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Pharmacological and therapeutic effects of *Vitex agnus-castus* L.: A review

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Vitex agnus-castus L., known as the chaste tree, is a small deciduous tree which its fruits have been used for more than 2500 years in ancient Egypt, Greece, Iran, and Rome for a variety of gynecologic problems. It has also been used for its claimed activity in the reduction of libido. The German health authorities have approved the use of *V. agnus-castus* for menstrual cycle irregularities, premenstrual syndrome, mastalgia, and menopausal disorders. The German Commission E recommended 30-40 mg/day of extract of dried fruit which is standardized based on 0.6% casticin. Scientific studies confirmed several pharmaceutical effects of this medicinal plant including antioxidant, chemopreventive, immunomodulatory and cytotoxicity, tumoricidal, antimutagenic, antimicrobial, antifungal, insect repellent, larvicidal, fracture healing, osteopenic, antinociceptive, opioidergic, antiepileptic, preventing nonalcoholic fat liver disease and oxidative stress, and anti-inflammatory activities. Adverse effects following by application of this plant are mild and reversible. There are no drug interactions recognized by systematic reviews. Theoretically, chaste tree could interfere with dopaminergic antagonists. In addition, the application of *V. agnus-castus* is contraindicated (or should be avoided) during pregnancy due to theoretical opinions and cellular studies that exhibited progesteron and estrogenic properties of the plant. This study provides the documentation for scientists to use the properties of *V. agnus-castus* as an effective herbal medicine and its safety and acceptable dosage are discussed. Advanced preclinical and clinical investigations for sufficiently assessing the safety and therapeutic efficacy of *V. agnus-castus* are recommended.

Introduction

Morphology

Vitex agnus-castus, belongs to the family Verbenaceae, under the common names of chaste tree and monk's pepper,[1],[2],[3] which could be found in the environments placed in Central Asia, Mediterranean region, and Southern Europe and also harvested in the various regions.[2],[3] It is a small deciduous tree or large shrub which could grow on an average of 1.5 m to 2 m tall. The diameter of leaves is 7.6-10 cm and the leaves are finger like containing 5-7 finger-like leaflets [Figure 1]. They are aromatic with gray-green color on and the lighter underside.[1],[2] The flowers are in clusters, violet to blue to deep purple, fragrant, bloom from summer until early fall, and the fruits are purple-blackberry that carries four seeds similar to black pepper.[1],[2],[4] This plant is considered a herbal product since the fruit berry and the dried leaves have been used for medicinal aims.[4] The medical part of the *V. agnus-castus* is the fruit.[5],[6]{Figure 1}

Traditional uses

In Latin, *V. agnus-castus* tree is also named 'chaste lamb,' which is because of decreasing the sexual desire after drinking a beverage produced from the *V. agnus-castus* seeds.[5] The fruits have been applied for more than 2500 years in ancient Egypt, Greece, Iran, and Rome for a variety of gynecologic problems. It has also been used for its claimed activity for reduction of libido.[7]

In traditional Persian medicine, the leaves and fruits of *V. agnus-castus* are proper candidates to be used in foods, as flavor and spice, and the berries as a replacement for pepper.[8],[9] The fruit has been recommended as a hormone-like remedy for alleviating menstrual disorders and as antiepileptic, carminative, energizer, sedative, anticonvulsant, tranquilizer, and for treating digestive disorders.[9],[10],[11] Based on ethnomedicine of different nations, this plant is used for relieving menstrual pain, eye diseases, spasmodic dysmenorrhea, insufficient lactation, treatment of acne, snakebites and scorpion sting, stomachache, and also as antispasmodic, anaphrodisiac, and emmenagogue agent.[12],[13]

Complementary medicine

Nowadays, *V. agnus-castus* is used more than any plant in complementary and alternative medicine for premenstrual syndrome (PMS) in the USA.[14] European Medicines Agency and German health authorities approved the beneficial effect of *V. agnus-castus* on regulating the menstrual cycle and treating the PMS and mastalgia.[5],[6] In Europe and North America, it is also known as a proper alternative for pharmaceutical products in treating other different disorders such as acne, digestive complaints, infertility, and also is used for lactation support.[1]

Phytochemical compounds

The fruits of *V. agnus-castus* possess a wide range of chemical ingredients including essential oils, flavonoids, iridoid glycosides, and diterpenoids such as agnuside, isoflavonoids, and phenolic compounds.[4],[8],[15],[16]

