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Phyto-pharmacological and Biological Aspects of *Vitex negundo* Medicinal Plant - A Review

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Authors' contribution

This work was carried out in collaboration among all authors. The review was guided by author PS. Authors BN and RJ contributed to the phytochemical and biological studies in this review and also collaborated in all facets of the work-literature search, collection of data, referencing and collectively made inputs to the lay-out and design. All authors read through and approved the final manuscript.

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Review Article

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ABSTRACT

Vitex negundo Linn is an important medicinal plant belonging to the Verbenaceae family. Every part of the plant is enriched with therapeutic value; hence the plant plays a pivotal role in traditional medicine systems. The presence of secondary metabolites such as alkaloids, flavonoids, terpenoids and phenolic compounds in the various plant parts are responsible for the anti-oxidant, anti-inflammatory, anti-microbial and anti-cancer properties which are being exploited in the treatment of cancer, cardiovascular diseases and so on. The major phytochemical components are Vitexin (8-(β-D-Glucopyranosyl)-4′,5,7-trihydroxyflavone), Isovitexin (5,7-dihydroxy-2-(4-hydroxyphenyl) 6[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl) oxan-2-yl]chromen-4-one), Vitedoin and Negundin((7R,8S)-8-(4-hydroxy-3-methoxyphenyl)-6, 7-bis(hydroxymethyl)-3-methoxy-7,8-dihydronaphthalen-2-ol). The scope of *Vitex negundo* as an adjuvant in modern medicine is huge. Therefore, this review focuses on research conducted till date to evaluate the phytochemical composition, and pharmacological activities of *Vitex negundo* medicinal plant.

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Keywords: Medicinal plant; traditional medicine; phytochemical analysis; pharmacological properties; biological activities; flavonoids; free-radical scavenging property.

ABBREVIATIONS

Vn : Vitex negundo
WHO : World Health Organization
FRS : Free Radical Scavenging

1. INTRODUCTION

Meuss defines herbal medicine or phytotherapy as the science of using herbal remedies to treat the sick [1]. Fossil studies show that the use of plants as therapeutic agents dates back to at least 60,000 years. Herbs were administered in various forms of traditional medicine such as the Indian Ayurveda, the Japanese Kampo, the Chinese traditional medicine and the Greek Unani [2,3]. They were also used in healing rituals by Africans and Native Americans for cultural purposes. However, the popularity of traditional medicine started to fade away from the 19th century when new chemical analytical techniques emerged and enabled scientists to produce synthetic drugs [4].

Nowadays, the demand for herbal drugs is back on the rise as they are cheaper, completely natural and free of noteworthy undesirable effects. The WHO approximated that 80% of the world's populace still depend on traditional medicine for their health care [5]. Recently, the collaboration of traditional and modern medicine is increasing with the use of herbal extracts as adjuvants in the treatment of cancer and cardiovascular diseases [6,7].

One of the most important plants used in traditional medicine is *Vn*. Belonging to the family Verbenaceae, it is a woody, aromatic shrub growing to a slender tree. Also known as the Five-Leaved Chaste Tree, it has quadrangular branches bearing tri or penta-foliate leaves with five leaflets arranged like a palm. This erect plant of height 2-5m bears bluish purple flowers and succulent, four-seeded fruits that are black when ripe. The plant prefers humid habitats and is found to grow in India, Pakistan, Afghanistan, Sri Lanka, Thailand, Malaysia, Eastern Africa and Madagascar [8]. The phytochemical composition, medicinal and biological properties of *Vn* have been described comprehensively in this review.

2. MEDICINAL USES OF *Vitex negundo*

Herbal medicine focuses on curing the root cause of the disease, rather than its symptoms. The assortment of phytochemicals found in medicinal herbs enable them to enhance the overall well-being. Regardless of the advancement of contemporary medicine, a large segment of the population in countries like India, China, Nepal and Bangladesh still rely on folk and traditional medicine.

