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THE EFFECT OF CINNAMON ZEYLANICUM ESSENTIAL OIL ON TREATMENT OF PATIENTS WITH UNIPOLAR NONPSYCHOTIC MAJOR DEPRESSIVE DISORDER TREATED WITH FLUOXETINE

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ABSTRACT

Background: One of the most common psychiatric disorders that adversely affects quality of life and functioning is Major Depressive Disorder. Given the side effects of antidepressants, medicinal plants have attracted attention in recent years, and animal studies have revealed the antidepressant effects of Cinnamomum zeylanicum essential oil. The study is aimed at investigating the effect of this essential oil on treatment of patients with MDD treated with fluoxetine.
Methods: In this double-blind clinical trial, 60 patients were randomized to three groups of 20 each: fluoxetine (20mg) +placebo daily, fluoxetine (20mg) +5 oral drops of Cinnamon essential oil daily, and fluoxetine (20mg) +15 oral drops of Cinnamon essential oil daily. At baseline and the weeks 2, 4, 6 and 8, a checklist of drug side effects and Beck Depression Inventory (BDI) was completed by all the patients. Data were analyzed by the SPSS 21.
Results: The mean (±standard deviation) score on BDI at baseline was 32.50±9.37 in fluoxetine+placebo group, 26.31±7.21 in fluoxetine+C. zeylanicum (5 drops) group, and 31.45±10.01 in fluoxetine+C. zeylanicum (15 drops) group. In the week 2 of treatment, the mean (±standard deviation) score on BDI was 26.90±8.36 in fluoxetine+placebo group and 18.36±4.62 in fluoxetine+C. zeylanicum (5 drops) group, representing a significant decrease ($p<0.01$) due to treatment with C. zeylanicum, but the score on BDI was not significantly different between fluoxetine+C. zeylanicum (15 drops) group (22.65±9.32) and the other two groups. In the weeks 6 and 8 of treatment, treatment with fluoxetine and C. zeylanicum (5 and 15 drops) caused a significant decrease in BDI score when compared to fluoxetine+placebo group ($p<0.01$). There was no significant difference in sexual and gastrointestinal complications and weight changes among three groups.
Conclusion: Cinnamon essential oil caused improvement of MDD but this effect was not dose dependent.

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Introduction

Major depressive disorder (MDD) is one of the most common psychiatric disorders with approximately 17% prevalence. Women are almost twice as likely to develop depression. MDD is characterized by two weeks of depressed mood or lack of pleasure, with several symptoms including changes appetite or weight changes, sleep or activity changes, decreased energy, feelings of guilt, impaired concentration and recurrent thoughts of death or suicidal ideation. MDD can lead to severe drop in function and is associated with 15% risk of suicide [1].

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The exact causes of depression remain unknown but this disorder is thought to be the result of interaction between genetic, biological and psychosocial factors [2]. Current hypotheses are related to the roles of the monoamine system, circadian rhythm, immune system disorders, hypothalamic–pituitary–adrenal (HPA) axis dysfunction, and structural or functional abnormalities of emotional circuits in brain [3].
According to the monoamine hypothesis of depression, inadequate activity of monoamine neurotransmitters, such as serotonin, noradrenaline and dopamine, play important roles in depression. Initial antidepressants have also been developed based on reuptake inhibition of these neurotransmitters. These drugs lead to increase in norepinephrine, serotonin and dopamine in the synaptic space, thereby stimulating the post-synaptic neurons and causing therapeutic effects [4].
Treatments for depression can be divided into pharmacological and non-pharmacological. In moderate and severe cases of depression, the use of antidepressants is the best choice. In recent decades, these medications have been quantitatively and qualitatively developed but numerous adverse side effects may occur due to their long-term use [5].

