The mechanisms underlying the role of *Vitex agnus-castus* in mastalgia

Aureol ZEQIRI¹, Miribane DERMAKU-SOPJANI², Mentor SOPJANI¹

Faculty of Medicine of the University of Prishtina, Str. Bulevardi i Dëshmorëve, p.n., Prishtina, Kosovo.
mentor.sopjani@uni-pr.edu

ABSTRACT

Medicinal plants exert therapeutic effects or have beneficial healing functions on the human or animal body. Medicinal plants are widely used in traditional medicine as an interesting alternative and/or complementary to science-based medicine. Compared to chemical drugs, medicinal plants have a lower risk of side effects, are eco-friendly, and have cost-effective production. This encouraged researchers to extensively exploit them for their therapeutic use. One of the most well-known medicinal plants is *Vitex agnus-castus* L., which belongs to the *Verbenaceae* family. This shrub tree is mainly grown in tropical and sub-tropical regions. The parts of VAC, especially berries and leaves, contain essential oils, flavonoids, and diterpenes. Many medical benefits of VAC have already been reported, including mastalgia, regulating menstrual cycles and premenstrual complaints, and infertility. Respiratory and cardiovascular effects are also reported. In this review, we will analyze and characterize the known roles of VAC in mastalgia, as well as the mechanism of action reported in in vitro and/or in vivo studies, and show the potential for alternative therapeutic uses in mastalgia, also known as breast pain (Fig. 2, Ref. 40).

KEY WORDS: mastalgia, *Vitex agnus-castus*, therapy, traditional medicine.

Introduction

Medicinal plants have been used for the treatment of certain diseases for a long time in human history. Thousands of plant species worldwide are reported to have medicinal properties (1–5). These plants are still in use as part of alternative medicine. They are also important sources for extracting many active compounds that can be used in certain therapies (1).

One of the best-known medicinal plants is *Vitex agnus-castus* (VAC, chaste tree). This specie belongs to the genus *Vitex* (*Verbenaceae* family). The genus *Vitex* has about 250 different species of shrubs and trees distributed all over the world (3, 6, 7). Traditional medicine is obtaining attention for the design and production of novel therapies that might have been used in medicine. An important plant widely used in traditional medicine is VAC. This shrub tree has been used traditionally for medical remedies and is nowadays gaining attention for proper scientific characterization so that its extracts can be used pharmaceutically by clinicians (5). The following discussion will be focused on the characterization of VAC and its medicinal use for the treatment of mastalgia as well as the mechanism of action.

Some characteristics of *Vitex agnus-castus*

VAC is a perennial, deciduous, grey-felted shrub or rarely a small tree, which is widely distributed in numerous parts of the world. VAC is native mainly to the Mediterranean region and southern Europe in general, as well as to western Asia (1), but it is also widely cultivated for medicinal use and as an ornamental plant. VAC is approximately 1–6 m in height with a strong aromatic odor. It is properly adapted to a wide range of soil types and is best in dry and moist habitats, but not wet conditions. VAC can grow, and it does best in places with full sun or partial shade (1–3).

Traditional use of VAC

*Vitex agnus-castus* has been used for over 2500 years and is shown to be widely used and primarily effective in reducing symptoms of numerous gynecological problems. The use of Vitex in herbal medicine could be traced back even to Hippocrates' time (over 2,500 years ago) for the treatment of gynecologic disorders (1, 2).

Along with modern medicine, alternative medicine still plays an important role in treating certain conditions or diseases in humans (7, 8). Medicinal preparations from the VAC are mainly ob-
tained from the fruits and used mainly as remedies to treat female reproductive system disorders (7–13), including menstrual irregularities, premenstrual dysphoric disorder, corpus luteum insufficiency, hyperprolactinemia, infertility, disrupted lactation, cyclic breast pain, cyclical mastalgia, but also acne, digestive complaints (diarrhea and flatulence), and inflammatory conditions. The leaves and fruits can also help with lactation (14–16). Additionally, infusion remedies made from the shoots and fruits of V AC are used for treating headaches, stomachaches, and syphilis (6, 15, 17), as well as for antioxidant (14), antihypertensive (4), tracheorelaxant (5), anticonvulsant, and antiepileptic functions (6, 15).

