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Original Article

Comparative Effect of Cinnamon Essential Oil, Diclofenac and Morphine on Acute and Chronic Pain in Mice

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A B S T R A C T

Backgrounds and Aims: *Cinnamomum Zeylanicum* is a medicinal herb used in Iranian traditional medicine as an analgesic spice, which its analgesic effect has been experimentally confirmed. Thus, this study was conducted to compare the antinociceptive effect of cinnamon essential oil (CEO) with those of Morphine and Diclofenac in mice.

Materials and Methods: 80 male albino mice were selected and randomly divided into 10 groups: a normal control group received distilled water, 3 test groups received different doses of CEO, 3 positive control groups were under the effect of different doses of Morphine Sulfate and another 3 positive control groups underwent the effect of 3 different doses of Sodium Diclofenac. Hot plate test was used to assess acute pain and writhing test was applied to measure the chronic pain.

Results: Hot plate test showed that response latency to painful heat and thereby the maximum possible effect was increased in groups receiving Morphine, Diclofenac and CEO as compared with the control group ($p<0.05$). In writhing test, Morphine, Diclofenac and CEO significantly reduced the severity of abdominal contractions in comparison with the control group. This pain relief in the group receiving 500 µg/ kg, of CEO at any time and for doses of 250 and 125 µg/ kg in the 2nd and 3rd periods was similar to groups receiving different doses of Morphine or Diclofenac.

Conclusions: Our findings concluded that CEO possesses antinociceptive properties. Its potency in chronic pain inhibition was similar to Diclofenac, thoughits acute antinociceptive effect was reported to be less than Morphine.

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Introduction

Humans have always faced with a variety of pains seeking to relieve their pain. Pain is normally considered as a symptom of disease, serving as a warning mechanism, which informs consent from a tissue injury. As a matter of fact, pain is the most common symptom that causes patients to seek medical attention. Pain is caused by many types of stimuli which have nothing in common such as mechanical, high temperature, low PH materials and chemicals such as Bradykinin and hyperosmolality. Synthesis of chemical compounds with analgesic activity, entry into the market and their vast use for pain relief led to the prominence of their side effects. For example, opiate may induce nausea, respiratory failure and constipation and in long-term use, it can also lead to addiction [1]. Non-steroidal anti-inflammatory drugs also cause gastrointestinal disorders, kidney damage, hemorrhagic lesions of the colon, increased risk of myocardial infarction and increased heart attack [2]. These problems led scientists to look for drugs that are cheap, and widely available with little side effects. In this context, medicinal plants are considered as the major alternatives. Herbal medications and spices contain numerous beneficial compounds, whereas synthetic drugs hold only one or two useful pharmaceutical compositions. Medicinal plants due to a combination of other compounds with their specific pharmacological active component exert far fewer side effects than synthetic drugs [3]. Cinnamon is introduced as one of these herbs used in Iranian traditional medicine as an analgesic spice [4]. It is the dried bark of *Cinnamomum Zeylanicum* stem from Lauraceae family which is native to Sri Lanka [5]. Indeed, it consists of more than 50 different compounds, of which 65-80% belongs to Cinamaldehyde. Other components entail Eugenol, Cinnamic acid, Trans-Cinnamaldehydes, Tannins, Coumarin, Resins, as well as such compounds as Hydroxyphenyl Propen, Hydroxycinamaldehyde, and terpene (Limonene, Safrole and Estragole) [6]. The sweet taste of cinnamon can be related to Mannitol [7]. Its use dates back to 2700 years before Christ which has been used to improve joint pain, respiratory failure, gastrointestinal diseases and severe anger [8] and is one of the scriptures ointment components [9]. In Islamic traditional medicine, it has been used as a diuretic, carminative, anti flatulent, appetizer, stomach tonic, ear pain relief, anti-edema, antitussive antipyretic, anti-hemorrhoids and antiseptic agent [4, 10, 11]. P.Subash Babu et al. in a dissertation research found a very effective associate of cinnamon to lower liver enzyme levels and blood glucose in type II diabetes mellitus 12]. In addition, strong antioxidant and anticancer effects of Cinnamon can be stated [13, 14]. Cinnamon improves fertility [15] and produces antimicrobial effects against a variety of bacteria, fungi, viruses and larvae [16]. It also suppresses tumor growth [17], and reduces pain as well as inflammation caused by traumatic injuries and burns [18]. Addition of cinnamon to O1 -RE gel makes it more effective against mild tonic pain such as

