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Original Article

Vitex agnus-castus (Chaste-Tree/Berry) in the Treatment of Menopause-Related Complaints

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Abstract

Background: The origin of the current practice of administering *Vitex agnus-castus* in menopause-related complaints is uncertain, but appears to be relatively recent. Here we review the evidence for this application of *Vitex* based on evidence from pharmacological studies and clinical research.
Methods: The mechanisms of potential relevance in the context of menopause are explored with reference to the current understanding of the endocrinology and neuroendocrinology of menopause and associated symptoms.
Conclusions: We conclude that, while evidence from rigorous randomized controlled trials is lacking for the individual herb in this context, emerging pharmacological evidence supports a role for *V. agnus-castus* in the alleviation of menopausal symptoms and suggests that further investigation may be appropriate.

Introduction

The practice of administering *Vitex agnus-castus* (chaste-tree/berry or Monk's pepper, family Verbenaceae) in the treatment of menopause-related complaints appears to be of relatively recent origin. In current Anglo-American and European phytotherapeutic practice, *Vitex* fruit is most widely used for female reproductive problems, finding an application in conditions such as premenstrual syndrome, anovulatory cycles, infertility, and hyperprolactinemia, among others.[1,2] It is said to have a normalizing action on the menstrual cycle.[1,2] References to its value for "diseases of the uterus" appear as far back as the works of Hippocrates in 4th century BC and Dioscorides in AD 77.[3] Gerard, one of the great Renaissance herbalists, recommended it for inflammation of the uterus and as an emmenagogue to promote menstruation.[4]

The earliest overt reference in the literature to the application of *Vitex* in menopause-related complaints, however, does not appear until the 20th century. A 1972 publication of a collective report on the clinical experience of 5 practitioners with Agnolyt® (a patent medicine extracted from dried *Vitex* fruit) reported on its efficacy for menopausal bleeding and menopausal complaints.[5] Its use in this context appears to have now become relatively popular in the Anglo-American tradition.[6–9] A practitioner survey of 276 UK herbalists reported that 86.3% prescribed it for the treatment of perimenopausal complaints, including hot flushes.[10] It is also used in clinical practice to assist with withdrawal from hormone therapy (HT).[1,7,10] The fruit is a common ingredient of phytotherapeutic formulations for menopause-related complaints in several Western countries (Table 1).[11–14] While evidence for *Vitex* as a sole agent in this context is lacking from randomized controlled trials (RCTs), emerging pharmacological evidence, relating to its dopaminergic activity,[15–17] affinity for opioid receptors,[18,19] and enhancement of melatonin secretion,[20] supports a role for *V. agnus-castus* in the alleviation of menopausal symptoms. This paper reviews the clinical and pharmacological evidence supporting this practice, and possible rationale for such an application.

Inconsistency of Definitions Used in Reference to Menopause

The practice of administering *Vitex* for menopausal complaints is not universally supported. One possible explanation for the differences in observations from clinical experience and from research is the lack of consistency in the use of terminology relating to the menopausal stages. As a result, it is often unclear from the literature which menopausal phases,

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Table 1. Herbal Menopause Formulations Containing *Vitex Agnus-Castus* on the Market

Manufacturer	*Product*
Forces of Nature	Menopause Ease (Essential oil blend – transdermal)
Fusion Health	Menopause
Gaia Herbs	Supreme Vitex/Alfalfa - *A Menopausal Corrective Formula*
Herb Farm	Healthy Menopause Tonic (Pulsatilla + Vitex Comp)
Herbs of Gold	Menopause Night Relief
Nature's Alternatives	Vitex/Black Cohosh Plus: Women's Menopause Herb Tonic
Naturopathica	MenoEze Forte; MenoEze Day Night formula; MenoThin
Nature's Sunshine	Menopause support
Neways	Wild yam and chaste tree cream
NutraLife	MenoLife
Oona	Herbal Supplement for Menopause, with Black Cohosh & Vitex
Oriental Botanicals	Femaren
Planetary Formulas	MenoChange Cimicifuga-Vitex Compound
Pretorius	EstroTrim: Menopause Weight Control
SuperHerb, Netanya	Phyto-Female Complex
Totally Natural Products	Estro Balance plus Vitex: Menopause Relief

