

# Vitex *agnus-castus*

## Introduction

*Vitex agnus-castus* (chaste tree) has been widely used by European and North American herbalists to treat acne, digestive complaints, menstrual irregularities, premenstrual syndrome (PMS), mastalgia, and infertility, and also for lactation support.<sup>1-3</sup> Although Vitex has been used for centuries and enjoys wide support from practitioners and the general public for many gynecological complaints, few clinical studies support its documented uses. Based on current scientific evidence, the German Commission E supports its use for menstrual irregularities, mastalgia, and PMS.<sup>1,3</sup>



## Description

Vitex is a deciduous shrub native to European, Mediterranean and Central Asian countries. It has slender, finger-like leaves, purple-black berries, and belongs to the Verbenaceae family.<sup>4</sup> The berries are used medicinally, with use dating back to the ancient Greeks and Romans. The berries were used by monks during the Middle Ages to suppress sexual desire; hence its common names – monk's pepper and chaste tree.<sup>5</sup>

## Active Constituents

Berry isolates contain flavonoids, essential oils, diterpenes, and glycosides.<sup>2</sup> The flavonoids (casticin, quercetagetin, isovitexin) have been shown *in vitro* to affect estrogen receptors. The essential oils bornyl acetate, limonene, and pinene have antifungal, antimicrobial, and insect-repellent qualities.<sup>6</sup> The diterpenes exhibit dopaminergic activity in *in vitro* studies, and the glycosides have an indirect effect on hormones on *in vitro* investigation.<sup>7</sup> According to a German survey, an alcohol extract of the whole berry is more efficacious than isolates of individual constituents.<sup>8</sup> Experimental data cites the iridoid glycoside agnuside and the flavonol casticin as the two quality control markers for pharmaceutical grade manufacturing.<sup>9</sup>

## Mechanisms of Action

*In vitro* studies describe dopaminergic effects of Vitex via a dose-dependent binding of dopamine-2 receptors, yielding potent inhibition of prolactin in cultured pituitary cells. The flavonoid apigenin can be isolated from Vitex and has selective binding affinity for the beta-estrogen receptor subtype.<sup>7</sup> Apigenin also shows regulatory effects on fat tissue homeostasis, but estrogenic effects on uterine weight or bone density were not noted in animal studies.<sup>7,10,11</sup> Additional *in vitro* studies provide evidence of prolactin inhibition with direct binding to dopamine receptors. Extracts were also demonstrated to displace ligands in human opioid-receptor binding.<sup>10</sup> Vitex did not modulate follicle stimulating hormone (FSH) or luteinizing hormone (LH) production in rat pituitary cells.<sup>11</sup>

Initial human studies reported inhibition of FSH and stimulation of LH secretion and presumed the hormone modulation of FSH and LH affected the downstream hormones progesterone and estrogen.<sup>12,13</sup> Further research, however, indicates a decrease of prolactin secretion by dopamine receptor antagonism.<sup>14</sup> Animal studies support the proposal that Vitex impacts prolactin secretion; a study by Winterhoff demonstrated high-dose Vitex inhibits stress-induced secretion of prolactin by male rats and decreases milk production in healthy lactating rats compared to controls.<sup>15</sup>

## Clinical Indications

### Menstrual Cycle Irregularities

Although few randomized controlled trials (RCTs) exist, Vitex is commonly prescribed for menstrual irregularities based on data collected by the German Commission E and current research studies.<sup>2,4,16</sup> Menstrual cycle irregularities due to hyperprolactinemia, corpus luteum insufficiency, oligomenorrhea, and secondary amenorrhea have been effectively treated with Vitex extract in open label, uncontrolled studies.<sup>17-19</sup> Based on current pharmacological studies and RCTs, Vitex is indicated for hyperprolactinemia.<sup>20</sup> A luteal phase defect has been clinically correlated with hyperprolactinemia, supporting the use of Vitex to modulate progesterone and other menstrual cycle irregularities.<sup>15,20</sup>

A 1993 double-blind RCT examined the effects of Vitex on luteal phase defects.<sup>20</sup> Women with luteal phase defects, ages 19-42 (n=37), received 20 mg Vitex dry extract or placebo daily; then both groups were evaluated for prolactin levels compared to baseline. A significant reduction in prolactin release and a normalization of progesterone was seen after three months of Vitex supplementation compared to placebo.

### Premenstrual Syndrome

PMS represents a diverse set of clinical symptoms that affect women throughout the reproductive lifespan and range from lasting only a few days to several weeks per month. Vitex represents a safe alternative to current hormone or drug therapy used to manage PMS symptoms.

