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RESEARCH ARTICLE

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Effect of cinnamon on migraine attacks and inflammatory markers: A randomized double-blind placebo-controlled trial

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Migraine is the most common type of primary headaches. Increased levels of interleukin-6 (IL-6), calcitonin-gene-related peptide (CGRP) and nitric oxide (NO) lead to inflammation and neurogenic pain. Cinnamon has anti-inflammatory and neuroprotective properties. Thus, the aim of this study was to assess the effect of cinnamon on migraine attacks and inflammatory status. Fifty patients with migraine were randomized to receive either cinnamon powder (three capsules/day each containing 600 mg of cinnamon) or three placebo capsules/day each containing 100 mg of corn starch (control group) for 2 months. Serum levels of IL-6, CGRP and NO were measured at baseline and at the end of the study. The frequency, severity and duration of pain attacks were also recorded using questionnaire. Serum concentrations of IL-6 and NO were significantly reduced in the cinnamon group compared with the control group ($p < .05$). However, serum levels of CGRP remained unchanged in both groups. The frequency, severity and duration of migraine attacks were significantly decreased in the cinnamon group compared with the control group. Cinnamon supplementation reduced inflammation as well as frequency, severity and duration of headache in patients with migraine. Cinnamon could be regarded as a safe supplement to relieve pain and other complications of migraine.

KEYWORDS
calcitonin-gene-related, cinnamon, interleukin-6, migraine, nitric oxide

1 | INTRODUCTION

Migraine is the most common form of primary headaches, which is prevalent in approximately 12% of the western world's population (Lipton, Stewart, Diamond, Diamond, & Reed, 2001). It is reported that each week, 1 day of migraine attack occurs in at least 1% of the general population (Goadsby, Lipton, & Ferrari, 2002). Severe impairment or need for bed rest has been reported in about 53% of patients during migraine attacks (Lipton et al., 2007). It has been reported that about 14% of the Iranian population are suffering from migraine, which is higher than the global average (Farhadi et al., 2016; Lantéri-Minet, Duru, Mudge, & Cottrell, 2011). A migraine attack is associated with reductions in the quality of life, productivity and utilisation of the labour force in the community, as well as financial burden (Farhadi et al., 2016; Lantéri-Minet et al., 2011). While some previous studies have found that migraine is initiated in the central nervous system (CNS), others indicated that migraine might be caused by neurovascular and metabolic changes in the brain with dysfunctional intracranial and extracranial blood vessels (Gerring, Powell, Montgomery, & Nyholt, 2017). However, in spite of diverse evidence about on etiology and pathophysiology of migraine, its main cause still remains unknown (Tajti et al., 2010). Recently, a growing body of evidence proposed that inflammation plays a significant role in both the initiation and persistence of pathological pain through activation of nociceptive sensory neurons (Sommer & Kress, 2004; Zhang & An, 2007). Calcitonin gene-related peptide (CGRP), nitric oxide (NO) and cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) are all pro-inflammatory molecules, which have been shown

to be implicated in the pathogenic mechanisms underlying migraine (Longoni & Ferrarese, 2006; Vallejo, Tilley, Vogel, & Benyamin, 2010). Finding novel treatment strategies, particularly from complementary and alternative approaches with low side effects, has attracted significant attention (Sun-Edelstein & Mauskop, 2011). Medicinal plants might be used as safe, accessible and inexpensive agents with low adverse effects to alleviate migraine pain and symptoms. Cinnamon as a food spice has been used for thousands of years (Bagherniya, Nobili, Blesso, & Sahebkar, 2018). It has been shown that cinnamon has several potential health benefits including anti-inflammatory, antioxidant, anti-neuroinflammatory, neuroprotective, insulin-sensitising and anti-obesity properties (Bagherniya et al., 2018; Mondal & Pahan, 2015; Vallianou, Tsang, Taghizadeh, Davoodvandi, & Jafarnejad, 2019). It has been previously shown that cinnamaldehyde as a main component of cinnamon has a strong neuroinflammatory capacity (Ho, Chang, & Chang, 2013; Ribeiro-Santos et al., 2017). More interestingly, in a very recent animal study, it was revealed that cinnamaldehyde protected against subarachnoid haemorrhage-induced early brain injury and it was proposed that vasospasm can be prevented by cinnamaldehyde (Gürer et al., 2019). Overall, due to the anti-neuroinflammatory and neuroprotective effects of cinnamon, it seems that this natural product can exert positive effects on migraine headache. To the authors' knowledge, there has been no prior randomised controlled trial to assess the effects of cinnamon on migraine attacks. Therefore, the aim of the present study was to evaluate the effect of cinnamon consumption on the frequency, severity and duration of migraine attacks and inflammatory markers in patients suffering from migraine.

2 | MATERIALS AND METHODS

2.1 | Sample size

The estimated sample size was calculated based on 80% power, an alpha level of .05, and a potential drop-out rate of 10%. It was calculated that 50 participants (i.e., 25 participants in each group) would be required to detect 20% difference between the groups (Billings, Lopez Mitnik, & Dye, 2017).

