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The role of curcumin supplementation in patients with migraine: A meta-analysis of randomized controlled trial

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Abstract

Objectives: Migraine is a repeated, chronic and neurovascular disease that adversely affects the quality of life and increases the risk of cerebral lesion. According to some previous studies, curcumin, the orange-yellow substance of turmeric, may possess anti-headache property according to several studies. This study aimed to meta-analytically evluate the anti-headache effect of curcumin supplementation in patients with migraine. *Methods:* Five databases were searched as of September 30, 2022 to identify all eligible randomized controlled trials. The random-effect Hunter-Schmidt model was used to calculate the effect sizes based on the heterogeneity. The PROSPERO registration number for this meta-analysis is CRD42023409829 (https://www.crd.york.ac.uk/PROSPERO/). *Results:* Four studies involving 170 patients finally met our inclusion criteria. Curcumin supplementation showed a significant difference in the severity of migraine symptoms compared with placebo (Hedges's g= -0.75, 95% confidence interval (CI) =-1.44 to -0.07, *P*= 0.03). The results of subgroup analyses indicated that curcumin significantly reduce the duration of migraine in patients over 35 years of age (Hedges's g= -0.63, 95%CI= -1.07 to -0.19, *P*< 0.01) and high-dose curcumin significantly reduced the severity of migraine symptoms (Hedges's g= -1.65, 95%CI= -2.32 to -0.97, *P*< 0.01).
Conclusions: Curcumin supplementation may relieve the severity of headache symptoms in migraine sufferers and appear to be more effective for reducing the headache duration in patients over 35 years of age.

Keywords: Curcumin supplementation, migraine, meta-analysis, frequency, severity, duration.

INTRODUCTION

Migraine is a common disabling primary headache disorder that adversely affects the quality of life.[1] It is known as a highly prevalent headache disorder that has a substantial impact on the patient and society.[2] Current epidemiological studies, including the global burden of disease study, have shown that migraine is the second leading cause of disability, ranking first among young people, with an estimated global prevalence of 15.2% and 4.9% of all children with disabilities.[3,4] The understanding of the pathophysiology of migraine is advancing rapidly, with better characterization of its clinical features and diagnosis. These have led to the view of migraine as a complex and variable disorder of nervous system rather than just a vascular headache.[5] With the complexity of the pathophysiological mechanisms of migraine, highly effective drugs against migraine are still limited.[6]

Curcumin, a polyphenol, is the main component of the perennial herb Curcuma longa (commonly known as turmeric), was first isolated in 1815 and has been used for thousands of years.[7,8] Hailed as the "spice for life", this ingredient from the age-old but ubiquitous Asian plant, turmeric, is now being given more attention because of its wide range of physiological activities.[9,10] Toxicity studies have confirmed that curcumin has a good safety profile in long-term use or at high doses (12 g/day), however, its bioavailability is low.[11-13] In addition to its antioxidant, anti-inflammatory, anti-

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bacterial, anti-ageing and anti-cancer activities. Curcumin the "panacea", has received increasing attention in recent years for its efficacy in neurological diseases.[14] A meta-analysis suggested that curcumin may have benefits in improving the symptoms in people with depression[15], and curcumin nanoparticles may be useful in treating neurodegenerative diseases, such as Alzheimer's disease, by enhancing the brain's self-healing mechanisms.[16] Additionally, some clinical trials have preliminarily demonstrated that curcumin supplementation can be used as a treatment for migraine.[17]

However, the therapeutic role of curcumin in migraine is still controversial. The evidence in vitro has shown curcumin to be potentially beneficial in migraine treatment by mitigating H_2O_2-induced oxidative stress and cell death in human umbilical vein endothelial cells.[18] In an experimental migraine model of rats, the combination of liposome curcumin and sumatriptan showed an improved anti-nociceptive effect.[19] Studies among human subjects also indicated that curcumin could significantly relieve migraine symptoms.[20,21] However, a randomized double-blind, placebo-controlled trial showed that despite a trend for a beneficial therapeutic effect, no significant relief of headache symptoms was observed in curcumin compared to the placebo group.[22] More evidence is still warranted regarding the optimal dosage, duration and formulation of curcumin for clinical use.[23]

Therefore, this study aimed to evaluate the effect of curcumin or its supplementation by a meta-analysis. Three outcomes of migraine symptoms were examined; frequency, duration and severity of the headache. Besides, subgroup analyses were performed to examine the differences based on patient's age, prophylactic administration and dose of curcumin.

