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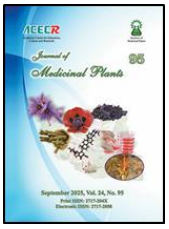

Review Article

Efficacy of chamomile in pain relief: A systematic review and meta-analysis of clinical trials

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ABSTRACT

Background: Chamomile is a well-known medicinal herb traditionally used for its analgesic properties. This article aims to provide an updated and critical evaluation of evidence from randomized controlled trials (RCTs) on chamomile's efficacy for pain relief. **Methods:** A comprehensive literature search was conducted in Medline, Embase, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials for published RCTs from inception to December 2024. Inclusion criteria comprised RCTs investigating chamomile in any form (oral, inhalation, or topical) compared to placebo or active controls, assessing pain as a primary outcome using validated tools such as the Visual Analog Scale (VAS), Numeric Rating Scale (NRS), or McGill Pain Questionnaire. Standardized mean differences (SMDs) with 95 % confidence intervals (CIs) were calculated using random-effects models. **Results** A systematic search identified 18 randomized controlled trials (n = 1,525) evaluating chamomile for pain relief. Meta-analysis demonstrated that chamomile was associated with significant pain reduction versus controls (SMD = −0.96; 9 5% CI: −1.36 to −0.57; P < 0.001), with high heterogeneity (I^2 = 91.1 %). Subgroup analyses showed significant effects in trials that used the Visual Analog Scale (VAS: SMD = −1.12, P < 0.001), with non-significant effects for other pain scales. Chamomile was superior to placebo (SMD = −0.95, P < 0.001) but did not differ significantly from other active treatments (P = 0.074). **Conclusion** This meta-analysis provides evidence supporting the analgesic efficacy of chamomile. However, substantial heterogeneity across studies suggests variability in design, populations, and protocols, warranting cautious interpretation. Future high-quality, standardized RCTs are needed to clarify effects by formulation, dosing, and clinical context.

Abbreviations: RCT, randomized controlled trials; SMD: standardized mean difference; CIs, confidence intervals; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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1. Introduction

Clinical pain is one of the most distressing symptoms encountered in medical settings, imposing a significant financial burden on healthcare systems. Pain is a major clinical, social, and economic challenge, with a global prevalence ranging from 8 % to over 60 % [1, 2]. Uncontrolled pain can lead to treatment failure [3] and a decline in health-related quality of life [4].

The mechanisms underlying pain are complex, involving multiple factors such as inflammatory, neuropathic [5], compressive, and ischemic changes in various organs [6]. Inflammatory mediators play a key role in clinical pain, with substances such as endothelin-1, nitric oxide, prostaglandin E2, and tumor necrosis factor-alpha contributing to pain perception [7]. Pharmacological interventions, including nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, and opioids, are considered the first-line treatments for pain management [8]. However, their long-term use is often limited by adverse effects and high costs [6].

Herbal medicine has a long-standing history in pain management [9]. Research suggests that certain medicinal plants may be effective in alleviating pain [10, 11]. Chamomile (*Matricaria chamomilla*), a member of the *Asteraceae* family, is one of the oldest and most widely used medicinal herbs globally [12]. It is available in various forms, including tea, raw extracts, and decoctions, and is widely consumed for its therapeutic properties [13]. Chamomile is recognized for its anti-inflammatory [14, 15], antioxidant [12, 16], muscle relaxant [17, 18], anti-cancer [12, 19], anxiolytic [13, 20], and antimicrobial [16] effects. In Iranian traditional medicine, chamomile has been used for its sedative and pain-relieving properties [21].

Evidence suggests that chamomile exerts its analgesic effects by modulating inflammatory pathways, reducing prostaglandin E2 levels, and inhibiting nitric oxide synthesis. Its bioactive compounds, such as chamazulene and apigenin, also contribute to pain relief by interacting with pain receptors and enhancing endogenous analgesic mechanisms [21-26].

Both human [21-23] and animal [24] studies support the analgesic effects of chamomile, which may be attributed to its ability to reduce inflammatory mediators, enhance endogenous analgesic factors, and induce central nervous system analgesia [12]. Chamomile contains several bioactive compounds, including chamazulene, bisabolol oxide, and polyphenols. Its flavonoids, such as apigenin and its derivatives, have been shown to inhibit inducible nitric oxide synthase (iNOS) expression in activated macrophages [15]. Additionally, chamomile flavonoids effectively reduce endogenous prostaglandin E2 levels in macrophages, while its polyphenols exhibit anti-inflammatory properties comparable to corticosteroids such as hydrocortisone [21, 25].

Several clinical trials have reported the pain-relieving effects of chamomile in various medical conditions [27-38]. However, to date, no systematic review has comprehensively evaluated the efficacy of chamomile for pain management. This systematic review and meta-analysis aim to assess the efficacy of chamomile as a complementary therapy for pain management.

2. Materials and methods

This systematic review and meta-analysis evaluated the efficacy of chamomile compared to a control (placebo or other treatments) for pain relief. The study was conducted in accordance with the recommendations of the

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Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [26].

2.1. Literature search

Potential studies were identified through a systematic search of Medline, Embase, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials, covering publications from inception to December 30, 2024. Additionally, reference lists and citation records of relevant articles were manually searched. Full search details are in Additional File 1. No language or publication year restrictions were applied.

2.2. Inclusion and exclusion criteria

Studies were included if they met the following criteria:

i) RCTs with either a parallel or crossover design,

ii) Chamomile administered in any form (oral, inhalation, or topical),

iii) A control group receiving either an active intervention, no intervention, or a placebo,

iv) Pain as an outcome measure assessed using any validated tool (defined as any tool previously used in clinical trials for pain assessment, such as Visual Analog Scale [VAS], Numeric Rating Scale [NRS], or the McGill Pain Questionnaire, with established reliability and validity in published literature),

v) All types of pain were considered, including acute, chronic, inflammatory, and neuropathic pain, with no restrictions based on pain etiology.

Studies were excluded if they were non-randomized trials, observational studies, case reports, case series, or animal/cell studies. Trials combining chamomile with other herbs or insufficient methodological data were also excluded.

2.3. Study selection, data extraction, and quality appraisal

Two independent reviewers (S.Sh. and F.Gh.) screened studies by title/abstract and full-text review, with a third reviewer resolving disagreements. Extracted data included: first author, publication year, country, sample size, type of pain, chamomile form, control group, treatment duration, and outcomes.

The methodological quality of the included studies was assessed following the *Cochrane Handbook for Systematic Reviews of Interventions*. Evaluations covered: Generation of the allocation sequence (selection bias), Concealment of the allocation sequence (selection bias), Blinding of participants and personnel (performance and detection bias), Blinding of outcome assessors, Completeness of outcome data (attrition bias), Selective outcome reporting (reporting bias) and Other potential sources of bias.