osteoarthritis and rheumatoid [19]. Cinnamon extract inhibits tumor necrosis factor and prostaglandin E production that thereby, can lead to anti-inflammatory effects [20]. Cinnamaldehyde, Eugenol and terpene compounds in cinnamon are calming and anti-inflammatory [21, 22, 23]. The Eugenol and terpene compounds in cinnamon involve the characteristic compounds in inhibiting the metabolism of arachidonic acid and cyclooxygenase activity, resulting in the inhibition of inflammation [24, 25]. Cinnamon and its compounds can inhibit the synthesis and release of neurotransmitters in central nervous system [26]. Analgesic effect of Cinnamon has been confirmed in rats [27, 28] in a clinical trial study [29]. The present study was conducted to evaluate the efficacy of cinnamon essential oil (CEO), against acute and chronic pain in mice via comparing its antinociceptive effect with Morphine and Diclofenac.

Materials and Methods

Animals

In this study, 80 male albino mice, weighed 25 to 30 grams, were selected from laboratory animal house of the Shahid Sadoughi University of Medical Sciences (Yazd, Iran) that were randomly divided into 10 groups as follows: A normal control group receiving distilled water (10 ml/kg), 3 test groups receiving different doses of CEO (125, 250 and 500 µg/kg), 3 positive control groups under the effect of different doses of Morphine Sulfate (2, 4 and 8 mg/kg) and another 3 positive control groups under the effect of 3 different doses of Sodium Diclofenac (10, 20 and 30 mg/kg). All injections were intraperitoneal in volume of 10 mg/kg. At first, animals were assigned to hot plate test and after 2 weeks to writhing test, keeping their own groups. The study data were collected by a laboratory assistant who was blind to the animal grouping. In this study, animal handling was approved by the Institutional Ethical Committee and all efforts were made to minimize the animal's suffering in the experimental procedures.

Cinnamon essential oil preparation

To yield CEO, 100 g of *Cinnamomum Zeylanicum* dried bark which was purchased from a city's apothecary shop and confirmed by an expert in the Herbal Medicine Research Center, were gently grinded and poured into the container of a distillation apparatus containing adequate amount of distilled water. After the oil was obtained from the distillation, it was separated from the solution and held in a closed container in the fridge until the appropriate concentrations get prepared [30].

Experimental procedure

Hot plate test for acute pain assessment

At first, before turning on the device, each mouse was placed in a hot plate apparatus three times at intervals of 5 minutes in order to get them familiarized with the device and reduce their stress. Then, with respect to testing, the mice were subjected to the hot plate apparatus which its temperature was set on 54 ± 0.1°C. The time interval between exposure of mice on the device until the animals' paw licking or shaking was

considered as time to reach the threshold of pain by heat stimulus (response latency). In this test, the mice were placed on the device, once before and four times after intraperitoneal injection of vehicle or drugs at intervals of 15 minutes and then, the response latencies were recorded [31, 32]. In this test, a cut off time of 30 seconds was considered to avoid the tissue damage. Using the following equation, the percentage of maximum possible effect (%MPE) of every animal was calculated in each of the four time points after injection .

$$MPE = \frac{Test\ latency(\text{sec}) - Baseline(\text{sec})}{Cut\ Off(\text{sec}) - Baseline(\text{sec})}.100$$

MPE represents the maximum possible effect, baseline and test latency mean the response latency before and after the injections respectively and cut off time is the maximum time the mouse was allowed to spend on the device (30 seconds).

Writhing test

To assess chronic pain, animals were assigned to the same groups as in the hot plate test. Writing test was performed on each animal 30 minutes after injections. It included intraperitoneal injection of 10 ml/ kg acetic acid solution (0.7%) counting the number of wrights and duration of abdominal contractions as indices of pain over a period of 30 minutes [31, 32].

