

## Review Article

# The Favorable Role of Alkaloids from *Vitex negundo* in the Management of Human Ailments

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## Abstract

*Vitex negundo* is a perennial plant belonging to family Verbenaceae highly distributed in the Himalayas region in India. The leaves, roots, fruits, and seeds have possessed hepatoprotective, antioxidant property, anti-inflammatory, anticancer and antioxidant properties. Generally, it required warm regions, common in waste places around villages, river banks, and most localities in the deciduous forests to grow. The *V. negundo* leaves contain Alkaloids such as Nishindine, Hydrocotylene, Glyoflavonoids, Orientin, Isoorientin, and the seeds contain hydrocarbons such as n-tritriacontane, n-hentriacontane, n-pentatriacontane and nonacosane. These potent phytoconstituents are highly responsible for the treatment in fever, cough, urinary problems, dyspepsia, rheumatism, for boils, as anthelmintic, in liver complaints, headache, catarrh, and coryza. *Vitex* generally used as a contraceptive, because it promotes the progesterone production during the second half of the menstrual cycle. The leaves intake reduces the loss of libido and gives relief in increases Vata, Kapha, and Pitta. The plant extracts potentiated the effect of commonly used anti-inflammatory drugs such as ibuprofen and phenylbutazone; analgesics as meperidine, aspirin, morphine and pethidine; sedative-hypnotic drugs like pentobarbitone, diazepam and chlorpromazine; and anti-convulsive agents like diphenylhydantoin and valproic acid.

**Keywords:** *Vitex negundo*; Alkaloids; Dyspepsia; Rheumatism; Forboils; Vata; Pitta; Kapha

## Introduction

*Vitex negundo* Linn., family Verbenaceae is known to possess several medicinal values so that highly cultivated for commercial purposes. The leaves, roots, fruits, and seeds have been extensively investigated by many scientists and reported that they possess hepatoprotective, antioxidant property, anti-inflammatory, anticancer and antioxidant properties [1]. It was reported that the use of *V. negundo* in naturopathic and homeopathic medicinal preparations are extensively used in the management of human complications occurred by vitiation of Vata, Pita and Kapha [2]. The leaves extract are generally used in headache, skin affections, wounds, swelling in joints, asthmatic pains, acute rheumatism, male and female sexual problems, and also used in the inflammation of the epididymis (testicular tube that stores and carries sperm) and orchitis (inflammation of testicles) [3].

## Botanical description

**Botanical name:** *Vitex negundo* Linn.

**Common name:** Nirgundi, Nirgundika, Nirgunda, Nilanirgundi, Nirkunnchi, Nallanochi, Nisinda, Nilika, Nilapushpi, Sindhuvara,

Sindhuvaram, Sinduya, Sugandhika, Surasa, Suvaha, Sinduka, Sephalika, Shvetasurasa, Svetapuspa, Shephali, Indrasursa, Indranika, Renuka, Vrikshaha [4].

**Plant:** It is a branched shrub or tree grown up to 5 meters tall, cylindrical with thin gray bark.

**Leaves:** Mostly trifoliate, occasionally Pentafoliate, palmate compound petiole up to 2:5:3.8 cm long; in trifoliate the leaflets are lanceolate or narrowly lanceolate, middle leaflet 5 cm to 10 cm long and 1.6:3.2 cm broad with 1 cm to 1.3 cm long petiolule and remaining two sub-sessile; in pentafoliate leaf inner three leaflets have petiolule and remaining two sub-sessile; on top of surface glabrous and tomentose in bottom with leathery texture.

**Roots:** Cylindrical, hard, longitudinal, narrow, cracks and small rootlets, tough with irregular fractures; the cork region shows grayish-brown, middle region greyish-white, and xylem region cream colored.

