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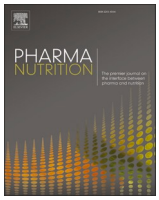

Nano-curcumin supplementation for the management of migraine: A systematic scoping review and meta-analysis

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ABSTRACT

Objectives: Migraine is a common neurological disorder contributing significantly to global disability. Nano-curcumin, known for its anti-inflammatory and neuroprotective properties, has emerged as a promising candidate for migraine prophylaxis. Herein, we assessed the effects of nano-curcumin supplementation on headache attack, severity, and duration in adult patients.

Methods: Five biomedical databases were searched until March 2024 for randomized controlled trials (RCTs). 13 records fulfilled the inclusion criteria, eight of which were considered for meta-analysis. The risk of bias was assessed using ROB2. Outcomes were quantified using both Standardized Mean Difference (SMD) and Mean Difference (MD) along with the 95 % Confidence Intervals (CIs). Pooled intervention effects were estimated using both common-effects and random-effects models.

Results: Our analysis revealed that 80 mg nano-curcumin supplementation per day for two months in young adults reduced migraine attacks (SMD −0.55; 95 % CI: −1.07 to −0.02), severity (SMD −0.64; 95 % CI: −1.10 to −0.19), and duration (MD −2.90; 95 % CI: −4.66 to −1.13) when compared with placebo. When combined with nutraceuticals such as omega-3 and coenzyme Q10, nano-curcumin demonstrated enhanced efficacy in reducing migraine attacks (SMD 1.19; 95 % CI: 0.90–1.48). Among those who received nano-curcumin supplementation only, a before and after intervention analysis showed a reduction in migraine attacks (SMD −0.77; 95 % CI: −1.00 to −0.54), severity (SMD −0.92; 95 % CI: −1.50 to −0.33), and duration (SMD −0.63; 95 % CI: −1.05 to −0.20).

Conclusions: Evidence from literature suggests that nano-curcumin supplementation might be effective in reducing migraine symptoms. However, caution is advised, and further research is recommended to confirm these findings, considering the single institutional source of all studies.

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1. Introduction

Migraine represents a significant public health concern that affects a heterogeneous demographic population [1]. Clinically, it is characterized by the occurrence of recurrent episodes of headache, generally of varying intensity, and often accompanied by nausea, photophobia, and phonophobia [2]. The underlying pathophysiology of migraine is complex and thought to involve a network of neurovascular pathways [3,4]. Hence, the search for efficacious treatment modalities has been a central focus of research for years, with a particular emphasis on the identification of active compounds that can alleviate symptoms and improve the quality of life for those afflicted.

One such active compound under investigation is curcumin, a polyphenolic compound extracted from the rhizome of *Curcuma longa* [5]. Curcumin, a traditional ingredient in Ayurvedic medicine, has been extensively documented in literature for its antioxidant [6,7] and neuroprotective properties [8,9]. These properties, in conjunction with its anti-inflammatory and analgesic effects [10–12], have positioned it as a leading contender for research on migraine prevention and treatment. Curcumin's therapeutic effects are believed to be a result of multifaceted modulation of multiple signaling pathways, including the inhibition of cyclooxygenase-2 (COX-2), lipoxygenase, and inducible nitric oxide synthase (iNOS); downregulation of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukins; and the suppression of oxidative stress through its free radical scavenging activity [13–15].

Nevertheless, the bioavailability of curcumin is constrained by its suboptimal solubility, stability, and absorption properties [16]. To circumvent these limitations, a nanoparticle formulation of curcumin, or "nano-curcumin", has been developed, to enhance its bioavailability and therapeutic potential. It has been demonstrated that nano-curcumin has a superior plasma concentration, tissue distribution, and cellular uptake compared to conventional curcumin formulations [17–20]. Recent clinical trials have reported on the therapeutic potential of nano-curcumin, either as monotherapy or combination therapy with nutraceuticals including omega-3 fatty acids and coenzyme Q10 [21, 22]. These trials have yielded preliminary indications that nano-curcumin may attenuate the frequency, intensity, and temporal span of migraine episodes.

Furthermore, evidence points out that nano-curcumin may cause a reduction in serum concentrations and genetic expression of inflammatory cytokines, markers of oxidative stress, and endothelial adhesion molecules [22–24]. However, the sample size and methodology of these trials vary considerably, limiting the overall evidence pool. As both patients and neurologists turn to and express growing interest in Complementary, Alternative, and Integrative (CAI) Neurology [25,26], it is imperative that recommendations are based on evidence that is scientifically sound, rigorously observed, and replicable across the spectrum.

We herein conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) that evaluated the efficacy of nano-curcumin in migraine treatment, with a comparison of its effects on headache duration, severity, and attack against a placebo, dietary supplements, or in combination. We complemented our analysis by investigating the before-and-after outcomes of nano-curcumin intervention, aiming to isolate its specific effects from those of other concurrent interventions. The findings of this meta-analysis are expected to contribute to the existing evidence base that guides the clinicians in the treatment of migraines and to inform future research directions in the field of migraine therapeutics.

Table 1
PICOS scheme for the present review.

Component	Identifier
Patient	Adult patients diagnosed with episodic or chronic migraine, with or without aura, as defined by the International Headache Society
Intervention	Nano-curcumin as a single or combined intervention, with a clear description of the dosage, duration, and formulation
Control	Placebo or other standard clinical treatment intervention
Primary Outcomes (meta-analysis)	Migraine attacks (number of episodes per month), migraine severity (pain intensity on a numerical or visual analog scale), and migraine duration (hours per attack)
Secondary Outcomes (review)	Biomarker levels in migraine patients attributed in the trials to nano-curcumin as a stand-alone intervention
Study design	Randomized controlled trials (RCTs)

2. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were adhered to when reporting the findings in this review [27]. The study protocol was approved by PROSPERO (CRD42024521986) on March 18, 2024. Deviations from the registered protocol are documented in **Appendix 1**.

2.1. Study objectives

We used the patient, intervention, control, outcome, and study design (PICOS) scheme to systematically strategize our search goals. The study aims were based on the clinical question to determine the effect of nano-curcumin supplementation compared to placebo or standard clinical treatment regimens on the attack frequency, severity, and duration in adult patients (Table 1).

2.2. Literature search

We systematically searched five biomedical databases including PubMed, Scopus, Web of Science Core Collection, Medline via Ovid, and Embase via Ovid for randomized controlled trials (RCTs) indexed from database inception to March 2024. The search was performed independently by two authors (EKK and JK). Our search string comprised a combination of MeSH-derived terms related to nano-curcumin and migraine without any language restrictions. The specific search strings utilized for each database are detailed in **Appendix 2**.

2.3. Inclusion and exclusion criteria

We considered studies for inclusion if they reported findings on adults (≥ 18 years) diagnosed with episodic or chronic migraine, with or without aura, according to the International Headache Society [2]. We focused on RCTs examining the therapeutic efficacy of nano-curcumin, either stand-alone or in conjunction with other treatments, providing empirical data on headache duration, severity, and attack and associated effect on various biomarker levels. A stringent exclusion criterion was followed, ruling out non-randomized studies, quasi-experimental studies, observational studies, non-comparative studies, case reports, case series, reviews, commentaries, letters, and research involving children, animals, or in vitro models. Studies with secondary headaches, other neurological disorders, non-nano-encapsulated curcumin formulations, ambiguous outcomes, or insufficient data for effect size calculation were also excluded. Non-English trials were also excluded. We also did not consider studies reporting on patients with contraindications to nano-curcumin such as allergies, bleeding disorders, or gallstone disease.

2.4. Study screening, data extraction, and quality appraisal

The search results were imported into Covidence software to remove duplicates, with additional manual checks. The title and abstract screening were done independently by EKK, DGM, JK, GB, BA, BOO, and DSB. The reviewers were blinded to the results from other reviewers, achieving a 96 % concordance in the study screening phase. Full text of eligible records was obtained from online sources including publisher's

