Original Article

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# Curcumin Ameliorates Depression, and Anxiety in Patients with Premenstrual Syndrome and Dysmenorrhea: A Triple-Blinded Placebo-Controlled Trial

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**ABSTRACT**

**Background & Objective:** Premenstrual syndrome (PMS) and primary dysmenorrhea (PD) are gynecological conditions that are associated with psychological and mood disorders. This study assessed the effects of curcumin, a natural polyphenol, on depression, anxiety, stress and quality of life (QL) in woman with PMS and PD.

**Materials & Methods:** The study was undertaken in 128 women who were randomised to treatment with either curcumin (n=64) or placebo (n=64) groups. Each subject received one capsules (500 mg of curcuminoids plus 5 mg piperine, or a placebo, plus 5 mg piperine) daily, for 3 successive menstrual cycles. Psychological status and QL were assessed using Depression, Anxiety, Stress Scales-21 (DASS-21) and the Short Form-12 (SF-12) questionnaires respectively.

**Results:** Overall scores as well as the mental health domain of the SF-12 improved significantly after curcumin supplementation ($P<0.05$). In addition, curcumin decreased significantly ($P<0.05$) all of the DASS-21 domains (depression, anxiety and stress). Significant differences were also found between the two groups for the DASS-21 domains, SF-12 mental health (total) and overall scores ($P<0.05$).

**Conclusion:** Curcuminoids may be useful as a natural, widely accessible therapeutic option for the management of the psychological impact of PMS and PD, and improve the QL of women with these conditions.

**Keywords:** Curcumin, Menstruation, Personality, Gynecology, Anxiety



## Introduction

Whilst the menarche is a natural physiological process, it is an important determinant of female health and wellbeing. A large percentage (40-99%) of young women have menstrual disorders, that include: irregular menstrual cycles and bleeding, primary dysmenorrhea (PD) and premenstrual syndrome (PMS). We have previously reported that the prevalence of PD and PMS was 68.8% and 47.6% respectively amongst adolescent Iranian girls **(1)**. PD is a common cyclic gynecological condition, characterized by pelvic and uterine pain that occurs during menstruation, and which has psychological, physical, behavioral and, social impacts. PMS refers to a category of mood, physical and psychological

manifestations which occurs during the secretory phase of the menstruation cycle and is alleviated with the start of menses **(2)**. Women with PMS or PD have adverse psychological symptoms, such as depressive mood, anxiety and stress and a reduced quality of life (QL) **(3, 4)**. Fluctuations in mood are related to menstrual features, and the most common psychological conditions are anxiety disorders and depression **(5, 6)**.

Several strategies have been proposed for the alleviation of PMS and PD symptoms. For women with moderate pains, supportive therapy and self-care interventions including increased exercise, and adherence to healthy diet are often enough **(7)**. NSAIDs are often prescribed for these conditions in Iran; mefenamic acid and ibuprofen being the most commonly used drugs **(8, 9)**. However, the use of prescription drugs is not advised due to side effects other than when symptoms are severe. The desire for non-pharmacological alternatives has led many women to consider nutritional supplement for PMS and PD **(7).** Natural products are widely used to treat many other medical conditions. Curcumin (CUM) is the main active curcuminoid in turmeric. This belongs to the ginger family which has numerous health positive effects in many human disorders. The pleiotropic effects of CUM i.e. its anti- inflammatory and oxidative-nitrosative effects are attributed, at least in part, to its interaction with different molecular targets **(10, 11).**

