

## **MEDICINAL POTENTIAL OF VITEX AGNUS-CASTUS: BOTANICAL TRAITS, FRUIT COMPOSITION, AND PHARMACOLOGICAL ACTIVITIES**

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**ABSTRACT:** This review is based on published data on the fruits of the chaste tree (*Vitex agnus-castus* L.), a traditional medicinal plant used to treat premenstrual syndrome (PMS). The review summarizes and analyzes the existing literature on the chemical composition and pharmacological properties of the fruit extract and its individual chemical compounds. According to the current data, the presence of 20 flavonoids, 10 iridoids, 11 phenolic acids, three diterpene alkaloids, and 12 terpenes was confirmed in the extract of *Vitex* fruits. Many of these compounds exhibit pharmacological activity according to the results of preclinical studies. Thus, various authors have confirmed the presence of dopaminergic, opioid, estrogenic, immunomodulatory, antineoplastic, and antioxidant activity. It is assumed that the cumulative effect of several chemical compounds also has beneficial effects on the complex regulation of the female reproductive system. In this review, special attention is paid to data obtained from clinical trials because they are the most important and reliable studies of drug efficacy and safety. Nine clinical studies that examined the effect of preparations based on chaste tree fruit extract on the female reproductive system are reviewed. Studies have shown that the fruits of the chaste tree significantly reduce the symptoms of PMS, normalize the menstrual cycle, and lower prolactin levels. The use of *Vitex* is often preferable due to its high efficacy, long-term and short-term tolerance, and positive effect on the female reproductive system, including fertility.

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**Keywords:** *Vitex agnus-castus* L., biologically active substances, fruits, premenstrual syndrome, pharmacologic properties.

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### **INTRODUCTION**

This field (Aleshnikova et al., 2020; Palvinskiy et al., 2020; Pisarev et al., 2020; Rogozhnikova et al., 2020). As a rule, herbal medicines are safer than newly synthesized substances due to years of experience gained from their use in folk and traditional medicine in different countries. Human metabolism has evolutionarily adapted to interaction with plant compounds, and in most cases, the excretory system successfully removes them from the body without disrupting homeostasis. Modern trends in pharmaceutical science in the field of phytochemistry are aimed at finding new sources of

bioactive substances, developing methods for extracting them from plant at the pharmaceutical industry's present stage of development, plants are one of the most important sources of biologically active substances. The diversity of plant species results in significant variations in the number of biosynthetic pathways that enable plants to produce hundreds of thousands of different chemical compounds. Total plant extracts are of great interest to researchers, as evidenced by the volume of studies in materials, and converting them into drugs. In gynecological practice, plant-based medicines are used to impart relief from the undesirable manifestations of premenstrual syndrome (PMS), correct menstrual irregularities, and prevent metabolic disorders in menopause. One of the sources of such medications is the chaste tree (also called Vitex, Abraham's balm, monk's pepper, or lilac chaste tree). The chaste tree (*Vitex agnus-castus* L.) is a low tree or tall shrub that grows to a height of 3–6 m. The modern taxonomy of plants classifies it as a member of the Lamiaceae family, but it previously belonged to the Verbenaceae family. It grows along riverbanks and seacoasts as a wild plant in the Mediterranean region (Southern Europe, North Africa, and Western Asia) and the Caucasus. In Russia, it is found on the coastal pebble beaches of the Caucasus Black Sea; in Crimea, it is a wild plant (Fedorov et al., 1978). In Russia, *Vitex* is cultivated in limited areas in the North Caucasus, and the fruits are used as a raw material for the production of dietary supplements. At present, *V. agnus-castus* grows on the East, South, and West Coasts of the United States (United States Department of Agriculture, 2021). It is also found in northeastern India (Nadkarni et al., 1954), Afghanistan and Pakistan (Flora of Pakistan), and Iran (Abbas Azimi et al., 2006; Salehpour et al., 2018). It has been speculated that another species of chaste tree grows in India, namely, *Vitex pseudonegundo* (Hauskn.) Hand.-Mazz. (*V. agnus-castus* var. *pseudo-negundo* Hauskn.). However, modern taxonomy considers these taxa synonyms of *V. agnus-castus* L. even though they differ from each other not only in area but also in several morphological and anatomical features as well as levels of bioactive substances, especially essential oil components. The fruits of this plant are widely used in traditional systems of medicine in different countries for the mitigation of PMS symptoms, improvement of the psychoemotional state of women, and normalization of the menstrual cycle. In addition, they serve as a raw material for medicines. The chaste tree is also included in pharmacopoeias in Europe, including Great Britain, and the USA. Researchers from different countries have isolated individual compounds from chaste tree fruits, the pharmacological properties of which have been studied both in vivo and in vitro. However, these studies did not establish the exact and complete mechanism of action of these compounds on the female reproductive system. In this regard, this review aimed at searching for relevant information about chaste tree fruits to understand their effects on the hormonal regulation of the female reproductive system.

