Systematic Review

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Evaluating Natural Compounds for Migraine Treatment: A Systematic Review

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Background: Migraine is one of the most common neurological disorders occurring globally and its treatment is currently based on synthetic drugs. Due to undesired effects associated with these agents, some of the patients might prefer natural compounds-based therapies that are cost-effective, efficacious, have more patient compliance and less adverse effects. Hence, this systematic review was conducted to evaluate the effects of natural compounds (single/combination) used for the prophylaxis or acute treatment of migraine.

Method: Five electronic databases (PubMed, Scopus, Cochrane Library, Cumulated Index to Nursing and Allied Health Literature (CINAHL) library and Web of Science) were searched from 1 March 2020–31 January 2024. We included studies that evaluated the effects of natural compounds on migraine through randomized clinical trials (RCTs) that reported the duration of migraine headache, severity and frequency of attacks as primary outcomes. Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) checklist was used to report the study while Cochrane Collaboration's Risk of Bias (ROB) 2 tool was used to assess the ROB in included studies. The review protocol was registered on PROSPERO (CRD42023454998).

Results: Twelve RCTs with 889 participants were included. Seven RCTs had low ROB and two RCTs had high ROB, while three RCTs expressed "some concerns". It was observed that natural compounds including curcumin, topical basil, cinnamon, ginger, Vitamin D3 (Vit D3), zinc (Zn), magnesium (Mg) and cobalamin significantly reduced the severity of migraine headache. In addition, the duration of migraine attacks was significantly decreased by curcumin, cinnamon, ginger, Vit D3, Mg and cobalamin. Further, curcumin, topical basil, cinnamon, Vit D3, Zn, Mg and cobalamin exhibited significant beneficial effect on migraine frequency. In contrast, nanocurcumin and jodeungsan showed no significant results.

Conclusion: The current findings suggest that natural compounds including cinnamon, Vit D3, Zn, Mg and cobalamin might mitigate migraine attacks and serve as interesting alternate therapies. Nonetheless, further large scale studies are highly desired.

Keywords: migraine; natural molecules; prophylaxis; treatment; systematic review

Introduction

Migraine is one of the most common neurological disorders and characterized by severe headache attacks that may last for 4–72 hours and accompanied by irritability, fatigue, hypersensitivity to light, sound and smell, depression, nausea, vomiting, euphoria, food cravings, neck stiffness and increased yawning [1,2]. Migraine is considered as second among the world's disabling diseases and first among women [3]. More than one billion individuals suffer from migraine globally with higher prevalence in North America and Europe (12.6%–14.7%) [4]. It was estimated that 6.5–8% of men and 18% women might suffer from this disorder [4]. In contrast, lower prevalence of migraine has been documented in Asian and African countries [4].

The prevalence of headache disorders has been on a rise and their effects on disability makes them a major public health concern. Migraine was ranked 14th out of 369 injuries and diseases on the basis of age-standardized disability adjusted life years (DALYs) in Global Burden of Disease (GBD) study 2019 [5,6]. After depressive disorders and back pain, headache disorders were 3rd most common cause of disability internationally, and migraine was considered as the most frequent cause of disability in adults of <50 years of age [6]. Despite the high global burden of migraine headache, health care provision (the quality of care delivered and rates of utilization) remains constantly poor which is particularly true for low- and middle-income countries (LMICs) [7].

The etiology and pathophysiology of migraine is still unclear, but activation of trigeminal vascular system (TVS) play a key role in migraine attacks. TVS activation causes central sensitization and neurogenic inflammation. Several studies have demonstrated that the stimulation of trigeminal ganglion causes the release of neuropeptides like calcitonin gene-related peptide (CGRP) and substance P resulting in vasodilation and neuronal inflammation. Nuclear factor kappa beta (NF-κB), a transcription factor, plays key role in gene regulation involved in inflammatory response and migraine attacks [8]. Stress, weather changes,

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fatigue, hormonal changes during menstruation, fasting, sleep disturbances, heat, alteration in daily activity, alcohol, odors, smoking, caffeine withdrawal and auditory stimuli are among the most common triggers of migraine attacks [9,10].

In general, migraine treatment might be broadly classified into two categories, abortive and prophylactic [11]. Nonsteroidal anti-inflammatory drugs (NSAIDs) and triptans are most frequently prescribed abortive treatments [12]. Triptans have vasoconstrictive effects, making them unsuitable in patients who are at risk for abnormal blood pressure or cardiovascular issues or high blood pressure complications [13]. Marketed drugs for migraine might also result in drug interactions and cardiovascular side effects and particularly a high recurrence rate following treatments.

Natural compounds have been continuously contributing to the discovery of new therapeutic entities [14]. According to an estimate, about one-third of the new candidate molecules approved by Food and Drug Administration (FDA) were natural products and their derivatives [15]. Interestingly, less than 10% of the world's biodiversity has been evaluated for potential biological activity [16]. The use of natural products, like medicinal plants, nutraceuticals, phytocompounds, nutritional supplements, and vitamins has been increasing for several health conditions [14]. Various natural compounds like feverfew, butterbur, coriander, curcumin, citron, menthol, damask rose, lavender, chamomile, Saint john's wort, cannabis and gingko biloba have anti-nociceptive, antioxidant and anti-inflammatory effects and used against migraine [17,18]. At the time of writing of the current report, two previous reviews focusing phytomedicines and herbal treatments for migraine were available [17,18]. First review was published in 2019 that included studies till 2018 and it was a "simple review article" [18]. The second review was published in 2020 including studies till March 03, 2020 [17] but did not include "natural supplements". In recent years, several natural compounds like basil, cinnamon, ginger, curcumin, magnesium (Mg), Vitamin D3 (Vit D3), zinc (Zn), Jodeungsan and Cobalamin have been evaluated through randomized clinical trials (RCTs) conducted on these natural agents to assess their effectiveness against migraine headache. Thus, the aim of this systematic review was to summarize and evaluate placebo controlled RCTs assessing the effects of natural compounds for prophylaxis or treatment of migraine. In addition, future research directions have been stated in an effort to encourage further research in this field.

Methods

Study Conduct

This systematic review was conducted according to the guidance of Cochrane Handbook for Systematic Reviews of Interventions [19]. For reporting, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed (Attached in **Supplementary file**). The analysis protocol was registered on PROSPERO at the Centre for Reviews and Dissemination, United Kingdom (CRD42023454998) on 27 August 2023.

