Original Article

Comparison of the Effects of Vitagnus, Soy, and Vitagnus-soy Capsules on Premenstrual Syndrome in University Students: A Randomized Clinical Trial

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Abstract

Background: Premenstrual syndrome (PMS) is a common disease that negatively impacts women's quality of life. This study aimed to compare the effects of the Vitagnus, soy, and Vitagnus-soy combination on PMS in students.

Methods: This triple-blind, three-arm clinical trial was conducted on 108 students with PMS living in the dormitory of Mashhad University of Medical Sciences from September 2022 to October 2023. Eligible participants diagnosed with moderate to severe PMS over two menstrual cycles, using the Calendar of Premenstrual Experiences form, were randomly assigned to one of three groups. Each participant took one daily capsule of Vitagnus (N=36), Soy (N=36), or a Vitagnus-soy combination (N=36) for two menstrual cycles. The data were analyzed using the ANOVA test (or Kruskal-Wallis test) with post-hoc tests based on Tukey (or Bonferroni correction), Chi-square test (or Fisher's exact method), and Wilcoxon test analysis (or paired t-test) in SPSS software version 26 with the significance level of $P<0.05$.

Results: In all three groups, PMS symptoms significantly reduced after the intervention ($P<0.001$). The Vitagnus-soy combination was more effective than either Soy or Vitagnus group in decreasing psychological ($P<0.001$) and total PMS symptoms ($P<0.001$). Vitagnus-soy combination had no statistically significant difference in decreasing physical PMS symptoms compared to Soy ($P>0.999$), but it was more effective than Vitagnus ($P<0.001$).

Conclusion: The Vitagnus-soy combination was more effective in alleviating PMS psychological and total symptoms than using either Soy or Vitagnus alone, making it a recommended option for reducing PMS symptoms.

Trial Registration Number: IRCT2022072005514N1

Keywords: Herbal medicine, Premenstrual syndrome, Soy, Vitex

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Introduction

Premenstrual syndrome (PMS) is one of the most common disorders in women.[1] It is a combination of physical and psychological symptoms that occur regularly in the luteal phase or the last 7-10 days of the menstrual cycle and disappears within 4 days from the start of menstrual bleeding.[2] The prevalence of PMS is 48% worldwide and is reported to be between 30% and 99.5% in Iran.[3] Over 200 signs and symptoms of PMS have been identified.[1] The most common physical symptoms of PMS include abdominal bloating, extreme fatigue, breast tenderness, and headache; among the psychological symptoms, the most common ones are mood swings, irritability, depressed mood, increased appetite, forgetfulness, and difficulty concentrating.[2] Premenstrual syndrome could affect women's quality of life negatively. Every month (menstrual cycle), many women experience physical and mental problems as well as dysfunctions in professional and social areas due to PMS.[1]

There is no consensus among experts regarding the optimal treatment for PMS.[4] The main goal of treatment is to control and relieve PMS symptoms in women.[5] Several studies have been conducted on the effect of herbal medicines on PMS symptoms, examining cinnamon, ginger, Hypericum perforatum, vitagnus, and soy.[6-9] While most studies have discussed the potential of herbal remedies in reducing PMS symptoms, conflicting results have also emerged. Some studies have highlighted the psychological impacts of these products and suggested the need for further research and updated studies.[10]

The European Medicines Agency and the German Commission for Health have mentioned the benefits of Vitagnus in regulating the menstrual cycle, treating PMS, and relieving mastalgia.[11] The fruit extract of Vitex agnus-castus (VAC) is the only herbal remedy proven to control mood swings and irritability associated with PMS.[12] In a review study related to the treatment of PMS with VAC, the high effectiveness of Vitagnus with a focus on depression and anxiety symptoms has been mentioned.[13]

VAC contains a mixture of essential oils, iridoid glycosides, diterpenes, and flavonoids.[14] Its therapeutic effects are achieved through dopamine ligands, opioid-like substances, and estrogen. The agonistic effect of dopamine improves PMS symptoms by inhibiting prolactin secretion. VAC exerts its therapeutic effects by activating the Mu opioid receptors (MOR) and Delta opioid receptors opioid ligands.[15] MOR ligand plays a key role in regulating mood and emotional disorders.[16] The isolated flavonoid apigenin is a selective phytoestrogen for the estrogen receptor and reduces the effects of estrogen. This reduction enhances the ability of endorphins to significantly normalize or improve mood.[7, 17] VAC is usually well tolerated, with infrequent, mild, and reversible adverse effects, such as nausea, headache, gastrointestinal disturbances, acne, itch, and rash.[18]

