Gingko biloba Extended Abstract

Primary literature: Article #1

Ozgoli G, Selselei EA, Mojab F, and Majd HA. *A Randomized, Placebo-Controlled Trial of Gingko biloba L. in Treatment of Premenstrual Syndrome.* J Alternative and Complementary Med. 15 (8): 2009 pp 845-851. DOI: 10.1089=acm.2008.0493.

Study Objective

A previous clinical study showed that Gingko extracts exhibit therapeutic activity in Alzheimer's, memory loss, dementia and poor cerebral and ocular blood flow due to antioxidant properties. The previous study was effective for treating congestive symptoms of PMS with few side effects. This study by Ozgoli *et al.,* was done to evaluate the effect of Gingko Biloba L. tablets containing 40-mg leafs extracts on PMS symptoms in university students due to the limited evidence available on this natural product.

Methods

- **Design:** This study is a single-blinded, randomized, placebo-controlled trial.
  - Collected data via a self-administered questionnaire with inclusion criteria and Beck's Depression Inventory and a form which had 19 symptoms of PMS (from DSM-IV) allowing for a preliminary diagnosis of PMS. Saved data electronically to prevent loss.
  - Symptoms of PMS included: tension, labile mood, irritability, anxiety, depression, fatigue, headache, forgetfulness, palpitation, decreased libido, increased appetite, suicidal thoughts, edema, breast tenderness, sleeping disorders, cravings for sweets, bloating, decreased concentration and crying spells.
  - Participants were considered to be affected by PMS if they experienced at least 5 symptoms for most of the time during the last week of the luteal phase and remitted within a few days after the onset of the follicular phase. Symptoms of PMS were to be absent in the postmenstrual week. Participants had to experience symptoms for at least two consecutive cycles
  - Participants rated the severity of symptoms by numbers ranging between 0 and 3. Severity of symptom then grouped into three groups: Mild: score <33%. Moderate: 33-66% and severe >67%.

- Statistical tests: used Mann-Whitney and Friedman tests to compare inter and intra group differences.

- **Allocation:**
  - I) Inclusion Criteria: Female students with PMS living in dormitories of Shahid Behesti University of Medical Sciences in Tehran from November 2007 to April 2008. Unmarried, ages: 18-30, BMI: 19.8-26, having menstrual cycles of 21-35 days, and with no known physical or psychological disorders such as mood disorders, hypothyroidism, and not taking any "special" medications: warfarin/antidepressants, oral contraceptives. 980 students were interviewed, 290 had a preliminary diagnosis of PMS based on a symptom rating questionnaire and 90 (30 had not met the inclusion criteria and 170 did not complete the forms or refused to participate) were definitely diagnosed with PMS and entered into the study.
  - III) Randomization with 90 participants enrolled in the study, each patient was randomly assigned by a computer-generated list to match severity of symptoms between the treatment and placebo group.
- **Blinding:** Placebo tablets were made by a laboratory within the university and were identically sized and coloured and filled with starch to the Gingko Biloba L. tablets. This study was meant to be a double-blinded trial but the researchers were able to uncover the blinding. The authors were unable to determine if patients were able to uncover the blinding.
- **Follow up period**: Followed patients for 2 consecutive cycles.
- **Setting:** Questionnaire done at the Shahid Behesti University of Medical Sciences in Tehran, Iran.
- **Participants:** Average age = 22 years, BMI: 22.5, 85% had a positive family history of PMS.
- **Intervention:** Gingko Biloba L 40mg-coated tablets (produced by Gink T.D.) with flavonoid glycoside 24% and terpene lactone 6%. Dosing regimen: 1 tablet three times days from day 16 of cycle to day 5 of the next cycle for two consecutive cycles.
- **Outcomes**: Daily rating symptom questionnaire improvement.
- **Patient Follow Up**: Participants asked to note down the use of analgesic and occurrence of events such as marriage and relative deaths.

