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The effect of an oral tablet containing a combination of extracts from *Vitex agnus-castus*, *Echium amoenum*, and *Chamomile* plus vitamin B6 on premenstrual syndrome: A randomized clinical trial

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Abstract

Background: While some medications are effective in managing premenstrual syndrome (PMS), ongoing efforts are focused on finding treatments with maximum efficacy and minimal side effects.

Objectives: This study aimed to evaluate the impact of an oral tablet containing a mixture of extracts from Vitex agnus-castus (VAC), Echium amoenum, and Chamomile, along with vitamin B6, on PMS.

Methods: In this clinical trial, 105 female university students diagnosed with PMS completed the intervention. Participants were allocated to study groups using the blocked randomization method. The supplement group (n=52) received a daily oral tablet containing 40 mg VAC, 100 mg *E. amoenum*, 160 mg *Chamomile*, and 40 mg vitamin B6 for two consecutive menstrual cycles. Changes in PMS symptom severity were assessed using the Daily Record of Severity of Problems (DRSP) chart during the intervention.

Results: A significant decrease in the mean overall DRSP score from 47.4±9.6 to 40.5±7.2 in the supplement group, while it increased significantly from 39.0±6.0 to 44.1±8.4 in the control group. Between-group comparisons for the mean changes in the overall DRSP score showed a significant difference between the supplement and placebo groups (-0.23±0.21 vs. +0.17±0.2, P< 0.001). Additionally, somatic PMS symptoms such as "back pain" and "joint pain" significantly improved in the supplement group compared to the placebo.

Conclusion: the consumption of an oral tablet containing a combination of extracts from VAC, E. amoenum, and Chamomile, along with vitamin B6, was found to reduce the overall severity of PMS symptoms.

Keywords: Premenstrual syndrome, Vitex agnus-castus, Echium amoenum, Chamomile, Vitamin B6.

Introduction

Premenstrual syndrome (PMS) is characterized by recurring physical and emotional symptoms that typically manifest a few days before menstruation and subside afterward.[1] A more severe form of PMS is premenstrual dysphoric disorder (PMDD).[2] Common symptoms of PMS include breast tenderness, bloating, changes in appetite, constipation, headaches, fatigue, mood swings, depression, anxiety, irritability, and crying spells.[3] Approximately 30-40% of women experience PMS symptoms that require treatment, with 3-8% suffering from PMDD.[4] Women with PMS may face social challenges such as communication issues and increased absenteeism from work or school.[5]

Treatment for severe PMS often involves medications like antidepressants or hormonal therapies.[6,7] However, these medications can have significant side effects that may not be well-tolerated by some women with PMS.[6,8] Therefore, the use of herbal remedies and vitamin supplements in safe doses, which may have fewer side effects, is preferred to alleviate PMS symptoms.

Vitex agnus-castus (VAC) is a Mediterranean native

plant widely grown in warm climates.[9] The beneficial effects of VAC on PMS are attributed to its dopaminergic compounds, which lower prolactin levels and modulate FSH and estrogen levels.[10] *Echium amoenum* is another herbal remedy suggested to improve the psychological symptoms of PMS due to its flavonoid content with antidepressant effects.[11] *Chamomile* is known for its anti-depressant and anti-anxiety properties,[12] as well as its ability to manage dysmenorrhea, PMS symptoms, abdominal, and pelvic pain.[13] Vitamin B6 (pyridoxine) plays a crucial role as a co-factor in neurotransmitter synthesis, such as norepinephrine and serotonin, potentially reducing depression and anxiety-related PMS symptoms.[14]

These agents may alleviate PMS symptoms through distinct pathways, suggesting that their combined intake could have synergistic effects on symptom relief. Additionally, formulating these herbal medicines and vitamin B6 into a single oral supplement may enhance their consumption and acceptance by individuals with PMS.

Objectives

This study aimed to assess the impact of an oral supplement containing a blend of extracts from VAC, E. amoenum, and Chamomile along with vitamin B6 on PMS symptoms.

