International Journal of Research in Pharmacy and Pharmaceutical Sciences
www.pharmacyjournal.in
ISSN: 2455-698X
Received: 01-06-2023, Accepted: 16-05-2023, Published: 01-06-2023
Volume 8, Issue 2, 2023, Page No. 119-125

Introduction, plant history, pharmacological and biological activities of vitex negundo: A review

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Abstract
The Verbenaceae family includes Vitex negundo, a tiny tree with thin, grey bark. This herb is abundantly available and has pharmacological effects against a variety of ailments in the traditional medical system. Secondary metabolites are present in varying numbers in all plant sections, but particularly in the leaves. This plant is thought to have a variety of therapeutic applications because to its high phytoconstituent content, including anti-microbial, anti-inflammatory, astringent, bronchodilator, CNS-depressant, detoxicant, diuretic, emmenagogue, anti-cancer, and hepatoprotective properties. Vitex negundo leaf extract is used as a sedative, nervine tonic, and vermifuge. In order to aid in the advancement of modern medicine, this review intends to give information on therapeutic uses, medicinal uses, pharmacological activities, and biological activity.

Keywords: nirgundi, chaste tree, negundoside, nishindaside, vitexin, therapeutic uses

Introduction
Plants used as medicines for centuries nowadays are popular. Therefore, there is an urgent need for their accurate identification and use. The earlier literature suggests the study of plants was neither exhaustive nor required, in fact, a study of greater scope was not. The current situation changed due to a high level of ethical consciousness, statutory requirements, and business advantages. In such situations, it is obvious that archive knowledge needs to have been revitalised and reaffirmed. A compilation of literature-based information is made available to individuals who need it. The plant Vitex negundo, also referred to as Nirgundi, is a member of the Verbenaceae family. It is a well-known plant because of its two major characteristics: reducing sexual desire and usage in treating female illnesses, particularly those involving the female reproductive system. Both central Asia and the Mediterranean region contain large populations of this plant. Pliny and Dioscorides, two of the most important herbalists in history, did excellent work on it and described its usage as an antipyretic and its ability to induce perspiration, urine, and many other bodily functions. De Materia Medica makes reference to the benefits of this plant, and numerous workers have occasionally remarked on its analgesic, antiandrogenic/antifertility, and anti-inflammatory properties [1-5].

Fig 1: Whole Plant of Vitex negundo

Taxonomic / scientific classification
Kingdom - Plantae – Plants
Sub Kingdom - Tracheobionta - Vascular plants
Super Division - Spermatophyta – Seed
plant Division - Magnoliophyta - Flowering Plant
Class - Magnoliopsida - Dicotyledons
Sub Class - Asteridea Order – Lamilales

Family - Verbenaceae Genus - Vitex linn

Species - Vitex negundo Linn. (Chaste tree

Latin name: vitex negundo Linn. (Verbenaceae).

Indian name: Sambhalu, Nirgundi, Sephali, Panjgusht (fanjangusht).

English Names: Five-Leaved Chaste Tree, Monk`s Pepper.

Medicinal importance

Herbal medicine aims at restoring the body to its natural state of health rather than only treating an illness. When it comes to enhancing health and wellness, the phytochemical components of medicinal plants frequently operate separately, additionally or synergistically. Focus must now be placed on the medical uses of Vitex negundo after examining the numerous chemical components found in its various portions. Vitex negundo has been credited with a wide range of therapeutic characteristics, and it has also been widely utilised to cure a wide range of illnesses. Three categories traditional medicine, folk medicine, and pharmacological evidence have been used to group these features [6-8].

- **Traditional medicine**

Indian Ayurveda, Arabic Unani medicine, and traditional Chinese medicine make up the majority of traditional medicine. Due to historical events and cultural beliefs, populations in Asia and Latin America still practice traditional medicine. In China, traditional medicine makes up about 40% of all healthcare services. In Around 80% of people in Africa depend upon traditional medicine for their medical needs [9-10].

- **Folk medicine**

Despite the development of modern medicine, folk systems of medicine continue to be used by a sizable portion of the population, particularly those in rural and tribal areas. To highlight the ethnobotanical variety and ubiquity of the plant, the entries detailing the several uses of Vitex negundo in folk medicine have been organized regionally [11].