2.4. Statistical analysis and bias assessment

To evaluate the effect of chamomile interventions on pain relief, we calculated standardized mean differences (SMDs) along with 95 % confidence intervals (CIs). Given the expected variability across studies—stemming from differences in study design, populations, and intervention protocols—a random-effects meta-analysis was conducted using the DerSimonian-Laird method.

Heterogeneity was assessed with Cochran's Q statistic (significance threshold: $P < 0.10$) and quantified using the I^2 statistic (interpreted as low [≤ 40 %], moderate [40 - 75 %], or high [≥ 75 %]). Tau^2 values were calculated to estimate between-study variance. Forest plots

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were generated to visually inspect heterogeneity.

Subgroup analyses were pre-specified based on:

(1) Pain assessment tool (VAS, NRS, McGill),

(2) Administration route (oral, inhalation, topical),

(3) Type of control (placebo, active treatment),

(4) Type of pain (acute, chronic, inflammatory, musculoskeletal) — to explore potential sources of heterogeneity.

However, due to limited reporting in included studies regarding specific pain types, dosage, and population characteristics, these variables could not be fully assessed, representing a limitation of this review.

To account for the statistical dependence of multiple time points within the same study, we adjusted variance estimates using an assumed correlation coefficient (P = 1). To assess the robustness of our findings, we conducted a sensitivity analysis, varying the correlation coefficient (P = 0.5 and P = 0.8).

To evaluate the stability of the pooled effect size, we performed a sequential study exclusion analysis, systematically removing individual studies to identify any undue influence on the overall results.

Publication bias was assessed using Begg's rank correlation test and Egger's regression test to detect funnel plot asymmetry. To estimate and adjust for potentially missing studies, we applied the Trim-and-Fill method under a random-effects model, consistent with the primary analysis. Given the heterogeneity of included studies and the need for sufficient power in Publication bias detection, subgroup analyses were restricted to datasets comprising at least 10 studies. All statistical analyses were performed using Comprehensive Meta-Analysis (CMA) software (Version 3.0), with statistical significance set at $P < 0.05$.

3. Results

3.1. Summary of the literature search

The initial electronic literature search identified 1,036 publications, including 54 from PubMed, 71 from Embase, 415 from Scopus, 120 from Cochrane, and 376 from Web of Science. After screening titles and abstracts, 41 studies were deemed potentially eligible. Full-text assessments led to the exclusion of 23 studies for the following reasons: one was duplicate, one was a non-randomized clinical trial, five were in languages other than the study criteria, four did not report the desired outcomes, and twelve involved chamomile in combination with other herbs. Eighteen RCTs were included in the meta-analysis [22, 23, 25, 29-43]. The literature search and study selection process are summarized in Fig. 1.

3.2. Study characteristics

Table 1 summarizes the key characteristics of the included trials, conducted between 2007 and 2024. A total of 18 RCTs comprising 1.525 patients (776 in the chamomile groups and 749 in the control groups) were included. All included studies utilized a parallel design. Sample sizes ranged from 20 to 150 participants. Chamomile was administered via topical application in 10 trials (55.6 %) (22, 25, 31, 33, 35-38, 40, 42)., oral route in 5 trials (27.8 %) (30, 32, 34, 41, 43), and inhalation in 3 trials (16.6 %) (23, 29, 39).

Pain assessment was predominantly performed using the VAS in 14 trials (77.8 %) [22, 23, 25, 29-30, 32, 35-36, 38-43], followed by the McGill Pain Questionnaire in 2 trials (11.1 %) [31, 34], NRS in 1 trial (5.5 %) [33], and a 1–3 intensity scale in 1 trial (5.5 %) [37].

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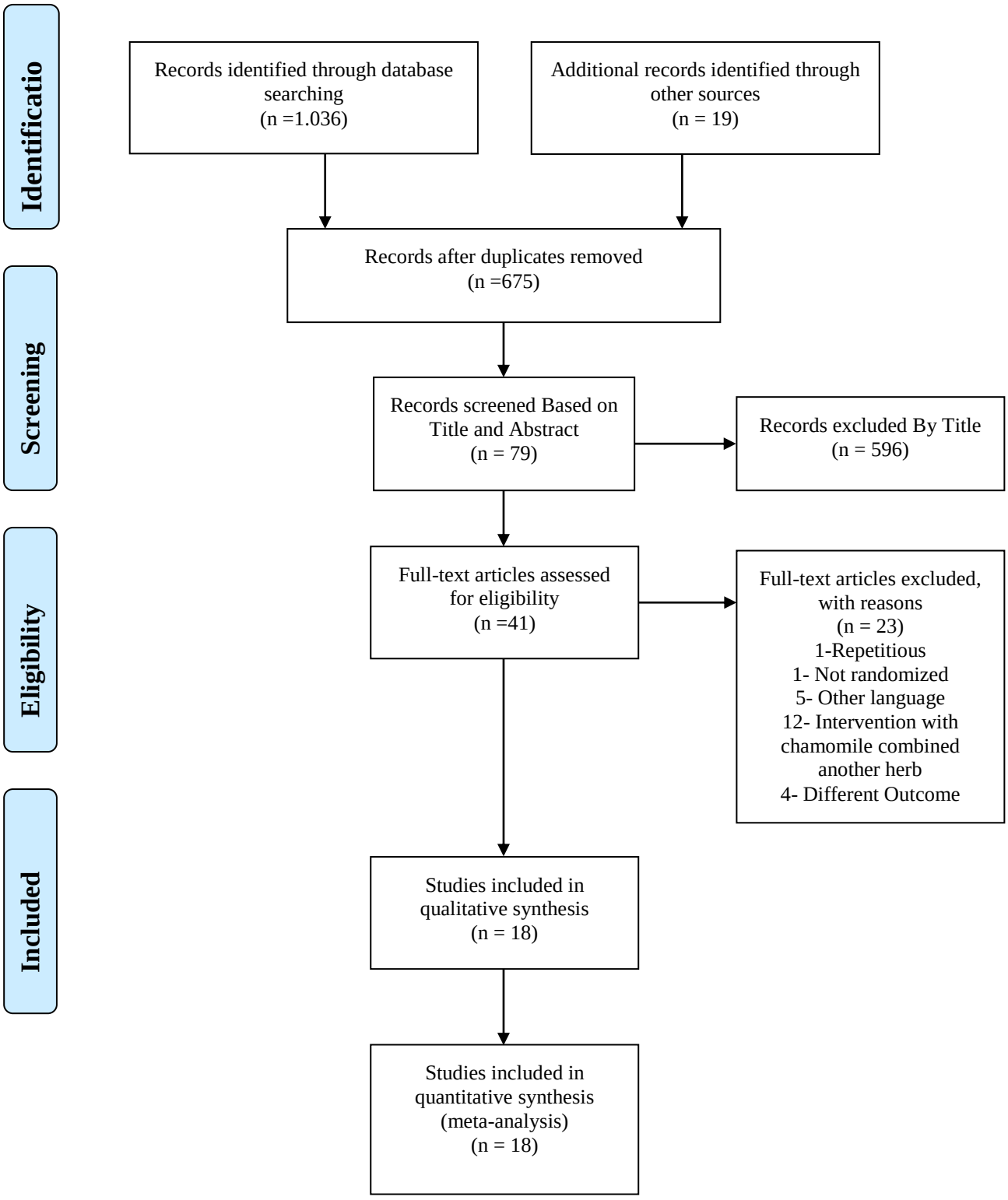

