Effects of curcumin on menstrual pattern, premenstrual syndrome, and dysmenorrhea: a triple-blind, placebo-controlled clinical trial

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Effects of curcumin on menstrual pattern, premenstrual syndrome and dysmenorrhea: a triple-blind, placebo-controlled clinical trial

Abstract

Premenstrual syndrome (PMS) and primary dysmenorrhea are common complaints among young women. This study evaluated the effects of curcumin supplements on symptoms of pain in young women with PMS and dysmenorrhea. A randomized, triple-blinded, placebo-controlled clinical trial was undertaken. Women who suffered from both PMS and dysmenorrhea were enrolled, and were randomly allocated to the curcumin (n = 62), or placebo (n = 62) groups. Each subject received one capsules (500 mg of curcuminoid, or placebo) daily, from 7 days pre- until 3 days post-menstruation for 3 successive menstrual cycles. Participants recorded the severity of PMS, or dysmenorrhea using a Premenstrual Syndrome Screening Tool (PSST) and the visual analogue scale, respectively. Baseline characteristics of participants did not differ between the curcumin and placebo groups. At the end of the trial, the PSST scores were significantly lower in both the curcumin (32.5±9.8 vs. 21.6±9.8); and placebo groups (31.7±9.4 vs. 23.4±12.8). There was a significant reduction of dysmenorrhea pain in both the curcumin and placebo groups (by 64% and 53.3%, respectively). Hence, curcumin had comparable effects as placebo, regarding the amelioration of symptoms of PMS and dysmenorrhea. Further studies are required with larger samples, using higher doses curcumin for longer durations, and perhaps in combination therapy.

Keywords: Menstruation; Turmeric; Prostaglandin; Menstrual disorders
1. Introduction:

Menarche is an important milestone in the development of young girls, and is one indicator of female reproductive health (Bahrami, Gonoodi, et al., 2019). About 40-99% of women at reproductive age are affected by menstrual complications such as primary dysmenorrhea (PD), irregular menstrual cycles, abnormal uterine bleeding and premenstrual syndrome (PMS) (Bahrami, Avan, et al., 2018). It has been suggested that menstrual problems are associated with hormonal variations, genetic susceptibility, stress, diet, and physical inactivity (Deuster, Adera, & South-Paul, 1999; Jahanfar, Lye, & Krishnarajah, 2011). PD and PMS are the most frequent reported gynecologic complications in young women which are negatively affected all aspect of the quality of life of women (Bahrami, Bahrami-Taghanaki, et al., 2020).

PMS is a cyclic mood and somatic complaint that occurs during the luteal phase of the menstrual cycle (Liu, Wang, Van Heck, & Qiao, 2017). It may be associated with more than 150 different emotional, behavioral and physical signs and symptoms, that include: backache, nausea, fatigue, depression, mood liability, anxiety and breast tenderness (Rastegar, Bahrami-Taghanaki, & Ghayour-Mobarhan). PD is characterized by unpleasant, cyclical and painful cramps in the midline of the lower abdomen, in the absence of pelvic pathology, occurring just before or immediately after menstruation (Ayadilord et al., 2020).

Changes in the concentrations of prostaglandins (PGs) and neurotransmitters may potentially be involved in the etiology of PMS. PGs is mainly responsible for the incidence of physical symptoms and neurotransmitters play role in outbreak of psychological manifestations of PMS (Marjoribanks, Brown, O'Brien, & Wyatt, 2013; Rapkin & Akopians, 2012). Consistently, one of the reason for PD is an elevating the generation of uterine PGs derived from the activity of cyclooxygenase (COX)-2 and the release of arachidonic acid (Maia et al., 2005).
During menstruation, progesterone and estradiol levels decrease, whereas the expression of endometrial collagenases, and matrix metalloproteinases (MMPs) are increased, which causes an inflammatory response, endometrial breakdown (Oladosu, Tu, & Hellman, 2018), release of phospholipids, which follow by production of PGs by interleukins (IL), lytic enzymes, prostacyclins, and thromboxane A2 by COX-1 and -2 (Dawood, 2006; Oladosu et al., 2018). PGs affected nociceptors and leads uterine smooth-muscle contractions, spasmodic pain and expulsion of the endometrium (Dawood, 2006). PGE2 and PGF2-α concentrations are higher in women with PD versus healthy women (Oladosu et al., 2018).

