HERBS, VITAMINS AND MINERALS IN THE TREATMENT OF PREMENSTRUAL SYNDROME: A SYSTEMATIC REVIEW

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ABSTRACT

Background
As many women experiencing symptoms of premenstrual syndrome (PMS) seek relief from natural products (NP), health care providers should have quality information available to aid women in making evidence-based decisions regarding use of these products.

Objective
To identify herbs, vitamins and minerals advocated for the treatment of PMS and/or PMDD and to systematically review evidence from randomized controlled trials (RCTs) to determine their efficacy in reducing severity of PMS/PMDD symptoms.

Methods
Searches were conducted from inception to April 2008 in Clinical Evidence, The Cochrane Library, Embase, IBID, IPA, Mayoclinic, Medscape, MEDLINE Plus, Natural Medicines Comprehensive Database and the Internet to identify RCTs of herbs, vitamins or minerals advocated for PMS. Bibliographies of articles were also examined. Included studies were published in English or French. Studies were excluded if patient satisfaction was the sole outcome measure or if the comparator was not placebo or recognized therapy.

Results
Sixty-two herbs, vitamins and minerals were identified for which claims of benefit for PMS were made, with RCT evidence found for only 10. Heterogeneity of length of trials, specific products and doses, and outcome measures precluded meta-analysis for any NP. Data supports the use of calcium for PMS, and suggests that chasteberry and vitamin B6 may be effective. Preliminary data shows some benefit with ginkgo, magnesium pyrrolidone, saffron, St. John's Wort, soy and vitamin E. No evidence of benefit with evening primrose oil or magnesium oxide was found.

Conclusion
Only calcium had good quality evidence to support its use in PMS. Further research is needed, using RCTs of adequate length, sufficient sample size, well-characterized products and measuring the effect on severity of individual PMS symptoms.

Key Words*: Premenstrual syndrome, herbs, vitamins, minerals, systematic review*

At least 75% of women will experience symptoms of premenstrual syndrome (PMS) at some point during their reproductive years.[1-3] Symptoms generally vary from mild to slightly bothersome; but for up to 5% of women, symptoms are severe, with a negative impact on quality of life and may meet criteria for premenstrual dysphoric disorder (PMDD).[1,2,4]

Approaches to treatment include lifestyle modifications and over-the-counter (OTC) products, with prescription medications generally reserved for more severe cases of PMS.[4] Conventional medicines, such as OTC and prescription products, do not always provide adequate relief of all symptoms,[4] leading many women to turn to natural product (NPs) such as herbs, vitamins and minerals.

A telephone survey found that up to 80% of women suffering from symptoms of PMS self-medicate with OTC products, including complementary and NPs such as herbs, vitamins and minerals.[5] With the increasing popularity of NPs[5] health care providers must be prepared to answer patient-questions about these products. Health care providers should have quality information available for use in making evidence based decisions about both conventional medicines and NPs. A search of the literature, however, identified only a few review articles that focused on the use of NPs the treatment of PMS – the majority of which were narrative or clinical reviews.[6-11] One review was more rigorous in methodology but included only one small section on management of PMS.[12] There was one review that used systematic review methodology,[13] however, it was published in 2001. In summary, there is no current systematic review examining the use of herbs, vitamins and minerals in the management of PMS.

Thus, the objectives of this review are to identify herbs, vitamins and minerals advocated for the treatment of PMS and/or PMDD and to systematically review evidence from randomized controlled trials (RCTs) to determine their efficacy in reducing severity of premenstrual symptoms.

METHODS

Identification of RCTs

A scan of the literature was conducted to identify herbs, vitamins and minerals advocated for the treatment of PMS and/or PMDD in women. The search included Clinical Evidence (1999-April 2008), the Cochrane Library (1999-April 2008), Mayoclinic (1998-April 2008), Medscape (1994-April 2008), MEDLINE Plus (1966-April 2008), Natural Medicines Comprehensive Database (1995-April 2008), and the Internet, using Google® as a search engine. Key search terms included the following: "premenstrual syndrome," "PMS," "premenstrual dysphoric disorder", "PMDD", "natural health products", "herb", "vitamin", "mineral", "dietary supplement" and "alternative medicine." The search was limited to English and French language references.

Following the identification of specific herbs, vitamins and minerals, they (in combination with "premenstrual syndrome", "PMS", "premenstrual dysphoric disorder", and "PMDD") were entered sequentially as search terms in Pubmed, Embase, International Pharmaceutical Abstracts, the Cochrane Library, Natural Medicines Comprehensive Database, and the International Bibliographic Information on Dietary Supplements (IBIDS) to identify clinical trials supporting their use in PMS/PMDD. When an herb, vitamin or mineral was indexed under more than one name, each name was included in the search. For example, when searching the databases for evidence for chasteberry the following terms were used: "Chasteberry," "Chaste Tree", "Agnus castus," and "Vitex." Searches were limited to randomized controlled trials published in English or French from inception of the database to April 2008. Bibliographies of identified articles were examined for additional articles of interest.

Study Selection

Abstracts of potentially relevant articles were retrieved and screened for relevance. Full articles were retrieved for abstracts deemed to be potentially relevant and then assessed for relevance using a form developed for this purpose.

Inclusion criteria included:

1) Randomized controlled trial;
2) English or French language;
3) Subjects with symptoms of PMS and/or PMDD;
4) Therapies containing only one herb, vitamin, or mineral (i.e. no combination products); and
5) Outcome measure of change in severity of PMS/PMDD symptoms.

Exclusion criteria included:

1) Patient satisfaction survey as sole outcome measure; and
2) Not compared to placebo or recognized therapy.

Two investigators conducted screening and relevance assessments, with discrepancies

resolved by a third investigator. Data was extracted from each article independently by two investigators using a data extraction form developed for this purpose. Details extracted from the articles included study design, study participants (e.g. age, symptoms/diagnosis of PMS/PMDD, use of concomitant medications), interventions (dose, duration, content), outcomes (type of instrument used and definition of clinically relevant outcome), results, adverse effects and general comments (e.g. impact of confounders). The same two investigators critically appraised each study using an assessment instrument developed previously by the investigators that was specific for appraising RCTs of NPs *(manuscript submitted)*. The assessment instrument contained a number of questions about the design of the RCT- to assess the quality of the trial. Questions specific to the identity and content of the natural product being evaluated in the trial were also included. The assessment instrument included a summary question intended to prompt the reviewer to reflect on their answers to the previous questions concerning quality of the trial. This aided the reviewer in reaching a conclusion as to the overall quality of the RCT and in determining if it was of sufficient quality to apply the results to practice. If investigators answered the summary question with a "yes," then the study was rated as "good quality"; if they answered "partially," the study was rated as "average quality" and if they answered "no," the study was rated as "poor quality." The final question in the assessment instrument, "I feel that sufficient detail was provided to allow me to select a specific product comparable to the one used in the study" was used to evaluate whether results of the RCT had broad applicability or were specific to the product tested. To determine if the identified RCTs supported a meta-analysis for each NP, data from the trials for each NP were examined for homogeneity of patient population, product content, doses, duration of trials and outcome measures. Conclusions regarding the efficacy of the herbs, vitamins and minerals for PMS and PMDD were reached through a descriptive analysis of the data.

