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Effects of *Melissa officinalis* L. on Reducing Stress, Alleviating Anxiety Disorders, Depression, and Insomnia, and Increasing Total Antioxidants in Burn Patients

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Abstract

Background: Burns are a major cause of stress, and afterwards, many patients suffer from anxiety, depression, and insomnia. Also, the levels of serum antioxidants increase after burns, which causes problems in patients. It has been observed that *Melissa officinalis* L. can increase serum antioxidant levels and improve mood and sleep quality.
Methods: Thirty-six patients who were admitted to Shahid Motahari Burn hospital were selected. Patients in the control group consumed black tea, and those in the experimental group received Melissa tea. The serum levels of antioxidants were measured using spectrophotometry once before the intervention and at 20 days after the intervention. Depression, anxiety, and insomnia levels were each measured by the Beck, Kettles, and Petersburg questionnaires, respectively.
Results: In the study group, the percentages of those experiencing anxiety (P value: 0.023) and depression (P value: 0.002) were significantly less than those of the control group. Also, sleep quality in the experimental group taking Melissa tea increased significantly (P value: 0.031). However, the mean serum antioxidant levels were not significantly different between the control and experimental groups (P value: 0.96).
Conclusions: *Melissa officinalis* L. can significantly reduce anxiety and depression and improve sleep quality. Therefore, its consumption may be useful for burn patients as a daily drink. However, the effects of Melissa on increasing serum antioxidants needs further investigation.

Keywords: Anxiety Disorders, Depression, Insomnia, Burn Patients, *Melissa officinalis* L

1. Background

Burns are one of the most common medical problems throughout the world, which can be caused by thermal, chemical, electrical, or radiation injuries (1). High temperatures can break the chemical bonds between the molecules in the skin, which can facilitate the development of free radicals with unpaired electrons (2). Free radicals are active and unstable, and can lead to important biochemical reactions in the skin (3). High levels of free radicals can cause oxidation of biomolecules and result in tissue damage, cell death, and various other diseases (4, 5). Compounds containing antioxidants can deactivate free radicals (6-8). In the past, synthetic antioxidants such as butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) were employed (9-11), but their usage has been forbidden because of their possible carcinogenic and toxic effects.

Most burn patients are disturbed by anxiety, depression, and insomnia. Admission into a hospital, isolation, pain upon dressing, fear of death, and concern about the long-term complications of the burn, especially on an exposed area of the body, are sufficient to cause these sorts of problems. Anxiety here includes the behavioral, cognitive, and physiological responses to the state of discomfort that immediately develops after an accident (12). Depressive disorders are quite prevalent and can cause disability in patients (13, 14). Depression is a heterogeneous, complex, and recurrent disorder which can lead to different problems such as social and familial issues, suicidal tendencies, and increased risk of cardiovascular and other conditions (15-17). Ahrari et al. showed that depression is very common in the early stages following a burn (18). Insomnia is a heterogeneous disorder that induces problems at the start

and with the continuity of sleep (19). Another definition of insomnia refers to subjective complaints about reduced sleep duration, quality, and depth (20).

Treatment of these disorders could improve the quality of the patients' experiences and provide better outcomes. However, it has been shown that some of the medication which is used for the treatment of anxiety and insomnia can produce a lot of side effects, as well as tolerance (21, 22). Derivations of plants such as valerian, lime blossoms, Passiflora, and lemon balm have developed commercially as alternative treatments because they have limited side effects (23-25). Therefore, it has been suggested that for the treatment of anxiety and sleep disorders, herbal derivations as well as chemical drugs should be used.

Certain of these properties can be found in the derivatives obtained from the leaves of *Melissa officinalis* L. (lemon balm) (26). This plant is from the *Lamiaceae* family, and it is one of the most popular medicinal plants in central and southern Europe, the Mediterranean region, and the northern parts of Iran (27). The boiled form of these leaves has a similar scent to lemon. In Iran, Melissa is called Faranjmoshk, Badranjbouye, or Rangbu 26. The chemical contents of the plants contain essential fats and derivatives of caffeic acid (rosmarinic acid and trimeric compounds) and some flavonoids (Luteolin 7-O-glucoside) (28).