The chemical composition of V AC

Essential oils, flavonoids, diterpenoids, ligans, and iridoid glycosides constitute major classes of phytoconstituents of the Vitex genus, including V AC (1, 9 13). V AC is a good source of estrogen-like compounds with a high affinity for estrogen receptors that are known as phytoestrogens (1, 18). Chemicals with medicinal effects can be found, particularly in fruits and leaves. Phytochemicals can also be found on root bark and flowering stems.

The main compounds in the fruits of V AC are essential oils, flavonoids, iridoids, and diterpenoids, as well as diterpene lactam and vitexlactam (1, 2, 5, 9 17–20). Casticin has also been isolated from aerial parts and seeds of V AC (19). In this regard, we have reviewed numerous studies in which different assessment methods were used, including nuclear magnetic resonance (NMR) spectroscopy, mass spectrometry (MS), matrix-assisted laser desorption ionization-mass spectrometry (MALDI-MSI), gas chromatography-mass spectrometry (GC-MS), column chromatography, high-performance liquid chromatography (HPLC), reverse phase HPLC, and ultra-high performance liquid chromatography-diode array detector (UHPLC-DAD), to identify compounds extracted mainly from fruits and, to a lesser extent, leaves, root barks, flowering stems, and seeds of V AC. The compounds include ninety-five terpenoids, twenty-six flavonoids (out of which six are flavonoid glucosides), twelve glucosides, twenty-seven phenolic compounds, seventeen steroids, seven unsaturated fatty acids, six saturated fatty acids, six aldehydes, six alkanes, six alklenes, three furan neolignanes, two glycerides, two dienes, and other compounds including heterocyclic compounds and sugars.

VAC and women’s fertility dysfunctions

VAC has been widely used for its healing effects on women’s fertility dysfunctions such as cyclic mastalgia, dysmenorrhea, amenorrhea, menopausal complications, hyperprolactinemia, premenstrual syndromes, abnormal menstrual cycles, lactation difficulties, and infertility (6, 21) (Fig. 1). This medicinal plant also has other effects, such as being an antioxidant, a tracheorelaxant, a chemopreventive, a vasorelaxant, an immunomodulatory, a cytotoxic, an antimitagenic, a tumoricidal, an antimicrobial, an antifungal, an insect repellant, a larvicidal, an osteopenic, a fracture healer, an antiepileptic, an anticncoceptive, opioidergic, and anti-inflammatory activity, and preventing nonalcoholic fatty liver disease (1, 4, 5).

Features of different types of mastalgia

Mastalgia (also known as mammalgia or mastodynia) is a medical term described mainly as breast pain during a female lifetime (10, 22). This condition has multifaceted and inhomogeneous clinical features. Mastalgia is a very common condition among women. It may include a dull ache, heaviness, tightness, discomfort, or burning sensation in the breast tissue or breast tenderness. It can be localized or diffuse and may be unilateral or bilateral. The exact cause of mastalgia remains unclear. With its not fully understood etiology, mastalgia affects about 50 % to 80 % of women at some point. However, only about 0.5 % of patients having mastalgia are reported to be diagnosed with breast cancer. Mastalgia most often appears in premenopausal and perimenopausal women, but postmenopausal women can also, but rarely, experience it. Breast pain can range from minor discomfort to severely disabling pain, and it can occur continuously or intermittently throughout the day (22, 23).

There are three known types of mastalgia (10, 11, 24): cyclical, noncyclical, and extramammary mastalgia. Cyclic mastalgia is the most common type of breast pain that is associated with the menstrual cycle. This is induced by hormonal variation. The disease is mainly associated with the second half of the menstrual cycle (luteal phase) and improves with the onset of menses. The breasts’ periodic discomfort is caused by an increase in estrogen levels that triggers the ductal elements of the breast. The decrease of progesterone in the luteal phase is followed by a decrease in progesterone-mediated stimulation of stroma cells. At the same time, an increase in prolactin release leads to increased ductal secretion, which in turn contributes to pain and swelling symptoms appearing during this phase. Another evidence of etiological link-
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**VAC and mastalgia**

Based on the scientific evidence, there are numerous alternative plant-based treatments for mastalgia (7, 30). It has been reported that mastalgia can be healed by *Vitex agnus-castus*, *Nigella sativa*, *Hypericum perforatum*, *Ginkgo biloba*, *Citrus sinensis*, curcumin, and wheat germ (30). The goal of this study is to look at how *V. agnus-castus* is used to treat mastalgia and its mechanisms of action.