**Flowers:** Small, Bluish-purple, cymes peduncled, large forming terminal, often pyramidal panicles.

**Fruit:** The fruit is light brown to black with rounded drupe, 1 mm to 3 mm in diameter, 1/3<sup>rd</sup> to 3/4<sup>th</sup> of its size surrounded by a dull grey cup-like, persistent calyx along with pedicel; calyx cup may show one or two vertical splits; two locules each containing two seeds; smooth texture with uncharacteristic taste and odour [5].

**Distribution:** It is a perennial tree distributed throughout the great outer part of Himalayas, India ascending to an altitude of approx 1500 meters. Highly distributed in the hill region of Afghanistan, Bangladesh, Bhutan, Cambodia, China, Indonesia, Malaysia, Myanmar, Nepal, Pakistan, Philippines, Sri Lanka, Taiwan, Thailand, and Vietnam.

**Habitat:** Required warm regions, common in waste places around villages, river banks, and moist localities in the deciduous forests (figure 1) [6].

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**Figure 1:** *Vitex negundo* plant with flower.

**Taxonomy:** The *Vitex* is derived from the Latin word 'vieo' meaning to tie or bind because of the flexible nature of its stems and twigs [7]. The taxonomy of the plant is as follows;

Kingdom	: Plantae (extinct plants)
Subkingdom	: Tracheobionta (lignified tissues or xylem)
Superdivision	: Spermatophyta (produce seeds)
Division	: Magnoliophyta (flowering plants)
Class	: Magnoliopsida (embryo with paired cotyledons)
Subclass	: Asteridae
Order	: Lamiales
Family	: Verbenaceae
Genus	: <i>Vitex</i> L.
Species	: <i>Negundo</i> [8]

### Phytochemical constituents

The aqueous extract of *Vitex negundo* leaves contains Aucubinaginaside, Alkaloids: Nishindine, Hydrocotylene, Glyoflavonoids, Orientin, Isoorientin, 5-Hydroxy, 3,6,7,31,4 1 pentamethoxy flavone. The essential oil of fresh leaves, flowers, and dried fruits  $\delta$ -guaiene contain guaia-3,7-dienecaryophyllene epoxide; ethyl-hexadecenoate;  $\alpha$ -selinene; germacren-4-ol; caryophyllene epoxide; (E)-nerolidol;  $\beta$ -selinene;  $\alpha$ -cedrene; germacrene D; hexadecanoic acid; p-cymene and valencene. The seeds contain hydrocarbons such as n-tritriacontane, n-hentriacontane, n-pentatriacontane and nonacosane [9]. Other constituents of the seeds include  $\beta$ -sitosterol, 5 hydroxybenzoic acid and 5 oxyisophthalic acids (Table 1 and 2) [10,11].

**Table 1:** Chemical constituents from different parts of the *Vitex negundo* plant.

S.N.	Part of Plant	Chemical Constituents
1.	Leaves	vitamin-C, artemetin, terpinen-4-ol, $\alpha$ -terpineol, sabinene, globulol, spathulenol, $\beta$ -farnesene, farnesol, carotene, casticin, 5-hydroxy-6,7,8, 4'-tetramethoxy (gardenin B), linalool, stearic acid, 5-hydroxy-3,6,7,3', 4'-pentamethoxy flavone, 5-hydroxy-3,7,3', 4'-tetramethoxy flavones, betulinic acid, ursolic acid.
2.	Seeds	$\beta$ -sitosterol, p-hydroxybenzoic acid and 5-oxyisophthalic acid, artemetin, vitedoin A, vitedoamine A, vitedoin B, 2 $\beta$ ,3 $\alpha$ -diacetoxyoleana-5, 12-dien-28-oic acid, 3 $\beta$ -acetoxyolean-12-en-27-oic acid n-tritriacontane, n-hentriacontane, n-pentatriacontane, $\beta$ -sitosterol.
3.	Stem and bark	3,6,7,3',4'-Pentamethoxy-5-Oglucopyranosylrhamnoside, vitexin cafeate, 4'-O-methyl myricetin- 3-O-[4'-O- $\beta$ -D-galactosyl]- $\beta$ -D-galactopyranoside, $\beta$ -amyrin, epifriedelinol and oleanolic acid, p-hydroxybenzoic acid, $\beta$ -sitostero.
4.	Roots	Vitexin and isovitexi, Vitexoside, negundin A, negundin B, 6-hydroxy-4-(4-hydroxy-3-methoxy)-3-hydroxymethyl-7-methoxy-3,4-dihydro-2-naphthaldehyde, 2 $\beta$ ,3 $\alpha$ -diacetoxyoleana-5,12-dien-28-oic acid.

