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"Phytopharmacological Review of Vitex Agnus-Castus (Verbenaceae) For The Treatment of Various Female Reproductive Disorders"

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Abstract

Two main factors have led to an increased shift towards use of medicinal plants for herbal remedy against deadly and infectious diseases. These factors are the sometimes-irreversible side effects of modern medicine and highly increasing drug resistance. *Vitex agnus-castus* also known as chaste tree is a small deciduous tree native to central Asia and Mediterranean region. Its fruits have been used in ancient Egypt, Rome, Iran, and Greece for more than 2500 years to treat variety of gynaecological problems. '*Vitex'* is a Roman word and it was considered to be related to willow, *Salix* – because of its leaves and flexible branches while '*agnus-castus'* is a Greek word *agnos-castus* because it has been associated with chastity. The fruit is berry which is purple to black in colour that carries four seeds similar to black pepper. The flowers are in clusters which are violet to blue to deep purple. The pharmaceutical effects of this medicinal plant include antioxidant, chemopreventive, immunomodulatory and cytotoxicity, tumoricidal, antimutagenic, antimicrobial, antifungal, insect repellent, larvicidal, fracture healing, osteopenic, antinociceptive, opioidergic, antiepileptic, preventing non-alcoholic fat liver disease and oxidative stress, and anti-inflammatory activities. The recommended dose is 30–40 mg/day of extract of dried fruit. Adverse effects of this plant are mild and reversible and are contraindicated in pregnant and lactating women. The present review compiles the data from ancient till today.

Keywords: Chaste tree, vitexin, *Vitex agnus-castus*, gynaecological disorder

Introduction

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Figure 1: *Vitex agnus-castus* [1]

Reproductive disorders in females result due to diseases of their reproductive organs that is uterus, breast, fallopian tubes, ovaries, vagina or cervix due to disease growth. [2] These disorders may include dysmenorrhoea (pain associated with menstruation), chronic pelvic pain and vulvodynia (chronic discomfort or pain of the vulva). [3] Some diseases take turn to cancer usually in late reproductive or menopausal years of a women. They mostly have high incidence of metastasis and high mortality rate. These reproductive organs are located deep inside the body and are relatively inaccessible to palpation for example ovaries. Others have few sensory nerves for example fallopian tubes and thus remain asymptomatic. Early detection of breast cancer becomes difficult because of fat or adipose tissue. Uterine cervix is easily accessed by using Papanicolaou smear and human papillomavirus (HPV) screening, resulting in reduced cervical cancer mortality rates. Female reproductive disorders may also occur due to present of disease in other organs that affect reproductive organs such as hypothalamus, pituitary, brain, adrenals, thyroid, liver and kidney. [2]

There are many herbs which are beneficial for the treatment of female reproductive disorder and show a broad spectrum effective with less side effects e.g. black cohosh root (*Actaea racemosa*), Goldenseal root (*Hydrastis canadensis*), valerian (*Valeriana officinalis*). In this study we are going to discuss about *Vitex agnus-castus.*

Vitex agnus-castus is commonly referred to as the monk's pepper or chaste tree belonging to the Verbenaceae family, a native of Mediterranean region and central Asia. [4] The plant was commonly used to correct gynaecological and reproductive problems by European and North American herbalist. [5] *Vitex* is a Roman word and it was considered to be related to willow, *Salix* – because of its leaves and flexible branches while *agnus-castus* is a Greek word *agnos-castus* because it has been associated with chastity. [6] This herb is widely used to treat menstrual irregularities, premenstrual syndrome (PMS), infertility, mastalgia, acne, and lactation difficulties. [5]

Biological Source

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Botanical name- *Vitex agnus-castus* [7]

Family- *Verbenaceae* [7]

Part used – Fruit [8]

Synonyms

Arabic : Athlak

Spanish : Agno casto

Italian : Agno-casto

Catalan : Agnocast, aloc, aloch

Chaman : Marwandi

Dutch : Kuischboom

English : Agnus-castus, chaste tree, monk's pepper

French : Agnos, Agnus castus

German : Keushbaum, keuschlamm

Greek : Elaiagnos [9]

Habit- small deciduous tree or large shrub [10]

Plant Description

Macroscopic

Figure 2: *Vitex agnus-castus* flower [4]

The plant is 1.5 m to 2 m tall. A palmately compound leaf with 5 to 9 radiating leaflets, shape is narrowly lanceolate with acute apex, margin is coarsely tooth towards upper side or entire undulated, the central and largest leaflet being 5 to 10 cm long and 2 to 4 cm wide, the upper surface is dark green, the lower greyish and tomentose. Taste is characteristic and odour is fragrant. The flowers are in clusters which are violet to blue to deep purple. It blooms from summer until early winter, and the fruits is berry which are purple to black in colour that carries four seeds similar to black pepper. [11]

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Microscopic

Leaflet

Transverse section of the leaflet passing through the midrib shows an upper and lower epidermis, being 2 to 3 in rows in the lamina region. Midrib shows a well-developed central arc, bicollateral meristele and a smaller, oval shaped meristele on the upper side, the remaining parenchymatous tissue ground adjacent to them being very narrow, colenchymatous tissue lies underneath both the epidermis. The upper epidermal cells of lamina are bigger in size than the lower one, and are devoid of stomata. Both the epidermis are covered with thick cuticle and bear plenty of simple covering and few glandular trichomes: simple trichomes are short, conical, straight or bent 2 to 3 cells long, uniseriate while few glandular trichomes are sessile with 1 to 4 celled, globular head and others with 1 to 3 celled stalk and unicellular head. Underneath the multi-layered upper epidermis lie a parenchymatous layer of hypodermis and then 2 to 3 rows of compactly arranged palisade calls, followed by narrow band of spongy parenchyma of mesophyll, transverse with obliquely cut vascular bundles. [11]

