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Original Article

Efficacy of Curcumin on Cognitive Function Scores in Women with Premenstrual Syndrome and Dysmenorrhea: A Triple-Blind, Placebo-Controlled Clinical Trial*

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ABSTRACT **Objective:** To assess the efficacy of a curcumin supplementation on cognitive abilities in women suffering from premenstrual syndrome (PMS) and dysmenorrhea. **Methods:** A randomized, triple-blind, placebo-controlled trial was conducted from December 2019 to March 2020. A total of 124 women who had both PMS and dysmenorrhea were enrolled, and were equally and randomly assigned to the curcumin group or placebo group, 62 cases in each. Each subject received either a capsule containing 500 mg of curcuminoid, or a placebo daily, for 10 days (7 days before and until 3 days after the onset of menstrual bleeding) over 3 menstrual cycles. The cognitive abilities questionnaire was used to measures cognitive functions in 7 specific areas. Adverse reactions were monitored during and after the trial in both groups. **Results:** Administration of curcumin was associated with a significant increase in memory score (P=0.002), inhibitory control and selective attention (P=0.020), and total cognitive ability task (P=0.024). In addition, significant increments were found in scores of memory (3.5±3.1 *vs*. 0.4±3.8 in the curcumin and placebo groups, respectively; P=0.035), inhibitory control and selective attention (3.0±3.7 *vs*. 0.4±3.7; P=0.027) and total cognitive abilities (8.3±12.3 *vs*. 2.2±12.4; P=0.025) in the curcumin group *versus* placebo groups. Curcumin was safe and well-tolerable in current clinical trial. **Conclusion:** Curcumin has a beneficial efficacy on cognitive function scores in women with PMS and dysmenorrhea, with improvements in memory, inhibitory control and selective attention. (Registration No. IRCT20191112045424N1, available at: https://www.irct.ir)

KEYWORDS curcumin, memory, cognition, dysmenorrheal, premenstrual syndrome, triple-blind, placebo-controlled clinical trial

Menstrual abnormalities, dysmenorrhea and premenstrual syndrome (PMS) are common gynecological conditions that can affect the ability of women to perform daily tasks, and also cause a negative impact on quality of life.[1,2] Dysmenorrhea is a cyclic gynecological condition, defined by pelvic pain and uterine cramps during menses in women with normal pelvic anatomy that affects up to 90% of women. PMS is a complex disorder that comprises affective physical and psychological symptoms (such as mood swing, irritability, tiredness, abdominal bloating and tender breast) that, by definition, occur after ovulation and the last days of luteal phase due to the change of ovarian hormones and, persist for 2–4 days after menstruation onset.[3] Premenstrual changes negatively affect the success of girls at school, their emotional health, social activities, and family relationships.[1,2]

There is a general belief that negative mood and emotional feelings are associated with the premenstrual period. The effects of the menstrual cycle on emotion and cognitive abilities have been recently been studied systematically.[4] Some reports have shown that many women with PMS and dysmenorrhea can experience emotional, physiological and cognitive problems (e.g., impaired concentration, distractibility, forgetfulness, judgment

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and mental slowness, inability to reason normally, and difficulty in thinking clearly).[5,6] Women with PMS also report higher levels of psychological distress.[6] Keenan, et al[7] found that women with PMS, who usually undergo physical and emotional changes, have some difficulty in learning new material such as recalling and learning new words. Nowadays medications are used to relieve some of the symptoms of dysmenorrhea and PMS, but due to their side effects, they are not recommended routinely.[8] There is an increasing desire for safe and effective supplementary and herbal medicines as an alternative to conventional pharmaceuticals to alleviate physical and psychological complications related to PMS, menopausal symptoms and, dysmenorrheal.[9]

