Vitex agnus-castus Extracts for Female Reproductive Disorders: A Systematic Review of Clinical Trials

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- Verbenaceae
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Abstract

Vitex agnus-castus L. (chaste tree; chasteberry) is a popular herbal treatment, predominantly used for a range of female reproductive conditions in Anglo-American and European practice. The objective of this systematic review was to evaluate the evidence for the efficacy and safety of *Vitex* extracts from randomised, controlled trials investigating women's health.

Eight databases were searched using Latin and common names for *Vitex* and phytotherapeutic preparations of the herb as a sole agent, together with filters for randomised, controlled trials or clinical trials. Methodological quality was assessed according to the Cochrane risk of bias and Jadad scales, as well as the proposed elaboration of CONSORT for reporting trials on herbal interventions.

Thirteen randomised, controlled trials were identified and twelve are included in this review, of which eight investigated premenstrual syndrome, two premenstrual dysphoric disorder, and two latent hyperprolactinaemia. For premenstrual syndrome, seven of eight trials found *Vitex* extracts to be superior to placebo (5 of 6 studies), pyridoxine (1), and magnesium oxide (1). In premenstrual dysphoric disorder, one study reported *Vitex* to be equivalent to fluoxetine, while in the other, fluoxetine outperformed *Vitex*. In latent hyperprolactinaemia, one trial reported it to be superior to placebo for reducing TRH-stimulated prolactin secretion, normalising a shortened luteal phase, increasing mid-luteal progesterone and 17β-oestradiol levels, while the other found *Vitex* comparable to bromocriptine for reducing serum prolactin levels and ameliorating cyclic mastalgia. Adverse events with *Vitex* were mild and generally infrequent. The methodological quality of the included studies varied, but was generally moderate-to-high. Limitations include small sample sizes in some studies, heterogeneity of conditions being treated, and a range of reference treatments.

Despite some methodological limitations, the results from randomised, controlled trials to date suggest benefits for *Vitex* extracts in the treatment of premenstrual syndrome, premenstrual dysphoric disorder and latent hyperprolactinaemia. Further research is recommended, and greater transparency in reporting for future trials.

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Introduction

Use of complementary medicines is becoming increasingly prevalent in Western cultures, with women constituting the largest user group [1]. Treatments for female reproductive health are often sought [2,3]. In this context, the phytotherapeutic agent *Vitex agnus-castus* fruit (chaste tree, chasteberry; family: Verbenaceae) is commonly employed for a range of female reproductive disorders [4], including premenstrual syndrome (PMS) and associated cyclic mastalgia, premenstrual dysphoric disorder (PMDD), lactation difficulties, low fertility [5], and menopause-related complaints [4,6].

PMS affects up to 40% women [7,8], with a further 3–8% (or even 13–18%) qualifying for the diagnosis of the more severe PMDD [9,10]. Cyclical breast symptoms are experienced by approximately 70% of women, while 22% experience moderate-to-extreme discomfort classified as cyclical mastalgia [11]. All of these common problems can be severe enough to interfere with usual activities. Conventional treatments such as hormonal interventions and synthetic antidepressant agents are not preferred options for a number of women. In this context, women often turn

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to complementary medicines for these and other reproductive health concerns.

Whilst these conditions involve different hormonal pathophysiologies, commonalities across some of them relate to prolactin elevation, proposed to be involved in premenstrual symptoms as well as in lactation difficulties. Although the exact cause has not yet been fully established, there is some evidence that premenstrual symptoms can be accompanied by a latent hyperprolactinaemia (LHP) [12,13], the prolactin elevation occurring either premenstrually or in response to stressful situations [14,15]. Increased prolactin levels might inhibit corpus luteal development, thereby indirectly reducing the secretion of progesterone in the luteal phase of the menstrual cycle [16]. LHP has been associated with premenstrual mastalgia, benign breast cysts, and infertility [12,17,18].

Vitex agnus-castus extracts may affect these conditions through dopaminergic activity via binding to dopamine-2 (DA-2) receptors [17], resulting in prolactin inhibition. (The pharmacology of *Vitex* is further reviewed below). Phytochemically, *Vitex* has been shown to contain dopaminergic compounds belonging to the diterpenes, as well as essential oil, flavonoids, and iridoid glycosides. The dried fruits are the most commonly used medicinal form and have a peppery taste. Today, *Vitex* is available in a range of pharmaceutical forms, including tinctures, fluid extracts, tablets, and homoeopathic preparations, and is commonly used throughout Europe and the English-speaking world.

In view of the clinical interest in *Vitex* for female reproductive disorders, the objective of this current review was to identify and systematically review all the data generated from randomised, controlled trials (RCTs) on the efficacy of *Vitex agnus-castus* in these conditions. Many of the earlier clinical studies on *Vitex*, such as those focussing on its galactagogue activity [19,20], were open-label or observational studies. While certainly of interest, studies lacking a placebo control have obvious limitations, particularly for conditions susceptible to a substantial placebo response.

Methods

Search strategy

The following electronic databases were searched (earliest to 2012): Medline, PubMed, EMBASE, The Cochrane Library, CINAHL, Ovid, Google scholar, and Web of Science.

Search terms used were: *Vitex* OR agnus-castus OR agnicasti OR chaste tree OR chasteberry OR monk's pepper OR hemp tree OR agneau chaste OR gatillier OR Keuschlamm OR kyskhedstrae OR agnuscasti OR Agnolyt OR Agnufemil OR Castufemin OR Cefanorm OR Femicur OR Gynocastus OR Hewekliman OR Kytta-femin OR Strotan OR agnomen AND randomised, controlled trial (where database search terms permitted).

In addition, further relevant papers were identified using the "related articles" function in PubMed, and by hand-searching reference lists of relevant journal articles and textbooks.

Where possible, authors were contacted [21–24] for further details of results, if these had not been reported as means and standard deviations.

Study selection

The search was restricted to randomised, controlled trials investigating extracts of *Vitex agnus-castus* in female reproductive conditions. All randomised, controlled trials, including cross-over trials, of *Vitex* versus placebo or a comparator treatment were included. Data from studies investigating multicomponent herbal formulations and homœopathic preparations were excluded.

No language restrictions were imposed.

Data extraction and quality assessment

Details of trial design, duration and setting, condition under investigation, sample size, participants, outcome measures, adverse events, results, and methodological quality were extracted. Included studies were reviewed by two investigators (DvD and KB or HB). To ascertain the validity of eligible randomised trials, two reviewers (DvD and KB) worked independently to determine selection bias, attrition bias, detection bias, performance bias, and reporting bias, using the Cochrane risk of bias assessment tool, RevMan [25]. The Jadad scale [26] was used to assess randomisation, double blinding, and reporting of withdrawals and dropouts. To supplement the quality assessment, additional criteria were assessed according to the proposed elaboration of the CONSORT checklist item 4 for reporting randomised, controlled trials of herbal medicines [27]. Disagreements were resolved by discussion between the two reviewers. If no agreement could be reached, it was decided that a third author would be consulted.

Data analysis

Quantitative meta-analysis was performed where possible, for independent studies investigating a common disorder, with a common comparator, compatible endpoints, and availability of appropriate end-of-treatment data. Heterogeneity was calculated using χ^2 and I^2 statistics. A random effects model was applied to heterogeneous study data. For studies for which a meaningful meta-analysis was precluded, it was decided that data would be qualitatively synthesised.

Of the 106 articles located after the removal of duplicates, 14 articles reporting on randomised, controlled trials (RCTs) met the selection criteria (**Fig. 1**). However, two articles were based on the same data [28,29]. In this case, both papers were examined to extract all relevant information.

Results

Description of studies

Overall, twelve of the thirteen separate trials are included in the present review. The excluded trial by Gerard House reported results for the active treatment group but failed to include data for the placebo arm, or between-group significance values [30]. It would appear that one report [31] is a subpopulation analysis of a larger multicentre trial [28]. It is unclear whether another of the trials was blinded [32]. Three of the studies were of 2 cycles/months duration, one continued for 6 cycles; and nine studies lasted 3 cycles/months, one of which, after a 2-month washout period, readministered the same extract only on the last seven days of the luteal phase for a further 3-month period.

