Free Radicals and Antioxidants., 2025; 15(2):42-48.
https://www.antiox.org

Review Article

Therapeutic Potential of *Vitex negundo*: A Comprehensive Review of Its Medicinal Properties

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ABSTRACT

Vitex negundo L., commonly known as *Nochi* in Tamil, is a widely distributed medicinal plant valued in traditional medicine for its diverse therapeutic properties. It contains a rich array of secondary metabolites, including flavonoids, alkaloids, tannins, and phenolic compounds, which contribute to its broad pharmacological potential. This review aims to provide a comprehensive overview of the general medicinal significance of based on existing scientific and ethnobotanical evidence. To summarize its phytochemical composition, highlight its general pharmacological activities, and discuss its role in traditional medicine, along with current research trends and conservation concerns. The available literature on the plant's bioactive constituents, extraction methods, and reported biological activities highlights its potential as a source of natural products. *V. negundo* represents a valuable medicinal resource with promising applications in natural product research and drug development. Further studies on its bioactive compounds, standardization, and sustainable extraction are necessary to explore and harness its therapeutic potential fully. This review highlights the multifaceted role of *V. negundo* in disease prevention and treatment, emphasizing the need for further pharmacological and clinical investigations to establish its efficacy and safety for modern therapeutic use.

Keywords: Apoptosis, Anti-diabetic, Anti-inflammatory, Phytochemical, *Vitex negundo*.

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Received: 08-01-2026;
Revised: 27-02-2026;
Accepted: 18-04-2026.

INTRODUCTION

In the Lamiaceae family, *Vitex*. L. is the largest genus in different countries. Species of Vitex are used in traditional medicine systems.[1] It consists of 230 species of shrubs and trees.[2] It reaches a height of 3-9 feet tall, but when it is cultivated, it grows around 20 feet tall. It is an aromatic shrub. Leaves are petiolate, unequal, elliptic-lanceolate or lanceolate, digitately compound and leaflets are 3-5 flowers are short and crowded, sub globose fruits and are drupaceous in 2-3 mm and seeds are 2-4 bony endocarps it can grow in the tropical regions it is widely distributed throughout globally in the places like America, Indo-Malaysia, West Indies, Europe, and Asia it spread greater part of India. Maharashtra is a regional state; it has many similarities to the warm parts of Europe and the hot regions of Asia.[3] There are six Vitex species, which are *Vitex trifolia, Vitex negundo, Vitex agnus-castus, Vitex glabrrata, Vitex rotundifolia*, and *Vitex donianai*.[2] It is used as a pharmacological, ornamental, and ethnobotanical species. Vitex is used as traditional medicine in various countries for various ailments and diseases, as illustrated in Figure 1. It consists of 556 chemical constituents, which belong to several different chemical classes: diterpenoids, flavonoids, lignans, iridoids, ecdysteroids, monoterpenoids, and sesquiterpenoids.[4] The Philippine Food and Drug Administration agreed to *V. negundo* as an herbal drug for asthma and cough after clinical trials for efficacy and safety.[5]

Anti-Inflammatory Activity

Mechanism of innate immunity in the generic response, which is inflammation, every pathogen has its own antigenic property. Our adaptive immunity is more specific to every pathogen.[6] The first line of defence is inflammation, which involves molecular mediators, immune cells, and blood vessels. When inflammation occurs, it removes injured cells and tissues, and tissue repair is initiated. Little inflammation can be caused by harmful stimuli, leading to tissue destruction. Various diseases are associated with chronic inflammation, for example, osteoarthritis, atherosclerosis, hay fever, and periodontal disease.[7] Inflammation has two types: acute inflammation and chronic inflammation. Acute inflammation is defined as inflammation that is sustained for a brief amount of time and increases the flow of plasma and leukocytes to wounded tissue by blood; chronic inflammation is