Traditional medicine predominantly encompasses Indian Ayurveda, Arabic Unani and Chinese Pharmacopeia. Charaka Samhita and Anubhoga Vaidya Bhaga, the great books of Ayurveda, elaborate on the use of *Vn* to treat sinusitis, syphilitic skin disease, catarrhal fever, dysmenorrhea and rheumatism [9]. The seeds of *Vn* are used as an aphrodisiac and to cure swellings in Unani medicine [10]. Chinese medicine mentions the consumption of the *Vn* fruit to treat puffy eyes, arthritis and headaches [11].

The traditional medicinal uses of various parts of *Vn* have been enlisted in Table 1.

2.1 Safety and Toxicity

Side effects of using *Vn* plant parts are rare. A mild skin rash with itching and slight gastrointestinal upset has been reported in less than 2% of the women monitored while taking *Vn* root extract in powdered form. It is not recommended for use during pregnancy.

3. PHYTOCHEMICAL ANALYSIS

Vn has a consortium of bioactive components (secondary metabolites) which play a pivotal role in the biopharma sector. The presence of more such phytochemicals in various other parts of this plant can be revealed using advanced spectroscopic techniques like FTIR, NMR, EMR combined with X-Ray Crystallography. The therapeutic potential of these compounds can further be validated through *in silico* analysis. The phytochemical analysis of the major parts of *Vn* has been tabulated below:

3.1 Leaf of *Vitex negundo*

The Soxhlet extractor was used to obtain extracts of dried and powdered leaves. Methanol extracts of leaves were preferred for phytochemical analysis [36].

The phytochemical constituents of leaf extract have been enlisted in Table 2.

3.2 Roots of *Vitex negundo*

Methanolic extract is preferred for phytochemical analysis of *Vn* roots and was obtained using Soxhlet apparatus [42].
The phytochemical constituents of root extract have been enlisted in Table 3.

3.3 Essential Oils of Flower of *Vitex negundo*

Hydro distillation process was used to extract the essential oils of flower buds [46].

The phytochemical constituents of flower extract have been enlisted in Table 4.

3.4 Seeds of *Vitex negundo*

Ethanol extract was preferred for phytochemical analysis of seed and was obtained by Soxhlet extraction using ethanol and water (70:30) as solvent [51].

The phytochemical constituents of seed extract have been enlisted in Table 5.

3.5 Stem and bark of *Vitex negundo*

Vn stem and bark were extracted with dichloromethane and cold methanol using Soxhlet apparatus [56].

The phytochemical constituents of stem and bark extract have been enlisted in Table 6.

3.6 Essential Oils of Fruit

Essential oils from fruits were extracted by subjecting to the hydro distillation process. Yellowish oil obtained was separated from distillate using hexane and used for phytochemical analysis [62].

The phytochemical constituents of fruit extract have been enlisted in Table 7.

Table 1. Uses of parts of *Vitex negundo* in folk medicine

Plant part used	Form	Disease/Usage	Reference
Flower	As Astringent and tonic	Fever, Cholera, Gastrointestinal disorders, Diarrhea, Jaundice/ Liver disorders	[12,13,14,15]
Leaf	Leaf juice	Common cold, Flu, Sore throat, Whooping cough, Respiratory disorders, Cough, Dysmenorrhea, Gonorrhea, Dysfunctional uterine, Rheumatism, Gout, Wounds and ulcers, As Diuretic, Insecticide	[12,13,15,16,17, 18,19,20,21,22, 23,24,25,26,27, 28,29,30,31]
	Crushed leaf poultice	Headache, Sinusitis, Swellings, Antitoxin (snake venom), Mosquito Repellent effect, Antifeedant, Fumigant	
	Essential oils	Skin diseases, Eczema, Carbuncles, Abscesses, Leprosy, Sinusitis, Dentistry	
	Pillow stuffed with leaves	Eye disease/Cataract/Watery eyes, Headache	
Root	Powdered form	Dyspepsia, Colic, Dysentery, Piles, Skin diseases, Eczema, Carbuncles, Abscesses, Leprosy, Rheumatism	[12,13,21,22, 23,32,33,15, 16,19,34]
	Decoction	Respiratory disorders, Cough, Bronchitis, Asthma, Wounds and ulcers, Malaria (as tonic)	
	As Tincture	Flatulence/ Irritable bladder, Dysentery, Rheumatism	
Stem and Bark	Decoction	Burns, Cancer	[12,13,19,28, 32,35]
	As Tincture	Flatulence/ Irritable bladder, Dysentery, Rheumatism	