Conditions investigated: The characteristics of the identified studies are included in **Table 1**. Of the 12 RCTs, eight investigated the effects of *Vitex* extracts in women suffering from PMS, two examined *Vitex* in PMDD, and the remaining two investigated latent hyperprolactinaemia (LHP) with/without mastalgia.

Controls: Six of the eight PMS studies were placebo-controlled while two were comparator studies, comparing the effects of *Vitex* with pyridoxine (vitamin B6) and magnesium, respectively. Both RCTs on PMDD compared *Vitex* extracts with fluoxetine. Of

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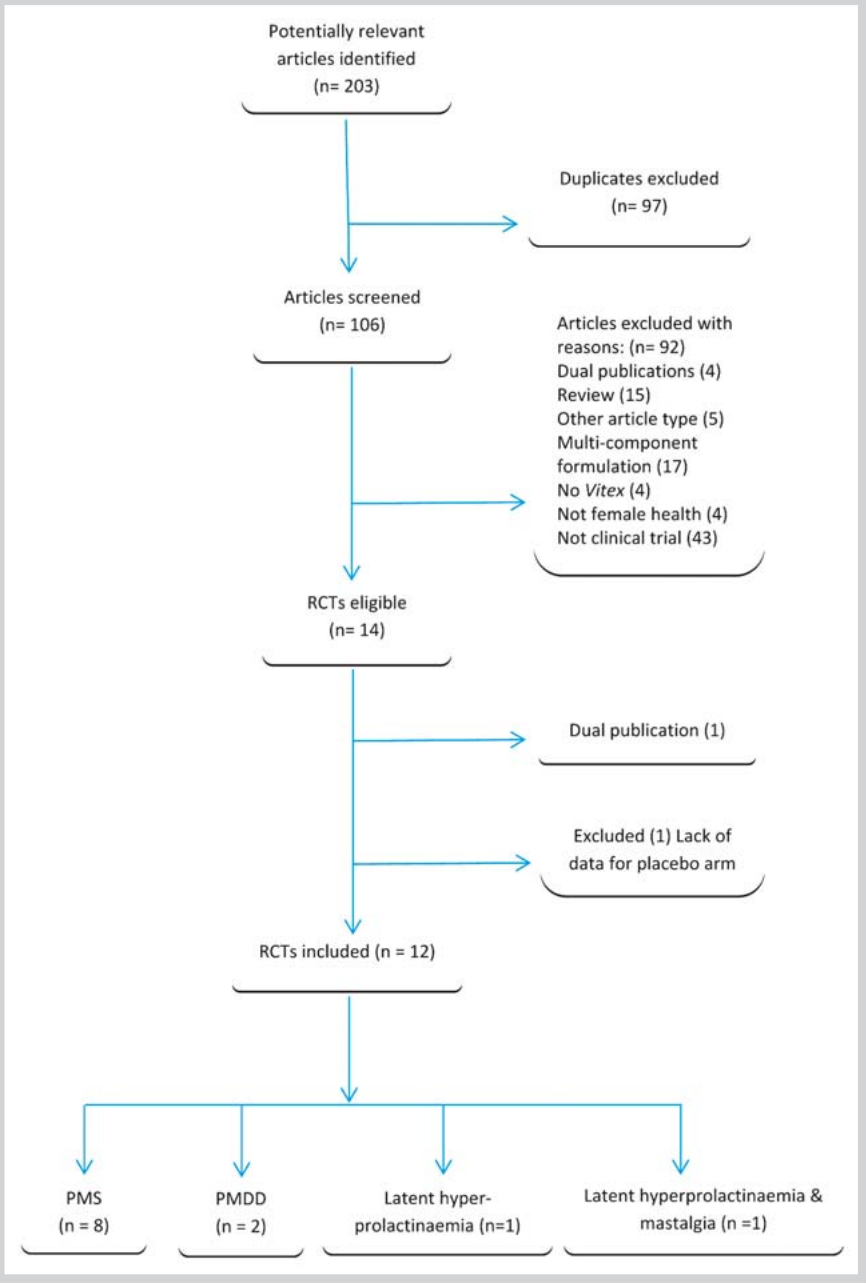

Fig. 1 Flowchart of eligibility assessment and inclusion.

the two trials investigating LHP, one was placebo-controlled, while the other compared *Vitex* with bromocriptine in LHP or mastalgia.

Participants and settings: In the five studies reporting sample size calculations [23,24,31,33,34], estimates ranged from 55 to 120 patients per arm, allowing for drop-outs and withdrawals. All but one of these [33] retained adequate numbers for analysis. Six of the twelve studies gathered trial data from over 100 participants (range 110 to 217). No differences in results were observed according to setting, which included clinical, university, and community-based levels, with the only negative finding from a community-based trial in which PMS sufferers self-identified.

Baseline symptoms were diagnosed according to the DSM-III or DSM-IV criteria in five PMS studies [22,23,28,31,35] and for both PMDD studies [21,36]. PMS was diagnosed by general practitioners in one other study [34] and was self-diagnosed (1) [24] or self-rated on the PMTS (1) [33] for the remaining PMS trials. LHP was established by the mid-follicular phase prolactin response to TRH stimulation, and serum prolactin levels on days 5–8 of the menstrual cycle, respectively, in the two trials using this endpoint.

It was specified in five (of eight) PMS and both PMDD studies that participants experienced regular cycles, with a cycle length ranging between 22 and 35 days (25–34 [23,36]; 24–35 [34]; 22–35 [28,31]). Symptoms were required to have been present for the previous three [35], six [36], or 12 months [28]. Five studies reported a requirement for an exacerbation of symptoms in the late luteal phase as compared to the follicular phase (in days 5–10) [23,36], (days 3–9) [28], (days unspecified) [31,33]. However, only four specified the magnitude of the exacerbation: an increase in the luteal phase (seven days before menses) of at least 16 points on the PMSD scale compared with the follicular phase [28,31] or an increase of 30% or over (days 23–28) compared with the postmenstrual scores (days 5–10) [23,36].

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Table 1 Characteristics of included studies.