The main active components of this plant are flavonoids which contain casticin, apigenin, vitexin, isovitexin, luteolin, orientin, isoorientin, santin, 6-methyl-7-caffeoyloxyorientin, and its methyl 5-O-demethyltangeretin,[5] 8-14-labdadiene-6,7,13-triol-6,7-diacetate, viteagnusins A-J viteagnuside A, and vitexlactams A-C are among diterpenoid ingredients of the plant. In addition, the isoflavonoid vitexcarpan as well as the phenolic compounds agnucastoid C, agnuside, p-hydroxybenzoic acid and p-hydroxybenzoic acid glucose ester,[8],[16] and linoleic acid has been isolated and identified in the fruits.[3] the possible estrogenic component which is recognized as an estrogen receptor ligand due to its selective affinity, molecular weight, and retention time; an in vitro study showed that linoleic acid could bind to estrogen receptors (ERs) and induce certain estrogen-inducible genes.[17] The important constituents of the *V. agnus-castus* essential oil are 1,8-cineole, sabinene, α -pinene, α -terpinyl acetate, and (Z)-[β]-farnesene.[18] The reference constituents used for the standardization of natural preparation of *V. agnus-castus* are agnuside, aucubin, casticin, and vitexilactone [Table 1].[1],[18],[19]{Table 1}

Methods

Scientific literatures were searched for medicinal and pharmacological effects of *V. agnus-castus*. In order to review literature, databases including Scopus, PubMed, Web of Science, and Google Scholar were investigated to carefully study the published articles, dealing with the biological and pharmacological activities, the possible interaction and of herb, and toxicity of this plant. Data were collected from 2000 to 2016 (up to Des). The search terms included: *Vitex agnus-castus* or *V. agnus-castus*, chaste tree, chaste berries, *Fructus agni casti*, and the main chemical compounds casticin, vitexin, and agnoside. There was no language restriction. Two independent researchers categorized and monitored the results obtained from primary searches. In order to further investigate the mentioned topics, the reference lists of all the reviewed studies were also examined carefully. The gathered results were categorized into three categories: in vitro, in vivo, and human studies, and were discussed separately in the current article. In this review article, the major pharmacological effects of *V. agnus-castus* were collected.

Pharmacological effects of *Vitex agnus-castus*

The main application of *V. agnus-castus* is the treatment of PMS or menstruation disorders and menopausal problems, which is based on its hormonal effects; other effects of this plant include antioxidant, chemopreventive, immunomodulatory and cytotoxicity, tumoricidal, antimutagenic, antimicrobial, antifungal, insect repellent, larvicidal, fracture healing, osteopenic, antinociceptive, opioidergic, antiepileptic, preventing nonalcoholic fat liver disease and oxidative stress as well as anti-inflammatory activities.

[Table 2] presents the pharmacological effects of *V. agnus-castus* and its chemical constituents based on in vivo and in vitro studies and [Table 3] illustrates the clinical studies investigating the efficaciousness of *V. agnus-castus* in different diseases.{Table 2}{Table 3}

Hormonal effects

The methanolic extract of fruits has shown significant ERs- α and ER- β binding and stimulation effects of the expression of progesterone receptor and presenilin-2 mRNA, an estrogen-inducible gene, in Ishikawa endometrial cancer cell line.[17],[23] The main component responsible for these activities is linoleic acid.[17] The same result was achieved in a ligand-binding assay which was conducted to investigate the effect of flavonoids isolated from 68% ethanol extract of fruits *V. agnus-castus*, including apigenin, vitexin, and penduletin on binding to the ER isoforms ER- α or ER- β . It was found that apigenin is the most active ER- β -selective phytoestrogen in the plant. The results indicated that the phytoestrogens in this plant are ER- β -selective.[22] The estrogenic activity of ethanolic extract of fruits was investigated by the vaginal smear and uterine weight methods in normal and ovariectomized female rats. Remarkable increase in the uterine weight, plasma progesterone, and total estrogen levels and decrease in luteinizing and plasma prolactin hormones of ovariectomized rats were shown compared with the control group.[21] In an in vivo study with 24 ovariectomized female rats, animals were divided randomly into four groups, including placebo, two groups received 8 and 80 mg/kg ethanolic extract of *V. agnus-castus* fruits (orally), and the last group was treated with 40 μ g/kg of estradiol valerate to assess learning and memory and the hippocampal ER- α expression by step-through passive avoidance test and real-time polymerase chain reaction, respectively. The *V. agnus-castus* and estradiol groups enhanced learning and memory in ovariectomized rats than that in the control group ($P < 0.05$). It could be related to an increase in ER- α gene expression in the hippocampal formation by *V. agnus-castus* extract.[24]