Curcumin, or diferuloylmethane, is the main curcuminoid in turmeric and is known to have several therapeutic properties, and has been used for a wide variety of conditions.[10,11] There is accumulating evidence that indicate that curcumin may have useful antidepressant, anti-inflammatory, antioxidant, antimicrobial, and hypoglycemic effects. Curcumin has also been reported to have protective activity in diverse animal models of neuropsychiatric conditions.[12,13] Though the mechanism of the neuro-protective effect of curcumin is not well understood, it has been reported to act by modulating the release of some neurotransmitters.[14] In women with PMS, the plasma level of some serum neurotransmitters differs from women without PMS in late luteal phase.[15] Due to the significant therapeutic effects of curcumin in previous investigations and the possibility of using it as a cost-efficient and effective herbal medicine, we performed this randomized, triple blind, placebo-controlled trial to explore potential effects of curcumin oral consumption on cognitive abilities in young woman suffering from both PMS and dysmenorrhea.

METHODS

Study Design

This study was approved by the Birjand University of Medical Sciences (BUMS) Ethics Committee (No. IR.BUMS.REC.1398.160), and registered with the Iranian Registry of Clinical Trial (Registration No. IRCT20191112045424N1, available at: https://www.irct.ir). The study population comprised 124 female students who lived in 4 different university dormitories in Birjand, South-Eastern of Iran, from December 2019 to March 2020. Based on the previous study,[16] sample size was calculated based on 80% power and α=0.05, and it was estimated that at least 55 patients were required for each arm; the final sample size assuming a 10% dropout rate was set as 62 individuals in each group. All participants signed written informed agreement for study participation.

Diagnostic, Inclusion and Exclusion Criteria

Dysmenorrhea and PMS were diagnosed by a gynecologist using a visual analogue scale (VAS)[17] and Premenstrual Syndrome Screening Tool (PSST)[18] as described before.[19] Briefly, the cases were instructed to report their dysmenorrhea pain intensity using a VAS tool. Individuals who experienced severe dysmenorrhea pain (score⩾8) were enrolled. PMS status was confirmed and graded by the PSST questionnaire. This tool comprises 19 items with 4-point Likert scale (0–3) to provide a total score ranging from 0–57. The individuals who obtained scores ⩾20 were enrolled to the present study.

The inclusion criteria were: age between 18 to 24 years, single, no history of severe gynecological disorders, no known allergy to herbal agents, and having regular menses, experiencing both moderate to intense primary dysmenorrhea and PMS. Women with any acute, or chronic condition, on any medications, or who experienced any stressful events during the intervention period were excluded.

Randomization and Blinding

Women who complied with the inclusion criteria and agreed to study participation were enlisted to take part in the trial. Participants were randomized to either placebo or curcumin group by a number: those with an even number on the registration list were enrolled to the curcumin group and the remaining participants were assigned to the placebo group. Researchers, patients, and statistical analysts were blinded to the participants' group allocations. Masking of group allocation was maintained until the final data analyses were conducted and all procedures, including randomization, patient's enrollment, and assigning individuals to interventions were performed by an experienced nurse at the clinic.

Intervention

Participants in curcumin or placebo groups were given 500 mg curcuminoids plus 5 mg piperine, C3 Complex (Sami Labs Ltd., Bangalore, India) at a daily

dose of 500 mg, or placebo. The placebo capsules contained inert filler (500 mg lactose powder, Sami Labs Ltd, Bangalore, India) plus 5 mg piperine. Curcumin and placebo were placed into capsules with the same appearance. Investigators were blinded to the group allocation. Piperine is an alkaloid and was added to the curcuminoids to improve its oral bioavailability and intestinal absorption. The participants were given 1 capsule per day for 10 days (7 days before and until 3 days after the onset of menstrual bleeding) for 3 menstrual periods. A valid questionnaire was used to evaluate participants' cognitive abilities during the trial.

Outcomes Assessment

Cognitive Abilities

The cognitive abilities questionnaire (CAQ) was used to measures cognitive functions in 7 specific aspects: memory, inhibitory control and selective attention, decision making, planning, sustained attention, social cognition, and cognitive flexibility.[20] The daily measurable operations in all the cognitive areas were present in the form of test items. CAQ is composed of 30 items, evaluated on a 5-point Likert scale (1–5) to assign a total score between 30 to 150. Higher scores represent better cognition abilities. All of the subscales had good reliability in the existing sample, with a Cronbach's alpha of 0.71–0.85.

