# Repeated systemic administration of the cinnamon essential oil possesses anti-anxiety and anti-depressant activities in mice

Reyhaneh Sohrabi [1], Nasim Pazgoohan [1], Hasan Rezaei Seresht [2], Bahareh Amin [3]*

[1] Research Committee, Sabzevar University of Medical Sciences, Sabzevar, Iran
[2] Traditional and Complementary Medicine Research Center, Sabzevar University of Medical Sciences, Sabzevar, Iran
[3] Cellular and Molecular Research Center, Department of Physiology and Pharmacology, Faculty of Medicine, Sabzevar University of Medical Sciences, Sabzevar, Iran

| A R T I C L E   I N F O | A B S T R A C T |
|---|---|
| | *Objective(s):* The present study aimed to evaluate the putative antidepressant and anti-anxiety effects of the cinnamon essential oil when administered acute (for 3 doses) and sub-acute (for 14 days) to mice.<br>*Materials and Methods:* In an acute experimental study, forced swim test (FST) was conducted to evaluate the antidepressant-like behavior of animals treated with the intraperitoneal (IP) essential oil of cinnamon in triple doses (0.5, 1, and 2 mg/kg). In a sub-acute study (14 days in 24-hr intervals) antidepressant-like effects of essential oil (0.5, 1, and 2 mg/kg) with the same route were assessed in FST and tail suspension test (TST). Anti-anxiety and motor activities were evaluated using elevated plus-maze (EPM) and open field tests, respectively. Determination of different constituents within the sample oil was via gas chromatography–mass spectrometry (GC–MS) analysis.<br>*Results:* Repetitive administration of cinnamon essential oil (0.5, 1, 2 mg/kg) during 14 days significantly decreased the time of immobility in both FST and TST as compared to the control group. Mice treated with oil at the dose of 2 mg/kg spent a longer time and had more entries into the open arms of EPM as compared with the vehicle-treated ones. According to GC-MS analysis, 46 chemical compounds were identified in the studied cinnamon essential oil with the main constituent being trans-cinnamaldehyde (87.32%).<br>*Conclusion:* Cinnamon essential oil might be used as an adjunctive therapy in improving symptoms of depressive and anxiety disorders. However, dose-response effects need further evaluation. Trans-cinnamaldehyde might be responsible for the beneficial effect observed. |

## Introduction

Depression is a major chronic psychiatric disorder affecting nearly 21% of the world population and imposes a substantial health burden on the society (1). People with a depressed mood are characterized by despair, loss of interest in daily working and social relationship, sadness, anxiety, hopelessness, helplessness, and guilt (2). There are three main kinds of classical antidepressants in clinical practice, including tricyclic antidepressants (amitriptyline, nortriptyline, and desipramine), selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, sertraline, citalopram, and monoamine oxidase inhibitors (MAOIs) including moclobemide and tranylcypromine. Although approved antidepressant drugs are effective, a significant number of people do not efficiently respond. In addition, these drugs are accompanied with many adverse effects (3, 4). Accordingly, there is a need for the development

of new drugs with more efficacies and less adverse effects. Natural products displaying antidepressant effects are of great interest and may be important sources of new antidepressant drugs (5, 6).

Cinnamon (sweet wood) the brown bark of *Cinnamomum verum* (true cinnamon tree or Ceylon cinnamon tree), belonging to the Lauraceae family, is native to Southern India and Sri Lanka. Since ancient times cinnamon has been commonly used as a spice and flavoring material for desserts, candies, chocolate, etc.; it has a long history as a medicine, as well. Medieval physicians used cinnamon to treat a variety of disorders including headaches, neuralgia, gastritis, coughing, hoarseness, sore throats, etc. (7). In many experimental as well as clinical studies, cinnamon has been demonstrated to possess anti-inflammatory (8, 9), anti-oxidant (10), anti-diabetic (11, 12) anti-microbial (13), analgesic (14) and wound-healing (15) properties. Anticancer (16), lipid-lowering (17), and cardiovascular-

*Corresponding author:* Bahareh Amin. Cellular and Molecular Research Center, Department of Physiology and Pharmacology, Faculty of Medicine, Sabzevar University of Medical Sciences, Sabzevar, Iran. email: amin.bahareh@gmail.com

disease protective effects of this compound have also been investigated (18). In addition, cinnamon has shown promising effects against neurological disorders, such as Parkinson's and Alzheimer's diseases (19, 20).

