A Randomized, Placebo-Controlled Trial of \textit{Ginkgo biloba} \textit{L.} in Treatment of Premenstrual Syndrome

Giti Ozgoli, M.Sc.,$^1$ Elham Alsadat Selselei, M.Sc.,$^1$ Faraz Mojab, Ph.D.,$^2$ Hamid Alavi Majd, Ph.D.$^3$

Abstract

\textbf{Background and objectives:} During the reproductive years, most of menstruating women experience symptoms of premenstrual syndrome (PMS), which is incapacitating in up to 10\% of cases. According to complicated etiology, various therapeutic approaches have been proposed. Because PMS is a chronic situation, special attention should be paid to the side-effects of pharmacological interventions. Herbal medicine is a recent favorable therapeutic approach owing to fewer side-effects. We aimed to determine the effect of \textit{Ginkgo biloba} \textit{L.} on the symptoms of PMS.

\textbf{Methods:} This was a single-blind, randomized, placebo-controlled trial conducted from November 2007 to April 2008. The students with PMS, living in dormitories of a medical university (Tehran), who met the inclusion criteria entered the study. The students filled out the daily symptom rating forms in two consecutive menstrual cycles. After we verified the PMS diagnosis in 90 students, the participants were randomly assigned to experiment and placebo groups and took \textit{G. biloba} \textit{L.} tablets (containing 40 mg leaf extracts) or placebo three times a day from the 16th day of the menstrual cycle to the 5th day of the next cycle. Data were collected using daily symptom rating forms.

\textbf{Results:} Eighty-five (85, 94.4\%) participants completed the study. The two groups were similar in terms of demographic characteristics and baseline overall severity of symptoms. After the intervention, there was a significant decrease in the overall severity of symptoms and physical and psychologic symptoms in both \textit{Ginkgo} (23.68\%) and placebo (8.74\%) groups ($p < 0.001$). However, the mean decrease in the severity of symptoms was significantly more in the \textit{Ginkgo} group compared to the placebo group ($p < 0.001$).

\textbf{Conclusions:} \textit{G. biloba} \textit{L.} can reduce the severity of PMS symptoms. Further research on active ingredients and also the efficacy and safety of various doses and treatment durations of \textit{Ginkgo} are required.

Introduction

Premenstrual Syndrome (PMS) is characterized by one or a number of a set of physical, behavioral, and psychologic symptoms that happen repetitively and in a cyclic pattern, in association with the luteal phase of the menstrual cycle, and the patient is symptom-free between two luteal phases. Almost 70\%–90\% of women of reproductive age suffer from at least one of the symptoms of PMS, which is severe and incapacitating in at least 3\%–10\% of the cases.\textsuperscript{1} The prevalence of PMS in Iran was determined as 62.4\%–66.5\% in different studies.\textsuperscript{2,3} Some women state that during the course of PMS, they experience more daily stress that affects their family and personal relationships, work productivity, and social activities.\textsuperscript{4,5}

The etiology of the syndrome is complicated, and according to hypothesized causes, various therapeutic approaches have been recommended. Consultation is usually effective in mild cases while surgical intervention is the final solution in the rare refractory cases with severe, disabling symptoms.\textsuperscript{6} Because PMS is a chronic condition, special attention should be paid to the side-effects of pharmacological interventions.\textsuperscript{7} Fewer side-effects and public interest in safe, effective, and natural therapies make herbal medicine desirable for treating the syndrome.\textsuperscript{8,9}

\textit{Ginkgo biloba} \textit{L.} is a native plant of China that has been used in Traditional Chinese Medicine (TCM) for more than 1000 years. The active ingredients of the plant are flavonoid glycoside and terpene lactone. Seeds and leaves of the plant are traditionally used.\textsuperscript{10} It is a safe and well-tolerated
medicine that has been used as a dietary supplement in the United States. Clinical studies have shown that Ginkgo extracts exhibit therapeutic activity in a variety of disorders including Alzheimer disease, failing memory, age-related dementias, poor cerebral and ocular blood flow, and the prevention of altitude sickness. Due in part to its potent antioxidant properties and ability to enhance peripheral and cerebral circulation, the primary application of Ginkgo is in the treatment of cerebrovascular dysfunctions and peripheral vascular disorders.

Although Chinese herbs and TCM have been used for the treatment of PMS, the quality of clinical trials was not acceptable, and to the best of our knowledge there was only one published placebo-controlled trial on the efficacy of Ginkgo for the treatment of PMS in which G. biloba extract (EGb 761) was effective against the congestive symptoms of PMS. Regarding this and since very few side-effects have been reported for the therapeutic dose of Ginkgo, the current study evaluated the effect of G. biloba L. tablets, containing 40-mg leaf extracts, on PMS symptoms in university students.

