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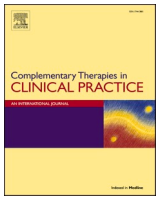

Rosemary as an adjunctive treatment in patients with major depressive disorder: A randomized, double-blind, placebo-controlled trial

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ABSTRACT

Background: Rosemary has shown antidepressant and anxiolytic properties. Thus, the present study aimed at assessing the therapeutic effects of orally administered rosemary capsules in patients with major depressive disorder.

Materials and Methods: Rosmarinic acid content of rosemary was determined using high performance liquid chromatography method. Hard gelatin capsules of rosemary were prepared, and their physicochemical properties were assessed. In this clinical trial, patients with major depressive disorder were randomly divided into rosemary and control groups. They received one capsule of rosemary or placebo twice a day for 8 weeks. The anxiety subscale of Hospital Anxiety and Depression Scale and Beck Depression Inventory - Second Edition were respectively used to measure the symptoms of anxiety and depression in the patients before initiating the treatment and four and eight weeks after the treatment.

Results: The amount of rosmarinic acid in rosemary was found to be 21.13 ± 0.56 mg/g dried plant. The scores of anxiety subscale of Hospital Anxiety and Depression Scale and Beck Depression Inventory significantly decreased in the rosemary group compared to those in the control group 8 weeks after the treatment. Memory improvement was a beneficial side effect observed in the study.

Conclusion: The use of rosemary as an adjunctive therapy could improve the symptoms of anxiety and depression in people with major depression.

1. Introduction

Depression is a prominent cause of disability worldwide and significantly contributes to the global burden of this disease. According to WHO estimates, approximately 4.4% of people worldwide suffer from depression. Depression is a syndrome with a wide range of symptoms including depressed mood and anxiety as well as cognitive and neurovegetative ones [1–3]. Only one third of patients with depression respond adequately to antidepressants. Clinical variability in response to antidepressants, susceptibility to their side effects, and their delayed onset of action are major clinical issues motivating researchers to conduct a search for novel antidepressants [1,2]. Medicinal plants are of the most attractive candidates for discovery of novel antidepressants because of their low side effects and promising efficacy. In addition, several studies have demonstrated the value of these plants in treating mental and emotional disorders such as anxiety and depression [4]. There are also about 650 reports of antidepressant-like medicinal herbs in PubMed [5].

Rosemary, *Rosmarinus officinalis* L. (Lamiaceae), is an evergreen perennial shrub native to southern Europe and Asia especially Mediterranean region that is now cultivated in many regions of the world [6,7]. Rosemary is a safe approved food additive in many countries. No adverse effects have been observed with the oral use of rosemary extracts at the dose levels of 180–400 mg/kg body weight per day. Also, in human studies, rosemary powder was orally administrated at acute dose of 6 g and repeated dose of 2.8 g daily without apparent adverse effects.

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Moreover, dried rosemary was used for cooking in the United Kingdom at the dose levels of 0.4–2.5 g/serving [6]. The major bioactive compounds in rosemary include essential oil components such as 1, 8-cineole, camphor, and α-pinene; triterpenes such as oleanolic, betulinic, and ursolic acids; phenolic diterpenes such as carnosic acid, carnosol and rosmanol; and polyphenols such as rosmarinic acid. Some of rosemary properties are anti-inflammatory, antioxidant, anti-nociceptive, neuroprotective, antidepressant, antiepileptic, antibacterial, antidiabetic, anxiolytic, and memory boosting. Several reports in the literature have demonstrated the potential of *R. officinalis* as an antidepressant and anxiolytic medication [7–10]. In animal models, different mechanisms of action have been suggested for the effectiveness of rosemary in depressive disorders including enhancement of dopaminergic, serotonergic and cholinergic functions, interaction with the monoaminergic system, and modulation of oxytocinergic system [7,8]. However, clinical trials on the effects of rosemary on depression are limited and more research is to be carried out. As a result, the aim of this study was to assess the therapeutic effects of orally administered rosemary capsules in patients with major depressive disorder (MDD).

2. Materials and methods

2.1. Preparation and extraction of rosemary

Rosemary was purchased from the market and was used after scientific name confirmation. The herbarium specimen of the plant was kept in the herbarium center (voucher number KF-1245). The leaves of the plant were cleaned and dried. After grinding, the resulting powder was passed through a sieve with a mesh size of 35 and used for capsule formulation. For standardization, the plant extract was prepared by warm maceration method with 80% ethanol (distilled ethanol).