Assessment of Covariate

Dietary intake of participants and cardio-metabolic indices were measured at baseline.

Dietary Intake

A validated semi-quantitative food frequency questionnaire (FFQ) was used in this study.[21] FFQ included 65 food items with 5 frequency categories (consumption basis per day, week, month, rarely, and never) for each food item. FFQ is an advanced type of the checklist in dietary history method that gives us the ability to estimate long-term dietary intakes in a simple, cost-effective, and time-saving method. FFQ was completed by an experienced nutritionist using a face-to-face interview. Diet Plan 6 software (Forestfield Software Ltd., Horsham, West Sussex, UK) was used for macronutrients and micronutrients intake analysis.

Cardio-metabolic Variables

Systolic and diastolic blood pressure was assessed using a sphygmomanometer and a cuff on the left arm, after 4 min in a relaxing situation with their left arm poisoned at heart level. The mean of 2 numbers was computed and used for analysis. Height and weight (wearing light clothing and no shoes) were conducted by trained individuals using a balance beam scale and height stick, and were used to determine body mass index (BMI). BMI was computed as weight (kg) divided by height squared (m^2).

Safety Assessment

Compliance and potential adverse reactions were monitored during and after the trial in both groups.

Statistical Analysis

Statistical analysis was performed using SPSS 16 software (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed as mean ± standard deviation ($\bar{x} \pm s$) or number (percent). Independent sample *t*-tests (for continuous variables) was done to examine the differences in parameters and then conducted at the end of trial to identify the changes in parameters between groups. The significance of changes from pre- to post-intervention within the groups was examined using paired *t*-tests for continuous variables. The α level was set significant at *P* value <0.05 in all analyses.

RESULTS

Participants Enrollment

A total of 117 participants (57 in curcumin group and 60 in placebo group) completed the trial and were included in the final analyses (Figure 1). Five participants did not complete the trial in the curcumin group and 2 in the placebo group. The drop-out rate due to lost in follow-up did not significantly differ between the groups (*P*=0.15).

Baseline Characteristics of Participants

At baseline, the total score of cognitive abilities in this population was 111.7 ± 13.8 (range: 78–138). Twenty-eight (22.9%) of participants scored <100 demonstrated cognitive impairments. Cognitive abilities score was inversely correlated with the PSST score (*r*=–0.23, *P*=0.014), but not with the VAS score (*r*=0.17, *P*=0.073). The baseline parameters of the study groups are shown in Tables 1 and 2. There were no significant differences between the curcumin and the placebo groups regarding to age, systolic and diastolic blood pressure, cognitive abilities task and dietary intake (*P*>0.05).

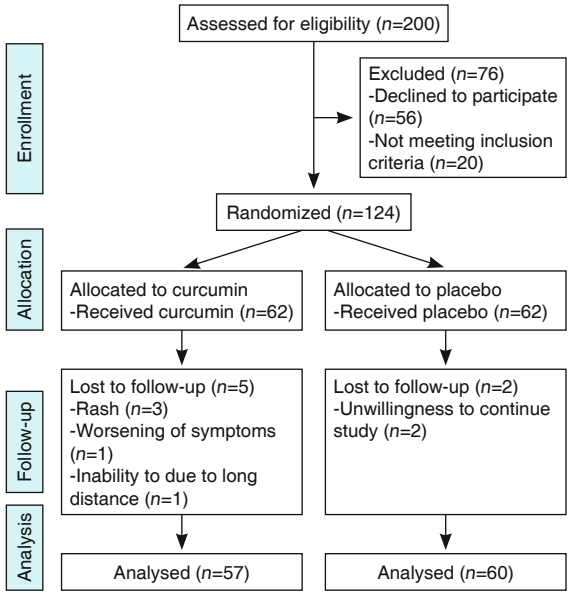

Figure 1. Flow Chart of Trial on Efficacy of Curcumin on Cognitive Function Scores in Woman with PMS and Dysmenorrhea