Plant history

The word "Nirgundi" in Sanskrit can refer to any plant or substance that defends the body against disease. This herb is described in Ayurveda and has a variety of applications. According to Charaka's, Nirgundi is a Visaghna-Antitoxin and a Krmighna-Antithelmintic. In the traditions of Ayurveda, Nirgundi is a plant having high potency (Virya), a pungent, bitter, and astringent taste (Rasa), as well as a pungent aftertaste (Vipaka). Additionally, it is stated that while it reduces the vatta and kapha dosas, it stimulates or intensifies the pitta dosa. Additionally mentioned are its antipyretic, anti-inflammatory, and anti-arthritic effects. Ancient Roman wives whose husbands were deployed overseas with the legions spread the fragrant leaves over their couches for this purpose because the medicine was known for its ability to suppress sexual desire. This substance is known as monk's berry or monk's pepper because in the past, monks was chewing nirgundi fruits to suppress their sex desires. The plant's stem was found to have beneficial effects on the pituitary gland, particularly in terms of luteinizing production of hormones and prolactin secretion reduction. These beneficial effects may help some infertile women as well as those who experience breast tenderness related to premenstrual disorder. Plants may also be utilised to decrease hot flashes caused by menopause's reduced progesterone production. Additionally, it can be used to control ovulatory cycles. In past centuries, plant leaf oil was used for relieving severe pain from gout, rheumatism, sciatica, and general body pains [1-5].

Fig 2: Vitex negundo

Distribution of plant

East Africa, Madagascar to Iran, Burma, Pakistan, Sri Lanka, China, Taiwan, Japan, Afghanistan, India, Philippines, Thailand, along with Malaysia's region, east to the Palace Islands, Caroline Island, and Moriana islands are all places where the species Vitex negundo are found. Additionally, it is widely grown all over Europe, North America, and the West Indies. It can be found in various

regions of Himachal Pradesh and the outer Himalayan region of India at a height of 1500 meters [1-4].

Plant characteristics

The 8-meter-long Nirgundi tree or spreading shrub has thin, grey, and slightly rough bark. Branchlets have four angled, very tomentose leaves that are 3 to 5 foliate, opposing, and quite long terminal leaflets. Small hairs cover the dorsal side of the leaves, which have a dense ventral pubescence, a shallow, blunt toothed border, and long leaf stalks. Panniculate raceme with bluish-white to bluish-purple flowers. Black and about pea size, the berry. Fruits have four valves, a cap, and an egg-like structure [1, 4, 12-14].

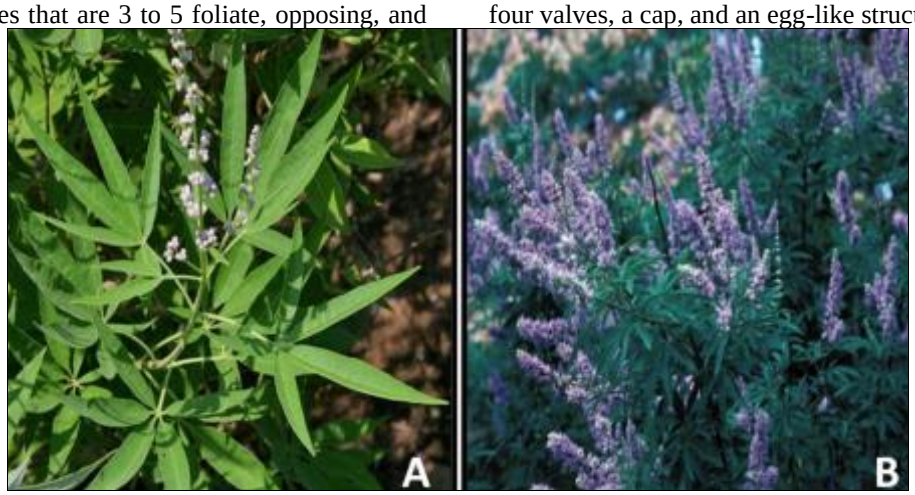

Fig 3: Plant of Vitex negundo
A-plant with leaves showing palm like structure, B- plant in flowering stage

Therapeutic uses

Table 1: The therapeutic uses of Vitex negundo are given in [1, 4, 12-14, 15-17]