**Table 2:** Phytochemical constituents present in aqueous leaves extract of *V. negundo*.

S.No.	Tests / Reagents	Color	Observation
1	Alkanoids- Dragendrof'sf Reagent	Yellow	+
2	Tannins-Fericchloride solution	Greenish Black	+
3	Sterols-Concentrated sulfuric acid	Red Ring	+
4	Glycosides-Libermann's burchard reagent	Pink Color	+
5	Flavonoids-Shinoda test: Ethanolic extract + magnesium ribbon + concentrated HCl	Pink Color	+
6	Resins-Concentrated Nitric Acid	No Color Change	-
7	Carbohydrate-Molisch's Test	Pinkish Ring	+
8	Test for Polysaccharides-Anthrone Test	Green Ring	+
9	Test for Protein-Potassium Iodide + Iodine solution	Yellow Color	+

### Extraction process

Extraction is the process through which the phytoconstituents easily obtained from the crude drugs. The leaves of *Vitex negundo* were collected and the preliminary extraction, separation, and isolation of the individual constituents of interest, their purification and characterization recorded [12]. The process involves the separation of the medically active portion of the plant from the inactive or inert components using effective solvent by following standard extraction method [13]. The principal methods of extraction are mentioned as;

1. Maceration
2. Percolation
3. Digestion
4. Infusion
5. Decoction
6. Soxhlet extraction

### Pharmacological evidence

The medicinal importance of *Vitex negundo* described as folklore medicine the scientific community and necessitated experimental evidence for further underline mechanism. The sign from these traditional as well as folk medicine, scientific studies have been designed and conducted in order to pharmacologically validate it uses [14].

**Anti-inflammatory activity:** A low dose of *V. negundo* potentiates anti-inflammatory activity against phenylbutazone and ibuprofen observed in carrageenan-induced hind paws edema and cotton pellet granuloma models. The potential anti-inflammatory activity indicates that *V. negundo* may be useful as an adjuvant therapy in chronic condition along with standard anti-inflammatory drugs [15].

**Antinociceptive activity:** The Antinociceptive effect of ethanolic leaf extract of *V. negundo* at a dose of 100, 250 mg/kg and 500 mg/kg were compared with standard drug such as meperidine (40 mg/kg) by tail flick method and aspirin (50 mg/kg) by writhing response. For the mechanism of central analgesic action an interaction with naloxone hydrochloride was also studied by using tail flick method. *V. negundo* significantly maintains both central and peripheral analgesic activity in a dose-dependent manner. It was suggested that the *V. negundo* used as useful adjuvant therapy along with the standard analgesic drug [16].

**CNS depressant activity:** The methanolic leaves extract of *V. negundo* was reported as significantly potentiate the sleeping time induced by pentobarbitone sodium, diazepam, and chlorpromazine in mice.

**Antifungal activity:** The ethanolic leaves extract of *V. negundo* possess a new flavone glycoside and evaluated for their antimicrobial activities. The new flavone glycoside was reported as good antifungal activity against *Cryptococcus neoformans* and *Trichophyton mentagrophytes*.

**Antioxidant activity:** The antioxidant scavenging activity for 2, 2'-azino-bis 3-ethyl benzothiazoline-6-sulfuric acid in a concentration-dependent manner, showing a direct role in trapping free radicals. The polar fractions of *V. negundo* possess a potent antioxidant property that was also reported similar antioxidant properties of same fraction by using ethanol induced-oxidative stress in rat.

