Iran Red Crescent Med J. 2019 March; 21(3):e84657. doi: 10.5812/ircmj.84657.

Published online 2019 April 24. **Research Article**

Effect of Peppermint Oil on Premenstrual Syndrome: A Randomized, Double-Blind Placebo-Controlled Study

Mouloud Agajani Delavar [1,*], Soheila Ebrahimi [2], Sedigheh Esmaeilzadeh [3] and Azam Khamse [2]

[1] Infertility and Reproductive Health Research Center, Babol University of Medical Sciences, Babol, Iran
[2] Department of Biology, Payame Noor University, Babol, Iran
[3] Infertility and Reproductive Health Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran

[*] *Corresponding author*: Associated Professor, Department of Midwifery, Infertility and Reproductive Health Research Center, Babol University of Medical Sciences, Babol, Iran. Email: moloodaghajani@yahoo.com

Received 2018 September 26; **Revised** 2019 April 07; **Accepted** 2019 April 09.

Abstract

Background: Despite the mental, physical, and behavioral problems of premenstrual syndrome (PMS) in reproductive women, there is no general agreement on effective treatment.
Objectives: To determine the safety and effectiveness of herbal medicine capsules of peppermint oil as a novel formulation used for the severity management of PMS symptoms.
Methods: A randomized, double-blind, placebo-controlled trial was carried out on 50 high school students who were diagnosed with PMS in Babol, Iran. The subjects were divided into two groups based on blocked randomization to receive capsules of Colpermin® containing the peppermint oil (187 mg peppermint oil/0.2 mL), or placebo twice daily for 10 days, from the 15th day of one period to the first day of the next period for two cycles. The degree of PMS was assessed using Delany's PMS checklist with 28 items as primary, at the first luteal phase of the menstrual cycle and at the third luteal phase.
Results: The PMS score was decreased for the two menstrual cycles, from 30.3 ± 10.1 to 15.5 ± 6.0 in peppermint oil group and from 23.2 ± 7.0 to 20.7 ± 8.0 in the placebo group. The mean difference of the total PMS score between the two groups was -9.77; 95% CI: -12.52 to -7.02 ($P < 0.0001$). The number of participants needing treatment (NNT) for the peppermint oil group was approximately two compared with that of the placebo group.
Conclusions: The proposed novel peppermint oil formulation was proved to be safe and may be used as an effective treatment for reducing the severity of PMS symptoms.

Keywords: *Mentha piperita*, Menthol, Oil, Pain, Peppermint, Premenstrual Syndrome

1. Background

It is generally assumed that premenstrual syndrome (PMS) is a menstrual disorder with an estimated prevalence of between 80% - 90%, which can affect the quality of life during the reproductive years (1, 2). The PMS is literally deemed as a number of symptoms, including mental, physical, and behavioral symptoms, which can occur in the luteal phase in women at their reproductive age (3, 4). It is thought that the etiology of PMS is not totally understood (4). It is suggested that intracellular calcium concentration can play a role in mood disorders in PMS (5). It is presumed that most women tend to use non-drug approaches such as dietary changes, exercise, cognitive behavioral therapy, and herbal remedy in order to reactivate PMS (3, 4, 6-9). A recent favorable treatment is an herbal medicine (10). It must be stated that herbal remedies have been used to manage menstrual disorders since a long time ago (8, 9, 11).

Peppermint is one among several plants, cultivated in Asia, Europe, Canada, and North America for its oil, which is extracted from its leaves (12-15). Peppermint oil contains menthol, menthone, cineol, menthofuran, 8-cineo limonene, pulegone, and caryophyllene (16-18). It is widely used as a cooling agent and a flavoring agent in food. It has anti-itch, antimicrobial properties, and is commonly used as analgesics for decreasing joint pain, tension headaches, cramping, digestive complaints, colonic spasm, anorexia, primary dysmenorrhoea, menstrual disorders, nausea, and diarrhea (14, 19-24).

Until 1990, peppermint oil had not been confirmed as a digestive aid; therefore, the Food and Drug Administration (FDA) put a ban on the sale of the peppermint oil as an over-the-counter medicine to be used as a digestive aid.

Nevertheless, it is currently available as over-the-counter (OTC) medicine, and has many commercial uses; thus it is sold as a dietary supplement with various functions (18). In this regard, the result of a study indicated that peppermint was the second most commonly used herb for the management of the menstrual disorder, especially for PMS, among Egyptian women (23). Also, it is worth mentioning that peppermint oil is safe and well tolerated (13, 25).