METHODS

We followed the guidelines provided in the Preferred Reporting Items for Systematic Reviews and Meta-analysis, the PRISMA statement, to search the literature and present the results.

Search strategy

The following databases have been systematically searched for relevant studies from 1984 to March 2023: PubMed, Web of Science, Cochrane Library databases, CNKI and Wanfang Data. A combination of the following keywords was employed to locate relevant studies: (curcuma OR curcuma longa OR curcuminoids OR curcumin OR turmeric) AND (head OR headache OR migraine OR migraines OR cephalalgia OR encephalalgia). All studies were imported into EndNote X9 (Clarivate, Philadelphia, USA) and duplicates were deleted. An initial screening of titles and abstracts for relevance was carried out.

Inclusion and exclusion criteria

The inclusion criteria were: (1) Only randomized controlled trials were included; (2) Patients who exhibit symptoms of headache; (3) The intervention groups were treated with various formulations of curcumin or curcumin with other drugs. (4) Primary outcomes were the duration, severity and frequency of headache and secondary outcomes were inflammatory indicators.

The exclusion criteria were: (1) Review studies, basic science investigations , case studies, guidelines, protocol studies or other unrelated topics; (2) all studies containing the same data were excluded, except for the one with the most representative data; (3) studies without quantitative data referring to the headache symptoms.

Data extraction and quality assessment

All titles and abstracts of studies that we searched electronically and manually were downloaded. Data were extracted into extraction files by two independent reviewers and discussed and made available by all panel members. Baseline features and target parameters were extracted from selected articles. For every included study, the following characteristics were extracted: (1) Characteristics of studies (the author, year of publication); (2) Characteristics of patients (sample size, gender composition and age); (3) The intervention of experimental and control arms (dosage, formulation, duration); (4) The primary and secondary outcomes described above.

The Jadad scale and Cochrane Collaboration Risk of Bias Tool (CCRBT) was used to evaluate the quality of each observational study.[24] The Jadad scoring criteria required the investigator to generate a proper random sequence (2 points), conduct proper randomization concealment (2 points), use proper blinding (2 points), describe the participants who dropped out (1 point), and a score of 4 or more was good for the quality of the study. The CCRBT was used to evaluate selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases in randomized controlled studies. The ratings "high risk", "low

risk" and "unclear" were used to classify the risk of bias. The Cochrane Collaboration Review Manager software (RevMan) version 5.4.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen) was used for literature bias risk assessment. Two investigators carried out this work separately.

Assessment of heterogeneity

The heterogeneity was analyzed by I^2 test. The random-effect model would be used if $I^2 > 50\%$. The fixed effect model would be used if $I^2 \leq 50\%$. When faced with heterogeneity, the subgroup analysis was carried out to explore clinical heterogeneity in terms of interventions and patient types.

Statistical analysis

Stata16.0 (Stata Corp, College Station, TX, USA) was used for meta-analysis and sensitive analysis. For the primary outcomes (duration, frequency and severity), based on a random effects model, Hedges's g (an indicator of standardized mean differences suitable for effect size estimation of small sample studies) and 95% confidence intervals (CI) were applied to estimate all comparisons.[25] Participants were adults with a current diagnosis of migraine meeting the International Headache Society (HIS) criteria (headache ≥ 15 days per month, lasting more than 3 months or ≥ 1 attack per week).[26] The following continuous variables are analyzed: Duration (average duration of attacks in hours); Frequency (headache frequency per month); Severity (average severity of migraine attacks using the visual analogue scale on a 0–10 numeric scale).

In terms of patient characteristics, there was a lot of evidence that migraine incidence and treatment effectiveness are related to patient's age and gender.[27-29] However, because the included studies lacked individual sex data, grouping based on patient's sex were not available. Previous studies showed that the efficacy of migraine treatment was related to curcumin dose and whether it was administered prophylactically.[30-32] Therefore, we conducted subgroup analyses of the included studies by participants' age, dosage of curcumin and condition of prophylactic administration respectively.

