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REVIEW

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A comprehensive review on ethnobotany, phytochemistry, traditional and modern uses of chasteberry (*Vitex agnus-castus* L.)

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Abstract

Vitex agnus-castus L. (chaste tree) has a rich history of use in traditional medicine across various cultures for over 2500 years, particularly for gynecological issues. Its applications range from regulating menstrual cycles to alleviating premenstrual syndrome and menopausal symptoms, with endorsements from health authorities such as the German Commission E. This review aims to consolidate existing knowledge on the ethnopharmacological uses, phytochemistry, and pharmacological effects of *V. agnus-castus*, while also discussing its safety profile and therapeutic potential. The relevant articles were identified by searching PubMed (www.pubmed.com), Scopus (http://www.scopus.com), ISI Web of Science (www.webofknowledge.com), and Google Scholar (www.scholar.google.com) up to November 2024. *V. agnus-castus* exhibits a wide range of pharmacological properties, including antioxidant, anti-inflammatory, antimicrobial, and cytotoxic effects. Its active compounds, particularly casticin, have been linked to these benefits. Future research should focus on advanced preclinical and clinical studies to better assess its safety and therapeutic efficacy in diverse populations.

Keywords Casticin, Chaste tree, Traditional uses, Pharmacological effects, *Vitex agnus-castus*

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Background

Chasteberry, also known scientifically as *Vitex agnus-castus* L., belongs to the family Lamiaceae [1]. It is a flowering plant used for its pharmaceutical applications in both traditional and modern medicine. The plant is more commonly known as "Monk's pepper." [2]. In fact, chasteberry has been used in various cultures for several centuries, although its main applications are pharmacological in nature and pertain to women's health. Ethnobotanical studies have reported its use in alleviating symptoms of premenstrual syndrome (PMS), menstrual irregularities, and discomforts associated with menopause, thereby signifying its importance in the traditional herbal system of medicine [3].

The active phytochemicals in chasteberry are rich and diverse, including essential oils, flavonoids, iridoids, phenolic acids, diterpene alkaloids, and terpenes [4]. According to a number of preclinical and clinical studies, most of them have dopaminergic, opioid, estrogenic, immunomodulatory, anti-neoplastic, and antioxidant activities. Therefore, these active principles have been reported in the literature to show dopaminergic action and modulate the levels of prolactin and hence are being used in cases of mastalgia and infertility. This unique biochemical profile underpins its traditional uses and also offers a basis for modern pharmacological applications [4].

Today, chasteberry is strongly perceived in contemporary settings as a possible herbal alternative to synthetic medication in the treatment of gynecological disorders [5, 6]. A rising interest in herbal remedies has instigated an influx of clinical studies validating efficacy and safety. It is thus at the very intersection of ethnobotany and modern phytotherapy, with a rich history while promising avenues for the future course of research and applications in women's health [7]. This survey of chasteberry encompasses its ethnobotanical significance, phytochemical properties, and both traditional and contemporary uses, underscoring its multifaceted role in health and wellness.

Botany, ethnobotany, authentication profile, and taxonomy

Botany

Chasteberry, or *V. agnus-castus* L., is a deciduous shrub that reaches heights of 1 to 3 m. This plant belongs to the family Lamiaceae and is differentiated by its palmately compound leaves with venation that is pinnate, with prominent midribs [3]. The upper leaf epidermis is covered by a cuticle, which bears non-glandular hairs on its surface [8], along with clusters of fragrant lilac-colored flowers.

Flowers are fragrant, hermaphroditic, and borne in terminal panicles up to 12 inches, with lavender to purple corollas, two stamens, and superior ovaries; they are very attractive to butterflies and other pollinators; fruits are small, globose, dark purple drupes (about 0.2 inches diameter) containing four hard, one-seeded pyrenes with thin endocarps and oily endosperm rich in iridoid glycosides and flavonoids [1, 3, 9]. Flowering occurs from June to October, with fruits ripening in October and November. The mature fruits persist on the tree through December and January [10]. Chasteberry grows best in sunny, well-drained positions. The panicle inflorescence attracts pollinators, giving rise to drupe fruits with single seeds. The stems of the plant are quadrangular, bearing non-glandular hairs, while the leaves bear a single-layered hypodermis beneath the epidermis [8]. It is widely distributed wild throughout the Mediterranean region of Southern Europe (Greece, Italy, and Spain), North Africa, Western Asia (Turkey), and the Caucasus. In Russia, it grows on the coasts of the Caucasus Black Sea and in the wild in Crimea. Russian cultivation of chasteberry is restricted to the North Caucasus region; its fruits are a raw material for the manufacture of dietary supplements. Nowadays, chasteberry also grows on the East, South, and West Coasts of the USA, as well as in northeastern India, Afghanistan, Pakistan, and Iran [4, 9]

Chasteberry can be distinguished from *V. negundo* by its 5–7 grayish-aromatic leaflets with entire to dentate margins that are serrate in *V. negundo*; paniculate lavender flower spikes (*vs*. more herbaceous stems); *V. negundo* shows higher leaflet serration variability and growth habit [11]. Also, it can be distinguished from *V. trifolia* through palmately 5–7 (rarely 3) foliolate leaves and taller stature (vs. consistently 3-foliolate leaves and smaller); corolla ridge pubescence and ovary glabrescence [11].

Ethnobotany

Chasteberry has an ethnobotanical history, particularly in feminine care. Because of its medicinal value, the plant has been conventionally used across cultures in managing symptoms related to menstrual and reproductive health. Traditionally, chasteberry has been used by ancient civilizations such as the Greeks and Romans, who recognized its potential in regularizing menstrual cycles and managing symptoms of menopause. Sometimes referred to as "Monk's pepper," the herb reflected a use by monks in attempting to suppress libido and ensure chastity. Ethnobotanical studies have shown that Indigenous communities have used this plant for many centuries, if not longer, in treating a wide range of illnesses, everything from PMS and infertility to even digestive problems. The leaves and fruits are also used in Iranian traditional medicine to increase the milk production [12]. During the Thesmophoria festival, Athenian women employed the plant's

foul-smelling leaves by scattering them over their bed linen as a means of preserving their chastity [13]. Traditional herbalists and practitioners in Europe and North America have long supported the use of chaste tree not only for gynecological disorders—including menstrual irregularities, infertility, and premenstrual syndrome—but also for managing acne, digestive issues, and as a sedative [13, 14].

Also, traditional European herbalism uses it very often as a women's reproductive tonic. In modern herbal practice, it is used very often in combination with other herbs in formulations destined to balance hormonal equilibrium and symptoms of PMS. The plant has been considered important in the past and hence a staple in traditional medicine systems [3].

The plant's medicinal history is longstanding: Hippocrates prescribed chaste tree for inflammation and injuries before the Common Era, and four centuries later, Pedanius Dioscorides documented its use for promoting lactation and alleviating womb inflammation [15]. In the medieval period, Arabian, Salerno, and Anglo-Saxon healers employed *V. agnus-castus* L. to treat psychological ailments. The plant's fruit was also commercialized, sold in Arabian bazaars as a sedative for hysteria [15]. Traditional applications further include creating antidotes for venomous bites from snakes and spiders. Additionally, in specific regions such as Loralai, Bori, and Barkhan across India and Pakistan, a common remedy for pain due to chills involves therapeutic baths using water boiled with the plant's leaves [16].

Authentication profile

Authentication of chasteberry is important to ensure the quality and efficacy of herbal products. It also points to the concern that some health foods may be different from the official standard, or the contents of active compounds may vary, or the products are manufactured by unauthorized methods. Authentication could be performed by morphological identification based on botanical features and by chemical profiling using phytochemical analysis. Examples include the assessment of HPLC fingerprints and marker compound ratios, which can be an excellent method for assessing the quality of chasteberry preparations. The method by Fukahori et al. (2014) can be a potential tool in assessing the quality of chasteberry products through comparisons against established standards in HPLC profiles, marker compounds, and amounts. The present study assessed the quality of chasteberry preparations based on HPLC fingerprint analysis. Seven medicinal products from Japan and six from Europe and 17 health foods (6 from Japan and 11 from the USA) were analyzed. Medicinal products showed a very similar profile by HPLC, though health foods showed a variety of profiles with large peak differences. The contents of agnuside and casticin in traditional medicinal products were very low compared to those in well-established medicinal products. Those healthy foods are scattered. Some health foods showed a higher ratio of agnuside to casticin, which resembles that of *Vitex negundo* L., a related Chinese herb [17]. In addition, the composition and biological activity of some essential oils from chasteberry were studied, and the major constituents identified included 1,8-cineole, among others, responsible for the pharmacological action. For this purpose, techniques like GC–MS are normally used to confirm authenticity and purity in chasteberry extracts [18]. On the other hand, to explain the genetic relationships among various genotypes of *V. agnus-castus*, Sevindik et al. (2019) conducted a genetic diversity study of *V. agnus-castus* populations in Aydin Province, Turkey, using RAPD markers. Genomic DNA was isolated from the leaves with the help of a commercial kit, and seven RAPD primers were used in the investigation of genetic diversity. The DNA samples were subjected to PCR with the respective primers, and the amplification products were resolved on an agarose gel. The banding patterns were recorded, and matrix files with 36 characters from the primers were obtained. Phylogenetic relationships and genetic distances were obtained by the PAUP* program. The populations showed a variable extent of genetic relatedness. The phylogenetic tree constructed using UPGMA algorithms displayed four distinct groups [19].

