Chaste Tree

Vitex agnus-castus L.

[Fam. *Verbenaceae*]

Overview

Chaste tree derived its common name from the traditional belief that the plant promoted chastity. The fruit of *Vitex agnus-castus* (hereafter referred to as chaste tree) was used to suppress sexual desire by both the men and women of ancient Greece and Rome. During the Middle Ages, monks used chaste tree as a "functional" food flavoring for the same purpose. In Germany, chaste tree is a common treatment for gynecological disorders including corpus luteum insufficiency, premenstrual syndrome (PMS), and hormonally-induced acne. Although chaste tree is widely used in Germany, it has not been used extensively in the U.S. until recently.

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Primary Uses

- Dysmenorrhea
- Hyperprolactinemia and corpus luteum insufficiency
- Premenstrual syndrome (PMS)

NOTE: The German Commission E recommended that women who experience tension or swelling of the breasts, or menstrual disturbances should consult a healthcare provider for proper diagnosis (Blumenthal, *et al.,* 1998).

Other Potential Uses

- Acne vulgaris
- Prevention of miscarriage in the first trimester of pregnancy in cases of progesterone insufficiency
- Mastodynia
- Insufficient lactation

Pharmacological Actions

Hormonal modulator; increases progesterone levels with corresponding reduction in estrogen levels via corpus luteum hormone effect (i.e, central action at pituitary level that inhibits release of follicle-stimulating hormone (FSH) and promotes release of luteinizing hormone (LH)); decreases prolactin secretion by the pituitary gland via dopamine antagonistic effect.

Dosage and Administration

Chaste tree does not have an immediate effect. The following are recommendations for minimum treatment duration: 3 months for PMS; 5–7 months for anovulation and infertility; up to 18 months for amenorrhea lasting longer than 2 years; 4–6 months for complete relief from symptoms of most conditions.

Internal

The German Commission E recommended the following daily dosage: 30–40 mg dried fruit [aqueous-alcoholic extract (50–70% *v/v*)].

DRY NATIVE EXTRACT: 1 tablet swallowed with some liquid each morning [2.6–4.2 mg, depending on concentration ratio, standardized to contain approximately 0.6–1.0% casticin].

FLUID EXTRACT: 0.5–1.0 ml [1:1 (*g/ml*), 70% alcohol (*v/v*)].

FLUID EXTRACT: 1.2–4.0 ml [1:2 (*g/ml*)].

TINCTURE: 40 drops, once daily with some liquid each morning [alcohol 58% volume, 100 g of aqueous-alcoholic solution contains 9 g of 1:5 tincture].

Contraindications

None known. In theory, chaste tree should not be given with dopamine antagonists.

PREGNANCY AND LACTATION: Not recommended for use during pregnancy. No known restrictions during lactation. There is insufficient information regarding chaste tree's influence on prolactin levels in lactating women to reliably predict the lactogenic response. Clinical information and traditional use suggest a galactogogue effect, while *in vitro* and animal studies using a high dosage range suggest an anti-galactogogue effect. Long-term use of chaste tree (more than two weeks) during lactation may lead to disruption of the lactation amenorrhea state and an early return to fertility, which may or may not be desired.

Adverse Effects

Side effects are rare, occurring in 1–2% of all patients treated (in clinical trials), and may include rash, headache, hair loss, fatigue, agitation, dry mouth, tachycardia, nausea, and increased menstrual flow. Itching and urticarial exanthemas occasionally occur. Caution patients to report tension, swollen breasts, or menstrual disturbances.

Drug Interactions

None known. Evidence of a dopaminergic effect in animals suggests that a reciprocal weakening effect may occur with ingestion of dopamine-receptor antagonists such as haloperidol and potentially with dopamine-receptor blocking agents, such as metoclopramide, widely used as an antiemetic. Because of its apparent hormonal activity, chaste tree may interfere with the effectiveness of oral contraceptives and hormone-replacement therapy, although this is speculative and has not been substantiated in clinical case reports.

Clinical Review

Eighteen clinical studies on chaste tree that included 8,336 participants all demonstrated positive effects for indications including corpus luteum abnormalities, menstrual cycle abnormalities, and PMS. Most of the studies were open, uncontrolled studies. One double-blind, placebo-controlled (DB, PC) study investigated a native dry extract of chaste tree in the treatment of luteal phase defects due to hyperprolactinemia. Two other DB, PC studies investigated native dry extracts in the treatment of PMS. A randomized (R), DB, PC, parallel study on a commercial chaste tree preparation (Ze440) on 170 women with PMS concluded that the fruit extract is safe and effective in reducing PMS symptoms. Another recent, multi-center trial on the efficacy of a chaste tree extract (Ze440) investigated 50 patients with PMS, concluding that PMS can be treated successfully as indicated by clear improvement in the main-effect parameter during treatment and the gradual return of that symptom after cessation of treatment. The main effect of treatment seems related to symptomatic relief rather than to the duration of the syndrome. From 1943 to 1997, approximately 32 clinical studies were conducted on a proprietary chaste berry product (Agnolyt®, Madaus, Germany). Eight studies focused on the product's effect on PMS, 4 on mastitis and fibrocystic disease, 3 on menopausal symptoms, 3 on increasing lactation, 4 on hyperprolactinemia, 7 on uterine bleeding disorders, 3 on acne, and 4 on miscellaneous menstrual irregularities.

