Journal of Psychosomatic Obstetrics & Gynecology, March 2011; 32(1): 42–51

informa
healthcare

REVIEW

Herbal treatments for alleviating premenstrual symptoms: a systematic review

GIULIA DANTE & FABIO FACCHINETTI

Mother Infant Department, University of Modena and Reggio Emilia, Via del Pozzo 71, Modena 41100, Italy

(Received 28 February 2010; revised 2 November 2010; accepted 3 November 2010)

Abstract

Premenstrual syndrome (PMS) is a condition of cyclical and recurrent physical and psychological discomfort occurring 1 to 2 weeks before menstrual period. More severe psychological symptoms have been described for the premenstrual dysphoric disorder (PMDD). No single treatment is universally recognised as effective and many patients often turn to therapeutic approaches outside of conventional medicine. This systematic review is aimed at analysing the effects of herb remedies in the above conditions.

Systematic literature searches were performed in electronic databases, covering the period January 1980 to September 2010. Randomised controlled clinical trials (RCTs) were included. Papers quality was evaluated with the Jadad' scale. A further evaluation of PMS/PMDD diagnostic criteria was also done.

Of 102 articles identified, 17 RCTs were eligible and 10 of them were included. The heterogeneity of population included, study design and outcome presentation refrained from a meta-analysis. *Vitex agnus castus* was the more investigated remedy (four trials, about 500 women), and it was reported to consistently ameliorate PMS better than placebo. Single trials also support the use of either *Gingko biloba* or *Crocus sativus*. On the contrary, neither Evening primerose oil nor St. John Worth show an effect different than placebo. None of the herbs was associated with major health risks, although the reduced number of tested patients does not allow definitive conclusions on safety.

Some herb remedies seem useful for the treatment of PMS. However, more RCTs are required to account for the heterogeneity of the syndrome.

Keywords: *Premenstrual syndrome, herbal remedies, Vitex agnus castus, Crocus sativus, Hypericum perforatum*

Introduction

Premenstrual syndrome (PMS) is a condition of cyclic, recurrent physical and psychological discomfort occurring 1–2 weeks before a woman's menstrual period. Symptoms have to be significant enough to cause disruption in either family, personal or occupational functions [1,2]. In its most severe form, PMS affects roughly 5% of women in reproductive age while in a milder form, it has been estimated to affect approximately 40% of the population [3,4]. A variant of PMS entailing more severe psychological symptoms has been described by psychiatrists as premenstrual dysphoric disorder (PMDD) [5].

More than 200 symptoms of PMS have been reported in the literature, none of them being specifically related to the condition [6]. Commoner affective symptoms are irritability, anxiety/tension, mood swings and depression. Commoner physical symptoms include abdominal bloating, breast tenderness, headache, swelling of extremities and food cravings [3]. The pathophysiology of PMS or PMDD have not been established and hypotheses included hormone imbalances, sodium retention, nutritional deficiencies, abnormal neurotransmitter responses to normal ovarian function and abnormal hypothalamic-pituitary-adrenal axis function [7,8].

Apart for the complete elimination of the menstrual cycle, no single treatment is universally recognised as effective. Studies have yielded conflicting results with most approaches, and many trials have not been well controlled [6]. A limitation of studies concerning PMS/PMDD is the lack of objective markers. Therefore, outcomes could be based only on self-reported

Correspondence: Fabio Facchinetti, Mother Infant Department, University of Modena and Reggio Emilia, Via del Pozzo 71, Modena 41100, Italy.
E-mail: facchinetti.fabio@unimore.it

ISSN 0167-482X print/ISSN 1743-8942 online
DOI: 10.3109/0167482X.2010.538102

questionnaires. Anyway, proven effective pharmacologic treatments include reproductive hormones, psychoactive drugs and vitamins among others [9–12].

Many patients often turn to therapeutic approaches outside of conventional medicine. Women are frequent users of complementary/alternative medicine (CAM) more than men [13–16]. Indeed, multiple surveys have shown that women, especially those of white ethnicity, middle-age, with high levels of education and income, are more likely to be users of CAM [17–19]. These surveys found that patients with PMS try a wide range of CAM remedies including diet, yoga, massage, exercise, faith healing, hypnosis, herbs, acupuncture, chiropractic, meditation, homeopathy and vitamins/supplements. The current stage of knowledge is still inadequate to sufficiently inform clinicians, researchers and the public about either benefits or potential risks of everyone among such interventions [20,21].

However, there is an increasing public interest in the use of herbal medicine treatment that lies outside the traditional Western medical practice. There is also evidence indicating that not all herbs are risk-free and concerns about self-administration and non-recognisable adverse events are increasing [22].

The present systematic review is aimed at analyse the effects of herbs in the management of PMS or PMDD in medical practice.

Methods

Systematic literature searches were performed in September 2010 in the following electronic databases: Medline, Amed, The Cochrane Library and in the PDR for Herbal Medicines [23]. We performed a search over the period from January 1980 to September 2010 and only randomised controlled clinical trials (RCT) were included.

The search terms were: 'premenstrual syndrome treatment', 'late luteal phase dysphoric disorder', 'Premenstrual Dysphoric Disorder', 'mastalgia treatment', 'hyperprolactinaemia' 'complementary treatments', 'alternative treatments', 'phytomedicine', 'herbal treatments', 'herbs', 'vitex agnus castus', 'fructus agni casti', 'chasteberry', 'chaste three', 'evening primrose oil,', 'oenothera biennis', 'hypericum perforatum', 'hyperici herba', 'St. John's wort', 'ginkgo biloba', 'black cohosh root', 'cimicifuga racemosa rhizoma', 'Crocus sativus', 'whether saffron' and 'Dioscorea villosa'.