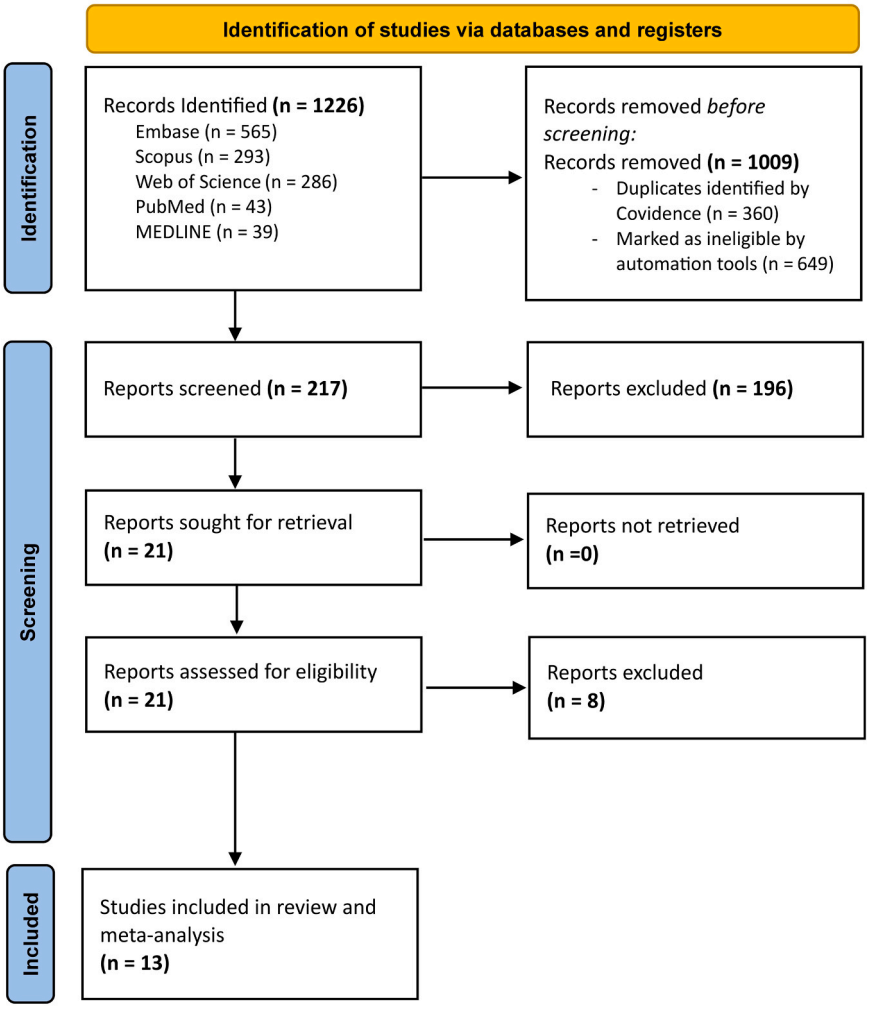

Fig. 1. PRISMA flowchart for the present review. The flowchart shows the number of studies considered and excluded at each step of the systematic review process.

website, aggregation platforms like ResearchGate, and by contacting corresponding authors. Wherever the corresponding author did not reply (after two reminders over a two-week period), other listed authors in the study were contacted by email.

Data extraction from included records was done manually using an in-house prepared Excel sheet. The reviewers (EKK, JK, GB, BA, BOO, and DSB) independently extracted data on study characteristics, participant demographics, interventions, comparators, and outcomes. At least two reviewers blindly extracted the data from each study. 100 % agreement was observed in this phase. Discrepancies were resolved through third-party adjudication (NJ). Two authors (EKK and DGM) independently assessed the risk of bias using the Cochrane Risk of Bias tool (ROB2), with disagreements settled by discussion and input from other authors. A second round for quality appraisal was performed by two different authors (NJ and JK). Disagreements from the initial assessment done were resolved by doing a panel discussion within the four authors.

2.5. Data synthesis and analysis

We performed pairwise meta-analyses using the <*meta*> package in R studio v4.3.2. The data was pooled using both common and random-effects models, considering that all included studies were published from a single research institute/team. Forest plots were produced for result visualization. Continuous outcomes were quantified using both Standardized Mean Difference (SMD) and Mean Difference (MD) along with the 95 % Confidence Intervals (CIs). Studies reporting consistent interventions, comparators, and outcomes were pooled together for subgroup analysis. Results from the included studies were expressed as means by the authors with standard error (SE) being the predominantly reported measure of variation.

However, to facilitate a uniform data synthesis approach, we converted SE to standard deviation (SD) using standard statistical equation $SD = SE \times \sqrt{N}$ where N was the sample size. The rationale behind this standardization was that SD, unlike SE, remains constant across different sample sizes, provided the samples are drawn from the same population under identical conditions. Consequently, SD serves as a more robust measure for aggregating and comparing results across multiple studies. The <*robvis*> package in R studio v4.3.2 and Microsoft PowerPoint were used for creating risk-of-bias visualizations. Study heterogeneity was assessed using the χ^2 test and Higgins-I-squared (I^2) model, with subgroup analyses to explore potential sources of heterogeneity. Publication bias (if $N \geq 10$) was evaluated using Egger's test and contour-enhanced funnel plots at 90 %, 95 %, and 99 % CIs.

3. Results

In our search, we identified 1226 records. After removal of duplicates and title and abstract screening, 217 records were eligible for full-text screening. Thirteen studies were finally included subsequent to exclusions based on our inclusion and exclusion criteria (Fig. 1). All

Table 2
Summary of the included randomized controlled trials in the present review.

Author, Year	Trial Name	Study Design	Form of Migraine ‡	Primary Endpoint	Time Period	Location	Funding Source	Trial Registration No.†
Abdolahi et al., 2017 [28]	The combined effects of omega3 fatty acids and curcumin supplementation on inflammatory and endothelial factors in migraine patients	Phase−4, double-blind, parallel assignment randomized trial	Episodic migraine without aura	Number of headaches, serum TNF-α concentration and gene expression levels	July 2015 to February 2017	Tehran, Iran (single centre)	None	NCT02532023
Abdolahi et al., 2018 [30]				Serum IL−6 concentration and gene expression levels, serum hs-CRP concentration				
Soveyd et al., 2018 [22]				Number of headaches, serum ICAM−1 concentration and gene expression levels				
Abdolahi et al., 2019 [29]				Severity, number, and duration of headaches, serum COX−2 and iNOS concentration and gene expression levels				
Djalali et al., 2020 [23]				Serum IFN-γ and IL−17 concentration and gene expression levels			Government	
Djalali et al., 2020 [32]				Serum PTX−3 concentration and gene expression levels			None	
Honarvar et al., 2021 [31]				Number of headaches, serum IL−1β concentration and gene expression levels				
Abdolahi et al., 2021 [24]				Severity, number, and duration of headaches, serum VCAM concentration and gene expression levels				
Djalali et al., 2023 [34]				Serum TGF-β and IL−4 concentration and gene expression levels			Government	
Parohan et al., 2021 [21]	The combined effects of nanocurcumin and ubiquinone supplementation on serum levels of homocysteine, calcitonin gene-related peptide, oxidative stress index, gene expression and activity of some antioxidant enzymes in migraine patients: Randomized double-blind placebo-controlled trial	Phase 2–3, double-blind, parallel assignment randomized trial	Episodic migraine without aura	Severity, number, and duration of headaches, headache diary result (HDR)	April to November 2018	Tehran, Iran (single centre)	University	IRCT2017080135444N1
Sedighiyan et al., 2022 [33]	The effects of nano-curcumin supplementation on leptin, adiponectin gene expression and serum levels of some adipokines in obese and overweight patients with migraine	Phase−3, double-blind, parallel assignment randomized trial	Episodic migraine without aura	Severity, number, and duration of headaches, serum levels of MCP-1, Resistin, and Visfati	April to September 2021	Tehran, Iran (single centre)	None	IRCT20160626028637N2
Sedighiyan et al., 2023 [36]				Severity, number, and duration of headaches, serum leptin and adiponectin concentration and gene expression levels				

(*continued on next page*)

Table 2 (*continued*)

Author, Year	Trial Name	Study Design	Form of Migraine ‡	Primary Endpoint	Time Period	Location	Funding Source	Trial Registration No.†
Mojtahedi et al., 2024 [35]				Severity, number, and duration of headaches, levels of stress, anxiety, and depression				

* COX-2 – cyclooxygenase-2; hs-CRP – high sensitivity C-reactive protein; ICAM-1 - Intercellular adhesion molecule-1; IL- interleukins; iNOS – inducible nitric oxide synthase; MCP-1 – Monocyte chemoattractant protein-1; TGF-β – Transforming growth factor-beta; TNF-α – Tumour necrosis factor-alpha; VCAM – Vascular cell adhesion molecule.

‡ It is important to note that studies conducted before 2018 relied on International Headache Society Second Edition for patient enrolment. Post-2018, studies relied on the International Headache Society Third Edition for patient enrolment. Differences in definitions may have been an underlying factor in patient enrolment differences. Refer to the respective guidelines for further guidance.

† IRCT – Iranian Registry of Clinical Trials; NCT – National Clinical Trial Number as registered on United States Clinicaltrials.gov.

studies included in this analysis were retrieved, with ten studies obtained from established online databases and three via direct author engagement. Among them, seven studies compared nano-curcumin to nutraceuticals or a combination with nano-curcumin [21,22,24,28–31], while the other six were placebo-controlled using paraffin-oil based capsules which were the same size, shape, and texture as the experimental capsules [23,32–36].

All 13 trials were conducted by the same research team/institute in Iran over the course of several years (2015–2024) and included patients with episodic migraine without aura, as defined by the International Headache Society guidelines (Table 2). The studies recruited young adult participants in the age range of 18–50 years, with a strong female predominance (> 70 % participants). The authors excluded patients with tension-type headache, serious inflammatory or organic disease (such as malignancy, liver failure, kidney disease, thyroid disorders), previous heart attack or stroke. Smokers, chronic alcohol users, and patients using non-steroidal anti-inflammatory drugs (NSAIDs), opioids, blood thinners, and statins were also excluded. Patients who were underweight (body mass index < 18.5 kg/m^2), pregnant, planning to become pregnant, or breastfeeding were also not considered. Those with previously known allergies to nano-curcumin, coenzyme Q10, or other nutraceuticals were also excluded from the trials.

