ORIGINAL ARTICLE

Evaluation of Therapeutic Effect of Eugenia caryophillats product on Mild and Moderate Depressed Patients; A Randomized, Double Blinded and Placebo Controlled Clinical Trial Study

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ABSTRACT

Background: Depression is a serious disease in society today. Its approximate lifetime prevalence in some developed countries is high at about 21%. Some herbs have been used in traditional medicine for many years to treat many diseases including depression and anxiety. Clove is an important medicinal plant due to its extensive proven medicinal effects over the centuries.
Aim: To investigate the mechanisms of antidepressant drugs in Persian medicine and to evaluate the therapeutic effect of adding clove products in patients receiving citalopram with mild to moderate depression.
Methods: First, antidepressants were extracted from Traditional Persian medicine (TPM) books by library study and tabulated according to their mechanism. Then a clinical trial study was performed to evaluate the antidepressant properties of cloves. This study was performed on 60 patients with mild to moderate depression. In this way, patients' depression was first confirmed based on interviews, examinations and Beck questionnaire. They were then randomly divided into two groups of 30 people. In one group, clove product was prescribed with citalopram and the other group received placebo with citalopram. Patients were re-evaluated after 2, 4 and 6 weeks and patients completed the Beck questionnaire.
Results: Our results showed a relative improvement at weeks 2 and 4, but no significant difference was observed with the placebo group. But there was a significant improvement and difference in the clove product group in the sixth week after the start of the study compared to the placebo group.
Conclusion: Many herbal medicines have been mentioned in TPM books that had antidepressant properties. These types of herbal medicines remedies need further study to determine their beneficial properties in relieving depressive disorders. Clove was found to be effective in treating depression during this trial. Clove product can be effective as a drug in the treatment of mild to moderate depression.
Keywords: Depression, Clove, Carnation, Citalopram, Traditional Persian medicine (TPM).

INTRODUCTION

Mental disorders are known to be important health disruptors. Among mental disorders, mood disorders and especially depression have received more attention due to adverse individual, family and social consequences such as suicide, divorce, severe decline in individual and social functioning and disease burden[(1)]. Depression is the fourth most common illness in the world and will become the second most common disability in the world by 2020[(2,3)]. Depression is a chronic illness that affects a person's mood, thoughts, physical and mental health. Symptoms of depression include biological symptoms such as mental retardation, lack of libido, sleep disorders, loss of appetite, and emotional symptoms (I.E., feelings of misery, negativity, low self-esteem, guilt, and lack of motivation)[(4)]. Depression is a mood disorder that affects about 10 to 20% of the population[(5)]. Major depressive disorder includes mood swings that take at least 2 weeks to diagnose and have no history of mania or mild mania[(6)]. In conventional medicine, there is no single known cause for depression, but a combination of genetic, biochemical, environmental and psychological factors are considered to be effective in causing the disease. Norepinephrine and serotonin are two neurotransmitters of biological amines that are most involved in the pathophysiology of mood disorders[(7)]. The severity of depressive illness is determined by the severity of its symptoms[(8-10)]. Various drug therapies are currently used for depression, such as Selective serotonin Reuptake Inhibitors (SSRIs); Serotonin-Norepinephrine Reuptake Inhibitors (SNRH), Monoamine Oxidase Inhibitors (MAOIs)[(11)]. A combination of conventional medical treatments with traditional methods can be more helpful in diagnosing, treating, reducing side effects and costs. In Persian medicine, there are several drugs with good efficacy in mood disorders and depression, but many studies have not been done in this field. Among these plants, Clove, traditionally known as carnation and

scientifically named Eugenia Caryophyllata Thunb, is a tree of the Myrtaceae family, 10 to 20 meters long[14]. Eugenol, chemically known as 4-allyl-2-methoxyphenol (C10H12O2), is the main constituent of essential oils derived from various plants, including cloves[4]. Eugenol is approved by the Food and Drug Administration and is an interesting molecule with a wide range of properties, including analgesic, anti-inflammatory, anti-fungal and anti-bacterial, and anti-hypertensive[5]. Research also shows that eugenol, in addition to environmental effects is capable of affecting the body's central control system and treating stress, epilepsy and depressive disorders. The antidepressant mechanism of eugenol is different from that of imipramine, which could make eugenol a suitable adjunct therapy for patients resistant to routine antidepressant therapy[7]. Clove has traditionally been able to combat depression, but no study has been done to investigate this effect. The present study was designed to investigate the antidepressant effects of clove plant consumption.