RESULTS

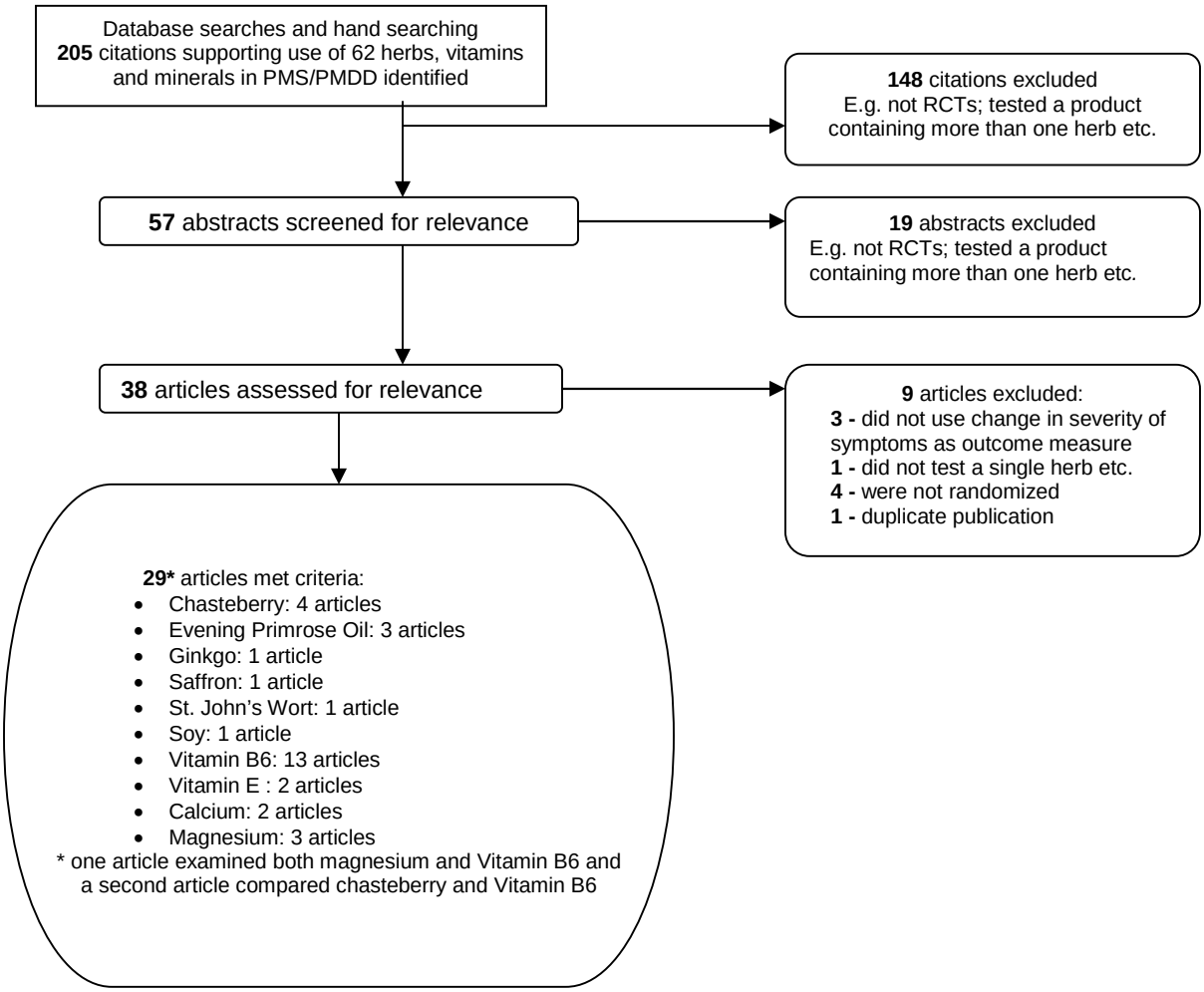
Sixty-two vitamins, minerals and herbs, for which some claims of benefit in the management of PMS and/or PMDD had been made, were identified from the literature scan (Table 1). A search of the literature identified 29 RCTs meeting inclusion criteria for the following 10 herbs, vitamins and minerals: chasteberry, evening primrose oil, ginkgo, saffron, St. John's Wort, soy, vitamin B6, vitamin E, calcium and magnesium (Figure 1).

TABLE 1 Herbs, vitamins and minerals advocated for treatment of premenstrual syndrome/premenstrual dysphoric disorder

1. Alfalfa	23. Garlic	45. Potassium
2. Belladonna	24. Ginger	46. Pycnogenol
3. Birch Leaf	25. **Ginkgo**	47. Raspberry Leaf
4. Black Cohosh	26. Goldenseal	48. Red Clover
5. Black Haw	27. Hawthorn	49. Rosemary
6. Blessed Thistle	28. Hops	**50. Saffron**
7. Blue Cohosh	29. Kava	51. Sarsaparilla Root
8. Borage Oil	30. Lavender	52. Skull Cap
9. Burdock	31. Lemon Balm	53. **Soy**
10. **Calcium***	32. Licorice Root	54. Squaw Vine
11. Chamomile	33. Lilium	55. Stinging Nettle
12. Chaparral	34. **Magnesium**	56. **St. John's Wort**
13. **Chasteberry**	35. Manganese	57. Valerian
14. Copper	36. Milk Thistle	58. **Vitamin B6**
15. Corn Silk	37. Motherwort	59. **Vitamin E**
16. Cramp Bark	38. Niacin	60. Wild Yam
17. Dandelion	39. Pantothenic Acid	61. Yarrow
18. Dong Quai	40. Parsley	62. Zinc
19. **Evening Primrose Oil**	41. Pennyroyal	
20. False Unicorn	42. Peony	
21. Fennel	43. Peppermint	
22. Flaxseed Oil	44. Pomegranate	

* Items in bold are herbs, vitamins or minerals for which randomized controlled trials that met inclusion criteria were found.

FIG. 1 Results of literature search and relevance



An examination of the RCTs for each individual herb, vitamin and mineral, did not support conducting a meta-analysis for each herb, vitamin and mineral, due to the relatively few RCTs, and obvious heterogeneity in trial design, such as variation in length of the trials, product content and doses and outcome measures. Details of the RCTs are provided in Tables 2[14-24], 3[25-38] and 4.[39-42] In general, the RCTs were of relatively poor quality in terms of the likelihood of producing unbiased results. Results obtained from the use of the assessment instrument showed that out of the 29 RCTs that were appraised: 21% described the process of randomization, 7% described allocation concealment and 50% provided reasons for participants dropping out of the study. Approximately 62% of the RCTs provided sufficient detail to allow selection of a product comparable to the NP used in the study; however, only 40% of RCTs included in the review were considered to be of sufficient overall quality to warrant applying the results to practice.

Chasteberry

Three RCTs evaluating the efficacy of chasteberry in reducing symptoms of PMS and one RCT analyzing chasteberry's efficacy in treating PMDD met the inclusion criteria for this review (Table 2).[14-17] The RCT conducted by Schellenberg et al compared a chasteberry preparation to placebo and found the chasteberry preparation to be superior to placebo in reducing the symptoms of PMS, such as irritability, mood alteration, anger, breast fullness and headache.[16] In contrast, another trial, comparing a different preparation of chasteberry to placebo found no statistically

significant difference in reduction of symptoms between participants treated with chasteberry and those treated with placebo, with the exception of one symptom: the feeling of "jitteriness or restlessness."[14] The RCT published by Lauritzen et al compared a commercial preparation of chasteberry to vitamin B6 and found both to be effective.[15] The fourth study compared the effects of chasteberry to fluoxetine in patients with PMDD and found that both chasteberry and fluoxetine statistically significantly improved symptoms, as measured by several tools.[17] Chasteberry appeared to be more effective at relieving the physical symptoms of PMDD while the comparator, fluoxetine, relieved the psychological symptoms.

