

**REVIEW ON THE NEURONAL ASPECT OF *VITEX NEGUNDO*-BENEFICIAL TO THE  
BRAIN HEALTH**

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**ABSTRACT**

*Vitex negundo* L. (Verbenaceae) is a hardy plant, which is credited with innumerable medicinal activities and holds importance in traditional medicine. Almost all the parts of this plant possess enormous medicinal values and it has been extensively used against wide spectrum of disease in traditional and folk medicine. Phytochemical investigation shows the presence of great number of secondary metabolites such as volatile oil, triterpenes, diterpenes, sesquiterpenes, lignan, flavonoids, flavones, glycosides, iridoid glycosides and stilbene derivative which impart a prodigious medicinal use to the plant. Now a day's greater attention is drawn towards the established traditional systems of herbal remedies for many brain disorders, which bring about positive hopes for the patients. It is estimated approximately that more than 60 million Indian populations suffers from mental disorders while the country dawdle far behind the world for treatments and pay out in the hospitals for mental cure. This review aims at presenting comprehensive information on therapeutic potential of *Vitex negundo* on Neurological and Brain disorder, which can be helpful in development of modern medicine.

**KEYWORDS:** *Vitex negundo*; Phytochemical constituents; Pharmacological activities; Neurological Disorder; Brain Health.

**INTRODUCTION**

*Vitex negundo* Linn is a large aromatic shrub (commonly known as Nirgundi, five leaved chaste tree) belonging to the family Verbenaceae. Almost all the parts of this plant possesses great medicinal values and it is employed as a remedy in various traditional systems of medicine like Ayurveda, Chinese, Siddha and Unani to treat various diseases.<sup>[1]</sup> A popular quote of India which translates as – A man cannot die of disease in an area where *Vitex negundo* Linn, *Adhatoda vasica* and *Acorus calamus* are found (provided that he knows how to use them).<sup>[2]</sup> In Indian traditional medicine system *Vitex negundo* Linn is referred as 'sarvaroganivarani' – the remedy for all diseases.<sup>[3]</sup>

**Current Situation:** Each year 10<sup>th</sup> October is the date when world mental health day is widely known everywhere the planet. The awareness regarding the balanced mental health is increasing and it is now recognized as a serious explanation for worldwide. As per WHO estimate, depression will be second only to cardiac diseases as the leading cause of morbidity and disability worldwide by 2020. Upon the statistical report available on 2005 it is estimated that about 1-2% of population suffers from severe mental disorders such as schizophrenia and manic depressive illness and nearly

5% of the population suffered from common mental disorders like depression and apprehension related problems. Indians aged 18 and above and 7.3% of those aged 13 to 17 years of the total population are suffering from various mental disputes and are in need of mental care service.<sup>[4]</sup>

**Common Brain Disorders:** The term mental disease or brain disorder is not limited to mean insanity and allied conditions of mental derangement but also includes, to certain extent, the emotional disorders. Frequently the emotional factors, when cross the state of normalcy, get deranged to become the syndromes of mental disorder. It is stated that the brain has 100 billion nerve cells (neurons) and each of them connect with many others to form communication networks. These nerve cells have special jobs like thinking, learning, remembering as well as to see, hear, and smell. To accomplish their work brain cells, like tiny factories, receive supplies, generate energy, construct equipment, and get rid of the waste. Brain cells also process and store information to communicate with other cells. Keeping everything functional, it requires a lot of fuel and oxygen for legitimate coordination. Once the system is disturbed, a range of human brain disorders start appearing, for

example, Alzheimer's disease, Parkinson's disease, depression, epilepsy, schizophrenia, anxiety, etc.<sup>[4]</sup>

## MORPHOLOGY

*Vitex negundo* is an erect shrub or small tree growing from 2 to 8 m (6.6 to 26.2 ft.) in height. The bark is reddish-brown. Its leaves are digitate, with five lanceolate leaflets, sometimes three. Each leaflet is around 4 to 10 cm (1.6 to 3.9 in) in length, with the central leaflet being the largest and possessing a stalk.



