The Effect of Deracocephalum Kotschyi Boiss or Melisa Officinalis on Depression in Patients with Depression

ABSTRACT

Aims The aim of this study was to determine the effectiveness of the hydrolysis extract from Melisa Officinalis in patients with depression taking escitalopram.

Materials & Methods This study was a quasi-experimental study with pre-test and post-test phases with 39 patients in 2023. In the control group, escitalopram (10 mg daily, single tablet) was prescribed for 30 days, and in the intervention group escitalopram (10 mg daily, single tablet) and melissa officinalis hydrochloride capsules (500 mg daily, single tablet) were prescribed for 30 days. Depression was measured by the Hamilton Depression Rating Scale and the Beck Depression Inventory. For the analysis of the data, chi-square test, paired t-tests and independent t-tests with significance of 0.05, SPSS version 26 were used.

Findings Seventy-eight participants were divided into two groups of 39. Regarding demographic variables, there was no statistically significant difference in treatment rates between the intervention and control groups. There was no significant difference between the two groups in severity of depression as measured by the Beck and Hamilton scales in pre-test ($p=0.533$, $p=0.570$). The severity of depression on the depression scale decreased significantly ($p<0.001$) in both groups in post-test, but the severity of depression on both scales decreased significantly ($p<0.001$) in the intervention group after intervention.

Conclusion Melisa Officinalis extract may be effective in reducing symptoms of depression when used in combination with the medicine escitalopram. However, to confirm this finding and to establish lemon balm as a new treatment option, larger, longer term clinical studies are needed to investigate the potential side effects and the exact mechanism of action of the product.

Keywords Depression, Deracocephalum kotschyi, Escitalopram

Introduction

Depression is a common psychiatric disorder and one of the most disabling mental health issues in various societies (1). Depression is a mental state of low mood and reduced activity affecting over 280 million people (about 3.5 percent of the world's population). Depression, which is classified as a mental and behavioural disorder, affects the way people think, act and feel. The main symptoms of depression may include a lack of interest and enjoyment in life (anhedonia), a mood disorder or both (2). Depression is a serious disease in today's society. It is one of the most common conditions, one in 10 patients suffer from major depression (3).

The most commonly prescribed antidepressants are selective serotonin reuptake inhibitors (SSRIs), serotonin-noradine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs). SSRIs are one of the newer treatments for major depression and are usually used as a first line treatment for major depression. Escitalopram is one of these medicines, which is prescribed as a 10- to 60-mg daily suspension (4) .

Antidepressants can take several weeks to take effect and can be accompanied by side effects. Some patients may not be able to cooperate with the use of drugs due to side effects or fear of using chemicals, which may lead to inefficient treatment (3).

Plants have been an important source of medicine for thousands of years. The World Health Organization estimates that near to 80 percent of people still rely mainly on traditional remedies such as herbs for their medicines. Plants are also the source of many modern medicines. It is estimated that up to one quarter of prescribed drugs contain plant extracts or active ingredients obtained from plant substances (5). Dracocephalum kotschyi Boiss has a number of medicinal properties such as antioxidant, antibacterial, anticancerous, antinociceptive, cytotoxic, antihyperlipidemic, antispasmodic, immunomodulatory effects (6) and is effective in treatment of headaches, congestion, and liver disorders (7) .

Dracocephalus kotschyi Boiss is known for its aromatic characteristics, which are attributed to the extract composition. The plant extract contains a significant amount of limonene and geranal and