Table 2. Phytochemical constituents of extract of *Vn* leaves

Secondary metabolite	Compounds	Uses	Reference
Flavonoids	hydroxy - 3, 6, 7 ,3′ ,4′ - pentamethoxyflavone	FRS	[37,38]
	casticin [3',5-dihydroxy-3,4',6,7-tetramethoxyflavone]		
	5, 3′ - dihydroxy- 6, 7, 4′- trimethoxyflavone		
	5, 3′- dihydroxy - 7, 8, 4′ - trimethoxyflavone		
Monoterpenoids	gamma-terpinene [1-methyl-4-(propan-2-yl) cyclohexa-1,4-diene]	Hepatoprotective, Gastroprotective	[39]
	sabinene [4-methylene-1-(1-methylethyl) bicyclo[3.1.0]hexane]		
	6′-p-hydroxybenzoyl mussaenosidic acid		
	2′-p-hydroxybenzoyl mussaenosidic acid		
Sesquiterpenoids	viridiflorol [(1*aR*,4*S*,4*aS*,7*R*,7*aS*)-1,1,4,7-tetramethyl-2,3,4*a*,5,6,7,7*a*,7*b*-octahydro-1*aH*-cyclopropa[e]azulen-4-ol]	Pharmaceutical agents	[39]
	β -caryophyllene		
	caryophyllene oxide		
	globulol [1,1,4,7-tetramethyl-2,3,4*a*,5,6,7,7*a*,7*b*-octahydro-1*aH*-cyclopropa[e]azulen-4-ol]		
	4-terpineol		
Triterpenoids	betulinic acid [3β-hydroxylup-20-(29)-en-28-oic acid]	Anti-bacterial, Anti-viral, Anti-tumor, Anti-oxidation activities	[40]
	ursolic acid [2β -hydroxyurs12-en-28-oic acid]		
Steroids	β-sitosterol	Anti-tumor, Immuno-suppressive agents	[40]
	sitosterol [17-(5-Ethyl-6-methylheptan-2-yl)-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol]		
Phenolic compounds	p-hydroxybenzoic acid	Cancer prevention and treatment	[41,10]
	protocatechuic acidprotocatechuic acid [3,4-dihydroxybenzoic acid]		
	oleanolic acid [3beta-Hydroxyolean-12-en-28-oic acid]		
	vitamin C [ascorbic acid]		

Table 3. Phytochemical constituents of extract of *Vn* roots

Secondary metabolite	Compounds	Uses	Reference
Flavone	vitexin [8-(β-D-glucopyranosyl)-4′,5,7-trihydroxyflavone]	Anti-oxidant, Anti-proliferative, used for Cancer, Cardiovascular disease	[43]
	isovitexin [5,7-dihydroxy-2-(4-hydroxyphenyl)-6-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl) oxan-2-yl] chromen-4-one]		