Methods

Study Participants

The present study was a double-blind, placebo-controlled clinical trial conducted with female students from Kashan University of Medical Sciences.

The study consisted of three phases. The first and second phases focused on confirming the diagnosis of PMS, while the third phase involved the intervention. In the initial phase, a retrospective short questionnaire called the Premenstrual Symptoms Screening Tool (PSST) was administered to a large number of female university students to screen for PMS. The Persian version of the PSST had previously been validated for its reliability.[15] The questionnaire comprised 19 questions, with 14 assessing the severity of physical, behavioral, and psychological PMS symptoms, while the remaining 5 evaluated the impact of these symptoms on quality of life. The diagnostic method using the PSST had been detailed in prior studies.[15] Participants diagnosed with moderate or severe PMS based on the PSST proceeded to the second part of the study. In this phase, students were instructed to complete the Daily Record of Severity of Problems chart (DRSP) for two consecutive menstrual cycles. The DRSP is a prospective self-administered questionnaire considered the gold standard for diagnosing and monitoring PMS symptoms.[16,17] This chart provided a daily record of 30 PMS symptoms, with each symptom rated on a scale of severity from 0 (Never) to 3 (Severe). Participants were diagnosed with definite PMS if they experienced at least 5 symptoms from the DRSP during the period ranging from 7 days before menstruation onset to 4 days after, while remaining asymptomatic for the rest of the cycle.

After confirming the diagnosis of PMS, participants who met the inclusion criteria were eligible to enter the intervention phase of the study. The inclusion criteria included being above the age of 18, having a confirmed diagnosis of PMS based on the DRSP, having a regular menstrual cycle within specific intervals and duration, having a normal BMI, not being pregnant or lactating, not having mental illness, depression, or chronic diseases, and not smoking or consuming alcohol.

Participants were excluded from the study if they did not adhere to the study protocol, became ill or hospitalized during the study, experienced mental or physical stress during the study, took hormonal or antidepressant medications in the last 3 months or during the study, used herbal products or dietary supplements in the last 3 months or during the study, took vitamin B6 supplements in the last 3 months, had allergies to any intervention agents used in the study, or received psychological counseling during the study.

Sample size

For sample size calculation, we utilized data from the study by Schellenberg et al., which examined the effects of VAC extract on the intensity of PMS symptoms.[18] A total of 34 subjects per arm were deemed sufficient for our trial to detect a 34% reduction in the overall severity score of PMS symptoms with 80% power and 5% significance. To account for potential dropouts, an additional 25% of subjects were added to the sample size.

Study Design

Eligible participants were randomly assigned to study groups in a 1:1 ratio using random blocks of 4 subjects based on blocked randomization. The sequence of permuted blocks was generated using a random number table. Supplements and placebos were packaged in opaque bottles, with an investigator not involved in the study numbering the bottles based on the random list. Another individual, unaware of the random sequences and not part of the trial, then assigned subjects to the numbered bottles containing supplements and placebos. Randomization and

allocation were concealed from both researchers and participants until statistical analysis was completed.

Participants were instructed to consume either one oral tablet daily containing 550 mg of herbal extracts plus vitamin B6 (40 mg VAC, 100 mg *E. amoenum*, 160 mg *Chamomile*, and 40 mg vitamin B6) or a placebo for two months. The herbal supplement and placebo were manufactured by the same pharmaceutical company (Barij Essence Company, Kashan, Iran). The placebo was identical in size, color, and shape to the herbal tablet and contained the same components (cellulose and starch) except for the active agents.

Data gathering

A general questionnaire collecting demographic data, medical histories, and anthropometric variables was completed by eligible participants. Weight and body mass index (BMI) were measured at baseline and at the end of the study. Participants were advised not to take any herbal or vitamin/mineral supplements during the study. Weekly reminders were provided to ensure compliance with supplement intake and to report any side effects.