Soy is a reliable source of isoflavones and contains daidzein, genistein, and glycitein.[19] Soybeans are a good source of iron, B vitamins, calcium, zinc, fiber, unsaturated fatty acids, and other bioactive compounds.[20] Most of the iron in soy is absorbed in the form of ferritin and equal to that from $FeSO_4$.[21] The bioavailability of calcium from soy and soy-based foods is the same as that from dairy products.[22] Calcium deficiency during the luteal phase of the menstrual cycle can aggravate PMS symptoms by causing depression, hallucinations, and restlessness.[23] Soy proteins are equivalent to animal proteins as to quality.[20] Elevating the consuming complex proteins results in higher levels of tryptophan, leading to increased serotonin production.[24] Soybeans contain 54% unsaturated fatty acids, especially linoleic acid, and significant amounts of alpha-linolenic essential fatty acid. The results of some studies have indicated the relationship between abnormal metabolism of essential fatty acids and PMS symptoms.[20] Soy is recognized for its positive impact on immunity, with rare cases of allergy as the

only reported adverse reaction.[25]

In the last decade, a considerable increase has been observed in the use of herbal medicine and complementary medicine in Europe, the United States of America, and Australia.[26] The World Health Organization and legislative bodies are interested in identifying affordable and readily available treatments with minimal side effects to control PMS symptoms.[27] Currently, there is an increasing focus on combination drugs in research, as combining drugs is commonly done to enhance their effectiveness and reduce their side effects.[28] Vitagnus acts as an antioxidant by stimulating the expression of genes related to progesterone receptors or by its ability to eliminate defects in progesterone synthesis and soy by inhibiting angiogenesis and protecting against oxidative damage.[29] Therefore, considering the different pharmacological aspects of Vitagnus and soy, their synergistic and overlapping effects in various potential pathophysiologies, combining these two plants with lower doses than those available in the market, and the lack of similar studies reported, this research was conducted to compare the effects of Vitagnus, soy, and the Vitagnus-soy capsules in students suffering from PMS.

Materials and Methods

This triple-blind, three-arm randomized clinical trial study was conducted on 100 eligible single female students at Mashhad University of Medical Sciences who lived in the dormitory from September 2022 to October 2023. The sample size was calculated based on previous studies for the three primary outcomes (physical, psychological, and total PMS). The largest sample size corresponded to the average changes in psychological symptom scores in the group receiving Vitagnus, which was 22.92±15.59.[9] To detect 50% more changes (a further reduction in the overall symptom score of 34.38) in the new drug combination, assuming equal variance for these changes in the Vitagnus group and considering a 5% type I error, 80% power of the test, and a 20% dropout rate, we determined the final sample size to be 108 individuals (36 in each group) using the following formula.

$$n = \frac{(s_1^2 + s_2^2)\left(Z_{1-\frac{\alpha}{2}} + Z_{1-B}\right)^2}{(\mu_2 - \mu_1)^2} =$$

$$\frac{(15.59^2 + 15.59^2)(1.96 + 0.84)^2}{(34.38 - 22.92)^2} = 29$$

The inclusion criteria were being Iranian and single; having regular menstruation (intervals of 21-38 days and bleeding duration less than 7 days); having no diseases (cardiac, respiratory, renal, hepatic, blood pressure, anemia, asthma, diabetes, epilepsy, migraine, thyroid, Cushing's, multiple sclerosis, galactosoma, pituitary tumor, hepatitis, AIDS, endocrine disorders, coagulation, schizophrenia, neurological and mental diseases, depression, cancers of uterus, ovaries, cervix and vagina, and reproductive system problems (abnormal bleeding, ovarian cyst, endometriosis, and uterine leiomyoma(according to the participants' reports; using no special medicine (Agonist-Antagonist Dopamine, Levothyroxin, Warfarin, Ferrous Sulfate, and Tamoxifen), using no herbal or chemical medicine in the last three months for relieving PMS symptoms (e.g., Selective Serotonin Reuptake Inhibitors, Benzodiazepines, Gonadotropin-releasing hormone agonist, Oral Contraceptive Pills, Spironolactone, and Vitamin B); not facing traumatic events (e.g., death of loved ones, surgery, and severe family conflicts in the last six months); not being a professional athlete; not being on a diet or vegetarian diet; having a body mass index (BMI) of less than 30 kg/m^2; having no allergy to Vitagnus products and soy; not consuming alcohol, cigarettes and any drugs; having PMS symptoms according to the temporary diagnosis form; having no severe depression, stress, and anxiety according to the Depression Anxiety Stress Scales-21 (DASS-21); and having moderate to severe (but not very severe) PMS

in two cycles according to the Calendar of Premenstrual Experiences (COPE) form. The exclusion criteria included very severe PMS, non-completion or incomplete completion of the COPE form, irregular consumption of medication (more than 5 intermittent doses or more than 3 consecutive days), and unwillingness to cooperate.

