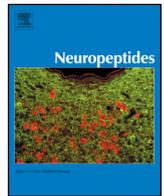




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## Effect of curcumin on serum brain-derived neurotrophic factor levels in women with premenstrual syndrome: A randomized, double-blind, placebo-controlled trial

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### ABSTRACT

Premenstrual syndrome (PMS) is a variety of physical, mental, and behavioral symptoms that start during the late luteal phase of the menstrual cycle, and the symptoms disappear after the onset of menses.

Serum brain-derived neurotrophic factor (BDNF) levels during luteal phase in women associated with PMS have more alterations than women not suffering from PMS. In this regard, altered luteal BDNF levels in women with PMS might play a role in a set of psychological and somatic symptoms of the PMS.

Studies of last decade revealed neuroprotective effects of curcumin and its ability to increase BDNF levels.

In the present study, we evaluated the effect of curcumin on serum BDNF level and PMS symptoms severity in women with PMS.

Present study is a Randomized, Double-Blinded, Placebo-Controlled Clinical Trial. Curcumin treatment was given for three successive menstrual cycles and each cycle ran 10 days. After having identified persons with PMS, participants were randomly allocated into placebo ( $n = 35$ ) and curcumin ( $n = 35$ ) groups. Each sample in placebo and curcumin groups received two capsules daily for seven days before menstruation and for three days after menstruation for three successive menstrual cycles. Participants noted the severity of the symptoms mentioned in the daily record questionnaire. Self-report was used to determine menstrual cycle phase of participants. At the fourth day of each menstrual cycle venous blood samples were collected for BDNF measurement by ELISA method.

Before intervention, BDNF levels and mean scores of PMS symptoms (mood, behavioral and physical symptoms) between two groups showed no significant differences. But in curcumin group first, second and third cycles after interventions BDNF levels were significantly higher and mean scores of PMS symptoms were significantly less than placebo group. Based on our results part of these beneficial effects of curcumin may be mediated through enhancing serum BDNF levels in women with PMS.

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### 1. Introduction

Premenstrual syndrome (PMS) is a variety of physical, mental, and behavioral symptoms that start during the late luteal phase of the menstrual cycle, and the symptoms disappear after the onset of menses (Khayat et al., 2014a; Wichianpitaya & Taneepanichskul, 2013; Seedhom et al., 2013; Epperson, 2013; Cubeddu et al., 2011).

Epidemiological studies have reported worldwide prevalence of PMS as approximate as 80%–90% (Khayat et al., 2014a; Wichianpitaya

& Taneepanichskul, 2013; Angst et al., 2001; Takeda et al., 2015). Also some women experience severe premenstrual symptoms that meet criteria for premenstrual dysphoric disorder (PMDD) (2–5%) (Epperson, 2013). PMDD in fourth text revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) was defined as a severe form of PMS (American Psychiatric Association, 2000). Recently, PMDD has been reclassified in DSM-V and listed as a depressive disorder (Zachar & Kendler, 2014; Association, 2013). Our study focused on PMS because the prevalence of PMS is more common than PMDD (Wichianpitaya & Taneepanichskul, 2013; Epperson, 2013; Angst et al., 2001; Takeda et al., 2015; Association, 2013; Khayat et al., 2014b).

Prevalence of PMS and PMDD reported in Iran varies among studies, about 40–70% of menstruating women have PMS symptoms and it is

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estimated that 9–16% of women suffer from PMDD (Khayat et al., 2014a; Tatari et al., 2008; Maleki et al., n.d.; Talaei et al., 2009; Farrokh-Eslamlou et al., 2015).

Treatment options for PMS are pharmacologic and nonpharmacologic therapies (Jarvis et al., 2008; Kroll & Rapkin, 2006; Freeman, 2010). Nonpharmacologic therapies include lifestyle modification, vitamin/herbal supplementation and alternative therapy (Jarvis et al., 2008; Kroll & Rapkin, 2006; Freeman, 2010).

A variety of medications are used to treat the different symptoms of PMS (Jarvis et al., 2008; Kroll & Rapkin, 2006; Freeman, 2010). Medications include diuretics, pain killers, oral contraceptive pills, drugs that suppress ovarian function and antidepressants (Jarvis et al., 2008; Kroll & Rapkin, 2006; Freeman, 2010).

