Reviews

# A review of the important chemical constituents and medicinal uses of *Vitex* genus

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**Abstract**

**Plants and their active constituents play an important role in the prevention of a variety of ailments. Most of the species of the Genus Vitex are used therapeutically in ancient Indian systems of medicine especially, Ayurveda and Siddha. The genus *Vitex* contains about 270 species distributed around the world. These species contain a variety of potentially bioactive molecules, such as iridoids, flavonoids, diterpenoids, derivatives, and phytosteroids. Most of these species possess analgesic, anti-inflammatory, antimicrobial, antioxidant, hepatoprotective, antihistamine, and antiasthmatic properties. This work reviews the pharmacological evidence for the effects of extracts of plants from the genus Vitex, giving an overview of the most widely studied biological effects and the known phytochemical constituents.**

***Key words***: medicinal plants; pharmacology; phytochemistry; indian systems of medicine

## 1. Introduction

In recent times, interest in plant research has increased all over the world owing to its potential use in traditional systems of medicine for treating a wide variety of diseases. Various medicinal plants have been identified and modern scientific approaches have been used to study their authenticity, safety and efficacy of their therapeutic use. The results highlight the great potential of medicinal plants in the field of pharmacology. The genus *Vitex* includes approximately 270 known species of trees and shrubs in tropical and sub-tropical regions, although a few species are also found in temperate zones.

*Vitex trifolia* L. is a shrub or shrubby tree that may grow up to 6 meters in height. Its origin is unknown and several varieties have been described in countries as are apart as India and Mexico. *Vitex mollis, Vitex piramidata*, *Vitex pubescens*, *Vitex agnus-castus* and. *Vitex gaumeri* are reported to possess antidysentery, analgesic, anti-inflammatory and anti-tumor activities and they are used in folk medicine for the treatment of scorpion stings and gastrointestinal disorders. In the Ayurveda and Unani systems of medicine, the leaves [1] and seeds of *Vitex negundo* are widely used for the treatment of rheumatism and inflammatory joint conditions. In India, the species *Vitex glabrata, Vitex leucoxylon, Vitex penduncularis, Vitex pinnata,* and *Vitex trifolia* are found to have insecticidal properties. *Vitex*

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*negundo* has larvicidal activity against the mosquito species *Culex quinquefasciatus* and *Anopheles stephensi* and is used as a mosquito deterrent againt *Aedes aegypti* and *Vitex rotundifolia* also acts as deterrent against *Aedes aegypti*. Several other *Vitex* species are currently being investigated for use in specific pest control programs [2].

## 2. Species of the genus *Vitex*

### *2.1. Vitex agnus-castus*

*Vitex agnus-castus* L. (Verbenaceae) is a small tree or shrub which is widely distributed along the Anatolian coast line and is used in the treatment of premenstrual problems and hyperprolactinemia. In Anatolian folk medicine, it is used as a diuretic, digestive, antifungal, and anxiolytic agent. This plant exhibits a number of activities such as an action against P388 leukemia cells, inhibition of prolactin synthesis and an inhibitor for dopamine $D_2$ and opiod receptors. The antiepileptic activity of the hydrophilic extract of the fruit has been evaluated using the kindling model of epilepsy. It contains iridoids flavonoids diterpenoids, essential oils and ketosteroids [3]. The methanolic extract of the flowering stems of *Vitex agnus-castus* contains three new iridoids: 6'-*O*-foliamenthoylmussaenosidic acid (agnucastoside A), 6'-*O*-(6, 7- dihydrofoliamenthoyl) mussaenosidic acid (agnucastoside B) and 7-*O*-trans-p-coumaroyl-6'-*O*-trans-caffeoyl-8-epiloganic acid (agnucastoside C) in addition to four known iridoids (aucubin, agnuside, mussaenosidic acid and 6'-*O*-*p*-hydroxybenzoylmussaenosidic acid) and one known phenylbutanone glucoside (myzodendrone) [4]. The dried ripe fruit of *Vitex agnus-castus* L. is widely used for the treatment of premenstrual syndrome.

Major components of the essential oil are 1, 8-cineole, sabinene, a-pinene, a-terpinyl acetate and (Z)-β-farnesene. In all systems, the aqueous extract exhibited greater activity than other extracts (hexane, dichloromethane, ethyl acetate and methanol) and the oil. As expected, the total phenolics content was very high in this extract. The dichloromethane extract has been found to be rich in flavonoids and a positive correlation has been found between the antioxidant activity potential and the total phenolic and flavonoid contents of the extracts [5].