### **Botanical Description of the Chaste Tree**

Modern plant taxonomy indicates that the genus *Vitex* comprises 223 species (ThePlantList, 2013). *Vitex agnus-castus* L. is a low tree or tall shrub 3–6 m in height (Fig. 1). It occurs in the form of a low,

erect shrub or as a prostrate creeping habit at a height below 1 m. The bark of old trunks is light gray with a barely noticeable pink tint, cracking into approximately regular rectangles with the edges bent upwards. The young shoots are slightly tetrahedral and gray. The leaves, which comprise 3–7 leaflets, are thin, opposite, palmate, 8–12 cm long, and 12–14 cm wide, with white tomentum on the lower surface. The inflorescence is paniculate, terminal, or axillary, 15–20 cm long, and 6–8 cm wide. The flowers are numerous, up to 0.8–1.0 cm long and 0.3–0.4 cm wide, and massed in airy half-umbrellas. The calyx is campanulate, 0.2–0.3 cm long, three times shorter than the corolla, densely hairy, and sometimes even woolly, with rounded, slightly wavy teeth along the edges. The corolla is bilabiate, with a two-incised upper lip and a three-incised lower lip. The color of the petals ranges from pale pink, pink, dark pink, and lilac to purple and occasionally white. The lobes on the inner side of the lower lip at the point of attachment of the stamens are hairy. In the middle lobe, which is much larger than the other two, patches of long shaggy hairs reach the base of the incision. The pistil and four stamens exceed the corolla, and the ovary is round and up to 0.1 cm in diameter. The fruit is round and dark brown or black in color, with a blue bloom and shiny drupe; it is 3–4 mm in diameter and almost entirely covered with a woolly calyx. In appearance, the fruits of the prutnyak resemble black pepper and often serve as its substitute due to their spicy taste. The fruits bloom from June to October and ripen between October and November but remain on the tree from December to January (Karaguzel et al., 2009; Mammadova et al., 2019). Previously, varieties and forms of the chaste tree were distinguished based on flower color and size as well as the degree of dissection and serration of the leaf blade. However, in modern taxonomy, all old infraspecies ranks are considered synonymous to *V. agnus-castus* L.

### **Chemical Composition**

The fruits of the chaste tree contain several secondary metabolites: terpenoids (the main components of the essential oil), flavonoids, iridoids, and phenol carboxylic acids (Fig. 2). More



**Figure 1.** Blooming chaste tree.

Than 60 substances have been identified in chaste tree fruits using chromatographic and spectral methods. Flavonoids and iridoids predominate in chaste tree fruits in terms of the contents and