The three studies that produced effects supporting the use of chasteberry were felt to be of sufficient quality to apply results to practice.[15-17] Three of the four studies reported occurrence of mild adverse events.

Evening Primrose Oil

Three RCTs evaluating the efficacy of evening primrose oil (EPO) met inclusion criteria (Table 2).[18-20] No significant reduction in total PMS symptoms was detected in any of the three studies, even with the wide range of doses used which varied from 0.27 g[18] and 0.36 g[19] to 6.48 g[20] of γ-linolenic acid per day. Two of the three RCTs were judged to be of sufficient quality to apply results to practice.[19,20] There was, however, a statistically greater reduction in depression symptoms with EPO as compared to placebo in one trial, although this trial was judged to be of lesser quality.[18] Only one study mentioned adverse effects, reporting perceived weight gain and difficulty swallowing.[20] However, it was not clear from the report of the RCT if these symptoms occurred in the treatment or placebo group.

Ginkgo

One study, using *Ginkgo biloba* as an intervention, was included in this review (Table 2).[21] A standard preparation of *G biloba* (EGb 761) was administered in an initial dose of 160 mg/day, with subjects given the option of doubling the dose if symptoms were not relieved after the first cycle of treatment. Subjects in both the placebo group (n=25) and the ginkgo group (n=23) opted to double their medication dose during the second treatment cycle. Treatment with ginkgo (160-320 mg/day) was found to significantly improve symptoms of mastodynia (p=0.03) and breast pain upon palpation (p=0.01). Although three participants withdrew due to adverse events, details regarding these effects and the causative agent were vague.

Saffron

One RCT was identified that evaluated the efficacy of an ethanolic extract of the stigmas of *Crocus sativa* in relieving symptoms of PMS (Table 2).[22] This study showed promising results with the saffron extract (30 mg/day) producing a statistically significant effect on both the total premenstrual daily symptoms and the Hamilton Depression Rating Scale as compared to placebo. Although several participants reported adverse effects with the saffron, all were mild and none resulted in withdrawal from the trial. The trial was well reported and of sufficient quality to apply the results to practice

St. John's Wort

One study comparing the efficacy of St. John's Wort (SJW) to placebo in the treatment of symptoms of PMS met the inclusion criteria (Table 2).[23] Anxiety-related symptoms were improved when SJW was administered at a daily dose of 600mg of a standardized extract. However, the improvement in symptoms in the treatment group was not significantly different from the improvement seen in the placebo group.[23] Although no severe adverse events were reported, five participants from the SJW group and one from placebo withdrew due to adverse events.

Soy

One RCT, using soy protein, containing isoflavones, as an intervention, was included in this review (Table 2).[24] Although the group taking soy protein experienced a reduction in overall symptoms compared to baseline, the placebo group also reported a reduction and the difference in reduction between the two groups was not significant. Cramps (p=0.025) and swelling (p=0.01) were significantly improved when the subjects used soy protein compared to placebo; however, reduction from baseline was not significant.

TABLE 2 Characteristics of Studies Evaluating Herbs for Premenstrual Syndrome/Premenstrual Dysphoric Disorder

Study/Design	Participants	Interventions	Outcomes	Results	Adverse Drug Reactions (ADR)
Chasteberry (Vitex agnus castus)					
Turner S, et al[14] 3 months, DB, PC	600 women with diagnosed PMS enrolled; 217 with complete data for analysis	Chasteberry 1800 mg/day for 3 months (n=105) Placebo – soya based (n=112)	Adapted version of the Moos Menstrual Distress Questionnaire	Both groups: improved symptoms but no difference between groups except with: -Chasteberry reduced "feeling jittery or restless" compared to placebo (p=0.05) -Trend to improvement with water retention symptoms with Chasteberry compared to placebo (p=0.09)	Not mentioned in study
Lauritzen CH, et al[15] 3 months, DB	175 women with premenstrual tension syndrome enrolled; 127 with complete data for analysis	Chasteberry group: One Agnolyt® capsule daily (containing dried fruit extract of chaste tree fruit [9.58-11,5:1] 3.5-4.2 mg per capsule) for 3 months (n=61) Vit B6 group: placebo caps on days 1-15; 200mg Vit B6 on days 16-35 of the menstrual cycle for 3 months (n=66) All capsules identical in size, color, shape and taste	PMTS scale and CGI scale	*PMTS*: -Mean scores in both groups were significantly lower than baseline (p=0.0377; 95% CI = -6.4261 to -0.1670) -Reduction in PMTS score points were ≥ 47% for both chasteberry and Vit B6 *CGI:* - 77.1% of chasteberry patients showed an improvement versus 60.6% of Vit B6 patients (no statistical tests reported)	9 participants reported an ADR: Agnolyte® (n): gastroenteritis (1); nausea (1); rash (2); acneiform facial inflammation (1) Vit B6 (n): feeling of lump in throat (1); abdominal discomfort (1); recurrence of ulcerative colitis (1); persistent bleeding (1)
Schellenberg R, et al[16] 3 months, DB, PC	178 women with diagnosed PMS enrolled; 170 included in intention-to-treat analysis	Chasteberry group: one 20mg tablet (containing Agnus castus fruit extract ZE 440: 60% ethanol m/m, extract ratio 6-12:1; standardized for casticin) per day for three months (n=86) Placebo (identical in size, color, taste and smell) (n=84)	VAS used to rate severity of 6 PMS symptoms	Chasteberry different than placebo in reducing irritability, mood alteration, anger, breast fullness (p<0.001), and headache (p<0.002) -52% of patients in Chasteberry group had ≥50% reduction in self-assessed symptoms from baseline compared to 24% in placebo group	7 participants reported ADRs; 4 in the Chasteberry group (acne, multiple abscesses, intermenstrual bleeding, urticaria) and 3 in the placebo group (acne, early menstrual period, gastric upset)
Atmaca M, et al[17] 4 months, DB	42 women who met DSM-IV criteria for PMDD enrolled; 38 included in	Chasteberry group: 20-40 mg/day for 2 months (n=19)	DSR, HAM-D, and CGI	Both Chasteberry and fluoxetine improved HAM-D, CGI and DSR scores (p>0.05)	Of the 36 ADRs reported, the most common were:

	analysis	Fluoxetine group: 20-40 mg/day for two months (n=19)		-Chasteberry group: 5 symptoms decreased by ≥ 50%: irritability, breast tenderness, swelling, food cravings and cramps (largely physical symptoms) -Fluoxetine group: 7 symptoms decreased by ≥50%: depression, irritability, insomnia, nervous tension, feeling out of control, breast tenderness and aches (largely psychological symptoms)	Chasteberry(n): Nausea (5); headache (4) Fluoxetine (n): Nausea (6); headache (4); insomnia (3)
Evening Primrose Oil					
Puolakka J, et al[18] 4 months, PC, crossover trial	30 women with PMS	Evening primrose oil: supplied as Efamol® capsules 3 g (2.16 g cis-linoleic acid and 0.27 g γ-linolenic acid) daily starting on day 15 of the cycle until the onset of menstruation. -1/2 participants started on EPO; the other half with placebo	Rating of severity of 19 PMS symptoms	-Efamol® and placebo both reduced total PMS symptom scores ($p<0.001$) -Depression was the only individual symptom that improved more with Efamol® than placebo ($p<0.05$)	Not mentioned in study
Khoo SK, et al[19] 6 months, DB, PC, crossover trial	38 women with PMS symptoms	Evening primrose oil: supplied as Efamol® capsules containing 9% γ linolenic acid (45 mg/capsule), 72% linoleic acid and 12% oleic acid. Dose: 8 capsules/day, containing 0.36 g linolenic acid Placebo capsules identical in appearance	Rating of severity of 10 PMS symptoms	No significant difference between treatment and placebo groups in reducing total PMS symptom scores ($p=0.982$)	Not mentioned in study
Collins A, et al[20] 10 months, DB, PC, crossover trial	27 women with diagnosed PMS	Evening primrose oil: supplied as Efamol® tablets each containing 4.32 g linoleic acid and 0.54 g γ-linoleic acid Dose: 12 capsules/day, containing 6.48 g γ-linoleic acid	VAS used daily to rate severity of 4 physical and 12 psychological symptoms	No significant effects could be attributed to Efamol®. The greater the length of time a woman was enrolled in the trial the better they felt regardless of treatment with Efamol® or placebo ($p<0.05$)	Perceived weight gain; difficulty swallowing tablets (did not specify treatment or placebo)