Database Searches

To find relevant records literature search was performed on 5 electronic databases: PubMed, Scopus, Cochrane Library, CINAHL library and Web of Science and the relevant records were sought. Google Scholar was also utilized to identify relevant articles. In addition, citation tracking of the initially shortlisted original articles was conducted to uncover any additional pertinent studies. The search was limited to scientific articles reported between 1 March 2020 and 31 January 2024. Initial searches were conducted till 31 September 2023 and follow-up search was performed until 31 January 2024. Articles published during this duration were identified and retrieved. For literature search of human trials, following keyword were used: Migraine, natural compounds, herbs, spices, phytocompounds, dietary supplements, prophylaxis, treatment. The Boolean operators 'AND', 'odds ratio (OR)' were used to connect search terms on all databases.

Study Selection

Selection criteria of studies was based on population, intervention, comparator, outcome and setting (PICOS) approach (Table 1).

Inclusion/Exclusion Criteria

Studies were included they were:

• Published between 2020–2024.

• Randomized, single/double/triple-blind, placebo-controlled clinical trials.

• Evaluated the effects of single/combination of natural compounds on migraine.

• At least 1 Intervention group (IG) received natural compound.

• Published in English language.

Studies were excluded if they were:

• Review articles, abstracts, patents, books, symposium, book chapters, poster and oral presentations in conferences were not included because of insufficient information for assessment and comparison.

• Articles that were irrelevant to migraine and natural compounds were excluded.

• *In-vitro* and *ex-vivo* studies were not included.

• Duplicated articles from search databases were excluded.

Data Screening and Extraction

Relevant citations were imported into Endnote Version X9 software (Clarivate Analytics, Philadelphia, PA, USA). Subgroups were formed for each database in the

Table 1. Population, intervention, comparator, outcome and setting (PICOS) strategy.

P	Population	People suffering from migraine.
I	Intervention	Natural compounds, herbs, spices, dietary supplements, phytocompounds and herbal medicines.
C	Comparator	Control/placebo.
O	Outcomes	Changes in migraine headache frequency, severity and duration.
S	Study design	Randomized clinical trials (RCTs).

Endnote, and duplicates were removed. MA and AA screened and reviewed all retrieved studies independently, BM was consulted if any discrepancy was found. From each included study, following components were extracted: article title, authors, year of publication, country of study, study design, sample size (commenced/completed), study duration, age, gender, dropouts, interventions, types of outcome measures and main results.

Risk of Bias (ROB) Assessment

Two reviewers individually evaluated the quality of randomized controlled trials by using the Cochrane Risk of Bias Tool (ROB.2, https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials) [20]. Disagreements were resolved by mutual agreement. Studies were evaluated as being of low risk (if no bias in the results), high risk (if bias affected the results severely) and some concerns (if any doubts affect results).

Data Synthesis and Analysis

The findings of selected clinical trial studies were qualitatively synthesized and by using the extracted data, text summaries and summary tables were constructed. Included studies were analysed independently based on age and gender of patients, study design, sample size, duration and country of study, intervention and outcome measures. Outcomes were classified as primary (most important and most reported outcomes of study) and secondary outcomes (other than primary outcomes like different biomarkers). Details of results were on the basis of alteration in outcome measures between Intervention group (IG) and/or from baseline to post-intervention. Meta-analysis was not conducted because of the paucity of replicable studies and heterogeneity of studies.

Results

Study Selection

The systematic search of databases initially screened 1652 articles. Among them, 391 articles were removed because of the duplication. Subsequently, the titles and abstracts of the remaining articles were screened, resulting in 41 articles considered for full-text assessment. Finally, after applying the inclusion criteria, 12 articles were included in the review. The overall workflow of the records search strategy has been presented as the PRISMA flow diagram shown in Fig. 1 [21].

Study Characteristics

Included studies comprised of 12 placebo-controlled RCT [22–33]. Out of these 11 studies were double blind [22,24–33], while one study was triple blind [23]. These studies were conducted between 2020 and 2023 and involved total of 889 patients. Minimum number of participants was 40 [24,25] while maximum number of participants was 144 [23]. 10 studies were conducted in different cities of Iran [22–28,31–33], one study conducted in Korea [29] and one study conducted in Brazil [30]. Duration of studies ranged from 1 month to 4 months while the age of participants ranged from 18–75 years. Participants were selected on the basis of International Headache Society (IHS), International Classification of Headache Disorders 3 beta edition (ICHD3) and International Classification of Headache Disorders 2nd edition (ICHD2) criteria. No participants were dropped in 3 studies [22,31,32], while total 57 participants were dropped from 9 clinical studies [23–30,33], due to personal reasons (2), change in medication (2), discontinued intervention (2), refusal to continue (10), non-adherence (1), allergic reaction (2), side effects (8), withdrawl (13), started prophylactic treatment (3), without any reason (7), lack of effects (1), depression (1), pregnancy (1), non-compliance (3) and other illnesses (1). Prophylactic medications like propranolol, amitriptyline or nortriptyline, topiramate, acetaminophen, sodium valproate, sumatriptan, ergotamine alone or in combination were used in 6 studies [22–25,27,32]. In other 6 studies, there were no prophylactic medications used [26,28–31,33]. All studies were randomized into IG (s) and control group (CG). Primary outcomes such as migraine headache frequency were reported in 11 studies [22,23,25–33], duration was reported in 9 studies [22,25–28,30–33] and headache severity was reported in 9 studies [22,23,25–28,31–33]. Secondary outcomes included different biomarkers i.e. interferon gamma (IFN-γ), interleukin 17 (IL-17) [24], interleukin 6 (IL-6) [26,32,33], calcitonin gene-related peptide (CGRP) [31–33], transforming growth factor beta (TGF-β), interleukin 4 (IL-4) [25], nitric oxide (NO) [33], interleukin 10 (IL-10), cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS) [26], and migraine-specific quality of life (MSQoL) [29], headache days/month, analgesic used/month [26] and number of days with severe pain [30]. MSQoL questionnaire comprised of 25 questions with high score indicating higher quality of life. Different biochemical tools included real-time polymerase chain reaction (RT-PCR) [24,25], enzyme-linked immunosorbent