and which specific complaints[1,6–9] are being referred to. For example, some studies reviewed here[12–14,21] have adopted the recommended definition of natural menopause as having occurred after 12 consecutive months of amenorrhea for which there is no other obvious pathological or physiologic cause.[22] However, some others have taken 6 months of amenorrhea as denoting entry to the postmenopause,[11] or neglected to define it at all.[10,23] Similarly, *late perimenopause* is commonly defined as menses within the preceding 12 months but not the preceding 3 months, in conjunction with the coexistence of symptoms,[24–26] after excluding other causes where there is a history of previous menstrual irregularity.[26] However, the Herbal Alternatives for Menopause (HALT) study took more than one skipped menses within the previous 12 months to denote late perimenopause.[12] It is possible that the practice of administering *Vitex* for menopausal complaints is confined to those experienced during the perimenopause, rather than postmenopause. Fluctuating or increased estradiol secretion characterizes the perimenopause[27] (formerly "climacteric," the period immediately prior to menopause up to the first year after the final menstrual period.[22]) Thus, the postulated benefits of *Vitex* in conditions where unopposed estrogen plays a role[1] may be of relevance here.

Menopausal Symptoms

Symptom experience varies throughout the transition and between individuals. It is during the *perimenopause* that most symptoms are reported.[28] These can be due to estrogen excess (breast tenderness, menorrhagia, migraine, nausea, shorter cycle length)[27,29,30] or deficiency (vasomotor symptoms,[31] breast tenderness, and vaginal dryness[32,33]) and often fluctuate, reflecting the underlying hormonal instability during these years.[30] Dysfunctional uterine bleeding is maximal during the menopausal transition due to persistent unopposed estrogen;[34,35] low progesterone is associated with failure of the secretory phase in anovulatory cycles.[26] Rates of psychologic distress are also found to peak during the perimenopause.[36–39] Anecdotal reports suggest that premenstrual syndrome (PMS)-like symptoms may be more prevalent at this time, or at least less well-tolerated than previously.[40] The incidence of hot flushes increases throughout the transition,[32] with a peak generally at the time of the menopause[36] and in postmenopausal women.

Hot flushes occurring during the night have been associated with sleep disturbances.[41–45] However, some evidence suggests that not all of the nocturnal flushes result in waking episodes or arousals.[41] Conversely, other studies have found that not all of the waking episodes are associated with flushing,[43,44] suggesting this may not be the only factor responsible for disturbed sleep. Other proposed causes of sleep disturbances include an age-related decrease in total brain serotonin, one of the main regulators of circadian sleep–wake cycles,[46] an age-related decrease in slow-wave sleep and GH secretion,[47,48] and depression.[49]

Endocrine Changes Associated with Menopause

Before discussing the pharmacological mechanisms of *Vitex* that may be of potential relevance to the treatment of menopause-related symptoms, it will be useful to outline the current understanding of the endocrinology of menopause and the etiology of its associated symptoms.

The endocrinology of menopause has not yet been fully elucidated, and is complicated by the irregular cycles that characterize the menopause transition; these include normal length ovulatory and anovulatory cycles, and elongated ovulatory cycles,[50] without any orderly progression from one type to another.

The previously held belief that the perimenopause is characterized by a gradual decline in estrogen levels with rising follicle-stimulating hormone (FSH)[51] has been challenged by current research indicating that serum estradiol (or urinary estrogen excretion) actually increases slowly with increasing age,[34,52–56] and declines only from about 2 years prior to final menses.[57] Research on the inhibins has helped to clarify the underlying mechanism.[58] The main action of the inhibins (ovarian dimeric glycoproteins that regulate gonadotropin release during the menstrual cycle) is to inhibit synthesis and secretion of FSH. The falling inhibin levels (especially INH-B), resulting from the declining antral follicle count as women age,[59] allows the gradual rise in FSH, which drives increased estradiol secretion.[56,58,60] This may lead to accelerated follicle development and occasions of multiple follicles developing at once, and hence give rise, on occasion, to markedly raised estradiol concentrations in perimenopausal women.[27,34,52] *Lower* than normal levels of estradiol have been found in late-perimenopausal women who had experienced 3 months' amenorrhea[60] and in late-perimenopausal women during *anovulatory* cycles,[61] and in cycles with an elongated "lag period" between the menstrual phase and the onset of the follicular phase.[62] There is evidence of reduced hypothalamic–pituitary sensitivity to estrogen feedback in perimenopausal women.[29,63,64]

Estrogens modify synthesis, release, and metabolism of many neurotransmitters such as noradrenaline, dopamine, acetylcholine, serotonin and melatonin, and neuropeptides including β-endorphin, which modulate the activity of hypothalamic centers and the limbic system.[65] Fluctuating levels of sex steroids, particularly estrogen, result in altered function of the hypothalamus and limbic system, and thereby the regulation of mood, psychologic well-being,[66,67] thermoregulation and vasomotor stability,[68] and many other functions.