		Placebo: four 500mg paraffin oil tablets TID			
Ginkgo					
Tamborini A, et al[21] 3 months, DB, PC	165 women with diagnosed PMS enrolled; 143 with complete data for analysis.	*Ginkgo biloba* extract EGb 761: 160 mg/day from day 16 of the menstrual cycle until day 5 of the next cycle for 2 months (n=77) Participants were given the option to double the dose to 320 mg/day if symptoms had not improved after 1 month. Placebo (n=66)	Daily PMS symptom diary	Ginkgo: Decrease in mastodynia (p=0.03), and breast pain upon palpation (p=0.01) Reduced symptoms of anxiety/ irritability and depression from baseline (not significant)	3 participants withdrew due to adverse effects: 1 with stomach upset; details not available for the other 2 (treatment group not specified)
Saffron					
Agha-Hosseini M, et al[22] 4 months, DB, PC	50 women diagnosed with PMS enrolled; 47 with complete data for analysis	Saffron (dried extract of petal) 15mg BID (n=24) Placebo capsule BID (n=23)	DSR and HAM-D	Total Premenstrual Daily Symptoms: Saffron group had 76% response rate (defined by authors as 50% reduction in severity of symptoms) compared to 8% in placebo group (p<0.0001) HAM-D Scale: Saffron group had 60% response rate (defined by authors as a 50% reduction in severity of symptoms) compared to 4% in placebo group (p<0.0001) Effects were not significant until cycle 3 and 4	Saffron (n): ↓ appetite (3) ↑ appetite (4) Sedation (1) Nausea (2) Headache (3) Hypomania (2) Placebo (n): ↓ appetite (2) ↑ appetite (2) Sedation (2) Nausea (2) Headache (2) Hypomania (2)
St. John's Wort (SJW)					
Hicks S, et al[23] 3 months, DB, PC	169 women with diagnosed PMS enrolled; 125 with complete data for analysis.	SJW; 300 mg extract/tablet, (standardized to 900 mcg hypericin/tablet) BID (n=61) Placebo tablets BID (n=64) All tablets identical in appearance	VAS used to rate severity of 25 symptoms (based on Abraham's MSQ) Anxiety related symptoms chosen as primary outcome measure	Both groups had significantly ($p \leq 0.007$) lower premenstrual symptoms scores but no difference between groups Anxiety-related symptoms improved the most (by 30.5% with placebo, and 34.3% with SJW) but no difference between groups	Adverse events leading to withdrawal from trial: *SJW (n):* Nausea, diarrhea, dry mouth (1); tiredness, forgetfulness, woolly head (1); headache (1); worsening of premenstrual symptoms

					(1); bloating, breast tenderness, rashes (1). *Placebo (n):* Irritable bowel-like symptoms (1). Other adverse events not leading to withdrawal from trial: *SJW (n):* Nausea (8); diarrhea (6); flatulence (5); headache (13); skin rash (3); dizziness/ confusion (4); tiredness/ sedation (5). *Placebo (n):* Nausea (5); diarrhea (3); flatulence (3); headache (16); skin rash (2); dizziness/ confusion (5); tiredness/ sedation (8)
Soy					
Bryant M, et al[24] 7 months, DB, PC, crossover trial	41 women with diagnosed PMS; 23 completed 7 months	30.5 g isolated soy protein/day (equivalent to 68 mg/d of isoflavones as aglycone equivalents) provided as powder (to be made into a drink or sprinkled over food) and a snack bar Placebo products were identical in appearance and taste	DSR	Total PMS symptoms and physical symptoms were reduced compared to baseline with both the soy protein as well as placebo, however the difference in reduction between the two groups was not significant Significant difference in cramps (p=0.025) and swelling (p=0.017) from baseline with soy compared to placebo; however reduction from baseline not significant	High withdrawal rate prior to commencement of treatment due to bad taste of product No adverse events mentioned in the study

CGI=global impression scale; DB= double-blind; DSR= daily symptom report; HAM-D=Hamilton depression rating scale; Moos Menstrual Distress Questionnaire = list of 47 symptoms rate on a severity scale of 1-6 with 1 being no experience of the symptom; MSQ= Menstrual symptomatology questionnaire by Abraham (19 symptoms divided into e subgroups: PMT-A: nervous tension, mood wings,irritability, anxiety; PMT-C: headache, cravings for sweets, increase appetite, heart pounding, fatigue, dizziness; PMT-D: depression, forgetfulness, crying easily, confusion and insomnia; PMT-H: sensation of weight gain, swelling of extremities, breast tenderness, abdominal bloating);PC= Placebo controlled; PMDD = Premenstrual dysphoric disorder; PMS=Premenstrual syndrome; PMTS Scale = premenstrual tension syndrome scale: rating of symptoms on a scale (modified from Moos Menstrual Distress Questionnaire)VAS= Visual analogue scale

Vitamin B6

Thirteen studies using vitamin B6 met the inclusion criteria for this review (Table 3).[15, 25-36] Five studies reported no benefit for vitamin B6 in reducing PMS symptoms.[25,30,31,34,35] One study reported an overall improvement in participants' condition, as assessed by the investigators; however there was no improvement in self-reported symptoms.[29] This study also allowed the use of analgesics, which may have influenced the outcome. Women who took analgesics were more likely to withdraw early from the study and were significantly less likely to benefit from the Vitamin B6 as compared to women who take other types of concurrent medication or none at all. Seven studies reported some benefit with taking vitamin B6.[15, 26-28,32,33,36] One of these studies was an N of 1 trial, making it difficult to extrapolate the findings to a larger population.[27] The doses used in the six remaining positive trials were examined. Three [28,33,36] used doses ≤ 100mg, two[15,32] used a dose between 100 and 200mg and one[26] used a dose of 500mg, with four of the trials using daily dosing.[26,32,33,36] There did not appear to be an association between dose and response. Four of the six positive trials reported improvement in symptoms related to mood,[28,32,33,36] while two[15,26] reported an overall improvement in scores but did not provide details of specific symptoms. Despite this improvement of mood symptoms, one author[32] cautioned that vitamin B6 may not be appropriate therapy as women still complained of depression and anxiety while on the treatment.

Three[26,32,36] of the six positive trials did not mention adverse events in their reports. It is unknown if this was because women did not report any or if adverse events were not monitored as part of the studies. In two studies,[28,33] the authors state that no adverse events were reported by participants. In the study by Lauritzen et al, four adverse events were reported in the Vitamin B6 group. Of the six positive studies, only one[15] was felt to be of sufficient quality to apply results to practice, while four[15,26,28,33] provided sufficient detail to select a similar product.

