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Meta-analysis

Targeting the gut–brain axis in migraine: Effects of probiotic supplementation on migraine outcomes and inflammatory markers (CRP and TNF-α)

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Abstract

The gut–brain axis has emerged as a potential therapeutic target in migraine management. Several randomized controlled trials (RCTs) have evaluated probiotic supplementation in migraine, yet their findings remain heterogeneous. The aim of this study was to systematically assess and quantitatively synthesize the effects of probiotics on migraine-related outcomes. A systematic review and meta-analysis of randomized controlled trials was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and registered in PROSPERO (CRD420261327461). Electronic databases were searched from inception to January 2026. Random-effects meta-analyses were performed to calculate pooled standardized mean differences (SMD) with 95% confidence intervals (CI). Primary outcomes included migraine attack frequency, migraine duration, and migraine severity. Secondary outcomes comprised inflammatory biomarkers, including high-sensitivity C-reactive protein (hs-CRP) and tumor necrosis factor-alpha (TNF-α). Risk of bias was assessed using the Cochrane Risk of Bias 2 (ROB 2) tool. Six RCTs involving 422 participants were included. Overall, probiotic supplementation significantly improved migraine-related outcomes compared with placebo (p<0.00001). Subgroup analyses demonstrated significant reductions in migraine attack frequency (p=0.002), migraine duration (p=0.0003), migraine severity (p=0.0006), and migraine disability assessment (MIDAS) score (p=0.04). Substantial heterogeneity was observed across studies (I^2=91%). Regarding inflammatory biomarkers, probiotic supplementation was not associated with significant reductions in hs-CRP (p=0.24) or TNF-α (p=0.66). The pooled analysis of inflammatory markers also showed no significant overall effect (p=0.28). Most trials were judged as having a low risk of bias or some concerns. In conclusion, probiotic supplementation is associated with significant improvements in migraine frequency, duration, severity, and disability, supporting its potential as an adjunctive therapeutic strategy in migraine management. The absence of significant effects on inflammatory biomarkers suggests that these clinical benefits may be mediated through alternative pathways within the gut–brain axis rather than systemic inflammation.

Keywords: Migraine, probiotics, gut–brain axis, randomized controlled trial, meta-analysis

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Introduction

Migraine is a highly prevalent and disabling neurovascular disorder affecting more than one billion individuals worldwide [1]. It represents a leading cause of years lived with disability, particularly among young and middle-aged adults [2]. Despite advances in pharmacological therapies, many patients continue to experience suboptimal symptom control, adverse effects, or medication overuse, highlighting the need for complementary therapeutic strategies [3].

The pathophysiology of migraine is complex and multifactorial, involving cortical spreading depolarization, trigeminovascular system activation, and neurogenic inflammation [4]. Increasing evidence suggests that systemic inflammatory processes may contribute to migraine susceptibility and attack severity. Elevated levels of pro-inflammatory biomarkers, including C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-α), have been reported in some patients with migraine, supporting the hypothesis that inflammatory pathways play a role in disease modulation [5-7].

In recent years, growing attention has been directed toward the gut–brain axis as a potential contributor to migraine pathogenesis. The bidirectional communication between the gastrointestinal system and the central nervous system involves neural, immune, endocrine, and metabolic pathways. Alterations in gut microbiota composition have been associated with immune dysregulation, increased intestinal permeability, and systemic inflammation, all of which may influence migraine activity [8].

Probiotics, defined as live microorganisms that confer health benefits when administered in adequate amounts, have demonstrated immunomodulatory and anti-inflammatory properties. By restoring microbial balance and modulating cytokine production, probiotics may influence both peripheral and central inflammatory signaling [9]. Several randomized controlled trials (RCTs) have investigated the effects of probiotic supplementation on migraine characteristics; however, the findings remain inconsistent, and the impact on inflammatory biomarkers is not clearly established.

Therefore, the aim of this study was to comprehensively evaluate the effects of probiotic supplementation on migraine clinical outcomes, including attack frequency, duration, and severity, as well as systemic inflammatory markers (CRP and TNF-α). By synthesizing available evidence, this study seeks to clarify whether modulation of the gut–brain axis translates into measurable clinical and biochemical benefits in patients with migraine.

Methods

Study design and protocol registration

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The research question was: “Does probiotic supplementation improve migraine clinical characteristics (frequency, duration, and severity) and reduce inflammatory biomarkers (CRP and TNF-α) compared with placebo in patients with migraine?” The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) following the initial identification of records CRD420261327461

Database and search strategies

The systematic literature search was conducted on January 7, 2026, across four electronic databases: Google Scholar, PubMed/MEDLINE, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy combined controlled vocabulary and free-text terms related to migraine and probiotic supplementation using Boolean operators (“AND” and “OR”). The detailed search strategy for each database is presented in **Table 1**. The development of the search strategy followed established methodological recommendations for systematic reviews to ensure comprehensiveness and reproducibility.