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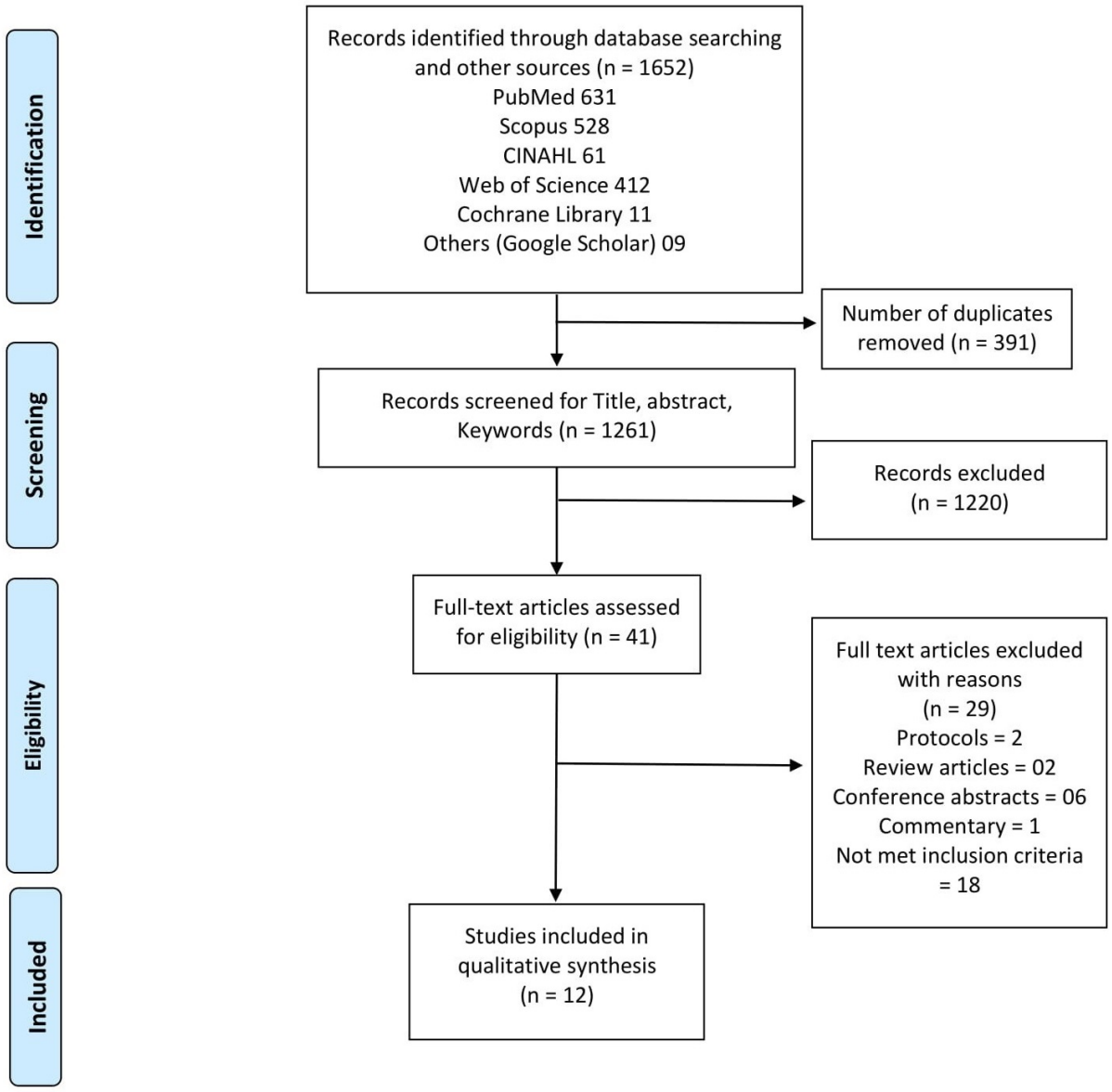

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) studies selection flow.

assay (ELISA) [24,25,32], visual analogue scale (VAS) [22,23,26–28,32,33], headache impact test version 6 (HIT-6) [28–30], migraine disability test (MIDAS) [27,28,30,31], beck depression inventory (BDI), beck anxiety inventory (BAI) [30], the deficiency and excess pattern identification questionnaire (DEPIQ), the cold and heat pattern identification questionnaire (CHPIQ), the blood stasis pattern questionnaire (BSPQ) [29] and headache daily results (HDR) [22] were used to access primary and secondary outcomes. VAS questionnaire was used to measure headache severity that ranged between 0–10, score 0 indicated no pain and score 10 was the highest pain level [32]. For HIT-6, participants reported the level of perceived headache and trouble in daily activities. HIT-6 score ranged from 36 (no migraine headache) to 78 (very severe migraine headache). High score also showed higher negative impact on daily activities [28,29]. MIDAS scores were recorded in 4 grades. Grade I ranged from 0–5, showed no disability; Grade II ranged from 6–10 and indicated mild disability; Grade III ranged from 11–20 and exhibited moderated disability, while grade IV ranged above 21 showed severe disability [31,34,35]. Depression related symptoms were measured by BDI and anxiety related symptoms were assessed using BAI [30]. HDR is the mean duration of attacks/day and was measured by formula: migraine attacks frequency × attack duration [22]. Detailed characteristics of included studies have been summarized in Table 2 (Ref. [22–33]).

Table 2. Detailed characteristics of included RCTs.