Melatonin levels decrease significantly with age; similarly the time during which melatonin remains elevated at night decreases with age.[69] An association between the quality of sleep and the amount of melatonin secreted has been noted, especially in the elderly.[70]

Studies in women during the perimenopause reveal that the decline in melatonin precedes FSH increase during menopause.[71] Whether this decline in melatonin secretion contributes to the development of menopause or its symptoms has not been established.[72]

Hot Flushes and Night Sweats

The term "hot flushes" is used here to include night sweats. The etiology of hot flushes is currently believed to involve a central noradrenergic mechanism. In symptomatic women, narrowing of the hypothalamic thermoneutral zone has been observed,[73] which is at least partly due to elevated brain noradrenaline levels.[74] Central noradrenergic activity is, in turn, modulated by ovarian steroids.[75] Within the reduced thermoneutral zone, small elevations in core body temperatures that precede most hot flushes are thought to constitute the triggering mechanism for hot flushes.[73]

The central noradrenergic instability associated with hot flushes could be due to the reduction of endogenous opioid activity[76,77] that results from declining estrogen levels, as hypothalamic opioidergic activity normally has an inhibitory effect on noradrenergic neurons in the brainstem. Casper and Yen[45] proposed that successful therapies for hot flushes may exert their effects by increasing endogenous opioid peptide activity with consequent inhibition of noradrenergic activity below the threshold needed to activate heat loss.

Dopamine has recently been found to be an important thermoregulatory neurotransmitter, with D2 receptors involved principally with the maintenance of body temperature in euthermia.[78] Earlier research had observed the dopamine agonist bromocriptine to increase the activity of the endogenous opioid system on the thermoregulation mechanisms that regulate body temperature in postmenopausal women[79] and to be effective in alleviating hot flushes.[80]

Estrogen withdrawal in menopausal women also results in dramatically lowered blood serotonin levels.[81,82] Low blood estrogen levels are correlated with upregulation of certain serotonin receptors (5-HT_{2A}) in the hypothalamus[83] that are believed to be involved in thermogenesis.

Mood Changes

Findings have been inconsistent regarding an association between depressed mood and hormone levels.[84–89] However, several effects of estrogens are of potential relevance to menopause-related mood changes (Table 2). Those of interest in the context of *Vitex agnus-castus* are as follows:

1. Estrogen potentiates the activity of opiate-containing neurons[90] and increases the synthesis and release of β-endorphin.[91]
2. Estrogen directly modulates dopaminergic activity,[92] increases dopamine release in the hypothalamus,[87] and increases dopamine transmission and D2 receptors.[93]
3. In postmenopausal women, the activity of the dopaminergic system was found to be significantly lower than in premenopausal women, but was significantly increased by HT administration, with a concomitant significant decrease in psychologic symptoms.[94]
4. Fluctuating ovarian hormones destabilize circadian rhythms during the perimenopause, and may contribute

Table 2. Proposed Roles for Hormones in the Etiology of Menopause-Related Mood Changes[a]

- Increased *variability* of estradiol,[b] follicle-stimulating hormone, and luteinizing hormone.[68]
- The *rate of change* of hormone secretion and levels.[c,d]
- Changes to estrogen levels influencing *neuropeptides and neurotransmitters* (cholinergic, catecholaminergic, and serotonergic[d]) in the limbic system and hypothalamus.[69]
- Periods of *elevated estrogens*, or excess relative to serum progesterone during the perimenopause. Estrogens are potentially anxiogenic in excess, while progesterone/allopregnanolone has a potent anxiolytic effect.[e]
- A pre-existing *sensitivity* in some individuals *to the change* in the gonadal hormones and resultant decreases in neural transmitters[38] such as noradrenaline.[f]
- In women previously reporting a *history of premenstrual syndrome*, perimenopausal depression could represent the elimination of follicular phase-related symptom remissions, and the development of a more persistent pattern of dysphoria.[99]
- Estrogen has reciprocal interactions with central nervous system growth factors. *Brain-derived neurotropic factor* (BDNF) levels may be of potential importance in the etiology and treatment of depression during the perimenopause.[g]