No language restrictions were imposed. Further relevant papers were located by hand-searching the reference lists of recent systematic reviews. Only human studies were included. Data from herbal treatments in combination with other herbs as well as animal and *in vitro* investigations were excluded. Chinese herb remedies were also excluded.

Where dual publications existed, the more detailed and recent paper was admitted.

We attempted to obtain hard copies of all the papers listed through our own university library or interlibrary loans.

The papers quality has been evaluated with the Jadad method [24], which is considered reliable for RCT assessment [25]. The parameters considered by this method are the following:

1. Was the study described as randomised?
2. Was the study described as double blind?
3. Follow up: adequate (number and reasons for dropouts and withdrawals described) or inadequate (number or reasons for dropouts and withdrawals not described).
4. Generation of the allocation sequence: adequate (computer-generated random numbers, table of random numbers ...), or inadequate;
5. Double blinding: adequate (taking placebo, or similar) or inadequate (not intervened or different).

For each positive answer, 1 point is assigned, the overall score going from '0' to '5'. Studies scoring <3 were considered of poor quality and then excluded from the analysis.

In addition to Jadad scale, studies were evaluated also according to the method used for the clinical diagnosis. PMS has been defined by the American College of Obstetrics and Gynecologists (ACOG) [2], while PMDD has been defined by the American Psychiatric Association (APA) which previously defined the Late Luteal Phase Dysphoric Disorder (LLPDD) in the third revised version of DSM [5]. Apart from the above-mentioned criteria, the diagnosis of PMS has been accepted when performed by a prospective evaluation of symptoms through validated questionnaires (i.e. MDQ, COPE, etc.), for at last two menstrual cycles [26,27]. Only studies using such standard criteria were considered reliable and then included in the final comparison.

All sources of information obtained were read and evaluated by one of us (GD), and successively checked independently by the other author (FF).

Results

Decision tree is reported in Figure 1. Of 102 studies identified, 25 trials were screened. Eight of them were excluded because not pertaining PMS ($n=5$) [28–32], duplicate publication ($n=2$) [33,34] or published only in abstract form ($n=1$) [35]. The remaining 17 RCTs were considered eligible for this review. Eight of them pertains the effects of *Vitex agnus-castus* [36–43], four used *Oenotera biennis* [44–47], two used *Hypericum perforatum* [48–49], two used *Ginkgo biloba* [50,51] and one *Crocus*

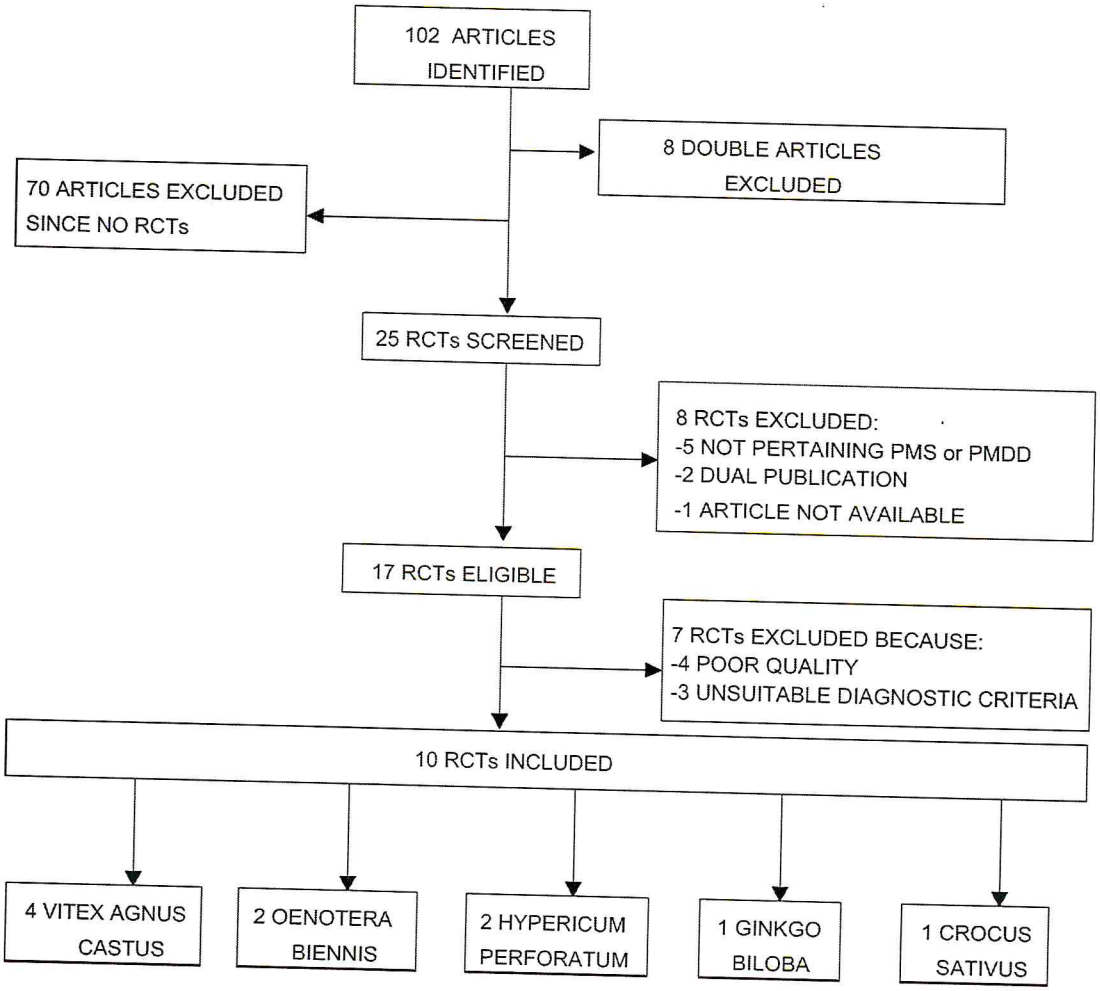

Figure 1. Decision tree.

sativus [52]. Each one of such RCT was detailed in Table I.

