

REVIEW

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

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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). Text in PDF www.elis.sk

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-

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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 VAC 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 VAC

Essential oils, flavonoids, diterpenoids, ligans, and iridoid glycosides constitute major classes of phytoconstituents of the *Vitex* genus, including VAC (1, 9 13). VAC 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 VAC 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 VAC (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 VAC. 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 alkenes, 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 antimutagenic, a tumoricidal, an antimicrobial, an antifungal, an insect repellent, a larvicidal, an osteopenic, a fracture healer, an antiepileptic, an antinociceptive, opioidergic, and anti-inflammatory activity, and preventing nonalcoholic fatty liver disease (1, 4, 5).

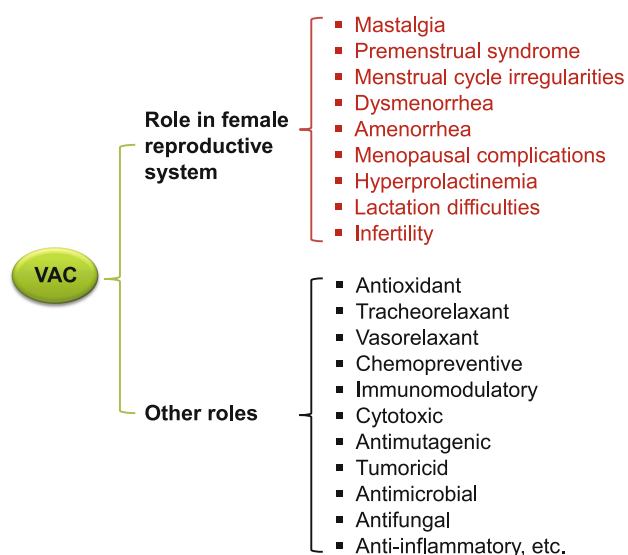


Fig. 1. Schematic representation of *Vitex agnus-castus* and its healing effects on female reproductive system dysfunctions and other roles. See the text for further details.

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-

age between cyclic mastalgia and hormones is hormonal therapy, including hormone replacement therapy and oral contraceptive usage. Cyclic breast pain resolves during pregnancy, lactation, and menopause (25). Cyclic mastalgia is generally bilateral and is often characterized by breast swelling, lumpiness, and tenderness. Most commonly, it appears in premenopausal women, and the pain usually intensifies a couple of weeks before the period. It normally lasts until the bleeding starts the next day, when the pain decreases over the next few days (10, 25). Non-cyclic mastalgia is quite uncommon and most likely appears in older women, in their 40s or 50s. In non-cyclic mastalgia, the breast pain is not related to the menstrual cycle and does not alternate with hormonal changes in the body. Instead, it is often associated with internal anatomical changes, such as injuries, surgery, or infections. Pains are generally localized and sharp and feel like burning breasts. Extramammary mastalgia is described as breast pain that feels as if it starts in the breast tissue but originates from outside the breast, usually the lung, chest wall, heart, or esophagus (10, 11, 22, 23).

The precise etiology of mastalgia is still unclear. However, numerous factors indicate the involvement of hormonal fluctuations (11, 24), especially in cyclic mastalgia, as the disease is related to the menstrual cycle as well as the cycle pain is significantly decreased with pregnancy or menopause. Changes in the anatomical structure, such as various injuries, surgery, the development of breast cysts, and some other disorders, may cause non-cyclic breast pain (24). Furthermore, breast pain has also been reported to be associated with the use of certain medications, including estrogen and progesterone hormonal therapies, oral contraceptive pills, antihistamines, and antidepressants. Numerous other factors (24), such as depression (26), stress, anxiety, smoking, and nutrition (fatty diet, caffeine-based drinks), have been linked to the development of breast pain (27).