Fig. 1. The literature search and study selection process

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Table 1. Characteristics of the included trials

Author; year (Reference)	Admin Type	Time Point	Mean ± SD Intervention	Mean ± SD (Control)	Total Patients
Najafi et al., 2017 [29]	Inhalation	15 minutes	4 .± 1.68	5.77 ± 1.94	80
Zafar et al., 2015 [30]	Oral	Baseline	45.62 ± 4.4	54.4 ± 4.1	131
		30 minutes	53.1 ± 3.7	57.8 ± 3.8	
		1 hour	60.7 ± 3.4	66.3 ± 3.5	
		2 hours	69.5 ± 3.9	73.5 ± 4.9	
		Second stage	81.9 ± 2.6	85.1 ± 1.9	
Aradmehr et al., 2017 [31]	Topical	Baseline	8.74 ± 5.96	9.48 ± 6.51	98
		12 hours	11.9 ± 4.84	12.46±5.84	
		1 day	12.44 ± 5.27	13.04 ± 4.82	
		7 days	11.36 ± 5.04	14.88 ± 7.34	
		10 days	7.1 ± 4.1	9.96 ± 4.81	
		14 days	4.44 ± 3.43	7.41 ± 4.92	
Modarres et al., 2011 [32]	Oral	Baseline	4.65 ± 0.47	4.65 ± 0.47	80
		After 2 Cycles	1.12 ± 0.43	2.8± 1.04	
Talebi et al., 2018 [42]	Topical	After Pain (IUD Insertaion)	2.18 ± 2.16	3.98 ± 2.79	150
Jenabi et al., 2009 [34]	Oral	Baseline	8.42 ± 3.84	7.35 ± 1.91	80
		1 Month	7.32 ± 2.59	7.36 ± 2.17	
		3 Months	5.94 ± 2.01	7.1 ± 2.39	
Pazandeh et al., 2007 [35]	Topical	7 days	2.2 ± 0.79	2.3 ± 0.82	88
		14 days	0.48 ± 0.59	0.73 ± 0.66	
Andishe Tadbiri et al., 2015 [36]	Topical	1 day	3.92 ± 1.592	3.8 ± 2.077	45
		3 days	2.36 ± 2.24	4.47 ± 1.457	
		6 days	0.71 ± 0.611	2.4 ± 1.502	
Charousaei et al., 2011 [37]	Topical	3 days	1.78 ± 0.42	2.78 ± 0.72	72
		6 days	1.42 ± 0.5	2.03 ± 0.81	
		9 days	1.25 ± 0.44	1.69 ± 0.62	
Valenzuela et al., 2015 [38]	Topical	Baseline	7.4 ± 1.5	6.9 ± 1.8	57
		15 days	6.7 ± 1.5	6.1 ± 1.9	
		30 days	6.7 ± 1.4	6.2 ± 1.9	
Jornet et al., 2016 [40]	Topical	Baseline	5.15 ± 1.7	4.21 ± 1.8	60
		4 weeks	1.88 ± 1.3	4.31 ± 1.9	
Pirouzpanah et al., 2017 [41]	Oral	Baseline	3.35 ± 0.35	3.07 ± 0.3	44
		42 days	2.65 ± 0.24	2.93 ± 0.33	
Zargaran et al., 2018 [25]	Topical	Baseline	6.67 ± 1.46	6.31 ± 1.5	100
		15 minutes	5.34 ± 1.65	5.51 ± 1.42	
		30 minutes	3.9 ± 1.94	5.39 ± 1.57	
		45 minutes	2.9 ± 2.03	5.24 ± 1.63	
		1 hour	2.1 ± 2.01	5.27 ± 1.97	
		2 hours	1.26 ± 1.89	4.15 ± 1.86	
		6 hours	0.6 ± 1.57	3.13 ± 2.06	
		24 hours	0.27 ± 1.02	2.34 ± 2.31	
Khatami et al., 2016 [43]	Oral	1 hour	13 ± 4.8	22 ± 7.8	20
		24 hours	24 ± 8.4	39 ± 9.9	
		48 hours	3 ± 4.8	9 ± 7.3	
Abo Rokbah et al., 2023 [22]	Topical	1 day	3.2 ± 0.9	4.26 ± 0.7	70
		2 days	2.34 ± 0.94	3.65 ± 0.84	
		3 days	1.77 ± 0.77	3.06 ± 0.87	

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Table 1. Characteristics of the included trials (Continued)

Author; year (Reference)	Admin Type	Time Point	Mean ± SD Intervention	Mean ± SD (Control)	Total Patients
Hosseinipour et al., 2024 [33]	Topical	6 hours	0.035 ± 0.1838	0.0718 ± 0.2582	148
		12 hours	0.076 ± 0.265	0.2 ± 0.4	148
Zardosht et al., 2021 [39]	Inhalation	4 hours	2.4 ± 1.5	9 ± 0.9	128
		8 hours	1.3 ± 1.2	5.1 ± 0.8	
		12 hours	0.9 ± 1.2	4.1 ± 0.4	
Habibabad et al., 2023 [23]	Inhalation	6 hours	8 ± 1	9 ± 0.75	136
		12 hours	6 ± 1	8.5 ± 0.75	
		18 hours	4.5 ± 0.75	7.5 ± 0.75	

Table 1. Characteristics of the included trials (Continued)