Taxonomy

Taxonomically, *V. agnus-castus* belongs to the Lamiaceae family. Its classification can be broken down as follows [20]:

Kingdom: Plantae
Subkingdom: Viridiplantae
Superdivision:Embryophyta
Division: Tracheophyta
Subdivision: Spermatophytina
Class: Magnoliopsida
Order:Lamiales
Family: Lamiaceae
Genus: Vitex L.
Species: *Vitex agnus-castus* L.

V. agnus-castus currently belongs to the family Lamiaceae, although previously it had been placed under the family Verbenaceae. Through the previous decades, many controversies have emerged regarding the Lamiaceae and Verbenaceae families on how the restructuring of the classification should be done. The reevaluation was afterward supported by Li et al. (2016), who used molecular

markers obtained from conserved regions of chloroplasts across various species representing subfamilies. These studies led to the transfer of a substantial number of genera within the Verbenaceae family into various subfamilies in the Lamiaceae, most notably the subfamily Viticoideae, with *Vitex* being its largest genus. However, within the circumscription of the subfamilies, it was assessed that Viticoideae was probably the worst, and a synthesis of evidence from morphology, phytochemistry, and molecules demonstrated beyond doubt that it is paraphyletic or maybe even polyphyletic in origin [21]. In addition, there has been speculation about the existence of another chaste tree species in India known as *Vitex pseudonegundo*. Despite their differences in geographical distribution, morphology, anatomy, and levels of bioactive compounds, particularly essential oil components, modern taxonomy considers these species as synonyms of *V. agnus-castus* [4].

Phytochemistry

The genus *V. agnus-castus* L. (Chasteberry) has been thoroughly investigated for its chemical contents belonging to several chemical classes. The primary phytochemicals are represented as flavonoids, iridoids, and diterpenoids along with volatile constituents and miscellaneous compounds (Fig. 1). Out of the reported compounds, the main active components of this plant are iridoids such as agnuside and aucubin (Table 1), and also the major constituents are flavonoids as luteolin, apigenin, and isovitexin (Table 2). Moreover, vitexilactone, viteagnuside A, and viteagnusin I are among the diterpenoid ingredients of the plant (Table 3), as well as the phenolic acids (Table 4). Different parts of the plant compromise volatile constituents, as represented in (Table 5) In addition, miscellaneous compounds comprise triterpenoids and chalcone (Table 6).

Structures of the major identified compounds are illustrated as follows: iridoids (Fig. 2), flavonoids and phenolics (Fig. 3), and diterpenoids (Fig. 4).

Traditional uses and ethnopharmacology

Chasteberry, Monk's pepper, also known as *V. agnus-castus* L., has been valuable for medicine for more than 2500 years. Usage references date back to ancient Egypt, Greece, and Rome, where it was thought as a gynecological remedy, libido suppressor, and antidote to bites and stings. Hippocrates, in 400 BCE, recommended it in cases of inflammation and injuries [39]. Dioscorides was also mentioned four hundred years later for increasing lactation and reducing inflammation of the uterus [6]. Chasteberry was widely used by medieval European monks as an anaphrodisiac to promote celibacy, where they would include it in their diet or carry dried berries around in their robes [39]. In ancient Athens, during the

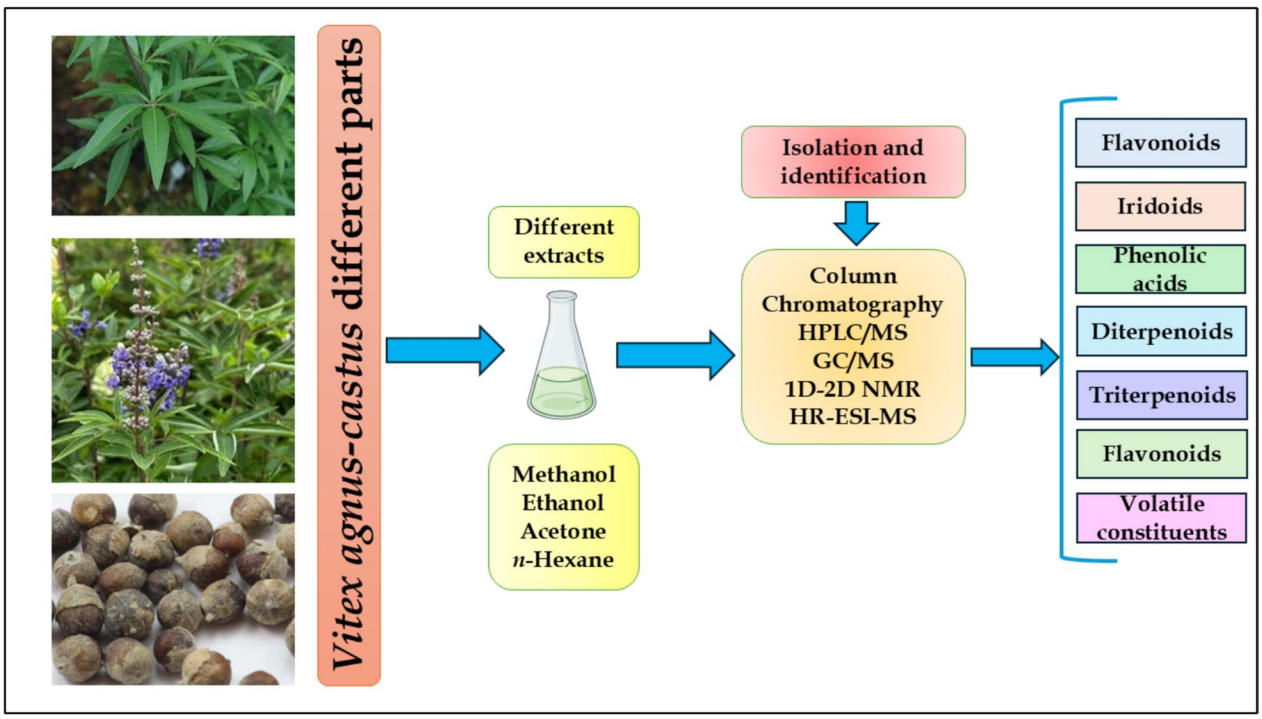


Fig. 1 Schematic representation for the major identified phytochemicals from *Vitex agnus-castus* L.

Table 1 List of iridoids reported from *Vitex agnus-castus* L.

Compound name	Plant part	Extract	Method of isolation or identification	References
Agnuside	Fruits and fruitless aerial parts	Ethanol extract	LC/ESI-MS-MS	[22]
	Flowering stems	Methanol extract	Column chromatography–1D and 2D NMR spectroscopic data analysis and MS	[23]
Agnuside	Flowers	Methanol extract	Column chromatography–1D and 2D NMR spectroscopic data analysis and HR-ESI-MS	[24]
2-*O*-*p*-Hydroxybenzoyl-8-epiloganic acid	Fruits and fruitless aerial parts	Ethanol extract	LC/ESI-MS-MS	[22]
Aucubin	Flowering stems	Methanol extract	Column chromatography–1D and 2D NMR spectroscopic data analysis and MS data	[23]
	Fruit	*n*-Hexane extract	Column chromatography–1D and 2D NMR spectroscopic data analysis and MS data	[25]
Angucastoside A	Flowering stems	Methanol extract	Column chromatography–1D and 2D NMR spectroscopic data analysis and MS data	[23]
Angucastoside B	Flowering stems	Methanol extract	Column chromatography–1D and 2D NMR spectroscopic data analysis and MS data	[23]
Angucastoside C	Flowering stems	Methanol extract	Column chromatography–1D and 2D NMR spectroscopic data analysis and MS data	[23]
6′-O-(6,7-dihydrofoliamenthoyl)mussaenosidic acid (agnucastoside B)	Flowering stems	Methanol extract	Column chromatography–1D and 2D NMR spectroscopic data analysis and MS data	[23]
Harpagide	Leaves	Ethanol extract	Column chromatography–1D and 2D NMR spectroscopic data analysis	[26]
8-O-Acetylharpagide	Leaves	Ethanol extract	Column chromatography–1D and 2D NMR spectroscopic data analysis	[26]

Table 2 List of flavonoids reported from *Vitex agnus-castus* L.