The specific aim of this study was to examine whether the essential oil obtained from cinnamon bark has anti-anxiety and/or antidepressant-like properties in acute (triple doses) or sub-acute regimen (14 days), in behavioral models of anxiety and depression in mice.

## Materials and Methods

### Animals

Male albino mice (20–30 g) obtained from the Animal House of Sabzevar University of medical Sciences, were used in this study. Food and water were provided *ad libitum* in colony rooms with 12/12 hr light/dark cycle at 22±2 °C. The procedures in this study were performed in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (21) and approved by Sabzevar University of Medical Sciences (ethical no: ir.medsab.rec.1394.16).

### Materials

Cinnamon volatile (essential) oil was extracted from cinnamon wood in our laboratory and administered intraperitoneally (0.5, 1, and 2 mg/kg) in acute treatment. Cinnamon was administered same as the previous protocol in the sub-acute administration for 14 days. Cinnamon was solved in normal saline + Tween 80 (1%). The solution was freshly prepared before administration. Fluoxetine (Dr. Abidi Pharm Co, Iran) and desipramine (Pars Daru Co, Iran) were used as positive control drugs in depressive behaviors. Diazepam (Darupakhsh Co. Iran) was used as a positive control drug in the elevated plus maze test. Dosage selection was based on previous studies (22, 23).

### Preparation of oil

Dried bark parts of cinnamon (50 g) were finely ground and subjected to a Clevenger-type apparatus for 4 hr to extract the oil by the hydrodistillation method. The total yield of volatile oil was 1% (W/W). The oil was dried over anhydrous sodium sulfate and stored at 4°C before analysis (24).

### Gas chromatography–mass spectrometry (GC–MS) analysis

The oil analysis was carried on a GC7890N AGILENT & MS 5975 (EI mass detector), in the following conditions: chromatography was achieved using a (5%-phenyl)-methyl polysiloxane HP-5MS column (30 m × 0.25 mm, 0.25 mm film thickness) with a helium carrier gas, adjusted to a linear velocity of 1 ml/min. the column was with a 50:1 split ratio. The injector temperature was regulated at

260 °C. also, The column oven temperature was maintained at 60 °C for 4 min and programmed to 100 °C at 3 °C/min for 2 min and then to 250 °C at 6 °C/min for 6 min; electron energy at 70 eV. Positive ions were observed while the analyzer was scanned from mass 50 to 550. The Kovats indices were determined for all volatile constituents using a mixture of homologous series of n-alkanes C9–C23 on HP-5MS column. The components were identified by comparison of their mass spectra with those of the NIST 5 mass spectra library. The Kovats indices were calculated using by following formula (25).

$$I = 100 \left( n + \frac{tc\text{-}tn}{tN\text{-}tn} \right)$$

Where: I=Kovats retention index, tn=the number of carbon atoms in the smaller n-alkane, tN=the number of carbon atoms in the larger n-alkane, and tc=the retention time.

### Behavioral study

#### Acute treatment

In the acute dose study, groups were as follows: Group I: Vehicle control group (normal saline plus Tween 80 (1%); Group II-IV: cinnamon essential oil (0.5, 1, and 2 mg/kg); Group V: Desipramine 10 mg/kg; Group VI: Fluoxetine 10 mg/kg.

All drugs were given intraperitoneally, 1, 8, and 24 hr before the test. In the acute study, antidepressant-like effects were assessed using the forced swim test (FST). Locomotor activity and anxiety-like behaviors were measured by the open field test and elevated plus maze, respectively.