Table 1. Keyword combinations used in different databases in this meta-analysis

Database	Keywords combination	Hits
Google Scholar	("migraine") AND ("probiotic" OR "synbiotic") AND ("CRP" OR "inflammatory markers") AND ("randomized controlled trial")	469
PubMed	("Migraine Disorders"[Mesh] OR migraine* OR "primary headache") AND (probiotic* OR synbiotic* OR prebiotic* OR "gut microbiota" OR "microbiome") AND ("Inflammation"[Mesh] OR "C-Reactive Protein" OR CRP OR hs-CRP OR cytokine* OR "inflammatory marker*" OR NLR OR "neutrophil lymphocyte ratio") AND (randomized controlled trial[pt] OR randomized[tiab] OR placebo[tiab] OR "clinical trial"[tiab])	9
Scopus	("migraine") AND ("probiotic" OR "synbiotic") AND ("CRP" OR "inflammatory markers") AND ("randomized controlled trial")	4
CENTRAL	(migraine OR "migraine disorder" OR "migraine headache") AND (probiotic OR probiotics OR synbiotic OR microbiota OR microbiome)	11

Inclusion and exclusion criteria

Eligible studies were RCTs investigating the effects of probiotic supplementation in patients with migraine. Interventions included orally administered probiotics or synbiotics, regardless of strain composition, dosage, or duration, compared with placebo or inactive control. Studies were required to report at least one relevant clinical outcome, including migraine attack frequency, duration, severity, or inflammatory biomarkers such as CRP and TNF-α.

Accepted study designs were limited to RCTs (parallel or crossover design) that provided primary quantitative data suitable for effect size calculation. Only peer-reviewed articles published in English were included. Conversely, studies that did not involve patients with a confirmed migraine diagnosis, lacked a placebo or comparable control group, did not report extractable outcome data (e.g., mean and standard deviation), or evaluated non-oral microbiota-modulating interventions were excluded. Observational studies, case reports, case series, reviews, conference abstracts without sufficient data, and non-English publications were also excluded. The eligibility assessment was conducted independently by two reviewers, and any discrepancies were resolved through discussion and consensus.

Screening and selection

Two reviewers (INW and PAPW) independently conducted each stage of the review process, including study selection and data extraction. References were organized and screened using Microsoft Excel spreadsheets developed specifically for this review. Disagreements were resolved through discussion and consensus, and when necessary, a third reviewer (INGNY) was consulted. For studies with unclear or missing outcome data, attempts were made to contact the corresponding authors for clarification. In addition, the reference lists of all included articles and relevant review papers were manually screened to identify any additional eligible studies.

Critical appraisal

Two independent reviewers (INW and AANABS) assessed the methodological quality of the included RCTs using the Cochrane Risk of Bias 2 (RoB 2) tool. This instrument evaluates potential bias across five domains: bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain was judged as “low risk,” “some concerns,” or “high risk” of bias, leading to an overall risk-of-bias judgment for each study. Any disagreements between reviewers were resolved through discussion and, when necessary, consultation with a third reviewer (IGAAPAY).

Data extraction

Following the identification and screening of eligible studies according to the predefined inclusion and exclusion criteria, two independent reviewers conducted data extraction using a standardized Microsoft Excel spreadsheet. The extracted data included the first author’s name, year of publication, study location, study design, total sample size, and sex distribution (male and female participants). Diagnostic criteria for migraine (e.g., ICHD criteria or neurologist-confirmed diagnosis) were recorded to ensure consistency across studies.

Details of the intervention regimen were extracted, including probiotic strain composition, dosage (colony-forming units), formulation, and duration of supplementation. Information regarding the control regimen, including placebo characteristics and background therapy, was also documented. The duration of follow-up or intervention period was recorded for each study. Data extracted by the primary reviewer (INW) were independently verified by a second reviewer (PAPW) to ensure accuracy and reliability. Any discrepancies were resolved through discussion and consensus.

Statistical analysis

Statistical analysis was performed using Review Manager (RevMan) version 5.4 (The Cochrane Collaboration, Copenhagen, Denmark). A pairwise meta-analysis was conducted to compare probiotic supplementation with placebo. Continuous outcomes were pooled using standardized mean differences (SMDs) with 95% confidence intervals (CIs), as variations in measurement scales were observed across studies.

A random-effects model was applied to account for anticipated clinical and methodological heterogeneity among trials, including differences in probiotic strains, dosages, and study populations. Statistical heterogeneity was assessed using the chi-square (χ^2) test and the I^2 statistic, with I^2 values greater than 50% considered indicative of substantial heterogeneity. A *p*-value of less than 0.10 in the χ^2 test was considered statistically significant for heterogeneity. Publication bias was planned to be evaluated using funnel plot symmetry if at least ten studies were available for a given outcome.

