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A REVIEW ON ETHANOMEDICINAL USES AND PHYTO-PHARMACOLOGY OF ANTI-INFLAMMATORY HERB *VITEX NEGUNDO*

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ABSTRACT

Vitex negundo is an important medicinal plant with potent anti-inflammatory activity. The major constituents of this plant are flavonoids, casticin, chryso-splenol and vitexin, Chrysophenol D, nishindine and hydrocotylene. It also contains monoterpenes agnuside, eurostoside, and aucubin. These constituents contribute various pharmacological activities as anti-inflammatory, antioxidant, antinociceptive, anti-ulcer, free radicals scavenging, hepatoprotective and many more. This review discuss the investigation made by various workers related to its ethnobotanical claims, ayurvedic properties, chemical constituents, pharmacological activities ,analytical studies and other aspects considering this plant since years till date.

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INTRODUCTION: *Vitex negundo* (VN) Linn. belongs to family Verbenaceae commonly known as Nirgundi. It is a large, aromatic shrub; with typical five foliate leaf pattern found throughout the greater part of India at warmer zones and ascending to an altitude of 1500 m in outer, Western Himalays. The shrub is one of the common plants used in Indian medicines. It has been claimed to possess many medicinal properties. It contains the various chemical classes such as alkaloids, tannins, flavonoids, carbohydrates, & tannins. Traditionally leaves reported to possess tranquilizing effect, insecticidal properties and lay over grain to ward off insects. The extracts of the leaves showed antibacterial activity against *Micrococcus pyogenes var aureus* and *E.coli*.

Fresh leaves of VN have been suggested to possess anti-inflammatory and pain suppressing activities possibly mediated via PG synthesis inhibition, antihistamine, membrane stabilizing and antioxidant activities. This also possess anti-ulcer activity against piroxicam induced ulcers, probably by increasing PG levels. Its various active constituents possess various pharmacological activities.

Ethnobotanical claim: Chasteberry has been used since ancient times as a female remedy. One of its properties was to reduce sexual desire, and it is recorded that Roman wives whose husbands were abroad with the legions spread the aromatic leaves on their couches for this purpose. It became known as the chasteberry tree. During the middle ages, Chasteberry's supposed effect on sexual desire led to it becoming a food spice at monasteries, where it was called "Monk's pepper" or "Cloister pepper." In tradition, it was also known as an important European remedy for controlling and regulating the female reproductive system. Long used to regularize monthly periods and treat amenorrhea and

dysmenorrhea, it also helped ease menopausal problems and aided the birth process.

Distribution: It is native to India: Assam, Bihar, Delhi, Himachal Pradesh, Hubei, Hunan, Jammu and Kashmir, Jiangsu, Jiangxi, Karnataka, Kerala; United States: (Alabama, Arkansas, Arizona, California, Colorado, Connecticut).

Plant description: Deciduous shrub, growing to 3m at a medium rate. It is hardy to zone 8. It is in flower from September to October. The scented flowers are hermaphrodite (have both male and female organs) and are pollinated by Insects. The plant prefers light (sandy) and medium (loamy) soils, requires well-drained soil and can grow in nutritionally poor soil. The plant prefers acid, neutral and basic (alkaline) soils. It cannot grow in the shade. It requires dry or moist soil (**Figure 1**).



FIG. 1: LEAVES AND BRANCHES OF VITEX NEGUNDO

Ayurvedic properties: Rasa- Madhura, Tikta, Katu; Virya-Usna; Guna-Laghu; Vipaka-Katu.

Vernacular names:

Sanskrit	Nirgundi, Nila
Bengali	Nirgundi, Nishinda
Gujrati	Nagod
Hindi	Nirgundi, Sambhalu
Marathi	Nirgundi,
Tamil	Nirkundi
Urdu	Sambhalu
Telugu	Nallavavilli

Taxonomical classification:

Kingdom	Plantae
Subkingdom	Tracheobionta
Superdivision	Spermatophyta
Division	Magnoliophyta
Class	Magnoliopsida
Subclass	Asteridae
Order	Lamiales
Family	Verbenaceae
Genus	<i>Vitex</i>
Species	<i>negundo</i>