Petiolule

The transverse section shows oval shape outline with globular ear shaped projections on one side. The epidermis bear a number of trichomes identical to that of leaflet, a collenchymatous band having different height run throughout underneath of the epidermis, U- shaped well develop meristele embedded in the central of the ground tissue shows two extra vascular bundles in the pit between the two terminals and a small rudimentary bundle under each of the projection. [11]

Petiole

Transverse section is having square outline, two pinna winged projection each on one side at the top. The epidermis surrounding the ground tissue have plenty of trichomes as that of the leaf, a collenchymatous hypodermis runs underneath it. Central pith is broad encircled with perimedullary phloem tissue underneath the horse-shaped stelar tissue, with a peripheral band of pericycle. [11]

Powder

A fragment of upper epidermis lamina shows sub-epidermis like epidermis in surface view, fragments of lower epidermis with stomata and striated cuticle, fragments of epidermis have glandular and covering trichomes, fragments of conical, 2 to 4 celled covering trichomes, glandular trichomes with unicellular and sessile trichomes 2 to 4 celled head, fragment of collenchymatous layer, fragment of cylindrical cut pitted parenchyma cells of pith, fragments of pitted and spiral vessels and tracheids, fragment of pitted fibre, fragment of thin wall acicular. [11]

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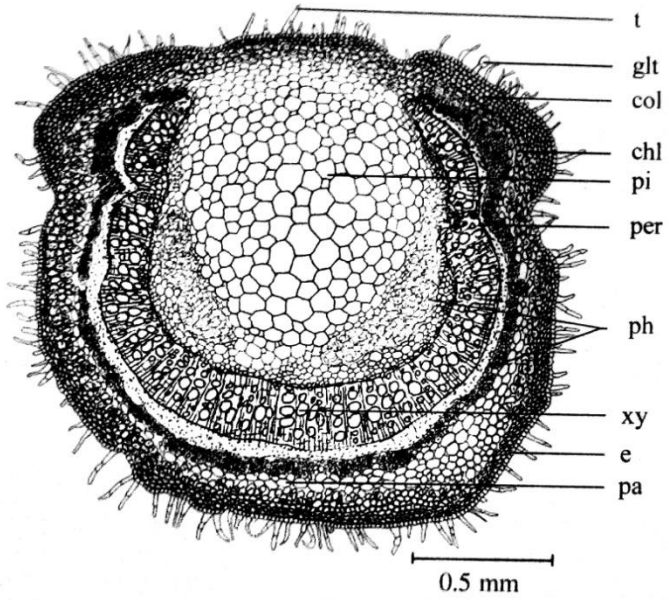

Figure 3: Microscopical characteristics of *Vitex agnus-castus* leaf petiole: chl-chlorenchyma; col-collenchymas; e-epidermis; glt-glandular trichome; pa-parenchyma; per-pericycle; ph-phloem; pi-pith; t-trichome; xy-xylem. [11]

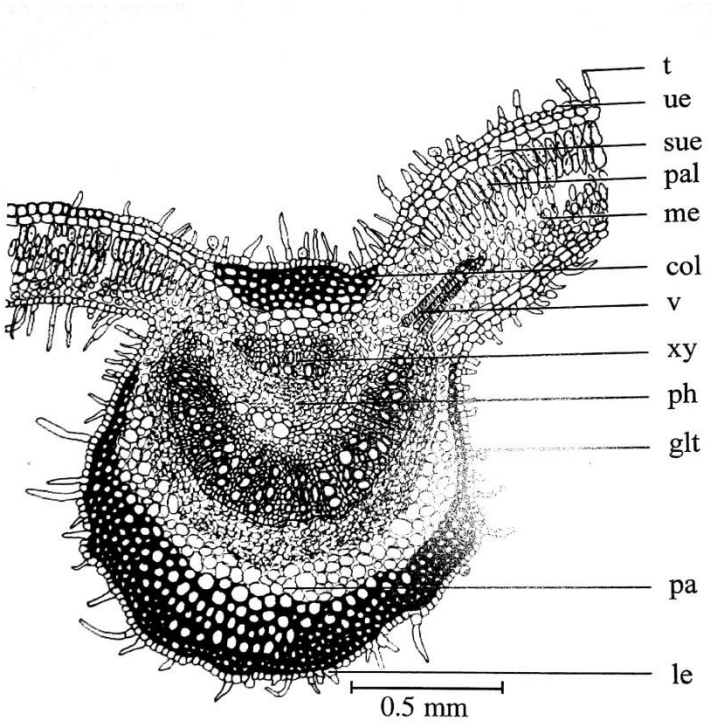

Figure 4: Microscopical characteristics of *Vitex agnus-castus* leaflet passing through mid-rib: col-collenchymas; glt-glandular trichome; le-lower epidermis; me-mesophyll; pa-parenchyma; pal-palisade; ph-phloem; sue-subepidermis; t-trichome; ue-upper epidermis; v-vessel; xy-xylem. [11]

