




Vitex agnus-castus: Botanical features and area, chemical composition of fruit, pharmacological properties, and medicinal uses

Grigory Vasilievich Adamov^{1*} , Tamara Danilovna Rendyuk², Olga Leonidovna Saybel³, Tamara Darizhapovna Dargaeva³, Andrey Nikolaevich Tsitsilin⁴, Dmitry Olegovich Bokov²

¹Laboratory of Atomic-Molecular Bioregulation and Selection, All-Russian Scientific Research Institute of Medicinal and Aromatic Plants, Moscow, Russia.

²Institute of Pharmacy, Sechenov First Moscow State Medical University Sechenov University, Moscow, Russia.

³Center for Chemistry and Pharmaceutical Technology, All-Russian Scientific Research Institute of Medicinal and Aromatic Plants, Moscow, Russia.

⁴Laboratory of the Botanical Garden, All-Russian Scientific Research Institute of Medicinal and Aromatic Plants, Moscow, Russia.

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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.

INTRODUCTION

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

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 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

*Corresponding Author

Grigory Vasilievich Adamov, Laboratory of Atomic-Molecular Bioregulation and Selection, All-Russian Scientific Research Institute of Medicinal and Aromatic Plants, Moscow, Russia. E-mail: adamov@yilarnii.ru

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* (Hausskn.) Hand.-Mazz. (*V. agnus-castus* var. *pseudo-negundo* Hausskn.). 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.

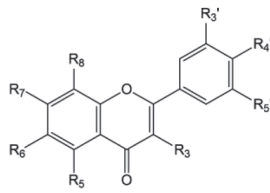
The lobes on the inner side of the lower lip at the point of attachment of the stamens are hairy. In the middle lobe, which is much larger than the other two, patches of long shaggy hairs reach the base of the incision. The pistil and four stamens exceed the corolla, and the ovary is round and up to 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

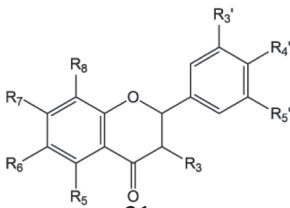
The fruits of the chaste tree contain several secondary metabolites: terpenoids (the main components of the essential oil), flavonoids, iridoids, and phenol carboxylic acids (Fig. 2). More



Figure 1. Blooming chaste tree.



1. R₃-OMe, R₅-OH, R₆-OMe, R₇-OMe, R₈-H, R_{3'}-OH, R_{4'}-OMe, R_{5'}-H.
2. R₃-H, R₅-OH, R₆-H, R₇-OH, R₈-H, R_{3'}-OH, R_{4'}-OH, R_{5'}-H.
3. R₃-H, R₅-OH, R₆-H, R₇-OGlu, R₈-H, R_{3'}-OH, R_{4'}-OH, R_{5'}-H.
4. R₃-OH, R₅-OH, R₆-OMe, R₇-OMe, R₈-H, R_{3'}-OH, R_{4'}-OMe, R_{5'}-H.
5. R₃-OMe, R₅-OH, R₆-H, R₇-OMe, R₈-H, R_{3'}-OH, R_{4'}-OH, R_{5'}-H.
6. R₃-OMe, R₅-OH, R₆-OH, R₇-H, R₈-H, R_{3'}-H, R_{4'}-OH, R_{5'}-H.
7. R₃-OH, R₅-OMe, R₆-OMe, R₇-OMe, R₈-H, R_{3'}-H, R_{4'}-OMe, R_{5'}-H.
8. R₃-OMe, R₅-OH, R₆-H, R₇-OH, R₈-H, R_{3'}-OH, R_{4'}-OH, R_{5'}-H.
9. R₃-OMe, R₅-OH, R₆-H, R₇-OH, R₈-H, R_{3'}-H, R_{4'}-OH, R_{5'}-H.
10. R₃-H, R₅-OH, R₆-H, R₇-OH, R₈-H, R_{3'}-H, R_{4'}-OH, R_{5'}-H.
11. R₃-OMe, R₅-OH, R₆-OMe, R₇-OMe, R₈-H, R_{3'}-OMe, R_{4'}-OMe, R_{5'}-H.
12. R₃-H, R₅-OH, R₆-H, R₇-OH, R₈-Glu, R_{3'}-H, R_{4'}-OH, R_{5'}-H.
13. R₃-H, R₅-OH, R₆-H, R₇-OH, R₈-Glu, R_{3'}-OH, R_{4'}-OH, R_{5'}-H.
14. R₃-H, R₅-OH, R₆-Glu, R₇-OH, R₈-H, R_{3'}-H, R_{4'}-OH, R_{5'}-H.
15. R₃-H, R₅-OH, R₆-Glu, R₇-OH, R₈-H, R_{3'}-OH, R_{4'}-OH, R_{5'}-H.
16. R₃-OH, R₅-OH, R₆-H, R₇-OH, R₈-H, R_{3'}-H, R_{4'}-OH, R_{5'}-H.
17. R₃-OMe, R₅-OH, R₆-OMe, R₇-OMe, R₈-H, R_{3'}-H, R_{4'}-OH, R_{5'}-H.
18. R₃-H, R₅-OH, R₆-OMe, R₇-OMe, R₈-H, R_{3'}-OH, R_{4'}-OMe, R_{5'}-H.