Note: PMS: premenstrual syndrome

Table 1. Baseline Characteristics of Participants Analyzed ($\bar{x} \pm s$)

Variable	Curcumin (57 cases)	Placebo (60 cases)
Age (Year)	20.7 ± 1.6	20.9 ± 1.8
BMI (kg/m^2)	20.9 ± 2.7	20.7 ± 3.0
SBP (mm Hg)	10.6 ± 1.0	10.6 ± 1.0
DBP (mm Hg)	7.1 ± 0.8	7.1 ± 0.7
WHR	0.73 ± 0.03	0.73 ± 0.04
CAQ (Score)		
Memory	25.2 ± 3.2	25.3 ± 3.9
Inhibitory control and selective attention	22.1 ± 3.9	21.5 ± 4.5
Decision making	19.2 ± 3.6	18.5 ± 3.9
Planning	10.7 ± 2.9	11.1 ± 2.8
Sustain attention	9.3 ± 2.1	9.7 ± 2.5
Social cognition	10.8 ± 1.9	10.6 ± 2.3
Cognitive flexibility	14.6 ± 2.7	14.5 ± 2.9
Total cognitive abilities task	112.0 ± 13.8	111.1 ± 15.6

Notes: BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, WHR: waist/hip ratio

Comparison of Outcomes between Two Groups

Administration of curcumin was associated with a significant increase in memory score (P=0.002), inhibitory control and selective attention (P=0.020), and total cognitive ability task (P=0.024). The slight increment in scores for decision making, planning, sustain attention, social cognition, and cognitive flexibility were not statistically significant (P>0.05). In the placebo group, the score of all cognitive abilities task were not statistically altered after the intervention (P>0.05, Table 3).

Table 2. Average Dietary Intake of Study Groups at Baseline ($\bar{x} \pm s$)

Variable	Curcumin (57 cases)	Placebo (60 cases)
Macronutrient (per 1000 kCal)		
Energy (kCal)	508.5 ± 161.6	547.6 ± 223.4
Carbohydrate (g)	61.2 ± 25.0	62.3 ± 34.5
Protein (g)	31.6 ± 13.4	33.9 ± 15.1
Total fat (g)	14.5 ± 11.2	16.7 ± 10.6
Dietary fiber (g)	6.7 ± 2.9	6.8 ± 3.4
Antioxidants (per 1000 kCal)		
Carotene (mcg)	700.6 ± 333.8	780.6 ± 406.0
Vitamin E (mg)	12.9 ± 6.9	12.9 ± 6.3
Vitamin C (mg)	62.1 ± 63.2	58.6 ± 45.4
Minerals (per 1000 kCal)		
Sodium (mg)	742.1 ± 374.9	793.4 ± 415.9
Calcium (mg)	207.5 ± 114.7	240.8 ± 143.7
Phosphorus (mg)	403.6 ± 159.3	439.2 ± 181.6
Magnesium (mg)	96.9 ± 42.2	102.1 ± 45.2
Manganese (mg)	1.4 ± 0.6	1.5 ± 0.7
Selenium (mcg)	21.5 ± 10.4	23.1 ± 10.4
Iron (mg)	3.2 ± 1.3	3.4 ± 1.4
Zinc (mg)	2.4 ± 1.0	2.5 ± 1.2
Vitamins (per 1000 kCal)		
Vitamin A (RE)	39.5 ± 41.4	56.4 ± 66.8
Thiamin (mg)	0.35 ± 0.19	0.37 ± 0.21
Riboflavin (mg)	0.59 ± 0.23	0.65 ± 0.26
Niacin (mg)	7.9 ± 3.3	7.8 ± 3.4

Significant increases were found in the scores for memory, inhibitory control and selective attention, and total cognitive ability task after curcumin *versus* placebo group (P<0.05, Table 3). However, no significant differences were observed between curcumin and placebo groups with respect to scores for decision making, planning, sustain attention, social cognition and cognitive flexibility (P>0.05).