The leaf edges are toothed or serrated and the bottom surface is covered with hairs.<sup>[5]</sup> The numerous flowers are borne in panicles 10 to 20 cm (3.9 to 7.9 in) in length. Each is around 6 to 7 cm (2.4 to 2.8 in) long and is white to blue in color. The petals are of different lengths, with the middle lower lobe being the longest. Both the corolla and calyx are covered with dense hairs. The fruit is succulent globose and black when ripe with four seeds, rounded and about 4 mm in diameter.<sup>[6,7]</sup>

## Geographical Distribution

It grows in humid places or along water courses in wastelands and mixed open forests and has been reported to occur in India, Pakistan, Afghanistan, Sri Lanka, Thailand, Malaysia, eastern Africa and Madagascar.<sup>[8]</sup> It is grown commercially as a crop in parts of Asia, Europe, North America and West Indies. It is used as a food crop and also as a source of timber. A large aromatic shrub, the plant is distributed throughout the greater part of India up to an altitude of 1500m in the outer region of Himalayas and some districts of Himachal Pradesh.<sup>[9,10]</sup>

## Vernacular Names<sup>[5,11]</sup>

English	: Five leaved chaste tree
Tamil	: Nirkundi, Vellai-nochi
Telugu	: Vaavili
Hindi	: Shivari, Nirgundi
Malayalam	: Vellanocchi, Indranee, Karunacci
Kannada	: Nkkilu, Lakkigida, Nekka, Nakkigida
Punjab	: Shwari
Assam	: Aslok
Bengal	: Nirgundi, Nishinda
Gujarati	: Nagod
Marathi	: Nirgundi
Punjabi	: Sambhalu, Banna
Sanskrit	: Nirgundi

## Taxonomic / Scientific Classification<sup>[11]</sup>

Kingdom	: Plantae
Sub Kingdom	: Tracheobionta
Super Division	: Spermatophyta
Division	: Magnoliophyta
Class	: Magnoliopsida
Sub Class	: Asteridea
Order	: Lamiales
Family	: Verbenaceae
Genus	: Vitex
Species	: Negundo

## Medicinal Importance

Herbal medicine, not only preferably curing a particular disease, but aims at returning the body back to its natural state of health.<sup>[12]</sup> The phytochemical components of medicinal plants often act individually, additively or synergistically for the improvement of health.<sup>[13]</sup> After evaluating the various chemical components present in different parts of *Vitex negundo*, it is essential that focus shifts to the medicinal applications of the plant. Myriad medicinal properties have been ascribed to *Vitex negundo* and the plant has also been extensively used in treatment of a plethora of ailments.<sup>[14]</sup>

### 1. Traditional medicine

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.<sup>[15]</sup>

#### a. Ayurveda

The plant finds mention in the verses of the Charaka Samhita which is unarguably the most ancient and authoritative textbook of Indian Ayurveda. *Vitex negundo* has been designated as an anthelmintic and is prescribed as a vermifuge in the exposition on the Charaka Samhita by Sharma.<sup>[16]</sup>

Other Ayurvedic uses of *Vitex negundo* are described by Tirtha.<sup>[17]</sup> People sleep on pillows stuffed with *Vitex negundo* leaves to dispel catarrh and headache and smoke the leaves for relief. Crushed leaf poultice is applied to cure headaches, neck gland sores, tubercular neck swellings and sinusitis. Essential oil of the leaves is

also effective in treatment of venereal diseases and other syphilitic skin disorders.

Jadhav and Bhutani,<sup>[18]</sup> report the Ayurvedic use of *Vitex negundo* in dysmenorrhea. Patkar,<sup>[19]</sup> refers to the formulations described in Anubhoga Vaidya Bhaga, a compendium of formulations in cosmetology, in outlining the use of *Vitex negundo* leaves along with those of *Azadirachta indica*, *Eclipta alba*, *Sphaeranthus indicus* and *Carum copticum* in a notable rejuvenation treatment known as Kayakalpa.

#### b. Unani medicine

Khare,<sup>[20]</sup> outlines the applications of *Vitex negundo*, commonly known as Nisinda in Unani medicine. The seeds are administered internally with sugarcane vinegar for removal of swellings. Powdered seeds are used in spermatorrhoea and serve as an aphrodisiac when dispensed along with dry *Zingiber officinale* and milk.