**Enzyme-inhibitory activity:** The root extract of *V. negundo* showed good inhibitory action against lipoxygenase, butyryl-cholinesterase,  $\alpha$ -chymotrypsin, xanthine-oxidase, and tyrosinase, while the aqueous extract of the aerial parts reported for the HIV type 1 reverse transcriptase inhibition [17].

**Anticonvulsant activity:** The leaves extract of *V. negundo* observed for anticonvulsant activity which shows the significant decrease in number and duration of convulsions and also potentiated the anticonvulsant activity of diphenylhydantoin and valproic acid. Moreover, these potentiating actions indicate that it may be useful as an adjuvant therapy along with standard anticonvulsants and also lowers the dose of valproic acid and diphenylhydantoin.

**Antibacterial studies:** Essential oils and successive ethyl acetate and ethanol extracts of *V. negundo* showed antibacterial activity against some bacterial strains such as *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Pseudomonas aeruginosa*. The phytoconstituents such as d-guanine, caryophyllene epoxide, ethylhexadecenoate,  $\alpha$ -selinene, germacren-4-ol, caryophyllene epoxide, E-nerolidol,  $\beta$ -selinene,  $\alpha$ -cedrene, germacrene D and hexadecenoic acid are highly responsible for antibacterial activity [18].

**Antiallergic activity:** The ethanolic extract of *V. negundo* showed antiallergic activity against immunologically induced degranulation of mast cells and also inhibit edema. The extract significantly inhibited both the initial and later sustained phases of tracheal contractions. The initial phase was primarily due to histamine and the latter phase was due to the release of lipid mediators from arachidonic acid [19].

**Snake venom neutralization activity:** The methanolic root extracts of *V. negundo* showed anti-snake venom activity. The extracts significantly antagonized the Viper arussellii and Naja kaouthia venom-induced lethal activity in both *in-vitro* and *in-vivo* studies. Viper arussellii venom-induced hemorrhage, coagulation, defibrinogenation, and inflammation were significantly neutralized by *V. negundo* extracts [20].

**Effect on reproductive potential:** The fractions of *V. negundo* seeds extract causes disruption of the latter stages of spermatogenesis in dogs and interfere with male reproductive function in rats. It was observed that ethanolic extracts of *V. negundo* showed estrogen-like activity and offers as hormone replacement therapy [21].

**Hepatoprotective activity:** The ethanolic extract of *V. negundo* at the dose of 250 mg/kg and 500 mg/kg shows significant decrease in serum bilirubin, AST, ALT, ALP and total protein levels against hepatotoxicity produced by combination of three antitubercular drugs Isoniazid (7.5 mg/kg), Rifampin (10 mg/kg) and Pyrazinamide (35 mg/kg). The alcoholic seeds extract of *V. negundo* also showed the hepatoprotective activity against  $\text{CCl}_4$ -induced hepatic toxicity [22].

**Hypoglycemic activity:** The leaf extracts of *V. negundo* was reported for the anti-hyperglycemic activity in animals.

**Laxative activity:** The aqueous leaves extract of the *V. negundo* at the dose of 100 mg/kg and 200 mg/kg were reported as good laxative properties in albino rats [23].

**Immunomodulatory activity:** The Immunomodulatory effect of *V. negundo* extracts have been reported by Ravishankar and Shukla and considered as a tonic, vermifuge and also given in catarrhal fever [24].

**Drug potentiating ability:** The *V. negundo* extracts potentiate the effect of commonly used anti-inflammatory drugs such as ibuprofen, phenylbutazone; analgesics such as meperidine, aspirin, morphine, pethidine; sedative-hypnotic drugs like pentobarbitone, diazepam, chlorpromazine; anti-convulsive agents such diphenylhydantoin and valproic acid [25].

