Effect of *Melissa officinalis* Capsule on the Intensity of Premenstrual Syndrome Symptoms in High School Girl Students

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Background: Several studies are conducted on Premenstrual Syndrome (PMS). However, a few herbal surveys exist on the treatment of PMS in Iran. Due to the sedative effects of *Melissa officinalis* (*M. officinalis*), this question comes to mind that "can it be used in the treatment of PMS symptoms?"

Objectives: The current study aimed to assess the effect of *M. officinalis* capsule on the intensity of PMS in high-school girls.

Materials and Methods: A double-blind randomized, placebo-controlled trial was performed on 100 high school girls from 2013 to 2014. The intervention group (n = 50) received 1200 mg of *M. officinalis* essence daily from the first to the last day of their menstrual cycle for three consecutive cycles. The second group (n = 50) received the placebo. The premenstrual symptoms screening tool was used to assess the intensity of PMS symptoms in the two groups before and one, two, and three months after the intervention. The data were analyzed using paired t-test and repeated measures analysis of variance.

Results: The results of repeated measures test revealed a significant reduction (P < 0.001) in PMS symptoms. Overall, the mean score of PMS intensity in the intervention group was $42.56 + 15.73$ before the intervention and changed to 32.72 ± 13.24, 30.02 ± 12.08, and 13.90 ± 10.22 at the three consecutive months after the intervention, respectively (P = 0.001).

Conclusions: *M. officinalis* capsules were effective in reduction of the PMS symptoms. Yet, application of this medication requires further investigations.

Keywords: Melissa officinalis; Premenstrual Syndrome; School

1. Background

Premenstrual Syndrome (PMS) is one of the most common disorders among females before menopause (1). PMS is defined as the periodical recurrence of a set of annoying physical, psychological, and social symptoms in the luteal phase of menstrual cycle. Females with severe emotional symptoms are considered with premenstrual dysphoric disorder (2). Millions of females worldwide experience this disorder in their reproductive ages (3). The relative prevalence rate of PMS and premenstrual dysphoric disorder is reported to be between 98.5% and 2.8%, respectively (4). The prevalence of this syndrome varies from 60% to 80% in the Asian countries; 66.6% in Turkey (5), 76% in China (6), and 63.1% in Malaysia (7). American College of Obstetrics and Gynecology (ACOG) reported the prevalence of this syndrome 65.5%, with 8.75% of the patients requiring specialized treatments (8). In Iran, it is estimated that 98.2% of university female students experience at least one of the PMS symptoms at age of 18 - 27 years old (9). Sometimes the physical and mental symptoms of PMS are so severe that need to be treated (10, 11).

The etiology of PMS and dysphoric disorder are unknown, but they are considered multi-factorial resulting from internal and external factors (12). Biological, physiological, environmental, and social factors are also reported to be involved in the disorder (13). Although the causes of this disorder are still unknown, research demonstrated that supportive strategies, such as writing the symptoms down, might be beneficial in diagnosis and management of the disorder. Moreover, changing lifestyle (healthy diet, vitamins, mineral supplements, primrose oil, restricting use of sodium and caffeine, reduction of stress, and doing sports) (2), hormone therapy (estrogen, oral contraceptive pills, GnRH analogues, danazol and progesterone), diuretics, anti-depressants, bromocriptine, surgery, psychotherapy, and Serotonin Reuptake Inhibitors (SRIS) are proposed as the first line

treatments in this regard (14). Besides, fluoxetine, paroxetine, and sertralin are reported to be effective to control the symptoms. However, side effects of pharmacological treatments are mentioned in some studies (15-19).

In the past decades, complementary and alternative methods such as homeopathy and herbal medicine were frequently used in alleviation of the PMS (11, 20-23) symptoms. A study performed in Iran, investigated the effects of aquatic extract and essence of *M. officinalis* and reported that this plant has anti-depression and sedative effects (24). *Melissa officinalis* is a bushy, aromatic plant from the mint family labiatae. Although more than 100 chemical compounds have been identified in *M. officinalis*, its main components include citral, linalool, geraniol, β-Caryophyllene oxide, phenolic acid, tannins, rosmarinic acid and caffeic acid. *Melissa officinalis* can be effective to improve cognitive function and its effect is similar to that of triazolam (25, 26).