Materials and Methods

This was a single-blind, randomized, placebo-controlled trial carried out on female students with PMS living in dormitories of Shahid Beheshti University of Medical Sciences (SBUMS), Tehran, from November 2007 to April 2008. Inclusion criteria were as follows: being unmarried, age range of 18–30 year old, body mass index (BMI) of 19.8–26, having regular menstrual cycles of 21–35 days, not being affected by known physical or psychologic disorders (e.g., hypothyroidism, mood disorders), and not taking any special medications (e.g., warfarin, antidepressants, oral contraceptives) or other herbal medicines. Informed consent was obtained from all participants, and the ethics committee of SBUMS approved the study. Calculated sample size per group was 42, considering \( z = 0.05 \), study power = 80%, effect size = 0.5, and 20% dropout.

Data were collected using a self-administered questionnaire that contained items on inclusion criteria, Beck’s Depression Inventory, and also a form for the preliminary diagnosis of PMS adopted from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). A daily symptom rating questionnaire contained 19 symptoms of PMS, according to DSM-IV, which included tension, labile mood, irritability, anxiety, depression, fatigue, headache, forgetfulness, palpitation, decreased libido, increased appetite, suicidal thought, edema, breast tenderness, sleeping disorders, craving for sweets, bloating, decreased concentration, and crying spells. Participants were considered to be affected by PMS and eligible to enter the study if they experienced at least five of the mentioned symptoms for most of the time during the last week of the luteal phase, which began to remit within a few days after the onset of the follicular phase, and were absent in the postmenstrual week. Also, participants had to have experienced the symptoms for at least two consecutive cycles before the intervention. Participants rated the severity of symptoms by numbers, ranging between 0 and 3 denoting none to severe symptoms. Then, the severity of symptoms was categorized into three groups of mild (score < 33%), moderate (33% < score < 66%), and severe (score > 66%). The validity of the questionnaire was confirmed by content validity method and the reliability of the daily symptom rating questionnaire was determined by test–retest method. The least Spearman correlation-coefficient was calculated at 0.82.

During the study period, 980 students were interviewed and 290 of them were given the symptom rating questionnaire based on the preliminary diagnosis of PMS. Finally, 90 of them were definitely diagnosed as being affected by PMS and eligible to enter the study. They were randomly assigned to the experiment and placebo groups (45 participants in each group) using a computer-generated random table list and also by matching according to the severity of symptoms (Fig. 1). Interviewing students, generation of the random sequence, and assignment of participants to their groups were done solely by one of the authors of this paper.

Ginkgo biloba L. (Ginkgoaceae; maidenhair tree) is currently produced in Iran as 40-mg coated tablets under the commercial name of “Ginko T.D.” by the Tolid-Daru Company (Tehran). It is produced from leaf extracts and standardized by flavonoid glycoside (24%) and terpene lactone (6%). The solvents used in the extract are ethanol and water, and the ratio of herbal drug to extract is 4:1. The placebo tablets, produced in the pharmaceutics laboratory of SBUMS, were identically sized and colored tablets (filled with starch) to match the G. biloba L. tablets. Participants took Ginkgo or placebo tablets (40 mg) three times a day, one tablet each time, from day 16 of the cycle to day 5 of the next cycle, for two consecutive cycles. This dosage regimen was determined according to a previous clinical trial. The participants were carefully followed up and were asked to note down the use of Ginkgo and placebo tablets, any analgesic, and the occurrence of any event (such as marriage, relatives’ death, etc.) in questionnaires. The questionnaires were collected after each menstrual cycle, and at the final visit participants filled out another questionnaire. After each cycle, the daily rating symptom questionnaire was assessed and the severity of symptoms was evaluated.

Data were analyzed using SPSS software v. 15.0. Because the Kolmogorov–Smirnov test did not verify the normality of the data, Mann–Whitney and Friedman tests were used for the comparison of inter- and intragroup mean differences before and after the intervention in the first and second cycles. In all tests, a \( p \) value of <0.05 was considered significant.

