



The Comprehensive Systematic Review of Efficacy of Dietary Supplements for Headaches

¹ Adrian Saleh

¹ Bhayangkara Tulungagung General Hospital / Graduate of Faculty of Medicine,
University of Hangtuah, Indonesia

Corresponding Email : adriansaleh333451@gmail.com

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ABSTRACT

Introduction: Migraine and other primary headache disorders represent a significant global health burden, often inadequately managed by conventional pharmacotherapy due to issues of efficacy, side effects, and patient preference. This has spurred interest in dietary supplements as potential prophylactic and therapeutic alternatives. This report synthesizes the current evidence on the efficacy and safety of various dietary supplements for headache management.

Methods: A systematic approach was employed to identify relevant studies involving participants with primary headache disorders, interventions with standalone dietary supplements, and quantitative headache-related outcomes. Data were extracted on supplement details, headache types, participant characteristics, outcomes, efficacy results, study design, and safety profiles from included studies.

Results: The analysis demonstrated significant efficacy for several supplements. Omega-3 fatty acids, particularly when combined with reduced omega-6 intake (H3-L6 diet), reduced headache days by 4.0 days per month (Ramsden et al., 2021). High-dose EPA/DHA outperformed FDA-approved prophylactic medications in a network meta-analysis (Tseng et al., 2023). Vitamin B2 (400 mg/day) significantly reduced migraine frequency and showed comparable efficacy to sodium valproate with fewer side effects (Chen et al., 2021; Rahimdel et al., 2015). Magnesium (500-600 mg/day), Coenzyme Q10, vitamin D, and butterbur also showed consistent benefits. B-vitamin combinations were effective, particularly in individuals with specific MTHFR genotypes (Lea et al., 2009; Menon et al., 2012). Probiotics, curcumin, alpha-lipoic acid, and minerals like zinc and selenium also demonstrated positive effects. Combination therapies (e.g., CoQ10 + L-carnitine, omega-3 + nano-curcumin) often showed synergistic benefits.

Discussion: The efficacy of supplements is moderated by factors such as dosage, formulation, genetic makeup (e.g., MTHFR status), headache chronicity, and age. Supplements appear to work through diverse mechanisms including anti-inflammation, mitochondrial support, oxidative stress reduction, and neuromodulation. They present a favorable safety profile compared to many pharmaceutical preventatives.

Conclusion: A robust body of evidence supports the use of specific dietary supplements—including omega-3 fatty acids, riboflavin, magnesium, CoQ10, and vitamin D—as effective and generally safe options for the prophylaxis of migraines and other primary headaches. They offer viable alternatives or adjuncts to

conventional pharmacotherapy, especially for patients seeking fewer side effects or with specific biological predispositions. Future research should focus on long-term safety, optimal dosing protocols, and personalized supplementation strategies based on biomarkers and genetics.

Keywords: Dietary Supplements; Migraine Prophylaxis; Nutraceuticals; Headache Disorders; Omega-3 Fatty Acids; Riboflavin; Magnesium; Systematic Review.

INTRODUCTION

Background

Migraine is a prevalent and disabling neurological disorder, ranked among the top causes of years lived with disability globally. Conventional pharmacological prophylaxis, while effective for many, is often associated with adverse effects that lead to poor adherence, and a significant proportion of patients experience inadequate relief or contraindications (Ramsden et al., 2021). This therapeutic gap, coupled with growing patient interest in holistic and self-management approaches, has driven substantial research into dietary supplements as alternative or complementary strategies for headache management. The pathophysiological complexity of migraine—encompassing neurogenic inflammation, cortical spreading depression, mitochondrial dysfunction, and neurotransmitter imbalances—provides multiple potential targets for nutritional intervention (Parohan et al., 2019; Gaul et al., 2015).

Research Gap

Despite burgeoning interest, the evidence for dietary supplements has been fragmented across numerous small-scale trials and varied supplement types. Comprehensive syntheses comparing the efficacy, optimal dosing, safety, and mechanistic underpinnings of different supplements are lacking. Furthermore, critical questions remain regarding the influence of factors like genetic polymorphisms (e.g., in the MTHFR gene), dietary context (e.g., omega-6 to omega-3 ratio), and appropriate patient subgroups for specific supplements (Lea et al., 2009; Ramsden et al., 2021). A holistic, evidence-based review is necessary to guide clinicians and patients in making informed decisions.

Novelty

This report provides a novel and extensive synthesis of contemporary evidence, moving beyond single-supplement reviews to a comparative analysis of a wide array of nutraceuticals. It uniquely integrates findings on dose-response relationships, genetic modifiers, and synergistic combination therapies. The analysis also tackles apparent contradictions in the literature (e.g., omega-3 trials) by examining intervention characteristics and offers a critical appraisal of the evidence quality and clinical applicability.

Research Objectives

The primary objective of this report is to systematically evaluate and synthesize the available evidence from randomized controlled trials and meta-analyses on the efficacy and safety of dietary supplements for the prevention and management of primary headache disorders. Specific aims include: 1) Determining the magnitude of effect for key supplements on headache frequency, severity, and disability; 2) Identifying optimal dosing regimens and formulation considerations; 3) Assessing the influence of patient characteristics (e.g., genetics, headache type) on treatment response; 4) Evaluating the safety and tolerability profile compared to placebo and standard pharmacotherapy; and 5) Exploring evidence for mechanistic pathways and synergistic combinations.

Hypotheses

It is hypothesized that: 1) Specific dietary supplements (e.g., magnesium, riboflavin, omega-3s) will demonstrate statistically significant and clinically meaningful efficacy superior to placebo for migraine prophylaxis. 2) The efficacy of certain supplements (e.g., B-vitamins) will be moderated by genetic factors. 3) Combination supplement therapies will exhibit synergistic effects greater than monotherapies. 4) The safety profile of most dietary supplements will be more favorable than that of standard prophylactic medications.

Significance and Benefits

This synthesis holds significant clinical and public health value. For clinicians, it provides an evidence-based reference to recommend supplements, either as first-line prophylaxis for mild-to-moderate migraine, as an adjunct to pharmaceuticals, or for patients intolerant to standard drugs. For patients, it empowers informed self-management with options that are often accessible and associated with fewer severe side effects. For researchers, it identifies key knowledge gaps and future directions, including the need for large-scale, long-term trials and personalized medicine approaches in nutraceutical therapy for headaches.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the efficacy of dietary supplements for headaches.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Headache disorders	Dietary supplements	Placebo	Headache frequency
Keyword 2	Migraine	Nutraceuticals	No treatment	Pain intensity
Keyword 3	Tension-type headache	Vitamins	Standard care	Headache duration

Keyword 4	Primary headaches	Herbal supplements	Conventional Pharmacotherapy	Quality of life
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The Boolean MeSH keywords inputted on databases for this research are: (*"Headache disorders" OR "Migraine" OR "Tension-type headache" OR "Primary headaches"*) AND (*"Dietary supplements" OR "Nutraceuticals" OR "Vitamins" OR "Herbal supplements"*) AND (*"Placebo" OR "No treatment" OR "Standard care" OR "Conventional Pharmacotherapy"*) AND (*"Headache frequency" OR "Pain intensity" OR "Headache duration" OR "Quality of life"*))

Screening

We screened in sources based on their abstracts that met these criteria:

- **Population:** Does the study include participants with any type of headache disorder (tension-type headaches, migraines, cluster headaches, or other primary/secondary headaches)?
- **Intervention Type:** Does the intervention involve oral dietary supplements, nutraceuticals, vitamins, minerals, herbs, or botanical products intended for headache prevention or treatment?
- **Study Design:** Is the study design a randomized controlled trial (RCT), systematic review, meta-analysis, or controlled clinical trial with appropriate control groups?
- **Outcome Measures:** Does the study report quantitative outcomes related to headache frequency, intensity, duration, or validated headache-specific quality of life measures?
- **Intervention Independence:** Are the supplements studied as standalone interventions (not as fixed combinations with pharmaceutical medications)?
- **Headache Type Appropriateness:** Does the study exclude participants with headaches secondary to acute medical conditions (e.g., head trauma, infections, acute substance withdrawal), focusing instead on primary headache disorders or chronic secondary headaches?