Plant Part	Uses
Powdered Roots	Antirheumatic, Hemorrhoid, Demulcent, Worms problem, Skin problems, Dyspepsia and Colic.
Tincture from Roots & Bark	Antirheumatic and Irritable bladder.
Roots and Leaves	Bitter tonic, expectorant, diuretic and anodyne.
Leaves	To treat headache and catarrh, use the pillow filling as a poultice in an aromatic bath. Over the spleen and in swelling, use crushed leaves as a medicament. The decoction of leaves is used as a febrifuge for ulcers and wounds. Leaf juices treat coughs, sore throats, and remove worms from wounds. Significant antifungal property against the fungus Trichophyton mentagrophytes is present in leaves ethanol extract.
Flowers	In Cholera, Diarrhoea, Liver disorders and as Cardiac tonic
Seeds	Boiled seeds or its water extract used internally to prevent spreading of toxins from dangerous bites of animals.
Whole plant	Galactagogue, Emenagogue, Antigastalgic, Antiflatulant, Antiparasitic and Analgesic.
Other uses	Reduces sex desire, improves sexual morality, and treats premenstrual syndrome and menstruation problems. used to treat fibrocystic breast disease and endometriosis. promotes hair development and is used to treat bronchitis, asthma, leucoderma, eye disorders, and children's uncomfortable teething. About 70 common and difficult disorders are treated using oil made from fresh leaves. Additionally utilised in the treatment of oxidative stress, stomach cancer, snake venom neutralisation, antibacterial activity, anxiolytic activity, CNS activity, antioxidant, anti-inflammatory activity, and anti-inflammatory activity.

Other uses of vitex negundo

Before making metallic powders into tablets, the granules are soaked in the leaf juice. Parts of Chhattisgarh are known for using herbal shoes made from nirgundi wood, which are said to be useful in the treatment of rheumatism. Its use for punishment in China is another fascinating fact. The Oroan communities use the branches of the tendu and nirgundi trees, which are thought to have magical power, to ward off the bad eye, fight off evil spirits, and ward off other negative influences from standing crops. When there was fighting in the past, V. negundo was employed as a totem plant. The ulingai creeper (Cardiospermum halicacabum) was used for soldiers who were ready to take over a fort, whereas the occupying force was required to wear nocci blossoms. [18]

Flowers from Sindhuvara, namely the white type known as Sweta Nirgundi, were eaten as vegetables because of their cooling (sita) and bile-destroying (pittanasana) properties. The Lokopakara notes that sambar is made from boiled nirgundi shoots, fresh lime, tree cotton roots, and turmeric powder. When boiled with 'high meat' (decomposed meat) or tainted meat or fish, fresh leaves are said to have the ability to neutralise the odor. In Hazaribagh, cotton and warm clothes are kept in dry leaves. During the rainy season, leaves are burned in a fire to prevent mosquitoes from biting people and animals. The smoke also deters other insects like Guleria and Vasisth. Bedbugs are repelled by dry leaf powder, according to the Lodha tribe. mosquitoes are attracted by dry leaf powder when used alone or when mixed with dhoop smoke [18, 19-23].

Table 2: Medicinal uses of vitex negundo in India

Region	Used in the treatment of
Andhra Pradesh	Asthma, cancer, jaundice and used as bath for women in puerperal state and for new born children

Assam	Urticaria, cellulitis, abcesses, carbuncles, eczema and liver disorders.
Himachal Pradesh	Kwashiorkor and for wounds, body ache and toothache.
Karnataka	Ferbrile, catarrhal and rheumatic afflictions and for migraine, rheumatism and encephalitis.
Maharashtra	Expectorant and joint ache
Odisha	Jaundice and antidote for snake bite
Tamil Nadu	Respiratory disorders, fever, headache and for eye pain.
Uttar Pradesh	Refrigerant for cattle and used as 48 different types of aliments

Table 3: Medicinal uses of vitex negundo outside India

Bangladesh	**Weakness, headache, vomiting, malaria and black fever**
China	Common cold, flu and cough.
Nepal	Sinusitis, whooping cough, backache and used as toothbrush
Pakistan	Used as anti- allergenic agent and as gun and skin disease.
Philippines	A number of aliments including cancer.
Sri Lanka	Eye disease, toothache, rheumatism and used as tonic, carminative and vermifuge. [24]