The analysis through the Jadad method showed three studies of poor quality (score <3) [40, 41,47] which were excluded. In addition, further four studies were excluded since they did not report a reliable standardised definition of either PMS or PMDD diagnosis [36,39,45,50]. Thus, 10 studies were included [37,38,42,43,44,46,48,49,51,52] for the final comparison which is reported in Table II.

Vitex agnus-castus (chasteberry)

Vitex agnus-castus (VAC), the fruit of chaste tree, is native to western Asia and south-western Europe, and now it is common in much of the south-eastern United States [23]. Over the past years, VAC has been widely used in Europe for gynaecologic conditions such as PMS, cyclical breast discomfort, menstrual cycle irregularities and dysfunctional uterine bleeding [53]. *Vitex agnus castus* shows central dopaminergic activity *in vitro* and *in vivo* [54].

In the study of Shellemberg [37], fruit extract ZE 440 contains 60% ethanol m/m extract (ratio 6:12:1) and it was standardised as casticin content. The reduction of symptoms was 52% (active) versus 24% ($p < 0.001$). Four minor self-resolving AE were reported in the VAC group, and three in the placebo group.

In the study by Atmaca et al. [38], VAC extracts was compared with flexible dosing fluoxetine (range 20–40 mg/day). The composition and the titration of the herb were not described. Although both treatments showed similar efficacy on PMDD, fluoxetine was more effective for psychological symptoms while VAC reduced physical symptoms. AE were reported in 17 patients (VAC: $n=9$; fluoxetine: $n=8$), nausea and headache being often described in either groups.

Both in the studies by He et al. [42] and Ma et al. [43], chinese women were enrolled. Each tablet of VAC (BNO 1095) they used contained 4.0 mg of a dried ethanol (70%) extract of VAC (corresponding to 40 mg of herbal drug) and it was identical to Agnucaston®/Cyclodynon®

Table I. Eligible RCTs where herb remedies have been evaluated for the treatment of PMS or PMDD.

Reference	Study design	Herb remedy treatment duration, dose	No. of subjects and inclusion criteria	Assessment of the response	Comments
[38]	Double-blind, randomised, controlled vs. fluoxetine	VAC 8 weeks Dose: 20–40 mg/day	*N*: 42/39 Age: 24–45 Diagnosis: DSM-IV OC users: no	DSR, HRSD, CGI-SI, CGI-I	Responders (>50% improvement) were similar in VAC (58%) and Fluoxetine (68%) group
[37]	Double-blind, randomised, placebo-controlled	VAC 3 cycles Dose: 20 mg/day	*N*: 178/170 Age: ≥18, mean age 36 Diagnosis: DSM III-R OC users: yes	Six symptoms recorded at the start of every cycle	According to the 3 global impression items active treatment was more effective than placebo ($p < 0.001$)
[41]	Prospective, randomised vs. bromocriptine	VAC 3 months Dose: 40 mg/day	*N*: 80/80 Age: not reported Diagnosis: mastalgia and Mild hyperprolactinaemia OC users: not described	Symptom scoring not defined	Both VAC and bromocriptine Improved symptoms ($p < 0.00001$)
[40]	Double-blind, randomised, placebo-controlled	VAC 3 cycles Dose: 300 mg/day	*N*: 2500/600 Age: not described Diagnosis: self-diagnosed sufferers from PMS based on the MDQ OC users: not described	MDQ	VAC improved symptoms equally than placebo
[39]	Double-blind, randomised controlled vs. vitamin B6	VAC 3 cycles Dose: 3.5–4.2 mg/day	*N* = 175/105 Age: 18–45 Diagnosis: PMTS OC users: no	PMTS, CGI	Treatment with VAC and B6 reduced PMTS score from 15.2 to 5.1 (47.4%) and from 11.9 to 5.1 (−48%). Similar data obtained by using the CGI scale
[36]	Double-blind, randomised, placebo-controlled	VAC 3 cycles Dose: 32.4 mg/day	*N* = 100/86 Age: 18–45 Diagnosis: patients had to suffer from cyclical mastalgia OC users: yes	VAS PMSD and PMTS	The differences of the VAS points for VAC were significantly greater than those with placebo ($p = 0.018$)
[42]	Prospective, randomised, multicenter, placebo-controlled	VAC 3 cycles Dose: 40 mg/day	*N*: 217/202 Age: 18–45 Diagnosis: Chinese version of PMSD and PMTS OC users: no		See Table II
[43]	Prospective, randomised, double-blind, placebo-controlled	VAC 3 cycles Dose: 40 mg/day	*N*: 67/64 Age: 21–44 Diagnosis: Chinese version of PMTS and PMTS OC users: no	PMSD and PMTS	See Table II

(*continued*)

Table I. (*Continued*).