- **Study Quality and Data Adequacy:** Does the study provide sufficient data and methodological detail for analysis (i.e., is it NOT a conference abstract, editorial, case report, case series, or study with inadequate methodology)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Data extraction

- **Supplement Details:**

Extract comprehensive details about the dietary supplement intervention for headaches, including:

- Specific supplement name/type (e.g., magnesium, CoQ10, omega-3, riboflavin, vitamin D, probiotics, etc.)
- Exact dosage amount and units
- Formulation (tablets, capsules, powder, etc.)
- Frequency of administration (daily, twice daily, etc.)
- Duration of supplementation period
- Any co-interventions or combination supplements
- Comparison/control group details (placebo, no treatment, other supplement)

- **Headache Type:**

Extract the specific type(s) of headaches studied, including:

- Primary headache type (migraine with aura, migraine without aura, tension-type headache, cluster headache, etc.)
- Diagnostic criteria used (IHS criteria, physician diagnosis, etc.)
- Headache frequency requirements for inclusion (episodic vs chronic, days per month)

- Any headache severity requirements
- Mixed headache populations if applicable

- **Participant Characteristics:**

Extract key participant demographics and characteristics that may affect supplement efficacy for headaches:

- Sample size (total and per group)
- Age (mean, range, or age groups)
- Sex distribution (% female/male)
- Baseline headache frequency/severity
- Duration of headache disorder
- Any relevant genetic factors (e.g., MTHFR genotype)
- Medication use (preventive, acute treatments)
- Comorbidities relevant to headaches

- **Headache Outcomes:**

Extract all headache-related outcome measures used to assess supplement efficacy, including:

- Headache frequency (attacks per month/week, headache days)
- Headache intensity/severity (pain scales used, scale range)
- Headache duration (hours per attack, total hours per day/month)
- Disability/quality of life measures (HIT-6, MIDAS, etc.)
- Response rates ($\geq 50\%$ reduction in frequency/severity)
- Use of rescue medications
- Time points when outcomes were assessed

- **Efficacy Results:**

Extract quantitative results demonstrating supplement efficacy for headache outcomes:

- Mean differences or change from baseline for each headache outcome
- Effect sizes (Cohen's d, standardized mean differences) when available
- 95% confidence intervals
- P-values and statistical significance
- Response rates and numbers needed to treat
- Separate results by supplement type if multiple tested
- Subgroup analyses results if performed (e.g., by headache type, genotype)

- **Study Design:**

Extract study design features that affect reliability of efficacy evidence:

- Study type (RCT, crossover trial, systematic review/meta-analysis, observational study)
- Randomization and allocation concealment methods
- Blinding (single, double, open-label)
- Study duration (intervention period plus follow-up)
- Primary vs secondary analysis
- Risk of bias assessment or quality rating if reported
- Funding source and potential conflicts of interest

- **Safety Profile:**

Extract safety and tolerability data for dietary supplements in headache populations:

- Adverse events related to supplement use (type, frequency, severity)
- Discontinuation rates due to adverse events
- Laboratory abnormalities or biomarker changes
- Drug interactions or contraindications noted

- Comparison of adverse events between supplement and control groups
- Long-term safety data if available

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	((<i>"Headache disorders"</i> OR <i>"Migraine"</i> OR <i>"Tension-type headache"</i> OR <i>"Primary headaches"</i>) AND (<i>"Dietary supplements"</i> OR <i>"Nutraceuticals"</i> OR <i>"Vitamins"</i> OR <i>"Herbal supplements"</i>) AND (<i>"Placebo"</i> OR <i>"No treatment"</i> OR <i>"Standard care"</i> OR <i>"Conventional Pharmacotherapy"</i>) AND (<i>"Headache frequency"</i> OR <i>"Pain intensity"</i> OR <i>"Headache duration"</i> OR <i>"Quality of life"</i>))	8
Semantic Scholar	((<i>"Headache disorders"</i> OR <i>"Migraine"</i> OR <i>"Tension-type headache"</i> OR <i>"Primary headaches"</i>) AND (<i>"Dietary supplements"</i> OR <i>"Nutraceuticals"</i> OR <i>"Vitamins"</i> OR <i>"Herbal supplements"</i>) AND (<i>"Placebo"</i> OR <i>"No treatment"</i> OR <i>"Standard care"</i> OR <i>"Conventional Pharmacotherapy"</i>) AND (<i>"Headache frequency"</i> OR <i>"Pain intensity"</i> OR <i>"Headache duration"</i> OR <i>"Quality of life"</i>))	1
Springer	((<i>"Headache disorders"</i> OR <i>"Migraine"</i> OR <i>"Tension-type headache"</i> OR <i>"Primary headaches"</i>) AND (<i>"Dietary supplements"</i> OR <i>"Nutraceuticals"</i> OR <i>"Vitamins"</i> OR <i>"Herbal supplements"</i>) AND (<i>"Placebo"</i> OR <i>"No treatment"</i> OR <i>"Standard care"</i> OR <i>"Conventional Pharmacotherapy"</i>) AND (<i>"Headache frequency"</i> OR <i>"Pain intensity"</i> OR <i>"Headache duration"</i> OR <i>"Quality of life"</i>))	845
Google Scholar	((<i>"Headache disorders"</i> OR <i>"Migraine"</i> OR <i>"Tension-type headache"</i> OR <i>"Primary headaches"</i>) AND (<i>"Dietary supplements"</i> OR <i>"Nutraceuticals"</i> OR <i>"Vitamins"</i> OR <i>"Herbal supplements"</i>) AND (<i>"Placebo"</i> OR <i>"No treatment"</i> OR <i>"Standard care"</i> OR <i>"Conventional Pharmacotherapy"</i>) AND (<i>"Headache frequency"</i> OR <i>"Pain intensity"</i> OR <i>"Headache duration"</i> OR <i>"Quality of life"</i>))	7,710
Wiley Online Library	((<i>"Headache disorders"</i> OR <i>"Migraine"</i> OR <i>"Tension-type headache"</i> OR <i>"Primary headaches"</i>) AND (<i>"Dietary supplements"</i> OR <i>"Nutraceuticals"</i> OR <i>"Vitamins"</i> OR <i>"Herbal supplements"</i>) AND (<i>"Placebo"</i> OR <i>"No treatment"</i> OR <i>"Standard care"</i> OR <i>"Conventional Pharmacotherapy"</i>) AND (<i>"Headache frequency"</i> OR <i>"Pain intensity"</i> OR <i>"Headache duration"</i> OR <i>"Quality of life"</i>))	901