During the intervention phase, participants completed the Daily Record of Severity of Problems (DRSP) table for two consecutive menstrual cycles while taking herbal supplements or placebos. At the end of the intervention, the mean overall DRSP score and mean score for each symptom were calculated for both trial groups and compared to baseline scores. The primary outcome in this clinical trial was the change in overall DRSP score.

Statistical Analysis

Between-group comparisons were conducted using independent t-tests, while paired t-tests were used for within-group comparisons. Differences in proportions were assessed using chi-square or Fisher's exact tests. The effectiveness of the intervention on PMS was evaluated using a general linear model analysis adjusted for baseline values. Statistical analysis was performed using SPSS version 16 software (SPSS Inc, Chicago, Ill), with two-sided p value <0.05 considered statistically significant.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki. Prior to participation, all participants were required to sign a written informed consent form. The study protocol was approved by the Ethics Committee of Kashan University of Medical Sciences and registered with the Iranian Registry of Clinical Trials (registered code: IRCT2015060812438N13).

Results

In the present study, 105 subjects (52 in the herbal supplement group and 53 in the placebo group) completed the intervention. The flowchart of participants' recruitment is displayed in Figure 1.

The compliance rates were 81% vs. 76.2% in the supplement and placebo groups, respectively. Three participants reported gastrointestinal complications such as stomachaches during the intervention phase of the study; however, one was in the supplement group, and the other two were in the placebo group (P>0.05). The remaining subjects did not report any adverse or side effects while taking supplements or placebos. Baseline characteristics of the study groups are shown in Table 1.

Table 1. Baseline characteristics of participants in the study groups

Characteristics	Herbal supplement+vitamin B6, n=52	Placebo, n=53	P value
Age (yrs)[a]	21.3±1.96	21.8±2.65	0.25
Weight (kg)[a]	56.2±7.47	54.9±7.51	0.38
BMI (kg/m^2)[a]	21±2.51	20.7±2.82	0.50
Marital status, n (%)[b]			
Single	44 (84.6)	45 (84.9)	0.97
Married	8 (15.4)	8 (15.1)	
Age of the first menstruation (yrs)[a]	13.4±1.38	13.5±1.48	0.52
Intervals between menstruations (days)[a]	25.7±3.75	24.9±3.83	0.33
Duration of bleeding (days)[a]	6.7±1.30	6.7±0.98	0.98

[a]Data is expressed as mean ±standard deviation and tested by independent sample t-test. [b]Data is tested by chi-square test
BMI: Body mass index.