Compound name	Plant part	Extract	Method of isolation or identification	References
Luteolin	Fruits and fruitless aerial parts	Ethanol extract	LC/ESI-MS-MS	[22]
	Stems flowers	Methanol extract	HPLC-DAD-QTOF-MS	[27]
	Seeds	Ethanol extract	LC/MS/MS	[28]
Luteolin glucuronide	Fruits and fruitless aerial parts	Ethanol extract	LC/ESI-MS-MS	[22]
Luteolin glucoside	Fruits and fruitless aerial parts	Ethanol extract	LC/ESI-MS-MS	[22]
Hesperidin	Stems flowers	Methanol extract	HPLC-DAD-QTOF-MS	[27]
Apigenin	Fruits and fruitless aerial parts	Ethanol extract	LC/ESI-MS-MS	[22]
Apigenin glucuronide	Fruits and fruitless aerial parts	Ethanol extract	LC/ESI-MS-MS	[22]
Isovitexin	Fruits and fruitless aerial parts	Ethanol extract	LC/ESI-MS-MS	[22]
Quercetin	Seeds	Ethanol extract	LC/MS/MS	[28]
3,7-Dimethylquercetin	Fruits	Methanol extract	Column chromatography–1D and 2D NMR spectroscopic data analysis and MS data	[29]
3-Methyl quercetin	Fruits	Methanol extract	Column chromatography–1D and 2D NMR spectroscopic data analysis and MS data	[29]
Naringenin	Seeds	Ethanol extract	LC/MS/MS	[28]
Kaempferol	Seeds	Ethanol extract	LC/MS/MS	[28]
3-O-Methylkaempferol	Fruits	Methanol extract	Column chromatography–1D and 2D NMR spectroscopic data analysis and MS data	[29]
Kaempferol 3-O-sophoroside	Flowers	Methanol extract	Column chromatography–1D and 2D NMR spectroscopic data analysis and HR-ESI–MS	[24]
Casticin (Vitexicarpin)	Fruits	Acetone extract	Column chromatography–1D and 2D NMR spectroscopic data analysis	[30]
Catechin hydrate	Seeds	Ethanol extract	LC/MS/MS	[28]
Resveratrol	Seeds	Ethanol extract	LC/MS/MS	[28]

Table 3 List of diterpenoids reported from *Vitex agnus-castus* L.

Compound name	Plant part	Extract	Method of isolation or identification	References
Vitexilactone	Fruits	Ethanol extract	Column chromatography–1D and 2D NMR spectroscopic data analysis	[31]
Viteagnuside A	Fruits	Acetone extract	Column chromatography–1D and 2D NMR spectroscopic data analysis	[30]
Viteagnusin I	Fruits	Methanol extract	Column chromatography–1D and 2D NMR spectroscopic data analysis and MS data	[29]
Vitexlactam A	Fruits	*n*-Hexane extract	Column chromatography–1D and 2D NMR spectroscopic data analysis and MS data	[25]
Vitexlactam B	Fruits	*n*-Hexane extract	Column chromatography–1D and 2D NMR spectroscopic data analysis and MS data	[25]
Vitexlactam C	Fruits	*n*-Hexane extract	Column chromatography–1D and 2D NMR spectroscopic data analysis and MS data	[25]
Viteagnusin I	Fruits	Acetone extract	Column chromatography–1D and 2D NMR spectroscopic data analysis	[30]
Viteagnusin J	Fruits	Acetone extract	Column chromatography–1D and 2D NMR spectroscopic data analysis	[30]
Vitetrifolin D	Fruits	Acetone extract	Column chromatography–1D and 2D NMR spectroscopic data analysis	[30]

Table 4 List of phenolic acids reported from *Vitex agnus-castus* L.

Compound name	Plant part	Extract	Method of isolation or identification	References
5-Caffeoyl quinic acid	Fruits and fruitless aerial parts	Ethanol extract	LC/ESI-MS-MS	[22]
3,4-Dicaffeoyl quinic acid	Fruits and fruitless aerial parts	Ethanol extract	LC/ESI-MS-MS	[22]
5b, 3,5-dicaffeoyl quinic acid	Fruits and fruitless aerial parts	Ethanol extract	LC/ESI-MS-MS	[22]
4,5- Dicaffeoyl quinic acid	Fruits and fruitless aerial parts	Ethanol extract	LC/ESI-MS-MS	[22]
Tri-*p*-(*E,E,E*)-coumaroyl spermidine	Fruits and fruitless aerial parts	Ethanol extract	LC/ESI-MS-MS	[22]
Chlorogenic acid	Stems Flowers	Methanol extract	HPLC-DAD-QTOF-MS	[27]
Vanillic acid	Stems Flowers	Methanol extract	HPLC-DAD-QTOF-MS	[27]
	Seeds	Ethanol extract	LC/MS/MS	[28]
3,4-dihydroxybenzoic acid	Stems Flowers	Methanol extract	HPLC-DAD-QTOF-MS	[27]
Hydroxybenzoic acids acid	Stems Flowers	Methanol extract	HPLC-DAD-QTOF-MS	[27]
	Seeds	Ethanol extract	LC/MS/MS	[28]
Caffeic acid	Seeds	Ethanol extract	LC/MS/MS	[28]
Ellagic acid	Seeds	Ethanol extract	LC/MS/MS	[28]
Castusic acid	Flowers	Methanol extract	Column chromatography–1D and 2D NMR spectroscopic data analysis and HR-ESI-MS	[24]

Thesmophoria festival, women probably used chasteberry flowers and leaves in symbolic display to maintain their chastity [40]. It was a diuretic, carminative, and sedative in traditional Turkish medicine. The plant was employed in conventional Arab, Iranian, and Albanian medicine in increasing milk production and treating psychological disorders [41]. The fruits and leaves of *V. agnus-castus* have been of importance in the traditional medicine of many cultures, especially gynecological health, including management of PMS, menstrual irregularities, hyperprolactinemia, menopausal symptoms, cyclical mastalgia, corpus luteum inadequacy, and infertility [13], also for general conditions such as acne, inflammatory disorders, diarrhea, and flatulence. It tries to manage respiratory disorders like asthma, bronchitis, and colds. Traditionally, leaves and fruits have been used in the treatment of increasing milk supply postnatal [11].

The potential medicinal uses of this plant are quite distinctive in individual countries. In a few locations in Pakistan and India, it is being utilized as an erratic medicine to relieve chills through bathing in hot water boiled with the leaves of the plant [42]. In Iranian traditional medicine, the plant's hot nature was harnessed for treating bowel flatulence and spleen diseases.

Ethnopharmacological studies validate traditional claims documented in Ibn Rushd's *Al-Kulliyat Fi A-Tibb* [43], which linked the plant to treatments for liver, spleen, and reproductive disorders [44]. Finally, rare side effects from *V. agnus-castus* are limited to sporadic incidences of gastrointestinal disturbances, headaches, or rashes. Indeed, modern use warrants surveillance, especially in subjects with hormonal sensitivities or concomitant use of other drugs [45]. Chasteberry is traditionally taken in various forms, such as oral administration as decoctions, supplements, and standardized extracts of fruit for systemic conditions. Local applications in the form of ointments or oils are used in acne treatment, bites of insects, and localized inflammation, in addition to fumigation,

Table 5 List of volatile constituents reported from *Vitex agnus-castus* L.

