Agnus Castus

Species (Family)

Vitex agnus-castus L. (Verbenaceae)

Synonym(s)

Chasteberry, Chaste Tree, Monk's Pepper

Part(s) Used

Fruit

Pharmacopoeial and Other Monographs

American Herbal Pharmacopoeia[G1]
BHP 1996[G9]
Complete German Commission E[G3]
ESCOP 1997[G52]
Martindale 32nd edition[G43]
Mills and Bone [G50]
PDR for Herbal Medicines 2nd edition[G36]

Legal Category (Licensed Products)

GSL[G37]

Constituents[G40]

Alkaloids Viticin

Diterpenes Rotundifuran (labdane-type), vitexilacton and 6β,7β-diacetoxy-13-hydroxy-labda-8,14-diene.[1]

Flavonoids Flavonol (kaempferol, quercetagetin) derivatives, the major constituent being casticin. Other identified flavonoids include penduletin and chrysophanol D.[2–4]

Iridoids In the leaf: 0.3% aucubin, 0.6% its *p*-hydroxybenzoyl derivative agnuside and 0.07% unidentified glycosides.[3,5]

Other constituents Fatty acids, including stearic and palmitic, volatile oil 0.5% with cineol and pinene as main components; castine (a bitter principle).[6,7]

Food Use

Agnus castus is not used in foods.

Herbal Use

Traditionally, agnus castus has been used for menstrual problems resulting from corpus luteum deficiency, including premenstrual symptoms and spasmodic dysmenorrhoea, for certain menopausal conditions, and for insufficient lactation.[G4,G49] The German Commission E approved it for internal use for irregularities of the menstrual cycle, premenstrual complaints and mastodynia.[G3]

Dosage

Fruit 0.5–1.0 g three times daily;[G49] by contrast, 30–40 mg daily of crushed fruit.[G3]

Tincture 1:5 (g/mL), 50–70% ethanol (v/v) 0.15–0.2 mL.[G4]

Pharmacological Actions

In vitro and animal studies

Agnus castus does not contain any oestrogenic constituents but has been reported to diminish release of follicle-stimulating hormone from the anterior pituitary whilst increasing the release of luteinising hormone and prolactin.[8,9]

Extracts of agnus castus act at dopamine receptors and affect prolactin release. Dopamine D_2-receptor binding of extracts has been demonstrated for three different dopamine receptors (rat striatum, calf striatum and human recombinant receptors) and for two separate ligands (sulpiridine and spiroperidol).[1,10,11] The active compounds acted as dopamine agonists and were characterised as labdane diterpenes. The two most active diterpenes, rotundifuran and 6β,7β-diacetoxy-13-hydroxy-labda-8,14-diene, had IC_{50} values (calf striatum preparation, ^{3}H-spiroperidol ligand) of 45 μg/mL (124 nmol/mL) and 79 μg/mL (194 nmol/mL), respectively.[11] A lyophilised extract of agnus castus (5 mg/mL) was similar in activity to 10^{-4} mol/L dopamine in receptor–ligand binding assays, displacing ^{3}H-spiroperidol from calf brain striatal preparations.[10]

An extract of agnus castus inhibited release of acetylcholine from ^{3}H-choline loaded rat brain striatal cells on electrical stimulation, and had an IC_{50} value of 30 μg/mL.[11]

Hexane fractions of agnus castus bind to human opiate receptors with IC_{50} values of 20 µg/mL (µ-receptors) and 10 µg/mL (κ-receptors).[12]

Agnus castus extracts and fractions dose-dependently stimulated galactosidase activity in yeast cells; this may be indicative of oestrogen-receptor binding. Radioligand–receptor binding assays have demonstrated that agnus castus only binds weakly to oestrogen receptors in comparison to dopamine receptor binding.[12]

Clinical studies

A proprietary preparation containing an alcoholic extract of agnus castus (0.2% w/w) has been available in Germany since the 1950s. It is used in the treatment of breast disease and pain, ovarian insufficiency, and dysfunctional uterine bleeding.[8,13–17] The clinical effects of agnus castus have been reviewed.[18,19] Details of clinical studies described in these reviews are summarised below.

Effects on prolactin secretion Several open, uncontrolled studies involving small numbers of women with fertility disorders, hyperprolactinaemia and menstrual disorders have explored the effects of treatment with extracts of agnus castus (e.g. Mastodynon and Agnucaston; Bionorica), generally at doses equivalent to 30–40 mg drug for several months. These studies report decreased prolactin concentrations at the end of treatment, compared with baseline values.[18,19]

A double-blind, placebo-controlled study involving women with cyclic mastalgia compared the effects of Mastodynon tablets ($n = 32$) and Mastodynon solution ($n = 31$) with those of placebo ($n = 38$) over three menstrual cycles. Prolactin concentrations in the two treated groups were significantly reduced, compared with those in the placebo group.

Other studies have reported that women with normal basal prolactin concentrations do not experience significant reduction in the concentration following treatment with agnus castus.

