

***Vitex negundo* Linn (*Nirgundi*): Journey from Past to Future Therapeutic Prospects**Shweta Telang-Chaudhari¹, Jeetendra Singh², Hitesh Chaudhari³, Vaibhav Aher⁴, Shishir Pande⁵¹Associate Professor, DRISHTI Research Unit, Maharashtra University of Health Sciences, Nashik²Professor & Head, Department of Pharmaceutical Medicine, Maharashtra University of Health Sciences, Nashik.³Associate Professor, Department of Ayurveda Pharmaceutics, Matoshri Asarabai Darade Ayurveda College, Yeola, Nashik.⁴Associate Professor, Department of Pharmaceutical Medicine, Maharashtra University of Health Sciences, Nashik⁵Professor & Head, Department of Ayurveda Pharmaceutics, Ayurveda Seva Sangh Ayurveda College, Nashik

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Abstract:

There has been accumulating awareness in the application of herbal medication that they may serve as a safe, effective and alternate treatment approach in the management of various diseases associated with pain and inflammation. *Vitex negundo* is one of such medicinal plants that has been of interest to many researchers and has been of use in traditional medicine. *Vitex negundo* is found in India, Sri Lanka, Madagascar, Malaysia, India, China and East Africa. Different parts, preparations and bioactive components of *Vitex negundo* possess potential protective and therapeutic effects against various disease and related conditions - We review the present state of scientific knowledge on the potential use of *Vitex negundo* and some of its bioactive components in protecting against various pathologies. Previous studies in various preclinical models, although limited in number and vary in design; seem to support the use of *Vitex negundo* and some of its active components in abdominal pain, asthma, cold, diarrhoea, indigestion, eye disorders, rheumatism, dysmenorrhoea, headache, etc.

However, there is need for further preclinical and clinical studies to validate the use of *Vitex negundo* and its active constituents in prevention and treatment of various diseases. Additionally, since only a few *Vitex negundo* compounds have been evaluated, specific effects or mechanisms of action and possible side effects of other *Vitex negundo* compounds need to be extensively evaluated. Also, this review delves into present commercial preparations of *Vitex negundo* which are mostly topical application preparations. However, further research, including large sampled randomised clinical trials, is essential to establish its safety and efficacy in human populations and to unlock its full therapeutic potential.

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Introduction

Vitex negundo is a traditional herb known for its medicinal properties in Unani, Ayurveda, Siddha, Chinese, and other traditional systems of medicine. [1] Traditionally, it is used as anthelmintic, antitoxin, aphrodisiac, contraceptive, antimalarial, analgesic, anti-inflammatory, anti-asthmatic, vermifuge, etc. [2] This review sheds light upon the ethnomedicinal uses, phytochemistry, and pharmacology of *Vitex negundo*.

The *Vitex* genus has gained attention in the health sector market due to the pharmacological potentials attributed to active phytochemicals present in the plant matrix. They can be used as a variety of health supplements to treat different kinds of illnesses or can be utilized as complementary drug along with

other standard treatment regimens. At present, many researchers are interested in discovering new pharmacologically active compounds of *Vitex* plant. Different types of secondary metabolites are found from the *Vitex* genus, namely terpenes, steroids, flavonoids, lignans and phenolic compounds. [3] Some of the bioactive compounds of *Vitex* genus which can contribute towards its anti-inflammatory activity are iridoid and pedunculariside, as they were found to demonstrate preferential inhibition of COX-2 and marginal inhibitory effect on COX-1 enzyme. [4,5]

Vitex negundo contains variety of active phytoconstituents [6] like alkaloids, fatty acids, flavonoids, glycosidic irridoids, lignans, phenols,

steroids, tannins and di- and sesquiterpenes which may play a role in its use in different types of diseases or symptoms such as rheumatism, asthma, abdominal pain, cold, diarrhoea, indigestion, eye disorders, - dysmenorrhea, headache, etc.