A prospective, multicenter trial in women with PMS (n=43) determined the efficacy of 20 mg of Vitex

daily for three menstrual cycles. The primary outcome measured the symptoms of PMS with the Moos' menstrual distress questionnaire (MMDQ) and the secondary outcomes were reported by a visual analogue scale and a global impression scale. There was significant reduction of PMS symptoms, 42.5 percent ( $p<0.001$ ), determined by MMDQ. At the conclusion of the study 38 patients judged the global efficacy from moderate to excellent and five patients indicated no global efficacy. No serious adverse events were reported. A gradual return of symptoms was noted three cycles post-treatment cessation. Based on the reduction of symptoms on the MMDQ, the authors concluded Vitex is effective at treating the symptoms of PMS.<sup>21</sup>

A 2001 double-blind RCT compared the efficacy and tolerability of Vitex versus placebo for women with PMS over three menstrual cycles. Patients (n=178) with clinically diagnosed PMS were given 20 mg dry Vitex extract or placebo daily and asked to assess various PMS symptoms including irritability, mood swings, anger, headaches, breast fullness, and bloating. The primary outcome was a self-assessment of PMS symptom improvement. Clinicians measured the secondary outcome by assessing changes in clinical severity and global impression of improvement. The active group experienced a statistically significant reduction in symptoms of 50.5 percent ( $p<0.001$ ) compared to placebo. The secondary outcome revealed a statistically significant global improvement of 52 percent versus 24 percent, in active and placebo groups, respectively. The authors concluded Vitex is efficacious for the treatment of PMS.<sup>22</sup>

Lauritzen et al studied the safety and efficacy of a specific formulation of Vitex (Agnolyt<sup>®</sup>) for the treatment of PMS. A multicenter RCT (n=105) examined the effects of one capsule of Agnolyt (3.5-4.2 mg dry Vitex extract) compared to 100 mg pyridoxine twice daily for three months on the symptoms of PMS. No placebo group was used due to the authors' ethical concerns, and pyridoxine was chosen as the comparison variable due to its clinical efficacy on PMS symptoms. At the study's conclusion, the endpoint assessment revealed the global impression was greater in the Agnolyt group (77.1%) versus the pyridoxine treatment group (60.6%). The study concluded Agnolyt is superior to pyridoxine in reducing premenstrual tension, as assessed by a premenstrual syndrome symptom scale.<sup>23</sup>



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statistical difference between groups for the CGI-SI, the authors concluded that patients responded well to both treatment options and further study is warranted.<sup>26</sup>

An open-label, multicenter trial examined the effects of Femicur® (a dried extract of Vitex) on mastalgia associated with PMS for three menstrual cycles.<sup>27</sup> Women diagnosed with PMS (n=1,634) took 20 mg Femicur twice daily for three months. Patients completed a symptom questionnaire unique to Vitex, determining its effects on depression, anxiety, cravings, and hyperhydration. A global assessment performed by clinicians revealed mastalgia to be the predominant PMS symptom reduced by Vitex treatment. Eighty-five percent of participants reported the frequency and severity of mastalgia decreased. Ninety-three percent of participants reported a decrease in PMS symptoms, with 42 percent reporting a complete cessation.<sup>27</sup> Based on the studies reviewed, there is sufficient evidence to support the use of Vitex for the treatment of mastalgia.<sup>24-27</sup>

### Drug-Herb Interactions

No known drug-herb interactions for Vitex have been reported in humans, although caution is recommended with dopamine agonists and hormone replacement therapy due to current understanding of the mechanisms of action.<sup>7,28</sup>

### Side Effects/Toxicity

The side effects associated with Vitex extracts are mild, reversible, and infrequent. They include gastrointestinal upset, urticaria, fatigue, headache, dry mouth, tachycardia, nausea, and agitation in less than two percent of patients.<sup>16,28</sup>

### Dosage

The German Commission E recommends 30-40 mg of dried fruit extract daily, 2.6-4.2 mg of dry native extract (standardized to 0.6% casticin), or 40 drops of tincture. Fluid extract ([1:1] g/mL) dosage ranges from 0.5-1.0 mL daily. Early studies show long-term supplementation is required for therapeutic effect. Several sources report response to treatment ranges from 4-6 months depending on the condition and duration since diagnosis.<sup>24</sup> Recent clinical trials show therapeutic effects after three months of treatment and a gradual return of symptoms after treatment cessation.<sup>21-23</sup>

# Monograph

## Warnings/Contraindications

The use of Vitex is contraindicated in pregnancy and lactation due to unknown effects in early pregnancy and possible hormonal effects through breast milk. No human studies have been conducted to determine the safety of Vitex during pregnancy and lactation according to current evidence-based clinical trials.<sup>28</sup>