In addition to worldwide common treatments, in Iran trends in the use of complementary and herbal medicines to treat the symptoms of PMS have increased among Iranian women (Khayat et al., 2014b; Babazadeh & Keramat, 2011; Beiranvand et al., 2015).

Previous studies have shown that brain-derived neurotrophic factor (BDNF) has a role in woman's reproductive physiology and some of the actions of sex hormones on brain are mediated by BDNF (Cubeddu et al., 2011; Begliuomini et al., 2007). Serum BDNF levels of fertile healthy woman in luteal phase are higher than follicular phase (Begliuomini et al., 2007).

Studies suggested that circulating serum BDNF levels have correlation with occurrence of PMS symptoms and may play a role in the pathophysiology of PMS (Cubeddu et al., 2011; Pluchino et al., 2009; Oral et al., 2015).

Reports are contradictory about alterations of serum levels of sex hormones and BDNF during the luteal phase of the menstrual cycle in women with PMS (Cubeddu et al., 2011; Pluchino et al., 2009; Oral et al., 2015). Recently, Oral et al. (2015) have shown that serum BDNF levels during luteal phase in the PMDD patients are significantly higher than control group (Oral et al., 2015). Also, their results showed that serum estrogen and progesterone levels during luteal phase in PMDD patients had no significant difference with control group (Oral et al., 2015).

On the other hand, Cubeddu et al. (2011) showed that serum levels of BDNF and estradiol during the luteal phase in PMS women were significantly lower than women without PMS (Cubeddu et al., 2011).

Comasco et al. (2011) demonstrated the role of the BDNF gene in the development of postpartum depression symptoms (Comasco et al., 2011). Recently, Comasco et al. (2014) showed that PMDD is characterized by impaired fronto-cingulate cortex activation in response to emotions (Comasco et al., 2014). They suggested that BDNF Val66Met polymorphism contributes to this impairment in the luteal phase (Comasco et al., 2014).

Treatment by several classes of antidepressants (e.g. monoamine oxidase inhibitors, SNRIs, SSRIs, and tricyclic agents) increases serum BDNF level in postmenopausal women and depressed patients (Cubeddu et al., 2010; Autry & Monteggia, 2012; Lopresti et al., 2012; Yoshimura et al., 2007).

Therefore, altered luteal BDNF levels in women with PMS might play a role in incidence of the PMS symptoms (Cubeddu et al., 2011; Begliuomini et al., 2007; Oral et al., 2015).

BDNF is a widespread growth factor in the nervous system (Cubeddu et al., 2011; Autry & Monteggia, 2012). It is involved in modulation a wide range of functions including neurogenesis, synaptogenesis, neuronal survival and growth (Autry & Monteggia, 2012; Zaben & Gray, 2013; He et al., 2013; Macedo et al., 2015; Yamamoto et al., 2015; Fanaei et al., 2014).

Alterations in serum BDNF levels are known to correlate with some neuropsychiatric disorders (Autry & Monteggia, 2012; Macedo et al., 2015; Yamamoto et al., 2015; Iughetti et al., 2011; Li et al., 2013).

Nowadays, varieties of chemical drugs are used to relieve PMS symptoms (Khayat et al., 2014a; Jang et al., 2014). Nonetheless, due to side effects of chemical drugs its consumption is not recommended

except in severe cases (Khayat et al., 2014a; Jang et al., 2014; Whelan et al., 2009; Dante & Facchinetti, 2011). As an alternative to chemical drug, complementary and herbal medicine are commonly used in the treatment of many chronic conditions such as PMS, menopausal symptoms, and dysmenorrhea (Khayat et al., 2014a; Jang et al., 2014; Whelan et al., 2009; Dante & Facchinetti, 2011). Protective effects of curcumin have been evaluated in the past decade (Kulkarni & Dhir, 2010). Curcumin is the principal curcuminoid of the spice turmeric, which is a member of the ginger family (Zingiberaceae) (Lopresti et al., 2012; Kulkarni et al., 2009). Many studies demonstrated that curcumin have beneficial effects in physiological and pathological conditions (e.g. antidepressant, anti-inflammatory, antioxidant, anti-carcinogenic, anti-arthritic, thrombosuppressive, anti-microbial, and hypoglycemic effects) (Lopresti et al., 2012; Kulkarni et al., 2009).