2. Objectives

Due to the paucity of clinical trial studies on this herbal medicine, the present study was aimed to investigate the therapeutic effects and the safety of a novel formulation of herbal medicine capsules of Colpermin® (187 mg peppermint oil/0.2 mL) for the severity management of symptoms in women with PMS.

3. Methods

This randomized, double-blind, placebo-controlled trial was carried out on 50 high school students in Babol, Iran, from February 2016 to October 2016. The estimated sample size in each group was 30, considering the 80% of power, $\alpha = 0.05$, and the reduction of two scores, which decreased the PMS between the two administration of drugs. Also, there was a 10% dropout rate.

The inclusion criteria were as follows: The participants' age had to be between 15 - 20 years to enter the study. Their menstrual cycles had to be regular during the last six months. They had to have no history of mental illness, no history of surgery, or the death of a close relative within the last six months. They were not supposed to have used antidepressants or anti-anxiety drugs during the last three months. Also, they had to have no history of allergy to peppermint and its derivatives. In addition, subjects who were married had a surgery, or experienced a stressful event throughout the research were excluded from the study.

3.1. Drug Preparation

We purchased capsules of Colpermin® (Tillotts Pharma AG; Rheinfelden, Switzerland), containing 187 mg peppermint oil/0.2 mL from Jalal-e Al-e Ahmad Boarding pharmacy. Placebo capsules were made from wheat flour in the pharmacology laboratory of Babol University of Medical Sciences. The Colpermin® capsules and the placebo capsules were similar in color, shape, and size. Forty Colpermin® capsules and placebo capsules were placed in a pack similar in shape and were coded by a pharmacist without the awareness of the researcher.

3.2. Questionnaires

The PMS was assessed during the luteal phase using the Delany's PMS checklist. The checklist, with 28 items, consisted of a series of mood or emotions (irritability, anxiety, tension, mood swings, hostility, anger, depression, sadness, crying spells, confusion, and decreased alertness), physical (clumsiness, fluid retention, backache, menstrual cramps, abdominal bloating, breast tenderness/swelling, headache/migraines, joint pain/muscle spasms, stomach upset/gastrointestinal, complications/changes in bowel movements, acne, panic attacks, cold sores, and sinus problems/allergies), and behavioral (forgetfulness/concentration, food cravings, increase in appetite/weight gain, fatigue/lethargy, dizziness/fainting, decreased self-esteem, sleep disturbances) symptoms.

It is worth noting that the reliability, internal consistency, and the validity of the questionnaire in this study were 0.72, 0.93, and 0.75, respectively. A 4-point Likert scale, from 0 to 3, was used for all items, covering the lowest and highest range of 0 and 84. Accordingly, those who obtained a score between 16 and 30 were judged to have premenstrual syndrome. The researchers, as a result, rated the severity as moderate, and severe (> 30) premenstrual syndrome. Those who scored 15 or less were considered to have no premenstrual syndrome, and those exceeding 15 were considered to have premenstrual syndrome. Consequently, the subjects with the scores of above 15 were qualified for this study (26). A baseline questionnaire containing information on age, education, weight, height, body mass index, menarche cycle, age at menarche, the duration of menstrual bleeding, the duration of menstrual cycles, and the pain was completed by each participant.

3.3. Sampling

A total of 156 eligible students complaining about premenstrual symptoms completed the Delany's PMS checklist during the luteal phase and were screened for inclusion/exclusion criteria. Therefore, 95 students were eligible to participate in this research. A demographic questionnaire was also completed through interviews and was screened through the inclusion/exclusion criteria for each participant. Thirty-four students were excluded from the study: 18 due to the lack of fulfillment of the inclusion criteria, six for their marriage, and 10 for their unwillingness to complete the study. Finally, 61 students meeting the criteria entered the study and were requested to sign the written informed consent forms. Then, according to the blocked randomization with a block size of 4, the researcher randomly divided the participants into two

groups receiving placebo or peppermint oil (A, B). At the outset, blocks covering four of two2 treatments (peppermint oil and placebo) were prepared with various potential combinations, and each one was given a number. Subsequently, the random number table was used to assign a number to each block. In the next step, biostatisticians were given medications in the same shape (capsule), in two groups, and were requested to assign a 5-digit code to each one. The capsules were given to the researcher following the coding procedure. It is worth noting that the researcher was totally blind to the contents of the capsules and the biostatisticians were the only person aware of the identities of the capsules. To accomplish the task, blocks of four, with various combinations, containing two capsules (two groups from each group) were provided by the biostatisticians. Then the name of each capsule was replaced with a 5-digit number, the envelopes were sealed, and each one was assigned a number. After that, the envelopes were submitted to the researcher randomly through a random number table. It is worth reiterating that both the researcher and participants were unaware of the whole process (double-blind) (Figure 1).