Author with year	Study design	City with country	Study setting	Sample size (N) IG/CG	RCT duration (months)	Age range	Participant's description	Sex M/F	Dropouts (N) IG/CG	Reason to dropout
Djalali *et al*., 2020 [24]	RCT	Tehran, Iran	Iranian Research Centre of Neurology in Imam Khomeini Hospital	N = 40 (19/19)	2 months	mean ± SE 37.36 ± 1.95	Episodic migraine patients based on IHS criteria	10/30	N = 2 (1/1)	Personal reason, Change in medications
Rezaie *et al*., 2021 [32]	RCT	Tehran, Iran	Clinic affiliated with the University of Medical Sciences	N = 44 (22/22)	2 months	20–50	Episodic migraine patients based on ICHD3 criteria	0/44	N = 0	–
Djalali *et al*., 2023 [25]	RCT	Tehran, Iran	Iranian Research Centre of Neurology in Imam Khomeini Hospital	N = 40 (19/19)	2 months	mean ± SE 37.36 ± 1.95	Episodic migraine patients based on IHS criteria	10/30	N = 2 (1/1)	Personal reason, Change in medications
Ahmadifard *et al*., 2020 [23]	RCT	Khorramabad, Iran	Rahimi Clinic, affiliated to the Lorestan University of Medical Sciences	N = 144 (106/35)	3 months	18–46	Episodic migraine patients based on IHS criteria	103/38	N = 3 (2/1)	Discontinue intervention
Zareie *et al*., 2020 [33]	RCT	Isfahan, Iran	Khorshid and Imam Mousa Sadr Clinics, Isfahan University of Medical Sciences	N = 50 (21/22)	2 months	20–50	Episodic migraine patients based on third edition of ICHD3 criteria	8/35	N = 7 (4/3)	Allergic reactions (n = 2), Refused to continue (n = 5)
Martins *et al*., 2020 [30]	RCT	Belo Horizonte, Brazil	Headache Clinic, University Hospital, Universidade Federal de Minas Gerais	N = 107 (39/46)	4 months	18–60	Episodic migraine patients based on ICHD2 criteria	16/91	N = 22 (14/8)	Side effects (n = 5), Withdraw (n = 13), Started prophylactic treatment (n = 3), Did not adhere (n = 1)
Helli *et al*., 2022 [27]	RCT	Ahvaz, Iran	Golestan Hospital's specialist neurological clinic	N = 110 (51/52)	3 months	18–50	Episodic migraine patients based on IHS criteria	28/75	N = 4 (4/3)	Refused to continue (n = 1), GIT complications (n = 3)
Kim *et al*., 2022 [29]	RCT	Iksan, Seoul, Jecheon, Korea	Wonkwang University Gwangju Medical Center (WUGMC), Kyunghee University Korean Medicine Hospital, and Semyung University Jechun Korean Medicine Hospital	N = 64 (32/29)	1 month	19–75	Migraine patients based on ICHD3 criteria	13/51	N = 3 (0/3)	Refused to participate further

Table 2. Continued.

Author with year	Study design	City with country	Study setting	Sample size (N) IG/CG	RCT duration (months)	Age range	Participant's description	Sex M/F	Dropouts (N) IG/CG	Reason to dropout
Ghorbani *et al*., 2020 [26]	RCT	Tehran, Iran	Tertiary headache clinic of Sina University Hospital	N = 80 (38/36)	3 months	18–45	Episodic migraine patients based on ICHD3 criteria	16/64	N = 7	–
Ahmadi *et al*., 2020 [22]	RCT	Isfahan, Iran	Isfahan University of Medical Sciences	N = 80 (40/40)	2 months	20–60	Episodic migraine patients based on IHS criteria	NA	N = 0	–
Karimi *et al*., 2021 [28]	RCT	Sari, Iran	University clinic of center, Mazandaran University of Medical Sciences	N = 70 (31/32)	2 months	18–65	Episodic migraine patients based on ICHD3 criteria	9/61	N = 7 (4/3)	Lack of effects (n = 1), Depression (n = 1), Pregnancy (n = 1), Non-compliance (n = 3), Other illness (n =1)
Matin *et al*., 2022 [31]	RCT	Isfahan, Iran	Headache clinic at Isfahan city	N = 60 (45/15)	2 months	20–50	Episodic migraine patients based on ICHD2 criteria	0/60	N = 0	–

IG, Intervention group; CG, control group; N, number; M, Male; F, female; RCT, randomized clinical trial; SE, Standard error; IHS, International Headache Society; ICHD3, International Classification of Headache Disorders 3 beta edition; ICHD2, International Classification of Headache Disorders 2nd edition.

Table 3. Detailed Intervention and outcomes of included RCTs.

Author with year	Prophylactic medication	Intervention	Comparator/control	Primary outcomes	Secondary outcomes	Tools used	Intervention vs. Comparator/Control Results	Within group (pre- and post-intervention) analysis results	No. of citations
Djalali *et al*., 2020 [24]	20–40 mg of propranolol and 25–50 mg of amitriptyline or nortriptyline	Group 1: 80 mg of nanocurcumin daily (n = 19)	Group 2: placebo daily (n = 19)	–	• IFN-γ • IL-17	• RT-PCR • ELISA	• Serum levels: • IFN-γ (–) • IL-17 (+) • PBMCs: • IFN-γ (–) • IL-17 (+)	• Serum levels: • IFN-γ (+) • IL-17 (+) • PBMCs: • IFN-γ (+) • IL-17 (+)	21
Rezaie *et al*., 2021 [32]	50 mg of Topiramate and 25 mg of amitriptyline daily	Group 1: 500 mg of Curcumin twice daily (n = 22)	Group 2: placebo (n = 22)	• Headache severity • Duration • Frequency	• IL-6 • CGRP	• VAS • ELISA	• Severity (+) • Duration (+) • Frequency (#) • IL-6 (+) • CGRP (+)	• Severity (+) • Duration (+) • Frequency (+) • IL-6 (–) • CGRP (+)	18
Djalali *et al*., 2023 [25]	20–40 mg of propranolol and 25–50 mg of amitriptyline or nortriptyline	Group 1: 80 mg of nanocurcumin daily (n = 19)	Group 2: placebo daily (n = 19)	• Frequency • Headache severity • Duration	• TGF-β • IL-4	• RT-PCR • ELISA	• No significant differences between groups regarding headache frequency, severity and duration • Serum levels: • TGF-β (–) • IL-4 (+) • PBMCs: • TGF-β (–) • IL-4 (–)	• Serum levels: • TGF-β (–) • IL-4 (+) • PBMCs: • TGF-β (+) • IL-4 (+)	6
Ahmadifard *et al*., 2020 [23]	325 mg of acetaminophen twice daily	Group 1: 2% basil essential oil topically thrice daily (n = 36), Group 2: 4% basil essential oil topically thrice daily (n = 36), Group 3: 6% basil essential oil topically thrice daily (n = 34)	Group 4: placebo (n = 35)	• Frequency • Headache severity	–	• VAS	Interaction of dose and time factors: • Frequency (+) • Severity (+) • RR (+) • OR (+)		14

Table 3. Continued.