Random allocation was done to ensure an equal number of people in 3 groups based on the WWW.Sealedenvelope.com website with blocks of sizes 3 and 6. Primary outcomes were PMS physical, psychological, and total symptoms. Secondary outcomes were menstrual pain and satisfaction with consumption. The tools used to gather the required data included a research unit selection form, demographic-menstrual characteristics form, PMS temporary diagnosis form, DASS-21, COPE form, Visual Analogue Scale (VAS) form, medication prescription information registration form, and consumer satisfaction.

The demographic-menstrual characteristics form (researcher-made) consisted of three sections: demographic characteristics (age, BMI, monthly family income, and employment), menstrual characteristics (age at onset of menstruation, menstrual intervals, duration of menstruation bleeding, absence from work or class due to menstrual problems, family history of PMS and dysmenorrhea), and lifestyle (day and night sleep, amount of soy consumption). The validity of the questionnaire was established through content validity and under the supervision of the supervisor and advisor professors, with the approval of 7 faculty members from the School of Nursing and Midwifery in Mashhad in the specialized field of midwifery Ph.D.

The PMS temporary diagnosis form was adapted from the Diagnostic and Statistical Manual of Mental Disorder, 5th edition (DSM-V). This form has been validated with a Cronbach's alpha coefficient of 0.75.[2, 30] If the research subjects had 5 out of 11 symptoms, provided that one of the symptoms was from the first 4 symptoms of the questionnaire, a temporary diagnosis of PMS was proposed.[2] The reliability of the PMS temporary diagnosis form was confirmed with an internal consistency of α=0.651.

The DASS-21, designed by Lovibond and Lovibond (1995), is a short tool comprising 21 questions that assess the individual's feelings over the past week through three subscales of depression, anxiety, and stress. The items are scored on a 4-point Likert scale, and the final score is calculated by adding up the relevant items and doubling the score. A score of 0-9, 0-7, and 0-14 denotes mild depression, anxiety, and stress, respectively; also, scores higher than 28, 20, and 33 correspond to severe depression, anxiety, and stress, respectively.[31] In Iran, Samani and Joukar (2007) confirmed the validity of this questionnaire using factor analysis, and its reliability was estimated using Cronbach's alpha coefficients for depression, anxiety, and stress at 0.85, 0.75, and 0.87, respectively.[32]

The COPE form, developed by Mortola and colleagues (1990), is a standardized tool and the most commonly adopted primary method for assessing PMS symptoms. It includes 10 physical symptoms and 12 psychological (behavioral) symptoms. The score for physical symptoms ranges from 0-300, for psychological symptoms from 0-360, and for total symptoms from 0-660. Each letter is recorded on each day accompanied by a severity rating from 0 (no symptoms) to 3 (severe). The average scores of the severity of physical, psychological, and total symptoms are calculated at the end of each menstrual cycle; then, the severity of PMS is calculated using the following formula:

$$\text{The percentage of changes within the cycle} = \frac{\text{total luteal phase scores} - \text{total follicular phase scores}}{\text{total luteal phase scores}} \times 100$$

A score of less than 30% represents a mild PMS, 30-50% suggests a moderate PMS, 50-60% indicates a severe PMS, and more than 60% shows very severe PMS.[2, 33] In Iran, Nourani and Dadi Givshad (2013) confirmed the validity of this form through content validity, and its reliability was

established with the method of retesting and r=0.82.[34] In this study, the reliability of this instrument was confirmed using the internal consistency of α=0.793. In this study, if the average severity of PMS symptoms was more than 30% and the participant had moderate to severe (but not very severe) PMS in two cycles, the participant was included in the intervention.

VAS was used to measure a secondary outcome of menstrual pain (dysmenorrhea). The VAS is the most used and reliable tool for measuring pain intensity worldwide. This scale is a 10-cm horizontal line marked, with the left side (0) indicating no pain and the right side[10] indicating the worst possible pain. Individuals identify the peak intensity of their pain from the first day of menstruation until the end of the seventh day. The validity and reliability of this tool have been confirmed in various studies abroad.[35] In Iran, the reliability of this scale has also been verified with a correlation coefficient of 0.86.[36]

Initially, necessary permission was obtained from the ethics committee of the university, and the study was registered on the Iranian Registry of Clinical Trials (IRCT) website. Then, the researcher visited the students in their dormitory rooms, and following an introduction and a general explanation of the research objectives, written informed consent was obtained, and sampling was initiated.