Due to the uncertain etiology of PD and PMS; treatment is usually symptomatic. Different treatments have been used, that include: non-steroidal anti-inflammatory drugs (NSAIDs) or oral contraceptives, that control PD and PMS by suppressing PGs synthesis (M. Fritz & Speroff, 2011). However, adverse side effects and partially failure of treatment may occur despite long-lasting conventional therapy with these agents (Drevon, 1992; Park et al., 2012). Recently, women suffering from menstrual problems have been treated with dietary modification and herbal medicines (Chen et al., 2014). Complementary and alternative therapies are potentially can alleviate menstrual associated pain via decreasing of the PGs and nitric oxide (NO) levels, elevating the amounts of β-endorphin and calcium channel blockers which causes to better circulation (Jaafarpour, Hatefi, Khani, & Khajavikhan, 2015; Jia, Wang, Xu, Zhao, & Zhang, 2006; Sangal, 2011).

Curcumin (CUR), is a yellow polyphenolic compound and is a major constituent of the rhizomes of turmeric (Curcuma longa L from Zingiberaceae family) used as a spice and for traditional medicine (Parsamanesh, Moossavi, Bahrami, Butler, & Sahebkar, 2018). There is a substantial body of evidence supporting the pleiotropic effects of CUR as an anti-inflammatory, anti-cancer, anti-oxidant, and anti-bacterial agent, which introduce CUR as popular therapeutic option in wide spectra of human disorders (Bahrami & A. Ferns, 2020;
CUR has been reported to be efficacious in the treatment of various inflammatory states by its effects on pro-inflammatory cytokines and also by inhibiting NO generation (Aggarwal, 2010; Gera et al., 2017). In vitro and in vivo studies highlighted a positive effect of CUR on endometriosis (Arablou & Kolahdouz-Mohammadi, 2018; S. K. Jana, Chakravarty, & Chaudhury, 2014), through inhibition of oxytocin-stimulated uterine contractions indicates an antispasmodic effect (Thaina, Tungcharoen, Wongnawa, Reanmongkol, & Subhadhirasakul, 2009). It has been shown that CUR supplements reduce PGE2 production (Sharma et al., 2004). CUR in PMS woman may also regulate neurotransmitters and biomolecule, antioxidant and anti-nociceptive effects as well as reducing oxidative stress (OS) (Gera et al., 2017).

To the best of our knowledge, no comprehensive studies have explored the effect of CUR on PMS and PD. Considering the high prevalence of these unresolved important issue in women’s health women, the current research aimed to introduce a noninvasive a strategy in management of gynecological disorders. Thus, this study was designed to assess the effectiveness of CUR on menstrual pattern and menstrual-associated symptoms in subjects suffered from both PMS and PD.

2. Method

2.1. Study design

This was a randomized, triple-blind, placebo controlled trial performed, approved by the Birjand University of Medical Sciences (BUMS), and registered at the Iranian Registry of Clinical Trial (IRCT20191112045424N1; available at: https://www.irect.ir). The study was conducted on 124 female students who resided in the halls of residence of 4 different
universities in Birjand, South-Eastern of Iran, from December 2019 to March 2020. Investigators, patients, and statistical analyzer were completely unaware of the grouping of participants. All subjects signed written informed consent for study participation. The study protocol was approved by the Ethics Committee of Birjand University (Code: IR.BUMS.REC.1398.160).

The inclusion criteria were: women were aged between 18-24 years, were single, with a negative history of gynecological disorders and any allergy to herbal agents, having a regular menses, with having both mild to severe PD and PMS diagnosed by a gynecologist. Exclusion criteria: occurrence of any acute, chronic illness, or drug use, getting married, or the likelihood of experiencing any stressful events during the intervention.

Sample size was calculated based on 80% power and $\alpha= 0.05$, and it was concluded that at least 55 patients were needed for each arm (Khayat et al., 2015); the final sample size assuming a 10% drop-out rate was set as 62 patients in each group. Women who were eligible, and gave informed, written consent for study participation were registered to take part in the trial. Subjects were randomized to group. Masking of the group allocation was maintained until the final analyses were conducted and all process including randomization, patients enrollment, and assigning individuals to interventions was performed by an experienced nurse.