2.2. Rosemary standardization

2.2.1. Total phenolic content

In general, phenolic compounds are of the major constituents of rosemary and could be employed as markers for standardization of herbal formulations. With gallic acid as the standard, the total phenolic content was measured quantitatively using the Folin-Ciocalteu reagent. Briefly, 500 μl of water diluted folin-ciocalteu reagent (1:10) was mixed with 100 μl of the sample extracts followed by adding 400 μl of sodium carbonate aqueous solution (7.5% w/w) to it. The mixture was incubated in a dark place at room temperature for 30 min. The absorbance was measured at 765 nm by a spectrophotometer (Synergy HTX, USA), and the phenolic content of the plant was calculated from the slope of gallic acid calibration curve [11].

2.2.2. Rosmarinic acid (RoA) content of the plant using high performance liquid chromatography (HPLC) method

A stock solution, different concentrations of RoA (0.5–10 μg/ml), and the plant extract (100 μg/ml) were prepared in methanol 80% and passed through a syringe filter (PTFE membrane, 0.2 μm). For analysis, a high-performance liquid chromatography system (HPLC, Yang, South Korea) and a Waters C18 column (4.6 × 250 mm, 4 μm) (USA) were used. Roa (10 μg/ml) and the plant extract were injected into the system. Chromatographic elution was set at a flow rate of 0.1 ml/min at the temperature of 25 °C. The elution was carried out using the mobile phases of A: 0.1% (v/v) formic acid solution in water and B: 0.1% (v/v) formic acid solution in methanol. The ratio of 90% A and 10% B was applied for 30 min. The UV wavelength was set at 2800 nm for detection. For the calibration curve, rosmarinic acid (10 mg) was accurately weighed and dissolved in 80% methanol. A serial dilution was prepared from standard RoA (0.5–10 μg/ml), and the calibration curve was presented using HPLC data [12].

2.3. Preparation of rosemary granules

Rosemary oral capsules were formulated using 350 mg of the dried, milled, and sieved plant per capsule which was mixed with lactose monohydrate and starch powder. The powder was passed through a sieve with a mesh size of 12 to produce granules. The dried granules were mixed with some lubricants such as talc and magnesium stearate in required quantities. Hard gelatin capsules (size 00) were filled with the prepared granules using a hand operated capsule filling machine. The final weight of each capsule was 650 mg.

2.4. Pre-formulation evaluation of the rosemary granules

Hausner ratio and Carr's index of the prepared rosemary granules were determined to assess their flow property. Hausner ratio less than 1.2 and Carr index $\leq$16 indicate good granule flowability [13]. The amount of lubricants was determined based on Hausner ratio and Carr's index.

2.5. Evaluation of physicochemical properties of the rosemary capsules

2.5.1. Weight variation

The average weight of each capsule was determined by randomly weighing 10 selected capsules. Each capsule should be in the range of 90–110% of the theoretically calculated weight of each unit [14].

2.5.2. Estimation of rosemary content in the capsules

To determine λ_{max} of rosemary, UV-spectrophotometric method was used. The absorbance of the standard concentrations of rosemary extract was measured at λ_{max}. The calibration curve of the absorption against the concentration was drawn. A number of 10 filled capsules were randomly selected, and the content of each was determined in accordance with the calibration curve. The range of 85–115% of the theoretically calculated content of each capsule is acceptable [15].

2.5.3. Dissolution test for the capsules

The rate and extent of rosemary dissolution from the capsules were tested by a dissolution test. Six capsules were inserted in the basket type dissolution apparatus containing distilled water. The speed was set on 50 rpm for 30 min, and the sample was withdrawn at every 10 min. The amount of the dissolved rosemary in the solution was determined by the spectrophotometric method and calculated as the percentage dissolved in 30 min [14].

2.5.4. Stability of the capsules

To test the stability, the capsules were placed in a refrigerator (4 ± 2 °C), environment (25 °C ± 2), and an oven (40 °C ± 2). The organoleptic properties and rosemary content (evaluated by UV spectrophotometric technique) of the capsules were assessed at monthly intervals for a period of 6 months [14].