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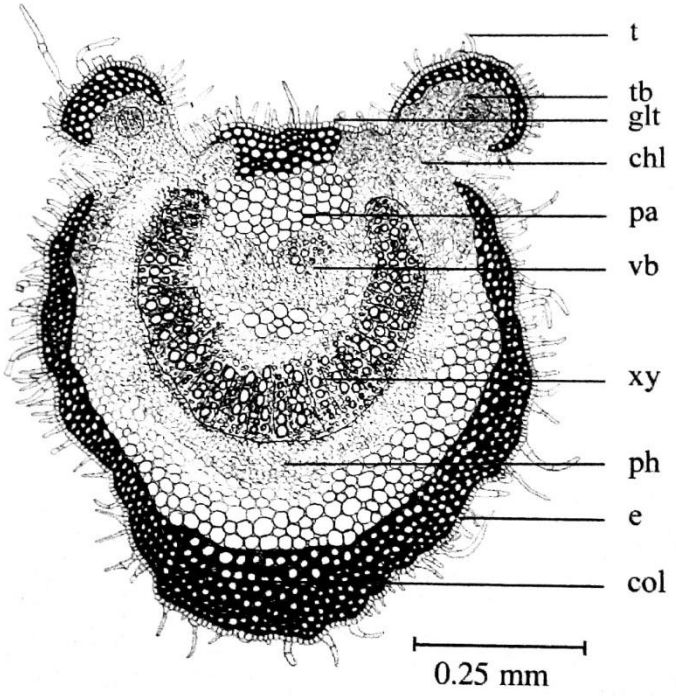

Figure 5: Microscopical characteristics of *Vitex agnus-castus* leaf petiole: chl-chlorenchyma; col-collenchyma; e-epidermis; glt-glandular trichome; pa-parenchyma; ph-phloem; t-trichome; tb-trace bundle; vb-vascular bundle; xy-xylem. [11]

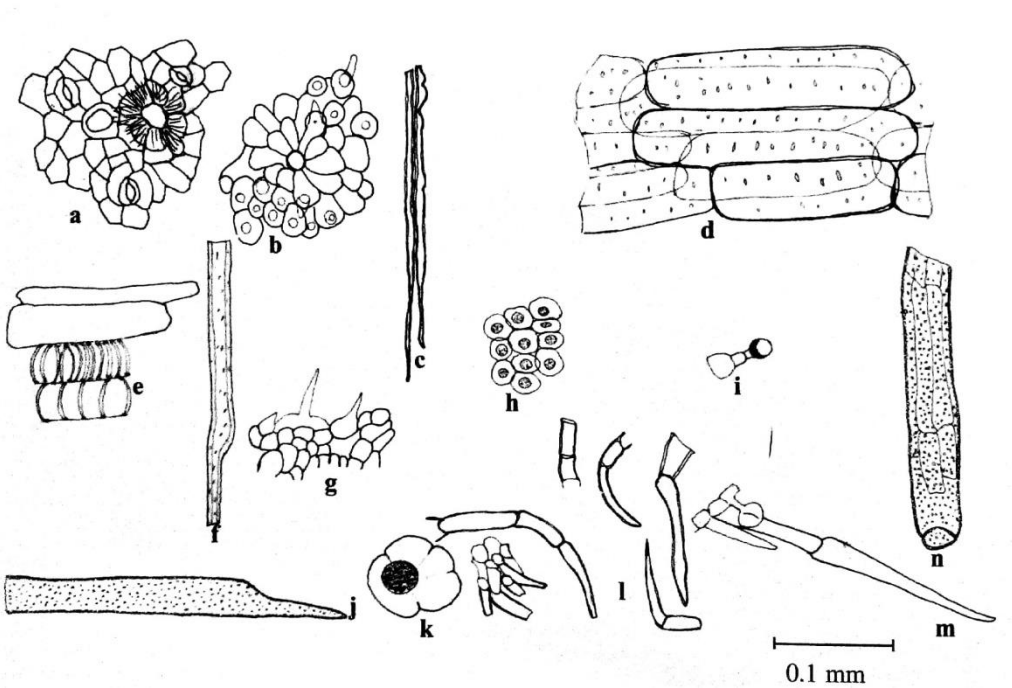

Figure 6: Powder microscopy of *Vitex agnus-castus* leaf. **a**-fragment of lower epidermis with stomata and striated cuticle; **b**-upper epidermis in surface view showing papillae; **c**-thin-walled pericycle fibre; **d**-pitted pith parenchyma; **e**-fragment of spiral vessel; **f**-fragment of pitted fibre; **g**-obliquely cut epidermis showing subepidermis and unicellular trichome; **h**-colenchyma cells; **i**-glandular trichome with multicellular stalk; **j**-fragment of pitted tracheid; **k**-sessile glandular trichomes; **l**-fragments of covering trichomes; **m**-fragment of epidermis bearing glandular and covering trichome; **n**-pitted vessel. [11]

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Quantitative Standards

Table 1: Standard Quantity of *Vitex agnus-castus* [11]

Sl. No.	Name	Limit
i.	Foreign matter	Not more than 2.0 %
ii.	Total Ash	Not more than 7.5 %
iii.	Acid insoluble ash	Not more than 0.5 %
iv.	Water soluble extractive	Not less than 25.0 %
v.	Alcohol soluble extractive	Not less than 20.0 %

Adulterants/ Substitutes

Leaf of *Vitex negundo* Linn has 3 to 5 foliate, greyish tomentose beneath, petiolulate except the terminal which is almost sessile, petiole 2.5 to 3.8 cm long while *Vitex trifolia* Linn. 3 leaflets the terminal being sessile, very white tomentose beneath, petiole 1.3 to 1.6 cm long are used as an adulterant. [11]