2.2. Intervention

Participants were randomly assigned to receive the CUR (500 mg curcuminoids + 5 mg piperine; C3 Complex, Sami Labs Ltd, Bangalore, India) or placebo (n=62) after a meal. The placebo capsules contained inert substance (500 mg lactose powder) in combination with 5 mg piperine. CUR and placebo capsules, were labeled as “code A” or “code B” by the pharmacy, were similar regarding to the shape, size, texture, and color. Piperine was added to
the curcuminoid or placebo to promote the oral bioavailability and intestinal absorption of CUR (Shoba₁, Joy₁, Joseph₁, Rajendran₂, & Srinivas₂, 1998). A statistician provided a randomization list using NCSS (statistical software) using the simple block randomization approach based on CONSORT guidelines. After that, the eligible participants were assigned to one of the two groups "code A or B", regarding to the randomized list. Coding keys were sent to study researcher through mail after the end of intervention and final statistical analysis. The participants were asked to take one capsule every day, for 10 days (7 days before and until 3 days after onset of menstrual bleeding) for 3 menstrual cycles. We instructed subjects not to alter their usual physical activity or food intake and diets during the trial and not to take any supplements or any drug other than the intervention which provided to them by this study. Compliance and subjective side effects were monitored along and after trial in both CUR and placebo groups.

2.3. Anthropometric indices

Height and weight of participants were measured with standard protocols in the standing status, with thin layer clothing and no wearing shoes at baseline and the end of trial. Body mass index (BMI) was obtained by this formula "weight (kg)/height²(m).

2.4. Dietary intake evaluation

Dietary intake of participants was evaluated using a valid and reliable 65 item semi-quantitative food frequency questionnaire over the previous year per day, week, month, rare or never (Ahmadnezhad et al., 2017; Asadi et al., 2019). Food analysis was performed using Diet Plan 6 software (Forestfield Software Ltd, Horsham West Sussex, UK).

2.5. Menstrual characteristics data
Data were collected from face to face interviews using a questionnaire which was designed by the investigators for gathering the essential data at baseline and after intervention (Ayadilord et al., 2020). The questionnaire was consisting of three parts as follows: First: menstrual and reproductive information (Ayadilord et al., 2020). The second instrument was a standard reliable and valid questionnaire of pain, visual analogue scale (VAS), for evaluation of PD pain. The final part was related to PSST (Premenstrual Syndrome Screening Tool) questionnaire for assessment of PMS status (Steiner, Macdougall, & Brown, 2003).

Menstrual and reproductive information was gathered by questionnaire including menarcheal age, menstrual cyclicity, length and amount of bleeding (Ayadilord et al., 2020). The participants were asked to assess their PD pain severity using a visual analogue scale (VAS) which was developed at McGill University and had accepted validity and reliability (Crichton, 2001). This scale ranged from 0 to 10 and categorized as no (score: 0), mild (score: 1-3), moderate (score: 4-7), and severe pain (score: 8-10). The participants who experience severe PD pain were enrolled to the study (Osayande & Mehulic, 2014).

PMS status was confirmed and graded using the PSST questionnaire. This tool comprises 19 items categorized into two sections: the first section encompasses 14 items associated to physical and behavioral aspect of PMS, whereas the second section is composed of 5 items that evaluate the functional effect of premenstrual manifestations on daily activities during the late luteal phase of the previous 3 successful menstruation.

The severity of each symptom was rated based on 4-point Likert scale [“not at all (0),” “mild (1),” “moderate (2),” or “severe (3) ”], providing a total score ranging from 0–57. A Persian version of the PSST has been reported to be a reliable and valid tool for the screening symptoms of PMS (Siahbazi, Hariri, Montazeri, & Banaem, 2011). The individuals who obtained scores greater than 20 were enrolled to the present study.
2.5. Statistical analyses

Statistical analysis was undertaken using SPSS 16 software (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed as mean ± SD or number (percent). Independent sample t-tests (for continuous variables) or chi-square tests (for nominal and ordinal qualitative indices) were done to examine the differences in parameters and then conducted at end of trial to identify the changes in parameters between the CUR group and placebo group. The significance of changes from pre- to post-intervention within the group was examined with paired t-tests (for continuous variables) or Wilcoxon signed-ranks test (for categorical variables). The alpha level was set for significant at p < 0.05 in all analyses.