It has recently been reported to have cytotoxic properties against various types of cancer cells. Likely mechanism may be inducing apoptosis via the mitochondrial and TRIAL pathways and cell cycle arrest in G2/M phase and apoptosis induction. [7]

Vitex negundo has a rich history in traditional medicine, where it has been utilized for its anti-inflammatory, analgesic, anti-arthritic, anti-pyretic, and anti-microbial properties. The ethno medical use of *V. negundo* as a useful remedy in inflammatory and arthritic disorders could possibly be because of its excellent anti-inflammatory and antioxidant potential. [8] In recent years, researchers have increasingly focused on elucidating the underlying mechanisms and validating these traditional claims through rigorous scientific investigations. *Vitex negundo* is of huge therapeutic importance and its leaves extract has been used as anti-inflammatory, analgesic and anti-itching agent in Ayurvedic tradition. [9]

This review aims to put forth the scientific basis to explain its possible mechanism of action of *V. negundo* for various ailments described in traditional Ayurveda texts. Also, it delves into present commercial preparations of *Vitex negundo* which are mostly topical application preparations. However, further research, including large sampled randomised clinical trials, is essential to establish its safety and efficacy in human populations and to unlock its full therapeutic potential and its likely role in future as a possible therapeutic option in pain management via oral route which could open up new options in pain management sparing the adverse effect of routinely used pain killers in modern medicine.

Traditional Therapeutic Applications of *Vitex negundo*: Traditional medicine mainly comprises of Indian Ayurveda, Arabic Unani medicine and traditional Chinese medicine. In Asia and Latin America, populations continue to use traditional medicine as a result of historical circumstances and cultural beliefs. Traditional medicine accounts for around 40% of all health care delivered in China. Up to 80% of the population in Africa uses traditional medicine to help meet their health care needs. [12]

Locally known as *Nirgundi* or *Sindhvar* in India and the Philippines, *V. negundo* L. plant is widely planted along the road as a hedge plant and is utilized as traditional medicine to treat a variety of medical issues, some of which have been empirically verified. Traditionally, the plant is

reported by many studies as an important medicinal plant, specifically in India, where they exhibit multifarious activities, including anti-inflammatory, analgesics, tonic, and antimicrobial properties.

Medicinal uses in Ayurveda: [13]

Vitex negundo (Nirgundi) is first described in the verses of the Charaka Samhita which is unarguably the most ancient and authoritative textbook of Indian Ayurveda [14]. The plant has been designated as an anthelmintic (verse Su:4-15) and is prescribed as a vermifuge (verse Vi:7-21) in the exposition on the Charaka Samhita by Sharma [15]

Later on plant related Ayurvedic texts like Bhavaprakasha nighantu, Kaiyadeva nighantu, Raj nighantu, Dhanvantari Nighantu and Chakradatta, etc. have mentioned about *Nirgundi* (*Vitex negundo*). [16] The therapeutic properties and uses of this plant are anti-inflammatory, antiseptic, antipyretic, diuretic, anti-rheumatic, skin diseases, wound healing etc

Phytochemistry: The pharmacological activities of *Vitex negundo* can be attributed to its complex phytochemical profile. The plant contains a variety of bioactive compounds, including flavonoids, alkaloids, terpenoids, steroids, and essential oils. These compounds contribute to the diverse therapeutic effects observed in preclinical and clinical studies.

Rationale for using Herbs for Pain Management:

The use of conventional drugs for the treatment of pain and inflammation has largely resulted in various side effects. These challenges have triggered scientific researchers all over the world in search of alternative therapy. [17] Herbal medication may serve as a safe, effective and alternate treatment approach in the management of various diseases associated with pain and inflammation. [18]

Chromone and its analogues are considered as important pharmacophores and privileged structures which have been featured in a number of clinically used drugs. Researchers Khan et al found that Bioactive chromone constituents from *Vitex negundo* alleviate pain and inflammation, which could possibly make it a potential source of anti-nociceptive and anti-inflammatory candidate.[19,20,21]

Anti-inflammatory and Analgesic Effects:

Several studies have reported the potent anti-inflammatory and analgesic properties of *Vitex negundo* extracts. Mechanistically, these effects may be linked to the inhibition of pro-inflammatory mediators, such as cytokines and prostaglandins. The plant has demonstrated efficacy in various animal models of inflammation and pain. [22,23]

Anti-Inflammatory Activity: The sub-effective dose of *Vitex negundo* potentiated anti-inflammatory activity of phenbutazone and ibuprofen significantly in carrageenin induced hind paw edema and cotton pellet granuloma models. The potentiation of anti-inflammatory activities of phenbutazone and ibuprofen by *Vitex negundo* indicates that it may be useful as an adjuvant therapy along with standard anti-inflammatory drugs. Yunos et al. and Jana et al. established anti-inflammatory properties of *Vitex negundo* extracts in acute and sub-acute inflammation which are attributed to prostaglandin synthesis inhibition. [24, 25]

Antinociceptive Activity: Telang *et al* studied the Tail flick test in rats and acetic acid induced writhing in mice to assess the antinociceptive activity of ethanolic leaf extract of *Vitex-negundo* (100, 250 and 500mg/kg). The effect was compared with meperidine (40 mg/kg) in tail flick method and aspirin (50 mg/kg, p.o) in writhing test as a standard control respectively. An interaction with naloxone hydrochloride was also studied in tail flick method for its mechanism of central analgesic action. It showed significant analgesic activity in dose dependent manner in both the experimental models. It suggested that *Vitex-negundo* possesses both central and peripheral analgesic activity. [26] The central analgesic action does not seem to be mediated through opioid receptors. It may prove to be a useful adjuvant therapy along with standard analgesic drug.