Vitamin E

Two studies comparing vitamin E [37,38] to placebo for two to three months were included in the review (Table 3). Study outcomes of each RCT were measured using a PMS questionnaire that grouped the symptoms into four categories called PMT-A, PMT-C, PMT-D and PMT-H. One RCT reported a statistically significant improvement in PMT-C (headache, craving for sweets, increased appetite, heart pounding, fatigue, dizziness, fainting) and PMT-D (depression, forgetfulness, crying, confusion, insomnia) symptoms with vitamin E 150-600 IU/day.[37] The second study reported a non-significant reduction in the same symptoms.[38] One study found that lower doses of vitamin E (150-300 IU/day) taken for two months produced significant improvement in PMT-A symptoms (nervous tension, mood swings, irritability, anxiety),[37] while 600 IU of vitamin E/day was not significantly different from placebo. Again, the second study found similar but non-significant results. Vitamin E was not effective, in either study, at improving PMT-H symptoms (weight gain, swelling of extremities, breast tenderness, abdominal bloating). No adverse drug events were reported in either study by participants taking vitamin E.

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TABLE 3 Characteristics of Studies Evaluating Vitamins for Premenstrual Syndrome

Study/Design	Participants	Interventions	Outcomes	Results	Adverse Drug Reactions (ADRs)
Vitamin B6 (Vit B6)					
Stokes J, et al[25] 8-12 months, DB, PC	13 women with premenstrual tension-depression; each women served as her own control. -Order of Vit B6 and placebo were random	Vit B6 50 mg/day (or identical placebo) for 18 days during the premenstrual and beginning of menstrual phase.	Moos menstrual distress questionnaire	9 subjects reported improvement in symptoms: - 5 thought to be placebo response - 4 improved with Vit B6, but only one showed a significant improvement (p=0.032) 3 subjects: no improvement 1 subject experienced worsening symptoms while taking Vit B6 (p=0.006)	Not mentioned in study
Abraham GE, et al[26] 6 months, DB, PC, crossover	25 women with diagnosed PMS symptoms	Vit B6 (or identical placebo) 500 mg/day in sustained release form for 3 months	Abraham's MSQ	Significant difference in mean total daily MSQ scores with Vit B6 versus placebo in 20 subjects (p<0.001) and one subject (p<0.05)	Not mentioned in study
Mattes J, et al[27] 8 months, DB, PC, crossover	1 woman with premenstrual depression	Vit B6 (or placebo) 50 mg/day for 10 days prior to expected onset of menses	Self-reported change in premenstrual depression	Subject reported reduced premenstrual depression and irritability when receiving Vit B6	Not mentioned in study
Barr W, et al[28] 4 months, DB, PC, crossover	48 women with symptoms of PMS	Vit B6 (or identical placebo) 100 mg/day from day 10 of one cycle to day 3 of the next for 2 months	Effect ("improvement", "no effect" or "felt worse") on 9 symptoms (depression, irritability, tiredness, swollen breasts, swollen abdomen, swollen fingers/ankles, headache, stomach ache) recorded	Significant difference in response with Vit B6 versus placebo (p<0.001): -Vit B6: 30 subjects reported positive response; 6 reported a negative response -Placebo: 10 subjects reported positive response; 20 reported a negative response	None reported by participants
Williams MJ, et al[29] 3 months, DB, PC	617 women with diagnosed PMS; 434 with complete data for analysis	-Vit B6100 mg/day initially. Subjects could decrease dose to 50 mg/day, or increase to 200 mg/day during the	Diary card for rating 11 symptoms as present or absent Final assessment: Investigator rated change in	Diary: No significant improvement in individual symptoms. Final assessment: 168 (82%)of patients taking Vit B6 improved, compared to 162 (70%) patients taking placebo	11 subjects taking Vit B6, and 8 subjects taking placebo withdrew due to adverse events (specifics not provided)

		three months of treatment. (n=204) -Matching placebo (n=230)	patient's condition	(p<0.02)	
Hagen I, et al[30] 4 months, DB, PC, crossover	42 women with symptoms of PMS enrolled; 34 with complete data for analysis 20 subjects randomized to receive Vit B6 first; 14 subjects randomized to receive placebo first.	Vit B6 (or placebo) 100 mg/day for 2 months	VAS used to rate severity of global symptoms Rated severity of 6 individual symptoms	Vit B6 no better than placebo in reducing symptoms of PMS. Substantial period effect, subjects preferred second treatment received (regardless of what treatment they had received first)	Vit B6: Nausea (n=5) Placebo: Nausea (n=1)
Smallwood J, et al[31] 4 months, DB, PC, crossover	42 women with severe mastalgia not due to cancer occurring in premenstrual half of cycle	Group A (n=22) placebo x 2 months switched to Vit B6 100mg BID x 2months Group B (n=20) Vit B6 100mg BID x2 months switched to placebo x 2months	Assessed monthly by one clinician Subjective responses measured by linear analogue scale, daily breast pain and tenderness chart and paracetamol tablet requirements	No significant difference between treatment groups, trend towards decreased breast tenderness with Vit B6.	None reported by participants
Kendall KE, et al[32] 3 months, DB, PC	74 women with symptoms of PMS enrolled; 55 with complete data for analysis.	Vit B6 150 mg/day for 2 months (n=29) Matching placebo (n=26)	Moos menstrual distress questionnaire	Vit B6 had a statistically significant effect on all symptom categories except "arousal" Participants still reported PMS symptoms of a substantial degree including depression and anxiety	Not mentioned in study
Doll H, et al[33] 7 months, DB, PC, crossover	63 women with symptoms of PMS enrolled; 37 with complete data for analysis.	Vit B6 (or placebo) 50 mg/day for 3 months	Daily rating of severity of 3 groups of PMS symptoms: emotional, somatic and menstrual	Statistically significant difference in emotional symptoms (depression, irritability, tiredness) scores (p<0.05) with Vit B6.	None reported by participants
Lauritzen CH, et al[15] 3 months, DB	175 women with premenstrual tension syndrome enrolled;	Chasteberry group: One Agnolyt® capsule daily	PMTS scale and CGI scale	*PMTS*: -Mean scores in both groups were significantly lower than baseline	9 participants reported an ADR: Agnolyte® (n): gastroenteritis (1); nausea (1); rash (2); acneiform facial

	127 included in intention-to-treat analysis	(containing dried fruit extract of chaste tree fruit [9.58-11.5:1] 3.5-4.2 mg per capsule) for 3 months (n=61) Vit B6 group: placebo caps on days 1-15; 200mg Vit B6 on days 16-35 of the menstrual cycle for 3 months (n=66) *all capsules identical in size, color, shape and taste		(p=0.0377; 95% CI = -6.4261 to -0.1670) -Reduction in PMTS score points were ≥ 47% for both chasteberry and Vit B6 *CGI:* - 77.1% of chasteberry patients showed an improvement versus 60.6% of Vit B6 patients (no statistical tests reported)	inflammation (1) Vit B6 (n): feeling of lump in throat (1); abdominal discomfort (1); recurrence of ulcerative colitis (1); persistent bleeding (1)
Diegoli MSC, et al[34] 8 months, DB, PC	120 women with diagnosed PMS	Vit B6 300 mg/day from day 15 to the last day of menstruation for 3 months (n=30) Alprazolam 0.75 mg/day as per pyridoxine (n=30) Fluoxetine 10 mg/day for 3 months (n=30) Propanolol 20 mg/day, increasing to 40 mg/day during menstruation, for 3 months (n=30)	Rating of intensity of PMS symptoms (based on Abraham's MSQ)	Placebo was more successful (not significant) than Vit B6 in reducing premenstrual symptom scores Vit B6 mainly reduced tachycardia, insomnia, acne and nausea	Not mentioned in study
De Souza MC, et al[35] 5 months, DB, PC, crossover	58 women with symptoms of PMS enrolled; 37 with complete data for analysis	Vit B6 50 mg/day for 1 cycle Magnesium 200 mg/day for 1 cycle Vit B6 50 mg/day + Magnesium	Daily rating of severity of 30 PMS symptoms	-No overall difference between individual treatments -Significant difference in anxiety-related symptoms (p=0.040) and craving (p=0.056) with Mg + Vit B6	Participants not asked about adverse events None reported spontaneously