2.6. Clinical investigation

2.6.1. Ethical considerations

The study (registered code: 98000127) was approved by the ethics committee of Kerman University of Medical Sciences (ethic approval code: IR.KMU.REC.1398.359) and the Iranian Registry of Clinical Trials (trial registration number: IRCT20110310006026N11). It was conducted in accordance with the ethical standards laid down in the Declaration of Helsinki. Eligible patients were fully informed about the study aims and procedures as well as the confidential nature of data selection and processing. They all signed a written informed consent form as well.

2.6.2. Study design, setting and participants

The study was conducted as a randomized, double-blind, placebo-

controlled clinical trial in Besat Clinic affiliated to Kerman University of Medical Sciences, Kerman, Iran, from April to November 2020. This study had a per-protocol design.

The patients aged 18–55 years old who were newly diagnosed with MDD based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, who did not receive any antidepressant medications, and who were candidates for initiation of selective serotonin reuptake inhibitor (SSRI) therapy were included. The exclusion criteria were pregnancy, lactating, having any underlying medical diseases or psychiatric disorders, hypersensitivity reactions to rosemary, being at high risk for suicide, using herbal medicines, mental retardation, and drug addiction.

2.6.3. Interventions

The participating patients were divided into two groups including rosemary and control ones in a 1:1 ratio using block randomization with a block size of four. A person who was not involved in the study generated allocation sequences. The rosemary group received one capsule of rosemary twice a day for 8 weeks. The control group received a standardized placebo in terms of shape, color and outer packaging of the capsules. The containers of the placebo and rosemary capsules were labeled as A and B by an independent researcher. The patients, physician, and outcome assessor were blinded to the treatment allocation. The patients' compliance with the therapy was assessed by counting the prescribed medications in each follow-up visit. Non-adherents to the medications was defined as taking less than 80% of the prescribed pills [16]. The patients with non-adherence to the therapy were excluded from the study.

Demographic information including age, gender, marital status, history of alcohol use, and type of SSRI prescribed for the patients was recorded. The patients were asked to report any side effects due to the treatment during the study.

It should be noted that no interaction between rosemary and SSRIs including sertraline, fluoxetine, citalopram, and escitalopram (prescribed in the current study) was documented based on Lexi-Natural Products database, last updated: July 28, 2022 and RxList database available at https://www.rxlist.com/rosemary/supplements.htm, accessed August 29, 2022).

2.6.4. Measurements

The validated Persian version of anxiety subscale of Hospital Anxiety and Depression Scale (HADS-A) and Beck Depression Inventory - Second Edition" (BDI-II) were respectively used to measure the symptoms of anxiety and depression in the patients before initiating the treatment and four and eight weeks after the treatment.

HADS is a self-report 14-item questionnaire consisting of two subscales: anxiety (7 items) and depression (7 items), and scores range from 0 to 3 for each item. The total subscale score can range from 0 to 21. HADS-A is used to assess the symptom severity and caseness of anxiety disorders. Anxiety subscale scores of 11 or more indicate a case of anxiety. The scores of 8–10 are considered as possible case of anxiety and 0–7 as normal person. HADS is a screening tool and also sensitive to change in response to medical intervention [17].

BDI-II is a 21-item self-report questionnaire that assesses the severity of depressive symptoms and rates from 0 (absent) to 3 (severe) for each item. The maximum score is 63. Higher total scores indicate more severe depressive symptoms [18].

2.6.5. Sample size and statistical analysis

The G-power software (3.1.9.7) was performed to calculate the sample size. It was estimated 23 patients in each group based on a type I (alpha) error of 0.05, type II error (beta) of 0.1 (power 90%) and repeated measures design. With a dropout rate of 20%, 28 patients were finally needed for each group.

All the data were collected according to the methods presented in the text and analyzed by SPSS 26 software. According to the Kolmogorov–Smirnov Test, the data distribution was normal. So, mixed model analysis of variance method was used to compare the scores of each scale between the rosemary and control groups during the study. Independent samples *t*-test, chi-square test and Fisher's exact test were employed to assess the differences in demographic variables. Also, independent samples *t*-test was used to measure the difference in scales scores between the two groups at each time point. Paired sample *t*-test was applied to compare the changes over time in the scales scores of each group. A p-value < 0.05 was considered to indicate statistical significance.