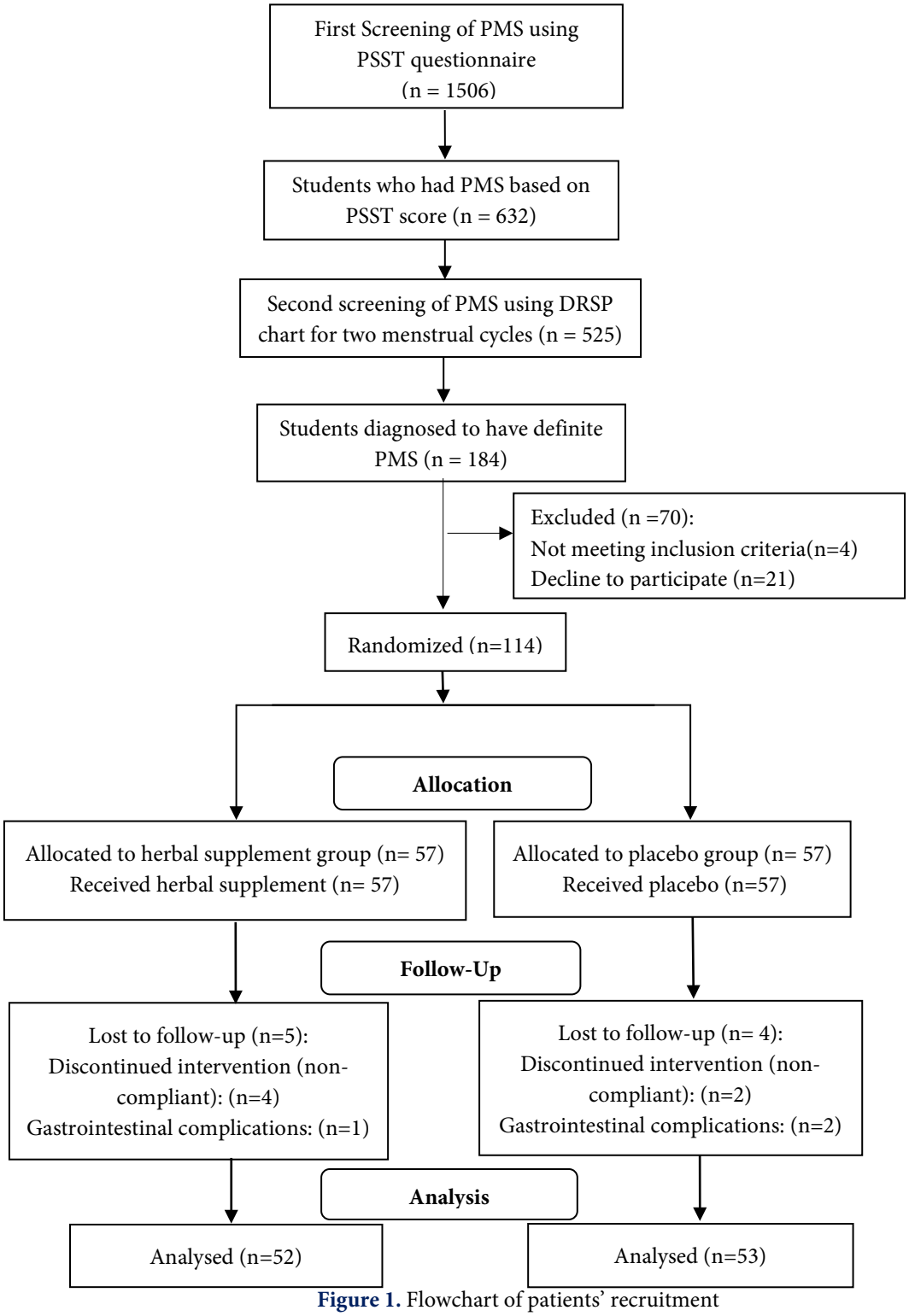

Figure 1. Flowchart of patients' recruitment

Within and between-group comparisons for the severity of somatic and psychological signs of PMS are presented in Tables 2 and 3, respectively. In the supplement group, the severity of "crying" and "boredom" from the psychological signs category, and "frequent urination," "feeling weak and lack of energy," "back pain," "joint pain," "acne," and "greasy skin" from the physical signs category decreased significantly after two months of intervention. On the other hand, in the placebo group, the severity of signs such as "boredom" and "depression," as well as "nausea" and "greasy skin," significantly reduced after two months of intervention. However, only the changes in the severity of "back pain" and "joint pain" were significantly different between the two groups.

The mean overall scores of the DRSP and the mean overall scores of somatic as well as psychological symptoms, before and after the intervention, are displayed separately for the supplement and placebo groups in Table 4. After two months of intervention, the mean overall score of DRSP significantly decreased in the supplement group while it increased significantly in the placebo group. In addition, between-group comparisons for the mean changes of the overall score revealed a significant difference between the groups. Although the mean overall scores of both somatic and psychological signs significantly reduced in the supplement group after the intervention, their changes were not statistically different from the corresponding changes in the placebo group.

The results of general linear model analysis are shown in Table 5. Using herbal supplements plus vitamin B6 for two months had a significant effect on the overall score of DRSP even after adjusting for the baseline overall score on that chart.