From the fruits, one new diterpene, 6β, 7β-diacetoxy-13-hydroxy-labda-8, 14-diene, as well as two previously described diterpenes, rotundifuran and vitexilactone, have been isolated. All the diterpenoids obtained are of the labdane type. Structural determinations were mainly based on 1D and 2D NMR spectra and MS data interpretation. The compounds, 6β, 7β-diacetoxy-13-hydroxy-labda-8, 14-diene and rotundifuran, showed a high affinity for dopamine-$D_2$-receptors [6]. The compound vitexilactone was isolated from the leaves of *Vitex cannabifolia* and the fruits of *Vitex rotundifolia* Linn. All the physical and spectroscopic data were identical to those of rotundifuran described in the literature.

A novel labdane diterpene alkaloid, vitexlactam A, was isolated in the form of prisms from the *n*-hexane extract of the fruits through normal and reverse phase column chromatography. Its structure was shown to be 6β-acetoxy-9α-hydroxy-13(14)-labden-16, 15-amide, based on chemical and spectral evidences, including 1D and 2D NMR spectra. The structure was confirmed by X-ray crystallographic analysis. The compound, vitexlactam A, is the first naturally occurring labdane diterpenoid containing an α, β-unsaturated γ-lactam moiety [7].

Four new flavonoids, luteolin 6-C-(4"-methyl-6"-*O*-trans-caffeoylglucoside), luteolin 6-C-(6"-Otrans-caffeoylglucoside), luteolin 6-C-(2"-*O*-trans-caffeoylglucoside), and luteolin 7-*O*-(6"-*p*-benzoylglucoside), together with four known ones 5, 4'-dihydroxy-3, 6, 7, 3-tetramethoxyflavone,

luteolin, artemetin and isorhamnetin, have been isolated from the root bark. Their structures were elucidated using spectroscopic metheods [8].

A methanol extract was tested for its ability to displace radio-labeled estradiol from the binding site of estrogen receptors alpha (ERα) and beta (ERβ). Progesterone receptors were up-regulated in the Ishikawa endometrial cancer cell line. Bioassay-guided isolation, using ER binding as a monitor, resulted in the isolation of linoleic acid as one possible estrogenic component of the extract. Linoleic acid also stimulated mRNA ER β expression in T47D: A18 cells,and PR expression in Ishikawa cells [9].

Subjects who took mixed essential oil of *vitex* with any form of progesterone supplementation (including progesterone cream) consistently noted breakthrough bleeding. Any woman who is concurrently taking any form of hormone replacement therapy should be closely monitored by a health professional when *vitex* is started [10].

The starting material for the isolation of single constituents was the extract which was obtained by extracting finely ground seeds with aqueous ethanol 70 % (*v/v*) and then drying gently in vacuo. The ethanol extract of the dried ripe fruit displays cytotoxic activity against some human cancer cell lines resulting in the induction of apoptosis.

The extract inhibits prolactin release which is caused by selective stimulation of $D_2$-type pituitary dopamine receptors. In clinical investigations and double-blind trials with preparations containing this extract, a decrease in pathologically increased prolactin levels and an effect on prolactin release in healthy subjects have been demonstrated. The extract appears effective and was well tolerated and further evaluation of this agent in the treatment of cyclical mastalgia is warranted [11].

*2.2. Vitex trifolia* Linn

*Vitex trifolia* Linn. is a tropical shrub widely disibuted in Pacific-Asian countries, such as India, Sri Lanka, China, Philippines, Indonesia, North Australia, New Caledonia and French Polynesia. It has also been reported in East Africa and introduced to many islands in the Central Pacific and Hawaii. The anti-inflammatory potential of an aqueous extract of *Vitex trifolia* leaves was evaluated by monitoring its effects on the modulation of cytokines, mediators of inflammation, as well as on the expression profiles of inducible nitric oxide synthase, which produces the free radical nitric oxide. The leaves are used internally or externally in baths to cure Ciguatera fish poisoning-related pruritus. It is used as an anti-pyretic, anti-inflammatory, and nematicidal agent and to increase body weight and it has also been reported to have anti-tumor activity [12]. The petroleum ether and ethanol extracts of *Vitex trifolia* leaves exhibited moderate inhibition of both Gram-positive and Gram-negative bacteria [13].