## References

1. Blumenthal M. *The ABC Clinical Guide to Herbs*. New York, NY: Thieme; 2003:61-72.
2. Weiss R. *Herbal Medicine*. Gothenburg, Sweden: Beaconsfield Publishers; 1988:317-318.
3. Blumenthal M. *The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicines*. Austin, TX: American Botanical Council; 1998.
4. Duke J. *The Green Pharmacy Herbal Handbook: Your Comprehensive Reference to the Best Herbs for Healing*. New York, NY: St. Martin's Press; 2000:72.
5. Hobbs C. The chaste tree: *Vitex agnus castus*. *Pharm Hist* 1991;33:19-24.
6. Hoffman D. *Medical Herbalism: The Science and Practice of Herbal Medicine*. Rochester, VT: Healing Arts Press; 2003:62-120.
7. Wuttke W, Jarry H, Christoffel V, et al. Chaste tree (*Vitex agnus-castus*) – pharmacology and clinical indications. *Phytomedicine* 2003;10:348-357.
8. Christie S, Walker A. *Vitex agnus-castus* L.: (1) A review of its traditional and modern therapeutic use; (2) current use from a survey of practitioners. *Eur J Herbal Med* 1997-1998;3:29-45.
9. Abel G. Experience with the analytical methods from raw extract to drug product. *Z Phytother* 1999;20:147-148.
10. Brugisser R, Burkard W, Simmen U, Schaffner W. Assessment of opioid receptor activity with *Vitex agnus-castus*. *Z Phytother* 1999;20:154. [Article in German]
11. Jarry H, Leonhardt S, Gorkow C, Wuttke W. *In vitro* prolactin but not LH and FSH release is inhibited by compounds in extracts of agnus castus: direct evidence for a dopaminergic principle by the dopamine receptor assay. *Exp Clin Endocrinol* 1994;102:448-454.
12. Boon H, Smith M. *The Botanical Pharmacy: The Pharmacology of 47 Common Herbs*. Kingston, ON: Quarry Press, Inc.; 1999;76-81.
13. No authors listed. *British Herbal Pharmacopeia*: 1996. 4th ed. Exeter, UK: British Herbal Medicine Association; 1996;19-20.
14. Merz PG, Gorkow C, Schrödter A, et al. The effects of a special agnus castus extract (BP1095E1) on prolactin secretion in healthy male subjects. *Exp Clin Endocrinol Diabetes* 1996;104:447-453.
15. Winterhoff H. Phytobotanicals and their endocrine effect. *Z Phytother* 1993;14:83-94. [Article in German]
16. Roemheld-Hamm B, Chasteberry. *Am Fam Physician* 2005;72:821-824.
17. Bubenzer R. Therapy with agnus-castus extract (Strotan®). *Therapiewoche* 1993;43:32-33,1705-1706.
18. Loche E, Kaiser E. Diagnosis and treatment of dyshormonal menstrual periods in the general practice. *Gynakol Prax* 1990;14:489-495. [Article in German]
19. Bleier W. Phytotherapy in irregular menstrual cycles or bleeding periods and the gynecological disorders of endocrine origin. *Zentralbl Gynakol* 1959;18:701-709. [Article in German]
20. Milewicz A, Gejdel E, Sworen H, et al. *Vitex agnus castus* extract in the treatment of luteal phase defects due to latent hyperprolactinemia. Results of a randomized placebo-controlled double-blind study. *Arzneimittelforschung* 1993;43:752-756.
21. Berger D, Schaffner W, Schrader E, et al. Efficacy of *Vitex agnus castus* L. extract Ze 440 in patients with pre-menstrual syndrome (PMS). *Arch Gynecol Obstet* 2000;264:150-153.
22. Schellenberg R. Treatment for the premenstrual syndrome with agnus castus fruit extract: prospective, randomised, placebo controlled study. *BMJ* 2001;322:134-137.
23. Lauritsen C, Reuter H, Repges R, et al. Treatment of premenstrual tension syndrome with *Vitex agnus castus*. Controlled, double-blind study versus pyridoxine. *Phytomedicine* 1997;4:183-189.
24. Carmichael AR. Can *Vitex agnus castus* be used for the treatment of mastalgia? What is the current evidence? *Evid Based Complement Alternat Med* 2008;5:247-250.
25. Halaska M, Beles P, Gorkow C, Sieder C. Treatment of cyclical mastalgia with a solution containing a *Vitex agnus castus* extract: results of a placebo-controlled double-blind study. *Breast* 1999;8:175-181.
26. Atmaca M, Kumru S, Tezcan E. Fluoxetine versus *Vitex agnus castus* extract in the treatment of premenstrual dysphoric disorder. *Hum Psychopharmacol* 2003;18:191-195.
27. Loch EG, Selle H, Boblitz N. Treatment of premenstrual syndrome with a phytopharmaceutical formulation containing *Vitex agnus castus*. *J Womens Health Gend Based Med* 2000;9:315-320.
28. Dugoua JJ, Seely D, Perri D, et al. Safety and efficacy of chastetree (*Vitex agnus-castus*) during pregnancy and lactation. *Can J Clin Pharmacol* 2008;15:E74-E79.