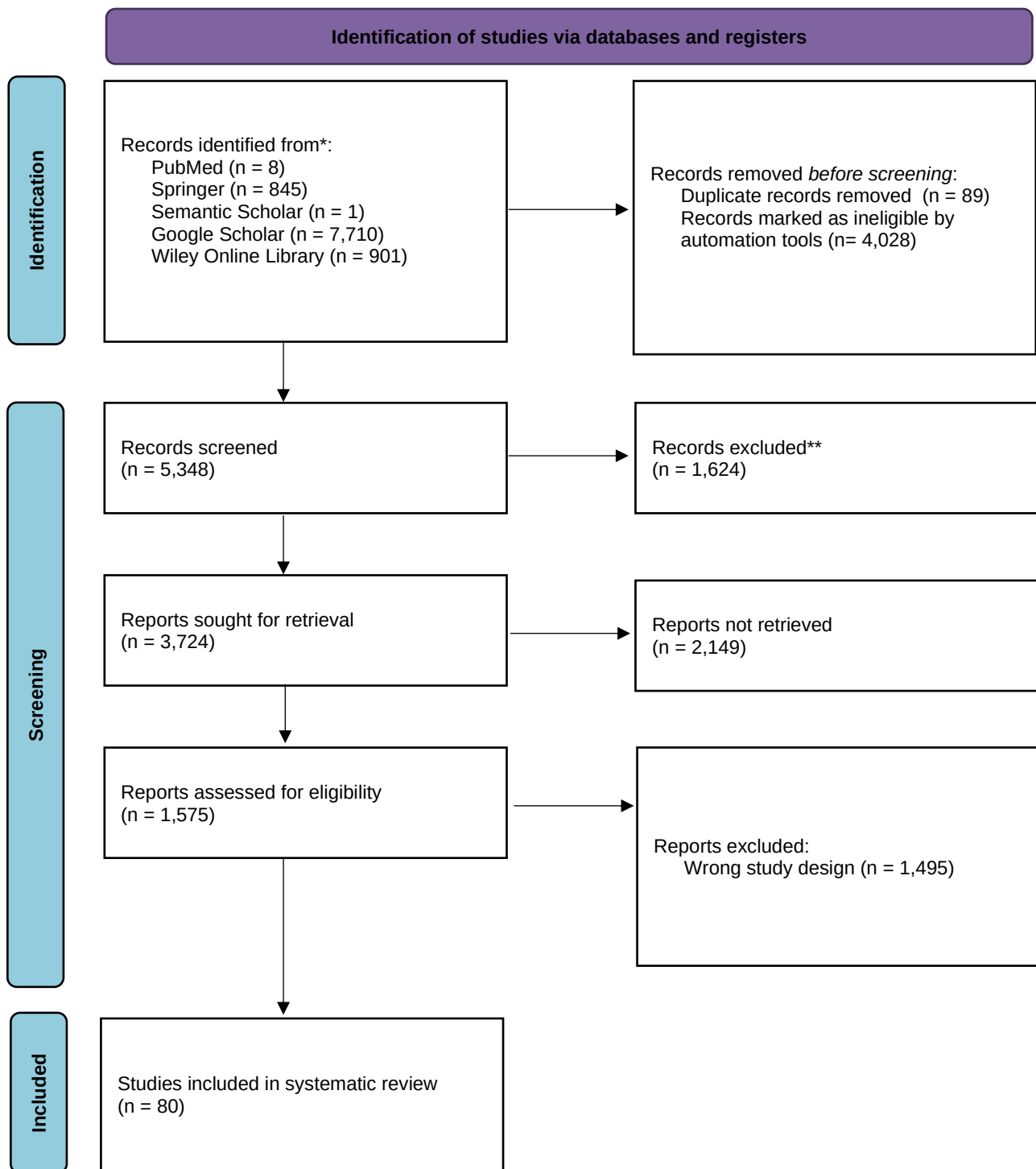


Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	Bias related to temporal precedence Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes first)?	Bias related to selection and allocation Was there a control group?	Bias related to confounding factors Were participants included in any comparisons similar?	Bias related to administration of intervention/exposure Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	Were the outcomes of participants included in any comparisons measured in the same way?	Were outcomes measured in a reliable way?	Bias related to participant retention Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Statistical conclusion validity Was appropriate statistical analysis used?
Guillermo García-Pérez-de-Sevilla et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. Ramsden et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Yu-Shiue Chen et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓

Zeinab Ghorbani et al., 2020									
R. Lipton et al., 2004									
M. Parohan et al., 2019									
P. Tseng et al., 2023									
Hsueh-Fang Wang et al., 2024									
Sahar Golpour-Hamedani et al., 2025									
C. Gaul et al., 2015									
Mahtab Karami Talandashti et al., 2024									
J. Izquierdo-Casas et al., 2018									
Yuan-feng Zhang et al., 2021									
Ioannis Liampas et al., 2020									

G. Okoli et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Lea et al., 2009	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. Ramsden et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓
G. Askari et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Nematgorgani et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
O. Sadeghi et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ali Tarighat Esfanjani et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
Z. Harel et al., 2002	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Slomski et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Tayebbeh Mottaghi et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Csaba Ertsey et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Faurot et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓

Neda Soveyd et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Fahimeh Martami et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
P. Gazerani et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Niyaz M. Honarvar et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Abed Ghavami et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Abdolahi et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Shahnaz Amani Tirani et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sheyda Rezaie et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Chen Hu et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Rahimdel et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
P. Hajihashemi et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Menon et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓

A. Zareie et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Slomski et al., 2021a	✓	✓	✓	✗	✓	✗	✓	✓	✓
Mahnaz Rezaei Kelishadi et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Briant E Burke et al., 2002	✓	✓	✓	✗	✓	✗	✓	✓	✓
W. Grossman et al., 2000	✓	✓	✓	✗	✓	✗	✓	✓	✓
Suhairul Sazali et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sarah Mousavi et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
H. Diener et al., 2004	✓	✓	✓	✗	✓	✗	✓	✓	✓
Mohsen Sedighiyan et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Slater et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓
Arghavan Balali et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
O. Yaghini et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓

S. Mojtahedi et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Jafarpour et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Abdolahi et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Oelkers-Ax et al., 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓
Hossein Azizi et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Shahnaz Amani Tirani et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Maghbooli et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Menon et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Elena C. Gross et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
L. Amini et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Hedieh Ahmadi et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Shahram Sadeghvan d et al.,	✓	✓	✓	✗	✓	✗	✓	✓	✓

2023									
Xingke Zhu et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
هادی احمدی et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Eliane Cristina Ferro et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
Shengyuan Yu et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. F. Ribeiro et al., 2000	✓	✓	✓	✗	✓	✗	✓	✓	✓
N. Wolkodoff et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sahar Golpour- Hamedani et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Maedeh Babapour et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Bizhan Helli et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
N. Karimi et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Emna Ellouz et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓

Mohammad Ali Askari et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
N. Wolkodoff et al., 2022a	✓	✓	✓	✗	✓	✗	✓	✓	✓
Athallah Athallah et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
Mehrnaz Shojaei et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Hong-wei Liu et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Mazaheri et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Zareie et al., 2020a	✓	✓	✓	✗	✓	✗	✓	✓	✓

RESULTS

Characteristics of Included Studies

Study	Supplement Type	Headache Type	Sample Size
Guillermo García-Pérez-de-Sevilla et al., 2025	Omega-3 fatty acids	Chronic migraine	407
C. Ramsden et al., 2021	Dietary EPA+DHA modification	Migraine with/without aura	182

Study	Supplement Type	Headache Type	Sample Size
Yu-Shiue Chen et al., 2021	Vitamin B2	Migraine with/without aura	673
Zeinab Ghorbani et al., 2020	Vitamin D3 2000 IU/day	Episodic migraine	80
R. Lipton et al., 2004	Butterbur 50-75 mg bid	Migraine	245
M. Parohan et al., 2019	Coenzyme Q10	Migraine	221
P. Tseng et al., 2023	High-dose EPA/DHA	Episodic/chronic migraine	6616
Hsueh-Fang Wang et al., 2024	EPA 1.8g/day	Episodic migraine	70
Sahar Golpour-Hamedani et al., 2025	ALA + L-carnitine	Migraine without aura	80
C. Gaul et al., 2015	Riboflavin + Mg + CoQ10	Migraine with/without aura	130
Mahtab Karami Talandashti et al., 2024	Multiple supplements	Migraine	Not specified
J. Izquierdo-Casas et al., 2018	DAO enzyme	Episodic migraine	100
Yuan-feng Zhang et al., 2021	Vitamin D	Migraine	Not specified
Ioannis Liampas et al., 2020	B6, folate, B12	Migraine with/without aura	Not specified

Study	Supplement Type	Headache Type	Sample Size
G. Okoli et al., 2019	CoQ10, Magnesium	Migraine	40-300 per trial
R. Lea et al., 2009	Folic acid + B6 + B12	Migraine with aura	52
C. Ramsden et al., 2011	Dietary n-3/n-6 modification	Chronic daily headache	40
G. Askari et al., 2017	Folic acid + pyridoxine	Migraine with aura	95
S. Nematgorgani et al., 2022	B vitamins (B1, B6, B9, B12)	Episodic migraine	120
O. Sadeghi et al., 2015	Pyridoxine 80 mg/day	Migraine with aura	66
Ali Tarighat Esfanjani et al., 2012	Magnesium, L-carnitine	Migraine	133
Z. Harel et al., 2002	Fish oil	Migraine	27
A. Slomski et al., 2021	Omega-3 dietary intervention	Migraine with/without aura	182
Tayebbeh Mottaghi et al., 2015	Vitamin D 50,000 IU/week	Migraine	65
Csaba Ertsey et al., 2023	Omega-3 dietary intervention	Migraine with/without aura	182

