

Effects of a Combination of *Hypericum perforatum* and *Vitex agnus-castus* on PMS-Like Symptoms in Late-Perimenopausal Women: Findings from a Subpopulation Analysis

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Abstract

Background: It has been suggested that some of the symptoms typically attributed to menopause may be more related to premenstrual syndrome (PMS) than menopause, as perimenopausal women appear to be more prone to PMS-like symptoms, or at least to tolerate them less well.

Objective: The objective of this study was to evaluate the effectiveness of a phytotherapeutic intervention comprising a combination of *Hypericum perforatum* (St. John's wort) and *Vitex agnus-castus* (chaste tree/berry) in the management of PMS-like symptoms in perimenopausal women.

Design: A double-blind, randomized, placebo-controlled parallel trial was conducted over 16 weeks on menopause-related symptoms. Data on PMS-like symptoms were collected at 4-weekly intervals from a small subgroup of late-perimenopausal women ($n = 14$) participating in this study. The primary endpoint was PMS scores measured on the Abrahams Menstrual Symptoms Questionnaire, comprising the subclusters of PMS-A (anxiety), PMS-D (depression), PMS-H (hydration), and PMS-C (cravings). Herbal combination therapy or placebo tablets were administered twice daily.

Results: At the end of the 16-week treatment phase, analyses of covariance showed the herbal combination to be superior to placebo for total PMS-like scores ($p = 0.02$), PMS-D ($p = 0.006$), and PMS-C clusters ($p = 0.027$). The active treatment group also showed significant reductions in the anxiety ($p = 0.003$) and hydration ($p = 0.002$) clusters, using paired-samples t tests. Results of trend analyses showed significant treatment group effects across the five phases for total PMS and all subscales, all in the clinically expected direction. No significant trends were evident in the placebo group.

Conclusions: These results suggest a potentially significant clinical application for this phytotherapeutic combination in PMS-like symptoms among perimenopausal women. Further research is warranted through a randomized, controlled trial dedicated to investigation of these symptoms.

Introduction

IT HAS BEEN SUGGESTED THAT some of the symptoms typically attributed to menopause may be more related to premenstrual syndrome (PMS),¹ which is observed to be quite prevalent, or less well-tolerated, in perimenopausal women.

However, the menstrual cyclicity of the symptoms may not always be apparent, not only because of the unpredictable nature of cycles, but also because ovulatory cycles can occur in the absence of subsequent menstruation during the perimenopause.² When PMS *co-exists* with menopausal symptoms, management with hormone therapy (HT) is

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difficult, as progestins are found to aggravate PMS symptoms and combined HT regimens may induce PMS-like symptoms in susceptible women.³

PMS is thought to result from sensitivity to normal hormonal fluctuations in the late luteal phase of the menstrual cycle, possibly due to neurotransmitter dysfunction.⁴ As these hormonal fluctuations depend on the occurrence of ovulation, which is less frequent during the late perimenopause, symptoms during this phase are more appropriately termed "PMS-like."

The herb *Vitex agnus-castus* (chaste tree/berry) has been shown to effect significant improvement in premenstrual symptoms such as irritability, mood alteration, anger, headache, breast tenderness and bloating.^{5,6} It is also widely prescribed for the treatment of menopausal symptoms by UK herbalists.⁶ Various mechanisms have been proposed including prolactin inhibition, conferring benefit in latent hyperprolactinemia, an opiate-agonist effect, and stimulation of melatonin secretion.⁶

Hypericum perforatum (St. John's wort), in addition to its efficacy for mild–moderate depression,⁷ has been observed to significantly reduce the severity of premenstrual symptoms.⁸ *Hypericum* extracts have been shown to influence serotonergic, noradrenergic, dopaminergic, and γ -aminobutyric acid–ergic mechanisms.⁹ Other potentially relevant mechanisms of action include the regulation of genes controlling hypothalamic–pituitary–adrenal axis function and opioid receptor binding activity.⁹

This study aimed to investigate the effects of a combination of *H. perforatum* and *V. agnus-castus* on PMS-like symptoms in a small subpopulation of late-perimenopausal women participating in a double-blind, placebo-controlled, randomized trial on menopausal symptoms.¹⁰

Methods

The study protocol was approved by the Royal Melbourne Institute of Technology University Human Research Ethics Committee. All participants gave written informed consent prior to study entry.