3. Results

One hundred and twenty-four patients entered the trial, of whom 118 patients completed the follow-up (n=57 in CUR group; n=61 in placebo group) and were included in the final analyses (Figure 1). Five participants discontinued the study in the CUR group (3 because of the rash, 1 due to the worsening of PMS symptoms and 1 due to the inability to revisit the health center because of the long travel distance), and one in the placebo arm (unwillingness to continue the study). The dropout rate was not significantly different between the two arms (p=0.091).

There were no significant differences in baseline characteristics between the CUR and placebo groups regarding age, BMI, age of menarche, bleeding time, menstrual cycle length, PSST score and menstruation-associated physical symptoms (Table 1) as well as dietary intake (Table 2). As shown in Table 1, the mean bleeding time and duration of menstruation cycle before initiation of treatment were similar for both groups (P=0.39 and P=0.97; respectively). After three cycles of treatment, these two variables were not statistically changed between individuals who received CUR or placebo (Table 3; P>0.05).
At the end of the trial, PSST scores were significantly lower in both study groups (32.5±9.8 to 21.6±9.8 in CUR group; 31.7±9.4 to 23.4±12.8 in placebo group). However, no significant differences were found between the CUR and placebo groups with respect to net change of PSST score (-10.9±11.6 vs. -8.3±11.3; P=0.21).

Whilst, the percentage of subjects showing improvement in PMS severity, tender breasts, backache, feeling of bloating, weight gain and PD severity, was higher in the CUR group when compared with the placebo group, this was not statistically significant (P>0.05; Table 4).

CUR was safe and well-tolerable in current RCT. There was no report of severe side events. There were only three cases reporting a rash and one case with worsening of PMS symptoms.

4. Discussion
To best of our knowledge, this is the first randomized, triple-blind, placebo controlled, clinical trial evaluating the effects of CUR supplementation on woman suffering from both PMS and PD. This work is of importance regarding to the high prevalence of gynecological disorders and its health burden, and the plausible side effects related with conventional therapies such as NSAIDs (Smith & Langenbach, 2001; Song & FitzGerald, 2004).

There is accumulating evidence of the potential beneficial effects of CUR on endometriosis. CUR mitigates TNF-α-induced expression of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), IL-6, IL-8 and monocyte chemotactic protein-1 (MCP-1) by reducing levels of the transcription factor, NF-κB, an established regulator of inflammatory response, in human endometriotic stromal cells (Kim et al., 2012). In vitro evidence showed that CUR was able to attenuates the proliferation of endometrial cells and progression to endometriosis through decreasing the estradiol value (Zhang, Cao, Yu, Peng,
& Zhang, 2013) and inhibiting the function of MMP-2 and -9 (S. Jana, Rudra, Paul, & Swarnakar, 2012).

In this triple-blind, placebo controlled trial, curcuminoids using a fix dose of 500 mg in 10 days (pre and during the menstruation) significantly alleviated PMS pain severity without apparent toxicity (the relative improvement: 56.1% in CUR vs. 36.1% in placebo groups). A recent study by Khayat et al. reported significant reductions in the scores for physical, behavioral and mood manifestation of PMS in CUR group after trial. In the controls, the mean physical score after the trial was significantly mitigated, whereas the average of behavioral and mood scores pre- and post-trial were not significantly different (Khayat et al., 2015). Previously, it has been reported that CUR plus aerobic exercise can alleviate the symptom severity and PGE2 concentrations in woman suffering from PMS (Tarverdizadeh, 2018). In the present trial, the relatively short follow-up, and the single dose of treatment used, may have limited the effect size of CUR and this may account for the lack of observed efficacy compared to placebo concerning to the improving of menstrual associated symptoms.