These double-blind, parallel-assignment trials were conducted under three unique trial registrations. Two trials were funded by governmental organizations, and one was supported by the university grant. The remaining 10 trials did not report any funding or support. The typical duration for nano-curcumin (± combination with nutraceuticals such as Omega-3 or Coenzyme Q10) was two months with 80 mg/day – delivered as a single capsule of 80 mg or two capsules of 40 mg each – being the standard dosage for nano-curcumin (Table 3). Patients in most trials were prescribed tricyclic antidepressants and beta-blockers per neurologist's recommendations with a restricted use of NSAIDs during the trial period. Six trials investigated Omega-3 fatty acids combinations (dosages – 1800 mg and 2500 mg) with nano-curcumin [22,24,28–31] while one trial studied Coenzyme Q10 (300 mg dose) with nano-curcumin [21].

3.1. Comparators for meta-analysis

For the purposes of our meta-analysis, we considered different sampling comparators as either monotherapy, combination, or placebo in comparison with the intervention. Monotherapy was defined as a group that received only omega-3 or Coenzyme Q10 capsules with or without nano-curcumin placebo. Combination therapy was defined as a group that received nano-curcumin with either omega-3 capsules or Coenzyme Q10 capsules. Placebo (control) was defined as a group that received either nano-curcumin placebo alone or double-placebo capsules i.e., nano-curcumin placebo with omega-3 placebo. The intervention group was defined as patients who received nano-curcumin alone or with omega-3 placebo capsules.

Accordingly, nine studies reported on the outcomes of interest for meta-analysis and were included for further analysis (Table 2) [21,22,24,28,29,31,33,35,36]. Nevertheless, we observed that two studies yielded comparable results pertaining to the outcomes in question [33,36]. Similar study design characteristics including recruitment interval, coupled with the identical trial registration number prompted considerable doubt regarding the veracity of the findings. Consequently, a compelling hypothesis arose that the results may have been derived from the same underlying dataset but presented in duplicate in disparate publications [33,36]. To avoid any potential bias in our interpretation, we only considered the outcomes of this particular sample once, resulting in a total of eight included studies in our meta-analysis.

3.2. Migraine attack

The pooled estimate showed that nano-curcumin when compared to nutraceutical monotherapy showed no effect on the frequency of migraine attacks (SMD 0.10, 95 % CI: −0.15–0.36) for both common effects and random effects models (Fig. 2). Though inconclusive, a rather narrow predictive interval was observed from −0.26–0.47. On the other hand, a combination of nano-curcumin and nutraceuticals, without statistical heterogeneity, favored the intervention for both models (SMD 1.19, 95 % CI: 0.90–1.48) with a narrow confident predictive interval of 0.78–1.60.

When compared with placebo, although Parohan et al. [21], found a non-significant preference for placebo over nano-curcumin supplementation alone (SMD 0.40, 95 % CI: −0.19–1.00), the overall pooled estimates favored nano-curcumin supplementation using both the common effects model (SMD −0.49, 95 % CI: −0.72 to −0.26) and the random effects model (SMD −0.55, 95 % CI: −1.07 to −0.02). Nonetheless, high statistically significant heterogeneity was observed ($I^2 = 80$ %, $P < 0.01$; Fig. 2).

3.3. Migraine severity

Our results indicated that nano-curcumin supplementation alone attenuated the severity of migraine attacks when compared to placebo using both the common effects model (SMD −0.63, 95 % CI: −0.95 to −0.31) and the random effects model (SMD −0.64, 95 % CI: −1.10 to −0.19). Though statistically insignificant, the results showed moderate study heterogeneity ($I^2 = 51$ %, $P = 0.100$; Fig. 3). Relative to nutraceutical monotherapy, use of nano-curcumin alone was not associated with reduction in headache severity using both models (SMD −0.10, 95 % CI: −0.46–0.25). Interestingly, although the results favored combination therapy, the results did not achieve statistical significance over nano-curcumin alone using both models (SMD 0.28, 95 % CI: −0.08–0.64).

Table 3
Patient and intervention characteristics of the included randomized controlled trials in the present review.

Author, Year	Number of Participants	Duration of Supplementation	Placebo composition	Nano-curcumin composition	Monotherapy therapy composition	Group 1 (per day)	Group 2 (per day)	Group 3 (per day)	Group 4 (per day)	Adjunct therapy
Abdolahi et al., 2017 [28]	80	2 months	Oral paraffin-oil based N-C and ω−3	Sinacurcumin 80 ⁜	Omega MAX † (ω−3 supplement)	2× ω−3 + 1× N-C	2× ω−3 + 1× N-C placebo	2× ω−3 placebo + 1× N-C	2× ω−3 placebo + 1× N-C placebo	All groups took 25–50 mg tricyclic antidepressants and 20–40 mg beta-blockers.
Abdolahi et al., 2018 [30]	80	2 months	Oral paraffin-oil based N-C and ω−3		Omega MAX † (ω−3 supplement)	2× ω−3 + 1× N-C	2× ω−3 + 1× N-C placebo	2× ω−3 placebo + 1× N-C	2× ω−3 placebo + 1× N-C placebo	Not reported
Soveyd et al., 2018 [22]	72	2 months	Oral paraffin-oil based N-C and ω−3		Omega MAX † (ω−3 supplement)	2× ω−3 + 1× N-C	2× ω−3 + 1× N-C placebo	2× ω−3 placebo + 1× N-C	2× ω−3 placebo + 1× N-C placebo	
Abdolahi et al., 2019 [29]	80	2 months	Oral paraffin-oil based N-C and ω−3		900 mg ω−3 supplement ¶	2× ω−3 + 1× N-C	2× ω−3 + 1× N-C placebo	2× ω−3 placebo + 1× N-C	2× ω−3 placebo + 1× N-C placebo	
Djalali et al., 2020 [23]	40	2 months	Oral paraffin-oil based N-C		-	1× N-C	1× N-C placebo	-	-	All groups took 25–50 mg tricyclic antidepressants and 20–40 mg beta-blockers. NSAIDs shouldn't exceed two weeks dose over two months
Djalali et al., 2020 [32]	38	2 months	Oral paraffin-oil based N-C		-	1× N-C	1× N-C placebo	-	-	
Honarvar et al., 2021 [31]	80	2 months	Oral paraffin-oil based N-C and ω−3		Omega MAX † (ω−3 supplement)	2× ω−3 + 1× N-C	2× ω−3 + 1× N-C placebo	2× ω−3 placebo + 1× N-C	2× ω−3 placebo + 1× N-C placebo	
Abdolahi et al., 2021 [24]	80	2 months	Oral paraffin-oil based N-C and ω−3		Omega MAX † (ω−3 supplement)	2× ω−3 + 1× N-C placebo	2× ω−3 placebo + 1× N-C	2× ω−3 + 1× N-C	2× ω−3 placebo + 1× N-C placebo	
Djalali et al., 2023 [34]	38	2 months	Oral paraffin-oil based N-C		-	1× N-C	1× N-C placebo	-	-	
Parohan et al., 2021 [21]	91	3 months (1-month adjunct therapy then 2 months of intervention)	Oral paraffin-oil based N-C		CoQ10 supplement ‡	1× N-C	3× CoQ10	1× N-C + 3× CoQ10	1× N-C placebo	All groups took 50 mg/day anti-convulsant and 25 mg/ day tricyclic antidepressant for all three months
Sedighiyan et al., 2022 [33]	44	2 months	Oral paraffin-oil based N-C	Nano-curcumin formulation Φ	-	2× N-C	2× N-C placebo	-	-	Not reported
Sedighiyan et al., 2023 [36]	44	2 months	Oral paraffin-oil based N-C		-	2× N-C	2× N-C placebo	-	-	
Mojtahedi et al., 2024 [35]	44	2 months	Oral paraffin-oil based N-C		-	2× N-C	2× N-C placebo	-	-	

* CoQ10 – coenzyme 10; N-C – nano-curcumin; ω-3 – omega-3

⁜ Sinacurcumin 80 is a 80 mg naro-curcumin capsule supplement manufactured by Sinacurcumin Pharmaceutical Company (seller Exir Nano Sina, Iran) with the following composition – 100 % curcumin as 10 nanometre nano-micelles with much lower amounts of other compounds such as curcuminoid, emulsifier (polysorbate), gelatine, and glycerine.

Φ Nano-curcumin formulation is a 40 mg nano-curcumin capsule manufactured by Cina Curcumin Pharmaceutical Company, Iran with the following composition - 100 % curcumin as 10 nanometre nano-micelles with much lower amounts of other compounds such as curcuminoid, emulsifier (polysorbate), gelatine, and glycerine. Each 40 mg capsule is equivalent to 1 g curcumin.

† Omega MAX is a 1250 mg ω-3 capsule supplement manufactured by Zahravi Pharmaceutical Company, Iran with the following composition – 600 mg eicosapentaenoic acid (EPA) + 300 mg docosahexaenoic acid (DHA) + 100 mg other ω-3 fatty acids, gelatine, glycerine, and pure water.

¶ 900 mg ω-3 supplement composed of 600 mg eicosapentaenoic acid (EPA) + 300 mg docosahexaenoic acid (DHA).
‡ CoQ10 is a 100 mg co-enzyme Q10 supplement provided by Pourateb Pharmaceutical Company, Iran (manufactured by Health Burst, USA).