Results

After randomization and before taking Ginkgo/placebo tablets, 5 participants (2 in the experiment and 3 in the placebo group) refused to continue the study. Therefore, the statistical tests were carried out on the data collected from 85 of the participants (43 in the experiment group and 42 in the control group). Baseline characteristics of participants are presented in Table 1. As shown, there was not a significant difference between the two groups in terms of age, BMI, menarche age, duration of menstrual cycle, onset of symptoms in a cycle, or number of roommates (\( p > 0.05 \)). Also, none of the participants were employed. Reviewing
daily questionnaires showed that all participants took the medicine regularly according to the administration order. As shown in Table 2, mean percentage of overall severity of symptoms in the experiment group was 34.80% before the intervention, which reduced to 11.11% after the intervention ($p < 0.001$), whereas the corresponding percentages in the placebo group were 34.38% and 25.64%, before and after intervention, respectively ($p < 0.001$). Mean percentage of overall severity of symptoms after the intervention and also mean reduction of overall severity of symptoms were significantly different between the two groups, and Ginkgo reduced the symptoms more than placebo ($p < 0.001$).

![Flow diagram](image)

**FIG. 1.** Flow diagram. PMS, premenstrual syndrome.

### Table 1. Comparison of Baseline Characteristics Between the Two Groups

<table>
<thead>
<tr>
<th></th>
<th><em>Ginkgo</em> (n = 43)</th>
<th><em>Placebo</em> (n = 42)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>22.2 (1.4)</td>
<td>22.1 (1.6)</td>
<td>0.844</td>
</tr>
<tr>
<td>BMI</td>
<td>22.6 (1.3)</td>
<td>22.5 (1.3)</td>
<td>0.71</td>
</tr>
<tr>
<td>Menarche age (year)</td>
<td>13 (0.8)</td>
<td>13 (0.8)</td>
<td>0.892</td>
</tr>
<tr>
<td>Duration of menstrual cycle (days)</td>
<td>27 (1.2)</td>
<td>27.4 (1.5)</td>
<td>0.27</td>
</tr>
<tr>
<td>Onset of symptoms in a cycle (days)</td>
<td>5.2 (1.6)</td>
<td>4.8 (1.5)</td>
<td>0.31</td>
</tr>
<tr>
<td>Number of roommates</td>
<td>3.2 (0.4)</td>
<td>3.1 (0.3)</td>
<td>0.817</td>
</tr>
<tr>
<td>Using dormitory food</td>
<td>37/43 (86%)</td>
<td>37/42 (88%)</td>
<td>0.778</td>
</tr>
<tr>
<td>Positive family history of PMS</td>
<td>37.43 (86%)</td>
<td>35/42 (83.3%)</td>
<td>0.728</td>
</tr>
</tbody>
</table>

* *p > 0.05; independent samples t-test.
* *p > 0.05; $\chi^2$ test.

Data are shown as mean (standard deviation) and number (percentage).

BMI, body–mass index; PMS, premenstrual syndrome.
As shown in Table 3, severity of psychologic symptoms reduced significantly in both groups after the intervention (\(p < 0.001\)). However, a significant difference was observed between the two groups, and Ginkgo reduced the psychologic symptoms more than placebo (\(p < 0.001\)).

Table 4 indicates that severity of physical symptoms reduced in both groups after treatment; however, there was a significant difference between the groups and Ginkgo reduced the physical symptoms more than placebo (\(p < 0.001\)). Additionally, as shown in Figure 2, there was a significant difference between the two groups in categorized symptom severity after the intervention (\(p < 0.001\)).

Regarding the probable side-effects of the intervention, 93% (40/43) of participants stated that Ginkgo did not cause any side-effects. Only one case of nausea and two cases of increased desire for sleep were reported in experiment group. In the placebo group, 90.5% (38/42) pointed out no side-effects and four cases of nausea were reported. It is notable that Ginkgo and placebo did not have any effects on duration and amount of menstrual bleeding.

Considering the participants’ satisfaction with the treatment, in the experiment group, 30.2%, 48.8%, and 20.9% of the participants reported being “very satisfied,” “satisfied,” “moderately satisfied,” and “moderately satisfied” with the treatment, respectively, which shows that participants in the experiment group were more satisfied (\(p < 0.001\)). Furthermore, 83.7% (36/43) in the experiment group were willing to continue the treatment, while only 26.2% (11/42) of participants in the placebo group were willing to do so (\(p < 0.001\)).

**Discussion**

According to the findings of the study, G. biloba L. was more effective than placebo in reducing the overall severity of symptoms and also severity of physical and psychologic symptoms in young women with PMS. In a similar study, Tamborini and Taurelle\(^{14}\) found beneficial effects of G. biloba extract (EGb 761) on congestive symptoms of PMS, especially breast tenderness and fluid retention. In their study, significant improvements were also seen in neuropsychologic symptoms (irritability and aggression) compared to placebo, and the tolerability of the treatment was judged to be good or very good by 86% of the patients.