other monoterpenes, which contribute to its flavouring profile and potential medicinal properties (4).
Studies have shown that certain types of Melisa officinalis have antibacterial, anti-fungal, antioxidant, rosmarinic acid, luteolin, apigenin, antidiarrhoeal and antidiuretic properties (8). Dracocephalum kotschyi Boiss or Melisa officinalis belongs to the mint family (Laminacaceae) and is cultivated in the Mediterranean region in a wide variety of different varieties. The plant is native to Iran and is found in areas such as Yasuj, Ispahan, Mazandaran and Tabriz (5).
Heidari et al. (2015), In a study entitled "Effect of Melisa Officinalis on depression in patients after coronary artery bypass surgery", concluded that the consumption of Melisa Officinalis capsules for seven days significantly reduced depression in patients who had coronary artery bypass surgery (6). Kermanian et al. (2018) in the study, comparing the effects of chamomile tea and black tea on depression and oxidative stress in type 2 diabetic patients, concluded that chamomile tea consumption caused a relative reduction in depression but did not affect oxidative stress (9). Hajrasouliha and Khakpour (2019) in a study titled "Comparison of the antidepressant effects of hydroalcoholic extract of Melisa Officinalis plant with fluoxetine in male mice" concluded that Melisa Officinalis plant extract has an antidepressant effect similar to fluoxetine (10).
Najafi Doulatabad et al. (2009) in a study titled Mint and Depressive Disorders concluded that mint can be used as an adjunct in the treatment of depression (1). Haybar et al. (2018) concluded in a study titled "Effects of lemon balm herbal supplement on depression, anxiety, stress, and sleep disorders in patients with chronic stable angina" that lemon balm herb reduces depression, anxiety, and stress (11).
Ghazizadeh et al. (2020) showed in a study that the hydroalcoholic extract of Melisa Officinalis has anti-anxiety and anti-depressant effects in mice (12).
Although studies have been conducted on the effect of Melisa Officinalis on depression in patients with various diseases and have shown that it reduces depression, no study was found in which escitalopram was prescribed to both groups at the same time and the intervention group received Melisa Officinalis in addition to escitalopram and compared them. In most studies, the control group was given placebo alone. Moreover, the dena Melisa Officinalis may have a different effect from that of Melisa Officinalis from other places. Therefore, considering the tendency of people to use herbal medicines, the nativeness and availability of the lemon balm plant (13), This study aimed to determine the effectiveness of consumption of the hydrocarbon extract from the lemon balm plant in patients with depression receiving escitalopram.

Materials and Methods

Study design, participants and sampling

This study is a two-group non-randomized controlled clinical trial that was conducted with two groups: intervention group and control group.. The study population included patients referred to Shahid Mofatteh Psychiatric Clinic in Yasuj during a one-year period from April to March 2023. The sample size was estimated using G-power software and based on the statistical requirements of the ANCOVA method. The sample size calculation formula was based on the expected effect size of 0.67, the correlation coefficient between repeated measurements of 0.7, the type I error rate of 0.95, and the power of the test of 0.8, and considering the possibility of dropout and lack of cooperation of patients during the study; the sample size was determined to be 78 patients in two groups of 39 patients.
The sample was collected using a non-random convenience sampling method (in an alternating manner; meaning that the first patient received escitalopram, the second patient received escitalopram along with lemon balm, the third patient again received escitalopram, and so on) from patients visiting the psychiatric clinic in Yasuj in the year 1402.
The inclusion criteria for the study included: a diagnosis of mild to moderate depression based on a clinical interview and the Beck Depression Inventory (scoring between 10 and 29) and the Hamilton Depression Rating Scale (scoring between 8 and 23), willingness to participate in the research, age between 15 and 65, absence of underlying diseases affecting depression such as cancer, diabetes, etc., and not having schizophrenia, schizoaffective disorder, psychosis, or anxiety disorders. Outcomes from the study included: worsening of the disease and serious suicidal thoughts, non-cooperation during the study, failure to complete the questionnaire, and general medical illness that occurred during the study and led to discontinuation of the study (e.g., MI).

Data collection tools

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The data collection instruments used in this study consisted of two questionnaires: the Hamilton Depression Rating Scale and the Beck Depression Inventory. The Hamilton Depression Rating Scale, designed to assess the severity of depressive symptoms through a structured clinical interview, was developed by Hamilton (14).

This scale consists of 24 items and is scored by Ballinger using the Likert scale. Its concurrent and construct validity have been independently confirmed through agreement between raters in HDRS scores and structured clinical interview scores. The sensitivity of the scale in detecting positive cases of depression is 87%. The highest sensitivity and specificity of HDRS in multiple studies have been observed at the clinical cutoff point of 17, where the sensitivity was 62.4% and specificity was 92% (15).