Compound name	Plant part	Extract	Method of isolation or identification	References
Phytol	Leaves	Ethanol extract	GC/MS	[32]
Squalene	Leaves	Methanol extract	GC/MS	[32]
1,8-Cineole	Fruits	Aqueous extract	HS-SPME-GC/MS	[33]
	Leaves	Hydrodistilled Essential oil	GC/MS	[34]
	Seeds	Hydrodistilled Essential oil	GC/MS	[35]
	Leaves	Hydrodistilled Essential oil	GC/MS	[36]
	Fruits	Hydrodistilled Essential oil	GC/MS	[36]
	Leaves	Hydrodistilled Essential oil	GC/MS	[37]
	Fruits	Hydrodistilled Essential oil	GC/MS	[38]
Germacrene D	Fruits	Aqueous extract	HS-SPME-GC/MS	[33]
β-Farnesene	Fruits	Aqueous extract	HS-SPME-GC/MS	[33]
	Leaves	Hydrodistilled Essential oil	GC/MS	[34]
	Leaves	Hydrodistilled Essential oil	GC/MS	[36]
	Fruits	Hydrodistilled Essential oil	GC/MS	[36]
	Flowers	Hydrodistilled Essential oil	GC/MS	[36]
β-Caryophyllene	Fruits	Aqueous extract	HS-SPME-GC/MS	[33]
	Leaves	Hydrodistilled Essential oil	GC/MS	[34]
	Seeds	Hydrodistilled Essential oil	GC/MS	[35]
	Flowers	Hydrodistilled Essential oil	GC/MS	[36]
Caryophyllene oxide	Leaves	Hydrodistilled Essential oil	GC/MS	[37]
Sabinene	Leaves	Hydrodistilled Essential oil	GC/MS	[34]
	Seeds	Hydrodistilled Essential oil	GC/MS	[35]
	Leaves	Hydrodistilled Essential oil	GC/MS	[37]
	Fruits	Hydrodistilled Essential oil	GC/MS	[38]
α-Terpinyl acetate	Leaves	Hydrodistilled Essential oil	GC/MS	[34]
	Leaves	Hydrodistilled Essential oil	GC/MS	[37]
α-Pinene	Seeds	Hydrodistilled Essential oil	GC/MS	[35]
	Fruits	Hydrodistilled Essential oil	GC/MS	[38]

Table 6 List of miscellaneous constituents reported from *Vitex agnus-castus* L.

Compound name	Plant part	Extract	Method of isolation or identification	References
Chalcone and Dihydrochalcone Phloridzin dehydrate	Seeds	Ethanol extract	LC/MS/MS	[28]
Butein	Seeds	Ethanol extract	LC/MS/MS	[28]
Triterpenoids 2,3-dihydroxy-12-ursen-28-oic acid	Fruits	Acetone extract	Column chromatography–1D and 2D NMR spectroscopic data analysis	[30]
2α-Hydroxyursolic acid	Fruits	Acetone extract	Column chromatography–1D and 2D NMR spectroscopic data analysis	[30]
3-epi-Maslinic acid	Fruits	Acetone extract	Column chromatography–1D and 2D NMR spectroscopic data analysis	[30]
Phenylbutanone glucoside (Myzodendrone)	Flowering stems	Methanol extract	Isolation by Column chromatography 1D-2D NMR spectra and MS data	[23]

sitz baths, and vaginal inserts for gynecological health. Figure 5 summarizes some traditional medicinal uses of chasteberry.

Pharmacological effects

For the effects of chasteberry on the body based on its hormonal actions, *V. agnus-castus* is mostly used to treat menstrual abnormalities, menopausal issues,

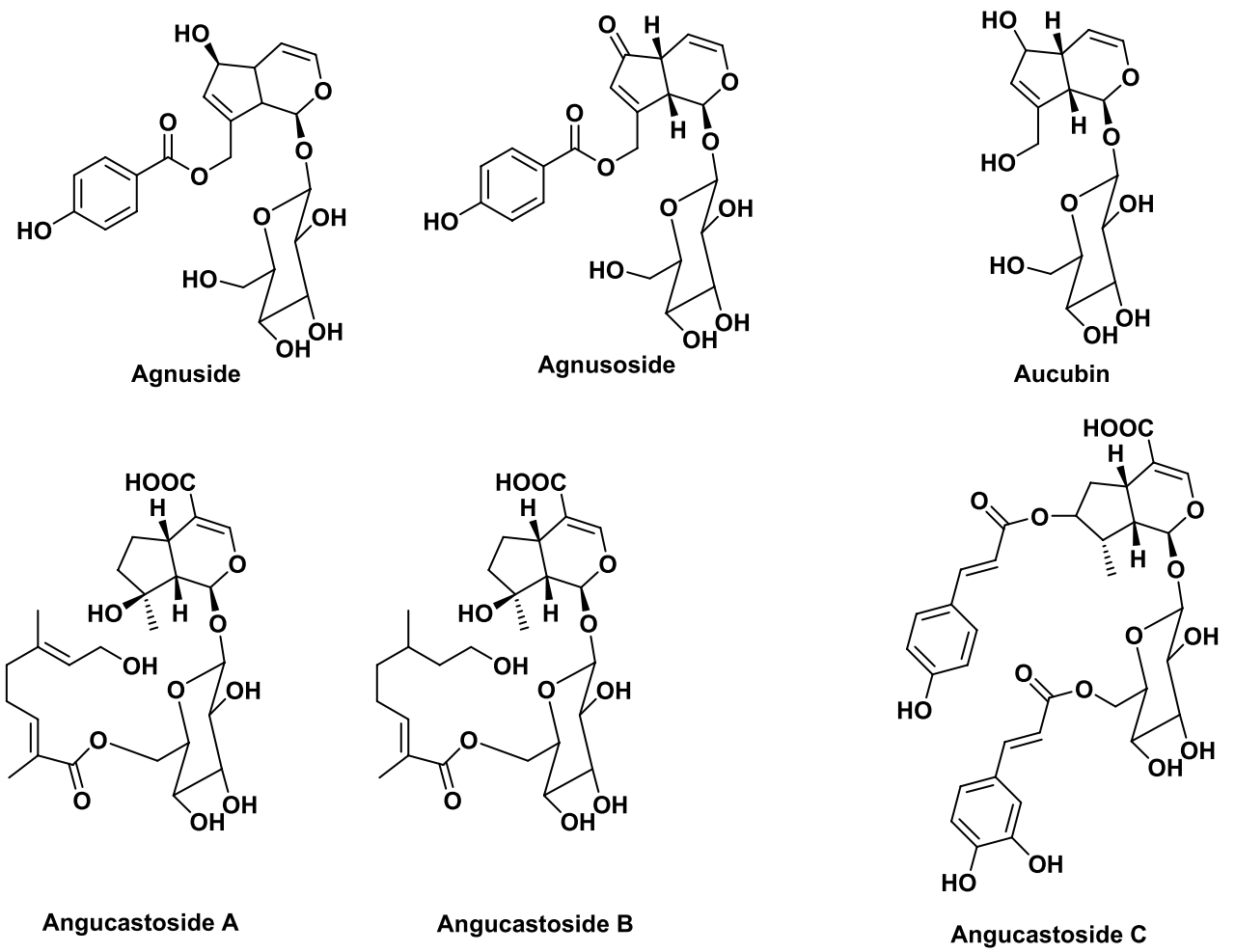


Fig. 2 Chemical structures of the major identified iridoids in *Vitex agnus-castus* L.

and premenstrual syndrome (PMS) [46]. According to Rafieian-Kopaei and Movahedi [47] and Adamov et al. [4], this plant also has anti-inflammatory, chemopreventive, immunomodulatory, cytotoxic, bone-healing, osteopenic, antinociceptive, opioidergic, antiepileptic, antimutagenic, antibacterial, antifungal, insect repellent, and larvicidal properties and prevents oxidative stress and non-alcoholic fat liver disease. Figure 6 shows the pharmacological and biological activities of chasteberry exposed in this section.

Dopaminergic effects

Chronic stress can cause a decrease in female dopamine release, which raises blood prolactin levels and contributes to the development of mastodynia and proliferative alterations in the mammary gland. Additionally, due to insufficient luteal phase, it causes infertility [48]. By stimulating pituitary gland dopaminergic receptors, chaste tree bioactive substances lower blood levels of prolactin and lessen its adverse effects. The characteristics of the chaste tree's total extract, fractions, and specific bioactive substances were discovered through in vitro tests and validated by clinical research. Rat pituitary gland cells' production of prolactin was markedly suppressed by a complete extract of chaste tree fruits, per Sliutz et al. [49]. Synthetic agonists of dopaminergic receptors had a comparable effect on these cells. Employing the radioligand technique, which measures the half-maximal binding concentration (IC_{50}), Meier et al. [50] discussed in detail how the ethanolic extract of chaste trees binds to several receptors, including opioid receptors, benzodiazepines, dopamine (D-2), histamine (H-1), and the binding site of the serotonin transporter. The findings showed that the extract's hexane fraction was more active than the extract's entire extract, which showed dopaminergic activity ($IC_{50} = 52$ µg/ml). It was also investigated whether the eluates could remove