Screening of the participants started with the temporary diagnosis form of PMS and the DASS-21. If students had a PMS diagnosis, no severe depression, anxiety, stress, and the other inclusion criteria, they were selected as the research unit. Then, the demographic-menstrual characteristics form was provided to the students and completed in the presence of the researcher. Afterward, the COPE form was distributed among the participants to confirm the diagnosis and severity of PMS. Individuals were instructed that this form was used to determine the severity of symptoms from the first day of menstrual bleeding; they were asked to assess the severity of their symptoms using a scale of 0 to 3 (0=none [no symptoms], 1=mild [noticeable but mild and tolerable], 2=moderate [interferes with daily activities], and 3=severe [intolerable and unable to perform daily activities]) at a specific time during sunset for two consecutive menstrual cycles before the intervention in a prospective manner, and also two cycles after the intervention. In addition, the VAS form was used to determine the average menstrual pain intensity as a secondary outcome at every two cycles before and every two cycles after the intervention.

First, the researcher assessed the completed COPE forms. Each symptom was scored and then added up at the end of each menstrual cycle. If the average intensity of the symptoms was between 30% and 60%, and the diagnosis of moderate to severe (but not very severe) PMS was confirmed, the participants were randomly assigned to one of the intervention groups. To closely monitor the completion of the research process, the researcher communicated with the participants every two weeks through face-to-face visits, phone calls, and messages, encouraging them to complete the form regularly.

The medications were formulated in the Research and Development Laboratory of Elixir Hayat Moshir Pharmaceutical Company, situated within the Health Park of Mashhad University of Medical Sciences. The raw materials were sourced from the Razavi Khorasan region. The dosage of medications was determined as follows: 500 mg capsule of dry extract of Vitagnus plant (contains 40 mg dry extract of Vitagnus and 460 mg Microcrystalline cellulose) was based on the formulation available in the market by Gol Daru Company and guided by a study by Pakgohar et al.,[9] and a 500 mg capsule of soy (contains 500 mg of soy powder) was based on the study by Nazemi et al.[8] For the combination treatment, a 500 mg capsule containing Vitagnus-soy was formulated with 20 mg of dry extract of Vitagnus plant, 250 mg of soy powder, and 230 mg Microcrystalline cellulose. This dosage was determined

according to the consulting pharmacist team, using existing literature, herbal textbooks, and consideration of effective and safe dosages. Each packet contained 30 capsules, and two packets were provided to the participants. The participants were instructed to consume one capsule daily after breakfast throughout two menstrual cycles.

To conceal the allocation, the pharmacist assistant coded the sealed opaque envelopes and packaged medications in similarly coded containers (assigned with codes A, B, and C). Medications were similar in appearance, size, color, scent, and taste. The pharmacist assistant was the only person not blinded by the group allocation and was not involved in the study. Neither the researcher nor the study participants were aware of the codes. The first envelope with the match-coded container was given to the first individual meeting the study entry criteria, and this process continued according to the prepared blocks until the desired sample size was reached. In addition, the statistician was unaware of the group types. The pharmacist assistant revealed the group codes after the analysis was completed: A) Vitagnus group, B) Vitagnus-soy group, and C) soy group. In the end, 33 individuals in the Vitagnus group, 33 in the soy group, and 34 in the Vitagnus-soy group completed the study (Figure 1).

Potential side effects of medications and consumer satisfaction were monitored at the end of each menstrual cycle based on the relevant form; in case of any side effects, they were managed in consultation with the supervisor/pharmacology consultant professor and the pharmacist assistant.