Table 2. The mean scores of the DRSP chart's items regarding *physical symptoms* of PMS at baseline and after two months intervention in participants who received either herbal supplement or placebo[a]

DRSP Chart's Items	**Herbal supplement+vitamin B6**			**Placebo**, n=53			
	Baseline	After 2 months[b]	Change	Baseline	After 2 months[b]	Change	P-value[c]
Sweets craving	1.49 ± 0.45	1.44 ± 0.42	-0.05 ± 0.38	1.49 ± 0.51	1.49 ±0.55	-0.004 ± 0.40	0.62
Heart palpitations	1.22 ± 0.27	1.26 ± 0.38	0.04 ± 0.26	1.36 ± 0.41	1.24 ± 0.38	-0.12 ± 0.43	0.22
Increased appetite	1.46 ± 0.47	1.32 ± 0.42	-0.14 ± 0.47	1.37 ± 0.46	1.40 ± 0.48	0.03 ± 0.48	0.18
Abdominal bloating	1.36 ± 0.47	1.31 ± 0.29	-0.05 ± 0.54	1.51 ± 0.52	1.35 ± 0.40	-0.16 ± 0.43	0.42
Feeling tired	1.72 ± 0.54	1.62 ± 0.51	-0.09 ± 0.44	1.58 ± 0.39	1.47 ± 0.40	-0.11 ± 0.50	0.84
Frequent urination	1.51 ± 0.45	1.28 ± 0.37*	-0.23 ± 0.50	1.37 ± 0.42	1.42 ± 0.42	0.04 ± 0.40	0.05
Flushing	1.47 ± 0.48	1.35 ± 0.42	-0.12 ± 0.47	1.36 ± 0.42	1.45 ± 0.48	0.92 ± 0.55	0.10
Feeling weak and lack of energy	1.63 ± 0.50	1.45 ± 0.41*	-0.17 ± 0.47	1.54 ± 0.42	1.47 ± 0.43	-0.07 ± 0.45	0.34
Breast tenderness	1.46 ± 0.44	1.42 ± 0.47	-0.03 ± 0.45	1.48 ± 0.40	1.49 ± 0.45	0.01 ± 0.40	0.69
Feeling cold	1.42 ± 0.34	1.25 ± 0.41	-0.17 ± 0.41	1.42 ± 0.47	1.29 ± 0.42	-0.13 ± 0.44	0.78
Edema	1.27 ± 0.41	1.14 ± 0.36	-0.13 ± 0.45	1.37 ± 0.43	1.03 ± 0.08	-0.34 ± 0.38	0.40
Nausea	1.37 ± 0.40	1.28 ± 0.39	-0.09 ± 0.40	1.60 ± 0.51	1.27±0.03**	-0.33 ± 0.37	0.07
Abdominal pain and discomfort	1.64 ± 0.51	1.48 ± 0.58	-0.16 ± 0.50	1.40 ± 0.37	1.33 ± 0.36	-0.06 ± 0.40	0.39
Back pain	1.74 ± 0.41	1.45 ± 0.48**	-0.29 ± 0.53	1.62 ± 0.39	1.59 ± 0.39	-0.02 ± 0.42	0.03
Headache	1.51 ± 0.51	1.44 ± 0.45	-0.07 ± 0.43	1.28 ± 0.38	1.21 ± 0.33	-0.07 ± 0.43	0.97
Acne	1.53 ± 0.47	1.28 ± 0.42**	-0.25 ± 0.46	1.37 ± 0.31	1.33 ± 0.36	-0.03 ± 0.42	0.07
Greasy skin	1.35 ± 0.47	1.16 ± 0.26**	-0.19 ± 0.38	1.24 ± 0.37	1.12 ± 0.25*	-0.12 ± 0.25	0.37
Joint pain	1.58 ± 0.54	1.32 ± 0.36*	-0.26 ± 0.52	1.31 ± 0.30	1.37 ± 0.36	0.06 ± 0.44	0.03
Muscle pain	1.49 ± 0.42	1.47 ± 0.54	-0.01 ± 0.55	1.41 ± 0.31	1.42 ± 0.36	0.009 ± 0.32	0.85
Insomnia	1.35 ± 0.40	1.38 ± 0.43	0.03 ± 0.43	1.36 ± 0.44	1.17 ± 0.21	-0.18 ± 0.41	0.11