Phytochemistry: *Vitex* contains the flavonoids, casticin, chryso-splenol and vitexin. *Vitex* contains Chrysofenol D. which is a substance with anti-histamine properties and muscle relaxant. Leaves contains two alkaloids nishindine and hydrocotylene. It also contains monoterpenes agnuside, eurostoside, and aucubin. It is thought to contain a progesterone-like compound. The main compounds are viridiflorol (19.55%), beta-caryophyllene (16.59%), sabinene (12.07%), 4-terpineol (9.65%), gamma-terpinene (2.21%), caryophyllene oxide (1.75%), 1-oceten-3-ol (1.59%), and globulol (1.05%). The methanolic extract of the flowering stems of *Vitex* yielded three new iridoids: 6'-*O*-foliamenthoylmussaenosidic acid (agnucastoid A), 6'-*O*-(6,7-dihydrofoliamenthoyl) mussaenosidic acid (agnucastoid B) and 7-*O*-*trans*-*p*-

coumaroyl- 6'-*O*-*trans*-caffeoyle- 8-epiloganic acid (agnucastoid C) in addition to four known iridoids (aucubin, agnuside, mussaenosidic acid and 6'-*O*-*p*-hydroxybenzoylmussaenosidic acid) and one known phenylbutanone glucoside (myzodendrone). The structure elucidations were mainly done by spectroscopic methods (1D and 2D NMR spectra) and MS data interpretation. The purified compounds were tested for biological activities against various microorganisms and cancer cell lines. The volatile constituents of *Vitex pseudo-negundo* (Hauskn.) Hand.- Mzt. were isolated by hydrodistillation and analyzed via GC and GC/MS.

The major constituents of the leaf oil were α -pinene (35.9%), limonene (12.2%) and bicyclogermacrene (9.5%), while the fruit oil contained α -pinene (31.7%), bicyclogermacrene (14.5%) and limonene (11.5%), and the flower oil contained α -pinene (14.7%), bicyclogermacrene (8.3%) and limonene (5.8%). Two new phenyldihydronaphthalene-type lignan glucosides, vitecannasides A (**1**) and B (**2**) were isolated from the fruit of *Vitex* along with the six known lignan derivatives (**3-8**), four known iridoid glucosides (**9-12**), three known flavonoids (**13-15**), and one known phenylbutanone glucoside (**16**). Their chemical structures were determined on the basis of spectroscopic data as well as chemical evidence. The scavenging effect of **1**, **2**, and **11-16** on the stable free radical 1, 1-diphenyl-2-picrylhydrazyl was examined. Compounds **1**, **2**, **14**, and **15** exhibited stronger activity than that of l-cysteine. Especially, **14** and **15** showed more potent activity than that of α -tocopherol.

Pharmacological studies:

- Negundoside, an irridoid glycoside from leaves of *Vitex negundo*, protects human liver cells against calcium-mediated toxicity induced by carbon tetrachloride. It exerts a

protective effect on CYP1B1-dependent CCL₄ toxicity via inhibition of lipid peroxidation, followed by an improved intracellular calcium homeostasis and inhibition of Calcium dependent proteases.