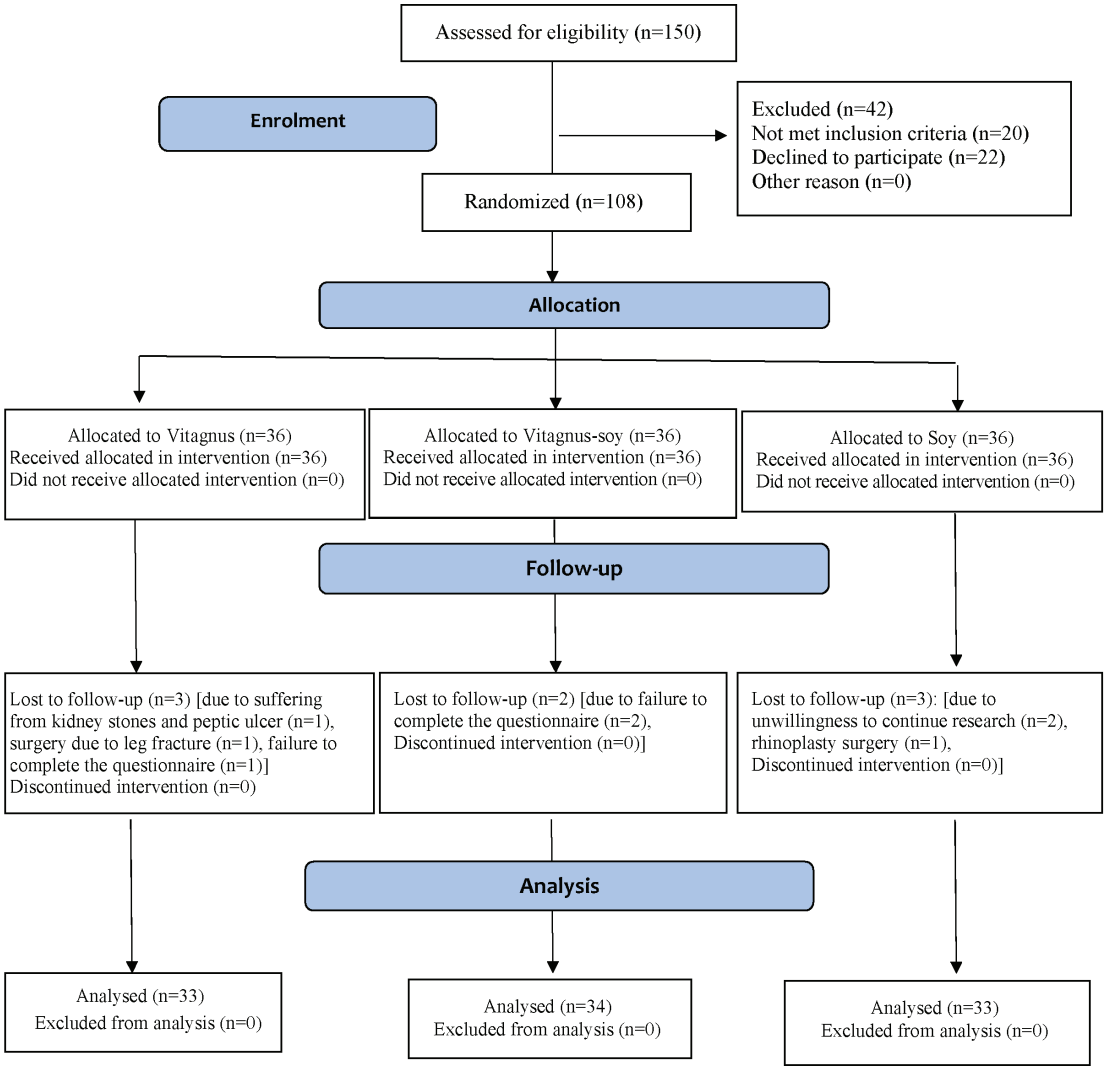

Figure 1: Consort flow diagram of the study participants

Based on the safety protocol of the medication, it was predicted that in case of moderate and severe side effects, the drug consumption needed to be stopped, and if medical attention was needed, the individual was referred to a physician, recorded, and then excluded from the study. Eventually, after two treatment cycles, the COPE and VAS forms were collected, and the data were analyzed by calculating the average of the two cycles before and after the data. In addition, the complication and satisfaction report form was completed at the end of each menstrual cycle after receiving the intervention.

The samples were contacted every two weeks through face-to-face visits and phone calls for follow-up side effects and ensuring the correct use. The contact number of the researcher was also given to them so that they could be contacted in case of any questions or complications.

After collecting and recording the data, the normality of the data related to quantitative variables was initially assessed using the Shapiro-Wilk test along with appropriate central tendency and dispersion indices and graphs. Following that, according to the results of checking the normality of the data, the ANOVA test analysis (or Kruskal-Wallis test) was used to check the distribution of quantitative variables with post-hoc tests based on Tukey **(**or Bonferroni correction**)**, and the Chi-square test (or Fisher's exact method) was used to check the distribution of qualitative variables in the three study groups. Also, the Wilcoxon test analysis (or paired t-test) was used to compare the Intragroup differences in the three study groups**.** Data analysis was done in SPSS software version 26 at a significance level of less than 0.05.

The present study was approved by the Research Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.NURSE.REC.1401.055). All participants signed an informed written consent at the beginning of the study, and they were assured of data confidentiality, voluntary participation, and the right to withdraw from the study without any penalty.

Results

A total of 150 students were assessed for eligibility; 20 did not meet the inclusion criteria, and 22 were unwilling to participate. Demographic and menstrual cycle characteristics did not show statistical differences in the Vitagnus, soy, and Vitagnus-soy combination groups ($P>0.05$) (Table 1). Additionally, the three groups were homogeneous in monthly family income ($P=0.46$), family history of PMS ($P=0.25$), and amount of soy consumption ($P=0.72$) (Table 1). The comparison of PMS physical ($P<0.001$), psychological ($P=0.01$) symptoms score, and the total PMS score ($P<0.001$) before the intervention indicated statistically significant differences (Table 2).

Considering the intragroup comparison of the mean scores of physical, psychological, and total PMS symptoms two cycles after the intervention, the results of the paired t-test in the Vitagnus group and those of Wilcoxon test in the soy and Vitagnus-soy groups showed a significant decrease in all three groups ($P<0.001$) (Table 2).