MATERIAL AND METHODS

This double-blind randomized clinical trial study was performed on patients with mild and moderate depression referred to psychiatric clinics located in Sari, Iran. Patients with inclusion criteria were included in the sample group. Sampling was performed by non-probability sampling technique.

Inclusion criteria: 1- Declaration of written consent,, 2- Age between 18 to 65 years, 3-Diagnosis of major depressive disorder based on DSM-5, 4. Score between 14 and 28 in the depression test.

Exclusion criteria: 1- Occurrence of high mood symptoms during the treatment period based on the clinical judgment of the therapist, 2- The emergence of suicidal thoughts, 3- Occurrence of unknown drug side effects, 4- The patient's own request to leave the study, 5- Pregnancy and breastfeeding

The sample size of 30 patients for each group was estimated using previous studies on the anti-depressant effects of natural products, 95% confidence interval, 80% potency and difference in efficacy for this drug.

$$n = \frac{2\left(z\left(1-\frac{\alpha}{2}\right)+z(1-\beta)\right)^2 s^2}{\Delta^2}$$

$N=2(Z(1-\alpha/2)+Z(1-\beta)^2)S^2$

$a=0.05\ \beta = 0.8$

$\Delta=X1-X2= s=8$

Procedure: In order to increase comparability, participants were randomly divided into two similar groups in terms of number and basic characteristics (demographic and clinical).

After randomization and assignment of individuals to the two groups, intervention group drugs and placebo were placed in the envelope and coding was done for blinding, so that the patient, physician and researcher did not know any type of treatment. Clove and placebo capsules were similar in appearance, color and size and remained hidden from the presenters and participants until the end of the data analysis. Demographic information and socioeconomic status including variables of gender, age, occupation, level of education, adequacy of economic income, and the main variables of this study (severity of depression) were assessed by a questionnaire. The interpretation of the scores obtained from this questionnaire was as follows: scores of 0-9 without depression, 10-16: mild depression, 17-29: moderate depression and above 29: severe depression. In this study, the characteristics of the recipients did not receive the same characteristics as those without treatment, and the only difference was in the type of treatment, which was done during the randomization process. The duration of the study was six weeks in both groups treated with carnation or placebo with citalopram tablets (maximum dose: 20 mg /day. Patients were evaluated by Beck test at 0, 2, 4, 6 weeks. Drug side effects were also evaluated with a weekly checklist. Clove essential oil and placebo were presented to patients in granulated form in capsules. In case of insomnia, 1-2 mg of lorazepam was prescribed. All the necessary items about the dosage, duration of treatment and method of use were explained to the patients. Due to the fact that cloves are not native to Iran, the clove buds were purchased from the Iranian pharmaceutical market and identified using macroscopic and microscopic properties and its scientific name was determined. First, extraction was performed by distillation method. During the review of various methods, there were several problems in the design of the drug, because the clove plant has a lot of aroma and it was not possible to simulate the drug like a placebo. Therefore, some clove essential oil was reduced by distillation and then extraction was performed. Then starch was added and its powder was encapsulated.

Statistical analysis: SPSS software version 22 was used to analyze the results. Types of descriptive statistical analyzes (such as graphs and descriptive statistics) and inferential analyzes (parametric and non-parametric comparative tests) were performed in this study. Based on this, first all data was transferred from Excel file to SPSS. The data were then analyzed for each question.

Ethical considerations: The study was conducted after obtaining permission from the Research Council and the University Ethics Committee. First, an oral explanation was given to participants about the purpose of the study, its importance, benefits, the generalities of the procedure, and the duration of treatment. Written informed consent was obtained from those who wished to participate in the study. Furthermore, a form of personal information and medical history was completed for patients.(Ethical code:IR.MAZUMS.REC.1398.302)and registered at Iranian registry clinical Trials center(No IRCTID:IRCT20190309042979N1).

RESULTS

In the current study, a total of 60 patients were included. The age of participants in the two intervention groups (clove + citalopram) and control (placebo + citalopram) was 48.2 ± 6.2 and 43.2 ± 11 years, respectively. The mean age of patients was recorded as 45.7 9± 9.2 years which did show a statistically significant difference ($P < 0.05$).