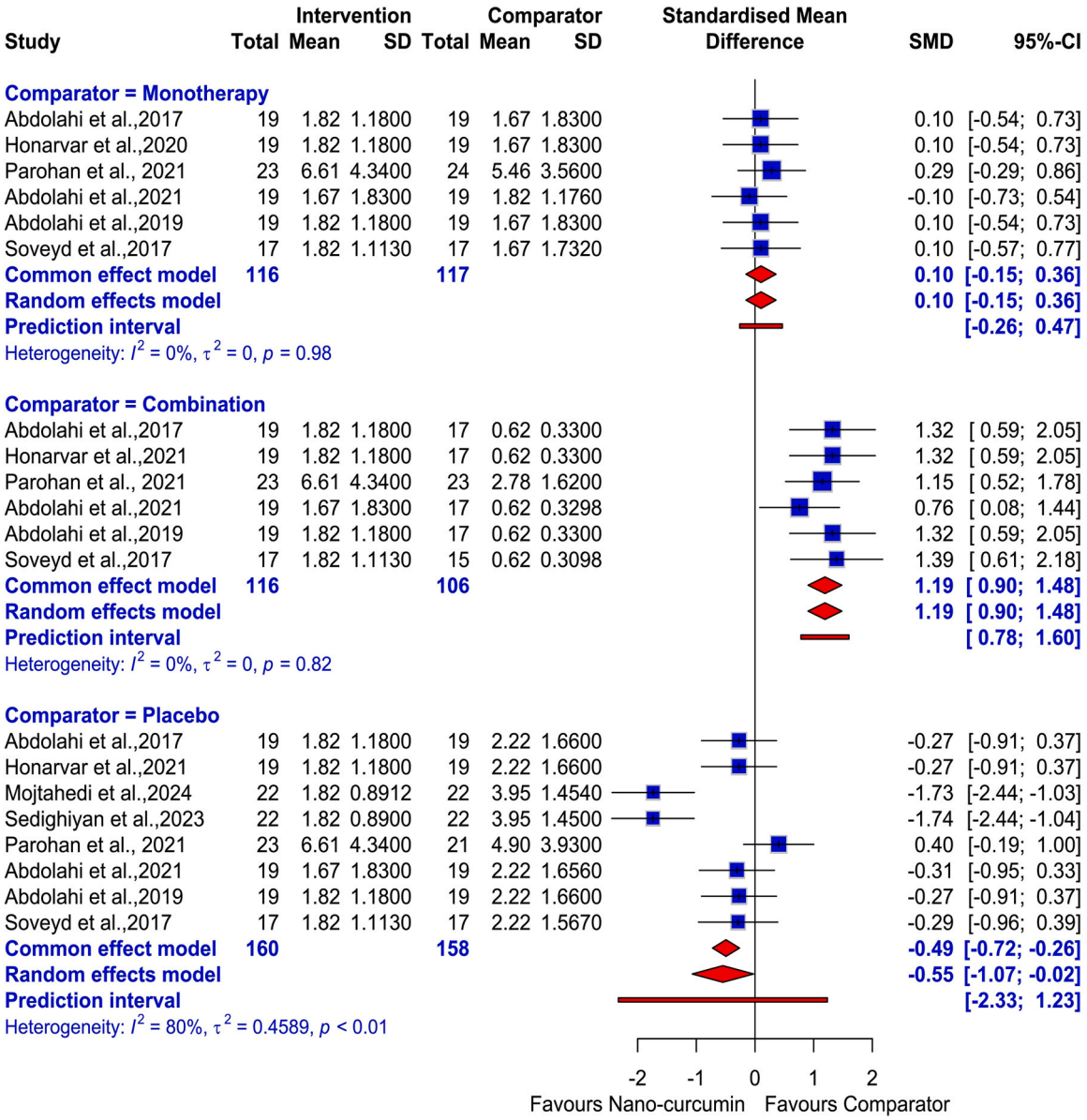

Fig. 2. Comparative effectiveness of nano-curcumin versus nutraceuticals, their combination or placebo, for migraine attack. The forest plot shows the standardized mean difference (SMD) and 95 % confidence intervals (CIs) from studies assessing interventions for migraine attack. The zero line indicates no effect from the intervention. The size of the blue squares indicates the respective study's weight on the meta-analysis. The red diamonds represent the pooled SMD and 95 % CI for each intervention type, while the red lines provide the prediction intervals, estimating the expected SMD and 95 % CI for a new study with similar characteristics.

3.4. Migraine duration

We found that nano-curcumin supplementation reduced the duration of migraine attacks when compared to placebo, using the common effects model only (MD −2.90, 95 % CI: −4.66 to −1.13). However, we observed significantly high statistical heterogeneity (I^2 = 76 %, P < 0.01; Fig. 4). When compared to nutraceutical monotherapy, no effect of nano-curcumin supplementation alone was observed using both models (MD 0.08, 95 % CI: −2.30–2.46). The combination therapy also did not show any effect over nano-curcumin supplementation alone in reducing attack duration using both models (MD 1.97, 95 % CI: −0.39–4.33).

3.5. Before and After Nano-curcumin (Alone) Intervention

Before and after intervention analysis showed that nano-curcumin supplementation alone reduced migraine attack frequency (both model SMD −0.77, 95 % CI: −1.00 to −0.54), severity (random effects model SMD −0.92, 95 % CI: −1.50 to −0.33), and duration (random effects model SMD −0.63, 95 % CI: −1.05 to −0.20). Although no statistical heterogeneity was observed between studies reporting on migraine attack frequency (I^2 = 0 %, P = 0.92; Fig. 5), statistical heterogeneity remained moderately significant for migraine severity (I^2 = 69 %, P = 0.02) but statistically non-significant for attack duration (I^2 = 56 %, P = 0.06).

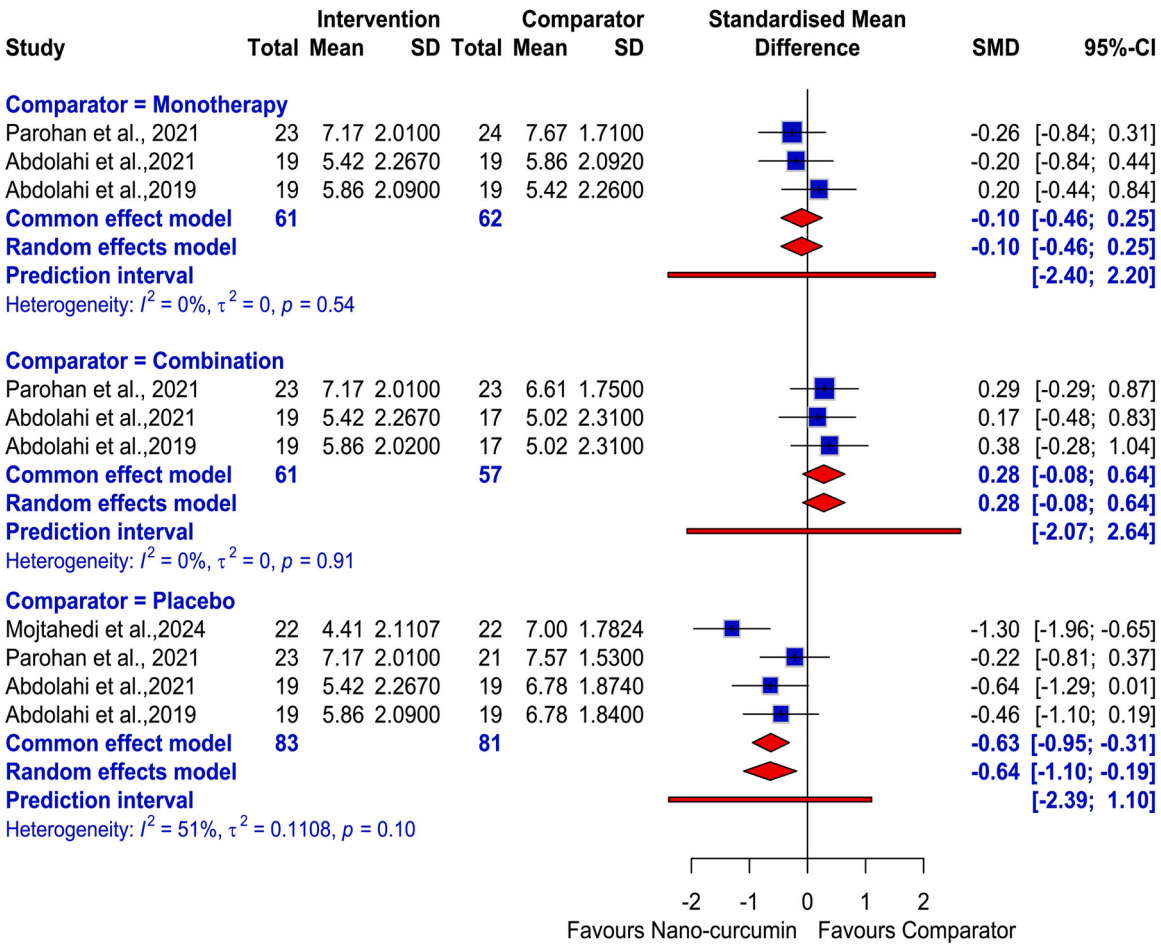

Fig. 3. Comparative effectiveness of nano-curcumin versus nutraceuticals, their combination or placebo, for management of migraine severity. The forest plot shows the standardized mean difference (SMD) and 95 % confidence intervals (CIs) from studies assessing interventions for migraine severity. The zero line indicates no effect from the intervention. The size of the blue squares indicates the respective study's weight on the meta-analysis. The red diamonds represent the pooled SMD and 95 % CI for each intervention type, while the red lines provide the prediction intervals, estimating the expected SMD and 95 % CI for a new study with similar characteristics.