Active Constituent

Vitex agnus-castus fruits contain flavonoids, iridoid glycoside, essential oils and essential fatty acid. Iridoid glycosides (agnoside, aucubin, agnucastoside A, agnucastoside B, agnucastoside C), flavonoids (castitin, kaemferol, orientin, isoorientin, quercetagetin, vitexin, isovitexin, luteolin, artemetin, apigenin, and isorhamnetin), essential oils (limonene, limes, linalool, terpinyl acetate, monoterpenoids, alpha pinenes and beta along with sabinene, cymene, castine, myrcene, citronellol, camphene, cineol, pinene, sesquiterpenoids such as cardinene, farnescene, caryophyllene and ledol), essential fatty acids (oleic, palmitic, stearic, linoleic acid). [10, 12]

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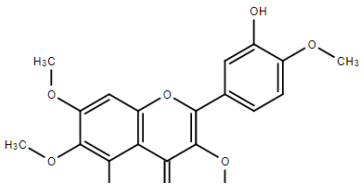
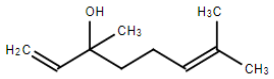
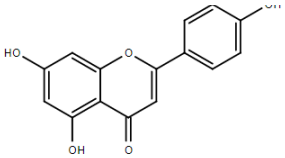
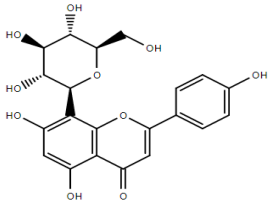
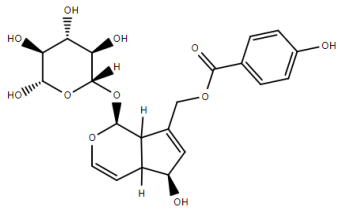
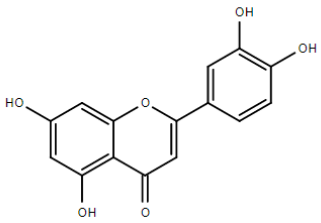
Table 2: Molecular structure of the main components of *Vitex agnus-castus*

Chemical name	Chemical structure
Casticin	
Linalool	
Apigenin	
Vitexin	
Agnuside	
Luteolin	

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Cultivation

Usually the chaste tree grows in the garden. Sandy and loamy soils are preferred by *V. agnus-castus*. The crop also requires well-drained soil and can rise in pure nutritional soil. The plants prefer the soil that are acid, neutral and basic (alkaline). In the shade, it cannot grow. [13]

Traditional Used

V. agnus-castus tree in *Latin* is additionally named "chaste lamb," because it diminishes the sexual desire subsequent to drinking a refreshment produced from the *V. agnus-castus* seeds. [14] Over 50 years it has been widely used in Europe to treat premenstrual syndrome (PMS), menstrual irregularities, mastalgia, infertility, and also for lactation difficulties. In ancient times, natural fruit products have been used in Egypt, Greece, Iran, and Rome for more than 2500 years to treat variety of gynaecological problems. It has also been utilized for libido reduction. [15] In Persian recently, *V. agnus-castus* leaves and fruits have been used as a flavour and also as a spice in food. [16, 17] The fruit has also been utilized as a hormone like remedy for reducing menstrual disorders and as antiepileptic, carminative, energy booster, sedative, anticonvulsant, tranquilizer, and for treatment of digestive disorders, but the berries are used as a pepper. [17,18] Based on ethno medicine of different nations in the World, this plant shows its effect commonly for relieving menstrual cramps, eye diseases, spasmodic dysmenorrhoea, insufficient lactation, treatment of acne, scorpion sting, stomach ache, and also as antispasmodic, aphrodisiac, and emmenagogue agent. [19,20] It is also used as an ornamental plant in America. Hippocrates recommended treatment of wounds and inflammation in 400 BCE. Greek botanist Dioscorides specifically recommended chaste tree for uterus inflammation and the problem of lactation. In the Middle Ages, where tradition remains that medieval monks chewed tree parts to preserve their celibacy, dried berries are used in food or put in the pockets of their robes to reduce sexual appetite, V. agnus-castus continued to pave importance; hence, the synonym of Monk's pepper comes into being. Throughout England and America, its popularity has risen since the mid-1900s. In traditional Chinese medicine method or traditional Indian medicine (Ayurveda), the use of V. agnus-castus is not generally used, but other Vitex species (negundo, trifoliata) are used in these therapies. [21]

Mechanism of Action

Vitex agnus-castus is an effective treatment option for premenstrual syndrome (PMS) and related symptoms, premenstrual dysmorphic disorder (PMDD) and cyclic mastalgia, migraine associated with PMS, headaches, menstrual irregularities, luteal phase deficiencies and hyperprolactinemia. [4] Chaste berry contains a mixture of iridoid glycosides and flavonoids, including orientin, isovitexin and casticin. These constituents seem to stimulate luteinizing hormone (LH) or follicle stimulating hormone (FSH) production and secretion. [22] Chaste berry may affect dopamine, acetylcholine and opioid receptors. Chaste berry may have hormonal properties through estrogenic and progesterone activity. [8] Elevated prolactin may inhibit progesterone secretion. The chaste tree mechanism of action involves inhibition of