2.2 | Participants

Among all patients with migraine who were visited at the Khorshidand Imam Mousa Sadr Clinics (Isfahan University of Medical Sciences, Iran), 50 eligible patients were recruited for the current study. A single expert neurologist confirmed migraine based on the third edition of the International Classification of Headache Disorders (Galioto et al., 2018).

The inclusion criteria were migraine without aura that was diagnosed by one expert neurologist, history of migraine for at least a year, age of 20–50 years old and willingness to participate in the study. Also, anxiety, stress and depression status were normal to moderate, which was measured by the DASS-21 questionnaire (Henry & Crawford, 2005). On the other hand, patients with tension-type headache, migraine with aura, chronic diseases such as chronic kidney diseases and gastrointestinal diseases were excluded. In addition, patients with a history of cinnamon sensitivity and allergy, taking any antioxidants, cinnamon supplement and anti-inflammatory drugs, Menopause, pregnant or breastfeeding subjects were not included in the study. All participants were informed regarding the study protocol before taking part and signed written informed consent.

The protocol of this study was approved by the Ethics Committee of the Isfahan University of Medical Sciences, Isfahan, Iran (ethics code: IR.MUI.RESEARCH.REC.1397.185). The trial was registered in the Iranian Registry of Clinical Trials (No. IRCT20121216011763N36).

2.3 | Study design and intervention

This was a double-blind placebo-controlled randomised trial. The participants were randomly divided into intervention and control groups based on the permuted four-block randomisation method in a 1:1 ratio using the table of random numbers. During the study, researchers and participants were blinded of the randomisation codes. Patients in each group were asked to consume three cinnamon or placebo capsule after each main meal everyday for 60 days. The cinnamon capsules contained 600 mg of dried *Cinnamomumzeylanicum* bark powder (Ceylon cinnamon) +100 mg of corn starch and placebo capsules containing 100 mg of corn starch; these capsules were produced by Faculty of Pharmacy, Isfahan University of Medical Sciences. Both capsules were similar in shape, colour and smell. All patients were allowed to take their usual medications considering the fact that adjuvant treatment alone is not ethical. They were also urged to refrain from taking Nonsteroidal anti-inflammatory drugs and not change their medication type and dose unless with prescription of their neurologist.

2.4 | Socio-demographic and dietary parameters

A structured interview was performed by one expert neurologist and a researcher to complete demographic information and questionnaires. Demographic data including age, sex, education, economic status, number of annual trips, history of illness and medications, family history of migraine and smoking were taken from all subjects. To estimate arginine, nitrate/nitrite, antioxidant content of the diet and amount of normal food spice usage such as cinnamon, a 3-day food record (two ordinary days and one weekend day) was collected from each participant at the beginning and at the end of the study. Also, at the beginning of the study, patients were asked about their amount of cinnamon intake. All of the patients indicated a low amount of cinnamon intake. Therefore, the subjects were asked to follow their usual dietary habits and not use cinnamon or any other antioxidant

supplements during the study. Obtained data were entered into the Nutritionist IV software.

2.5 | Migraine assessment

Initially, the characteristics of the migraine headache included monthly frequency and duration of the attacks were asked by one expert neurologist. Then, during the intervention, the frequency and duration of the attacks were recorded on the questionnaire by the patients. Using a visual analogue scale (VAS) ranging from 0 to 10, the severity of pain was evaluated. In this scale, 0 indicated no pain and 10 revealed agonising pain (Hawker, Mian, Kendzerska, & French, 2011). A neurologist assessed and collected the information.

2.6 | Blood collection and inflammatory marker measurements

Blood samples (5 ml) were collected after 12 hr of fasting in the morning at baseline and at the end of study to measure CGRP and IL-6 concentrations. Blood samples were centrifuged at room temperature for 10 min to isolate serum, and aliquots were stored at −80°C until the time of final analysis. Enzyme-linked immunosorbent assay (ELISA) was used to measure the serum levels of IL-6 and CGRP human Interleukin-6 (IL-6) ELISA Kit (EASTBIOPHARM) and Human CGRP ELISA Kit (Bioassay Technology Laboratory). Nitric Oxide Assay Kit (Kiazist) was also used to measure NO.

2.7 | Statistical analysis

The statistical analysis of data was performed using the Statistical Package for the Social Sciences (Windows version 22.0, IBM Corp., Armonk, NY). The Kolmogorov–Smirnov distribution test was used to evaluate data normality. Independent-simple *t* test and Mann–Whitney test were used for the mean and median comparisons, respectively, to assess the differences between the two groups. The paired-samples *t* test and Wilcoxon test were used for the mean and median comparisons, respectively, to assess the differences between time points. Analysis of covariance (ANCOVA) was performed to distinguish the effect of the intervention between the two groups, adjusted for age and sex. Statistcial significance was defined at $p < .05$.