It has been proposed that altered levels of prostaglandins (PGs) and neurotransmitters (NTs) may contribute to the pathophysiology of PMS and PD. PGs often cause physical symptoms and NTs primarily have responsible for the mood and psychological distress among PMS women. Previous studies have shown that CUM decreases the synthesis of PGs by inhibiting the enzyme cyclooxygenase-2 (COX-2) **(10, 11)**. CUM supplementation mitigates depressive- and anxiety-like symptoms caused by different stressors. In vivo studies also report that CUM exerts antidepressant effects by modulating the rates of production of NTs **(12, 13)**. Considering the important therapeutic potential of CUM that has been reported in previous studies and, the probability of using it as an affordable and available herbal drug, this study aimed to determine whether CUM may be used to manage the psychological symptoms of PDS and PMS. This study was design to explore the effect of CUM on depression, anxiety, stress and QL in young woman suffering from both PMS and PD. As CUM has low bioavailability, we examined it in combination of piperine, the active isolate of black pepper, to boost the absorption of CUM.

## Materials and Methods

### Study design

This triple-blind, placebo controlled clinical trial was undertaken on 128 female students recruited from 4 different universities in Birjand, from January to April 2020. Data were collected over a 5 month period. Researchers, patients and, statistical analysts were blinded to study groups. All individuals gave written informed consent. The current study protocol was approved with the Ethics Committee of Birjand University of Medical Science and registered at Iranian Registry of Clinical Trial (Trial ID: IRCT20191112045424N1); available at https://www.irct.ir). IR.BUMS.REC.1398.160

The study was a sub-study of another clinical trial **(14)**. The sample size was determined according to 80% power and α= 0.05 that at least 55 patients were required for intervention group **(15)**.

$$n = \frac{(z_{1-\frac{\alpha}{2}} + z_{1-\beta})^2 (S_1^2 + S_2^2)}{(\bar{x_1} - \bar{x}_2)^2}$$

Inclusion criteria were; healthy premenopausal women aged between 18-25 years with regular menopause cycles of >21 and <35 days, having both PMS and PD, being single, not receiving any medication, and being a non-smoker. Exclusion criteria included: suffering from any acute or chronic disorders, taking any drug, multivitamin or mineral supplements during last three months, and experience of stressful life events in the last three months, being married or not being willing to continue the study.

### Intervention

Participants were randomized to take CUM (n=64; Curcuminoids 500 mg/day ; C3 Complex, obtained from Sami Labs Ltd, India, plus 5 mg piperine), a dose which has previously been reported to be effective and stable **(16);** or placebo (n=64). The placebo capsules included an inert filler (500 mg lactose powder) and 5 mg piperine (Bioprin). CUM and placebo capsules bottles labeled as “A” or “B” by the pharmacy, were indiscernible on appearance, texture, and color. A statistician created a randomized list by using NCSS via the simple block randomization approach (block size = 2). After that, the eligible participants were assigned to one of two groups "A or B", based on the randomized list. Coding keys were sent to the principal investigator by mail after final analysis. Bioperine (piperin) is a purified extraction of black, or long pepper, which consist of at least 95% piperine and used to increase bioavailability through intestinal absorption of CUM. The purity of the three major curcuminoids and Bioperine was determined by HPLC **(17)**. The individuals were instructed to take one capsule daily, for 10 days (seven days pre- and, until three days post- the start of menstrual blood loss) for 3 menstruation cycles. We used valid and reliable questionnaires to measure participants’ depression, anxiety, stress, and QL before and after trial. We instructed participants not to change their physical activity or food consumption whilst on the trial and not to take any supplements or any other drugs. Compliance and plausible adverse events were explored in all individuals via telephone follow-up. Depression, anxiety, stress and QL were evaluated

using standard questionnaires one week pre- and post-intervention.

### Diagnosis of PMS and PD

The following criteria were used for the diagnosis of PD: lower abdominal pain, low back pain or anterior thigh related by menarche onset during 6-12 hours of menstruation and lasting longer than 8-72 hours. Patients were instructed to report their severity of PD pain using a visual analogue scale (VAS) tool, which were rated from 0 to 10 **(18)**. The presence of PMS was determined using the Premenstrual Syndrome Screening Tool (PSST) questionnaire. This tool contains nineteen items in three parts (physical, behavioral, and psychological manifestations). The degree of every symptom was scored according to Likert-type scale from zero (No) to three (severe) to prepare a total score range from 0 to 57. Participants who reported severe PD pain (VAS score ≥ 8) and intense PMS (PSST score ≥ 38 ) were considered to have both PD and PMS and enrolled **(19)**.