Kariyawasamthe et al studied the anti-inflammatory effects of an aqueous leaf extract of *V. negundo* L. and found it markedly inhibited NO (Nitrous oxide) production ($87.5 \pm 17.7\%$), The highest membrane stabilizing activity (91 %) was observed at 0.01 µg/mL and was comparable with that of aspirin [27]

Anti-arthritis Activity: *Vitex negundo* has shown promising anti-arthritis effects in experimental models of rheumatoid arthritis. The inhibition of inflammatory cytokines, modulation of immune responses, and suppression of oxidative stress are proposed mechanisms underlying its anti-arthritis activity.

The chief chemical constituents are nishindine, flavones, luteolin-7-glucoside, casticin, iridoid glycosides, vitamin C, β-sitosterol, and phthalic acid [28]. The active compound agnuside isolated from ethanolic extract of leaves administered at doses of 1.56 mg/10 ml, 3.12 mg/10 ml, 6.25 mg/10 ml and 1.25 mg/10 ml p.o. decreased the elevated levels of ESR, leukotriene B4, PGE2, cytokines, IL-17, TNF-α and interferon gamma. Hence, it can be concluded that the *Vitex negundo* possess an anti-arthritis activity. [28]

Antimicrobial Activity: The plant exhibits significant antimicrobial activity against a wide range of pathogens, including bacteria, fungi, and viruses. Extracts of *Vitex negundo* have demonstrated inhibitory effects on the growth and proliferation of various microorganisms, suggesting its potential as a natural antimicrobial agent.[29]

Antioxidant Activity: The antioxidant potency of *Vitex negundo* Linn. was investigated by all the fractions of *Vitex negundo* Linn. exhibited a potent scavenging activity for (2, 2'-azino-bis 3-ethyl benzothiazoline-6-sulfuric acid) ABTS radical cations in a concentration dependent manner, showing a direct role in trapping free radicals. [30] The polar fractions of *Vitex negundo* Linn. possess potent antioxidant properties. Tandon et al have also reported similar antioxidant properties of *Vitex negundo* Linn. in rats, by using ethanol induced oxidative stress model. [31].The extracts also possess the ability to combat oxidative stress by reducing lipid peroxidation owing to the presence of flavones, vitamin C and carotene. Rooban *et al.* evaluated the antioxidant and therapeutic potential of *Vitex negundo* flavonoids in modulating solenoid-induced cataract and found it to be effective [32]

Other Pharmacological Activities: Interestingly, Ayurveda classical texts have described oral as well as local application consumption of *V. negundo* in pain management, while recent market preparations e.g. ointments, oils, creams have used it as topical applications for its likely analgesic activity as depicted in commercially available preparation in the table no. 1 and 2 below.

Table 1: Ayurveda classical preparations containing *V. negundo* (Ref: 33-38)

Formulations	Major Plant Drug (Botanical Name)	Indication Refs
<i>Nirgundi Thaila</i> [33]	<i>V. negundo</i>	<i>Sandhigata vata</i> (osteoarthritis)
<i>Nirgundi Patra pinda sweda</i> [34]	<i>V. negundo</i>	<i>Sandhigata vata</i> (osteoarthritis)
<i>Nirgundi churna</i> [35]	<i>V. negundo</i>	Renal colic
<i>Nirgundi Ghana vati</i> [36]	<i>V. negundo</i>	<i>Gridhrasi</i> (sciatica)
<i>Trivikrama Rasa</i> [37]	<i>V. negundo</i> , Tamra (copper)	<i>Mutrashmari</i> (Urolithiasis)
<i>Vishagarbha Taila</i> [38]	<i>Vishatinduka</i> (<i>Strychnous nux-vomica</i>)	<i>Vatarakta</i> (Gout)

Table 2. Herbal products containing *V. negundo*, available in market. [39]