Various medications for depression have entered the market including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, serotonin- norepinephrine reuptake inhibitor, and monoamine oxidase inhibitor [1]. Fluoxetine is one of the most widely used SSRIs. Fluoxetine inhibits serotonin reuptake by pre-synaptic cells and thus increases serotonin concentration. Fluoxetine is one of the oldest SSRIs that causes comparatively very few side effects. One of the most prominent features of fluoxetine is that it causes lower drowsiness compared to other antidepressants, but certain complications such as insomnia, agitation, and decreased appetite due to its use have been reported [6].
Given the side effects of chemical drugs and the lack of acceptance of these drugs by some patients, and because psychotherapy is time-consuming and costly, extensive studies are being conducted to seek out herbal remedies with comparatively fewer or no side effects [7].
The genus Cinnamomum includes aromatic species belonging to the family Lauraceae [8]. Bark is the pharmaceutical part of this plant [9].
In Iranian traditional medicine, Cinnamomum zeylanicum has a warming and dry nature. Iranians believe that cinnamon is refreshing, curative of some infections and antidote of mineral, animal and vegetative toxins and strengthens the heart, brain, liver and stomach [10], and that C. zeylanicum is used to treat several diseases such as diabetes, metabolic syndrome and insulin resistance and to control certain conditions such as pain and hyperlipidemia [11, 12, 13, 14, 15].
Investigations have indicated that the main compounds isolated from C. zeylanicum essential oil are eugenol, linalool and cinnamaldehyde comprising 82.5% of the compounds of this essential oil [16]. These compounds significantly decrease the lipid peroxidation and increase the glutathione content and antioxidant activity of the brain and liver in rat [17] In the human subjects, consumption of C. zeylanicum tea also significantly reduced serum lipid peroxidation [18]
A study showed that inhaled C. zeylanicum improved mood, increased consciousness and reduced anxiety, fatigue and anger in humans [19]. C. zeylanicum extract has been reported to exhibit fluoxetine-like antidepressant effects in mouse, attributed to the serotonergic and antioxidant properties of this extract [20, 21]. An animal study has also shown that oral consumption of C. zeylanicum improves cognitive functions and subsequently memory and learning [22].
Although the antidepressant effects of various herbal drugs including Ginkgo biloba, mint, Hypericum perforatum, Panax ginseng and Lavandula officinalis have already been studied with animal models and human subjects [19,23, 24, 25, 26], C. zeylanicum seems to be useful to improve depression symptoms. Because no study with human subjects has yet been conducted to investigate this issue and fluoxetine is widely used as an antidepressant medication, we conducted a double-blind clinical trial to investigate the combined effects of C. zeylanicum and fluoxetine in patients with MDD so that the recommended doses of fluoxetine and related side effects could be reduced in these patients.

Materials and Methods

The protocol of this double-blind clinical trial was approved by the Research and Technology Deputy and the Ethics Committee of Shahrekord University of Medical Sciences (approval code: IR.SKUMS.REC.1395.295) which was conducted in 2017. A total of 60 people with depression referring to a clinic diagnosed with unipolar non-psychotic MDD by a psychiatrist and fulfilling inclusion criteria were studied. The purposes of the study were first explained to them and they were then enrolled if they completed informed consent form, and randomized to three groups.
The inclusion criteria were being 18-60 years old and having diagnosis of unipolar non-psychotic MDD made by a psychiatrist according to the data drawn from clinical interviews and Beck Depression Inventory (BDI).
Exclusion criteria were suffering from other psychiatric disorders, certain events such as death of a relative, divorce, marriage during the study (major stressor), taking other psychiatric medications, psychosis, mental retardation, any physical illness, substance abuse, taking antidepressant within the past six months, not volunteering to participate in the study, intolerable side effects for patient, suffering from diabetes and taking anti-diabetic drugs, pregnancy, and lactation.
Before participants provided informed consent to participate in the study, sufficient explanations had been given to them to observe ethical considerations.
Participants were randomized to three groups of 20 each as follows: 1) Oral fluoxetine (20mg)+oral drops of distilled water (placebo) each day; 2) oral fluoxetine (20mg)+5 oral drops of C. zeylanicum essential oil (Zardband Co., Iran) each day; and 3) oral fluoxetine (20mg)+15 oral drops of C. zeylanicum essential oil (Zardband Co., Iran) each day.
Both participants and the therapist were blind to the type of the administered drug or placebo. Participants filled out Medicine Adverse Side Effect Checklist and BDI at baseline and the weeks 2, 4, 6 and 8 of treatment.
BDI is one of the most well-known and widely used scales to investigate depression [27] In the current study, the 21-item version of BDI was used. This inventory can determine the type and severity of depression with high levels of validity and reliability, and has been used in a study with Iranian population [28].
The items of BDI were rated on a four-point Likert scale (scored 0-3), and therefore minimum and maximum possible scores are 0 and 63, respectively. The scores on BDI are classified as 0-9 (symptom-free), 10-18 (mild depression), 19-29 (moderate depression), and 30-63 (severe depression) [27]. The patients with BDI scores $\geq$ 19 were enrolled in the study.