3 | RESULTS

From 114 subjects who were examined by a neurologist in the headache clinic, 50 subjects met the inclusion criteria and participated in this study. Throughout the intervention (60 days), seven patients were excluded from the study; four in the cinnamon group (two subjects because of allergic reactions including itching, and others because of refusal to continue the study), and three in the placebo group refused to continue the study. Except for the mentioned allergy, no other side effect was reported. Finally, 43 patients (21 in the cinnamon group and 22 in the control group) completed the study and were considered for statistical analysis, corresponding to 86% of the subjects (Figure 1).

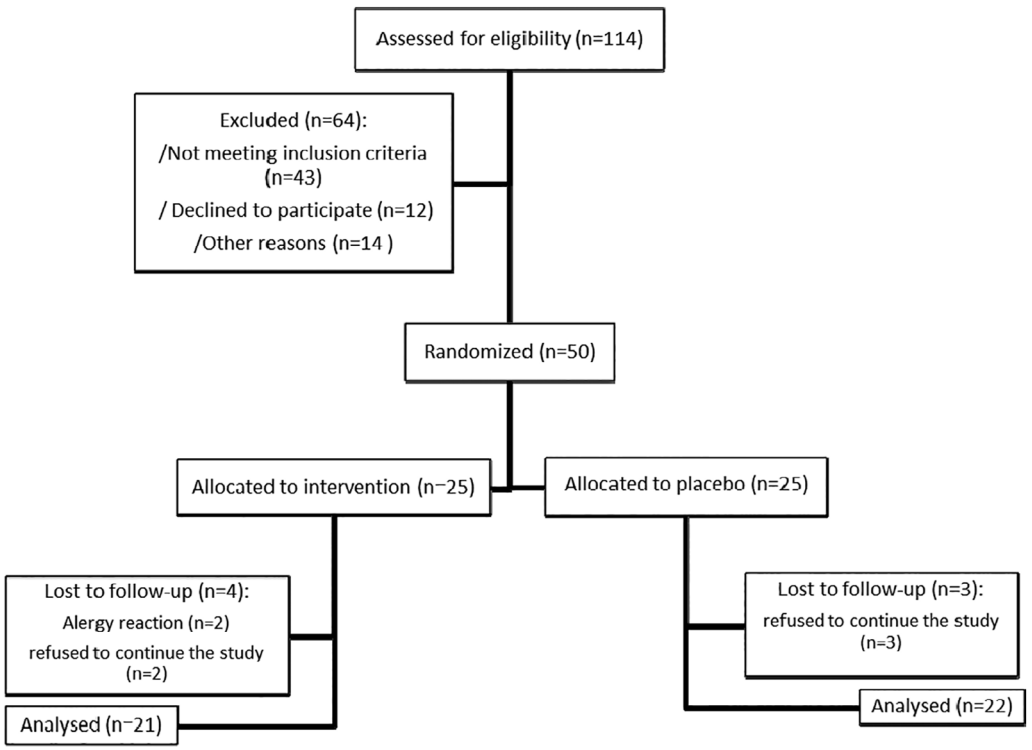

FIGURE 1 Chart of participants follow-up

3.1 | Subjects' characteristics

At baseline, no significant difference was found between the two groups regarding demographic characteristics. Patients in the cinnamon group were aged 37.13 ± 7.80 years, and 79.19% (16/21) of them were female. On the other hand, 22 patients in the placebo group were aged 39.36 ± 6.87 years, and 86.36% (19/21) of them were female. Other characteristics are presented in Table 1. In addition, no significant differences were observed in the medications used between the studied groups before and during the intervention. According to the 3-day dietary records, there were no significant differences between the two groups regarding dietary intakes of antioxidants such as Zinc, Selenium, Vitamin C, Vitamin E, Vitamin A and NO precursors such as arginine, NO_3^- and NO_2^- (Table 2).

3.2 | Changes in migraine characteristics

After 2 months of intervention, frequency, duration and severity of migraine headaches significantly decreased in the cinnamon group compared with the placebo group (Table 3). The mean scores of frequency attacks were significantly reduced in both groups; however, the reduction was significantly greater in the intervention group compared with the control group (8.47 ± 1.01 to 1.71 ± 0.29 and 8.72 ± 0.96 to 7.22 ± 0.99 in the cinnamon and placebo groups, respectively, $p < .001$). Likewise, as shown in Table 3. The mean severity of attacks (based on the VAS) was significantly reduced in both groups though the reduction was significantly greater in the cinnamon group compared with the control group (7.61 ± 0.26 to 3.33 ± 0.43 and 7.54 ± 0.18 to 6.77 ± 0.21 in the cinnamon group and placebo groups, respectively, $p < .001$).