Curcumin has been found to possess protective activity in various animal models of neuropsychiatric disorders (Lopresti et al., 2012; Kulkarni & Dhir, 2010; Kulkarni et al., 2009; Kulkarni et al., 2008; He et al., 2015; Ghosh et al., 2015; Liu et al., 2014). Although the mechanism of the neuroprotective effect of curcumin is not fully understood, it is observed that it acts through modulating the release of certain neurotransmitters, such as BDNF (Kulkarni et al., 2009; Liu et al., 2014; Franco-Robles et al., 2014).

Moreover, there are evidences that in women with PMS during late luteal phase, serum BDNF level is different than women without PMS (Cubeddu et al., 2011; Oral et al., 2015). Taken together, these reports provided a rationale for studying the effect of curcumin in women with PMS. So, the hypothesis for this study was that curcumin would promote serum BDNF level, thereby improving severity of PMS symptoms.

## 2. Materials and methods

This study was a randomized, double-blinded and placebo-controlled research.

All subjects participated in the study voluntarily. All participants were informed that they could leave the study whenever they want. Aims and methods of the study were fully explained to the participants and written informed consent was received from all participants. Sample size was determined based on 80% power and  $\alpha = 0.05$  and it was estimated that 35 patients were required for each group. The study was done on 70 female students in dormitories of Tehran University of Medical Sciences in the year 2013. Data were collected during 10 months.

The ethics committee of Tehran University of Medical Sciences has approved the study and was registered at the Iranian Registry of Clinical Trial.

Inclusion criteria observed were: healthy premenopausal women with regular menstrual cycle of 21–35 days, not taking oral contraceptives, lack of sensitivity to curcumin, not taking any medication, not drinking alcohol, no smoking, and no stressful events in the last 3 months. The participants recorded their symptoms with daily record questionnaires for two menstrual cycles before the intervention (this form contains a table with 19 symptoms of premenstrual syndrome questionnaire based on the DSM-IV, Self-Rating Scale) (Khayat et al., 2014a; American Psychiatric Association, 2000; Abbasinia et al., 2013).

This questionnaire determines the severity of PMS using 3 items, including: mood symptoms (restlessness, irritability, anxiety, depression or sadness, crying, feeling of isolation), physical symptoms (headache, breast tenderness, backache, abdominal pain, weight gain, swelling of extremities, muscle stiffness, gastrointestinal symptoms and nausea) and behavioral characteristics (fatigue, lack of energy, insomnia, difficulty in concentrating, increased or decreased appetite) (Khayat et al., 2014a; American Psychiatric Association, 2000; Abbasinia et al., 2013). Then the severity of premenstrual syndrome was evaluated for all participants (0: absence of symptoms, 1: mild symptoms may not interfere with everyday activities, 2: moderate symptoms that interfere with

daily activities, 3: severe symptoms that impede doing daily activities). Each participant with at least five symptoms was finally diagnosed as a person with PMS (Khayat et al., 2014a; American Psychiatric Association, 2000; Abbasinia et al., 2013). After identifying participants with PMS, they were randomly allocated into two groups ( $n = 35$ ) with a ratio of 1:1 distributed in two balanced blocks. Out of every two participants, one was assigned to placebo group and another to the curcumin group and this order varied randomly.

Curcumin powder was provided by Darou Pakhsh Pharma. Co. (Tehran, Iran). The Curcumin and placebo capsules were prepared with identical appearance by the Faculty of Pharmacy (Tehran University of Medical Sciences, Tehran, Iran). The Curcumin powder as drug and brown sugar as placebo were separately filled in oral gelatin capsules by hand-operated capsule-filling machine (Scientific Instruments and Technology Corporation, USA).

Participants, investigators and statistician were blind to the treatment until the analysis was completed. The placebo and curcumin capsules had the same properties, such as smell, taste, shape, texture, color and size.

Doses of curcumin and placebo were 100 mg/12 h. Curcumin and placebo capsules were given through three successive menstrual cycles and each cycle ran 10 days (in each menstrual cycle 7 days before and 3 days after onset of menstrual bleeding). After intervention, again the severity of PMS was evaluated. The subjects completed the daily record questionnaire at their first, second and third menstrual cycles. Exclusion criteria were: incidence of side effects of drugs or drugs allergy, other drug use, drug use disorder, identifying any diseases during the study, getting married during the study, menstrual irregularities, and irregular bleeding event during the study.

### 2.1. Blood sampling and BDNF assay

Blood samples were collected one day after the last treatment in each menstrual cycle, so as to observe the effect of it (i.e. on the fourth day of menstrual cycle).