Effects on premenstrual syndrome and dysmenorrhea

An open-label, multicenter trial with 1634 patients who faced PMS investigated the effect of Femicur (a dried extract of *V. agnus-castus*) on the four symptoms associated with PMS, including depressive symptoms, anxiety, craving, and hyperhydration in three

menstrual periods. Nearly 93% of patients reported a reduction in the number of PMS symptoms and 94% of them could achieve the good or very good tolerance of *V. agnus-castus* remedy.[52] The efficacy of 20 mg *V. agnus-castus* extract (Ze 440) on PMS-related symptoms has been approved in a prospective, multicenter trial conducted on fifty patients suffering from PMS for three menstrual cycles in 2000. Thirteen patients received associated oral contraceptives. At the end of the study, PMS-related symptoms were diminished (42.5%) of the Moos' Menstrual Distress Questionnaire as the vital affecting parameter ($P < 0.001$). There were no differences between patients with or without oral contraceptives.[53] This study was repeated in the form of prospective randomized double-blind placebo-controlled study with 178 women aged 18 years or older with PMS. The results exhibited remarkable improvement, more than 50% decrease, in the combined symptom score ($P < 0.001$) in the patients who were administered with *V. agnus-castus* (20 mg tablet once daily). In five symptoms including irritability, mood alteration, anger, headache, and breast fullness, this plant showed more efficacy than placebo ($P < 0.01$).[54] Relieving the common symptoms of PMS by *V. agnus-castus* has been shown in a randomized double-blinded placebo-controlled study involving 170 women, while some of them taken the oral contraceptive pills. They received *V. agnus-castus* (fruit extract) one tablet (20 mg) daily or matching placebo for three menstrual cycles. There was a remarkable improvement in symptoms such as headache, irritability, mood changes, and breast symptoms in women in the *V. agnus-castus* group. The authors indicated that the improvement in mastalgia was more significant in the *V. agnus-castus* group in comparison to the placebo group (52% vs. 24%).[69]