3.6. Publication bias and risk of bias assessment

We assessed publication bias using a contour-enhanced funnel plot and Egger's test. The contour-enhanced funnel plot analysis indicated no publication bias (Fig. 6). The results from Egger's further corroborated the absence of publication bias (P = 0.42), suggesting that the studies included in our analysis were unlikely to be affected by selective reporting. The overall risk of bias for some of the included studies was assessed as low, despite some specific concerns. Most studies demonstrated low risk across key domains such as randomization, intended intervention, and measurement of outcomes. However, several studies did not reference a full trial protocol, which raised concerns about the lack of transparency in reporting rather than indicating a flaw in the study design (Fig. 7). Moreover, some studies had some concerns of the missing outcome data due to patient exclusions, but these withdrawals did not affect the primary outcomes and were unlikely to introduce significant bias. Therefore, in the context of the entire body of evidence, these minor issues did not elevate the overall risk of bias according to us, thereby allowing for a low overall concern rating for the studies.

3.7. P curve analysis

Given that all included studies originated from a single institution, we performed a P curve analysis. The P curve analyses for both headache attacks and the nano-curcumin intervention (before and after) demonstrated evidential value (Fig. 8). For headache attacks, the analysis of 20 studies revealed significant right-skewness ($P_{Binomial}$ = 0.035) and a non-flat distribution of P values ($P_{Binomial}$ = 0.932), with an estimated power of 95 % (95 % CI: 83 %-98.8 %), indicating high power. Similarly, the nano-curcumin intervention analysis (before and after) of 17 studies showed significant right-skewness ($P_{Binomial}$ = 0.003) and a non-flat distribution of P values ($P_{Binomial}$ = 0.982), with an estimated power of 58 % (95 % CI: 26.4 %-82.2 %), indicating moderate power. These findings suggest that the results likely reflect true effects rather than biases such as publication bias or P hacking. No P curve analysis was conducted for headache severity and duration outcomes due to the presence of two or fewer significant values, which may yield unreliable results.

3.8. Nano-curcumin effects on biomarkers

The trials reported on 18 different biomarkers from migraine patients, including cytokines, adipokines, cell adhesion molecules, inflammatory enzymes, growth factors, and acute phase inflammatory proteins (Table 4). The anti-migraine efficacy of nano-curcumin appears to be mediated through the downregulation of inflammatory processes. Moreover, there seems to be marginal correlation when compared with corresponding changes in serum levels, indicating downstream modulation of pathways.

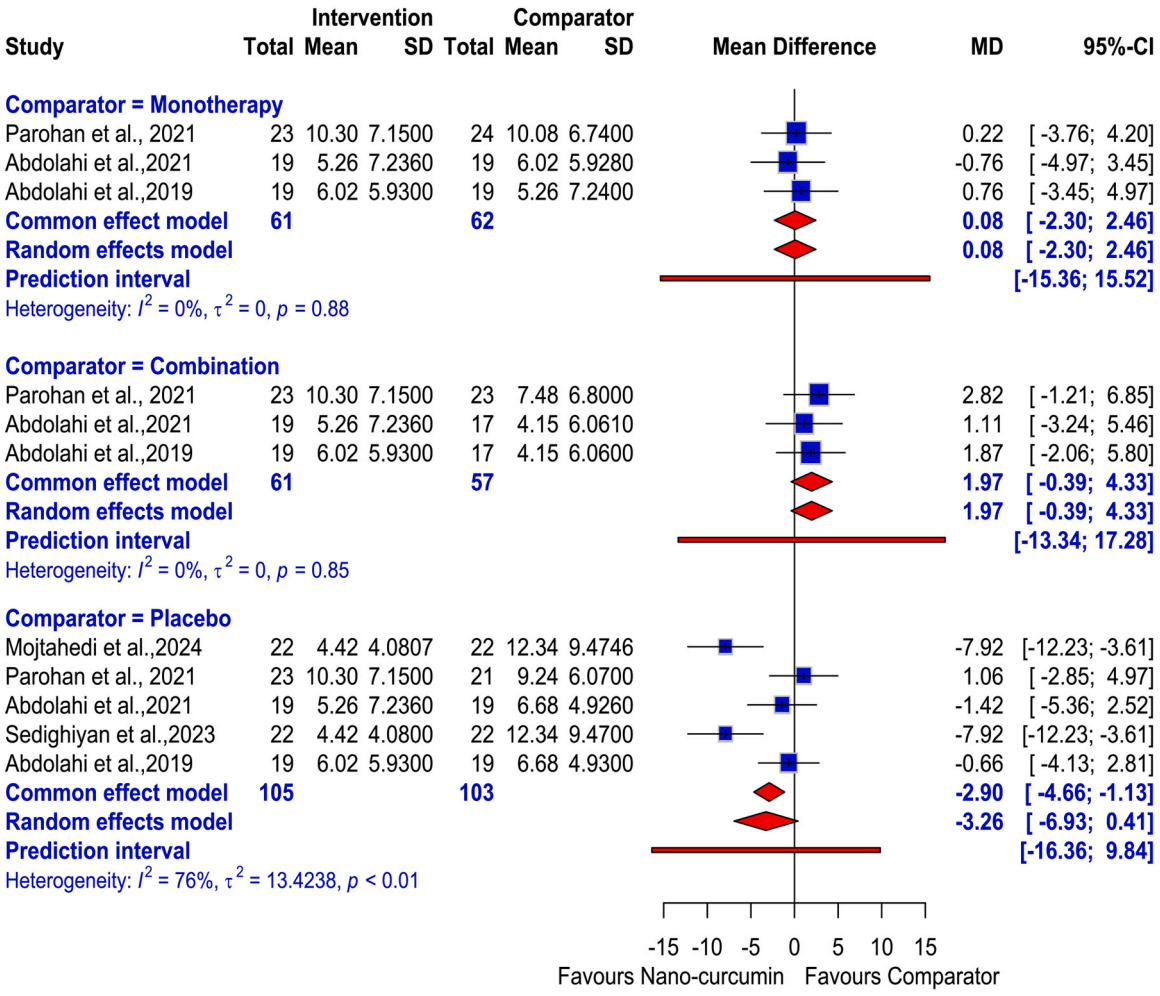

Fig. 4. Comparative effectiveness of nano-curcumin versus nutraceuticals, their combination or placebo, for the duration of migraine attacks. The forest plot shows the mean difference (MD) and 95 % confidence intervals (CIs) from studies assessing interventions for migraine duration. The zero line indicates no effect from the intervention. The size of the blue squares indicates the respective study's weight on the meta-analysis. The red diamonds represent the pooled SMD and 95 % CI for each intervention type, while the red lines provide the prediction intervals, estimating the expected SMD and 95 % CI for a new study with similar characteristics.

3.9. Adverse reactions

No adverse reactions, including allergic reactions, nausea, vomiting, or toxicity, were reported in nine studies of nanocurcumin and nutraceuticals [22,23,28,30,31,33–36]. One study did mention assessing side effects, but no data on the observations were provided [29]. Two other trials did not assess adverse reactions as an outcome of interest [24,32]. Only a single trial reported mild transient side effects during the first three months of follow-up. Symptoms included gastrointestinal disturbances (nausea, vomiting, diarrhea, constipation), loss of appetite, dizziness, dry mouth, and drowsiness [21]. However, the authors also reported noting these symptoms in the placebo group [21]. Hence, conclusions over the safety profile of nano-curcumin supplementation could not be assessed from the included studies.

4. Discussion

The present meta-analysis assessed the efficacy of nano-curcumin in the symptomatic management of migraine and yielded several implications for clinical practice and future research directions. The data suggests that nano-curcumin supplementation significantly reduces the frequency, duration, and severity of migraine attacks when compared to a placebo. This effect highlights nano-curcumin's potential as a promising therapeutic agent, possibly attributed to its anti-inflammatory properties and ability to modulate nociceptive pathways [10–12]. Moreover, the bioavailability of nano-curcumin, enhanced due to its nanoscale formulation, may facilitate a more efficient interaction with biological targets, thereby amplifying its analgesic effects.

Nano-curcumin can decrease the levels of cell adhesion molecules (CAMs) like VCAM (vascular) and ICAM (intercellular) [22,24], which play a role in the adhesion of leukocytes to the vascular endothelium—a key event in inflammation. Nano-curcumin may also enhance the transcription of adiponectin mRNA, subsequently elevating its serum concentration [36]. Given adiponectin's established anti-inflammatory properties, its elevation may play a contributory role in modulating nociception, thereby augmenting the analgesic profile of nano-curcumin in the context of migraine treatment [37–38]. Nano-curcumin may also influence the Th2/T regulatory axis by upregulating the gene expression of IL-4 and TGF-β, aiding in the resolution of the inflammatory response associated with migraines [34].