BDNF has a diurnal variation in women (Pluchino et al., 2009). To avoid diurnal variation, blood samples were collected after overnight fasting between 0800 AM and 0900 AM from cubital vein of each subject for measurement of serum BDNF levels (Cubeddu et al., 2011; Pluchino et al., 2009). To minimize the effects of seasons on serum BDNF levels, all blood samples were collected during successive menstrual cycles from middle of spring to late summer (Molendijk et al., 2012). The samples were centrifuged at 5000 rpm, 4 °C, for 15 min; then serum was removed and stored at  $-70$  °C until BDNF measurement. Serum BDNF levels were measured with a BDNF ELISA kit (BDNF Emax Immunoassay System, Promega, USA), after proper dilution of samples (1:4) using Block & Sample Buffer, according to the manufacturer's instructions. Statistical analysis was performed using software SPSS-18. To compare severity of symptoms before and after intervention inter-group and intra-group statistical analyses were performed. Inter-group analyses were performed to compare the total score of PMS, mood, behavioral and physical symptoms in cycle before intervention and first, second and third cycles after intervention between two groups by unpaired *t*-test. Intra-group analyses were performed to compare the total score of PMS symptoms in cycles before and after intervention in each group by repeated-measurement analysis of variances (ANOVA). Pairwise comparison using Bonferroni test was used to compare total PMS severity between cycle before intervention and first, second and third cycles after intervention in each group.  $P < 0.05$  was considered significant.

### 3. Results

As shown in Fig. 1, out of 70 students who participated in the study 4 subjects in the placebo group and 3 subjects in the curcumin group did not complete the study. In the placebo group two subjects because of

getting married, one due to other drug use and another one because of menstrual irregularity were excluded. In the curcumin group two subjects due to misuse of curcumin capsules and one subject because of menstrual irregularity were excluded.

As shown in Table 1, any significant difference between placebo and curcumin groups was not seen concerning demographic characteristics and menstrual history records.

Total score of PMS, severity of behavioral, mood, and physical symptoms between two groups did not show significant difference before the intervention (respectively  $P = 0.77$ ,  $P = 0.68$ ,  $P = 0.42$  and  $P = 0.48$ ) (Table 2). After the intervention, total score of PMS, severity of behavioral, mood, and physical symptoms in curcumin group were significantly lower than placebo group (Table 2 and Fig. 2).

Overall, repeated measures ANOVA showed that there was a substantial main effect for time,  $F(3, 60) = 23.87$ ,  $p < 0.001$  with both groups showing reduction in PMS severity. The main effect comparing the placebo and curcumin across the four time periods was significant,  $F(1,62) = 26.35$ ,  $p < 0.001$ . Pairwise comparisons using Bonferroni test to total PMS severity indicated that in placebo group between cycle before intervention and first, second and third cycles after intervention had no significant difference ( $p > 0.05$ ), whereas in curcumin group significant differences were seen between cycle before intervention and first, second and third cycles after intervention ( $p < 0.001$ ,  $p < 0.001$ ,  $p < 0.001$  respectively).

Repeated measures ANOVA revealed that there was a substantial main effect for time,  $F(3, 60) = 9.475$ ,  $p < 0.001$  with both groups showing reduction in behavioral symptoms. The main effect comparing the placebo and curcumin across the four time periods was significant,  $F(1,62) = 13.679$ ,  $p < 0.001$ . Pairwise comparisons using Bonferroni test to behavioral symptoms indicated that in placebo group between cycle before intervention and first, second and third cycles after intervention had no significant difference ( $p > 0.05$ ), whereas in curcumin group significant differences were seen between cycle before intervention and first, second and third cycles after intervention ( $p < 0.001$ ,  $p < 0.001$ ,  $p < 0.001$  respectively).