Author with year	Prophylactic medication	Intervention	Comparator/control	Primary outcomes	Secondary outcomes	Tools used	Intervention vs. Comparator/Control Results	Within group (pre- and post-intervention) analysis results	No. of citations
Zareie *et al*., 2020 [33]	None	Group 1: 600 mg of cinnamon powder (Ceylon cinnamon) with 100 mg of corn starch thrice daily (n = 21)	Group 2: 100 mg of corn starch as placebo thrice daily (n = 22)	• Headache severity • Frequency • Duration	• CGRP • IL-6 • NO	• VAS	• Severity (+) • Frequency (+) • Duration (+) • CGRP (–) • IL-6 (+) • NO (+)	• Severity (+) • Frequency (+) • Duration (+) • CGRP (–) • IL-6 (+) • NO (+)	23
Martins *et al*., 2020 [30]	None	Group 1: 200 mg of ginger extract (5% gingerol) thrice daily for 3 months (n = 39)	Group 2: 200 mg cellulose as placebo thrice daily for 3 months (n = 46)	• Duration • Frequency	• Percentage of patient responded to treatment • Number of days with severe pain • Analgesic use	• HIT-6 • MIDAS • BDI • BAI	• Percentage of patient responded to treatment (–) • Duration (–) • Frequency (–) • Number of days with severe pain (–) • Analgesic use (–) • HIT-6 (–) • MIDAS (–) • BDI (–) • BAI (–)	-	20
Helli *et al*., 2022 [27]	20 mg of propranolol	Group 1: 500 mg of dry extract of ginger twice daily (n = 51)	Group 2: 500 mg of starch as placebo twice daily (n = 52)	• Frequency • Duration • Headache severity	–	• VAS • MIDAS	• Frequency (–) • Duration (+) • Severity (+) • MIDAS (+)	• Frequency (+) • Duration (+) • Severity (+) • MIDAS (+)	1
Kim *et al*., 2022 [29]	None	Group 1: 7.5 g of Jodeungsan thrice daily (n = 32)	Group 2: 7.5 g of placebo thrice daily (n = 29)	• Number of HAD (frequency)	• MSQoL	• HIT DEPIQ • CHPIQ • BSPQ	• Number of HAD (–) • HIT (–) • MSQoL (–)	• Number of HAD (–) • HIT (+) • MSQoL (+)	0
Ghorbani *et al*., 2020 [26]	None	Group 1: 2000 IU (50 µg) of vitamin D3 daily (n = 38)	Group 2: placebo (n = 36)	• Headache severity • Frequency • Duration	• Headache days/month • Analgesic used/month	• VAS	• Frequency (+) • Duration (+) • Severity (+)	• Frequency (+) • Duration (+) • Severity (+)	30

Table 3. Continued.

Author with year	Prophylactic medication	Intervention	Comparator/control	Primary outcomes	Secondary outcomes	Tools used	Intervention vs. Comparator/Control Results	Within group (pre- and post-intervention) analysis results	No. of citations
					• IL-6 • IL-10 • COX-2 • iNOS		• Number of headache days/month (+) • Analgesic used/month (+) • IL-6 (#) • IL-10 (–) • COX-2 (–) • iNOS (+)	• Number of headache days/month (+) • Analgesic used/month (+)	
Ahmadi, *et al*., 2020 [22]	200 or 500 mg of sodium valproate, 50 or 100 mg of sumatriptan, or 1 mg of ergotamine	Group 1: 220 mg of zinc sulfate or 50 mg of elemental zinc (n = 40)	Group 2: Lactose as placebo (n = 40)	• Headache severity • Frequency • Duration	–	• VAS • HDR	• Severity (+) • Frequency (+) • Duration (–) • HDR (–)	• Severity (+) • Frequency (+) • Duration (+) • HDR (+)	15
Karimi *et al*., 2021 [28]	None	Group 1: 500 mg of Magnesium oxide and then after 4 weeks washout, 400 mg of valproate sodium 2 tablets daily (every 12 h) (n = 31)	Group 2: control group, 400 mg of valproate sodium 2 tablets daily (every 12 h) and then after 4 weeks washout, 500 mg of magnesium oxide (n = 32)	• Frequency • Headache severity • Duration	–	• VAS • MIDAS • HIT-6	• Frequency (+) • Severity (+) • Duration (+) • VAS (+) • MIDAS (+) • HIT-6 (+)	–	27
Matin *et al*., 2022 [31]	None	Group 1: HIIT (n = 15), Group 2: Supp (1 mg of vitamin B12 and 250 mg of magnesium oxide) once daily (n = 15), Group 3: HIIT + Supp (n = 15)	Group 4: MD (n = 15)	• Frequency • Headache severity • Duration	• CGRP	• MIDAS	• Frequency (+) • Severity (+) • Duration (+) • CGRP (+) • MIDAS (#) • More significant reduction in HIIT + Supp group as compared to HIIT and Supp alone	• Frequency (+) • Severity (+) • Duration (+)	9

+, significant ($p < 0.05$); –, no significant ($p > 0.05$); #, marginal significant; IFN-γ, interferon gamma; IL-17, interleukin 17; RT-PCR, real-time polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay; PBMCs, peripheral blood mononuclear cells; IL-6, interleukin 6; CGRP, calcitonin gene-related peptide; VAS, visual analogue scale; TGF-β, transforming growth factor beta; IL-4, interleukin 4; IL-10, interleukin 10; COX-2, cyclooxygenase-2; iNOS, inducible nitric oxide synthase; RR, rate ratio; OR, odds ratio; NO, nitric oxide; HIT-6, headache impact test version 6; MIDAS, migraine disability test; BDI, beck depression inventory; BAI, beck anxiety inventory; HAD, headache attack days; MSQoL, migraine-specific quality of life; DEPIQ, deficiency and excess pattern identification questionnaire; CHPIQ, cold and heat pattern identification questionnaire; BSPQ, blood stasis pattern questionnaire; HDR, headache daily results; HIIT, High Intensity Interval Training; Supp, Vitamin B12 and magnesium oxide; MD, migraine disease.