[a]These are additional to those reported in the text.
[b]Sherwin BB. Affective changes with estrogen and androgen replacement therapy in surgically menopausal women. J Affect Disord 1988;14:177–187.
[c]Schmidt PJ, Roca CA, Bloch M, Rubinow DR. The perimenopause and affective disorders. Semin Reprod Endocrinol 1997;15:91–100.
[d]Schmidt PJ, Rubinow DR. Neuroregulatory role of gonadal steroids in humans. Psychopharmacol Bull 1997;33:219–220.
[e]Bitran D, Purdy RH, Kellogg CK. Anxiolytic effect of progesterone is associated with increases in cortical allopregnanolone and GABAA receptor function. Pharmacol Biochem Behav 1993;45:423–428.
[f]Manji HK, Drevets WC, Charney DS. The cellular neurobiology of depression Nat Med 2001;7:541–547.
[g]Rubinow D, Roca C, Schmidt PJ. Estrogens and depression in women. In: Lobo R, ed. Treatment of the Menopausal Woman: Basic and Clinical Aspects, 3rd ed. Burlington, MA: Academic Press, 2007:307–322.

to the development of mood disorders in predisposed women.[95]

Perimenopausal Premenstrual Syndrome (PMS)-like Symptoms

It has also been hypothesized that some symptoms attributed to the menopause transition such as mood changes are more likely to be related to PMS, given that they improve after cessation of menstruation.[96] The PMS-like symptoms experienced during the perimenopause may differ in their etiology from PMS during normal reproductive years, due to increasing infrequency of ovulatory cycles as the perimenopause progresses. According to current understanding, ovulation is a prerequisite for PMS, which is believed to result from sensitivity in predisposed individuals to normal hormonal fluctuation during the late luteal phase.[97,98] It is possible that these PMS-like symptoms in the perimenopause may similarly represent an increased sensitivity to normal fluctuations in ovarian hormones.[29,63,64,99] Alternatively, estrogen excess has been suggested as a possible cause for these symptoms in late perimenopausal women.[100] Other factors potentially implicated in the etiology of PMS include changes in circadian rhythms, found to be similar to those occurring in anxiety and mood disorders, with aberrant timing of the secretion of melatonin, cortisol, and prolactin.[96]

Pharmacological Actions of Vitex with Potential Relevance to Menopause

Phytochemically, *Vitex* has been shown to contain essential oil, flavonoids, iridoid glycosides, and dopaminergic compounds belonging to the diterpenes. Mild D2 receptor agonistic properties have been demonstrated, resulting in inhibition of latent hyperprolactinemia, (the nonphysiologically stimulated prolactin release often manifest during the time of decreasing progesterone and estradiol levels. It is frequently also accompanied by an insufficient function of the corpus luteum).[15–17] *Vitex* has demonstrated activity as an agonist at the μ, and potentially the κ, opioid receptor.[18,19] It has also been found to effect a dose-dependent increase in melatonin secretion.[20] These actions of *Vitex* may be of relevance to the etiology of menopausal symptoms and are elaborated below. Findings from recent cell culture experiments indicate that *Vitex* extracts may contain phytoestrogens, the most active of which has been identified as the flavonoid, apigenin.[101] However, the compounds identified are only weakly estrogenic, not unique to this herb, and present in relatively low levels compared to other herbal and dietary sources. We therefore suggest that this finding does not contribute to our understanding of the true mechanism of the action of *Vitex*.

Latent hyperprolactinemia

Hyperprolactinemia results in inhibition of secretion of gonadotropin releasing hormone and decreased secretion of luteinizing hormone and FSH. In the ovary, this results in inhibition of progesterone secretion by the granulosa-lutein cells of the corpus luteum.[102] Premenstrual symptoms, particularly mastodynia, are often accompanied by *latent* hyperprolactinemia,[103,104] which can be stimulated by stressful situations.[15,105]

The above may have potential relevance to menopause-related symptoms in several ways:

1. In light of the suggestion that many of the menopausal symptoms may represent an exacerbation of premenstrual symptoms, targeting premenstrual latent hyperprolactinemia may also be appropriate during the perimenopause;
2. The dopaminergic effects of *Vitex* may be of relevance to alleviating hot flushes, as was the dopamine agonist, bromocriptine.[80] Dopamine has been found to affect thermoregulation, possibly via activation of the endogenous opioid system. The effects of *Vitex* on opioid receptors may also be of relevance in this context;
3. Because lower activity of the dopaminergic system is associated with psychologic symptoms,[94] the dopaminergic properties of *Vitex* may also prove beneficial in the amelioration of the emotional symptoms of menopause.

