Fructus Agni Casti

Definition
Fructus Agni Casti consists of the dried, ripe fruits of *Vitex agnus-castus* L. (Lamiaceae) (*1*, *2*).

Synonyms
Agnus-castus vulgaris Carr., *Vitex verticillata* Lam. (*3*).

Selected vernacular names
Abraham's balm, Abrahamsstrauch, agneau-chaste, agnocasto, agnos-casto cumune, agnus-castus, angarf, ârbol casto, ârbolde la castidad, arbre au poivre, athlak, banjankusht, barátcserje, bish barmagh aghaji, chaste tree, chasteberry, common chaste tree, daribrahim, felfele barry, fanfangosht, gatileira comum, gattilier, gattilier commun, hab an nasl, hab el fakd, hab a khouraf, hayit, hemp tree, jurema, kaff maryam, kef-meriem, kerwa, Keuschbaum, Keuschlamm, kyskhedstrae, lilac chastetree, lygos, Mönchspfeffer, Mönchspfeller, monk's pepper, monk's pepper tree, Müllen, non's peppertree, panj angosht, panjangusht, pape falso, peperella, petite poivre, pimiento menor, poivre de moine, poivre sauvage, ranukabija mah, sagetree, sauzgatillo, seiyo-ninzin-boku, shajerat Ebrahim, shagareh Ibrahim, sinduvara, tree of chastity, true chaste tree, vitex, vitiu, wild lavender, Yemen safrani (*1–7*).

Geographical distribution
Native to the Mediterranean region and Asia (*2*, *4*, *8*). Cultivated in warm temperate regions of the world, and obtained primarily from Mediterranean countries, especially Albania and Morocco (*3*, *9*).

Description
A small tree or deciduous shrub, approximately 1–6 m in height, with aromatic odour. Leaves: opposite, long-petiolate, palmately-compound with 3–9 stipulate leaflets; leaflet blade linear-lanceolate, apex and base acuminate, 1.5–10.0 cm long, 0.5–2.0 cm wide; the central leaflet is the longest,

dark green and glabrous above, velvety white-tomentose below; margin entire to sparsely toothed. Inflorescence: terminal panicle, 12.0–17.5 cm long, and composed of many sessile-subsessile cymes. Flower: perfect, campanulate symmetric, white-tomentose; calyx 5-toothed, campanulate, 2.0–2.5 cm long; corolla blue, pink, yellowish or white, salverform, tube 6–7 mm long, limb 2-lipped, upper lip 2-lobed, lower lip 3-lobed; stamens 4, exerted, 2 long, 2 short, inserted near top of corolla tube, alternate with corolla lobes; ovary superior, style exerted, stigma bifid. Fruit: drupe, globose to subglobose, 2–4 mm in diameter, reddish (*3*, *4*).

Plant material of interest: dried ripe fruits

General appearance

Mature fruit is round to ovoid, 2–4 mm in diameter, glandular hairy, extremely hard, reddish-brown to black, slightly rough, and usually accompanied by a short pedicel and some smaller, immature fruits in close groups of up to six. The apex has a slight depression with 4 faint grooves at right angles to one another. A tubular persistent calyx with 5 short, often indistinct, teeth covers half to three quarters of the surface. The calyx is grey-green and tomentose (*1*).

Organoleptic properties

Odour: faintly aromatic; taste: slightly aromatic and bitter (*4*, *9*, *10*).

Microscopic characteristics

Fruit: The exocarp is brown and narrow, consisting of parenchymatous cells with thin walls and partially lignified cells with many pitted thickenings on the inside. In surface view, the exocarp shows an epidermis of polygonal cells with thickened walls and some with large, conspicuous, simple pits; among the cells are short-stalked glandular trichomes with unicellular or multicellular heads and some short covering trichomes. In cross-section, the fruit shows small epicarp cells covered with a thick cuticle. The mesocarp consists of several layers of isodiametric parenchyma cells with slightly thickened and pitted cell walls; occasionally these cells have brownish granular contents. The walls of the outer mesocarp cells are brown whereas those of the inner cells lack colour. The inner mesocarp consists of finely pitted sclerenchymatous cells, some with moderately thickened walls, others consisting of isodiametric stone cells with a small lumen. In the outer part, very small brown-coloured vascular bundles are arranged in a circle. Towards the endocarp the cells become smaller and their cell walls thicker; the innermost cell layers consist of small sclereids with a small branched lumen. The seeds are small, having large

cotyledons surrounded by thin-walled, large parenchymatous cells that have ribbed thickenings. The nutritive tissue and the cells of the germ contain aleurone grains and oil globules. Calyx: composed of outer epidermis of small, isodiametric polygonal cells, densely covered by short, bent or undulate, unicellular or bicellular covering trichomes of fairly uniform length; inner epidermal cells a little larger, walls slightly wavy, some thickened; trichomes absent (*1*).