Chaste Tree

Vitex agnus-castus L.
[Fam. *Verbenaceae*]

Overview

Chaste tree, also called chaste berry or vitex, derives its common name from the traditional belief that the plant promoted chastity. The fruit was used by both men and women in ancient Greece and Rome, and by monks during the Middle Ages, to suppress sexual desire. In Germany, chaste tree is a common treatment for gynecological disorders and it has recently become popular in the U.S.

Uses

Premenstrual syndrome (PMS); painful menstruation; hyperprolactinemia and corpus luteum insufficiency.

NOTE: The German Commission E recommended that women who experience tension or swelling of the breasts or menstrual disturbances should consult a healthcare provider for proper diagnosis.

Other Potential Uses

Breast pain.

Dosage

DRY NATIVE EXTRACT: One 2.6–4.2 mg tablet, standardized to contain approximately 0.6–1.0% casticin, swallowed with some liquid each morning.

FLUID EXTRACT: 0.5–4.0 ml, daily.

TINCTURE: 40 drops, daily.

Contraindications

No known contraindications.

PREGNANCY AND LACTATION: Not for use during pregnancy. No restrictions known during breast-feeding. There is insufficient information on chaste tree's effect on breast-feeding. Long-term use of chaste tree (more than 2 weeks) may lead to disruption of the cessation of the menstrual cycle that normally accompanies breast-feeding and an early return to fertility which may or may not be desired. Consult a healthcare provider prior to use while breast-feeding.

Adverse Effects

Itching, rash, headache, hair loss, fatigue, agitation, dry mouth, rapid heartbeat (tachycardia), nausea, and increased menstrual flow may occur rarely (noted in 1–2% of patients in clinical studies).

Drug Interactions

Consult with a healthcare provider if using dopamine-receptor antagonists such as haloperidol, and dopamine-receptor blocking agents such as metoclopramide. Chaste tree may also interfere with the effectiveness of oral contraceptives and hormone-replacement therapy; however, this potential interaction is theoretical and has not been documented in case reports.

Comments

When using a dietary supplement, purchase it from a reliable source. For best results, use the same brand of product throughout the period of use. As with all medications and dietary supplements, please inform your healthcare provider of all herbs and medications you are taking. Interactions may occur between medications and herbs or even among different herbs when taken at the same time. Treat your herbal supplement with care by taking it as directed, storing it as advised on the label, and keeping it out of the reach of children and pets. Consult your healthcare provider with any questions.

AMERICAN BOTANICAL COUNCIL

Chaste Tree

Vitex agnus-castus L.
[Fam. *Verbenaceae*]

Overview

Chaste tree, sometimes called chaste berry or vitex, derived its common name from the traditional belief that the plant promoted chastity (Winterhoff, 1998; Christie and Walker, 1997). The fruit of *Vitex agnus-castus* (hereafter referred to as chaste tree) was used in ancient Greece and Rome by males and females, including the monks of the Middle Ages (as a "functional" food flavoring), to suppress sexual desire (Winterhoff, 1998; Upton, 2001). Chaste tree is a widely used and popular treatment for gynecological disorders, including corpus luteum insufficiency (Merz *et al.*, 1996; Milewicz *et al.*, 1993); premenstrual syndrome (PMS) (Schellenberg *et al.*, 2001, Loch *et al.*, 2000; Dittmar and Böhnert, 1992; Coeugniet *et al.*, 1986; Wuttke *et al.*, 1995); menstrual problems (Loch *et al.*, 1991; Loch and Kaiser, 1990); and cyclic mastalgia (Halaska *et al.*, 1998; Kress and Thanner, 1981; Kubista *et al.*, 1983). It has also been used to treat hormonally induced acne (Amann, 1967). Chaste tree has been traditionally used to treat fibroid cysts and infertility, to stop miscarriages caused by progesterone insufficiency, to flush out the placenta after birth (McGuffin *et al.*, 1997; Peirce, 1999), and as a digestive aid, sedative, and anti-infective (Christie and Walker, 1997). Although chaste tree is widely used in Germany, it has not been used in the U.S. much until relatively recently. It has not yet achieved significant popularity in mainstream retail outlets but ranked 54th in natural food store sales in 2001 (Richman and Witkowski, 2001).

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Description

Chaste tree is the ripe, dried fruit of *Vitex agnus-castus* L. [Fam. *Verbenaceae*], containing no less than 0.4% (*v/w*) of volatile oil (GHP, 1993), and no less than 8% water-soluble extractive (BHP, 1996). The average water- and ethanol-soluble extractive content is approximately 10% (Abel, 1999). It is unknown which constituents are responsible for chaste tree's activity, and up to this point there are no official published guidelines for the standardization of chaste tree preparations (Meier, 1999). However, two compounds are presently used as marker compounds for quality control: the iridoid glycoside *agnuside* and the flavonol *casticin* (Abel, 1999). Most chaste tree preparations used in European medicine are nonstandardized fluid extracts, tinctures, and/or native dry extracts. The "native" or "total" extract has an approximate 10:1 (*w/w*) drug-to-extract ratio containing 0.6 –1.0% casticin (Abel, 1999; Morant and Ruppanner, 2001). It has been suggested in the future, pharmaceutical-grade chaste tree preparations should be characterized qualitatively and quantitatively, based on hydrophilic flavonoids, lipophilic compounds, and iridoid glycosides (Hoberg *et al.*, 1999; Upton, 2001).