Biological assays of plant organic extracts have shown a number of important activities. Hexanic and dichloromethanic extracts, when prepared from stems and foliage, have proved to be very toxic against cultures of several cancer cell lines. Also, an important anti-feeding activity against the insect pest *Spodoptera frugiperda* has been recorded. The hexanic extract of the leaves completely inhibited the growth of the fungal plant pathogen *Fusarium* sp. The essential oils of *Vitex trifolia* have been shown to having insecticidal activity [14]. An abietane-type diterpene, named vitetrifolin A, and two labdane-type diterpenes, named vitetrifolins B and vitetrifolin C, were isolated from the acetone extract of the fruits of *Vitex trifolia* Linn. along with three known diterpenes, rotun-difuran, dihydrosolidagenone and abietatriene 3β-ol.

*2.3. Vitex cymosa*

*Vitex cymosa* Bertero is a small tree widely distributed in the Central and Amazon regions of Brazil, where it is popularly known as Taruma-do-Igapo and Taruma-do-alagado. A new ecdysteroid, 26-hydroxypinnatasterone, together with 20-hydroxyecdysone, have been isolated from the stem bark of *Vitex cymosa* [15].

### *2.4. Vitex polygama*

The species *Vitex polygama* Cham. is found mainly in the states of Bahia, Minas Gerais and Rio de Janeiro and the bark and fruits of this plant are traditionally used as emenagogues and diuretics. The compounds 20-hydroxyecdysone, ajugasterone C, ajugasterone C monoacetonide and turkesterone have been isolated from the branches of *Vitex polygama* [16].

### *2.5. Vitex canescens*

*Vitex canescens* Kurz is a medium-sized tree widely distributed throughout Thailand. A number of *Vitex* species have been investigated in a search for ecdysteroids. From the bark of *Vitex canescens* 20-hydroxyecdysone and turkesterone, a new ecdysteroid, canescensterone, have been isolated along with the teroid, 24-epi-abutasterone, from the root. The compound 20-hydroxyecdysone, 24-epi-makisterone A, shidasterone, calonysterone and turkesterone have also been isolated from this plant species [17] .

### *2.6. Vitex negundo* Linn

*Vitex negundo* Linn. Verbenaceae, known as Nirgundi in Hindi, grows widely in wastelands and has also been used as a hedge-plant. It is an erect, slender tree, 2–5 m in height, with quadrangular branchlets growing throughout India. The leaves have five leaflets in a palmate arrangement, which are lanceolate, 4–10 cm long, with a hairy underside and pointed at both ends. It has many bluish purple flowers. The fruit is succulent, and black when ripe, rounded and about 4 mm in diameter. Phytochemical studies of *Vitex negundo* have afforded several types of compounds, such as volatile oils, lignans, flavonoids, terpenes (triterpenes, diterpenes, sesquiterpenes) and steroids [18-19].

The most common flavonoid glycosides from an ethanolic extract of the leaves of *Vitex negundo* are 5-hydroxy-3, 6, 7-trimethoxy-2-(3, 4-dimtoxypheny)-4H-chrome-4-on and 5, 7-dihydroxy-2-(3, 4-dihydroxyphenyl)-4H-chromen-4-one. The methanolic extract also contains, Negundoside, Agnuside, and Vitegnoside. From bark of *Vitex negundo* Linn., *p*-hydroxybenzoic acid and β-sitosterol have been isolated, and identified from the methanol and hexane extracts of *Vitex negundo*.

In the acetoacetate fraction of the seeds , two phenylnaphtha-lene-typelignans have been- obtained and identified as 6-hydroxy-4-(4-hydroxy-3-methoxy-phenyl)-3-hydroxy-methyl-7-methoxy-3, 4-dihydro-2-naphthaldehyde and vitedoamine A. It is used to treat dyspepsia, colic, rheumatism, worms, boils and leprosy. The roots contain a furanoeremophilane. Tyrosinase inhibitory lignins have been found in the methanol extract of the roots of *Vitex negundo* Linn [20].

The hepatoprotective activity of the ethanolic exract of *Vitex negundo* leaves has been investigated as a treatment of hepatotoxicity produced by administering a combination of three anti-tubercular drugs, isoniazid-7.5 mg/kg, rifampin-10 mg/kg and pyrazinamide-35 mg/kg. This plant contains many polyphenolic compounds, terpenoids, glycosidic iridoids and alkaloids. Since polyphenolic compounds have a high antioxidant potential, the antioxidant potency of *Vitex negundo* was investigated using a variety of established *in vitro* systems, such as 2, 20-azino-bis 3-ethyl benzothiazoline- 6-sulfuric acid/lipid peroxide/ superoxide/hydroxyl radical scavenging and iron ion

chelation.