In a 3-month randomized controlled trial on 127 women with PMS, capsules with 3.5 mg of *V. agnus-castus* extract (Agnolyt [R]) were compared with Vitamin B6 (100 mg twice a day). The Agnolyt [R] and Vitamin B₆ groups both had similar reductions in PMS scores. Almost 77% versus 66% in the *V. agnus-castus* and Vitamin B6 groups, respectively, revealed improvements in PMS symptoms.[5] Forty-one patients with premenstrual dysphoric disorder (PMDD) and ages of 24 and 45 years were randomly grouped into fluoxetine or *V. agnus-castus* group, both groups received 20-40 mg/day for 2 months in a single-blind, rater-blinded, and prospective treatment period. This study revealed that both *V. agnus-castus* and fluoxetine treatments are efficacious and successfully close to the intended responses for patients with PMDD. Although fluoxetine exhibited more ability to overcome psychological symptoms, the Vitex extract could decrease the physical symptoms.[60] The efficacy of *V. agnus-castus* on moderate-to-severe PMS was studied in a prospective, open, noncomparative, monocenter trial with 120 patients who received Agnucaston [R] tablet (40 mg herbal drug) orally once daily for three cycles. The severity of the PMS symptoms had shown reduction during treatment, with the mean decrease of 12.6 score points ($P < 0.0001$) consistently. It was found that 67.8% of the women during the third treatment had responded.[61] In another clinical study, late-perimenopausal women took *V. agnus-castus* (extract of dry fruit 1000 mg/day) and *Hypericum perforatum* extract (5400 mg dry herb flowering top) or placebo tablet twice daily for 16 weeks to evaluate the improvement of PMS-like symptoms. This double-blind, randomized, placebo-controlled, parallel trial showed that the herbal formulation has beneficial effect in managing PMS in terms of PMS-like scores, significantly compared with control group. The treatment group also showed notable reductions in the anxiety, depression, cravings, and hydration on Abraham's Menstrual Symptoms Questionnaire.[62] In a three cycles' prospective, double-blind, placebo-controlled, parallel-group, multicenter clinical trial of 217 women treated with one tablet daily containing a standardized form of *V. agnus-castus* ethanolic extract (40 mg) or matching placebo, chaste tree was an effective, safe, and well-tolerated treatment for the moderate-to-severe PMS.[70] Moreover, a prospective, randomized, double-blind, placebo-controlled study of 67 patients randomly assigned to treatment group receiving film-coated tablets, including 4.0 mg of dried ethanolic (70%) extract of *V. agnus-castus* or placebo group for three cycles, found that all the specific symptoms improved significantly greater with *V. agnus-castus* than placebo, mainly in the symptoms of negative effect and insomnia ($P < 0.05$) in the treatment of PMS except lower abdominal cramping ($P > 0.05$).[55] Similar results were reported in a study of 134 women suffered from PMS who took the plant extract (40 drops administrated for 6 days before menstruation) for six consecutive cycles. In this randomized, placebo-controlled, double-blind study, active and placebo groups showed a significant difference before and after the study ($P < 0.0001$) for the relief of mild and moderate PMS.[56] In a multicenter, double-blind, placebo-controlled, parallel-group study, 162 female patients with PMS (18-45 years) were divided into either placebo or different doses of Ze 440 (*V. agnus-castus* fruit extract) 8, 20, and 30 mg for three menstrual cycles. Results were observed with the single PMS symptom scores. The total symptom score improved for the 20-mg group, remarkably higher than those for the placebo and 8-mg group. In addition, the higher dose of 30 mg did not significantly reduce symptom severity compared with the 20 mg treatment. Thus, the daily intake of 20 mg extract could have favored patients with PMS.[57] In an open-label, clinical observation study, efficacy of the herb was noted in the treatment of headache in 107 migrainous women who used *V. agnus-castus* for PMS symptoms for 3 months. The results with respect to migraine showed that the recurrence of monthly attacks decreased up to 50% in 42% of the patients and also up to 50% decrease in monthly days with headache was observed in 57% of the patients. In fact, the use of this herb in migrainous women affected by PMS resulted to be safe and well tolerated, and could positively affect the frequency and duration of migraine attacks.[71] Another study determined that 20 mg of chaste tree extract, once daily (Prefemin [R]) for three menstrual cycles, provided successful effect on PMS symptoms, by significant decrease in total Visual Analog Scale (VAS) score ($P < 0.001$) with no substantial adverse events.[58] The effectiveness of *V. agnus-castus* on menstrual cycle irregularities (MCIs), such as polymenorrhea, oligomenorrhea, or amenorrhea, was observed in an observational study. A total of 211 patients with MCIs and menstrual bleeding were administrated daily with 20 mg of the plant extract (Ze 440) for three consequent menstrual periods. Improvement of symptoms related to menstrual bleeding such as dysmenorrhea and pre- or postmenstrual bleeding was in the range of 60%-88% and improvement of MCIs and specific symptoms such as polymenorrhea, oligomenorrhea, and amenorrhea was in the range of 79%-85%. This study showed that treatment with *V. agnus-castus* extract significantly alleviated MCIs and was well tolerated.[72] Another investigation checked the effect of *V. agnus-castus* on PMS in the form of double-blinded study with 72 female students with PMS who received randomly Vitagnus [R] oral drop as 40 drops daily or placebo for three menstrual cycles. In this study, mean scoring of total physical and psychological symptoms and duration of PMS had shown significant difference between two groups ($P < 0.001$, $P < 0.05$, and $P < 0.01$, respectively).[59] The plant capsule was compared with mefenamic acid capsule for its efficacy on intrauterine device (IUD)-induced bleeding in a double-blinded, randomized controlled clinical trial on 84 women with IUD who were randomly allocated into two groups of 42 treated with mefenamic acid (250 mg) and 42 with *V. agnus-castus* capsules taking three times a day during menstruation. Both had significantly decreased bleeding, this decrease at 4th month was 52% in the mefenamic acid group and 47.6% in the *V. agnus-castus* group. However, mefenamic acid was more effective.[65] A prospective comparative Doppler study of sixty women with severe primary dysmenorrhea and thirty healthy women (control) was designed for three menstrual cycles. Thirty patients were treated with ethinyl estradiol 0.03 mg/drospirenone 3 mg (Yasmin) (Group 1) and another

thirty were treated with *V. agnus-castus* (Agnucaston [R] tablet 4 mg) (Group 2) once a day. After three menstrual cycles, VAS scores significantly fell in both groups compared to before treatment ($P < 0.0001$ for both); although there were no significant differences between Groups 1 and 2.[66]

Effects on menopause

Two subsequent studies were designed in 2000 and 2002 to investigate the *V. agnus-castus* essential oils' (derived from the leaf and fruit of the plant, separately) effect on menopausal symptoms. In the first study, oils were administered to 23 women through different routes (oral, transdermal, and inhalation). Five menopausal symptoms (urogenital, vasomotor, mood dysfunction, uterine bleeding, and sleep) improved in these women. A return to regular menstruation after 3-10 months of amenorrhea was reported in several women, and another one was reported after 6 years. The second one revised the details with 52 pre- or postmenopausal women who applied a 1.5% solution of the essential oil of *V. agnus-castus* aerial parts in the form of base cream or lotion. Nearly 33% of patients announced major improvement and 36% reported mild-to-moderate improvement in troublesome symptoms. The most significant improvements were observed in the emotional symptoms, night sweats, hot flushes, and moderation of menstruation.[63] Combination of *V. agnus-castus* and *H. perforatum* in the management of menopausal symptoms was assessed in a double-blinded, randomized, placebo-controlled, parallel trial with 100 eligible late-pre- or postmenopausal women, having hot flushes and other menopausal symptoms, for 16 weeks. A combination of *V. agnus-castus* and *H. perforatum* tablets (containing extract equivalent to 500 mg of dry fruit and 300 mg extract, respectively) was given daily. The combination of this order of daily dosages was found remarkably effective and could be satisfactorily tolerated; however, there was no difference to placebo for menopausal symptoms.[64]