3. Results

3.1. Rosemary standardization

3.1.1. Total phenolic content

The yield of extraction was 16.8 (w/w %). The total phenolic content of the powdered rosemary was determined as 4.25 ± 0.50 (w/w %) based on the slope of gallic acid calibration curve ($y = 0.0071x + 0.151$, R^2 of 0.9999).

3.1.2. Rosmarinic acid content

The HPLC chromatogram (a) and calibration curve (b) of standard RoA are shown in Fig. 1. As per the obtained results, the amount of RoA content of rosemary was determined to be 21.13 ± 0.56 mg/g dried plant on the basis of RoA calibration curve.

3.2. Flow property of the granules

Hausner ratio and Carr's index of the prepared granules were in the mentioned ranges for good flowability.

3.3. Physicochemical properties of the capsules

3.3.1. Weight variation

The weight uniformity was checked, and it was found that the weight range of the capsules (90.78–103.8%) was acceptable.

3.3.2. Rosemary content in the capsules

The λ_{max} of the prepared rosemary was found to be 230 nm. The results showed a good relationship between the concentration and absorbance based on the obtained linear calibration plot ($Y = 0.0044x + 0.148$, $R^2 = 0.9968$). The rosemary content of all the ten capsules (92.00–105.30%) was within the standard range. The mean ± SD of the capsules total phenolic content was 459.1 ± 23.50 mg.

3.3.3. Dissolution test for the capsules

The results indicated that 91.25 ± 1.92% of the rosemary content of the capsules was dissolved in 30 min.

3.3.4. Stability of the capsules

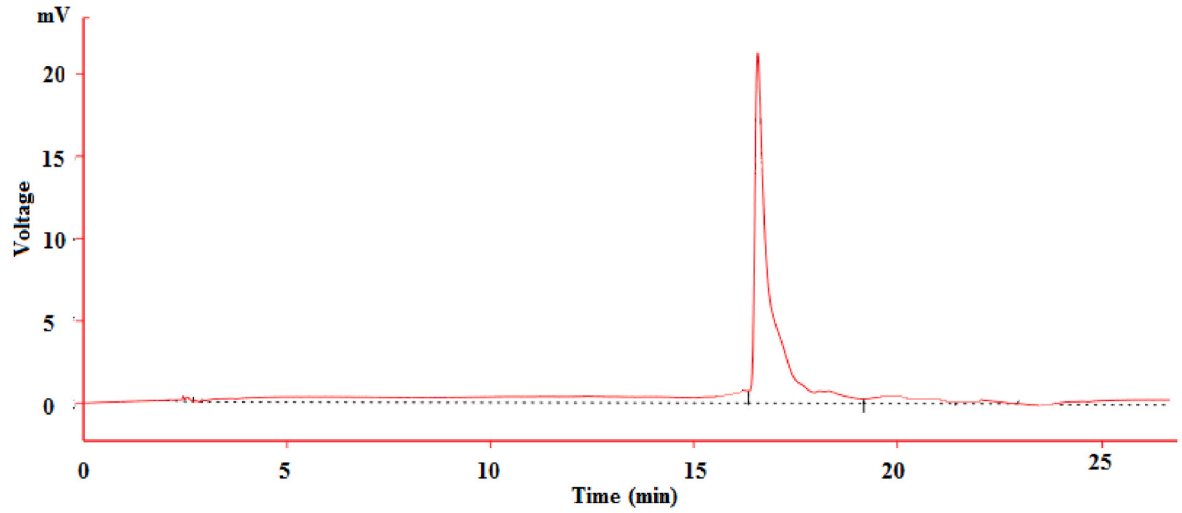
No changes in terms of the organoleptic properties were observed in any of the samples under any of the storage conditions during 6 months. Moreover, in the aforementioned conditions and after 6 months, more than 94% of the rosemary content of the capsules remained constant.

3.4. Clinical findings

Fifty-one patients completed the study (26 patients in the rosemary group and 25 in the control group). Fig. 2 demonstrates the flowchart of the study.