The types of subgroup meta-analyses were based on age group (< 35 years and ≥ 35 years), prophylactic administration (yes or no), and dose of curcumin (80 mg/day and more than 80 mg/day). The subgroup meta-analyses were carried out separately for outcome indicators of patient symptoms (frequency, duration, severity), following the method of analysis described above.

RESULTS

Description of the included studies

The study flow diagram was presented in Figure 1. Up to September 30, 2022, 507 records were identified by electronic searching in PubMed, Web of Science, Cochrane Library databases, CNKI and Wanfang databases. Seventy-nine duplicate studies and 560 reports not related to population studies were ruled out. No grey literature was found. After reading the titles and abstracts of the remaining 88 studies, 74 studies that met the exclusion criteria were excluded. After reviewing the full text of the remaining studies, 10 studies were excluded due to a lack of data or duplication of data for the primary outcomes. Finally, 4 studies were eligible for this meta-analysis that met all requirements.[21,33-35]

The characteristics of the included trials were summarized in Table 1. Data from the four randomized controlled trials were then pooled. In total, 170 patients were enrolled and completed these studies, including 86 patients in the intervention group and 84 patients in the control group. The included trials were implemented between 2015 and 2021. All of these studies recruited patients diagnosed with migraine according to the previously described standardized tool. Except for one study, preventive medication was used in both intervention and control groups in the remaining studies, while the intervention group also had curcumin supplementation, and the control group had a placebo. All chosen trials quantified migraine symptoms as the primary outcome in different aspects and estimated the effect of intervention using standardized tools. Secondary outcomes were not included in this meta-analysis because of the different data types.

Studies quality assessments

The studies quality assessments were summarized in Figure 2. By Jadad criteria, the four included studies all had scores ≥ 4. According to the Cochrane criteria, 75% of the studies elucidated appropriate random sequence generation, 25% performed appropriate allocation concealment, one hundred percent performed appropriate blinding, 50% had complete outcome data, while 50% had selective reporting of risk. These results suggest that the quality of the included studies was