Results

Study selection

A total of 493 records were identified through database searching across Google Scholar, PubMed/MEDLINE, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL) (**Figure 1**). After removing 28 duplicate records, 465 studies remained for title and abstract screening. Following this initial screening, 450 records were excluded for clearly not meeting the inclusion criteria, leaving 15 articles for full-text assessment.

Of these, 9 studies were excluded after full-text review. The reasons for exclusion included non-randomized study design, absence of a placebo or comparable control group, lack of relevant migraine outcomes (frequency, duration, or severity), insufficient quantitative data for effect size calculation (e.g., missing mean and standard deviation), or ineligible population. Ultimately, six randomized controlled trials met the eligibility criteria and were included in the qualitative synthesis. Of these, five studies provided sufficient quantitative data and were included in the meta-analysis.

Characteristics of included studies

The characteristics of the included studies are presented in **Table 2**. A total of six RCTs were included, comprising 422 participants overall. Across most studies, female participants predominated over males, reflecting the higher prevalence of migraine among women. The sample sizes ranged from 41 to 100 participants per study.

The studies were conducted in multiple geographic locations, predominantly in Iran (four studies), with additional studies from the Netherlands and other regions. All included studies employed randomized controlled designs, with most utilizing double-blind or triple-blind placebo-controlled methodologies. Migraine diagnosis was primarily based on established criteria, including the International Classification of Headache Disorders (ICHD-3), while one study used migraine disability assessment (MIDAS) or PedMIDAS-based diagnostic or severity assessment tools.

Intervention regimens varied in probiotic composition, dosage, and formulation. Most studies administered multi-strain probiotic capsules containing various *Lactobacillus* and *Bifidobacterium* species, with treatment durations ranging from 8 to 16 weeks. In two trials, probiotics were administered as adjunctive therapy alongside standard pharmacological treatments such as propranolol or sodium valproate. Control groups generally received matching

placebo capsules containing inert substances such as starch, maltodextrin, or microcrystalline cellulose.

Migraine-related outcomes were assessed using validated instruments, including the Headache Impact Test (HIT-6), MIDAS, Headache Diary Index (HDI), and PedMIDAS. Additionally, several studies reported inflammatory biomarkers, including CRP and TNF-α, as secondary outcomes.