TABLE 1 Baseline demographic characteristics of migraine patients in groups of the study

Variable	Cinnamon group (n = 21)	Placebo (n = 22)	p Value
Age [mean ± *SD* (years)]	37.13 ± 7.80	39.36 ± 6.87	.32[a]
Gender [number (%)]			
Female	16 (76.19)	19 (86.36)	.35[b]
Male	5 (23.80)	3 (13.63)	
Family history of migraine [number (%)]	18 (85.71)	15 (68.18)	.15[b]
History of smoking [number (%)]			
Yes	4 (19.04)	3 (13.63)	.89[b]
No	17 (80.95)	19 (86.36)	
Marital status [number (%)]			
Married	17 (80.95)	20 (90.90)	.10[b]
Not married	4 (19.04)	1 (4.54)	
Widowed/divorced	0	1 (4.45)	
Employment status [number (%)]			
Working	10 (47.61)	8 (36.36)	.65[b]
Not working	8 (38.09)	12 (54.54)	
Student	3 (14.28)	2 (9.09)	
Economy status [number (%)]			
Very low income	5 (23.80)	1 (4.54)	.72[c]
Low income	7 (33.33)	9 (40.90)	
Average income	8 (38.09)	12 (54.54)	
High income	1 (4.76)	0	
Yearly trips (mean ± *SD*)	3.20 ± 0.71	1.82 ± 0.64	.15[a]
Medications [number (%)]			
Antidepressants			
Tricyclic antidepressant	2 (9.52)	4 (18.18)	.31[b]
SSRI	3 (13.63)	3 (13.63)	1[b]
SNRI	2 (9.52)	2 (9.09)	1[b]
Antiepileptic	7 (33.33)	10 (45.45)	.32[b]
Gabapentin	2 (9.52)	3 (13.63)	.50[b]
Beta-blockers	5 (23.80)	8 (36.36)	.32[b]

[a]Independent samples *t* test.
[b]Chi-square test.
[c]Mann–Whitney test.

TABLE 2 Dietary intake of antioxidants and nitric oxide precursor in migraine patients before and after the intervention

		Cinnamon group (n = 21)			Placebo (n = 22)		
		Baseline	After intervention	p Value[a]	Baseline	After intervention	p Value[a]
Antioxidants	Zinc (mg)	6.51 ± 3.04	6.99 ± 2.29	.38	6.87 ± 2.42	7.12 ± 2.22	.14
	Selenium (mg)	0.07 ± 0.03	0.06 ± 0.02	.52	0.07 ± 0.03	0.08 ± 0.04	.15
	Vitamin C (mg)	100.02 ± 68.86	99.02 ± 105.40	.96	102.89 ± 45.62	97.50 ± 64.76	.63
	Vitamin E (mg)	2.67 ± 1.99	2.17 ± 1.67	.40	2.33 ± 1.56	2.79 ± 1.27	.27
	Vitamin A (RE)	481.40 ± 269.81	490.83 ± 362.26	.83	565.82 ± 533.44	570.74 ± 516.04	.89
Nitric oxide precursor	Arginine (mg)	177.47 ± 214.62	210.81 ± 251.77	.41	286.59 ± 558.69	327.03 ± 545.78	.33
	Nitrate (NO_3; mg)	397.33 ± 111.58	375.92 ± 146.41	.57	391.15 ± 153.52	374.00 ± 117.73	.54
	Nitrite (NO_2; mg)	9.30 ± 3.40	8.41 ± 2.68	.33	8.46 ± 3.00	9.43 ± 3.08	.09

Note: Data are reported as means ± *SD*.
[a]Paired *t* test was used to compare pre-post tests.

TABLE 3 Evaluation of attack frequency/duration/severity in migraine patients before and after the intervention

		Cinnamon group (n = 21)	Placebo (n = 22)	p Value[a]	p Value[b]
Frequency (attacks per 2 months)	Before	8.47 ± 1.01	8.72 ± 0.96		
	After	1.71 ± 0.29	7.22 ± 0.99		
	p Value[c]	<.001	.02		
	Between-group difference	−6.76 ± 0.96	−1.50 ± 0.57	<.001	<.001
Duration (hour/attack)	Before	18.42 ± 4.18	16.72 ± 3.74		
	After	7.73 ± 2.49	11.20 ± 1.90		
	p Value[c]	.001	.10		
	Between-group difference	−10.69 ± 2.72	−5.52 ± 3.26	.02	.03
Severity (visual analogue scale)	Before	7.61 ± 0.26	7.54 ± 0.18		
	After	3.33 ± 0.43	6.77 ± 0.21		
	p Value[c]	<.001	.01		
	Between-group difference	−4.28 ± 0.46	−0.77 ± 0.28	<.001	<.001

Note: Data are reported as means ± SE.
[a]Idependent samples *t* test was used to compare between groups.
[b]ANCOVA test (adjusted for age and sex).
[c]Paired *t* test was used to compare pre-post tests.

The mean duration of attacks was reduced from 18.42 ± 4.18 hr to 7.73 ± 2.49 hr in the cinnamon group, while it did not significantly change in the placebo group. The difference between the two groups was statistically significant (p = .02). Likewise, the same results were found after adjustments for age and sex as shown in Table 3.

