REFERENCE SHEET:

Vitex *agnus-castus*

Pronunciation

Vitex *agnus-castus* (vy-teks ag-*nus* kast-*us*)

Summary

Vitex *agnus-castus* (VAC) is also commonly known as chaste tree or chasteberry. The plant's main constituents include vitexin, casticin, agnuside, p-hydroxybenzoic acid, alkaloids, and diterpenoids. The fruit consists of flavonoids, terpenoids, neolignans, phenolic compounds, and glycerides. The extracts of the dried ripe fruits themselves demonstrate antioxidant activity and have been used in treating symptoms of premenstrual syndrome (PMS). Essential oils from the fruit contain 20.73–23.36% 1,8-cineole + 16.09–22.28% sabinene, and 6.60–19.73% α-pinene. Its main flavonoids include casticin, vitexin, and orientin. Standardized extracts typically measure the iridoid or flavonoid content where aucubin (iridoid glycoside) or agnuside is used as the reference material.

Main Medical Uses

Research supports the use of VAC in treating the symptoms of PMS, premenstrual dysphoric disorder, premenstrual migraines, premenstrual tension syndrome, postmenopausal hot flushes, cyclical mastalgia and hyperprolactinemia. Evidence also demonstrates similar effectiveness of VAC to low dose oral contraceptives and metformin in polycystic ovarian syndrome, and to ethinyl estradiol/drospirenone in dysmenorrhea. VAC can reduce intrauterine device induced bleeding, and may promote the healing of fractures.

Proprietary Extracts

Proprietary Extract	Formulation	Safety
VAC BNO 1095 Agnucaston®	70% ethanol, 30% H2O extract 4 mg of extract equivalent to 40 mg of dry weight VAC (10:1 ratio)	No adverse events over 3 menstrual cycles
BCM-95®	60% ethanol m/m, fruit extract ratio 6-12:1; (20 mg of extract equivalent to 120-240 mg of dry weight VAC) standardized for casticin	Equal instances (~5%) of reported adverse events between VAC (20mg per day) and placebo groups with good tolerability over 3 cycles No serious adverse events with VAC (20mg per day) over 3 cycles 20/50 reported 37 adverse events, none serious in nature (20 mg per day) over 8 cycles Physicians suspected adverse events in 1% of patients with no serious effects. 94% of patients describe tolerance as good or very good
Agnolyt®	100g of tincture provides 9 g of VAC with 1:5 ratio. A capsule contains dried extract of VAC fruit [9.58–11, 5:1] 3.5–4.2mg	Considered as safe with no serious adverse events. 12 of 85 patients reported mild GI distress, skin manifestations or headaches, while 5 reported similarly in B6 group
Agnugol®	4 mg dried fruit extract	No side effects over 8 weeks No side effects over 3 months as compared to metformin
Strotan®	Each capsule contains 20 mg of VAC	No side effects observed with VAC (20 mg) over 3 months

Dosing and Administration

Condition	Dosing & Administration	Outcome	Class of Evidence	MOA
PMS	20 mg tablet (as ZE 440 fruit extract) per day for 3 cycles	↓ visual analog scale (VAS) compared with placebo	B	↑ plasma progesterone, estrogen, uterine weight; ↓ LH & prolactin
	8 mg, 20 mg or 30 mg (as ZE 440 fruit extract) per day for 3 cycles	↓ total symptom score. 30 mg did not improve effects observed in 20 mg	B	↑ binding & activity of μ-opioid and δ-opioid receptors
	40 mg (as BNO 1095 extract) per day for 3 cycles	↓ PMSD score, PMTS score *note: 50% placebo effect	B	↑ μ-opioid receptors activity ↓ prolactin & nociceptive activity by castacin
	40 mg (as BNO 1095 extract) per day for 3 cycles	↓ PMSD score, negative affect score & water retention score	B	↓ nociceptive activity with VAC essential oils
	40 drops (extract added to fruit juice - unspecified concentration) per day for 6 days prior to menstruation for 6 cycles	↓ mean VAS in VAC and placebo, but to a significantly greater extent by VAS	B	Partial modulation of 5HT1A receptor
Cyclical Mastalgia	3.2–4.8 mg (as dried fruit extract) for two months	↓ breast pain intensity and length (days) in VAC and placebo, but significantly greater extent in VAC	B	↓ hyperprolactinemia via decreased prolactin release ↓ prolactin via DA2 receptor binding
	30 drops (as VAC extract - unspecified concentration) twice per day for 3 cycles	↓ breast pain intensity, mastalgia pain measured by VAS	B	↓ prolactin via inhibition of basal/THR-stimulated prolactin release Competitive inhibition of ER-α & ER-β, stimulates progesterone receptor

