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Effectiveness of *Cuscuta planiflora* Ten. and *Nepeta menthoides* Boiss. & Buhse in Major Depression: A Triple-Blind Randomized Controlled Trial Study

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Abstract

Background. Depression is one the most common mental disorders that can be seen all over the world. In traditional Persian medicine, some medicinal herbs are recommended for depression treatment. This study aimed to evaluate the effects of *Cuscuta planiflora* Ten. and *Nepeta menthoides* Boiss. & Buhse in patients with major depression. *Methodology*. This study is a randomized triple-blind controlled clinical trial conducted in the year 2010 in Shiraz University of Medical Sciences on patients with major depression. Pharmaceutical capsules of *Cuscuta planiflora* (500 mg) and *Nepeta menthoides* (400 mg) were prepared by a pharmacist. Patients were randomly assigned to 3 groups: group A (treated with *Nepeta menthoides* capsules and conventional drugs), group B (treated with *Cuscuta planiflora* capsules and conventional drugs), and group C (treated only with conventional drugs). The study period was 8 weeks and depression was measured before and after the study by Beck Depression Inventory and Hamilton Depression Inventory. The data were analyzed by SPSS version 20 and the $P < .05$ was considered statistically significant. *Results*. A total of 43 subjects participated in this study, of whom 81.4% were females ($n = 35$) and 18.6% were males ($n = 8$). The mean $\pm$ standard deviation of age of the participants was 38 $\pm$ 10.9 years. The majority of patients (65.1%, $n = 28$) were married. There were 15 patients (34.9%) in group A, 13 (30.29%) in group B, and 15 (34.9%) in group C. There was a significant decrease in mean scores of Beck and Hamilton depression inventories in the 3 groups after treatment ($P < .01$); moreover, there was more decrease in scores of the Beck and Hamilton depression inventories in groups A and B compared with group C after treatment ($P < .01$). *Conclusion*. Despite the paucity of the population under study, the findings showed that *Cuscuta planiflora* and *Nepeta menthoides* capsules could be effective, affordable herbal medicines with improved cost–benefit in treatment of major depression and it is worth designing further and more extensive studies to get to a more accurate conclusion.

Keywords

Nepeta menthoides Boiss. & Buhse, *Cuscuta planiflora* Ten., major depression, traditional medicine, herbal medicine

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Introduction

Today, depression is a serious disorder and counts among the most common chronic diseases. A number of medications in the several classes have been employed to treat the patients.[1] However, since depression often lasts for several months or years, the consumers are always concerned and worried about their complications. Thus, extensive researches have been conducted in the past 3 decades on antidepressant medicinal herbs and effective herbal medicines have been marketed and in some cases, trials have also been conducted, for example, on St John's wort and Valerian.[2-6]

In *Makhzan Aladviyeh*, one of the main pharmaceutical manuscripts of traditional Persian medicine, lavender (*Ostokhodus*)

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and Cuscuta (*Afteemoon*) are referred to as herbs that were widely applied for neurological disorders. Previous studies have reported the therapeutic benefits of lavender in addition to imipramine for depression management.[7] Moreover, the herb has been recommended to manage depression in prior investigations, solely or in combination with other antidepressants.[8] In such researches, lavender species have been studied. However, in this study, the *Nepeta menthoides* Boiss. & Buhse has been applied as it was mentioned by early Persian practitioners. Concerning the herb *Cuscuta planiflora* Ten., no respective studies were found in the literature, except for antiseizure effects in animal models.[9]

Regarding the issue that herbal medicines are used by people as medications with fewer side effects, and the treatment team was aimed at providing less costly drugs with fewer complications and acceptable efficacy, this study was performed to evaluate the effects of *Cuscuta planiflora* and *Nepeta menthoides* in the treatment of depression.