Interestingly however, when nano-curcumin's efficacy was juxtaposed with that of nutraceuticals, the results did not favor nano-curcumin, indicating a non-significant difference. This observation could stem from the inherent therapeutic benefits of nutraceuticals, which may already target and synergistically optimize certain physiological pathways that nano-curcumin targets. Apart from the study by Parohan et al. [21], the remaining studies investigated omega-3 fatty acid supplements in combination therapy with nano-curcumin. As

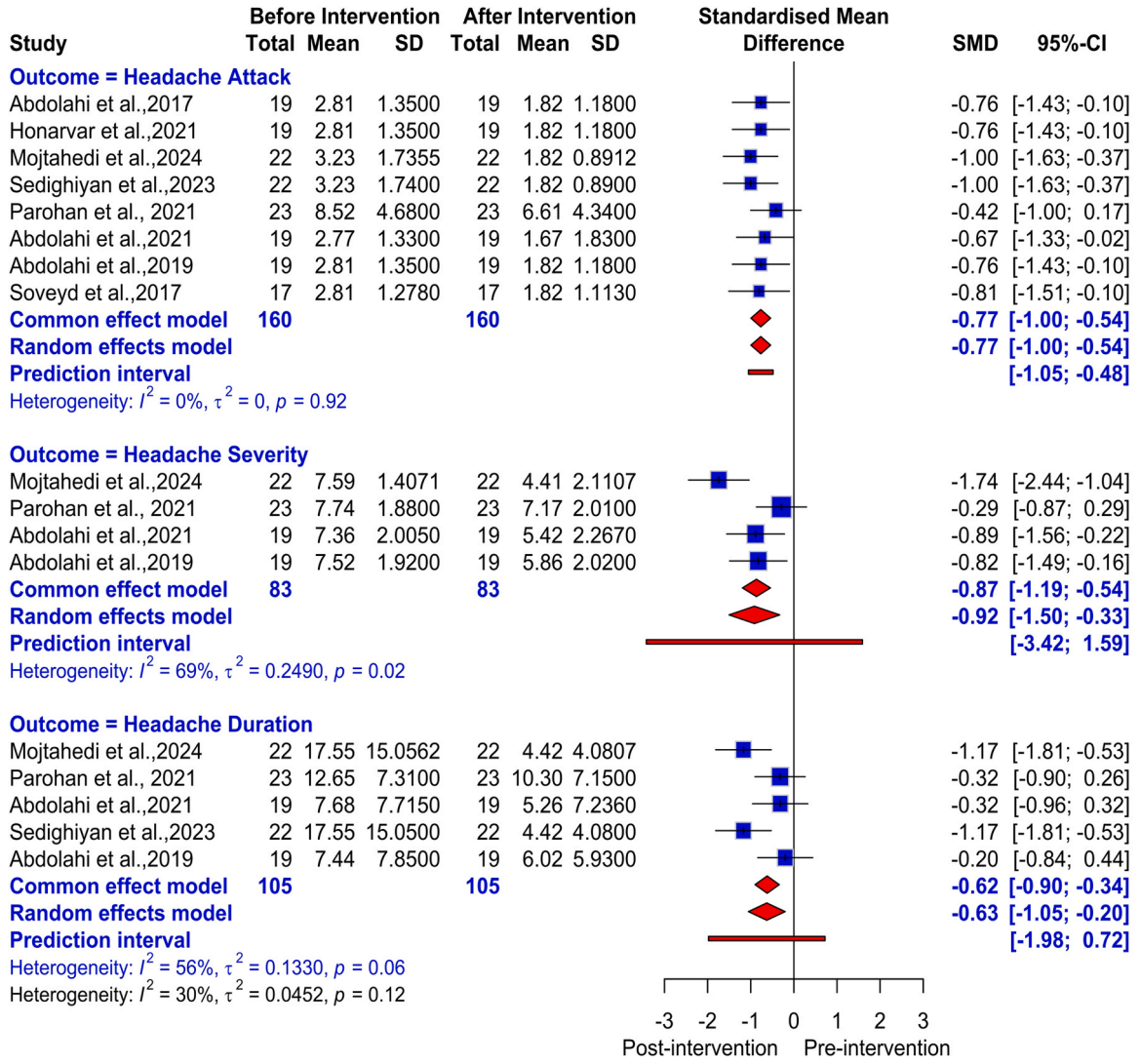

Fig. 5. Comparative effectiveness of nano-curcumin, pre-and post-intervention, on migraine attack, severity, and duration. The forest plot shows the standardized mean difference (SMD) and 95 % confidence intervals (CIs) from studies assessing interventions for migraine attack, severity, and duration. The zero line indicates no effect from the intervention. The size of the blue squares indicates the respective study's weight on the meta-analysis. The red diamonds represent the pooled SMD and 95 % CI for each intervention type, while the red lines provide the prediction intervals, estimating the expected SMD and 95 % CI for a new study with similar characteristics.

demonstrated in previous research, supplementation with omega-3 fatty acids can result in a reduction in migraine duration, while not affecting severity or frequency of the attacks [39–40].

Our findings differ from these findings, demonstrating reductions across all outcome measures, with a pronounced decrease in the frequency of migraine attacks when nano-curcumin is included as a treatment component. This synergy could suggest that nano-curcumin may potentiate the effects of nutraceuticals, offering a complementary approach for patients who find limited relief with conventional treatments. It is possible that the observed synergistic effect may be due to modulation of inflammatory pathways and enhancement of mitochondrial function, two processes frequently associated with the pathophysiology of migraines [35–36,41–42].

The before-and-after comparison provides empirical evidence supporting the theoretical benefits of nano-curcumin, demonstrating the efficacy of this approach in improving migraine parameters. In contrast to traditional curcumin, nano-curcumin has been designed for enhanced bioavailability and targeted delivery, which could explain the pronounced clinical effects [20]. The studies included demonstrated minimal heterogeneity with evidential value for the true effect of nano-curcumin, as indicated by the high to moderate power in the P curve analysis. This is suggestive of consistent results across the trials and a lack of potential P hacking, thereby enhancing the reliability of the pooled estimates. Furthermore, the absence of publication bias, as confirmed by Egger's test, further validates the conclusions drawn from this analysis.

4.1. *Limitations*

One significant limitation of this study is that all studies were conducted by the same research group. The homogeneity of the data sources may introduce a form of selection bias, potentially skewing the results towards a particular outcome favored by the methodologies employed by this group. Moreover, the narrow scope of study designs and populations may restrict the generalizability of the findings. These limitations are compounded by the lack of clarity surrounding the sampling population. It was unclear from the methodologies described in the included trials whether the same sample of patients was utilized repeatedly over the course of multiple years (multiple cross-sectional analyses), or different samples were drawn from the population. In the

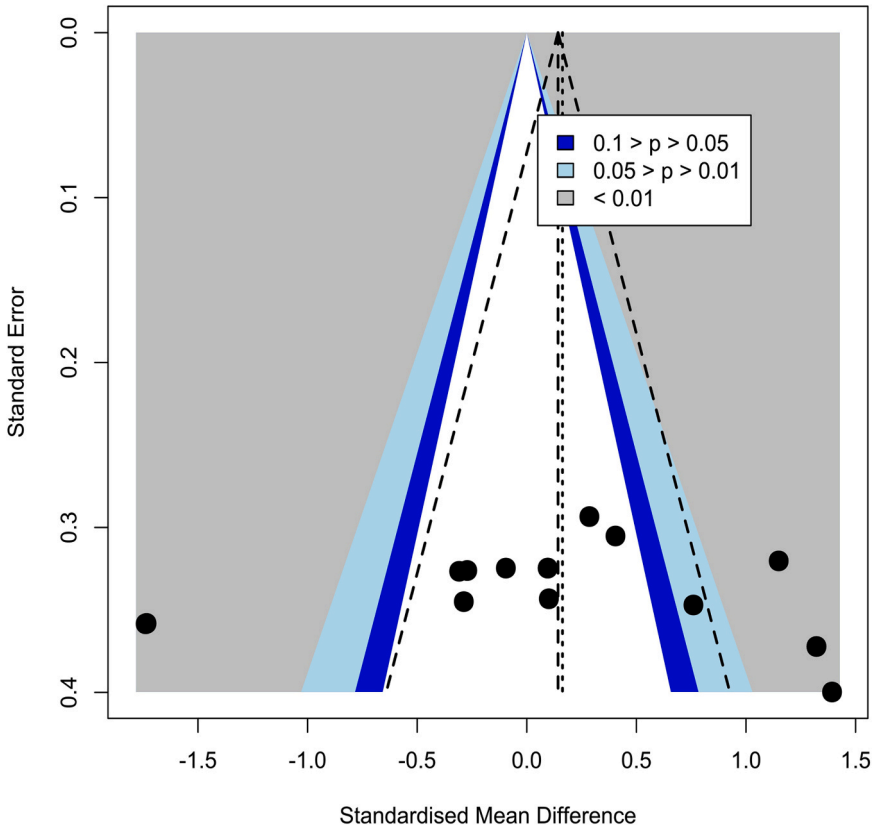

Fig. 6. Contour-enhanced funnel plot for the assessment of publication bias in studies investigating nano-curcumin supplementation for migraine attacks. Each round dot signifies an individual trial. The x-axis represents the standardized mean difference (SMD) in effect size, while the y-axis denotes the standard error (SE). The dashed vertical line indicates the pooled average effect size. The shaded areas reflect levels of statistical significance: $p < 0.01$ (grey), $p < 0.05$ (blue), and $p < 0.10$ (light blue).

former case, it can be argued that the stratified randomization technique employed by the authors prior to each trial could nullify any residual effects from previous trials. However, it is necessary to ascertain the gap between the trials to determine whether this was the case. Other limitations include the relatively short duration of supplementation employed in most studies, which does not allow for the assessment of long-term efficacy and safety trends.

