



Nepeta menthoides Boiss. & Buhse freeze-dried aqueous extract versus sertraline in the treatment of major depression: A double blind randomized controlled trial



Sepideh Kolouri^{a,b}, Ali Firoozabadi^{c,*}, Alireza Salehi^{a,b}, Mohammad M. Zarshenas^{d,e}, Seyed Ali Dastgheib^f, Mojtaba Heydari^{a,b}, Hossein Rezaeizadeh^g

^a Research Center for Traditional Medicine and History of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

^b Department of Traditional Persian Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

^c Research Center for Psychiatry and Behavioral Sciences, Department of Psychiatry, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

^d Medicinal Plants Processing Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

^e Department of Phytopharmaceuticals (Traditional Pharmacy), School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran

^f Substance Abuse Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

^g Department of Traditional Persian Medicine, School of Traditional Medicine, Tehran University of Medical Sciences, Tehran, Iran

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ABSTRACT

Background: Depression is the most common psychiatric disorder in the world. The conventional medications for depression, however, often have significant side effects. These adverse effects of conventional therapies, have motivated researchers to study alternative options including complementary and traditional treatments for solving the problem.

Objective: To compare the efficacy of *Nepeta menthoides* Boiss. & Buhse freeze-dried aqueous extract with sertraline in the treatment of major depression.

Design and setting: From April to September of 2015, 72 patients from two psychiatry clinics of Shiraz University of Medical Sciences who met the criteria for major depression based on the structured clinical interview as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, participated in a two-armed double-blind randomized controlled trial.

Intervention: Subjects were randomly assigned to receive *Nepeta menthoides* or sertraline for four weeks. **Outcome measures:** Patients were evaluated in terms of the Beck Depression Inventory-II (BDI-II) total score and common side effects of medications at the base line, the second and fourth weeks, and two weeks following the intervention (i.e. in the sixth week).

Results: The mean changes in the Beck Depression Inventory scores in *Nepeta menthoides* group were significantly higher in terms of the BDI-II scores diminution as compared to that of the control ($p \leq 0.001$). Two weeks follow up after intervention showed a lower recurrence rate in the *Nepeta menthoides* group ($p \leq 0.001$).

Conclusion: *Nepeta menthoides* may have potential benefits in the control of mood in patients suffering from major depression. Sustention of antidepressant effect and delay in the recurrence of depression could be considered worthwhile using this herb.

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Abbreviations: *N. menthoides*, *Nepeta menthoides* Boiss. & Buhse; BDI-II, Beck Depression Inventory second version; SD, standard deviation; BMI, body mass index; SUMS, Shiraz University of Medical Sciences; SSRI, selective serotonin reuptake inhibitor; MDD, major depressive disorder; OTC, over the counter.

* Corresponding author.

E-mail address: firooza@sums.ac.ir (A. Firoozabadi).

1. Background

Major depression is a common depressive disorder associated with at least two weeks of depressed mood or apathy, and four or more other disturbances in thinking ability, cognition, sleep, appetite, daily energy or psychomotor activations.^{1,2} Major depression is predicted to be the second disabling agent in the world by 2020.^{3,4}

The prevalence of major depressive disorder (MDD) in an individual's lifetime is approximately 17%, occurring 12.7% in men and 21.3% in women.^{1,5} In Iran, the rate of MDD has a wide range, between 6 and 75% in different populations. MDD occurs twice as much in women compared to men.⁶ The most common age for major depression is between 18–29, which is typically the most reproductive period of one's life. MDD can cause poor function in personal and social activities with an increased risk of suicidal tendency. Therefore it forces a great deal of psycho-socioeconomic burden on societies.⁴

Although the exact cause of depression is not well known, coefficient factors such as biological, neurophysiological, immunological, hormonal, genetic and psycho-social factors are involved in it.^{7–9} A number of treatment approaches have been applied as MDD remedies.^{10,11} Among those, antidepressant agents have the most consumption,^{9,12} but their adverse effects may cause intolerance or inadequate responses in patients, decreasing their compliance.¹³ Selective serotonin reuptake inhibitors (SSRIs) – the most frequent and popular antidepressants – have a widespread use in treatment of many psychiatric disorders. The efficacy, tolerability and general safety of SSRIs make them a first-line treatment for patients with major depression. Selective effects of SSRIs enable them to have a relatively mild side effect profile.^{14,15} The most common side effects of this pharmacologic group are sexual dysfunction and drowsiness. Other adverse effects such as weight gain and insomnia have the secondary prevalence rate. Drug-drug interaction is another important issue that should be considered in SSRIs administration.