Secondary metabolite	Compounds	Uses	Reference
Terpenoids	2β,3α-diacetoxyoleana-5, 12-dien-28-oic acid	Natural expectorant and bronchodilator for respiratory health	[43]
	2α,3α-dihydroxyoleana-5, 12-dien-28-oic acid		
	2α,3β-diacetoxy-18-hydroxyoleana- 5,12-dien-28-oic acid		
	3-formyl-4.5-dimethyl-8- oxo-5H-6,7-dihydronaphtho (2,3-b) furan		
Steroids	sitosterol [17-(5-Ethyl-6-methylheptan-2-yl)-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol]	Anti-tumor, Immunosuppressive	[44]
Lignans	negundin-A	Treat fever, Skin diseases	[45]
	negundin-B [(7R,8S)-8-(4-hydroxy-3-methoxyphenyl)-6,7-bis(hydroxymethyl)-3-methoxy-7,8-dihydronaphthalen-2-ol]		
	(+)-diasyringaresinol		
	(+)-lyoniresinol		
	vitrofolal-E		
	vitrofolal-F		

Table 4. Phytochemical constituents of essential oil of *Vn* flower

Secondary metabolite	Compounds	Uses	Reference
Monoterpenoids	sabinene [4-methylene-1-(1-methylethyl) bicyclo [3.1.0] hexane]	Anti-inflammatory agent, enhancing fragrances in beverages	[47]
	p-cymene [1-Methyl-4-(propan-2-yl) benzene]		
	trans-α-bergamotene		
Terpineol	linalool	An ingredient in perfumes and as a foaming agent in the flotation of ores of nonferrous metals	[48]
	terpinen-4-ol(4-Methyl-1-(propan-2-yl) cyclohex-3-en-1-ol)		
Sesquiterpenoids	B-caryophyllene	Pharmaceutical agents, Treating Fever	[48]
	Valencene [(3*R*,4a*S*,5*R*)-4a,5-Dimethyl-3-(prop-1-en-2-yl)-1,2,3,4,4a,5,6,7-octahydronaphthalene]		
	A-selinene		
	B-selinene		
	Germacren-4-ol		
	caryophyllene epoxide (E)-nerolidol		
	Globulol [1,1,4,7-tetramethyl-2,3,4*a*,5,6,7,7*a*,7*b*-octahydro-1*aH*-cyclopropa[e]azulen-4-ol]		

Secondary metabolite	Compounds	Uses	Reference
Fatty alcohol	1-octen-3-ol	Insect attractant used in insect repellants	[49]
	n-hentriacontanol		
Hydrocarbon	n-heptane	n-heptane used as an industrial solvent for storage and transport, toluene used as a solvent in paints, thinners, glues	[50]
	toluene		
Carboxylic acid	Formic acid	Preservative, Anti-bacterial agent and Miticide	[47]
Triterpenoid	acetyl oleanolic acid	Anti-pyretic, Analgesic, Sedative and Tonic effects	[47]

Table 5. Phytochemical constituents of extract of *Vn* seeds

Secondary metabolite	Compounds	Uses	Reference
Alkaloids	a phenyl naphthalene-type lignan alkaloid: vitedoamine A	Anti-inflammatory, Anticancer, Analgesics	[52]
Flavonoids	vitexin B [6-hydroxy-4-(4-hydroxy-3-methoxy-phenyl)-3-hydroxymethyl-7-methoxy-3, 4-dihydro- 2-naphthaldehyde]	FRS	[53]
	artemetin [2-(3,4-dimethoxyphenyl)-5-hydroxy-3,6,7-trimethoxychromen-4-one]		
Triterpenoids	3β -acetoxyolean-12-en-27-oic acid 2α, 3α- dihydroxyoleana- 5,12-dien-28-oic acid	Hepatoprotective, Gastroprotective	[54,55]
	2β,3α- diacetoxyoleana- 5,12-dien-28-oic acid		
	2α,3β-diacetoxy-18- hydroxyoleana-5,12-dien-28-oic acid		
Steroids	β-sitosterol [17-(5-Ethyl-6-methylheptan-2-yl)-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol]	Anti-tumor, Immunosuppressive	[10]
Phenolic compounds	p-hydroxybenzoic acid	Cancer prevention and treatment	[10]
	5-oxyisophthalic acid		
Lignans	vitedoin A [3R,4S)-6-hydroxy-4-(4-hydroxy-3-methoxyphenyl)-3-(hydroxymethyl)-5-methoxy-3,4-dihydronaphthalene-2-carbaldehyde]	Lowers risk of heart disease, Menopausal symptoms	[52]
	vitedoin B [[(2*S*,4*aS*,5*R*,6*R*,8*aS*)-1,1,4*a*,6-tetramethyl-5'-oxospiro[3,4,6,7,8,8*a*-hexahydro-2*H*-naphthalene-5,2'-oxolane]-2-yl] acetate]		
Hydrocarbon	n-tritriacontane	Cancer prevention and treatment	[10]
	n-hentriacontane		
	n-pentatriacontane		
	n-nonacosane		