Melissa is a plant that has different biological activities. Its reported effects include improving mood (29, 30) decreasing stress (31), relieving anxiety (32), increasing levels of body antioxidants (33, 34) treating digestive problems such as spasms or functional disorders of the gastrointestinal tracts (35) acting as an anti-tumor agent (28), acting as an anti-viral agent against conditions such as herpes (36, 37), acting as an anti-microbial substance (38), and effectively improving DNA damage from low doses of ionizing radiation exposure (39). Rosmarinic derivatives of Melissa are used to combat the effects of the herpes virus, as a sedative for alcoholic derivation, and as a digestive (Melissa fats) (40, 41). In addition, the essential fat of Melissa is used in the pharmaceutical industry.

In two studies on rats and then on humans using Cyracos (a standardized extract of Melissa), there were reported improvements in symptoms of anxiety and also insomnia (42, 43). In 2012, Fazli et al. treated (31) workers exposed to aluminum with Melissa administered in tea-bags and, after completion of the treatment, the levels of antioxidants dramatically increased and body fat decreased (27).

2. Objectives

Since burn patients frequently suffer from depression, anxiety, and insomnia, and there are not adequate studies about the effects of Melissa on these disorders in burn patients, we designed this clinical trial to address this absence in the research. In addition, because antioxidant levels elevate in the body after a burn, these particular effects of Melissa were also evaluated in burn patients.

3. Methods

This study was a randomized clinical trial which was conducted on 36 patients who were hospitalized in the Shahid Motahari Burn hospital in 2013. The study was approved by the ethical committee of the university, and informed consent was obtained from all patients. This study was registered on the Iranian registry of clinical trials (Code: IRCT201205198177N4). The sample size was calculated as 36 patients (18 patients per group) according to α error of 0.05, β error of 0.08, effect size of 0.9805807, and the calculated effect size of 0.35 ± 0.18 versus 0.20 ± 0.12 with G*Power 3.1.3 software. Data were analyzed by SPSS version 19 software. All of the information was calculated in terms of means $\pm$ SD. To investigate the antioxidant, depression, anxiety, and insomnia variables, we used a t-test and chi-squared test, respectively. A P value of < 0.05 was considered statistically significant. The inclusion criteria were patients with second and third degree burns with 35 to 55% total body surface area (TBSA) burned that could tolerate oral medication and nutrition, and were estimated to stay in the hospital for 20 days. If the patient was discharged during the study, another patient was replaced. Exclusion criteria included pregnancy; lactation; consumption of anti-anxiety drugs, antidepressants, or sedatives 10 days before the start of the study; diabetes; asthma, hypo- and hyper-thyroidism; depression, schizophrenia, or psychosis; and consumption of serotonin-reuptake inhibitors.

3.1. Interventions

Patients in the control group were given black tea in the form of a tea-bag twice a day for 20 days. Those in the experimental group received the Melissa plant in the form of a tea-bag (2.5 gr per tea-bag) twice a day for 20 days. The patients were not informed about the type of tea that they were given, but they could likely discern the difference of taste, color, and odor. Therefore, this study was not completely double-blinded.

3.2. Measurements

The interview was performed by an independent observer that was blind to the type of tea that was administered to each patient. Depression was measured using the Beck depression inventory (categorized into four groups of no depression, mild, moderate, and severe depression),

anxiety was measured with Kettles' anxiety questionnaire (classified into four groups of no anxiety, mild, moderate, and severe anxiety), and insomnia was measured by the Petersburg sleep quality index (from poor to good sleep quality). These tests were taken once before beginning the trial and then after 20 days of using the tea (black tea for the control group and Melissa for the experimental). Also, 5 mL of blood was obtained from each patient once before beginning the trial and another time after 20 days of using either black tea or Melissa. The blood serums were removed after 10 minutes of centrifugation at 3000 rpm, and the samples were stored at -80°C. Then, the total antioxidant levels of the samples were measured through spectrophotometry.

4. Results

Table 1 shows the percentages of patients with good or poor sleep quality in the control and experimental groups both before and after the intervention. The number of patients with good sleep quality after the intervention in the experimental group increased significantly (P value = 0.031); however, in the control group, the number of patients with good sleep quality after the intervention did not increase significantly (P value = 0.500).

Table 2 shows the percentages of patients with mild, moderate, and severe levels of anxiety in the control and experimental groups before and after the intervention. The number of patients with no anxiety in the experimental group increased significantly (P value = 0.023) after the intervention; however, in the control group, the number did not increase significantly (P value = 0.351).

Table 3 demonstrates the percentages of patients with mild, moderate, and severe levels of depression in the experimental and control groups before and after the intervention. The percentage of patients with no depression in the experimental group increased significantly (P value = 0.002) after the intervention; however, in the control group, the percentage did not increase significantly (P value = 0.236).