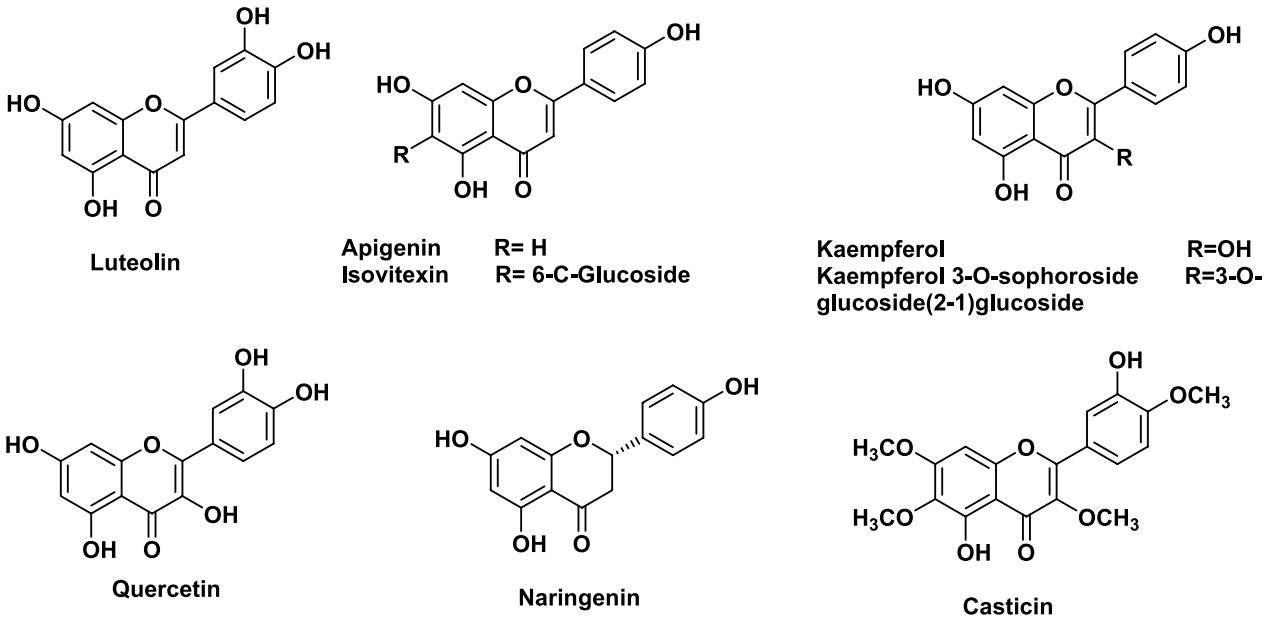


Fig. 3 Chemical structures of the major identified flavonoids in *Vitex agnus-castus* L.

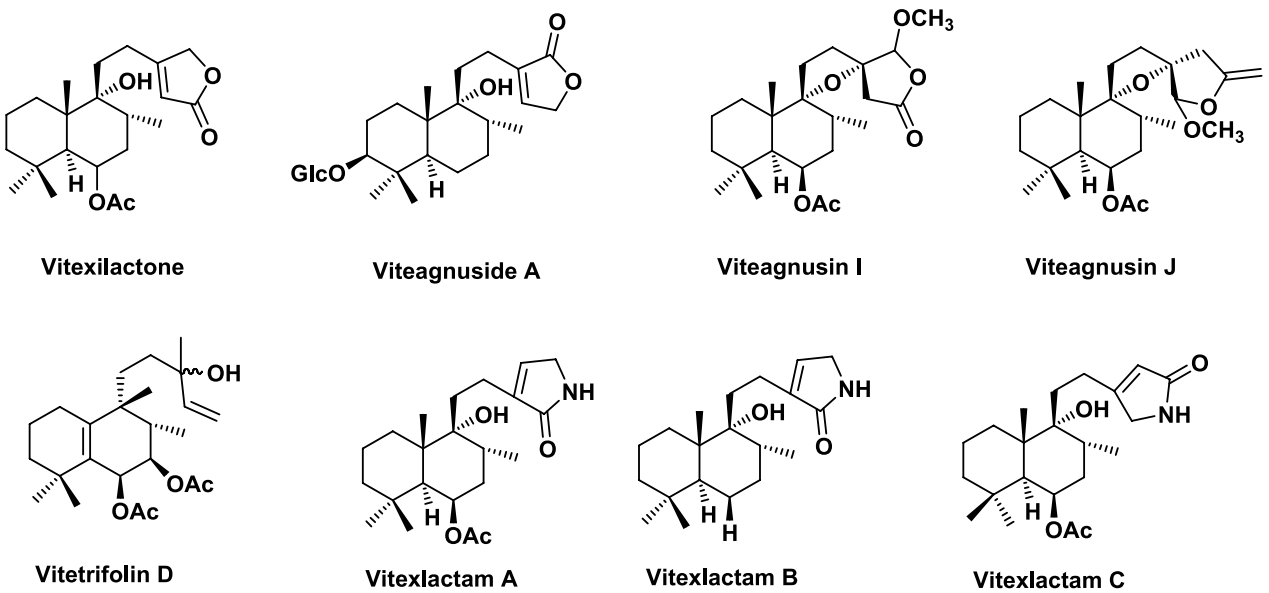


Fig. 4 Chemical structures of the major identified iridoids in *Vitex agnus-castus* L.

tagged ligands from the dopamine receptors of cultured pituitary cells in a dose-dependent manner in a study by Wuttke et al. [51], which used preparative chromatography to obtain chaste tree fractions and individual compounds. Furthermore, clerodadienol, a chaste tree component, was only slightly less effective than dopamine at preventing the pituitary cells from releasing prolactin. Understanding the mechanism of action of chaste tree extract requires in vivo investigations that evaluate its likely impact on male reproductive function. Male mouse groups were given separate intraperitoneal injections of chaste tree extract; haloperidol or bromocriptine or a mix of the three in the study by Nasri et al. [52]. Because of dopamine's regulatory activity, the injection of haloperidol raised the levels of testosterone and luteinizing hormones while