First author, year & country	Condition	Study design duration no. of participants	Participant characteristics Age: mean ± SD (years) Diagnostic criteria Two cycles prospective ratings? Criteria Oral contraceptive users + Source of participants	Preparation & dosage vs. comparator	Outcome measures	Main results between groups	Adverse events	Authors' conclusions
Zamani et al. [23], 2012 Iran	PMS	randomised, double-blind, placebo-controlled trial; 6 cycles; n = 134/128; VAC 62; placebo 66	age: VAC 30.77 ± 4.37; placebo 30.89 ± 4.02; met DSM-IV criteria; prospective ratings? yes; DSR: 30 % + days 23–28 *cf* days 5–10; OC users? yes; hospital clinic	preparation not specified; 40 drops of VAC extract for 6 days before menses vs. placebo	self-report VAS	On all the endpoints, the reduction in symptoms in the VAC group was superior to placebo ($p < 0.0001$) except for headaches ($p < 0.01$) using Mann-Whitney mean rank.	none	VAC was effective and well- tolerated for the relief of mild-to-moderate PMS symptoms.
Ma et al. [28–29], 2010 China	PMS moderate-to-severe PMS	randomised, double-blind, placebo-controlled trial; 3 cycles; n = 67/64; VAC 33/31; placebo 34/33	age: VAC 36.8 ± 6.8; placebo 35.3 ± 6.7; PMTS self-assessment scale ≥ 18; prospective ratings? yes; PMSD: 16 points+ 7 days premenses *cf* days 3–9; OC users? no; hospital clinic	VAC BNO 1095 Agnucaston® ethanol (70 %) extract, ratio 10 : 1; 40 mg orally once daily vs. placebo	Chinese versions of PMSD and PMTS; luteal phase serum prolactin levels	VAC group was superior to placebo for total PMTS, PMSD, negative affect, and fluid retention factors, $p < 0.05$, but not food cravings or pain. Clinical efficacy 84.85 % vs. 55.89 %. No significant changes in PRL.	VAC: 1 prolonged period	VAC was effective in treating moderate-to-severe PMS in Chinese women, especially in symptoms of negative affect and water retention.
He et al. [31], 2009 China	PMS	randomised, double-blind, placebo controlled multicentre clinical trial; 3 cycles; n = 217/202; VAC 108/101; placebo 109/101	age: VAC 34.51 ± 7.34; placebo 35.27 ± 6.16; moderate-to-severe PMS – 11 items from DSM-IV; prospective ratings? yes; total score on PMTS ≥ 18; OC users? no; community setting	VAC BNO 1095 Agnucaston® ethanol (70 %) extract, ratio 10 : 1; 40 mg orally once daily vs. placebo	Chinese versions PMSD and PMTS	At the end of 3 cycles, improvements in VAC group were superior to placebo, $p < 0.0001$ on the PMSD, $p < 0.05$ on PMTS, and $p < 0.001$ for clinical efficacy rates (79.8 % vs. 50 %).	VAC: 3 headaches; placebo: 2 headaches	VAC is a safe, well- tolerated, and effective treatment for Chinese women with moderate-to-severe PMS.
Pakgohar et al. [34], 2009 Iran	PMS	randomised, double-blind, placebo controlled trial; 2 cycles; n = 116/99; VAC 58/49; placebo 58/50	age: ≥ 18 yrs. [majority 21–25 yrs]; PMS diagnosed by general practitioner; prospective ratings? not specified; OC users? no; university students, Tehran	Isfahan Gol Daroo Company. Each tablet contained 4.3–4.8 mg dried extract *Vitex* fruit; one tablet daily vs. placebo	Daily Symptom Rating (DSR) scale	Improvement greater with VAC than placebo for total PMS symptoms (60.73 % vs. 20.79 %, $p < 0.001$), psychological symptoms (65.62 % vs. 28.19 %, $p < 0.001$) and physical symptoms (57.98 % vs. 16.22 %, $p < 0.001$). VAC was superior on 16/18 symptoms (no "suicide" or swelling of extremities).	VAC (4): 1 exacerbation of symptoms; 3 GI complaints; NS difference between VAC and placebo	VAC is an effective treatment for the relief of symptoms of premenstrual syndrome.

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Table 1 *Continued*

First author, year & country	Condition	Study design duration no. of participants	Participant characteristics Age: mean ± SD (years) Diagnostic criteria Two cycles prospective ratings? Criteria Oral contraceptive users + Source of participants	Preparation & dosage vs. comparator	Outcome measures	Main results between groups	Adverse events	Authors' conclusions
Schellenberg [22], 2001 Germany	PMS	randomised, double-blind, placebo-controlled trial; 3 cycles; n = 178/170; VAC 91/86; placebo 87/84	age: VAC 37 ± 8.4; placebo: 36 ± 7.4; met DSM-III-R criteria; prospective ratings? not specified; OC users: yes, if dose maintained; six general medicine clinics	VAC extract ZE 440: 60% ethanol, extract ratio 6–12 : 1; standardised for casticin; one 20 mg tablet once daily vs. placebo	VAS 0–10 Domains = irritability, mood alteration, anger, headache, bloating and breast fullness CGI	Improvement greater on VAS with VAC than with placebo ($p < 0.001$). Differences on all domains except bloating were significant ($p = 0.001$ or $p = 0.002$). VAC superior ($p < 0.001$) in all three CGI items. Responder rates: VAC 52% vs. placebo 24%.	VAC (4 mild): acne, multiple abscesses, intermenstrual bleeding, urticarial vs. placebo (3)	VAC extract is an effective and well-tolerated treatment for the relief of PMS symptoms.
Turner et al. [24], 1993 U. K.	PMS	randomised, double-blind, placebo controlled trial; 3 months; n = 600/217	age: not specifed; entry 18–46; self-diagnosed sufferers of PMS based on the MDQ (only 2 s, 3 s, or 4 s on the negative affect); prospective ratings? not specified; community-based	1800 mg/day (600 mg tds) vs. soy-based placebo	Moos Menstrual Distress Questionnaire plus: increased appetite, sweet cravings; feeling less affectionate; drinking more caffeine	Statistical difference on only 1 symptom: "feeling jittery or restless" (placebo outperformed VAC). 25/62 VAC patients reported an improvement in PMS symptoms vs. 16/74 on placebo.	not reported	VAC showed little difference to placebo in the treatment of PMS symptoms in this clinical trial.
Di Pierro et al. [35], 2009 Italy	PMS	randomised (double-blind?), comparator trial; 3 months; followed by 2 months washout, then further 3 months where VAC administered only 7 days of late- luteal phase; n = 82; VAC 42; magnesium 40	age: VAC 37 ± 9.1; magnesium 36 ± 8.2; met DSM-III criteria for 3 previous cycles; prospective ratings? not specified; OC users? yes, if dose maintained; outpatients at Hospital General Medicine clinic	Monoselect Agnus; (fast-release) VAC fruit extract standardised to 0.5% agnuside, 60% ethanol extract; one 40 mg tablet once daily vs. magnesium oxidize 300 mg/day	VAS 0–10	Improvement was greater in the VAC group than the magnesium group in all variables (back pain, menstrual pain, breast fullness, headache, asthenia, irritability, and sleep disturbances), $p < 0.001$, except appetite modulation.	VAC (2 mild): 1 acne, 1 urticaria; magnesium (3): 1 urticaria; 2 acne	The action of VAC is evident after 90 days of continual treatment. Effects can be maintained with a treatment protocol of 7 days per month.
Lauritzen et al. [33], 1997 Germany	PMS	randomised, double-blind, comparator trial; 3 cycles; n = 175/127/105; VAC 61/46; pyridoxine 66/59	age: not specified; entry 18–45 years; "PMTS" symptoms, recurring with every cycle and severe enough to affect quality of life; prospective ratings? not specified; OC users? no; 16 study centres	Agnolyt 1 capsule per day, dried extract 3.5–4.2 mg/day extraction ratio 9.58–11 5 : 1 vs. 1 capsule placebo twice daily on days 1–15, and 1 capsule pyridoxine-HCL (100 mg) twice daily on days 16–35 of the menstrual cycle.	PMTS CGI	On PMTS scale, VAC and B6 reduced scores from 15.2 to 5.1 (− 47.4%) and from 11.9 to 5.1 (− 48%), respectively. On CGI, VAC treatment was rated as excellent by 24.5% and pyridoxine treatment by 12.1% of the investigators. 36.1% of patients in VAC group and 21.3% in pyridoxine group were free from complaints. 5 patients in VAC group became pregnant.	VAC (5): 1 nausea; 1 persistent gastroenteritis; 1 headache; 2 skin reactions. Pyridoxine (4): 1 lump in throat, 1 return of ulcerative colitis; 1 abdominal discomfort; 1 persistent bleeding	VAC was superior to pyridoxine for the treatment of PMS.