		200 mg/day for 1 cycle Placebo			
Kashanian M, et al[36] 5 months, DB, PC	160 women with diagnosed PMS enrolled; 94 with complete data for analysis.	Vit B6 80 mg/day (n=46) Matching placebo (n=48)	Daily recording of 17 symptoms listed in the American Psychiatric Association questionnaire	Significant differences in psychiatric symptom scores and total PMS scores were seen in both treatment groups, but reductions were significantly greater in the Vit b6 group ($p<0.05$)	Not mentioned in study
Vitamin E					
London RS, et al[37] 2 wks lead-in, 2 months treatment, DB, PC	75 women with diagnosed benign breast disease and symptoms of PMS.	dl-α-tocopherol 150 (n=18), 300 (n=19), or 600 (n=19) IU/day Placebo (n=19) All treatment in identical capsules	Abraham's MSQ	Improvement of PMT-A symptoms with vitamin E 150 and 300 IU, but not 600 IU ($p<0.05$) compared to placebo Improvement in PMT-C ($p<0.03$) and PMT-D ($p<0.01$) symptoms with vitamin E 150-600 IU compared to placebo Vitamin E did not significantly improve PMT-H symptoms ($p>0.05$).	None reported by participants
London RS, et al[38] 3 months, DB, PC	46 women with PMS enrolled; 41 with complete data for analysis.	d-α-tocopherol 400 IU/day (n=22) Placebo (n=19) All treatment in identical capsules	PMS questionnaire combining questions from Abraham MSQ and Steiner	MSQ: Non-significant decrease in PMT-A ($p<0.058$), PMT-C ($p<0.066$), and PMT-D ($p<0.085$) symptom scores Steiner: Vit E significantly reduced irritability, tension, dysphoria, mental-cognition, motor coordination, and other physical symptoms	Placebo (n=1): headache, chest pain, anxiety and paranoid ideation.

CGI=global impression scale; DB= double-blind; Moos Menstrual Distress Questionnaire = list of 47 symptoms rate on a severity scale of 1-6 with 1 being no experience of the symptom; MSQ= Menstrual symptomatology questionnaire by Abraham (19 symptoms divided into e subgroups: PMT-A: nervous tension, mood swings, irritability, anxiety; PMT-C: headache, cravings for sweets, increase appetite, heart pounding, fatigue, dizziness; PMT-D: depression, forgetfulness, crying easily, confusion and insomnia; PMT-H: sensation of weight gain, swelling of extremities, breast tenderness, abdominal bloating); PC= Placebo controlled; PMS=Premenstrual syndrome; PMTS Scale = premenstrual tension syndrome scale: rating of symptoms on a scale (modified from Moos Menstrual Distress Questionnaire);Steiner symptoms: irritability, tension, physical symptoms, efficiency, dysphoria, mental-cognitive, motor coordination, social impairment, eating habits, sexual drive and activity, other physical symptoms; VAS= Visual analogue scale

Calcium

Two RCTs, both using calcium carbonate for three months, met the inclusion criteria for this review (Table 4).[39,40] In the 1989 study by Thys-Jacob[39] calcium was found to be statistically significantly more effective than placebo in reducing PMS symptoms in the categories of Factor 1 (nervousness, irritability, crying, mood swings, depression, violent tendencies), Factor 2 (fatigue, abdominal bloating, headache, breast tenderness) and Factor 4 (abdominal cramps, back pain). However, this was a relatively small (n=33) study of mostly black or Hispanic health care workers from a single hospital in northeastern United States. The authors conducted a second study in 12 health centers located in both northern and southern regions of the United States enrolling a larger sample of women (n=466) from variety of ethnic backgrounds.[40] Similar positive results were found. Fifty-five percent of the participants in the calcium group had a greater than 50% improvement in global symptoms compared to 36% of the women in the placebo group.[40]

Calcium was statistically significantly more effective than placebo in reducing PMS symptoms in all four of the symptom categories:

- Factor 1 (negative affect): mood swings, depression, tension, anxiety, anger, crying spells;
- Factor 2 (water retention): swelling of extremities, tenderness of breasts, abdominal bloating, headache, fatigue;
- Factor 3 (food cravings): increased or decreased appetite, cravings for sweets or salt; and
- Factor 4 (pain): lower abdominal cramping, generalized aches and pains, low backache.

Both studies were of sufficient quality to apply the results to practice. Both trials reported mild adverse effects such as nausea and headache.

Magnesium

Three studies, two using magnesium oxide (MgO)[35,42] and one using magnesium pyrrolidone carboxylic acid[41] met the inclusion criteria for this review (Table 4). No significant differences in PMS symptoms were found in the studies using MgO compared to placebo.[35,42] In the study by De Souza et al, this may be explained in part, because participants received treatment for only one menstrual cycle. Despite non-significant findings in the MgO treatment group, Walker et al[42] reported a statistically significant reduction in anxiety-related ($p<0.001$) and total ($p<0.001$) PMS symptom scores with a sorbitol placebo (1305 mg sorbitol/day) after two months of supplementation. The authors attributed the positive effects seen in the placebo group to an influence of sorbitol in magnesium homeostasis, either through reduced absorption, reduced excretion, or enhanced cell uptake of magnesium.[42]

The study by Facchinetti et al suggests that another magnesium formulation – magnesium pyrrolidone carboxylic acid may be effective for treatment of PMS.[41] Significant reductions in negative affect ($p<0.02$) and total symptom ($p<0.05$) scores with magnesium pyrrolidone carboxylic acid were reported after two months of treatment. When the placebo group then received magnesium pyrrolidone carboxylic acid for two months, the total score, negative affect and arousal scores all decreased significantly, adding further support for the benefit of magnesium. Only one trial was of sufficient quality to apply the results to practice.[41] One woman in the Facchinetti trial[41] reported experiencing diarrhea; this was the only adverse effect reported.