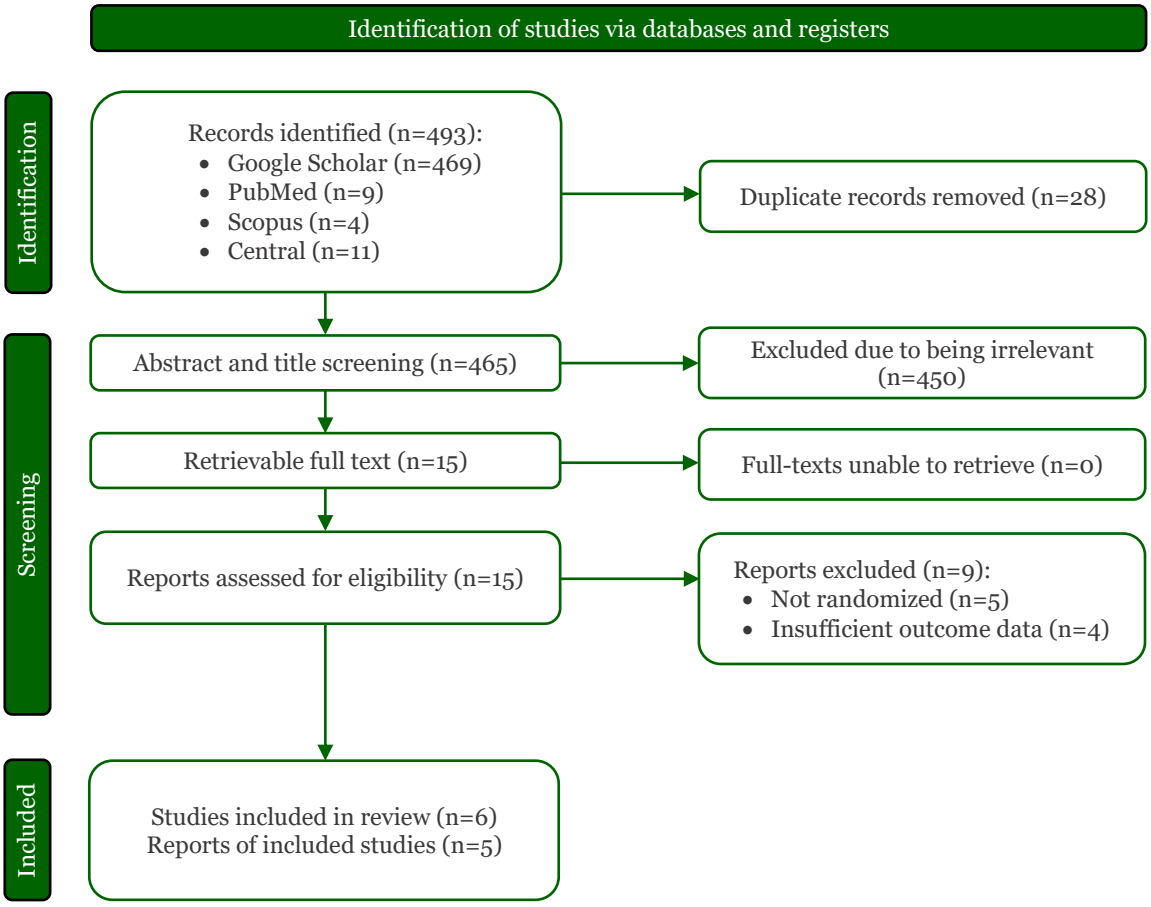

Figure 1. PRISMA flow diagram of study selection for the systematic review and meta-analysis.

Risk of bias assessment

The risk of bias assessment of the included randomized controlled trials is presented in **Figure 2**. Most studies were judged to have a low risk of bias or some concerns, with no study demonstrating critical methodological flaws across multiple domains. Regarding bias arising from the randomization process (D1), most trials adequately described random sequence generation, including Tirani *et al.* (2024) [10], Roos *et al.* (2017) [11], Ghavami *et al.* (2021) [12], and Martami *et al.* (2019) [13]. However, Bazmamoum *et al.* (2024) [14] and Bidabadi *et al.* (2023) [15] did not clearly report allocation concealment procedures, resulting in judgments of some concerns.

For bias due to deviations from intended interventions (D2), the majority of trials, such as Tirani *et al.* (2024), Roos *et al.* (2017), Ghavami *et al.* (2021), and Bidabadi *et al.* (2023), were described as double-blinded and placebo-controlled, leading to a low risk of bias. In contrast, Martami *et al.* (2019) and Bazmamoum *et al.* (2024) provided limited information regarding adherence to intention-to-treat principles, raising some concerns. Bias due to missing outcome data (D3) was generally low, particularly in Tirani *et al.* (2024), Ghavami *et al.* (2021), Bazmamoum *et al.* (2024), and Bidabadi *et al.* (2023). However, Roos *et al.* (2017) and Martami *et al.* (2019) presented some concerns due to incomplete clarification of attrition handling.

Table 2. Characteristics and outcomes of included randomized controlled trials

Author, year	Location	Sample size	Gender		Study design	Diagnosis criteria	Regimen intervention	Regimen control	Duration
			Male	Female					
Tirani *et al.*, 2024	Iran	72	7	65	Randomized, triple-blinded, placebo-controlled trial	ICHD-3	Probiotic capsule (4.5×1011 CFU) (Farabiotic Pharmaceutical Company, Tehran, Iran) per day and a pearl of vitamin D (50,000 IU) (Zahravi Pharmaceutical Company, Tabriz, Iran).	Placebo capsule for probiotic (containing starch and maltodextrin) every day and a placebo pearl for vitamin D (containing corn oil)	Every 2 weeks for 12 weeks
Roos *et al.*, 2017	Netherlands	60	4	56	Randomized placebo-controlled study	MIDAS	Probiotic mixture (2.5×109 colony-forming units per gram) contains the following bacterial strains: *Bifidobacterium bifidum* W23, *B. lactis* W52, *Lactobacillus acidophilus* W37, *L. brevis* W63, *L. casei* W56, *L. salivarius* W24, *Lactococcus lactis* W19 and *L. lactis* W58.	Placebo contained 2 g of the carrier of the probiotic product; maize starch and maltodextrin powder	Once daily for 12 weeks
Ghavami *et al.*, 2021	Iran	69	0	69	Multi-center, randomized, placebo-controlled, double-blind parallel-group clinical trial	ICHD-3	Each capsule (500 mg) contained 109 CFU of 12 types of probiotics including *Lactobacillus casei*, *Lactobacillus acidophilus*, *Lactobacillus rhamnosus, Lactobacillus helveticus, Lactobacillus bulgaricus, Lactobacillus plantarum, Lactobacillus gasseri, Bifidobacterium breve*, *Bifidobacterium longum, Bifidobacterium lactis, Bifidobacterium bifidum, Streptococcus thermophilus,* and Fructooligosaccharides (FOS).	Starch capsules	Twice a day (30 min before lunch and dinner), for 12 weeks
Martami *et al.*, 2019	Iran	100	28	72	Randomized, double-blind, placebo-controlled trial	ICHD-3	Multispecies probiotic product (Bio-Kult-protexin: 2x 10'9 CFU/capsule) that contained 14 bacterial strains: *Bacillus subtilis* PXN 21, *Bifidobacterium bifidum* PXN 23, *Bifidobacterium breve* PXN 25, *Bifidobacterium infantis* PXN 27, *Bifidobacterium longum* PXN 30, *Lactobacillus acidophilus* PXN 35, *L. delbrueckii* ssp. bulgaricus PXN 39, *L. casei* PXN 37, *L. plantarum* PXN 47, *L. rhamnosus* PXN 54, *L. helveticus* PXN 45, *L. salivarius* PXN 57, *Lactococcus lactis* ssp. lactis PXN 63, and *Streptococcus thermophilus* PXN 66.	Microcrystalline cellulose in a vegetable capsule (hydroxypropyl methylcellulose)	Once a day, for 10 weeks in the episodic migraine and 8 weeks for chronic migraine