DOI: 10.5530/fra.2025.2.6

defined as inflammation that is sustained over an extended period of time. Differentiated into two types, type-1 and type-2, which depend on the type of cytokines and helper T cells.[8] The crude extract of *V. negundo* has different types of bioactive molecules within it. Bioactive molecules are isolated from other solvents based on solvent polarity.[9] The ether extract of *V. negundo* leaves shows the antioxidant effect to reduce inflammation.[10] The extract of *V. negundo* leaf is worked with various solvents like water-based solvents, methanol, and petroleum ether to examine the free radical scavenging efficacy and anti-inflammatory properties.[11] The findings indicate that the three solvents, petroleum ether, aqueous, and methanol, all exhibit dose-dependent anti-inflammatory and antioxidant properties, with aqueous exhibiting the greatest effectiveness.[9]

Antioxidant

Reactive Oxygen Species (ROS) can be neutralized to prevent the oxidation of molecules in our bodies, thereby protecting cells. Although humans have an antioxidant system, they also absorb antioxidants from the diet. Oxidative stress is characterized by the accumulation of ROS and free radicals.[12] Asthma, acute respiratory disease syndrome, chronic obstructive pulmonary disease, cancer, diabetes, atherosclerosis, and hypertension are the numerous diseases that are linked with oxidative stress.[13] Studies have suggested that many of the phytochemical activities are present in the ethanolic extract of *V. negundo*, which shows a higher range of flavonoids and phenols from the content. This was confirmed by the different *in vitro* assays, like radical scavenging activity, 2,2-Diphenyl-1-Picrylhydrazyl (DPPH).[14] *V. negundo* has been attributed largely to its polar phytoconstituents, which exhibit robust free radical scavenging activity. This activity has been demonstrated through concentration-dependent quenching of the ABTS (2,2′-azino-bis-3-ethylbenzothiazoline-6-sulfonic acid) radical cation, indicating the plant's capacity to directly neutralize ROS. Comparable antioxidant effects have also been reported *in vivo*, where ethanol-induced oxidative stress models in rats confirmed the efficacy of the same polar fraction in mitigating oxidative damage. Significant antioxidant properties of *V. negundo* reveal its therapeutic relevance in oxidative stress-related conditions.[15]

Anticancer

In developed and developing countries, cancer is one of the deadliest diseases compared to other diseases worldwide. World Health Organisation (WHO) supervised a survey revealing that in the year of 2012, 8.2 million people were affected by cancer, and it will increase to 19 million in the year 2025. Each year, more than 0.6 million die because of tobacco-related cancer. There are several treatments available, which are radiation, surgery, hormones, chemotherapy, and immunotherapy, based on the patients and the severity of the disease. Although there isn't a proven medication to treat cancer,[16] nature offers us a wealth of plants that have many therapeutic qualities.

The ancient shrub *V. negundo*, in particular, has a compound called artemetin that is extracted from the solvent ethyl acetate and exhibits both antioxidant and cytotoxic properties against cancerous breast cell lines. Western blotting was used to examine Michigan Cancer Foundation-7 (MCF-7) caspase-3 and caspase-9, which demonstrate the propensity for apoptosis.[17] Methanolic extract was used for the synthesis of Silver Nanoparticles (AgNPs), and it was employed against the *in vitro* Human Colorectal adenocarcinoma cell line.[18] (HCT15) *V. negundo* leaf extracts in methanol and chloroform were found to be anti-proliferative and have a strong cytotoxic effect in human ovarian cancer when compared to the standard medication doxorubicin.[19] *V. Pseudo-Negundo* possesses notable medicinal properties, including the ability to modulate apoptotic and antioxidant signaling pathways. The combined treatment using methanolic extract and cisplatin demonstrated a significantly enhanced cytotoxic effect on cervical cancer cell lines (HeLa and CaSki) when compared to monotherapy.[20] The term tyrphostins was coined in the year 1988. Tyrosine Kinase Inhibitors (TKI) are a group of pharmacological agents that phosphorylation is the process of adding a phosphate group to the protein and the proteins, activating it. By several modes of inhibition, the signal transduction pathway is inhibited.[21] TKIs are used as inhibitors; they are used in anticancer studies, for example, chronic myelogenous leukaemia, and also to treat other diseases like idiopathic pulmonary fibrosis.[22] The compounds which are present in the roots of *V. negundo* Compound 1 (negundin A) are moderately potent with lactose functionality at the c-2 position when compared to the standard. Tyrosinase inhibitors kojic acid and L-mimosine, which is compound 2, (negundin B) contain an OH group in the c-2 position and are potent in the c-1 and c-2 positions between the double bond.