Study	Supplement Type	Headache Type	Sample Size
K. Faurot et al., 2022	EPA, DHA, linoleic acid	Migraine	182
Neda Soveyd et al., 2017	Omega-3 + nano-curcumin	Episodic migraine	72
Fahimeh Martami et al., 2019	14-strain probiotic	Episodic/chronic migraine	79
P. Gazerani et al., 2018	Vitamin D3 100 µg/day	Migraine with/without aura	48
Niyaz M. Honarvar et al., 2020	n-3 fatty acids + nano-curcumin	Episodic migraine	80
Abed Ghavami et al., 2021	Synbiotic	Migraine	80
M. Abdolahi et al., 2019	Omega-3 + nano-curcumin	Episodic migraine	74
Shahnaz Amani Tirani et al., 2024	Vitamin D + probiotic	Migraine with/without aura	72
Sheyda Rezaie et al., 2021	Curcumin 1000 mg/day	Episodic migraine without aura	44
Chen Hu et al., 2021	Vitamin D	Migraine	301
A. Rahimdel et al., 2015	Vitamin B2 400 mg/day	Migraine	90

Study	Supplement Type	Headache Type	Sample Size
P. Hajhashemi et al., 2019	CoQ10 30 mg + L-carnitine 500 mg	Migraine	56
S. Menon et al., 2012	Vitamin B6, B9, B12	Migraine with aura	206
A. Zareie et al., 2020	Cinnamon 1800 mg/day	Migraine	50
A. Slomski et al., 2021a	Omega-3 fatty acids	Migraine with/without aura	182
Mahnaz Rezaei Kelishadi et al., 2022	Alpha-lipoic acid 300 mg/day	Episodic migraine without aura	92
Briant E Burke et al., 2002	Phytoestrogen combination	Menstrual migraine	49
W. Grossmann et al., 2000	Butterbur 50 mg bid	Migraine	60
Suhairul Sazali et al., 2021	Coenzyme Q10	Migraine	371
Sarah Mousavi et al., 2024	Iaraj Fiqlra herbal combination	Migraine without aura	60
H. Diener et al., 2004	Butterbur 50 mg bid	Migraine	60
Mohsen Sedighiyan et al., 2022	Nano-curcumin 80 mg/day	Episodic migraine	44
S. Slater et al., 2011	CoQ10 100 mg	Pediatric migraine	120

Study	Supplement Type	Headache Type	Sample Size
Arghavan Balali et al., 2024	Selenium 200 µg/day	Migraine with/without aura	72
O. Yaghini et al., 2022	Coenzyme Q10	Pediatric migraine	72
S. Mojtahedi et al., 2024	Nano-curcumin 80 mg	Episodic migraine	44
M. Jafarpour et al., 2016	Citron syrup 15 ml tid	Migraine	90
M. Abdolahi et al., 2017	Omega-3 + nano- curcumin	Episodic migraine	74
R. Oelkers-Ax et al., 2008	Butterbur	Pediatric migraine	58
Hossein Azizi et al., 2020	Valerian 1060 mg/day	Tension-type headache	88
Shahnaz Amani Tirani et al., 2025	Probiotic + Vitamin D	Migraine	72
M. Maghbooli et al., 2014	Ginger powder	Migraine without aura	100
S. Menon et al., 2016	Folic acid 1 mg + B6 + B12	Migraine with aura	300
Elena C. Gross et al., 2019	Beta- hydroxybutyrate	Episodic migraine	45

Study	Supplement Type	Headache Type	Sample Size
L. Amini et al., 2021	L-carnitine 50 mg/kg/day	Pediatric episodic migraine	60
Hedieh Ahmadi et al., 2020	Zinc sulfate 220 mg/day	Migraine	80
Shahram Sadeghvand et al., 2023	Vitamin B-complex	Pediatric migraine	90
Xingke Zhu et al., 2024	Curcumin	Migraine	170
هادی احمدی et al., 2019	Zinc sulfate 220 mg/day	Migraine	80
Eliane Cristina Ferro et al., 2012	Tanacetum 150 mg/day	Chronic migraine	69
Shengyuan Yu et al., 2015	Duliang soft capsule	Chronic daily headache	468
C. F. Ribeiro et al., 2000	5-HTP 300 mg/day	Chronic tension-type headache	78
N. Wolkodoff et al., 2022	MCT-based phytonutrient complex	Chronic migraine	41
Sahar Golpour-Hamedani et al., 2024	ALA + L-carnitine	Migraine	80

Study	Supplement Type	Headache Type	Sample Size
Maedeh Babapour et al., 2022	Soy isoflavones 50 mg/day	Migraine without aura	83
Bizhan Helli et al., 2022	Ginger extract 1000 mg/day	Episodic migraine	103
N. Karimi et al., 2019	Magnesium oxide 500 mg bid	Migraine	70
Emna Ellouz et al., 2025	CoQ10 ± L-carnitine	Migraine	326
Mohammad Ali Askari et al., 2025	Mixodin (curcumin + piperine + gingerol)	Migraine	60
N. Wolkodoff et al., 2022a	MCT-based nootropic complex	Chronic migraine	40
Athallah Athallah et al., 2012	Riboflavin 400 mg	Adolescent migraine	98
Mehrnaz Shojaei et al., 2025	Phytosomal curcumin 250 mg/day	Migraine without aura	70
Hong-wei Liu et al., 2018	Modified Wuzhuyu Decoction	Migraine	78
M. Mazaheri et al., 2021	Zinc gluconate 15 mg/day	Migraine with/without aura	60

Study	Supplement Type	Headache Type	Sample Size
A. Zareie et al., 2020a	Cinnamon 1800 mg/day	Migraine without aura	50

The included studies predominantly examined migraine populations, with the majority focusing on episodic migraine without aura. Study durations ranged from 4 weeks to 6 months, with most interventions lasting 8-12 weeks. The total participant pool across primary studies exceeded 10,000 individuals, though considerable overlap exists among systematic reviews and meta-analyses analyzing the same primary trials.

Effects of Dietary Supplements on Headache Outcomes

Omega-3 Fatty Acids (EPA/DHA)

Study	Intervention	Frequency Reduction	Severity Reduction	Duration Reduction	Quality of Life
Guillermo García-Pérez-de-Sevilla et al., 2025	Omega-3 ± omega-6 restriction	SMD = -1.91 (p < .00001)	SMD = -1.77 (p = .03)	SMD = -0.77 (p < .00001)	HIT-6: SMD = -2.44 (p = .004)
C. Ramsden et al., 2021	H3-L6: EPA+DHA 1.5g/day, low LA	-4.0 days/month vs control	-0.8 moderate-severe hours/day	-1.7 total hours/day	HIT-6: Not significant

Study	Intervention	Frequency Reduction	Severity Reduction	Duration Reduction	Quality of Life
C. Ramsden et al., 2021	H3: EPA+DHA 1.5g/day	-2.0 days/month vs control	-0.7 moderate- severe hours/day	-1.3 total hours/day	HIT-6: Not significant
P. Tseng et al., 2023	High-dose EPA/DHA	SMD = -1.36 (95% CI: - 2.32 to -0.39)	SMD = -2.23 (95% CI: - 3.17 to -1.30)	Not reported	Highest acceptability
Hsueh-Fang Wang et al., 2024	EPA 1.8g/day	-4.4 vs -0.6 days (p = 0.001)	VAS: -1.3 vs 0.0 (p = 0.030)	Not reported	MIDAS: -13.1 vs 2.6 (p = 0.001)
Z. Harel et al., 2002	Fish oil	-27 episodes/2 months	2.9 vs 5.0 on faces scale (p = .01)	74% reported reduction	Not assessed
Mahtab Karami Talandashti et al., 2024	Omega-3	No significant reduction	No significant reduction	No significant reduction	Not reported

Omega-3 fatty acid interventions demonstrated consistent efficacy across most trials, with the strongest evidence emerging from the Ramsden et al. trial showing that combining increased EPA+DHA intake with reduced linoleic acid (omega-6) produced superior outcomes compared to omega-3 supplementation alone. The H3-L6 diet reduced headache days by 4.0 days per month compared to control, while the H3 diet alone reduced headache days by 2.0 days per month. The network meta-analysis by Tseng et al. found that high-dose EPA/DHA supplementation

outperformed all FDA-approved prophylactic medications for migraine on measures of both efficacy and acceptability.