3.3 | Inflammatory markers

The changes in serum levels of IL6, NO and CGRP are illustrated in Table 4. The concentrations of IL-6 and NO were significantly decreased in the cinnamon group compared with the placebo group. However, although CGRP levels decreased in the cinnamon group, the change was not significant compared with either baseline or the control group. Above-mentioned results did not change after adjustments for age and sex as shown in Table 4.

4 | DISCUSSION

The main finding of the current study was that cinnamon significantly reduced the frequency, severity and duration of migraine attacks in the study participants. To the best of our knowledge, this is the first randomised controlled trial investigating the effect of cinnamon on migraine complications. Considering the high prevalence of migraine, our novel finding might be useful in a clinical setting to relieve pain and migraine attacks, and subsequently improve the functional capacity of migraine patients.

In this study, cinnamon consumption dramatically reduced the frequency, severity and duration of migraine. Although the precise pathophysiological mechanisms of migraine are still unclear, a growing body evidence has indicated that the neuroinflammatory state is involved in the development of migraine attacks (Longoni & Ferrarese, 2006; Zhang & An, 2007).

TABLE 4 Change in biochemical parameters after 2 months of intervention

Parameter		Cinnamon group (n = 21)	Placebo (n = 22)	p Value	p Value
IL-6 (ng/L)	Before	108.71 ± 28.23	86.43 ± 27.83		
	After	100.81 ± 25	87.33 ± 27.39		
	p Value[a]	.003	.52		
	Between-group difference	−7.90 ± 4.65	0.90 ± 10.19	.003[b]	.005[c]
NO (nmol/ml)	Before	29.25 ± 2.92	21.91 ± 2.05		
	After	23.34 ± 2.17	27.78 ± 3.63		
	p Value[d]	.001	.019		
	Between-group difference	−5.91 ± 1.45	5.86 ± 2.30	.001[e]	.004[c]
CGRP (ng/L)	Before	118.50 ± 37.07	80.84 ± 31.48		
	After	111.66 ± 35.03	81.65 ± 31.62		
	p Value[a]	.09	.49		
	Between-group difference	−6.83 ± 5.40	−0.80 ± 3.88	.06[b]	.09[c]

Note: Data are reported as means ± SE.
[a]Wilcoxon ranks test was used to compare pre-post tests.
[b]Mann–Whitney testused to compare between groups.
[c]ANCOVA test (adjusted for age and sex).
[d]Paired t test was used to compare pre-post tests.
[e]Independent samples t test was used to compare between groups.

One of the most well-known cytokines involved in the pathological pain process is IL-6 (Wang et al., 2015). It has been revealed that IL-6 levels are higher in patients with migraine compared with normal subjects, suggesting that IL-6 has a significant role in the pathophysiology of migraine pain and making the patients more vulnerable to pain attacks during chronic migraine (Kocer et al., 2009; Kocer, Kocer, Memisogullari, Domac, & Yuksel, 2010).

In the present study, serum levels of IL-6 were significantly decreased after the intervention. Cinnamon has anti-inflammatory and neuroprotective properties (Ho et al., 2013; Ranasinghe et al., 2013). Cinnamaldehyde as the main bioactive component of cinnamon could reduce the production of inflammatory cytokines such as IL-6, IL-1β and TNF-α by suppressing the expression of cyclooxygenase and nitric oxide synthase (iNOS; Ho et al., 2013; Kim et al., 2007; Lee et al., 2006; Liao et al., 2008; Liao, Wang, Tan, & Wei, 2017). In addition, animal studies showed that cinnamon's components and metabolites can regulate the release of inflammatory mediators (Modi, Jana, Mondal, & Pahan, 2015; Mondal & Pahan, 2015). Therefore, it seems that the beneficial effects of cinnamon on migraine complications are, at least in part, due to its effects on IL-6.

In the present study, the levels of CGRP did not significantly change after the intervention. However, serum NO levels were reduced in the intervention group in comparison to the control group. CGRP and NO are effective vasodilator molecules that are involved in the pathophysiology of migraine (Mason & Russo, 2018). Considering the interplay between NO and CGRP (Li, Vause, & Durham, 2008), it might be hypothesised that a reduction in NO can lead to CGRP reduction. Unlike the effect of cinnamon in reducing NO levels (Ho et al., 2013; Raffai et al., 2014), CGRP levels remained unaltered by the end of the trial.