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Table 1 *Continued*

First author, year & country	Condition	Study design duration no. of participants	Participant characteristics Age: mean ± SD (years) Diagnostic criteria Two cycles prospective ratings? Criteria Oral contraceptive users + Source of participants	Preparation & dosage vs. comparator	Outcome measures	Main results between groups	Adverse events	Authors' conclusions
Ciotta et al. [21], 2011 Italy	PMDD	randomised, double-blind, comparator trial; 2 months; n = 57; VAC 31; fluoxetine 26	age: 30.5 ± 2,3; VAC 30 ± 2,7; fluoxetine 29 ± 3.8; met DSM-IV criteria for PMDD; prospective ratings? not specified; OC users? not specified; Institute of Obstetrics & Gynaecology	preparation not specified. 6–12 : 1; 20 mg/day oral (corresponding to 180 mg/day plant material) vs. fluoxetine 20–40 mg/day	4 items on HAM-D: depressed mood; work interest; psychic anxiety; general somatic symptoms	Fluoxetine outperformed VAC on all endpoints: depressed mood, $p < 0.02$, work interests, $p < 0.05$, psychic anxiety, $p < 0.003$, general somatic symptomş $p < 0.05$. However VAC group signficantly improved on all endpoints: depressed mood, $p < 0.04$, work interests, $p < 0.04$, psychic anxiety, $p < 0.02$, general somatic symptoms, $p < 0.05$.	"no side effects"	VAC was a valid alternative to fluoxetine treatment for patients with PMDD, (although fluoxetine outperformed VAC on all endpoints).
Atmaca et al. [36], 2003 Turkey	PMDD	randomised, single-blind, rater-blinded trial; 8 weeks; n = 41/38; VAC 20/19; fluoxetine 21/19	age: VAC 34.1 ± 12.5; fluoxetine 32.7 ± 10.8; met DSM-IV criteria for PMDD for at least 6 months; prospective ratings? yes, rated on Penn Daily symptom rating (DSR); OC users: not specified; recruited through university	20–40 mg/day VAC with flexible dosing (not described; nor frequency) vs. fluoxetine 20–40 mg/day	DSR; HAM-D; CGI-SI; CGI-I	With fluoxetine: 50 %+ decrease in 7 PMS symptoms; (VAC showed a 50 % + decrease in 5 PMS symptoms; Clinical improvement: 57.9 % responded to VAC; 68.4 % to fluoxetine	VAC (16): mostly nausea and headache; Fluoxetine (20): mostly nausea, headache, insomnia, sexual dysfunction	Patients with PMDD respond well to treatment with both fluoxetine and VAC extract. However fluoxetine may be more effective for psychological symptoms while VAC may be more effective for physical symptoms.
Kilicdag et al. [32], 2004 Turkey	latent hyperprolactinaemia and mild mastalgia	prospective, randomised, comparator study; 3 months; n = 80/80 (40 with cyclic mastalgia; 40 with LHP)	age: not reported; mastalgia not due to breast disease; hyperprolactinaemia not due to endocrinopathy	Agnucaston®, Biomeks, 40 mg/day vs. bromocriptine, Parlodel® 2.5 mg twice daily, Novartis	serum prolactin on days 5–8 of the menstrual cycle; breast pain assessed by VAS	Both groups improved on both endpoints of mastalgia and PRL levels, $p < 0.001$ for both groups. No significant between–group differences	VAC none; bromocriptine (12.5 %): nausea and vomiting	VAC performs similarly to bromocriptine in cyclic mastalgia and mild hyperprolactinaemia. VAC has fewer (no) adverse events, better compliance and lower cost.
Milewicz et al. [37], 1993 Germany	latent hyperprolactinaemia	randomised, double-blind, placebo-controlled trial; 3 months; n = 52/37; VAC 17; placebo 20	age: VAC 29.0 ± 7.3; placebo 30.1 ± 6.4; cycle irregularities due to latent hyperprolactinaemia, verified by TRH testing at admission; gynaecological practice	Strotan capsules, aqueous ethanolic 50–70 % extract of VAC dried fruits 20 mg/day once daily in the evening on empty stomach vs. placebo	Changes in PRL reserve determined by prolactin (PRL) response to TRH stimulation during the mid-follicular phase after 3 months' treatment	Significant reduction in PRL concentration after TRH ($p < 0.001$); a shortened luteal phase had normalised/lengthened by 5 days. Mid-luteal progesterone levels (low at baseline) normalised ($p < 0.001$ vs. placebo). PMS still present in 2/9 VAC and 11/13 on placebo. Two pregnancies in VAC group.	none	VAC is an efficient medication in the treatment of luteal phase defects due to latent hyperprolactinaemia.

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Four studies (of the 10 PMS and PMDD studies for which it was relevant) reported two or more cycles of prospective daily rating of symptoms prior to randomisation. Oral contraceptive (OCP) users were excluded from four of the eight PMS studies [28,31, 33,34], while three permitted its use providing the dose was maintained [22,23,35]. However, outcomes were similar in studies including or excluding OCP use.

In most studies, women in the early perimenopausal age group were eligible for inclusion. Women were accepted up to age 46 (1 study) [24], 45 (3 studies) [31,33,36], 44 (1 study) [28], and 42 (1 study) [37]. In a further three [22,34,35], women 18 years and over were recruited, and women of "child bearing age" in another [23]. Age range was not reported in two studies [21,32]. The lower included age varied from 18 to 24 years. There were no reports of the actual age ranges recruited, but means reported ranged from 29 to 37 years.

Interventions: Six different *Vitex* preparations were specified in eight of the 12 trials, with the remaining four not specifying the product used [21,23,24,36]. VAC BNO 1095 Agnucaston® dried ethanolic (70%) extract/tincture was used in two PMS studies [28,31] as well as in the study on mastalgia and LHP [32]. Of the other studies, each of the following was used in one trial: VAC extract ZE 440: 60% ethanol m/m, extract ratio 6–12 : 1, standardised for casticin (PMS trial) [22]; Isfahan Gol Daroo Company containing 4.3–4.8 mg dried extract of *Vitex* fruit per tablet (PMS) [34]; Agnolyt, 1 capsule per day, dried extract 3.5–4.2 mg/day, extraction ratio 9.58–11.5 : 1 (PMS) [33]; Monoselect Agnus, a fast-release VAC extract standardised for 0.5% in agnuside (PMS) [35]; and Strotan capsules, aqueous ethanolic 50–70% extract of VAC dried fruits (LHP) [37].

Dosages and dosing regimens varied from 40 drops (approximately 2 mL) of VAC extract/tincture for 6 days before menses [23] to 1800 mg/day [24]. The most commonly prescribed dose was 40 mg/day dried fruit equivalent (DFE) [28,31–33], although 20 mg/day was administered in one trial [37] and a flexible dose of 20–40 mg/day (presumably DFE, not extract) in one of the PMDD studies [36]. In the other PMDD study, an extract 6–12 : 1, 20 mg/day oral (corresponding to 180 mg/dry plant material) was administered [21]. In one key PMS trial, the daily dose was 180 mg/day DFE [22]. For one other trial, it was difficult to definitively determine the DFE dose, although it was probably 40 mg/day [34]. Treatment was generally administered once daily for the entire month.

Comparators: In the RCTS on PMS, placebo tablets described in one trial were soy-based [24]. Other comparators were one capsule placebo twice daily on days 1–15 and one capsule pyridoxine-HCL (100 mg) twice daily on days 16–35 of the menstrual cycle [33], as well as 300 mg magnesium oxide daily [35]. Both PMDD studies compared *Vitex* extracts with fluoxetine 20–40 mg/day [21,36]. In the trial investigating LHP and mastalgia, the comaparator was bromocriptine, Parlodel® 2.5 mg twice daily, Novartis [32].

Outcome measures

Eight different outcome measures were used in the RCTs investigating PMS and PMDD. Among the PMS studies, two measured symptoms on the premenstrual tension syndrome self-rating scale (PMTS) and premenstrual syndrome diary (PMSD) but could not be combined into a meta-analysis due to apparently not being independent. Although two others used visual analogue scales, these could not be combined for analysis as one reported total symptoms (mean difference) while the other reported the means of individual symptom improvements [without standard deviations (SDs)]. Further analysis was precluded as different measures were employed by all the other PMS studies, and not all reported end-of-treatment means and SDs. Four authors were contacted for these details [21–24]; two provided data, where normal distribution permitted [22,23]. Similarly, the HAM-D was used as an outcome measure for both PMDD studies, but one reported on only four domains, while the other reported total scores. No meaningful analysis could be undertaken for the LHP endpoint as different controls were used. None of the studies reported effect sizes or confidence intervals.