Of 100 volunteers recruited to the larger study, 14 late-perimenopausal women provided baseline data for PMS-like symptoms and menstruated at least once within the last 12 weeks of the treatment phase. Exclusion criteria included concurrent major illnesses, substance abuse, and concurrent treatment for menopausal or PMS-like symptoms, and any medication known to interact with the study intervention.

The daily dose of *H. perforatum* was extract equivalent to 5400 mg dry herb flowering top administered via three tablets, each standardized to contain 990 μ g hypericins, 9 mg hyperforin, and 18 mg flavonoid glycosides.¹⁰ The daily dose of *V. agnus-castus* was extract equivalent to 1000 mg dry fruit.¹⁰ The *Vitex* tablet was not a standardized preparation as the key quality markers for this herb have not yet been established. Further details of the herbal intervention, according to the Elaborated Consort checklist, have been provided elsewhere.¹⁰ Tablets and matching placebos were manufactured by MediHerb Australia according to the Code of Good Manufacturing Practice, and are included as Listed Medicines on the Australian Register of Therapeutic goods. They were randomized by MediHerb using a computer-generated random number table.

Participants recorded the severity of their PMS-like symptoms at study entry by recall and during the premenstrual phase whenever the impending onset of menstruation was evident throughout the 16-week treatment phase. These were recorded on Abraham's Menstrual Symptoms Questionnaire,¹¹ consisting of four clusters, namely, PMS-A: nervous tension, irritability, mood swings, and anxiety; PMS-H: weight gain, swelling of extremities, breast tenderness, and abdominal bloating; PMS-C: headaches, cravings for sweets, increased appetite, pounding heart, fatigue, and dizziness; and PMS-D: depression, forgetfulness, crying, confusion, and insomnia. Potentially confounding dietary and lifestyle factors and adverse events were monitored.

Data were analyzed using Statistical Package for Social Science Version 16. Assumptions for parametric tests were met. Last observation carried forward was used to deal with missing week-16 PMS data, provided the last observation was at week 8 or later. Three (3) sets of data analysis were conducted on the overall PMS scores and its four subscales. First, single-factor between-subjects analyses of covariance (ANCOVAs) were used to evaluate the overall treatment effects, with the baseline scores serving as the covariates, and the equivalent week 16 scores as the dependent variables. The treatment and placebo groups formed the between-subjects factor. Second, focused linear mixed model single degree of freedom *F*-test comparisons, with appropriate Bonferroni corrections, were used to examine specific phase-within-group and group-within-phase differences. Finally, analyses of orthogonal polynomials (trend analyses), using a linear mixed-model approach, were conducted across the five phases, separately for the treatment and placebo groups, to examine the pattern of change across the phases.

Results

There were no significant baseline differences between the two groups in terms of sociodemographic characteristics or outcome measures. The mean age was 49 in each group and the mean body–mass index 24.5 (\pm 3.7) and 24.7 (\pm 4.1) for the placebo (n = 6) and active groups (n = 8), respectively. All 14 participants in this subgroup completed the study and were included in the analyses.

Figure 1 shows the pattern of change for the five measures across the five phases for the treatment and placebo groups. At a descriptive level, it is evident that there was no notable difference between the groups on any measure at either baseline or week 4, with differences emerging subsequently in the clinically expected direction. Notable group differences are evident for all measures at week 16.

This interpretation was confirmed by statistical analysis. Three (3) of the five ANCOVAs revealed significant group differences at week 16: Total-PMS, $F(1, 11) = 7.33$, $p = 0.020$; PMS-C, $F(1, 11) = 6.53$, $p = 0.027$; and PMS-D, $F(1, 11) = 11.61$, $p = 0.006$. Focused single degree of freedom tests revealed no significant differences between groups on any measure at either baseline or at week 4, but significant differences in the clinically expected direction at week 16 for PMS-Total, $F(1, 39.81) = 4.82$, $p = 0.034$; PMS-C, $F(1, 35.57) = 4.69$, $p = 0.037$; and PMS-D, $F(1, 39.33) = 8.07$, $p = 0.007$.