Author; year (Reference)	N chamomile /control	Pain Assessment Tool	chamomile dosage	Control Type
Najafi et al., 2017 [29]	40/40	Visual Analog Scale (VAS)	2 drops of chamomile essence on a cotton ball	Placebo (normal saline)
Zafar et al., 2015 [30]	42/42	Visual Analog Scale (VAS)	3 drops of Chamomilla recutita (1M potency)	Placebo (saline injection and oral placebo)
Aradmehr et al., 2017 [31]	50/48	McGill Pain Questionnaire	0.5 g cream twice a day	Placebo cream (Cold)
Modarres et al., 2011 [32]	40/40	Visual Analog Scale (VAS)	500 mg capsules every 8 hours	Mefenamic acid
Talebi et al., 2018 [42]	50/50	Ruler pain (Visual analog scale or similar)	3 drops of chamomile oil on a cotton ball	Placebo (propylene glycol) and Control (no intervention)
Jenabi et al., 2009 [34]	40/40	McGill Pain Questionnaire	2 cups of chamomile tea daily	No treatment
Pazandeh et al., 2007 [35]	44/4	Visual Analog Scale (VAS)	Sitz bath twice daily	Placebo
Andishe Tadbiri et al., 2015 [36]	14/15	Visual Analog Scale (VAS)	Chamomile in Orabase applied four times a day	Placebo (Orabase alone) and Triamcinolone in Orabase
Charousaei et al., 2011 [37]	36/36	Pain intensity rated using a 1-3 scale	Chamomile solution: 6g dried chamomile in 150 cc water	1% hydrocortisone ointment (applied once a day)
Valenzuela et al., 2015 [38]	31/36	Visual Analog Scale (VAS)	2 % chamomile gel, 0.5 ml twice daily for 30 seconds	Placebo (gel with the same excipients but without chamomile)
Jornet et al., 2016 [40	30/30	Visual Analog Scale (VAS)	2 % Chamaemelum nobile gel (0.5 mL, 3 times a day)	Placebo
Pirouzpanah et al., 2017 [41]	22/22	Visual Analog Scale (VAS)	6 g of chamomile tea per day	Placebo (herbal tea without chamomile)
Zargaran et al., 2018 [25]	38/34	Visual Analog Scale (VAS)	10% traditional chamomile oil in liquid paraffin	Placebo (liquid paraffin with colloidal silicon dioxide)

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Table 1. Characteristics of the included trials (Continued)

Author; year (Reference)	N chamomile /control	Pain Assessment Tool	chamomile dosage	Control Type
Khatami et al., 2016 [43]	10/10	Visual Analog Scale (VAS)	300 ml of chamomile extract per day	Placebo (water with small amounts of chamomile essence)
Abo Rokbah et al., 2023 [22]	35/35	Visual Analog Scale (VAS)	2 ml gel	Placebo
Hosseinipour et al., 2024 [33]	74/74	Numeric Rating Scale (NRS)	3 cc ointment	Placebo (ointment)
Zardosht et al., 2021 [39]	62/45	Visual Analog Scale (VAS)	3 drops of chamomile essential oil	Placebo (neutral oil)
Habibabad et al., 2023 [23]	34/34	Visual Analog Scale (VAS)	1 drop of chamomile essential oil with 6L/min of oxygen.	Placebo

Regarding control groups, placebo controls were employed in 16 trials (88.9 %), whereas active comparators such as mefenamic acid or hydrocortisone were used in 2 trials (11.1 %).

Various pain conditions were assessed, including dysmenorrhea, postoperative pain, migraine, musculoskeletal pain, aphthous stomatitis, oral lichen planus, and procedural pain (e.g., IUD insertion, cesarean section).

3.3. Overall Meta-Analysis

Pooling data from 18 trials with a total of 1,525 participants, the random-effects model estimated an overall SMD of -0.962 (95 % CI: -1.358 to -0.565), indicating a large effect size based on Cohen's criteria (≥ 0.8). The chamomile treatment resulted in a statistically significant reduction in pain compared to the control group ($Z = -4.749$, $P < 0.001$) (Fig. 2). Substantial between-study heterogeneity was observed ($Q = 191.413$, $df = 17$, $P < 0.001$; $I^2 = 91.119$ %), with a τ^2 of 0.659, suggesting considerable variation that warrants further investigation.

3.4. Subgroup Analysis by Pain Assessment Tool

The SMD varied across different pain assessment tools. Studies using the VAS (K = 14) demonstrated a significant effect (SMD: -1.117, 95 % CI: -1.597 to -0.638, $P < 0.001$) [22, 23, 25, 29-30, 32, 33, 35-36, 38-43]. In contrast, studies utilizing the NRS (k = 1, SMD = -0.265, 95 % CI: -1.10 to 1.46, P = 0.764), pain intensity rated on a 1–3 scale (P = 1, SMD = -1.140, 95 % CI: -2.91 to 0.63, P = 0.206), and the Short-Form McGill Pain Questionnaire (K = 2, SMD = -0.220, 95 % CI: -1.46 to 0.02, P = 0.727) did not yield statistically significant results [31, 34] (Fig. 3). No significant between-group difference was detected (P = 0.484). However, substantial heterogeneity was observed within the VAS subgroup ($Q = 158.579$, $df = 13$, $P < 0.001$, $I^2 = 91.802$ %).

3.5. Subgroup Analysis by Type of Control

A subgroup analysis based on the type of control group demonstrated different SMDs. Studies comparing chamomile with placebo (k = 16) showed a significant reduction in pain (SMD: -0.945, 95 % confidence interval (CI): -1.376 to -0.515, $P < 0.001$) [22, 23, 25, 29-31,

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33-36, 38-43]. However, when chamomile was compared with other treatments [32, 37], no significant difference was observed (K = 2, SMD: -1.098, 95 % confidence interval (CI: -2.303 to 0.107, P = 0.074). Other treatments included mefenamic acid and hydrocortisone ointment. The difference between groups was not statistically significant (Q = 0.055, df = 1, P = 0.815) (Fig. 4). Significant heterogeneity was detected in the placebo-controlled subgroup (Q = 187.824, df = 15, P < 0.001, I^2 = 92.014 %), while heterogeneity was negligible in the active treatment subgroup.

3.6. Subgroup analysis by administration route

When stratified by the mode of administration, inhalation (K = 3) demonstrated the largest effect size (SMD: -2.475, 95 % CI: -3.315 to -1.635, P < 0.001), followed by oral administration (K = 5; SMD: -0.768, 95 % CI: -1.419 to -0.118, P = 0.021) [30, 32, 34, 41, 43], and topical application (K = 10; SMD: -0.609, 95 % CI: -1.056 to -0.162, P = 0.008) [22, 25, 31, 33, 35-38, 40, 42] (Fig. 5).

A statistically significant difference between these subgroups was observed (p = 0.001), suggesting that inhalation may be the most effective administration route.

Heterogeneity was highest in the inhalation subgroup (Q = 59.771, df = 2, P < 0.001, I^2 = 96.654 %) [23, 29, 39], followed by oral administration (Q = 24.893, df = 4, P < 0.001, I^2 = 83.931 %) and topical application (Q = 36.529, df = 9, P < 0.001, I^2 = 75.362 %).