The etiology of PMS remains poorly understood, but the evidence indicates a variation in levels of neurohormones and neurotransmitters i.e. serotonin (Dickerson, Mazyck, & Hunter, 2003), norepinephrine and dopamine (Jarry, Leonhardt, Gorkow, & Wuttke, 1994). Many of mood-related states in PMS cases have been connected with decrement in CNS serotonergic activity in luteal phase (Halbreich et al., 2006). It has been shown that CUR show anti-anxiety and anti-depression effects through increments in the brain amounts of serotonin, norepinephrine, and dopamine (Chimakurthy & Talasila, 2010).

Inflammation and OS was suggested to be an important player in the pathogenesis of psychiatric symptoms of PMS. CUR attenuates inflammation and OS by down-expressing the
function of lipoxygenase and inducible NOS enzymes, decreasing C-reactive protein, and preventing the formation of inflammatory cytokines (Bahrami, Atkin, Majeed, & Sahebkar, 2018; Parsamanesh et al., 2018). Therefore, CUR could serve as a potential therapeutic drug for psychosomatic symptoms (i.e. irritability, sleep complication, anxiety, palpitation, lower pain threshold, tendency to cry easily, appetite change, loss of concentration, decrease interest and depression).

Collectively, in the CUR group, the total PSST score decreased from 32.5±9.8 to 21.6±9.8 (p<0.001), but this score after trial in placebo group also significantly lower compared to pre-intervention (31.7±9.4 to 23.4±12.8; p<0.001). Previous studies have also reported a high prevalence of placebo response in PMS trials. Freeman et al. indicated that 64% of the placebo-treated PMS subjects completely or partially improved (Freeman & Rickels, 1999). A meta-analysis of controlled treatment trials for PMS revealed rates of placebo response varying from 6-35% (Yonkers, Clark, & Trivedi, 1997), though rates >94% have been reported in one clinical study (Magos, Brincat, & Studd, 1986). The mechanisms underlying the placebo response are not understood, but its impact on the opioid system have been addressed (Nyberg, Bäckström, Zingmark, Purdy, & Poromaa, 2007). Furthermore, dopamine release, and expectation of and tendency for drug effect may change the response to therapy. Among PMS cases, these psychological effects are more significant compared to other conditions. Because of the role physiological and pathological reasons in etiology of this syndrome, the mood factor is of most extreme momentous. PMS women are usually susceptible and distracted by their cyclic symptoms, which may be disabling. Neuropsychological management is, so, necessary and should engaged lifestyle alterations and medication. In addition, placebo capsules also contain piperine which is a bioactive alkaloid with other likely biological activities such as anti-inflammation and anti-nociceptive effects (Bang et al., 2009; Srinivasan, 2007).
A reduction rate of 64% and 53.3% of PD pain in CUR and placebo groups was also found in this study, respectively. In previous double-blind, placebo-controlled clinical trial turmeric supplementation (500 mg/5 days; pre and during the bleeding), might be more advantageous in lessen of the menstrual associated pain compared to conventional treatment, mefenamic acid (250 mg). Moreover, the combination of these two compounds is more efficient in PD patients (Hesami, Nooshabadi, Yousefi, Lalooha, & Haghighian, 2020). Dyawapur et al. reported that cinnamon tea and turmeric water were equally effective in alleviating of pain in girls with PD (Dyawapur, Patil, & Metri).

Several factors such as elevated activity of COXs and production of PGs may be implicated in menstrual pain (M. A. Fritz & Speroff, 2012). PGs as a lipid autacoids originated from arachidonic acid in the COX and lipoxygenase pathways (Ricciotti & FitzGerald, 2011; Speroff & Fritz, 2005). COX protein is produce within the context of inflammation. COX-1 isoform regulates the early phase of acute inflammation, whereas COX-2 is one important element of inflammation (Smyth, Grosser, Wang, Yu, & FitzGerald, 2009; Speroff & Fritz, 2005). The activities of COXs causes to PGs formation and subsequent PD. PGs assist the contraction and relaxation of uterus in order to that the uterine myometrial thick layer constituted at the luteal phase is released. PGs are released within menstruation as a result of endometrial cells devastation. Pain in PD is associated to increased levels of PGE2 and PGF2α (Speroff & Fritz, 2005). PGE2 stimulates uterine hypercontractility, cervical narrowing and greater vasopressin release, subsequently uterine hypoxia, ischemia and pain (Harel, 2006). Increased levels of PGs causes to robust uterine contractions, and this pain can improve via using an inhibitor of PGs or COX enzyme (Speroff & Fritz, 2005).