It has been previously proposed that increasing NO can raise CGRP synthesis and release from trigeminal neurons. Conversely, increasing CGRP can raise NO synthesis and release from trigeminal glia and vascular endothelium. This suggests a mutual interaction between NO and CGRP (Russo, 2015). CGRP is a mediator of neurogenic inflammation and a modulator of nociceptive input, which is also recognised as one of the most potent vasodilators of cranial arteries (Ashina, Newman, & Ashina, 2017). A reduction in CGRP after decreasing NO was expected in the present study; however, it seems that the short duration of intervention might have been a possible reason for not observing significant changes in CGRP levels. Therefore, additional studies with longer periods will be required to clarify the exact effect of cinnamon on CGRP. Another possibility is that there is only an incremental feedback mechanism between NO and CGRP. Moreover, the concentrations of CGRP in cerebrospinal fluid (CSF) can be much higher than serum because most of the CGRP is intracranial and comes from the CNS, and the levels are thus better reflected in the CSF (Dux, Will, Eberhardt, Fischer, & Messlinger, 2017).

Regarding our results about NO, it should be mentioned that NO is an important signalling molecule involved in nociceptive processing (Olesen, 2008; Pradhan, Bertels, & Akerman, 2018). The pronociceptive effect of NO has previously been determined in inflammatory pain and, on the other hand, inhibition of NO production ameliorated inflammatory and neuropathic pain (Saad, Hamza, Bahr, & Masoud, 2016). Thus, reducing NO levels might be considered as a way to relieve pain and other complications of migraine.

Previous studies have demonstrated that cinnamon possesses anti-neuroinflammatory activity and is able to inhibit NO production and iNOS expression. The findings of previous studies support our results, which showed that cinnamon can reduce the levels of NO. It

seems that cinnamon reduces the metabolites of NO including superoxide and peroxynitrite, which result in the reduction of inflammation and pain evoked by NO (Ho et al., 2013; Lee, Kim, & Kim, 2002; Raffai et al., 2014). In addition, it should be mentioned that the serum NO levels are derived from food intake and endogenous production (Mirmiran, Bahadoran, Ghasemi, & Azizi, 2016). In our study, the arginine and nitrate/nitrite intake from foods were unchanged before and after the intervention, indicating that the reduction in serum NO occurred in response to cinnamon supplementation. Therefore, it might be proposed that a reduction in migraine complications is due to the inhibitory actions of cinnamon on NO production as well as its beneficial effects on IL-6.

Although this study was the first randomised double-blind clinical trial that investigated the effect of cinnamon as a natural, inexpensive and accessible herbal medicine on migraine, some limitations should be noted. The duration of the intervention was relatively short and there was no long-term follow-up. Also, the sample size was small. Moreover, because of ethical issues, the effect of cinnamon alone could not be investigated.

5 | CONCLUSIONS

Our findings showed that cinnamon consumption significantly reduced serum levels of IL-6 and NO as well as the frequency, severity and duration of migraine attacks. These findings merit further confirmation in larger trials.

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CONFLICT OF INTEREST

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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REFERENCES

Ashina, H., Newman, L., & Ashina, S. (2017). Calcitonin gene-related peptide antagonism and cluster headache: An emerging new treatment, *38*(12), 2089–2093. https://doi.org/10.1007/s10072-017-3101-8

Bagherniya, M., Nobili, V., Blesso, C. N., & Sahebkar, A. (2018). Medicinal plants and bioactive natural compounds in the treatment of non-alcoholic fatty liver disease: A clinical review. *Pharmacological Research*, *130*, 213–240. https://doi.org/10.1016/j.phrs.2017.12.020

Billings, M., Lopez Mitnik, G., & Dye, B. A. (2017). Sample size for clinical trials. *Oral Diseases*, *23*(8), 1013–1018. https://doi.org/10.1111/odi.12611

Dux, M., Will, C., Eberhardt, M., Fischer, M. J. M., & Messlinger, K. (2017). Stimulation of rat cranial dura mater with potassium chloride causes CGRP release into the cerebrospinal fluid and increases medullary blood flow. *Neuropeptides*, *64*, 61–68. https://doi.org/10.1016/j.npep.2017.02.080

Farhadi, Z., Alidoost, S., Behzadifar, M., Mohammadibakhsh, R., Khodadadi, N., Sepehrian, R., … Behzadifar, M. (2016). The prevalence of migraine in Iran: A systematic review and meta-analysis. *Iranian Red Crescent Medical Journal*, *18*(10), e40061. https://doi.org/10.5812/ircmj.40061

Galioto, R., O'Leary, K. C., Gunstad, J., Thomas, J. G., Lipton, R. B., Pavlovic, J. M., … Bond, D. S. (2018). The role of migraine headache severity, associated features and interactions with overweight/obesity in inhibitory control. *The International Journal of Neuroscience*, *128*(1), 63–70. https://doi.org/10.1080/00207454.2017.1366474

Gerring, Z. F., Powell, J. E., Montgomery, G. W., & Nyholt, D. R. (2017). Genome-wide analysis of blood gene expression in migraine implicates immune-inflammatory pathways. *Cephalalgia*, *38*, 292–303. https://doi.org/10.1177/0333102416686769

Goadsby, P. J., Lipton, R. B., & Ferrari, M. D. (2002). Migraine—Current understanding and treatment. *New England Journal of Medicine*, *346*(4), 257–270.

