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.

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.
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 \textit{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

<table>
<thead>
<tr>
<th>Plant part used</th>
<th>Form</th>
<th>Disease/Usage</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flower</td>
<td>As Astringent and tonic</td>
<td>Fever, Cholera, Gastrointestinal disorders, Diarrhea, Jaundice/ Liver disorders</td>
<td>[12,13,14,15]</td>
</tr>
<tr>
<td>Leaf</td>
<td>Leaf juice</td>
<td>Common cold, Flu, Sore throat, Whooping cough, Respiratory disorders, Cough, Dysmenorrhea, Gonorrhea, Dysfunctional uterine, Rheumatism, Gout, Wounds and ulcers, As Diuretic, Insecticide</td>
<td>[12,13,15,16,17, 18,19,20,21,22, 23,24,25,26,27, 28,29,30,31]</td>
</tr>
<tr>
<td>Crushed leaf poultice</td>
<td>Headache, Sinusitis, Swellings, Antitoxin (snake venom), Mosquito Repellent effect, Antifeedant, Fumigant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Essential oils</td>
<td>Skin diseases, Eczema, Carbuncles, Abscesses, Leprosy, Sinusitis, Dentistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pillow stuffed with leaves</td>
<td>Eye disease/Cataract/Watery eyes, Headache</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Root</td>
<td>Powdered form</td>
<td>Dyspepsia, Colic, Dysentery, Piles, Skin diseases, Eczema, Carbuncles, Abscesses, Leprosy, Rheumatism</td>
<td>[12,13,21,22, 23,32,33,15, 16,19,34]</td>
</tr>
<tr>
<td>Decoction</td>
<td>Respiratory disorders, Cough, Bronchitis, Asthma, Wounds and ulcers, Malaria (as tonic)</td>
<td>As Tincture</td>
<td>Flatulence/ Irritable bladder, Dysentery, Rheumatism</td>
</tr>
<tr>
<td>Stem and Bark</td>
<td>Decoction</td>
<td>Burns, Cancer</td>
<td>[12,13,19,28, 32,35]</td>
</tr>
<tr>
<td>As Tincture</td>
<td>Flatulence/ Irritable bladder, Dysentery, Rheumatism</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 2. Phytochemical constituents of extract of Vn leaves

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

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

<table>
<thead>
<tr>
<th>Secondary metabolite</th>
<th>Compounds</th>
<th>Uses</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Flavone</strong></td>
<td>vitexin [8-(β-D-glucopyranosyl)-4',5,7-trihydroxyflavone]</td>
<td>Anti-oxidant, Anti-proliferative, used for Cancer, Cardiovascular disease</td>
<td>[43]</td>
</tr>
<tr>
<td></td>
<td>isovitexin [5,7-dihydroxy-2-(4-hydroxyphenyl)6-[(2S,3R,4R,5S,6R)-3,4,5,6-trihydroxy-6-(hydroxymethyl) oxan-2-yl] chromen-4-one]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### 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,β-diacetoxy-18-hydroxyoleana-5,12-dien-28-oic acid
- 3-formyl-4,5-dimethyl-8-oxo-5H-6,7-dihydranonaphtho (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-dodecacydro-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-dihydranonaphthalen-2-ol]
- (+)-diasyringaresinol
- (+)-lyoniresinol
- vitrofolal-E
- vitrofolal-F

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

<table>
<thead>
<tr>
<th>Secondary metabolite</th>
<th>Compounds</th>
<th>Uses</th>
<th>Reference</th>
</tr>
</thead>
</table>
| **Monoterprenoids**  | sabine [4-methylene-1-[(1-methyl) bicyclo [3.1.0] hexane]  
  p-cymene [1-Methyl-4-(propan-2-yl) benzene]  
  trans-α-bergamotene | Anti-inflammatory agent, enhancing fragrances in beverages | [47] |
| **Terpineol**        | linalool  
  terpinen-4-ol [4-Methyl-1-(propan-2-yl) cyclohex-3-en-1-ol] | An ingredient in perfumes and as a foaming agent in the flotation of ores of nonferrous metals | [48] |
| **Sesquiterpenoids** | B-caryophyllene  
  Valencene [(3R,4aS,5R)-4a,5-Dimethyl-3-(prop-1-en-2-yl)-1,2,3,4,4a,5,6,7-octahydro-1aH-cyclopenta[e]azulen-4-ol]  
  A-selinene  
  B-selinene  
  Germacren-4-ol  
  caryophyllene epoxide (E)-nerolidol  
  Globulol [1,1,4,7-tetramethyl-2,3,4a,5,6,7,7a,7b-octahydro-1aH-cyclopopa[e]azulen-4-ol] | Pharmaceutical agents, Treating Fever | [48] |
<table>
<thead>
<tr>
<th>Secondary metabolite</th>
<th>Compounds</th>
<th>Uses</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty alcohol</td>
<td>1-octen-3-ol, n-hentriacontanol</td>
<td>Insect attractant used in insect repellants</td>
<td>[49]</td>
</tr>
<tr>
<td>Hydrocarbon</td>
<td>n-heptane, toluene</td>
<td>n-heptane used as an industrial solvent for storage and transport, toluene used as a solvent in paints, thinners, glues</td>
<td>[50]</td>
</tr>
<tr>
<td>Carboxylic acid</td>
<td>Formic acid</td>
<td>Preservative, Anti-bacterial agent and Miticide</td>
<td>[47]</td>
</tr>
<tr>
<td>Triterpenoid</td>
<td>acetyl oleanolic acid</td>
<td>Anti-pyretic, Analgesic, Sedative and Tonic effects</td>
<td>[47]</td>
</tr>
</tbody>
</table>