19. R₃-H, R₅-OH, R₆-H, R₇-OMe, R₈-H, R_{3'}-OH, R_{4'}-OH, R_{5'}-OH.
20. R₃-H, R₅-OH, R₆-H, R₇-OH, R₈-H, R_{3'}-OH, R_{4'}-H, R_{5'}-OH.

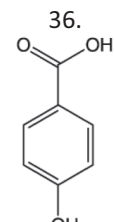
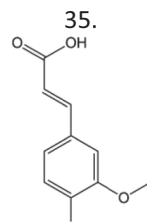
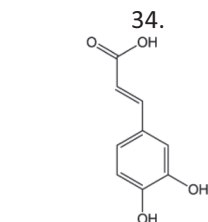
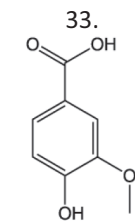
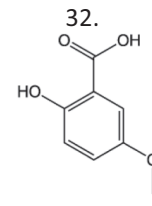
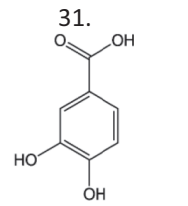
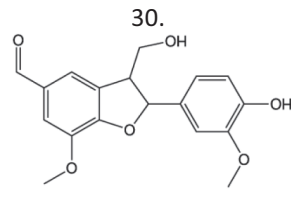
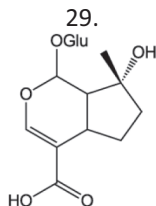
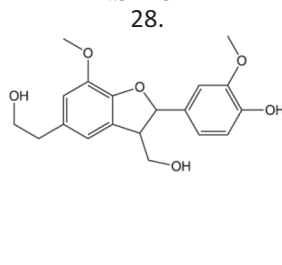
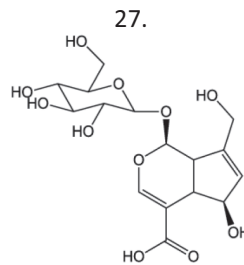
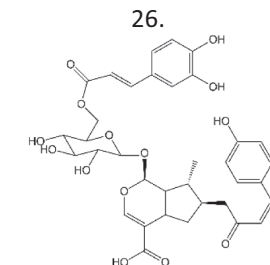
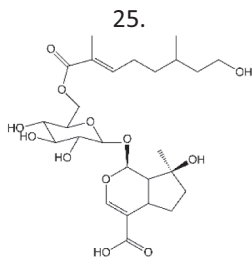
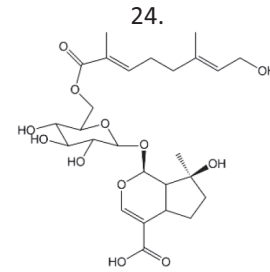
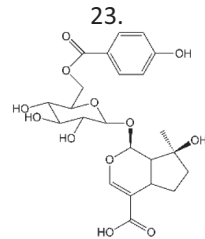
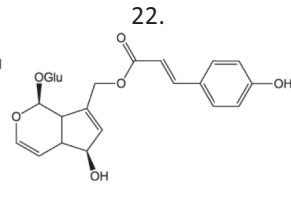
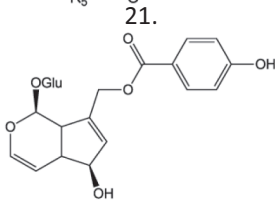


Figure 2. Compounds chaste tree.