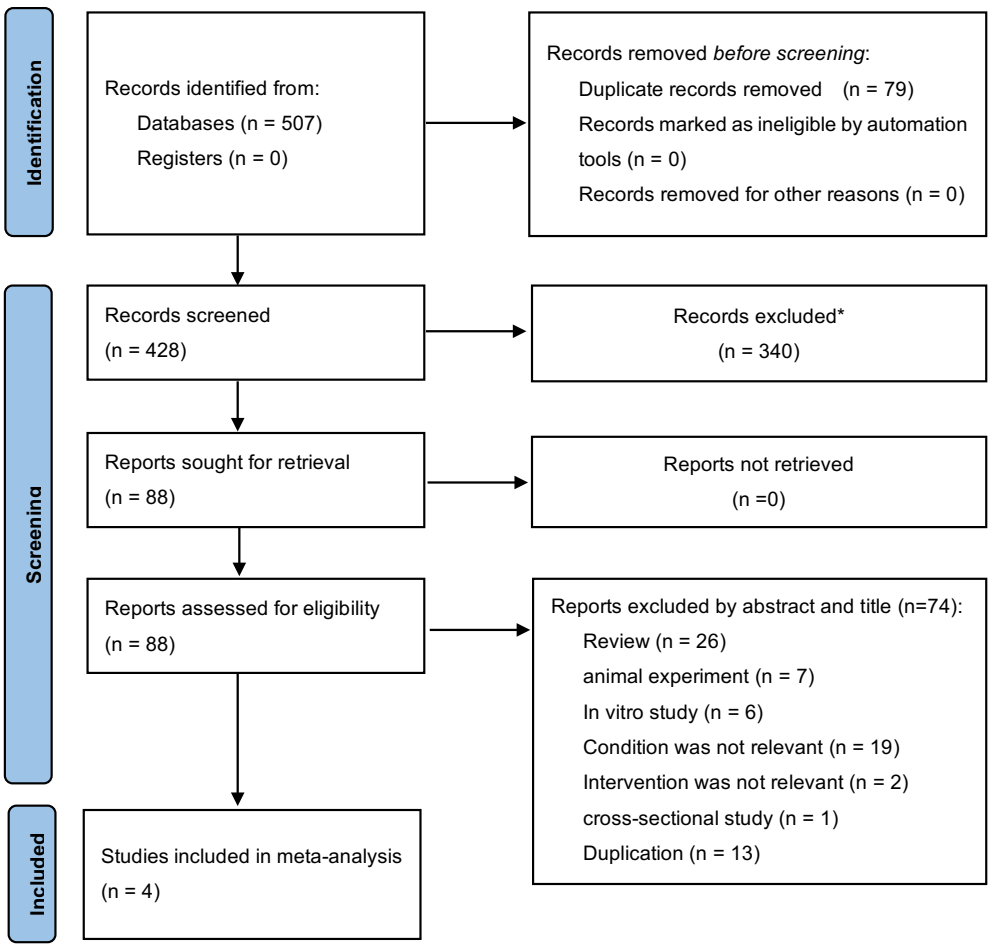

Figure 1. Search strategy diagram.
*Reports not related to population studies were excluded by EndnoteX9.

generally good, particularly in terms of blinding and randomization compared to other aspects.

Curcumin supplementation versus placebo

As shown in Figure 3, four studies were meta-analyzed separately using frequency, duration and severity as effect sizes. The results indicated that curcumin supplementation showed a significant reduction on the severity of migraine headache (Hedges's g = -0.75, 95%CI= -1.44 to -0.07, *P*= 0.03). However, there was no significant effects observed in the frequency and duration of migraine headache reduction (for frequency, Hedges's g= -0.42, 95%CI= -1.15 to 0.32, *P*= 0.27; for duration, Hedges's g= -0.43, 95%CI= -0.90 to 0.04, *P*= 0.08). According to Cochrane Handbook, the results of duration represented a moderate heterogeneity (I^2= 58.56%, *P*= 0.02), while the frequency and the severity suggested substantial heterogeneities (I^2= 82.29%, *P*< 0.01; I^2=72.08%, *P*< 0.01, respectively).

Thus, we further conducted the subgroup analyses of these three dimensions (duration, frequency and severity) according to participants' age, dosage of curcumin, and condition of prophylactic administration respectively.

Subgroup analysis

The subgroup analyses of the effect of curcumin supplementation on migraine symptoms were shown in Table 2. The outcomes revealed that curcumin supplementation significantly reduced the duration of migraine symptoms in participants older than 35 years (Hedges's g= -0.63, 95%CI= -1.07 to -0.19, *P*= 0.01), and the heterogeneity was not important (I^2= 33.83%). The combined results for the remaining subgroup analyses were not found to be statistically significant

Table 1: The characteristics of the included trials

References	Participants (treatment/ control)	Age (Mean ± SE)		Curcumin dosage (mg/day)	Dosage form	Prophylactic medication	Migraine symptoms			Other outcomes
		Treatment	Control				Duration	Severity	Frequency	
Abdolahi 2021[33]	19/19	37.36±1.95	36.57±1.87	80	Nano-curcumin	Amitriptyline, Propranolol, etc	NS	S	S	VCAM
Parohan 2021[34]	23/21	33.60±1.73	31.75±1.89	80	Nano-curcumin	Topiramate, Amitriptyline, etc	NS	NS	S	None
Rezaie 2021[35]	22/22	37.00±1.70	37.00±1.50	1000	curcumin pellet	Topiramate	S	S	NS	IL-6, CGRP
Sedighiyan 2022[21]	22/22	39.27±2.15	41.00±2.42	80	Nano-curcumin	None	S	S	S	None

The intervention time of all studies was 8 weeks.
SE: Standard error. NS: No significant difference compared with the control group. S: Significant difference compared with the control group.

and their heterogeneity remained high. As for the severity of migraine symptoms, curcumin supplementation significantly reduced the severity of migraine symptoms in participants who were given higher doses (Hedges's g= -1.65, 95%CI= -2.32 to -0.97, $P< 0.01$). The effect on severity of migraine on lower dose of curcumin was not significant (Hedges's g= -0.33, 95%CI= -0.76 to 0.10, $P= 0.13$) and the outcomes did not show heterogeneity ($I^2= 0.00\%$). The combined results for the remaining subgroup analyses were not statistically significant and their heterogeneity remained high. The subgroup analyses of the effect of curcumin supplementation on the frequency of migraine symptoms were also shown. None of the combined results were statistically significant.