#### c. Chinese medicine

The Chinese Pharmacopoeia prescribes the fruit of *Vitex negundo* in the treatment of reddened, painful, and puffy eyes; headache and arthritic joints.<sup>[21]</sup>

### 2. Folk medicine

Folklore systems of medicine continue to serve a large segment of population, especially those in rural and tribal areas, regardless of the advent of modern medicine.<sup>[22]</sup>

Used in the treatment of,

- Crushed leaf poultice, Leaf is smoked, Pillow stuffed with leaves are used in conditions like Weakness, Headache, Vomiting, Malaria, Black fever in Bangladesh, India and Malaysia.<sup>[23]</sup>
- Leaf Juice is used in Common cold, Flu and Cough in Guangdong of China.<sup>[24]</sup>
- Essential oils from leaf, crushed leaf poultice are used in Sinusitis and Whooping cough in Nepal.<sup>[25]</sup>
- Chest-pain, Backache, Used as toothbrush in Buner of Pakistan.<sup>[26]</sup>
- Eye disease, Toothache, Rheumatism, Used as a tonic, carminative and vermifuge in Sri Lanka.<sup>[27]</sup>
- Root decoction is used in the treatment of Asthma and Bronchitis in India.<sup>[28]</sup>
- Flowers are used in gastrointestinal disorder and diarrhoea in India and Pakistan.<sup>[29]</sup>

#### Phytochemical Constituents

Phytochemical studies on *Vitex negundo* Linn revealed the presence of volatile oil, triterpenes, diterpenes, sesquiterpenes, lignan, flavonoids, flavones, glycosides, iridoid glycosides and stilbene derivative.<sup>[30]</sup> The detailed of phytochemical constituents is present in each part of the plant is given below.

**Leaves:** The leaves of *Vitex negundo* Linn possess various chemical constituents such as.

S.NO	PHYTOCHEMICAL CONSTITUENT	REFERENCE
1.	Friedelin, vitamin-C, carotene, casticin, artemetin	[31]
2.	terpinen-4-ol, $\alpha$ -terpineol, sabinene, globulol, spathulenol, $\beta$ - farnesene, farnesol, bis(1,1dimethyl) methylphenol, $\alpha$ -pinene, $\beta$ -pinene, linalool, terpinyl acetate, caryophyllene epoxide, caryophyllenol, vitexicarpin, viridiflorol	[32],[33],[34],[35]
3.	4,4'- dimethoxy-trans-stilbene, 5,6,7,8,3'4'5- heptamethoxy, 5-hydroxy-6,7,8,3'4'-pentamethoxy (5-Odesmethylnobiletin), 5-hydroxy-6,7,8,3',4',5-hexamethoxy(gardeninA), 5-hydroxy-6,7,8,4'-tetramethoxy (gardeninB), 5- hydroxy-7,3',4',5'-tetramethoxyflavone (corymbosin)	[36],[37],[38],[39]
4.	terpinen-4-ol, $\alpha$ -copaene, $\beta$ -caryophyllene, $\beta$ -elemene, camphene, $\alpha$ -thujene, $\alpha$ -pinene, sebinene, linalool, stearic acid and behenicacid	[40]
5.	$\alpha$ -elemene, $\delta$ - elemene, $\beta$ -elemene, $\beta$ -eudesmol, camphor, camphene, careen, 1,8- cineol, 1-oceten-3-ol, $\gamma$ -terpinene, $\alpha$ -phellendrene, $\beta$ -phellendrene, $\alpha$ - guaiene, abieta-7,13-diene, neral, geranial, bornyl acetate, nerolidol, $\beta$ -bisabolol, cedrol	[41],[42],[43],[44]&[45]
6.	2'-p-hydroxybenzoyl mussaenosidic acid, agnuside, lagundinin, aucubin and nishindaside	[46]
7.	viridiflorol, squalene, 5-hydroxy-3,6,7,3',4'- pentamethoxy flavone, 5-hydroxy-3,7,3',4'-tetramethoxy flavones, 5,3-dihydroxy- 7,8,4- trimethoxy flavanone, p-hydroxybenzoic acid, 3,4 - dihydroxybenzoicacid, luteolin-7-glucoside, isoorientin	[47]
8.	3'-benzoyloxyhydroxy-3,6,7,4- tetramethoxyflavone, 5,3'-dibenzoyloxy-3,6,7,4-teramethoxyflavone,5,3'-Dipropanyloxy-3,6,7,4'-tetramethoxyflavone, 5,3-Dibutanoyloxy3,6,7,4-tetramethoxyflavone,5,3'-Dipenty4enoyloxy-3,6,7,4' tetramethoxy flavone, 5,3-Dihexanoyl 3,6,7,4-tetramethoxyflavone	[48]
9.	betulinic acid, ursolic acid	[49]
10.	dimethoxyflavonone, 5,3'-dihydroxy-7,8,4'-trimethoxyflavonone, 7,8-Dimehylherbacetin-3-rhamnoside, vitegnoside	[50]
11.	1,4a,5,7a tetrahydro 1 $\beta$ Dglucosyl (3',4'dihydroxybenzoyloxymethyl)-5-ketocyclopenta[c] pyran-4-carboxylic acid, luteolin-7-O- $\beta$ -D-glucosid	[51]
12.	6'-p-hydroxy benzoylmussaenosidic acid	[52]