4.2. Recommendations and future directions

To bridge the current knowledge gaps regarding the long-term safety of nano-curcumin, future research should prioritize evaluating its sustained efficacy and safety. There remains a paucity of data regarding the optimal dosing, dose-response relationships, and formulations of nano-curcumin. It would be beneficial for future researchers to prioritize the conducting of long-term studies. Such studies could be utilized to ascertain the sustained effects of nano-curcumin and its safety profile over extended periods. Research should explore the impact of nano-curcumin on patients' quality of life and develop strategies to enhance patient education and adherence.

Another key area of focus should be to explore the molecular pathways through which nano-curcumin exerts its effects on migraine. This could also provide insights into potential new therapeutic targets. Moreover, studies should be conducted to assess the effects of nano-curcumin in diverse populations, such as children, the elderly, and pregnant women. A further examination of the potential benefits of nano-curcumin in different subpopulations, such as those with chronic versus episodic migraines, with and without aura, could contribute towards the development of treatments that are more tailored to individual needs.

A comparative analysis with other emerging treatments could place nano-curcumin within a wider therapeutic context, thereby offering insights into its relative efficacy. The economic impact of nano-curcumin, including its cost-effectiveness, patient compliance, and the utilization of healthcare resources, requires further investigation. Such an investigation could provide a more comprehensive insight into the potential of nano-curcumin in the management of migraines and its capacity to influence healthcare policies.

5. Conclusions

Our meta-analysis indicates that 80 mg nano-curcumin supplementation per day for two months alone may be beneficial in reducing migraine attacks, duration, and severity, hence, supporting its use as a complementary therapy to current clinical recommendations. Nano-curcumin combination therapy with omega-3 and coenzyme Q10 may offer superior results in reducing migraine attacks. Cautious interpretation and further research are warranted to explore the long-term safety and efficacy of nano-curcumin, both alone and in combination with nutraceuticals, ensuring its integration into modern evidence-based clinical practice.

Abbreviations

SMD, standardized mean difference; MD, mean difference; CI, confidence interval; RCT, randomized controlled trial; COX-2, cyclooxygenase-2; iNOS, inducible nitric oxide synthase; TNF-α, tumor necrosis factor-alpha; VCAM, vascular cell adhesion molecule; ICAM, intercellular cell adhesion molecule; CoQ10, coenzyme 10; N-C, nano-curcumin; ω-3, omega-3

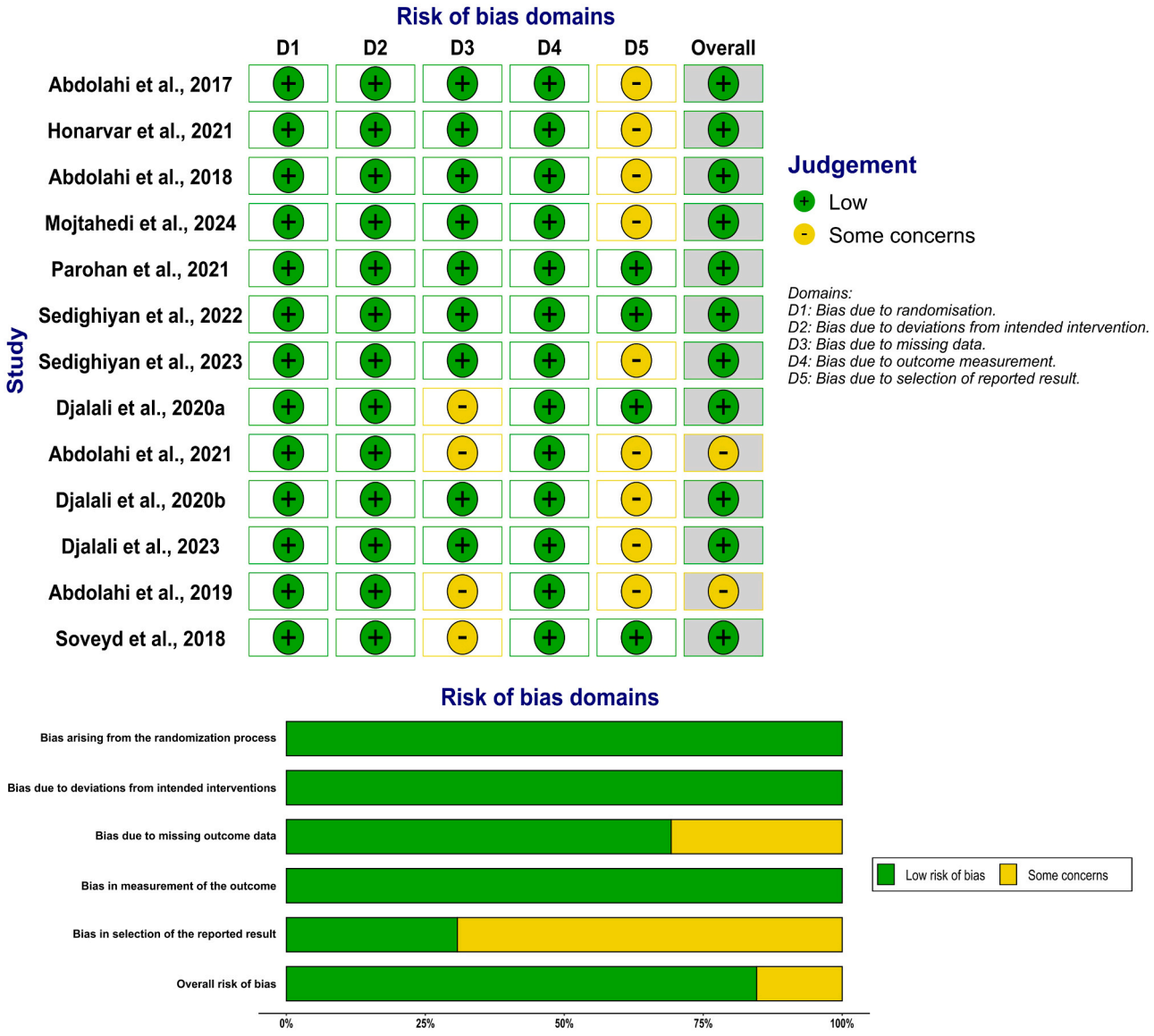

Fig. 7. Risk of Bias assessment for the included trials using the ROB2 tool. Visualization done using the ROBVIS tool. Green color indicates low risk of bias across all domains.

Ethical approval

Not applicable.

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CRediT authorship contribution statement

Nityanand Jain: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Bismark Osei Owusu:** Writing – review & editing, Investigation, Data curation. **Godwin Odum Bortey:** Writing – review & editing, Investigation, Data curation. **Bismark Acheampong:** Writing – review & editing, Investigation, Data curation. **Ernest Kissi Kontor:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Derrick Sackitey:** Writing – review & editing, Validation, Investigation, Data curation. **Jessica Kumah:** Writing – review & editing, Investigation, Data curation. **Daha Garba Muhammad:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

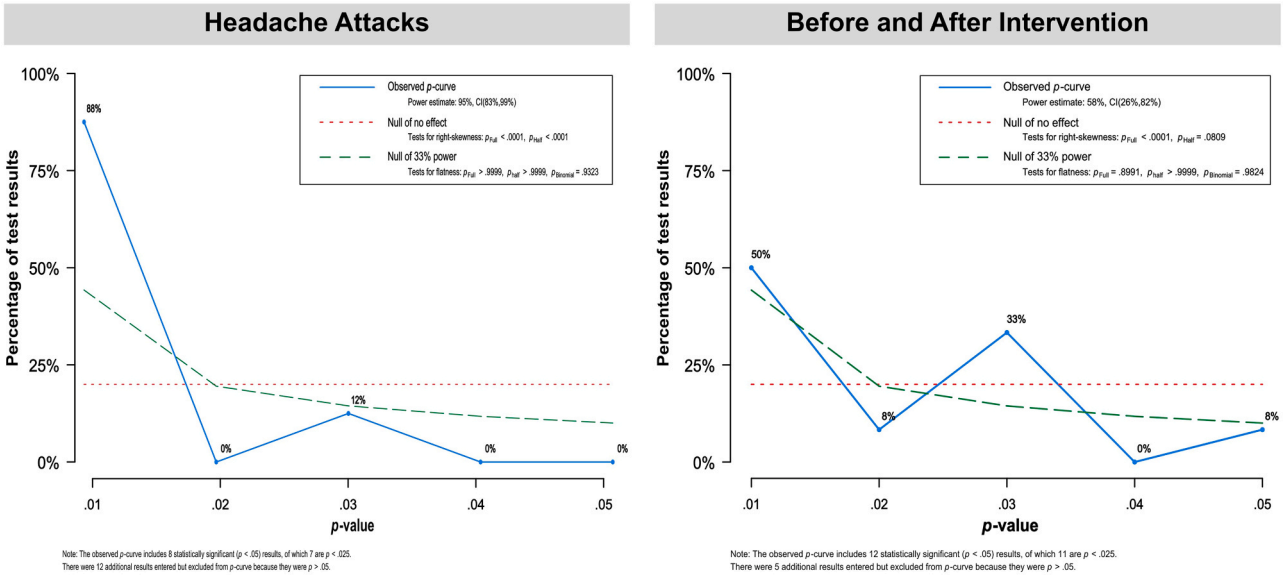

Fig. 8. P curve analysis for the two outcome measures. Outcome measures include headache attacks and nanocurcumin intervention (before and after).