Side effects

None of the included studies reported any significant adverse effects from the administration of curcumin.

DISCUSSION

Our study focused on subdividing the migraine headache symptoms into three aspects (duration, frequency and severity) to determine the therapeutic effects of curcumin supplementation. Four clinical trials, with a total of 170 patients, were included to examine the effects of curcumin administration on migraine symptoms. The results suggested that curcumin supplementation was effective in reducing the severity of migraine headache. Further subgroup analysis indicated that curcumin supplementation was effective in reducing migraine duration among patients older than 35 years.

Our findings indicated that curcumin supplementation was effective in reducing the severity of migraine headache with significant difference between the control and intervention group. Many population-based trials have shown that curcumin can relieve the pain symptoms of knee osteoarthritis compared to the placebo group.[36,37] There was also report of curcumin significantly reduced the severity of pain in dysmenorrhea.[38] An evaluation based on visual analogue scale scores in a meta-analysis suggested that curcumin could relieve the severity of muscle pain.[39]

The mechanism of action of curcumin in the treatment of migraine has been attributed to its antioxidant and anti-inflammatory properties.[40] The relationship among oxidative stress, inflammatory factors (calcitonin gene-related

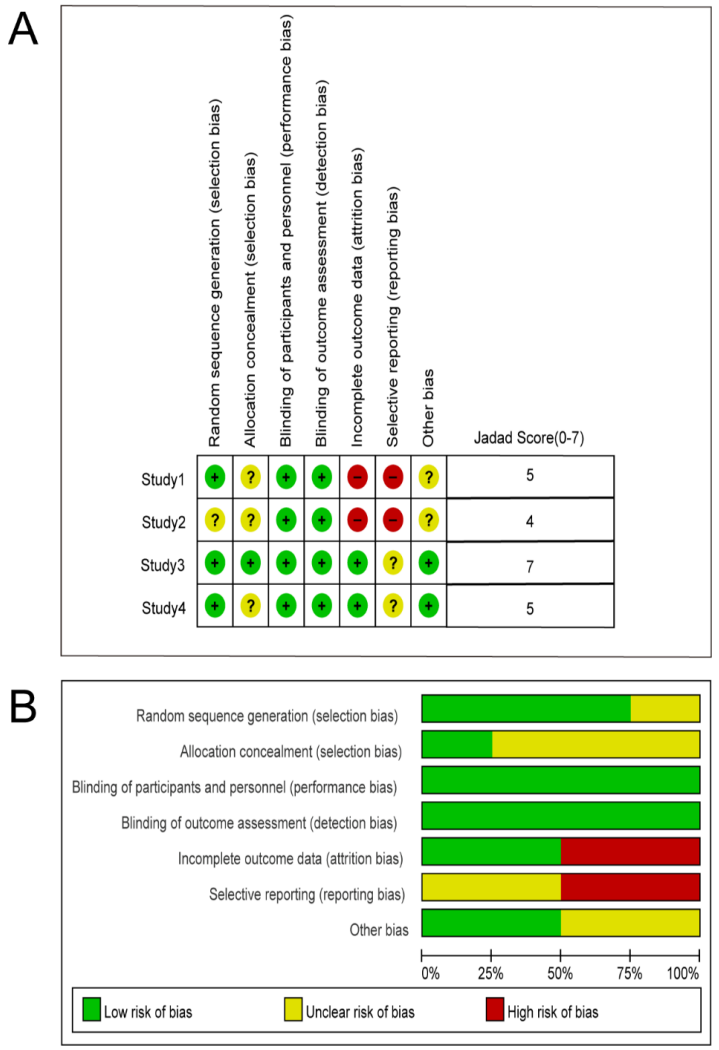

Figure 2. Studies quality assessments: A. Risk of bias graph for each included study; B. Risk of bias summary for each included study. The name of first author, followed by year of publication, and the reference no. Study 1: Abdolahi, 2021[33]; Study 2: Parohan, 2021[34]; Study 3: Rezaie, 2021[35]; Study 4: Sedighiyan, 2022[21].