Medicinal plants and medicine

Many medicinal plants are commonly used in alternative medicine due to their curative roles reported in many disorders (4, 5, 28, 29). Moreover, herbal medicinal products are widely considered to be compatible with our body conditions and have more efficacy and likely fewer side effects compared with synthetic drugs. However, they are not completely free of risks. Several side effects of herbal medicine have been reported (1). This highlights the demand and necessity of scientific characterization, especially performing toxicological analysis, for herbal products prior to their usage. The use of medicinal plants as one element of traditional complementary and alternative medicine is increasing worldwide. According to the World Health Organization (WHO), it is estimated that approximately 80 % of the world's population uses medicinal plants for primary health care or other medical purposes.

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*,

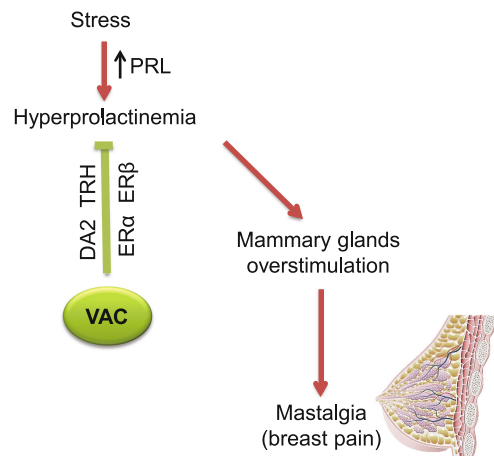


Fig. 2. The mechanisms of *Vitex agnus-castus* in mastalgia. The pharmacological functions of VAC in various conditions, including mastalgia, are reported. VAC affects mastalgia by controlling hypersecretion of prolactin, interacting with estrogen receptors, or through other unknown mechanisms. For further information, read the text.

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.

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 penduletin, as well as polyunsaturated fatty linoleic acid, are estrogenic compounds that exert their activity by specific binding to the ER β (9, 14, 15). Upon receptor binding, they cause the estrogen-mediated PRL-lowering activity of VAC. Furthermore, VAC extract may also act through ER α (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 ER α 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 ER α 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 ER α and ER β 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, pruritus, 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