Demographic information sex of the participants in the intervention and control groups was examined. The

intervention group consisted of 10 men (33.5%) and 20 women (66.5%). Furthermore, the control group consisted of 12 men (40%) and 18 women (60%), which did not show a statistically significant difference (P=0.592).

Demographic information of participants' education was also examined in two groups of intervention and control. In the intervention group, 1 person (3.3%) was illiterate, followed by a diploma and less (21 people, 70.1%) and had a high school diploma or higher (8 people, 26.6%). In the control group, 7 participants (23.3%) were illiterate, followed by diploma (9 people, 30%) and had a high school diploma or higher (14 people, 46.7), which showed a statistically significant difference (P = 0.001).

The distribution of occupational frequency of patients in the two groups was examined in Table 1. Occupations of participants in the intervention group included 2 self-employed (6.5%), housewife (19, 63.5%), workers (9, 30%) and 0 employees. The occupations of the participants in the control group included self-employment (0 people), housewife (17 people, 56.6%), workers (10, 33.4%) and (3, 10%) employees.

Table 2 shows the mean depression of patients in both groups at weeks 0, 2, 4, and 6. The mean of patients' depression at the beginning of the study was not significantly different in the two groups (P <0.276; intervention: 16.4 ± 6.2; control group: 15±3.8). The results showed that the average depression in different weeks has a normal distribution. Kolmogorov-Smirnov test was calculated for weeks 0 (0.138), week 2 (0.373), week 4 (0.384) and week 6 (0.362).

Patients' depression at the beginning of the study showed that 36 patients (60%) had mild depression in week 0 and before the intervention and 24 (40%) had moderate depression. There was no significant difference in the severity of depression between the two groups at week 0 (before the intervention). The number of people with mild depression in the intervention group was determined to be 18 (60%) and the number of people with moderate depression was 12 (40%). The number of people with mild depression in the control group was 18 (60%) and the number of people with moderate depression was also found to be 12 (40%), but no significant difference was found between both group (P = 1.0).

Patients' depression in the second week is shown in Table 3. Our findings revealed that 13 patients (21.7%) had no depression and one patient (1.7%) had severe depression. There was no significant difference between the two groups in terms of severity of depression in the second week (P <0.688).

Table 1: Demographic information of the participants in the intervention and control groups

Job	Free	Housewife	Worker	Employee
Groups	Number(%)	Number(%)	Number(%)	Number(%)
Intervention Group	2(6.7)	19(63.5)	9(30)	0
Control Group	0(0)	17(56.7)	10(33.4)	3(10)
P-value	0.245			

Table 2: Comparison of patients' mean anxiety in weeks 0, 2, 4, and 6 in intervention and placebo groups

	Week 0 Mean± SD	Week 2 Mean± SD	Week 4 Mean± SD	Week 6 Mean ± SD
Intervention group	16.4 ± 6.2	13.8 ± 6	9 ± 5.5	7 ± 6.1
Control group	15 ± 3.8	12.6 ± 4.8	9.2 ± 5.3	10.9 ± 4.9
P value Indepent T test	0.276	0.398	0.849	*0.009
Indepent T test .Shows a significant difference at week 6 between the two groups*				

Table 3: Patients' depression in the second week

Depression group	No depression Number (%)	Mild Number (%)	Moderate Number (%)	Severe Number (%)
Intervention group	7(23.3)	18(60)	4(13.3)	1(3.3)
Placebo group	6(20)	18(60)	6(20)	0(0)
P-value	0.688			

Table 4: Comparison of the severity of depression at the end of the fourth week

Depression group	No depression Number (%)	Mild Number (%)	Moderate Number (%)	Severe Number (%)
Group 1	19(63.3)	10(33.3)	0	1(3.3)
Group 2	14(46.7)	14(46.7)	2(6.7)	0(0)
P-value	0.197			

Table 5: Depression severity at the end of the sixth week

Depression group	No depression Number (%)	Mild Number (%)	Moderate Number (%)	Severe Number (%)
Group 1	23(76.7)	5(16.7)	2(6.7)	0(0)
Group 2	10(33.3)	18(60)	2(6.7)	0(0)
P-valu	0.001			

The mean of depression in the intervention and control groups is shown in Figure 1.

