Monograph

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.[1-3] 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.[1,3]

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.[4] 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.[5]

Active Constituents

Berry isolates contain flavonoids, essential oils, diterpenes, and glycosides.[2] 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.[6] The diterpenes exhibit dopaminergic activity in *in vitro* studies, and the glycosides have an indirect effect on hormones on *in vitro* investigation.[7] According to a German survey, an alcohol extract of the whole berry is more efficacious than isolates of individual constituents.[8] Experimental data cites the iridoid glycoside agnuside and the flavonol casticin as the two quality control markers for pharmaceutical grade manufacturing.[9]

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.[7] Apigenin also shows regulatory effects on fat tissue homeostasis, but estrogenic effects on uterine weight or bone density were not noted in animal studies.[7,10,11] 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.[10] Vitex did not modulate follicle stimulating hormone (FSH) or luteinizing hormone (LH) production in rat pituitary cells.[11]

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.[12,13] Further research, however, indicates a decrease of prolactin secretion by dopamine receptor antagonism.[14] 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.[15]

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.[2,4,16] 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.[17-19] Based on current pharmacological studies and RCTs, Vitex is indicated for hyperprolactinemia.[20] A luteal phase defect has been clinically correlated with hyperprolactinemia, supporting the use of Vitex to modulate progesterone and other menstrual cycle irregularities.[15,20]

A 1993 double-blind RCT examined the effects of Vitex on luteal phase defects.[20] 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.[21]

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.[22]

Lauritzen et al studied the safety and efficacy of a specific formulation of Vitex (Agnolyt®) 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.[23]

Mastalgia

Mastalgia is a complex condition with a poorly understood etiology. Supported by recent clinical trials and an endorsement by the German Commission E, Vitex has shown clinical efficacy for its treatment. The mechanism of action is believed to be inhibition of prolactin secretion and modulation of estrogen receptors.[7,24] Increased prolactin is associated with cyclical mastalgia and the symptoms of PMS.

In a double-blind RCT, women diagnosed with mastalgia (n=97) were treated with 30 drops Vitex liquid extract or placebo twice daily for three menstrual cycles.[25] The intensity of mastalgia was recorded using a visual analogue scale once per cycle. After one treatment cycle, patients treated with Vitex showed a decrease in pain by 21 mm on the visual analogue scale compared to placebo at 11 mm decrease. By the completion of two cycles, 71 percent of patients in the treatment group had visual analogue scores under 35 mm and 50 percent reported no severe pain. No difference was reported in the frequency of adverse events between the treatment group and placebo (Vitex, n=5; placebo, n=4). This study concluded, via a visual analog pain scale, that Vitex significantly reduced pain by 54 percent compared to placebo, p=0.0018 and p=0.006, respectively. The authors suggest Vitex reduces pain duration and intensity throughout the menstrual cycle, is well tolerated and efficacious, and more study is warranted in cyclical mastalgia.[25]

Atmaca et al compared the efficacy of Vitex to fluoxetine for treatment of cyclical mastalgia and premenstrual dysphoric disorder (PMDD).[26] The authors claim there were no previous studies comparing an SSRI to a natural treatment choice for cyclical mastalgia associated with PMDD. Forty-one PMS patients with PMDD were randomized and received fluoxetine or Vitex for two months. Patients were evaluated by the Penn Daily Symptom Report, the Hamilton Depression Rating Scale (HAM-D), and the Clinical Global Impression-Severity of Illness Scale (CGI-SI). At the conclusion of the study the CGI-SI showed a similar percentage of patients responded to fluoxetine (68.4 percent, n=13) versus Vitex (57.9 percent, n=11), not a statistically significant difference. Psychological symptoms improved in the fluoxetine group while mastalgia improved in the Vitex group. Although there was no statistical difference between groups for the CGI-SI, the authors concluded that patients responded well to both treatment options and further study is warranted.[26]

An open-label, multicenter trial examined the effects of Femicur® (a dried extract of Vitex) on mastalgia associated with PMS for three menstrual cycles.[27] 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.[27] Based on the studies reviewed, there is sufficient evidence to support the use of Vitex for the treatment of mastalgia.[24-27]

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.[7,28]

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.[16,28]

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.[2-4] Recent clinical trials show therapeutic effects after three months of treatment and a gradual return of symptoms after treatment cessation.[21-23]

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.[28]

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