### Depression Anxiety Stress Scales-21 (DASS-21)

The DASS is a reliable and valid self-report questionnaire which measured the severity of three important disorders associated with negative feeling. This tool includes 21 items in 3 subscales (every has 7 questions) with four-Likert measure scored 0-3 and, the final score should be doubled for every sub-scale. Higher score reflects lower emotional feelings. Previously, the DASS-21-Persian version was approved for Iranian population **(20)**.

### Quality of Life (QL)

Health-related QL (HRQL) was assessed using the Short Form-12 (SF-12) that is a widely used and reliable instrument. This version applied in this study that is a shorter SF-36 version called SF-12, which uses twelve questions from the SF-36. The Iranian version of the SF-12 item was applied in the present study, and has good reliability and validity. The questionnaire has 8 health domains to distinguish physical and psychological health functioning, and given the lower score of each items, the total number is mostly employed. Higher scores display superior health **(21)**.

### Other variables

Data related to the family structure and socio-economic status, including family members, parent death/divorce (Yes or No), parents' occupations, parents' educational attainment were gathered by a standard tool which was previously validated in the PIRLS for Iran **(22)**. Height and weight were measured to define Body Mass Index (BMI). Dietary intake of the students was assessed using a 65 item semi-quantitative food frequency questionnaire **(23)**, as described previously **(14)**.

### Statistical analysis

SPSS 18 software (SPSS Inc., IL, USA) was used for Statistical analysis. Descriptive data were expressed as mean-standard deviation or frequency (%). Correlation between variables was identified using Pearson correlation analysis. Independent sample T-tests (for normally distributed variables or Chi-square test (for categorical indices) were undertaken to determine the differences in parameters at baseline. The significance of changes from pre- to post- supplementation within the group was evaluated using paired T-tests (for normally distributed variables). Analysis of covariance (ANCOVA) adjusting for baseline was recruited to assess the effect of the supplementation on score of depression, anxiety, stress and QL. Significant of p value set as <0.05.

## Results

As shown in Figure 1, 123 participants (62 in CUM group and 61 in placebo group) were entered into the final data analysis. Three persons in the placebo group and, two persons in the CUM group did not complete the study. The causes for non-completion are summarized in Figure 1. In the placebo group, one of the contributors because of long distance from the research center and two due to reluctance to continue with the trial. For the CUM group one participant developed a rash and one participant developed severe abdominal pain and were excluded. At baseline, no significant differences were found between CUM and placebo groups with respect to the demographic variables (Table 1) and dietary intake (Data not shown). The correlation matrix between the scores for PSST, VAS, depression, anxiety, stress and QL among participants at baseline are presented in Table 2. PSST score was significantly correlated with score of total QL (r=-0.44; p<0.001), depression (r=0.32; p<0.001), anxiety (r=0.27; p=0.001), and stress (r=0.31; p<0.001). Furthermore, total QL score was inversely associated by scores of depression, anxiety and stress (r=-0.51, r=-0.44, r=-0.48; p<0.001; Table 2).

Table 3 shows DASS-21 and SF-12 domains in the study groups before and after the trial. DASS-21 and SF-12 domains and overall scores did not show significant differences between two groups at baseline (P>0.05). As shown in Table 3, depression, anxiety and stress were significantly lower, whereas the overall score and mental health domain of QL were significantly higher after CUM supplementation (P<0.05). In the placebo group, the depression, anxiety, stress as well as SF-12 domains and overall scores remained unaltered after 3 successive menstrual cycle intervention (P>0.05). After trial, differences in depression, anxiety, stress and QL overall score and mental health domain of QL were significant between intervention arms (P< 0.05).