S No.	Brand	Indication	Manufacturers (country)
1.	Liv 52 [40]	Detoxification of liver	Himalaya Drug co., Bangalore (India) [42]
2.	Antiseptic cream [41]	Burns, wounds	
3.	Dental cream [42]	Bleeding gums, toothaches	
4.	Muscle and joint rub	Muscle strains	
5.	Pilex tablets and cream	Haemorrhoids	
6.	Rumalaya gel and tablets	Inflammatory musculoskeletal disorders	
7.	Himcolin cream	Erectile dysfunction	
8.	V-gel	Cervicitis, vaginitis	
9.	Relief cream	Stiff back, joint and muscle pain	Surya Herbal Ltd., Noida (India)
10.	Ostranil gel	Lumbago, osteoarthritis	
11.	Jigreen	Liver ailments	Hamdard Laboratories, New Delhi (India)
12.	Arthrill capsules	Joint pain, arthritis	IndSwift Ltd., Chandigarh (India)
13.	Massage oil	Frozen shoulder, cervical spondylitis	
14.	Arthofix Juice	Joint pain, arthritis	Sri Sri Tattva Ltd.
15.	Asthi Move Tablet	Joint pain, arthritis	Glenn Biocare Pvt Ltd

Mechanisms of Action: The ethno medical use of *V. negundo* as a useful remedy in inflammatory and arthritic disorders could possibly be because of its excellent anti-inflammatory and antioxidant potential. The studies by Kulkarni et al have demonstrated a strong correlation between anti-inflammatory and antioxidant activities of *V. negundo*. [43] The standardized extract of 100 mg/kg dose caused a comparable reduction in edema with that of diclofenac sodium (25 mg/kg) when evaluated for anti-inflammatory 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 suggested that radical quenching may be one of the mechanisms responsible for its anti-inflammatory activity. The prevention of oxidative damage to tissue could therefore be one of the mechanisms responsible for the anti-inflammatory effect shown by the plant. This may include the inhibition of pro-inflammatory cytokines, modulation of inflammatory pathways (such as NF- κ B and MAPK), and antioxidative effects. Some of the bioactive compounds of *Vitex* genus which can contribute towards its anti-inflammatory activity are iridoid and pedunculariside, as they were found to demonstrate preferential inhibition of COX-2 and marginal inhibitory effect on COX-1 enzyme. [44,45]

In vitro studies: Raghavendra et al suggested the presence of phytochemicals in the ethanolic extract of *Vitex negundo* L. Total phenols and flavonoids content were also very rich in ethanolic extract. This extract was found to contain an effective antioxidant

fraction that has been confirmed by different in vitro assays including DPPH radical scavenging activity, ferrous chelating, reducing power assay and total antioxidant capacity.[46] The free radical scavenging ability probably is one of the mechanisms by which herbal medicines exhibit higher antioxidant activity. Further studies are warranted for the isolation and identification of individual phenolic compounds and also *in vivo* studies are needed for understanding their mechanism of action to exploit as potent antioxidants for therapeutic applications.

In vivo studies: *Vitex negundo* bioactive compound, Tris (2,4-di-tert-butylphenyl) phosphate (TDTBPP), has been shown to exert anti-inflammatory activity in a Carrageenan induced rat paw edema model.[47]

V. negundo seeds possessed potential therapeutic effect on adjuvant induced arthritis in rats by decreasing the levels of TNF- α , IL-1 β and IL-6 and increasing that of IL-10 in serum as well as down-regulating the levels of COX-2 and 5-LOX, and therefore may be an effective cure for the treatment of human rheumatoid arthritis. [48]

The isolated chromone derivatives (1–2) from *V. negundo* are able to alleviate nociception and inflammation and the findings corroborated that *V. negundo* may be used as a potential source of antinociceptive and anti-inflammatory candidates. [49]

Clinical Studies: Owing to its anti-inflammatory effect it was tried during covid-19 era, its use decreased the symptoms and discomfort during mild covid disease, especially for anosmia, and overall relief and discomfort due to other symptoms (significantly compared to placebo). However, it did not decrease the time to recovery of the patients. *Vitex negundo* was safely used in these

patients without any serious adverse events. Mild adverse events of diarrhoea, vomiting, pruritus, and nausea were not significantly different between *negundo* and placebo (events probably caused by the disease itself) [50]

A phase III clinical trial using the randomized, double-blind, placebo-controlled design was used to determine the efficacy, safety and acceptability of *Vitex negundo* (*Lagundi* tablets).[51] The subjects were patients who were otherwise healthy except for complaints of acute non-bacterial cough of mild to moderate severity as defined in the protocol, with no previous cough medications within two days of consultations. A total of 119 subjects participated in the study. Forty paediatric patients completed the study: twenty one received the *Lagundi* therapy and nineteen the placebo.