Main Results

5 participants (2 experiment and 3 in the placebo) dropped out of the study after randomization due to refusal to continue. The total number of participants was 85 (43 for treatment). No significant differences between age, BMI, menarche age, duration of menstrual

cycle, onset of symptoms in a cycle and the number of roommates. None of the participants were employed**.** All participants were compliant with the medications.

Overall severity of symptoms in the experiment group was 34.80 +/- 12.02% before the intervention was reduced to 11.11 +- 5.74% after the intervention after the 2nd cycle. Placebo group was 34.38 +/- 11.63% before and 25.64 +/- 7.05% after. Mean percentage of overall decreased severity of symptoms after the intervention and mean reduction of overall severity of symptoms were significantly different (23.68% vs. 8.74%, $p < 0.001$) between the two groups and Gingko reduced symptoms much better than placebo. Gingko also reduced psychological symptoms better than placebo (27.52% vs. 11.61% $p < 0.001$). Severity of physical symptoms was reduced more in Gingko as well (16.3% vs. 4.23%).

In terms of side effects, in the treatment arm 40/43 participants had no side effects. 1 participant had nausea and 2 felt symptoms of sleepiness. In the placebo arm there were 4 causes of nausea.

Patients taking Gingko were very happy with the treatment as 30.2% (vs. 0%) were very satisfied with the treatment, 48.8% (vs. 14.3%) were satisfied, and only 20.9% (vs. 85.7%) were moderately satisfied. The treatment arm had 83.7% which wished to continue treatment vs. 26.2% of the placebo arm that wanted to continue the treatment.

Conclusions

The authors concluded that Gingko biloba was more effective than placebo in reducing the overall severity of symptoms in PMS including physical and psychological symptoms in young women. However the authors did note the limitations of only following the patients for two cycles and its stringent inclusion criteria.

Comments/Critical appraisal:

- **Internal validity:**

  The study's inclusion criterion was very stringent. Only participants with no physical or psychological disorders could be included. The authors explained that there was a ton of overlap between psychological disorders and PMS but gave no reasoning to excluding participants with any physical conditions. They also excluded participants from not taking any "special" medications such as warfarin, antidepressants and oral contraceptives but they did not give a list of these

medications or reasons for the exclusions leading to an amount of bias. Furthermore they excluded married women from the study and had limitations on BMI which has no scientific or clinical basis without the authors giving reasoning. Lastly, participants were only included in the trail if they had at least 5 symptoms of PMS where it can only take one symptom to be diagnosed with PMS.

Another area of potential bias was in the results. They had a questionnaire regarding the satisfaction of either the treatment or placebo arm with options such as very satisfied, satisfied or moderately satisfied. 0% (0/85) of patients were unsatisfied and this is even with a high percentage of participants saying that would not want to continue with a placebo treatment. Likely meaning that the unsatisfied was not an option and therefore making the results of patient satisfaction skewed.

Also, since this study was meant to be designed as a double-blind placebo trial and was uncovered by the author, this could have lead to expectation bias from the authors but most importantly the authors did not know whether or not participants were not blinded in this study. This could have had a huge impact on the results since the questionnaires were self-administered.

- **External validity:**

  With such stringent inclusion criteria this study has a very limited external validity. Participants were from Iran and the results can't be applied to populations of North America or other parts of the world. Furthermore they chose young, health and non-overweight participants and likely limit the amount of patients this study could be applied to.

  Another important factor is that patients had numerous symptoms of PMS. While baseline severity was mild to moderate, the results of this study could be argued that the participants studied had more severe forms of PMS. This could mean that the treatment was made to look better than it would in clinical or real world practice.

  One of the major limitations of natural health products is standardization and this study only suggests the effectiveness of the Gingko biloba product made in Iran and not about another product made by a different manufacturer. The product was different used in the previous study used by Tamborini and Taurelle.

Overall the study had promising results that were statistically significant compared to placebo. Main criticisms include stringent inclusion criterion which makes the external validity very limited.