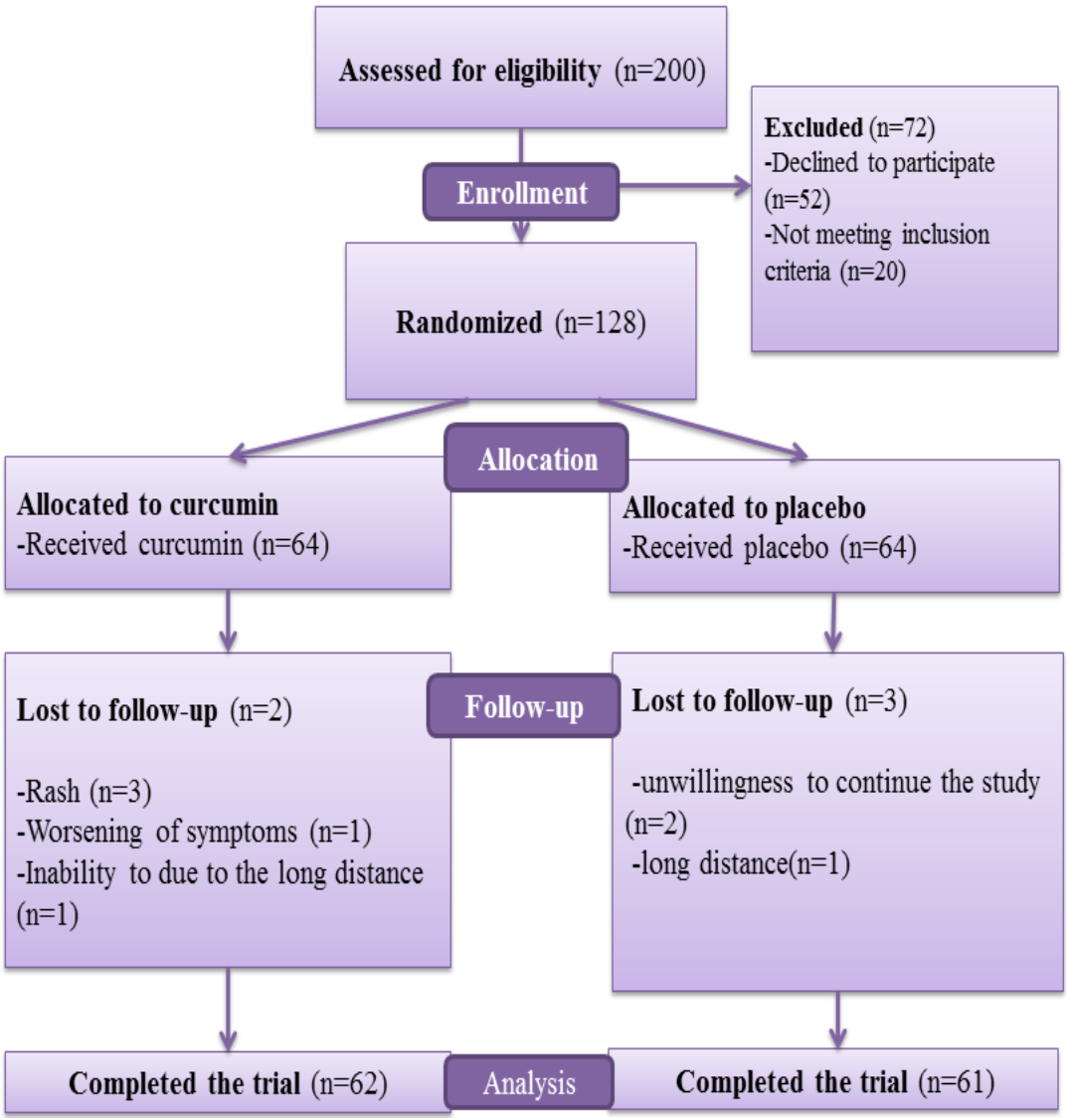


**Figure 1. Summary of CONSORT flow diagram**

**Table 1. Baseline characteristics of the study groups.**

| Variable (score) | | CUM (n=62) | Placebo (n=61) | P value * |
|---|---|---|---|---|
| Age(year) | | 20.7±1.6 | 20.9±1.8 | 0.32 |
| Body mass index(kg/m$^2$) | | 21.0±2.7 | 20.7±3.0 | 0.57 |
| Family members | 2-4 | 15(24.3) | 18(28.8) | 0.30 |
| | 5-7 | 43(69.3) | 37(61.0) | |
| | ≥8 | 4(6.4) | 6(10.2) | |
| Parent death, Yes | | 2(3.3) | 1(1.6) | 0.52 |
| Parent divorce, Yes | | 0(0) | 4(6.8) | 0.06 |
| Father's occupation | Worker | 7(11.3) | 8(13.5) | 0.64 |
| | Employee | 25(40.3) | 18(28.8) | |
| | Tradesmen market | 10(16.2) | 12(18.6) | |
| | Unemployed | 11(17.7) | 14 (23.7) | |
| | Other | 9(14.5) | 9(15.2) | |
| Mother's occupation | Worker | 1(1.6) | 1(1.6) | 0.39 |
| | Employee | 11(17.7) | 9(15.2) | |
| | Housewife | 48(77.4) | 48(79.7) | |
| | Other | 2(3.3) | 3(5.1) | |
| Father's education (year) | Illiterate | 1(1.6) | 3(5.1) | 0.91 |
| | <9 | 20(32.2) | 20(33.9) | |
| | 9-12 | 19(30.7) | 19(28.8) | |