Each group was further subdivided into 2 groups: younger and older children. Demographic characteristics of the subgroups were comparable as to age, sex, duration of illness and intake of previous medications. Evaluation of patients every three days gave the following results: *Lagundi* treatment of acute cough of non-bacterial etiology effectively decreased the frequency of coughing in children of all groups and improved the color of phlegm in older children by the 3rd day of dosing. With placebo treatment, cough frequency decreased by the 6th day. There were no adverse effects noted or reported by the children or their guardians and both placebo and *Lagundi* tablets were acceptable as to taste and smell. Patient compliance to medications was comparable in the two treatment groups.

A study compared the efficacy and safety of the capsule and tablet formats of *Vitex negundo*, after three days of treatment among Filipinos with acute uncomplicated cough. In terms of efficacy, both treatments showed significant and similar improvements in cough severity and quality of life. They were also comparable in safety with few adverse events in both groups, all mild and assessed unrelated to drug intake. [52]

Safety and Toxicology: In the acute toxicity study, the aqueous ethanol leaf extract of *Vitex negundo* at 620.25 g/kg/day - the highest tolerable dose in mice, yielded no oral toxicity. In the sub-chronic toxicity study, *Vitex negundo* was administered orally to 2 groups of rabbits at doses of 3.2 g/kg/day and 9.6 g/kg/day, respectively, for eight weeks. The results showed no sign of general toxicity. There were no changes in growth or hematological parameters, liver and kidney functions, and no effect in the macromorphology and micromorphology of the treated animals' livers and kidneys. [53]

Dharmasiri et al [54] in their study on *V. negundo* confirmed the oral anti-inflammatory, analgesic and antihistamine properties of mature fresh leaves

(MFL) of *Vitex negundo* L. (Verbenaceae) claimed in the Ayurveda medicine by orally treating a water extract of the leaves to rats. discovered that after 1 h of therapy, a study group of rats treated with an aqueous extract of *V. negundo* L. leaf demonstrated considerable dose-dependent analgesic efficacy. The early phase (2 h) of carrageenan-induced rat paw oedema was significantly ($P < 0.01$) suppressed in an inversely dose-dependent ($r^2 = 1, P < 0.01$) manner by MFL. The EC₅₀ was 2 g/kg of MFL. In the formaldehyde-induced rat paw oedema test, the 2.5 and 5 g/kg leaves significantly ($P < 0.05$) suppressed the inflammation on days 4–6 of the test. In the hot plate test, 2.5 and 5 g/kg of MFL showed a significant ($P < 0.05$) and directly dose-dependent analgesic activity at 1 h of treatment while the activity was absent in the tail flick test in rats. The EC₅₀ for the analgesic activity was 4.1 g/kg. In the formalin test, 1.25, 2.5 and 5 g/kg of MFL significantly ($P < 0.05$) suppressed the pain in both the phases of the test like aspirin. The leaves showed an inversely dose-dependent in vivo antihistamine and in vitro prostaglandin (PG) synthesis inhibition, membrane stabilising and antioxidant activities. These observations revealed that the fresh leaves of *Vitex negundo* have anti-inflammatory and pain suppressing activities possibly mediated via PG synthesis inhibition, antihistamine, membrane stabilising and antioxidant activities.

Conclusion

Vitex negundo emerges as a valuable medicinal plant with natural anti-inflammatory compounds to mediate the inflammatory process through a wide array of pharmacological actions. The integration of traditional knowledge with modern scientific evidence highlights its potential as a source of novel therapeutic agent in treating the inflammatory reaction seen in both chronic and sub-acute pain syndromes encountered in a pain management. Its safety profile is also acceptable as evident from various preclinical and clinical studies. On-going experiments and clinical trials should be continued to guide and provide their scientifically based effectiveness to reduce inflammation and promote wellness. Additionally, there is still a huge research need for preclinical, clinical and pharmacokinetic studies to justify the use of *V. negundo* or any of its compounds as a therapeutic agent against various diseases and to validate the likely mechanism behind the pharmacological actions of *V. negundo* and its active compounds towards alleviating the pathogenesis responsible for disease generation and progression. Various other alternative routes of administration to be explored to deliver *Vitex negundo* which can maximise its clinical efficacy, and minimise its adverse effects in the best interest of patients.

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