In Iran, the validity of this instrument has been assessed through its correlation with the Beck Depression Inventory and the Dysfunctional Attitudes Scale, yielding coefficients of 55% and 39%, respectively. Additionally, the inter-rater reliability has been reported at 95%, indicating a high level of consistency in assessments (16). Based on previous studies, scores ranging from 0 to 7 indicate the absence of depression, scores between 8 and 16 suggest mild depression, scores from 17 to 23 reflect moderate depression, and scores of 24 or higher are classified as severe depression (17). The Beck Depression Inventory consists of 21 items, with each item scored between 0 and 3. The total score ranges from 0 to 63, indicating varying levels of depressive symptoms (15).

The concurrent validity of the questionnaire, determined through its correlation with a psychiatric interview, was found to be 77%. Additionally, its reliability was assessed using the split-half method, yielding a reliability coefficient of 90%, while the test-retest method produced a reliability coefficient of 75% (16). Shapourian and colleagues conducted a study to evaluate the validity and reliability of the Beck Depression Inventory among Iranian students residing in Iran and the United States. The findings revealed that the Cronbach's alpha coefficient for both groups was 0.85 and 0.83, respectively, indicating a high level of reliability for the questionnaire. Furthermore, employing the test-retest method after three weeks, a reliability coefficient of 0.61 was obtained, demonstrating acceptable reliability for the instrument (17). According to the authors' recommendations (Beck, Steer, and Garbin), a score below 10 indicates minimal or no depression, a score between 10 and 18 suggests mild to moderate depression, a score between 19 and 29 reflects moderate to severe depression, and a score between 30 and 63 signifies severe depression (18).

Preparation of Melisa officinalis extract

The Dena Melisa officinalis plant was collected during the summer from the Dena mountain range surrounding Yasuj and transported to the Medicinal Plants Research Center at Yasuj University of Medical Sciences, where it was identified by a botany specialist. Various parts of the plant sample, including leaves, stems, and flowers, were then separated, dried in the shade at room temperature away from direct sunlight, and extracted using a hydroalcoholic method.

To prepare the hydroalcoholic extract, 100 grams of the dried powder was mixed with 500 mL of 70% ethanol and stored for 72 hours at room temperature (22°C) in a dark environment. The resulting extract was filtered using Whatman No. 1 filter paper and subjected to ethanol removal through a rotary evaporator (EV311 lab tech) operating at 100 rpm and 40°C. The alcohol extract was then dried in an incubator at 40°C and stored in a refrigerator until the experiment was conducted. Finally, the powdered extract was encapsulated using a laboratory-grade filling machine to determine appropriate dosage levels (19).

Intervention method and data collection

After approval of the ethical code and necessary permits, this study was conducted on patients referred to the Shahid Mofatteh Psychiatric Clinic in Yasuj. Patients aged 15 to 65 years were interviewed by a psychiatrist, underwent psychiatric evaluations and clinical tests, and were included in the study if they were willing to participate in the study. They entered the process with informed consent and were informed about the extract. First, the patients were interviewed by a psychiatrist; second, they underwent psychiatric evaluation and clinical examination; and third, the Beck and Hamilton Depression Scales was completed on the first day of the study. In the control group, patients received a dose of 10 mg of Escitalopram tablets, once a day, for 1 month, and in the experimental group, patients received a daily dose of 500 mg of lemon balm extract, once a day, for thirty days, in addition to taking 10 mg of Escitalopram tablets, once a day. 1 month after intervention, a re-evaluation was conducted by the interviewing psychiatrist; Psychiatric examination, clinical examination, and completion of the Beck and Hamilton Depression Scales were also performed. Finally, the collected data were analyzed statistically.

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Blinding

In this study, although patients could not be blinded, the data gatherer and the statistician were blinded to patients in the groups.

Statistical analysis

Collected data were analyzed through SPSS19 software with P<0.05 as statistically significant difference. Chi-square and independent sample T-tests were used for demographic variables.as the statistical distribution of the outcome variables was normal, the independent samples T-test, dependent samples T-test, paired samples T-testwere used for between and within group comparison.

Findings

Comparison of demographic characteristics of the intervention and control groups

As shown in Table 1, 78 subjects were enrolled in 2 groups of 39. One group received escitalopram alone as control group and one group received escitalopram and a capsule of lemon balm extract as intervention group. Chi-square analysis showed that there was no significant difference between the two groups in terms of gender (p=0.784) or educational attainment (p=0.263). An independent t-test showed that there was no significant difference in age between the two groups (p=0.811).