On the other hand, repeated measures ANOVA showed that there was a substantial main effect for time,  $F(3, 60) = 18.416$ ,  $p < 0.001$  with both groups showing decrease in mood symptoms. The main effect comparing the placebo and curcumin across the four time periods was significant,  $F(1,62) = 15.282$ ,  $p < 0.001$ . Pairwise comparisons using Bonferroni test to mood symptoms indicated that in placebo group between cycle before intervention and first, second and third cycles after intervention had no significant difference ( $p > 0.05$ ), but in curcumin group significant differences were seen between cycle before intervention and first, second and third cycles after intervention ( $p < 0.001$ ,  $p < 0.001$ ,  $p < 0.001$  respectively). Finally, repeated measures ANOVA showed that there was a substantial main effect for time,  $F(3, 60) = 13.796$ ,  $p < 0.001$  with both groups showing reduction in physical symptoms. The main effect comparing the placebo and curcumin across the four time periods was significant,  $F(1,62) = 17.260$ ,  $p < 0.001$ . Pairwise comparisons using Bonferroni test to physical symptoms indicated that in placebo group between cycle before intervention and first, second and third cycles after intervention had no significant difference ( $p > 0.05$ ), whereas in curcumin group significant differences were seen between cycle before intervention and first, second and third cycles after intervention ( $p < 0.001$ ,  $p < 0.001$ ,  $p < 0.001$  respectively).

Before the intervention, serum BDNF levels between curcumin and placebo groups did not show significant differences (Table 3). However, in curcumin group serum BDNF levels in first, second and third cycles after intervention were significantly higher than placebo group (Table 3 and Fig. 3).

Repeated measures ANOVA showed a remarkable main effect of time,  $F(3, 59) = 10.80$ ,  $p < 0.001$  with both groups showing increase in BDNF levels.

Besides, while comparing the main effect of placebo group with curcumin group across four times periods was found significant,  $F(1,$

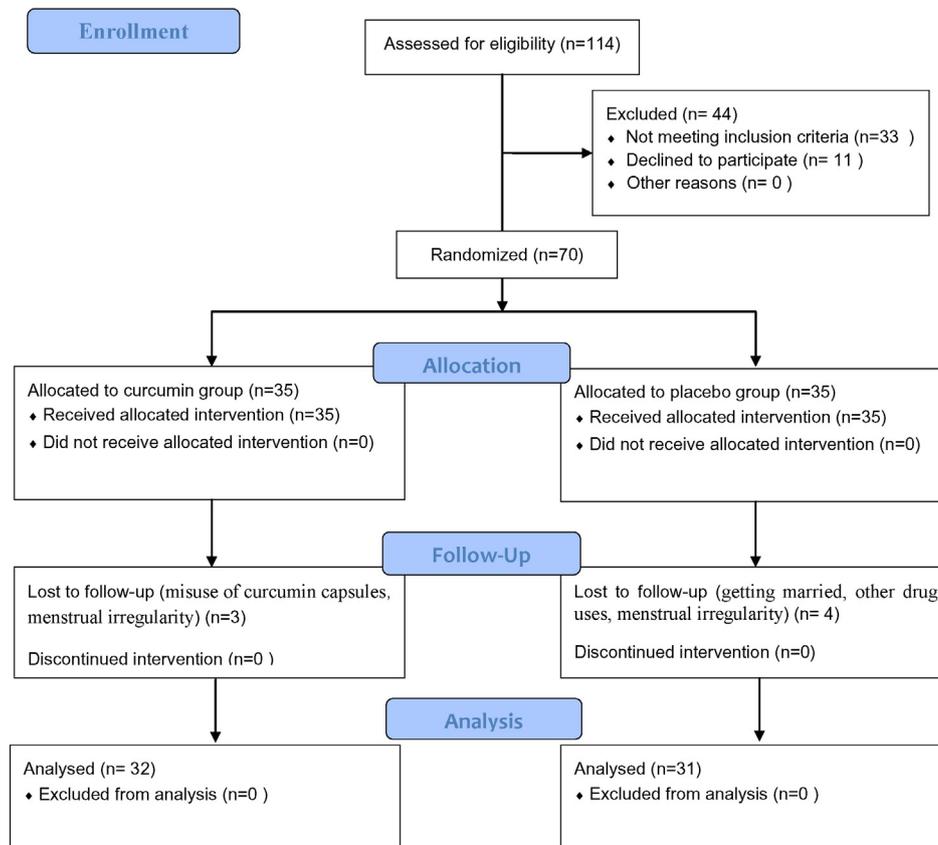


Fig. 1. CONSORT flow diagram.

61) = 14.66,  $p < 0.001$  (Fig. 3). Pairwise comparisons using Bonferroni test indicated that serum BDNF levels in placebo group between cycle before intervention and first, second and third cycles after intervention had no significant difference ( $p > 0.05$ ), while in curcumin group revealed that cycle before intervention had significant differences with first, second and third cycles after intervention ( $p < 0.001$ ,  $p < 0.001$ ,  $p < 0.001$  respectively).