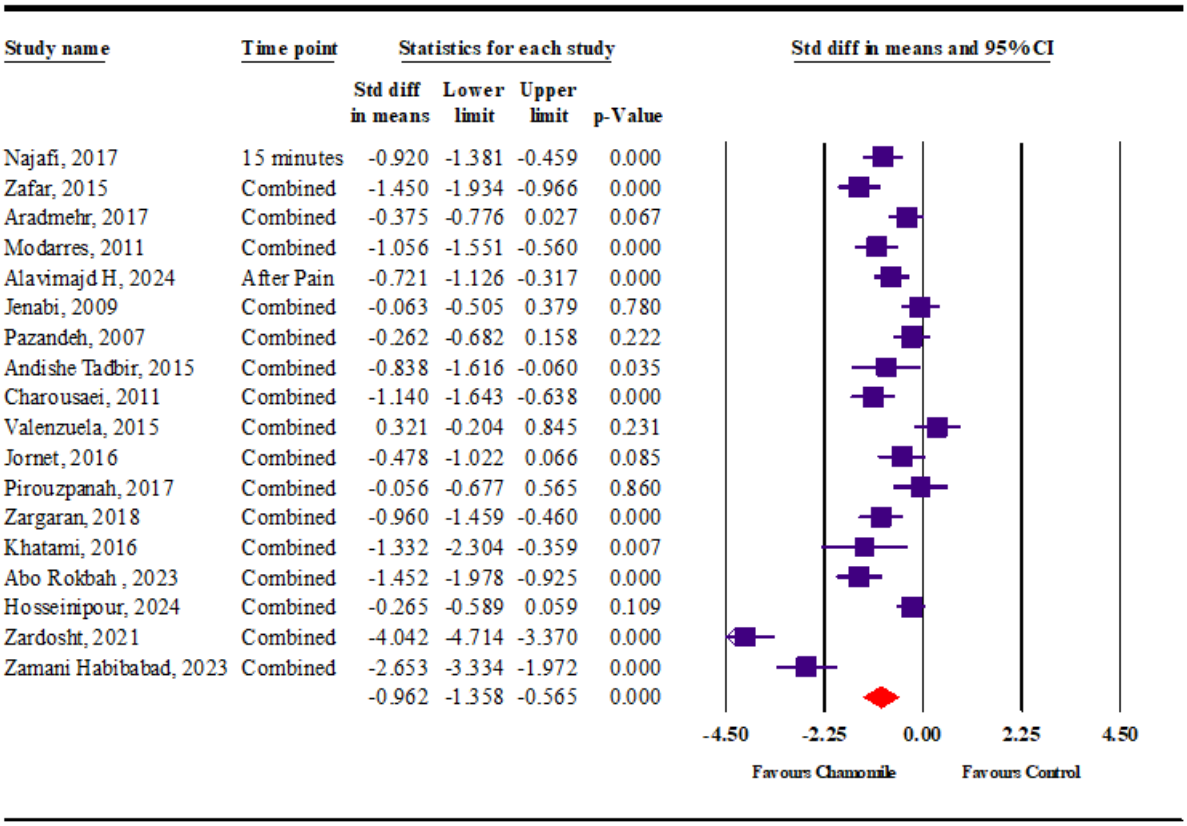

Fig. 2. Forest plot of the overall meta-analysis

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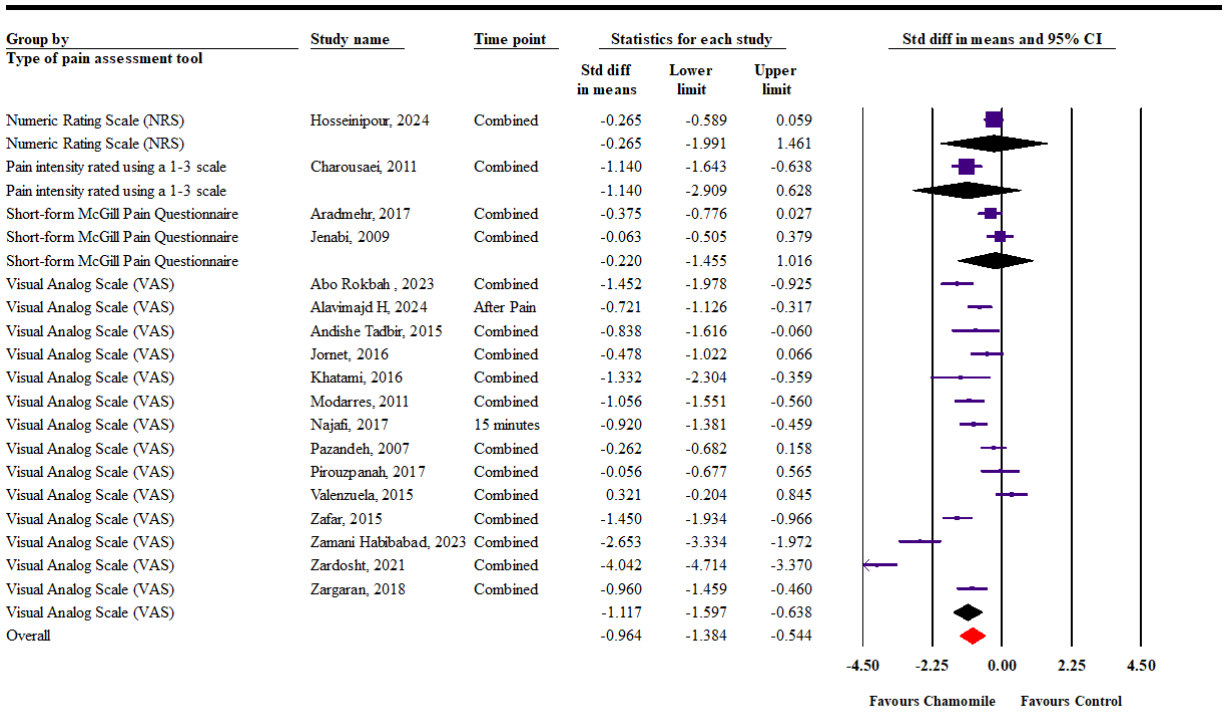