Pharmacological evidence

According to estimates, 14–28% of higher plant species are utilized medicinally. Following up on the plants' use in traditional medicine led to the discovery of about 74% of the pharmacologically active plant-derived components. Secondary plant metabolites, or phytochemicals, have received a lot of attention recently as potential sources for pharmaceuticals. Nearly every component of Vitex negundo, from the root to the fruits, is rich in phytochemicals called secondary metabolites that give the plant a variety of medicinal benefits. The traditional therapeutic powers of the medicinal plants are currently fashionable. Therefore, it is thought that its accurate identification and utility are urgently needed. Experimental evidence has been required by the scientific community in order to further highlight Vitex negundo's importance in medicine. Scientific studies have been created and undertaken in order to validate pharmacological claims, drawing inspiration from these traditional and folk medical systems [25].

Pharmacological activities

All parts of the Vitex negundo plant, from the leaves to the roots, contain different phytochemicals that give the plant a range of therapeutic benefits. Experimental proof was required by the scientific community to support Vitex negundo's traditional and folk medical systems. Consequently, numerous scientific investigations have been carried out to support these statements.

1. Antioxidant activity and FRS activity

Free radicals can be stopped from damaging cells by neutralizing them with antioxidants, which are chemicals. Vitex negundo leaf extract decreased the levels of catalase, superoxide dismutase, and glutathione peroxidase in Freund's adjuvant-induced arthritic rats. Particularly flavonoids exhibit FRS action and have the potential to be antioxidants. Rooban *et al*. confirmed the antioxidant and therapeutic effects of Vitex negundo flavonoids in controlling solenoid-induced cataract [26-27].

2. Anti-inflammatory and analgesic activity

About half of analgesics, which relieve pain by lowering inflammation, include anti-inflammatory medications. The research carried out by Mandal *et al*., Sori *et al*., and Dharmasiri *et al*. confirmed the anti-inflammatory and analgesic properties of Vitex negundo [28].

3. Histomorphology and anti-cancer activity

Tandon *et al*. have demonstrated on rats that Vitex negundo extracts have a positive histomorphology effect. The study found dose-dependent changes on the tissues of the heart, liver, and lungs but not the stomach. The U-937 cell line was used to test the ethanolic Vitex negundo extract's anticancer properties. While Yunos *et al*. showed that the plant extracts were non-cytotoxic on mouse mammary and Genito-urinary cells, Diaz *et al*. demonstrated that the chloroform extracts of leaves are toxic to human cancer cell line panels [29-30].

4. Effect on reproductive potential

Research on the ability of Vitex negundo to reproduce generated conflicting results. Several investigations shown the suppressive effect of Vitex negundo extract on spermatogenesis and reproduction in male rats. However, Hu *et al*. found that the same extract showed estrogen-like properties and suggested using it in hormone replacement treatment. The potential of Vitex negundo seeds to cure polycystic ovarian syndrome was investigated by Kakadia *et al* [31-32].

5. Enzyme-inhibitory activity

It has been demonstrated that Vitex negundo root preparations inhibit a number of enzymes, including butyryl-cholinesterase, lipoxygenase, chymotrypsin, xanthinoxidase, and tyrosinase. Aqueous Vitex negundo extract was found to have an inhibiting effect on HIV-1 reverse transcriptase, according to Woradulayapinij *et al* [33-34].

6. Anti-pyretic activity

The antipyretic efficacy of leaf extract in yeast-provoked increase of body temperature has been studied by Raama *et al*. The methanolic extract caused the body temperature to drop. According to the study, the antipyretic effect may be due to flavonoids, which lower lipid peroxidation [35].

7. Anti-snake venom activity

Durairaj *et al*. investigated the possible ability of Vitex negundo leaf extract to neutralize the venom of Daboia russelli and Naja naja [36].

8. Cardioprotective activity

For the first time, the cardioprotective effect of Vitex negundo was verified by Marathi Prasad *et al*. They showed that an ethanol extract of Vitex negundo can prevent rats from developing ISO-induced MI via controlling the expression of the NF-B and Akt1 signalling cascades. They verified that flavonoids such 5,7-dihydroxy-6,4'-dimethoxy flavanone, which are present and responsible for this impact [37].