Affinity for opioid receptors

An action on μ, and potentially κ, opioid receptors may also be of relevance to the use of *Vitex* for menopause-related symptoms such as flushes and mood symptoms. In 2000, Meier and colleagues suggested additional pharmacological actions for *V. agnus-castus* via opioid receptors based on *in vitro* research.[18] They reported a relatively potent inhibition for opioid (μ and κ subtypes) receptor-binding with extracts of *Vitex,* which was most pronounced in lipophilic fractions. Additionally, binding to δ opioid receptors was found to be inhibited mainly by an aqueous fraction of *Vitex. In vitro* research, with high levels of direct exposure of test cells to the herbal extract, is of uncertain relevance to oral dosing of herbs in humans due to the pharmacokinetic factors that affect bioavailability of the phytochemicals with oral administration. In addition, the type of *in vitro* system used and the experimental conditions may not reflect the complexity of the *in vivo* environment of the living organism. However, it was subsequently also demonstrated in human and animal models that *Vitex* acted as an agonist at the μ-opioid receptor.[19] Extracts with and without fatty acids removed showed significant affinities to the μ-opioid receptor.

These findings support the beneficial action of *Vitex* in PMS, as endorphins are known to decrease in the late luteal phase[106,107] and are found to be associated with symptoms such as mood disorders, migraines, and fluid retention.[108,109] However, they are also of potential relevance to its reputed value in treating menopausal symptoms. The reduction of endogenous opioid activity may be responsible, at least in part, for the central noradrenergic instability associated with hot flushes.[76,77] Increasing endogenous opioid peptide activity may effect a reduction in hot flushes via inhibition of noradrenergic activity below the threshold needed to activate heat loss.[45] In an estrogen-deficient environment, it is possible that mood enhancement may be effected by stimulating the activity of opiate-containing neurons[90] and thereby increasing the synthesis and release of β-endorphin.[91]

Melatonin

The effect of *Vitex* on melatonin secretion is also of potential relevance to symptoms experienced in relation to

menopause. A dose-dependent increase in melatonin secretion, especially during the night, was found after administration of *Vitex* extracts 120 mg and 480 mg per day (dried herb equivalent 0.6 g and 2.4 g) in an open placebo-controlled trial. Total melatonin output was approximately 60% higher than in the placebo group.[20] This has obvious potential relevance to menopause-related sleep disturbances. However, data from a recent case report demonstrated that melatonin administration was able to delay the characteristic endocrine parameters associated with menopause onset.[110] While further studies are needed to confirm this finding, it is extremely interesting in view of the possible role of declining melatonin secretion (that precedes FSH increase[71]) in the development of menopause and its symptoms,[72] and the effect of *Vitex* on melatonin secretion, which may be part of the rationale for using it in menopause.

Clinical Studies with Vitex *for Menopausal Symptoms*

Despite its apparent popularity with UK herbalists, and its use as a component of menopause formulations, *Vitex* as a sole agent does not appear to have been tested in oral dosage form in this context in clinical trials. However, several studies were located in the literature on the essential oil and multicomponent formulations containing *Vitex* in the treatment of menopausal symptoms. These are outlined below. The databases searched were PubMed and Embase. Search terms used were combinations of *Vitex*, chaste or agnus with *menopaus*, climacteric, flush, flash, vasomotor or *menstrua*.