In most studies on the effectiveness of herbal medicines in the treatment of PMS, significant response to placebo was observed as a common finding. This can be explained by the fact that using therapeutic approaches gives women a feeling of increased self-control over their life. Therefore, even minor

### Table 2. Comparison of Mean Percentage of Overall Severity of PMS Symptoms Before Intervention, and One and Two Cycles After Intervention in the Two Groups

<table>
<thead>
<tr>
<th></th>
<th>Ginkgo (n = 43)</th>
<th>Placebo (n = 42)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before intervention</td>
<td>34.80 (12.02)</td>
<td>34.38 (11.63)</td>
<td>0.930(^a)</td>
</tr>
<tr>
<td>1st cycle of intervention</td>
<td>19.65 (7.77)</td>
<td>28.72 (8.41)</td>
<td>&lt;0.001(^a)</td>
</tr>
<tr>
<td>2nd cycle of intervention</td>
<td>11.11 (5.74)</td>
<td>25.64 (7.06)</td>
<td>&lt;0.001(^a)</td>
</tr>
<tr>
<td>Mean decrease of overall severity of symptoms after 1st cycle intervention</td>
<td>15.13%</td>
<td>5.66%</td>
<td>&lt;0.001(^a)</td>
</tr>
<tr>
<td>Mean decrease of overall severity of symptoms after 2nd cycle intervention</td>
<td>23.68%</td>
<td>8.74%</td>
<td>&lt;0.001(^a)</td>
</tr>
<tr>
<td>Intragroup difference</td>
<td>(p &lt; 0.001)(^b)</td>
<td>(p &lt; 0.001)(^b)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Mann–Whitney test.  
\(^b\)Friedman test.  
Data are shown as mean (standard deviation) and percentage.  
PMS, premenstrual syndrome.

### Table 3. Comparison of Mean Percentage of Severity of Psychologic Symptoms of PMS Before Intervention, and One and Two Cycles After Intervention in the Two Groups

<table>
<thead>
<tr>
<th></th>
<th>Ginkgo (n = 43)</th>
<th>Placebo (n = 42)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before intervention</td>
<td>38.41 (10.52)</td>
<td>37.79 (11.43)</td>
<td>0.899(^a)</td>
</tr>
<tr>
<td>1st cycle of intervention</td>
<td>19.39 (6.89)</td>
<td>30.14 (8.20)</td>
<td>&lt;0.001(^a)</td>
</tr>
<tr>
<td>2nd cycle of intervention</td>
<td>10.89 (6.33)</td>
<td>26.18 (6.89)</td>
<td>&lt;0.001(^a)</td>
</tr>
<tr>
<td>Mean decrease of psychologic symptoms severity after 1st cycle intervention</td>
<td>19.02%</td>
<td>7.64%</td>
<td>&lt;0.001(^a)</td>
</tr>
<tr>
<td>Mean decrease of psychologic symptoms severity after 2nd cycle intervention</td>
<td>11.61%</td>
<td>27.52%</td>
<td>&lt;0.001(^a)</td>
</tr>
<tr>
<td>Intragroup difference</td>
<td>(p &lt; 0.001)(^b)</td>
<td>(p &lt; 0.001)(^b)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Mann–Whitney test.  
\(^b\)Friedman test.  
Data are shown as mean (standard deviation) and percentage.  
PMS, premenstrual syndrome.
Interventions such as placebo may lead to desirable effects. Results of the present study demonstrated that the severity of physical and psychologic symptoms decreased after the intervention in both groups, but Ginkgo decreased the severity of symptoms more than placebo. This result is in accord with the findings of the studies by Pak-Gohar et al. and Stevinson et al. regarding the effects of Hypericum perforatum and the studies by Aghajani et al. and Prilepskaya et al. regarding the effectiveness and tolerability of extract of Vitex agnus castus on PMS symptoms. However, in another study, H. perforatum L. was not significantly superior to placebo in reducing PMS symptoms, which was attributed to insufficient statistical power of the study, rather than lack of efficacy of H. perforatum L.

In the present study, more detailed analyses also showed that the severity of sleeping abnormalities, fatigue, bloating, and palpitation decreased in the Ginkgo group but not in the placebo group. Severity of other symptoms except suicidal tendency decreased in both groups. However, Ginkgo was more effective than placebo in reducing the symptoms. These results were in agreement with those of Pak-Gohar et al., which evaluated the effect of Hypriran (Hypericum Perforatum extract) in the treatment of PMS in students living in dormitories. Ginkgo maintains the balance of prostacyclines and, thus, increases the blood circulation. In addition, it is an inhibitor of monoamine oxidase and thromboxane A2 methyl esterase, and by increasing the release of catecholamines and other neurotransmitters and decreasing the re-uptake of these molecules, improves the mood and symptoms of depression. Lipoxigenase and cyclooxygenase, which play a role in the production of inflammatory prostaglandins, are inhibited by flavonoids that are found in Ginkgo and so the medicine has an anti-inflammatory effect. Furthermore, the quercetin contained in Ginkgo is an effective inhibitor of histamine release. Therefore, the reduced severity of symptoms by Ginkgo could be justified in part by this mechanism.