Medicine Adverse Side Effect Checklist developed by the Food and Drug Deputy of Iran Ministry of Health and Medical Education was used to investigate side effects. This checklist consists of 13 items. The patients who experienced side effects were asked to fill out this checklist [29].
Data analysis was conducted by the SPSS version 21. If data were normally distributed, descriptive statistics, chi-square test and repeated measures ANOVA were used. Greenhouse-Geisser correction was used to investigate significant difference among the five measurements and least significant difference to determine inter-group differences.

Results
Table 1 shows the mean (±standard deviation) scores on BDI at baseline and the weeks 2, 4, 6 and 8 of treatment. There were significant differences in the mean scores on BDI between groups at the weeks 2, 4, 6 and 8 of treatment ($p<0.01$), but not at baseline.
Table 2 shows paired comparisons of mean BDI scores of groups. Results showed that at the weeks 2 and 4 of treatment, the mean BDI score of fluoxetine+C. zeylanicum (5 drops) group was significantly lower than that of fluoxetine+placebo group ($p<0.01$), without any significant difference in mean BDI score between fluoxetine+C. zeylanicum (15 drops) group and fluoxetine+placebo group. Comparison of the mean BDI scores at the weeks 2 and 4 showed no significant difference between fluoxetine+C. zeylanicum (15 drops) group and the other two groups. At the weeks 6 and 8, the mean BDI scores of fluoxetine+C. zeylanicum groups were significantly lower than that of fluoxetine+placebo group ($p<0.01$), and the mean BDI scores of fluoxetine+C. zeylanicum (5 drops) group and fluoxetine+C. zeylanicum (15 drops) group were not significantly different.
According to repeated measures ANOVA and the intra-group difference test Greenhouse-Geisser (df: 2.52 and F: 238.499), the mean BDI scores at different weeks were significantly different ($p=0.002$). Inter-group difference test (df: 2 and F: 7.13) showed significant differences among different treatments. The paired comparisons of the mean BDI scores showed significant differences between baseline and other weeks (Table 3 and the figure).

Discussion
MDD is a major health issue worldwide that affects around 20% of the world's population. It has been projected that depressive disorders will represent the second leading global burden of disease up to 2020 [30]. Given that family and social problems can predispose one to depression and that depression is associated with the risk of suicide, it is essential to treat depression. Many drugs for depression are available but many of the patients do not exhibit satisfactory therapeutic response to these drugs and also cannot tolerate their side effects. In addition, these drugs exert their effects after a time delay, which may cause the patients to discontinue their consumption. Therefore, development of new drugs without adverse side effects has turned into a big challenge [3].
This study was first to demonstrate the efficiency of C. zeylanicum essential oil to improve the symptoms of MDD. The double-blind clinical trials that have been conducted to date, have demonstrated positive effects of medicinal plants such as saffron, chamomile, sycamore, lavender and dill on the symptoms of mild to moderate depression [31, 32, 33] and positive effects of curcumin and gingko biloba on the symptoms of MDD [34, 35] Rhodiola rosea has also been reported to be effective on both MDD and mild depression [36, 37] Some plants such as lavender and dill alone do not exert any significant antidepressant effects but, when combined with antidepressants such as fluoxetine, reinforce their effects [33, 38].
The current study was conducted to investigate the effect of C. zeylanicum on treatment regimen of patients with unipolar non-psychotic MDD under treatment with fluoxetine. Results showed that treatment with fluoxetine+C. zeylanicum (5-15 drops) improved the symptoms in patients with MDD. From the second week of treatment, the mean BDI score of fluoxetine+C. zeylanicum (5 drops) group was significantly lower than that of fluoxetine+placebo group; from the sixth week of treatment, the mean BDI scores of fluoxetine+C. zeylanicum groups were significantly lower than that of fluoxetine+placebo group.
An experimental study with rats demonstrated antidepressant effects of C. zeylanicum extract by the tail suspension test (TST) [20]. Hydroalcoholic C. zeylanicum extract has been reported to exert therapeutic effects on reserpine-induced depression in mice [21]. Sohrabi et al., reported that C. zeylanicum essential oil at 0.5, 1, and 2mg/ml exhibited antidepressant effects in the forced swim test and the TST [39]. The study of Chericoni et al., indicated that linalool, eugenol and cinnamaldehyde are three main compounds of C. zeylanicum essential oil, comprising 82.5% of its entire compounds [16] Norte et al., reported the antidepressant effects of linalool in rats and Saiyudthong et al., did the antidepressant effects of this compound on chronic stress-induced depression [40, 41],which may explain the antidepressant effects of C. zeylanicum observed in the present study.
Oxidative stress, inflammation, and neuronal degeneration contribute greatly to the pathogenesis of MDD. Different biomarkers such as inflammatory cytokines and markers of oxidative/nitrosative stress in patients with MDD and animal models of depression confirm the roles of these factors in MDD pathogenesis [42]. Studies have shown that the antioxidant defense system is weakened and lipid peroxidation is increased significantly in patients with MDD. Weakening of antioxidant defense system is associated with declined capacity to protect and increase reactive oxygen species and reactive nitrogen species [43, 44]
Taken together, antioxidant and anti-inflammatory compounds seem to contribute to improving the symptoms of MDD through preventing the stimulation of the immune system and oxidative/nitrosative stress.
The antioxidant and anti-inflammatory properties of C. zeylanicum extract and essential oil have been demonstrated, and seem to be the action mechanisms involved in the antidepressant effects of this plant. For example, in a clinical trial, consumption of C. zeylanicum-containing tea caused a significant decrease in serum lipid peroxidation in operating room staff [18] Besides that, treatment with C. zeylanicum powder caused a significant decrease in the apotosis of the hippocampal neurons and the markers of oxidative stress in the mice with induced Alzheimer's disease [45] The study of Jawale et al., indicated that cinnamaldehyde treatment caused significant decrease in the inflammatory cytokines interleukin-6 and tumor necrosis factor-alpha (TNF-α) in the diabetic mouse [46]. Taken together, C. zeylanicum active compounds