Data analysis

In the current study, distilled water and different doses of CEO, Morphine and Diclofenac were considered as independent variables and the number and duration of the animal's writhes, in Writhing test and pain response latency in the hot plate test were taken into account as dependent variables. Regarding the study objectives to compare the effect of CEO, Diclofenac and Morphine on acute and chronic pain in mice, the differences between the data obtained by different groups were statistically analyzed using the stat graph software applying two-way repeated measure ANOVA followed by Bonferroni post test (for data obtained by different groups at different time points in both hot plate and writhing tests), Kruskal-Wallis test (for response latencies of different groups in the hot plate test) and one -way ANOVA followed by Tukey's multiple comparison test (for %MPE demonstrated by different groups during 60-minute hot plate test). The significance level was set at $p < 0.05$.

Results

Hot Plate Test

Average latency in response to the heat stimulus, by different groups of animals, before intervention (0 time point/ baseline), are shown in table 1. Although statistical comparison of these data using Kruskal-Wallis test revealed no significant difference between groups at zero time point ($p>0.05$, Table 1), in order to eliminate the effect of slight differences between the delay in the response of different animals at zero time, the percentage of maximum possible effect (%MPE) was calculated for each animal and these values in different groups were used

for further statistical analysis at 4 time points of 15, 30, 45 and 60 minutes after the intervention,.

Table 1. Statistical measures of response latencies of different groups (in seconds) in the hot plate test before the intervention (n = 8).

Statistics / Groups	Minimum	Maximum	Mean	Std. Error	P value
Distilled water (Control)	3.00	6.00	4.25	0.38	
Morphine sulfate 2 mg/kg	2.50	8.00	5.56	0.64	>0.05
Morphine sulfate 4 mg/kg	2.50	7.00	4.81	0.54	>0.05
Morphine sulfate 8 mg/kg	3.00	9.00	5.38	0.85	>0.05
Diclofenac 10 mg/kg	4.00	8.00	5.03	0.48	>0.05
Diclofenac 20 mg/kg	4.00	7.00	5.11	0.48	>0.05
Diclofenac 30 mg/kg	3.00	7.80	4.91	0.66	>0.05
CEO 125 µg/kg	4.00	8.00	5.60	0.41	>0.05
CEO 250 µg/kg	4.00	7.00	5.65	0.33	>0.05
CEO 500 µg/kg	5.40	7.50	6.33	0.21	>0.05

According to Kruskal-Wallis test, there was no significant diference between groups (p>0.05).
CEO= cinnamon essential oil

Administration of Morphine sulfate induced a dose dependant antinociceptive effect which was prominent at 45 minute time point. %MPE in all Morphine treated groups at this time point demonstrated a significant difference as compared with the normal control group ($p<0.05$, Fig.1). In the case of Diclofenac treated groups, %MPE was significantly greater than the normal control group (17.12 ±6.04 vs. -5.5 ± 3.09, $p<0.05$, Fig. 2) only in maximum dose (30 mg/kg) 15 minutes after the intervention,. Groups receiving doses of 500 and 250 µg/kg CEO revealed a significant difference compared with the normal control group ($p<0.05$, Fig. 3), at 15 minutes after the intervention. In an overall view, %MPE demonstrated by CEO (500 mg/kg) during 60-minute hot plate test was significantly ($p<0.05$) greater than normal control, though it was reported to be less than Morphine 4 and 8 mg/kg , and the same as Morphine 2 and Diclofenac 30 mg/kg ($p>0.05$, Fig. 4).

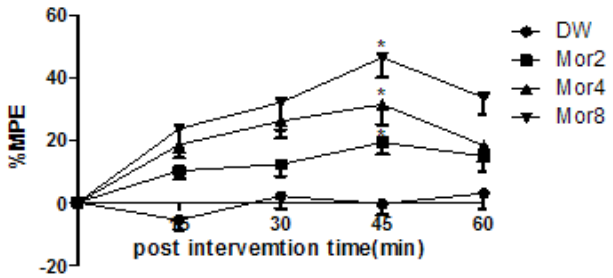

Fig. 1. Percentage of maximum possible effect of Morphine treated groups as compared with normal control group in hot plate test (n=8). According to two-way repeated measure ANOVA followed by Bonferroni post test, * a significant difference was represented ($p<0.05$) as compared to normal control group. DW= Distilled water (Control), Mor=Morphine sulfate