Among-groups comparison of differences of the mean score of PMS physical symptoms before and after the intervention showed that there was a statistically significant difference among the Vitagnus group (-11.28±10.34), soy group (-40.13±24.34), and Vitagnus-soy group (-43.51±19.21) ($P<0.001$), and the greatest decrease was observed in the mean score of the Vitagnus-soy group (Table 2). The results of the Mann-Whitney U test with Bonferroni correction showed that the Vitagnus group was significantly difference from the Vitagnus-soy and soy groups ($P<0.001$); however, there was no statistically significant difference between the Vitagnus-soy group and the soy group ($P>0.999$).

Among-groups comparison of the differences of the mean score of PMS psychological symptoms before and after the intervention showed a statistically significant difference among the Vitagnus group (-42.21±17.56), soy group (-34.71±16.69), and

Table 1: Demographic-menstrual characteristics of students in the Vitagnus, soy, and Vitagnus-soy groups

Variable	Group			P value
	Vitagnus (N=33) Mean±SD Median (IQR)	Soy (N=33) Mean±SD Median (IQR)	Vitagnus-soy (N=34) Mean±SD Median (IQR)	
Age (years)	22.79±4.49 21(3)	22.42±4.43 21(5)	23.21±4.71 21.50(4)	0.37*
Body mass index (kg/m^2)	21.47±3.21 21.50(4.85)	20.73±4.72 20.55(5.50)	22.78±3.64 22.35(6.52)	0.21*
Age at onset of menstruation (years)	13.06±1.32 13(2)	13.12±1.21 13(2)	12.44±1.10 12(1)	0.05*
Menstrual intervals (days)	28.33±1.94 28(2)	29.09±1.04 29(2)	28.47±1.91 28(2)	0.14*
Duration of menstrual bleeding (days)	6.39±1.22 7(2)	6.09±1.23 7(2)	6.47±1.32 7(2)	0.52*
Nighttime sleep (hours)	8.21±1.34 8(2)	7.79±1.55 8(2)	7.76±0.98 8(1)	0.18*
	N (%)	N(%)	N (%)	
Monthly family income level				0.46**
Sufficient for living expenses	30(91)	28(85)	32(94)	
Less than sufficient for living expenses	2(6)	3(9)	0(0)	
More than sufficient for living expenses	1(3)	2(6)	2(6)	
Employment				0.10**
Yes	2(6)	8(24)	4(12)	
No	31(94)	25(76)	30(88)	
Absence from work or class due to menstrual problems				
At all	11(33)	8(24)	11(32)	0.55**
Always	1(3)	4(12)	1(3)	
Sometimes	21(64)	21(64)	22(65)	
History of dysmenorrhea				0.93**
Yes	29(88)	28(85)	30(88)	
No	4(12)	5(15)	4(12)	
Family history of PMS[a]				0.25**
Yes	18(55)	22(67)	21(62)	
No	3(9)	1(3)	6(18)	
Do not know	12(36)	10(30)	7(20)	
Amount of soy consumption				0.72**
No consumption	18(55)	17(52)	15(44)	
Once a week	14 (42)	13 (39)	15(44)	
Twice a week	1(3)	3(9)	4(12)	
Three times a week	0(0)	0(0)	0(0)	

[a]PMS: Premenstrual syndrome; *Kruskal-Wallis; **Fisher's exact test

Vitagnus-soy group (-74.51±28.49) (P<0.001), with the greatest decline in the mentioned mean scores of the Vitagnus-soy group (Table 2). The results of the Tukey post-hoc test showed that there was a statistically significant difference between the Vitagnus-soy group with the soy and Vitagnus groups (P<0.001); also, no statistically significant difference was found between the Vitagnus and soy groups regarding the reduction of PMS psychological symptoms (P=0.18).

Among-groups comparison of differences of the mean score of PMS total symptoms before and after the intervention showed that there was a statistically significant difference among the Vitagnus group (-53.50±21.26), soy group (-74.84±35.28), and Vitagnus-soy group (-118.02±40.71) (P<0.001), with the greatest decline in the mentioned mean scores of the Vitagnus-soy group (Table 2).

Table 2: Mean and standard deviation of physical, psychological, and total scores of premenstrual syndrome in students in the Vitagnus, soy, and Vitagnus-soy groups