Reference	Study design	Herb remedy treatment duration, dose	No. of subjects and inclusion criteria	Assessment of the response	Comments
[45]	Double-blind, randomised, placebo-controlled, crossover	EPO 3 cycles Dose: 500 mg/day	*N* = 40/38 Age: 20–40 Diagnosis: symptoms during the 2nd half of cycle, relieved within 72-h of menses OC users: no	10 PMS symptoms	There was no difference between active and placebo (RR: −0.026; 95% CI: −2.3 to 2.2)
[44]	Double-blind, randomised, placebo-controlled, crossover	EPO 4 months Dose: Efamol 1 g/day Efavit: 2 + 3 capsules/day	*N* = 54/10 Age: 26–38 Diagnosis: MDQ OC users: no	MDQ, BDI, SAI	At interview, 6/20 felt better with placebo, and 14/20 felt better with EPO (not significant)
[46]	Randomised, double-blind crossover	EPO 10 cycles Dose: Efamol 6 g/day	*N* = 38/27 Age: 30–45 Diagnosis: DSM III-R OC users: no	Modified scale from Hammerback et al.**	Using spectral densities, improvement was observed over time irrespective of whether patients received EPO or placebo
[47]	Placebo-controlled, randomised, crossover	EPO 4 cycles Dose: Efamol 1.5 g/day	*N*: 30/30 Age: 25–47 Diagnosis: suffering severe PMS since a mean of 8.8 years OC users: not described	19 symptoms scored on a 3-point scale global score index	Both EPO and placebo decreased PMS score respect with baseline. At patient's assessment, the lack of (60%) vs. EPO (38%), $p < 0.05$
[48]	Double-blind, randomised, placebo-controlled	*Hypericum perforatum* 3 cycles. Dose: 600 mg/day	*N* = 169/125 Age: not described Diagnosis: MHQ OC users: no	Abraham's classification***	See Table II
[49]	Double-blind, randomised, placebo-controlled	*Hypericum perforatum* 10 cycles. Dose: 900 mg/day	*N*: 36/34 Age: 18–45 Diagnosis: DSR, BDI, STAIT OC users: no	DSR, STAIS, BPAQ BIS-11	SJW equal to placebo for DSR, SJW better than placebo for physical ($p = 0.013$) and behavioural symptoms ($p = 0.032$)
[50]	Double-blind, randomised, placebo-controlled	*Ginkgo Biloba* 3 cycles. Dose: 160 mg/day	*N* = 165/143 Diagnosis: women suffering since 3 cycles from congestive PMS troubles OC users: no	DSR	Active and placebo were equally effective, except for breast symptoms where Gingko was more

(*continued*)

Table I. (*Continued*).

Reference	Study design	Herb remedy treatment duration, dose	No. of subjects and inclusion criteria	Assessment of the response	Comments
[51]	Single-blind, randomised, placebo-controlled	*Ginkgo Biloba* 2 cycles Dose: 120 mg/day	$N = 90/85$ Age: 18–30 Diagnosis: DSM-IV, BDI	DSM-IV, BDI	See Table II
[52]	Double-blind, randomised, placebo-controlled	*Crocus sativus* L. 4 cycles Dose: 30 mg/day	$N = 78/53$ Age: 20–45 Diagnosis: ACOG OC users: no	DSR, HRSD	See Table II

*Enrolled/completed the trial.
**Hammerback S, Backstrom T, MacGibbon-TaylorB. Diagnosis of premenstrual tension syndrome: description and evaluation of a procedure for diagnosis and differential diagnosis. J Psychosom Obstet Gynecol 1989;10:25–42.
***Abraham GE. Nutritional factors in the etiology of the premenstrual tension syndromes. J Reprod Med 1983;28:446–464.
OC: oral contraceptives; DSR: daily symptom reports; HRSD: Hamilton rating scale for depression; CGI_SI: clinical global impression scale; CGI-I: clinical global improvement; VAC: vitex agnus castus; MDQ: menstrual distress questionnaire; PMS: premenstrual syndrome; PMTS: premenstrual tension syndrome scale; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders; DSM III-R: Diagnostic and Statistical Manual of Mental Disorders III revisited; VAS: visual analogue scale; EPO: evening primerose oil; BDI: beck depression inventory; SAI: Salkind anxiety inventory; MHQ: daily symptom report; HDRS: Hamilton depression rating scale; PMSD: Premenstrual syndrome diary, STAIT: Trait scale of the State-Trait Anxiety Inventory, STAIS: State scale of the State-Trait Anxiety Inventory, BPAQ Aggression Questionnaire, BIS-11: Barratt Impulsiveness Scale version 11.

Table II. Efficacy of herbs remedies for PMS/PMDD treatment tested in high-quality trials.

Herb remedy tested	Jadad score	Diagnosis	Reduction vs. baseline		
			Herb remedy	Placebo	*p*
Vitex agnus castus					
Schellemberg [37]	3	PMS	48.8%	30.4%	<0.001
Atmaca et al. [38]	4	PMDD	N.A.	N.A.	
He et al. [42]	4	PMS	79.2%	55.1%	<0.0001
Ma et al. [43]	4	PMS	85.7%	57.2%	<0.0001
Oenotera biennis					
Callender et al. [44]	3	PMS	BDI: 46.6%	35.6%	NS
			SAI: 21.2%	24.3%	NS
Collins et al. [46]	4	PMS	N.A.	N.A.	
Hypericum perforatum					
Hicks et al. [48]	3	PMS	28.5%	30.2%	NS
Canning et al. [49]	5	PMS	N.A.	N.A.	
Ginkgo biloba					
Ozgoli et al. [51]	4	PMS	23.6%	8.74%	<0.001
Crocus sativus					
Hosseini et al. [52]	5	PMS	57.9%	21.6%	<0.001

Reference to single study is reported in brackets. For Jadad score refers to the text.
The percent changes are calculated by using scores referring to overall symptoms. Effect on subscales is not reported except for Ref. 44 where a total PMS score was not available.
N.A.: In these studies, data are not available for the calculation, neither from the text, nor from figures/tables. The significance of active/placebo treatment is reported in Table I.
BDI: Beck depression inventory; SAI: Salkind anxiety inventory.