Author, year	Location	Sample size	Gender		Study design	Diagnosis criteria	Regimen intervention	Regimen control	Duration
			Male	Female					
Bazmamoum *et al.*, 2024	Iran	41	21	20	Randomized Clinical Trial Study	PedMIDAS	Propranolol at a dose of 1 mg per kilogram of body weight daily in two divided doses along with a 250 mg Yomogi capsule	Propranolol along with placebo	Once a day, for 3 months
Bidabadi *et al.*, 2023	Iran	80	45	35	Randomized Controlled Clinical Trial	ICHD	Initial dose of sodium valproate 20 mg/Kg/24hr and a maintenance dose of 5 mg/Kg/24hr + 1g probiotic sachet (KidiLact) contains the following bacteria: *Lactobacillus acidophilus* (2.5×10'10), *Lactobacillus rhamnosus* (3.5×10'10), *Lactobacillus bulgaricus* (2×10'9), *Bifidobacterium infantis* (5×10'10), *Lactobacillus casei* (3×10'10), *Bifidobacterium breve* (2.5×10'10), and *Streptococcus thermophilus* (2×10'9)	Placebo	Daily for four months

HIT-6: the short-form headache impact test-6; ICHD: international classification of headache disorders; MIDAS: migraine disability assessment scale; PedMIDAS: pediatric migraine disability assessment scale.

Figure 2. Risk of bias assessment of included randomized controlled trials using the ROB 2 tool. (A) Traffic light plot summarizing domain-specific risk of bias judgments for each included study. (B) Summary plot showing the proportion of studies rated as low risk or some concerns across each ROB 2 domain and overall risk of bias.

In terms of bias in measurement of outcomes (D4), studies such as Roos *et al.* (2017), Martami *et al.* (2019), Bazmamoum *et al.* (2024), and Bidabadi *et al.* (2023) were judged as low risk. Meanwhile, Tirani *et al.* (2024) and Ghavami *et al.* (2021) raised some concerns, mainly due to insufficient reporting of blinding procedures, particularly given the subjective nature of migraine-related outcomes. Finally, bias in the selection of the reported result (D5) was predominantly judged as low risk in most studies, including Tirani *et al.* (2024), Roos *et al.* (2017), Ghavami *et al.* (2021), Martami *et al.* (2019), and Bidabadi *et al.* (2023). Some concerns were identified in Bazmamoum *et al.* (2024) due to limited clarity regarding pre-specified outcome reporting. Overall, the included trials were considered to have predominantly low risk of bias, with some concerns mainly related to incomplete reporting of allocation concealment and blinding procedures.

Meta-analysis results

Five RCTs comprising 362 participants were included in the quantitative synthesis. Probiotic supplementation was associated with a significant improvement in migraine-related outcomes compared with placebo (SMD=−1.76; 95%CI: −2.33 to −1.18; $p<0.00001$). Substantial between-study heterogeneity was observed ($I^2=91\%$, $p<0.00001$) (**Figure 3**).

Subgroup analyses showed that probiotic supplementation significantly reduced migraine attack frequency (SMD= −1.98; 95%CI: −3.21 to −0.74; $p=0.002$), with considerable heterogeneity ($I^2=95\%$); migraine duration (SMD= −1.90; 95%CI: −2.93 to −0.86; $p=0.0003$), with high heterogeneity ($I^2=86\%$); and migraine severity (SMD= −1.70; 95%CI: −2.67 to −0.72; $p=0.0006$), also with substantial heterogeneity ($I^2=91\%$).

Migraine-related disability, assessed using the MIDAS score in one study, showed a modest but statistically significant improvement (SMD= −0.66; 95%CI: −1.30 to −0.03; p=0.04).