Postmenopausal Hot Flashes	40 drops per day (as standardized extract - unspecified concentration) for 8 weeks	↓ frequency of hot flashes	B	↑ competitive ER-α & ER-β binding, displacing estradiol ↑ progesterone receptor ↑ D2 receptor activation
Bone Fractures	4 mg (as Agnugol® dried fruit extract) per day for 8 weeks	↑ alkaline phosphatase, serum VEGF	B	↑ alkaline phosphatase & serum VEGF ↑ trabecular area, number, number of nodes, & protects cortical bone ↓ IL-1β -induced NO, PGE2, MMP-3, MMP-13, ADAMTS-4 & ADAMTS-5 synthesis, iNOS & COX-2 expression, TNF-α & IL-6 levels by castacin
Polycystic Ovarian Syndrome	One capsule (as standardized fruit extract to 2, 1-3 and 3 mg of aucubin) per day for 3 months	↓ serum DHEA-S; Normalized 60% of participants' (with oligomenorrhea or amenorrhea) menstrual cycle duration	B	↓ serum DHEA-S; normalization of menstrual cycle duration
Hyperprolactinemia	20 mg (as Strontan®) per day for 3 months	↓ prolactin release ↑ luteal phase: to normal length, progesterone synthesis, 17 beta-estradiol	C	↓ prolactin release; ↑ luteal phase: to normal length, progesterone synthesis, 17 beta-estradiol ↓ prolactin via inhibition of basal/ THR-stimulated prolactin release ↓ prolactin & nociceptive activity by castacin ↓ prolactin via DA2 receptor binding

For an explanation of the classes of evidence, please see the Rating Scales for Evidence-Based Decision Support.

Associated Depletions and Interactions

Class of Drug	Pharmaceutical	Effect	Class of Evidence
Mineral	Magnesium oxide (250 mg)	VAC group increased alkaline phosphatase, but VAC+Mg did not. Co-administration may promote bone healing via synergistic increases in osteocalcin, VEGF and callus formation.	B
Dopamine Receptor Agonist	Bromocriptine (5, 10, 20 mg/kg)	Bromocriptine caused a significant decrease in LH & testosterone. Co-administration with VAC caused a decrease in LH & testosterone in male mice.	D
Dopamine Receptor Antagonist	Haloperidol (1, 1.5, 2, 2.5, 3 mg/kg)	Haloperidol increased LH & testosterone. Co-administration with VAC caused a decrease in LH and testosterone in male mice.	D
Serotonin Receptor Agonist	8-OH-DPAT, a 5HT1A receptor agonist (5, 10 and 25 ng)	Oral VAC (100, 200, 300 mg/kg) for 2 weeks produced anxiogenic effects that were attenuated most potently with 10 ng of drug, though all doses had this effect compared to control in rats.	D
Serotonin Receptor Antagonist	NAN190, a 5HT1A receptor antagonist (0.25, 0.5 and 1 µg/rat)	Oral VAC (100, 200, 300 mg/kg) for 2 weeks produced anxiogenic effects that were potentiated to the greatest extent by 0.5µg, though 0.25µg dose also had an effect compared to control in rats.	D
Contraceptives	General	While untested, theoretical interaction exists with VAC as it may alter hormone levels and decrease effectiveness: ↓ serum DHEA-S ↓ Prolactin release; ↑ progesterone synthesis, 17 beta-estradiol	F

Pharmacokinetics

The pharmacokinetics of VAC have been scarcely studied. In mice, the oral bioavailability of agnuside was 0.7%. Peak plasma concentrations were reached within 30-45 mins and VAC was found in highest amounts in the intestine, kidney, liver, spleen, brain, lungs and heart. In vitro, BNO 1095 (a VAC extract) solubility and permeability was improved once it was nano-emulsified, suggesting the possibility for improved bioavailability. An in vitro study also demonstrated that VAC inhibited CYP2C19 and CYP3A4, which may have implications for future studies on herb-drug interactions.

Adverse Effects

VAC extract is considered safe to use, with trials reporting safety without serious adverse events in daily doses of up to 40 mg for three menstrual cycles. It has been shown that there is no difference in side effects between VAC standardized up to 3mg of aucubin and low doses of oral contraceptives (30 mcg ethyinyl estradiol/150 mcg levonorgestrel). Commonly reported side effects include nausea, headache, gastrointestinal disturbances, menstrual disorders, acne, pruritus, and erythematous rash. However, these side effects are mild and reversible. A systematic review of 33 studies suggests that VAC does not pose serious health risks. However, it is recommended that pregnant and lactating women avoid its use due to limited safety data in these states.