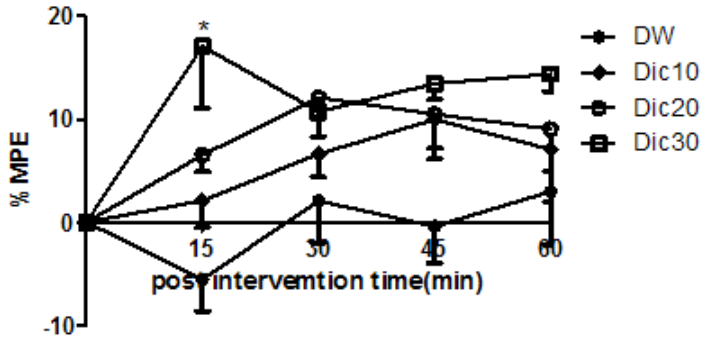

Fig. 2. Percentage of maximum possible effect of Diclofenac treated groups as compared with normal control group in hot plate test (n=8). According to two-way repeated measure ANOVA followed by Bonferroni post test, * a significant difference was represented ($p < 0.05$) as compared to the normal control group. DW= Distilled water (Control), Dic=Diclofenac

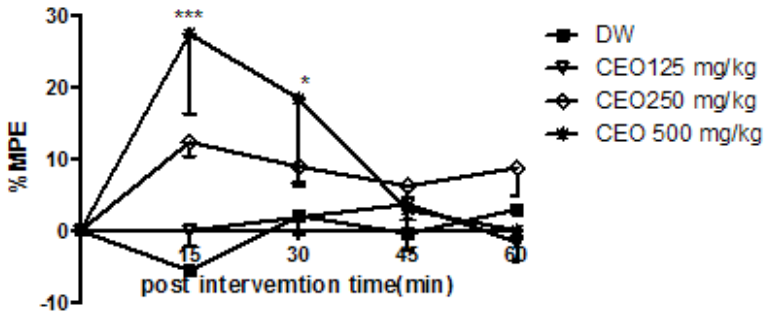

Fig. 3. Percentage of maximum possible effect of CEO treated groups as compared with normal control group in hot plate test (n=8). According to two-way repeated measure ANOVA followed by Bonferroni post test, * amd *** represents a significant difference with $p < 0.05$ and $p < 0.001$ as compared to the vehicle control group. DW=Distilled water (Control), CEO= Cinnamon essential oil

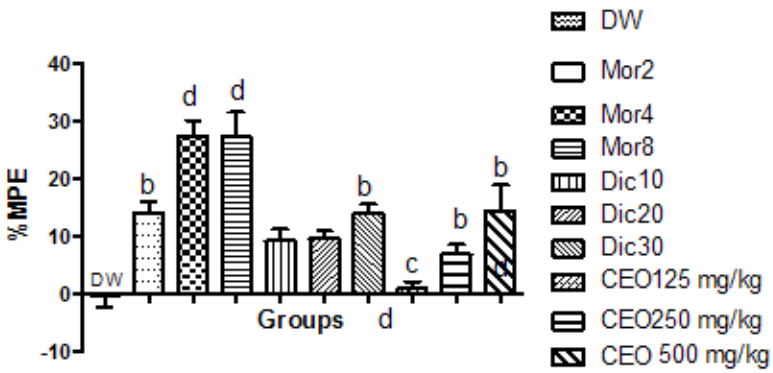

Fig 4. Mean values of percentage of maximum possible effect demonstrated by different groups during 60-minute hot plate test (n=8). According to one-way ANOVA followed by Tukey's multiple comparison test, a significant difference was indicated ($p < 0.05$) as compared with the normal control group, b as compared with the normal control and CEO 125groups, c as compared with CEO 500 group and d as compared with the normal control, CEO 125, CEO 250 and CEO 500 groups. DW= Distilled water (Control), Mor=Morphine sulfate, Dic=Diclofenac, CEO= Cinnamon essential oil

Writhing test

The results related to the number and duration of abdominal contractions in writhing test for 3 subsequent 10-minute periods are shown in Tables 2 and 3, respectively. In this case, the maximum average time of feeling pain response (in seconds) during the 30-minute test belonged to the normal control group (395.2 ± 37.74) and the minimum was related to the dose of 8 mg/kg Morphine (99.0 ± 0.52). At the same time, the mean of wrights maximum number was indicated by the dose of 10 mg/ kg Diclofenac (18.58 ± 2.09) and its minimum value was related to the dose of 8 mg/kg Morphine (0.42 ± 0.19).