DRSP= Daily Record of Severity of Problems; PMS= premenstrual syndrome

[a] Values are expressed as mean ±standard deviation

[b] Paired sample t-test was used for within group comparisons and p-values have been determined by *. *= P< 0.05, ** = P< 0.01

[c] independent sample t-test was used to compare the mean changes of scores from baseline to endpoint between study groups

Table 3. The mean scores of the DRSP chart's items regarding *psychological symptoms* of PMS at baseline and after two months intervention in participants who received either herbal supplement or placebo[a]

DRSP Chart's Items	Herbal supplement+vitamin B6 n=52			Placebo n=53			
	Baseline	After 2 months[b]	Change	Baseline	After 2 months[b]	Change	P value[c]
Avoiding social activities	1.60 ± 0.52	1.47 ± 0.49	-0.13 ± 0.41	1.53 ± 0.47	1.41 ± 0.38	-0.12 ± 0.47	0.97
Crying	1.70 ± 0.54	1.44 ± 1.45*	-0.25 ± 0.55	1.57 ± 0.49	1.47 ± 1.44	-0.10 ± 0.54	0.31
Boredom	1.73 ± 0.46	1.50 ± 0.39**	-0.23 ± 0.48	1.63 ± 0.37	1.44 ± 0.36**	-0.19 ± 0.38	0.67
Depression	1.61 ± 0.33	1.44 ± 0.44	-0.17 ± 0.49	1.46 ± 0.46	1.27 ± 0.30*	-0.19 ± 0.45	0.85
Seclusion	1.64 ± 0.51	1.48 ± 0.58	-0.16 ± 0.50	1.39 ± 0.37	1.33 ± 0.36	-0.09 ± 0.40	0.39
Nervousness	1.69 ± 0.44	1.59 ± 0.55	-0.10 ± 0.63	1.56 ± 0.44	1.49 ± 0.42	-0.07 ± 0.43	0.79
Irritability	1.70 ± 0.56	1.53 ± 0.43	-0.17 ± 0.56	1.45 ± 0.42	1.39 ± 0.42	-0.06 ± 0.50	0.41
Anxiety	1.49 ± 0.42	1.39 ± 0.40	-0.10 ± 0.45	1.29 ± 0.37	1.20 ± 0.31	-0.09 ± 0.37	0.94
Forgetfulness	1.30 ± 0.37	1.23 ± 1.31	-0.06 ± 0.49	1.44 ± 0.46	1.25 ± 1.40	-0.19 ± 0.43	0.44
Lack of concentration	1.50 ± 0.56	1.27 ± 0.29	-0.22 ± 0.59	1.37 ± 0.39	1.33 ± 0.53	-0.04 ± 0.49	0.26

DRSP= Daily Record of Severity of Problems; PMS= premenstrual syndrome

[a] Values are expressed as mean ±standard deviation

[b] Paired sample t-test was used for within group comparisons and *p*-values have been determined by *. *= P< 0.05, ** = P< 0.01

[c] independent sample t-test was used to compare the mean changes of scores from baseline to endpoint between study groups

Table 4. The mean overall scores of the PMS severity based on the DRSP chart, at baseline and after two months intervention, in participants who received either herbal supplement or placebo [a]

	Herbal supplement+vitamin B6, n=52			**Placebo,** n=53			
	Baseline	After 2 months[b]	Change	Baseline	After 2 months[b]	Change	P-value[c]
Overall score of the DRSP	1.58±0.32	1.35±0.24 **	-0.23 ± 0.21	1.30±0.20	1.47±0.28 **	0.17±0.20	< 0.001
Overall score of the physical symptoms	1.47±0.30	1.33±0.27 **	-0.14 ± 0.33	1.38±0.24	1.30±0.25	-0.08±0.28	0.32
Overall score of the psychological symptoms	1.58±0.38	1.43±0.30 **	-0.15 ± 0.29	1.44±0.30	1.37±0.57	-0.07±0.28	0.21