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**The mechanisms of action of VAC on mastalgia**

The pharmacological activities of VAC in premenstrual syndromes are attributed to the presence of various receptor ligands, including dopamine, estrogen, and opioid receptor ligands (13-21). Thus, VAC properties modulate hormone levels and, through them, regulate many female conditions. The VAC has been reported to have a therapeutic role in the management of mastalgia (14, 21, 23), especially cyclic mastalgia, mainly due to its effects on controlling hypersecretion of prolactin and estrogen receptors (Fig. 2). The effects of VAC may also be through other undefined mechanisms.

**VAC-mediated latent hyperprolactinemia**

It is confirmed that in women suffering from premenstrual mastalgia, latent hyperprolactinemia is one of the major causes of the disease (21, 23, 25). The primary function of prolactin, a polypeptide hormone, is to stimulate lactation (the production of milk by the mammary glands). Prolactin is also responsible for breast development and many other functions needed to maintain homeostasis. Prolactin is derived from pre-prolactin (the prolactin prohormone) (31). Prolactin is synthesized and secreted by anterior pituitary-mediated hypothalamic regulation, but it can also be produced in the nervous and immune systems, as well as by mammary glands and the uterus. In these tissues, the initiation of prolactin synthesis is stimulated by various stimuli (nipple stimulation, olfaction, light, and stress), including hormonal-mediated-stimuli (thyrotropin-releasing hormone [TRH], dopamine...
antagonists, and estrogen (in pregnancy), respectively. Prolactin is low in non-lactating, non-pregnant females and males. Abnormal prolactin elevation in males indicates the potential initiation of a pathological process (12, 31).

In line with this, cyclic mastalgia is caused by latent stress-induced hyperprolactinemia. At least in some cases, women respond to this hormonal stimulus with hypersecretion of prolactin, which in turn leads to cyclical mastalgia due to overstimulation of the mammary glands (10, 11, 14, 21, 23). VAC effects, among others, include controlling hypersecretion of prolactin, i.e., lowering the prolactin level in women, as has been reported in clinical and laboratory studies (13, 21, 23). As a result, it plays a therapeutic role in the treatment and management of cyclical mastalgia. The prolactin-suppressive effect of VAC can be mediated either by dopaminergic activation through binding to recombinant DA2-receptor protein (13) or by inhibiting the TRH-stimulated prolactin secretion (32). Among other bioactive constituents, VAC contains diterpenoids (5), which can interact with dopamine receptors in the pituitary gland, therefore lowering prolactin levels (8). Vitex diterpenoids can interact with both D2 and D3 dopamine receptors in the brain (1, 8, 14, 21, 32). This could be a source for new drugs that could be used to treat other diseases linked to dopaminergic pathways.

Of note, in the Vitex genus, there are 114 unique structural labdane, -abietanes, and -clerodanes-related diterpenoids (20). Most diterpenoids extracted from V. agnus-castus link hydroxyl groups at C-9 and C-13 and have common structural features of lactone furan or 3-hydroxy-3-methyl-pent-4-enyl groups (18). The first two are especially relevant for their bioactive activity (2, 14, 16, 18). Of note, in the Vitex genus, there are 114 unique structural labdane, -abietanes, and -clerodanes-related diterpenoids (20). Most diterpenoids extracted from V. agnus-castus link hydroxyl groups at C-9 and C-13 and have common structural features of lactone furan or 3-hydroxy-3-methyl-pent-4-enyl groups (18). The first two are especially relevant for their bioactive activity (2, 16, 18). One of the most important prolactin-suppressive diterpenes are clerodadienols, which are identical in their effects to dopamine itself, i.e., they bind to recombinant DA2-receptor protein on the nerve cell membrane. Upon binding, they initiate the suppression of prolactin release, as reported in cultivated lactotrophs as well as in animal experiments (13, 18).

Another way of VAC extract inhibition of prolactin secretion has been reported in vitro in rats to be through TRH at the pituitary level (32). Except for dopamine and TRH, there are many other factors known to regulate prolactin secretion either through the pituitary and/or hypothalamic levels (33) that might be worthy of an investigation into VAC’s effects on them in future studies. Still, VAC might be a good alternative phytotherapeutic drug for treating hyperprolactinemia because it has a dopaminergic effect.