Primary Uses

Gynecology

- Dysmenorrhea (Bubenzer, 1993; Loch *et al.*, 1991; Loch and Kaiser, 1990; Bleier, 1959; Probst and Roth, 1954)
- Hyperprolactinemia and corpus luteum insufficiency (Merz *et al.*, 1996; Milewicz *et al.*, 1993; Propping *et al.*, 1991; Propping and Katzorke, 1987)
- Premenstrual syndrome (PMS) (Schellenberg *et al.*, 2001; Loch *et al.*, 2000; Berger *et al*, 2000; Berger *et al.*, 1999; Lauritzen *et al.*, 1997; Turner and Mills, 1993; Dittmar and Böhnert, 1992; Coeugniet *et al.*, 1986)

NOTE: The German Commission E recommended that women who experience tension or swelling of the breasts, or menstrual disturbances should consult a healthcare provider for proper diagnosis (Blumenthal, *et al.,* 1998)

Other Potential Uses

Dermatology

- Acne vulgaris (Giss and Rothenburg, 1968; Amann, 1967; Bleier, 1959)

Gynecology

- Prevention of miscarriage in the first trimester of pregnancy in cases of progesterone insufficiency (McGuffin *et al.*, 1997)
- Mastodynia (Halaske *et al.*, 1999; Blumenthal *et al.*, 1998; Kubista *et al.*, 1986)
- Insufficient lactation (Bruckner, 1989)

Dosage

Internal

The German Commission E recommended the following daily dosage: Aqueous-alcoholic extract (50–70% *v/v*), corresponding to 30–40 mg dried fruit (Blumenthal *et al.*, 1998).

DRY NATIVE EXTRACT [2.6–4.2 mg, depending on concentration ratio, standardized to contain approximately 0.6–1.0% casticin]: 1 tablet swallowed with some liquid each morning (Abel, 1999; Bionorica, 1998; Lauritzen *et al.*, 1997; Madaus, 1996). NOTE: Some products (Zeller PreMens® Ze440) recommend up to 20 mg native extract daily (Morant and Ruppanner, 2001; Berger *et al.*, 1999).

FLUID EXTRACT [1:1 (*g/ml*), 70% alcohol (*v/v*)]: 0.5–1.0 ml (Karnick, 1994).

FLUID EXTRACT [1:2 (*g/ml*)]: 1.2–4.0 ml (Bone, 1989).

TINCTURE [Alcohol 58% volume, 100 g of aqueous-alcoholic solution contains 9 g of 1:5 tincture]: 40 drops, once daily with some liquid each morning (Madaus, 1996).

DURATION OF ADMINISTRATION

Chaste tree does not have an immediate effect. For treatment of PMS, a minimum treatment duration of three months is recommended (Morant and Ruppanner, 2001). A survey of medical herbalists in the U.K. reported a mean average of 4.8 months of treatment is necessary before patients with PMS symptoms respond to chaste tree (Christie and Walker, 1997). For anovulation and infertility, a treatment duration of five to seven months may be necessary. For amenorrhea lasting longer than two years, a treatment period of up to 18 months may be required (Pizzorno and Murray, 1999; Boon and Smith, 1999; Brown, 1994). For most other conditions, symptoms usually start to diminish within one to two months. After four to six months, extensive or complete relief from symptoms may be seen (Pizzorno and Murray, 1999; Brown, 1994).

CHEMISTRY

Mature chaste tree fruit yields 0.4–0.7% (% *v/w*) essential oil, depending on distillation time and size of comminuted particles (Sørensen and Katsiotis, 2000), and is composed mainly of bornyl acetate, 1,8-cineole, limonene, α- and β-pinene, β-caryophyllene, and α-terpinyl acetate (Meier and Hoberg, 1999). It also contains labdane diterpenoids: 0.04–0.3% rotundifuran, 0.04–0.17% vitexilactone, 0.02–0.1% 6β, 7β-diacetoxy-13-hydroxy-labda-8,14-diene (Hoberg et al., 1999); flavonoids: 0.10–0.16% casticin (Abel, 1999); iridoid glycosides: 0.2–0.4% agnuside (Abel, 1999); and 0.3% aucubin (Newall *et al.*, 1996). NOTE: For optimal yield of isoorientin, agnuside, and casticin in extraction, tincture maceration with a drug-to-extract ratio of 1:5 (*w/v*) in 52% ethanol (*v/v*) is most effective and will also extract a significant amount of the diterpenes (Meier, 1999).

PHARMACOLOGICAL ACTIONS

Human

Hormonal modulator (BHP, 1996). Early research suggested that chaste tree acts centrally, at the pituitary level, to inhibit release of follicle-stimulating hormone (FSH) and promote the release of luteinizing hormone (LH) (Boon and Smith, 1999; Weiss and Fintelmann, 2000). This action, referred to as a "corpus luteum hormone effect" (Weiss, 1988), was previously thought to lead to an increase in progesterone levels and a corresponding reduction in estrogen levels (Boon and Smith, 1999; Weiss, 1988). However, more recent research indicates that chaste tree appears to exert its medicinal actions through the reduction of prolactin secretion by the pituitary gland (Upton, 2001; Boon and Smith, 1999; Winterhoff, 1998; Newall *et al.*, 1996), through a mechanism involving dopamine antagonism.