The mean age of the 51 participants was 30.67 ± 8.97 years. Among the participating patients, 41 (80.39%) and 10 (19.61%) were female and male, respectively. The demographics of the patients in each group are presented in Table 1. There were no significant differences between the two groups concerning the demographic data. The participants were

a)



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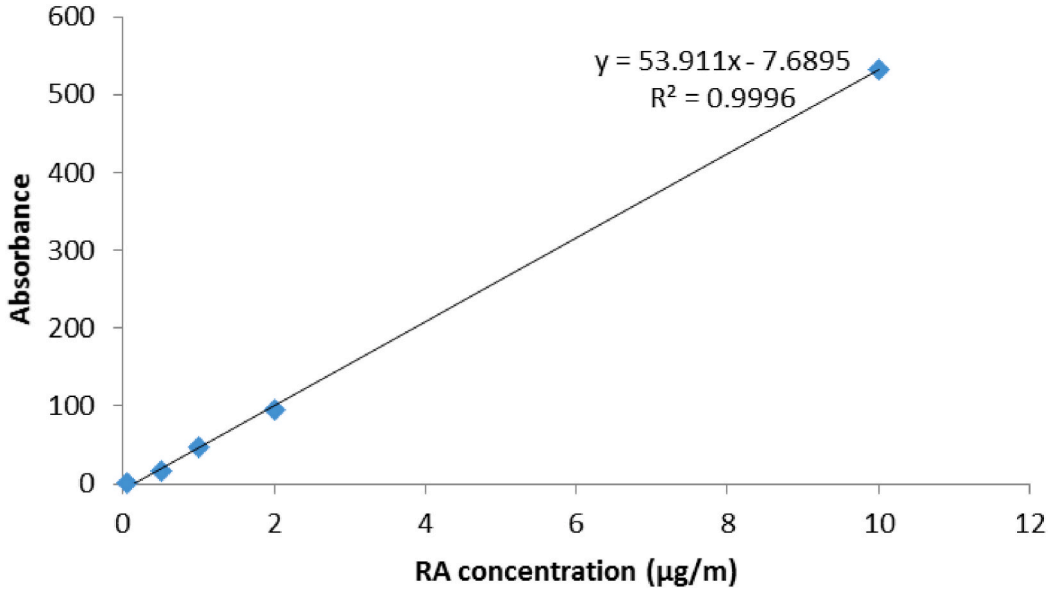

Fig. 1. HPLC chromatogram of rosmarinic acid (RoA) detected at 280 nm (a) and calibration curve (b) of RoA (0.5–10 µg/ml).

classified regarding HADS-A as 37 (72.55%) anxiety cases, 9 (17.65%) possible anxiety cases, and 5 (9.80%) normal people.

The analyses showed that time-group interaction, time, and grouping effects were statistically significant for HADS-A and BDI-II after 8 weeks. The clinical outcomes of the participants during the study (at baseline, after 4 weeks, and after 8 weeks) are shown in Table 2.

The decrease in the BDI-II scores was statistically significant in the control group after 4 (0.0001) and 8 (0.0001) weeks of initiating the treatment. The decrease in the scores of HADS-A was not statistically significant 4 weeks after the treatment (p-value = 0.186), but it reached statistical significance 8 weeks after the treatment (p-value = 0.028) in the control group.

There was a statistically significant decrease in the BDI-II scores in the rosemary group 4 (p-value = 0.0001) and 8 (p-value = 0.0001) weeks after the treatment. Also, the scores of HADS-A significantly decreased 4 (p-value = 0.0001) and 8 (p-value = 0.0001) weeks after the treatment in the rosemary group. At baseline, there was not any significant difference regarding the HADS-A scores between the two groups (p-value = 0.474). But the HADS-A scores were significantly lower in the rosemary group compared to those in the control one 4 (p-value =