**Seeds**

The seeds of *Vitex negundo* Linn have chemical constituents such as

S.NO	PHYTOCHEMICAL CONSTITUENT	REFERENCE
1.	n-Tritriacontane, n-hentriacontanol, n-hentricontane, n-nonacosane, $\beta$ -sitosterol, phydroxybenzoic acid and 5-oxyisophthalic acid, 3, 4-dihydroxybenzoic acid [53-55], artemetin	[56]
2.	3 $\beta$ -acetoxylean-12-en-27-oic acid, 5 $\beta$ -hydro-8,11,13-abietatrien-6 $\alpha$ -ol, 2 $\alpha$ ,3 $\alpha$ -dihydroxyoleana-5,12-dien-28-oicacid, 2 $\beta$ ,3 $\alpha$ -diacetoxyleana-5,12-dien-28-oicacid and 2 $\alpha$ ,3 $\beta$ -diacetoxyleana-5,12-dien-28-oic acid	[57,58]
3.	vitedoin A, vitedoamine A, vitedoin B	[59,60]
4.	5,7,3'-trihydroxy 6,8,4'-trimethoxy	[61]
5.	6-hydroxy-4-(4-hydroxy-3-methoxy-phenyl)-3-hydroxymethyl-7-methoxy-3, 4-dihydro-2-naphthaldehyde	[62]

**Stem and bark**

The various chemical constituents present in the stem of *Vitex negundo* are tabulated

S.NO	PHYTOCHEMICAL CONSTITUENT	REFERENCE
1.	3,6,7,3',4'-Pentamethoxy-5-Oglucopyranosyl-rhamnoside, vitexin cafeate, 4'-O-methyl myricetin- 3-O-[4'-O- $\beta$ -D-galactosyl]- $\beta$ -D-galactopyranoside	[63]
2.	bark $\beta$ -amyrin, epifriedelinol and oleanolic acid	[64]
3.	Hepta methyl-phenyl-cyclotetra siloxane, Cyclo heptasiloxane,tetra decamethyl Nona methyl, phenyl-cyclopenta siloxane, Cyclo octa siloxane,hexadeca methyl, Borazine, 2,4,6- triphenyl-11, 3, 5-tryophl, Nonamethyl, phenyl-cyclopenta siloxane , Tetracosamethylcyclododeca siloxane, penta methyl phenyl-Disilane, Heptasiloxane, 1,1,3,3,5,5,7,7,9,9,11,11,13,13,-tetradeca methyl,3 $\alpha$ ,3 $\alpha'$ -Dichloro-2 $\alpha$ ,3 $\alpha$ -ethano-3 $\beta$ -methyl-cholestan-2 $\alpha$ -one, Octadecamethyl, cyclonona siloxanes Cyclo octa siloxane, hexadeca methyl	[65]
4.	p-hydroxy benzoic acid, $\beta$ -sitosterol	[66]
5.	5-hydroxy-3,6,7,3'4'-pentamethoxy flavone, 5-hydroxy-3'dihydroxy-7,8,4'-trimethoxy flavanone,3 $\beta$ -acetoxylean-12-en-27-oic acid, 3 $\beta$ -hydroxy-olean-5, 12-dien-28-oic acid	[67]