Methods

Mono-Ingredient Herbal Preparation

Oral capsules of *Cuscuta planiflora* and *Nepeta menthoides* were prepared by one of the authors at the School of Pharmacy, Shiraz University of Medical Sciences. To prepare the *Nepeta menthoides* capsules, initially plants' aerial parts were washed with water, dried, and ground. A decoction was prepared with a ratio of 1:10 (extract to distilled water). The extract was then filtered and was concentrated using a rotary evaporator apparatus with a ratio of 1:10. The concentrated extract was stored at $-20^{\circ}C$ for 72 hours, and subsequently the remaining aqueous part of the extract was sublimated using freeze dryer under vacuum conditions for 96 hours and at $-50^{\circ}C$. Finally, a dry crystalline powder was obtained. Given that the maximum level of consumption of this herb has been reported to be about 8 g as mentioned in the traditional manuscript, the drug was given as 400 mg capsules to patients twice daily.

For preparing the capsules of *Cuscuta planiflora*, given that the plant will be destroyed in case of exposure to heat, the formulation was prepared in a crude form. Therefore, *Cuscuta planiflora* was ground and 500 mg of which was inserted into the capsules. Medieval reports have noted the maximum level of the herb as 8 g daily, and since only the aerial parts were administered, the adjusted dose was determined as 2 g/d or 4 capsules per day.

Patients and Study Design

This study was a prospective triple-blind controlled clinical trial conducted in the year 2010 at Shiraz University of Medical Sciences. All patients who were diagnosed with major depression by at least 2 psychiatrists based on Beck and Hamilton depression inventories and the *Diagnostic and Statistical Manual of Disorders*, fourth edition, criteria were included in the study. The patients with additional underlying (physical or mental) disease, drug addicts, pregnant women, and the patients who received electroconvulsive therapy were excluded. Blocked randomization method was used in this study. All patients were randomly assigned to 3 groups: group A was treated with *Nepeta menthoides* capsules and conventional drugs, group B was treated with *Cuscuta planiflora* capsules and conventional drugs, and group C was treated only with conventional drugs. By conventional drugs, we mean a combination of tricyclic antidepressant and selective serotonin receptor inhibitor group of antidepressants medications. The patients, the person who prescribed the drugs and the person who completed the inventories were unaware of the nature of the drugs. Patients were evaluated by Beck and Hamilton inventories before treatment. The duration of treatment was 8 weeks and at the end of the study, evaluation was conducted again. Since depression is a serious and potentially life-threatening condition, conventional depression medications were prescribed as primary drugs for all patients. Informed consent form was signed by all patients for this study. This study was registered by the ethics committee of Shiraz University of Medical Sciences (Code: 89-5457). Patients' data, including demographic data and the scores of the inventories, were analyzed using SPSS version 20 and the level of statistical significance was considered to be $P < .05$.

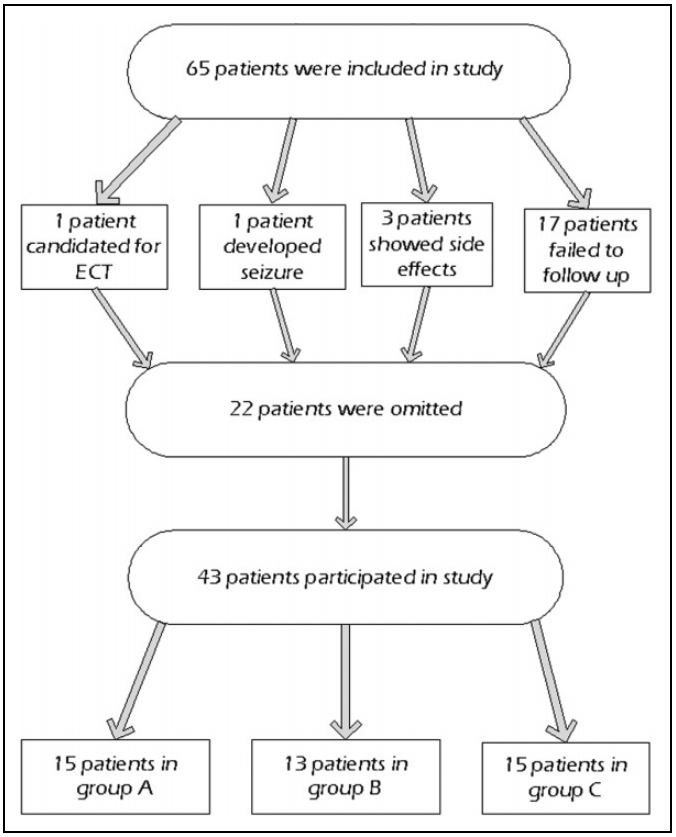

Figure 1. Study flowchart.