Compound 3 (6-hydroxy-4-(4-hydroxy-3-methoxy)-3-h ydroxymethyl-7-methoxy-3,4-dihydro-2-naphthaledehyde) is lesser in the degree of inhibition because the replacement of Carboxyl group (COOH) with aldehyde group (CHO) at the c-2 position compound 4 (vitrofolal E) potency is decline when the double bond introduced by c-3 and c-4 and also in the c-3 position COH is removed compound 5 ((+)-lyoniresinol) contains c-2 and c-3 position which is highly potent because of the COH group present in opposite orientation is exhibited compound 6 doesn't show any inhibition against tyrosinase. After all, the presence of bulk glucose, which doesn't allow the molecules to penetrate the active site of the enzyme, inhibits its inhibitory potency by the presence or absence of the functional group in the c-2 and c-3 position. For the treatment of hyperpigmentation related to the high production of melanocytes, lignans are compounds isolated from the root of *V. negundo*, showing effective inhibition of the tyrosinase enzyme.[23]

Antimicrobial

The agent used to kill or inhibit the growth of microorganisms is called an antimicrobial. Based on the microorganisms, the antimicrobial medicines are used to kill or inhibit the growth of bacteria.[24] *V. negundo* is used to check the anti-microbial activity and to know the zone of inhibition for four different types of microorganisms, which are *Escherichia coli, Pseudomonas aeruginosa, Bacillus cereus*, and *Bacillus subtilis*, using different types of solvents, such as aqueous, ethanol, petroleum ether, and chloroform. For different organisms, 100 mg/mL of the extracts is used. In the zone of inhibition, ethanol extract shows the highest zone of inhibition, which is 41.6 mm in the *B. subtilis.* From the anti-microbial activity, petroleum ether and chloroform show a high zone of inhibition of the growth of *B. cereus*.[25] Both *in vitro* and *in vivo*, a methanolic extract of *V. negundo* leaves demonstrates potent vibriocidal action.[26] Evidence highlights the anti-candidal and anti-biofilm potential of phenolic acids derived from *V. negundo* leaves, underscoring their relevance as promising natural therapeutic agents for managing *Candida albicans* infections.[27] The bioprospecting potential of fungal endophytes associated with *V. negundo*, with a particular focus on their antibacterial properties. A total of seventeen endophytic fungal isolates were obtained from different parts of the *V. negundo* plant tissues. Among these, the *Phomopsis* sp isolated from the leaf samples of *V. negundo* exhibited notably strong and methanol, and were evaluated for antibacterial efficacy. The ethyl acetate extract shows the most effective activity, which efficiently inhibits the activity of *E. coli, Salmonella typhimurium, B. cereus, B. subtilis, K. pneumonia*, and *S. aureus*. The highest inhibitory effect was observed against *E. coli*, followed by *S. typhimurium* and *B. cereus*. These findings suggest that *V. negundo* has therapeutic agents against human pathogenic microorganisms and highlight its potential as a source of bioactive endophytic fungi.[28]