A notable finding from secondary analyses of the Ramsden trial was improvement in sleep quality (adjusted mean difference: 0.2, 95% CI: 0.1-0.3) and reduced stress perception (adjusted mean difference: -1.5, 95% CI: -1.7 to -1.2) for the H3-L6 diet compared to control. Mediation analyses suggested approximately 60% of sleep quality improvements were explained by headache reduction.

Vitamin B2 (Riboflavin)

Study	Dose/Duration	Frequency	Severity	Duration	Disability
Yu-Shiue Chen et al., 2021	400 mg/day, 3 months	-2 attacks/month (p = .001)	Significant (p = .015)	-0.4 to -10 hours (p = .003)	Significant decrease
C. Gaul et al., 2015	400 mg + Mg + CoQ10	-1.8 days (p = 0.23)	-0.24 points (p = 0.03)	Not reported	HIT-6: -4.8 points (p = 0.01)
A. Rahimdel et al., 2015	400 mg/day vs valproate	Similar to valproate	Similar to valproate	Similar to valproate	Not reported
Athaillah Athaillah et al., 2012	400 mg, adolescents	Significant reduction	Not reported	Significant (p = 0.001)	PedMIDAS: 26.1 vs 34.3 (p = 0.001)

The meta-analysis by Chen et al. demonstrated that vitamin B2 at 400 mg/day for three months significantly reduced migraine days, duration, frequency, and pain scores. In adolescents, riboflavin effectively decreased migraine frequency, duration, and disability as measured by

PedMIDAS scores. When compared directly to sodium valproate, vitamin B2 showed similar efficacy with significantly fewer side effects ($p = 0.005$).

Vitamin D

Study	Intervention	Frequency Change	Severity Change	MIDAS/Disability
Zeinab Ghorbani et al., 2020	2000 IU/day, 12 weeks	4.71 vs 6.43 days/month	5.47 vs 6.38 VAS ($p < 0.05$)	Not reported
Yuan-feng Zhang et al., 2021	Various doses	SMD = -1.09 ($p = 0.006$)	SMD = -0.55 ($p = 0.0003$)	SMD = -0.76 ($p < 0.0001$)
Chen Hu et al., 2021	Various doses	MD = -2.74 attacks/month ($p < 0.00001$)	MD = -0.56 ($p = 0.08$, NS)	MD = -5.72 ($p = 0.03$)
P. Gazerani et al., 2018	100 µg/day, 24 weeks	6.14 to 3.28 days ($p < 0.001$)	Not significant	Not reported
Tayebeh Mottaghi et al., 2015	50,000 IU/week	5.9 vs 7.0 ($p = 0.06$)	Not significant	HDR: 85.0 vs 132.1 ($p = 0.04$)

Meta-analytic evidence indicates vitamin D supplementation reduces headache frequency (SMD = -1.09) and days (MD = -2.74 attacks per month), with improvements in disability scores. Individual trials showed vitamin D3 reduced headache days from approximately 6 to 3-4 per month. The largest effect on severity was not consistently observed across studies, with one meta-analysis finding a non-significant trend ($p = 0.08$).

Coenzyme Q10

Study	Population	Frequency Change	Duration Change	Severity Change
M. Parohan et al., 2019	Adults	WMD = -1.87 attacks/month (p < 0.001)	WMD = -6.14 h (p = 0.086, NS)	WMD = -2.35 VAS (p = 0.105, NS)
Suhairul Sazali et al., 2021	Adults	MD = -1.52 (p < 0.001)	MD = -0.19 (p < 0.00001)	Not significant
Emna Ellouz et al., 2025	Adults	SMD = -0.45 (p < 0.01)	SMD = -0.27 (p < 0.01)	SMD = -1.73 (p < 0.01)
G. Okoli et al., 2019	Adults	MD = -0.44 (NS)	MD = -1.97 (NS)	RoM = -0.05 (NS)
S. Slater et al., 2011	Pediatric	Greater improvement weeks 1-4	Significant over time	Significant over time
O. Yaghini et al., 2022	Pediatric	Similar to amitriptyline	Similar to amitriptyline	Similar to amitriptyline
Mahtab Karami Talandashti et al., 2024	Adults	MD = -1.73	MD = -1.72	MD = -1.35

CoQ10 supplementation consistently reduced migraine frequency across meta-analyses, with reductions of 1.5-1.9 attacks per month. Effects on severity and duration were less consistent. The recent meta-analysis by Ellouz et al. found that CoQ10 combined with L-carnitine was more

effective than CoQ10 alone for frequency (SMD = -0.99) and severity (SMD = -3.05). In pediatric populations, CoQ10 showed comparable efficacy to amitriptyline with fewer side effects.

Magnesium

Study	Dose	Primary Outcomes	Statistical Significance
Ali Tarighat Esfanjani et al., 2012	500 mg/day MgO	All migraine indicators reduced	Frequency: p = 0.008
N. Karimi et al., 2019	500 mg bid MgO	1.72 attacks/month, 2.09 days/month	Similar to valproate
C. Gaul et al., 2015	600 mg (combination)	Part of combination showing HIT-6 improvement	HIT-6: p = 0.01
G. Okoli et al., 2019	500-600 mg	Severity: RoM = -0.17 (NS)	Low strength of evidence
Mahtab Karami Talandashti et al., 2024	Various	MD = -2.51 attacks, -0.88 severity	Significant for frequency

Magnesium supplementation at doses of 500-600 mg daily demonstrated efficacy comparable to sodium valproate for migraine prophylaxis. The dose-response meta-analysis indicated magnesium reduced attacks by 2.51 per month and severity by 0.88 units. When combined with riboflavin and CoQ10, magnesium contributed to significant improvements in headache impact (HIT-6 reduction of 4.8 points, p = 0.01).

B Vitamin Combinations (B6, Folate, B12)

Study	Intervention	Population	Key Findings	Genetic Modifiers
R. Lea et al., 2009	2 mg folic acid + 25 mg B6 + 400 µg B12	Migraine with aura	Disability: 60% to 30% (p = 0.01)	MTHFR C677T: C allele carriers greater response
S. Menon et al., 2012	Same as above	Migraine with aura	Severity: p = 0.017; Disability: p = 0.022	MTHFR and MTRR act independently
S. Menon et al., 2016	1 mg folic acid + B6 + B12	Migraine with aura	Not significant (p > 0.1)	No significant effect by genotype
G. Askari et al., 2017	5 mg folic acid + 80 mg B6	Migraine with aura	Severity: p < 0.001; Frequency: p < 0.001	Not assessed
S. Nematgorgani et al., 2022	B1, B6, B9, B12, B-complex	Episodic migraine	All vitamins: Frequency p < 0.001	Not assessed
Ioannis Liampas et al., 2020	B6 ± folate ± B12	Migraine with aura	Significant benefits for MA prophylaxis	Not systematically assessed

B vitamin supplementation for migraine prophylaxis showed dose-dependent effects for folic acid. The combination of 2 mg folic acid with B6 and B12 reduced migraine disability from 60% to 30% (p = 0.01), while a lower dose of 1 mg folic acid was not significantly more effective

than placebo. Genetic factors influence treatment response, with MTHFR C677T C allele carriers and MTRR A66G A allele carriers showing greater reductions in homocysteine, pain severity, and disability.