Effects on mastalgia

In a study, a group of women suffering from cyclic mastalgia (Group 1, 40 women) and a second group suffering from mild hyperprolactinemia (Group 2, 40 women) were investigated for the efficacy of *V. agnus-castus* in the treatment of these two symptoms, and the results were compared to those for bromocriptine (dopamine agonist) therapy. In each group, the patients were subjected randomly to a repetitive 3-month administration of either bromocriptine (2.5 mg twice daily) or *V. agnus-castus* (40 mg daily). Prolactin levels decreased significantly in both groups after treatment ($P < 0.0001$ for both), but no adverse effect was observed for *V. agnus-castus* within this period, while 12.5% of the bromocriptine-treated patients experienced nausea and vomiting. Therefore, this plant acts similarly to bromocriptine concerning the reduction of serum prolactin and reducing breast pain; besides, it offers more patient compliance and no adverse effects.[73] In a randomized, double-blind study, 104 premenopausal patients younger than 40 years, suffering from cyclic mastalgia, were divided into two groups, respectively, with 40 mg of fruit extract as 1 tablet daily and flurbiprofen 200 mg/day in two portions for 3 months. Both of these medications markedly diminished the complaints and had acceptable side effects. The results did not exhibit a statistically notable difference between these two treated groups ($P = 0.945$).[67]

Effects on fertility disorders

V. agnus-castus is a main component of an herbal formulation, Fertility Blend [R]. In a 3-month double-blind, placebo-controlled study on female fertility in 93 women who had experienced unsuccessful tries to conceive for 6-36 months, Fertility Blend [R] showed significant improvement in their fertility parameters compared to placebo group. The mean mid-luteal progesterone was found dependent on treatment and significantly increased, and simultaneously the number of days in which the luteal-phase basal temperatures were higher than 98[degrees]F elevated and both short (<27 days pretreatment) and long cycles (>32 days pretreatment) normalized in the Fertility Blend [R] group. The placebo group did not show any remarkable changes in these parameters. Fourteen women of the 53 in the Fertility Blend [R] group were pregnant (26%) after 3 months, compared to four of the forty women in the placebo group (10%).[74] An investigation on fecal sample collection of monkeys which eat leaves and fruits of *V. agnus-castus* was performed on 2011. Analyses for fecal progesterin and estrogen metabolites were made through collecting fecal samples of ten monkeys and physical conditions were used as a measure of energetic status. The results exhibited that fecal progesterin levels elevated in all females, and during the time of high progesterin, females showed longer cycle lengths and follicular phases. This study indicated the predicted effects of chaste berry on endocrine and reproductive activities and also increased progesterin levels on female reproduction system. The high progesterin period was associated with a significant elevation in the chance of conception.[20]

Antimicrobial activity

The essential oil of the seeds showed antimicrobial activity on *Salmonella enteritidis*, *Staphylococcus aureus*, *Bacillus subtilis*, and *Pseudomonas aeruginosa*, in a disc diffusion method. *S. aureus* was the most sensitive one and caryophyllene oxide was recognized as the most important constituent of the essential oil.[10] Another study was designed to test the antimicrobial activity of essential oil of fruits using the disc diffusion method. The susceptibility of inhibition zone was observed obviously, but it was found to be less effective in comparison with ampicillin and ofloxacin. The most susceptible organism was *Enterococcus faecalis* .[27]

The antifungal activity of the essential oils extracted from different parts of the plant (leaves, fruits, and flowers) toward dermatophyte strains (*Trichophyton mentagrophytes*, *Microsporum canis*, *Trichophyton rubrum*, *Microsporum gypseum*, and *Epidermophyton floccosum*) was determined by calculating the minimal inhibitory concentration and the minimal lethal concentration. It was observed that the essential oils extracted from the leaf possessed the highest antifungal activity.[28] The methanolic extract of *V. agnus-castus* leaves exhibited noticeable antifungal activity against *Candida albicans* when compared with standard antimicrobial compounds, such as ampicillin and penicillin.[26]