Trial results

Results of identified studies are summarised in ◉ **Tables 1** and **2**. Despite the heterogeneity of the studies and outcome measures, the results were generally consistent. In the treatment of both physical and psychological PMS symptoms, *Vitex* extracts were shown to be superior to placebo in all but one of the six studies described as placebo-controlled. Due to heterogeneity of the disorders, comparators, endpoints, limited availability of appropriate end-of-treatment data, and two studies not appearing to be independent, it was only possible to perform a meta-analysis on two PMS studies. Combining the results of the multicentre study reporting total PMS symptoms on the PMSD and PMTS scales [31] with the outcome reported on the Penn's DSR [34], *Vitex* also showed a greater benefit than placebo (MD 8.38, 95% CI 3.48 to 13.28 for PMSD; MD 7.71, 95% CI 1.24 to 14.17 for PMTS) (◉ **Fig. 2**).

PMS: *Vitex* versus placebo

In the four placebo-controlled trials reporting significance values for total PMS scores, *Vitex* extracts were found to be superior to placebo. In a multicentre trial with 208 participants, VAC BNO1095 (40 mg/day, 70% extract Agnucaston®) was superior to placebo over 3 cycles for total PMS symptoms measured on the PMTS ($p < 0.001$) and PMSD ($p < 0.05$) scales, and clinical efficacy rates ($p < 0.001$) [31]. The same results were observed in what appears to be a subset of these women at a hospital in Beijing for total PMS symptoms on PMTS and PMSD, and for negative affect and water retention (all $p < 0.05$) but not pain or food cravings [28]. However, on the individual symptoms, 16 of 17 (all except pain) showed superiority over placebo ($p < 0.001$) in this same cohort [29]. Improvement was greater with the *Vitex* extract (4.3–4.8 mg/day dried extract, Isfahan Gol Daroo) than with placebo for total PMS symptoms measured on the DSR over 2 cycles, and for psychological and physical domains (both $p < 0.001$) but not symptoms of "suicide" or swelling of extremities [34]. Over three cycles, *Vitex* extract ZE 440 (20 mg/day dried extract; ratio 6–12 : 1, 60% ethanol) was found to be superior to placebo in 170 women with mild-to-moderate PMS symptoms, for total PMS symptoms measured on a VAS and CGI ($p < 0.001$) and for all domains [irritability, mood alteration, anger, and breast fullness ($p < 0.001$); as well as headache ($p = 0.002$)] except bloating [22].

On individual symptoms/symptom-clusters, four of five studies reported superiority of *Vitex* extracts over placebo. In addition to those cited above, symptom improvement was noted in 128 women with 40 drops of *Vitex*/day (extract not specified) over 6 cycles in symptoms measured on a VAS: nervousness, restlessness, depression, breast pain, bloating (all $p < 0.001$), as well as headaches, ($p < 0.05$) [23]. One (weak) study found that the soy-based "placebo" used significantly outperformed *Vitex*, 1800 mg/

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Table 2 Results of included studies.

First author, year	Condition	Comparator	Jadad Scale	Outcome measures		Baseline		End of treatment		Mean difference	
						VAC	Control	VAC	Control	VAC	Control
Zamani et al. [23], 2012	PMS	placebo	4	self-report VAS 0–10	headaches†	5.7 ± 2.0	6.6 ± 2.0	3.8 ± 2.0	5.7 ± 2.1	2	0.8
					nervousness§	6.2 ± 1.9	6.6 ± 1.9	3.8 ± 2.0	5.8 ± 2.1	2.4	0.8
					restlessness§	6.1 ± 1.5	6.8 ± 1.6	3.6 ± 2.0	6.0 ± 1.8	2.6	0.8
					depression§	5.8 ± 1.5	6.9 ± 1.6	2.8 ± 1.8	6.0 ± 1.5	3.2	1.0
					breast pain§	6.2 ± 1.2	6.5 ± 1.5	2.6 ± 1.6	5.4 ± 1.8	3.1	1.0
					bloating/tympanis§	6.4 ± 1.3	6.4 ± 1.7	2.6 ± 1.8	5.1 ± 2.0	3.6	1.2
Ma et al. [28, 29], 2010	PMS	placebo	4	PMSD, PMTS	PMSD*	29.38 ± 7.63	28.76 ± 8.23	4.28 ± 5.76	11.79 ± 11.78	24.08 ± 2.13	16.49 ± 2.65
					PMTS*	26.73 ± 4.96	28.53 ± 4.24	8.71 ± 8.62	14.44 ± 10.64		
He et al. [31], 2009	PMS	placebo	4	PMSD, PMTS	PMSD§	29.13 ± 7.88	28.14 ± 7.59	6.41 ± 7.94	12.64 ± 10.35	22.71 ± 10.33	15.5 ± 12.94
					PMTS*	26.17 ± 4.79	27.10 ± 4.76	9.92 ± 9.01	14.59 ± 10.69	16.25 ± 10.28	12.51 ± 10.53
Pakgohar et al. [31], 2009	PMS	placebo	4	DSR	total PMS§	33.82 ± 15.19	31.02 ± 12.32	13.28 ± 10.82	24.57 ± 12.42	60.73%	20.79%
					psychological symptoms§	34.93 ± 17.96	30.26 ± 14.52	12.01 ± 12.22	21.73 ± 14.44	65.62%	28.19%
					physical symptoms§	30.06 ± 14.69	29.04 ± 12.97	12.63 ± 10.62	24.33 ± 12.02	57.98%	16.22%
Schellenberg [22], 2001	PMS	placebo	4	self-report VAS CGI	VAS†	263 ± 104	256 ± 112	134.5	177.9	− 128.5	− 78.1
					CGI severity†	5 ± 1	5.0 ± 1.0	3.70	4.02	− 1.5	− 1.0
Turner et al. [24], 1993	PMS	placebo	2	Moos MDQ	Moos MDQ	not reported	not reported	not reported	not reported	not reported	not reported
Di Pierro et al. [35], 2009	PMS	magnesium	2	VAS 0–10 (Day 0 – Day 90)	back pain§	6.8 ± 1.4	7.2 ± 1.8	1.4 ± 0.6	5.5 ± 1.5		
					menstrual pain§	8.4 ± 1.4	8.8 ± 1.4	2.0 ± 0.4	7.4 ± 2.6		
					breast fullness§	6.0 ± 1.0	6.2 ± 1.4	0.4 ± 0.6	5.4 ± 1.8		
					headache§	8.2 ± 2.8	6.8 ± 1.8	1.0 ± 0.8	6.4 ± 1.6		
					asthenia§	5.4 ± 0.5	6.0 ± 1.4	1.2 ± 0.9	6.4 ± 1.2		
					irritability§	5.0 ± 1.7	5.8 ± 1.4	0.4 ± 0.4	5.0 ± 1.1		
					appetite modulation	2.0 ± 1.5	2.3 ± 0.4	0.2 ± 0.2	1.4 ± 0.6		
					sleep§	5.8 ± 1.8	5.9 ± 1.9	1.1 ± 0.5	5.4 ± 0.7		
Lauritzen et al. [33], 1997	PMS	pyridoxine	4	PTMS per protocol	PMTS	15.2	11.9	5.1 ± 6.6	5.1 ± 6.6	− 47.4%	− 48%
Ciotta et al. [21], 2011	PMDD	fluoxetine	2	HAM-D – 4 items	depressed mood*	96	92	69	36	27	56
					work interest*	83	70	58	26	25	44
					psychic anxiety†	110	100	80	22	30	78
					general somatic*	57	49	37	14	20	35
Atmaca et al. [36], 2003	PMDD	fluoxetine	4	DSR	DSR	171.7 ± 58.1	177.4 ± 62.8	82.8 ± 49.5	85.6 ± 55.3		
				HAM-D	HAM-D	15.2 ± 4.7	15.9 ± 5.6	7.6 ± 4.3	7.1 ± 3.8		
				CGI-SI	CGI-SI	4.1 ± 1.4	4.3 ± 1.6	1.2 ± 0.7	1.5 ± 0.6		
Kilicdag et al. [32], 2004	LHP and mild mastalgia	bromocriptine	2	VAS serum PRL	mastalgia^{NS}	6.8 ± 2.3	6.3 ± 2.3	1.9 ± 1.9	0.89 ± 1.05	4.90 ± 2.10	5.32 ± 2.24
					prolactin^{NS}	945.66 ± 173.46	885.04 ± 177.45	529.19 ± 279.65	472.68 ± 265.64	416.47 ± 248.93	412.36 ± 322.78
Milewicz et al. [37], 1993	latent hyperprolactinaemia	placebo	4		PRL 15 min after TRH§	179 ± 41 ng/mL	181 ± 35	120 ± 20	175 ± 20		
					PRL 30 min after TRH§	108.6 ± 21.5	116.2 ± 4.5	80 ± 20	115 ± 20		
					progesterone§	2.5 ± 0.7 ng/mL	1.99 ± 0.65	9.69 ± 6.34	2.34 ± 0.59		
					17β-estradiol*	132 ± 25 pg/nL	120 ± 266	151.6 ± 25.4	131.1 ± 33.2		
					duration of luteal phase§	5.5 ± 5.2 days	3.4 ± 5.1	10.5 ± 4.3	3.4 ± 5.0		