Animal

Chaste tree significantly inhibits the stress-induced secretion of prolactin in male rats via its activity on the pituitary gland (Jarry *et al.*, 1991; Winterhoff, 1993; Wuttke *et al.*, 1995). In healthy lactating rats, high doses of chaste tree significantly reduced milk production compared to controls (Winterhoff, 1993, 1998).

In vitro

Chaste tree extract displaces ligands of human opioid-receptor-binding (Brugisser *et al.*, 1999), inhibits prolactin release from rat pituitary cells and exerts a dopamine-agonistic effect through direct dopamine receptor-binding (Jarry *et al.*, 1994; Sluitz *et al.*, 1993; Winterhoff, 1993; Wuttke *et al*, 1995). It does not appear to modulate rat pituitary cell production of FSH or LH (Jarry *et al.*, 1994) or inhibit spontaneous activity of the isolated rat uterus (Lal *et al.*, 1985). It has antimicrobial activity (Pepeljnjak, *et al.*, 1996).

MECHANISM OF ACTION

The exact mechanism of action of chaste tree has not been established (Upton, 2001). However, *in vitro* and *in vivo* studies have shown a dopaminergic action resulting in a reduction in elevated prolactin levels (Jarry *et al.*, 1994, 1991; Milewicz *et al.*, 1993; Sluitz *et al.*, 1993; Upton, 2001; Winterhoff, 1998; Wuttke *et al.*, 1995) and a cholinergic mechanism of action (Berger *et al.*, 1999). Isolated diterpenoids, rotundifuran, and 6β,7β-diacetoxy-13-hydroxy-labda-8,14-diene have shown dopaminergic activity in studies on receptor-binding (Hoberg *et al.*, 1999). Chaste tree extract inhibit release of FSH, and promote the release of LH (Boon and Smith, 1999; Weiss and Fintelmann, 2000). This action, referred to as a "corpus luteum hormone effect" (Weiss, 1988), leads to an increase in progesterone levels and a corresponding reduction in estrogen levels (Boon and Smith, 1999; Weiss, 1988). Furthermore, new research indicates that chaste tree appears to exert its medicinal actions through the reduction of prolactin secretion from the pituitary gland (Boon and Smith, 1999; Winterhoff, 1998; Newall *et al.*, 1996).

Animal

- Healthy male rats have been involved in studies in which plasma levels of prolactin were measured before and after exposure to chaste tree. Post-treatment prolactin levels were significantly reduced in the chaste tree treatment groups compared to control groups, which indicates inhibition of prolactin secretion *in vivo* (Winterhoff, 1998; Wuttke *et al.*, 1995).

In vitro

- Studies using a test system consisting of rat pituitary cultures revealed a dose-dependent decrease in prolactin secretion (Jarry *et al.*, 1994, 1991; Sluitz *et al.*, 1993; Winterhoff, 1998; Wuttke *et al.*, 1995). Since the prolactin inhibitory effects could be blocked by haloperidol, a dopamine receptor antagonist, chaste tree appears to exert its prolactin-lowering action via dopamine agonism (Merz *et al.*, 1996; Winterhoff, 1998).

CONTRAINDICATIONS

According to the German Commission E, no contradictions are known (Blumenthal *et al.*, 1998).

PREGNANCY AND LACTATION: Not recommended for use during pregnancy, according to the Commission E (Blumenthal *et al.*, 1998). The corpus luteum hormone effect of chaste tree can adversely effect the fetal sexual development and therefore chaste

tree extract should not be taken during pregnancy. However, in cases of progesterone insufficiency, the increase in progesterone levels can prevent miscarriage in the first trimester of pregnancy (McGuffin *et al.,* 1997), but this exceptional indication during pregnancy should be discussed with the healthcare provider prior to use. Progesterone levels should be closely monitored in the early weeks of pregnancy if a decision is made to withdraw chaste tree before four months.

No known restrictions during lactation (McGuffin *et al.*, 1997). There is insufficient information regarding chaste tree's influence on prolactin levels in lactating women to reliably predict the lactogenic response. Clinical information and traditional use suggest a galactogogue effect, while *in vitro* and animal studies using a high dosage range suggest an anti-galactogogue effect. Long-term use of chaste tree (more than two weeks) during lactation may lead to disruption of the lactation amenorrhea state and an early return to fertility, which may or may not be desired.

Adverse Effects

Commission E noted occasional occurrence of itching and urticarial exanthemas. If feelings of breast tension, breast swelling, or menstrual disturbances occur, a healthcare provider should be consulted for diagnosis (Blumenthal *et al.*, 1998). Side effects are rare, occurring in 1–2% of all patients treated (Loch *et al.*, 2000), and may include itching, rash, headache, hair loss, fatigue, agitation, dry mouth, tachycardia, nausea, and increased menstrual flow (Anon., 1998; Dittmar and Böhnert, 1992; Loch *et al.*, 1991; Newall, *et al.*, 1996). The usual percentage of side effects reported in clinical trials is 1–2% of subjects, or 246 side effects in 30 studies, with some subjects reporting multiple effects (total subjects=11,506) (Upton, 2001). The most frequent side effects reported were gastrointestinal distress/nausea (75), acne, skin reactions, urticaria (58), cycle changes (24), headache (10). There is one case report of mild ovarian hyperstimulation in a woman who self-prescribed chaste tree (Cahill, *et al.*, 1994).