Safety

Curcumin was safe and well-tolerable in current clinical trial. There was no report of severe side effects. There were only 3 cases declaring a rash and 1 with exacerbating of PMS symptoms.

DISCUSSION

In this trial the investigation had a good

Table 3. Comparison of Cognitive Abilities Task between Groups (Score, $\bar{x} \pm s$)

Item	Curcumin (57 cases)			Placebo (60 cases)		
	Before-treat.	After-treat.	Change	Before-treat.	After-treat.	Change
Memory	25.2±3.2	28.6±3.0**	3.51±3.12△	25.3±3.9	25.6±3.5	0.40±3.80
Inhibitory control and selective attention	22.1±3.9	25.1±3.5*	3.03±3.73△	21.5±4.5	21.9±4.0	0.43±3.72
Decision making	19.2±3.6	19.7±3.9	0.33±2.79	18.5±3.9	19.2±3.6	0.68±3.34
Planning	10.7±2.9	11.5±2.4	0.06±2.66	11.1±2.8	11.3±2.4	0.28±2.42
Sustain attention	9.3±2.1	9.5±2.3	0.17±2.50	9.7±2.5	10.1±2.4	0.47±2.67
Social cognition	10.8±1.9	10.5±2.3	–0.02±2.45	10.6±2.3	10.5±2.3	–0.01±2.51
Cognitive flexibility	14.6±2.7	15.3±2.7	0.63±3.24	14.5±2.9	14.5±2.6	–0.03±2.63
Total cognitive abilities task	112.0±13.8	120.2±12.9*	8.33±12.28△	111.1±15.6	113.3±14.2	2.25±12.40

Notes: *P<0.05, **P<0.01 *vs*. before treatment in the same group; △P<0.05 *vs*. the change value of the placebo group

completion rate, with more than 94.3% of participants who enrolled, completing the trial. In the present study, we noted significant increment in score of memory, inhibitory control and selective attention, and total cognitive ability tasks after curcumin supplementation compared to placebo.

Some researchers have reported an association between PMS and primary dysmenorrhea and have shown a correlation between the severity of PMS and severity of dysmenorrheal.[22] Whilst primary dysmenorrhea has a potential impact on educational efficiency, there is little evidence regarding its relationship with academic and cognitive performances in adolescent girls. Although studies are limited, current evidence suggests that there may be a correlation between premenstrual disorders and cognitive deficits in some aspects of life in women.[23] Based on these investigations, women undergoing PMS and dysmenorrhea, due to advanced progesterone and estrogen fluctuations, experience behavioral changes, cognitive processing disorders and are associated with emotional feelings and depression, which reduce the psychosocial health scores of quality of life.[4,23] Keenan and co-researchers[7] administered a test to measure motor speed, visual scanning and cognitive flexibility in women with PMS and showed women with PMS did less well on these tasks comparing to those without PMS. Unmarried women with PMS experience emotional problems at more significant degrees than those without it.[24] Women with PMS usually deal with more stress and depression and based on some cognitive tests, depressed individuals more often face problems with their memory performance.[7] Some evidence also suggests that cognitive operations, like acquirement and memory, are affected in depression.[25] Therefore, using agents with antidepressant-like effects, such as curcumin, may improve cognitive impairments.[25]

Although there is little agreement on how persistent pain can reduce cognitive function, previous study has shown that patients with chronic pain may complain of cognitive dysfunction and women with persistent pain are more vulnerable to cognitive impairment.[3] According to these investigations and because women with PMS and dysmenorrhea experience more chronic and periodic pain, this is possible that they are more susceptible to affect with neurocognitive disorders, such as cognitive decline and associated conditions such as Schizophrenia, Alzheimer's disease and Parkinson's disease, as well as sleep disturbance and impaired strength.[26,27]