Results

Among the 65 participants who were recruited in the study, 22 patients were omitted: 17 patients because of failing to follow-up, 1 patient because of receiving electroconvelsive therapy, 1 patient because of seizure, and 3 patients because of complications (diarrhea, headache, nausea); 5 excluded patients were in group A, 11 patients in group B, and 6 patients in group C. Thus, a total number of 43 subjects participated in this study (Figure 1), of whom 81.4% were females (n = 35) and 18.6% were males (n = 8). The mean ± standard deviation of age of the participants were 38 ± 10.9 years. The majority of patients (65.1%, n = 28) were married, 12 patients (27.9%)

Table 1. The Demographic Data of the Patients.

Characteristic	% (n)
Age in years, mean ± SD	38.0 ± 10.9
Gender	
Female	81.4 (35)
Male	18.6 (8)
Marital status	
Married	65.1 (28)
Single	27.9 (12)
Divorced	7.0 (3)
Place of residence	
Shiraz	41.9 (18)
Other cities	44.2 (19)
Rural areas	9.0 (4)
Education	
Under diploma	55.8 (24)
Illiterate	9.3 (4)
Diploma	25.6 (11)
Higher education	9.4 (4)

Table 2. The Depression Level Among the Study Groups.[a]

	Before Treatment		After Treatment	
Group	Beck	Hamilton	Beck	Hamilton
A	38.4 ± 9.6	29.6 ± 5.5	9.4 ± 1.1	7.0 ± 6.6
B	37.9 ± 9.0	27.2 ± 5.2	9.0 ± 6.5	7.9 ± 4.5
C	32.0 ± 1.15	24.7 ± 5.7	17.5 ± 9.5	14.5 ± 6.1

[a] "A" represents the *Nepeta mentoides* group, "B" represents the *Cuscuta planiflora* group, and "C" represents the control group.

were single, and 3 patients (7%) were divorced. Table 1 shows the demographic data of the subjects. The places of residence of the patients during the study period were as follows: 18 people lived in Shiraz (41.9%, n = 24), 19 patients (44.2%) in other cities of Fars province, and 4 patients (9%) lived in rural areas around Shiraz. The majority of patients (55.8%, n = 24) had not completed their high school, 4 patients (9.3%) were illiterate, 11 patients (25.6%) had diploma, 2 people (4.7%) had associate diploma, and 2 patients (4.7%) had bachelor's degree or higher.

Table 2 shows the mean and standard deviation of scores of Beck and Hamilton inventories before and after treatment in the groups. There were 15 patients (34.9%) in group A (treated with *Nepeta menthoides* capsules and conventional drugs), 13 (30.29%) in group B (treated with *Cuscuta planiflora* capsules and conventional drugs), and 15 (34.9%) in group C (treated only with conventional drugs). To test the efficaciousness of treatment and comparison of the groups before and after treatment, repeated-measures analysis of variance was used. The intergroup test showed that the difference of mean scores between the study groups before and after treatment was significant ($P < .01$). Statistical tests showed no significant difference between the 3 groups in terms of baseline demographic variables and depression scores at the beginning of the study. However, there was a significant difference between the scores of Beck and Hamilton inventories after treatment among the 3 groups ($P < .05$). The depression scores in groups A and B were not significantly different, and the depression scores in group C was significantly higher than that of groups A and B ($P < .01$). Age, gender, marital status, and place of residence had no significant effects on test results of Beck and Hamilton inventories. One patient in group A reported numbness as a side effect during the study period, and 2 patients in group B discontinued taking conventional drugs because of side effects and only used herbal medicines for treatment.