#### Sub-acute treatment

In the sub-acute study, groups were as follows: Group I: Vehicle control group (Tween 80+normal saline); Group II-IV: cinnamon essential oil (0.5, 1, and 2 mg/kg) for antidepressant activity; Group V-VII: cinnamon essential oil 0.5, 1, and 2 mg/kg for antianxiety activity; Group VIII: Desipramine 10 mg/kg; Group IX: Fluoxetine 10 mg/kg; Group X: Diazepam 2 mg/kg.

In this regimen, drugs were given once daily during a period of 14-day, through the same route as in the previous regimen. Antidepressant-like effects were evaluated in FST and tail suspension test (TST). Locomotor activity and anxiety-like behavior were measured using the open field test and elevated plus-maze, respectively.

#### Forced swim test

TFST is one of the most widely acceptable rodent behavioral models used for assessing depression and antidepressant-like efficacy of new drugs. One hour after the last treatment of acute study or 24 hr after

**Table 1.** Chemical composition of cinnamon in the essential oil of cinnamon bark

| No. | Compound | Retention time | Concentration (%) | KI (Kovats retention index) | Class |
|---|---|---|---|---|---|
| 1 | Benzenepropanal | 15.54 | 0.19 | 1151 | PC |
| 2 | Cis-cinnamaldehyde | 18.08 | 0.98 | 1206 | PC |
| 3 | 2-Methyl-3-phenyl-propanal | 19.04 | 0.30 | 1225 | PC |
| 4 | Trans-cinnamaldehyde | 21.30 | 87.32 | 1270 | PC |
| 5 | Cinnamaldehyde diethyl acetal | 26.39 | 2.34 | 1385 | PC |
| 6 | Calamenene | 30.73 | 0.35 | 1505 | MH |
| 7 | o-Methoxycinnamaldehyde | 31.08 | 1.88 | 1516 | PC |
| 8 | Alpha-longyi pinene | 33.60 | 0.24 | 1596 | SH |
| 9 | δ-Cadinene | 34.02 | 0.45 | 1610 | SH |
| 10 | t-cadinol | 34.46 | 0.81 | 1625 | SH |
| 11 | Copaene | 34.59 | 0.46 | 1629 | SH |
| 12 | Alpha-cadinol | 34.83 | 0.18 | 1638 | SH |
| 13 | Beta-tumerone | 35.17 | 3.31 | 1649 | PC |
| 14 | Alpha-bisabolol | 35.76 | 0.34 | 1670 | SH |
| 15 | Alpha-tumerone | 36.20 | 0.38 | 1685 | PC |
|  | Total identified |  | 99.55 |  |  |

PC, phenolic compounds; SH, sesquiterpene hydrocarbons; MH, monoterpene hydrocarbons

tTST of sub-acute study, mice were individually placed in an inescapable transparent cylinder (15 cm in diameter), filled with 35 cm of room temperature water, such that the animals could not touch the bottom of the container with their hind paws or their tails. Immobility of animals was recorded during 6 min and the first 2 min was considered as trial (pre-test) (26).

*Tail suspension test*

TST was performed one day before FST in the sub-acute study. In this test, the mice were suspended by their tails, using tape, from a wire at the height of 33 cm. In such a position the animal was not able to escape or hold onto nearby surfaces. The absence of initiated movements was defined as immobility and recorded during a short-time period of 6 min and the first 2 min was considered as trial (pre-test). Mice were returned to the box after each animal was tested (27).

*Open field test*

A wooden (30×30 cm) box with sidewalls of 40 cm was used to measure locomotor/exploratory activity of animals in a quiet environment. After passing 45 min of the last treatment of the acute study or after the 14th day of sub-acute study, animals were placed in the center of box and number of squares crossed with four paws of the animal was recorded. Each trial lasted 5 min (28).