(Bionorica AG, Neumarkt, Germany) available in Europe.

In the study enrolling perimenopausal women [42,] AE (19 patients) were equally reported in the two groups, headache being the most frequent. In the study enrolling women in fertile age [43], only the prolongation of periods was reported as AE, in the treatment group.

Oenotera biennis (evening primerose oil)

Unbalanced prostaglandin production has been hypothesised in women with PMS. Indeed, cis-linoleic acid levels are higher in these patients, with respect to controls. Since the levels of the metabolites are reduced, this suggests a failure of conversion into gamma-linolenic acid [55,56]. On these basis,

evening primrose oil (Efamol) was promoted for the treatment of PMS. Each Efamol capsule contains 500 mg of oil (73% cis-linoleic acid, 9% gamma-linolenic acid and the remaining 18% is a variety of other fatty acids). In each capsule, 13.6 IU of vitamin E are added. Since a number of coenzymes are required in the conversion to gamma-linolenic acid, Efavit tablets (125 mg ascorbic acid; 5 mg zinc sulphate; 25 mg niacin; 25 mg pyridoxine) were added to Efamol in some trials.

In the study by Callender et al. [44], only 10 women completed the trial (seven placebo and three Evening primrose oil). Depression and anxiety scores improved in both arms, irrespective of medication quality. Skin reaction (eight women) was reported on active treatment. The study of Collins et al. [46] had a similar design, but the dose of Efamol (12 capsules/day) was the highest never reported. Neither essential fatty acids nor placebo reduced premenstrual symptoms.

Hypericum perforatum (St. John's wort)

A number of reviews suggested that St. John's Wort (SJW) can be useful for the treatment of mild, but not severe depression. Hyperforin (the active compound) inhibits the reuptake of serotonin, dopamine and norepinephrine and interacts with both GABA and glutamate receptors. The effectiveness of SJW correlates with hyperforin rather than with hypericin content [57,58].

Hicks et al. [48] investigated a SJW extract standardised to 0.3% of hypericin in volunteers recruited through newspaper advertisements, followed by an interview. Although minor AE are reported, five subjects in the SJW group, and one in the placebo group withdrew because of this. Averaging both treatment cycles there was only a trend for SJW to be superior to placebo.

Canning et al. [49] also recruited trough advertisements but employed a different extract titrated to 0.18% hypericin and 3.38% hyperforin. The subject evaluation included three observational run-in cycles, followed by two placebo-cycles before randomisation, allowing few, very selected subjects to be treated. Minor AE were reported both in placebo and SJW group. In a sophisticated multivariate analysis, SJW was not different than placebo on overall PMS symptoms. Sub-analyses revealed SJW efficacy for physical (include food craving) and behavioural (include headache) symptoms. Unexpectedly, SJW did not relieved mood symptoms.

Gingko biloba

The leaf extract of *Gingko biloba* comes from the oldest living tree species in the world. Ginkgo was primarily known for improving memory. Extracts contain many active compounds including flavonoids and terpenoids. The former have antioxidant and scavenging properties. Gingko also inhibits platelet-activating factor and has anti-inflammatory effects, also relaxing vascular smooth muscle [59,60].

Ozgoli et al. [51] enrolled student volunteers from Teheran and used a leaf extract titrated to flavonoid glycoside (24%) and terpene lactone (6%). Very few minor AE were reported. Either physical or psychological symptoms of PMS were reduced significantly more by Gingko respect with placebo. Interestingly, the extent of placebo reduction was very low (<10%).

Crocus sativus (whether saffron)

Crocus sativus is considered an excellent stomach ailment and an antispasmodic, helping digestion and increasing appetite. It also relieves renal colic. In Persian traditional medicine, it is used for depression [61], an effect which has been confirmed in a recent clinical trial [62]. A serotoninergic mechanism involved in the antidepressant activity has been suggested [63].

In their small RCT, Agha-Hosseini et al.'s [52] investigated an extract of *Crocus sativus* prepared as follow: 120 g of dried and milled petal was extracted with 1800 ml ethanol (80%) by percolation procedure in three steps. Both in Saffron and placebo group, minor AE were observed including decreased/increased appetite, sedation, nausea, headache and hypomania. Despite a placebo effect, Saffron was found to be superior in relieving all symptoms of PMS.

Discussion

Although the relatively high number of reports evaluating herb remedies for PMS/PMDD relief, only a few of them are designed as RCTs, and often the quality of such trials is far to be satisfactory. In addition to the quality assessment used in systematic reviews, we also evaluated the consistency of diagnostic criteria adopted for PMS/PMDD definition. Indeed, a correct diagnosis is a crucial issue in every field lacking objective/instrumental markers of the disorder/syndrome under investigation [6]. PMS largely fulfil such needs. Therefore, in agreement to such stringent evaluation of quality, the evidences on efficacy and safety in the treatment of PMS/PMDD became restricted to 10 studies only, and pertain to five different herb remedies.

