

Review

Can *Vitex Agnus Castus* be Used for the Treatment of Mastalgia? What is the Current Evidence?

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There have been many treatments suggested for the management of mastalgia; one of these is the fruit extract of *Vitex Agnus castus* L. commonly known as *Agnus castus*, an extract of a deciduous shrub native to Mediterranean Europe and Central Asia. It is postulated that *A. castus* suppresses the stress-induced latent hyperprolactinemia which is a release of supra-physiological levels of prolactin in some patients in response to stressful stimuli. It is postulated that *A. castus* could be effective in the treatment of cyclical mastalgia by inhibiting the release of excess prolactin by blocking Dopamine-2 receptor type on pituitary. The adverse events following *A. castus* treatment are mild and reversible. The aim of this review is assess the efficacy of *A. castus* in the treatment of mastalgia. Data from randomized and non-randomized studies regarding the efficacy and safety of *A. castus* is reviewed in a systematic fashion. It is concluded that *A. castus* can be considered as an efficient alternative phytotherapeutic agent in the treatment of mastalgia.

Keywords: mastalgia – premenstrual syndrome – drug therapy – vitex

Introduction

Mastalgia is a multi-faceted and inhomogeneous clinical condition with poorly understood etiology. Between 50% and 80% of women are estimated to have experienced mastalgia at some point in their life but in only 1% of patients is mastalgia a symptom of breast cancer. Chronic or recurrent mastalgia and lack of reliable remedies can lead to severe impact on a patient's quality of life. Psychological morbidity such as depression, helplessness and loss of self-esteem in patients suffering from mastalgia are well documented (1).

There have been many treatments suggested for the management of mastalgia; one of these is the fruit extract of *Vitex Agnus castus* L. commonly known as *Agnus castus*, a deciduous shrub native to Mediterranean Europe and Central Asia. The use of herbal treatments

in the management of pain is well documented (2). *Agnus castus*, like other herbal treatments (3), has been used in the treatment of many conditions of women's health such as menstrual disorders (amenorrhea, dysmenorrhea), premenstrual syndrome, corpus luteum insufficiency, hyperprolactinemia, infertility, acne, menopause and disrupted lactation (4–12). *Agnus castus* is thought to be affective in the management of mastalgia because of its dopaminergic effects. It is postulated that *A. castus* suppresses the stress-induced latent hyperprolactinemia in patients suffering from cyclical mastalgia. The purpose of this review is to analyze the current evidence available for the efficacy and safety of *A. castus* in the management of mastalgia.

Mechanism of Action?

The reasons why *A. castus* could be helpful in the management of mastalgia may be because of its effect on latent hyperprolactinemia, estrogen receptors or other unknown mechanisms.

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Latent Hyperprolactinemia

There is evidence to suggest that cyclical mastalgia in some women is caused by a latent stress-induced hyperprolactinemia (13,14). Some women respond to stimuli of prolactin release with a hyper-secretion of this hormone resulting in stimulation of mammary gland leading to cyclical mastalgia. *Agnus castus* may have therapeutic role in the management of cyclical mastalgia by controlling hyper-secretion of prolactin. The ability to lower the prolactin level in women with cyclical mastalgia has been shown in clinical and laboratory studies (15–17). A prolactin-suppressive effect of *A. castus* is thought to be due to a number of diterpenes including clerodadienols (15). These compounds manifest their dopaminergic properties by binding to recombinant DA2-receptor protein, which has been shown to suppress prolactin release from cultivated lactotrophs and also *in-vivo* in animal experiments. These substances are almost identical in their prolactin-suppressive properties as dopamine itself (15). Addition of *A. castus* significantly inhibits basal as well as TRH-stimulated prolactin secretion of rat pituitary cells *in vitro*, as demonstrated in the primary cell culture experiments (18). These experiments also found that adding a dopamine receptor blocker could prevent this *A. castus*-induced inhibition of prolactin secretion. Authors suggested that because of its dopaminergic effect *A. castus* could be considered as an efficient alternative phytotherapeutic drug in the treatment of hyperprolactinemia. Other studies have demonstrated that inhibition of prolactin secretion by *A. castus* is dependent on the initial level of prolactin and the dose of *A. castus* and is independent of gonadotrophins (19,20).