Table 4
Change in gene expression levels and serum levels of reported biomarkers (presented as the difference between after intervention vs baseline before intervention).

Study	Biomarker Gene	Biomarker Protein	Proposed function in migraine	Change in Gene Expression*		Change in Serum Levels (ng/dl)**	
				Nano-curcumin alone	Placebo group	Nano-curcumin alone	Placebo group
Abdolahi et al., 2017 [28]	*TNFA*	Tumor necrosis factor alpha	Pro-inflammatory	0.51 ± 0.58	0.04 ± 0.37	−11.33 ± 8.75	−9.22 ± 8.15
Abdolahi et al., 2018 [30]	*IL6*	Interleukin 6	Pro-inflammatory	-	-	−9.84 ± 3.52	0.11 ± 4.29
	CRP	High-sensitivity C-reactive protein	Inflammation marker	-	-	−1.17 ± 0.42	−0.45 ± 0.36
Soveyd et al., 2018 [22]	*ICAM1*	Intercellular adhesion molecule 1	Pro-inflammatory	0.80 ± 0.42	−0.61 ± 0.37	−18.81 ± 9.95	−9.51 ± 17.83
Abdolahi et al., 2019 [29]	*PTGS2*	Cyclooxygenase−2	Oxidative	-	-	−3.81 ± 1.36	−1.19 ± 1.49
	NOS2	Nitric oxide synthase, inducible	Oxidative	-	-	−2.50 ± 1.31	−0.52 ± 1.61
Djalali et al., 2020 [23]	*IFNG*	Interferon gamma	Pro-inflammatory	0.96 ± 0.34	0.52 ± 0.47	−8.02 ± 3.41[a]	−2.73 ± 2.47[a]
	IL17A	Interleukin 17 alpha	Pro-inflammatory	1.20 ± 0.40	0.07 ± 0.49	−11.60 ± 3.19[a]	−2.45 ± 2.73[a]
Djalali et al., 2020 [32]	*PTX3*	Pentraxin 3	Inflammation marker	0.39 ± 1.09	0.40 ± 0.37	0.14 ± 0.73[b]	0.13 ± 0.12[b]
Honarvar et al., 2021 [31]	*IL1B*	Interleukin 1 beta	Pro-inflammatory	0.96 ± 0.58	0.36 ± 0.29	−3.81 ± 1.36[c]	−1.49 ± 1.19[c]
Abdolahi et al., 2021 [24]	*VCAM1*	Vascular cell adhesion molecule 1	Pro-inflammatory	−2.21 ± 0.56	0.55 ± 0.61	−1.24 ± 0.42	−0.09 ± 0.18
Djalali et al., 2023 [34]	*IL4*	Interleukin 4	Anti-inflammatory	−1.04 ± 0.42	−0.22 ± 0.38	42.98 ± 11.02[a]	7.27 ± 9.35[a]
	TGFB1	Transforming growth factor beta	Anti-inflammatory	−0.57 ± 0.25	- 0.12 ± 0.32	30.69 ± 49.70[a]	−16.31 ± 25.45[a]
Sedighiyan et al., 2022 [33]	*CCL2*	Monocyte chemoattractant protein 1	Pro-inflammatory	-	-	−12.15 ± 4.60	4.39 ± 2.07
	RETN	Resistin	Pro-inflammatory	-	-	−5.42 ± 7.43	−3.34 ± 6.54
	NAMPT	Visfatin	Pro-inflammatory	-	-	−0.74 ± 0.40	−0.15 ± 0.27
Sedighiyan et al., 2023 [36]	*ADIPOQ*	Adiponectin	Anti-inflammatory	-	-	2.87 ± 0.04[d]	−0.66 ± 1.11[d]
	LEP	Leptin	Pro-inflammatory	-	-	−1.14 ± 0.77[d]	−0.06 ± 0.83[d]

[a] Measured in pg/ml
[b] Measured in ng/L
[c] Measured in mg/dL
[d] Measured in ng/ml
* Gene expression was evaluated from peripheral blood mononuclear cells (PBMCs). Results shown as mean with standard error.
** Serum levels were evaluated using enzyme-linked immunosorbent assay (ELISA). Results shown as mean with error.

Acknowledgements

None to declare.

Appendix 1. Deviation from protocol. A description of any changes made to the original protocol and the reasons for them

Protocol method	Deviation from protocol method, with justification
Only Random effects model was planned to be used.	Both Common effects and Random effects models were used because all studies were from a similar research team, and there was interest in how the analysis would be pooled in both models. **Type of Deviation**: *Addition*
Only primary outcomes such as migraine attack frequency, duration and severity were to be extracted.	Biomarkers were included as secondary outcomes. **Type of Deviation**: *Addition*
Odds Ratio (OR) was to be used for binary data (e.g., having a migraine attack or not).	Such data was not available in any of the included articles. **Type of Deviation**: *Omission*
Standardized Mean Difference (SMD) was to be used for continuous data.	Mean Difference (MD) was used for the analysis of migraine duration as all studies reported using the same units. **Type of Deviation**: *Modification*
Planned to perform trim and fill analysis.	It was not performed as Egger's test indicated no publication bias. **Type of Deviation**: *Omission*
Meta regression was planned to be conducted.	It was not conducted due to the small number of subgroups (N<10) and minimal heterogeneity. **Type of Deviation**: *Omission*

Addition: When a new method or criterion is added that was not originally planned.
Modification: When a planned method or criterion is changed.
Omission: When a planned method or criterion is not used.

Appendix 2. Search strategy and a detailed account of the search terms, databases, and filters used to identify the relevant studies for the systematic review. All searches were done on 12/04/2024

Medline via Ovid = 39

((nano-curcumin OR nanocurcumin OR "curcumin nanoparticles" OR curcumin OR turmeric OR "Curcuma longa" OR curcuminoids OR diferuloylmethane OR "Indian saffron" OR haldi OR "yellow ginger" OR "Jiang Huang" OR Halada OR Kurkum OR Kurkuma OR Theracurmin OR Meriva OR BCM-95) AND (migraine OR headache OR cephalalgia OR migraines OR headaches OR "tension headache" OR "cluster headache" OR "vascular headache" OR "cervicogenic headache" OR "post-traumatic headache"))

Scopus = 293

TITLE-ABS-KEY(((nano-curcumin OR nanocurcumin OR "curcumin nanoparticles" OR curcumin OR turmeric OR "Curcuma longa" OR curcuminoids OR diferuloylmethane OR "Indian saffron" OR haldi OR "yellow ginger" OR "Jiang Huang" OR Halada OR Kurkum OR Kurkuma OR Theracurmin OR Meriva OR BCM-95) AND (migraine OR headache OR cephalalgia OR migraines OR headaches OR "tension headache" OR "cluster headache" OR "vascular headache" OR "cervicogenic headache" OR "post-traumatic headache"))) AND (LIMIT-TO (EXACTKEYWORD,"Humans"))

Web of Science (All databases) = 286

((nano-curcumin OR nanocurcumin OR "curcumin nanoparticles" OR curcumin OR turmeric OR "Curcuma longa" OR curcuminoids OR diferulolylmethane OR "Indian saffron" OR hardi OR "yellow ginger" OR "Jiang Huang" OR harada OR karkar OR kuruma OR Theracurmin OR merida OR BCM-95) AND (migraine OR headache OR cephalalgia OR migraines OR headaches OR "tension headache" OR "cluster headache" OR "vascular headache" OR "cervicogenic headache" OR "post-traumatic headache"))

Embase via Ovid =565

((nano-curcumin OR nanocurcumin OR "curcumin nanoparticles" OR curcumin OR turmeric OR "Curcuma longa" OR curcuminoids OR diferuloylmethane OR "Indian saffron" OR haldi OR "yellow ginger" OR "Jiang Huang" OR Halada OR Kurkum OR Kurkuma OR Theracurmin OR Meriva OR BCM-95) AND (migraine OR headache OR cephalalgia OR migraines OR headaches OR "tension headache" OR "cluster headache" OR "vascular headache" OR "cervicogenic headache" OR "post-traumatic headache"))

PubMed = 43

((nano-curcumin OR nanocurcumin OR "curcumin nanoparticles" OR curcumin OR turmeric OR "Curcuma longa" OR curcuminoids OR diferuloylmethane OR "Indian saffron" OR haldi OR "yellow ginger" OR "Jiang Huang" OR Halada OR Kurkum OR Kurkuma OR Theracurmin OR Meriva OR BCM-95) AND (migraine OR headache OR cephalalgia OR migraines OR headaches OR "tension headache" OR "cluster headache" OR "vascular headache" OR "cervicogenic headache" OR "post-traumatic headache")).

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