The limit of this survey is that a quantitative estimate of clinical effects, i.e., a meta-analysis was refrained due to several factors. Some study design includes run-in cycles thus selecting placebo responders whereas others did not. Population included

either volunteers or patients chronically suffering from several years where the response to any intervention is obviously different. In many circumstances, herb preparations are not standardised. Last, but not the least the different outcomes are reported with different statistical approach and cannot be summarised.

Nonetheless, we have tried to compare studies by calculating the overall symptoms change respect with baseline, in active and placebo arm, within each trial. Confirming the above-discussed heterogeneity, placebo response showed a 6-fold variation, perhaps also linked to the cultural attribution of PMS across populations [64].

Bearing the above limitations in mind, this survey allows some consideration. Respect to other remedies, the experience with Chasteberry extract is the main one. Indeed, it was tested in almost 500 patients where it consistently relieves PMS better than placebo. Moreover, in a subset of women suffering of PMDD *Vitex agnus castus* performed equally to fluoxetine, a first-line drug treatment of such condition [11]. The available data also indicate that Chasteberry was not associated with major health risks. At present, no drug interactions have been reported.

On the opposite, despite its popularity in the eighties, Evening primerose oil was evaluated in only two adequate trials performed in early nineties. Results indicate an equivalence of such essential fatty acids supplement with placebo. Therefore, its clinical application in women with PMS seems useless.

Also St. John's Worth was evaluated in two trials. As a whole, the efficacy of this herb was not different from placebo. Unexpectedly, small significant benefits were found for physical, while not for psychological symptoms.

The remnant two herbs, *Gingko biloba* and *Crocus sativus* were evaluated in single studies. Each herb relieved PMS better than placebo did. Such evidences however were reached upon very few subjects, requiring confirmation in further trials.

In terms of tolerability, only minor side effects have been described so far, and none of the herbs was associated with major health risks, although the reduced number of tested patients does not allow definitive conclusions on safety. Moreover, one has to be aware that drug interaction represents an issue to be considered for the case of St. John's Worth [65].

In conclusion, despite a very large use of herb remedies in everyday life, few studies have been devoted to specific clinical investigations. The evidences are scanty and suggest that the relief of PMS could possibly be obtained only with few herb extracts. The heterogeneity of PMS/PMDD presentation and the different cultural value attributed to premenstrual symptoms in the diverse populations, suggests that more trials have to be performed before assuming a single herb remedy as an effective treatment.

Declaration of interest: None of the authors has any conflict of interest in the subject matter of this systematic review.

References

1. Reid R. Premenstrual syndrome. N Engl J Med 1991;324: 1208–1210.
2. ACOG Diagnostic Criteria for PMS. ACOG Practice Bulletin – Number 15, April 2000.
3. Mortola J. Premenstrual syndrome-pathophysiologic considerations. N Engl J Med 1998;338:256–257.
4. Singh BB, Berman BM, Simpson RL, Annechild A. Incidence of premenstrual syndrome and remedy usage: a national probability sample study. Altern Ther Health Med 1998;4:75–79.
5. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994. pp 715–718.
6. Halbreich U. The diagnosis of premenstrual syndromes and premenstrual dysphoric disorder-clinical procedures and research perspectives. Gynecol Endocrinol 2004;19:320.
7. O'Brien PM. Helping women with premenstrual syndrome. BMJ 1993;307:1471–1475.
8. Chrousos GP, Torpy DJ, Gold PW. Interactions between the hypothalamic-pituitary-adrenal axis and the female reproductive system: clinical implications. Ann Intern Med 1998;129:229–240.
9. Lopez LM, Kaptein AA, Helmerhorst FM. Oral contraceptives containing drospirenone for premenstrual syndrome. Cochrane Database Syst Rev 2009;15:CD006586.
10. Ford O, Lethaby A, Roberts H, Mol BW. Progesterone for premenstrual syndrome. Cochrane Database Syst Rev 2009;15:CD003415.
11. Brown J, O' Brien PM, Marjoribanks J, Wyatt K. Selective serotonin reuptake inhibitors for premenstrual syndrome. Cochrane Database Syst Rev 2009;15:CD001396.
12. Wyatt KM, Dimmock PW, Jones PW, Shaughn O, Brien PM. Efficacy of vitamin B-6 in the treatment of premenstrual syndrome: systematic review. BMJ 1999;318:1375–1381.
13. MacLennan AH, Wilson DH, Taylor AW. Prevalence and cost of alternative medicine in Australia. Lancet 1996;347: 569–573.
14. Corney RH, Stanton R. A survey of 658 women who report symptoms of premenstrual syndrome. J Psychosom Res 1991;35:471–482.
15. Lloyd KB, Hornsby LB. Complementary and alternative medications for women's health issues. Nutr Clin Pract 2009;24:589–608.
16. Himmel W, Schulte M, Kochen MM. Complementary medicine: are patients' expectations being met by their general practitioners? Br J Gen Pract 1993;43:232–235.
17. Eisenberg DM, Davis RB, Ettner SL, Appel S, Van Rompay M, et al. Trends in alternative medicine use in the United States, 1990–1997: results of a follow-up national survey. JAMA 1998;280:1569–1575.
18. Tesch BJ. Herbs commonly used by women. An evidence-based review. Am J Obstet Gynecol 2003;188:S44–S45.
19. Stevinson C, Ernst E. Complementary/alternative therapies for premenstrual syndrome: a systematic review of randomized controlled trials. Am J Obstet Gynecol 2001;185:227–235.
20. Whelan AM, Jurgens TM, Naylor H. Herbs, vitamins and minerals in the treatment of premenstrual syndrome: a systematic review. Can J Clin Pharmacol 2009;16:407–429.