| | ≥13 | 22(35.5) | 19(32.2) | |
| Mother's education (year) | Illiterate | 5(8.1) | 5(8.5) | 0.21 |
| | <9 | 25(40.3) | 35(59.3) | |
| | 9-12 | 14(22.6) | 13(18.6) | |
| | ≥13 | 18(29.0) | 8(13.5) | |

Data presented as mean±SD/ number (%).
*Obtained from independent sample T-test or chi-square tests and Fischer's exact test.

**Table 2. Correlation matrix between score of PSST, VAS, depression, anxiety, stress and quality of life**

| Variables | | Total QL | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Depression** | r | -0.51* | Depression | | | | | |
| **Anxiety** | r | -0.44* | 0.56* | Anxiety | | | | |
| **Stress** | r | -0.48* | 0.51* | 0.56* | Stress | | | |
| **Physical QL** | r | 0.75* | -0.34* | -0.32* | -0.37* | Physical QL | | |
| **Mental QL** | r | 0.91* | -0.48* | -0.38* | -0.45* | 0.42* | Mental QL | |
| **PSST** | r | -0.44* | 0.32* | 0.27* | 0.31* | -0.35* | -0.39 | PSST |
| **VAS** | r | -0.08 | -0.03 | -0.02 | 0.05 | -0.04 | -0.1 | 0.16 |

Premenstrual Syndrome Screening Tool (PSST); Quality of Life (QL); Visual Analogue Scale (VAS).
*p<0.05