### Medicinal uses in different medication system

**Allopathic medication system:** Roots are used for fever, cough, urinary problems, dyspepsia, rheumatism, and forboils. The powdered root is consumed as an anthelmintic. Flowers are used in fever, diarrhea and the liver complaints; fruits in headache, catarrh, and coryza (Table 3) [26].

**Table 3:** Medical uses of *V. negundo* in Allopathic medication system.

S.N.	Plants Parts	Beneficial Uses
1.	Flowers	Gastrointestinal disorders, Diarrhoea, Cholera, Dyspepsia
2.	Root powdered, tincture from roots and bark	Dysentery
3.	The whole plant, tincture from roots and bark	Flatulence, Irritable bladder
4.	Crushed & poultice leaf, Pillow stuffed with leaves	Headache
5.	Fruits pillow stuffed, the decoction of leaves	Eye disease, Cataract, Watery eyes, improves eyesight
6.	Root decoction, Leaf juice	Respiratory disorders, Cough, Expectorants
7.	Leaf juice	Common cold, Flu, Sore throat
8.	Leaf extract	Whooping cough
9.	Root decoction	Bronchitis, Asthma
10.	Essential oils from leaf, crushed leaf poultice	Sinusitis

**Ayurvedic medication system:** The white-flowered variety is known as Sindhuvaara and the blue-flowered as Nirgundi or Shephaali. Nirgundi belongs to the Surasaadi group of herbs of Ayurvedic medicine, considered specific for cough, rhinitis, asthma. This group helps in the cleansing of ulcers. The leaf is considered astringent, bitter and pungent in taste (Rasa), pungent after digestion (Vipaka), and is hot in effect (Virya). It is pungent in both the initial and post-digestive tastes (Rasa and Vipaka) and gives relief in increases Vata, Pitta and Kapha [27]. It is carminative, antiemetic and thermogenic. It is useful in indigestion, low appetite, nausea, and piles.

- Rasa (taste on the tongue): Kashaya (Astringent), Katu (Pungent), Tikta (Bitter)
- Guna (Pharmacological Action): Laghu (Light), Ruksha (Dry)
- Virya (Action): Ushna (Leaf Heating); Sheet (Fruit, Flowers, Seeds Cooling)
- Vipaka (transformed state after digestion): Katu (Pungent)
- Effect on Dosha: Reduces Vata and Kapha Dosha but increases Pitta (in excess)
- Preparations: Infusion, Decoction, Oil
- System: Digestive, Circulatory
- Tissues: Plasma, Blood, Muscles, Nerves and Marrow, Reproductive.

**Other benefits:** It should be taken cautiously by women of childbearing age. Vitex promotes the production of progesterone in the second half of the cycle. It should not be taken before ovulation, as it may delay or prevent ovulation. There is some evidence that using plant during in vitro fertilization procedures might prevent an ensuing pregnancy despite having a viable embryo [28].

- Arthritis: Nirgundi leaf powder is taken in a dose of one tablespoon, twice a day.
- Abdominal gas and pain: Decoction of leaves juice will relief abdominal problem.
- Asthma, cough: Take 1/4<sup>th</sup> decoction leaves juice three times a day in asthma.
- Boils and pimples: Grind neem, Karanja, and Nirgundi and apply topically.
- Bone fracture: Paste of leaf, salt and pepper seeds applied at fracture area.
- Burning urination and kidney stone: Two spoonful root extract dissolved in tender coconut water and used twice a day for a week to suppress kidney problem.
- Chronic fever, intestinal parasites: Dictionery root is beneficial in this condition.
- Common colds (runny nose, watery eyes, etc.): Pound 6 table spoons of the leaves in 2 glasses of water and boil for 15 minutes. Cool and strain the mixture, juice will relief in it.
- Cold, cough, headache, fever: Leaves are boiled with water and the vapor is inhaled twice a day.
- Cyclic mastalgia: The alcohol-based tincture or encapsulated

tinctures extract used around 1 ml for 3 to 4 times a day.