TABLE 4 Characteristics of Studies Evaluating Minerals for Premenstrual Syndrome

Study/Design	Participants	Interventions	Outcomes	Results	Adverse Drug Reactions (ADRs)
Calcium					
Thys-Jacobs S, et al[39] 8 months, DB, PC, Crossover	60 women meeting criteria for PMS enrolled; 33 with complete data for analysis	Calcium carbonate; 500 mg elemental calcium - two tablets daily (or identical placebo) for 3 months	Daily rating of severity of 14 PMS symptoms divided into 4 "factor" categories*	Calcium: significantly more effective in reducing symptoms than placebo in three symptom categories: Factor 1: p=0.045 Factor 2: p=0.003 Factor 4: p=0.036	No participants withdrew due to ADRs Calcium (n): nausea (3); constipation (4); flatulence (1); GI discomfort (3). Placebo (n): nausea (2)
Thys-Jacobs S, et al[40] 5 months, DB, PC	497 women with diagnosed PMS enrolled; 466 with complete data for analysis.	Calcium carbonate; 300 mg elemental calcium: 2 tablets BID (n=231) Placebo (n=235)	Daily rating of severity of 17 PMS symptoms divided into 4 "factor" categories**	Calcium group had significantly lower symptom scores compared to placebo for: Factor 1: negative affect (p<0.001) Factor 2: water retention (p<0.001) Factor 3: food cravings, (p<0.05) Factor 4: pain, (p<0.001)	16 participants withdrew due to ADRs. 422 participants reported an ADR; 216 in the calcium group, 206 in the placebo group. Headache, rhinitis, and pain were most commonly reported.
Magnesium (Mg)					
Facchinetti F, et al[41] 6 months, DB, PC	32 women with diagnosed PMS; 28 with complete data for analysis	Magnesium pyrrolidone carboxylic acid 360 mg/day from day 15 to onset of menses (n=14) for 2 months or placebo (n=14) Both groups then received magnesium for 2 months	Moos Menstrual Distress Questionnaire	Pain was significantly (p<0.05) reduced in both groups at end of 2 months Total score (p=0.04) and negative affect (p<0.02) were significantly reduced in Mg group but not placebo at end of 2 months When placebo group received Mg for 2 months the Total Score (p<0.04), negative affect (p<0.05) and arousal (p<0.01) scores all significantly decreased	2 participants withdrew due to ADR's: Magnesium (n): diarrhea (1) Placebo (n): headache (1)

De Souza MC, et al[35] 5 months, DB, PC, crossover	58 women with symptoms of PMS enrolled; 37 with complete data for analysis.	Vitamin B6 50 mg/day for 1 cycle Magnesium (as MgO heavy precipitate) 200 mg/day for 1 cycle Vitamin B6 50 mg/day + Magnesium 200 mg/day for 1 cycle Placebo	Daily rating of severity of 30 PMS symptoms	No overall difference between individual treatments -Significant difference in anxiety-related symptoms (p=0.040) and craving (p=0.056) with Mg + Vit B6	Participants not asked about adverse events None reported spontaneously
Walker AF, et al[42] 6 months, DB, PC, crossover	88 women with symptoms of PMS	Magnesium 200, 350, or 500 mg/day as MgO (containing 1050, 830, and 717 mg of sorbitol respectively) Placebo (contained 1305 mg of sorbitol)	Daily rating of severity of 20 PMS symptoms	No significant difference in symptom scores after 1 or 2 months with magnesium Statistically significant difference in total symptom score (p=0.004) and anxiety-related symptoms (p=0.006) after 2 months with placebo	Not mentioned in study

DB= double-blind
Moos Menstrual Distress Questionnaire = list of 47 symptoms rate on a severity scale of 1-6 with 1 being no experience of the symptom
PC= Placebo controlled
PMS = premenstrual syndrome

[*]Factor 1: nervousness, irritability, crying, mood swings, depression, violent tendencies; Factor 2: fatigue, abdominal bloating, headache, breast fullness; Factor 3: increased appetite, craving for sweets; Factor 4: abdominal cramps, back pain
[**]Factor 1 (negative affect): mood swings, depression, tension, anxiety, anger, crying spells; Factor 2 (water retention): swelling of extremities, tenderness of breasts, abdominal bloating, headache, fatigue; Factor 3 (food cravings): increased or decreased appetite, craving for sweets or salt; Factor 4 (pain): lower abdominal cramping, generalized aches and pains, low backache

DISCUSSION

Chasteberry

Results from four RCTs, all evaluating preparations of chasteberry for efficacy in reducing symptoms of PMS/PMDD, were mostly positive, yet results were not unanimous. All four studies were of three to four months duration, likely to be of sufficient length to determine effect as 2 months of use of a treatment has been suggested to be sufficient to allow for variability of symptoms between cycles.[43] A potential source of difference in efficacy seen between the trials could arise from the difference in the content and dosing of the chasteberry product tested in each trial. Each study used a different preparation, some commercially available, some standardized and some with very little detail provided other than the amount of the crude extract contained in each tablet. In fact, only the studies by Lauritzen et al and Schellenberg et al provided enough detail about the content of the chasteberry product used in the study to allow selection of a similar product and dose.

The identity of the placebo or comparator in each of the trials also has potential to affect the interpretation of the results of each trial. For example, Lauritzen et al. used vitamin B6 as a placebo comparator to chasteberry and both showed some reduction in symptoms.[15] Vitamin B6 is a recognized treatment for PMS, however, evidence for its efficacy is conflicting, as will be seen later in this review. Therefore, the choice of vitamin B6 as comparator in this trial limits interpretation of the results. Another example of where the content of the placebo could affect the interpretation of results is provided by the trial of Turner et al.[14] This trial was the only one of the four that did not show chasteberry to have some benefit. They reported no difference in symptom reduction between the treatment and placebo group (with the exception of one symptom). However, lack of difference between treatment groups for the other symptoms may be attributable to the soy-based composition of the placebo; findings from an RCT conducted by Bryant et al[24] suggest that soy may decrease severity of some PMS symptoms and therefore perhaps soy was not a true placebo.

Evening Primrose Oil

EPO was evaluated in three RCTs using a range of doses of standardized commercial products.[18-20] Duration of the studies varied from 4 to 10 months. Despite the range of dose and the long duration of study, no improvement in symptoms of PMS, with the exception of a reduction in depression in one trial, could be detected. Based on the results of these three RCTs, EPO does not appear to be effective for reducing symptoms of PMS.

Ginkgo

Results from one RCT suggested a possible role for ginkgo in the treatment of mastalgia associated with PMS. Further study is needed to confirm these findings.

Saffron

Preliminary evidence from one trial[22] suggests that saffron may be effective for symptoms of PMS, especially after three to four cycles of treatment. More study is needed to confirm these results and to establish the most appropriate dose.

St. John's Wort

Results from one RCT showed what the authors referred to as a "non-significant trend for SJW to be superior to placebo" in decreasing PMS-associated symptoms of anxiety when SJW was dosed at 600 mg (1800 μg hypericin)/day.[23] The authors point out that a high dropout rate (26%) left the study underpowered, which could account for the apparent lack of clear superiority to placebo. A major limitation of this trial was that although the SJW product used in the trial was standardized to hypericin, this is only one of at least two known pharmacologically active compounds necessary for the activity of SJW.[44] It is unclear whether the SJW product used in the trial contained any of the second compound, hyperforin, that is associated with producing antidepressant effects of SJW. Inadequate levels of hyperforin could contribute to the non-significant findings of this trial, as evidence has clearly shown that both hypericin and hyperforin must be present to elicit the antidepressant effects of SJW.[44] Future studies with adequate power and adequate hyperforin are needed to determine SJW's place in the treatment of PMS.

Soy

Interpretation of the results of the one RCT that met inclusion criteria was limited by a 56% dropout rate that resulted from the poor taste of the isoflavone product. This led to a small sample size (n=23) and, consequently, low study power. The positive trends toward benefit with physical symptoms and generally high quality of the trial suggest that further study with larger sample sizes and a more palatable soy product are warranted.

Vitamin B6

The results of this review are inconclusive with regards to the role of vitamin B6 in the management of PMS. This is consistent with results of a systematic review by Wyatt et al[45] who reported that conclusions from their findings were limited by the low quality of the studies included, but added, that vitamin B6 may be of benefit. Another review of RCTs published in 2003 concluded that definitive clinical recommendations could not be made on the basis of the data.[12] If women do want to try vitamin B6, limited evidence suggests that vitamin B6 may improve mood symptoms in some women at a dose of 100mg daily for 3 months. Although higher doses of Vitamin B6 were also found to be effective, they are generally not recommended, as toxicity has been associated with doses of greater than 200mg/d.[45]

Vitamin E

Results from the two studies evaluating the efficacy of vitamin E are promising - however, application of findings is limited, to some degree, by poor methodology. For example, sample sizes were small in both studies, and details regarding randomization process and allocation concealment were not provided. Application of the results is further restricted by a lack of baseline characteristics of the participants. Further research with a large, well-described study population is needed to determine the role of vitamin E in PMS treatment.