The steam-distilled essential oil of the fruit and leaves has been investigated in two studies[21,23] that reported benefits for menopausal symptoms. The first study, with 23 women, reported improvements following use of the oil of the leaf or fruit, with the majority of "major improvements" related to the the leaf oil.[23] Symptoms clusters for which improvements were reported were mood, vasomotor, urogenital, sleep and dysfunctional uterine bleeding, and to a lesser extent, cognitive and sexual. Interestingly, several women reported reinstatement of regular menstruation after 3–10 months of amenorrhea, and one after 6 years without a period. However, this study contained several weaknesses, including the use of different extracts and variable doses, different routes of administration (transdermal, inhalation, oral), lack of a standardized rating scale, and failure to exclude other concomitant treatments such as HT, herbs, and acupuncture. The subsequent study with 52 peri- or postmenopausal women aged 38 to 73 used a 1.5% solution of the essential oil of *Vitex* aerial parts in a base cream or lotion.[21] Participants applied 2.5 mL of the cream dermally, once daily, 5–7 days per week for 3 months. Overall, 33% reported major improvement and 36% reported mild to moderate improvement in troublesome symptoms, with greatest improvement observed in the emotional symptoms (16 responses), hot flushes/night sweats (15 responses), and moderation of menstruation (12 responses). However, these results need to be interpreted with caution due to the lack of a control group. The findings from aromatherapy studies utilizing the essential oil are of uncertain relevance to the administration of fruit extracts in oral dosage forms.

Three (3) RCTs[11–13] and one pilot study[14] on multicomponent formulations containing *Vitex* for the treatment of menopausal symptoms have been reported in the literature. A small subpopulation analysis of PMS-like symptoms in perimenopausal women with the combination of *Vitex* and *Hypericum perforatum* has also been conducted (see article by the authors in the next issue). Results of these studies have been inconsistent.

V. agnus-castus was one component of a menopause herbal formulation, Phyto-Female Complex, found to be significantly superior to placebo in a RCT on menopausal hot flushes and night sweats in 50 healthy peri- and postmenopausal women, aged 44–65 years.[11] In the 35 who completed the study, a 73% decrease in the number of hot flushes was observed at the end of the 3-month treatment period in the active treatment ($n = 19$) compared with 38% in the placebo group ($n = 16$), $p = 0.026$, and the number of night sweats was reduced by 69% and 29%, respectively, $p = 0.027$. A significant benefit was also observed in terms of sleep quality. The other herbs in the formulation were *Cimicifuga racemosa* (black cohosh) root extract, 100 mg (2.5 mg triterpene glycosides, 2.5%); *Silybum marianum* (St. Mary's thistle/milk thistle) herb extract, 75 mg (60 mg silymarin, 80%); *Angelica sinensis* (dong quai) root extract, 75 mg (7.5 mg ligustilides, 1%); *Trifolium pratense* (red clover) flower extract, 50 mg (4 mg isoflavone, 8%); and *Panax quinquefolium* (American ginseng) root extract, 50 mg (12.5 mg ginsenosides, 25%). The dose of *V. agnus-castus* fruit extract (2.5 mg vitexin, 5%) was 50 mg. Tablets were administered twice daily. The multicomponent make-up of this combination does not permit conclusions about the contributions of individual herbs. However, a significant contributor to the effect is likely to have been *Cimicifuga racemosa* (black cohosh), for which efficacy in menopause-related symptoms is supported by evidence from RCTs and randomized comparison group trials.[111–114] In view of the small sample size at the end of the treatment phase, these results are encouraging, although not adding specifically to the evidence for *Vitex* in this context.

The Herbal Alternatives for Menopause (HALT) study investigated three different herbal regimens compared with HT and placebo over a period of 12 months.[12] Three hundred and fifty-one (351) peri- or postmenopausal women with two or more vasomotor symptoms per day were assigned to one of five groups: (1) black cohosh 160 mg daily; (2) multibotanical with black cohosh, 200 mg daily, and 9 other ingredients including *V. agnus-castus*; (3) multibotanical plus dietary soy counseling (that is, advice from a clinical dietitian and literature to include two soy food servings per day in their diet, equivalent to 12–20 g of soy protein); (4) conjugated equine estrogen, 0.625 mg daily, with or without medroxyprogesterone acetate, 2.5 mg daily; and (5) placebo. The multibotanical contained the following daily doses: *Cimicifuga racemosa* (black cohosh), 200 mg; *Medicago sativa* (alfalfa), 400 mg; boron, 4 mg; *V. agnus-castus* (chaste tree), 200 mg; *Angelica sinensis* (dong quai), 400 mg; *Chamaelirium luteum* (false unicorn), 200 mg; *Glycyrrhiza glabra* (licorice), 200 mg; *Avena sativa* (oats), 400 mg; *Punica granatum* (pomegranate), 400 mg; *Eleutherococcus senticosus* (Siberian ginseng, standardized constituents 0.8% eleutherosides E and B), 400 mg. On the endpoints of the Wilkund vasomotor subscale, frequency and intensity of hot flushes and night sweats, no significant difference was found between any of the herbal interventions and placebo at any of the 3-monthly time