Table 5. Phytochemical constituents of extract of Vn seeds

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

<table>
<thead>
<tr>
<th>Secondary metabolite</th>
<th>Compounds</th>
<th>Uses</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Flavonoids</strong></td>
<td>5-hydroxy-3,6,7,3′4′-pentamethoxy flavone</td>
<td></td>
<td>[57]</td>
</tr>
<tr>
<td></td>
<td>5-hydroxy-3′dihydroxy-7,8,4′-trimethoxy flavanone</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Triterpenoids</strong></td>
<td>β-amyrin</td>
<td>Anti-inflammatory, Anti-oxidant,</td>
<td>[58]</td>
</tr>
<tr>
<td></td>
<td>epifriedelinol</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>oleanolic acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3β-acetoxy-olean-12-en-27-oic acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3β-hydroxy-olean-5, 12-dien-28-oic acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Steroids</strong></td>
<td>1,1,3,3,5,5,7,7,9,9,11,13,13, -tetradeca methyl,3a,3a′-Dichloro-2α,3α -ethano-3β-methyl-cholestan-2a-one</td>
<td>Anti-tumor, Immunosuppressive</td>
<td>[59]</td>
</tr>
<tr>
<td></td>
<td>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]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Phenolic compounds</strong></td>
<td>hexadeca methyl p-hydroxy benzoic acid</td>
<td>Cancer prevention and treatment</td>
<td>[60]</td>
</tr>
<tr>
<td><strong>Glycosides</strong></td>
<td>3,6,7,3′,4′-pentamethoxy-5-O-glucopyranosylhamnoside</td>
<td>Anti-oxidant, Anti-cancer</td>
<td>[61]</td>
</tr>
<tr>
<td></td>
<td>Vitisin caffeate [5,7-dihydroxy-2-(4-hydroxyphenyl)-8-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl) oxan-2-yl] chromen-4-one]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4′-O-methyl myricetin-3-O-[4′-O-β-D-galactosyl]-β-D- galactopyranoside</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Siloxanes</strong></td>
<td>heptamethylphenoicycloctetrasiloxane</td>
<td>Implants, dentures, skin patches to deliver therapeutic substances</td>
<td>[62]</td>
</tr>
<tr>
<td></td>
<td>tetradecamethylnonamethylcycloheptasiloxane</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>phenylcyclopentasiloxane</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>cyclooctasiloxane</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>nonamethyl, phenylcyclopenta siloxane</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>tetracosamethylcyclooctadecasiloxane</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>tetradeacethylheptasiloxane</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>octadecamethylcyclooctasiloxane</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Secondary metabolite</th>
<th>Compounds</th>
<th>Uses</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sesquiterpene</strong></td>
<td>α-copaene [1,3-dimethyl-8-propan-2-yltricyclo [4.4.0.02,7] dec-3-ene]</td>
<td>Anti-cancer, Anti-plasmodial</td>
<td>[50]</td>
</tr>
<tr>
<td></td>
<td>β-selinene [(3R,4aS,8aR)-8a-methyl-5-methyldiene-3-prop-1-en-2-yl-</td>
<td></td>
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</table>
4.2 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].

4.3 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 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].

4.4 Effect on Reproductive Potential

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

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. PHARMACOLOGICAL ACTIVITIES

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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], lipooxygenase, 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 antimicrobial 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 tritaeniorynchus, 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

Venkataramanapp 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, arteminin 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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