improve antidepressant effect of fluoxetine through reducing markers of oxidative/nitrosative stress and inflammatory markers.

Cinnamaldehyde, the most important active compound of C. zeylanicum essential oil, is peroxisome proliferator- activated receptor (PPAR)-Y agonist. PPAR-Y is a ligand-dependent transcription factor that regulates the expression of the target genes related to glucose and lipid metabolism, inflammatory processes and cell differentiation. Experimental and clinical investigations have indicated that the agonists of this molecule such as rosiglitazone and pioglitazone improve depression symptoms and mood disorders [47]. It can be therefore hypothesized that C. zeylanicum essential oil can improve depression through affecting PPAR-Y.

MRI results have consistently demonstrated reduction in hippocampal volume in the people with recurrent depression when compared to age and gender-matched controls. Preliminary and clinical evidence has indicated that depression is associated with various structural and neurochemical changes in the levels of neurotrophins especially brain-derived neurotrophic factor (BDNF). Cinnamaldehyde, present in C. zeylanicum essential oil, is metabolized in the liver, producing a secondary metabolite called sodium benzoate. This compound potentially increases the gene expression of BDNF precursor [48]. As a result, the cinnamaldehyde in this essential oil can partly contribute to treating depression and other neurodegenerative diseases through elevating the BDNF levels in brain and serum.

It was shown, in our study, that C. zeylanicum effects were not dose-dependent and 15 drops of its essential oil did not cause further decrease in BDI score compared to 5 drops. This finding can be tentatively explained by higher doses of plant essential oils and extracts having potential to intensify the production of free radicals and lipid peroxidation in the brain [49]. This question may be raised whether C. zeylanicum extract at high concentrations can intensify lipid peroxidation in the brain and certain receptors and, given the role of oxidative stress in depression, fail to exert more marked effects in decreasing and improving the symptoms. More detailed and comprehensive studies are required to answer this question.

A review of available evidence on the essential oil and extract of C. zeylanicum, indicates that the effects of C. zeylanicum active compounds on cerebral neurotransmitters have not yet been sufficiently studied, highlighting the need for studies to determine antidepressant action mechanisms of this plant.

In our study, C. zeylanicum caused significant improvement of fluoxetine antidepressant effects, which promises to use this plant to achieve this purpose so that the prescribed doses of this drug and the resulting side effects could be reduced. With regards to the public welcome to nature-based compounds, patients are also becoming more willing to use C. zeylanicum.

Conclusion

In this study, C. zeylanicum exhibited good antidepressant effects and well tolerated with fluoxetine. This plant also caused no side effect and sensitivity. This drug can reinforce fluoxetine antidepressant effect without causing any side effect.