Powdered plant material

Greyish to dark brown, with a musty, slightly aromatic odour and unpleasant, bitter taste, reminiscent of sage; abundant, more or less isodiametric stone cells with walls of varying thickness and degree of pitting; ovoid lignified cells with thin bands of reticulate thickening; fragments of calyx with closely-spaced, short covering and glandular trichomes on the outer side and birefractive elongated sclereids on the inner side; epicarp cells with large pits in the outer wall; thin-walled parenchymatous cells and globules of fixed oil; small glandular trichomes (*1*).

General identity tests

Macroscopic and microscopic examinations (*4*, *9*, *11*), thin-layer chromatography for the presence of agnuside and aucubin (*1*), and high-performance liquid chromatography for the presence of the marker compounds, casticin and agnuside (*1*, *12*) and for the biologically active diterpenes vitexilactone, rotundifuran and 6β,7β-diacetoxy-13-hydroxy-labda-8,14-diene (*12*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues (*13*).

Foreign organic matter

Not more than 2.0% (*1*).

Total ash

Not more than 8.0% (*1*).

Acid-insoluble ash

Not more than 2.0% (*1*).

Water-soluble extractive

Not less than 8.0% (*9*).

Loss on drying
Not more than 10.0% (*1*).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*13*). For other pesticides, see the *European pharmacopoeia* (*13*) and the WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues (*14*) and pesticide residues (*15*).

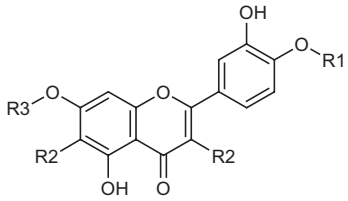
Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues (*14*).

Radioactive residues
Where applicable, consult the WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues (*14*).

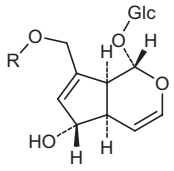
Chemical assays
Contains not less than 0.05% agnuside and 0.08% casticin calculated on the basis of dried drug by high-performance liquid chromatography (*1*).

Major chemical constituents
Up to 2.0% essential oil with bornyl acetate, 1,8-cineol, limonene, α-pinene and β-pinene being primary constituents. Flavonoids, iridoids and diterpenes represent major groups of secondary constituents found in the fruit (*4*, *5*). Casticin, in concentrations up to 0.2% (*12*) is considered the major flavonoid, with chrysosplenetin, chrysosplenol D, cynaroside, 5-hydroxy-3,4′,6,7-tetramethoxyflavone, 6-hydroxykaempferol, isorhamnetin, luteolin and luteolin 6-C-glycoside (isoorientin) derivatives being other compounds of this class. Diterpene constituents include vitexilactone (0.001–0.004%), 6β,7β-diacetoxy-13-hydroxylabda-8,14-diene, rotundifuran, and vitexlactam A (*3*, *5*, *16–18*). The structures of representative flavonoids, iridoids and diterpenes are presented below.

Medicinal uses
Uses supported by clinical data
Orally for the symptomatic treatment of gynaecological disorders including corpus luteum insufficiency and hyperprolactinaemia (*19*), premenstrual syndrome (*20–25*), menstrual irregularities (*26*, *27*), cyclic mastalgia (*28*, *29*) and also to treat hormonally-induced acne (*30*, *31*).

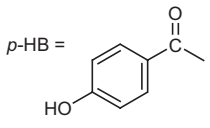


	R1	R2	R3
Casticin	CH_3	OCH_3	CH_3
Chrysosplenol D	H	OCH_3	CH_3
Cynaroside	H	H	Glc

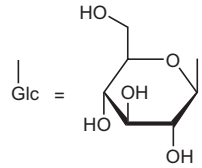


Aucubin R = H

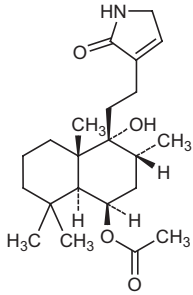
Agnuside R = *p*-HB



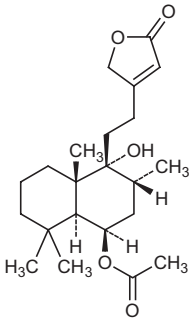
p-hydroxybenzoyl



β-D-glucopyranosyl



Vitexlactam A



Vitexilactone

Uses described in pharmacopoeias and well established documents

Orally for the treatment of endometrial hyperplasia and secondary amenorrhoea (*32*); endocrine-dependent dermatoses (dermatitis symmetrica dysmenorrhoica (Matzenauer-Polland syndrome)) acne vulgaris, eczema, acne rosacea), hypermenorrhoea (*33*), infertility due to hyperprolactinaemia and luteal phase defect (*34*). Used to treat fibroid cysts and infertility, to stop miscarriages due to progesterone insufficiency, to help expel the placenta after birth (*35*) and also as a digestive aid, sedative, anti-infective and for the treatment of hot flushes (*36*).

Uses described in traditional medicine

Used as an anaphrodisiac, calefacient, contraceptive, emmenagogue, sedative and as a tonic (*5*).