**Roots**

S.NO	PHYTOCHEMICAL CONSTITUENT	REFERENCE
1.	Vitexoside, agnuside, R-dalbergiphenol	[68,69]
2.	negundin A, negundin B, 6-hydroxy-4-(4-hydroxy-3-methoxy)-3-hydroxymethyl-7-methoxy-3,4-dihydro-2-naphthaldehyde, vitrofolal E, (+)-lyoniresinol, (+)(-)-pinosresinol, and (+)-diasyringaresinol	[70]
3.	2 $\beta$ ,3 $\alpha$ -diacetoxyleana-5,12-dien-28-oic acid;2 $\alpha$ ,3 $\alpha$ -dihydroxyoleana-5,12-dien-28-oic acid, 2 $\alpha$ ,3 $\beta$ -diacetoxyleana-5,12-dien-28-oic acid, vitexin and isovitexin	[71]
4.	acetyl oleanolic acid, sitosterol, 3-formyl-4.5-dimethyl-8-oxo-5H-6,7-dihydronaphthofuran (a new furanoeremophilane)	[72]

**Essential oil of fresh leaves, flowers and dried fruits**

The various chemical constituents of essential oil of from leaves, flowers and dried fruits are listed

S.NO	PHYTOCHEMICAL CONSTITUENT	REFERENCE
1.	$\delta$ -guaiene, 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	[73]
2.	viridiflorol(19.55%), $\beta$ -caryophyllene (16.59%), sabinene (12.07%), 4-terpineol (9.65%), $\gamma$ -terpinene (2.21%), caryophylleneoxide (1.75%), 1-oceten-3-ol (1.59%), and globulol (1.05%)	[74]

**Pharmacological Evidence**

It has been estimated approximately that 14-28% of higher plant species are used medicinally. About 74% of pharmacologically active plant derived components were discovered after follow up on ethnomedicinal use of the plants.<sup>[75]</sup> In recent years, secondary plant metabolites (phytochemical) have been extensively investigated as a source of medicinal agents. Almost all parts of *Vitex negundo*, from root to fruits, possess a multitude of phytochemicals as secondary metabolites which impart a

variety of medicinal uses to the plant. The medicinal plants with time tested healing properties are now in vogue. An urgent need is therefore being felt for their proper identification and utility.

Demands of the scientific community have necessitated experimental evidence to further underline the medicinal importance of *Vitex negundo*. Taking cure from these traditional and folk systems of medicine, scientific studies have been designed and conducted in order to

validate pharmacological claims.

### Pharmacological Activity Upon Nervous System

#### Anti-Amnesic Activity

**Kanwal A et al., 2010** investigated the anti-amnesic activity of *Vitex negundo* Linn extract was studied against scopolamine induced amnesia in rats. Based on the stages of memory acquisition, consolidation and retention the scopolamine was given that different stages and anti-amnesic activity of *Vitex negundo* Linn was compared with standard donepezil and study proved that the groups treated with *Vitex negundo* Linn extract showed decrease in the phenomenon of amnesia through the antioxidant effect thus increases memory.<sup>[76]</sup>

**Otari KV et al., 2012** demonstrated the improvement in learning and memory by hydroalcoholic extract of *Vitex negundo* Linn. Leaves (HEVN). Effects of HEVN were evaluated in normal as well as in scopolamine- induced cognitive deficit mice paradigms using elevated plus maze (EPM) and object recognition test (ORT). Study revealed the effectiveness of HEVN in improving learning and memory processes in both paradigms. The effect might be due to AchE inhibition, antioxidant effect, and/or increase in cholinergic transmission.<sup>[77]</sup>

**Wang Q et al., 2019** reported the Vitegnoside Mitigates Neuronal Injury, Mitochondrial Apoptosis, and Inflammation in an Alzheimer's disease Cell Model via the p38 MAPK/JNK Pathway. Study was carried using human neuroblastoma SH-SY5Y cell line carrying the Swedish mutation that induces A $\beta$ PP overexpression was used as an in vitro AD cell model. Vitegnoside promoted neuroprotection through the improvement of cell viability, maintenance of cytomembrane integrity and nuclear homogeneity in these cells, but these effects were not observed in the copper-treated SH-SY5Y cells without A $\beta$ PP overexpression used as the wild-type control, indicating that vitegnoside exerted neuroprotection under copper-triggered A $\beta$  toxic conditions.<sup>[78]</sup>

#### Anxiolytic activity

**Adnaik RS et al., 2009** revealed the anxiolytic activity of ethanolic extracts of *Vitex negundo* Linn roots was performed using the elevated plus maze (EMP) and light-dark exploration test in maze. *Vitex negundo* Linn extract are diazepam (used as positive control) was orally administered to male mice one hour before the behavioral evaluation. *Vitex negundo* Linn extract has increase the percentage time spent on and the number of entries to the open arms of EPM. Both the diazepam and *Vitex negundo* Linn treated rates increase the time spent in light-arena reveals that *Vitex negundo* Linn root extract has significantly good anxiolytic activity.<sup>[79]</sup>