Variable	Group			Among group comparison P value
	Vitagnus (N=33) Mean±SD Median (IQR)	Soy (N=33) Mean±SD Median (IQR)	Vitagnus-soy (N=34) Mean±SD Median (IQR)	
PMS[a] physical symptoms score				
Before the intervention	36.28±21.20 35 (34)	52.57±17.72 54 (20.50)	54.51±20.33 56.50 (33.13)	<0.001*
After the intervention	25±15.62 22.50 (27.75)	12.43±19.79 3.50 (18.25)	11±9.73 8.75 (14.25)	<0.001*
Difference between before and after the intervention	-11.28±10.34 -10.50 (10)	-40.13±24.34 -49 (37.75)	-43.51±19.21 -43.50 (25)	<0.001*
Intragroup comparison (P value)	<0.001**	<0.001***	<0.001***	
PMS psychological symptoms score				
Before the intervention	70.60±26.33 73.50 (39)	74.50±23.98 74.50 (34.75)	91.50±31.73 85.50 (36.50)	0.01*
After the intervention	28.39±11.15 30 (16.25)	39.78±20.60 39.50 (18.75)	16.98±14.23 14 (13)	<0.001*
Difference between before and after the intervention	-42.21±17.56 -42 (24.25)	-34.71±16.69 -33 (21.50)	-74.51±28.49 -72.25 (33.38)	<0.001****
Intragroup comparison (P value)	<0.001**	<0.001***	<0.001***	
PMS total symptoms score				
Before the intervention	106.89±36.33 111 (64)	127.07±34.87 125.50 (43.75)	146.01±43.26 149.75 (48.25)	<0.001****
After the intervention	53.39±22.44 48.50 (40.75)	52.22±35.32 44 (16.50)	27.98±22.32 25 (27.88)	<0.001*
Difference between before and after the intervention	-53.50±21.26 -52 (30)	-74.84±35.28 -80.50 (53)	-118.02±40.71 -116.25 (56)	<0.001****
Intragroup comparison (P value)	<0.001**	<0.001***	<0.001***	

[a]PMS: Premenstrual syndrome; *Kruskal-Wallis test; **Paired t-test; ***Wilcoxon test; ****ANOVA test

The results of the Tukey post-hoc test showed that the Vitagnus-soy group was significantly difference from the Vitagnus and soy groups (P<0.001). Moreover, based on the Tukey post-hoc test, there was a statistically significant difference between the Vitagnus group and the soy group in terms of a decrease in PMS total symptoms (P=0.01).

The results of the Wilcoxon test for the intra-group comparison of the mean menstrual pain intensity in the two cycles after the intervention compared to two cycles before the intervention indicated a statistically significant difference in the three groups: Vitagnus (P=0.001), soy (P<0.001), and the combination of Vitagnus and soy (P<0.001).

In the comparison of the difference in menstrual pain intensity between the two cycles before and after the intervention, the Kruskal-Wallis test results showed a statistically significant difference among the three groups (P<0.001). The greatest reduction in the mean pain intensity score was observed in the Vitagnus-soy group (-1.49±0.86), followed by soy (-0.96±0.95) and Vitagnus groups (-0.54±0.80). The Mann-Whitney U test with Bonferroni correction results showed that there was a statistically significant difference between the Vitagnus-soy group and the Vitagnus group (P<0.001). However, the soy group showed no statistically significant difference with the Vitagnus-soy group (P=0.13) and the Vitagnus group (P=0.11).

The Chi-square test results showed that there was a statistically significant difference among the three groups regarding satisfaction with the capsule consumption (P<0.001), with higher satisfaction reported in the Vitagnus-soy group than in the other two groups.

No specific side effects were reported in the three study groups. In the first cycle after the intervention, one person reported a slight increase in the bleeding in the Vitagnus group, one person reported mild dry skin in the soy group, and one person reported mild nausea in the first two days of consumption in the Vitagnus-soy group. In the second cycle following the intervention, no complications were reported in the three study groups.

Discussion

The results of the present study showed that PMS physical, psychological, and total symptoms significantly decreased after eight weeks of consuming Vitagnus, soy, and Vitagnus-soy capsules, indicating the beneficial effects of all three. Moreover, a between-group comparison of the difference in the mean scores of PMS physical symptoms after the intervention indicated that this score in the Vitagnus-soy group was not significantly different from that in the soy group but higher than that in the Vitagnus group in reducing physical symptom scores. Additionally, in the between-group comparison of the mean scores of PMS psychological and total symptoms after the intervention, the Vitagnus-soy was more effective than the other two interventions.

Some studies have already investigated the use of combined herbs in the treatment of PMS symptoms. In a study, it was reported that the percentage of changes in the average psychological and physical symptoms in the cinnamon-ginger group was significantly higher than those in the control group.[6] Another study reported Prementrid capsule as a unique combination of phytoestrogen ingredients and a safe and natural option with the best herbal combination used to treat PMS.[26] Therefore, considering their low side effects and synergistic therapeutic effects on clinical symptom improvement, this study aimed to combine two plants, Vitagnus and Soy.