peptide, IL-6, IL-1β, TNF-α, etc.) and migraine has received numerous examinations, although the definitive mechanisms of migraine pathogenesis is still unknown.[41] Furthermore, our results indicated that curcumin supplementation did not significantly reduce the frequency and duration of migraine attacks compared to the control group, although results from some of the included studies showed significant differences between the control and intervention groups. The results might be due to the insufficient sample size and different baseline characteristics of the study objects. Therefore, more studies on curcumin for migraine and larger sample sizes are needed.

The results of subgroup analysis of migraine duration supported that the effect of curcumin supplementation on reducing the duration of migraine was more pronounced in the middle-aged and elderly patient population. In the group of patients older than 35 years, the curcumin intervention group and the control group showed significant differences in the reduction of migraine duration, although no difference was observed in the total population. The heterogeneity of the subgroup analysis was reduced from moderate to mild, which indicated that age might be a source of heterogeneity in studies of curcumin to reduce migraine duration. Earlier epidemiological studies

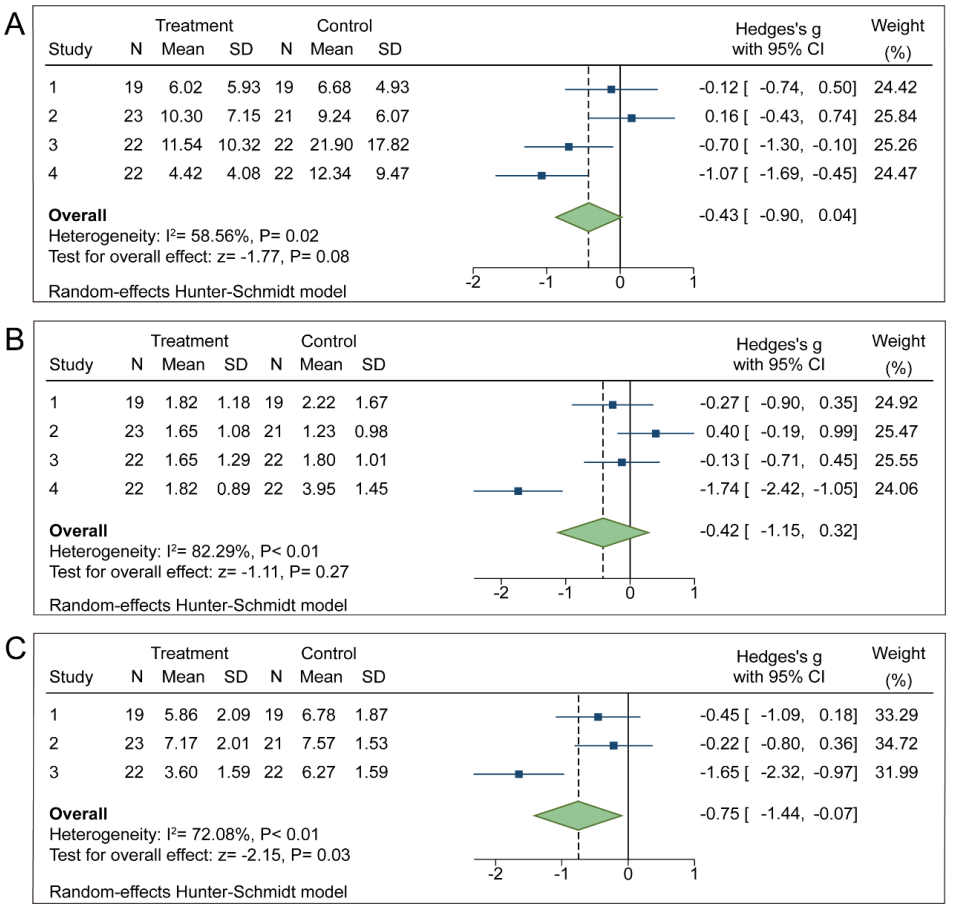

Figure 3. Curcumin supplementation compared to placebo for migraine symptoms: A. Effect on duration; B. Effect on frequency; C. Effect on severity.
Study 1: Abdolahi, 2021[33]; Study 2: Parohan, 2021[34]; Study 3: Rezaie, 2021[35]; Study 4: Sedighiyan, 2022[21].