**Table 3. Comparison of main measures in treatment groups pre- and post- intervention.**

| Variables | Measurement period | CUM | Placebo | P[a] |
|---|---|---|---|---|
| ***Dass-21*** | | | | |
| Depression | Before intervention | 9.4±9.6 | 10.7±8.3 | 0.15 |
| | After intervention | 8.4±6.2 | 11.1±9.0 | **0.041** |
| | P[b] | **0.048** | 0.66 | |
| Anxiety | Before intervention | 8.8±6.2 | 8.9±6.5 | 0.79 |
| | After intervention | 7.0±6.5 | 8.8±8.2 | **0.047** |
| | P[b] | **0.039** | 0.96 | |
| Stress | Before intervention | 17.5±9.9 | 16.6±9.3 | 0.18 |
| | After intervention | 15.3±9.1 | 16.1±9.8 | **0.038** |
| | P[b] | **0.041** | 0.68 | |
| ***Quality of life*** (SF-12) | | | | |
| Physical health | Before intervention | 15.6±2.5 | 16.1±2.4 | 0.55 |
| | After intervention | 16.0±2.4 | 15.9±2.2 | 0.59 |
| | P[b] | 0.28 | 0.40 | |
| Mental health | Before intervention | 16.6±3.6 | 16.5±3.9 | 0.91 |
| | After intervention | 18.7±2.9 | 16.9±3.8 | **0.029** |
| | P[b] | **0.043** | 0.42 | |
| | Before intervention | 32.3±5.0 | 32.7±5.6 | 0.19 |

| | | | | |
|---|---|---|---|---|
| Total quality of life score | After intervention | 34.9±4.8 | 32.9±5.1 | **0.035** |
| | P[b] | **0.033** | 0.77 | |

**-Values expressed as mean ± SD**

**[a] p values obtained from comparison between groups via using independent sample t test at pre- and ANCOVA test post-treatment.**
**[b] p values obtained from comparison within groups by paired-sample T test.**

## Discussion

This trial was designed to determine the impact of a curcuminoid supplementation on depression, anxiety, stress and QL in a group of young and healthy females with PMS and PD. There was a significant increase in the QL score and decrease levels of depression, anxiety behavior and stress-related symptoms after 3 successive menstrual cycle of intervention with CUM supplementation versus to placebo group.

PMS and PD are common menstrual disorders which may affect the psychological wellbeing and quality of life of women of reproductive age. **(24, 25)**. One of the most critical concerns of severe PMS is the potential for suicidal ideation. In spite of high prevalence and severe symptoms of PD and PMS, most females do not seek medical therapies for these conditions. In the last decade, CUM has been proposed as a treatment of a variety of pathologic disorders because of its various health advantages **(12, 13)** .

In our study CUM was significantly more effective in decreasing some mood-related complications including depression, anxiety and stress, compared to placebo. Three recent meta-analyses concluded that CUM may improve depression and anxiety **(26-28)**. Inflammation and oxidative stress are considered to be involved in the pathogenical mechanism of psychological dysfunctions such as anxiety and/or depression. Compared to healthy states, atypical depression is related with higher amounts of circulating inflammatory biomarkers **(29)**. Studies have concluded that depressive and, anxiety associated with PMS and PD as being most important to the psychological wellbeing which may adversely effects the QL, enjoyment and satisfaction **(30-32)**. Therefore, any agent which may causes cyclic disruption among inflammatory and oxidative stress possibly be of therapeutic effectiveness for aggression and depression. Neuroprotective and antidepressant properties of polyphenol CUM may be related to its anti-inflammation, antioxidant, monoaminergic, and hypothalamus-pituitary-adrenal (HPA) axis modulating actions **(33)**. Curcuminoids reduce systemic inflammation through down-expression of COX-2, lowering levels of CRP, endothelial-leukocyte adhesion molecule 1, calcitonin gene-related peptide (CGRP), heme oxygenase 1, NF-$\kappa$B, and expression of TGF-β related genes as well as attenuating the synthesis of pro-inflammatory cytokines such as TNF-α, monocyte chemoattractant protein, and IL-1, -2, -6, -8 and -12. Additionally, CUM can elevate the concentrations of brain-derived neurotrophic factor, a well-known neurotropin involved in the pathophysiology of depression **(34)**. With concern to the above properties, CUM could improve inflammatory states in depressed cases.