The two groups (A, B) received capsules of placebo or capsules of Colpermin® 187 mg twice daily for 10 days (from the 15th day of one period to the 1st day of the next period), 30 minutes before meals. The treatments were administered for two cycles (months). After the intervention, the participants were requested to complete the Delany's PMS checklist again to be assessed for PMS symptoms (mood or emotional, physical, and behavioral symptoms), as a primary outcome, and the side effects of drugs such as complaints of heartburn, allergies, hot flash, rectal burning, oesophageal pain, and mouth ulcer as a secondary outcome during the two menstrual cycles. Throughout the phase of the study, the participants were disallowed to take any sedatives or pain-killers.

The researchers followed the participants during the intervention through phone calls to ensure that all subjects received the appropriate therapy and completed the Delany's PMS checklist forms at the end of the intervention. During the study, 10 subjects failed to complete the research and were excluded from the study. No serious side effects were reported for the two groups.

3.4. Ethical Consideration

The Ethics Committee of Babol University of Medical Sciences approved this research study, and the Iranian Registry of Clinical Trial (IRCT) registered it with the code of IRCT2016020926446N2. The informed written consent was obtained from all participants after explaining the study's objectives to them. The study protocol conformed to the 1964 Helsinki declaration.

3.5. Data Analysis

The IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, N.Y., USA) was used to analyze the data. The normality assumptions for variables were tested by Kolmogorov-Smirnov test. The data were not normally distributed, and the sample size was low; therefore, the researchers had to use a bootstrap method for reporting P value, and CI differences were used, as well. The repeated measure analyses of variance and ANCOVA analysis were performed for the comparison of the follow-up variables between the two groups. In addition, the intention-to-treat (ITT) analysis was used to analyze the data. The severity rates of PMS symptoms, analyzed by chi-square tests, were compared before and after the intervention for each group. It must be noted that the severity of PMS (mild severity) was used for the calculation of the number-needed-to-treat (NNT). In addition, two-tailed hypothesis testing, with the level of significance set at 0.05, was used for all analyses in this study. It must be reiterated that the study was accomplished through CONSORT checklist. The level of significance for all analyses was $P < 0.05$.

4. Results

A total number of 50 students (25 in the peppermint oil group and 25 in the placebo group) participated and completed this double-blind clinical trial study. The mean and the standard deviation of the age for both the peppermint oil group and the placebo group were 17.4 ± 0.9 and 17.0 ± 0.5, respectively. The two groups were homogenous with respect to age, educational status, body mass index, and menstrual cycles (Tables 1 and 2). The majority of the participants reported that they had dysmenorrhea.

Table 1. Subjects' Characteristics (N = 25)[a]

	Peppermint Oil Group	Placebo Group
Age, y[b]	17.4 ± 0.9	10.9 ± 0.2
Education, y[b]	11.2 ± 0.6	11.9 ± 0.3
Weight, kg	60.0 (55.0, 65.0)	59.0 (51.5, 63.0)
Height, cm	163.0 (157.5, 166.0)	164.0 (160.0, 167.5)
Body mass index	22.7 (20.6, 24.2)	21.3 (19.9, 23.8)
Waist circumference	80.0 (74.5, 86.0)	81.0 (71.5, 83.0)

[a] Values are expressed as mean ± SD or median (25th, 75th).
[b] The data were normally distributed.