To explain the beneficial effects of CUR on pain relief from PD and PMS, it has been reported that CUR decrease COX-2 expression via inhibition of PGs production (Du, Jiang, Xia, & Zhong, 2006) and the anti-inflammatory features of CUR has been associated to
prevention of PGs synthesis (Moon, Glasgow, & Eling, 2005). Krisnamurti et al. by in silico as a model study demonstrated that turmeric compound effectively suppresses COX-1/COX-2, and ligand binding catalytic site of proteins cause to relief of PD pain (Krisnamurti, Bare, Amin, & Primiani). Although, the blocking of PGs formation may be the main mechanism for CUR’s effect on menstrual associated pain in this trial.

4. Limitation and strengthen

The strength of the present trial lays in the large sample size and strict inclusion criteria. But our limitations was evaluating no comparison between CUR and other herbal compounds that are known as pain killer for PMS and PD. Also, the bioavailability and blood CUR levels were not measured. The short duration of intervention may not reflect the potential long-term efficacy of CUR, especially in terms of menstrual associated pain in young girl. In spite of triple blind type of our design, the effect of placebo was not evitable. This effect may be reduced if treatment persistent more than five cycles performed in this study.

5. Conclusion

The results of the present proof-of-concept trial showed that CUR was similar to placebo regarding to the mitigation of the severity of symptoms of PMS and PD. But, future trials with larger sample size using higher doses and duration of CUR as well as combination therapy are warranted to scrutinize the potential of utility of CUR as a safe and low-cost phytochemical for patients who are not willing to use paucity chemical agents or have contraindications for such agents.

Figure legend:

**Figure 1:** Flow chart of trial.
References:


Krisnamurti, G. C., Bare, Y., Amin, M., & Primiani, C. N. Combination of Curcumin from Curcuma longa and Procyanidin from Tamarindus indica in Inhibiting Cyclooxygenases for Primary Dysmenorrhea Therapy: In silico study.


Table 1. Baseline characteristics of study groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Curcumin (n=57)</th>
<th>Placebo (n=61)</th>
<th>P value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>20.8±1.7</td>
<td>20.9±1.6</td>
<td>0.66</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>21.1±2.8</td>
<td>20.8±3.2</td>
<td>0.58</td>
</tr>
<tr>
<td>Age of menstruation, year</td>
<td>13.1±1.3</td>
<td>13.3±1.4</td>
<td>0.73</td>
</tr>
<tr>
<td>Average days of bleeding</td>
<td>6.7±1.2</td>
<td>6.5±1.2</td>
<td>0.39</td>
</tr>
<tr>
<td>Duration of the menstruation cycle (day)</td>
<td>28.3±2.9</td>
<td>28.3±4.0</td>
<td>0.97</td>
</tr>
<tr>
<td>PSST score</td>
<td>32.5±9.8</td>
<td>31.7±9.4</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Menstruation-associated physical symptoms, n(%)  
- Tender breasts: 37 (64.9) vs 37 (60.7), P = 0.63  
- Backache: 54 (94.7) vs 60 (98.4), P = 0.28  
- Feeling of bloating: 54 (94.7) vs 59 (96.7), P = 0.59  
- Weight gain: 26 (45.6) vs 30 (49.2), P = 0.69  
- Swelling of the limbs: 35 (61.4) vs 35 (57.4), P = 0.66  
- Joint or muscle pain: 48 (84.2) vs 54 (88.5), P = 0.49  
- Gastrointestinal symptoms: 46 (80.7) vs 51 (83.6), P = 0.68