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stress induced prolactin secretion from the pituitary gland [23] and normalizes luteal phase deficiencies in menstrual cycle by competitively binding to dopamine (D2) receptors and also contributing to positive benefits in PMS AND PMDD. Additionally, due to prolactin inhibition, chaste berry improved latent hyperprolactinaemia and cyclic mastalgia. [24] It does not appear that chaste berry affects testosterone levels. In vitro work suggests that the growth of ovary, cervical, breast, gastric, lung and colon cancer cells may be reduced by chaste berry. Essential oils obtained from chaste berry shows antibacterial and antifungal properties. [8] However, the hormonal effect is dose-dependent: low doses of extract have resulted in lower levels of estrogen and increased levels of progesterone and prolactin that may be caused by inhibiting the release of follicle-stimulating hormone (FSH) and stimulating the levels of luteinizing hormone (LH). However, FSH and LH levels remained unchanged in some studies of people receiving higher doses, but the secretion of prolactin decreased. [12]

Clinical Indication

Premenstrual Syndrome

A prospective, multicenter trial in 1634 patients with premenstrual syndrome (PMS) investigated the effect of Femicur which is a dried fruit extract of *V. agnus-castus*, on the four symptoms associated with PMS, including symptoms like depression, anxiety, craving, and hyperhydration in three menstrual periods. Nearly 93% of patients with premenstrual syndrome symptoms show a reduction and 94% have a good or excellent tolerance of *V. agnus-castus* remedy. [25] The effectiveness of 20 mg *V. agnus-castus* fruit extract on premenstrual syndrome-related symptoms has been approved in a potential, multicenter trial conducted on 50 patients with premenstrual syndrome for three menstrual cycles in 2000. 13 patients took oral contraceptives. At the end of the study, the decline of premenstrual syndrome-related symptoms (42.5 %) was measured as the vital affecting parameter by the Moos ' Menstrual Distress Questionnaire. There were no differences involving in patients with or without oral contraceptives. [26] The study was repeated as a prospective randomized double-blind placebo-controlled study with 178 patient aged 18 years or older with premenstrual syndrome to check *V. agnus-castus* effectiveness and tolerability. The study results showed significant improvement in the patients treated with *V. agnus-castus* (20 mg tablet once daily) by more than 50 percent of the combined symptom decrease. *V. angus-castus* showed more effectiveness in treating premenstrual syndrome than placebo in the five symptoms including mood alteration, breast fullness, irritability, anger and headache. [27] 128 women were administered with 40 drops of Vitex extract daily over 6 cycles, showed improvement in symptoms like nervousness, restlessness, depression, breast pain, bloating and headache when measured on a Visual Analogue Scale (VAS). [28] In a 3-month randomized controlled trial, a 3.5 mg capsule of V. agnus-castus fruit extract (Agnolyt®) was compared to 100 mg of Vitamin B6 (twice a day) in 127 patients with premenstrual symptoms. Agnolyt® and Vitamin B6 both reported similar reductions in premenstrual syndrome which is 77% versus 66% in the *V. agnus-castus* and Vitamin B6, respectively.[14] 41 patients with premenstrual dysphoric disorder (PMDD) of ages 24 and 45 years were

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randomly grouped into fluoxetine or *V. agnus-castus*. In a single-blind. Rater-blind and prospective treatment period, the two groups received, 20-40 mg daily for 2 months. The study reported that both *V. agnus-castus* and fluoxetine treatments show equal efficacy. Fluoxetine has more ability to overcome psychological symptoms but the Vitex extract could decrease the physical symptoms. [29] A prospective, open, non-comparative, mono-center trial in 120 patients with moderate to severe premenstrual syndrome (PMS) who received Agnucaston® tablet (40 mg herbal drug) orally once daily for three cycles to check the efficacy of *V. agnus-castus*. The signs of severity of premenstrual syndrome (PMS) consistently showed a decline with the mean decrease of 12.6 score points ($P < 0.0001$). The study reported that during the third treatment, 67.8 percent of women had responded. [30] In another clinical trial study, a double-blind, randomized, placebo-controlled, parallel trial in women with late perimenopausal to investigate the improvement efficacy of PMS related symptoms of dry fruit extract of *V. agnus-castus* (1000 mg/day) and dry herb flowering top extract of Hypericum perforatum (5400 mg) or placebo tablet twice daily for 16 weeks. The study reported a reduction of PMS symptoms like the anxiety, depression, cravings, and hydration on Abraham's Menstrual Symptoms Questionnaire as compared with control group. [31] A prospective, placebo-controlled, double-blind, parallel-group, multi center clinical-trial of 217 female patients with PMS symptoms reported a result. One tablet daily containing *V. agnus-castus* ethanolic extract (40 mg) or matching placebo, chaste tree reported safe, effective and well-tolerated. [32] Furthermore, a prospective, double-blind, randomized, placebo-controlled study of 67 patients to investigate efficacy of *V. agnus-castus*. All patients receive *V. agnus-castus* or placebo group film-coated tablets, i.e. 4.0 mg of dried ethanolic (70%) extract for three cycles. The results found out that all the symptoms of PMS improved significantly greater with *V. agnus-castus* than placebo. [33] Vitex extract (40 drops given 6 days before menstruation) was taken for six consecutive cycles in another study of 134 patients suffering from premenstrual syndrome and reported a result. In this randomized, placebo-controlled, double-blind study, *Vitex agnus-castus* and placebo groups showed a major difference before and after the study ($P < 0.0001$) for reduction of mild and moderate premenstrual syndrome symptoms. [34] In a retrospective, double-blind, parallel-group, multi-center, placebo-controlled study, over three menstrual cycles, 162 female patients with premenstrual syndrome (18–45 years) were divided into two groups, i.e., placebo and specific doses of Ze 440 (V. agnus-castus fruit extract) 8, 20, and 30 mg. The report was observed with the single premenstrual syndrome symptom scores. The total symptom of PMS showed higher improvement for the 20 mg group than the placebo and 8 mg group. In addition, the higher 30 mg dose did not decrease the symptom of PMS compared to treatment with 20 mg. Therefore, the daily intake of 20 mg extract showed response by patients with PMS. [35] In addition, the effectiveness of V. agnus-castus in treating headache in 107 migraine women who used V. agnus-castus extract for symptoms of premenstrual syndrome for 3 months was noted in an open-label clinical study. The results related to migraine indicated that the repetition of monthly attacks reduce 50% in 42% of the women and 50% decrease in monthly days with headache in 57% of the women. Therefore, the use of V. agnus-castus in migraine women affected by PMS was confirmed to be safe and well tolerated and could have a positive effect on migraine attack frequency and duration.