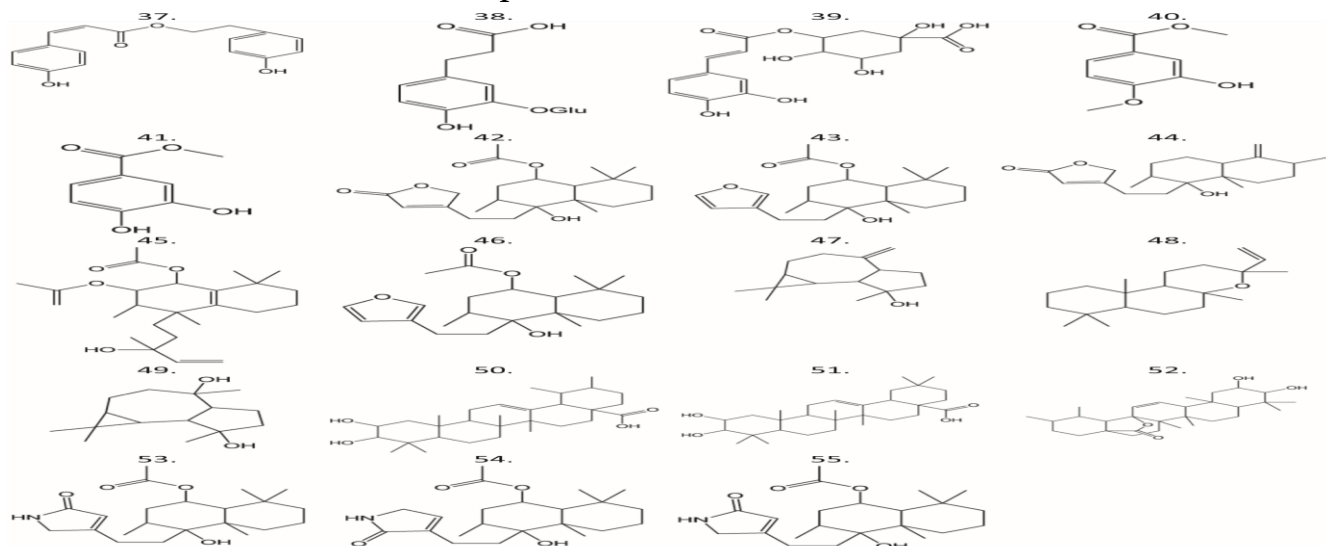


Figure 2: Compounds chaste tree.

amounts of compounds present. The dominant flavonoids are casticin and luteolin-7-glycoside. The other compounds present are luteolin, 3,3'-dihydroxy-5,6,7,4'-tetramethoxyflavone, 3,7-dimethylquercetin, 3-O-methylkaempferol, 3-hydroxy-5,6,7,4'-tetramethoxyflavone, 3-methylquercetin, 3-methylkaempferol, 5,3',5'-trihydroxymethoxyflavanone, 5,7,3',5'-tetrahydroxyflavanone, apigenin, artemetin, vitexin, orientin, isovitexin, isoorientin, kaempferol, penduletin, and eupatorin (Chen et al., 2011; Choudhary et al., 2009; Hajdú et al., 2007; Makhmoor and Choudhary, 2010; Mari et al., 2015; Sogame et al., 2019; Sorensen and Katsiotis, 1999). Agnuside is the dominant iridoid of the chaste tree. The other iridoids are 10-p-coumaroylaucubin (eurostoside), 6'-O-p-hydroxybenzoylmussaenosidic acid, agnucastoside A, agnucastoside B, agnucastoside C, aucubin, vladirrol F, mussaenosidic acid, and ficusal (Fukahori et al., 2014; Görler et al., 1985; Kuruüzüm-Uz et al., 2003; Li et al., 2013). Some other compounds with phenolic structure have been identified. These are 3,4-dihydroxybenzoic acid, 5-hydroxy-2-methoxybenzoic acid, vanillic acid, caffeic acid, ferulic acid, p-hydroxybenzoic acid, p-hydroxyphenylethanol-p-coumarate, myzodendrone, chlorogenic acid, methylisovanillate, and methyl 3,4-dihydroxybenzoate (Chen et al., 2011; Choudhary et al., 2009; Kuruüzüm-Uz et al., 2003; Li et al., 2013; Makhmoor and Choudhary, 2010; Şarer et al., 2008; Sogame et al., 2019). The following terpenoid compounds are present in the lipophilic fraction: vitexilactone, vitexilactone B, vitetrifoline C, vitetrifoline D, vitetrifoline I, rotundifuran, spatulenol, 8-epimanoyl oxide, aromadendren-4 $\alpha$ , 10 $\alpha$ -diol, 3-epi-corosolic acid, 3-epi-maslinic acid, and ilelatifol D (Chen et al., 2011; Hajdú et al., 2007; Li et al., 2013; Şarer et al., 2008). The diterpene alkaloids vitexilactam A, vitexilactam B, and vitexilactam C are unique to chaste tree fruits (Li et al., 2002, 2013).