Table 2. Mean ± SEM of writhing numbers for 3 periods of 10 minutes in writhing test (n = 8)

Time points	Writhing number								
	1st 10 min		2nd 10 min		3rd 10 min		Overall 30 min		P vs.
Groups	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	DW
Distilled water (Control)	18.38	2.154	20.63	2.625	16.38	0.999	18.46	1.154	
Morphine sulfate 2 mg/kg	9.88	2.715	16.88	2.394	13.88	1.597	13.54	1.395	>0.05
Morphine sulfate 4 mg/kg	3.5	1.871	3.13	2.083	1.38	0.707	2.67	0.936	<0.001
Morphine sulfate 8 mg/kg	0.38	0.375	0.75	0.4119	0.13	0.125	0.42	0.189	<0.001
Diclofenac 10 mg/kg	10.63	2.017	23.63	2.946	21.5	4.036	18.58	2.087	>0.05
Diclofenac 20 mg/kg	8.88	3.204	12.38	2.383	11.38	2.203	10.88	1.485	<0.001
Diclofenac 30 mg/kg	4.88	2.133	7.5	2.625	9.38	3.07	7.25	1.505	<0.001
CEO 125 µg/kg	2.75	0.7008	3	0.6268	2.63	0.73	2.79	0.381	<0.01
CEO 250 µg/kg	3.25	1.426	4	0.8889	4.75	0.826	4	0.602	<0.001
CEO 500 µg/kg	0	0	2.25	0.921	1.25	0.369	1.17	0.382	<0.001

P values are given according to two-way repeated measure ANOVA followed by Bonferroni post test.
CEO=Cinnamon essential oil

In this test, the mean duration of abdominal constrictions in all test groups, as well as the mean writhes number for positive control 1 (receiving doses of 4 and 8 mg/kg of Morphine) and positive control 2 (receiving doses of 20 and 30 mg/kg Diclofenac), were considerably less than the normal control group ($p<0.05$).

Table 3. Mean ± SEM of writhing duration (in seconds) for 3 periods of 10 minutes in writhing test (n = 8)

Time points (min) / Groups	Writhing duration								PV/DW
	1st 10 min		2nd 10 min		3rd 10 min		Overall 30 min		
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	
Distilled water (Control)	167.9	42.82	497.9	22.8	519.9	23.96	395.23	37.74	
Morphine sulfate 2 mg/kg	62.63	29.65	140.4	35.31	94.25	21.98	99.09	17.58	<0.001
Morphine sulfate 4 mg/kg	11.13	6.802	11.38	9.159	5.625	3.396	9.38	3.832	<0.001
Morphine sulfate 8 mg/kg	1.75	1.75	0.875	0.4407	0.125	0.125	0.92	0.5926	<0.001
Diclofenac 10 mg/kg	44	28.36	209.5	48.44	171.8	42.76	141.77	25.6	<0.001
Diclofenac 20 mg/kg	45.25	11.55	88.5	35	79.25	31.07	71	17.86	<0.001
Diclofenac 30 mg/kg	17.63	8.93	94.25	41.73	79.5	32.89	63.79	18.51	<0.001
CEO 125 µg/kg	174.4	37.32	307.1	56.58	262.5	45.28	248	32.15	<0.01
CEO 250 µg/kg	92.13	35.07	200.9	62.89	339.4	65.49	210.81	34.34	<0.001
CEO 500 µg/kg	0	0	98.38	33.46	231.3	73.19	109.89	32.36	<0.001

P values are given according to two-way repeated measure ANOVA followed by Bonferroni post test.
CEO=Cinnamon essential oil

Since the duration of abdominal cramps during each contraction is different every time, the total duration of contractions seems to be more appropriate measure in order to compare the intensities of abdominal pain responses in different groups. The duration of abdominal constrictions in the normal control group increased with time, and it reached its maximum at the third 10 minutes after the administration of acetic acid. All doses of Diclofenac reduced the severity of abdominal contractions as compared to the normal control group, except for the first 10 minutes after a dose of 10 mg/kg, which was not proved to be significant. It is worth mentioning that in all other periods, the differences were held to be significant ($p<0.05$). The analgesic effect of all doses of Diclofenac was demonstrated to be more significant on the third 10 minutes.