Fig. 3. Forest plot of the subgroup analysis by pain assessment tool

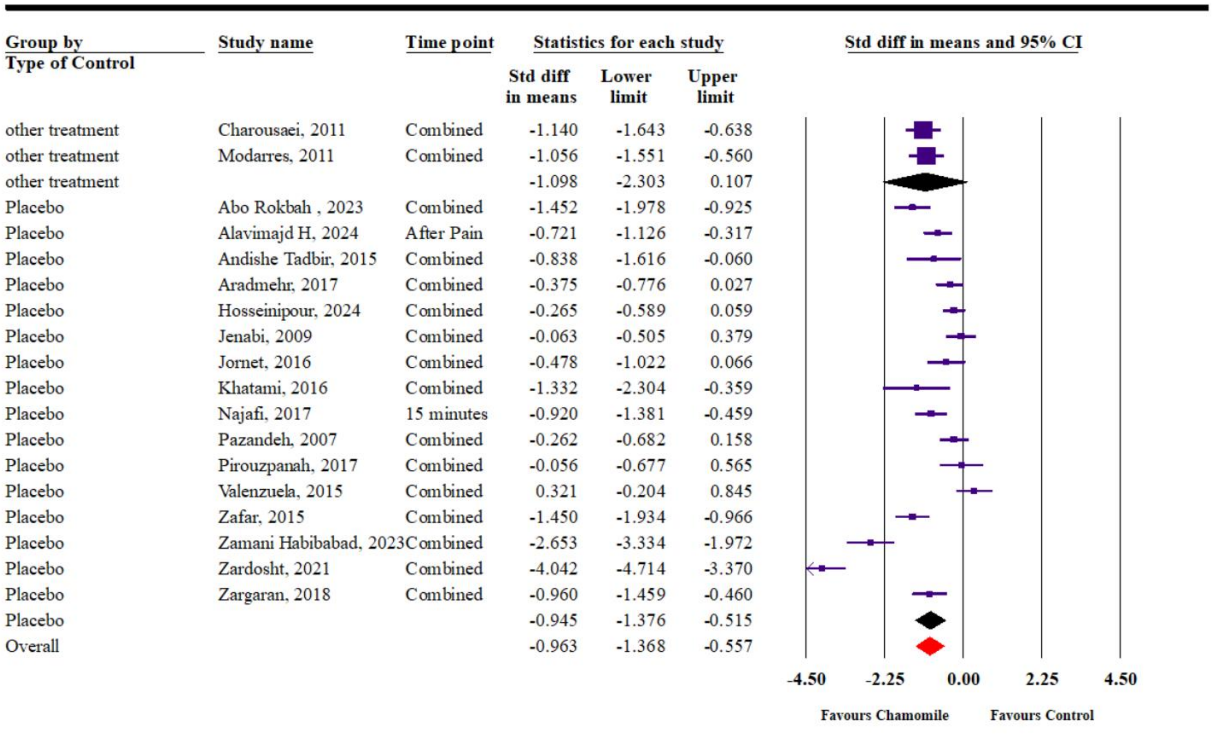

Fig. 4. Forest plot of the subgroup analysis by type of control

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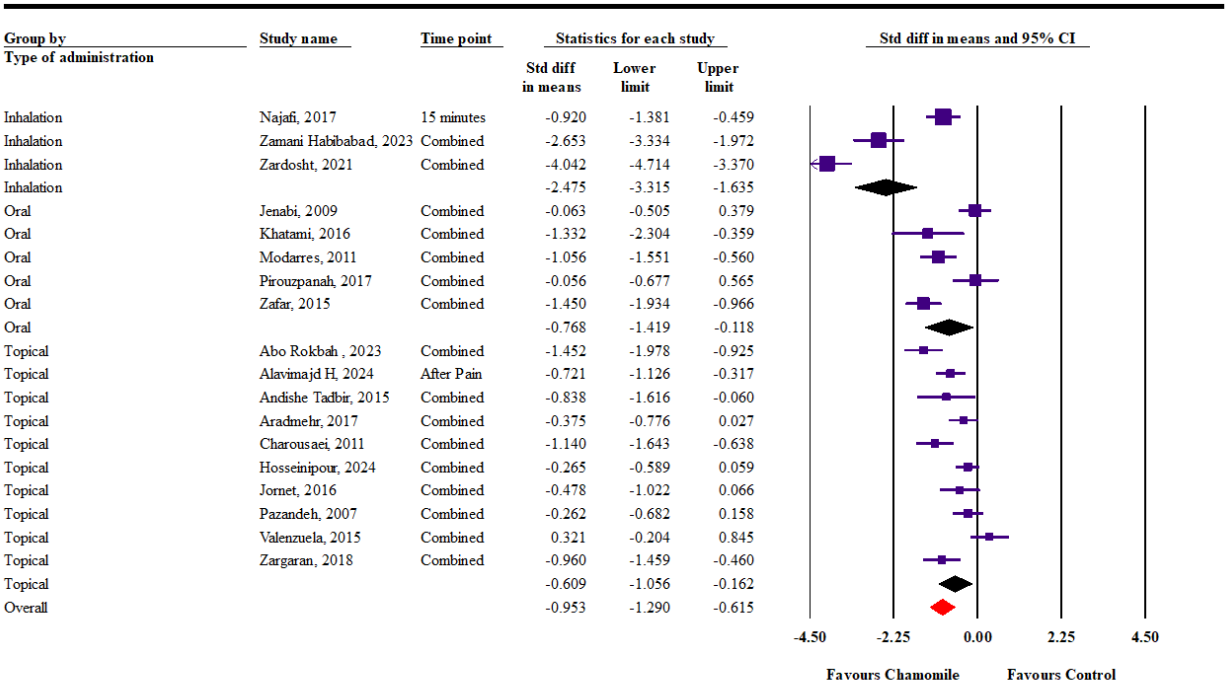

Fig. 5. Forest plot of the subgroup analysis by type of administration

3.6. Publication Bias and Sensitivity Analysis

High heterogeneity remained across most subgroups. Sensitivity analyses confirmed the robustness of the results. Sequential study exclusion demonstrated that the pooled effect size remained stable across all iterations, with no single study exerting undue influence (Fig. 6).

Egger's regression test indicated significant funnel plot asymmetry (P = 0.040), while Begg's test was not statistically significant (P = 0.058). Trim-and-Fill analysis under the random-effects model imputed five hypothetical studies, resulting in an adjusted SMD of –1.32 (95 % CI: – 1.76 to – 0.88) (Fig. 7). Despite a 37.5% increase in effect magnitude, the adjusted estimate remained statistically significant and directionally consistent. In subgroups comprising at least 10 studies, neither Begg's test (P = 0.283, 0.324, 0.065) nor Egger's test (P = 0.306, 0.174, 0.052) indicated statistically significant asymmetry, suggesting no strong evidence of publication bias within these subsets (Table 2).

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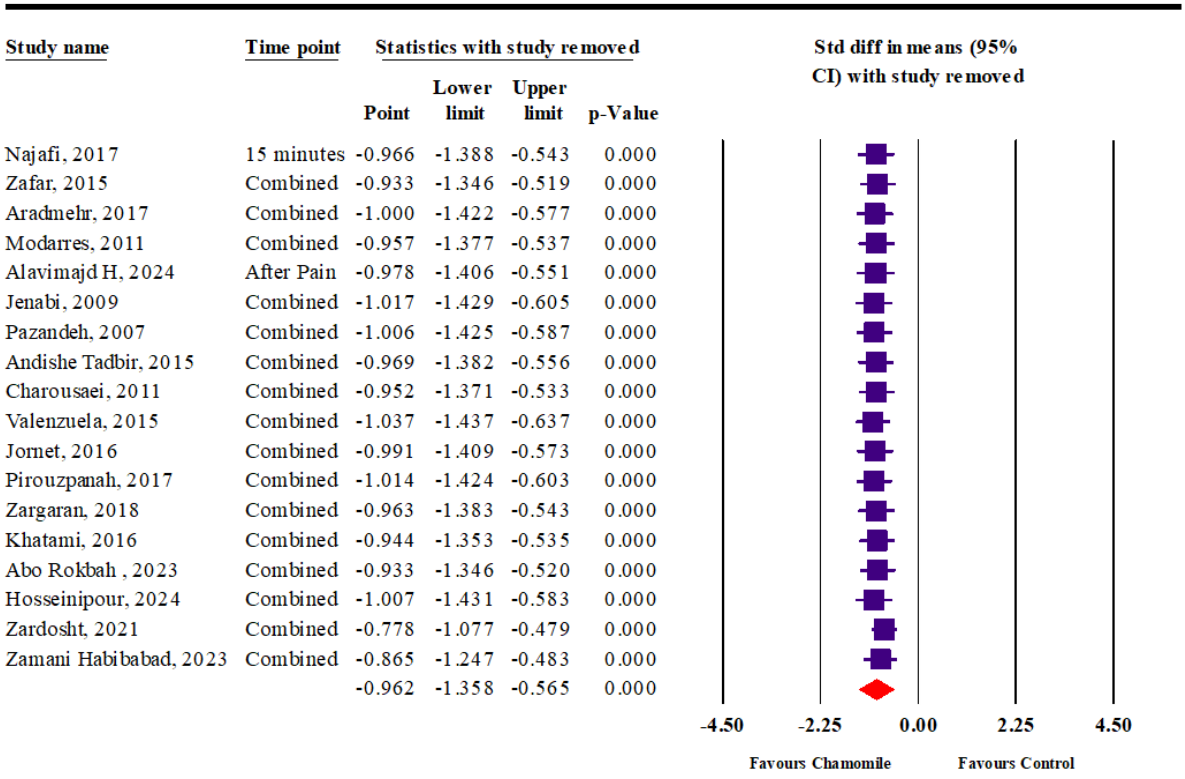