## Discussion

To our knowledge, this study is the first report about the effect of curcumin on BDNF level in women with PMS. Present study has shown that curcumin increased serum BDNF levels and concurrently reduced severity of PMS symptoms during three successive menstrual cycles.

Nowadays, there is a high trend among researchers exploring the beneficial effects of curcumin against various diseases (e.g. arthritis, diabetes, cancer, depression, stroke, schizophrenia) (Lopresti et al., 2012; Kulkarni & Dhir, 2010; He et al., 2015; Ghosh et al., 2015; Mythri & Bharath, 2012; Lopresti et al., 2015).

The common symptoms of PMS are mood, behavioral and physical problems and curcumin possesses some interesting properties in

animal models on those problems that justify its effects in our study (Angst et al., 2001; Lopresti et al., 2012; Kulkarni & Dhir, 2010; Kulkarni et al., 2009; Pérez-López et al., 2009; Rapkin & Akopians, 2012). In vivo and in vitro studies during past decade confirmed that curcumin is capable of modulating levels of BDNF, norepinephrine, dopamine, and serotonin that are involved in mood and behavior regulation (Lopresti et al., 2012; Kulkarni et al., 2009).

Early studies on the neuroprotective effect of curcumin have shown its ability to increase BDNF and attenuate neurodegeneration (Lopresti et al., 2012; Kulkarni & Dhir, 2010; Kulkarni et al., 2009). In these studies, rodents were exposed to various stressors that lead to a significant decrease in hippocampal BDNF levels (Kulkarni & Dhir, 2010; Kulkarni et al., 2009; Kulkarni et al., 2008). Curcumin administration prevented decrease in hippocampal BDNF levels in stressed animals at levels similar to imipramine treatment (Lopresti et al., 2012; Kulkarni & Dhir, 2010; Kulkarni et al., 2009; Kulkarni et al., 2008; Mythri & Bharath, 2012; Kumar et al., 2010; Lee et al., 2011).

In addition, curcumin treatment exerts potent antidepressant effects that are comparable with the effects of well-known antidepressants drugs such as the serotonin reuptake inhibitors (fluoxetine and imipramine) (Lopresti et al., 2012; Sanmukhani et al., 2011).

**Table 1**  
Demographic characteristics and menstrual history of the participants.

Group	Placebo	Curcumin	Test results (unpaired t-test)
Characteristics	Mean ± SD	Mean ± SD	
Age (year)	23.86 ± 5.7	25.21 ± 9.2	$P = 0.48$
BMI (kg/m <sup>2</sup> )	23.33 ± 3.4	24.04 ± 2.9	$P = 0.71$
Age at menarche (year)	13.82 ± 2.3	14.06 ± 1.8	$P = 0.22$
Duration of cycle (day)	28 ± 2.1	28.9 ± 1.4	$P = 0.12$
Duration of menstruation (day)	6.1 ± 2.3	5.8 ± 3.5	$P = 0.9$

**Table 2**  
PMS scores in cycles before and after intervention in placebo and curcumin groups.

Group		Placebo	Curcumin	Test results
Symptoms		Mean ± SD	Mean ± SD	Unpaired <i>t</i> test
Total severity of PMS	Before intervention	106.06 ± 40.1	102.1 ± 40.1	<i>P</i> = 0.77
	One month after intervention	93.87 ± 39.7	39.32 ± 22.5	<i>P</i> < 0.001
	Two months after intervention	94.66 ± 51.3	44.61 ± 26.4	<i>P</i> < 0.001
	Three months after intervention	89.9 ± 42.6	43.45 ± 23.1	<i>P</i> < 0.001
Behavioral symptoms	Before intervention	24.45 ± 15.6	22.83 ± 13.2	<i>P</i> = 0.68
	One month after intervention	22.96 ± 15.1	8.35 ± 6.2	<i>P</i> < 0.001
	Two months after intervention	22.81 ± 18.98	7.96 ± 6.5	<i>P</i> < 0.001
	Three months after intervention	22.72 ± 18.28	11.32 ± 12.3	<i>P</i> = 0.005
Mood symptoms	Before intervention	34.82 ± 17.6	37.83 ± 20.3	<i>P</i> = 0.42
	One month after intervention	31.69 ± 16.77	12.12 ± 10.4	<i>P</i> < 0.001
	Two months after intervention	36.21 ± 21.55	15.8 ± 12.4	<i>P</i> < 0.001
	Three months after intervention	33.63 ± 20.46	17.45 ± 8.5	<i>P</i> < 0.001
Physical symptoms	Before intervention	46.75 ± 25.39	41.45 ± 18.4	<i>P</i> = 0.48
	One month after intervention	39.21 ± 23.31	18.83 ± 16.5	<i>P</i> < 0.001
	Two months after intervention	35.87 ± 23.3	20.87 ± 17.5	<i>P</i> = 0.005
	Three months after intervention	33.45 ± 17	14.6 ± 17.4	<i>P</i> < 0.001