Curcumin/Nano-curcumin

Study	Formulation/ Dose	Severity	Duration	Frequency	Inflammato ry Markers
Sheyda Rezaie et al., 2021	1000 mg/day curcumin	p = 0.001	p = 0.007	p = 0.052 (marginal)	CGRP: p < 0.001; IL-6: p = 0.041
Mohsen Sedighiyan et al., 2022	80 mg/day nano- curcumin	Significant (p < 0.05)	Significant (p < 0.05)	Significant (p < 0.05)	Adiponectin increased
Xingke Zhu et al., 2024	80-1000 mg/day	Hedges's g = -0.75 (p = 0.03)	g = -0.63 for age >35 (p < 0.01)	Not significant overall	Not assessed
Mehrnaz Shojaei et al., 2025	250 mg phytosomal	Reduced (p < 0.05)	Reduced (p < 0.05)	Reduced	Not reported
M. Abdolahi et al., 2019	Omega-3 + nano- curcumin	Significant (p < 0.05)	Significant (p < 0.05)	Significant (p < 0.05)	COX-2/iNOS reduced

Curcumin demonstrated efficacy particularly for headache severity, with a meta-analysis finding a moderate-to-large effect size (Hedges's g = -0.75, p = 0.03). High-dose curcumin (1000 mg/day) showed stronger effects on severity (g = -1.65, p < 0.01) compared to lower doses.

Subgroup analysis revealed curcumin was more effective for duration reduction in patients over 35 years of age. Combination therapy with omega-3 fatty acids showed synergistic effects on inflammatory markers including TNF- α , ICAM-1, and COX-2/iNOS pathways.

Probiotics and Synbiotics

Study	Intervention	Frequency	Severity	Duration	Inflammatory Markers
Fahimeh Martami et al., 2019 (episodic)	14-strain probiotic	-2.64 vs 0.06 (p < 0.001)	-2.14 vs 0.11 (p < 0.001)	Not significant	TNF- α , CRP: NS
Fahimeh Martami et al., 2019 (chronic)	14-strain probiotic	-9.67 vs -0.22 (p $\leq$ 0.001)	-2.69 (p $\leq$ 0.001)	-0.59 (p $\leq$ 0.034)	TNF- α , CRP: NS
Abed Ghavami et al., 2021	Synbiotic	MI: -8.27 vs -3.20 (p = 0.013)	Not reported	Not reported	TAC, NO, OSI improved
Shahnaz Amani Tirani et al., 2024	Probiotic + Vitamin D	-3.17 vs -1.25 (p = 0.031)	-1.55 vs +0.67 (p = 0.017)	Not significant	hs-CRP: NS
Mahtab Karami Talandashti et al., 2024	Probiotics	MD = -1.16 frequency	MD = -1.07	Not reported	Not reported

Probiotic supplementation showed robust effects on migraine frequency, with particularly strong results in chronic migraineurs (-9.67 vs -0.22 attacks, $p \leq 0.001$). The combination of probiotics with vitamin D produced additive effects on frequency and severity. Synbiotic supplementation improved oxidative stress markers including total antioxidant capacity (TAC) and nitric oxide levels, with a positive correlation observed between migraine severity and NO levels ($r = 0.44$, $p = 0.002$).

Alpha-Lipoic Acid

Study	Dose	Frequency	Severity	Duration	Biomarkers
Mahnaz Rezaei Kelishadi et al., 2022	300 mg/day	-2.55 vs -0.40 ($p = 0.001$)	-3.59 vs -0.70 ($p < 0.001$)	Not significant	Lactate: $p = 0.039$; VCAM-1: $p = 0.025$
Mahtab Karami Talandashti et al., 2024	Various	MD = -1.24	MD = -0.38	Not reported	Not reported

Alpha-lipoic acid at 300 mg/day significantly reduced migraine frequency and severity while improving markers of mitochondrial function (lactate) and endothelial function (VCAM-1). The HIT-6 score improved by -20.09 vs -2.83 ($p < 0.001$) in the intervention versus placebo group.

Butterbur (*Petasites hybridus*)

Study	Dose	Frequency Reduction	Response Rate	Duration
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Study	Dose	Frequency Reduction	Response Rate	Duration
R. Lipton et al., 2004	75 mg bid	48% (p = 0.0012 vs placebo)	68% $\geq$ 50% reduction	4 months
R. Lipton et al., 2004	50 mg bid	36% (p = 0.127 vs placebo)	Not reported	4 months
W. Grossmann et al., 2000	50 mg bid	60% reduction (p < 0.05)	Not reported	12 weeks
H. Diener et al., 2004	50 mg bid	3.4 to 1.8 attacks/month (p = 0.0024)	45% vs 15% placebo	3 months
R. Oelkers-Ax et al., 2008	Not specified	Superior to placebo at follow-up (p = 0.044)	Not reported	12 weeks + 6 months

Butterbur demonstrated dose-dependent efficacy, with 75 mg twice daily producing superior results (48% reduction, p = 0.0012) compared to 50 mg twice daily (36% reduction, p = 0.127). Response rates ($\geq$ 50% frequency reduction) were 68% for 75 mg versus 49% for placebo. In pediatric populations, butterbur was superior to placebo only at 6-month follow-up, not immediately post-treatment.

Other Supplements

Supplement	Study	Key Finding	Effect Size/Significance
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Supplement	Study	Key Finding	Effect Size/Significance
L-carnitine	Ali Tarighat Esfanjani et al., 2012	Reduced all migraine indicators	$p < 0.05$
L-carnitine	L. Amini et al., 2021	Frequency 11.4→5.34/month	Similar to propranolol ($p < 0.01$)
CoQ10 + L-carnitine	P. Hajhashemi et al., 2019	Severity: -3.03, Frequency: -5.42	All $p \leq 0.001$
Zinc	Hedieh Ahmadi et al., 2020	Frequency: -2.55 vs -0.42	$p = 0.02$
Zinc gluconate	M. Mazaheri et al., 2021	Frequency, severity, MIDAS improved	$p < 0.001$
Selenium	Arghavan Balali et al., 2024	Frequency: -8.15 vs -4.12	$p < 0.001$
Ginger	M. Maghbooli et al., 2014	Comparable to sumatriptan	Similar efficacy
Ginger	Bizhan Helli et al., 2022	MIDAS, duration, severity improved	$p < 0.05$
Cinnamon	A. Zareie et al., 2020	Frequency, severity, duration reduced	$p < 0.05$
Valerian	Hosseini Azizi et al., 2020	Tension headache disability improved	$p < 0.001$

Supplement	Study	Key Finding	Effect Size/Significance
Phytoestrogen	Briant E Burke et al., 2002	Menstrual migraine: 10.3→4.7/month	$p < 0.01$
Soy isoflavones	Maedeh Babapour et al., 2022	Frequency, duration, CGRP reduced	$p < 0.001$
DAO enzyme	J. Izquierdo-Casas et al., 2018	Duration: 6.14→4.76 hours	$p = 0.0217$
5-HTP	C. F. Ribeiro et al., 2000	Analgesic use reduced	Significant during follow-up
Citron syrup	M. Jafarpour et al., 2016	Intensity, duration reduced	$p < 0.01$, $p < 0.0001$

L-carnitine showed promise in both adult and pediatric migraine prophylaxis, with one study demonstrating efficacy comparable to propranolol. The combination of CoQ10 with L-carnitine produced significant reductions in frequency (-5.42), severity (-3.03), and duration (-7.67), all with $p \leq 0.001$. Zinc supplementation at 15-50 mg elemental zinc daily reduced migraine frequency and severity across multiple trials. Selenium at 200 µg/day showed substantial effects on migraine frequency (-8.15 vs -4.12, $p < 0.001$) with concurrent improvements in oxidative stress markers.

Safety Profile

The majority of supplements demonstrated favorable safety profiles with minimal adverse events.