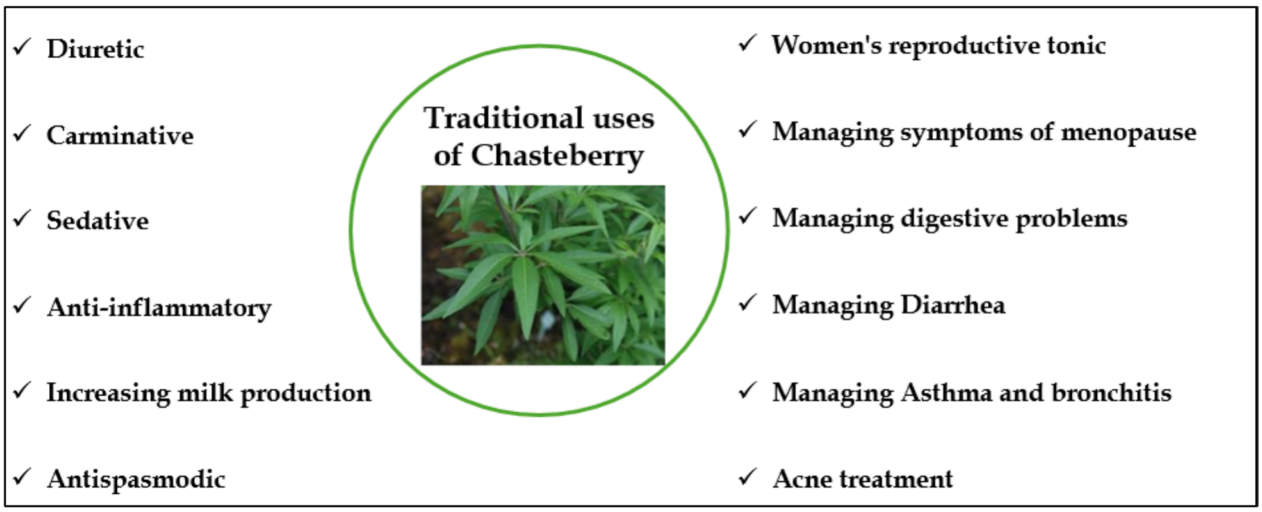


Fig. 5 A selection of major traditional medicinal uses of chasteberry

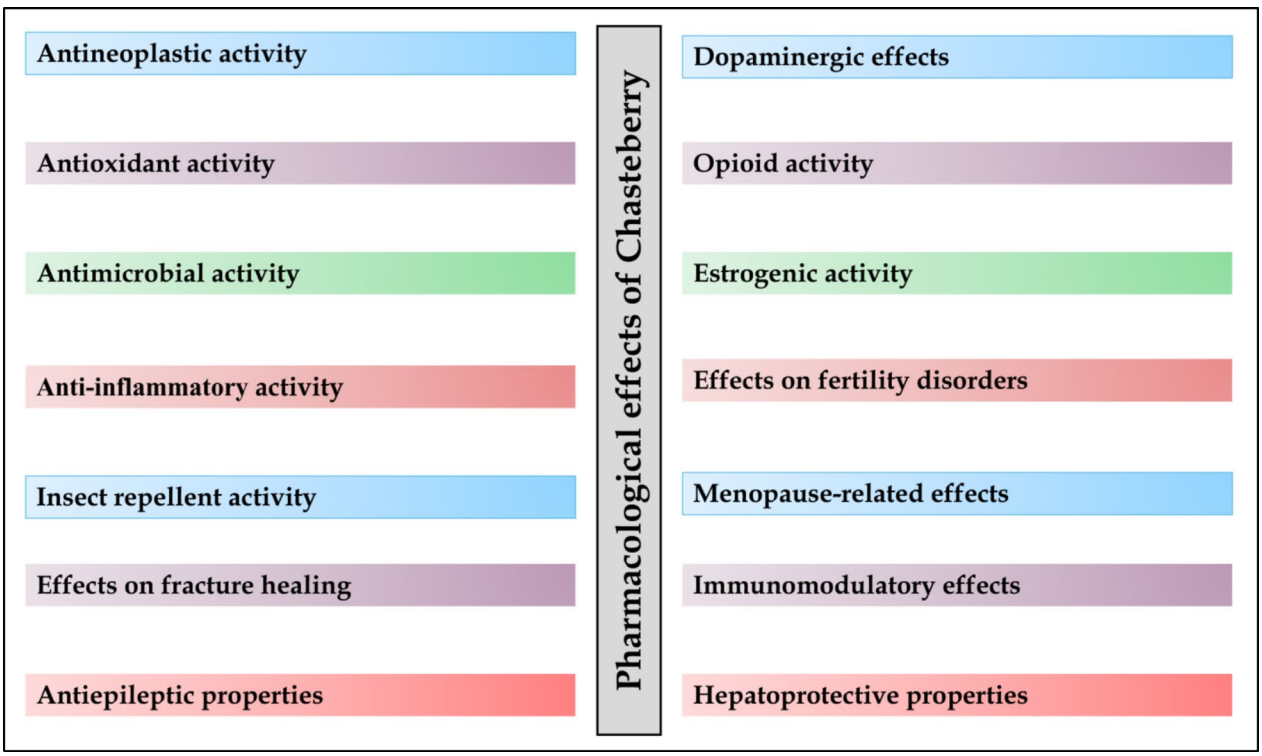


Fig. 6 Pharmacological and biological activities of chasteberry

decreasing them in all other situations. When haloperidol and chaste tree extract are administered together, the levels of the hormones under study decrease, suggesting the existence of other regulatory mechanisms unrelated to dopamine.

Opioid activity

Research has shown that the endogenous opiate system and the hypothalamic-pituitary axis are intimately connected [53]. The chaste tree's special effect on females may be explained by the physiologically active chemicals

in its fruits, which may have an impact on the opioid system [54]. According to Meier et al. [50], the μ- and κ-opioid receptors were activated by the lipophilic portions of chaste tree fruit extract with half-maximum binding concentrations (IC_{50}) of 36 and 22 μg/ml, respectively. Webster et al. [55] discovered that the flavonoid casticin contributed the most among the marker compounds of the examined raw material. Similar outcomes were seen in the guanosine 5'-O-[gamma-thio] triphosphate (GTPγS) binding assay and the methanolic fruit extract in the receptor, which demonstrated agonistic activity at the Mu opiate receptor. The effectiveness of plants in treating PMS may be supported by this characteristic [56].

Estrogenic activity

According to Jarry et al. [57], with relative IC_{50} values of 0.08, 0.25, and 10 μg/mL, apigenin, penduletin, and vitexin flavonoids found in chaste fruit exhibited estrogenic action. In contrast, the initial excerpt (marketed under the name BNO 1095) contained an inhibitor at a concentration of 10 μg/ ml, which is the point at which 50% of the response is inhibited. These substances exclusively exhibited affinity for β-estrogen receptors. The capacity of linolenic acid to enhance the β-estrogen receptor gene's expression may be the reason for the additional synergistic impact of chaste tree fruits in treating PMS, as established experimentally in Ishikawa cells by Liu et al. [58] and Souto et al. [59]. The chaste tree fruit methanolic extract was found to displace estrogen from the α- and β-estrogen receptors in the same study. The estrogenic action of chaste tree fruits has been validated by a number of indirect pharmacological investigations. Male mice with orchiectomy had their bone tissue quality tracked [60]. Positive effects were found in both investigations. Molecular docking has been used in a published study. According to the study, the estrogen receptor is highly favored by quercetin, casticin, agnuside, isovitexin, and apigenin [61]. In both ovariectomized and normal female rats, the vaginal smear and uterine weight procedures were used to examine the estrogenic activity of fruit ethanolic extract. The weight of the uterus, the levels of total estrogen and plasma progesterone, plasma prolactin, and luteinizing hormones of ovariectomized rats were decreased compared with the control ones [56]. In female mice with ovariectomies, some cognitive processes and uterine size were examined. In an in vivo study, 24 female mice with ovariectomies were randomly assigned to one of four groups: a placebo; two groups were administered oral *V. agnus-castus* fruit ethanolic extracts of at doses of 8 and 80 mg/kg; the last group received 40 μg/kg of estradiol valerate to use the passive avoidance test and a real-time polymerase chain reaction, respectively, to assess learning and memory and the expression of ER α in the hippocampus. In comparison to the control group, the ovariectomized mice's learning and memory were improved by the *V. agnus-castus* and estradiol treatment groups ($P<0.05$). Fruit extract may have increased the expression of the ER α gene in the hippocampus development [62].

Effects on fertility disorders

The primary ingredient in the herbal composition Fertility Blend® is chasteberry. Ninety-three women who had spent 6 to 36 months trying in vain to conceive participated in a placebo-controlled trial on female fertility. In a three-month double blind, Fertility Blend® significantly improved their reproductive indices when compared to the placebo group. In the Fertility Blend® group, after 32 days of therapy, days with basal temperatures exceeding 98°F during the luteal phase rose right away. The mean mid-luteal progesterone was found to be considerably enhanced and dependent on treatment. There were no discernible changes in these measures in the placebo group. Four of the 40 women in the placebo cohort (10%) were expecting a child after three months, while 14 (26%) of the 53 women in the Fertility Blend® group did so [63]. In 2011, fecal samples taken from monkeys that consume the *V. agnus-castus*'s leaves and fruits were examined. Fecal samples from 10 monkeys were collected for analyses of progestin and estrogenic metabolites, and physical condition was used to gauge the animals' energetic state. According to the findings, all females had higher fecal progestin levels, and females displayed longer follicular phases and cycle lengths when progestin levels were high. In addition to raising progestin levels in the female reproductive system, the study demonstrated the anticipated chaste berries' impact on reproductive and endocrine potentials. A considerable increase in the chance of conception was linked to the high progestin period [64].

Menopause-related effects

Two trials in 2000 and 2002 were scheduled to evaluate the effects of essential oils from *V. agnus-castus*, which are extracted from the plant's leaves and fruit, respectively, on menopausal symptoms [65]. In the initial research, 23 women received oils by inhalation, transdermal application, and oral administration. Five symptoms of menopause, urogenital, vasomotor, mood, uterine hemorrhage, and sleep, were alleviated in these women. Following three to ten months of menstruation, some women stated that they were able to resume normal menstruation, and after 6 years, another one was noted [66]. Fifty-two premenopausal or after menopause women who used a base cream containing a 1.5% solution of the essential oil of *V. agnus-castus* aerial parts

as a base cream or lotion were the subjects of the second study, which updated the specifics. About 33% of patients reported significant improvement in their problematic symptoms, while 36% reported modest to moderate improvement. The biggest benefits were shown in the areas of emotional symptoms, hot flashes, nocturnal sweats, and menstrual control [67]. For 16 weeks, the combined efficacy of *H. perforatum* and *V. agnus-castus* in treating signs of menopause was evaluated in a parallel, randomized, double-blind, placebo-controlled study including one hundred qualified postmenopausal or late premenopausal women experiencing hot flashes and other menopause symptoms. Daily doses of a mixture of *V. agnus-castus* and *H. perforatum* tablets were administered; each tablet contained 300 mg of extract and 500 mg of dried fruit extract, respectively. Although there was no difference between the combination and a placebo for menopausal symptoms, it was determined to be effective and tolerable [68].