Insect repellent activity

In a study performed to investigate seventy plant extracts for their potential to repel the attacks of blood-sucking insects, carbon dioxide extract of *V. agnus-castus* possessed insect repellent activity, especially against *Ixodes ricinus* and *Rhipicephalus sanguineus* ticks from animals and humans for at least 6 h. Moreover, mosquitoes, biting flies, and fleas were also repelled for about 6 h.[31] Licatack [R], a preventive spray which contains extract of the *V. agnus-castus* seeds and paramenthan-3,8-diol, was determined for repellency on head lice on hair of children. It protects human hair for at least 7 h from the attack of head lice, *Pediculus humanus capitis*. [32] The essential oil of leaves had shown larvicidal activity due to increasing larval and pupal duration, larval mortality, adult deformity and decreasing adult emergence, fecundity, and egg fertility, when the higher amounts of oils were topically administrated on the dorsal side of mesothoracic region.[13] The essential oil had revealed larvicidal activity on late third to early fourth *Culex pipiens* larvae and the main component of the essential oil was trans-[sz]-caryophyllene.[29] The ethanolic extract of leaves had exhibited toxicity against third instar larvae of *Musca domestica*. [30]

Antioxidant activity

Flavonoids are one of the major groups in *V. agnus-castus* chemical compounds which possess the antioxidant and radical scavenging properties.[35] There is a positive relation between the antioxidant property and the phenolic content of the extracts.[26], [35] In a study carried out on decolorization of the radical monocation of 2,2,8,8-tetrazolyl-5-aminobis-(3-ethylbenzothiazoline-6-sulfonic acid) ethanol, n-hexane and water extracts of leaves and fruits of the plant had revealed antioxidant activity due to their flavonoid and tannin content, although the water and ethanol extracts possessed the higher antioxidant activity in comparison with the n-hexane extracts.[34] In the ethyl acetate extract of fruits, the antioxidant effect of the flavonoid components of the extract, vitexin, casticin, and orientin, was evaluated. It was observed that only the casticin resulted a significant lipid peroxidation inhibition in an in vitro 1,1-diphenyl-2-picrylhydrazyl (DPPH)-free radical assay and toward the auto-oxidation of a standard rat brain homogenate.[33] In DPPH, b-carotene, linoleic acid, and reducing power assays, the essential oil of the fruit and also water, hexane, dichloromethane, ethyl acetate, and methanol extract of the fruit have shown antioxidant activity in all systems; water extract possessed the most highest activity potential in comparison with the other mentioned extracts. Flavonoids were recognized to have the main role in antioxidant effect of the plant.[35] In a cell-based contemporary assay, several secondary metabolites isolated from methanol extract of aerial parts of *V. agnus-castus* were analyzed for lipoxygenase inhibition. Artemetin and casticin showed a potent lipoxygenase inhibitory potential.[51] The methanolic extract of *V. agnus-castus* leaves exhibited great antioxidant activity in different antioxidant tests, including ferric-chelating, scavenging activity of hydrogen peroxide, and cupric-reducing antioxidant capacity.[26] In an assay of scavenging effect on NO, DPPH radical, H₂O₂, and ferrous metal ions, the hexane, acetone, and methanol extracts of *V. agnus-castus* fruit showed antioxidant activity and the active constituent was casticin.[3] The crude extract and butanolic fraction of fruits prevented nonalcoholic fat liver disease and oxidative stress, frequent causes of abnormal liver functions in postmenopausal women, in an in vivo assay of ovariectomized rats. The results showed reinstatement of activities of some antioxidant enzymes and reduction in the mitochondrial hydrogen peroxide production in animals treated with the extract.[47]

Cytotoxic effect

The n-hexane and methanol extracts of the fruit had shown chemopreventive potential in chemoprevention evaluation of nicotinamide adenine dinucleotide phosphate: quinone oxidoreductase type 1 induction activity and cytotoxicity against Madin-Darby Bovine Kidney (MDBK) adherent cells. Two compounds, vitetrolin D and vitexlactam C, were recognized to be responsible for this property.[8] The ethanol extract of fruits [37],[38],[39],[40],[41] and flavonoids [39] or its major component, casticin,[40],[41] showed cytotoxicity against colon carcinoma (COLO 201),[37],[39] gastric signet ring carcinoma (KATO-III), human uterine cervical canal fibroblast, ovarian cancer (MCF-7), breast carcinoma (SKOV-3), human embryo fibroblast (HE-21), cervical carcinoma (SKG-3a), colon carcinoma (COLO 201), small cell lung carcinoma (Lu-134-A-H),[37] human gastric signet ring carcinoma cell line, KATO-III, [38] and tumor cells HL-60.[41] The cytotoxicity of Vitex extract may be regarded to the effect on cell death through apoptosis,[37], [38],[39],[40],[41] which could be attributed to increased intracellular oxidation [37],[38] and mitochondrial membrane damage by Vitex extract due to its flavonoid content.[38] The hydroethanolic extract of fruits had antitumor and antiproliferative activities against prostate cell lines due to inhibitory effect on the proliferation of all the three cell lines in a concentration-related method. According to the results of DNA fragmentation and cell cycle analysis, a portion of the cells encountered apoptosis.[43] Phagocyte chemiluminescence assay, neutrophil chemotaxis assay, and T-cell proliferation assay of the ethanolic extract of the plant powder exhibited strong activity against malignant spontaneous tumor Neuro-2a cells.[42] In another study on the methanolic extract obtained from aerial parts and the main constituent, casticin, the inhibition activity could be observed on monocyte oxidative burst in a dose-related method. This study revealed the suppressive potency on the chemotoxic function at higher concentrations on stimulated neutrophils. It had also shown a strong suppressive activity on the phytohemagglutinin-stimulated T-cell (PMBC) and was toxic against the MDBK cell line.[36] Vitexin 6, a flavonoid of *V. agnus-castus*, had also shown cytotoxicity toward 14 different tumor cell lines in an in vitro 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide assay. It caused induction of apoptosis in cancerous cell lines and autophagy for the cases with a time- and concentration-dependent relationship. The vitexin 6-treated cells exhibited a gradual improvement in the Beclin-1 and LC3-II levels and the cell autophagy indicators.[12] The essential oil of the leaves and the ethanolic extract of the seeds had revealed antimutagenic effects on *Salmonella typhimurium* in microsome mutagenicity tests. This research found that the essential oil was shown to have more antimutagenic activity than the ethanolic extract and it was dose dependent.[44]