21. Cho SH, Kim J. Efficacy of acupuncture in management of premenstrual syndrome: a systematic review. Complement Ther Med 2010;18:104–111.
22. Lampert N, Xu Y. Chinese herbal nephropathy. Lancet 2002;359:796–797.
23. Gruenwald J, Brendler T, Jaenicke C, editors. PDR for herbal medicines. 2nd edition. Montvale, New Jersey: Medical Economics Company; 2000.
24. Jadad AR, Carroll D, Moore A, McQuay H. Developing a database of published reports of randomised clinical trials in pain. Research Pain 1996:66:239–246.
25. Jadad AR, McQuay HJ. A high-yield strategy to identify randomized controlled trials for systematic reviews. Online J Curr Clin Trials 1993:27;Doc. No. 33.
26. Mortola JF, Girton L, Beck L, Yen SS. Diagnosis of premenstrual syndrome by a simple, prospective, and reliable instrument: the calendar of premenstrual experiences. Obstet Gynecol 1990;76:302–307.
27. Carver CS, Scheier MF, Weintraub JJ. Assessing coping strategies: a theoretically based approach. J Pers Soc Psychol 1989;56:267–283.
28. Gerhard I, Patek A, Monga B, Blank A, Gorkow C. Mastodynon (R) bei weiblicher Sterilitaet. Forsch Komplementarmed 1998;5:272–278.
29. Westphal LM, Polan ML, Trant AS, Mooney SB. A nutritional supplement for improving fertility in women: a pilot study. J Reprod Med 2004;49:289–293.
30. Cerin A, Collins A, Landgren BM, Eneroth P. Hormonal and biochemical profiles of premenstrual syndrome. Treatment with essential fatty acids. Acta Obstet Gynecol Scand 1993;72:337–343.
31. Halaska M, Raus K, Beles P, Martan A, Paithner KG. Treatment of cyclical mastodynia using an extract of Vitex agnus castus: results of a double-blind comparison with a placebo. Ceska Gynekol 1998;63:388–392.
32. Van Die MD, Bone KM, Burger HG, Reece JE, Teede HJ. Effects of a combination of *Hypericum perforatum* and *Vitex agnus castus* on PMs-like symptoms in late perimenopausal women: findings from a subpopulation analysis. J Altern Complement Med 2009;15:1045–1048.
33. Milewicz A, Gejdel E, Sworen H, Sienkiewicz K, et al. *Vitex agnus castus* extract in the treatment of luteal phase defects due to latent hyperprolactinemia. Results of a randomized placebo-controlled double-blind study Arzneimittelforschung 1993;43:752–756.
34. Ma L, Lin S, Chen R, Zhang Y, Chen F, Wang X. Evaluating therapeutic effect in symptoms of moderate-to-severe premenstrual syndrome with *Vitex agnus castus* (BNO 1095) in Chinese women. Aust NZJ Obstet Gynecol 2010;50:189–193.
35. Hunter JO, Wilson AJ. A double-blind controlled trial of gamma-linolenic acid (GLA) in the management of premenstrual gastrointestinal symptoms. Proceedings of 2nd International Symposium on Premenstrual, Postpartum and Menopausal Mood Disorders, Kiawah Island, South Carolina; 1987. Abstract 44.
36. Halaska M, Beles P, Gorkow C, Sieder C. Treatment of cyclical mastalgia with a solution containing a *Vitex agnus castus* extract: results of a placebo-controlled double-blind study. The Breast 1993;8:175–218.
37. Shellemberg R. Treatment for the premenstrual syndrome with agnus castus fruit extract: prospective, randomised, placebo controlled study. BMJ 2001;322:134–137.
38. Atmaca M, Kumru S, Tezcan E. Fluoxetine versus *Vitex agnus castus* extract in the treatment of premenstrual dysphoric disorder. Hum Psychopharmacol Clin Exp 2003;18:191–195.
39. Lauritzen CH, Reuter HD, Repges R, et al. Treatment of premenstrual tension syndrome with Vitex agnus castus: controlled, double-blind study versus pyridoxine. Phytomedicine 1997;4:183–189.
40. Turner S, Mills S. A double-blind clinical trial on a herbal remedy for premenstrual syndrome: a case study. Complement Ther Med 1993;1:73–77.
41. Kilicdag EB, Tarim E, Bagis T, Erkanli S, et al. Fructus agni casti and bromocriptine for treatment of hyperprolactinemia and mastalgia. Int J Gynecol Obstet 2004;85:292–293.
42. He Z, Chen R, Zhou Y, Geng L, Zhang Z, et al. Treatment for premenstrual syndrome with *Vitex agnus castus*: a prospective, randomized, multi-center placebo controlled study in China. Maturitas 2009;63:99–103.
43. Ma L, Lin S, Chen R, Zhang Y, Chen F, Wang X. Evaluating therapeutic effect in symptoms of moderate-to-severe premenstrual syndrome with *Vitex agnus castus* (BNO 1095) in Chinese women. Aust N Z J Obstet Gynaecol 2010;50:189–193.
44. Callender K, Mc Gregor M, Kirk P, Thomas CS. A double blind trial of evening primerose oil in the premenstrual syndrome: nervous symptoms subgroup. Hum Psychopharmacol 1988;3:57–61.
45. Khoo SK, Munro C, Battistutta D. Evening primrose oil and treatment of premenstrual syndrome. Med J Aust 1990;153:189–192.
46. Collins A, Cerin A, Coleman G, Landgren B-M. Essential fatty acids in the treatment of premenstrual syndrome. Obstet Gynecol 1993;81:93–98.
47. Puolakka J, Makirainen L, Viinikka L, Ylikorkala O. Biochemical and clinical effects of treating the premenstrual syndrome with prostaglandin synthesis precursors. J Reprod Med 1985;30:149–153.
48. Hicks SM, Walker AF, Gallagher J, Middleton RW, Wright J. The significance of "nonsignificance" in randomized controlled studies: a discussion inspired by a double-blinded study on St. John's wort (*Hypericum perforatum L.*) for premenstrual symptoms. J Altern Complement Med 2004;10:925–932.
49. Canning S, Waterman M, Orsi N, Ayres J, Simpson N, Dye L. The efficacy of *Hypericum perforatum* (St John's Wort) for the treatment of premenstrual syndrome. A randomized, double-blind, placebo-controlled trial. CNS Drugs 2010;24:207–225.
50. Tamborini A, Taurelle R. Value of standardized Ginkgo biloba extract (Egb 761) in the management of congestive symptoms of premenstrual syndrome. Rev Fr Gynecol Obstet 1993;88:447–457.
51. Ozgoli G, Selselei EA, Mojab F, Majd HA. A randomized, placebo-controlled trial of *Ginkgo biloba* L. in treatment of premenstrual syndrome. J Altern Complement Med 2009;15:845–851.
52. Agha-Hosseini M, Kashani L, Aleyaseen A, Ghoreishi A, et al. *Crocus sativus* L. (saffron) in the treatment of premenstrual syndrome: a double-blind, randomised and placebo-controlled trial. BJOG 2008;115:515–519.
53. Jarry H, Leonhardt S, Gorkow C, Wuttke W. In vitro prolactin but not LH and FSH release is inhibited by compounds in extracts of *Agnus castus*: direct evidence for a dopaminergic principle by the dopamine receptor assay. Exp Clin Endocrinol 1994;102:448–454.
54. Rotblatt M, Ziment I, editors. Evidence-based herbal medicine. Philadelphia: Hanley & Belfus Publ; 2002.
55. Brush MG, Watson SJ, Horrobin DF, Manku MS. Abnormal essential fatty acid levels in plasma of women with premenstrual syndrome. Am J Obstet Gynecol 1984;150:363–366.
56. Graham J. Premenstrual syndrome: evening primrose oil. Thorsens 1984:36–40.
57. Shelton RC, Keller MB, Gelenberg A, et al. Effectiveness of St. John's Wort in major depression: a randomized placebo controlled trial. JAMA 2001;285:1978–1986.
58. Laakmann G, Schule C, Baghai T, et al. St. John's Wort in mild to moderate depression: the relevance of hyperforin for the clinical efficacy. Pharmacopsychiat 1998;31:54–59.