*Elevated plus maze*

For conducting this test, different groups of animals received normal saline or essential oil for 14 days, and were individually placed in the center of a wooden cross elevated 40 cm above the floor. This apparatus consisted of two open (30×5 ×0.25 cm) and two closed arms (30×5×40 cm) as described previously (29). At the time of the experiment, each animal was placed in the center of apparatus, facing one of the open arms. Anxiety was evaluated during 5 min by recording the entries to open arms/total entries and the time spent in the open arms/time spent in all arms of the apparatus.

For all three tests, after ending each trial session, fecal boli and urine were removed and surfaces were cleaned with 70% ethanol to start the next session.

*Statistical analysis*

SThe SPSS software package (version 17; Chicago, IL, USA) was used for statistical analysis. All data were expressed as the mean±standard error of the mean (SEM). A one-way ANOVA test at $P<0.05$ was considered significant.

## Results
### Chemical composition of the essential oil

The hydrodistillation of the bark of *C. verum* gave a yellowish essential oil with 1% yield. Among the 15 components that were identified, the main component was trans-cinnamaldehyde (87.32%). The other considerable constituents were beta-tumerone (3.31%), *O-* cinnamaldehyde diethyl acetal (2.34%), and o-Methoxycinnamaldehyde (1.88%) (Table 1). In this study, the oil consisted mainly of phenolic compounds (96.7%), sesquiterpene hydrocarbons (2.5%), and small amounts of monoterpene hydrocarbons (0.35%) (Figure 1).

### Effect of cinnamon essential oil on the forced swimming test

There were no differences among groups in the acute study when essential oil was administered three times as mentioned in the methods section (data not shown).

Time spent immobile with 0.5, 1, and 2 mg/kg of cinnamon essential oil for 14 days was significantly less than that in the vehicle-treated mice (Figure 2A; $P<0.001$). Desipramine and fluoxetine (10 mg/kg) as the reference drugs decreased immobility as compared with the vehicle-treated group during 5 min observation.
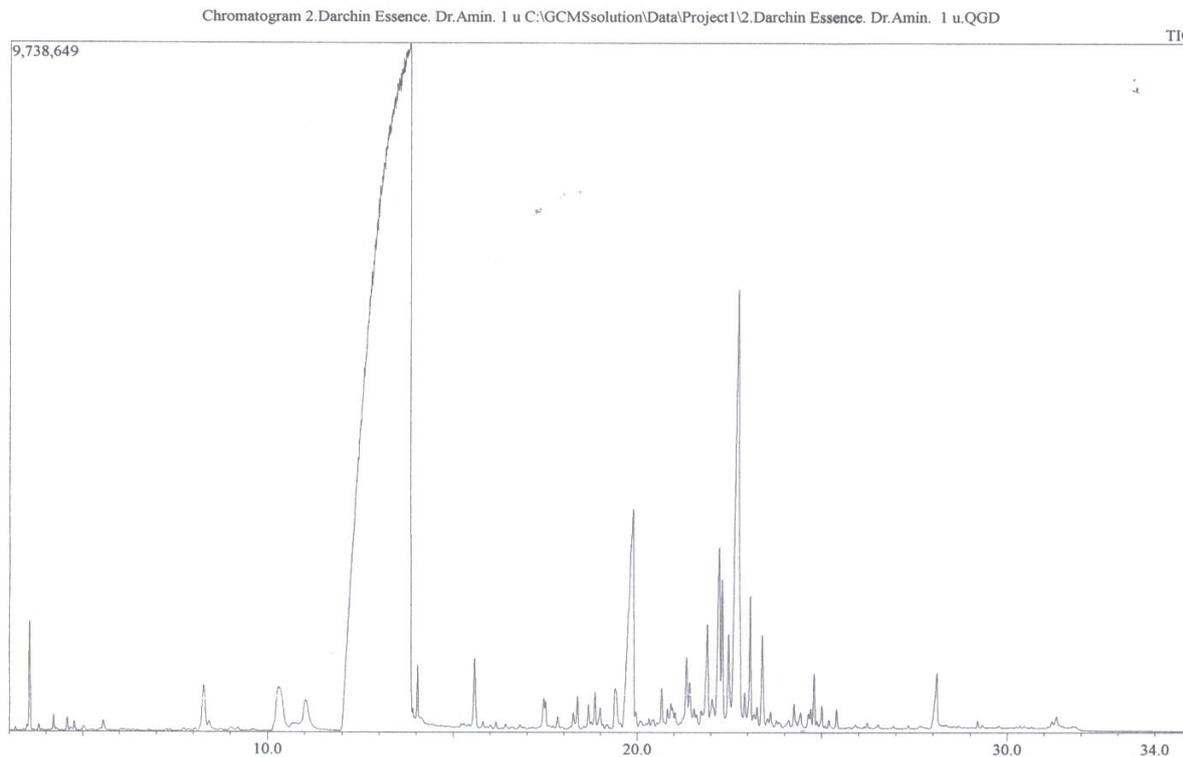
Chromatogram 2.Darchin Essence. Dr.Amin. 1 u C:\GCMSsolution\Data\Project1\2.Darchin Essence. Dr.Amin. 1 u.QGD