Calcium

Results of the two studies provide good evidence to support the use of elemental calcium 1000-1200 mg/day for treating PMS symptoms of negative affect (mood swings, depression, tension, anxiety, anger, crying spells), water retention (swelling of extremities, tenderness of breasts, abdominal bloating, headache, fatigue), food cravings (increased or decreased appetite, cravings for sweets or salt), and pain (lower abdominal cramping, generalized aches and pains, low backache). Women with high dietary calcium intake may need to adjust their supplemental dose downward to avoid exceeding the recommended safe, tolerable maximum daily limit of 2500mg/day elemental calcium.[46]

Magnesium

Based on the results of three trials, the efficacy of magnesium for treatment of PMS is unclear. Two studies using magnesium oxide as an intervention reported negative results.[35,42] However, the results of the De Souza et al[35] trial may be limited due to the short duration (one month) of the trial. The results of the Walker et al[42] trial are confounded by the positive results observed with the sorbitol placebo. One study did find improvement in symptoms with magnesium pyrrolidone carboxylic acid, when given at a dose of 360 mg/day for at least 2 months.[41] Based on these positive results, further study, of at least 2 months duration, is warranted to determine which symptoms of PMS are most likely to be relieved, and which formulation of magnesium is most efficacious.

Limitations

Limiting the literature search to reports of RCTs published in English or French had the potential to reduce the number of total articles identified. It is therefore possible that some potentially relevant RCTs were missed in the search. Interpretation of the evidence was challenging due to the limited number of trials for most of the NPs, the varying content of the product tested in each RCT, small sample size and poor study design. Varieties of methods for defining and/or diagnosing PMS were used in the studies, resulting in studies enrolling women with various types and severity of PMS symptoms. The use of a variety of methods for determining if a participant had symptoms of PMS was not unexpected - as there is no accepted gold standard for diagnosing PMS. In 2000, the American College of Obstetrics and Gynecology[47] published criteria for the diagnosis of PMS; however, none of the studies in this review used these criteria. Studies used a variety of instruments to measure study outcomes, most of

which evaluated the severity of symptoms using a scale. Scores were then evaluated to detect statistical differences between baseline and post-treatment scores. There is no widely accepted definition of a clinically relevant difference in symptom reduction although a 50% reduction in scores has been proposed and used in some studies.[48-50] Only four[14,17,19,28] of the studies included in this review used predetermined definitions of clinical response, with only Atmaca et al[17] using the 50% reduction in score. Use of these different methods of measuring study outcomes adds to the difficulty of comparing results from various studies and deriving clinically meaningful conclusions. It is important to note that additional evidence evaluating the use of NPs in the treatment of PMS may be available from studies that did not meet the inclusion criteria of this systematic review. These include studies that were conducted using a non-RCT design, evaluated products that contained multiple NPs and/or other active ingredients, and/or were published in languages other than English or French.

CONCLUSION

Based on our search strategy, 62 herbs, vitamins and minerals were identified that have been advocated for the treatment of PMS/PMDD in women. Of these, 10 NPs had published evidence that met the inclusion criteria for this review. Results from RCTs support the use of calcium as treatment for symptoms of PMS (Table 5). Data suggests that chasteberry and vitamin B6 are possibly effective. Preliminary data suggests benefits with ginkgo, magnesium pyrrolidone carboxylic acid, saffron, St. John's Wort, soy and vitamin E, but more study is needed to confirm their place in therapy. Results from the available evidence failed to detect improvement of symptoms with evening primrose oil, or magnesium oxide. To better determine the role of NPs in treatment of PMS, future RCTs must be of adequate duration; have a sufficient sample size; include monitoring and reporting of adverse reactions; use a well characterized product and provide information on patient baseline characteristics. Studies should clearly state the criteria that was used to diagnose PMS and what criteria was used to determine if there was a clinically significant treatment effect. Additionally, studies that evaluate and report on the change of severity of individual symptoms associated with PMS would be more informative.

TABLE 5 Summary of Evidence of Benefit of Herbs, Vitamins and Minerals in Premenstrual Syndrome/Premenstrual Dysphoric Disorder

Herb, Vitamin or Mineral (# of trials)	Efficacy	Comments
Chasteberry (4 RCTs)	Possibly effective	-Benefit or possible benefit shown in 3 good quality studies[15-17]; no benefit found in a study of average quality[14] -Symptoms relieved: physical -Dose in effective trials: 20mg/day (fruit extract ZE 440:60% ethanol 6-12:1, standardized to casticin)[16] 4mg/day Agnolyt^{R} (dried fruit extracted with 60% ethanol)[15], 20-40 mg/day (*Vitex agnus castus* extract)[17]
EPO (3 RCTs)	Not effective	-No benefit shown in 2 good quality studies[19, 20] or in 1 study of poor quality[18]
Ginkgo (1 RCT)	Limited evidence; more study warranted	-Benefit shown in one study of average quality[21] -Symptoms relieved: mastodynia and breast pain -Dose used in effective trial:160-320mg/day (EGb 761) for 2 months[21]
Saffron (1 RCT)	Limited evidence; more study warranted	-Benefit shown in 1 good quality study[22] -Symptoms relieved: overall PMS symptoms and overall symptoms

		measured by Hamilton Depression Scale -Dose used in effective trial: 30mg/day (80% ethanol extract of petal of *C. sativus*)[22]
St. John's Wort (SJW) (1 RCT)	Not effective; more study warranted	-Trend to benefit in one good quality study [23] -Symptoms relieved: anxiety-related symptoms -Dose used in trial showing trend to benefit: 300mg SJW extract standardized to 900mcg hypericin/300 mg[23]
Soy (1 RCT)	Not effective; more study warranted	-Trend to benefit in one good quality study[24] -Symptoms relieved: physical symptoms -Dose used in trial showing trend to benefit: powder and snack bar containing a total of 30.5 g isolated soya protein containing 68 mg isoflavones. [24]
Vitamin B6 (13 RCTs)	Possibly effective	-Benefit shown in one good quality study [15] and in 3 studies of average quality[26, 32, 33]; the remaining 2 beneficial studies were of poor quality [28, 36] -Symptoms relieved in studies: mood symptoms -Dose used in effective trials: 100-500mg/day.[15, 26, 28, 32, 33, 36] Data suggests that 100mg per day is sufficient to observe any benefit while minimizing adverse effects[45]
Vitamin E (2 RCTs)	Limited evidence; more study warranted	-Benefit shown in one study of average quality[37] while trend to improvement observed in a poor quality study[38] -Symptoms relieved in study: mood, physical and depressive symptoms -Dose used in effective trial: 150-300 IU per day[37]
Calcium (2 RCTs)	Effective	-Benefit shown in 2 good quality studies[39, 40] -Symptoms relieved in studies: negative affect, water retention, food cravings and pain -Dose used in effective trials: 1000-1200mg elemental calcium per day[39, 40]
Magnesium (3 RCTs)	Limited evidence; more study warranted	-Benefit shown for magnesium pyrrolidone carboxylic acid in one study of average quality. [41] No benefit seen with magnesium oxide in one study of average quality[35] and one study of poor quality[42] -Symptoms relieved in studies: negative affect and overall symptoms -Dose used in effective trial: 360mg/d of magnesium pyrrolidone carboxylic acid[41]

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