The mean serum antioxidant level in the experimental group before the intervention was 2.58 $\pm$ 0.62, and after the intervention, it was 2.56 $\pm$ 0.62. The result for the control group before the intervention was 2.8 $\pm$ 0.94, and after the intervention, it was 2.67 $\pm$ 0.92. Mean serum antioxidant levels in the experimental group (P value = 0.931) and control group (P value = 0.591) were not statistically significant (Table 4).

Table 5 shows the differences between antioxidant levels, anxiety, depression, and sleep quality in the experimental and control groups. Anxiety levels significantly changed after the intervention (P value = 0.006). Also, depression significantly changed after the intervention (P value = 0.014). Similarly, sleep quality significantly changed in both groups after the intervention (P value = 0.013). However, the total antioxidant levels in the body did not significantly change for both groups after the intervention (P value = 0.96).

5. Discussion

Burn patients complain about anxiety, depression, and insomnia, and effective treatment of these conditions could improve their quality of life. Also, the increase of serum total antioxidant levels can deactivate free radicals, which is helpful for healing burn injuries. Any drug which can decrease anxiety and depression levels in burn patients and increase sleep quality and serum antioxidant levels can help burn patients to improve faster. Several studies have reported that Melissa may have such effects, but evidence has thus far been insufficient.

According to a recent study 62.3% of burn patients complain about depression (18). Alvi et al. reported that, from among 100 burn patients who were hospitalized, 82% had anxiety: 26% had mild anxiety, 22% had moderate anxiety, and 34% had severe anxiety. Moreover, 58% of the patients had depression: 26% had mild depression, 14% had moderate depression, and 18% had severe depression (44) Furthermore, Robert et al. examined the effects of imipramine and chlorate hydrate on the treatment of acute anxiety disorder in burn children. In this study, imipramine was effective for the treatment of acute anxiety disorder (45).

It was also reported that 73% of patients who were hospitalized due to burn injuries had sleep problems (46). Medical treatment of insomnia in burn patients includes benzodiazepines, non-benzodiazepines, and antidepressants (47). It has been reported that zolpidem and haloperidol are effective for the treatment of insomnia in patients with burn injuries (48). Case et al. found that Cyracos, which is the standard extract of Melissa, could be effective for patients with mild to moderate anxiety. This drug could also improve sleep quality in patients. It has also been reported that Cyracos could be an effective alternative to chemical drugs in the treatment of patients with anxiety (42).

According to pubmed and google scholar searches, no study has yet been done on the effects of Melissa specifically on burn patients. In this study, *Melissa officinalis* L. was able to reduce anxiety levels in burn patients, which was significantly different from the results for the control group. This plant also decreased the percentage of patients with mild to moderate anxiety after intervention, but had no effect on patients with severe disorders. In this study,

Table 1. Percentages of Patients With Good and Poor Sleep Quality in the Experimental and Control Groups Before and After the Intervention

Groups	Results		
	Percentage of Patients with Good Sleep Quality	Percentage of Patients with Poor Sleep Quality	P Value
Control group before intervention	38.9%	61.1%	0.500
Control group after intervention	50%	50%	
Experimental group before intervention	33.3%	66.7%	0.031
Experimental group after intervention	66.7%	33.3%	

Table 2. Percentages of Patients with Mild, Moderate, and Severe Levels of Stress in the Control and Experimental Groups Before and After the Intervention

Groups	Results				
	No Stress	Mild Stress	Moderate Stress	Severe Stress	P Value
Control group before intervention	66.2%	11.1%	11.1%	11.1%	0.351
Control group after intervention	72.2%	5.6%	5.6%	16.7%	
Experimental group before intervention	50%	22.2%	22.2%	5.6%	0.023
Experimental group after intervention	77.8%	11.1%	5.6%	5.6%	

Table 3. Percentages of Patients With Mild, Moderate, and Severe Levels of Depression in the Experimental and Control Groups Before and After the Intervention

Groups	Results				
	No Depression	Mild Depression	Moderate Depression	Severe Depression	P Value
Control group before intervention	66.7%	11.1%	11.1%	11.1%	0.236
Control group after intervention	66.6%	11.1%	11.1%	11.1%	
Experimental group before intervention	55.6%	22.2%	11.1%	11.1%	0.002
Experimental group after intervention	72.2%	11.1%	5.6%	11.1%	