The positive effect of the Vitagnus plant has been demonstrated in several previous studies.[7, 9, 37] A study compared the 20 mg dose with the 8 and 30mg doses of Vitagnus in treating PMS. The results of their study showed that the reference dose (20 mg) had more beneficial effects, and the adverse events were slightly increased for the high dose, which was not significant.[37] The above study was similar to our research in terms of the Vitagnus dose in the Vitagnus-soy combination medication and the reduction of possible side effects. A systematic review of eight studies on Vitagnus for PMS treatment showed that PMS symptoms significantly decreased in the group receiving Vitagnus than in the pyridoxine or placebo group.[37] Several previous studies have reported that Vitagnus is effective in the treatment of PMS,[7, 9, 37] which was similar to the results of the present study in the Vitagnus group.

Similarly, the positive effect of the soy plant has been shown in some previous studies; however, there have been some differences in the implementation method. In a study on female students with moderate-severe PMS, it was shown that soy was effective on physical symptoms and would also be effective on psychological symptoms after consuming two consecutive cycles; nevertheless, it did not affect behavioral symptoms.[38] In the current study, soy capsules affected PMS physical, psychological, and total symptoms. This discrepancy between the results of our study and the above research could be attributed to the differences in the amount of isoflavone received, the way of consumption, the placebo, and the type of study. In that study, the placebo biscuit was prepared from regular flour and the experimental biscuit contained 50 mg of soy isoflavone, while in the present study, the soy capsule contained 500 mg of soy powder.

A double-blind, placebo-controlled study with crossover design and two conditions of isolated soy protein containing 68 mg/day soy isoflavones or an identical placebo product showed that soy isoflavone significantly reduced total and physical PMS symptoms after active and placebo treatments; however,

the difference between active and placebo treatments was not significant.[39] This result was consistent with that of the current study regarding reduction of PMS physical and total symptoms. However, it was inconsistent with the present research as no significant difference was observed between the intervention and placebo groups regarding the PMS physical and total symptoms. This discrepancy in the results could be due to several factors, such as the use of the daily symptom report questionnaire, the method of consumption (in powder form, as a drink, sprinkled on food, or between meals), and the dose of soy used (30.5 g of soy isoflavones), in the mentioned study compared to the present study. Additionally, the sample size in their study was much smaller than that in the current study.

A further single-blind quasi-experimental study conducted on female students living in dormitories of Shahroud University found that soy consumption was effective in reducing total and psychological symptoms of PMS in the soy group, while it did not affect physical symptoms.[8] These findings are consistent with the results of the present study on reducing total and psychological symptoms, considering the same dosage and duration of soy supplementation. However, in our study, soy also reduced physical symptoms. The lack of a significant difference in physical symptoms may be attributed to the inclusion of individuals with severe PMS in the mentioned study, compared to the inclusion of those with moderate and severe PMS in the present study. A review study on 20 studies examining the role of vitamins and minerals on PMS symptoms concluded that the consumption of certain vitamins (e.g., E, D, and B6) and minerals (e.g., magnesium, calcium, and zinc) could alleviate PMS symptoms.[40] In the present study, soybeans are rich in the mentioned salts, and the results of the present and above studies are somehow related.

One of the strengths of our study was its three-arm and triple-blind nature to reduce interfering factors. In addition, this is the first study that aimed at investigating the effect of the Vitagnus-soy combination on PMS symptoms. However, the study had limitations, including the inability to follow participants for more than two menstrual cycles and measuring the durability of the intervention effect due to the time and financial limitations of the research as a master of thesis. Moreover, there was no control or placebo group in this study.

Conclusion

The results of the present study showed that all the three herbal medicine groups, including Vitagnus, soy, and Vitagnus-soy combination, were effective and safe in reducing physical, psychological, and total symptoms of PMS. However, the Vitagnus-soy combination was more effective in reducing PMS psychological and total symptoms than using either soy or Vitagnus alone. It was also found that the Vitagnus-soy combination had no statistically significant difference in reducing physical PMS symptoms compared to soy, but it was more effective than Vitagnus. Therefore, it is recommended that the Vitagnus-soy combination should be used as an effective and safe herbal treatment to reduce PMS symptoms, which is preferable to using either Soy or Vitagnus alone. Moreover, it is suggested that future research should assess the effect of the Vitagnus-soy combination capsule by comparing it with the placebo group in treating PMS and evaluating its effects over a longer follow-up period.

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Authors' Contribution

Conceptualization and study design were done by RPG, MM, HR, and SMMF. Data collection was carried out by RPG. RPG, VG, and MM performed data management, analysis, and interpretation. RPG and MM prepared the initial manuscript draft, and critical revisions for important intellectual content were conducted by MM, HR, VG, and SMMF. SMMF and HR were responsible for preparing medications. MM supervised and holds full responsibility for the work. All authors read and approved the final version of the manuscript and take responsibility for the integrity and accuracy of the data analysis. The corresponding author attests that all listed authors meet authorship criteria.

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Declaration on the use of AI

The authors of this manuscript declare that no artificial intelligence (AI) was used during the writing process.

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