points measured, with one exception. At 12 months, placebo significantly outperformed the multibotanical-plus-soy counseling intervention for symptom intensity ($p = 0.016$). The average difference over all the time points between herbal interventions and placebo was less than 0.55 vasomotor symptoms per day, compared with −4.06 for HT compared to placebo. (For the multibotanical, no significant differences were found between the study group and placebo at 3 months, $p = 0.45$, 6 months, $p = 0.18$, or 12 months, $p = 0.88$). While the sample size and duration of this study are definite strengths, a major limitation is the recruitment of women with mild symptoms. It is recommended by the U.S. Food and Drug Administration (FDA) guidelines that seven moderate to severe hot flushes per day, or 50–60 per week, be the minimum requirement for menopause studies, with specific definitions of severity.[115]

A 16-week RCT, conducted by the authors (see article in the next issue), on a combination of *Hypericum perforatum* (St. John's wort) and *V. agnus-castus* with 100 late-perimenopausal and postmenopausal women found no significant effect for the herbal combination over placebo on vasomotor symptoms, $p = 0.42$; Greene Climacteric scores, $p = 0.13$; or depressed mood, $p = 0.42$. However, both arms showed significant improvements on all outcome measures of vasomotor symptoms ($p < 0.001$ and $p < 0.01$ for placebo and study groups, respectively), depressed mood, and overall menopausal symptoms measured on the Greene Climacteric scale ($p < 0.001$ for both groups). Substantial placebo effects were observed for all the endpoints: 43% for flushing and night sweats, 41% for depression measured on the Hamilton Depression Inventory, and 41% for Greene Climacteric scores. The daily dosages were consistent with clinical use and other RCTs on these herbs. No conclusions can be drawn regarding the effectiveness of *V. agnus-castus* in isolation, as individual arms were not included. However, a negative interaction between the two herbs is unlikely based on the known pharmacological mechanisms.

A pilot study of a combination botanical containing 15 herbs in 8 women suggested a potential benefit of a combination botanical for improving moderate menopausal symptoms in women.[14] The herbs were administered in 550-mg capsules, 2 capsules taken twice daily, providing a total of 2,200 mg of herbs per day. However, given the large number of herbs in the formulation (*C. racemosa* [black cohosh root], *Viburnum opulus* [cramp bark], *Mitchella repens* [squaw vine], *Valeriana officinalis* [valerian root], *Polygonatum multiflorum* [King Solomon seed], *Taraxacum officinalis* [dandelion root], *V. agnus-castus* [chaste tree berry], *Rosmarinus officinalis* [rosemary leaves], *Nigella sativa* [black seed], *Eupatorium purpureum* [queen of the meadow], *Epimedium grandiflorum* [epimedium leaf], *Ligusticum chuanxiong* [chuanxiong rhizome], *Schisandra chinensis* [schisandra berry], *Mentha piperita* [peppermint leaves], *Rubus idaeus* [raspberry leaves]), the dose of each individual herb was quite low, ranging from 80 mg to 300 mg per day. The dose of *Vitex* was 140 mg per day, or 6% of the total. In addition, the administration of a multicomponent preparation means that it is not possible to draw conclusions about the individual contribution of *V. agnus-castus.* The lack of a placebo group is a major limitation, as placebo effects with vasomotor symptoms in menopause studies are substantial, with 51% being the average for studies of HT according to a meta-analysis published in 2004,[116] and generally in the range of 30%–41% in RCTs of medicinal herbs.[11,13,117–119] From baseline to 3 months, a 42% decrease was observed in daily hot flushes, $p = 0.0003$, and Kupperman Index total symptoms score decreased by 24%, ($p = 0.0028$). Due to substantial placebo effects found in studies of vasomotor symptoms, it is possible that the 42% reduction in vasomotor symptoms observed in this study would not be significant over placebo. The small sample size in this study also suggests that this result should be interpreted with caution.