The trend analyses revealed no significant trends for any test involving the placebo group, but four of the five measures in the treatment group revealed significant quadratic trends:

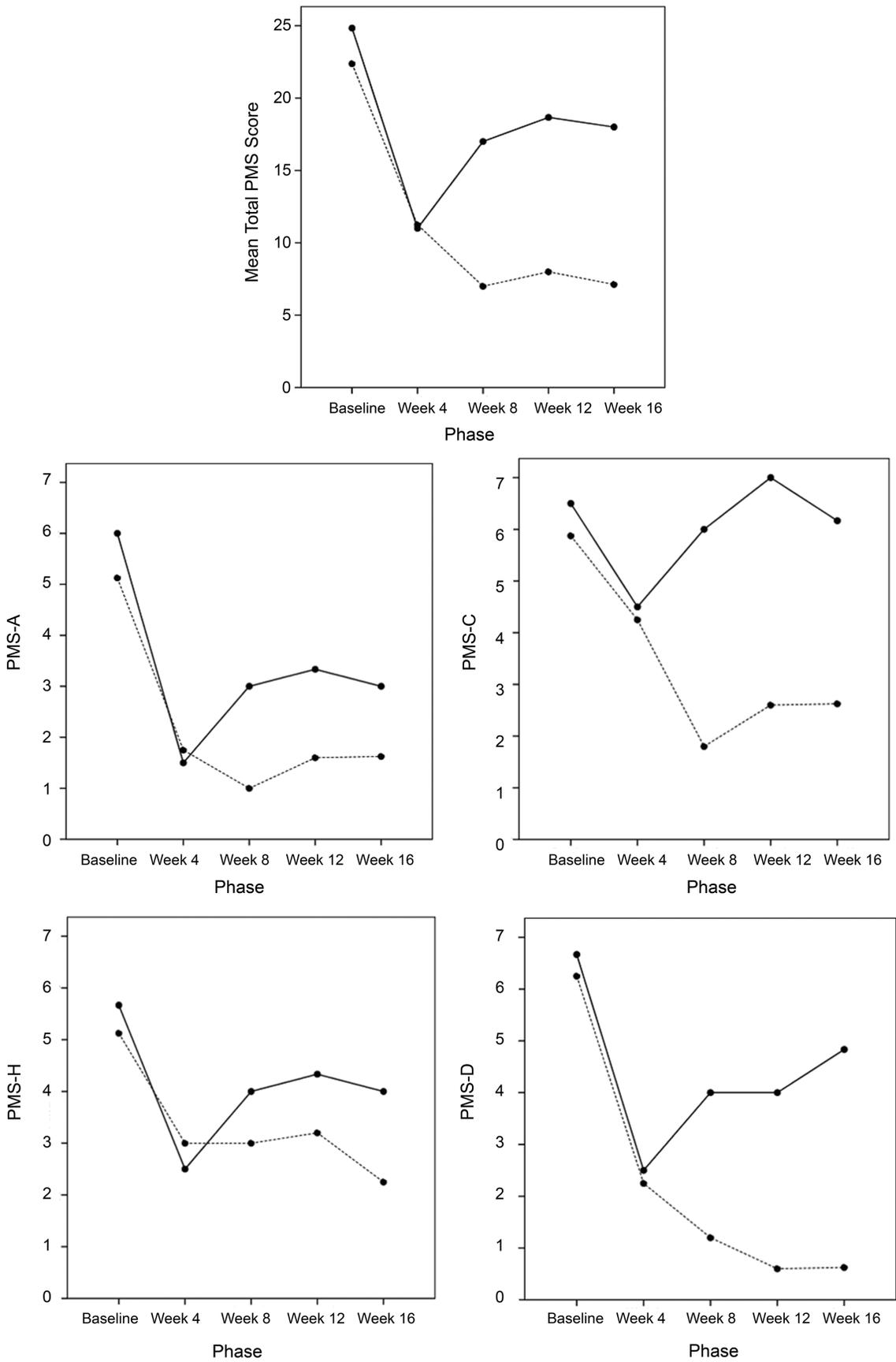


FIG. 1. Effect of intervention on premenstrual syndrome (PMS) total and subcluster scores. Abraham's Menstrual Symptoms Questionnaire subclusters of PMS-A (anxiety), PMS-D (depression), PMS-H (hydration), and PMS-C (cravings). Active treatment (.....); placebo (_____).

PMS-Total, $t(18.89) = 5.39$, $p < 0.001$; PMS-A, $t(19.48) = 4.10$, $p = 0.001$; PMS-C, $t(18.52) = 2.98$, $p = 0.008$; and PMS-D, $t(18.95) = 3.53$, $p = 0.002$. The fifth measure, PMS-H, failed to show a significant quadratic trend, but did reveal a significant linear trend, $t(18.26) = 4.65$, $p < 0.001$. All quadratic trends reflected the same pattern of clinical change: a steep decrease in symptoms from baseline to week 8, followed by a pattern of maintained change to week 16.