The identified compounds are listed in Table 1. The pharmacological properties of many medicinal plants are conferred by their essential oils. In view of the specific nature of their study, medical uses, and physical and chemical properties as well as their characteristic production technologies, it is advisable to present data on essential oils separately. The composition of the essential oil extracted from chaste tree fruits has been well studied and comprises mainly terpenoid compounds. The most common and informative method for studying the qualitative and quantitative composition of essential oils is gas chromatography coupled to a mass detector. Published data indicate that the following compounds have been identified in the essential oil of mature, air-dried chaste tree fruits using distillation with water vapor:  $\alpha$ -pinene, sabinene,  $\beta$ -pinene,  $\beta$ -myrcene, p-cymene, limonene, 1,8-cineole, cis-sabinene hydrate, trans-sabinene hydrate, cis-p-ment-2-en-1-ol, trans-p-ment-2-en-1-ol, trans-verbenol,  $\delta$ -terpineol, terpinene-4-ol, krypton,  $\alpha$ -terpineol, trans-carveol,  $\beta$ -citronelol, and  $\alpha$ -terpinyl acetate. The other compounds are trans- $\beta$ -caryophyllene, trans- $\alpha$ -bergamotene, cis- $\beta$ -farnesene, trans- $\beta$ -farnesene, dihydroaromadendren, curcumen, viridiflorene,  $\beta$ -bisabolene,  $\beta$ -basanene, myristicin, palustrol, spatulenol, caryophyllene oxide, iceol, humulene epoxide II,  $\tau$ -cadinol, 14-hydroxy-cis-caryophyllene, epi- $\alpha$ -bisabolol, trans-isovalencenol, cubiten, (3E)-cembrene A, sklaren, (E, Z)-geranylinalool, (Z, E)-geranylinalool, abietatriene, and 13-epimanool (Ghannadi et al., 2012; Sorensen and Katsiotis, 2000; Stojković et al., 2011). The relative proportions of the components of the essential oil vary depending on the place of growth, phenotypic characteristics, and duration of the distillation process used for obtaining the oil. Studies have shown that prolonged distillation resulted in a product containing greater amounts of low-volatile components but thermolabile compounds were degraded. The content variability levels for the main components have been experimentally established: sabinene (16.4%–44.1%), 1,8-cineole (8.4%–15.2%),  $\beta$ -caryophyllene (2.1%–5.0%), and trans- $\beta$ -farnesene (5.0%–11.7%) (Sorensen and Katsiotis, 2000).

### **Preclinical Studies**

Currently, the mechanism by which chaste tree products affect the female reproductive system is not fully understood. However, studies have shown that bioactive substances contained in the chaste tree exert dopaminergic, opioid, and estrogenic effects (Rafieian-Kopaei and Movahedi, 2017). Moreover, the extant literature confirms the antioxidant, immunomodulatory, and antitumor effects of the chaste tree and its individual bioactive components.