Pharmacology

Experimental pharmacology

Receptor binding

Numerous mechanisms have been proposed for the many activities of the crude drug. Extracts of the fruit have been shown to act as dopamine agonists in vitro and in vivo. The binding of an 80% ethanol extract of the fruit and various fractions of the extract to the dopamine D_2 and other receptors was evaluated both by radioligand binding studies and by super-

fusion experiments (*35*). The extract bound to the dopamine D_2 and opioid (μ and κ subtype) receptors with a range of median inhibitory concentrations between 40 and 70 μg/ml. Binding was not observed for the histamine H_1 and benzodiazepine receptor or the serotonin transporter. Two diterpenes isolated from the hexane fraction of the extract, rotundifuran and 6β,7β-diacetoxy-13-hydroxy-labda-8,14-diene, exhibited inhibitory actions on dopamine D_2 receptor binding with a median inhibitory concentration of 45 and 79 μg/ml, respectively (*16*, *37*). While lipophilic fractions of the extract bound to the μ- and κ-opioid receptors, binding to δ-opioid receptors was inhibited mainly by an aqueous fraction of the extract. In superfusion experiments, the aqueous fraction of a methanol extract inhibited the release of acetylcholine in a concentration-dependent manner. In addition, the D_2 receptor antagonist, piperone, antagonized the effect of the extract suggesting a dopaminergic action mediated by D_2 receptor activation. A labdane diterpene, α-acetoxy-13-hydroxylabdadiene, isolated from a fruit extract, was found to displace ^{125}I-sulpiride from recombinant human D_2 receptor binding sites in a dose-dependent manner (*38*). This group also demonstrated that rotundifuran, at a concentration of 100 μM, significantly inhibited the secretion of prolactin from cultured rat pituitary cells ($p < 0.05$). In addition, rotundifuran inhibited forskolin-induced prolactin and cyclic adenosine monophosphate secretion in rat pituitary cells, when added to the medium at a concentration range of 10–100 μM (*38*). Bicyclic clerodane diterpenes have also been isolated from extracts of the fruit and were found to have a 10-fold higher activity than rotundifuran for inhibiting synthesis of cyclic adenosine monophosphate and release of prolactin in prolactin secreting cells of the rat pituitary by binding directly to the D_2 receptors (*39*).

In membrane preparations from rat corpus striatum, a lyophilized 60% ethanol extract of the fruit at a concentration of 0.5 mg/ml displaced ^{125}I-sulpiride from dopamine D_2 receptor binding sites in a dose-dependent manner (*40*). An extract of the fruit as well as the synthetic dopamine agonist (lisuride) significantly inhibited basal and thyroid releasing hormone-stimulated secretion of prolactin by rat pituitary cells in vitro (*41*).

A reduction in the concentrations of endogenous opioids during the late luteal phase has also been proposed as one of the mechanisms which may induce the symptoms of premenstrual syndrome, such as mood swings, headaches and water retention (*39*). A number of fruit extracts and chromatographic fractions have been tested in vitro for their ability to displace receptor binding ligands to the μ-, κ-, and δ-opioid receptors (*37*, *42*). The extract and butanol, chloroform and hexane fractions bound to

the μ- and κ-receptors, while the aqueous extract was more active in the δ-opioid receptor. No binding in the orphan opioid receptor was noted.

Rat brain striatal tissue was preincubated with ^{3}H-choline. Treatment of the preincubated tissue with a fruit extract inhibited electrically stimulated release of ^{3}H-acetylcholine with a median inhibitory concentration of 30 μg/ml (*37*). The inhibitory effect was reduced by co-incubation of the tissues with spiroperidol. Atropine partially reduced the inhibitory effects of the fruit extract suggesting that the extract may also work on the cholinergic receptors (*37*).

Several extracts of chaste berry have been shown to bind to the estrogen receptor and have weak estrogenic effects, suggesting that chaste berry may also affect the estrogen/progesterone balance (*43–45*). A fruit extract dose-dependently bound to both estrogen receptor isotypes, but binding appeared to be more selective for estrogen receptor β than estrogen receptor α (*45*). The extract also dose-dependently inhibited the secretion of progesterone from human granuloma cells (*44*), an effect that is mediated by estrogen receptor β, as it can be blocked by tamoxifen. Furthermore one in vivo study has shown that treatment of ovariectomized rats with an undefined extract of the fruit (dose not stated) increased uterine growth, and the expression of uterine c-myc mRNA levels and liver ceruloplasm mRNA levels, indicating an estrogenic effect (*43*).