Table 6. Phytochemical constituents of extract of *Vn* stem and bark

Secondary metabolite	Compounds	Uses	Reference
Flavonoids	5-hydroxy-3,6,7,3'4'-pentamethoxy flavone	FRS	[57]
	5-hydroxy-3'dihydroxy-7,8,4'-trimethoxy flavanone		
Triterpenoids	β-amyrin	Anti-inflammatory, Anti-oxidant,	[58]
	epifriedelinol oleanolic acid 3β-acetoxy-olean-12-en-27-oic acid		
	3β-hydroxy-olean-5, 12-dien-28-oic acid		
Steroids	1,1,3,3,5,5,7,7,9,9,11,11,13,13, -tetradeca methyl,3a,3a'-Dichloro-2α,3α -ethano-3β-methyl-cholestan-2a-one	Anti-tumor, Immunosuppressive	[59]
	β-sitosterol [17-(5-Ethyl-6-methylheptan-2-yl)-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol]		
Phenolic compounds	hexadeca methyl p-hydroxy benzoic acid	Cancer prevention and treatment	[60]
Glycosides	3,6,7,3',4'-pentamethoxy-5-O-glucopyranosylrhamnoside Vitexin caffeate [5,7-dihydroxy-2-(4-hydroxyphenyl)-8-[(2*S*,3*R*,4*R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl) oxan-2-yl] chromen-4-one]	Anti-oxidant, Anti-cancer	[61]
	4'-O-methyl myricetin-3-O-[4'-O-β-D-galactosyl]-β-D- galactopyranoside		
Siloxanes	heptamethylphenylcyclotetra siloxane	Implants, dentures, skin patches to deliver therapeutic substances	[62]
	tetradecamethylnonamethylcyclo heptasiloxane		
	phenylcyclopentasiloxane		
	cyclooctasiloxane		
	nonamethyl, phenylcyclopenta siloxane		
	tetracosamethylcyclododeca siloxane		
	tetradecamethylheptasiloxane		
	octadecamethylcyclononasiloxane		

Table 7. Phytochemical constituents of essential oil of *Vn* fruit

Secondary metabolite	Compounds	Uses	Reference
Sesquiterpene	α-copaene [1,3-dimethyl-8-propan-2-yltricyclo [4.4.0.02,7] dec-3-ene]	Anti-cancer, Anti-plasmodial	[50]
	β-selinene [(3*R*,4*aS*,8*aR*)-8*a*-methyl-5-methylidene-3-prop-1-en-2-yl-		