### **Dopaminergic effects**

A decrease in dopamine secretion in females, such as under conditions of chronic stress, may lead to an increase in blood prolactin content, which in turn contributes to the occurrence of proliferative changes in the mammary gland and mastodynia. It also results in insufficiency of the luteal phase, thereby leading to infertility. Chaste tree compounds reduce the blood level of prolactin and decrease its negative manifestations by activating the dopamine receptors of the pituitary gland. These properties of chaste tree extracts (whole extract, fractions, and individual bioactive compounds) were revealed via

in vitro experiments and confirmed in clinical studies. Sliutz et al. (1993) found that the release of prolactin by cells of the pituitary gland in rats was significantly inhibited by the whole extract of chaste tree fruits. A similar effect on these cells was achieved by the action of synthetic agonists of the dopamine receptors. The binding of components of the ethanol extract of the chaste tree to various receptors (D2-dopamine, H1histamine, benzodiazepine, opioid receptors, and the binding site of the serotonin transporter) was studied in detail (Meier et al., 2000) using the radioligand method based on the assessment of the concentration of half-maximal binding ( $IC_{50}$ ). The results showed that the whole extract exhibited dopaminergic activity ( $IC_{50} = 52 \mu\text{g/ml}$ ), with the hexane fraction of the extract being more active ( $IC_{50} = 32 \mu\text{g/ml}$ ). A study of BNO 1095 (a commercial preparation based on chaste tree extract) that investigated the pharmacological effects of chromatographic eluates found that the active principles involved in dopaminergic activity were bicyclic terpenoids, mainly clerodane, rotundifuran, and  $6\beta$ ,  $7\beta$ -diacetoxy-13-hydroxylabda-8, 14-diene. There was no binding to the histamine receptor, benzodiazepine receptor, or histamine transporter.

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**Table 1.** Bioactive substances identified in chaste tree fruits.

Name	CAS number	Source
Flavonoids		
1	Casticin	479-91-4 (Chen et al., 2011)
2	Luteolin	491-70-1 (Chen et al., 2011)
3	Luteolin-7-glycoside	5373-11-5 (Mari et al., 2015)
4	3,3'-dihydroxy-5,6,7,4'-tetramethoxyflavone	(Choudhary et al., 2009)
5	3,7-dimethylquercetin	2068-02-2 (Chen et al., 2011)
6	3-O-metyl kaempferol	(Chen et al., 2011)
7	3-hydroxy-5,6,7,4'-tetramethoxyflavone	- 21764-09-0 (Makhmoor et al., 2010)
8	3-methylquercetin	1486-70-0 (Chen et al., 2011)
9	3-metyl kaempferol	1592-70-7 (Chen et al., 2011)
10	Apigenin	520-36-5 (Chen et al., 2011)
11	Artemetin	479-90-3 (Choudhary et al., 2009)
12	Vitexin	3681-93-4 (Hajdú et al., 2007)
13	Orientin	28608-75-5 (Hajdú et al., 2007)

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14	Isovitexin	38953-85-4	(Mari et al., 2015)
15	Isoorientin	4261-42-1	(Fukahori et al., 2014)
16	Kaempferol	520-18-3	(Chen et al., 2011)
17	Penduletin	569-80-2	(Makhmoor et al., 2010)
18	Eupatorin	855-96-9	(Hajdú et al., 2007)
19	5,3',5'-trihydroxymetoxyflavanone		(Chen et al., 2011)
20	5,7,3',5'-tetrahydroxyflavanone		(Chen et al., 2011)

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Iridoids

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21	Agnuside	1027-63-7	(Kuruüzüm-Uz et al., 2003)
22	10-p-coumaroyl aucubin (eurostoside)	85802-33-1	(Kuruüzüm-Uz et al., 2003)
23	6'-O-p-hydroxybenzoilmussaenosidic acid	87667-61-6	(Kuruüzüm-Uz et al., 2003)
24	Agnucastoside A		(Kuruüzüm-Uz et al., 2003)
25	Agnucastoside B		(Kuruüzüm-Uz et al., 2003)
26	Agnucastoside C		(Kuruüzüm-Uz et al., 2003)
27	Aucubin	479-98-1	(Kuruüzüm-Uz et al., 2003)
28	Vladirol F		(Chen et al., 2011)
29	Mussaenosidic acid	82451-22-7	(Kuruüzüm-Uz et al., 2003)
30	Ficusal	321991-55-3	(Chen et al., 2011)