Primary literature: Article #2

Tamborini A, and Taurelle R. ***Value of standardized Gingko biloba extract (EGb 761) in the management of premenstrual syndrome.*** **Revue francaise de gynecologie et d'obstretqieu. 88 (7-9): 1993 pp 447-457.**

Study Objective

To determine the efficacy of standardized Gingko Bilbo extract (EGb 761) in treating congestive symptoms of premenstrual syndrome after the extract demonstrated efficacy in treating idiopathic cyclic edema.

Methods

- **Design:**
  - Placebo controlled multicentric double blind clinical trial.
  - Data collection: Cycle self-assessment done by potential participants and evaluated by the clinician before enrollment for two menstrual cycles (to properly diagnose PMS). Collecting data for two months after the beginning of treatment. Patients assessed severity of symptoms with a daily data rating scale.
  - Severity of symptoms were rated as 0 if not felt, 1 if mild, 2 for moderate and 4 for severe total score was added up for all symptoms.
  - Statistical tests: Confirmatory analysis with the Mantel-Haenszel test between the two treatment groups.
- **Allocation:**
  - Inclusion Criteria: Women aged 18 to 45 and complaining of PMS for at least 3 months. Symptoms had to be present for at least 7 days per cycle with a post-menstrual free interval of at least 10 days. Symptoms had to be one of three things: breast pain, swelling of the abdomen and pelvis or edema in the extremities such as the face, fingers and ankles. Patients with neuropsychiatric disorders (mainly anxiety and irritability) were included and if they were on oral contraceptives in the absence of symptom changes for at least 3 months.
  - Exclusion criteria: Women with menorrhagia, hormone-dependent cancers with concomitant treatment with either hormone therapy or chemotherapy. Women with endocrine disorders, chronic progressive diseases or mental disorders.

Patients on antihypertensives, aldosterone antagonists, anti-prolactin medications or diuretics were excluded from this study as well.

- **Blinding:** Not given.
- **Follow up period:** Followed patients after 2 cycles.
- **Setting:** Participants were under the care of 43 gynecologists.
- **Participants:** Group of 165 women aged 18 to 45 with congestive PMS symptoms for 3 cycles lasting at least 7 days per cycle. Average age of the women was around 38 years old with a few women (16/165) not having given birth before. Average weight is around 57.5 kg. Many women suffered from weight gain (~80%), and discomfort in each cycle (~95%) with only a fraction feeling intense discomfort (~25%). In terms of symptoms, 67 had breast tenderness, while 58 had swelling of the abdomen or pelvic region and 31 had edema in their extremities. 27% of patients had taken oral contraceptives and two-thirds of the patients had already been treated for PMS.
- **Intervention:** EGb 761 160 mg per day from 16^{th} day of cycle until the 5^{th} day of the next cycle for 2 cycles. Each patient could double the dose after the first cycle of treatment if they deemed the treatment inadequate.
- **Outcomes:** Efficacy of Egb 761 on congestive symptoms of PMS such as breast tenderness, swelling of the abdomen and pelvic regions and edema of extremities.
- **Patient Follow Up**: None.

Main Results

165 participants were enrolled for this study: 77 for the placebo arm and 88 for the treatment arm. Of the 165, 143 complete observations were collected at the end of study. 11 in each group left the study with 12 for undocumented reasons, 4 refused further testing, 3 discontinued the medication and 3 left the study due to side effects. EGb1 was more effective in improving tender/painful breasts ($p=0.03$) and breast pain on palpitation ($p=0.01$) when compared to placebo. There were 44 patients with mastalgia before taking EGb 761 and this reduced to 15 while there were 31 with placebo with mastalgia and this reduced to 14. Severity of symptoms decreased significantly by 6 points in the treatment arm compared to 2.7 points in the placebo group. When patients were analyzed to have a severity score of greater than 10, the treatment reduced severity by 9.6 points while placebo decreased it by 6 points. The decrease in tight/sore breasts was seen only in patients were the initial severity score was greater than 10 as there was no significant difference found all in patients ($p=0.07$). Participant's weight remained stable in the placebo group and slightly decreased in the

treatment arm. There was a significant difference in the severity of headaches experienced by those taking EGb 761 within the 1st cycle but after the second cycle it became non-significant compared to placebo.