Several studies are conducted on PMS in Iran. However, most of them focused on the prevalence of premenstrual symptoms and dysphonic (27), types of symptoms (28), efficacy of stress management or counseling to reduce symptoms (29). However, less attention is paid to treatment and a few herbal surveys exist on the treatment of PMS in Iran. Nonetheless, due to the sedative effects of *M. officinalis*, this question comes to mind that "can *Melissa officinalis* be used to treat PMS symptoms?

2. Objectives

The current study aimed to investigate the effect of *M. officinalis* capsule, as a substitute for chemical medicines, on the intensity of menstrual cycles in high-school girl students in Shiraz, Iran.

3. Materials and Methods

The current double-blind randomized clinical trial was conducted on 100 high school girls during 2013 - 2014. Sample size was calculated based on the results of a study that used *Crocus sativus* L. (saffron) to treat PMS (20). Considering the effect size of 2 (reflecting the difference between the two groups), Standard Deviation (SD) of 1.3, type I error probability of 5%, power of 0.9, it was estimated that 42 subjects were needed in each group. Yet, considering a possible attrition rate of 20%, 50 subjects were recruited in each group.

The study subjects were selected through random cluster sampling. At first, under the supervision of the department of education, four girl high schools (including 800 students) were selected from the four educational districts of Shiraz, Iran. Then, in each high school, the students with symptoms of PMS were invited to take part in the study among which, considering the inclusion criteria, 100 subjects were selected and then randomly allocated into the intervention (n = 50) and the placebo groups (n = 50).

The inclusion criteria were willing to participate in the study, being a high school student, obtaining a score < 23 from the General Health Questionnaire (GHQ), gaining a score > 20 from the Premenstrual Syndrome Screening Tool (PSST), not using vitamin supplements during the study, not having used hormonal drugs such as oral contraceptive pills at least two months prior to the study, length of menstrual cycle between 24 and 35 days, not suffering from other diseases such as thyroid, diabetes and mental disorders. The exclusion criteria were a decision to withdraw from the study, parents' request for exclusion of their child from the study, experiencing a stressful event such as death, marriage, or surgery during the study, experiencing a change in the intervals of menstrual cycles for less than 24 and more than 35 days, and experiencing changes in the length of menstrual cycles for less than three and more than seven days.

Melissa officinalis capsules were made in the pharmacology department in the Shiraz Medical School under the supervision of a professional counselor. Each capsule of *M. officinalis* contained 600 mg of the essence. Moreover, the placebo was prepared from starch in capsules similar to *M. officinalis*. To keep the study blind, the drug and placebo were marked with codes 1 and 2 and only the specialized consultant knew about the drugs. The subjects were not aware of cods.

A self-report questionnaire was designed consisting of demographic characteristics, the GHQ-28 questionnaire, and the Premenstrual Syndrome Screening Tool (PSST). The GHQ-28 was used to screen the subjects' mental health. The GHQ-28 consists of four subscales including somatic symptoms (items 1 - 7), anxiety/insomnia (items 8-14), social dysfunction (items 15 - 21) and severe depression (items 22 - 28). All items are responded on a 4-point Likert scale of none, mild, moderate, and severe which are scored from zero to three. The score 23 or above was the cut-off point for probability of having a mental health disorder (30). Accordingly, girls who obtained scores > 23 were excluded from the study. The Farsi version of GHQ-28 questionnaire was validated by Yaghoubi, as cited in Ozgoli et al. and its sensitivity and specificity were calculated 86.5 and 82, respectively (31).