Drug Interactions

None known. There is evidence of a dopaminergic effect in animals, which suggests a reciprocal weakening effect can occur with ingestion of dopamine-receptor antagonists such as haloperidol and potentially with dopamine-receptor blocking agents, such as metoclopramide, widely used as an antiemetic (Blumenthal *et al.,* 1998). Due to its apparent hormonal activity, chaste tree may interfere with the effectiveness of oral contraceptives and hormone-replacement therapy (McGuffin *et al.,* 1997; Boon and Smith, 1999); however, this speculative interaction has not been substantiated in clinical case reports (Upton, 2001).

American Herbal Products Association (AHPA) Safety Rating

Class 2b: Should not be used during pregnancy (McGuffin *et al.*, 1997).

Class 2d: May counteract the effectiveness of birth control pills (McGuffin *et al.*, 1997). However, a subsequent in-depth review of chaste tree pharmacology and clinical trials by a co-editor of the AHPA rating writes that this precaution "lacks substantiation" (Upton, 2001).

Regulatory Status

Canada: 32 chaste tree-containing homeopathic drugs have marketing authorization with Drug Identification Numbers (DIN) assigned (Health Canada, 2001). No chaste tree-containing Traditional Herbal Medicines (THM) are presently authorized, though there are no known restrictions.

France: Chaste tree fruit for homeopathic preparations is official in the Pharmacopée Française (Ph.Fr. X, 1989).

Germany: Approved nonprescription drug by the Commission E (Blumenthal *et al.*, 1998). Dried ripe fruit, containing no less than 0.4% (*v/w*) volatile oil, for preparation of mother tincture and liquid dilutions is official in the *German Homeopathic Pharmacopoeia* (GHP, 1993). Chaste tree is the subject of a botanical monograph in development for the DAB by the German pharmacopeial commission (Meier, 1999).

Italy: No monograph in the *Italian Pharmacopoeia* (Meier, 1999).

Sweden: Classified as a drug which must be registered as a pharmaceutical specialty (De Smet *et al.*, 1993). No chaste tree-containing products are presently registered in the Medical Products Agency's (MPA) "Authorised Natural Remedies" (MPA, 2001a), but chaste tree homeopathic drugs in tablets (D6, D12, and D30) have been registered (MPA, 2001b).

Switzerland: Category D nonprescription drug with sale limited to pharmacies and drugstores (Meier and Hoberg, 1999; Morant and Ruppanner, 2001). Two chaste tree phytomedicines and two chaste tree-containing homeopathic drugs are listed in the *Swiss Codex* 2000/01 (Ruppanner and Schaefer, 2000). Chaste tree is the subject of a botanical monograph in development by the Swiss pharmacopeial commission (Meier, 1999).

U.K.: Herbal medicine on *General Sale List* (GSL), Table A (internal or external use), Schedule 1 (requires full Product License) (GSL, 1994). No monograph in the *British Pharmacopoeia* (Meier, 1999), but one is found in *British Herbal Pharmacopoeia*.

U.S.: Dietary supplement (USC, 1994). Tincture of the dried or fresh berries, 1:10 (*w/v*) in 65% alcohol (*v/v*), is official in the *Homeopathic Pharmacopoeia of the United States* (HPUS, 1989). No monograph in the USP-NF.

Clinical Review

Eighteen studies are outlined in the table, "Clinical Studies on Chaste Tree," including 8,336 participants. All of these studies demonstrate positive effects for indications including corpus luteum abnormalities, menstrual cycle abnormalities, and PMS. Most of the studies are open, uncontrolled studies. One double-blind, placebo-controlled (DB, PC) study investigated a native dry extract of chaste tree in the treatment of luteal phase defects due to hyperprolactinemia (Milewicz *et al.*, 1993). Two other studies investigated native dry extracts in the treatment of PMS (Lauritzen *et al.*, 1997; Turner and Mills, 1993). A randomized, DB, PC, parallel study on a commercial chaste tree preparation (Ze440) on 170 women with PMS concluded that the fruit extract is safe and effective in reducing PMS symptoms (Schellenberger *et al.*, 2001). Another recent, multi-center trial on the efficacy of a chaste tree extract (Ze440) investigated 50 patients with PMS, concluding that PMS can be treated successfully as indicated by clear improvement in the main-effect parameter during treatment and the gradual return of that symptom after cessation of treatment. The main effect of treatment seems related to symptomatic relief rather than to the duration of the syndrome (Berger *et al.,* 2000). From 1943 to 1997, approximately 32 clinical studies were conducted on a proprietary chaste berry product (Agnolyt®, Madaus, Germany). Eight studies were on the product's effect on PMS, 4 on mastitis and fibrocystic

disease, 3 on menopausal symptoms, 3 on increasing lactation, 4 on hyperprolactinemia, 7 on uterine bleeding disorders, 3 on acne, and 4 on miscellaneous menstrual irregularities.

Branded Products*

Agnolyt® Capsules: Madaus AG / Ostermerheimer Strasse 198 / Köln / Germany / Tel: +49-22-18-9984-76 / Fax: +49-22-18-9987-21 / Email: b.lindener@madaus.de. Chaste tree fruit, hydro-alcoholic, native dry extract 9.58–11.5:1 (*w/w*), 60% ethanol volume. This product is no longer available.

Agnolyt® Solution: Madaus AG Chaste tree fruit tincture, ethanol 68% volume. Each 100 g of aqueous-alcoholic solution contains 9 g of a 1:5 tincture.