Fig. 6. Results of the sensitivity analysis

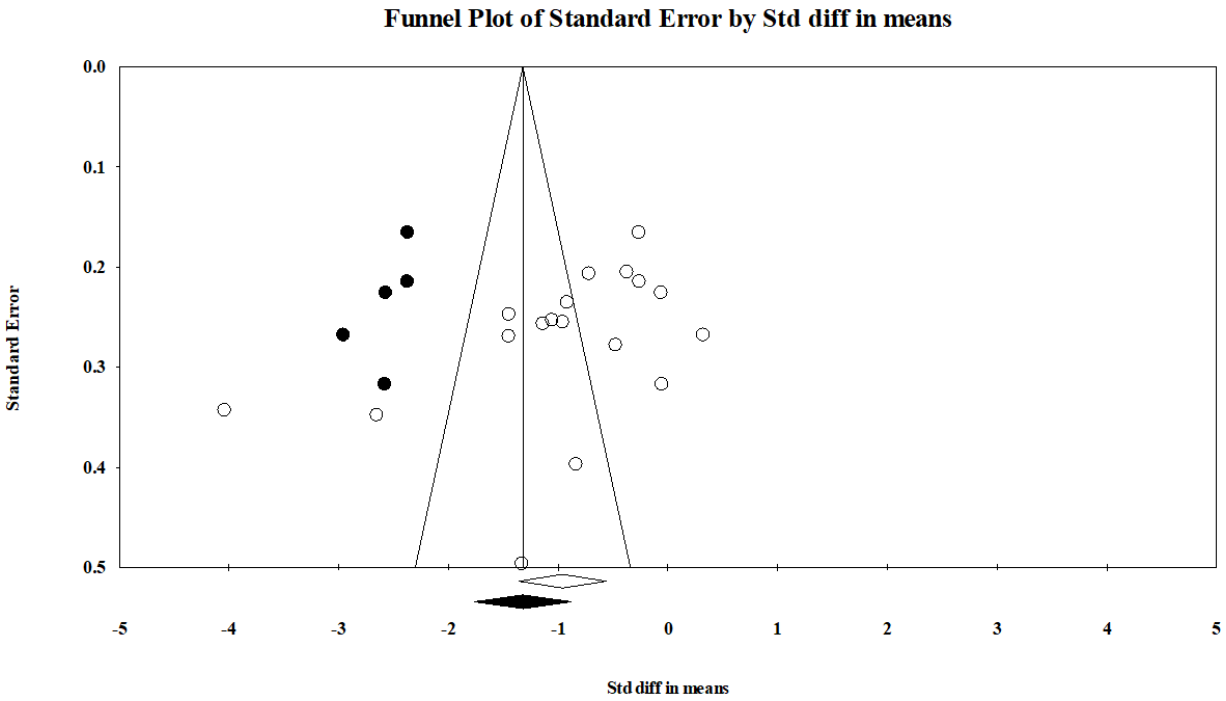

Fig. 7. Funnel plot for detecting publication bias

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4. Discussion

This systematic review and meta-analysis aimed to evaluate the efficacy of chamomile (*Matricaria chamomilla*) in pain management. A total of eighteen randomized controlled trials (RCTs) assessing various pain conditions, administration routes, and populations were included. The pooled results demonstrated a statistically significant and clinically large reduction in pain scores (standardized mean difference [SMD] = − 0.962) among individuals receiving chamomile compared to controls. According to Cohen's criteria, this represents a large effect size, suggesting potential clinical importance beyond mere statistical significance. Our findings suggest that chamomile may serve as an effective natural remedy for managing pain across various conditions.

The analgesic effects of chamomile are primarily attributed to its bioactive compounds, such as flavonoids (e.g., apigenin) and terpenoids (e.g., bisabolol), which exhibit anti-inflammatory, antispasmodic, and sedative properties [12]. These mechanisms may contribute to the alleviation of various types of pain, such as menstrual pain, musculoskeletal pain, and postoperative pain [13, 14]. Notably, several studies reported that chamomile's pain-relieving effects were comparable to conventional analgesics, suggesting its potential role as an adjunct or alternative therapy in pain management.

Our findings are consistent with previous systematic reviews that have explored the efficacy of herbal interventions for pain management. For instance, a recent meta-analysis by Kiani et al. (2024) also reported significant pain reduction with chamomile use, particularly through inhalation and topical routes, reinforcing the credibility of our results [45]. However, unlike the present review, which focused exclusively on chamomile and included a broader range of pain conditions and administration methods, their analysis had a narrower scope. Similarly, a systematic review by Sah et al. (2022) provided a comprehensive overview of chamomile's therapeutic applications, including its analgesic properties, but did not conduct a quantitative meta-analysis, thus limiting the comparability of effect sizes [46]. The current study differentiates itself by providing a rigorous statistical synthesis of RCTs, subgroup analyses based on administration routes and control types, and an assessment of publication bias, offering a more nuanced understanding of chamomile's efficacy in pain relief.

Traditional pain management relies on pharmacological agents such as nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and acetaminophen, each of which has well-documented efficacy but also carries significant adverse effects [45]. NSAIDs, including ibuprofen and diclofenac, are widely used for inflammatory pain conditions but are associated with gastrointestinal ulcers, renal impairment, and cardiovascular risks [46]. Opioids, while highly effective for moderate to severe pain, pose concerns regarding addiction, tolerance, and respiratory depression [47]. Acetaminophen, although considered safer, carries risks of hepatotoxicity, particularly at high doses or in patients with liver disease [46].