SSRIs' inhibitory effect on hepatic cytochrome p450 enzymes, may affect other medications metabolism, which could be responsible for drug–drug interactions.^{14,16} Sertraline is a good SSRI candidate for the initial choice of antidepressant medications in patients suffering from major depression. It has fewer side effects in terms of anticholinergic effects, drowsiness and QT prolongation.^{17–19} In addition when drug–drug interaction is a concern, sertraline could be a good choice, due to its lesser inhibitory effects on liver enzymes.¹⁴ It should be mentioned that there are ongoing research efforts for better antidepressant medications with less side effects.²⁰

More recently, the use of complementary and alternative medicine (CAM) has significantly increased, especially in common mental disorders.^{21,22} One important branch of CAM is herbal therapy, which is becoming more popular among some populations.^{23–25}

Nepeta menthoides (Lamiaceae) Boiss. & Buhse is one of the promising medicinal herbs with positive effects on the neurologic system. The anti-nociceptive, analgesic, cognitive stimulant, nerve regenerative and neuroprotective effects of this plant are investigated in multiple animal studies.^{26,27} Although traditional and conventional mechanisms of *N. menthoides* in such trials are not clearly known, but it has been recommended by multiple Persian traditional medical scholars such as Rhazes (865–925CE), Haly Abbas (949–982CE) and Avicenna (980–1037CE) that a medicinal plant with hot nature or temperament might be suitable for the treatment of different neurologic and psychologic diseases including depression.^{28–30} However, considering the secondary metabolites including phenols, flavonoids and terpenoids in this plant, various underlying mechanisms are hypothesized.³¹

To the best of our knowledge, there is only one clinical research study on antidepressant effect of *N. menthoides* as a combination therapy with other conventional antidepressants showing the beneficial adjuvant effect of this herb in the treatment of depression by Firoozabadi et al. in 2014.¹⁰ Regarding the background of *N. menthoides* usage in traditional Persian literatures, its known neuropharmacological effects and the previous positive clinical results, as an adjuvant treatment of depression, the current study was

carried out to assess the effectiveness of *N. menthoides* freeze-dried aqueous extract as a monotherapy compared to sertraline, in the treatment of major depression.¹⁷

2. Methods

2.1. Ethical considerations

The trial protocol was in compliance with the Declaration of Helsinki (1989 revision) and approved by the Local Medical Ethics Committee of Shiraz University of Medical Sciences (SUMS) with reference number: CT-9470-7440 and registered in the Iranian Registry of Clinical Trials (registration ID: IRCT2015031521469N1).

2.2. Study setting

The study was conducted in two psychiatry clinics of Shiraz University of Medical Sciences (Hafez and Emam Reza Clinics) from April to September 2015.

2.3. Study design and patients

This was a two-arm randomized double-blind clinical trial using a parallel design with blocked randomization in a six week period.

Adult outpatients aged 18–65 referring to Hafez and Emam Reza psychiatric clinics of Shiraz University of Medical Sciences participated in the study. They met the Beck Depression Inventory (BDI-II) – the Persian translated Beck Depression Inventory, which has been validated in previous studies –^{32,40} as well as Diagnostic and Statistical Manual of Disorders, fifth edition (DSM-V) criteria for major depression confirmed by at least two psychiatrists. Other inclusion criteria included: lack of other clinical conditions assuming depression (i.e. hypothyroidism); lack of other comorbidities such as diabetes, heart disease, renal disease, hepatic disease, seizure, stroke, disorders with bleeding tendency and active gastrointestinal ulcers; lack of mental disorders (i.e. dementia) or mental retardation; and lack of pregnancy. Patients who satisfied the inclusion criteria and signed the informed consent for participating in the trial were included in the study. The exclusion criteria were: other psychiatric disorders; using any other treatment methods such as psychotherapy or complementary and alternative therapies; allergy to *N. menthoides* or other genera of the mint family (Lamiaceae); allergy to selective SSRIs; alcohol or substance dependency; suicidal risk; needing electroconvulsive therapy; consumption of any psychiatric medications in the four weeks preceding the study; and patients who needed to use medications for a chronic condition.

Patients with eligible criteria were randomly assigned to two groups: group A was treated with *N. menthoides* capsules and group B was treated with sertraline capsules.

2.4. Preparation of test drugs

Oral capsules of *N. menthoides* were prepared by two of the authors at the Department of Phytopharmaceuticals, School of Pharmacy, Shiraz University of Medical Sciences. *N. menthoides* dried herb was purchased from a medicinal plants market in Shiraz. Following authentication by a botanist at the Shiraz School of Pharmacy, a voucher number was specified for the sample (PM-775). The sample was preserved in the herbarium of Pharmacy School at Shiraz University of Medical Sciences. Aerial parts of the herbs were washed, dried, ground and decocted in distilled water with a ratio of 1:10 for ten minutes. The yielded extract was then filtered and concentrated by a rotary evaporator. The concentrated extract was preserved at –54 °C for 24 h. By using a freeze-dryer under vacuum condition at –50 °C, the extract was sublimated for 96 h to obtain

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