Apoptosis

Kerr *et al*., (1972) coined the term apoptosis because they showed the morphological distinct features of cell death that had been reported many years ago. To interpret the mechanism in the process of apoptosis in mammalian cells. The mechanism behind apoptosis is clearly demonstrated in the nematode *Caenorhabditis elegans* during its developmental stage. When it grows into an adult worm, it has 1090 somatic cells, of which 131 cells undergo programmed cell death at a particular point in the development process. Genetically set the elimination of cells, which is a very important mode of programmed cell death.[29] In Vietnam, from *V. negundo*, the compounds are isolated Flavodiiron protein 1 (FLV1), FLV2, and FLV3, which have the properties of potential anticancer and mechanisms. At the concentrations of 2.3 and 3.9μm, the FLV 1 compound shows the results of cytotoxicity in HepG2 and MCF-7 cells. Caspases-3, -8, and -9 are strict, which are crucial for cell death; they regulate the apoptosis activities.[30,31] The fluorescence intensity of MCF-7 cells treated with compounds FLV1-3 for 24 hours showed caspase-3 and -8 activity. While the caspase-3 cascade is only seen in HepG2 cells, when the compound FLV is exposed to HepG2, the caspase-3 is in active form in comparison to other caspases and untreated cells following treatment with FLV compounds. It is possible to confirm that the apoptosis induction in HepG2 and MCF-7 cell lines has significantly activated the upregulation of caspase-3 or caspase-3//8. The western blot confirms that the level of expression of caspase-3/8 is increased in treated cells. Through caspase cascades, apoptosis and caspase-3 activation were seen; these actions, which include DNA fragmentation.[32]

Motility and Viability of Sperm

Sperm is a motile cell that has the unique capacity to pass through a woman's reproductive system. Reviews concentrate on sperm motility to comprehend sperm physiology, molecular mechanisms governing sperm motility, risk factors influencing sperm motility in fertility outcomes, because spermatozoa need movement as a critical component in both natural and assisted conception. Pharmacological agents and biomolecules increase sperm motility both *in vitro* and *in vivo* to improve assisted reproductive technology.[33] From the study, Vasudeva *et al*., (2012) state that aqueous, methanol, petroleum ether, and chloroform were four different types of solvents for the extraction of *V. negundo* to investigate the motility of the sperm. Petroleum ether and chloroform extract show complete immobility of sperm within 3 min of 20mg/mL^{-1} incubated at 37°C within 5 min, and methanol shows complete immobilization of sperm. Immediate immobilization is shown in the 1 mg/mL^{-1} petroleum ether extract. In petroleum ether, chloroform, and methanol, it shows that 50% of the sperms are immobile at 5 mg mL^{-1} of extract. There is no effect on sperm motility after exposure to aqueous extracts for 20 min.[34]

Menstrual Cycle

The female reproductive system differs from the male reproductive system; it undergoes constant cyclic changes, known as the menstrual cycle. Menstruation is a process in a woman's life that shows that the woman is fertile. Menstruation starts when the girl reaches puberty at the age of 12.4 and stops at the age of 51, it is known as menopause.[35] *V. negundo* is widely recognized for its efficacy in managing irregular or incomplete menstrual cycles and is similarly employed in the treatment of dysmenorrhea and various obstetric conditions, as illustrated in Figure 2. According to Choudhary *et al*., (2024), administering two grams of *V. negundo* seeds twice daily, once in the morning and once in the evening, may help promote menstrual cycle regularity.

Polycystic Ovary Syndrome (PCOS)

Worldwide, 70% of women are affected but not diagnosed with Polycystic Ovary Syndrome (PCOS). About 8.13% of reproductive-aged women are affected with PCOS.[36] It starts in