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Phenolic acids

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31	3,4-dihydroxybenzoic acid	99-50-3	(Choudhary et al., 2009)
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32	5-hydroxy-2-metoxybenzoic acid	2612-02-4	(Choudhary et al., 2009)
33	Vanilic acid	121-34-6	(Choudhary et al., 2009)
34	Caffeic acid	331-39-5	(Şarer et al., 2008)
35	Ferulic acid	1135-24-6	(Chen et al., 2011)
36	p-hydroxybenzoic acid	99-96-7	(Makhmoor et al., 2010; Choudhary et al., 2009)
37	p-hydroxy phenyl ethanol-p-coumarate		(Chen et al., 2011)
38	Mysodendron	101705-37-7	(Kuruüzüm-Uz et al., 2003)
39	Chlorogenic acid	327-97-9	(Şarer et al., 2008)
40	Methylisovanilate	6702-50-7	(Kuruüzüm-Uz et al., 2003)
41	Methyl -3,4-dihydroxybenzoate	99-50-3	(Makhmoor et al., 2010)

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The results of a study by Jarry et al. (2003) indicated that the flavonoids apigenin, penduletin, and vitexin exerted estrogenic effects, with  $IC_{50}$  values of 0.08, 0.25, and 10  $\mu\text{g/ml}$ , respectively, while the original extract (commercial name BNO 1095) had a concentration of an inhibitor at which 50% inhibition of the response is seen ( $IC_{50}$ ) of 10  $\mu\text{g/ml}$ . These compounds showed affinity only for the  $\beta$ -estrogen receptors. An additional synergistic effect of chaste tree fruits in PMS treatment may be due to the ability of the linolenic acid component to induce the expression of the  $\beta$ -estrogen receptor gene, as demonstrated experimentally in Ishikawa cells (Liu et al., 2004). The same study showed that the methanol extract of the chaste tree fruit displaced estrogen from the  $\alpha$ - and  $\beta$ -estrogen receptors.

Several indirect pharmacological tests have confirmed the estrogenic activity of chaste tree fruits. Cognitive function and uterine size were studied in female ovariectomized mice (Allahtavakoli et al., 2015). In another study, the quality of bone tissue was monitored in male mice with orchietomy (Sehmisch et al., 2009). In both studies, positive effects were observed.

A study using molecular docking has been published. The study reports that quercetin, casticin, agnuside, isovitexin, and apigenin have an affinity for the estrogen receptor (Powers et al., 2015)

### **Immunomodulatory effects**



The immunomodulatory effect of chaste tree products has been attributed to the flavonoid casticin (Mesaik et al., 2009). It was confirmed experimentally that casticin significantly inhibited monocyte chemotaxis and T-lymphocyte proliferation at levels comparable to inhibition by prednisolone.

### **Antineoplastic activity**

The cytotoxic effect of agnuside on some types of cancer cells has been confirmed via in vitro experiments, as has its effect on the nuclear condensation and apoptosis of these cells (Arokiyaraj et al., 2012). In addition, vitetrifoline D has shown high potential as an agent for cancer chemoprophylaxis (Li et al., 2013). Chaste tree alcohol extract and essential oil produced strong, dose-dependent antimutagenic effects in a genetic test (Sarac et al., 2015).

### **Antioxidant activity**

A study by Hajdú et al. (2007) on the antioxidant effects of bioactive substances in the lipophilic hexane fraction of the aqueous-alcoholic extract of chaste tree found that the flavonoid casticin produced the strongest antioxidant activity, which was several times superior to that of ascorbic acid. Moreover, a study on the effect of chaste tree extract on iron II-mediated free radical oxidation of deoxyribose revealed that the aucubin iridoid agnuside significantly inhibited this damage (Arokiyaraj et al., 2012). An investigation that screened compounds isolated from the chaste tree for antioxidant effects through free radical neutralization using 1,1-diphenyl-2-picrylhydrazyl demonstrated that methyl 3,4-dihydroxybenzoate and 3,4-dihydroxybenzoic acid had strong antioxidant properties, while casticin and vanillic acid produced moderate effects (Makhmoor and Choudhary, 2010).