Alyt® Solution: Ciba-Geigy AG / Contact: Novartis Consumer Health AG / Route de l'Etraz / CH 1260 Nyon 1 / Switzerland / www.consumer-health.novartis.com. Chaste tree fruit tincture, ethanol 68% volume. Each 100 g of aqueous-alcoholic solution contains 9 g of a 1:5 tincture. Unable to verify manufacturer and availability.

BNO 1095 capsules (Bionorica Agnus castus extract), Bionorica AG / P.O. Box 1851 / D-92308 Neumarkt / Germany / Tel: +49(0)9181-231-90 / Email: international@bionorica.de / www.bionorica.de. Capsules contain 40 mg BP1095E1 [6–12:1 extract (spissum) (70% ethanol)]. This product is not distributed; Bionorica does distribute a tablet product containing BP1095 extract (6–12:1) equivalent to 40 mg crude drug.

Femicur® N Kapseln: Schaper & Brümmer GmbH & Co. KG/ Bahnhofstrasse 35 / 38259 Salzgitter / Ringelheim / Germany / Tel: +49-5341-30-70 / Fax: +49-5341-30-71-24 / Email: info@schaperbruemmer.de / www.schaper-bruemmer.com. 1 capsule contains dry extract of fruits of Vitex agnus-castus (7–13:1) 4 mg, extractant: ethanol 60% (m/m).

PreMens® Ze440: Zeller AG / Seeblickstrasse 4 / CH-8590 Romanshorn 1 / Switzerland / www.zellerag.ch. One coated tablet contains 40 mg chaste tree fruit hydro-alcoholic extract of which 20 mg is native dry extract, 6.0–12.0:1 (*w/w*) and 20 mg is lactose as excipient, 60% ethanol by weight. Normalized to contain a minimum of 0.6% casticin.

Strotan® Kapseln: Strathmann AG & Co. / Sellhopsweg 1 / 22459 Hamburg / Germany / Tel: +49-40-55-9050 / Fax: +49-40-55-9051-00 / Email: info@strathmann.de / www.strathmann.de. Soft-gel capsule contains 20 mg chaste tree fruit, hydro-alcoholic (50–70% *v/v*), native dry extract. Chemically defined constituents include the iridoids aucubin and agnuside, flavonoids, essential and fatty oils, and the bitter principle castin.

*American equivalents are found in the Product Table beginning on page 398.

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Clinical Studies on Chaste Tree (*Vitex agnus castus* L.)

Corpus Luteum Irregularities/Hyperprolactinemia

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Merz *et al*., 1996	Hyperprolactinemia	O, PC, Cm (intra-individual comparison) n=20 healthy men	14-day treatment period for each phase with 7-day wash-out phase between phases	Phase 1: placebo Phase 2: One capsule 3x/day (120 mg/day) Phase 3: Two capsules 3x/day (240 mg/day) Phase 4: Four capsules 3x/day (480 mg/day)	Bionorica BNO1095 capsules containing 20 mg BP1095E1 extract [6–12:1 extract (spissum) (70% ethanol)] equivalent to 40 mg crude drug	Pharmacological data were obtained on the influence of 14-day vitex treatment on Thyroxin Releasing Hormone (TRH)-stimulated prolactin release compared to placebo. Significant increase (p=0.003) in prolactin levels in men receiving the lowest dose (120 mg per day), but slight reduction in prolactin level in those receiving higher dose. There were no significant dose-dependent changes in the 24-hour serum prolactin profile.
Milewicz *et al*., 1993	Luteal phase defects due to hyperprolactinemia	R, DB, PC n=37 women with luteal phase defects due to latent hyperprolactinemia (ages 19–42 years old)	3 months	1 capsule vitex extract/day or 1 capsule placebo/evening	Strotan® soft-gel capsule containing 20 mg vitex fruit aqueous, alcoholic, dry native extract	After 3 months, vitex group experienced significant reduction in symptoms compared to placebo group. Significant reduction in prolactin release in response to TRH stimulation compared to placebo (p<0.0001). Midluteal progesterone levels, low at baseline, were normal after 3 months in vitex group. Luteal phase normalization and luteal progesterone synthesis normalization were seen in vitex group with no observable changes in these parameters in placebo group. No side effects were noted.
Propping *et al*., 1991	Corpus luteum insufficiency, menstrual disorders, and PMS	O, MC, U n=1,592 women with corpus luteum insufficiency; including 418 with hypermenorrhea; 355 with polymenorrhea; 202 with secondary amenorrhea,186 with dysmenorrea; 175 with PMS, anovulation; 145 experiencing sterility; 66 with menorrhagia; 32 with disturbed menstruation (average age 32.9 years)	16 years (average treatment period, 6 months)	43 drops tincture/day	Agnolyt® vitex fruit tincture (Each 100 ml of aqueous-alcoholic solution contains 9 ml of 1:5 tincture)	In 90% of cases, physician's clinical observation assessment was good or satisfactory, with 33% of patients free of complaints and a positive response to treatment in 51% noted. Patients experienced relief at about 8–9 weeks after beginning treatment. Out of 145 patients who were trying to conceive during treatment period, 56 became pregnant. Adverse effects, including nausea, skin rashes, headaches, and dyspepsia, were reported by 2.4% of patients.
Propping and Katzorke, 1987	Corpus luteum insufficiency	O, U n=18 infertile normoprolactinemic women (24–39 years old)	3 months	40 drops tincture/day	Agnolyt® vitex fruit tincture	Treatment was deemed successful in 13 of 18 patients (outcome was assessed by normalization of the midluteal progesterone level and by correction of pre-existing short menstrual cycle). 2 women became pregnant, and 11 patients had significantly improved serum progesterone values. There was a trend towards normalization of progesterone levels in 4 cases. These findings are indicative of corpus luteal function enhancement.