Evaluation of neuropsychiatric disorders was not the objective of the study but found that irritability (average decrease of 3 points of severity), anxiety (average decrease of 2.9 points of severity) and depression were all improved by EGb 761.

48 patients (23 in 761 EGb group and 25 in the placebo group) chose to double the dose for the second cycle of treatment. All these patients had a non-significant improvement in symptoms. The baseline differences between the two groups was large and was at the limit of significance ($p = 0.07$). 86% of patients found EGb 761 to be good or very good by the patients.

Conclusions

The authors concluded that EGb 761 was effective for treating the congestive symptoms of PMS specifically breast symptoms. EGb 761 also improved neuropsychological symptoms. EGb 761 had a low dropout rate due to side effects and patients found it very acceptable.

Comments/Critical appraisal:

First and foremost, the article was only found in French it is possible any information can be lost in translation or misinterpreted. Graphs were poorly illustrated as both the placebo and treatment arms had an identical symbol under their legends.

- Internal validity: While non-significant, there was a large difference between the placebo and treatment arms. The treatment arm had 11 more participants which is roughly a 15% difference. The authors suggested that differences between groups was at the limit with a $p=0.07$ but there were many differences between groups making it the placebo group and treatment group poor comparators. For example, the EGb 761 treatment tended to have higher scores of severity such as breast pain and hence was made to look better than placebo when that may not necessarily be the case if there was a more comparable group. Authors noted that they selected participants based on a homogenous group and this suggests there was a likelihood of bias when allocating the participants for this trial. With no details on how blinding occurred or how each participant was chosen for each group, suggests there's a room for bias as the groups were very different. Therefore in terms of internal validity, there are enough issues with this study's methodology to accept the findings of this trial.

- External validity: With the internal validity of this trial in question, there is not much external validity to this trial. If the internal validity was excellent, there are many patients that this study could be applied to. The only limitations are the specific extract of Gingko Biloba used and the population in France is different from other areas.

There many methodological issues with this study with the placebo group not being very equal to the treatment arm and hence likely limits the validity of this study's results.

Secondary literature: Article #3 (systematic review)

Whelan AM, Jurgens TM, & Naylor H. *Herbs, Vitamins and Minerals in the Treatment of Premenstrual Syndrome: A Systematic Review.* Can J Clin Pharmacol 16(3):2009: pp e430-e431.

Study objectives

The authors wished to identify herbs, vitamins and minerals advocated for the treatment of PMS or PMDD and to systematically review evidence from RCTs to determine efficacy in reducing symptoms.

Scope

The only studied look at by the authors was the trial done by Tamborini *et al.*

Methods

The authors conducted searches in Clinical Evidence, The Cochrane Library, Embase, IBID, IPA, Mayo clinic, Medscape, MEDLINE Plus, Natural Medicines Comprehensive Database and the internet. The authors performed the search until April 2008 and identified RCTs of herbs, vitamins or minerals used for PMS/PMDD. Inclusion criteria for the literature search included: RCTs, English or French languages, studies with symptoms of PMS or PMDD, therapies containing only one herb, vitamin or mineral (no combination products) and the outcome measures as a change in severity of PMS/PMDD symptoms. Studies were excluded if patient satisfaction was the sole outcome measure or the comparator was not placebo or a recognized therapy. To assess quality of the trial they had a final question to summarize the trial. If they answered "yes" it was considered good quality, "partially" was labelled average quality

and “no” was poor quality. The authors examined the homogeneity of the populations, product content, doses, duration of the trials and outcome measures. They made conclusions for a variety number of products for PMS and PMDD.