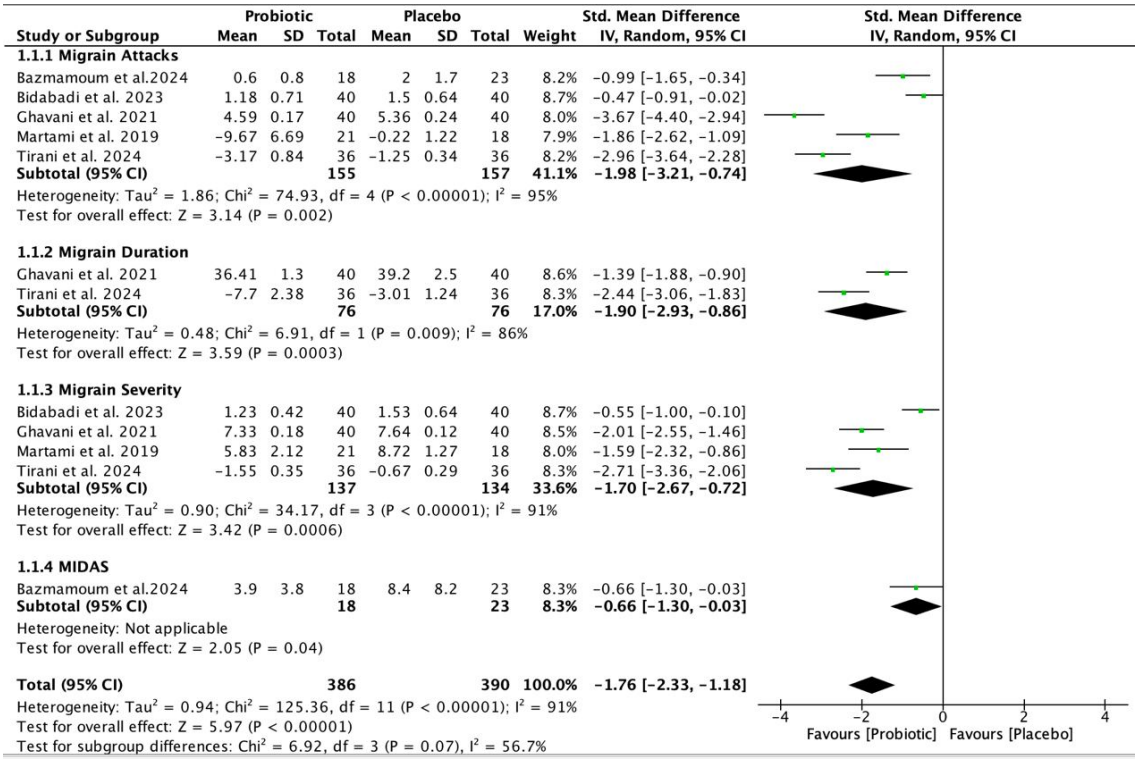

Figure 3. Forest plot of the effects of probiotic supplementation on migraine-related outcomes compared with placebo.

Inflammatory biomarkers

C-Reactive Protein (hs-CRP)

Four trials involving 245 participants evaluated the effects of probiotic supplementation on hs-CRP levels. Pooled analysis using a random-effects model demonstrated no significant reduction in hs-CRP levels compared with placebo (SMD=−0.86; 95%CI: −2.31 to 0.59; p=0.24). Between-study heterogeneity was considerable (I^2=96%, p<0.00001), indicating substantial variability across trials.

Tumor Necrosis Factor-α (TNF-α)

Two studies comprising 93 participants assessed TNF-α levels. No significant difference was observed between the probiotic and placebo groups (SMD=0.10; 95%CI: −0.34 to 0.53; p=0.66). Heterogeneity was low (I^2=10%, p=0.29), suggesting consistency across included studies.

Overall Effect on Inflammatory Markers

When pooling CRP and TNF-α outcomes, probiotic supplementation was not associated with a significant overall effect on inflammatory biomarkers (SMD=−0.53; 95%CI: −1.49 to 0.44; p=0.28). Substantial heterogeneity was detected in the combined analysis (I^2=94%, p<0.00001). No significant subgroup differences were observed between CRP and TNF-α outcomes (p=0.22) (**Figure 4**).