The PSST consists of 19 items in three sections. The first and second sections includes 14 items on physical, and psychological symptoms, and the third section contains five items that assesse the effects of symptoms on subject's life (social symptoms) (32). All items are responded on a four options Likert scale namely none, mild, average, and severe, receiving a score from zero to three, respectively. Thus, the minimum and maximum scores of the questionnaire are 0 and 57. Scores ranging from 0 - 19, 20 - 38, and 39 - 57 represented mild, average, and severe conditions, respectively. The subjects who gained scores > 20 were enrolled into the current study. This scale was validated in Iran. The content validity ratio and content validity index of this scale were obtained as 0.7, and 0.8, respectively. Moreover, the reliability of the scale was confirmed by a Cronbach's alpha of 0.9 (8).

3.1. The Procedure

Subjects in the intervention group were required to consume 1200 mg *M. officinalis* essence daily (two 600 mg capsules) from the first to the last day of their menstrual cycle for three cycles. In the control group, the subjects received the placebo in the same way as the intervention group. The first researcher called the subjects in both groups at least 3 - 4 times to guide them and explain about consumption of the medication. All subjects in the two groups were required to complete the PSST questionnaire at the beginning of the study and then in three consecutive months (three menstrual cycle).

3.2. Ethical Considerations

The protocol of the study was approved by the Ethics Committee of Shiraz University of Medical Sciences. Permissions were also received through the authorities in the schools. Written informed consent letters were obtained from all the subjects. They were all assured of the confidentiality of their personal information. In order to prevent any probable error, the completed questionnaires were encoded by the researcher's assistant. Moreover, subjects in the intervention group were allowed to withdraw from the study at any time.

3.3. Data Analysis

Statistical analysis was performed using the SPSS ver.

11.5. Paired t-test was used to compare the changes of PMS scores in each group before and after the intervention. Moreover, the repeated measures ANOVA was used to compare the severity of symptoms in the two groups during the four subsequent measurements.

4. Results

The mean age of the participants was 16.2 ± 1.06 years in the intervention group and 16.3 ± 0.66 years in the placebo group. The two groups were homogeneous with respect to age ($P = 0.32$), education level ($P = 0.83$), and Body Mass Index (BMI) ($P = 0.42$).

The results of repeater measures ANOVA showed that the mean (SD) of symptoms in the intervention group was 42.56 ± 15.73 before, 30.72 ± 13.24 one month after, 30.2 ± 12.08 two months after, and 13.90 ± 10.22 three months after the intervention, and the differences were statistically significant (Table 1).

The results of paired t-test showed that the intensity of physical symptoms significantly decreased in the subjects who consumed the capsules of *M. officinalis* ($P < 0.001$), but no significant difference was observed in the placebo group in this regard. The results of the paired t-test also indicated a significant decrease in psychological and social symptoms of the subjects in the intervention group. However, no significant difference was found in the control group in this respect ($P < 0.001$) (Table 2).

Table 1. Comparison of Severity Symptoms of Premenstrual Syndrome in the Study Groups [a]

Group	Time				P Value
	Before Intervention	**One Month After Intervention**	**Two Months After Intervention**	**Three Months After Intervention**	
Intervention	42.56 ± 15.73	30.72 ± 13.24	30.02 ± 12.08	13.90 ± 10.22	< 0.001
Placebo	39.28 ± 16.2	35.24 ± 13.66	34.44 ± 12.71	28.38 ± 18.33	

[a] Data are presented as Mean ± SD.

Table 2. Comparison of Physical, Psychological and Social Symptoms of Premenstrual Syndrome in the Study Groups Before the Study and at the End of Third Month [a]

Type of Symptoms / Time of Measurement	Intervention	Placebo
Physical		
Before intervention	14.21 ± 2.81	9.64 ± 2.60
End of the third month	11.20 ± 1.47	2.92 ± 3.33
P value	< 0.001	0.477
Psychological		
Before intervention	14.20 ± 3.85	18.80 ± 4.42
End of the third month	12.50 ± 2.97	10.62 ± 4.04
P value	0.005	0.1
Social		
Before intervention	13.34 ± 2.69	8.26 ± 3.25
End of the third month	10.12 ± 1.47	8.52 ± 2.89
P value	< 0.001	0.479

[a] Data are presented as Mean ± SD.