As mentioned above, studies of multicomponent formulations do not contribute to the knowledge about the individual component herbs. Herbs are chemically complex, and may contain in excess of 100 different plant chemicals, often with synergistic actions. While studies of multicomponent formulations may reflect clinical practice, the numerous potential interactions between the chemical components they contain make it impossible to extrapolate findings of their effects to any of the individual herbs or chemical components. Methodological differences between these studies present an additional limitation to comparing the findings. The oral dosage of *Vitex* in the formulations varied, ranging from 50 mg to 1,000 mg per day, and different scales were used for measuring outcomes. While all studies on orally administered herbs recruited women in the perimenopause and postmenopause, the definitions of these phases varied, as did the age range. In most cases, stratification by menopausal status was not reported, although the small sample sizes in each subgroup would probably have resulted in inadequate power to detect a significant effect in either the peri- or postmenopausal subgroups. The studies were of reasonable duration and most were placebo controlled. However, the percentage reduction in vasomotor symptoms in the uncontrolled pilot study was comparable with the placebo effect reported in the menopause RCT by van Die et al., highlighting the need for a control group, especially in menopause symptom trials. The negative finding in the HALT study may reflect the recruitment of women with mild baseline symptoms, which is associated with an enhanced placebo response. The need for evidence from rigorous RCTs on *Vitex* as a sole agent in this context is highlighted.

Clinical Trials on PMS and PMS-like Symptoms

It is possible that the practice of using *V. agnus-castus* for menopausal symptoms refers to its benefits for PMS-like symptoms reported by some women during the perimenopause. *Vitex* has been shown in placebo-controlled,[120] comparator,[121,122] and observational studies[123–125] to be effective in alleviating symptoms of PMS, which may well be relevant in this context.

A small study of PMS-like symptoms by the authors has shown that these improve in late-perimenopausal women with a combination of *V. agnus-castus* (extract equivalent to dry fruit 1,000 mg per day) and *H. perforatum* (extract equivalent to 5,400 mg dry herb flowering top standardized to contain hypericins 2,970 μg, 27 mg hyperforin, and 54 mg flavonoid glycosides) (see article by the authors in the next issue). Improvements were observed for total PMS scores and scores on all the subclusters of anxiety (PMS-A), depression (PMS-D), cravings (PMS-C), and hydration (PMS-H) on Abraham's Menstrual Symptoms Questionnaire. The herbal combination was significantly superior to placebo for total PMS, PMS-D,

and PMS-C. Limited conclusions can be drawn regarding the individual contributions of the herbs, which were administered in combination. An impact of *Hypericum* on the depression subcluster can be inferred from its established efficacy in the context of mild to moderate depression.[126] However, the findings are also consistent with those of previous research on *Vitex* for PMS in premenopausal women.[120–125]

Directions for Future Research

Although *Vitex* is currently used clinically and promoted as being effective in the management of menopause-related complaints, appropriate evidence to confirm its efficacy in this arena is lacking. While administering herbal formulations reflects clinical practice, RCTs of formulations do not permit the effects of the herb as a sole agent to be evaluated. Such evidence from rigorous scientific RCTs is needed to clarify the efficacy and safety of *Vitex* in this context. Because of the substantial response observed in the placebo group in menopause trials, possibly largely attributable to the natural history of the symptoms under investigation, large sample sizes are required to ensure adequate power, and a control group is essential in future studies. Findings from uncontrolled studies must be interpreted with caution. In accordance with the recommendations of bodies such as the FDA,[115] women with adequate symptom severity should be recruited to clinical trials.

The findings reported for the PMS-like symptoms, while encouraging, were from a very small sample, and need to be replicated in a larger RCT dedicated to study of these symptoms.

Conclusions

The origins of the practice of administering *Vitex* in menopause are unclear, but it appears to be widespread among some groups of herbal practitioners. While several recent studies have suggested a benefit for multicomponent formulations containing *Vitex* in the treatment of menopausal symptoms, evidence from rigorous randomized controlled trials is lacking to support the use of the individual herb in this context. Recent evidence from pharmacological studies points to possible mechanisms that could account for beneficial effects in some of the symptoms of menopause, as well as possibly influencing its onset. As the endocrinology and neuroendocrinology of menopause and its symptoms have not yet been fully elucidated, firm conclusions cannot be drawn. However, in view of current understanding, the emerging pharmacological evidence supports a role for *V. agnus-castus* in the management of menopause-related symptoms. In particular, further research may be appropriate into its possible role in alleviating the PMS-like symptoms associated with the perimenopause.

Disclosure Statement

Associate Professor Kerry M. Bone is Research Director, Director of MediHerb, which supplied the herbal products used in the studies by van Die et al.

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