Immunomodulatory effects

The flavonoid casticin was attributed to the immunomodulatory effect of chaste tree [5]. Experimentally, it was established that casticin considerably reduced T-lymphocyte proliferation and the monocyte chemotaxis at levels comparable to inhibition by prednisolone. Moreover, monocyte oxidative burst was significantly inhibited by casticin in a dose-dependent manner. At higher concentrations, it was discovered to significantly block the chemotaxic action on neutrophils activated by fMLP (10–8 M). Additionally, it had a strong suppressive effect on PMBCs, or PHA-stimulated T cells [69]. Similar to other vertebrates, fish have a diverse range of substances, receptors, and cells that make up their immune systems [70]. Rashmeei et al. [71] found that the amount of *V. agnus-castus* in the diet significantly increased the expression of the lysozyme gene. The majority of fish species contain the bactericidal enzyme lysozyme in their lymphoid tissues, mucus, and serum. Thus, it may be concluded that increased expression of lysozyme mRNA can strengthen the fish's innate immune system [72]. Because *V. agnus-castus* contains many bioactive chemicals, including iridoids, flavonoids, diterpenoids, and ketosteroids, a rising tendency in the expression of specific immune-related genes may be linked to its immunomodulatory [73, 74].

Antineoplastic activity

Agnuside's cytotoxic effect on some cancer cell types as well as its impact on nuclear condensation and apoptosis were validated by Arokiyaraj et al. [75] and Wang et al. [76] in vitro. However, according to Li et al. [25], vitetrifoline D demonstrated great promise as a cancer chemoprophylactic drug. In a genetic test, an alcohol-based extract of chaste tree and essential oil demonstrated potent, dose-dependent antimutagenic properties [77]. Casticin, a component of fruit ethanol extract and flavonoids, demonstrated the potential cytotoxic effect of various cancers, including lung cancer in tiny cells, cell line for gastric cancer, cervical fibroblast in the uterus, ovarian carcinoma, breast carcinoma, fibroblasts in human embryos, cervical cancer, colon cancer, and tumor cells (HL 60) [78–80]. Increased intracellular oxidation and mitochondrial membrane damage brought on by apoptosis may be the origin of Vitex extract's cytotoxic impact [81, 82]. Furthermore, in a concentration-dependent way, the hydroethanolic fruit extract prevented each of the three cell lines from proliferating, resulting in anticancer and antiproliferative properties against prostate cell lines [83]. According to Mazzio et al. [84], the plant powder's ethanolic extract demonstrated potent action against malignant spontaneous tumor Neuro 2a cells by the use of T cell proliferation, neutrophil chemotaxis, and phagocyte chemiluminescence assays. Another study found that the methanolic extract of the aerial portions and its primary component, casticin, inhibited monocyte oxidative burst in a dose-related manner. According to Saraca et al. [77], research showed that the chemotoxic effect of activated neutrophils was suppressed at greater doses.

Antioxidant activity

The fruit of *V. agnus-castus* contains flavonoids and phenolics, which have strong antioxidant and radical-scavenging qualities [73, 74, 85]. Fruit ethyl acetate extract's flavonoid constituents vitexin, casticin, and orientin, were evaluated for their antioxidant potential. In a test for 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radicals and in the direction of the autooxidation of a typical rat brain homogenate, it was shown that only casticin exhibited a strong lipid peroxidation inhibition [86]. Using a modern cell-based assay, a number of secondary metabolites that were separated from the aerial parts methanol extract of *V. agnus-castus* were examined for the suppression of lipoxygenase. According to Choudhary et al. [87], casticin and artemetin had a strong lipoxygenase inhibitory action. In several antioxidant assays, such as ferric chelating, cupric reducing antioxidant capacity, and hydrogen peroxide scavenging activity, the methanolic extract of *V. agnus-castus* leaves shown strong antioxidant potential [88]. The antioxidant activity of the active ingredient casticin obtained from *V. agnus-castus* fruit methanol, hexane and acetone extracts were demonstrated in an experiment of scavenging action on nitric oxide (NO), DPPH radical, hydrogen peroxide (H_2O_2), and ferrous metal ions [30, 89]. In an in vivo test using

ovariectomized rats, oxidative stress was avoided by the fruit's butanolic component and crude extract and liver disease caused by non-alcoholic fat, which are common causes of aberrant liver functioning in postmenopausal women. In rats given the extract, the results showed a decrease in mitochondrial hydrogen peroxide production and a restoration of several antioxidant enzyme activities [90]. The flavonoid casticin exhibited the strongest antioxidant activity, outperforming ascorbic acid by a factor of many, according to a study by Hajdú et al. [91] on the antioxidant potentials in the aqueous-alcoholic lipophilic hexane fraction of chaste tree extract bioactive components. Furthermore, an investigation into how chaste tree extract affected the oxidation of deoxyribose by iron II-mediated free radicals showed that this harm was significantly decreased by aucubin [75]. Strong antioxidant qualities were demonstrated by methyl 3,4-dihydroxybenzoate and 3,4-dihydroxybenzoic acid compounds that were separated from the chaste tree for antioxidant effects using DPPH, whereas vanillic acid and casticin had mild effects [92].

Antimicrobial activity

Using a disk diffusion method, the seeds' essential oil showed antibacterial efficacy against *Salmonella enteritidis*, *Staphylococcus aureus*, *Bacillus subtilis*, and *Pseudomonas aeruginosa* [13, 93]. The oxide of caryophyllene was identified as the major component of the essential oil, and *S. aureus* was the most sensitive [94]. The disk diffusion approach was applied in another investigation to assess the antimicrobial action of fruit essential oil. Although the inhibition zone susceptibility was clearly visible, it turned out to be less effective than ofloxacin and ampicillin. *Enterococcus faecalis* was the most vulnerable organism [95]. By computing the minimal inhibitory concentration and the minimal lethal concentration, *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Microsporum canis*, *Microsporum gypseum*, and *Epidermophyton floccosum* were among the dermatophyte strains against which the antifungal activity of the essential oils derived from the plant's leaves, fruits, and flowers was ascertained. According to Marongiu et al. [96], the essential oils that were isolated from the leaf had the strongest antifungal activity. When compared to penicillin and ampicillin antimicrobial agents, the leaves of *V. agnus-castus* in methanolic extract show exceptional effectiveness as antifungal against *Candida albicans* [88].

Insect repellent activity

In an investigation into the ability of 70 plant extracts to repel bloodsucking insect attacks, the *V. agnus-castus* carbon dioxide extract showed insect repellent activity for at least six hours, specifically against animal and human *Ixodes ricinus* and *Rhipicephalus sanguineus* ticks [97]. Additionally, for almost six hours, fleas, mosquitoes, and biting insects were repelled [98]. The head lice-repelling properties of Licatack®, a preventive spray that comprises paramenthan 3,8 diol and an extract of *V. agnus-castus* seeds, were tested on children's hair. It has been shown to shield human hair from *Pediculus humanus capitis*, the head lice, for at least seven hours [99]. According to Tandon et al. [100], the essential oil of leaves exhibited larvicidal activity by decreasing adult emergence, fecundity, and egg fertility and increasing larval and pupal duration, larval mortality, and adult deformity when applied topically to the dorsal side of the mesothoracic region. Meanwhile, according to Cetin et al. [101], the primary constituent of essential oil, trans β-caryophyllene, demonstrated larvicidal effectiveness on *Culex pipiens* larvae in the late third to early fourth stage. The ethanolic extract of the leaves was poisonous to *Musca domestica* larvae in their third instar [102].

Effects on fracture healing

Pursuant to a study by Eftekhari et al. [103], fracture repair was enhanced when magnesium and *V. agnus-castus* were administered together in a group of 64 women who had lengthy bone fractures. Flavonoids were found to efficiently enhance the initial phases of New Zealand's fracture healing procedure white rabbits with fractures to their right tibia in an in vivo investigation [104]. Comparing *V. agnus-castus* to untreated osteopenic rat bone, another in vivo investigation showed a significant improvement in bone biomechanical stability [60].