All doses of Morphine in all 3 time courses significantly decreased the severity of abdominal contractions as compared to the control group, except for the first 10 minutes after a dose of 2 mg/kg. The analgesic effect of Morphine doses was more obvious in the 3rd 10 time point.

In the groups receiving different doses of CEO, the intensity of abdominal cramps in the first 10 minutes was reported to be at the least level, which increased with time, though in all cases, the intensity of contractions was demonstrated to be less than the normal control group. This pain relief in the group receiving 500 µg/ kg, at any time and for doses of 250 and 125 µg/ kg, in the 2nd and 3rd periods was significant as compared to the normal control group, though no significant difference was observed between these groups and the groups receiving different doses of Morphine or Diclofenac.

Discussion

Writhing and hot plate tests are commonly applied in order to relatively evaluate the effects of acute and chronic pain killers. High temperatures in the hot plate test induce an acute pain used to evaluate the analgesic effect of substances acting on the central nervous system, particularly through the opioidergic system, whereas the pain caused by intraperitoneal injection of acetic acid is a chronic pain, used to evaluate the central and peripheral effects of analgesics [31, 32]. According to the findings of the present study, CEO has demonstrated significant antinociceptive effects in both tests. This suggests that some of the compounds forming the oil affect both the acute and chronic pain.

As the literature reviews revealed, there was no publication regarding the antinociceptive effect of CEO, except for a clinical trial study, that was effective in reducing inflammation and pain caused by traumatic injuries and burns using cold compresses of cinnamon extract [33]. In another study in 2004, it was proposed that adding cinnamon to RG- O1 gel increases the efficacy of these gels on gentle tonic pain such as osteoarthritis and rheumatism [19]. As the findings of another study in 2005 demonstrated, cinnamon extract inhibited tumor necrosis factor alpha and cyclooxygenase 2, thereby inhibiting the production of prostaglandin E [20]. On the other hand, *Cinnamomum Zeylanicum* compounds such as Cinamaldehyde, Eugenol and terpene derivatives are said to be analgesic, sedative and anti-inflammatory compounds [21, 22, 27, 28]. Cinnamaldehyde, as a major constituent of CEO, has been demonstrated to exert its effect through stimulating the sympathetic nervous system via activating the transient receptor potential A1 cation channel and thereby contributing to inhibition of pain transmission in the central nervous system [34].

Eugenol, as a second major constituent of CEO, can inhibit arachidonic acid metabolism leading to inhibition of histamine release and cyclooxygenase-2

expression. As a result, inflammation is inhibited [24, 35]. Furthermore, the active components of cinnamaldehyde and cinnamic acid are held to be cardio protective due to their ability to produce nitric oxide as well as the associated anti-inflammatory property [34, 36]. The results of some previous studies suggest that *Cinnamomum Zeylanicum* and its compounds can affect the central nervous system and reduce pain transmission or sensation [34, 37, 38]. Compounds from cinnamon which activate nitric oxide synthase, and hence release of NO as a recognized mediator of pain seem to be involved in central inhibition of acute and chronic pain [39, 40, 41]. Eugenol also acts centrally for its analgesic effects via inhibiting the entry of calcium into the cells, thereby inhibiting the release of neurotransmitters from pain afferent fiber terminals which have been implicated in the transmission of pain messages from the dorsal horn of the spinal cord [42, 43]. Research on the monoterpene linalool, as a composition of Cinnamon, has revealed that the compound exhibits its analgesic effects via the opioid receptors [44]. Moreover, Linalool induces the inhibitory potential in neurons of the central nervous system via opening potassium channels [45].

Conclusion

Overall, the findings of this study concluded that CEO possesses anti-inflammatory and antinociceptive properties resulting in a greater inhibition of inflammatory pain in a high dose, such as pain in the writhing test, which showed a similar potency to 30 mg/kg Diclofenac. The analgesic effect of CEO was less than Morphine sulfate. Although the chemical composition of CEO in the current study was not determined, according to references, major constituents of cinnamon such as Cinamaldehyde and Eugenol may be involved in CEO antinociceptive effect which needs to be further investigated.

Conflict of interest

The authors declare no conflicts of interest.

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