A methanol extract of the crude drug bound to both estrogen receptor α and estrogen receptor β, and induced the expression of estrogen-dependent genes, progesterone receptor, and pS2 (presenelin-2) in Ishikawa cells (an estrogen-dependent endometrial adenocarcinoma cell line) (*45*). Significant binding affinity for both estrogen receptor α and estrogen receptor β, with a median inhibitory concentration of 46.3 μg/ml and 64.0 μg/ml, respectively, and the affinity for estrogen receptor α and estrogen receptor β was not significantly different (*45*). In Ishikawa cells, the extract exhibited weak estrogenic activity, as indicated by up-regulation of the progesterone receptor mRNA; however alkaline phosphatase activity was not changed. In S30 breast cancer cells, the presenelin-2 gene was up-regulated in the presence of 20.0 μg/ml of the same extract. Based on bioassay-guided isolation, the "estrogenic" component from the fruit extract was identified as linoleic acid, which also bound to estrogen receptor α and estrogen receptor β (*46*). Like the extract, linoleic acid also induced expression of the progesterone receptor mRNA in Ishikawa cells, at a concentration of 1 μg/ml, indicating that binding produced a biological estrogenic effect in vitro. In addition, low concentrations of the extract or linoleic acid (10 μg/ml) up-regulate the expression of estrogen receptor β mRNA in the estrogen receptor+

hormone-dependent T47D:A18 cell line, a further indication of estrogenic activity (*46*).

Effect on prolactin secretion

An ethanol extract of the fruit (1:10 with ethanol, 62%), in a range of concentrations from 0.41 to 3.3 mg/ml, significantly inhibited basal and thyroid stimulating hormone-stimulated prolactin secretion from rat primary pituitary cell cultures in vitro ($p < 0.05$) (*41*, *47*). At a concentration of 3.3 mg/ml the inhibition was 80% for basal secretion and 65% for stimulated secretion. These results were confirmed in another study demonstrating significant inhibition of prolactin release from rat pituitary cells by the extract at concentrations of 0.5 mg/ml for basal secretion and 0.125 mg/ml for stimulated secretions (*41*). Furthermore, inhibition of prolactin secretion from rat pituitary cells was also observed after treatment with an extract of the fruit at concentrations of 460 µg/ml ($p < 0.0003$) for basal secretion and 115 µg/ml for stimulated secretion ($p < 0.01$) (*41*). The inhibitory effect of a fruit extract on prolactin secretion was investigated in male rats (*48*). Intravenous administration of a 53% ethanol fruit extract containing 20 mg/ml of water-soluble constituents significantly inhibited stress-induced prolactin secretion as compared with the baseline ($p < 0.05$) (*48*).

Toxicology

The median lethal dose of an ethanol extract of the fruit after a single intragastric or intraperitoneal injection was greater than 2.0 g/kg body weight (bw) in rats and mice, and no deaths were reported (*4*).

In a 28-day subacute toxicity study the no-observed-effect level was 50.0 mg/kg bw; chronic administration over 26 weeks resulted in a no-observed-effect level of 40.0 mg/kg bw (*4*). No genotoxic effects were observed when the same extract was tested in the thymidine kinase mutation assay in mammalian cell lines, the unscheduled DNA repair assay in rat hepatocytes or in the micronucleus assay of murine bone marrow cells (*4*).

Clinical pharmacology

Approximately 32 clinical trials have assessed the safety and efficacy of various fruit extracts or tinctures (53–70% ethanol) for the treatment of acne, corpus luteum insufficiency, cyclic breast pain, hyperprolactinaemia, menopausal symptoms, increasing lactation, premenstrual syndrome, uterine bleeding disorders and miscellaneous menstrual irregularities (*47*). A review of all of the clinical data is beyond the scope of this monograph; for the complete details of all trials please refer to the cited references (*4*, *47*). Most of the studies were open, uncontrolled studies investigating the effects of the extracts on menstrual cycle abnormalities or premenstrual

syndrome. One double-blind placebo-controlled study investigated a fruit extract in treatment of luteal phase defects due to hyperprolactinaemia (*19*). Two other double-blind placebo-controlled studies investigated fruit extracts in treatment of premenstrual syndrome (*24*, *49*).

Abnormal menstrual cycles and infertility

Since 1954 at least 17 studies have assessed the effects of extracts of the fruit on a variety of menstrual cycle disorders including amenorrhoea, oligomenorrhoea, polymenorrhoea, corpus luteum insufficiency and infertility (*4*). Two double-blind placebo-controlled clinical trials and several observational studies have investigated the effect of various extracts of the fruit on corpus luteal phase dysfunction and infertility (*19*, *34*). The products tested were all ethanol extracts (53–70% ethanol), and the doses used in these investigations were: 20 drops twice daily; 15 drops three times daily; 30 drops twice daily; or one to two tablets or capsules daily.