Figure 1: Medicinal properties of *Vitex negundo.*

the age of adolescence, symptoms may vary over time, including irregular periods, excess androgen levels, hormonal imbalance, and cysts in the ovaries, which can lead to PCOS. In PCOS conditions, pregnancy is difficult because of irregular periods and a lack of ovulation. PCOS causes infertility, and it is a chronic condition that isn't cured, requiring fertility treatments, meditation, and lifestyle changes to improve symptoms for women with type-2 diabetes, and those with a family history are at high risk of PCOS.[37] According to the findings of Kakadia *et al.*, (2019), the hydro-ethanolic extract of *V. negundo* efficiently replaces the endocrine-metabolic imbalance associated with PCOS, further altering apoptosis biomarkers, proinflammatory cytokines, and antioxidant enzyme levels. The dominant phytochemicals in *V. negundo* are plumbagin, nigundin B, and cinnamic acid, found as a result of Liquid Chromatography-Mass Spectrometry (LC-MS) analysis.[38] The effects of *V. negundo* on letrozole- induced PCOS were evaluated using female Sprague-Dawley rats. The aqueous extract was administered at doses of 200 mg/kg (Group 3) and 400 mg/kg (Group 4), while the hydroalcoholic extract was given at the same respective doses (Group 5 and 6). Treatment continued for up to 66 days. Throughout the study, body weight and oestrous cycle phases were monitored daily to assess the progression of PCOS and the therapeutic effects of *V. negundo.* Letrozole-induced PCOS was significantly improved by the aqueous and hydro-alcoholic extracts of *V. negundo* seeds.[39]

Oxidative Stress

The effects of oxidative stress on the body are an imbalance between the generation of free radicals and the body's capacity to counteract them with antioxidants, resulting in oxidative stress, which damages cells and tissues. Antioxidants present in cellular defence, which act against oxidants, contain antioxidant enzymes along with their coenzymes and substrates. Several biomarkers of oxidative stress damage have been found for several molecular groups, including proteins, carbohydrates, DNA, and lipids.[40] The essential oils are extracted by using supercritical fluid extraction from the *V. negundo* leaf powder. Terpenes are non-polar constituents present in the *V. negundo* extract, as declared by techniques like Thin Layer Chromatography (TLC) fingerprinting, Gas Chromatography (GC), and Gas Chromatography- Mass Spectrometry (GC-MS) analysis. According to a study by Nagarsekar *et al.*, (2011), when the extracts were given orally to rats in order to measure the amount of thiobarbituric acid reactive chemicals, the flavonoids were shown to be the polar ingredients in the ethanol extract by TLC. Testing *in vitro* demonstrates the capacity to scavenge radicals. The leaf extract of *V. negundo* can control oxidative stress due to its polar and nonpolar elements.[41]

A study conducted by Umamaheswari *et al.*, (2012) showed that cerebral oxidative stress was induced by the administration of 20% ethanol, which produced marked cerebral oxidative stress, as evidenced by alterations in both serum biochemical parameters and brain antioxidant status. Ethanol exposure resulted in insignificant elevations in serum Aspartate Transaminase (AST), Alanine Transaminase (ALT), Alkaline Phosphatase (ALP), uric acid, triglycerides, and lipoprotein levels, indicating systemic toxicity and hepatic dysfunction. In parallel, brain tissue exhibited a pronounced decline in enzymatic and non-enzymatic antioxidant defenses, accompanied by significant increases in lipid peroxidation markers, including Lipid Hydroperoxides (LH) and Malondialdehyde (MDA). Histopathological examination further confirmed ethanol-induced neurotoxicity, revealing prominent gliosis in the cerebral tissue of treated rats. Administration of hydromethanolic extract of leaves of *V. negundo.* These fractions attenuate serum enzyme leakage and normalize elevated uric acid, triglyceride, and lipoprotein levels. The protective effects were comparable to those produced by the reference antioxidant, α-tocopherol 100 mg/kg, orally. Neuroprotective and antioxidant properties capable of counteracting ethanol-induced oxidative stress and associated neuropathological changes.[42]