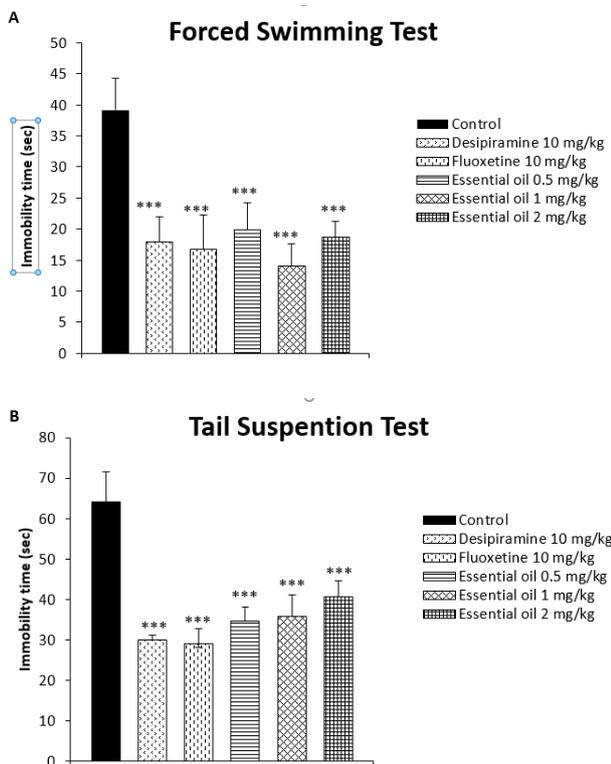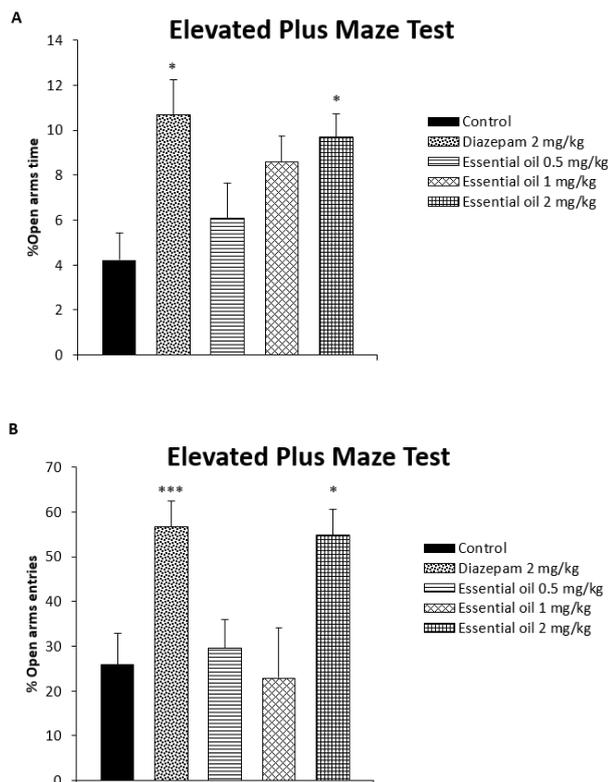**Figure 1.** Gas chromatography–mass spectrometry (GC–MS) fingerprint of cinnamon essential oil