A randomized, double-blind, placebo-controlled trial involving 52 women with luteal phase defects due to latent hyperprolactinaemia assessed the efficacy of a dried fruit extract (*19*). The aim of the study was to find out whether elevated pituitary prolactin levels could be reduced and if deficits in luteal phase length and luteal phase progesterone synthesis could be normalized. Blood for hormone analysis was taken on days 5–8 and day 20 of the menstrual cycle, before and after 3 months of therapy. Latent hyperprolactinaemia was analysed by monitoring the prolactin release 15 and 30 min after intravenous administration of 200 µg of thyroid hormone. Thirty-seven cases (placebo: $n = 20$; treatment: $n = 17$) were included in the final statistical analysis. After 3 months of treatment with the extract at a dose of 20 mg per day, prolactin release was reduced; a significant increase in the length of the luteal phase (10.5 days; $p < 0.05$) was observed. Deficits in luteal progesterone synthesis were eliminated. These changes only occurred in women in the treatment group, no change was observed in the placebo group. All other hormonal parameters remained unchanged, except for 17-β-estradiol, which increased during the luteal phase in women in the treatment group. The overall length of the menstrual cycle did not change, suggesting that there was a corresponding shortening of the follicular phase. Two women in the group given the extract had become pregnant by the end of the study. No side-effects were reported.

The second randomized, double-blind, placebo-controlled study assessed the efficacy of a 53% ethanol extract of the crude drug in 96 infertile women (*34*). The outcome criteria included pregnancy or menstrual bleeding in women with secondary amenorrhoea or improved luteal hormone concentrations. The women were administered 30 drops twice daily for 3 months. Sixty-six women completed the study, but no statisti-

cally significant results were found (p = 0.069). In the women with amenorrhoea or luteal phase dysfunction, pregnancy resulted twice as often in women in the treatment group (15%) as in those in the placebo group (7%); however no statistical analysis was reported.

In open (uncontrolled) trials involving 48 women who were infertile due to luteal-phase dysfunction, the efficacy of a fruit extract for the normalization of progesterone concentrations was determined (*50*). The inclusion criteria were normal prolactin levels (below 20 ng/ml), normal results in the prolactin and thyroid-stimulating hormone stimulation tests and an abnormally low serum progesterone level (below 12.0 ng/ml) on the 20th day of the cycle. Treatment consisted of a fruit extract, 40 drops daily, without any other medication for 3 months. Forty-five women completed the studies (3 were excluded because of concurrent hormone use). The outcome of therapy was assessed by the normalization of the mid-luteal progesterone level and by correction (lengthening) of any pre-existing shortening of the phases of the cycle. Treatment was deemed successful in 39 of the 45 patients. Seven women became pregnant; serum progesterone was restored to normal in 25 patients (> 12 ng/ml) and in seven women there was a trend towards normalization of progesterone levels. However, no statistical analysis was performed.

Two larger post-marketing trials, involving 479 women, assessed the safety and efficacy of fruit extracts for the treatment of oligomenorrhoea or polymenorrhoea (*50*). The women were treated with 30 drops of the extract twice daily and the outcome measured was the bleeding-free interval. An increase in the bleeding-free interval was observed after 35 days in 187/287 women receiving treatment for oligomenorrhoea and after 26 days in 139/192 women receiving treatment for polymenorrhoea.

Acne treatment

Two uncontrolled clinical studies and one observational report have assessed the effects of extracts of the fruit on acne due to hormone imbalance (*30*, *31*, *33*). In one open study, 118 people with acne were treated with a fruit extract (20 drops twice daily for 4–6 weeks, then 15 drops twice daily for 1–2 years) and the results were compared with those of conventional treatments for acne (*31*). Patients treated with the fruit extract reported a quicker healing rate after 6 weeks and after 3 months of therapy, 70% of patients treated with the fruit extract had complete healing.

Cyclic breast pain (mastalgia)

Breast pain (mastalgia) is a common complaint usually classified as cyclical (associated with the menstrual cycle) or non-cyclical (not associated with the menstrual cycle). Mild premenstrual breast discomfort, lasting

for 1–4 days prior to menstruation that resolves upon the initiation of menstruation, is considered to be within normal physiology. Non-cyclic breast pain lasting for five or more days should be brought to the attention of a health care provider. Several open (uncontrolled) trials (*28*, *51–56*) and three randomized controlled clinical trials (*28*, *29*, *56–58*) have assessed the safety and efficacy of extracts of the fruit for the treatment of cyclic mastalgia.

A randomized, double-blind, placebo-controlled clinical trial involving 104 women with cyclic breast pain (at least 3 cycles) assessed the effects of a preparation of the fruit (tincture 1:5 equivalent to 2 g of the fruit in 53% ethanol) for the treatment of cyclic breast pain (*58*). The patients were treated with either placebo, tincture (30 drops twice daily), or tablets (one tablet twice daily) for three cycles. Patients assessed the intensity of breast pain once per cycle using a visual analogue scale and also recorded the presence of menstrual bleeding and the intensity of pain in a diary. Prolactin levels were also measured during the premenstrual week of cycles one and three. At the end of the third cycle of treatment, a significant reduction in breast pain was observed in the treated patients as compared with those who received placebo (tincture, $p = 0.006$; tablets, $p = 0.0076$). Neither the tablets nor the tincture of crude drug had any effect on concentrations of progesterone, follicle stimulating hormone or luteinizing hormone. While the basal prolactin levels decreased in both treatment groups, this was not statistically significant when compared with placebo (*58*).