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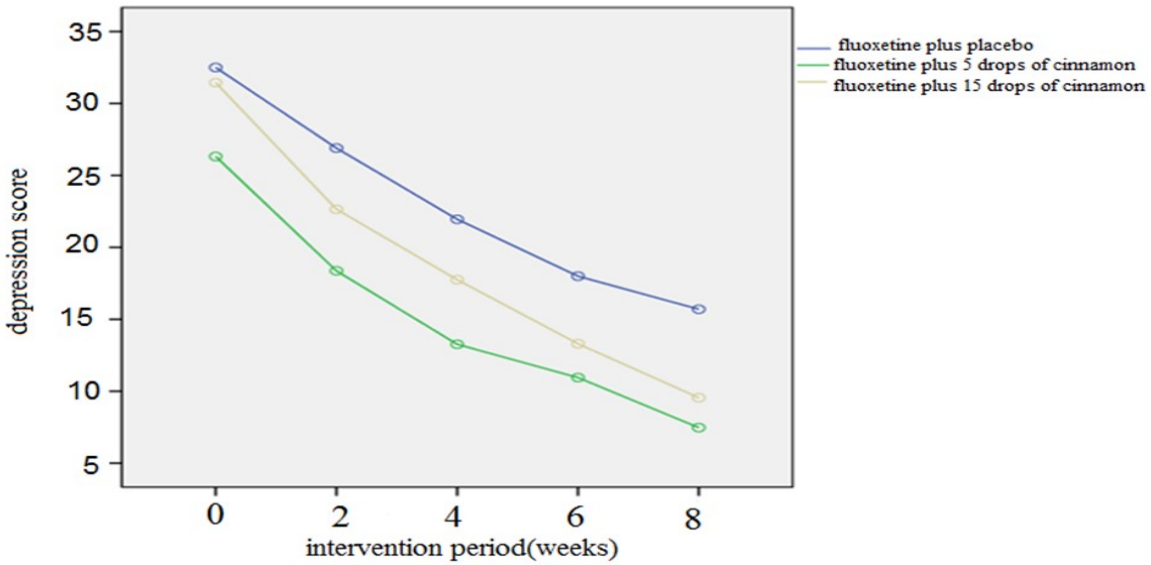
Figure



Variations in scores on Beck Depression Inventory during treatment in three groups analysis shows that there is no significant difference in frequencies of GI side effects, drug intolerance and sensitivity, sexual side effects and weight changes among three groups. No drug or food allergy was reported in these groups.

Table 1. Mean (±standard deviation) scores on Beck Depression Inventory

Groups		Mean(±standard deviation) scores			
	Week 0	Week 2	Week 4	Week 6	Week 8
Fluoxetine + placebo	32.50±9.37	26.90±8.36	21.95±9.49	18±6.17	15.7±6.15
fluoxetine+5 oral drops of C. zeylanicum essential oil	26.31±7.21	18.36±4.62	13.26±4.79	10.94±3.04	7.47±2.50
fluoxetine +15 oral drops of C. zeylanicum essential oil	31.45±10.01	22.65±9.32	17.5±8.05	13.30±7.24	9.55±5.92
Total	30.15±9.22	22.71±8.38	17.27±8.40	14.13±6.42	10.96±6.18
P value	0.117	0.004	0.003	0.001	0.00

Significant at $p \leq 0.05$.

Table 2. Comparison of mean scores on Beck Depression Inventory

Treatment course	Groups	P value
Week 0	Fluoxetine+placebo & Flouxetine+5 drop of essential oil	0.052
	Fluoxetine+placebo & Flouxetine+15 drop of essential oil	0.714
	Flouxetine+5 drop of essential oil && Flouxetine+15 drop of essential oil	0.112
Week 2	Fluoxetine+placebo & Flouxetine+5 drop of essential oil	0.001
	Fluoxetine+placebo & Flouxetine+15 drop of essential oil	0.086
	Flouxetine+5 drop of essential oil && Flouxetine+15 drop of essential oil	0.093
Week 4	Fluoxetine+placebo & Flouxetine+5 drop of essential oil	0.001
	Fluoxetine+placebo & Flouxetine+15 drop of essential oil	0.089
	Flouxetine+5 drop of essential oil && Flouxetine+15 drop of essential oil	0.061
Week 6	Fluoxetine+placebo & Flouxetine+5 drop of essential oil	0.00
	Fluoxetine+placebo & Flouxetine+15 drop of essential oil	0.013
	Flouxetine+5 drop of essential oil && Flouxetine+15 drop of essential oil	0.211
Week 8	Fluoxetine+placebo & Flouxetine+5 drop of essential oil	0.00
	Fluoxetine+placebo & Flouxetine+15 drop of essential oil	0.00
	Flouxetine+5 drop of essential oil && Flouxetine+15 drop of essential oil	0.216

Significant at $p \leq 0.05$

Table 3. Results of intra-group effects

	Measurement	Mean	F	P-value
Depression score	Greenhouse-Geisser	5320.777	238.494	0.000
Groups	Intra group	1460.894	7.13	0.002

Significant at $p \leq 0.05$