**Figure 2. A:** Time (sec) spent immobile in the forced swimming test (FST) (mean±SEM) and **B:** in the tail suspension test (mean±SEM) in mice during a 6-2=4 min test. Mice were injected with vehicle control, essential oil (0.5, 1, and 2 mg/kg, IP), fluoxetine, and desipramine (10 mg/kg, IP), for a 14 day treatment. *** $P<0.001$ is significantly different from the control group

### Effect of cinnamon essential oil in the tail suspension test

The data of behavioral observation during the suspension of the tail from wire is presented in Figure 2B. Mice treated with essential oil (0.5, 1, and 2 mg/kg) spent significantly less time as compared with those who received vehicle ($P<0.001$). Time spent immobile was significantly decreased in desipramine and fluoxetine (10 mg/kg, as the reference drugs) treated groups ($P<0.001$).

### Effect of cinnamon essential oil in the elevated plus maze test

As indicated in Figures 3A and 3B, one-way ANOVA of the data obtained from the cinnamon essential oil at the dose of 2 mg/kg showed a significant increase in the percent of time spent in the open arms/time spent in all arms or the percent of entries to open arm/total entries in mice placed at the center of EPM, in comparison with the vehicle-treated control group ($P<0.05$). The diazepam-treated (2 mg/kg, IP) positive control group showed significantly more time spent in the open arms/ time spent in all arms ($P<0.05$), and more entries to open arms/ all arms ($P<0.001$), compared with the vehicle-treated control group.

A

**Elevated Plus Maze Test**
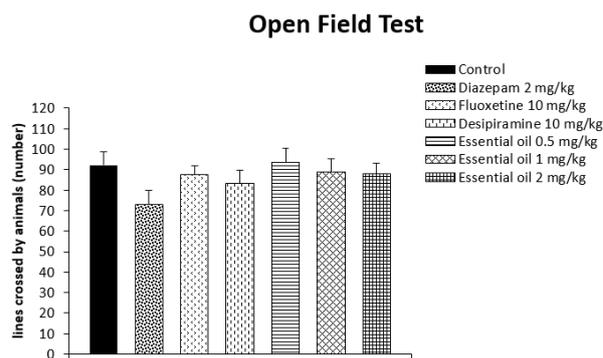


B

**Elevated Plus Maze Test**



**Figure 3.** A: Percent of time spent in the open arms to time spent in all arms and B: Percent of entries to open arm to total entries in mice placed at the center of the plus-maze and given a 5-min test. Mice were injected with vehicle control, essential oil (0.5, 1, and 2 mg/kg, IP), diazepam (2 mg/kg, IP), for 14 days. * $P<0.05$, *** $P<0.001$ is significantly different from the control group

### Effect of cinnamon essential oil in the open field test

As shown in Figure 4, the total squares crossed by animals treated with cinnamon or fluoxetine/ desipramine was not different from those receiving the vehicle during a 5-min observation period in the open field test. There was a reduction in the number of squares crossed by diazepam-treated animals, although it did not reach a significant difference with the control animals.

## Discussion

Our results in this study demonstrated anti-depressant-like activity of cinnamon in mice treated with the essential oil of cinnamon (0.5, 1, 2 mg/kg) with shorter duration of immobility in both FST and TST as compared to the control animals, during a 14-day regimen. These tests frequently used in animal studies, force animals to combat two different stressful situations (floating or hemodynamic stress) and show a difference in some cases (27). Although oil at the three applied doses showed antidepressant-like activity data of dose response was not the same as in FST, it showed a U-shape pattern of activity, while in TST it had a linear relationship. The same results were reported in the Bai *et al.* study on the antidepressant effect of imipramine

**Open Field Test**



**Figure 4.** Number of lines crossed by the four paws of the animal (mean±SEM) at the open field apparatus during a 5-min test. Mice were injected with vehicle control, essential oil (0.5, 1, and 2 mg/kg, IP), diazepam (1 or 2 mg/kg, IP), during a 14-day treatment

(30). It seems that involved neurochemical pathways of these famous behavioral tests are not the same.