KEY: C – controlled, **CC** – case-control, **CH** – cohort, **CI** – confidence interval, **Cm** – comparison, **CO** – crossover, **CS** – cross-sectional, **DB** – double-blind, **E** – epidemiological, **LC** – longitudinal cohort, **MA** – meta-analysis, **MC** – multi-center, **n** – number of patients, **O** – open, **OB** – observational, **OL** – open label, **OR** – odds ratio, **P** – prospective, **PB** – patient-blind, **PC** – placebo-controlled, **PG** – parallel group, **PS** – pilot study, **R** – randomized, **RC** – reference-controlled, **RCS** – retrospective cross-sectional, **RS** - retrospective, **S** – surveillance, **SB** – single-blind, **SC** – single-center, **U** – uncontrolled, **UP** – unpublished, **VC** – vehicle-controlled.

Clinical Studies on Chaste Tree (*Vitex agnus castus* L.) (cont.)

Menstrual Cycle Irregularities

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Bubenzer, 1993	Oligo-menorrhea, corpus luteum insufficiency, poly-menorrhea	O, U n=120 women with hormone imbalance syndromes	6 months		Strotan® soft-gel capsule containing 20 mg vitex fruit aqueous, alcoholic, dry native extract	Of the subjects, 63% had normalized cycle (most had extended follicular phase), and those with disturbed temperatures during their cycles normalized. Patients with very low progesterone benefited particularly. 29% became pregnant.
Loch *et al.*, 1991	Menstrual irregularity	O, U n=2,447 women with a variety of menstrual disorders	9 years (average treat-ment period, 5 months)	42 drops tinc-ture/day	Agnolyt® vitex fruit tincture	Both patients and physicians noted improvement of symptoms. Of the patients, 90% demonstrated very good, good, or satisfactory results; 2.3% experienced minor side effects.
Loch and Kaiser, 1990	Secondary amenorrhea	P, O, U n=15 female out-patients with secondary amenorrhea (17–29 years old)	6 1/2 months	40 drops tinc-ture/day with some liquid in mornings apart from meals	Agnolyt® vitex fruit tincture	In 10 of 15 patients, the onset of menstruation was observed at about 6 months of treatment. Hormone values for progesterone and LH increased, while FSH decreased slightly or did not change. Authors concluded that Agnolyt® can be recommended for long-term treatment of secondary amenorrhea.
Bleier, 1959	Oligo-menorrhea, polymenor-rhea, menor-rhagia	O n=126 women (35 with oligomenor-rhea, 33 with poly-menor-rhea, 58 with menorrhagia)	2–3 months	15 drops, 3x/day with water 1/2 hour before meals	Agnolyt® vitex fruit tincture	In 58 patients with menorrhagia, a statistically significant shortening of bleeding period was achieved. In 33 patients with polymenorrhea, duration between periods lengthened (on average, from 20 days to 26 days). In 33 cases of oligomenorrhea, the average cycle was shortened from 39 to 31 days. Fourteen patients became pregnant.
Probst and Roth, 1954	Secondary amenorrhea, oligohy-pomenorrhea, cystic granular hyperplasia of endometrium, anovulatory cycle	O, Cm, U n=82 women (57 in vitex group; 25 in group combining vitex with estrogen)	5–24 months	15 drops vitex tincture, 3x/day vs. 1 tablet ethenyl estradiol, 3x/day with same vitex dosage	Alyt® vitex fruit tincture, same as Agnolyt® tincture of aqueous-alcoholic solution	Of women in vitex group 87.7% showed normalization of bleeding in menstrual cycle compared to 52% in the vitex/estradiol combination group. Of those women in vitex group, 100% were diagnosed with anovulatory cycle, 50% with secondary amenorrhea and 44% with oligo-hypomenorrhea experienced a distinct increase in the basal temperature curve. Only 16% of the women in the combination therapy group observed an increase in basal temperature. The authors concluded that vitex was particularly indicated in patients with deficient corpus luteum function.

Premenstrual Syndrome (PMS)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Schellenberg, 2001	PMS	R, DB, PC, PG n=170 women aver-age menstrual cycle = 28 days; average duration of menses = 4.5 days (average age 36 years)	3 menstrual cycles	One, 20 mg tablet/day	PreMens® (Ze440) extract tablets 40 mg (20 mg native dry extract, 20 mg lactose as excipient)	Improvement in vitex group in the main efficacy vari-ables from baseline to end of third cycle in women's self assessment and physician's assessment of irritability, mood change, anger, headache, breast fullness, and other menstrual symptoms including bloating ($p<0.001$). Over half of women had 50% or greater improvement of symptoms. 4 women in vitex group and 3 in placebo group reported mild adverse events, none which caused discontinuation. Authors conclude that vitex fruit is a safe and effective treatment for relief of symptoms of PMS.
Loch *et al.*, 2000	PMS	OL, MC n=1,634 women with PMS; data from 857 gynecologists (mean age 35.8 years)	3 menstrual cycles	One, 20 mg capsule, 2x/day	Femicur® capsules containing 1.6–3.0 mg dried extract [6.7–12.5:1] corresponding to 20 mg drug	93% reported PMS symptoms lessened or disappeared after vitex treatment over 3 menstrual cycles. Changes from baseline were recorded on questionnaires by physicians before treatment and after 3 cycles. Significant decrease of all symptoms. Of the patients, 42% reported that they no longer suffered from PMS; 51% showed a decrease in symptoms.