Therefore, we examined the efficacy of curcumin on cognitive abilities task. Other investigations have also reported that oral consumption of a bioavailable and safe form of curcumin can improve memory and cognitive abilities.[28] The efficacy of curcumin on cognition and behavior have revealed positive outcomes in animal models. Administration of dietary curcumin for a 2-month period affected an A β -infusion-induced spatial memory deficit in female Sprague-Dawley rats.[29] Rui, et al[30] reported that curcumin can have a neuroprotective effect and improve memory in mice and prevent apoptosis in cultured PC12 cells by inhibiting $AlCl_3$ and D-galactose induced apoptosis. However, these results were from studies in animal models and the present study is one of the few studies that evaluated the effect of curcumin consumption on cognitive abilities in human subjects and has shown an improvement in memory, inhibitory control and selective attention in woman with PMS and dysmenorrhea.

Curcumin, due to its strong antioxidant activity, may offer some protection against cognitive impairment through neutralizing the detrimental effects of oxidative stress by increasing the expression molecular systems related to brain-derived neurotrophic factor (BDNF). BDNF, the most important broadly distributed neurotrophic factor for synaptic plasticity, learning and memory, can ease synaptic transfer and regulate gene expression through activation of synapsin Ⅰ and cyclic AMP response element-binding protein.[31] BDNF may be essential for many pathological manifestations of neurodegenerative conditions and it has been shown that curcumin can restore the BDNF protein to a normal.[32] Traumatic brain injury impairs cognitive ability and this seems to be connected with low levels of BDNF. Wu, et al[32] declared that curcumin dietary consumption can reduce the harmful effects of traumatic brain injury on cognition.

Oxidative stress can play a significant role on cognitive dysfunction and it is possible that oxidative damage can reduce cognitive capacity. Dietary supplementation of curcumin can act against oxidative damage with subsequent effects on the action of BDNF on synaptic plasticity. Curcumin is a strong scavenger for free radical's and has been proven to decrease oxidative damage by reducing the elevated protein carbonyl levels.[33] The antioxidant properties of curcumin may be due to the existence of two electrophilic a, b-unsaturated carbonyl groups in its structure, which can react with nucleophiles like glutathione. So, curcumin has the ability to block lipid peroxidation and neutralize reactive oxygen and nitric-oxide-based free radicals.[21,34] It was also suggested that curcumin may treat Alzheimer's disease due to its anti-oxidative activity and protective effect against transitional metal ions. In rat model, curcumin, at low dose, protect primary cultured neurons from Cu(Ⅱ)-induced damage.[35]

This study evaluated the efficacy of curcumin supplementation on cognitive abilities. The present study is subject to a number of limitations. First, this investigation was designed as a single-dose trial. Because some effects of curcumin are dose dependent, we are unable to ascertain whether there was any dose dependent effect of curcumin on cognitive function. Another limitation of our trial relates to short duration of curcumin consumptions and follow-up that interferes with any judgment on long-term efficacy of curcumin supplementation. Finally, our study included healthy young women, who were free of cognitive decline and major psychiatric disorders. So, it may not be possible to generalize our results to patients with emotional complications or cognitive impairment.

Our study found that curcumin has a beneficial influence on cognitive ability in women with PMS and dysmenorrhea. This may be a useful means of improving cognitive in young apparent healthy women, which could also be expanded as a beneficial assistance to the other specific population if other larger studies confirmed similar effects on different age and cases with different spectra of neurological disorders. Future randomized controlled trials in key populations of interest are needed to elucidate whether supplementation can promote cognition in these domains.

Conflict of Interest

The authors declare that they have no conflict of interest.

Author Contributions

AB conducted all analyses and drafted the manuscript. AJ and SK coordinated the fieldwork of the study. MA and AB provided methodological feedback. AJ and GF supervised the overall research project and helped to draft the manuscript. All of the authors have read and confirmed the final manuscript.

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Data Availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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