Between groups p values: * $p < 0.05$; † $p < 0.01$; § $p < 0.001$; NS: no significant between-groups difference

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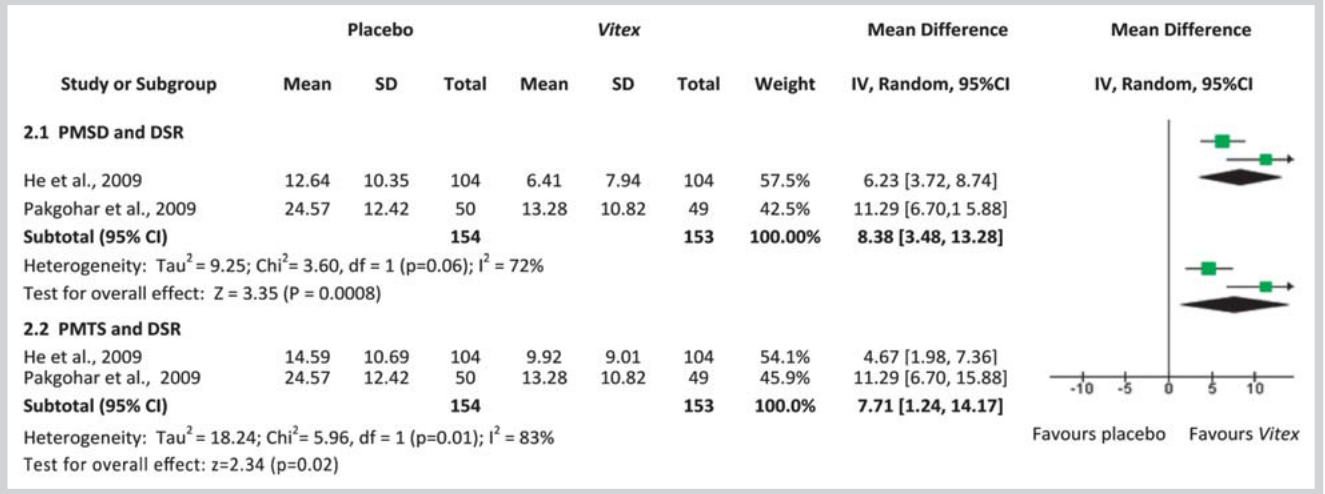

Fig. 2 *Vitex* extracts versus placebo for total PMS.

day (extract not specified), on the symptom of feeling jittery/restless ($p < 0.05$) [24].

PMS: *Vitex* versus other comparator

Two studies compared *Vitex* extracts with other comparators for PMS. In 127 women over three cycles, *Vitex* (3.5–4.2 mg/day Agnolyt®, extraction ratio 9.58–11; 5 : 1) performed similarly to pyridoxine (vitamin B6, 200 mg/day) for PMS, with overall reductions in total symptoms measured on the PMTS of 47.4% and 48%, respectively; pregnancy occurred in 5 patients in the *Vitex* group [33]. An RCT involving 124 women found that in comparison with magnesium oxide (300 mg/day), *Vitex* (40 mg/day, MonoselectAgnus®, 60% ethanol extract) over 3 months showed superiority on back pain, menstrual pain, breast fullness, headaches, asthenia, irritability, and sleep (all $p < 0.001$), but not appetite modulation [35]. After a 2-month washout period when symptoms returned to baselines scores, *Vitex* administered to 21 women for a further 3 months, only in the last 7 days of the luteal phase, was superior to no treatment ($n = 21$) on all the same endpoints ($p < 0.01$).

PMDD: *Vitex* versus fluoxetine

Two studies compared *Vitex* extracts with fluoxetine in PMDD. Clinical improvements were observed over 8 weeks in 57.9% of 20 participants administered *Vitex* (20–40 mg/day, extract not specified) compared with 68.4% of the 21 who received fluoxetine (20–40 mg/day), with a 50% or greater response on 5 domains with *Vitex* (irritability, breast tenderness, swelling, food cravings, and cramps) compared with 7 with fluoxetine (depression, irritability, insomnia, nervous tension, feeling out of control, breast tenderness, and aches). It was concluded that fluoxetine may be more effective for psychological symptoms, while *Vitex* may be more effective for physical symptoms [36]. The second study, involving 57 women for 2 months, found that, despite significant improvements from baseline in both arms for all outcomes, fluoxetine (20–40 mg/day) outperformed *Vitex* (40 mg/day, 6–12 : 1, extract not specified) on all endpoints: depressed mood ($p < 0.02$), work interests ($p < 0.05$), psychic anxiety ($p < 0.003$), and general somatic symptoms ($p < 0.05$) [21].

Latent hyperprolactinaemia

Two studies investigated *Vitex* extracts in latent hyperprolactinaemia. In one of these, a placebo-controlled trial involving 52 women, Strotan®capsules (20 mg/day DFE) were administered in the evening on an empty stomach for 3 months [37]. Compared with placebo, prolactin concentration after TRH stimulation was signifcantly reduced ($p < 0.001$), luteal phase was normalised (lengthened by five days, $p < 0.001$), mid-luteal progesterone levels were normalised ($p < 0.001$), and β-oestradiol was significantly increased ($p < 0.05$). In the other study, a prospective, randomised, comparator study of 3 months' duration, the effect of *Vitex* (40 mg/day DFE Agnucaston®, Biomeks) was compared with bromocriptine (5 mg/day Parlodel®, Novartis) in 40 women with mild hyperprolactinaemia and 40 with cyclic mastalgia [32]. A signficant within-group drop in prolactin levels was observed with both treatments ($p < 0.0001$ for each), with no significant between-groups difference. Similarly, mastalgia assessed on a VAS also decreased significantly in both groups ($p < 0.0001$ for each), with no significant differences observed between groups. Two women in the *Vitex* arm became pregnant.

Methodological quality

Assessment of risk of bias: Risk of bias, assessed according to the Cochrane risk of bias criteria, was predominantly low or unclear (**Figs. 3** and **4**). High risk of bias was only detected in two of the studies [32,33], on one, two, and three of the criteria, respectively (**Fig. 3**). Overall, low risk of bias was most commonly identified for reporting bias (all studies), selection [22,24,28,31,33–35,37] and attrition bias [22,28,31,32,34–37] (eight studies each). Blinding of participants and personnel (performance bias) was most commonly inadequately described (unclear in 10 studies [21–24,28,31,35–37], and high risk in one [32]); followed by random sequence generation (unclear in eight studies [21,24,28,31–35]) and blinding of outcome assessment (unclear in six studies [21,24,28,31,35,36]). It would appear that one of the studies with high risk of bias on two criteria was not blinded as both interventions were propriety products, and a double-dummy design was not described [32].