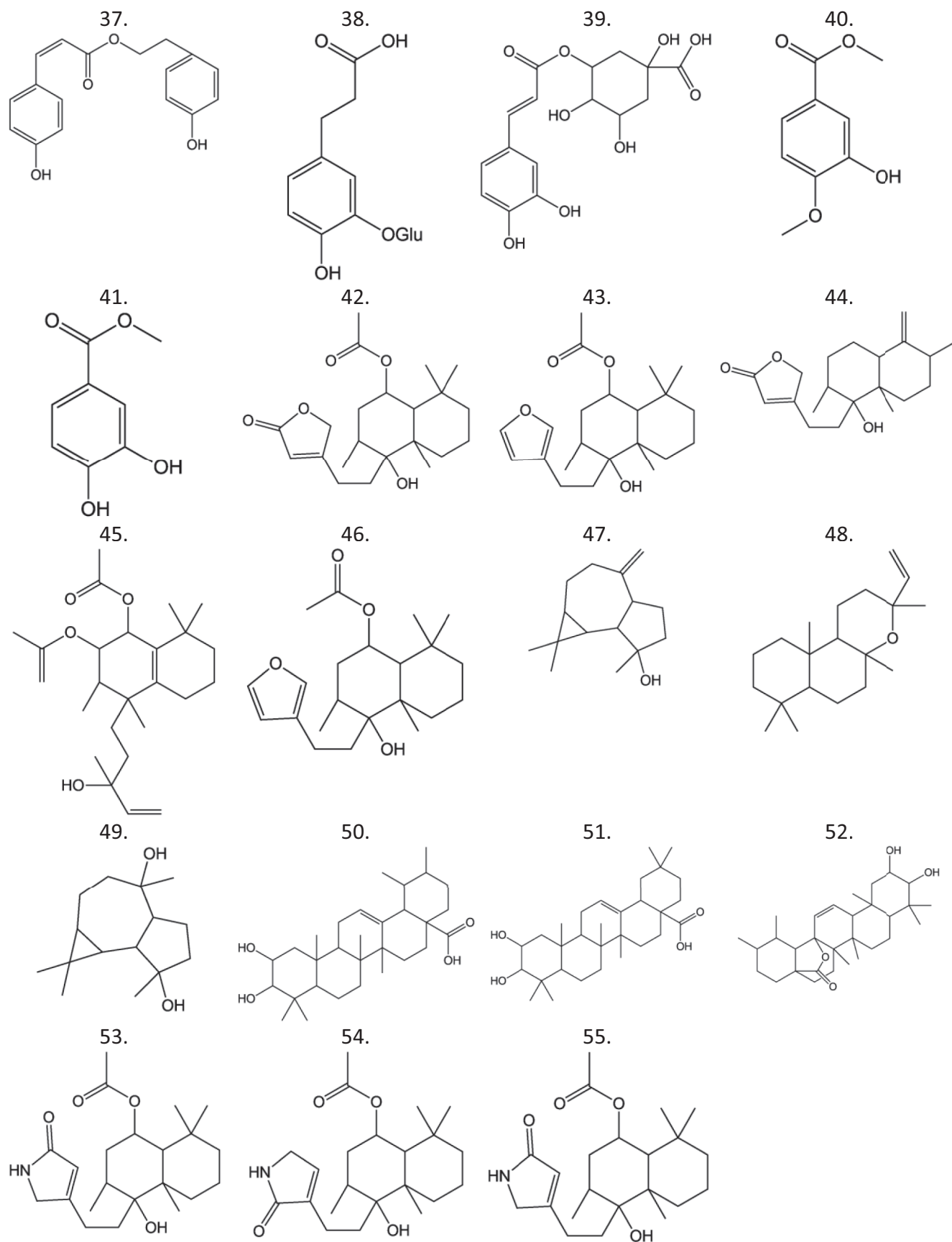


Figure 2. Compounds chaste tree.

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 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, agnucastoid A, agnucastoid B, agnucastoid 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-epi-manoyl oxide, aromadendren-4 α , 10 α -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: α -pinene, sabinene, β -pinene, β -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, δ -terpineol, terpinene-4-ol, krypton, α -terpineol, trans-carveol, β -citronelol, and α -terpinyl acetate. The other compounds are trans- β -caryophyllene, trans- α -bergamotene, cis- β -farnesene, trans- β -farnesene, dihydroaromadendren, curcumen, viridiflorene, β -bisabolene, β -basanene, myristicin,

palustrol, spatulenol, caryophyllene oxide, iceol, humulene epoxide II, τ -cadinol, 14-hydroxy-cis-caryophyllene, epi- α -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%), β -caryophyllene (2.1%–5.0%), and trans- β -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.