have also demonstrated that the prevalence of migraine peaks between the ages of thirty and forty and decreases subsequently.[42] A previous report of migraine revealed a correlation between age and metabolic changes in key regions of the brain.[43] This may underlie the effect of curcumin supplementation having better efficacy in the middle-aged population.

We found the high dose of curcumin significantly reduced the severity of migraine symptom. It is generally accepted that high doses of curcumin are more effective than low doses of curcumin in terms of nerve recovery.[30,44] Previous studies have shown that the association of low absorption by the small intestine and reductive and conjugative metabolism by the liver diminishes the oral bioavailability of curcumin.[45] The natural food-derived compound curcumin is recognized as a safe substance that is non-toxic to humans, especially when administered orally.[46] Thus, high-dose administration of curcumin may be more appropriate if it is used as therapeutic agent.

In the quality assessment, we judged that the included randomized controlled trials were generally of good quality. All included trials had placebo-controlled design, selection process, patient allocation, and reasons for exiting and met the requirements in terms of blind design.

There were some limitations in this study. First, due to limited data and requirements for data types, the number of included studies and sample size were small. However, because the studies we included were all randomized double-blind, placebo-controlled trials, the results were robust. Second, the inflammatory factor indicators were not included in this meta-analysis due to the inconsistent data types. Third, studies published in languages other than English and Chinese or unpublished clinical studies were not included.

In conclusion, this study suggested that

Table 2: Subgroup analysis of the effect of curcumin on migraine symptoms

Effect size	Subgroups	N	SMD (Hedges's g)	95%CI	I^2	*P*
Duration	Age of participants					
	≥ 35	3	-0.63	[-1.07, -0.19]	33.83%	< 0.01
	< 35	1	0.16	[-0.43, 0.74]	NA	0.60
	Dosage of curcumin					
	80mg/day	3	-0.34	[-0.93, 0.26]	64.74%	0.27
	1000mg/day	1	-0.7	[-0.90, 0.04]	NA	0.02
	Prophylactic medication					
	PA	3	-0.22	[-0.63, 0.19]	27.97%	0.30
	NP	1	-1.07	[-1.69, 0.45]	NA	< 0.01
Frequency	Age of participants					
	≥ 35	3	-0.69	[-1.48, 0.10]	78.75%	0.08
	< 35	1	0.40	[-0.19, 0.99]	NA	0.18
	Dosage of curcumin					
	80mg/day	3	-0.52	[-1.50, 0.46]	86.24%	0.30
	1000mg/day	1	-0.13	[-0.71, 0.45]	NA	0.67
	Prophylactic medication					
	PA	3	0.01	[-0.33, 0.36]	0.00%	0.95
	NP	1	-1.74	[-2.42, -1.05]	NA	0.18
Severity	Age of participants					
	≥ 35	2	-1.04	[-1.87, -0.21]	68.78%	0.01
	< 35	1	-0.22	[-0.80, 0.36]	NA	0.46
	Dosage of curcumin					
	80mg/day	2	-0.33	[-0.76, 0.10]	0.00%	0.13
	1000mg/day	1	-1.65	[-2.32, -0.97]	NA	< 0.01

N: The number of studies. NA: not applicable. PA: Prophylactic administration.
NP: No prophylactic administration.
The random-effect Hunter-Schmidt model was used for subgroup analysis.

curcumin supplementation was effective in reducing the severity of migraines and were more effective in reducing migraine duration in people older than 35 years. Clinical studies with larger sample sizes are needed to further validate the appropriate population characteristics and dosage of curcumin for the treatment of migraine.

DISCLOSURE

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Conflicts of interest: None

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