Assessment on Jadad scale: On the Jadad scale, of the twelve identified randomised, controlled trials, eight were rated with a score

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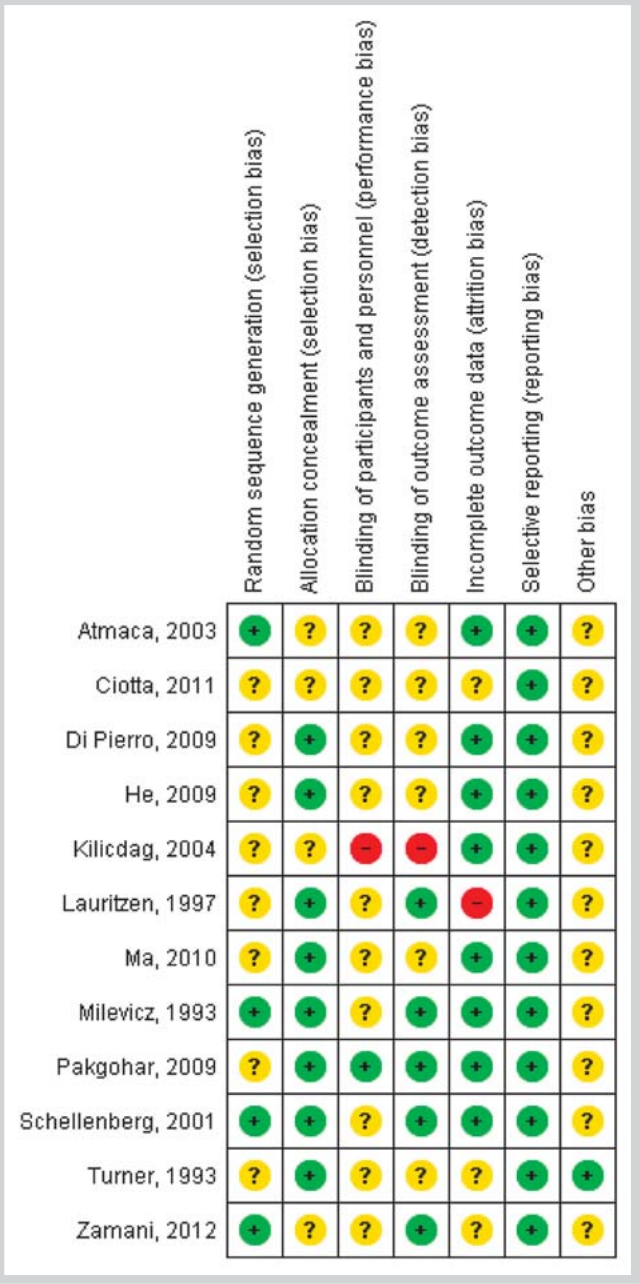

Fig. 3 Risk of bias: summary.

of 4 [22,23,28,31,33,34,36,37], and four with a score of 2 [21, 24,32,35].

Assessment of reporting according to elaborated CONSORT statement for trials of herbal interventions: All identified studies were assessed according to the elaborated CONSORT statement for trials of herbal interventions [27] (**Table 3**). Information was reported in all studies on the Latin binomial, dose and duration of administration; the plant part was reported in all but one study. Eight studies included information on the propriety product name or extract name and name of manufacturer of the product (4A.2); seven studies specified the type of extract. All other items were infrequently reported. Details relating to qualitative testing and practitioners were rarely provided, and no studies provided information about authorisation (licensing or registration of the product [4A.3]), authentication of raw material, and retention of a specimen (4B.4), or content constituents per dosage unit form, and extraneous materials (4C.2). No study reported more than 10 (of a possible 24) pieces of information.

Sample size calculations were reported in five studies [23,24,31, 33,34]. Intention-to-treat (ITT) analysis was specifically reported in three studies [24,28,31]. Results were ostensibly based on ITT analyses in a further three, reporting no dropouts or withdrawals [21,32,35]. Six other studies described dropouts and withdrawals and provided a per protocol analysis.

Adverse events

Four studies reported no adverse events in the *Vitex* arm [21,23, 32,37], while another failed to report on adverse events [24]. In the other seven trials, adverse events associated with *Vitex* were found to be mild and not significantly more frequent than with placebo, magnesium, or pyridoxine. Compared with fluoxetine [36] or bromocriptine [32], adverse events with *Vitex* extracts were reported to be less severe.

In total, 35 adverse events were reported from 641 participants. The highest percentage was reported in a comparator study with fluoxetine in PMDD, where 16 of 38 participants reported mostly nausea or headache [36]. Among the other 603 participants, the main symptoms reported were headaches (4) [31,33], skin reactions (2) [33], acne (2) [22,35], urticaria (2) [22,35], and gastrointestinal complaints (3) [34]. There was one report each of nausea [33], multiple abscesses, intermenstrual bleeding [22], persistent gastroenteritis [33], prolonged menstrual period [28], and exacerbation of PMS symptoms [34].

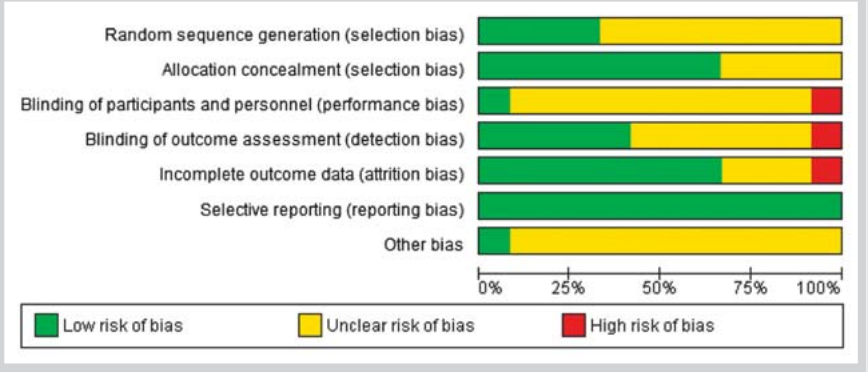

Fig. 4 Risk of bias: graph.

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Table 3 Reporting according to the Proposed Elaboration of CONSORT checklist item 4 for reporting randomised, controlled trials of herbal medicine.

	Zamani et al. [23], 2012	Ma et al. [28–29], 2010	He et al. [31], 2009	Pakgohar et al. [34], 2009	Schellenberg [22], 2001	Turner et al. [24], 1993	Di Pierro et al. [35], 2009	Lauritzen et al. [33], 1997	Ciotta et al. [21], 2011	Atmaca, et al. [36], 2003	Kilicdag et al. [32], 2004	Milewicz et al. [37], 1993
4A: Herbal medicinal product name												
1. i) Latin binomial;	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ii) botanical authority; and				✓								✓
iii) family									✓			
iv) common names.					✓		✓					✓
2. The propriety product name (brand name) or extract name and name of manufacturer of the product.		✓	✓	✓	✓		✓	✓			✓	✓
3. Whether the product is authorised (licensed or registered) in the country in which the study was conducted.												
4B: Characteristics of the herbal product												
1. Plant part used in extract.	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓
2. Type of product, e.g. raw, (fresh or dry) extract		✓	✓	✓	✓	✓		✓				✓
i) Type and concentration of extraction solvent use (e.g. 80% ethanol, etc.); and		✓	✓		✓		✓					
ii) the ratio of herbal drug to extract (e.g. 2 : 1)					✓			✓	✓			
3. The method of authentication of raw material, the lot number of raw material; whether a voucher specimen was retained; where deposited and reference number.												
4C: Dosage regimen and quantitative description												
1. I) The dosage of the product	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ii) duration of administration; and	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
iii) how these were determined.									✓			✓
2. The content of all quantified herbal product constituents per dosage unit form. Added materials such as binders, etc.												
3. For standardised products the quantity of active/marker constituents per dosage unit form.							✓					
4D: Qualitative testing												
1. i) Products chemical fingerprint and methods used								✓				
ii) who performed the chemical analysis; and												
iii) whether a sample of the product was retained;												
iv) where.												
2. i) Description of any special testing/purity testing undertaken												
ii) which unwanted components were removed; and iii) how												
3. Standardisation:					✓		✓					
i) what to standardise; and												
ii) how.												
4E: Placebo/control group						✓	✓	✓		✓		
The rationale for the type of control/placebo.												
4F: Practitioner/s		✓										
A description of the practitioners (training and practice experience) that are part of the intervention.		(partial)										

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Discussion

To our knowledge, this is the first systematic review to examine randomised, controlled trials of *Vitex agnus-castus* extracts in all women's reproductive health conditions. Despite the large number of clinical studies that have been conducted on *Vitex* in this context, the only randomised, controlled trials that could be identified focused on premenstrual syndrome (PMS) and related conditions, premenstrual dysphoric disorder (PMDD), latent hyperprolactinaemia, and cyclic mastalgia. In all, 106 unique studies were located, and twelve are included in the current review.