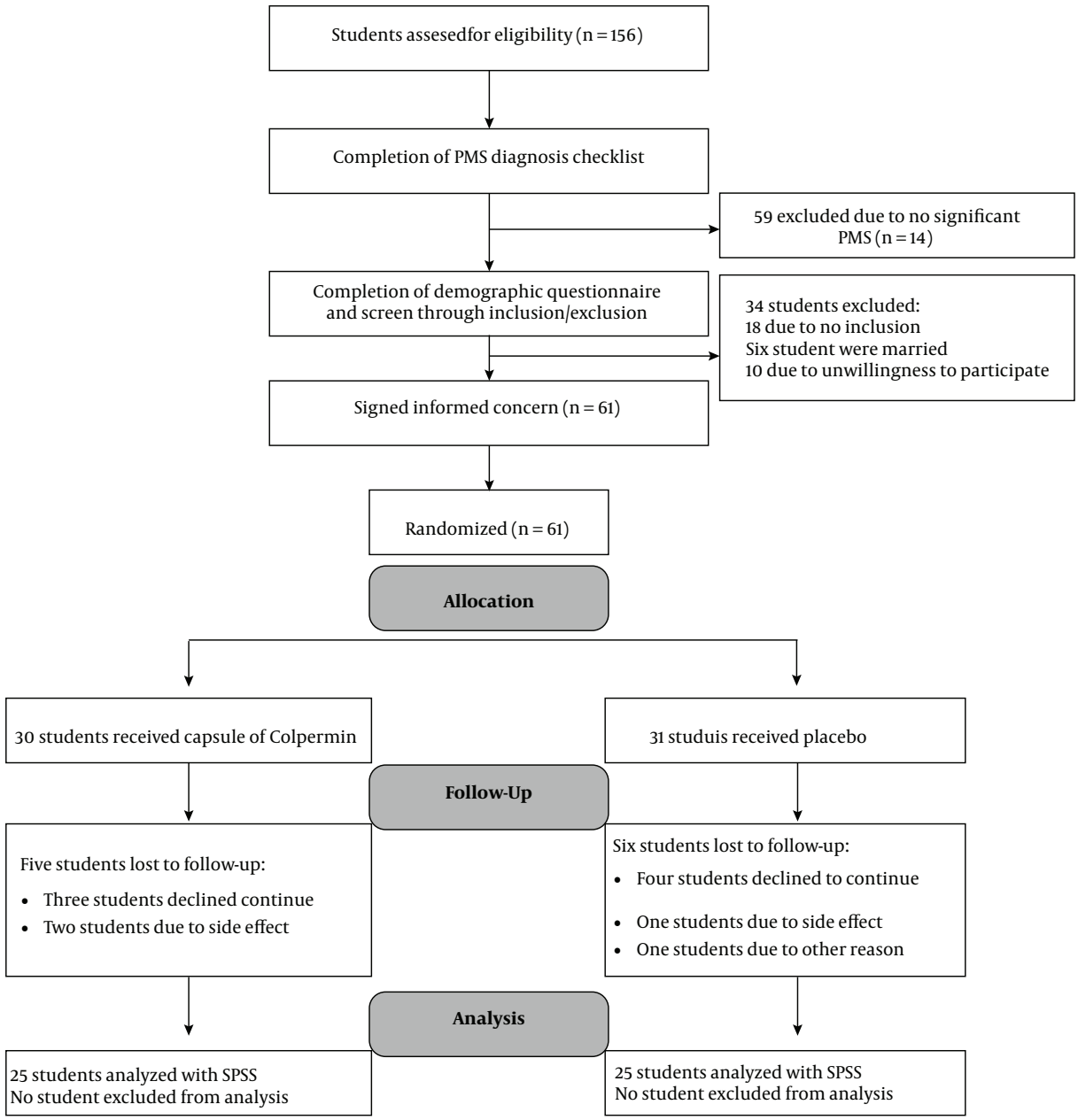

Figure 1. Consort fellow diagram of the participants

The main outcome was the change in PMS severity, based on Delany's PMS checklist (Figure 2). The results of ANCOVA bootstrapped also demonstrated that the mean difference of the total PMS score between the two groups (Peppermint oil group-placebo group) was -9.77; 95% CI: -12.52 to -7.02, $P < 0.0001$). Also, the mean difference of the emotional PMS score between the two groups was -5.84; 95% CI: -7.36 to -4.32, $P < 0.0001$). In addition, there were significant mean differences in physical and behavioral PMS scores between the two groups at different times (-5.37; 95% CI: -3.80 to -3.40, $P < 0.0001$ and -2.75; 95% CI: -7.35 to -1.71, $P < 0.0001$, respectively) (Table 3).

Before the intervention 14 (56.0%) and 11 (44.0%) of participants in peppermint oil group and 20 (80.0%) and 5 (20.0%) of participants in the placebo group experienced moderate and severe PMS symptoms before the interven-

Table 2. Menstrual Cycle Status of the Students (N = 25)[a]

	Peppermint Oil Group	Placebo Group
Age at menarche, y		
≤ 12	8 (32.0)	10 (40.0)
> 12	17 (68.0)	15 (60.0)
Duration of menstrual bleeding, days		
3 - 5	8 (32.0)	6 (24.0)
6 - 10	17 (68.0)	19 (76.0)
Duration of menstrual cycles, days		
21 - 27	7 (28.0)	5 (20.0)
28 - 30	10 (40.0)	10 (40.0)
31 - 35	8 (32.0)	10 (40.0)
Having pain, dysmenorrhea		
Yes	23 (92.0)	19 (76.0)
No	2 (8.0)	6 (24.0)

[a]Values are expressed as No. (%).