In a double-blind, placebo-controlled trial, 37 women with deficiencies in corpus luteal phase and latent hyperprolactinaemia received an agnus castus preparation ($n = 17$) or placebo ($n = 20$) for three menstrual cycles. In the treated group, the luteal phase was extended to 10.5 days from an initial 3.4–5.5 days.

The effects of agnus castus have also been investigated in men. In an open, uncontrolled study, 20 healthy men were given a commercial preparation of agnus castus extract (BP 1095E1) at doses ranging from 120 to 480 mg extract (3–12 times higher than doses used in women) for 14 days.[20] The lowest dose was reported to increase serum prolactin concentrations, whereas the higher dose decreased prolactin concentrations.

Effects on mastodynia In an open, uncontrolled trial, 825 women with mastodynia received Mastodynon for three months. At the end of the study, 465 patients (56%) said they were symptom-free, and a further 198 patients (24%) reported that their symptoms had improved. A subsequent trial involving 121 women reported that 75% of participants experienced relief of symptoms.

In a randomised, double-blind, placebo-controlled study, 104 patients with breast pain were treated for three menstrual cycles with either Mastodynon solution ($n = 34$), tablets ($n = 32$) or placebo ($n = 38$). Patients in both treated groups claimed to have reduced breast pain; the findings were reported to be statistically significant for treatment, compared with placebo.

Another randomised, double-blind, placebo-controlled trial involving 97 patients with cyclic mastalgia compared Mastodynon solution ($n = 48$) with placebo ($n = 49$).[21] After two menstrual cycles, pain intensity, as assessed by visual analogue scale (VAS) scores was reduced in both groups; the reduction was significantly greater in the agnus castus group ($p = 0.006$). However, at the end of the study (after three cycles), the reduction in pain intensity between the two groups was no longer statistically significant ($p = 0.064$). It was reported that Mastodynon was well-tolerated.

Effects on premenstrual syndrome Five postmarketing surveillance studies involving more than 5000 women have monitored the effects of agnus castus preparations in premenstrual syndrome (PMS).[19]

A randomised, double-blind, controlled trial involving 175 women with PMS compared Agnolyt (Madaus) one capsule daily (equivalent to 3.5–4.2 mg dry extract) ($n = 90$) and pyridoxine two capsules daily ($n = 85$) over three menstrual cycles.

Therapeutic response was measured using a premenstrual tension scale (self-assessment) and a clinical global impression (CGI) scale (physician assessment). Reductions in PMS scale scores (of around 48%) were reported for both groups.[22] It was concluded that the two treatments were equally effective in the treatment of symptoms of PMS.

In a randomised, double-blind, placebo-controlled, parallel-group trial, 170 women with PMS received agnus castus extract ZE 440 (60% ethanol, extract ratio 6 to 12 : 1; standardised for casticin) 20 mg daily ($n = 86$) or placebo ($n = 84$) for three menstrual cycles.[23] The main outcome measure

was the participant's self-assessment of PMS symptoms (irritability, mood alteration, anger, headache, breast fullness and bloating). At the end of the third cycle, improvements in the PMS symptoms were significantly greater in the agnus castus group, compared with the placebo group ($p < 0.001$). Clinical global impression scores for severity of condition, global improvement and overall risk/benefit were also significantly better for agnus castus, compared with placebo ($p < 0.001$). Mild adverse events were reported by four agnus castus recipients and three placebo recipients. All resolved without treatment. It was concluded that agnus castus dry extract is an effective and well-tolerated treatment for symptoms of PMS.[23]

Agnus castus has also been reported to be effective in the treatment of endocrine disorders such as menstrual neuroses and dermatoses [24] and has been used for the treatment of acne.[25,26]

A lactogenic action has been documented for agnus castus;[27] chemical analysis of the breast milk revealed no changes in composition.

The precise mode of action of agnus castus and the active constituents has not been established. However, it is thought to act on the pituitary–hypothalamic axis rather than directly on the ovaries.

Side-effects, Toxicity

Agnus castus is generally well-tolerated, although allergic reactions (which resolved following discontinuation of agnus castus therapy), headaches and an increase in menstrual flow have been reported.[8,24]

Contra-indications, Warnings

Agnus castus has dopaminergic activity and should not be used with dopamine receptor antagonists or agonists.

Pregnancy and lactation In view of the documented pharmacological actions and lack of toxicity data, the use of agnus castus during pregnancy should be avoided. Agnus castus has been reported to stimulate milk secretion without altering the composition of the breast milk.[24,27] Nevertheless, agnus castus should be avoided during lactation until further information is available.

Pharmaceutical Comment

The chemistry and pharmacology of agnus castus are well-documented. There is clinical evidence indicating that raised prolactin concentrations are reduced following agnus castus treatment, and that there are beneficial effects in mastodynia and in symptoms of PMS.

References

See also General References G1, G3, G5, G9, G31, G36, G40, G43, G49 and G50.

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