Table 4. Mean Serum Antioxidant Levels in the Experimental and Control Groups Before and After the Intervention

Groups	Results	P Value
	Mean Serum Antioxidant Level	
Control group before intervention	2.80 ± 0.94	0.591
Control group after intervention	2.76 ± 0.92	
Experimental group before intervention	2.58 ± 0.62	0.931
Experimental group after intervention	2.59 ± 0.62	

in agreement with the previous reports, *Melissa officinalis* L. could reduce the percentage of patients with mild to moderate depression, with results that were significantly different from those of the control group. However, this plant could not decrease the percentage of patients with severe depression. In this study, in agreement with the previous reports, Melissa significantly improved quality of sleep. Therefore, the effects of Melissa on treating anxiety, depression, and insomnia in the present study were the same as those reported in many other studies among

Table 5. Differences Between Antioxidant Levels, Stress, Depression, and Sleep Quality in the Experimental and Control Group

Groups After Intervention	dif	P Value
Stress level in control group	-0.38	0.006
Stress level in experimental group	2.3	
Depression in control group	2.7	0.014
Depression in experimental group	1.66	
Sleep quality in control group	-0.111	0.013
Sleep quality in experimental group	1.333	
Antioxidant level in control group	0.400	0.96
Antioxidant level in experimental group	-0.0008	

patients without burns as well as those conducted on animals.

In a healthy person, a balance exists between free radicals and scavengers, but this balance is disrupted after traumatic events and increased reactivated oxygen species. Moreover, trauma and burns activate neutrophils and produce free radicals (49). This situation can suppress the immune system of patients. Hence, consumption of antioxidants can increase the level of immunity in patients (50). A study published in 2012 by Frisman et al. was conducted on 66 burn patients, and it demonstrated that the activity of superoxide dismutase significantly decreased in the first week after burn injuries; however, after the first weak, the activity increased up to the normal level. In this study, the activation of catalase showed the same pattern; however, the difference from the control group was not significant (51).

Rasik and Skala demonstrated that free radicals, which are produced in skin injuries, injured cell membranes, DNA, proteins, and lipids could delay wound healing (52). Traber et al. found that levels of α-tocopherol decreased after burn injuries (53). They also concluded that it is beneficial to use α-tocopherol after burn injuries to prevent the depletion of vitamin E (54). Moreover, Al-Jawad et al. showed that antioxidants play an important role in the healing of burn injuries, and also decrease the mortality rate in burn patients (55).

According to recent studies, Melissa is able to increase serum antioxidant levels. In a study by Fazli et al., total serum antioxidants, triglycerides, and cholesterol increased in workers exposed to aluminum who were treated with Melissa officinalis (27). Zeraatpishe et al. found that Melissa could increase total antioxidant levels, including catalase, super oxidase dismutase, and glutathione peroxidase (39).

The effect of Melissa on antioxidant production in burn patients had not been examined, and this work was the first study in this regard. In this study, unlike the other above-mentioned studies, the levels of total antioxidants were not significantly different before and after the intervention for both groups. This difference may be attributed to the point that, in this study, Melissa was administered in a tea-bag, while in most of other studies, extracts of this plant were used. It seems that because of the lower concentration of Melissa in tea-bags, the levels of antioxidants did not increase as expected.

The study has some limitation in design and implementation. Although the selected patients did not have very severe burns, impairment in oral absorption capabilities of the tea may have existed. In addition, due to the different taste and smell of the tea, double-blinding of the patients and observer was not possible here. Furthermore, oral absorption of this plant may decrease as a result of impaired gastrointestinal absorption.

5.1. Conclusion

This study demonstrated that Melissa can decrease anxiety and depression and improve sleep quality in burn patients. Since Melissa herbal tea is effective for reducing anxiety and depression and improving sleep quality in burn patients, it may be recommended as a daily drink for these patients. However, further studies are needed to show the effects of Melissa on antioxidant levels in burn patients.

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Footnote

Authors' Contribution: Study concept and design: Mohammad Javad Fatemi; acquisition of data: Shirin Chehroudi, Rogayeh Samimi; analysis and interpretation of data: Mohsen Saberi; drafting of the manuscript: Shirin Chehroudi; statistical analysis: Mohsen Saberi; administrative, technical, and material support: Seyed Hamid Salehi; study supervision: Mohammad Javad Fatemi, Hossein Akbari.

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