DRSP= Daily Record of Severity of Problems; PMS= premenstrual syndrome

[a] Values are expressed as mean ±standard deviation

[b] Paired sample t-test was used for within group comparisons and *p*-values have been determined by *. *= P< 0.05, ** = P< 0.01

[c] independent sample t-test was used to compare the mean changes of scores from baseline to endpoint between study groups

Table 5. The effects of study groups on the endpoint overall score of DRSP chart adjusted for baseline overall score[a]

Source	Sum of Squares	df	Mean Square	F	P value
Corrected Model	2.677[b]	2	1.339	37.296	<0.001
Intercept	0.499	1	0.499	13.903	<0.001
Baseline overall score of DRSP	2.379	1	2.379	66.285	<0.001
Study groups	4.121	1	1.458	40.629	<0.001
Error	2.62	73	0.036		
Total	157.794	76			
Corrected Total	5.298	75			

DRSP= Daily Record of Severity of Problems, [a] General linear model analysis, [b] R Squared =0.505 (Adjusted R Squared = 0.492)

Discussion

The present study demonstrated that the use of an oral supplement containing a combination of extracts from *Vitex agnus-castus, Echium amoenum,* and *Chamomile*, along with vitamin B6 for two months, resulted in a significant 27.6% reduction in the severity of PMS symptoms. The most notable reductions were observed in the signs of "back pain" and "joint pain."

Consistent with our findings, previous studies have also highlighted the efficacy of VAC in alleviating PMS symptoms. Prilepskaya et al. discovered that the consumption of dried extract of was both safe and effective in alleviating the symptoms of PMS.[19] He et al. conducted a study on the impact of VAC on PMS treatment over three menstrual cycles involving 202 Chinese women.[20] Their findings indicated a significant improvement in PMS symptoms among those who took VAC compared to those who received a placebo.[20] Similarly, Schellenberg et al. investigated the dose-dependent effectiveness of VAC extract on PMS symptoms across three menstrual cycles in 162 females.[18] They observed a notable enhancement in the overall PMS symptom score in the group that received a 20 mg dose of VAC.[18]

In a randomized placebo-controlled trial, 128 women experiencing PMS were administered 40 drops of VAC extract or a placebo daily for six days before menstruation over six consecutive menstrual cycles. The final outcomes demonstrated a marked improvement in the visual analogue scores for PMS in both groups, with a more pronounced enhancement observed in the VAC group compared to the placebo group. Additionally, a significant reduction in symptoms such as headache, nervousness, restlessness, depression, breast swelling, and bloating was reported.[21]

In the present study, we observed a significant improvement specifically in "back pain" and "joint pain." One potential explanation for the disparities between our findings and those of previous studies could be attributed to variations in the duration of the intervention. While we administered the herbal supplement for two menstrual cycles, prior trials had intervention periods spanning over three menstrual cycles or more.

Limited research has explored the effects of chamomile extract on PMS symptoms. Sharifi et al. conducted a study comparing the impact of chamomile extract and mefenamic acid on the severity of PMS symptoms.[22] Their findings indicated a notable 30% reduction in emotional symptoms among chamomile extract users compared to those using mefenamic acid.[22] However, chamomile extract did not demonstrate effectiveness in alleviating somatic symptoms of PMS when compared to mefenamic acid.[22] Conversely, our study revealed a positive effect of an herbal supplement containing chamomile extract specifically on certain somatic symptoms such as "back pain" and "joint pain." It is worth mentioning that Sharifi et al., utilized a daily dose of 300 mg of chamomile extract, whereas we administered a dose of 160 mg. This dosage variance may account for the differences observed between the two study outcomes.[22]