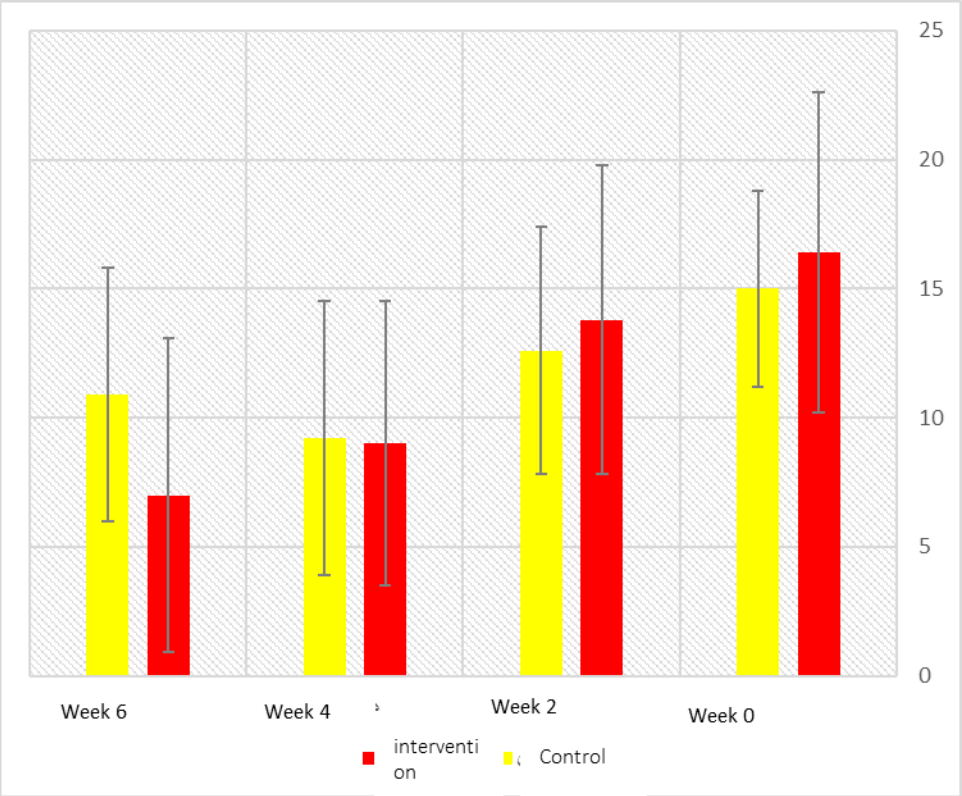

Figure 1: Mean depression at onset, week 2, week 4 and week 6 in intervention and control groups

Patients' depression in the 4th week is shown in Table 4. In the fourth week after the intervention, 33 patients (55%) had no depression, followed by mild depression (24 patients, 40%), moderate depression (2 patients, 3.4%) and severe depression (1 patient, 1.7%).

Depression at week 6 is shown in Table 5. At the end of the intervention, 33 patients (55%) recovered in the sixth week. But 23 patients (38.3%) had mild depression and 4 patients (6.7%) had moderate depression. Repeated Measure test also showed a significant difference between the two groups before and after the intervention in terms of reducing anxiety (P <0.05).

DISCUSSION

Depression is one of the most common debilitating mental illnesses in the world, affecting about 264 million people of all ages around the world. Most studies of traditional Persian medicine have focused on the effects of medicinal plants in the treatment of depression compared to chemical drugs, including the therapeutic effects of rose, dracocephalum, lavender, viper's-buglosses and aphthon (15-16). To the best of our knowledge, no study has been conducted to evaluate the therapeutic effect of clove or its products on depression as a clinical trial, and this study is the first clinical trial to evaluate the effectiveness of this drug compared to routine drugs.

In this study, no disruptive differences were observed between the two groups. In this study, clinically significant reductions in Beck questionnaire scores were found at the end of the sixth week of the study in treatment with clove product.

The mean of patients' depression at the beginning of the study was not significantly different between the two groups according to beck depression inventory scoring. (p=276). It was found to be 16.4 ± 6.2 in the intervention group and 15 ± 3.8 in the control group. Among all participants in the two study groups, 13 patients (21.7%) had no depression in the second week after the intervention, while one patient (1.7%) had severe depression. However, the mean depression did not differ significantly between the two groups in the second week (P = 0.276.) At the end of the fourth week after starting treatment, it was found that 16.6% of patients in the intervention group were treated more than the placebo group and their depression improved. However, the mean depression rate was not significantly different between the two groups in the fourth week (P = 0.398). However, there was a significant difference between the two groups of clove treatment and citalopram treatment along with placebo in the sixth week after onset of treatment (P = 0.009). The effects of clove on depression have not been studied so far and studies have often been performed on rats and mice and positive effects on depression have been reported[18,17]. However, similar clinical trial studies have been performed on some plants for mild to moderate depression, which is briefly stated herein.