Cell Cycle

Duplication of the vast DNA plays a vital role in the cell cycle and its function. The cell cycle consists of two main phases: the interphase and the M phase. During the S phase, DNA duplication occurs in a typical mammalian cell; half of the cell cycle time occupies about 10-12 hr. In the M phase of cell division, chromosome segregation occurs; it isn't similar to the S phase, but it requires less time. Mitosis and nuclear division begin with a series of dramatic events in the M phase.[43] EVn-50 is a lignan compound isolated from the seeds of *V. negundo*. The compound EVn-50 has an impact on the cell cycle. Study characterizes the range of cytotoxic activity of EVn-50 and explores the anticancer mechanism behind its effects. A panel of cancer cell lines was used in the SRB experiment to assess the cytotoxic effects of EVn-50 and VB1. MDA-MB-435 and SMMC-7721 cells were arrested at the G2/M phase upon treatment with EVn-50 or VB1, as evidenced by decreased expression of Cdc25c, increased phosphorylation of Histone 3 at Ser10, phosphorylation of Cdk1 at Tyr15, and expression of cyclin B1, and discovered that MDA-MB-435 cells underwent apoptosis when exposed to EVn-50 or VB1. Xin *et al.*, (2013) demonstrate the broad-spectrum lethal action of EVn-50, lignan compounds derived from *V. negundo*, which stop cancer cells at the G2/M phase of the cell cycle and thereafter trigger apoptosis.[44]

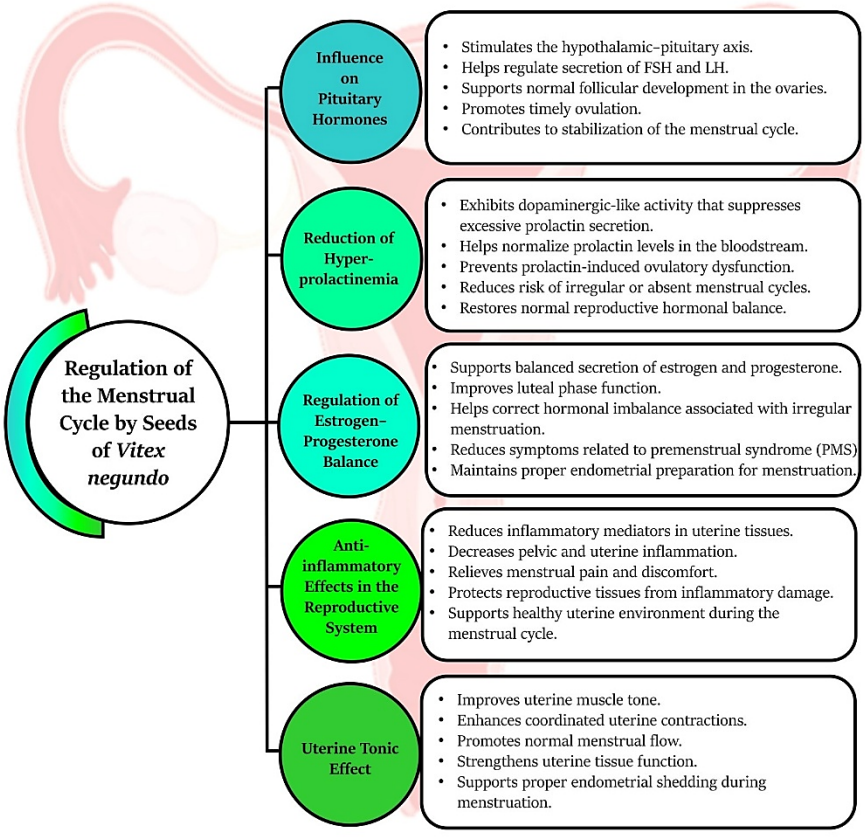

Figure 2: Regulation of the menstrual cycle by the seeds of *Vitex negundo*.