5. Discussion

The study results revealed a significant difference between the two groups regarding the total intensity mean of physical, psychological and social symptoms of PMS in the first, second and third months after the intervention. The interaction between time and group was also statistically significant. Of course, in the control group there was also a decrease in the severity of symptoms. This finding might be attributed to the psychological effect of the placebo.

No previous studies were available on the effect of *M. officinalis* on the intensity of PMS; however, the effects of other herbal products were investigated on anxiety, depression, sleep disorder, stress and other symptoms of PMS (21, 22, 31, 33). The results of these studies were consistent with those of the present study. Moreover, Taiwo et al. investigated the effect of *M. officinalis* on mice and showed the positive psychoactive potentials of this herb (34). Another study indicated the effectiveness of *M. officinalis* in reduction of restlessness and insomnia in children (35). Another study also reported *M. officinalis* as a mediator of mood and cognitive function with anxiolytic effects (36). *Melissa officinalis* leaves have also been shown to have anxiolytic and spasmolytic properties (37). The results of the above studies are similar to those of the current study in reducing psychological symptoms and mood changes. PMS is a multi-factorial disorder with unknown etiology (3). Still no blood or biochemical test is available to diagnose this disorder (38). The main mechanism of PMS is perhaps related to the level of serotonin (39). Although there is no evidence in favor of hormonal disorders in this syndrome, since its symptoms can begin at the beginning, middle, or end of the luteal phase, it might be attributed to the progesterone produced by ovaries. Overall, GABAergic and serotonergic neurotransmitter systems and reduction of serotonin are involved in the occurrence of these symptoms (40, 41). Some studies investigated the effects of herbs such as *Crocus sativus* (20) and *Hypericum perforatum* (21) on the symptoms of PMS and reported that these herbs probably affected the reduction of PMS symptoms through increasing the level of circulating serotonin. Some studies also revealed that *M. officinalis* can reduce the symptoms of PMS through GABA neurotransmitters (Gamma-aminobutyric acid, GABAergic system). GABA neurotransmitters have great inhibitory effects on the central nervous system and are essential to create balance between nervous stimulation and suppression in brain's normal function. It is reported that the brain's GABA levels are highly associated with anxiety; in such a way that benzodiazepines used as sedatives in the past decades imitate GABA. These medications result in sedative and anxiolytic effects through binding to GABAergic receptors and changing other neurotransmitters of brain, such as norepinephrine and serotonin (42, 43).

Review of the studies performed on treatment of PMS demonstrated that some of the herbs could, to some extent, decrease the symptoms of this disorder. However, which herb is more effective, efficient, and cost-effective, and which mechanisms are involved in the effects yet remains to be determined. Thus, further studies are recommended to compare other plants to *M. officinalis* to confirm the results of the present study and find an answer to the above-mentioned questions.

One of the limitations of the current study was its small sample size and its implementation in high school girls. Moreover, the placebo group also experienced some reductions in their symptoms that might be attributed to the psychological effects of placebo. A self-report questionnaire was used to assess the symptoms and this may affect the students' responses. Furthermore, the subjects of the present study were at different stages of puberty and, consequently, did not experience the changes related to this period similarly. Also, individual differences in learning ability and interest might have affected the participation in the adoption of plans. Therefore further studies with larger sample size, among older females from different levels of the community, and also studies without a placebo are suggested.

In conclusion, the results of the current study showed that *M. officinalis* capsules were effective to reduce the intensity of PMS symptoms. Yet, this plant is recommended to be compared to other herbal medicines and its degree of effectiveness should be assessed up to several months after the intervention.

Authors' Contributions

Marzieh Akbarzadeh and Mansoore Dehghani: manuscript drafting; Marzieh Akbarzadeh: critical revisions, corresponding author; Zeinab Moshfeghy: in researching for articles, Pouran Tavakoli: education of psychology topics; Masoumeh Emamghoreishi: supervision and guidance on doses and the construction of Melissa officinalis and placebo capsules; Najaf Zare: data analysis.

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