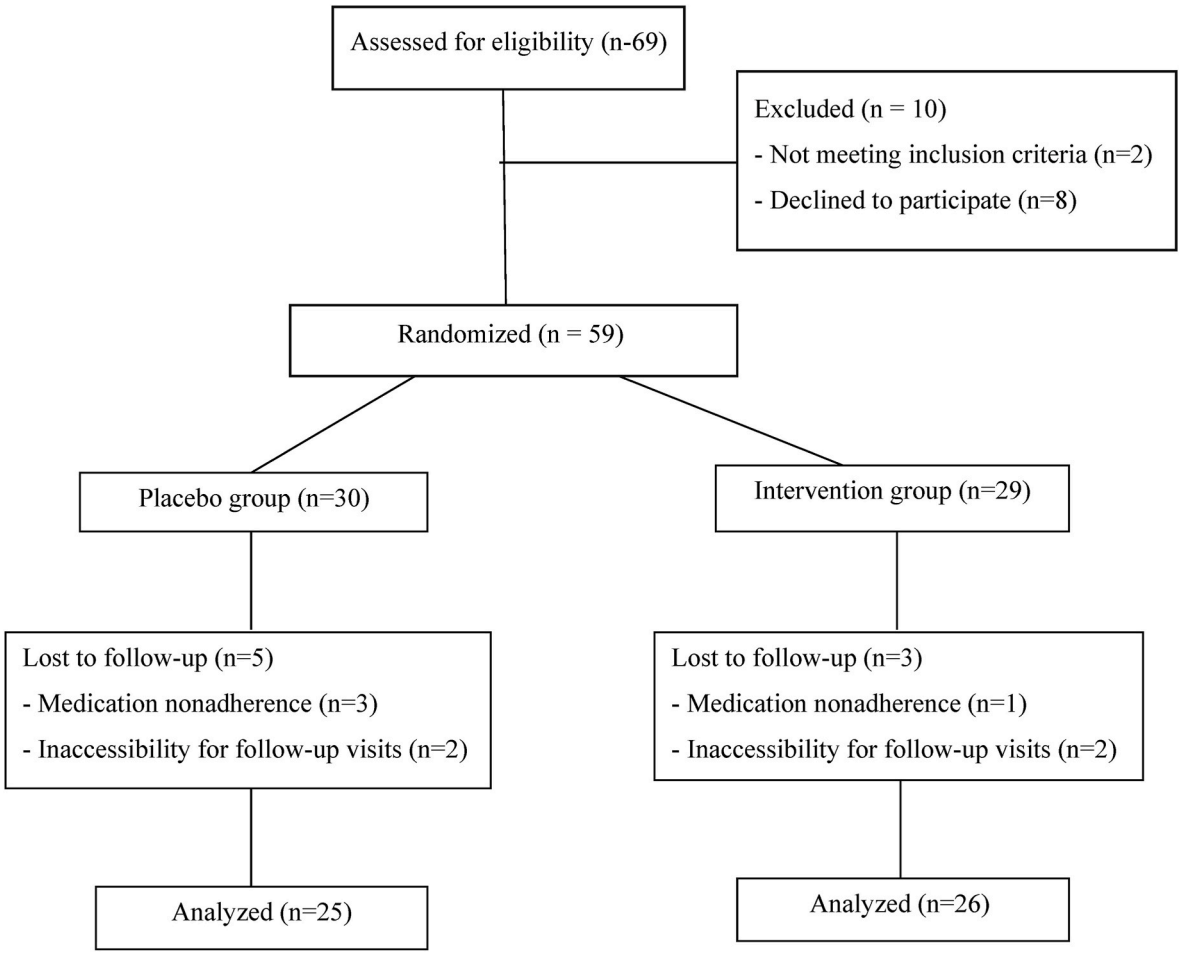

Fig. 2. CONSORT flowchart of the study.

Table 1
Demographics of the patients in the rosemary and control groups.

Variables		Rosemary group (N = 26) N (%)	Control group (N = 25) N (%)	p-value
Age (years) (Mean ± SD)		29.92 ± 9.30	31.44 ± 8.77	0.567[a]
Sex	Male	23 (88%)	(72%) 18	0.113[b]
	Female	3 (12%)	(28%) 7	
Marital status	Single	(54%) 14	(40%) 10	0.322[b]
	Married	(46%) 12	(60%) 15	
Alcohol consumption		3 (12%)	3 (12%)	0.647[b]
Prescribed selective serotonin reuptake inhibitor	Sertraline	11 (42%)	11 (44%)	0.587[b]
	Fluoxetine	1 (4%)	1 (3.85%)	
	Fluvoxamine	0	1 (4%)	
	Citalopram	4 (15%)	1 (4%)	
	Escitalopram	10 (38%)	11 (34%)	

SD: Standard deviation.
[a] Independent-samples *t*-test.
[b] Chi-square test or Fisher's Exact Test.

0.004) and 8 (p-value = 0.0001) weeks after the treatment.

The BDI-II scores were significantly lower in the rosemary group compared to those in the control group at baseline (p-value = 0.003), 4 (p-value = 0.0001), and 8 (p-value = 0.0001) weeks after the therapy.