Estrogen Binding

It is postulated that *A. castus* may interact with steroid hormones in order to reduce breast pain in some women. The role of estrogen in the development of breast pain is not clearly understood but anti-estrogen medication has shown to have a significant effect on the improvement of breast pain (21–24). It is possible that *A. castus* may block estrogen receptors by binding to these receptors and exert anti-estrogen activity. Experimental evidence found that *A. castus* demonstrates a significant competitive binding to estrogen receptors alpha (ER alpha) and beta (ER beta) as well as stimulating Progesterone Receptor expression (25). The exact mechanism of this increased affinity to estrogen receptors is not well understood but is thought to be mediated by yet unidentified phytoestrogens (15,26). Clinically, anti-estrogenic medication helps with breast pain. However, there is no evidence to support that *A. castus* has anti-estrogenic activity and in fact it may have weak estrogenic activity. Therefore it is possible that the estrogen binding function of *A. castus* may not contribute

to the ability of *A. castus* to alleviate mastodynia. Apigenin has increased binding activity to ER beta, which appears to be involved in regulation of the mammary fat tissue, but has no effect on uterus and only little effect on bones (15). *Agnus castus* has also been shown to be able to up-regulate pS2 (presenelin-2), an estrogen-inducible gene in S30 breast cancer cells. Therefore, it is possible that *A. castus* may preferentially bind with estrogen receptors hence controlling mastalgia by blocking estrogenic activity of the breast cells by yet unknown mechanisms. Further experimental studies suggest that linoleic acid from the fruits of Vitex *A. castus* can bind to estrogen receptors and induce certain estrogen inducible genes. However, linoleic acid was found to have estrogenic affinity only at a very high concentration for a single compound (25–30 µM), and therefore it is unlikely that this compound is responsible for any therapeutic activity *in vivo*. (27). As estrogen can exert its effect on the mammary epithelial cells by genomic and non-genomic pathways the exact mechanism by which estrogen affects breast pain is not clearly understood.

Safety of Agnus Castus

The most frequent adverse events associated with the use of *A. castus* are nausea, headache, gastrointestinal disturbances, menstrual disorders, acne, pruritus and erythematous rash. Data available from clinical trials, post-marketing surveillance studies, surveys, spontaneous reporting schemes, manufacturers and herbalist organizations have recently been reviewed (28). The adverse events following *A. castus* treatment are mild and reversible indicating that *A. castus* is a safe herbal medicine. (28). Data of The German Commission E has approved the use of *A. castus* for mastalgia. No drug interactions have been reported.

Evidence that Agnus castus is Useful for Mastalgia?

The evidence of effectiveness of *A. castus* in the management of mastalgia is available from both randomized and non-randomized studies. This evidence is summarized in Table 1.

Non-Randomized Studies

A large scale multi-centric non-interventional trial (open study without control) of 1634 patients suffering from cyclical mastalgia as a part of premenstrual syndrome, revealed that frequency and severity of cyclical mastalgia decreased after 3 months of therapy with *A. castus*. (6,29). Eighty percent of physicians and 81% of patients rated *A. castus* as good or very good

Table 1. Evidence that *Vitex Agnus Castus* is useful in the management of cyclical mastalgia

Author and Reference	Study type	Duration of treatment	Patients	Age	Pain assessment	Outcome	Adverse reaction
Loch (29)	Cohort	3 Months	1634	36 (9)	Questionnaire	85% reduction	1%
Halaska (31)	RCT with placebo	3 Months	VAC 48 Placebo 49	36 (6)	VAS	54% reduction	5/48 4/49
Atmaca (32)	RCT with Fluoxetine	2 Months	VAC 20 Fluoxetine 21	33 (11)	HAM-D DSR CGI-SI	50% reduction	
Berger (30)	Cohort	3 Months	50	31 (8)	VAS	45% reduction	20/50
Schellenberg (33)	RCT with placebo	3 Months	VAC 86 Placebo 84	36	DMS-III-R	52% reduction	4/86 3/84

treatment of mastalgia. Ninety-four percent of patients assessed the tolerance of *A. castus* treatment as good or very good. There were no serious adverse reactions to *A. castus* and minor adverse reactions were observed in 1% of patients. Authors suggested that *A. castus* could be useful in the management of cyclical mastalgia.