Slutz *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, H1-histamine, 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 (IC₅₀). The results showed that the whole extract exhibited dopaminergic activity (IC₅₀ = 52 μ g/ml), with the hexane fraction of the extract being more active (IC₅₀ = 32 μ 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 β , 7 β -diacetoxy-13-hydroxy-labda-8, 14-diene. There was no binding to the histamine receptor, benzodiazepine receptor, or histamine transporter.

Table 1. Bioactive substances identified in chaste tree fruits.

	Name	CAS number	Source
Flavonoids			
1	Casticin	479-91-4	(Chen <i>et al.</i> , 2011)
2	Luteolin	491-70-1	(Chen <i>et al.</i> , 2011)
3	Luteolin-7-glycoside	5373-11-5	(Mari <i>et al.</i> , 2015)
4	3,3'-dihydroxy-5,6,7,4'-tetramethoxyflavone		(Choudhary <i>et al.</i> , 2009)
5	3,7-dimethylquercetin	2068-02-2	(Chen <i>et al.</i> , 2011)
6	3-O-metyl kaempferol		(Chen <i>et al.</i> , 2011)
7	3-hydroxy-5,6,7,4' -tetramethoxyflavone	21764-09-0	(Makhmoor <i>et al.</i> , 2010)
8	3-methylquercetin	1486-70-0	(Chen <i>et al.</i> , 2011)
9	3-metyl kaempferol	1592-70-7	(Chen <i>et al.</i> , 2011)
10	Apigenin	520-36-5	(Chen <i>et al.</i> , 2011)
11	Artemetin	479-90-3	(Choudhary <i>et al.</i> , 2009)
12	Vitexin	3681-93-4	(Hajdú <i>et al.</i> , 2007)
13	Orientin	28608-75-5	(Hajdú <i>et al.</i> , 2007)
14	Isovitexin	38953-85-4	(Mari <i>et al.</i> , 2015)
15	Isoorientin	4261-42-1	(Fukahori <i>et al.</i> , 2014)
16	Kaempferol	520-18-3	(Chen <i>et al.</i> , 2011)
17	Penduletin	569-80-2	(Makhmoor <i>et al.</i> , 2010)
18	Eupatorin	855-96-9	(Hajdú <i>et al.</i> , 2007)
19	5,3',5'-trihydroxymetoxyflavanone		(Chen <i>et al.</i> , 2011)
20	5,7,3',5'-tetrahydroxyflavanone		(Chen <i>et al.</i> , 2011)
Iridoids			
21	Agnuside	1027-63-7	(Kuruüzüm-Uz <i>et al.</i> , 2003)
22	10- <i>p</i> -coumaroyl aucubin (eurostoside)	85802-33-1	(Kuruüzüm-Uz <i>et al.</i> , 2003)
23	6'- <i>O-p</i> -hydroxybenzoilmussaenosidic acid	87667-61-6	(Kuruüzüm-Uz <i>et al.</i> , 2003)
24	Agnucastoside A		(Kuruüzüm-Uz <i>et al.</i> , 2003)
25	Agnucastoside B		(Kuruüzüm-Uz <i>et al.</i> , 2003)
26	Agnucastoside C		(Kuruüzüm-Uz <i>et al.</i> , 2003)
27	Aucubin	479-98-1	(Kuruüzüm-Uz <i>et al.</i> , 2003)
28	Vladirol F		(Chen <i>et al.</i> , 2011)
29	Mussaenosidic acid	82451-22-7	(Kuruüzüm-Uz <i>et al.</i> , 2003)
30	Ficusal	321991-55-3	(Chen <i>et al.</i> , 2011)
Phenolic acids			
31	3,4-dihydroxybenzoic acid	99-50-3	(Choudhary <i>et al.</i> , 2009)
32	5-hydroxy-2-metoxybenzoic acid	2612-02-4	(Choudhary <i>et al.</i> , 2009)
33	Vanilic acid	121-34-6	(Choudhary <i>et al.</i> , 2009)
34	Caffeic acid	331-39-5	(Şarer <i>et al.</i> , 2008)
35	Ferulic acid	1135-24-6	(Chen <i>et al.</i> , 2011)
36	<i>p</i> -hydroxybenzoic acid	99-96-7	(Makhmoor <i>et al.</i> , 2010; Choudhary <i>et al.</i> , 2009)
37	<i>p</i> -hydroxy phenyl ethanol- <i>p</i> -coumarate		(Chen <i>et al.</i> , 2011)
38	Mysodendron	101705-37-7	(Kuruüzüm-Uz <i>et al.</i> , 2003)
39	Chlorogenic acid	327-97-9	(Şarer <i>et al.</i> , 2008)
40	Methylisovanilate	6702-50-7	(Kuruüzüm-Uz <i>et al.</i> , 2003)
41	Methyl -3,4-dihydroxybenzoate	99-50-3	(Makhmoor <i>et al.</i> , 2010)