In PMS, all studies, with the exception of one poor quality trial [24], showed *Vitex* extracts to be superior to placebo [22,23,28,29,31,34], pyridoxine (vitamin B6) [33], and magnesium [35] for the amelioration of total PMS symptoms, and psychological and physical subclusters. Findings regarding premenstrual bloating [23], fluid retention [22,28], swelling of extremities [34], and food cravings [29,36] appear to be inconsistent, however. In PMDD, fluoxetine outperformed *Vitex* in two studies [21,36], although improvements were also evident with *Vitex*, which was associated with fewer adverse events. For late luteal phase defects due to LHP, one randomised, controlled trial found *Vitex* to be superior to placebo [37], while a second showed it to be equivalent to bromocriptine but with better compliance and fewer (no) side effects [32]. In the latter study, its effects on cyclic mastalgia were also comparable with those of bromocriptine.

The safety profile was excellent overall for *Vitex* extracts, with adverse events being mild and generally infrequent. The quality of the trials varied from weak to very good, with the majority being rated as good. In terms of risk of bias assessment, three studies were predominantly judged to have a low risk of bias [22,34,37], while the others required greater transparency in reporting. Comparison of studies conducted prior to and post-publication of the CONSORT checklist item 4 for reporting RCTs of herbal medicine suggests that the transparency of reporting has not been impacted by this recommendation.

The findings of the present study are consistent with those of a systematic review of good quality, randomised, controlled trials of phytotherapeutic agents, including *Vitex* extracts, for premenstrual syndrome [38], and with a review of randomised and non-randomised studies of *Vitex* and multicomponent formulations containing *Vitex* for the treatment of mastalgia [39]. The current systematic review includes a greater number of studies investigating only *Vitex* mono-preparations, including RCTs of all women's health conditions, and imposing no language restrictions. In addition, we include a risk of bias assessment, assessment of reporting according to the elaboration of the CONSORT checklist item 4 for reporting on RCTs of herbal interventions, and a meta-analysis where studies permitted. The good tolerability and safety profile are consistent with the findings of a 2005 systematic review on the adverse events associated with *Vitex* extracts [40].

Based on current evidence regarding the pharmacology of *Vitex*, the following mechanisms may be of relevance: *Vitex* has been shown to have dopaminergic activity by binding to DA-2 receptors [17], which results in prolactin inhibition. For example, using the corpus striatum membrane dopamine receptor binding assay, it was determined that *Vitex* contained several active principles that bind to the dopamine D2 receptor. The action of the chaste tree on pituitary hormone secretion *in vitro* was selective, since both basal and LHRH-stimulated gonadotropin (FSH, LH) release remained unaffected [41]. An extract (containing 3.3 mg/mL water-soluble substances) markedly reduced stress-induced prolactin release in rats after intravenous injection [15]. However, the prolactin-inhibiting activity is not consistent with a traditional galactagogue action attributed to *Vitex*, possibly because effects on lactation are dose-related [41,42]. *Vitex* also effected a dose-dependent clinical increase in melatonin secretion [43], suggesting a benefit in the symptoms of disordered sleep associated with female reproductive cycles and in menopause [44,45]. Flavonoids in *Vitex* (especially apigenin) have also demonstrated binding activity to the beta oestrogen receptor *in vitro*, a finding of uncertain clinical relevance [46]. The pharmacology of *Vitex* has been comprehensively reviewed elsewhere [17,44].

The failure to find significance over placebo in the study by Turner et al. could be attributable, at least in part, to their choice of a soy-based placebo. Some evidence suggests that soy may be of benefit in PMS [47], and specifically in physical symptoms of headache, breast tenderness, cramps, and swelling [48]. This is probably due to the mild oestrogen agonist activity of its isoflavone constituents [49]. Therefore, the use of a potentially active placebo was probably ill-advised.

Of the 12 studies reviewed, seven were placebo-controlled while the remaining five were comparator studies. The use of reference treatments that do not have established benefits in premenstrual symptoms such as magnesium or vitamin B6 can potentially cloud the results of these studies. These comparators may have acted as a placebo in these trials. In such instances, the inclusion of a third placebo arm is helpful. By way of elaboration, the interpretation of the finding that *Vitex* was equivalent to pyridoxine (vitamin B6) on the PMTS scale in the trial by Lauritzen et al. is open to interpretation, since the efficacy of pyridoxine in premenstrual syndrome is controversial [50,51], although there is some evidence to support its role in the treatment of PMS symptoms and premenstrual depression [52,53]. Nonetheless, investigator and patient ratings suggested superiority of *Vitex* extracts over pyridoxine [33].

The finding that *Vitex* extracts were better tolerated than bromocriptine in mastalgia patients is of uncertain relevance to current clinical practice as bromocriptine is no longer commonly prescribed, and is known to have a high side effects profile [54,55].

The diagnosis of latent hyperprolactinaemia based on an abnormally large prolactin response to TRH stimulation is not commonly reported in current literature. However, the effect of *Vitex* to treat this condition is consistent with its dopaminergic activity.

As is common with research on PMS, consistency was lacking across studies in terms of the definition employed, including degree of aggravation in the late luteal phase, and the specific days of the follicular phase with which these were compared; it was unclear whether some studies required two cycles of prospective daily ratings prior to randomisation. Several studies included perimenopausal women, in whom ovulatory cycles are less frequent, suggesting that some symptoms under examination may have been more appropriately described as PMS-like [56]. The DSM-III and DSM-IV criteria [57] used in several trials for diagnosing premenstrual syndrome describe "late luteal phase dysphoric disorder", and as such these findings appear to relate to PMDD at the more severe end of the PMS spectrum. This suggests a possible lack of uniformity regarding the conditions actually being treated in these studies.

In addition to the limitations mentioned above, publication bias cannot be excluded, particularly in earlier studies published prior

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to the establishment of the international clinical trials register, as most study findings have been positive for *Vitex* in the context of women's health.

The range of conditions under investigation, outcome measures, and expression of results only allowed for a meta-analysis of two studies to be conducted. The quality of reporting of clinical trials was inadequate to permit a complete assessment of risk of bias. Sample sizes were small in some studies, and sample size calculations were reported in only five. Overall, the wide range of dosages and insufficient information about the *Vitex* extracts administered prevents determination of phytoequivalence across studies.

Greater transparency in methodological reporting would facilitate assessment of quality of trial design, results, and risk of bias in clinical trials, as would inclusion of full information according to the CONSORT checklist for RCTs of herbal medicine interventions [27]. This latter point would facilitate the determination of phytoequivalence of extracts studied for the purposes of clinical practice as well as further research. To overcome the word limitations, this could be considered as an appendix to the main report [6].

More meaningful interpretation of findings would be permitted by choice of comparators that have clearly established benefits in the condition under investigation and are commonly prescribed in clinical practice.

Despite small sample sizes in some studies, randomised, controlled trials to date appear to support the efficacy and tolerability of *Vitex agnus-castus* extracts in the treatment of premenstrual syndrome, premenstrual dysphoric disorder, and latent hyperprolactinaemia. However, lack of transparency in the reporting of some studies limits assessment of trial design and, in some cases, results. Future research into *Vitex* extracts for these conditions would benefit from use of tightly defined patient populations and common endpoints. To permit determination of assessment of risk of bias and phytoequivalence of extracts, greater transparency in reporting methodological details, including the phytotherapeutic intervention, is recommended. This would inform researchers and clinicians prescribing *Vitex* extracts for premenstrual disorders.

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Conflict of Interest

Associate Prof. Kerry Bone is a founder and director of research and development of MediHerb Australia Pty. Ltd. and is related to Diana van Die (in-law).

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