1. Das N, Salgueiro ACF, Choudhury DR, Mandal SK, Logesh R, Hassan MM, Devkota HP. Traditional uses, phytochemistry, and pharmacology of genus *Vitex* (Lamiaceae). *Phytother Res* 2022; 36: 571–671.
2. Neves RC, Camara CA. Chemical composition and acaricidal activity of the essential oils from *Vitex agnus-castus* L. (Verbenaceae) and selected monoterpenes. *An Acad Bras Cienc*.2016; 88: 1221–1233.
3. Rani A, Sharma A. The genus *Vitex*: A review. *Pharmacogn Rev* 2013; 7: 188–198.
4. Thaci S, Krasniqi B, Dermaku-Sopjani M, Rifati-Nixha A, Abazi S, Sopjani M. Vasorelaxant Effects of the *Vitex Agnus-Castus* Extract. *Evid. Based. Complement Alternat Med* 2022; 2022: 7708781.
5. Thaçi S, Krasniqi B, Cela D, Dërmaku-Sopjani M, Bahtiri E, Abazi S, Sopjani M. Mechanisms Underlying the Tracheorelaxant Effect of *Vitex agnus-castus* Extract. *Rev Bras Farmacogn* 30(1), 103–110. 2020.
6. Rafeian-Kopaei M, Movahedi M. Systematic Review of Premenstrual, Postmenstrual and Infertility Disorders of *Vitex Agnus Castus*. *Electron Physician* 2017; 9: 3685–3689.
7. Tesch BJ. Herbs commonly used by women: an evidence-based review. *Dis Mon* 2002; 48: 671–696.
8. Kilicdag EB, Tarim E, Bagis T, Erkanli S, Aslan E, Ozsahin K, Kuscü E. Fructus agni casti and bromocriptine for treatment of hyperprolactinemia and mastalgia. *Int. J. Gynaecol Obstet* 2004; 85: 292–293.
9. Liu J, Burdette JE, Sun Y, Deng S, Schlecht SM, Zheng W, Nikolic D, Mahady G, van Breemen RB, Fong HH, Pezzuto JM, Bolton JL, Farnsworth NR. Isolation of linoleic acid as an estrogenic compound from the fruits of *Vitex agnus-castus* L. (chaste-berry). *Phytomedicine* 2004; 11: 18–23.
10. Pearlman MD, Griffin JL. Benign breast disease. *Obstet. Gynecol.* 2010; 116: 747–758.
11. Smith RL, Pruthi S, Fitzpatrick LA. Evaluation and management of breast pain. *Mayo Clin Proc* 2004; 79: 353–372.
12. Vilar L, Vilar CF, Lyra R, Freitas MDC. Pitfalls in the Diagnostic Evaluation of Hyperprolactinemia. *Neuroendocrinology* 2019; 109: 7–19.
13. Wuttke W, Jarry H, Christoffel V, Spengler B, Seidlova-Wuttke D. Chaste tree (*Vitex agnus-castus*)--pharmacology and clinical indications. *Phytomedicine* 2003; 10: 348–357.
14. Ahangarpour A, Najimi SA, Farbood Y. Effects of *Vitex agnus-castus* fruit on sex hormones and antioxidant indices in a d-galactose-induced aging female mouse model. *J Chin Med Assoc* 2016; 79: 589–596.
15. Echeverria V, Echeverria F, Barreto GE, Echeverria J, Mendoza C. Estrogenic Plants: to Prevent Neurodegeneration and Memory Loss and Other Symptoms in Women After Menopause. *Front Pharmacol* 2021; 12: 644103.
16. Soleymanzadeh F, Mahmoodi M, Shahidi S. Effect of *Vitex Agnus-Castus* Ethanolic Extract on Sex Hormones in Streptozotocin-Induced Diabetic Rats. *J Family Reprod Health* 2020; 14: 102–105.
17. Janbaz KH, Arif J, Saqib F, Imran I, Ashraf M, Zia-Ul-Haq M, Jaafar HZ, De F, V. In-vitro and in-vivo validation of ethnopharmacological uses of methanol extract of *Isodon rugosus* Wall. ex Benth. (Lamiaceae). *BMC. Complement Altern Med* 2014; 14: 71.
18. Goncalves R, Ayres VFS, Carvalho CE, Souza MGM, Guimaraes AC, Correa GM, Martins CHG, Takeara R, Silva EO, Crotti AEM. Chemical Composition and Antibacterial Activity of the Essential Oil of *Vitex agnus-castus* L. (Lamiaceae). *An Acad Bras Cienc* 2017; 89: 2825–2832.
19. Kikuchi H, Yuan B, Nishimura Y, Imai M, Furutani R, Kamoi S, Seno M, Fukushima S, Hazama S, Hirobe C, Ohyama K, Hu XM, Takagi N, Hirano T, Toyoda H. Cytotoxicity of *Vitex agnus-castus* fruit extract and its major component, casticin, correlates with differentiation status in leukemia cell lines. *Int J Oncol* 2013; 43: 1976–1984.
20. Yao JL, Fang SM, Liu R, Oppong MB, Liu EW, Fan GW, Zhang H. A Review on the Terpenes from Genus *Vitex*. *Molecules* 2016; 21.
21. van Die MD, Burger HG, Teede HJ, Bone KM. *Vitex agnus-castus* extracts for female reproductive disorders: a systematic review of clinical trials. *Planta Med* 2013; 79: 562–575.
22. Weaver M, Stuckey A. Benign Breast Disorders. *Obstet Gynecol Clin North Am* 2022; 49: 57–72.
23. Peter C, Alec M, Botsikas D, Wegener S, Perbet E, Lam GT. Mastalgia: management and state of the art) *Rev. Med Suisse* 2022; 18: 83–87.
24. Eren T, Aslan A, Ozemir IA, Baysal H, Sagiroglu J, Ekinci O, Alimoglu O. Factors Effecting Mastalgia. *Breast Care (Basel)* 2016; 11: 188–193.