- The effect of *Vitex negundo* leaf extract on the free radicals scavengers in complete Freund's adjuvant arthritic rats, showed decrease in enzymic anti-oxidant-SOD, CAT, GPx, G6PD and non-enzymic anti-oxidant-GSH, Vit-C, exhibiting its anti-oxidant activity.
- The anti-inflammatory activity of *Vitex negundo* leaf extract and mechanism of action had been studied in carrageenan induced hind paw edema and cotton pellet granuloma test in albino rats. The study showed that VN leaf extract inhibited oxytocin induced contractions of rat uterus and plasma MDA (malondialdehyde) levels. This suggest that VN possesses anti-inflammatory activity against acute as well as sub acute inflammation, which appear to be due to prostaglandin synthesis inhibition and reduction of oxidative stress respectively.
- In vitro, the antioxidant activity of the freeze-dried root extract of *Vitex negundo* was investigated by determining their abilities to scavenge DPPH (1, 1-diphenyl-2-picrylhydrazyl free radical and to inhibit hydroxyl radical-mediated damage to deoxyribose. The leaf extract can produce reduction of oxidative stress by reducing lipid peroxidation whereas it has failed to modulate endogenous anti-oxidant enzyme activity.
- The chloroform extract of the defatted seeds of *Vitex negundo* exhibited anti-inflammatory activity and yielded four triterpenoids: 3-beta-acetoxyolean-12-en-27-oic acid, 2 alpha, 3 alpha-dihydroxyoleana-5, 12-dien-28-oic acid (2), 2-beta, 3-alpha-diacetoxy-18-hydroxyoleana-5, 12-dien-28-oic acid.
- Dose dependent histomorphological changes produced by VN extract were observed in specimens of heart, liver and lung, which showed that the major toxic assault of VN was on heart. The major cause of mortality was cardiopulmonary arrest as non-reversible dyspnoea was appeared, so the dyspnoea caused by cardiac toxicity in the form of vascular dilatation and hemorrhage is the cause of mortality.
- Tail flick test in rats and acetic acid induced writhing in mice were employed to study the antinociceptive activity of *Vitex negundo* linn. leaf extract which suggest that VN posseses both central and peripheral analgesic activity. The central analgesic action does not seem to be mediated through opioid receptors.
- Fresh leaves of VN have been suggested to posses anti-inflammatory and pain suppressing activities possibly mediated via PG synthesis inhibition, antihistamine, membrane stabilising and antioxidant activities. This also possess anti-ulcer activity against piroxicam induced ulcers, probably by increasing PG levels.
- The total methanol extract of the plant was standardized in terms of total polyphenols. The standardized extract in a dose of 100 mg/kg caused a comparable reduction in edema with that of diclofenac sodium (25 mg/kg) when evaluated for antiinflammatory activity by carrageenan-induced rat paw edema method. The extract also exhibited a strong free radical scavenging activity by 1,1-diphenyl-2-picrylhydrazyl method and caused a significant reduction in the formation of thiobarbituric acid reacting substances when

evaluated for its lipid peroxidation inhibitory activity. The results strongly suggest that radical quenching may be one of the mechanisms responsible for its anti-inflammatory activity.

- The antimicrobial activity was assessed using the minimum inhibitory concentration assay. Through bioactivity-guided fractionation, the fraction responsible for the antimicrobial activity was determined. The toxicity profile, anti-oxidant and anti-inflammatory activity was evaluated using the tetrazolium cellular viability, 2,2-diphenyl-1-picrylhydrazyl and 5-lipoxygenase assays respectively. The antimalarial activity of the extracts and isolated compound was also investigated on the chloroquine-resistant Gambian FCR-3 strain of *Plasmodium falciparum* using the tritiated hypoxanthine incorporation assay.

Uses: The whole plant is used for medicinal purposes. The leaves are astringent, febrifuge, sedative, tonic and vermifuge and used in diffusing swellings of the joints from acute rheumatism. The juice of the leaves is used for removing foetid discharges and worms from ulcers, while oil prepared with the leaf juice is applied to sinuses and scrofulous sores. The dried fruit is vermifuge and used in treatment of angina, colds, coughs, rheumatic difficulties etc.

The fresh berries are crushed to a pulp and used in the form of a tincture for the relief of paralysis, pains in the limbs, weakness etc. The root is expectorant, febrifuge and tonic and used in treatment of colds and rheumatic ailments. The whole plant is said to be a malarial preventive and is also used in treatment of bacterial dysentery. The extracts of the leaves have also shown bactericidal and antitumor activity. The leaves are used to repel insects in grain stores. Extracts of the leaves have

insecticidal activity. The fresh leaves are burnt with grass as a fumigant against mosquitoes. A decoction of the stems is used in the treatment of burns and scalds.

Safety and Toxicity:

- Side effects of using *Vitex negundo* are rare. Minor gastrointestinal upset and a mild skin rash with itching have been reported in less than 2% of the women monitored while taking *Vitex negundo*. It is not recommended for use during pregnancy.
- The LD₅₀ was established at 7.58 g/kg, b. w.

CONCLUSION: *Vitex negundo* have been meticulously studied for its chemical constituents and pharmacological studies. Taking into account its anti-inflammatory and anti-tumour and anti-arthritic and anti-ulcer activity plant is of great importance. However lot of investigation could be made in the field of tissue culture and biotechnology to improve the yield of require chemical constituents within the plant. Few toxicological and analytical studies have been reported. The work could also be done in this direction to ensure free utility of this plant.

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