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[36] Again, another study determined that 20 mg of *V. agnus-castus* extract (Prefemin®) once every day for three menstrual cycles, proved successful effect on premenstrual syndrome symptoms, by reducing total Visual Analog Scale (VAS) score ($P < 0.001$) without substantial adverse events. [37] The usefulness of *V. agnus-castus* on menstrual cycle irregularities (MCIs), such as polymenorrhea, oligomenorrhea, or amenorrhea, was observed in the study. 211 female patients with MCIs and menstrual bleeding were administrated with 20 mg of the Vitex extract (Ze 440) every day for three resulting menstrual periods. The results reported 60%–88% reduction of symptoms related to menstrual bleeding such as dysmenorrheal and pre- or postmenstrual bleeding and that of MCIs and 79%–85% for the symptoms such as polymenorrhea, oligomenorrhea, and amenorrhea. The study showed that treatment with *V. agnus-castus* extract considerably decrease MCIs and was well tolerated. [38] Another double-blind study received Vitagnus ® 40 drops orally every day or placebo for three menstrual cycles in 72 female patients with premenstrual syndrome. The result revealed variations between two classes ($P < 0.001$, $P < 0.05$, and $P < 0.01$, respectively) in the physical and psychological symptoms and duration of premenstrual syndrome. [39] *V. agnus-castus* capsule was compared with mefenamic acid capsule to check the efficacy on intrauterine device (IUD)-induced bleeding in a double-blinded, randomized controlled clinical trial in 84 female patients with IUD. Two groups were allocated, 42 patients treated with mefenamic acid (250 mg) and 42 patients with *V. agnus-castus* capsules thrice a day during menstruation. Both had alleviated bleeding, the treatment decreases at 4th month was 52% with mefenamic acid and 47.6% with V. agnus-castus. Hence, mefenamic acid was more effective than *V. agnus-castus*.[40] A prospective, comparative study of 60 female patients with severe primary dysmenorrhea and 30 healthy women (control) reported results for three menstrual cycles. 30 patients were administrated with Yasmin (0.03 mg ethinyl estradiol and 3 mg drospirenone) and other 30 patients were treated with *V. agnus-castus* (Agnucaston® tablet 4 mg) once a day. The study showed same effective in both the groups. [41]

Menopause

Two following studies were designed in 2000 and 2002 to examine the *V. agnus-castus* essential oils effect on menopausal symptoms which derived from the leaf and fruit of the plant. In the first study, 23 female patients took oil through different routes i.e. oral, transdermal, and inhalation. Five menopausal symptoms like urogenital, vasomotor, mood dysfunction, uterine bleeding, and sleep reported reduction in the result. After 3-10 months, regular menstruation of amenorrhea was achieved in some women, and another was after 6 years. In the second study, 52 pre- or postmenopausal female patients applied V. agnus-castus essential oil solution in the form of base cream or lotion extracted from aerial parts. Nearly 33 percent of patients reported significant relief and 36 percent reported mild to moderate relief. The major changes were observed in the night sweats, hot flushes, emotional symptoms and moderation of menstruation. A randomized, placebo-controlled, double-blind, parallel study of 100 late-pre- or post-menopausal women with hot flushes and other symptoms of menopause was tested by a combination of *V. agnus-castus* and *H. perforatum* for 16 weeks in treating menopausal symptoms. [42] A combination of *V. agnus-castus* as

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well as *H. perforatum* tablets were administered daily (containing extract equal to 500 mg of dry fruit and 300 mg of extract respectively). This combination reported a significant improvement even though there was no difference to placebo for menopausal symptoms. [43]

Mastalgia

The efficacy of *V. agnus-castus* in the treatment of these two symptoms was investigated in a study of 40 female patients in group 1 with cyclic mastalgia and 40 female patients in group 2 with mild hyperprolactinemia, and results were compared with those for bromocriptine (dopamine agonist) therapy. Patients were administered randomly for 3 months either with bromocriptine (2.5 mg twice daily) or *V. agnus-castus* (40 mg daily). A prolactin level was found to be decreased significantly in both groups after treatment ($P < 0.0001$ for both), without any adverse effect for *V. agnus-castus* but bromocriptine-treated patients (12.5%) was observed to have nausea and vomiting. Hence, vitex acts in the same way to bromocriptine about the reduction of serum prolactin and reducing breast pain. [44] In another study, a randomized, double-blind trial in 104 premenopausal patients less than 40 years, with cyclic mastalgia were divided into two groups. One group was administrated with 40 mg *V. agnus-castus* fruit extract one tablet every day and another group with flurbiprofen 200 mg twice a day for 3 months. In order to reduce cyclic mastalgia, *V. agnus-castus* and flurbiprofen were observed. [45]