Main results

The authors reviewed 62 natural products that claimed to be beneficial in the management of PMS and/or PMDD. The authors identified 29 RCTs meeting the inclusion criteria. In terms of results related specifically to Ginkgo, the authors felt that the dropout rate of 3 people due to adverse effects was vague and reasons were not specified. Concluded that the study by Tamborini *et al.* that it suggested that there was a possible role for Ginkgo in the treatment of mastalgia associated with PMS but needed further studies to confirm these findings. Authors suggested that the study by Tamborini *et al*. was of average quality.

Conclusions

Further study warranted before suggesting a role of Gingko in PMS.

Comments/Critical appraisal

This study did quite an extensive amount of work of all clinical trials for all natural health products. However if there was any criticism was their method of evaluating trials as “good quality”, “average quality” or “poor quality” as it sounded very subjective to the author and did not have a set criteria for suggesting if a study was good or not (i.e. randomization, blinding, or methodology). However, their assessment of Gingko on the RCT by Tamborini *et al*. is reasonable as the methodology was not very strong and if evaluating Gingko on this on trial it is fair to say more studies are needed. Not reviewed was the RCT done by Ozgoli *et al*. which was published after the systematic review was done.

Tertiary literature: Reference # 4(Internet Database)

Casper RF. *Premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD).* Accessed July 11, 2013. From: <http://uptodate.com>

Source description

UpToDate is an evidenced-based, clinical decision support internet resource authored by physicians. The article was last updated February 2, 2013

Summary

The author states that there is no proven benefit of Ginkgo biloba and references the study by Tamborini and Taurelle. The author discourages the use of Ginkgo for PMS.

Comments/Critical Appraisal

Not a fair assessment of the trial done by Tamborini and Taurelle. While the methodology of the study was not of the highest quality, the trial did show benefits. Also did not mention the most recent trial on Ginkgo biloba by Ozgoli *et al.* which was published before the article was updated in 2011.

Tertiary literature: Reference # 5 (Internet source)

Hudson, T. *Ginkgo is Effective for Relief of PMS Symptoms.* Accessed July 2013. From: <http://www.naturalmedicinejournal.com/article_content.asp?edition=1&section=3&article=166>

Source description

The Natural Medicine Journal is both an electronic journal and website focusing on natural products. The article was written by a naturopath on March 1, 2010.

Summary

The author reviews the methodology and results done by Ozgoli *et al.* while providing practice implications of Gingko Biloba in PMS. The author suggests the study confirms the benefits of standardized extract of Ginkgo **B**iloba for the treatment of PMS and suggests that it is one of the better natural agents for the treatment of PMS. The author encourages women and their practitioners to seek PMS formulas that include Ginkgo as part of the formulation with St. John's Wort and Chasteberry.

Comments/Critical Appraisal

While the author does a good job of summarizing the trial done by Ozgoli *et al.* it is does not provide any critical analysis and assumes that the study has both good internal and external validity[1]. The author jumped to the conclusion that Gingko should be asked for and in combinations with other natural products for the treatment of PMS. The combinations are likely not studied together and hence lacking evidence and may not be a reasonable recommendation based on the evidence out there.

Tertiary literature: Reference #6 (Internet Database)

Natural Medicines Comprehensive Database. *Gingko*. Accessed July 12, 2013. From: <http://naturaldatabase.therapeuticresearch.com/nd/Search.aspx?cs=&s=ND&pt=100&id=333&fs=ND&searchid=42013047>

Source description

The Natural Medicines Comprehensive Database is made up of multiple databases which include detailed, evidence-based monographs on individual natural ingredients. This database has roughly 1100 monographs.

Summary

The NMCD suggests that taking Ginkgo leaf extract orally seems to produce significant relief in breast tenderness and neuropsychological symptoms associated with PMS. The NMCD lists Gingko as possibly effective for PMS.

Comments/Critical Appraisal

Possibly effective is a fair rating for Ginkgo for the treatment of PMS. The NMCD defines possibility effective as a product having "some clinical evidence supporting its use for a specific indication; however, the evidence is limited by quantity, quality, or contradictory findings". In this case both the quantity and quality of clinical trials is somewhat lacking to make Ginkgo effective in treating PMS and hence a reasonable conclusion.