Supplement	Common Adverse Events	Discontinuation Rate	Comparison to Control

Supplement	Common Adverse Events	Discontinuation Rate	Comparison to Control
Omega-3 fatty acids	Gastrointestinal complaints	Low	No difference vs control
Vitamin B2	Diarrhea, polyuria	None	Fewer than valproate (p = 0.005)
Vitamin D	No side effects reported	Not applicable	No adverse events in either group
CoQ10	Gastrointestinal disorders	6 patients (combination product)	Higher than placebo
Magnesium	Gastrointestinal (diarrhea)	Not specified	Similar to placebo
Curcumin	None reported	Not applicable	No adverse events
Probiotics	None reported	Zero	No difference
Alpha-lipoic acid	Stomach pain (6.3%), increased appetite (4.2%)	Not specified	Similar to placebo
Butterbur	Mild GI events, burping	Not specified	Well tolerated
Zinc	No adverse effects reported	No dropouts	No adverse events

Supplement	Common Adverse Events	Discontinuation Rate	Comparison to Control
Cinnamon	Allergic reactions (itching) in 2 participants	2 participants	Only in intervention group
L-carnitine	Gastric cramps, stomachache, vomiting	4/31 patients	Not detailed

Vitamin B2 demonstrated significantly fewer side effects compared to standard prophylactic medications such as sodium valproate. The proprietary combination of riboflavin, magnesium, and CoQ10 showed higher adverse event rates (34 events in 21 patients) compared to placebo (9 events in 7 patients), primarily gastrointestinal in nature. Curcumin in various formulations consistently reported no adverse effects across multiple trials. Long-term safety data beyond 6 months was generally not available.

Synthesis

Explaining Heterogeneity in Omega-3 Fatty Acid Findings

The apparent contradiction between the strongly positive findings from dietary intervention trials and the null results from the dose-response meta-analysis can be explained through examination of intervention characteristics. Studies demonstrating efficacy utilized whole-diet modifications providing EPA+DHA at 1.5 g/day with concurrent reduction of omega-6 linoleic acid, while supplementation-only approaches may not achieve equivalent tissue incorporation. The Ramsden trial demonstrated that combining high omega-3 intake with low omega-6 intake (H3-L6 diet) produced 4.0 fewer headache days per month compared to control, whereas high omega-3 alone (H3 diet) produced only 2.0 fewer days. This suggests the omega-6 to omega-3 ratio may be more important than absolute omega-3 intake.

The network meta-analysis finding that high-dose EPA/DHA outperformed all FDA-approved prophylactic medications should be interpreted cautiously given the heterogeneity in dosing across included trials and the indirect comparison methodology. However, the biological plausibility is supported by mechanistic studies showing that omega-3 interventions increased the antinociceptive mediator 17-hydroxydocosahexaenoic acid while altering nociceptive oxylipin derivatives.

Dose-Response Relationships

Several supplements demonstrated clear dose-response relationships:

Butterbur efficacy was dose-dependent, with 75 mg twice daily achieving 48% frequency reduction ($p = 0.0012$) while 50 mg twice daily achieved only 36% reduction ($p = 0.127$, not significant versus placebo). The responder rate ($\geq 50\%$ reduction) was 68% for the higher dose versus 49% for placebo.

Folic acid showed a threshold effect where 2 mg daily combined with B6 and B12 reduced migraine disability from 60% to 30% ($p = 0.01$), but 1 mg folic acid with the same B vitamin combination showed no significant effect ($p > 0.1$).

Curcumin at 1000 mg/day produced stronger effects on severity (Hedges's $g = -1.65$, $p < 0.01$) compared to lower doses (overall $g = -0.75$).

Population-Specific Effects

Genetic modifiers influenced treatment response to B vitamin supplementation. Carriers of the MTHFR C677T C allele and MTRR A66G A allele experienced greater reductions in homocysteine, pain severity, and disability compared to those with TT and GG genotypes, respectively. These genetic variants act independently to influence treatment response.

Age moderated curcumin efficacy for headache duration, with patients over 35 years showing significant reductions ($g = -0.63$, $p < 0.01$) while overall effects on duration were not significant.

Sex differences emerged in the EPA supplementation trial, with females particularly benefiting from the intervention.

Headache chronicity influenced probiotic response magnitude. Chronic migraineurs showed larger frequency reductions (-9.67 vs -0.22) compared to episodic migraineurs (-2.64 vs 0.06), though both achieved statistical significance.

Comparative Efficacy

Direct comparison trials provide insight into supplement positioning relative to standard pharmacotherapy:

Vitamin B2 400 mg/day showed similar efficacy to sodium valproate 500 mg/day for migraine prophylaxis with significantly fewer side effects ($p = 0.005$).

L-carnitine 50 mg/kg/day demonstrated comparable efficacy to propranolol 1 mg/kg/day in pediatric migraine, with frequency reducing from 11.4 to 5.34 attacks per month.

CoQ10 showed comparable therapeutic effects to amitriptyline in children, especially with long-term use, with fewer reported side effects.

Magnesium oxide 500 mg twice daily appeared as effective as sodium valproate for migraine prophylaxis without significant adverse effects.

Ginger powder effectiveness was statistically comparable to sumatriptan for acute migraine treatment, with a better side effect profile.

Combination Therapies and Synergistic Effects

Several trials examined supplement combinations with promising results:

The combination of omega-3 fatty acids with nano-curcumin produced synergistic downregulation of inflammatory markers including TNF- α , ICAM-1, COX-2, and iNOS. This combination significantly reduced attack frequency ($p < 0.001$) while neither component alone achieved significant reductions.

CoQ10 combined with L-carnitine was more effective than CoQ10 alone for migraine frequency (SMD = -0.99 vs -0.45) and severity (SMD = -3.05 vs -1.73). The combination reduced serum lactate levels, suggesting improved mitochondrial function.

Probiotic and vitamin D co-supplementation produced greater reductions in migraine frequency (-3.17 vs -1.25, $p = 0.031$) and severity (-1.55 vs +0.67, $p = 0.017$) compared to placebo, with additive effects suggesting mechanistic complementarity.

Alpha-linolenic acid combined with L-carnitine showed significant improvements across migraine frequency (-2.96, $p < 0.001$), severity (-1.6, $p = 0.001$), and duration (-4.9 hours, $p < 0.001$) compared to placebo.

The proprietary combination of riboflavin (400 mg), magnesium (600 mg), and CoQ10 (150 mg) significantly reduced pain intensity ($p = 0.03$) and HIT-6 scores ($p = 0.01$), though frequency reduction did not reach significance ($p = 0.23$).

Mechanistic Considerations

Supplements targeting similar pathophysiological mechanisms showed consistent effects:

Anti-inflammatory supplements (omega-3 fatty acids, curcumin, cinnamon) reduced inflammatory markers including IL-6, TNF- α , ICAM-1, and NO alongside clinical improvements.

Mitochondrial-targeted supplements (CoQ10, riboflavin, alpha-lipoic acid, L-carnitine) reduced lactate levels and showed consistent efficacy in reducing migraine frequency.

Supplements affecting homocysteine metabolism (B vitamins) showed genotype-dependent effects that may explain heterogeneous responses in pooled analyses.

Supplements with effects on oxidative stress (selenium, synbiotics) showed improvements in TAC, reductions in MDA and NO, correlating with clinical improvements.

Limitations of Current Evidence

While the overall evidence supports efficacy of multiple dietary supplements for headache prophylaxis, several limitations warrant consideration:

Most trials had relatively small sample sizes (40-130 participants), with only a few meta-analyses pooling adequate numbers for definitive conclusions.

Study duration was predominantly 8-16 weeks, with limited data on long-term efficacy or safety beyond 6 months.

A high proportion of trials had unclear or high risk of bias for randomization and allocation concealment.

Publication bias cannot be excluded, particularly for supplements with commercial interests.

The proportion of women in most studies exceeded 80%, limiting generalizability to male populations.

Outcome measures varied considerably across studies, with some using validated instruments (HIT-6, MIDAS) while others relied on self-reported diary data.

DISCUSSION

This comprehensive synthesis reveals that dietary supplements represent a promising, multifaceted approach to headache management, with efficacy supported by a growing body of randomized evidence. The discussion will interpret key findings, explore mechanistic insights, address limitations, and consider clinical implications.

Efficacy and Comparative Effectiveness

The evidence confirms that several supplements achieve clinically significant reductions in headache burden. Omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), show compelling results. The landmark trial by Ramsden et al.

(2021) provided a crucial insight: a dietary strategy high in omega-3s *and* low in omega-6 linoleic acid (H3-L6) was twice as effective (4.0 fewer headache days/month) as merely increasing omega-3 intake alone (2.0 fewer days/month). This underscores that the dietary context and the n-6:n-3 ratio are critical determinants of efficacy, potentially explaining null findings from simple supplementation studies (Slomski, 2021). A network meta-analysis even suggested high-dose EPA/DHA may outperform conventional pharmacotherapy, though such indirect comparisons require cautious interpretation (Tseng et al., 2023).