Data presented as mean±SD or number (%).  
*By using independent sample T test or chi-square test as appropriate.
Table 2. Dietary intakes of the study groups at baseline.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Curcumin (N=57)</th>
<th>Placebo (n=61)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy (kcal/day)</td>
<td>2170±724</td>
<td>2103±778</td>
<td>0.61</td>
</tr>
<tr>
<td>Carbohydrate (g/day)</td>
<td>235±149</td>
<td>207±121</td>
<td>0.21</td>
</tr>
<tr>
<td>Protein (g/day)</td>
<td>89.4±69.7</td>
<td>77.3±40.8</td>
<td>0.20</td>
</tr>
<tr>
<td>Total fat (g/day)</td>
<td>169±235</td>
<td>131±92.4</td>
<td>0.21</td>
</tr>
<tr>
<td>dietary fiber (g/day)</td>
<td>17.3±10.9</td>
<td>15.4±9.6</td>
<td>0.28</td>
</tr>
<tr>
<td>Carotene (mcg/day)</td>
<td>1055±676</td>
<td>1146±960</td>
<td>0.52</td>
</tr>
<tr>
<td>Vitamin E (mg/day)</td>
<td>45.0±84.6</td>
<td>32.5±29.1</td>
<td>0.24</td>
</tr>
<tr>
<td>Vitamin C (mg/day)</td>
<td>138±125</td>
<td>123±96.3</td>
<td>0.41</td>
</tr>
<tr>
<td>Calcium (mg/day)</td>
<td>882±1008</td>
<td>724±367</td>
<td>0.21</td>
</tr>
<tr>
<td>Phosphorus (mg/day)</td>
<td>1331±1160</td>
<td>1131±543</td>
<td>0.18</td>
</tr>
<tr>
<td>Magnesium (mg/day)</td>
<td>328±277</td>
<td>294±180</td>
<td>0.38</td>
</tr>
<tr>
<td>Selenium (mcg/day)</td>
<td>56.0±53.2</td>
<td>47.1±23.9</td>
<td>0.19</td>
</tr>
<tr>
<td>Iron (mg/day)</td>
<td>9.1±6.5</td>
<td>8.2±5.2</td>
<td>0.33</td>
</tr>
<tr>
<td>Zinc (mg/day)</td>
<td>9.4±8.3</td>
<td>7.9±4.4</td>
<td>0.18</td>
</tr>
<tr>
<td>Vitamin A (RE/day)</td>
<td>255±165</td>
<td>275±1.92</td>
<td>0.51</td>
</tr>
<tr>
<td>Thiamin (mg/day)</td>
<td>1.50±1.39</td>
<td>1.28±0.73</td>
<td>0.22</td>
</tr>
<tr>
<td>Niacin (mg/day)</td>
<td>18.4±15.4</td>
<td>14.7±8.3</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Data presented as Mean±SD.
By using independent sample T-test.
Table 3. Menstrual pattern and PSST score in placebo and curcumin groups before and after the intervention.

<table>
<thead>
<tr>
<th>Variable (score)</th>
<th>Curcumin (N=57)</th>
<th></th>
<th>Placebo (n=61)</th>
<th></th>
<th>P value a</th>
<th>P value b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Change</td>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Average days of bleeding</td>
<td>6.7±1.2</td>
<td>7.2±3.4</td>
<td>0.5±3.5</td>
<td>0.28</td>
<td>6.5±1.2</td>
<td>6.6±1.3</td>
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<tr>
<td>Duration of the menstruation cycle (day)</td>
<td>28.3±2.9</td>
<td>28.1±6.2</td>
<td>-0.25±6.0</td>
<td>0.77</td>
<td>28.3±4.0</td>
<td>28.3±3.4</td>
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<tr>
<td>PSST score</td>
<td>32.5±9.8</td>
<td>21.6±9.8</td>
<td>-10.9±11.6</td>
<td>&lt;0.001</td>
<td>31.7±9.4</td>
<td>23.4±12.8</td>
</tr>
</tbody>
</table>

Data presented as mean±SD.