CUM may also inhibit oxidative stress through various mechanisms such as suppression of lipid peroxidation and promotion of endogenous antioxidants enzymes with free radical clearing capacity such as superoxide dismutase, catalase and glutathione. The antioxidant effect of CUM is 300 times more potent than vitamin E **(35)**. This is important because the brain is a high oxygen consumption organ, which can induce neuro-oxidative or neuro-nitrosative pathway, leading to neurological pathologies such as anxiety and a mood disorders, along with neurodegeneration and neuroinflammation.

In addition, it is worth mentioning that CUM's derivatives have a potential anti-anxiety like effect in different pathologies. CUM can suppress the monoamine oxidase A/B, which are most abundant mitochondrial enzymes, with a key role in the metabolizing of released NTs and in the detoxifying of different endogenous and exogenous amines. Interestingly, CUM advocates the alteration of hepatic alfa-linoleic acid in DHA, long chain omega-3 fatty acid with anti-anxiety effects, and also its cumulation in the brain. CUM also suppress the production of inducible NOS (iNOS), which is elevated in brain throughout stress, so providing anxiolytic-like properties **(36).**

Our findings indicate that the CUM treatment was associated with improvements in total score and mental health domain of QL in women with PMS and PD compared to baseline and placebo. HRQL is one of the main issues in health system and its measurement is essential assessment of the well-being. HRQL quantifies at least, physical, intellectual, psychological and civic activities and extensively used to assess individual's perception of the effect of illness and treatment efficacy. Similar to us, previous studies demonstrated that CUM improve QL in various ailments such as IBS, liver cirrhosis, and

cancer **(37, 38).** Recently, a systematic review and meta-analysis highlighted a significant effect of oral CUM intervention by improving HRQL. CUM showed significantly beneficial effects on HRQL in trials with a relatively short-term duration of CUM supplementation (lower than 5 months) and those that administrated high bioavailability formulation of CUM **(39).** It has been reported that short-term use of a curcuminoids supplementation (co-administered by piperine to raise the bioavailability of CUM) reduced systemic oxidative stress, clinical signs and betterment HRQL in patients with chronic pulmonary complications. Multiple proof of-concept investigations have noted that piperine combination can enhance the bioavailability of CUM more than 2000% **(40)**.

According to the findings of our research and others which used CUM in different diseases, CUM can be applied as an alternative for antidepressant and anxiolytic drugs in the treatment of PMS and PD. The present study had several strengths. First, to the best of our knowledge, this is the first study performed to explore the effect of CUM administration on level of depression, anxiety, stress and QL in women with menstrual-associated symptoms. Second, CUM plus piperine supplementation in preference to CUM alone was administrated because of its increased bioavailability. Lastly, this was a triple-blind, placebo-controlled fashion. Our finding had some limitations. We did not evaluate the physical activity of participants. Due to the self-report instruments to assess patients' depression, anxiety, stress and QL, a recall bias might have affected the responses. Also, relatively short time intervention hindered identification of any potential side effects. Enlarge clinical trials with differing dosage of CUM over a longer duration are needed to further confirm CUM psychoprotective effects.

## Conclusion

CUM has positive effects on psychological wellbeing and QL of PMS and PD patients; and may be considered as an alternative for antidepressant and anxiolytic in treatment PMS and PD. But further studies are required to clarify the impact of CUM on NTs and inflammation factors involved in PMS and PD to reach a definitive conclusion.

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## Conflict of Interest

The authors declare that they have no conflict of interest.

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## Ethics Approval and consent to participate

The current study protocol was approved with the Ethics Committee of Birjand University of Medical Science and registered at Iranian Registry of Clinical Trial (Trial ID: IRCT20191112045424N1); available at https://www.irct.ir). IR.BUMS.REC.1398.160

## Authors' Contribution

A.Bahrami conceptualized and designed the study. F.Nikoomanesh and H. Dehghan , H. Aramjoo provided the data. A. Bahrami and H.Aramjoo conducted the statistical analysis and interpretation of the data. A.Bahrami and G.Ferns contributed to the writing and revision of the manuscript. All authors read and approved the final version of the manuscript.

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