A second randomized, placebo-controlled, double-blind study with a similar design compared the tincture (30 drops = 1.8 ml, twice daily for 3 cycles) with placebo for the treatment of 97 women ($n = 48$ in the treatment group; 49 in the placebo group) who had had breast pain at least 5 days prior to menses in the last cycle before the study (*57*). A visual analogue scale was used for assessment of the efficacy. Intensity of breast pain diminished more quickly in the group that received the tincture. The study design and duration were similar to that of Wuttke et al. (*57*, *58*). The results of this study showed a decrease in the visual analogue scale scores of women in both the treatment and the placebo groups. However, compared with women in the placebo group, those in the treatment group had significantly lower visual analogue scale values at the end of each cycle ($p = 0.018$, 0.006 and 0.064 for cycles 1, 2 and 3, respectively).

In a randomized, placebo-controlled trial the effects of a Vitex agnus-castus solution and a placebo (double-blind) were compared with that of gestagen (lynestrenol) in 160 women with mastalgia (*59*). A complete remission, or improvement of symptoms, was reported in 82.1%, 74.5%, and 36.8% of the patients in the gestagen, chaste tree, and placebo groups,

respectively. The difference in effect between treatment and placebo was significant ($p < 0.01$). No significant differences were found between the two treatments (*59*).

Numerous open studies have assessed the effect of a solution of *Vitex agnus-castus* (VAC solution) for the treatment of over 1700 women with mastalgia (*28*, *29*, *51*, *52*, *54–56*). All of these studies assessed the efficacy of one product, VAC solution, at a dose of 45–75 drops per day for 1–6 menstrual cycles. Two studies compared VAC treatment with lynestrenol (5 mg daily on days 12–24 of each cycle). Elimination of symptoms was observed in 46–81.5% of treated women; improvement of symptoms in 12–39.6% and no effect in 6.5–29%. Reported side-effects included circulatory disturbances, acne and weight gain.

Premenstrual syndrome

Premenstrual syndrome refers to the regular occurrence of affective symptoms such as depressive moods, irritability, anxiety, confusion and social withdrawal, as well as somatic symptoms including breast tenderness or heaviness and breast pain (mastalgia), abdominal bloating, cravings, fatigue and headache.

Twelve clinical trials have assessed the efficacy of extracts of the fruit for the symptomatic treatment of premenstrual syndrome (*22–24*, *26*, *27 49*, *58–63*). Of these studies, only three were randomized controlled trials and two were double-blind (*22*, *49*, *63*). A positive placebo effect was ruled out by one randomized placebo-controlled study carried out in compliance with good clinical practice (*63*). In this study, patients ($n = 86$) with premenstrual syndrome were given either a chaste tree fruit extract (60% ethanol), in the form of a product called "Z 440", one 20-mg tablet daily or a placebo ($n = 84$) during three consecutive menstrual cycles. Diagnosis was made according to the Diagnostic and Statistical Manual for Mental Disorders. The main efficacy variable was change from baseline to end-point (end of the third cycle) in the patient's self-assessment of six premenstrual syndrome symptoms (irritability, mood alteration, anger, headache, breast fullness, and other symptoms including bloating). A secondary efficacy variable was change in Clinical Global Impressions score for the factors: severity of condition, global improvement, and risk–benefit. Mean improvement in patient's self-assessment was significantly greater in the women in the treatment group than in women who received the placebo ($p < 0.001$). Clinical Global Impressions scores for each of the three factors also revealed significant superiority of the treatment relative to placebo ($p < 0.001$). Responder rates (> 50% reduction in symptoms) were 52% and 24% for treatment and placebo, respectively. Adverse events reported in the active treatment arm ($n = 4$) included acne, multiple

abscesses, inter-menstrual bleeding and urticaria; in the placebo arm (n = 3) the adverse events were acne, early menstrual period and gastric upset.

A randomized, double-blind, placebo-controlled trial involving 217 women with self-diagnosed premenstrual syndrome according to a modified version of the Menstrual Distress Questionnaire, a rating scale covering most of the important symptoms, assessed the efficacy of the fruit for the management of symptoms of premenstrual syndrome (*49*). Subjects were treated with either a powder of the dried fruit (300-mg tablets; two tablets three times daily; n = 105) or a soy-based placebo (n = 112) for a period of 3 months, after which they all completed the Menstrual Distress Questionnaire again. Other than a statistically significant difference in effect between the active powder and the soy-based placebo for the symptom "feel jittery and restless" (p = 0.05), no other statistically significant results were reported. Unfortunately, soy was a poor choice for use as a placebo, as it is not considered to be biologically inert.