Terpenoid compounds			
42	Vitexilactone	61263-49-8	(Hajdú <i>et al.</i> , 2007)
43	Vitexilactone B	329763-47-5	(Hajdú <i>et al.</i> , 2007)
44	Vitexilactone C		(Hajdú <i>et al.</i> , 2007)
45	Vitexilactone D	351427-18-4	(Li <i>et al.</i> , 2013)
46	Rotundifuran	50656-65-0	(Li <i>et al.</i> , 2013)
47	Spatulenol	6750-60-3	(Li <i>et al.</i> , 2013)
48	8-epi-manoyl oxide	596-84-9	(Chen <i>et al.</i> , 2011)
49	Aromadendren -4 α ,10 α -diol	70051-38-6	(Chen <i>et al.</i> , 2011)
50	3-Epicorosolic acid	52213-27-1	(Chen <i>et al.</i> , 2011)
51	3-epi-maslinic acid	26563-68-8	(Chen <i>et al.</i> , 2011)
52	lIlelatifol D		(Chen <i>et al.</i> , 2011)
53	Vitexilactam A		(Li <i>et al.</i> , 2002)
54	Vitexilactam B		(Li <i>et al.</i> , 2013)
55	Vitexilactam C		(Li <i>et al.</i> , 2013)

Wuttke *et al.* (2003) conducted a study in which fractions of chaste tree extract and individual compounds were obtained using preparative chromatography, after which the ability of the eluates to dose-dependently displace labeled ligands from the dopamine receptors of cultured pituitary cells was investigated. In addition to the compounds described above, it was possible to additionally establish the structures of three bioactive substances of the labdane type and six compounds of the clerodane type. The data showed that one of the substances, clerodadienol, had the highest activity and was minimally inferior to dopamine in inhibiting the release of prolactin from pituitary cells.

In vivo experiments aimed at assessing the probable effect of chaste tree extract on male reproductive function are important for understanding its mechanism of action. To do this, male mouse groups were separately injected intraperitoneally with bromocriptine (a dopamine receptor agonist), haloperidol (a dopamine receptor blocker), chaste tree extract, or a combination of the three. The levels of luteinizing hormone and testosterone were increased with the introduction of haloperidol due to the regulatory action of dopamine but decreased in all other cases (Nasri *et al.*, 2007). Decreases in the levels of the studied hormones due to the combined intake of chaste tree extract and haloperidol indicate the presence of additional regulatory mechanisms that are not associated with dopamine.

Opioid activity

There are reports that the endogenous opiate system is closely related to the regulation of the hypothalamic–pituitary axis. The presence of biologically active substances in chaste tree fruits potentially affects the opioid system and may account for the unique effect of this plant in females (Facchinetti *et al.*, 1994). A study reported on the affinity of the lipophilic fractions of chaste tree fruit extract for μ - and κ -opioid receptors, with IC_{50} values of 36 and 22 μ g/ml, respectively (Meier *et al.*, 2000).

Research on the effect of chaste tree fruits on the opioid system also confirmed that the petroleum, chloroform, and ethyl

acetate fractions (lipophilic fractions) had affinities for the μ - and δ -opioid receptors, while the aqueous fraction showed no such affinity. Among the marker substances of the studied raw material, the greatest contribution was found to be made by the flavonoid casticin, with IC_{50} values of 2.84 ± 0.707 and 2.05 ± 0.631 μ M for μ - and δ -opioid receptors, respectively (Webster *et al.*, 2011).

Estrogenic activity

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 μ 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 μ g/ml. These compounds showed affinity only for the β -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 β -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 α - and β -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 IC₅₀ 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 α -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 μ g/ml, while the MIC ranges of 1,8-cineole, α -pinene, and streptomycin were 4–8, 5–10, and 50–200 μ g/ml, respectively. The MIC values of the essential oil against fungi were 45–219 μ g/ml, while those of 1,8-cineole, α -pinene, and bifonazole were 4–7, 4–8, and 100–250 μ 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

B. However, negative results were obtained in studies of the antioxidant activity of the essential oil 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
IC50	Concentration of half-maximal binding
MIC	Minimum inhibitory concentration

CONFLICTS OF INTEREST

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