Table 3. Comparison of the Emotional, Physical, and Behavioral Symptoms of PMS Symptoms Before and After the Intervention in Peppermint Oil and Placebo Groups[a]

	1- Peppermint Oil Group	2- Placebo Group	Mean Difference (1 - 2)	95% CI	P Value
Emotional			-5.84	-7.36, -4.32	< 0.0001
Before the intervention	13.6 ± 4.2	8.0 ± 3.2			
After the intervention	3.0 ± 2.5	6.0 ± 3.0			
Physical			-5.37	-7.35, -3.40	< 0.0001
Before the intervention	9.6 ± 4.2	9.0 ± 3.9			
After the intervention	1.8 ± 2.2	6.9 ± 5.2			
Behavioral			-2.75	-3.80, -1.71	< 0.0001
Before the intervention	7.2 ± 4.3	6.1 ± 2.5			
After the intervention	2.0 ± 1.3	4.5 ± 2.6			
Total			-9.77	-12.52, -7.02	< 0.0001
Before the intervention	30.3 ± 10.1	23.2 ± 7.0			
After the intervention	15.5 ± 6.0	20.7 ± 8.0			

[a]Values are expressed as mean ± SD.

tion. It should be mentioned that the severity of PMS decreased after the intervention in both groups. According to the criteria of PMS severity in the second menstrual in both peppermint oil and placebo groups, 15 (60.0%) and 8 (32.0%) suffered from complete mild PMS during the second menstrual, respectively (Table 2). According to the criteria of PMS severity during the second menstrual, the number of participants who NNT in the peppermint oil group was approximately 2. No serious side effects were reported for both groups.

5. Discussion

In this study, the statement: "Herbal medicine capsules of peppermint oil can be used to treat PMS syndrome" was proposed as a hypothesis. The findings of our study revealed that the severity of the total, emotional, behavioral, and physical symptoms were reduced in the peppermint oil group. In addition, the severity of PMS symptoms in the placebo group relatively decreased after two months of consumption of the placebo. This could be attributed to the person's expectations or the psychological effects of the placebo. Furthermore, based on NNT analy-