Moreover, pill count adherence rates were 95.00 ± 14.43 and 97.31 ± 10.41 in the control and rosemary groups, respectively. There was not any significant difference between these two groups in this regard.

During the current study, some side effects including nausea, headache, diarrhea, constipation, heartburn, memory improvement, drowsiness, increased libido, and increased appetite were reported by the participants. Some patients reported more than one side effect. There were no significant differences between the rosemary and control groups regarding the side effects except for heartburn and memory improvement. Constipation was borderline significant. Memory improvement was a beneficial side effect observed in the study, and it was significantly higher in the rosemary group compared to that in the control one. Table 3 presents the reported side effects in the study.

4. Discussion

According to the findings of the present study, rosemary as an adjunctive therapy to SSRIs was considerably effective in reducing anxiety and depression in the patients suffering from major depression. Also, the anxiety scores decreased more rapidly in the rosemary group.

Numerous animal studies have looked into various possible mechanisms of action of rosemary and its major polyphenols in improving nervous system disorders such as depression and anxiety. Machado et al. demonstrated that rosemary antidepressant-like effect is mediated via an interaction with the monoaminergic system [19]. Ursolic acid, a triterpenoid from *R. officinalis*, has shown an antidepressant-like effect through interaction with the dopaminergic system and activation of dopamine D1 and D2 receptors [20]. Lin et al. suggested that rosmarinic acid affected serotonergic neurotransmission and decreased serotonin turnover in an animal model [21]. Carnosol and betulinic acid compounds of *R. officinalis* extracts have been found to have antidepressant effects similar to fluoxetine in mice [22].

The effect of rosemary on gamma aminobutyric acid (GABA) receptors is another possible mechanism explaining its antidepressant and

Table 2
Changes in the scales scores in the intervention and placebo groups at the baseline, 4 and 8 weeks after the treatment.

Scales	Groups	Baseline (Mean ± SD)	After 4 weeks (Mean ± SD)	After 8 weeks (Mean ± SD)	p-value[a] (Effect of Grouping)	p-value[a] (Effect of time)	p-value[a] (Time-Group interaction)
Beck Depression Inventory Second Edition	Control	42.20 ± 9.94	34.48 ± 10.44	29.52 ± 10.12	0.0001	0.0001	0.005
	Rosemary	33.46 ± 10.35	20.50 ± 7.77	14.19 ± 7.03			
Anxiety subscale of Hospital Anxiety and Depression scale	Control	13.24 ± 3.92	11.96 ± 3.79	10.78 ± 3.93	0.0001	0.008	0.011
	Rosemary	12.42 ± 4.16	8.69 ± 3.83	6.8 ± 2.68			

SD: Standard deviation.
[a] Mixed model Analysis of Variance.

Table 3
Reported side effects by the participants during the study.

Side effects	Rosemary group (N = 26) N (%)	Control group (N = 25) N (%)	p-value[a]
Nausea	6 (23.07%)	4 (1.60%)	0.39
Headache	1 (3.85%)	1 (4.00%)	0.745
Diarrhea	2 (7.69%)	6 (24.00%)	0.112
Constipation	4 (15.38%)	0	0.06
Heartburn	11 (42.31%)	0	0.0001
Increased memory	21 (80.77%)	3 (12.00%)	0.0001
Drowsiness	13 (50.50%)	7 (28.00%)	0.093
Increased libido	5 (19.23%)	2 (8.00%)	0.226
Increased appetite	4 (15.38%)	1 (4.00%)	0.187

[a] Chi-square test or Fisher's Exact Test.

sedative characteristics. Additionally, rosemary antioxidant properties may be responsible for its impacts on anxiety [23]. Because of the presence of flavonoids in this plant and their antioxidant properties, rosemary extract has an anti-anxiety effect similar to the standard drug diazepam as reported by Noori Ahmad Abadi et al. [24]. Rosmarinic acid increases endogenous antioxidant defense against oxidative stress and induces the production of the antioxidant enzyme superoxide dismutase (SOD) [25]. The effects of non-volatile components of rosemary such as rosmanol, cirsimaritin, and salvigeninon on central nervous system function in mouse models were studied by Abdelhalim et al. The compounds had little toxicity in the 50–200 mg/kg range, but they did have antinociceptive, antidepressant, and anxiolytic properties. The anxiolytic activity of each of the three mentioned compounds was not decreased by flumazenil but was inhibited by pentylenetetrazol, suggesting that the effect was mediated by GABAA receptors at a location other than the high affinity benzodiazepine binding site [26]. Moreover, it has been suggested that the plant extract works by altering the complex interactions between oxytocin and neuroendocrine, neurotransmitter, and inflammatory processes resulting in antidepressant and anxiolytic effects [8].