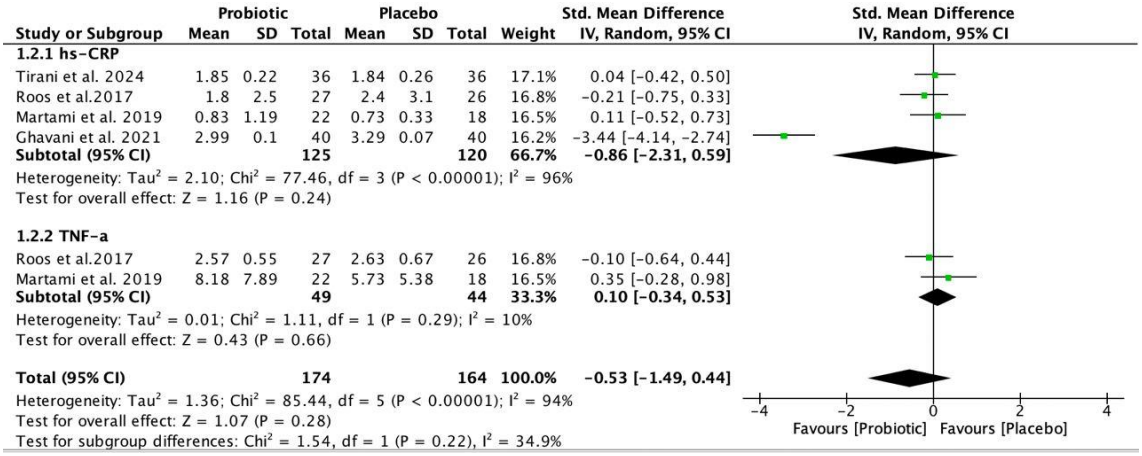

Figure 4. Forest plot of the effects of probiotic supplementation on inflammatory Biomarker outcomes compared with placebo.

Publication bias assessment

Potential publication bias was assessed visually using funnel plots for each pooled outcome (**Figure 5**). The plots were constructed by plotting the standardized mean difference (SMD) against the standard error of the effect size. For clinical outcomes, including migraine attack frequency, migraine duration, migraine severity, and MIDAS scores, the funnel plot demonstrated a relatively symmetrical distribution of studies around the pooled effect estimate. Although a small degree of dispersion was observed among smaller studies with higher standard errors, no clear asymmetry suggesting substantial publication bias was identified. Similarly, for inflammatory biomarkers (hs-CRP and TNF-α), the distribution of studies appeared generally symmetrical around the vertical line of the pooled effect size. No obvious clustering of small studies on one side of the plot was observed. However, it should be noted that the number of included studies per outcome was fewer than ten. According to established methodological recommendations, the interpretation of funnel plot asymmetry is unreliable when fewer than ten studies are included. Therefore, although no apparent publication bias was detected, the possibility of small-study effects cannot be definitively excluded.

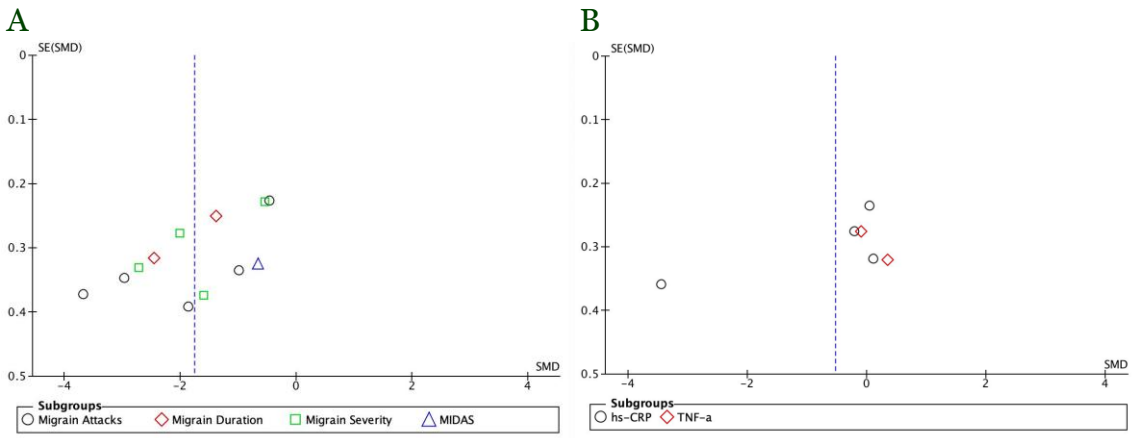

Figure 5. Funnel plots assessing potential publication bias. (A) Funnel plot for clinical outcomes, including migraine attack frequency, migraine duration, migraine severity, and MIDAS score. (B) Funnel plot for inflammatory biomarkers, including hs-CRP and TNF-α.

Discussion

This meta-analysis demonstrates that probiotic supplementation is associated with significant improvements in migraine clinical characteristics, including attack frequency, duration, and severity. The magnitude of effect observed across studies suggests a clinically meaningful benefit.

However, these improvements were not accompanied by consistent reductions in systemic inflammatory biomarkers, namely CRP and TNF-α. This dissociation between clinical response and circulating inflammatory markers provides important insight into the potential mechanisms underlying probiotic efficacy in migraine.