- 25. Dzoic DM, Ivanac G, Bojanic K, Kralik K, Smolic M, Divjak E, Smolic R, Brkljacic B.** Exploring Association of Breast Pain, Pregnancy, and Body Mass Index with Breast Tissue Elasticity in Healthy Women: Glandular and Fat Differences. *Diagnostics (Basel)* 2020; 10.
- 26. Katar MK, Baser M.** Relationship Between Mastalgia And Anxiety-Depression: An Observational Study. *Cureus* 2021; 13: e12734.
- 27. Idiz C, Cakir C, Ulusoy AI, Idiz UO.** The Role of Nutrition in Women with Benign Cyclic Mastalgia: A Case-Control Study. *Eur J Breast Health* 2018; 14: 156–159.
- 28. Krasniqi B, Thaci S, Dermaku-Sopjani M, Rifati-Nixha A, Abazi S, Sopjani M.** Insight into the Mechanisms Underlying the Tracheorelaxant Properties of the *Sideritis raeseri* Extract. *Evid. Based. Complement Alternat Med* 2020; 2020: 6510708.
- 29. Romanucci V, Di Fabio G, D'Alonzo D, Guaragna A, Scapagnini G, Zarrelli A.** Traditional uses, chemical composition and biological activities of *Sideritis raeseri* Boiss. *Heldr J Sci Food Agric* 2017; 97: 373–383.
- 30. Niazi A, Rahimi VB, Hatami H, Shirazinia R, Esmailzadeh-Dizaji R, Askari N, Askari VR.** Effective Medicinal Plants in the Treatment of the Cyclic Mastalgia (Breast Pain): A Review. *J Pharmacopuncture* 2019; 22: 131–139.
- 31. Freeman ME, Kanyicska B, Lerant A, Nagy G.** Prolactin: structure, function, and regulation of secretion. *Physiol Rev* 2000; 80: 1523–1631.
- 32. Sliutz G, Speiser P, Schultz AM, Spona J, Zeillinger R.** Agnus castus extracts inhibit prolactin secretion of rat pituitary cells. *Horm Metab Res* 1993; 25: 253–255.
- 33. Bernard V, Young J, Binart N.** Prolactin – a pleiotropic factor in health and disease. *Nat Rev Endocrinol* 2019; 15: 356–365.
- 34. Tejwani PL, Srivastava A, Nerkar H, Dhar A, Hari S, Thulkar S, Chumber S, Kumar S.** Centchroman regresses mastalgia: a randomized comparison with danazol. *Indian J Surg* 2011; 73: 199–205.
- 35. Wisbey JR, Kumar S, Mansel RE, Peece PE, Pye JK, Hughes LE.** Natural history of breast pain. *Lancet* 1983; 2: 672–674.
- 36. Allahtavakoli M, Honari N, Pourabolfi I, Kazemi AM, Ghafarian H, Roohbakhsh A, Esmaili NA, Shamsizadeh A.** Vitex Agnus Castus Extract Improves Learning and Memory and Increases the Transcription of Estrogen Receptor alpha in Hippocampus of Ovariectomized Rats. *Basic Clin Neurosc.* 2015; 6: 185–192.
- 37. Ishunina TA, Fischer DF, Swaab DF.** Estrogen receptor alpha and its splice variants in the hippocampus in aging and Alzheimer's disease. *Neurobiol Aging* 2007; 28: 1670–1681.
- 38. Li H, Li SL, Gong L, Wang JL, Li YZ, Wu ZH.** The effects of an herbal medicine Bu-Wang-San on learning and memory of ovariectomized female rat. *J Ethnopharmacol* 2008; 117: 427–432.
- 39. Favarin DC, de Oliveira JR, de Oliveira CJ, Rogerio AP.** Potential effects of medicinal plants and secondary metabolites on acute lung injury. *Biomed Res Int* 2013; 2013: 576479.
- 40. Daniele C, Thompson CJ, Pittler MH, Ernst E.** Vitex agnus castus: a systematic review of adverse events. *Drug Saf* 2005; 28: 319–332.

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