Gürer, B., Kertmen, H., Bektaşoğlu, P. K., Öztürk, Ö. Ç., Bozkurt, H., Karakoç, A., … Çelikoğlu, E. (2019). The effects of Cinnamaldehyde on early brain injury and cerebral vasospasm following experimental subarachnoid hemorrhage in rabbits. *Metabolic Brain Disease*, *34*(6), 1–10.

Hawker, G. A., Mian, S., Kendzerska, T., & French, M. (2011). Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care Research (Hoboken)*, *63*(Suppl 11), S240–S252. https://doi.org/10.1002/acr.20543

Henry, J. D., & Crawford, J. R. (2005). The short-form version of the Depression Anxiety Stress Scales (DASS-21): Construct validity and normative data in a large non-clinical sample. *The British Journal of Clinical Psychology*, *44*(Pt 2), 227–239. https://doi.org/10.1348/014466505x29657

Ho, S. C., Chang, K. S., & Chang, P. W. (2013). Inhibition of neuroinflammation by cinnamon and its main components. *Food Chemistry*, *138*(4), 2275–2282. https://doi.org/10.1016/j.foodchem.2012.12.020

Kim, D. H., Kim, C. H., Kim, M. S., Kim, J. Y., Jung, K. J., Chung, J. H., … Chung, H. Y. (2007). Suppression of age-related inflammatory NF-kappaB activation by cinnamaldehyde. *Biogerontology*, *8*(5), 545–554. https://doi.org/10.1007/s10522-007-9098-2

Kocer, A., Kocer, E., Memisogullari, R., Domac, F. M., & Yuksel, H. (2010). Interleukin-6 levels in tension headache patients. *The Clinical Journal of Pain*, *26*(8), 690–693. https://doi.org/10.1097/AJP.0b013e3181e8d9b6

Kocer, A., Memisogullari, R., Domac, F. M., Ilhan, A., Kocer, E., Okuyucu, S., … Yuksel, H. (2009). IL-6 levels in migraine patients receiving topiramate. *Pain Practice*, *9*(5), 375–379. https://doi.org/10.1111/j.1533-2500.2009.00301.x

Lantéri-Minet, M., Duru, G., Mudge, M., & Cottrell, S. (2011). Quality of life impairment, disability and economic burden associated with chronic daily headache, focusing on chronic migraine with or without medication overuse: A systematic review. *Cephalalgia*, *31*(7), 837–850. https://doi.org/10.1177/0333102411398400

Lee, H. J., Hyun, E. A., Yoon, W. J., Kim, B. H., Rhee, M. H., Kang, H. K., … Yoo, E. S. (2006). In vitro anti-inflammatory and anti-oxidative effects of *Cinnamomum camphora* extracts. *Journal of Ethnopharmacology*, *103*(2), 208–216. https://doi.org/10.1016/j.jep.2005.08.009

Lee, H. S., Kim, B. S., & Kim, M. K. (2002). Suppression effect of *Cinnamomum cassia* bark-derived component on nitric oxide synthase. *Journal of Agricultural and Food Chemistry*, *50*(26), 7700–7703. https://doi.org/10.1021/jf020751f

Li, J., Vause, C. V., & Durham, P. L. (2008). Calcitonin gene-related peptide stimulation of nitric oxide synthesis and release from trigeminal ganglion glial cells. *Brain Research*, *1196*, 22–32. https://doi.org/10.1016/j.brainres.2007.12.028

Liao, B. C., Hsieh, C. W., Liu, Y. C., Tzeng, T. T., Sun, Y. W., & Wung, B. S. (2008). Cinnamaldehyde inhibits the tumor necrosis factor-alpha-induced expression of cell adhesion molecules in endothelial cells by suppressing NF-kappaB activation: Effects upon IkappaB and Nrf2. *Toxicology and Applied Pharmacology*, *229*(2), 161–171. https://doi.org/10.1016/j.taap.2008.01.021

Liao, Z., Wang, J., Tan, H., & Wei, L. (2017). Cinnamon extracts exert intrapancreatic cytoprotection against streptozotocin in vivo. *Gene*, *627*, 519–523. https://doi.org/10.1016/j.gene.2017.07.014

Lipton, R. B., Bigal, M. E., Diamond, M., Freitag, F., Reed, M., & Stewart, W. F. (2007). Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology*, *68*(5), 343–349.

Lipton, R. B., Stewart, W. F., Diamond, S., Diamond, M. L., & Reed, M. (2001). Prevalence and burden of migraine in the United States: Data from the American Migraine Study II. *Headache: The Journal of Head and Face Pain*, *41*(7), 646–657.

Longoni, M., & Ferrarese, C. (2006). Inflammation and excitotoxicity: Role in migraine pathogenesis. *Neurological Sciences*, *27*(2), s107–s110.