Bioflavonoids are among the active ingredients of Ginkgo that are mainly known as stress modulators. That is why Ginkgo is used as an anxiolytic medicine. Accordingly, the significant decrease of symptoms such as tension, irritability, labile mood, and anxiety could be justified in the Ginkgo group. It seems that Ginkgo is effective in relieving depression symptoms by increasing the release of neurotransmitters and decreasing their re-uptake. Numerous studies have proved the important role of Ginkgo in improvement of brain blood circulation and enhancement of memory and concentration. As was mentioned, Ginkgo is a vasodilator and stimulates the blood circulation and its flavonoid components have an anti-inflammatory effect. This could explain the relief of congestive symptoms such as breast tenderness, abdominal bloating, and edema.

It is noteworthy that almost two thirds of the participants in the present study who took the medicine were “very satisfied” or “satisfied” with the medicine, but two thirds of the participants in placebo group were “moderately satisfied” with it, which indicates the importance of using herbal medicine.

In the present study, participants were healthy people with special consideration to exclude depressed cases, because there is considerable overlap between symptoms of depression and those of PMS. Also, the daily symptom rating questionnaire was used for 2 consecutive months prior to the intervention to confirm the diagnosis of the syndrome.

Table 4. Comparison of Mean Percentage of Severity of Physical Symptoms of PMS Before Intervention, and One and Two Cycles After Intervention in the Two Groups

<table>
<thead>
<tr>
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<th>Ginkgo (n = 43)</th>
<th>Placebo (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before intervention</td>
<td>27.11 (23.91)</td>
<td>26.93 (16.99)</td>
</tr>
<tr>
<td>1st cycle of intervention</td>
<td>13.74 (11.02)</td>
<td>24.10 (14.38)</td>
</tr>
<tr>
<td>2nd cycle of intervention</td>
<td>10.81 (9.74)</td>
<td>22.70 (12.76)</td>
</tr>
<tr>
<td>Mean decrease of physical symptoms severity after 1st cycle intervention</td>
<td>13.36%</td>
<td>2.83%</td>
</tr>
<tr>
<td>Mean decrease of physical symptoms severity after 2nd cycle intervention</td>
<td>16.30%</td>
<td>4.23%</td>
</tr>
<tr>
<td>Intragroup difference</td>
<td>p &lt; 0.001b</td>
<td>p = 0.006b</td>
</tr>
</tbody>
</table>

aMann–Whitney test.
bFriedman test.

Data are shown as mean (standard deviation) and percentage.
Besides that, there are some important limitations in our study that need to be considered in future trials. The participants in this study were university students who may not represent the general population of women with PMS. Therefore, our results are not completely generalizable to the general population. The participants were followed up just during the 2 months of taking the medicine, and it is recommended to evaluate the long-term effects of Ginkgo on PMS in further studies. This study was designed to be a double-blind trial, but the researcher who gave the tablets to the participants reported that she had detected the placebo and drug in the middle of the study period. However, the researcher was unaware at the time of interviewing students, generation of the random sequence, assignment of participants to their groups, and gathering information of the first cycle and, therefore, we think that this problem did not significantly affect the results. We did not check unawareness of the participants. Questioning participants whether they think they have received active treatment or placebo could verify their unawareness. Also, the placebo used in the study was made from starch which may, itself, have possible effects on some symptoms of PMS.

Conclusions

The results of the present study showed that G. biloba leaf extract reduces the severity of physical as well as psychological symptoms of PMS. However, further research is needed to obtain more evidence for administering Ginkgo as a safe and low-cost medication for patients who are not willing to use chemical drugs or have some contraindications for such drugs. Also, studies on active ingredients and efficacy and safety of various doses and treatment durations of G. biloba are required.

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Disclosure Statement

The authors state that no competing financial interests exist.

References


Address correspondence to:
Giti Ozgoli, M.Sc.
Nursing and Midwifery School
Shahid Beheshti University of Medical Sciences
Next to Mofid Children’s Hospital, End of Mirdamad Street
Dr. Shariati Street
Tehran
Iran
E-mail: gozgoli@yahoo.com