Table 1. Comparison of demographic characteristics in the two studied groups

Variables		**Studied groups**		**p-value**
		Intervention N=39 (%100)	**Control N=39 (%100)**	
Gender	**Female**	9 (%23)	8 (%20.50)	0.784*
	Male	30 (%77)	31 (%79.50)	
Education level	**)Illitrate(0**	8 (%20.50)	5 (%12.80)	0.263*
	)Primary school(1-6	5 (%12.80)	9 (%23)	
	)Secoundary school(7-12	15 (%38.50)	15 (%38.50)	
	13-16 (Associated bachelor's degree)	11 (%28.20)	7 (%18)	
	)Master and Doctorate(17-20	0 (%0)	3 (%7.70)	
Age		35.38±12.90	34.74±10.61	0.811**

* Chi square test

** Independent t-test

Determination and comparison of the severity of depression in intervention and control groups

As shown in Table 2, the independent t-test results showed that the two groups did not differ significantly in pre- and post-test depression severity on the Beck Depression Inventory (p=0.533), but that the post-test depression severity was significantly reduced in both groups (p<0.001). The results showed that the severity of the depression on the Beck Depression Inventory was significantly lower in the intervention group (p<0.001).

Table 2. Assessment and comparison of beck depression severity in intervention and control groups

Groups	**Pre-intervention mean**±SD	**Post-intervention mean**±SD	**p-value**
Intervention)39=N(	13.64±6.21	4.00±3.02	0.001**<
Control)39=N(	14.44±4.91	8.44±2.95	0.001**<

p-value	0.533*	0.001*<	

* Independent t-test
** Dependent t-test

As shown in Table 3, the independent t-test results showed that there was no significant difference between the two groups in terms of severity of depression on the Hamilton Depression Rating Scale prior to intervention (p=0.570), and that the paired t-test results showed that the severity of depression on the Hamilton scale decreased significantly after intervention (p<0.001). However, the severity of the depression on the Hamilton scale in the intervention group was significantly lower (p<0.001).

Table 3. Assessment and comparison of hamilton depression severity in intervention and control groups

Groups	**Pre-intervention mean**±SD	**Post-intervention mean**±SD	**p-value**
Intervention)39=N(	13.44±2.34	3.46±2.66	0.001**<
Control)39=N(	13.13±2.41	8.62±2.83	0.001**<
p-value	0.570*	0.001*<	

* Independent t-test
** Dependent t-test

Discussion

This study aims to determine the effectiveness of the hydraulic extract from Melissa Officinalis in depressed patients taking Escitalopram. The results of this study showed that both the intervention group (using Melissa Officinalis hydrochloride extract with Escitalopram) and the control group (taking Escitalopram alone) had an improvement in depressive symptoms after intervention compared to before intervention.

One of the characteristics of Escitalopram that makes it different from other SSRIs is its allosteric property. This unique property allows it to modulate serotonin reuptake through mechanisms that go beyond traditional serotonin reuptake inhibitors (20). Moreover, the combination of S citalopram with other antidepressants, such as mirtazapine, has been shown to be beneficial by engaging the different mechanisms of action and may improve treatment outcomes (21). In this study, the same effect was seen when escitalopram was used alone, although the combination of Melissa Officinalis extract and escitalopram resulted in a more pronounced improvement in the depression of the patients.

Heidari et al. (2015) conducted a study titled 'The Effect of Melissa officinalis on Depression in Patients After Coronary Artery Bypass Surgery' and found that consuming Melissa officinalis capsules for seven days resulted in a significant reduction in depression levels in coronary artery bypass surgery patients. Fear of returning to work and normal life is a major factor in the development of depression in these patients. Therefore, this herbal medicine could be incorporated into the treatment regimen of these patients to prevent adverse postoperative and discharge outcomes (13). This study is consistent with the findings of the aforementioned article, and based on the obtained results, Dena Melissa officinalis may be effective in reducing depression. The difference from the present study was that in the above study, a placebo was used for the control group, whereas in the present study, escitalopram was administered to both groups, with Dena Melissa officinalis added to the intervention group.