Furthermore, previous research has highlighted the beneficial effects of chamomile on primary dysmenorrhea,[23,24] suggesting that its anti-inflammatory properties, may be attributed to constituents like chamazulene and alpha bisabolol.[25,26] Despite variations in study durations and dosages, our findings add to the growing body of evidence supporting the potential benefits of herbal supplements containing chamomile extract in managing specific PMS symptoms. Further research is warranted to explore the mechanisms underlying these effects and optimize treatment strategies for individuals with PMS. A randomized controlled trial conducted by Farahmand et al., investigated the effects of Echium amoenum (E. amoenum) on the severity of PMS. The study revealed that E. amoenum (450 mg/day) was more effective in improving PMS symptoms compared to a placebo.[27] Previous studies have also reported the anxiolytic and antidepressant effects of E. amoenum.[28,29] In a preliminary randomized controlled trial, Sayyah et al. demonstrated that daily consumption of 375 mg of E. amoenum aqueous extract over 6 weeks significantly reduced depressive symptoms compared to a placebo.[29] Furthermore, in another clinical trial, Sayyah et al., investigated the effects of combining 500 mg of E. amoenum aqueous extract with fluoxetine on anxiety disorders over an 8-week intervention period, showing a significant reduction in signs of general anxiety disorders.[30] Given its antidepressant and anxiolytic properties, E. amoenum extract was selected for use in the herbal supplement in the present study to improve PMS symptoms. The dose of E. amoenum in the current study was 100 mg/day, which was lower than the doses used in the aforementioned studies. It is possible that higher doses of E. amoenum could lead to greater reductions in PMS symptoms.

Previous studies have indicated that vitamin B6 may be more effective in reducing psychological symptoms of PMS than somatic signs.[31,32] In the current study, although the overall score of psychological symptoms significantly decreased after taking the herbal supplement containing vitamin B6, this change did not differ

significantly from the change observed after taking the placebo. One potential reason for this finding could be the dosage of vitamin B6 used in the present study. A previous systematic review suggested that doses of vitamin B6 around 100 mg/day are likely to be beneficial in treating the psychological symptoms of PMS, whereas we administered a lower dose (40 mg/day).[33]

Like previous similar studies, the present study had some limitations. The dosages of certain components in the current supplements, such as chamomile, *E. amoenum*, and pyridoxine, were lower than those used in previous clinical trials that demonstrated their beneficial effects on PMS symptoms. Due to the combination of three herbal remedies with vitamin B6 in the supplement used in this study, lower doses were necessary to prevent potential interactions and minimize unwanted side effects. Additionally, it is possible that a longer intervention duration spanning more than two menstrual cycles would result in a more pronounced effect size for this herbal supplement. On a positive note, the strength of the present study lies in its randomized double-blind controlled design with a large sample size (105 subjects). Furthermore, PMS diagnosis was confirmed in our participants following two stages of screening.

Conclusions

The results of the present study indicate that taking an oral supplement containing a combination of extracts from Vitex agnus-castus, Echium amoenum, and Chamomile plus vitamin B6 significantly reduced the overall severity of PMS symptoms. It may also improve somatic signs of PMS such as back pain and joint pain. Additionally, our results showed no side effects after the consumption of the herbal supplement. Therefore, women who suffer from PMS and cannot tolerate other treatments, such as taking contraceptives or antidepressants, might benefit from using such an herbal supplement. An important achievement of the current study was the creation of a supplement in which the extracts of herbal medicines are incorporated into a single oral tablet that is consumed more easily than the separate use of herbal extracts or brewed herbal remedies, consequently increasing consumer compliance.

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Competing interests

The authors declare that they have no competing interests.

Abbreviations

Premenstrual syndrome: PMS; Vitex agnus-castus: VAC;
Daily Record of Severity of Problems: DRSP;
Premenstrual dysphoric disorder: PMDD;
Premenstrual Symptoms Screening Tool: PSST;
Body mass index: BMI.

Authors' contributions

All authors read and approved the final manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

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None.

Availability of data and materials

The data used in this study are available from the corresponding author on request.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. Prior to participation, all participants were required to sign a written informed consent form. The study protocol was approved by the Ethics Committee of Kashan University of Medical Sciences and registered with the Iranian Registry of Clinical Trials (registered code: IRCT2015060812438N13).

Consent for publication

By submitting this document, the authors declare their consent for the final accepted version of the manuscript to be considered for publication.

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