Secondary metabolite	Compounds	Uses	Reference
	1,2,3,4,4*a*,6,7,8-octahydronaphthalene]		
	α-guaiene [(1*S*,4*S*,7*R*)-1,4-dimethyl-7-prop-1-en-2-yl-1,2,3,4,5,6,7,8-octahydroazulene]		
	guaia-3,7-diene [3,8-dimethyl-5-propan-2-yl-1,3*a*,4,7,8,8*a*-hexahydroazulene]		
	caryophylleneoxide [(1*R*,4*R*,6*R*,10*S*)-4,12,12-trimethyl-9-methylidene-5-oxatricyclo [8.2.0.04,6] dodecane]		
	α-cedrene [(1*S*,2*R*,5*S*)-2,6,6,8-tetramethyltricyclo [5.3.1.01,5] undec-8-ene]		
	aristolene [1,1,7,7*a*-tetramethyl-2,4,5,6,7,7*b*-hexahydro-1*aH*-cyclopropa[a]naphthalene]		
	β-caryophyllene [(1S,4E,9R)-4,11,11-trimethyl-8-methylidenebicyclo [7.2.0] undec-4-ene]		
	germacrene D [(1*E*,6*E*,8*R*)-1-methyl-5-methylidene-8-propan-2-ylcyclodeca-1,6-diene]		
	α-humulene [(1E,4E,8E)-2,6,6,9-tetramethyl-1,4-8-cycloundecatriene]		
Fatty Acids	n-hexadecanoic acid	Anti-inflammatory	[50]
	palmitolic acid		

4. PHARMACOLOGICAL ACTIVITIES

The whole plant of *Vn*, from leaves to roots, possess various phytochemicals which impart a variety of medicinal uses to the plant. Scientific community demanded experimental evidence to support the traditional and folk system medicine of *Vn*. Therefore, various scientific studies have been conducted to validate these claims.

4.1 Antioxidant Activity and FRS Activity

Antioxidants are substances that are capable of neutralizing free radicals thus preventing them from causing cell damage. The levels of catalase, superoxide dismutase and glutathione peroxidase in Freund's adjuvant induced arthritic-rats [63] were lowered by *Vn* leaf extract. Flavonoids in particular have potential antioxidants and show FRS activity [64]. The antioxidant and therapeutic role of *Vn* flavonoids in regulating solenoid-induced cataract was affirmed by Rooban et al. [65].

4.2 Anti-inflammatory and Analgesic Activity

Anti-inflammatory drugs make about half of analgesics which alleviate pain by reducing the inflammation. The anti-inflammatory and analgesic activities of *Vn* were validated by the studies conducted by Mandal et al. [66], Sori et al. [67] and Dharmasiri et al. [68].

4.3 Histomorphological and Anti-Cancer Activity

The histomorphological effect of *Vn* extracts has been validated by Tandon et al. [69] in rats. The study showed dose-dependent changes in lung, heart and liver tissues but not in stomach tissues. The anticancer activity of ethanolic *Vn* extract was studied against U-937 cell line [70]. While Diaz et al. [71] confirmed that the chloroform extracts of leaves are toxic to human cancer cell line panels, Yunos et al. [72] have reported that the plant extracts were non-cytotoxic on mammary and genito-urinary cells of mice.

4.4 Effect on Reproductive Potential

Contrasting results have been obtained from researches on the reproductive potential of *Vn.* The inhibitory effect of *Vn* extract on reproduction and spermatogenesis in male rats [73] was proved in certain studies. Whereas, Hu et al. [74] revealed that the same extract acted as an

aphrodisiac [10] having estrogen-like activity and proposed its use in hormone replacement therapy. Kakadia et al. [75] studied the potential of Vn seeds to treat polycystic ovarian syndrome.

4.5 Enzyme-inhibitory Activity

Various enzymes like butyryl-cholinesterase [76], lipoxygenase, α chymotrypsin [77], xanthine-oxidase [78] and tyrosinase [76] were shown to be inhibited by *Vn* root extracts. Woradulayapinij et al. [27] reported the inhibitory action of aqueous *Vn* extract against HIV-1 reverse transcriptase.

4.6 Anti-pyretic Activity

Raama et al. [79] studied the antipyretic activity of leaf extract in yeast provoked elevation of body temperature. The methanolic extract led to reduction in body temperature. The study stated that the presence of flavonoids which reduced lipid peroxidation, may be the reason for the antipyretic effect.

4.7 Anti-Snake Venom Activity

The ability of Vn leaf extract to neutralise the venom of *Daboia russelli* and *Naja naja* was studied by Durairaj et al. [80].