In Ayurvedic medicine and in various recent experimental models, the oral administration of the plant leaves have been claimed to have anti-inflammatory, analgesic, anti-hyperglycemic and anti-bacterial, anti-asthmatic and anti-implantation activities [21].

The methanolic root extracts (*Vitex negundo* and *Emblica officinalis*) significantly antagonized the lethal action induced by Vipera russellii and Naja kaouthia venom in both *in vitro* and *in vivo* studies. The petroleum ether extract of the leaves has been evaluated in the laboratory for larvicidal activity against the larval stages of Culex tritaeniorhynchus The crude aqueous extract of *Vitex negundo* Linn. leaves has been investigated for laxative activity. An ethanolic extract was tested for anthelmintic activity against the Indian earthworm Pheritima posthuma.

### *2.7. Vitex peduncularis* Wall

Extraction of the dried leaves yielded pachypodol, ursolic acid, 2α-hydroxyursolic acid, vitexin and peduncularcin. In Orissa, a decoction of the leaves is taken as tea during the cold season. An infusion of leaves administered intramuscularly or orally to rabbits increases the osmtic resistance of cells and inhibits haemolysis produced by saponin ,cobra venom, bile salts, or saline solution [22] .

### *2.8. Vitex pinnata* Linn

An ecdysteroid, pinnatasterone, together with 20-hydroxyecdysone and turkesterone has been isolated from the bark of this plant. Pinnatasterone exhibited weak biological activity in the pupariation test using housefly larvae. The flavonoids, luteolin, iso-orientin, and vitexin, have been isolated from the flowers. In Brunei, the young leaf shoots are eaten raw to treat hypertension and fever. A root-tea is taken for backache, bodyache and fatigue [23].

### *2.9. Vitex leucoxylon* Linn

An ethanolic extract of the leaves was found to reduced spontaneous motor activity. In addition the ethanolic extract produced significant inhibition of granulation tissue formation while a cold aqueous infusion reduced total serum cholesterol. In acute inflammation, a cold aqueous infusion as well as a mixture of flavonoids of *Vitex leucoxylon* Linn exhibited anti-inflammatory activity without any effect on chronic inflammation [24].

### *2.10. Vitex altissima* Linn.

This is a large tree with a grey, scaly, fibrous bark. The leaves are 3-foliolate; petiole angular or winged; the leaflets are subsessile, elliptic-lanceolate while the flowers are bluish-white, terminal paniculate cymes. The fruit is mostly used to treat stomatitis, cardiac diseases, anorexia, blindness, leprosy and worm infestation, heart-wood, leaves and bark contain the flavonoid–vitexin [25].

### *2.11. Vitex mollis*

*Vitex mollis* is a tree native to Mexico that grows up to 18 m high. It can be found in humid and tropical regions. The fruit is known as ‘uvalama’ in Sinaloa. This fruit is a drupe with a fleshy edible part consisting of an epicarp and mesocarp, commonly known as peel and pulp, respectively. The fruit is eaten fresh, as a conserve, or as a boiled drink with milk and sugar. It has been reported that some indigenous cultures used this fruit as well as other parts of the plant to treat diseases, such as fever, diarrhea, dysentery and abdominal colic. It also has anti-inflammatory and analgesic properties. In addition, uvalama has been suggested for the treatment of scorpion stings and to alleviate menstrual pains. Fruits are important sources of minerals, fiber and vitamins, and they provide essential dietary nutrients [26].

## 3. Conclusion

This review summarizes the main biological findings and known phytochemical constituents of the *Vitex* genus. The studies conducted to date have demonstrated that the plants of the *Vitex* genus contain many biologically active compounds with antioxidant, anti-inflammatory, antimicrobial, hepatoprotective, analgesic antihistamine, anti-implantation, and antiasthmatic effects. Thus, the *Vitex* genus deserves further evaluation as a source of hepatoprotective agents. Indeed, there is a current need for new plant-derived bioactive agents; thus genus *Vitex* may be an important natural source for the development of new drugs and may provide a cost-effective means of treating heart problems and other important diseases in the developing world.

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