### **Pharmacological properties of essential oil**

Essential oils often exhibit antimicrobial and antifungal effects. A study by Stojković et al. (2011) measured in vitro antimicrobial and antifungal effects (as appropriate) in terms of IC<sub>50</sub> values with respect to *Micrococcus flavus*, *Bacillus subtilis*, *Salmonella typhimurium*, *Staphylococcus aureus*, *Escherichia coli*, *Alternaria alternata*, *Aspergillus flavus*, *Aspergillus niger*, *Aspergillus ochraceus*, *Fusarium tricinctum*, *Penicillium ochrochloron*, *Penicillium funiculosum*, and *Trichoderma viride*. The reference compounds were 1,8-cineole and  $\alpha$ -pinene, the predominant components of chaste tree essential oil. The standard drugs used were the antibacterial streptomycin and antifungal bifonazole. The Minimum inhibitory concentration (MIC) values of the essential oil against bacteria ranged from 44 to 890  $\mu\text{g/ml}$ , while the MIC ranges of 1,8-cineole,  $\alpha$ -pinene, and streptomycin were 4–8, 5–10, and 50–200  $\mu\text{g/ml}$ , respectively. The MIC values of the essential oil against fungi were 45–219  $\mu\text{g/ml}$ , while those of 1,8-cineole,  $\alpha$ -pinene, and bifonazole were 4–7, 4–8, and 100–250  $\mu\text{g/ml}$ , respectively. Thus, the antimicrobial and antifungal properties of chaste tree essential oil were largely due to 1,8-cineole, which was the most active component; the 1,8-cineole content of the essential oil was also more than that of the aqueous extract. In another study (Asdadi et al., 2015), the antifungal activity of the essential oil was investigated against eight *Candida* species, including strains that acquired drug resistance. The methods used were macrodilution (determination of minimum inhibitory and fungicidal

concentration) and the agar disc-diffusion method. In an overwhelming number of tests, the effectiveness of the essential oil was higher than that of fluconazole and amphotericin using the 1,1-diphenyl-2-picrylhydrazyl test system. Research using several in vitro test systems (1,1-diphenyl-2-picrylhydrazyl, beta-carotene/linoleic acid, and reducing power tests) has demonstrated the low antioxidant activity of chaste tree essential oil (Sarikurkcu et al., 2009). In all cases, the antioxidant activity of the essential oil was less than that of the aqueous extract obtained from the same raw material. Considering the low content of essential oil in chaste tree fruits (about 0.5%), it can be argued that their antioxidant effect is not due to essential oil.