In line with the present study, Hajrasouliha and Khakpour (2020) conducted a study titled 'Comparison of the Antidepressant Effect of Melissa officinalis Hydroalcoholic Extract with Fluoxetine in Male Syrian Mice.' They concluded that the extract of Melissa officinalis has an antidepressant effect similar to that of fluoxetine (10). This study is consistent with the findings of the aforementioned article, and based on the obtained results, Melissa officinalis Denayi may have

an effect on reducing depression. The difference between the two studies is that fluoxetine was compared with Melissa officinalis, and the study was conducted on animals. Furthermore, to evaluate the antidepressant effect of Melissa officinalis, the forced swimming test and the suspension test were used in male Syrian mice.

Haybar et al. (2018) conducted a study titled 'Effects of Melissa officinalis Herbal Supplement on Depression, Anxiety, Stress, and Sleep Disorders in Patients with Stable Chronic Angina.' The results showed that by the end of the study, the intervention group that received Melissa officinalis capsules had a significant reduction in depression, anxiety, stress, and overall sleep disorder scores compared to the placebo group (11). Similarly, as observed in the present study, the results of the study showed that Melissa officinalis plays a role in reducing the level of depression in patients. Moreover, it led to an improvement in patients' quality of life. The difference between this study and ours was that a placebo was administered to the control group, whereas in the present study, escitalopram was prescribed to both groups.

Similarly, as observed in the present study, the study by Talebi et al. (2022) demonstrated that Melissa officinalis extract has an antidepressant effect (14). Melissa Officinalis is an important medicinal plant with a large number of active constituents and great potential to safeguard human and animal health in Iran. The plant was also reported to be a remedy for inflammatory pain, headaches, congestion, fever, renal pain, dyspepsia, muscle spasm and wound healing effects (6). Dracocephalum kotschyi has anti-hyperlipidemic and anti-spasmodic activities and is effective in treatment of headaches, congestion, and liver disorders (7).

According to the result of the present study that Melissa Officinalis can be helpful as an auxiliary drug in the treatment of depression, it is somewhat consistent with these two studies. Melissa Officinalis have anti-diabetic and anti-depression activities. The study aimed to determine the efficacy of M. officinalis extract on depression, anxiety, and sleep quality in patients with type 2 diabetes with depressive symptoms (22).

Although the above-mentioned study showed the effect of Melissa Officinalis on depression in patients with diabetes, and the present study showed the effect of this plant on depression in patients with depression, in both studies, improvement in depression was observed. Melissa Officinalis (Lemon Balm) significantly improved mean anxiety and depression scores compared with the placebo, without serious side effects. Melissa Officinalis may be effective in improving anxiety and depressive symptoms, particularly in the acute setting (23).

Although improvement in depression was observed in both of the above studies, the difference between this study and our study was that the control group received placebo and did not use any antidepressants such as escitalopram or others. The intervention group received only Melissa Officinalis.

The use of Melissa Officinalis could reduce the incidence rate of postpartum blues, which is one of the most common postpartum psychiatric disorders, without the development of possible side effects (24). Melisa officinalis has serotonergic antidepressant activity to prevent depression in rat (25). Melissa officinalis can significantly reduce anxiety, depression, improve sleep quality and may be useful for burn patients as a daily drink (26).

The mentioned studies have shown the effect of Melissa Officinalis on the improvement of psychological problems after childbirth, depression and anxiety of patients with burns and depression of rats. Although the nature of patients' depression was different and also the number of samples in these two studies was different, it is somewhat consistent with the results of the present study.

Although the strength of the study was the observance of research ethics and the Giving of antidepressants to both groups in addition to the intervention group, it was also a limitation of the study because there was a possibility of synergistic effect and perhaps it had a different effect if it was prescribed to one group Without Escitalopram alone. Another limitation of the study was the use of a mental questionnaire, which may not accurately indicate the level of depression.

Conclusion

People have long realized that plants can be used as a cure for some diseases, and some plants are effective in treating neurological and psychiatric diseases; in the present study, Melissa Officinalis as an adjunct drug is effective in treating mild to moderate depressive disease; however, to confirm the results and introduce Melissa Officinalis as a new treatment option, more extensive and long-term clinical studies are needed to examine the exact dosage, exact mechanisms of action and

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