9. Other pharmacological activities

The various Vitex negundo extracts also have other pharmacological properties, including anxiolytic, hepatoprotective, anti-diarrheal, and other effects. The results of a research investigation by Abhinav Kanwal *et al*. revealed that among rats given the plant extract, there was a reduction in A ChE activity and an increase in learning of memory through antioxidant impact. The anti-histaminic effect is further supported by its alpha-amylase inhibitory properties. The Siddiqui *et al*. study found that methanolic Vitex negundo extract stimulated the formation of long neurites in the hippocampus, demonstrating its potential for neuroprotection [38-39].

Biological activity of vitex negundo

Many plants have chemical compounds that serve as defence mechanisms and defend against infections and predators. The examination of the plant extracts' anti-microbial qualities demonstrates that the Vitex negundo is an effective biocontrol agent. According to research on the plant, numerous biological agents that cause disease or harm may be inhibited, hampered, or even destroyed by the extracts. Below is a summary of the Vitex negundo's biological activity

1. Anti-bacterial activity

The bactericidal activity of Vitex negundo extracts and essential oils was confirmed using a disc-diffusion antibiotic sensitivity test. According to the research of Khokra *et al*., the plant's ethanol and ethyl acetate extracts exhibited promising antibacterial activity against the bacterial strains Staphylococcus aureus, Bacillus subtilis, Escherichia coli, and Pseudomonas aeruginosa [40].

2. Anti-feedant activity

The studies by Haridasan *et al*. and Matharu *et al*., respectively, validated the ability of Vitex negundo extracts to prevent the growth of Tribolium castaneum and Plutella xylostella [41].

3. Anti-filarial activity

The anti-filarial efficacy of the plant extract was studied by Sahare *et al*. The extracts could prevent Brugia malayi, a microfilarial parasite, from growing [42].

4. Anti-fungal activity

The fungicidal activity of the Vitex negundo extracts against Curvularia lunata, Alternaria alternata, Cryptococcus neoformans, Trichophyton mentagrophytes, Candida albicans, and Aspergillus niger was investigated by Guleria *et al*. and Sathiamoorthy *et al* [43].

5. Anti-larval activity

The works of Nathan *et al*. suggested that the Vitex negundo is an effective bio-control agent against the Rice leaf-folder, Cnaphalocrocis medinalis [44].

6. Insecticidal activity

The bioactive agents in the Vitex negundo extracts display repressive activity on the growth of Arthropods like Spodoptera litura (Asian armyworm), Tribolium castaneum (Red flour beetle), Sitotroga cerealella (Angoumois grain moth), Myzus persicae (Green peach aphid), Aphis citricola (Spirea aphid), Aedes aegypti (Dengue vector mosquito) and Aphis gossypii (Melon or Cotton aphid). Kamalakannan, Rajendran, Deepthy *et al*., Chowdhury *et al*., and En-Shun examined the insecticidal ability of Vitex negundo [45].

7. Mosquito repellent activity

The Vitex negundo extracts successfully prevented the development of mosquito larvae and adults from species including Culex tritaeniorhynchus, Anopheles subpictus, Aedes aegypti, and Anopheles stephensi. Rajakumar *et al*. and Kannathasan *et al*. investigated the larvicidal efficacy against Culex quinquefasciatus, whereas Ranasinghe *et al*. demonstrated that methanolic Vitex negundo extract has 85.44% mosquito-repellent activity [46].

8. Anthelmintic activity

Trapti *et al*. proved the ethanolic extract of Vitex negundo 's anthelmintic effectiveness against the Indian earthworm Pheritima posthuma [47].

Conclusion

The significance of compiling this data on *Vitex Negundo* is that it has powerful and varied pharmacological qualities that can serve as a useful foundation for future scientific study. Modern pharmacological research, focused on Vitex negundo's anti-microbial, anti-inflammatory, anti-tumor, anti-oxidant, anti-androgenic, hepatoprotective, and antihyperglycemic action, etc., have verified nearly all of the plant's traditional uses. Even though there have been more studies on the pharmacological effects of Vitex negundo, they are still few, and more pharmacological research on this species is still required to support the traditional uses and provide more information on the pharmacological mechanism of action.

Acknowledgement

With lots of respect to my family and my colleagues, I would like to grateful thanks to my college B.C.O.P college of pharmacy for permitting me to do this review article. Special thank to my Friends, respected Teacher's and Co-authors give us lots of information and valuable time, thank for support. I also thankful of International Journal of Research Pharmacy and Pharmaceutical Science, who gives me this opportunity to publish our review article.

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