Effects on fracture healing

In a double-blind, randomized, placebo-controlled trial, a group of 64 women with long bone fracture were administrated with (1) one Agnugol tablet (4 mg dried fruit extract of *V. agnus-castus*) plus 250 mg magnesium oxide (n = 10), (2) one Agnugol tablet plus placebo (n = 15), (3) placebo plus 250 mg magnesium oxide (n = 12), or (4) placebo plus placebo (n = 14) per day for 8 weeks. The results demonstrated that co-administration of magnesium and *V. agnus-castus* could enhance the fracture healing.[68] In an in vivo study, rabbits with right tibia fracture were divided into two groups randomly. The ethanolic extract of fruits, Group 1 and Group 2, was chosen as control. It seems that flavonoids could successfully enhance the early periods of fracture healing mechanism in New

Zealand White rabbits, but no significant statistical difference between both was observed.[45] Another in vivo research was accomplished on orchidectomized rats divided into five groups. The groups were administrated with testosterone, estradiol, soy-free food, and *V. agnus-castus* (70% ethanol, 30% H₂O extract) for 12 weeks. *V. agnus-castus* caused improvement of the bone biomechanical stability in comparison with nontreated osteopenic rat bone. Its efficacy is not as distinguishing as that of estradiol, but it could have fewer side effects than a hormone replacement therapy with estradiol, especially when it is considered for use in patients.[46]

Other effects

In an in vivo study, a model of middle cerebral artery occlusion was investigated in ovariectomized mice. The stroke was induced after 1 month treatment with ethanolic extract of the *V. agnus-castus* fruits. The results showed Vitex extracts and estrogen (in form of estradiol valerate) can decrease infarct volume ($P < 0.05$) and neurological deficits, compared to the control group ($P < 0.001$). The study revealed that Vitex extracts, similar to estrogen have neuroprotective effects, following middle cerebral artery occlusion in ovariectomized mice.[25]

Preventing nonalcoholic fat liver disease by the crude extract and butanolic fraction of fruits had been shown through an in vivo assay of ovariectomized rats. The plant extract caused reinstatement of activities of some antioxidant enzymes and reduction in the mitochondrial hydrogen peroxide production in animals.[47]

In a cell-based contemporary assay, ten isolated constituents of methanol extract obtained from aerial parts of the plant were studied for anti-inflammatory activity and lipoxygenase inhibition. The results showed that methyl 3,4-dihydroxybenzoate, p-hydroxybenzoic acid, and 3,4-dihydroxybenzoic acid exhibited significant anti-inflammatory activity.[51] Anti-inflammatory potency of casticin was observed in an in vivo study. Six mice were exposed to cigarette smoke or fresh air for 2 weeks and treated with 1, 2, and 10 mg/kg casticin through an intraperitoneal injection, and then cytokine productions and immune cell infiltrations were evaluated using bronchoalveolar lavage fluid (BALF), and lung histological analysis was accomplished. Casticin had inhibited the numbers of macrophages, neutrophils, and lymphocytes; decreased the levels of pro-inflammatory cytokines and chemokines in the BALF; and diminished the infiltration of peribronchial and perivascular inflammatory cells and the epithelium thickness.[50]

The essential oil of leaves exhibited antinociceptive activity in tail immersion, formalin, and acetic acid-induced visceral pain in rats. The study suggested that endogenous opioidergic system and also muscarinergic receptors of cholinergic system could be involved in the antinociceptive property of *V. agnus-castus* essential oil in these models of pain in rats.[11]