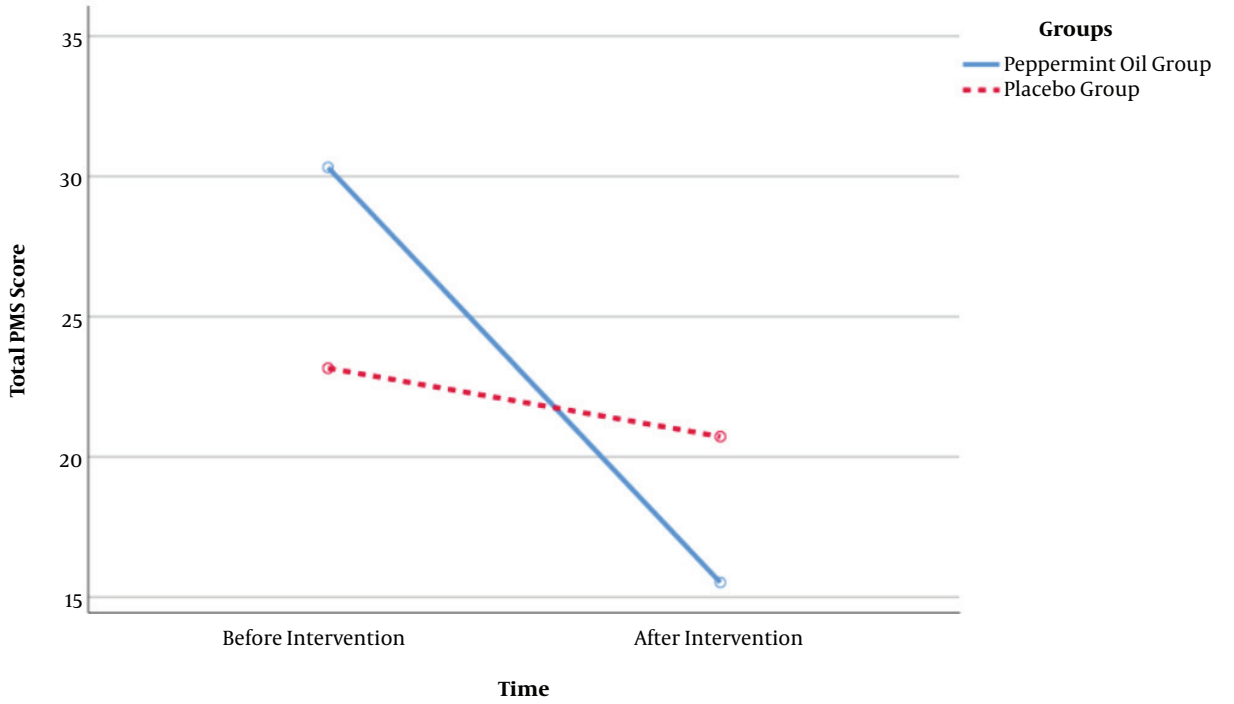

Figure 2. Changes in the mean PMS score from before the intervention and after the intervention to cycle two for the two groups

sis, the number of participants who needed treatment for the severity of PMS symptoms was approximately two. This finding could indicate that about two patients required to be treated with the capsules of peppermint oil, 187 mg BID for 10 days, during the luteal phase in order to get the full benefits (the ideal NNT is one).

Based on the findings of laboratory experiments, menthol can generate analgesic effects by activating the endogenous opioid system and/or partly by the effects of local anesthetics without having any anti-inflammatory properties. In addition, menthol can bind the cold receptor, resulting in the release of calcium from some cells. Also, peppermint oil is known for its power to inhibit muscle contraction caused by serotonin and substance. It is also assumed that peppermint oil and menthol could provide smooth muscle calcium channel antagonism and may be effective for the relief of tension headaches (15, 16, 21, 27, 28). In addition, peppermint oil can reduce gas and bloat by relaxing the lower oesophageal sphincter. Therefore, it is suggested that peppermint can reduce gastrointestinal symptoms and other symptoms associated with premenstrual syndrome (9, 29-31).

Peppermint oil has been used for PMS in Egypt. Accordingly, the study conducted in Egypt is the only study that we found in the literature in which peppermint was prescribed to 200 female participants for the treatment of PMS. The results indicated that peppermint alleviated symptoms of PMS and was effective in 98.5% of cases (23). In the existing literature, to the best of our knowledge, there was no randomized, clinical trial that assessed the effect of peppermint oil on PMS; however, peppermint has widely been used to treat indigestion and bloating, and strengthen the stomach and digestive analgesic and antispasmodic properties in traditional medicine. In fact, it is worth mentioning that this study was probably the first randomized, double-blind, placebo-controlled clinical trial that tried to assess the impact of the peppermint oil as a new formulation, on PMS syndrome, which could be regarded as strength for this study.

This study had also several limitations: first, this study used a self-report questionnaire to determine the symptoms of PMS, which may have induced response bias. Another limitation of the study was that it was the first clinical trial to use peppermint oil as a new formulation of peppermint. Moreover, small sample size, high school students with moderate, and severe PMS could be another limitation for this study. It would be more beneficial to conduct a clinical trial study involving a larger population to

reach more tangible results. Finally, we have to declare that our trial had approximately 30% loss from the original sample population due to the lack of cooperation. Therefore, the data were analyzed through the ITT approach. It is highly recommended that both stages (completed and remaining subjects) need to be treated and accurately calculated. This is an important measure in a clinical trial for defining the true advantages of one treatment over the control group. It must be noted that the peppermint oil had an NNT of two and four, with no intention and with intention, respectively. It is worth mentioning that the NNT of two and four both sound promising.

In conclusion, the results of this study suggest that peppermint oil is effective in reducing the severity of PMS symptoms among young women in Iran.

Acknowledgments

The authors acknowledge the assistance of Iranian high school students for their participation in this study as well as the financial support of Babol University of Medical Sciences and the Payame Noor University of Babol.

Footnotes

Authors' Contribution: Mouloud Agajani Delavar and Azam Khamse developed the original idea and the protocol. Azam Khamse collected data. Mouloud Agajani Delavar analyzed data. Mouloud Agajani Delavar, Soheila Ebrahimi and Sedigheh Esmaeilzadeh wrote the manuscript. All authors provided critical feedback and helped shape the research, analysis, and manuscript.

Conflicts of Interests: There are no conflicts of interest.

Ethical Approval: This research was approved by the Ethics Committee of Babol University of Medical Sciences and was registered at the Iranian Registry of Clinical Trial (IRCT) with the code of IRCT2016020926446N2. The study protocol was in compliance with the 1964 Helsinki declaration.