4.8 Cardioprotective Activity

Maruthi Prasad et al. [81] validated the cardioprotective effect of *Vn* for the first time. They demonstrated that the ethanolic extract of *Vn* has the potential to protect ISO-induced MI by regulating expression of NF-κB and Akt1 signalling cascades in rats. They confirmed that the presence of flavonoids like 5,7-dihydroxy-6,4'-dimethoxy flavanone is responsible for this effect.

4.9 Other Pharmacological Activities

The various extracts of *Vn* also possess other pharmacological activities such as anxiolytic activity [82], hepatoprotective effect [83], anti-diarrheal activity [84] and so on. The results of a study by Abhinav Kanwal et al. [85] have shown a decrease in the phenomenon of amnesia by increasing learning of memory through antioxidant effect and decreasing AChE activity in rats administered with the plant extract. Furthermore, the anti-histaminic activity is validated through its ability to inhibit alpha-amylase [86]. The study by Siddiqui et al. [87] revealed that methanolic Vn extract promoted the growth of long neurites in the hippocampus, thereby validating its neuroprotective potential.

5. BIOLOGICAL ACTIVITY OF *Vitex negundo*

Chemical substances isolated from many plants play the role of defence compounds and protect against pathogens and predators. The analysis of the anti-microbial properties of the plant extracts reveals that the *Vn* is a competent bio-control agent. Studies conducted on the plant show that the extracts have the potential to inhibit, hinder and even destroy many biological agents that cause disease or damage. The biological activity of the *Vn* has been summarised below:

5.1 Anti-bacterial Activity

Disc-diffusion antibiotic sensitivity test was used to validate the bactericidal activity of Vn extracts and essential oils. The works of Khokra et al. [50] suggested that the ethyl acetate and ethanol extracts of the plant showed promising anti-microbial activity against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli* and *Pseudomonas aeruginosa* bacterial strains.

5.2 Anti-feedant Activity

The potential of *Vn* extracts to hinder the growth of *Tribolium castaneum* and *Plutella xylostella* was confirmed in the research conducted by Haridasan et al. [88] and Matharu et al. [89] respectively.

5.3 Anti-filarial Activity

Sahare et al. [90,91] evaluated the anti-filarial activity of the plant extract. The extracts possessed the potential to inhibit the growth of the microfilarial parasite, *Brugia malayi.*

5.4 Anti-fungal Activity

Guleria et al. [92] and Sathiamoorthy et al. [93] examined the fungicidal activity of the *Vn* extracts against *Curvularia lunata, Alternaria alternata*, *Cryptococcus neoformans, Trichophyton mentagrophytes*, *Candida albicans and Aspergillus niger.*

5.5 Anti-larval Activity

The works of Nathan et al. [94] suggested that the *Vn* is an effective bio-control agent against the Rice leaf-folder, *Cnaphalocrocis medinalis.*

5.6 Insecticidal Activity

The bioactive agents in the *Vn* extracts display repressive activity on the growth of Arthropods like *Spodoptera litura* (Asian armyworm), *Tribolium castaneum* (Red flour beetle), *Myzus persicae* (Green peach aphid), *Sitotroga cerealella* (Angoumois grain moth), *Aphis citricola* (Spirea aphid), *Aedes aegypti* (Dengue vector mosquito) and *Aphis gossypii* (Melon or Cotton aphid). The insecticidal potential of *Vn* was evaluated by Deepthy et al. [95], Chowdhury et al. [96], Kamalakannan [97], Rajendran [98] and En-Shun [99].

5.7 Mosquito Repellent Activity

The growth of larvae and adult mosquitoes of species like *Culex tritaeniorhynchus, Anopheles subpictus*, *Aedes aegypti* and *Anopheles stephensi* were successfully inhibited by the *Vn* extracts. The larvicidal potential against *Culex quinquefasciatus* was examined by Rajakumar et al. [100] and Kannathasan et al. [101] while the study by Ranasinghe et al. [102] proved that methanolic *Vn* extract shows 85.44% mosquito-repellent activity.