In a prospective, multi-centre trial the efficacy of *A. castus* in the management of cyclical mastalgia was investigated in 50 patients with pre-menstrual syndrome (30). Forty-three patients were treated daily with *A. castus* during three menstrual cycles. At the end of the study, cyclical mastalgia decreased significantly and a smaller degree of improvement (20%) persisted even 3 months after cessation of the treatment. ($P<0.001$). At baseline, the *A. castus* score was elevated in the late luteal phase and low at the follicular phase, as expected. During treatment, *A. castus* score decreased in the late luteal phase (47%; $P<0.01$) and remained 22% ($P<0.001$) below baseline after 3 cycles post-cessation of treatment. Thirty-eight patients judged the global efficacy moderate to excellent, 5 patients indicated no global efficacy. Twenty (47%) patients reported 37 minor adverse events none of which was serious.

Randomized Control Trials

Agnus castus was well tolerated and was effective in controlling the symptoms of cyclical mastalgia in a placebo-controlled, randomized, double-blind study of 97 patients suffering from cyclical mastalgia (31). The intensity of mastalgia in patients treated with *A. castus* as measured by visual analogue score significantly decreased after one or two treatment cycles and remained reduced after third cycle. After one/two treatment cycles mean visual analogue score decreased by 21 mm/34 mm in *A. castus* group ($n=48$) as compared with 11 mm/20 mm for the placebo group ($n=49$) ($P=0.018$; $P=0.006$). Visual analogue score was less than 35 in 71% of patients after two treatment cycles. Not only the intensity but duration of pain also improved on *A. castus* treatment. In *A. castus* group, 50% of patients did not have severe pain at all during menstrual cycle and only 25% had severe pain for 4% of days compared with severe mastalgia for 20% of days before

treatment. There was no difference in the frequency of adverse events between both groups (*A. castus*: $n=5$; placebo: $n=4$).

The efficacy of *A. castus* for the treatment of cyclical mastalgia associated with premenstrual dysphoric disorder was compared with fluoxetine, a selective serotonin reuptake inhibitor (SSRI), in a randomized control trial (32). After a period of 2 months to screen the patients for suitability, 41 patients were randomized to fluoxetine or *A. castus* for 2 months of single-blind, rater-blinded and prospective treatment period. In patients treated with *A. castus*, cyclical mastalgia improved by >50%. Psychological symptoms improved in 68% of patients treated with Fluoxetine and mastalgia improved in 58% of patients treated with *A. castus*.

A randomized, double-blind, placebo controlled trial and parallel group comparison was carried out in 170 women who were given *A. castus* or placebo for three consecutive cycles (active 86; placebo 84) (33). Mean age of women was 36 years. The study demonstrated that the improvement in breast pain was greater in the *A. castus* group compared with placebo group (52% versus 24%, $P<0.001$). Seven women reported mild adverse events (four active; three placebo), none of which caused discontinuation of treatment. The authors concluded that *A. castus* is an effective and well-tolerated treatment for the relief of symptoms of mastalgia associated with premenstrual syndrome.

Data from randomized and non-randomized well-conducted studies provides convincing evidence to suggest that *A. castus* is safe, effective and well tolerated in a majority of patients suffering from mastalgia. Therefore, use of *A. castus* is justified in the treatment of cyclical mastalgia for at least three cycles.

Conclusion

There is convincing laboratory-based and clinical evidence available that *A. castus* is safe, effective and efficient in the treatment of cyclical mastalgia. It has a safe side effect profile and can be used safely for the treatment of cyclical mastalgia.

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Received April 27, 2006; accepted May 18, 2007