Anti-Diabetic Effects

Diabetes is a condition that is characterized by an elevated blood glucose level and a deficiency of insulin. There are two types of diabetes: type 1 and type 2. From natural sources, dietary polysaccharides have anti- diabetic properties that are largely obtained from algae, fungi, grains, fruits, vegetables, mushrooms, and medicinal plants, which also prevent diabetic complications by different molecular mechanisms. Primarily depends on the preparation sources and composition to regulate hyperglycaemia by polysaccharides. In Streptozotocin (STZ) induced rats, the anti-diabetic activity of 6-d-glucan increased the level of insulin and hepatic glycogen accumulation. It decreased the blood glucose levels.[45] The leaves of *V. negundo* extract show antioxidant and antidiabetic functionalities. *V. negundo* extract from hydroethanolic shows the best α-glucosidase and antioxidant inhibitor. 15 compounds were identified from 60% extract of the phenolic and flavonoids using UHPLC-QTOF-MS/MS analysis. The antidiabetic activity is by synergetic interaction.[46] The leaf of the *V. negundo* extract contains phytochemicals that are extremely capable of healing diabetes.[47] *V. negundo* leaf ethanol extracts have significant hypoglycaemic and hypolipidemic activities in streptozotocin-induced diabetic mice. Phytochemical analyses indicate that the extract is rich in secondary metabolites, particularly phenols and flavonoids known for their potent antioxidant properties, which likely contribute to its antidiabetic potential. In addition to improving glucose and lipid profiles, treatment with the leaf extract produced a marked reduction in hepatic Serum Glutamate Pyruvate Transaminase (SGPT) and Serum Glutamate Oxaloacetate Transaminase (SGOT) levels, indicating a protective effect on liver function in diabetic rats.[48]

CONCLUSION

This review highlights *V. negundo* as a multifunctional plant with significant medicinal, cosmetic, and industrial values. The compiled studies demonstrate its diverse phytochemical composition and broad spectrum of biological activities. However, inconsistencies in extraction methods and dosage standards remain major challenges for reproducibility and clinical validation. Future research should focus on standardized protocols, molecular mechanisms of action, and sustainable cultivation practices to fully harness the potential of *V. negundo*. Overall, a more integrative and multidisciplinary approach will be essential to advance its applications and ensure the long-term conservation of this valuable species.

ABBREVIATIONS

ROS: Reactive Oxygen Species; **DPPH:** 2,2-Diphenyl-1-Picrylhydrazyl; **ABTS:** 2,2′-Azino-bis-(3-ethylbenzothiazoline-6-sulfonic acid); **WHO:** World Health Organization; **TKI:** Tyrosine Kinase Inhibitor; **FLV:** Flavodiiron Protein; **PCOS:** Polycystic Ovary Syndrome; **LC-MS:** Liquid Chromatography-Mass Spectrometry; **TLC:** Thin Layer Chromatography; **GC:** Gas Chromatography; **GC-MS:** Gas Chromatography-Mass Spectrometry; **AST:** Aspartate Transaminase; **ALT:** Alanine Transaminase; **ALP:** Alkaline Phosphatase; **LH:** Lipid Hydroperoxides; **MDA:** Malondialdehyde; **DNA:** Deoxyribonucleic Acid; **EVn-50:** Extract of *Vitex negundo* Fraction-50; **VB1:** Vitexin-related lignan compound; **SRB:** Sulforhodamine B Assay; **Cdc25c:** Cell Division Cycle 25C; **Cdk1:** Cyclin-Dependent Kinase 1; **STZ:** Streptozotocin; **UHPLC-QTOF-MS/MS:** Ultra-High-Performance Liquid Chromatography-Quadrupole Time-of-Flight Tandem Mass Spectrometry; **SGPT:** Serum Glutamate Pyruvate Transaminase; **SGOT:** Serum Glutamate Oxaloacetate Transaminase.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Cite this article: Abidharini JD, Gunasekaran A, Prabhu JPA, Robert AA, Anand AV, Sampathkumar P. Therapeutic Potential of *Vitex negundo*: A Comprehensive Review of Its Medicinal Properties. Free Radicals and Antioxidants. 2025;15(2):42-8.