5.8 Anthelmintic Activity

The ethanolic extract of *Vn* was validated for anthelmintic activity against Indian earthworm *Pheritima posthuma* by Trapti et al. [103].

6. RECENT RESEARCH APPLICATIONS OF *Vitex negundo*

6.1 Antimicrobial Natural Dye Extraction Using *Vn*

Venkataramanappa Narayana Swamy et al. [104] discovered that the leaf extracts of *Vn* can be used to dye silk fabrics and can be utilized as a possible alternative to synthetic dyes for dyeing silk. The leaves possessed three major flavonoids- luteolin-7-glucoside, casticin, artemetin which made it a potential dye candidate for silk fabric. The dyed silk fabrics showed acceptable fastness properties and were also found to exhibit antimicrobial activity against Gram-positive and Gram-negative bacteria. When tannic acid was used as a mordant, the dyed samples showed highest antibacterial activity against both bacteria. The bacterial inhibition may be due to the active flavonoids present within the dye and also due to the toxic effects of metallic salts (tannic acid) against pathogens.

6.2 Removal of Fluoride from Polluted Waters Using *Vn*

Fluoride in drinking water has both beneficial and harmful effects on human health. The research conducted by Mekala Suneetha et al. [105] proved that activated carbon treated with nitric acid derived from barks of *Vn* (NVNC) plants can be used as an effective adsorbent for the de-fluoridation of ground waters. The adsorption process was fitted with Langmuir adsorption isotherm with a good correlation coefficient value and it indicated monolayer adsorption. The adsorption kinetics followed pseudo-second-order kinetics. The results can be applied in wastewater treatment technologies in controlling the fluorides.

6.3 Herbal Soap Formulation Using Leaf Extract of *Vn*

Kandasamy Ruckmani et al. [106] formulated a herbal soap using methanolic extract of *Vn* leaves. After preliminary phytochemical analysis, the extract was subjected to saponification and chemical characterizations. The results obtained showed that the estimation of saponification value, total fatty matter, moisture content and pH were 395.52 mg/mL, 70%, 6.23%, and 9.67 respectively. It was proved that the soap was effective against Gram-positive bacteria *S. aureus* and the non-filamentous fungus *Candida sp*. Thus, the formulation was categorized as a Grade 2 soap with antibacterial and antifungal activities.

6.4 Green Synthesis of Silver Nanoparticles Using *Vn* extract

Mohsen Zargar et al. [107] synthesised silver nanoparticles having antibacterial activity using *Vn* by a green method. Silver nitrate was used as the silver precursor and methanolic extract of *Vn* leaf was used as the reducing agent and stabilizer. The nanoparticles were then characterized by transmission electron microscopy (TEM), X-ray diffraction (XRD) and UV–Visible (UV-Vis) spectroscopy which showed that the particles were spherical and crystalline in nature with average size 18.2 nm. The antibacterial activity of the formulated Ag-NPs against Gram-negative *E. coli* and Gram-positive *S. aureus* was validated by the Kirby-Bauer method.

7. CONCLUSION

Vitex negundo is one of the major plants which has wide applications in traditional systems of medicines practiced in different countries. All parts of the plant, from roots to fruits, possess a multitude of phytochemicals like flavonoids, terpenoids, phenolic compounds which are important bioactive agents imparting a variety of medicinal uses to the plant. Extensive research conducted on the plant validates its biological activities and pharmacological potential such as antioxidant, anti-inflammatory, and anti-cancer properties. Apart from this, it is also reported to have larvicidal, pesticidal, and anti-microbial activities. Many investigations and researches are continuously made in the field of biotechnology to reveal other applications of *Vn* and its scope in modern medicine. *Vitex negundo*, like many other herbal products, has immense potential in treating diseases and fighting pathogens and it is upon us to make the best use of it.

CONSENT

It's not applicable.

ETHICAL APPROVAL

It's not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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