In one study, 80 patients were randomly divided into evening primrose oil and nortriptyline groups. All patients

were evaluated at the beginning of the study and in weeks 4, 8 and 12 through Beck Depression Inventory and clinical interview with a psychiatrist. Aforementioned study indicated that the rate of depression at the beginning of the study was 31 ± 6.17 in the evening primrose group and 33 ±7.9 in the nortriptyline group, while these values were recorded at the end of the study to be 20 ± 6.17 and 23 ± 9.7 in the evening primrose and nortriptyline, respectively. The results showed that the mean score of Beck depression in both groups at the beginning of the study and at weeks 4, 8 and 12 significantly decreased and patients' performance improved where the evening primrose was able to reduce the level of depression as much as nortriptyline (19). While a significant effect was observed in the sixth week in the above-mentioned study, but a significant difference was observed in all three times in the present study. But final results were similar to above study.

In a 6-week randomized trial, Darbinyan et al. in 2007 evaluated the safety and efficacy of *hodiola rosea* L. extract SHR-5 in the treatment of current episode of mild/moderate depression, where one group (31 patients) received 340 mg/day of SHR-5, a second (29 patients) were given 680 mg/day of SHR-5 tablets, and a third (29 patients) placebo tablets. Aforementioned study indicated that SHR-5 causes a significant reduction in the development of depression compared to placebo (20). In this study, differences in outcome were also observed in the final stage. Noorbala et al. evaluated the effect of saffron stigma in the treatment of mild to moderate depression in a 6-week, double-blind, placebo-controlled clinical trial. Forty adult outpatients based on DSMII and structured psychiatric interviews were included in the study. Patients had a minimum score of 18 on the Hamilton Scale for depression. In mentioned study, patients randomly received 30 mg saffron capsules twice daily (group one) or placebo capsules twice daily (group two) for 6 weeks.

During 6 weeks, saffron showed significantly better results in terms of Hamilton scale compared to placebo. The difference between the intervention group and the placebo group was seen (P <0.001). In addition, no significant difference was found between the two groups in terms of side effects. The results of this study showed the effect of saffron in the treatment of mild to moderate depression (21), which was similar to the recent trial.

In Zarghami et al.'s study, the antidepressant efficacy and safety of hydroalcoholic extract of A. *procumbens* were compared with fluoxetine. a double-blind clinical trial was conducted in people aged 18 to 65 years with depression. Thirty outpatients were included in the study and divided into two random groups. One group was given fluoxetine capsule and the other group was given1.2 g dried extract of *A. procumbens* capsule orally per day. The results of the second and fourth weeks were similar in the two groups (P = 0.89, P = 0.31), but the effect of fluoxetine was better anti-depressant activity in the sixth week (P = 0.3). The final result showed that this plant can be effective in treating depression (22). It can be seen that the results were almost in agreement with our findings. However, in mentioned study, the effect of the drug decreased in the sixth week, but in the study of cloves, its effect was similar in the two groups until the end of the trial.

A recent study by Abdelrahman et al. in 2018, evaluated the effect of combination of lavender and herbal syrup flavoring versus citalopram on major MDD depressive disorder with anxiety as a double-blind randomized clinical trial. In this six-week study, patients in the citalopram group received citalopram tablets 20 mg daily plus 5 ml placebo twice daily. In the opposite group, they received placebo tablets once a day plus 5 ml of lavender syrupm where 50 participants with MDD and anxiety were randomly divided into two groups, and the mean scores of depression in the citalopram and herbal groups per week decreased significantly. In the third week, there was a significant difference between the two groups (P = 0.75). However, the reduction observed in the herbal syrup group was significantly higher at the end of the sixth week (P = 0.007) As a result, it was found that lavender herbal syrup is an effective and tolerable supplement for the treatment of MDD. The results obtained in the recent study was in line with our findings.

CONCLUSION

There are many herbal medicines in traditional medicine that represent anti-depressant properties and are in needs of further studies to find out their beneficial properties in relieving depressive disorders. Clove was found to be effective in treating depression during this trial.

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