Fertility disorders

A 3-month placebo-controlled, double-blind study in 93 females with female fertility tries to conceive for 6-36 months after administration of Fertility Blend® (*V. agnus-castus* extract) and showed relief in their fertility parameters as compared to placebo group. The mean mid-luteal progesterone become dependent on treatment and considerably increased, and the number of days in which the luteal-phase basal temperatures increase than 98°F elevated and both short (<27 days pretreatment) and long cycles (>32 days pretreatment) showed improvement in the Fertility Blend® group. No remarkable changes in these parameters were shown by the placebo group. 14 women out of the 53 observed to be pregnant (26%) after 3 months. [46] Another study in which an investigation on fecal sample collection of monkeys which eat leaves and fruits of *V. agnus-castus* was conducted on 2011. Analyses for fecal progestin and estrogen metabolites was done by collecting fecal samples from ten monkeys and physical conditions was considered as a measure of energetic status. The results reported that fecal progestin levels increase in all female monkeys, and during that level, the female monkeys showed longer cycle lengths and follicular phases. Therefore, this study depicted the predicted effects of *V. agnus-castus* on endocrine and reproductive activities and also increased progestin levels on female reproduction system. [47]

Antimicrobial activity

The essential oil of *V. agnus-castus* seeds has antimicrobial property on Salmonella enteritidis, Staphylococcus aureus, Bacillus subtilis, and Pseudomonas aeruginosa, in a disc diffusion method. The most sensitive bacteria out of all was Staphylococcus aureus and the

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most important chemical element of the essential oil was caryophyllene oxide. [48] Again, another study was designed to check the antimicrobial activity of essential oil present in fruits of *V. agnus-castus* using the disc diffusion method. The zone of inhibition was observed, but it was less effective as compared to ampicillin and ofloxacin and the most susceptible and sensitive organism was Enterococcus faecalis. [49] The antifungal activity of the essential oils extracted from different parts of the plant like leaves, fruits, and flowers is sensitive toward dermatophyte strains like Trichophyton mentagrophytes, Microsporum canis, Trichophyton rubrum, Microsporum gypseum, and Epidermophyton floccosum and the study was determined by calculating the minimal inhibitory concentration and the minimal lethal concentration. The result was observed that the essential oils extracted from the leaf of *V. agnus-castus* possessed the highest antifungal activity. [50] Compared to standard antimicrobial compounds, such as ampicillin and penicillin, the methanolic extract of *V. agnus-castus* leaves showed antifungal activity against Candida albicans. [51]

Insect repellent activity

A study performed to investigate seventy extracts of *V. agnus-castus* for their efficacy in repelling blood-sucking insects attacks. Carbon dioxide extracts from animals and humans show at least 6 hours of insect repellent behaviour against Ixodes ricinus and Rhipicephalus sanguineus. [52] Additionally, biting flies, mosquitoes, and fleas were also repelled for about 6 hours. Licatack® (*V. agnus-castus* seeds extract) a preventive spray which contains paramenthan-3,8-diol possessed repellency on head lice (Pediculus humanus capitis) on hair of children for at least 7 hours. [53] The essential oil of leaves of *V. agnus-castus* possessed larvicidal activity due to rising larval and pupal duration, larval mortality, adult malformation and diminishing adult emergence, fecundity, and egg fertility, when the higher amounts of oils were applied topically on the mesothoracic dorsal side. [20] Trans-β-caryophyllene, the main component of essential oil had exhibited larvicidal activity on late third to early fourth Culex pipiens larvae. [54]

Antioxidant activity

Flavonoids are one of the chemical compounds present in *V. agnus-castus* which exhibit antioxidant and radical scavenging activity.[55] Phenolic content of the extracts possessed antioxidant property. [51, 55] In a study of 2, 2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) ethanol, n-hexane and water extracts of leaves and fruits of the *V. agnus-castus* had revealed antioxidant activity due to flavonoid and tannin content, performed by decolorization of the radical monocation. The water and ethanol extracts possessed higher antioxidant activity as compared to n-hexane extracts. [56] The flavonoids component like vitexin, casticin, and orientin present in *V. agnus-castus* fruits ethyl acetate extract had an antioxidant effect. It was revealed that only casticin resulted a lipid peroxidation inhibition in an in vitro 1,1-diphenyl-2-picrylhydrasyl (DPPH)-free radical study and the auto-oxidation of a standard rat brain homogenate. [57] In another study, a cell-based contemporary assay, several secondary metabolites isolated from methanol extract of *V. agnus-castus* aerial parts were analyzed for lipoxygenase inhibition. Two components, Casticin and Artemetin had a

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strong inhibitory potential for lipoxygenase. [27] *V. agnus-castus* methanolic extract of leaves showed great antioxidant activity in different antioxidant tests, like ferric-chelating, scavenging activity of hydrogen peroxide, and cupric-reducing antioxidant capacity. [51]