Funding/Support: Babol University of Medical Sciences, Babol, Iran.

Patient Consent: The informed written consent was obtained from all participants after explaining the study's objectives to them.

References

1. Firoozjaei SK, Delavar MA, Bayani AA. Attribution styles associated with premenstrual syndrome in women at reproductive age, Iran. *Caspian J Reprod Med*. 2015;**1**(2):23–7.
2. Pearlstein T, Steiner M. Premenstrual dysphoric disorder: Burden of illness and treatment update. *J Psychiatry Neurosci*. 2008;**33**(4):291–301. [PubMed: 18592027]. [PubMed Central: PMC2440788].
3. Anandha S, Priy M, Saraswathi I, Saravanan A, Ramamchandran C. Prevalence of premenstrual syndrome and dysmenorrhoea among female medical students and its association with college absenteeism. *Int J Biol Med Res*. 2011;**2**(4):1011–6.
4. Braverman PK. Premenstrual syndrome and premenstrual dysphoric disorder. *J Pediatr Adolesc Gynecol*. 2007;**20**(1):3–12. doi: 10.1016/j.jpag.2006.10.007. [PubMed: 17289510].
5. Cunningham J, Yonkers KA, O'Brien S, Eriksson E. Update on research and treatment of premenstrual dysphoric disorder. *Harv Rev Psychiatry*. 2009;**17**(2):120–37. doi: 10.1080/10673220902891836. [PubMed: 19373620]. [PubMed Central: PMC3098121].
6. Bogg T, Roberts BW. Conscientiousness and health-related behaviors: A meta-analysis of the leading behavioral contributors to mortality. *Psychol Bull*. 2004;**130**(6):887–919. doi: 10.1037/0033-2909.130.6.887. [PubMed: 15535742].
7. Cloninger CR, Svrakic DM, Przybeck TR. A psychobiological model of temperament and character. *Arch Gen Psychiatry*. 1993;**50**(12):975–90. doi: 10.1001/archpsyc.1993.01820240059008. [PubMed: 8250684].
8. Domoney CL, Vashisht A, Studd JW. Premenstrual syndrome and the use of alternative therapies. *Ann N Y Acad Sci*. 2003;**997**:330–40. doi: 10.1196/annals.1290.036. [PubMed: 14644840].
9. Rapkin AJ. New treatment approaches for premenstrual disorders. *Am J Manag Care*. 2005;**11**(16 Suppl):S480–91. [PubMed: 16336057].
10. Green L, Myerson J. A discounting framework for choice with delayed and probabilistic rewards. *Psychol Bull*. 2004;**130**(5):769–92. doi: 10.1037/0033-2909.130.5.769. [PubMed: 15367080]. [PubMed Central: PMC1382186].
11. Behmanesh E, Delavar MA, Kamalinejad M, Khafri S, Shirafkan H, Mozaffarpur SA. Effect of eryngo (Eryngium caucasicum Trautv) on primary dysmenorrhea: A randomized, double-blind, placebo-controlled study. *Taiwan J Obstet Gynecol*. 2019;**58**(2):227–33. doi: 10.1016/j.tjog.2019.01.011. [PubMed: 30910144].
12. Kavrayan D, Aydemir T. Partial purification and characterization of polyphenoloxidase from peppermint (Mentha piperita). *Food Chem*. 2001;**74**(2):147–54. doi: 10.1016/s0308-8146(01)00106-6.
13. Nair B. Final report on the safety assessment of Mentha piperita (Peppermint) oil, Mentha piperita (Peppermint) leaf extract, Mentha piperita (Peppermint) Leaf, and Mentha piperita (Peppermint) leaf water. *Int J Toxicol*. 2001;**20 Suppl 3**:61–73. doi: 10.1080/10915810152902592. [PubMed: 11766133].
14. Kligler B, Chaudhary S. Peppermint oil. *Am Fam Physician*. 2007;**75**(7):1027–30. [PubMed: 17427617].
15. Loolaie M, Moasefi N, Rasouli H, Adibi H. Peppermint and its functionality: A review. *Arch Clin Microbiol*. 2017;**8**(4):54–71.
16. Hsouna AB, Touj N, Hammami I, Dridi K, Al-Ayed AS, Hamdi N. Chemical composition and in vivo efficacy of the essential oil of Mentha piperita L. in the suppression of crown gall disease on tomato plants. *J Oleo Sci*. 2019. doi: 10.5650/jos.ess18261. [PubMed: 30867394].
17. Balakrishnan A. Therapeutic uses of peppermint-a review. *J Pharm Sci Res*. 2017;**7**(7):474–6.
18. Grigoleit HG, Grigoleit P. Pharmacology and preclinical pharmacokinetics of peppermint oil. *Phytomedicine*. 2005;**12**(8):612–6. doi: 10.1016/j.phymed.2004.10.007. [PubMed: 16121523].
19. Mimica-Dukic N, Bozin B, Sokovic M, Mihajlovic B, Matavulj M. Antimicrobial and antioxidant activities of three Mentha species essential oils. *Planta Med*. 2003;**69**(5):413–9. doi: 10.1055/s-2003-39704. [PubMed: 12802721].
20. Marwa C, Fikri-Benbrahim K, Ou-Yahia D, Farah A. African peppermint (Mentha piperita) from Morocco: Chemical composition and antimicrobial properties of essential oil. *J Adv Pharm Technol Res*. 2017;**8**(3):86–90. doi: 10.4103/japtr.JAPTR_11_17. [PubMed: 28795021]. [PubMed Central: PMC5527698].