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Clinical Studies on Chaste Tree (*Vitex agnus castus* L.) (cont.)

Premenstrual Syndrome (PMS) (cont.)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Berger *et al*, 2000	PMS	P, MC n=43	8 menstrual cycles; including 2 baseline, 3 treatment, and 3 post-treatment	One, 20 mg tablet/day in the morning	PreMens® Ze440 tablet containing 20 mg vitex fruit, hydro-alcoholic, native dry extract, 6.0–12.0:1 (*w*/*w*)	Significant score reduction (42.5%) using the MMDQ (Moos Menstrual Distress Questionnaire) as the main effect parameter ($p<0.001$). Symptoms gradually returned after cessation of treatment. However, a difference from baseline remained (20%; $p<0.001$) up to 3 cycles thereafter.
Berger *et al.*, 1999	Late luteal phase dysphoric disorder (PMS III –R)	C, E, MC n=132 women, 65 on oral contraceptives and 67 not on oral contraceptives (19–30 years old)	6 months (3 cycles followed by 3-month observation period)	One, 20 mg tablet/day in morning	PreMens® Ze440 tablet containing 20 mg vitex fruit, hydro-alcoholic, native dry extract, 6.0–12.0:1 (*w*/*w*)	Using Visual Analog Scale (VAS), the only marginal differences were observed between the contraceptive and non-contraceptive groups during the medication period and post-medication period. All clinically relevant reduction in VAS scores of approximately 60% of all patients was reached. Of all patients, 90% believed that vitex helped and 75% said they would use vitex in the future. A good use-risk ratio was determined for both groups. Clinically relevant score-values of PMS declined during the 3 cycle therapy and rose again thereafter.
Lauritzen *et al.*, 1997	PMS	MC, C,R, Cm n=105 women with PMS; Agnolyt® group n=46, pyridoxine group n=59 after exclusion (18–45 years old)	3 months	Vitex group: 1 capsule Agnolyt®/day plus 1 capsule placebo/day. B6 group: 1 placebo capsule, 2x/day, on days 1–15; 1 B6 capsule, 2x/day, on days 16–35 of menstrual cycle.	Agnolyt® capsules containing 3.5–4.2 mg vitex fruit, dry native extract, 9.58–11.5:1 (*w*/*w*) vs. B6 capsules containing 100 mg pyridoxine HCL	Agnolyt® was superior to pyridoxine. On the premenstrual tension syndrome (PMTS) scale, vitex group had reduction in score points from 15.2 to 5.1 vs. 11.9 to 5.1 in B6 group. Of patients in vitex group, 77.1% vs. 60.6% of patients in B6 group showed improvement on Clinical Global Impression (CGI) scale. No serious adverse events were noted. Side effects included gastrointestinal complaints (equally distributed between both groups), skin reactions (two patients in vitex group), and transitory headache (one patient in vitex group).
Turner and Mills, 1993	PMS	R, DB, PC n=217 women (105 in vitex group, 112 in placebo group) with PMS (physiological symptoms)	3 months	600 mg, 3x/day vs. soya-based placebo	Vitex capsules (brand not stated)	Vitex was statistically more effective than placebo only in alleviating jitters and restlessness; there was no statistical significant difference for other PMS symptoms including impaired concentration, fluid retention, or pain.
Dittmar and Böhnert, 1992	PMS	O, MC, U n=1,542 women with PMS (13–62 years old)	166 days average treatment duration	40 drops/day in morning	Agnolyt® vitex fruit tincture	Of patients, 33% reported total relief of symptoms, 57% reported partial relief, 4% reported no improvement. On 5% no data were obtained, and 2% terminated treatment because of side effects. Physicians observed a positive response (good or very good) to treatment in 92% of patients.
Coeugniet *et al.*, 1986	PMS	O, U n=36 women with PMS	3 months	40 drops/day	Agnolyt® vitex fruit tincture	After 3 months, physical and psychological alterations experienced during luteal phase of cycle were significantly reduced ($p<0.5$), including reduction in headaches, breast tenderness, bloating, fatigue, appetite, sweet cravings, nervousness, restlessness, anxiety, irritability, lack of concentration, depression, mood swings, and aggressiveness. Interval of luteal phase normalized from average of 5.4 days to 11.4 days and a diphasic cycle was established.

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Clinical Studies on Chaste Tree (*Vitex agnus castus* L.) (cont.)

Other

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Giss and Rothenburg, 1968	Acne vulgaris, acne indurate, acne conglobata, acne follicularis	C, Cm n=161 patients with acne (30% male; 70% female)	1–2 years (minimum 3-month treatment period)	20 drops tincture, 2x/day (morning and evening) for 4–6 weeks; then 15 drops daily for 1–2 years.	Agnolyt® vitex fruit tincture vs. standard acne therapy	118 patients received Agnolyt®, and 43 received standard acne therapy. Over 2 years, a statistically significant improvement of acne conditions was reported in the mostly female vitex group compared to placebo.

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