The present findings are partially consistent with previous RCTs investigating probiotic supplementation in migraine. Several individual studies, including Ghavami *et al.* (2021), Tirani *et al.* (2024), and Bidabadi *et al.* (2023), reported significant reductions in migraine frequency and severity following probiotic administration. Similarly, Martami *et al.* (2019) observed improvements in headache-related outcomes after probiotic supplementation. These findings support the hypothesis that modulation of gut microbiota may influence migraine activity through the gut–brain axis.

However, the magnitude of effect observed in this pooled analysis appears larger than that reported in some earlier trials, such as Roos *et al.* (2017) and Bazmamoum *et al.* (2024), where the reduction in migraine parameters was more modest. This discrepancy may reflect differences in probiotic strains, colony-forming unit (CFU) dosage, intervention duration, baseline migraine severity, and participant characteristics.

Migraine is increasingly recognized as a neuroinflammatory disorder involving activation of the trigeminovascular system and release of pro-inflammatory mediators. Growing evidence supports the role of the gut–brain axis in migraine pathophysiology [16]. The bidirectional communication between intestinal microbiota and the central nervous system involves neural, immune, and metabolic pathways [17]. Probiotics may exert therapeutic effects by enhancing intestinal barrier integrity, reducing endotoxin translocation, modulating cytokine production, and influencing neurotransmitter synthesis, such as serotonin and gamma-aminobutyric acid (GABA). These mechanisms may attenuate neuronal sensitization and cortical excitability without necessarily producing measurable changes in systemic inflammatory markers [18].

In contrast to the significant improvements observed in clinical outcomes, the present analysis did not demonstrate significant reductions in CRP or TNF-α levels. Previous studies assessing inflammatory biomarkers in migraine have produced inconsistent findings, with some reporting elevated cytokine levels during attacks, while others show minimal systemic changes. CRP and TNF-α are systemic markers and may not adequately reflect localized neurogenic inflammation within the trigeminovascular pathway [19]. Additionally, variability in baseline inflammatory status, small sample sizes, and methodological differences in biomarker assessment likely contributed to the substantial heterogeneity observed, particularly for CRP outcomes.

Substantial heterogeneity was evident across most clinical endpoints. This variability is likely attributable to differences in probiotic formulations (single-strain versus multi-strain), dosage, treatment duration, migraine subtype, and study design. Such heterogeneity limits the ability to define optimal probiotic regimens and standardize therapeutic recommendations. Additional sources of uncertainty include the relatively small number of included studies and modest sample sizes, which may reduce the precision of pooled estimates and increase susceptibility to small-study effects. The limited number of trials also constrained formal assessment of publication bias.

Inflammatory biomarker analyses were based on a subset of studies, restricting the strength of conclusions regarding systemic inflammation. Inconsistencies in laboratory methods, baseline inflammatory profiles, and timing of biomarker measurement may have further contributed to variability in these findings. Moreover, differences in outcome measurement tools and follow-up durations across studies may have affected comparability and overall estimate precision.

Despite these limitations, the consistent direction of effect across attack frequency, duration, and severity strengthens the overall conclusion that probiotic supplementation may offer a beneficial adjunctive strategy in migraine management. The absence of consistent biomarker changes suggests that the therapeutic effect may be mediated through complex gut–brain signaling mechanisms rather than solely through systemic inflammatory suppression.

Future large-scale, well-designed randomized trials with standardized probiotic formulations, adequate sample sizes, and comprehensive inflammatory profiling, including both systemic and neuroinflammatory markers, are warranted to clarify the biological pathways

involved and to determine the long-term clinical relevance of probiotic supplementation in migraine.

Conclusion

In conclusion, this meta-analysis suggests that probiotic supplementation may provide clinically meaningful improvements in migraine frequency, duration, and severity. However, these benefits were not consistently accompanied by significant reductions in systemic inflammatory markers such as CRP and TNF-α, indicating that the therapeutic effects of probiotics may involve mechanisms beyond measurable systemic inflammation. While the findings support the potential role of gut–brain axis modulation as an adjunctive strategy in migraine management, substantial heterogeneity and limited biomarker data warrant cautious interpretation. Future large-scale, well-designed randomized controlled trials with standardized probiotic formulations and comprehensive inflammatory profiling are needed to confirm these results and clarify underlying mechanisms.

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Competing interests

All the authors declare that there are no conflicts of interest.

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This study received no external funding.

Underlying data

Derived data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declaration of artificial intelligence use

We hereby confirm that no artificial intelligence (AI) tools or methodologies were utilized at any stage of this study, including during data collection, analysis, visualization, or manuscript preparation. All work presented in this study was conducted manually by the authors without the assistance of AI-based tools or systems.

How to cite

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