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Natural Products and Their Impact on Migraine

Here are the details of natural products and their impact on migraine. Key details related to intervention and outcomes have been summarized in Table 3 (Ref. [22–33]).

Curcumin (Curcuma longa L.)

Three double-blind, placebo-controlled RCT studies were found to assess curcumin's effects on migraine. Djalali *et al*., 2020 [24] conducted a clinical trial study on episodic migraine patients. In this study, the expression of IFN-γ and IL-17 serum levels and concentrations from peripheral blood mononuclear cells were measured. During the study, no side effects were reported by patients. No statistically significant differences were found in sex, age, weight, height and body mass index (BMI) between groups. Nano-curcumin group exhibited reduction in serum levels and expression of *IL-17* mRNA as compared to placebo group (PG). However, there was no statistically significant difference could be observed for *IFN-*γ mRNA [24]. Likewise, Djalali *et al*., 2023 [25] determined the gene expression and serum levels of TGF-β and IL-4 and concentrations from peripheral blood mononuclear cells. During the study, no side effects were reported by patients. There were no significant differences regarding frequency, duration and severity of migraine headache attacks were present at the baseline. The findings of the trial indicated that treatment with nano-curcumin could significantly elevate IL-4 levels, promoting anti-inflammatory effects, while having minimal impact on both the gene expression and serum levels of TGF-β [25].

Rezaie *et al*., 2021 [32] studied the effects of curcumin on migraine patients. Marginal decrease was seen in the frequency of migraine attacks while duration and severity of migraine headache were significantly reduced in curcumin group than control. The curcumin group also exhibited significant reduction in serum levels of CGRP and IL-6 as compared to placebo. Significantly decreased headache duration, headache frequency and CGRP level were observed during within-group analysis as compared to baseline but the level of IL-6 was not significantly reduced. There were no significant alterations observed in control group in terms of headache frequency, IL-6 and CGRP as compared to pre-intervention. No significant differences were seen in weight, height, BMI, percent body muscle (PBM) and percent body fat (PBF) between groups.

Basil (Ocimum basilicum L.)

Ahmadifard *et al*., 2020 [23] examined the effects of basil on migraine. Participants were advised to apply test agents topically to temporal and frontal areas three times daily. During these visits, participants were asked about number of attacks and severe headache attacks. Between groups, there were no significant differences in terms of gender, age, BMI, baseline headache frequency and baseline intensity of pain. Results indicated the interaction between the time and dose factors was significant on both frequency and intensity of pain. Over the course of the study, the Intervention groups exhibited a reduction in the odds ratio for experiencing higher pain intensity and a decrease in the rate ratio for the frequency of attacks when compared to the placebo group. In 4% basil group, the OR of pain intensity was reduced by 87% in 4th week as compared to placebo and in 2% basil group, the OR of pain intensity was decreased by 90% in 8th week as compared to placebo. Similarly, in IGs, the rate ratio (RR) of attacks was dependent on time as compared to the placebo. In 6% basil group, the RR of occurring migraine attacks was reduced by 34% in 2nd week as compared to placebo and in 4% basil group, the RR of occurrence of migraine attacks was decreased by 80% in 12th week as compared to placebo. During this clinical study, as the dose increased, both frequency and severity of pain decreased. Similarly, as time passed, fewer patients suffered from pain. In 6% basil essential oil group, no patient expressed severe pain for 3 months. According to the results, frequency and severity of migraine attacks would reduce following use of basil essential oil over time and higher doses [23].

Cinnamon (Cinnamomum zeylanicum)

Zareie *et al*., 2020 [33] RCT evaluated the effects of cinnamon on migraine duration, frequency and severity. There were no significant differences regarding age, gender and family history of migraine between the two groups. In addition, no significant differences were found between two groups in terms of NO precursors like NO_2, NO_3, arginine and antioxidant dietary intakes like vitamin C, vitamin A, vitamin E, selenium and Zn at the base line. The mean severity of headache was significantly decreased and there was significantly greater reduction in cinnamon group as compared to control. In addition, the frequency mean scores were significantly decreased in IG as compared to control. Moreover, the headache mean duration was decreased in cinnamon group, but no significant alteration was observed in PG. Hence, after intervention, headache severity, frequency and duration were significantly reduced in cinnamon group as compared to placebo. Further, serum levels of NO and IL-6 were significantly decreased in cinnamon group as compared to control group. In contrast, serum concentration of CGRP remained unchanged in both groups [33].

Ginger (Zingiber officinale Rosc.)

Two studies reported the effects of ginger on migraine [27,30]. Martins *et al*., 2020 [30] studied the effectiveness of ginger in the treatment of migraine prophylaxis. No statistical differences between two groups were seen regarding age, gender and BMI. 42% patients exhibited 50% or more reduction in number of migraine attacks/month. However, in both groups, days needing the use of analgesics, days with pain, days with severe pain, maximum duration

of migraine attacks and number of migraine attacks were reduced on follow-up, without significant difference between them. No significant difference was found between groups in terms of MIDAS and HIT-6 scales. BAI and BDI scores were also reduced in both groups. After 60 days of intervention, BAI and BDI correlated positively with total days with migraine headache and frequency of migraine attacks/month after 90 days of intervention. 16 participants in IG and 8 participants in PG reported side effects. The frequency of side effects was significantly greater in IG only during first 30 days of intervention [30]. It was concluded that Ginger did not offer any additional benefit in preventing migraines compared to a placebo.

Helli *et al*., 2022 [27] also reported the effects of ginger in migraine headache. No significant difference regarding age, gender, weight, physical activity, anxiety, waist circumference (WC), hip circumference (HC) and waist to hip ratio (WHR) was present between the groups. In IG, within group analysis showed significant decrease in weight, BMI, WC, HC and WHR while no significant differences were found in dietary intakes. Headache duration, intensity and MIDAS scores were significantly reduced at end of study but headache frequency was not significantly reduced following ginger intake than placebo [27].