A multi-centre, randomized, double-blind, controlled clinical trial compared the activity of a dried ethanol extract of the fruit with that of pyridoxine (vitamin B6) in the treatment of women with premenstrual syndrome (*22*). The intent-to-treat population included 127 women: 61 of whom were given one capsule of extract plus one placebo capsule daily for three cycles, while 66 were given one capsule of placebo twice daily on days 1–15 of their cycle, followed by one capsule (100 mg) of pyridoxine twice daily on days 16–35. Therapeutic response was assessed using the Premenstrual Tension Syndrome scale, the Clinical Global Impressions scale, and by recording six characteristic symptoms of premenstrual syndrome (breast tenderness, oedema, inner tension, headache, constipation and depression). Therapeutic efficacy was assessed by both patients and physicians at the end of the trial. Initial mean scores on the Premenstrual Tension Syndrome scale were higher in the group treated with the chaste tree extract (15.2) than in those treated with pyridoxine (11.9). By the end of therapy, the mean absolute change in Premenstrual Tension Syndrome score in each group was 5.1, representing a reduction of 10.1 and 6.8, respectively, for the chaste tree and pyridoxine-treated groups (p < 0.038, both groups, 95% confidence interval –6.4261 to –0.1670). Therefore no difference was evident between the two treatment groups. The Clinical Global Impressions scale showed that 77.1% of the women who received chaste berry and 60.6% of those treated with pyridoxine showed improvement. Adverse events were rare, but included gastrointestinal complaints, skin reactions and transient headache.

Six post-marketing studies assessed the safety and efficacy of various extracts of the fruit in 8391 female patients with menstrual abnormalities

or symptoms of premenstrual syndrome (*23*, *26*, *27*, *58*, *60*, *62*). Three open (uncontrolled) trials (*24*, *26*, *59*) also investigated the effect of various fruit extracts on menstrual abnormalities. The dose ranged from 40–42 drops or 1 capsule daily, for 1 day to 9 years and the outcomes measured included the physician's and patient's self-assessments. Elimination of symptoms was observed in 29–42% of patients; improvements in symptoms were observed in 51–59% of patients and symptoms were unchanged in 1–10% of patients. Adverse events were reported in 1–5% of patients and were generally not reported to be serious. The limitations of these studies include the lack of a control group and the fact that most did not distinguish between premenstrual syndrome and the other menstrual disorders.

An open (uncontrolled) clinical trial involving 50 women (43 of whom completed the study) with late luteal phase dysphoric disorder (Diagnostic and Statistical Manual for Mental Disorders) assessed the effect of an ethanol fruit extract on the management of premenstrual syndrome (*59*). Thirteen of the subjects were concurrently taking oral contraceptives. After 2 months of baseline observation, one tablet of the extract was administered daily for three cycles, followed by a post-treatment phase lasting three cycles. Treatment effectiveness was evaluated using both the Menstrual Distress Questionnaire and the visual analogue scale. The Menstrual Distress Questionnaire was filled out by patients at the end of the first cycle and again during cycles 3 and 6. The visual analogue scale was completed twice per cycle, once in the late luteal phase when symptoms peaked and once after menstruation during the follicular phase. By the end of the third cycle, the Menstrual Distress Questionnaire scores were reduced by 42.5% ($p < 0.001$), with a 50% reduction in the score in 20/43 patients. By the end of the post-treatment period, the scores remained approximately 20% below baseline ($p < 0.001$). The main improvements following treatment were reported for symptoms of breast tenderness, behavioural changes, negative feelings and oedema. The average late-luteal phase visual analogue scale score was reduced by 47.2% during the 3-month treatment phase ($p < 0.01$), and remained at 21.7% below baseline ($p < 0.001$) during the post-treatment phase. By contrast, the follicular phase score did not significantly change. The number of days with premenstrual syndrome symptoms was slightly reduced from 7.5 to 6 days, and the concomitant use of oral contraceptives had no significant effect on any of the parameters investigated. Twenty patients (47%) reported 37 adverse events during the treatment and post-treatment periods (*59*).

An open (uncontrolled) study involving 36 women with premenstrual syndrome assessed the effect of a 58% ethanol extract of the fruit for the

management of premenstrual syndrome symptoms (*24*). The women were treated with 40 drops of the extract daily over three cycles and the outcomes measured were a reduction in physical and psychological symptoms such as headache, swollen breasts, breast tenderness, bloating, fatigue and psychological changes such as increased appetite, sugar craving, nervousness and restlessness, anxiety, irritability, lack of concentration, depression, crying spells, mood changes and aggressiveness. The duration of the luteal phase was also determined. After 3 months of treatment, 69% of women had a reduction in physical symptoms and 80% showed a reduction in psychological symptoms ($p < 0.05$). The duration of the luteal phase was lengthened from 5.4 to 11.4 days. A randomized open (uncontrolled) trial assessed a tincture of the fruit (10 g tincture containing 2 g fruit in 53% ethanol) for the treatment of premenstrual syndrome. Women were treated with 30 drops twice daily in combination with vitamin E (400 mg daily). Treatment significantly reduced the symptoms of irritability or anxiety ($p = 0.028$), breast tenderness ($p = 0.0001$) and mastalgia ($p = 0.015$) (*61*).