Cytotoxic effect

The n-hexane and methanol extracts of *V. agnus-castus* fruit exhibit chemopreventive effect in chemoprevention assessment of nicotinamide adenine dinucleotide phosphate: quinone oxidoreductase type 1 induction effect and cytotoxicity against Madin-Darby Bovine Kidney (MDBK) adherent cells. Vitetrifolin D and vitexlactam C were revealed to be responsible for this property. [16] The ethanol extract of fruits and the major component of flavonoids which is casticin possessed cytotoxicity against colon carcinoma (COLO 201), breast carcinoma (SKOV-3), ovarian cancer (MCF-7), cervical carcinoma (SKG-3a), gastric signet ring carcinoma (KATO-III), human embryo fibroblast (HE-21), human uterine cervical canal fibroblast, colon carcinoma (COLO 201), small cell lung carcinoma (Lu-134-A-H), human gastric signet ring carcinoma cell line, KATO-III, and tumor cells HL-60. [58, 59, 60] *Vitex agnus-castus* extracts cytotoxicity effect may be recognised as having an effect on cell death through apoptosis due to flavonoids, which may increase intracellular oxidation and damage to the mitochondrial membrane. [61, 62] The hydroethanolic extract of *Vitex agnus-castus* fruits reported antitumor and antiproliferative effect against prostate cell lines due to inhibitory effect on the proliferation of all the three cell lines in a concentration-related method. [63]

Effects on fracture healing

One study, in a double-blind, randomized, placebo-controlled trial, 64 women suffering from long bone fracture were administrated with one Agnugol tablet (4 mg dried fruit extract of *V. agnus-castus*) with 250 mg magnesium oxide (n = 10), one Agnugol tablet with placebo (n = 15), placebo with 250 mg magnesium oxide (n = 12), or placebo with placebo (n = 14) per day for 8 weeks. The results reported that co-administration of magnesium and *V. agnus-castus* extract (Agnugol tablet) could enhance the fracture healing. [64] Moreover, in an in-vivo study, rabbits having right tibia fracture were divided randomly into two groups. The ethanolic extract of *V. agnus-castus* fruits was administrated in both groups. The results revealed that flavonoids could successfully improve the early periods of fracture healing mechanism in New Zealand White rabbits, but there was no statistical difference in both the groups. [65] Another in vivo research was investigated on orchidectomized rats and is divided into five groups. Testosterone, estradiol, soy-free food, and *V. agnus-castus* (70% ethanol, 30% H2O extract) were administrated for 12 weeks. *V. agnus-castus* enhance the bone biomechanical stability as compared with non-treated osteopenic rat bone. [66]

Dosage, toxicity, adverse effect, and drug interaction

Dosage and toxicity

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The German Commission E suggested 30-40 mg of dried fruit extract daily, 2.6-4.2 mg of dry native extract which is standardized to 0.6% casticin, or 40 drops of tincture. [5] It has also been recommended 3-6 g daily of dried herb and 1 g/day of dried fruit could be taken daily for the treatment of menstrual disorders. [67] After treatment with the essential oil of V. agnus-castus leaves, it was observed that there was no animal death even at the highest dose of 5000 mg/kg after 2 days from administration. Hence, the LD50 of this essential oil in mice exceeded the highest dose of 5 g/kg. [18]

Adverse effects

V. agnus-castus shows adverse effect which are mild and reversible. [68, 69, 70] The most common adverse effects are nausea, intermenstrual bleeding or menstrual disorders, headache, gastrointestinal problem, weight gain, acne, dizziness, and allergic reactions. [68, 69] Side effects are very rare and happens only in 1-2% of all patients treated and may include itching, dry mouth, rash, hair loss, fatigue, agitation, tachycardia, and increased menstrual flow. [7]

Drug interaction

There are no significant drug interactions reported by systematic reviews. Moreover, *V. agnus-castus* could interfere with dopaminergic antagonists such as bromocriptine and metoclopramide. [68,69] Additionally, use of antipsychotic drugs is contraindicated and it is suggested to be carefully with oral contraceptives and through hormone replacement therapy based on its theoretical action on ERs. [67, 68] Clinical trials have also reported the various contraindication like mild skin reactions, including itching, rash, eczema, urticaria and minor skin eruptions.

Pregnancy and lactation

V. agnus-castus is contraindicated during pregnancy [5, 68, 69, 71]. The safety of *V. agnus-castus* during pregnancy is unknown until human studies have been conducted. Moreover, the prescription of any medicine containing *V. agnus-castus* extracts by complementary and alternative medicine, gynaecologists, midwifery, and medical practitioners for pregnant and lactating mothers should be done carefully, particularly when the patient is planning for pregnancy. There are no reports in the scientific researches or any study revealing that compounds of chaste tree transfer into breast milk, but it is better to be cautious and not to be used during lactation because of the possibility of hormonal effects through breast milk. [5, 69]

Conclusion

Nowadays, the complementary and alternative medicine approaches are widely used by women with premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD). The effectiveness of this particular plant is shown in different studies and researches with different categories including treatment of PMS and menstruation disorders and menopausal problems, and also possessing antioxidant, and cytotoxicity, antimicrobial, antifungal, insect

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repellent, fracture healing, antinociceptive, opioidergic, and antiepileptic, preventing non-alcoholic fat liver disease, oxidative stress, and anti-inflammatory activities etc. However, the beneficial efficacy of V. agnus-castus in the treatment of the various problems of the menstrual cycle, PMS, and mastalgia has been proven by German health authorities due to its significant effects on hormones. The use of V. agnus-castus is contraindicated during pregnancy and lactation, so it should be taken very cautiously. Based on studies and researches, it can be concluded that V. agnus-castus could interfere with medications that are dopamine antagonists.

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