Jodeungsan

Jodeungsan (JDS) is a herbal medicine, i.e., a light-gray granular product of Jeil Herb (Tsumura), Co. Ltd., comprising of 11 medicinal plants: Gypsum Fibrosum, Citri Un-shius Pericarpium, Liriopis seu Ophio-pogonis Tuber, Uncariae Ramulus et Uncus, Poria Sclerotium, Pinelliae Tuber, Ginseng Radix, Chrysanthemi Indici Flos, Zingiberis Rhizoma, Saposhnikoviae Radix and Glycyrrhizae Radix et Rhizoma. Kim *et al*., 2022 [29] reported no significant results between two groups in terms of age, weight, height, past treatment experience, period of illness, use of analgesics, HAD, HIT, MSQoL, DEPIQ, CHPIQ except sex distribution. In IG, 5 participants experienced adverse effects such as nausea, mild indigestion and cold while, in PG, 4 participants' experienced adverse effects like cold, moderate indigestion and vestibular neuritis. There were no serious adverse effects and all were resolved spontaneously. This study showed that JDS was not effective against migraine pain [29].

Vitamin D3

One clinical trial study by Ghorbani *et al*., 2020 [26] reported that the mean number of headache days/month was less in IG that received Vitamin D3 supplementation as compared to placebo group. At end of study, IG exhibited significant decrease in headache days than placebo group, and mean frequency of attack. There was significant decrease in duration and severity of migraine attacks as compared to placebo. The use of analgesics by migraine patients was also reduced in IG than placebo group. There was no significant alteration in COX-2 and IL-10 but marginal decrease in IL-6 concentration as compared to placebo. However, serum level of iNOS was decreased significantly in IG as compared to placebo [26].

Zinc

Ahmadi *et al*., 2020 [22] reported no significant difference between both groups regarding age, gender, weight, BMI, serum Zn level. No significant difference was present in dietary intake of proteins, fiber, Mg, phosphorus, fats, calcium and energy between two groups. When compared with baseline of study, Zn supplemented group showed significant decrease in headache frequency but not severity and duration. No adverse effect was reported by participants in any group while Zn improved the appetite in few participants [22].

Magnesium

Karimi *et al*., 2021 [28] reported that the headache duration, headache days per month and mean number of attacks were significantly reduced with valproate sodium and magnesium oxide as compared to baseline during a cross-over trial. After intervention, migraine attacks significantly reduced in both groups and also in both periods after treatment. HIT-6, MIDAS, headache severity and symptoms associated with migraine were reduced at first and second treatment period as compared to baseline. According to VAS score, severity of headache was reduced significantly during treatment with valproate sodium and magnesium oxide in comparison to before treatment but there was no statistical difference between valproate and Mg groups. No significant difference was found between two groups in terms of rate of analgesics use and the mean of attacks [28].

Synchronize Exercise, Cobalamin and Magnesium

Cobalamin, also called Vitamin B12, belongs to vitamin B family. NSAIDs can impair the production of intrinsic factor and decrease cobalamin absorption and there may be cobalamin deficiency in migraine patients due to more consumption of NSAIDs [36,37]. Matin *et al*., 2022 [31] have reported clinical trial, where 60 participants were randomized into four groups: a High Intensity Interval Training (HIIT) group, a supplementation group receiving Vitamin B12 and magnesium oxide (Supp), a combined group receiving both HIIT and supplementation (HIIT + Supp), and a control group of migraine cases. The intervention lasted for 2 months. Receiver operating characteristic (ROC) curve analysis was conducted to assess the functionality of CGRP to differentiate between healthy and migraine patients. Total area under the curve (AUC) showed that CGRP concentration might aid as a pivotal biomarker to differentiate between control and migraine patients. ROC curve analysis assessed that amplifying the CGRP level as a potential biomarker for migraine diagnosis [31]. It was observed that there were no significant differences found

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between age, height, weight, BMI, percentage body fat and chronic migraine between the groups at the base line. The duration, frequency and intensity of headache was altered in HIIT + Supp group as compared to other groups. Moreover, in the HIIT + Supp group, there was a reduction in MIDAS scores, frequency, intensity, and duration compared to the other groups. Severe pain was decreased in HIIT + Supp group as compared to before intervention. Quality of life of migraine patients was increased by exercise and intake of cobalamin and Mg. In addition, levels of CGRP decreased significantly by consumption of supplements and physical exercise as compared to baseline. Patients with exercise showed improved aerobic capacity and based on Astrand's submaximal bicycle test, the maximum oxygen uptake was increased. It was suggested that the synergistic effects of cobalamin and magnesium, combined with regular exercise, could suppress the inflammation signaling pathway. Furthermore, the combination of High Intensity Interval Training (HIIT) and Vitamin B12 and magnesium oxide (Supp) significantly alleviated migraine pain.

Risk of Bias (ROB) Assessment

Two out of twelve studies showed some concerns about ROB due to randomization process [22,31]. Two studies presented some concerns due to missing outcome data and measurement of outcome [26,29]. Two studies showed overall high ROB due to missing outcomes [24,29]. The overall results of the ROB assessments have been shown in Figs. 2,3.

Discussion

Summary of Evidence

Previous two reviews [17,18] published in 2019 and 2020 have presented some evidences to support the utilization of natural compounds for migraine. However, these reviews consisted of studies till 2020. Hence, this systematic review of 12 RCTs with 889 participants to evaluate the safety and efficacy of natural compounds including basil, cinnamon, ginger, curcumin, Mg, Vit D3, Zn, and cobalamin was conducted. This included three studies conducted on curcumin (three studies), two studies conducted on ginger and single studies conducted on basil, cinnamon, jodeungsan, Vit D3, Zn, Mg and cobalamin. The present study suggested that the benefits from natural compounds such as curcumin, topical basil, cinnamon, ginger, Vit D3, Zn, Mg and cobalamin were statistically significant in terms of decreasing the severity of migraine headache. Curcumin, cinnamon, ginger, Vit D3, Mg and cobalamin significantly reduced the duration of migraine attacks and curcumin, topical basil, cinnamon, Vit D3, Zn, Mg and cobalamin also reduced the frequency of migraine attacks. Nanocurcumin and Jodeungsan didn't prove as effective treatment for migraine. Furthermore, these natural compounds seemed to be well-tolerated and safe. Current evidences suggest that these natural compounds could be an alternative therapy for migraine treatment. Some biomarkers like IL-17 (curcumin), IL-6 (curcumin, cinnamon), IL-4 (curcumin), CGRP (curcumin, Mg and cobalamin), nitric oxide (cinnamon) and iNOS (Vit D3) were also significantly reduced. Anti-inflammatory, antioxidant and analgesic properties of curcumin, basil essential oil, cinnamon, ginger, Vit D, Zn and cobalamin have been previously reported [38–45]. Vit D3, Zn, Mg and cobalamin deficiency leads to different psychological and neurological disorders like migraine, depression, memory impairment, chronic pain disorders, cognitive decline, psychosis, attention deficit disorder, impaired learning and Alzheimer disease [46–50].