**VAC effects on estrogen receptors**

The etiology of mastalgia, except increased prolactin, is also thought to be caused by increased estrogen, decreased progesterone levels, or changes in the estrogen/progesterone ratio (23, 25, 34). The estrogen hormone is likely to be responsible for the cyclic nature of breast discomfort, the occurrence of breast symptoms such as tenderness, swelling, and nodularity, and the cessation of these symptoms in the postmenopausal period. It has been reported that there is a link between mastalgia and increased breastfeeding (35), which is linked to an increase in the number of births and, as a result, to increased exposure to the effects of high estrogen and prolactin levels, i.e., three or more periods of lactation can cause structural problems in the breast tissue, especially in the ductal system. This can lead to mastalgia. According to one study (24), lower estrogen levels can lead to a significant reduction in breast discomfort symptoms.

As a result of their estrogenic properties, VAC extracts are used to treat mastalgia, which is one of the premenstrual disorders. The binding of VAC bioactive compounds to estrogen receptors provides this endocrinologically active characteristic. Apigenin and perdudetin, as well as polyunsaturated fatty linoleic acid, are estrogenic compounds that exert their activity by specific binding to the ERβ (9, 14, 15). Upon receptor binding, they cause the estrogen-mediated PRL-lowering activity of VAC. Furthermore, VAC extract may also act through ERα (9). It has been demonstrated that VAC extract significantly increases estrogen receptor mRNA expression in hippocampal formation. VAC extracts, like estradiol, improve learning and memory performance in rats with ovariectomies (36). Estrogen receptors are found in many parts of the brain that help with learning and memory, like the hippocampus and basal forebrain. This makes it likely that estrogens play a role in cognitive functions.

Mastalgia is associated with cognitive disturbances (23, 25). According to animal research, estradiol treatment can improve cognition by upregulating ERα expression in the hippocampus (37). In line with this, VAC may have similar effects. Most likely by increasing hippocampus synapse density (38). An increase in ERα mRNA in the hippocampus may be linked to the action of VAC extract on the protection of learning and memory deficits. However, this may not exclude other mechanisms (1, 4, 5), including antioxidant, anti-inflammatory, and other VAC characteristics, which could be implicated in the plant’s beneficial effects on learning and memory. So, more research needs to be done to fully understand how exactly the VAC extract affects cognition. Both ERα and ERβ are expressed in the hippocampus (9, 14). In line with this, the exact process by which VAC lowers breast pain through steroid hormone interaction is unknown. Further investigation into the anti-estrogen activity of VAC competitive binding to estrogen receptors is needed to determine the exact mechanisms of action. Furthermore, estrogen can affect mammary cells through both genomic and non-genomic mechanisms. Of note, there are reports suggesting that the entire composition of the plant extract is more efficient than its individual components due to the synergy of its elements.

**VAC safety**

Herbal medicine is generally safe, but there have been several reported adverse reactions to plant extracts. The most common
side effects of plant extracts are headaches, nausea, vomiting, dizziness, restlessness, diarrhea, and dermal sensitivity (7, 39). A similar observation was made in the *Vitex agnus-castus* side effects. Nausea, headache, menstrual abnormalities, acne, gastrointestinal problems, pruritis, and erythematous rash are the most common adverse effects linked with VAC use, which were reviewed elsewhere (40). The minor and transient adverse effects of VAC therapy, on the other hand, demonstrate that it is a safe herbal remedy. The side effects could have been caused by the specific substances in the whole extract. So, it might be safer to use VAC for treatments if we knew more about its specific ingredients and how to optimize their extracts by taking out the ones that cause side effects.

**Conclusions**

The global acceptance and use of medicinal plants and related products is rapidly increasing. Mistakes of considering or labeling herbal medicinal items as “safe” because they are derived from “natural” sources are faultless. Issues linked to adverse reactions are emerging and need to be addressed. So, the agencies in charge of making sure herbal medicines are safe and of the right quality need to be proactive and ensure they are covered by a drug regulatory framework. Nonetheless, the purpose of this study was to review current knowledge of the *Vitex agnus-castus* role in mastalgia in order to improve understanding and direct future research in this field. Despite the fact that the underlying mechanisms of VAC’s effects on mastalgia are unknown, it is clear that VAC has a beneficial effect and a low risk of negative effects, making it suitable for the treatment of mastalgia, particularly cyclic mastalgia, as well as other premenstrual syndromes. The extract of *Vitex agnus-castus* is safe, effective, and efficient in the treatment, according to both laboratory and clinical data. For future studies with *Vitex agnus castus* extracts, it would be helpful to have clearly defined patient groups and the same endpoints.

**References**


Received July 8, 2022.
Accepted August 15, 2022.