This curcumin's antidepressant activity has been attributed to the increase in the level of serotonin (Lopresti et al., 2012; Kulkarni & Dhir, 2010; Kulkarni et al., 2009). Serotonin in women play important roles in the regulation of mood, sleep, memory, learning, and sexual behavior (Martinowich & Lu, 2008). Selective serotonin reuptake inhibitors (SSRIs) administration increases BDNF gene expression (Martinowich & Lu, 2008; Naumenko et al., 2012; Deltheil et al., 2008). Reciprocally, BDNF promotes the survival and differentiation of serotonin neurons (Lopresti et al., 2012; Kulkarni & Dhir, 2010; Kulkarni et al., 2009).

Serotonin may play an important role in etiology of PMS; specially in onset of mood and behavioral symptoms (such as irritability, sleep disturbance, anxiety, aggression, decreased pain threshold, change in appetite, difficulty concentrating and depression) (Wichianpitaya & Taneapanichskul, 2013; Pérez-López et al., 2009; Rapkin & Akopians, 2012; Marjoribanks et al., 2013).

PMS is one of the most common health problems in women during their reproductive age (Khayat et al., 2014a; Wichianpitaya & Taneapanichskul, 2013; Angst et al., 2001; Takeda et al., 2015). PMS as a neuroendocrine disorder is widely investigated but its pathogenesis is not clear (Epperson, 2013; Cubeddu et al., 2011; Rapkin & Akopians,

2012). BDNF have important roles in regulation of psychoneuroendocrine process (Hong et al., 2011; Borrow & Cameron, 2014; Balaratnasingam & Janca, 2012). Recent studies in PMS women revealed that serum BDNF level in luteal phase is significantly different than women without PMS (Cubeddu et al., 2011; Oral et al., 2015).

Evidence obtained by neuroimaging genetic studies demonstrated a complex interaction between sex steroid hormones fluctuations during menstrual cycle and BDNF gene expression in several brain regions that are implicated in emotional and cognitive processing in women (e.g. limbic system) (Toffoletto et al., 2014).

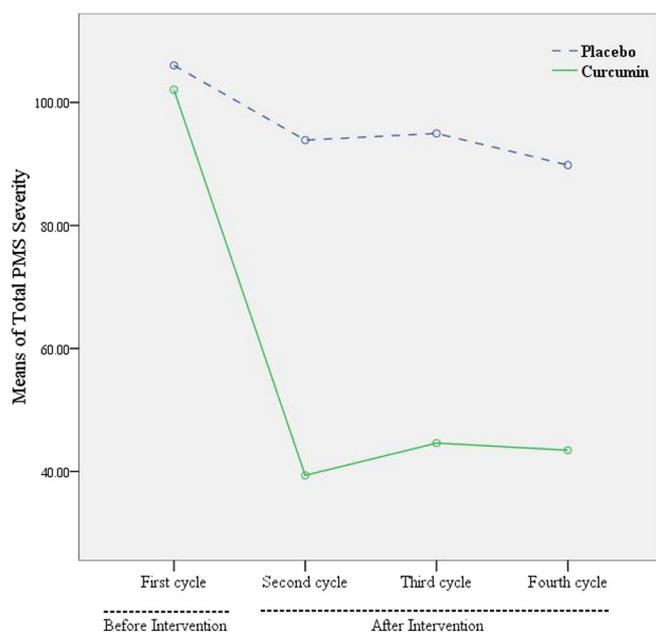
BDNF is widely expressed in limbic system where it has roles in mood and behavior regulation (Autry & Monteggia, 2012). In this regard, several studies reported biochemical and structural changes in limbic brain regions (especially hippocampus, amygdala and hypothalamus) across the menstrual cycle (ter Horst, 2010; Ossewaarde et al., 2013; Protopopescu et al., 2008).