59. Pang Z, Pan F, He S. *Ginkgo biloba* L.: history, current status, and future prospects. J Altern Complement Med 1996;2:359–363.
60. McKenna DJ, Jones K, Hughes K. Efficacy, safety, and use of *Ginkgo Biloba* in clinical and preclinical applications. Altern Ther Health Med 2001;7:70–90.
61. Noorbala AA, Akhondzadeh S, Tamacebi-pour N, Jamshidi AH. Hydroalcoholic extract of *Crocus sativus* L. versus fluoxetine in the treatment of mild to moderate depression: a double-blind, randomized pilot trial. J Ethnopharmacol 2005;97:281–284.
62. Akhondzadeh S, Tamacebi-pour N, Noorbala AA, Amini H, Fallah Pour H, Jamshidi AH, et al. *Crocus sativus* L. in the treatment of mild to moderate depression: a double-blind, randomized and placebo controlled trial. Phytother Res 2005;19:25–29.
63. Wang Y, Han T, Zhu Y, Zheng CJ, Ming QL, Rahman K, Qin LP. Antidepressant properties of bioactive fractions from the extract of *Crocus sativus* L. J Nat Med 2010;64:24–30.
64. Monagle L, Dan A, Krogh V, Jossa F, Farinaro E, Trevisan M. Perimenstrual symptom prevalence rates: an Italian-American comparison. Am J Epidemiol 1993;138:1070–1081.
65. Borrelli F, Izzo AA. Herb-drug interactions with St John's wort (*Hypericum perforatum*): an update on clinical observations. AAPS J 2009;11:710–727.

Current knowledge on this subject

- No single treatment is universally recognised as effective for PMS or PMDD. Several treatments have proven effective including reproductive hormones, central nervous system acting drugs, diuretics, vitamins and minerals.
- Patients with PMS try a wide range of Complementary Alternative medicines
- Efficacy and safety of herb remedies are poorly known.

What this study adds

- Few studies are designed as a RCTs, and often the quality is far to be satisfactory. Adding an evaluation of PMS/PMDD diagnosis, only 10 trials remain available for clinical conclusions.
- *Vitex agnus castus*, *Gingko biloba* and *Crocus sativus* extracts relief PMS better than placebo. In women suffering of PMDD, *Vitex agnus castus* performed equally to fluoxetine. Evening primerose oil is effective as placebo, whereas St. John Worth relief physical/behavioural symptoms but not psychological discomfort.
- None of the herb remedies is associated with major health risks, although the reduced number of tested patients does not allow definitive conclusions on safety.