Some clinical studies have previously proved rosemary beneficial effects in reducing anxiety, depression, and improving mood in various groups. In college students, oral rosemary increased future and retrospective memory, reduced anxiety and depression, and improved sleep quality [9]. In addition, continuous oral intake of rosemary extract improved the mood, fatigue, and cognitive function of healthy Japanese adult working men [27]. Furthermore, in healthy participants, 10 days of rosemary tea drinking dramatically altered peripheral anxiety and depression biomarkers such as elevated plasma concentrations of brain-derived neurotrophic factor (BDNF). These findings showed the possible anxiolytic/antidepressant effects of rosemary [28]. Moreover, aromatherapy with rosemary essential oil has shown positive effects on reducing stress and anxiety in different populations such as pre-hospital emergency staff [29], elderly women [30], and nursing students [31], and also on reducing depression in ambulance technicians [32].

Also, in the current study, more than 70% of the patients with MDD were the cases of anxiety based on HADS-A. This finding confirmed the fact that many patients with depression experience anxiety symptoms. These symptoms do not fully meet the criteria for anxiety disorders, but they are distressing. Consequently, the patients with these conditions often turn to complementary and integrative therapies [33]. In the present study, the number of participating men was more than the participating women. Therefore, the gender distribution was not equal.

Furthermore, in the current study, heartburn and memory improvement as side effects were significantly observed in the rosemary group. Previously reported side effects were increased appetite, arousal of sexual desire, diuretic effect and skin improvement. Considering the findings of the previous studies, memory improvement was expected [9].

It should be mentioned that the lethal dose 50 (LD50) of rosmarinic acid is approximately 2500 mg/kg [34]. The rosmarinic acid content of the 350 mg rosemary capsule in the present study was around 7.40 mg. So, the safe dose of rosmarinic acid was used in this study.

In the current study, rosemary was standardized and the physicochemical properties of prepared rosemary capsules were assessed. It was also tried to conduct a well-designed clinical trial. But the study had some limitations which are discussed below.

This study had a small sample size and short duration. More interventional trials with longer durations, larger sample size, and different doses and frequency of capsules per day are recommended.

Also, in the present study, biological parameters such as BDNF level, cortisol level and inflammatory makers were not measured. Consequently, the correlation of the parameters with the HADS-A and BDI- II scores was not evaluated which should be considered in future studies.

Besides, the amount of all bioactive compounds in rosemary capsule was not determined in the current study as it was a clinical trial, and the analysis of all herbal ingredients was not the authors' agenda. Needless to say that the analysis studies themselves are time-consuming and costly which can be done in future researches. However, in order to standardize the plant in the present study, its total phenolic compounds were measured, and the content of one of its main compounds (rosmarinic acid), considered the plant marker, was determined by an instrumental method (HPLC). Moreover, it has not exactly been determined that which compounds in rosemary have antidepressant and anxiolytic properties.

Additionally, in the current study, the effect of rosemary on the patients who were candidates for initiation of SSRI therapy was evaluated. Therefore, it is recommended to conduct similar studied to evaluate the effect of rosemary in patients being treated or previously treated with SSRI.

5. Conclusions

It was concluded that the use of rosemary as an adjunctive therapy to SSRIs could improve the symptoms of anxiety and depression in people with major depression. Findings of the present study highlight the prospects of rosemary as an adjunct to antidepressants in treating depressive disorders.

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Author contributions

Saeed Azizi: Investigation, Project administration, Validation, Writing - Original draft. **Gholamreza Dehghannoudeh and Fariba Sharififar**: Conceptualization, Methodology, Project administration, Resources, Validation, Visualization, Writing - Original Draft. **Fatemeh Dabaghzadeh**: Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Formal analysis, Validation, Visualization, Writing - Original Draft, Writing – review & editing. **Farzaneh Jahanbakhsh and Neda Mohamadi**: Conceptualization, Project administration, Resources, Writing - Review & Editing. All the authors approved the manuscript final version.

Declarations of competing interest

None.

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