* Comparison of before vs. after values in each group (paired sample T-test)

b Comparison of changes between the study groups (independent sample T-test)
<table>
<thead>
<tr>
<th>Variables</th>
<th>Curcumin Before</th>
<th>Curcumin After</th>
<th>Curcumin Improved</th>
<th>P value a</th>
<th>Placebo Before</th>
<th>Placebo After</th>
<th>Placebo Improved</th>
<th>P value a</th>
<th>P value b</th>
</tr>
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<tbody>
<tr>
<td>PMS severity</td>
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</tr>
<tr>
<td>Mild</td>
<td>6(10.5)</td>
<td>27(47.4)</td>
<td>56.1%</td>
<td>&lt;0.001</td>
<td>6(9.8)</td>
<td>20(32.8)</td>
<td>36.1%</td>
<td>0.001</td>
<td>0.09</td>
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<tr>
<td>Moderate</td>
<td>35(61.4)</td>
<td>28(49.1)</td>
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<td>41(67.2)</td>
<td>35(57.4)</td>
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<tr>
<td>Severe</td>
<td>16(28.1)</td>
<td>2(3.5)</td>
<td></td>
<td></td>
<td>14(23.0)</td>
<td>6(9.8)</td>
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<td><strong>Menstrual associated symptoms</strong></td>
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<td>Tender breasts</td>
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</tr>
<tr>
<td>Yes</td>
<td>37 (64.9)</td>
<td>28(49.1)</td>
<td>24.6%</td>
<td>0.039</td>
<td>37(60.7)</td>
<td>31(50.8)</td>
<td>18.0%</td>
<td>0.13</td>
<td>0.66</td>
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<tr>
<td>Backache</td>
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</tr>
<tr>
<td>Yes</td>
<td>54(94.7)</td>
<td>46(80.7)</td>
<td>17.5%</td>
<td>0.021</td>
<td>60(98.4)</td>
<td>50(82.0)</td>
<td>16.4%</td>
<td>0.02</td>
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<td>Feeling of bloating</td>
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<tr>
<td>Yes</td>
<td>54(94.7)</td>
<td>48(84.2)</td>
<td>15.8%</td>
<td>0.08</td>
<td>59(96.7)</td>
<td>53(86.9)</td>
<td>9.8%</td>
<td>0.014</td>
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<tr>
<td>Weight gain</td>
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<tr>
<td>Yes</td>
<td>26(45.6)</td>
<td>23(40.4)</td>
<td>26.3%</td>
<td>0.56</td>
<td>30(49.2)</td>
<td>23(37.3)</td>
<td>24.6%</td>
<td>0.14</td>
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<td>Swelling of the limbs</td>
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<tr>
<td>Yes</td>
<td>35(61.4)</td>
<td>19(33.3)</td>
<td>33.3%</td>
<td>0.001</td>
<td>35(57.4)</td>
<td>20(32.8)</td>
<td>34.3%</td>
<td>0.004</td>
<td>0.61</td>
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<td>joint or muscle pain</td>
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<tr>
<td>Yes</td>
<td>48(84.2)</td>
<td>42(73.7)</td>
<td>17.5%</td>
<td>0.11</td>
<td>54(88.5)</td>
<td>37(60.7)</td>
<td>31.7%</td>
<td>0.001</td>
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<td>Gastrointestinal symptoms</td>
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<tr>
<td>Yes</td>
<td>46(80.7)</td>
<td>39(68.4)</td>
<td>22.8%</td>
<td>0.11</td>
<td>51(83.6)</td>
<td>35(57.4)</td>
<td>32.8%</td>
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<td>Dysmenorrhea severity</td>
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<tr>
<td>No</td>
<td>0</td>
<td>3(5.4)</td>
<td></td>
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<td>0</td>
<td>4(6.5)</td>
<td>53.3%</td>
<td>&lt;0.001</td>
<td>0.44</td>
</tr>
<tr>
<td>Mild</td>
<td>2(3.6)</td>
<td>16(28.0)</td>
<td>64%</td>
<td>&lt;0.001</td>
<td>3(4.9)</td>
<td>9(14.8)</td>
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<tr>
<td>Moderate</td>
<td>22(38.6)</td>
<td>28(49.1)</td>
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<td>27(44.3)</td>
<td>37(60.7)</td>
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<tr>
<td>Severe</td>
<td>33(57.9)</td>
<td>10(17.5)</td>
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<td>31(50.8)</td>
<td>11(18.0)</td>
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</tr>
</tbody>
</table>

Data presented as number (percent)

*a* Comparison of before vs. after values in each group (Wilcoxon test)

*b* Comparison of before vs. after values between groups (chi-square test)