In the EPM test, based on natural avoidance of mice for open area, animals spent more time in the closed area. However, animals receiving cinnamon 2 mg/kg for 14 days exhibited an anti-anxiety like effect by spending more time and more entries to the open arm of EPM.

Locomotor activities of animals decreased but had no significant difference in relation to the control group in the open field test. Consequently, cinnamon seems to have no effect on overall locomotion compared with vehicle-treated controls. Reference drug, diazepam belonging to benzodiazepines has been used for anxiety disorders; however, sedative, amnesic and dependence-inducing characteristics in repeated administrations limit its safe prescription (31).

Today, the role of neuroinflammation and oxidative stress has been highlighted in the pathogenesis of psychologic disorders such as anxiety and depressive disorders (32, 33).

Trans-cinnamaldehyde, an organic compound that gives cinnamon its flavor and odor is responsible for many biological activities observed with cinnamon. It has been reported that cinnamaldehyde constitutes 65 to 80% of cinnamon bark (34, 35). GC-MS analysis indicated that polyphenols contents were higher than other constituents in the sample essential oil of cinnamon and main polyphenolic compounds measured were trans-cinnamaldehyde, turmerone, and *O-* cinnamaldehyde diethyl acetal (87.32%, 3.31%, and 2.34%, respectively). Anti-inflammatory effect of turmerone has been reported to be via microglia activation inhibition (36). Trans-cinnamaldehyde represented neuroprotective activity in a model of ischemia/reperfusion (I/R)-induced brain injury in rats via suppressing protein levels of inflammatory mediators such as inducible nitric oxide synthase (iNOS), cyclooxygenase 2 (COX-2), and nuclear factor

kappa B (NF-κB) signaling pathway (37). In an investigation by Sahib, antidiabetic activity of cinnamon in poorly controlled diabetic patients was associated with increased serum levels of antioxidants such as glutathione, superoxide dismutase, and decreased levels of malondialdehyde as a marker of lipid peroxidation in the cinnamon treated group (11).

Consequently, one of the potentially involved pathways in antidepressant and antianxiety activity might be antioxidant and anti-inflammatory properties of cinnamon, however, it needs further experimental studies to elucidate this hypothesis.

Another mechanism playing an important role in the molecular neurobiology of depressive disorder is decreased monoamine function in the brain, known as monoamine hypothesis (38). Intravenous cinnamaldehyde increased adrenaline secretion via activating thermosensitive transient receptor potential (TRP) channels, mainly expressed in the sensory neurons, and induced secretion of adrenaline via the CNS (39).

An important factor in the pathogenesis of major depression is the reduction of neurotrophic factors such as the brain-derived neurotrophic factor (40). Cinnamon and its metabolite sodium benzoate have been shown to increase the level of neurotrophic factors such as BDNF, which may be of benefit for the treatment of depressive disorders (41).

Although cinnamon is a safe drug, a report of intraoral allergy to cinnamic aldehyde has been reported (40, 41). As a result, it should be considered with caution in patients with increased sensitivity.

According to a meta-analysis study, combination therapy has shown better outcomes in the treatment of depressed and anxious patients (42), adding cinnamon to conventional drugs would be of worth in future experimental and clinical studies for add-on or single therapy of depressed patients.

## Conclusion

Cinnamon essential oil could have beneficial effects in improving depressive and anxiety disorders and might be used as an adjunctive therapy to conventional drugs. However, dose-response effects need further evaluation. Trans-cinnamaldehyde might be responsible for the beneficial effect observed with the essential oil of cinnamon.

## Acknowledgment

## Conflicts of interest

There are no conflicts of interest in this study.

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