#### Anticonvulsant activity

**S. L. Khokra et al., 2011** investigated the Anticonvulsant Activity of Essential Oils Isolated from *Vitex negundo* Linn. Study shows that the essential oils

isolated from dried fruits, fresh leaves and flowers of *Vitex negundo* Linn. Were compared with phenytoin in MES and diazepam in PTZ induced seizures methods. Fruit oil showed good protection against PTZ induced clonic convulsions and reduced the extensor phase duration in MES. The essential oil of leaves showed excellent protection in mice against PTZ induced clonic convulsions only. The sub protective doses of all the oils (100 mg/kg, p.o) potentiated the anticonvulsant action of phenytoin and diazepam. These oils may be used in adjuvant therapy along with standard anticonvulsants and can possibly lower the requirements of phenytoin and diazepam.<sup>[80]</sup>

**Khan et al., 2018** reported the Therefore, we have investigated the effects of Methanolic fraction of *Vitex negundo* extract in Murine Neuro 2A cell line. Cells were cultured in a defined medium with or without the *Vitex negundo* extract (100 $\mu$ g/ml). Sodium currents were recorded using whole-cell patch clamp method. The data show that Methanolic extract of *Vitex negundo* inhibited sodium currents in a dose dependent manner (IC<sub>50</sub> =161 $\mu$ g/ml). *Vitex negundo* (100 $\mu$ g/ml) shifted the steady-state inactivation curve to the left or towards the hyper polarization state. However, *Vitex negundo* did not show any effects on outward rectifying potassium currents. Moreover, *Vitex negundo* (100  $\mu$ g/ml) significantly reduced the sustained repetitive (48 $\pm$ 4.8%, P< 0.01) firing from neonatal hippocampal neurons at 12 DIV. Hence, our data suggested that inhibition of sodium channels by *Vitex Negundo* may exert pharmacological effects in reducing pain and convulsions.<sup>[81]</sup>

#### Anti-nociceptive activity

**Gupta RK et al., 2005** reported the Anti-nociceptive Activity of *Vitex negundo* Linn Leaf Extract. The anti-nociceptive activity of ethanolic *Vitex negundo* Linn leaf extract was performed by tail flick test in rats and writhing test induced by acetic acid in mice. In tail flick test meperidine was used as a standard control, aspirin used as a standard control in writhing test which was compared to the effect of *Vitex negundo* Linn extract. Mechanism of central analgesic action was studied by the interaction of naloxone hydrochloride. *Vitex negundo* Linn. Extract possesses both central and peripheral analgesic activity.<sup>[82]</sup>

**Zheng CJ et al., 2010** investigated the Anti-nociceptive activities of the liposoluble fraction from *Vitex negundo* seeds. The anti-nociceptive activities of the petroleum ether fraction (PEF) from the aqueous ethanol extract of *Vitex negundo* Linn. (Verbenaceae) seeds have been evaluated in several nociceptive mouse models. The PEF (at doses of 12, 24, and 48 mg/kg body wt) of *Vitex negundo* seeds demonstrated dose-related and marked anti-nociception against several models of chemical nociception in mice such as acetic acid-induced writhing and formalin test. The study demonstrated the notable anti-nociceptive activity of the PEF of *Vitex negundo*

seeds in the test models of nociception induced by chemical and thermal stimuli.<sup>[83]</sup>

#### CNS Depressant activity

**Gupta M et al., 1999** reported the CNS activity of *Vitex negundo* Linn. In mice. A methanolic extract (ME) of the leaves of *Vitex negundo* was found to significantly potentiate the sleeping time induced by pentobarbitone sodium, diazepam and chlorpromazine in mice.<sup>[84]</sup>

#### Analgesic Activity

**M.G. Dharmasiri et al. 2003** evaluated analgesic activity from the aqueous extract of fresh leaves of *Vitex negundo* in female Wistar rats using hot plate, tail flick and formalin tests. The standard drug used in hot plate and tail flick was aspirin (100 mg/kg).<sup>[85]</sup>