Other effects

In an investigation of Alimohammadi et al. [105], ovariectomized mice were used as an example of blockage of the middle cerebral arteries in vivo investigation. The stroke was brought on after a month of treatment with an ethanolic preparation of the fruits of *V. agnus-castus*. In comparison to the normal control group, the results showed that Vitex extract and estrogen can reduce infarct volume ($P < 0.05$) and neurological impairments ($P < 0.05$). In ovariectomized rats, vitex extract, like estrogen in our work, demonstrated neuroprotective benefits following middle cerebral artery blockage. The butanolic fraction and crude extract of fruits reduce non-alcoholic fat liver disease, according to an in vivo test conducted on ovariectomized rats. According to Moreno et al. [90], the plant extract was successful in restoring the activity of some antioxidant enzymes and lowering the amount of hydrogen peroxide produced by the animal's mitochondria. In a modern, cell-based experiment, ten distinct components of methanol extract extracted from the plant's aerial parts were examined for their ability to block lipoxygenase

and have inflammatory-reducing properties. According to Choudhary et al. [87], the findings indicated that (3,4) dihydroxybenzoic acid, p-hydroxybenzoic acid, and methyl (3,4) dihydroxybenzoate had noteworthy anti-inflammatory properties. An in vivo investigation was conducted to examine the anti-inflammatory properties of casticin. Six mice were given 1, 2, and 10 mg/kg casticin intraperitoneally after being exposed to either fresh air or cigarette smoke for two weeks. Lung histological analysis was subsequently performed, and infiltrations of immune cells and cytokine productions were measured by bronchoalveolar lavage fluid (BALF). The amounts of chemokines and pro-inflammatory cytokines in the BALF were reduced by casticin, as well as the perivascular inflammatory cells, peribronchial infiltration, and epithelial thickness [106]. It also decreased the number of macrophages, neutrophils, and lymphocytes. Rats' viscera were triggered by acetic acid, formalin, and tail immersion, and the essential oil from the leaves demonstrated antinociceptive activity. According to the study, the cholinergic system's muscarinergic receptors and the plant's endogenous opioidergic system may be the cause of *V. agnus-castus* essential oil's antinociceptive qualities [107]. In a kindling rat model of epilepsy, Saberi et al. [108] reported the antiepileptic efficacy of hydrophilic fruit extract. By reducing attention deficit disorder (ADD) and convulsion duration in a dose-dependent way, it was possible to examine the inhibition or reduction of epileptic activity. According to Ulusoy et al. [6] study, luteolin-7-glucoside and kaempferol content of *V. agnus-castus* leaves and flowers showed positive results in the treatment of obesity. In rats fed a high-fat diet, these active ingredients reduced body weight, decreased serum levels of leptin, triglycerides, and low-density lipoprotein (LDL), and increased levels of adiponectin and high-density lipoprotein (HDL).

Toxicity and safety studies

The LD50 (lethal dose for 50% of the population) for chasteberry (*V. agnus-castus*) specifically is not well-documented in the literature. Most studies indicate that chasteberry has a low toxicity profile, and acute toxicity studies in animals have demonstrated high LD50 values, suggesting a wide safety margin. For example, one study found that mice did not die even when given high dosages (5 g/kg) of chasteberry leaf essential oil, suggesting a good safety margin [107]. Another study reported that the LD50 of *V. agnus-castus* leaves methanol extract was 17.21 g/kg body weight, suggesting that this extract is quite safe for single-dose treatment [109].

There is limited research on the chronic toxicity of chasteberry, and more comprehensive long-term studies are needed to fully understand its potential effects on various populations. However, the available information suggests that chasteberry does not exhibit significant negative effects when used at recommended dosages [33].

Chasteberry is generally well-tolerated, according to clinical research. When they do happen, side effects are usually minor and can include skin rashes, headaches, and stomach issues [33].

Chasteberry seems to be typically well tolerated when taken in small doses. Itching, headaches, nausea, and gastrointestinal problems are examples of moderate side effects. The safety of chasteberry during pregnancy and breastfeeding is not well established. It is advised that women who are pregnant or nursing avoid using chasteberry due to potential hormonal effects [110].

It also may not be safe for women with hormone-sensitive conditions, such as breast, uterine, or ovarian cancer, to take this herb. It's possible that chasteberry might interact with some medicines, such as birth control pills, drugs used to treat Parkinson's disease, and drugs used to treat psychosis [110].

Formulations

Recent investigations into *V. agnus-castus L.* have expanded significantly, focusing on innovative drug delivery systems to enhance its therapeutic efficacy, particularly in the realm of women's health [32]. Traditionally used to address menstrual irregularities, premenstrual syndrome (PMS), and hormonal imbalances, Vitex contains bioactive compounds such as flavonoids, iridoids, and essential oils that exhibit dopaminergic activity and influence prolactin levels. However, the plant's therapeutic potential is often limited by poor solubility and bioavailability, prompting researchers to explore advanced delivery technologies [111].

Nanotechnology has emerged as a promising solution, with studies developing solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and polymeric microspheres using biodegradable materials like chitosan and poly(lactic-co-glycolic acid) (PLGA) [112]. These systems are designed to protect Vitex's sensitive phytochemicals, enhance absorption, and allow for controlled release, thereby improving clinical outcomes. For instance, encapsulating Vitex extracts in SLNs has shown improved stability and sustained release profiles, which are particularly beneficial for long-term hormonal therapies [113].

In addition to oral formulations, other delivery approaches have gained attention. Transdermal patches and mucoadhesive gels offer non-invasive alternatives that improve patient compliance and provide steady therapeutic levels. These formats are especially useful for individuals requiring continuous hormonal support

without the gastrointestinal side effects associated with oral administration [114].

Moreover, hydroethanolic extracts of Vitex have demonstrated interactions with cytochrome P450 enzymes, specifically CYP1A2, CYP2C9, and CYP3A4, raising concerns about potential drug-drug interactions [115]. This has led to increased emphasis on precision formulation and personalized medicine strategies to ensure safety and efficacy when Vitex is used alongside conventional pharmaceuticals [116].

Recent studies have also explored the antimicrobial and anticancer properties of Vitex through novel delivery systems. For example, silver nanoparticles synthesized using Vitex seed extract have exhibited potent antibacterial and cytotoxic effects, suggesting broader applications beyond hormonal regulation [117]. Similarly, essential oil profiling and molecular docking studies have revealed antioxidant and antibacterial activities, supporting its use in topical formulations and integrative therapies [118].

Together, these advancements reflect a growing trend toward merging traditional herbal medicine with cutting-edge pharmaceutical technologies [119]. By leveraging nanocarriers, biodegradable polymers, and patient-centered delivery formats, researchers aim to unlock the full therapeutic potential of *V. agnus-castus L.* in a safe, effective, and personalized manner [6].

A 2022 study explored the formation of inclusion complexes between *V. agnus-castus* extracts and β-cyclodextrins. These complexes improved the aqueous solubility and chemical stability of the active compounds, offering a viable strategy for oral and buccal drug delivery systems [120].

A 2023 study investigated the use of phytosomes complexes of plant extracts and phospholipids to improve the oral bioavailability of *V. agnus-castus* extracts. The phytosome formulation significantly enhanced the absorption of flavonoids and diterpenoids, which are typically poorly soluble in water. This approach is particularly promising for oral supplements targeting PMS and menopausal symptoms [121].

Researchers have developed nanoemulsions containing *Vitex* essential oil to improve its antimicrobial and anti-inflammatory activity. These nanoemulsions demonstrated enhanced skin penetration and stability, making them suitable for topical applications in dermatological and gynecological conditions [122].

Another recent investigation focused on transdermal films incorporating *Vitex* extract using hydroxypropyl methylcellulose (HPMC) as a film-forming agent. These films provided sustained release over 24 h and were well-tolerated in skin irritation tests, suggesting potential for hormone-balancing therapies [123].

A 2024 study formulated nanogels loaded with *V. agnus-castus* extract for vaginal delivery. The nanogels exhibited strong antioxidant and antimicrobial activity, with mucoadhesive properties that support prolonged retention and localized action, ideal for treating vaginal infections and hormonal imbalances [123].

Conclusions

Natural complementary approaches to disease prevention and treatment have a long-standing record of safe and effective use. Recent research has confirmed the effectiveness of *V. agnus-castus* in treating conditions such as premenstrual syndrome, menstrual disorders, and menopausal issues. This plant is recognized for its diverse beneficial effects, including hormonal regulation, antioxidant properties, chemoprevention, immune system support, cytotoxicity, tumor inhibition, antimutagenic effects, as well as antimicrobial and antifungal actions. It also shows promise in insect repellent applications and aiding fracture healing.

Overall, this review provides valuable documentation for researchers exploring the medicinal properties of *V. agnus-castus*. It emphasizes the importance of understanding its safety profile and proper dosing while advocating for further preclinical and clinical investigations to comprehensively assess its therapeutic effectiveness and safety.

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Data availability
The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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