Compared to these pharmacological treatments, chamomile presents a potentially safer alternative with fewer side effects [48, 49]. Its analgesic and anti-inflammatory properties are attributed to bioactive compounds such as flavonoids (e.g., apigenin) and terpenoids (e.g., bisabolol), which modulate inflammatory pathways and inhibit cyclooxygenase-2 (COX-2), similar to NSAIDs but without the associated

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gastrointestinal risks [50]. Additionally, chamomile's muscle-relaxant properties may contribute to its effectiveness in dysmenorrhea, paralleling the effects of antispasmodic drugs like mefenamic acid [32, 34].

However, the effectiveness of chamomile remains modest compared to conventional analgesics. A meta-analysis of NSAID efficacy in dysmenorrhea reported a greater reduction in pain scores than herbal remedies, suggesting that while chamomile may provide complementary benefits, it may not serve as a complete substitute for NSAIDs in acute pain conditions. Additionally, the evidence for analgesic effects of chamomile remains heterogeneous, with some studies reporting non-significant pain reduction compared to placebo [27, 32, 51].

Our findings align with previous reviews on herbal medicine for pain management. For example, a systematic review of Derris scandens demonstrated comparable pain relief to NSAIDs, while a meta-analysis of *Rosa damascena* showed promising analgesic properties but raised concerns regarding potential nephrotoxic and hepatotoxic effects at high doses [52]. In contrast, chamomile has demonstrated both effectiveness and a favorable safety profile, with no significant adverse events reported [40, 43, 49].

Given the increasing preference for natural and complementary therapies, chamomile presents an attractive option, particularly for individuals seeking alternatives to synthetic drugs due to concerns over side effects. In many countries, chamomile is affordable and widely accessible, making it a viable complementary remedy for pain management [53]. While many medicinal herbs carry potential adverse effects, chamomile is recognized as safe for use in the United States [49, 54]. It is used to control pain in infants and children [17]. Given that pain management plays a critical role in improving maternal outcomes during and after childbirth [55], particularly in regions with high perinatal risk, the use of safe and accessible herbal therapies like chamomile may offer adjunctive benefits in perinatal care settings. However, despite its favorable safety profile, chamomile is not entirely free of risks. Studies indicate potential interactions with anticoagulants, benzodiazepines, and cytochrome P450-metabolized drugs, necessitating caution in patients on polypharmacy [53]. Moreover, allergic reactions, particularly in individuals sensitive to Asteraceae family plants, should be considered [54].

A critical gap in existing research is the lack of standardized dosage and method of administration. Chamomile has been administered in various forms, including oral, topical, and inhalation methods, each of which may influence its absorption, bioavailability, and therapeutic effectiveness [29-44]. Subgroup analysis indicated that the route of administration significantly influenced the magnitude of effect, with inhalation demonstrating the largest effect size (SMD = − 2.475), followed by oral and topical routes. This superior efficacy of inhalation may be due to faster systemic absorption of active volatile compounds, such as chamazulene and bisabolol oxide, via the respiratory mucosa compared to gastrointestinal or dermal absorption. This suggests that the delivery route should be carefully considered when developing chamomile-based products for pain relief. Additionally, while chamomile is generally considered safe, dosage standardization is necessary to ensure consistent efficacy across patient populations.

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Future product development may benefit from focusing on inhalable chamomile formulations, such as essential oil vaporizers or inhalers, which could enhance bioavailability and therapeutic efficacy. While some chamomile inhalation products exist on the market (e.g., aromatherapy oils), their standardization and clinical evaluation remain limited. This highlights the need for the development and testing of regulated inhalable chamomile formulations specifically targeted for pain management.

The role of chamomile in multimodal pain management strategies requires further investigation. Conventional pharmacological treatments, including NSAIDs, opioids, and corticosteroids, remain the primary options for pain relief. While chamomile demonstrated significant pain reduction compared to placebo, its effects were not significantly different from standard analgesics in the limited trials that made direct comparisons. This suggests that chamomile may be most beneficial when used as an adjunct to existing therapies rather than as a stand-alone treatment. Future clinical trials should explore the potential synergistic effects of chamomile when combined with conventional analgesics, particularly in patients who experience adverse effects from long-term NSAID or opioid use.

The overall risk of bias among included RCTs was variable. While most studies reported adequate randomization and allocation concealment, issues such as lack of blinding, small sample sizes, and incomplete outcome data were noted in several trials. These methodological limitations may contribute to the substantial heterogeneity (I^2 = 91.1 %) observed in the meta-analysis and affect the reliability of the pooled estimates. Therefore, future RCTs with rigorous methodological designs, including appropriate blinding, allocation concealment, and sufficient sample sizes, are essential to validate the efficacy of chamomile for pain relief.

This review had several limitations. While our analyses suggested potential funnel plot asymmetry (Egger's test: P = 0.040), these results should be interpreted cautiously. First, Begg's and Egger's tests have limited power to detect bias in meta-analyses with fewer studies or substantial heterogeneity, as observed in our subgroup analyses. Second, the Trim-and-Fill method, while widely used, assumes that funnel plot asymmetry arises solely from publication bias and that missing studies are symmetrically distributed—assumptions that may not hold in the presence of clinical or methodological heterogeneity (e.g., variations in pain measurement tools or population characteristics across studies). The imputation of five studies under the random-effects model increased the effect magnitude by 37.5 % but did not alter the significance or direction of findings, suggesting that while small-study effects may exist, they are unlikely to invalidate the primary conclusions. Furthermore, substantial variability in the dosage forms, concentrations, and administration protocols of chamomile across the included studies precluded any meaningful dose-response analysis or formulation-specific recommendations. Future trials should strive to standardize and comprehensively report chamomile preparations to enhance comparability and clinical applicability. Finally, the nonsignificant subgroup-level asymmetry ($P > 0.05$ for all subgroups with ≥ 10 studies) implies that observed bias in the overall analysis may reflect residual heterogeneity rather than selective publication. These limitations underscore the need to interpret pooled estimates as hypothesis-generating, pending

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confirmation by large, prospectively registered trials.

5. Conclusion

This meta-analysis provides evidence supporting the efficacy of chamomile in pain relief, particularly when assessed using the VAS and compared to placebo. The findings indicate that inhalation is the most effective administration route, followed by oral and topical applications.

This study is strengthened by its comprehensive literature search, adherence to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, and robust statistical analysis, including assessment of publication bias and sensitivity analysis. However, limitations include heterogeneity in study populations, variations in pain assessment tools, dosing regimens, and chamomile preparations, which may impact the generalizability of the findings. Further high-quality, standardized RCTs are needed to confirm these findings and establish optimal dosing and administration strategies for chamomile in pain management.

Author contributions

F.Gh. and M.K. provided the original idea. S.Sh., F.Gh., Sh.Sh and M.S. carried out the data extraction, analysis and interpretation of data, and drafted the article. H.B. carried out the statistical analysis. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare that they have no competing of interests.

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