- Diarrhea: Dried fruits powder is orally taken with honey at a dose of 5 g to 10 g in diarrhea.
- Fever, toothaches: Nirgundi leaves (6 table spoons) in 2 glasses water boiled for 15 minutes and take thrice (in 3 divided dose) in a day at 4 hours interval.
- Gout, calculus: Root decoction used for a period of 2 weeks is effective against gout and calculus.
- Hair tonic: The ointment made from leaf juice is applied as a hair tonic.
- Headache: Take Nirgundi leaves and grind with water to make a paste. Apply this paste on the forehead to relief headache.
- Hormone replacement therapy: The ethanolic extracts showed estrogen-like activity and propounded its use in hormone replacement therapy.
- Gout, calculus: The root decoction used for a period of 2 weeks is effective against gout and calculus.
- Hyper prolactinemia: High levels of prolactin may cause oligomenorrhea, amenorrhea, discharge from the breasts, vaginal dryness, or acne and excessive body and facial hair growth (hirsutism).
- Menstrual disorders, urinary disorders, indigestion: Dried fruits powder is orally taken in a dose of 5g to 10 g with roasted common salt and warmed water.
- Obesity: Leaf juice extract at a dose of one spoonful may reduce body weight.
- Orchitis: Leaf paste along with pepper is used to treat orchitis.
- Pain in ears: Leaves are boiled in mustard oil and filtered then oil used as an ear drop.
- Rheumatism: The heated leaf is pressed and tied for rheumatoid arthritis pain and sprains. Oil prepared from leaves is also applied.
- Skin disease: Paste of leaves is applied locally as an ointment.
- Sprain: Heat fresh leaves and apply on the sprained area.
- To get rid of mosquitoes: The fumigating leaves used to get rid of mosquitoes.
- Throat pain, oral ulcers: The leaf decoction is used for gargling.
- Ulcers, boils, wounds: Wash affected area with the decoction leaf juice is used to clean infected ulcers.
- Loss of libido: Intake of leaves reduces sexual libido [29].

## Conclusion

The *Vitex negundo* leaves contain Aucubinaginaside, Alkaloids: Nishindine, Hydrocotylene, Glyoflavonoids, Orientin, Isoorientin, 5-Hydroxy, 3,6,7,31,41 pentamethoxy flavone. The essential oil of fresh leaves, flowers, and dried fruits  $\delta$ -guaiene contain guaia-3,7-dienecaryophyllene epoxide; ethyl-hexadecenoate;  $\alpha$ -selinene; germacren-4-ol; caryophyllene epoxide; (E)-nerolidol;  $\beta$ -selinene;  $\alpha$ -cedrene; germacrene D; hexadecanoic acid; p-cymene and



valencene. The seeds contain hydrocarbons such as n-tritriacontane, n-hentriacontane, n-pentatriacontane and nonacosane. Other constituents of the seeds include  $\beta$ -sitosterol, p-hydroxybenzoic acid, and 5 oxyisophthalic acids [30].

In Ayurvedic medicine, the flowers are considered specific for cough, rhinitis, asthma, and cleansing of ulcers while the Leaves considered as astringent, bitter and pungent in taste (Rasa), pungent after digestion (Vipaka), and is hot in effect (Virya) and gives relief in increases Vata, Pitta, and Kapha. It is carminative, antiemetic and thermogenic and useful in indigestion, low appetite, nausea, and piles. Roots are used for fever, cough, urinary problems, dyspepsia, rheumatism, and for boils [31].

The effect of several categories of drug such as NSAIDs, sedative-hypnotic, and anticonvulsant drugs may possibly potentiated by the extracts of *Vitex negundo* plant. There is some evidence that the use of plant during the process of *in-vitro* fertilization, it might be prevent the consequent pregnancy despite having a viable embryo, and also the intake of leaves may reduces sexual libido.

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