V. agnus-castus had also shown opioidergic potential in a receptor binding assay, mu and delta opioid receptors. Casticin, a flavonoid isolated from methanolic extract, exhibited selective agonist activity for delta opioid receptor at high concentrations.[18] Similar results had been found in the methanolic extract of fruits in receptor and GTPaS binding assay which exhibited agonistic activity at the Mu-opiate receptor. This property may support the plant efficacy in PMS.[48]

The hydrophilic extract of fruit in a kindling model of epilepsy in rats had indicated antiepileptic effect. Reduction or prevention of epileptic activity was revealed by decreasing ADD and S5D (length of convulsion) in a dose-dependent manner.[49]

Dosage, toxicity, adverse effect, and drug interaction

Dosage and toxicity

The German Commission E recommended 30-40 mg of dried fruit extract daily, 2.6-4.2 mg of dry native extract (standardized to 0.6% casticin), or 40 drops of tincture.[1] It has been also suggested that 3-6 g daily of dried herb and 1 g/day of dried fruit could be taken daily for menstruation disorders.[75] After treatment with the essential oil of *V. agnus-castus* leaves, no animal death was observed even at the highest dose (5000 mg/kg) after 2 days from administration. Therefore the LD₅₀ of this essential oil in mice exceeded the highest dose of 5 g/kg.[11]

Adverse effects

Adverse effects followed by application of this plant are mild and reversible.[76],[77],[78] The most recurrent adverse events are nausea, intermenstrual bleeding or menstrual disorders, headache, gastrointestinal disturbances, weight gain, acne, dizziness, and allergic reactions.[76],[77]

Drug interaction

There are no drug interactions recognized or reported by systematic reviews.[76],[77],[79] Theoretically, chaste tree could interfere with dopaminergic antagonists such as bromocriptine and metoclopramide.[76],[77] In addition, simultaneous use of antipsychotic drugs is contraindicated,[76] and it is recommended to apply carefully with oral contraceptives and through hormone replacement therapy based on its theoretical action on ERs.[75],[76] It was observed that *V. agnus-castus* extract inhibited CYPs 1A2, 2C19, 2D6, and 3A4, although the effects on CYPs 2C19 and 3A4 were specially potent based on in vivo studies. Thus, the concomitant use with drugs which are metabolized by these enzymes could be influenced by this herbal dosage forms.[77]

Pregnancy and lactation

The application of *V. agnus-castus* is contraindicated (or should be avoided) during pregnancy [1],[76],[77],[79] due to theoretical opinions and in vitro studies that exhibited estrogenic and progesteronic properties of the plant.[76] In fact, the safety of the plant

during pregnancy is unclear until human studies have been regulated; consequently, the prescription of any drug containing *V. agnus-castus* by complementary and alternative medicine, gynecologists, midwifery, and medical practitioners for women of childbearing age should be done particularly when the patient is planning for pregnancy.[1],[76] There are no reports in the scientific researches showing that compounds of chaste tree transfer into breast milk,[76] but it is better not to be used during lactation because of the possibility of hormonal effects through breast milk.[1] Although the low toxicity and tolerability of *V. agnus-castus* make it unlikely to be toxic for the newborn, based on its phytoestrogenic and phytoprogestogenic properties, more human researches and clinical trials are required to investigate what constituents can cross the placenta into the fetus and also into breast milk; until then, it should be used with caution, especially when prescribing for women of childbearing age.[76]

Conclusion

The complementary 'natural' approaches for prevention and treatment of diseases possess a significant time-proven history of safe and efficacious administration.[80],[81],[82],[83] Nowadays, the effectiveness of this plant is shown in different studies including treatment of PMS and menstruation disorders and menopausal problems, and also possessing hormonal properties, antioxidant, chemopreventive, immunomodulatory and cytotoxicity, tumoricidal, antimutagenic, antimicrobial, antifungal, insect repellent, larvicidal, fracture healing, osteopenic, antinociceptive, opioidergic, antiepileptic, preventing nonalcoholic fat liver disease, oxidative stress, and anti-inflammatory activities. However, the beneficial efficacy of *V. agnus-castus* in the treatment of the irregularities 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* should be contraindicated during pregnancy and lactation. Based on studies and theories, it can be concluded that *V. agnus-castus* could interfere with medications that are dopamine antagonists.[5]

Finally, the current review provides the documentation for other researchers to use the properties of *V. agnus-castus* as an effective herbal drug, and its safety and acceptable dosage were discussed. Further preclinical and clinical studies for sufficient evaluation of the safety and therapeutic efficacy of *V. agnus-castus* are recommended.

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Conflicts of interest

There are no conflicts of interest.

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