21. Singh R, Shushni MAM, Belkheir A. Antibacterial and antioxidant activities of Mentha piperita L. *Arab J Chem*. 2015;**8**(3):322–8. doi: 10.1016/j.arabjc.2011.01.019.
22. Masoumi SZ, Asl HR, Poorolajal J, Panah MH, Oliaei SR. Evaluation of mint efficacy regarding dysmenorrhea in comparison with mefenamic acid: A double blinded randomized crossover study. *Iran J Nurs Midwifery Res*. 2016;**21**(4):363–7. doi: 10.4103/1735-9066.185574. [PubMed: 27563318]. [PubMed Central: PMC4979258].
23. Yassin SAT. Herbal remedy used by rural adolescent girls with menstrual disorders. *J Am Sci*. 2012;**8**(1):467–73.
24. Asgarshirazi M, Shariat M, Dalili H. Comparison of the effects of pH-dependent peppermint oil and synbiotic lactol (bacillus coagulans + fructooligosaccharides) on childhood functional abdominal pain: a randomized placebo-controlled study. *Iran Red Crescent Med J*. 2015;**17**(4). e23844. doi: 10.5812/ircmj.17(4)2015.23844. [PubMed: 26023339]. [PubMed Central: PMC4443394].
25. Cosmetic Ingredient Review Expert P. Final report of the safety assessment of alcohol denat., including SD alcohol 3-A, SD alcohol 30, SD alcohol 39, SD alcohol 39-B, SD alcohol 39-C, SD alcohol 40, SD alcohol 40-B, and SD alcohol 40-C, and the denaturants, quassin, brucine sulfate/brucine, and denatonium benzoate. *Int J Toxicol*. 2008;**27 Suppl 1**:1–43. doi: 10.1080/10915810802032388. [PubMed: 18569160].
26. Kratzert K. *Pms symptoms checklist, delany women's wellness place*. 2019. Available from: http://thewomenswellnessplace.com/questionaires_pms.cfm.
27. Amato A, Liotta R, Mule F. Effects of menthol on circular smooth muscle of human colon: Analysis of the mechanism of action. *Eur J Pharmacol*. 2014;**740**:295–301. doi: 10.1016/j.ejphar.2014.07.018. [PubMed: 25046841].
28. Uritu CM, Mihai CT, Stanciu GD, Dodi G, Alexa-Stratulat T, Luca A, et al. Medicinal plants of the family lamiaceae in pain therapy: A review. *Pain Res Manag*. 2018;**2018**:7801543. doi: 10.1155/2018/7801543. [PubMed: 29854039]. [PubMed Central: PMC5964621].
29. Ford AC, Talley NJ, Spiegel BM, Foxx-Orenstein AE, Schiller L, Quigley EM, et al. Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: Systematic review and meta-analysis. *BMJ*. 2008;**337**. a2313. doi: 10.1136/bmj.a2313. [PubMed: 19008265]. [PubMed Central: PMC2583392].
30. Wilkins T, Pepitone C, Alex B, Schade RR. Diagnosis and management of IBS in adults. *Am Fam Physician*. 2012;**86**(5):419–26. [PubMed: 22963061].
31. Khanna R, MacDonald JK, Levesque BG. Peppermint oil for the treatment of irritable bowel syndrome: A systematic review and meta-analysis. *J Clin Gastroenterol*. 2014;**48**(6):505–12. doi: 10.1097/MCG.0b013e3182a88357. [PubMed: 24100754].