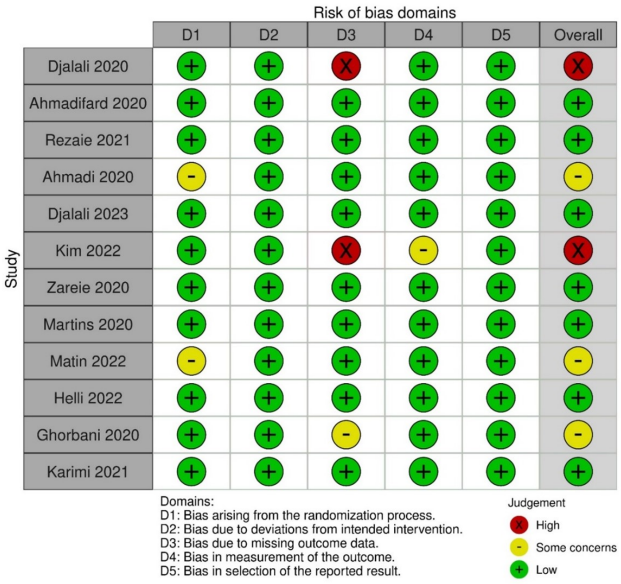

Fig. 2. Summary of Risk of Bias: review authors' judgements about each Risk of Bias item for included randomized clinical trials (RCTs).

The current data dispute the role of curcumin for the treatment of migraine headache. In one cited study on curcumin, there were positive findings but curcumin had low bioavailability that may impact its efficacy [32]. Further, two studies on nanocurcumin showed mixed findings and hence no firm conclusion about its efficacy could be drawn [24,25]. The preliminary findings showed that topical basil may play a vital role in acute treatment of migraine, but further studies are required to understand its mechanism of action and to evaluate its efficacy and safety [23]. Findings indicated that cinnamon may have therapeutic potential for migraine but showed minor allergic reactions which warrant more careful studies [33]. Evidence of the effects of ginger were mixed and showed GIT complications [27,30]. Therefore, no definitive conclusion about efficacy and safety can of ginger could be made. Jodeungsan didn't

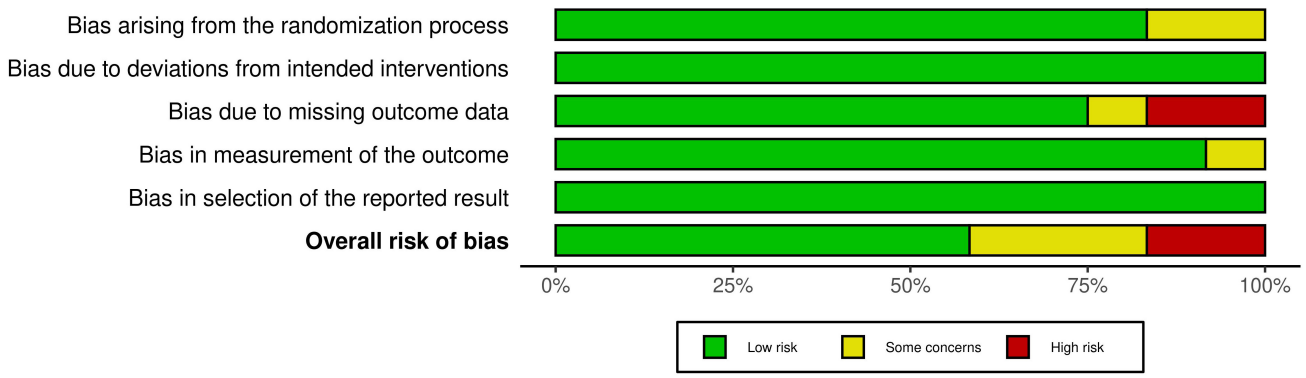

Fig. 3. Risk of Bias graph: review authors' judgements about each Risk of Bias item presented as percentages across all included RCTs.

show any positive results [29]. Vit D3 showed positive results and seemed to be safe [26]. Zn, Mg and cobalamin also presented positive findings and appeared to be well-tolerated, safe and possibly effective to be considered further [22,28,31].

Limitations

There are several limitations. Firstly, the methodological details were not satisfactory in few studies. Secondly, ten studies have been conducted in Iran that may restricts the generalizability of the results. Thirdly, the duration of intervention and follow-up period ranged from 1–4 months and therefore, long term efficacy and safety of natural compounds for migraine could not be estimated. Finally, the ratio of men was amplified in a study, two studies were only based on women while one study didn't describe the participants and gender ratio that resulted in gender selection bias.

Implications for Future Studies

The protocol of clinical trials should be registered from clinical trials registry platform and must follow CONSORT statement for reporting and publication. Migraine headache type should be demonstrated in clinical trials that would give accurate evidence for clinicians. Proper sample size, appropriate duration of intervention and follow-up, ideal randomization methods and blinding, and intend-to-treat analysis is recommended for future RCTs. The exact pharmacological mechanisms of natural compounds and the pathological mechanism of migraine are still unknown which must be further investigated. Many natural compounds that are used frequently should be considered first while manufacturing optimal drugs or combinations with other natural compounds.

Conclusion

Natural compounds are safe, well-tolerated, effective, easily available, cost-effective and more compliant for patients. Many natural compounds like topical basil, cinnamon, Vit D3, Zn, Mg and cobalamin might serve as potential options for mitigating migraine in clinical studies. However, further high-quality investigation are required to examine the safety and efficacy of these compounds as innovative therapeutics in migraine and to confirm their place in modern pharmacopeia. With the findings of this systematic review, it is envisaged that the use of natural products would lead to drug research and therapy of migraine in new directions.

Availability of Data and Materials

The data will be available on reasonable request from the first author.

Author Contributions

Conceptualization: AA and BM; Methodology: AA, MA, BM and IB; Formal analysis and investigation: MA and BM; Writing—original draft preparation: MA and IB; All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

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