A randomized single-blind study compared the efficacy of fluoxetine, a selective serotonin reuptake inhibitor with that of the crude drug (*64*). Forty-one patients with premenstrual dysphoric disorder according to the Diagnostic and Statistical Manual of Mental Disorders were randomly allocated to the group receiving fluoxetine or that receiving the extract for 2 months. The outcomes measured included the Penn daily symptom report, the Hamilton depression rating scale, and the clinical global impression severity of illness and improvement scales. After 2 months, 68.4% of patients had responded to fluoxetine and 57.9% to the crude drug extract. There was no statistically significant difference between the groups in the rate of responders. However, fluoxetine was more effective in alleviating the psychological symptoms, while the extract reduced the physical symptoms (*64*).

Effects on lactation

Only one randomized, double-blind controlled trial examined the effect of the fruit in lactating women (*65*). Women were treated with the fruit extract (15 drops three times daily) or vitamin B1 (no dose stated) or assigned to the control group (details not stated). Lactation in all groups increased up to day 10 postpartum; from days 10–20 a decrease in lactation was observed in women in the control and vitamin B1-treated groups. Lactation in women in the group treated with the fruit extract increased or was maintained up to day 20. Lactating women with poor milk production treated with a fruit extract were able to effectively increase production. No statistical analyses were performed.

Adverse reactions

Adverse reactions have been reported in some clinical trials. A review of 30 studies involving 11 506 subjects reported a total of 246 adverse events, thus representing an adverse reaction rate of approximately 2% (*4*). The major reactions reported included acne, changes to the menstrual cycle, dizziness, gastrointestinal distress, increased menstrual flow, nausea, skin reactions, urticaria and weight gain (*4*). Minor adverse events include fatigue, hair loss, increased intraocular pressure, palpitations, polyurea, sweating and vaginitis (*4*, *57*).

Contraindications

Fructus Agni Casti should not be used during pregnancy (*35*).

Warnings

No information available.

Precautions

General

Patients reporting a feeling of tension and swelling of the breasts or menstrual disturbances should consult a health care provider for a medical diagnosis (*66*).

Drug interactions

Although no interactions have been documented, the reported dopaminergic effect may reduce the efficacy of dopamine-receptor antagonists (*3*). Furthermore, due to its potential hormonal effects, Fructus Agni Casti may interfere with the effectiveness of oral contraceptives and hormone replacement therapy (*67*).

Carcinogenesis, mutagenesis, impairment of fertility

Intragastric administration of an ethanol fruit extract to male and female rats at doses up to 80 times the recommended human daily dose had no effect on fertility, mating behaviour, pregnancy or lactation (*3*). No pathological changes were observed in any of the offspring of treated animals when compared with those animals treated with vehicle control (*3*).

Pregnancy: non-teratogenic effects

See Contraindications.

Pregnancy: teratogenic effects

Intragastric administration of an ethanol fruit extract to rats and rabbits at doses up to 100 and 74 times higher than the human daily dose, respec-

tively, was not teratogenic and did not affect maternal health as compared with controls (*3*).

Nursing mothers

One study in rats assessed the effect of a fruit extract administered orally to lactating dams on their offspring (*68*). A decrease in milk consumption in the offspring was observed and a high rate of mortality resulted compared with untreated animals. Normal milk consumption patterns were resumed in the offspring when the dams were no longer given the extract (*68*). No further data are available; therefore the use of the crude drug by nursing mothers is not recommended.

Paediatric use

No safety data are available, therefore the use of the crude drug in children under the age of 12 years is not recommended.

Other precautions

Estrogen-dependent breast cancer patients should use Fructus Agni Casti preparations with caution, as weak estrogenic effects have been reported in vitro (*45*, *46*).

Dosage forms

Crude drug, extracts, fluidextracts, tinctures and infusions. The dried berries should be stored in airtight non-plastic containers and protected from light, heat, moisture and insect infestation (*4*).

Posology

(Unless otherwise indicated)

Dry native extract: 8.3–12.5:1 (w/w), approximately 1.0% casticin: 1 tablet containing 2.6–4.2 mg native extract, swallowed whole with some liquid each morning (*4*).

Dry native extract: 9.58–11.5:1 (w/w): 1 tablet containing 3.5–4.2 mg native extract each morning with some liquid (*22*).

Dry native extract: 6.0–12.0:1 (w/w), approximately 0.6% casticin. For premenstrual syndrome: 1 tablet containing 20 mg native extract daily with water (*63*).

Fluidextract: 1:1 (g/ml), 70% alcohol (v/v): 0.5–1.0 ml (*9*).

Tincture: ethanol 58% (100 g of aqueous-alcoholic solution contains 9 g of 1:5 tincture): 40 drops, once daily with some liquid each morning (*4*).

Tincture: ethanol 53% (10 g of the solution contains 2 g crude drug mother tincture): 30 drops twice daily (*25*, *28*, *34*).

Tablet: containing 162 mg of crude drug mother tincture (1:10 with 62% ethanol), twice daily (*57*).

Hydroalcoholic extracts (50–70% v/v): corresponding to 30–40 mg dried fruit (*4*, *69*).

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