Also, estrogen responsive elements have been localized on BDNF genes, telling that estradiol fluctuation during menstrual cycle can alter BDNF expression in limbic brain regions (Cubeddu et al., 2011; Blurton-Jones et al., 2004; Zhu et al., 2013).

Previous reports about BDNF concentration in serum of PMS women are contradictory. Cubeddu et al. (2011) showed that serum BDNF levels in luteal phase of PMS women were significantly lower than women not having PMS (Cubeddu et al., 2011). They suggested that lower luteal BDNF levels in PMS women might play a role in the onset of the symptoms related to PMS (Cubeddu et al., 2011). Our finding showed that increase in serum BDNF level is concurrent with reduction in PMS symptoms and this is consistent with the result of Cubeddu et al. (2011).

On the other hand, Oral et al. (2015) obtained conflicting results (Oral et al., 2015). They showed that serum BDNF level of luteal phase in PMDD patients is higher than control group (Oral et al., 2015).

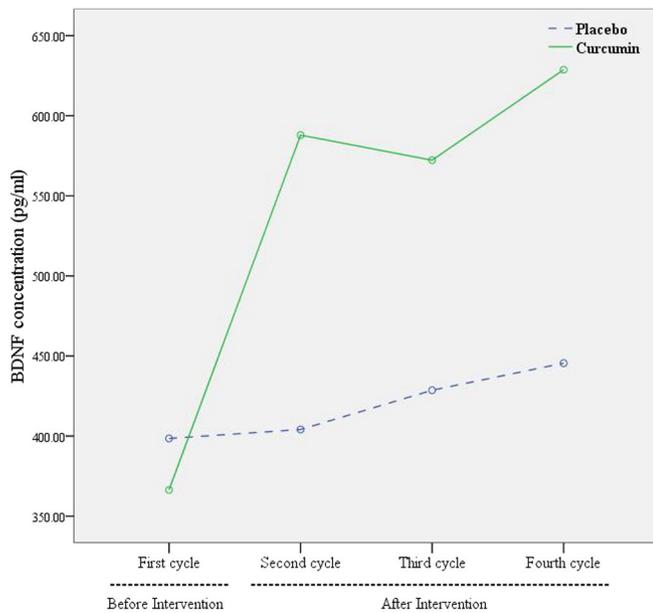
Oral et al. (2015) stated that higher serum BDNF level of luteal phase in PMDD patients may be a compensating biological process that results in an improvement of the depressive symptoms that occur during the



**Fig. 2.** Total PMS severity in cycles before and after intervention in placebo and curcumin groups.

**Table 3**  
Serum BDNF levels (pg/ml) in cycles before and after intervention in placebo and curcumin groups.

Group	Placebo	Curcumin	Test results
Cycle	(Mean ± SD)	(Mean ± SD)	Unpaired <i>t</i> -test
Before intervention	398.5 ± 185.4	366.3 ± 179.6	<i>P</i> = 0.48
One month after intervention	404.1 ± 138.9	587.9 ± 149.1	<i>P</i> < 0.001
Two months after intervention	428.6 ± 195.4	572.3 ± 164.9	<i>P</i> = 0.002
Three months after intervention	445.5 ± 193.2	628.7 ± 176.0	<i>P</i> < 0.001



**Fig. 3.** Serum BDNF levels in cycles before and after intervention in placebo and curcumin groups.

follicular phase (Oral et al., 2015). This contradiction between PMS and PMDD patients can be explained that in PMS patients during luteal phase the compensating mechanisms have failed to increase BDNF level.

Therefore, in our study curcumin through enhancing compensatory process may lead to increase in BDNF level and subsequently reduced severity of PMS symptoms.

The present study had several strengths including BDNF measurement in three successive menstrual cycles, randomized, double-blinded and placebo-controlled design. However, present study had some limitations, including recruiting only bachelor girls, and sex-hormone levels were not measured to confirm the self-reported menstrual cycle histories. These limitations attenuate our ability to generalize conclusions about the effects of curcumin on PMS.

## Conclusions

In summary, our findings demonstrate that curcumin reduces severity of PMS symptoms may be through increasing serum BDNF levels. Although larger studies are required, this study demonstrates that curcumin can be considered as an effective therapeutic option for PMS.

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