Discussion

In this subpopulation of irregularly menstruating late-perimenopausal women, the combination of *H. perforatum* and *V. agnus-castus* was superior to placebo for total PMS-like symptoms and the subclusters, PMS-D (depression) and PMS-C (cravings). The active treatment group also showed significant improvements on PMS-A (anxiety) and PMS-H (hydration), although this effect was not superior to placebo.

The observations from the present study support results from previous studies on the efficacy of *V. agnus-castus* in overall premenstrual symptoms,⁶ as well as pilot studies with *H. perforatum* in PMS, particularly for depression-related symptoms.⁸ However, they contrast with findings from the larger study of this combination in menopausal symptoms (measured on the Greene Climacteric scale) in late peri- and postmenopausal women,¹⁰ and in the particular subgroup investigated here. This suggests that benefits to PMS-like symptoms do not simply reflect improvements to actual menopausal symptoms.

To our knowledge, this is the first study of this phytotherapeutic combination in PMS-like symptoms. The duration of the trial was adequate to allow for washout of the placebo effect, randomization resulted in equivalent groups, and blinding was successful. Good quality-assurance data were available for the phytotherapeutic intervention, for which overall tolerability and acceptability were good and compliance high.

The main limitations in this study were the small subgroup sample size and the late-perimenopausal status of the sample, with associated infrequent ovulatory menstrual cycles. As this was a substudy of a menopause study, the diagnosis of PMS at baseline was not confirmed by 2 months of ratings, but relied on recall of symptoms, allowing for potential recall bias.

The current study suggests a potentially significant clinical application for the combination of *H. perforatum* and *V. agnus-castus* for largely neglected symptoms among perimenopausal women. Due to the limitations of this study, however, these findings should be interpreted with caution until replicated. This phytotherapeutic combination warrants further investigation in a dedicated study of PMS-like symptoms with a larger sample of women.

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Disclosure Statements

No competing financial interests exist for Margaret Diana van Die, Professor Henry Burger, Professor Helena Teede, or Dr. John Reece, Associate Prof. Kerry Bone is a co-founder and director of research and development of MediHerb Australia Pty Ltd., and is related to Diana van Die (in-law).

References

1. Khan SA, Pace JE, Cox ML, et al. Climacteric symptoms in healthy middle-aged women. *Br J Clin Pract* 1994;48:240–242.
2. Burger HG, Robertson DM, Baksheev L, et al. The relationship between the endocrine characteristics and the regularity of menstrual cycles in the approach to menopause. *Menopause* 2005;12:267–274.
3. O'Brien S, Ismail KMK, Jain K. Premenstrual syndrome and the menopause. In: Studd J, ed. *The Management of the Menopause*. 3rd ed. London: The Parthenon Publishing Group Limited, 2003:111–117.
4. Halbreich U. Gonadal hormones and antihormones, serotonin and mood. *Psychopharmacol Bull* 1990;26:291–295.
5. Linde K, Mulrow CD. St John's wort for depression. *Cochrane Database Syst Rev Abstracts* 2000;2:CD000448.
6. Christie S, Walker AF. *Vitex agnus-castus* L: (1) a review of its traditional and modern therapeutic use; (2) current use from a survey of practitioners: *Eur J Herb Med* 1997;3:29–45.
7. van Die MD, Burger HG, Teede HJ, Bone KM. *Vitex agnus-castus* (chaste tree/berry) in the treatment of menopause-related complaints: *J Altern Complement Med* 2009;15:853–862.
8. Stevinson C, Ernst E. A pilot study of *Hypericum perforatum* for the treatment of premenstrual syndrome. *Br J Obstet Gynaecol* 2000;107:870–876.
9. Butterweck V, Schmidt M. St. John's wort: Role of active compounds for its mechanism of action and efficacy. *Wien Med Wochenschr* 2007;157:356–361.
10. Van Die MD, Burger HG, Bone KM, et al. *Hypericum perforatum* with *Vitex agnus-castus* in menopausal symptoms: A randomized, controlled trial. *Menopause* 2009;16:156–163.
11. Abraham G. Premenstrual tension. *Curr Prob Obstet Gynecol* 1980;3:1–39.

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