Discussion

This study evaluated the effect of 2 herbal products as an adjuvant in the treatment of depressed patients. The findings of this study showed that *Cuscuta planiflora* and *Nepeta menthoides* extracts could potentially effective agents in depressed patients. Today, complementary indigenous treatments are highly important and the depressed patients take various types of such treatments.[10] Previous studies had shown the elimination of physical and somatic health problems in depressed patients as a result of taking herbal medicines.[11,12] The use of lavender tincture and imipramine was effective in controlling depression.[7] The findings of this study in terms of efficaciousness of *Cuscuta planiflora* and *Nepeta menthoides* capsules along with conventional antidepressant medications are consistent with the previous findings. However, it is not clear that these medicaments have synergistic or additive effect if taken simultaneously with other conventional medications. The antidepressant effects of *Nepeta menthoides* can be justified as being due to the effective factors in this plant on the neurotransmitters involved in depression. A previous study showed the effects of the herb on γ-aminobutyric acid and management of depression.[13] Polyphenolic compounds found in the herb are reported to be effective on benzodiazepine receptors.[8] Other influential factors such as monoterpenes and sesquiterpenes (such as linalool and linalyl acetate) likely magnify the effects of this herb over the central nervous system.[9] One study revealed that the effects of lavender are similar to the effects of chlordiazepoxide. Moreover, linalool in lavender increases noradrenalin and dopamine, which can have a positive effect in controlling depression. Previous studies showed the impact of lavender on the limbic system, particularly amygdala and hippocampus and increase of γ-aminobutyric acid in the amygdala.[14] Linalool in the plant inhibits the release of acetylcholine and has a sedative effect. The findings of the current study regarding the effects of lavender on depression management are consistent with the findings reported by Walsh et al[15] concerning the improvement of the patients' mood and reduction of psychological problems.

No study was found in review of literature concerning the effect of *Cuscuta planiflora* on depression management. In pharmaceutical manuscripts of medieval Persia, taking the infusion of *Cuscuta planiflora* in milk has been recommended for psychiatric disorders. The present study is the first in which *Cuscuta planiflora* has been evaluated for such a disorder.

Based on these findings and considering that the onset of the therapeutic effect of antidepressants is approximately 4 to 6 weeks after treatment,[14] prepared capsules of *Cuscuta planiflora* and *Nepeta menthoides* can be used as a supplement to treatment with conventional medicines in controlling depression in patients. However, precise drug monitoring should be considered for the merge of any possible undesirable effects.

This study had some limitations, the most important of which was the paucity of sample. Furthermore, since the present study was the first clinical trial for *Cuscuta planiflora* on human subjects, the lowest possible dose was chosen according to traditional reports and fortunately, no serious complications occurred in the patients. Thus, future studies may be conducted on larger samples and with higher doses so that results that are more precise can be achieved regarding the use of these medications. Also, further studies could be designed to evaluate the effects of these compounds as independent antidepressants (not only an adjuvant). If the future studies would show such effect, these herbal products may be able to play a significant and important role in the treatment of major depressive disorder.

Conclusion

Given the tendency of people toward traditional medicine and using herbal remedies such as *Cuscuta planiflora* Ten. and *Nepeta menthoides* Boiss. & Buhse for their antidepressant properties, the findings of this study indicate that the use of these preparations along with conventional medications seems to be an effective, inexpensive, and safe treatment for depression management. Further studies are still required to generalize these findings.

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Author Contributions

The work presented here was carried out through collaboration between all authors. AF, AM, and AS defined the research theme, designed methods, and experiments, MMZ and SJ carried out the laboratory experiments, analyzed the data, interpreted the results, and wrote the article. All authors have contributed to, seen, and approved the article.

Declaration of Conflicting Interests

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Ethical Approval

This study was approved by the Ethical Committee of Shiraz University of Medical Sciences, Shiraz, Iran.

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