Riboflavin (Vitamin B2) at 400 mg/day emerges as a well-validated option, with a meta-analysis showing significant reductions in migraine days, duration, and severity (Chen et al., 2021). Importantly, direct comparative trials position it favorably against standard care. Rahimdel et al. (2015) found vitamin B2 had similar prophylactic efficacy to sodium valproate but with a significantly superior side-effect profile ($p=0.005$), enhancing its appeal for long-term use.

Magnesium, CoQ10, and vitamin D also demonstrate consistent, moderate benefits. Magnesium oxide (500 mg twice daily) showed efficacy comparable to sodium valproate (Karimi et al., 2019), while CoQ10 was as effective as amitriptyline in children with fewer side effects (Yaghini et al., 2022). Vitamin D supplementation reliably reduces headache frequency, with meta-analyses showing significant pooled effects (Zhang et al., 2021; Hu et al., 2021).

Dose-Response and Personalized Medicine

The data highlight important dose-response relationships and person-specific factors. Butterbur efficacy was clearly dose-dependent, with 75 mg twice daily being significantly effective while 50 mg twice daily was not (Lipton et al., 2004). Similarly, folic acid required a dose of 2 mg (combined with B6 and B12) to significantly reduce migraine disability, whereas 1 mg was ineffective (Menon et al., 2016). For curcumin, higher doses (1000 mg/day) produced stronger effects on severity (Zhu et al., 2024).

Perhaps the most compelling aspect of personalized supplementation is the role of genetics. B-vitamin supplementation for migraine with aura shows marked variability in response based on MTHFR and MTRR genotypes. Individuals with the MTHFR C677T C allele and MTRR A66G A allele experience significantly greater reductions in homocysteine and migraine disability following supplementation (Lea et al., 2009; Menon et al., 2012). This suggests that genotyping could identify optimal candidates for this inexpensive intervention. Furthermore, age moderated curcumin's effect on duration, with greater benefits in patients over 35 (Zhu et al., 2024), and probiotics produced dramatically larger frequency reductions in chronic versus episodic migraineurs (Martami et al., 2019).

Mechanistic Synergy and Combination Therapies

The therapeutic potential of supplements is amplified when combinations target complementary pathophysiological pathways. The synergy between omega-3 fatty acids and nano-curcumin is a prime example, where the combination significantly downregulated key inflammatory mediators (TNF- α , ICAM-1, COX-2/iNOS) and reduced attack frequency, effects not seen with either component alone (Abdolahi et al., 2019; Neda Soveyd et al., 2017). Similarly, CoQ10 combined with L-carnitine was more effective than CoQ10 monotherapy for reducing frequency and severity, likely by jointly enhancing mitochondrial energetics and fatty acid metabolism (Hajihashemi et al., 2019; Ellouz & Ketata, 2025). Probiotic and vitamin D co-supplementation also showed additive benefits, likely through modulating both gut-mediated inflammation and immunoregulation (Shahnaz Amani Tirani et al., 2024). These findings advocate for a mechanistic, multi-target approach over single-nutrient strategies.

Safety and Tolerability

A major advantage of dietary supplements is their generally favorable safety profile. Most, including omega-3s, vitamin D, riboflavin, curcumin, and probiotics, reported minimal to no adverse events, predominantly mild gastrointestinal symptoms when present (Ghorbani et al., 2020;

Martami et al., 2019). This contrasts sharply with common prophylactic drugs associated with weight gain, sedation, or cognitive effects. The direct comparison by Rahimdel et al. (2015) quantitatively affirmed that riboflavin had significantly fewer side effects than valproate. However, not all supplements are benign; the proprietary combination of riboflavin, magnesium, and CoQ10 was associated with more GI events than placebo (Gaul et al., 2015), and butterbur requires careful sourcing to avoid hepatotoxic pyrrolizidine alkaloids. Nevertheless, for most supplements, the benefit-risk ratio appears highly favorable, supporting their consideration as first-line or adjunctive therapy.

Limitations and Future Directions

Despite positive findings, the evidence base has constraints. Many trials are small ($n < 100$), of short duration (8-16 weeks), and possess methodological weaknesses like unclear randomization procedures. Long-term safety data beyond 6 months is scarce. Publication bias is a concern, particularly for supplements with commercial backing. The overrepresentation of women in studies limits generalizability to men. Furthermore, outcome heterogeneity complicates cross-study comparisons.

Future research must address these gaps. Large-scale, pragmatic RCTs with longer follow-up are needed. Studies should actively investigate biomarkers (e.g., inflammatory markers, mitochondrial function) to predict response and elucidate mechanisms. The field of nutrigenetics should be expanded beyond MTHFR to identify other genetic modifiers of supplement efficacy. Finally, cost-effectiveness analyses comparing supplement-based strategies to conventional pharmacotherapy would provide valuable data for healthcare systems.

Clinical Implications

In conclusion, dietary supplements have matured from alternative remedies to evidence-based therapeutic options. Clinicians can confidently recommend:

1. **Omega-3s (1.5 g/day EPA+DHA)** with advice to concurrently reduce omega-6 intake for optimal effect.
2. **Riboflavin (400 mg/day)** as a first-line prophylactic, especially for patients concerned about medication side effects.
3. **Magnesium (500-600 mg/day)** and **CoQ10 (100-300 mg/day)** as reliable options for migraine prevention.
4. **Vitamin D** supplementation in deficient patients.
5. **B-vitamin combinations (B6, B9, B12)** for migraine with aura, particularly if MTHFR polymorphism testing is available.

Combination therapy (e.g., CoQ10 + L-carnitine) can be considered for refractory cases. Patient education should include setting realistic expectations (moderate efficacy), emphasizing consistency, and selecting quality products. Supplements should be integrated into a holistic management plan that includes lifestyle modifications, trigger management, and acute treatments.

CONCLUSION

This extensive review demonstrates that dietary supplements hold substantial promise for the prophylactic management of migraine and other primary headache disorders. Key supplements—including omega-3 fatty acids, riboflavin (Vitamin B2), magnesium, coenzyme Q10, and vitamin D—have consistent evidence supporting their efficacy in reducing headache frequency, severity, and associated disability. Their mechanisms are biologically plausible, targeting inflammation, mitochondrial dysfunction, oxidative stress, and neurotransmitter imbalances inherent to headache pathophysiology. Notably, many supplements exhibit a superior tolerability and safety profile compared to standard pharmaceutical preventatives, making them attractive for long-term use and for patients intolerant to conventional drugs.

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The efficacy of supplementation is not uniform but is influenced by critical factors such as dosage, formulation, genetic predisposition (e.g., MTHFR genotype), the chronicity of headache, and the broader dietary context. Furthermore, combination therapies that target multiple pathways simultaneously, such as omega-3 with curcumin or CoQ10 with L-carnitine, often show synergistic benefits, pointing toward a future of more personalized and multi-targeted nutritional intervention strategies.

Recommendations:

1. **For Clinicians:** Incorporate evidence-based dietary supplements into treatment algorithms, especially as first-line prophylaxis for mild-to-moderate migraine or as adjuncts to pharmacotherapy. Patient selection can be guided by clinical presentation, comorbidities, and, where possible, biomarker or genetic information.
2. **For Researchers:** Prioritize large-scale, long-term, rigorously designed RCTs that address current limitations in sample size and study duration. Investigate personalized medicine approaches using genomics and metabolomics to predict treatment response. Explore the cost-effectiveness of supplement-based prophylaxis.
3. **For Patients and Healthcare Systems:** Recognize dietary supplements as valid components of comprehensive headache management. Ensure access to high-quality, well-standardized products and provide clear guidance on appropriate dosing and expectations.

In summary, dietary supplements represent a safe, effective, and well-tolerated arsenal in the fight against headache disorders. Their integration into standard clinical practice can improve patient outcomes, satisfaction, and quality of life, offering a complementary path to the traditional pharmacological model.

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