Mason, B. N., & Russo, A. F. (2018). Vascular contributions to migraine: Time to revisit? *Frontiers in Cellular Neuroscience*, *12*, 233. https://doi.org/10.3389/fncel.2018.00233

Mirmiran, P., Bahadoran, Z., Ghasemi, A., & Azizi, F. (2016). The association of dietary l-arginine intake and serum nitric oxide metabolites in adults: A population-based study. *Nutrients*, *8*(5), 311. https://doi.org/10.3390/nu8050311

Modi, K. K., Jana, M., Mondal, S., & Pahan, K. (2015). Sodium benzoate, a metabolite of cinnamon and a food additive, upregulates ciliary neurotrophic factor in astrocytes and oligodendrocytes. *Neurochemical Research*, *40*(11), 2333–2347. https://doi.org/10.1007/s11064-015-1723-x

Mondal, S., & Pahan, K. (2015). Cinnamon ameliorates experimental allergic encephalomyelitis in mice via regulatory T cells: Implications for multiple sclerosis therapy. *PLoS One*, *10*(1), e0116566. https://doi.org/10.1371/journal.pone.0116566

Olesen, J. (2008). The role of nitric oxide (NO) in migraine, tension-type headache and cluster headache. *Pharmacology & Therapeutics*, *120*(2), 157–171. https://doi.org/10.1016/j.pharmthera.2008.08.003

Pradhan, A. A., Bertels, Z., & Akerman, S. (2018). Targeted nitric oxide synthase inhibitors for migraine. *Neurotherapeutics*, *15*(2), 391–401. https://doi.org/10.1007/s13311-018-0614-7

Raffai, G., Kim, B., Park, S., Khang, G., Lee, D., & Vanhoutte, P. M. (2014). Cinnamaldehyde and cinnamaldehyde-containing micelles induce relaxation of isolated porcine coronary arteries: Role of nitric oxide and calcium. *International Journal of Nanomedicine*, *9*, 2557–2566. https://doi.org/10.2147/ijn.s56578

Ranasinghe, P., Pigera, S., Premakumara, G. A., Galappaththy, P., Constantine, G. R., & Katulanda, P. (2013). Medicinal properties of 'true' cinnamon (*Cinnamomum zeylanicum*): A systematic review. *BMC Complementary and Alternative Medicine*, *13*, 275. https://doi.org/10.1186/1472-6882-13-275

Ribeiro-Santos, R., Andrade, M., Madella, D., Martinazzo, A. P., Moura, L. D. A. G., de Melo, N. R., & Sanches-Silva, A. (2017). Revisiting an ancient spice with medicinal purposes: Cinnamon. *Trends in Food Science & Technology*, *62*, 154–169.

Russo, A. F. (2015). CGRP as a neuropeptide in migraine: Lessons from mice. *British Journal of Clinical Pharmacology*, *80*(3), 403–414. https://doi.org/10.1111/bcp.12686

Saad, S. S., Hamza, M., Bahr, M. H., & Masoud, S. I. (2016). Nitric oxide is involved in ibuprofen preemptive analgesic effect in the plantar incisional model of postsurgical pain in mice. *Neuroscience Letters*, *614*, 33–38. https://doi.org/10.1016/j.neulet.2015.12.034

Sommer, C., & Kress, M. (2004). Recent findings on how proinflammatory cytokines cause pain: Peripheral mechanisms in inflammatory and neuropathic hyperalgesia. *Neuroscience Letters*, *361*(1–3), 184–187.

Sun-Edelstein, C., & Mauskop, A. (2011). Alternative headache treatments: Nutraceuticals, behavioral and physical treatments. *Headache: The Journal of Head and Face Pain*, *51*(3), 469–483.

Tajti, J., Párdutz, Á., Vámos, E., Tuka, B., Kuris, A., Bohár, Z., … Vécsei, L. (2010). Migraine is a neuronal disease. *Journal of Neural Transmission*, *118*(4), 511–524. https://doi.org/10.1007/s00702-010-0515-3

Vallejo, R., Tilley, D. M., Vogel, L., & Benyamin, R. (2010). The role of glia and the immune system in the development and maintenance of neuropathic pain. *Pain Practice*, *10*(3), 167–184.

Vallianou, N., Tsang, C., Taghizadeh, M., Davoodvandi, A., & Jafarnejad, S. (2019). Effect of cinnamon (*Cinnamomum zeylanicum*) supplementation on serum C-reactive protein concentrations: A meta-analysis and systematic review. *Complementary Therapies in Medicine*, *42*, 271–278. https://doi.org/10.1016/j.ctim.2018.12.005

Wang, F., He, Q., Ren, Z., Li, F., Chen, W., Lin, X., … Tai, G. (2015). Association of serum levels of intercellular adhesion molecule-1 and interleukin-6 with migraine. *Neurological Sciences*, *36*(4), 535–540. https://doi.org/10.1007/s10072-014-2010-3

Zhang, J. M., & An, J. (2007). Cytokines, inflammation, and pain. *International Anesthesiology Clinics*, *45*(2), 27–37. https://doi.org/10.1097/AIA.0b013e318034194e

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