**Yasmeen A. et al., 2017** evaluated both the peripheral and central analgesic activity of ethanolic extract of *Vitex negundo* flowers in experimental animals. This activity was evaluated for peripheral analgesic activity by the acetic acid induced writhing test and central analgesic activity by the tail flick method respectively using aspirin as the standard drug. This study showed that the increased analgesic effects which was comparable with that of the standard drug aspirin at in writhing test and produced greater analgesic activity than that of standard drug aspirin at dose in tail flick method.<sup>[86]</sup>

#### Neuroprotective Activity

**Rahiman RA et al., 2015** reported the We conclude that aqueous extract of *Vitex negundo* leaf has potential therapeutic effects on improving the cognitive impairment in Wistar albino rats through inhibiting lipid peroxidation, augmenting endogenous antioxidant enzymes and decreasing acetylcholinesterase activity in brain. Aqueous extract of *Vitex negundo* was fed to the rats at a dosage of 1000 mg per kilogram body weight of the animal for a period of 15 days. Learning and memory were evaluated using the classical T-maze test. Oxidative stress parameters like Malondialdehyde, glutathione-S-transferase and superoxide dismutase were assessed and acetylcholinesterase activity was estimated.<sup>[87]</sup>

**Siddiqui et al., 2018** reported the neurite outgrowth effects of *Vitex negundo* extract in hippocampal neurons. Neurons from P0 mice were isolated and cultured in defined medium containing the different concentrations of *Vitex negundo* (20, 30, 40, 50, 100, 150 and 200 µg/ml) for 48 hrs. The presence of the neurites was confirmed by using βIII-tubulin antibody which specifically labels only the neurites. Morphometric analysis was done by using Optika Pro-Vision software. The data show that *Vitex negundo* at 30 and 40 µg/ml significantly increased the mean average length of the longest neurite whereas at 150 and 200 µg/ml it significantly decreased the mean average length of the 10 longest neurite in hippocampal neurons. Nevertheless *Vitex negundo* did not show any significant effects on the sum of all the neurite lengths at any concentrations

tested. Taken together the result shows that methanolic extract of *Vitex negundo* has potential to produce long neurites at 30 and 40 µg/ml and therefore can be act as a neuroprotective agent in the future drug development.<sup>[88]</sup>

#### Antioxidant Activity

**Umamaheswari M et al., 2012** reported the Protective effect of the leaves of *Vitex negundo* against ethanol-induced cerebral oxidative stress in rats. The present study investigated the effect of the various fractions of hydromethanolic extract of the leaves of *Vitex negundo* (Verbenaceae) against ethanol-induced cerebral oxidative stress in rats. Cerebral oxidative stress was induced by the administration of 20% ethanol (5 ml/100g bw) for a period of 28 days. Histopathological examination of the brain tissue of the ethanol treated animals showed marked gliosis. Histopathological examination revealed that the fractions of *Vitex negundo* offered a significant protection against ethanol toxicity in rat brain. The present study reveals that the leaf of *Vitex negundo* has protective action on the brain, which could be attributed to its antioxidant potential.<sup>[89]</sup>

#### Toxicology

Preliminary acute toxicity study of ethanolic leaf extract in albino rats by oral route carried out by Tendon and Gupta (2004) indicated it to be practically nontoxic, as its LD50 dose recorded was 7.5 g/kg/wt. The stomach showed no histomorphological changes in any of the doses of the extract studied. However, dose dependent histomorphological changes were observed in the specimens of the heart, liver and lung.<sup>[90]</sup>

#### CONCLUSION

Available psychotherapeutics does not properly meet the therapeutic demands of a vast majority of patients with mental health problems and that herbal remedies remain to be the ultimate therapeutic hope for many such patients worldwide. The world is rightly looking towards brain healing properties of traditional medicines, for a reliable cure with no or minimal side effects. The present critical review on *Vitex negundo* reveals that the plant is a treasury among plant drugs for treating most of the brain related disorders and a benefit to brain health.

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#### Conflicts of Interest

The authors affirm no conflicts of interest, financial, or otherwise.

#### Authors' Contributions

Pavithra Dass who is the first author has collected all the relevant literature and sorted the significant articles for this review. Dr. Palayyan Muralidharan the second author recommended the theme and helps out in

collection and screening of the information in the article and reviewed the article for final submission.

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The authors declare no conflicts of interest.

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