### **Clinical Studies**

Clinical trials are used to assess the safety and efficacy of new treatments and are a prerequisite for bringing a drug to market and widespread use in humans. Clinical research requires a rigorous scientific approach and statistical processing of the results. Among all methods for assessing the effectiveness of a drug, the data obtained from clinical trials are the most reliable. One of the first clinical studies of a drug based on Vitex in which 52 women participated found that the prolactin level significantly decreased, and deficiencies in the luteal phase of the menstrual cycle and the synthesis of luteal progesterone were eliminated after administering the drug for 3 months. Additionally, it was indicated that two women could become pregnant during therapy (Milewicz et al., 1993). A preparation based on Vitex extract, Pregnoton (Russia), is used specifically to increase female fertility. In a clinical study involving 25 families who had been infertile for 1–4.5 years, 5 women could become pregnant. As in the previous study, evaluating the drug's efficacy in women revealed clear benefits. These included a decrease in prolactin levels, lengthening of the luteal phase of the menstrual cycle, normalization of the menstrual cycle, reduction of pain, and an increase in progesterone levels (Zhukov et al., 2013). The presence of dopaminergic properties was confirmed in a clinical study in patients with severe and mild mastalgia. The therapy involved daily administration of 40 mg of chaste tree fruit extract (Agnucaston®, Biomeks, Germany). The standard group was treated with 2.5 mg of bromocriptine, a dopamine receptor agonist, twice a day. In both groups, there was a comparable decrease in blood prolactin levels and a significant decrease in pain in the mammary glands. Not a single case of adverse reactions was recorded in the group receiving chaste tree extract, compared with a 12.5% incidence of adverse reactions under bromocriptine treatment (Kilicdag et al., 2004). The anti-inflammatory properties of some chaste tree metabolites such as p-hydroxybenzoic acid, methyl 3,4-dihydroxybenzoate, and 3,4-dihydroxybenzoic acid potentially also contributed to pain relief. In one retrospective study involving women with moderate-to-severe PMS, it was demonstrated that daily intake of 5 mg of chaste tree extract over three menstrual cycles resulted in a significant decrease in the severity of PMS in 67% of subjects (Prilepskaya et al., 2006). The effect of chaste tree extract on cyclic mastalgia was established in a randomized, placebo-controlled, double-blind study. The long-term study demonstrated the high efficacy of chaste tree extract as early as in the second menstrual cycle,

with a 53% decrease in pain intensity (Halaska et al., 1999). To compare the treatment effects of chaste tree extract with those of other drugs, a clinical study was conducted in which one group was treated with chaste tree extract and the other with fluoxetine, an antidepressant and serotonin reuptake inhibitor that is sometimes used for the alleviation of PMS. In patients from both groups, there were equal decreases in PMS symptoms. However, chaste tree extract influenced physiological symptoms such as breast tenderness, edema, convulsions, irritability, and increased appetite to a greater extent, while fluoxetine had a greater effect on neurological symptoms such as irritability, insomnia, depression, nervous tension, and breast pain (Atmaca et al., 2003). A similar study in which fluoxetine was used as the standard drug showed that chaste tree-based medicine produced better results with respect to performance, depressed mood, and general somatic symptoms. Thus, the use of chaste tree preparations is preferable for alleviating the physiological manifestations of PMS (Ciotta et al., 2011). A clinical study using dry chaste tree extract Ze 440 at a dose of 20 mg per day demonstrated clear superiority of the drug over placebo, with 52% and 24% decreases in PMS symptoms, respectively, with no adverse reactions requiring discontinuation of the drug (Schellenberg, 2001). In another clinical study, Agnolyt P capsules containing chaste tree fruit extract were used, with pyridoxine as the reference drug. Clinical improvements and a high benefit-to-risk ratio were observed in 77.1% of subjects when compared with 60.6% of the reference group (Lauritzen et al., 1997). An important argument in favor of the safety of chaste tree-based drugs is the low frequency of occurrence of undesirable reactions. A review of clinical trials (van Die et al., 2013) indicated that, out of 641 participants, only 35 cases of side effects were recorded, with nausea and headache being the major complaints.

## **CONCLUSION**

The chaste tree is a medicinal plant with unique pharmacological properties. Several clinical studies have demonstrated its effectiveness in PMS treatment, and the scientific community has displayed tremendous interest in the study of this plant. Both diseases and multicomponent plant extracts affect several hormonal regulation systems. Thus, Vitex extract activates many of the major systems, including the hypothalamic-hypophyseal, opioid, and immune systems. The receptors for these systems are found in all tissues of the body, and a complex network of receptor interactions produces the necessary therapeutic effect without side effects. A systematic approach to the study of these interactions can lead to the emergence of future generations of drugs. With regard to Vitex, the large number of pharmacological effects of its individual chemical compounds and the high pharmacological activity of the whole extract require further study to detect synergistic interactions and ways of regulating the female reproductive system. This will allow the use of new treatment methods for diseases such as PMS and female infertility.

## **LIST OF ABBREVIATIONS**

PMS Premenstrual syndrome

IC<sub>50</sub> Concentration of half-maximal binding

MIC Minimum inhibitory concentration

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