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Nishinda (V*itex negundo* Linn) – A valuable medicinal plant used in herbal medicine

[*1] Mohammad Abu Bin Nyeem, [2] Md. Obaydul Haq, [3] Md. Moksed Ali, [4] Nasim Ahmed, [5] Helal Uddin, [6] Meher Nowrose

[1, 2, 3] Assistant Professor, Department of Unani Medicine, Hamdard University, Bangladesh
[4] Department of Public Health, Northern University, Bangladesh
[5] Govt. Unani & Ayurvedic Medical College, Bangladesh
[6] Department of Public Health, ASA University, Bangladesh

Abstract
Herbal medicines have been the basis of treatment and cure for various diseases and physiological conditions in traditional methods practiced such as Ayurveda, Unani and Siddha. The aim of the present study investigation was carried out to compile the medicinal properties of different plant parts of *Vitex negundo* L. with scientific evidences. *Vitex negundo* Linn belongs to the family of Verbenaceae. It has been reported to posses potent pharmacological properties like anti-inflammatory, anti-rheumatic, antipyretic, hepatoprotective, antioxidant, anticonvulsant, anti-estrogenic, snake venom neutralization, mosquito repellent and anti-allergic activities. Phytochemical studies on *Vitex negundo* Linn revealed the presence of volatile oil, triterpenes, diterpenes, sesquiterpenes, lignan, flavonoids, flavones, glycosides, iridoid glycosides and stilbene derivative.

Keywords: Vitex negundo, Pharmacological activity, Phytochemical constituents, Nishinda

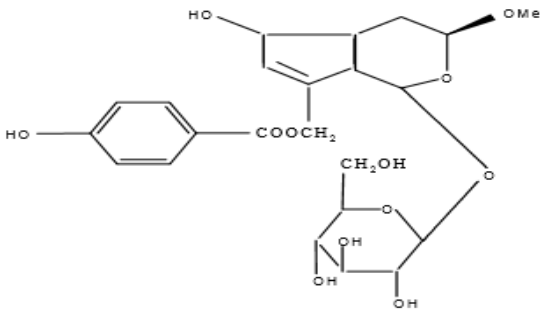
Introduction
Medicinal plants are the backbone of traditional medicine. *Vitex negundo* L. (Verbenaceae), commonly called "five leaved chaste tree", is a large aromatic shrub. This plant has been used for various medicinal purposes in the Ayurvedic and Unani systems of medicine where almost all the parts are employed for the drug preparation. It is found throughout, mainly at warmer zones and at an altitude of 1500 m in the outer Western. Himalayas, India. It is also found in Bangladesh, Sri Lanka, Burma, China, Pakistan, Afghanistan, Malaysia, Tropical Africa, Philippines. It is common in waste places around villages, river banks, moist localities and deciduous forests. In Indian traditional medicine system *Vitex negundo* Linn is referred as 'sarvaroganivarani' – the remedy for all diseases [1]. A popular local quote of the Bhangalis in the Western Himalayan region 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) [2]. Nirgundi in Sanskrit means which protects the body from diseases [3]. The fresh leaves are used for the treatment of rheumatism, fever, pain, inflammation, skin diseases and the leaves, root and bark are used in snake bite cures [4]. Fruits are employed as a vermifuge and the seeds reputed to be cooling in skin disease and leprosy [5]. Root is used as a tonic, expectorant, febrifuge and diuretic and the flowers are used in the treatment of diarrhea, cholera and liver disorders [6].

Fig 1: *Vitex negundo*

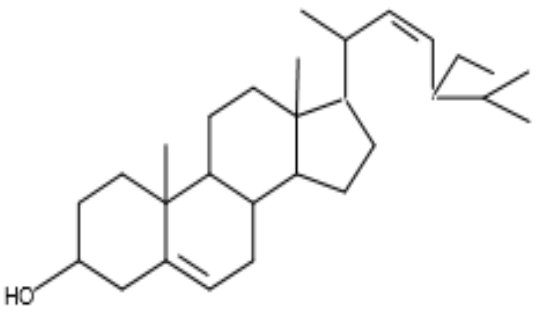
Vernacular Names

Assamese	-	Aslok, Pochatia
Bengali	-	Beguna, Nishinda
Hindi	-	Nirgundi, Sambhalu
Kannada	-	Karilakki, Lakkagida
Malyalam	-	Karunocci, Noch-chi
Marathi	-	Nirgunda, Nengar
Oriya	-	Thingkhawilupa, Niligundi
Sanskrit	-	Nirgundi, Sindhuvara
Tamil	-	Nallanocci, Nochi

Phytochemical Constituents
Phytochemical studies on *Vitex negundo* revealed the presence of volatile oil, triterpenes, diterpenes, sesquiterpenes, lignan, flavonoids, flavones, glycosides, iridoid glycosides and stilbene derivative. The detailed of phytochemical constituents is present in each part of the plant is given below:



Nishindaside



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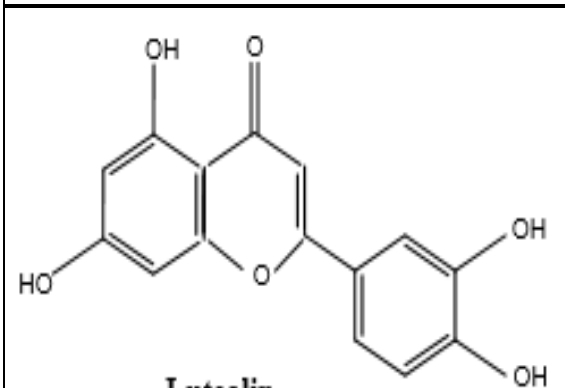
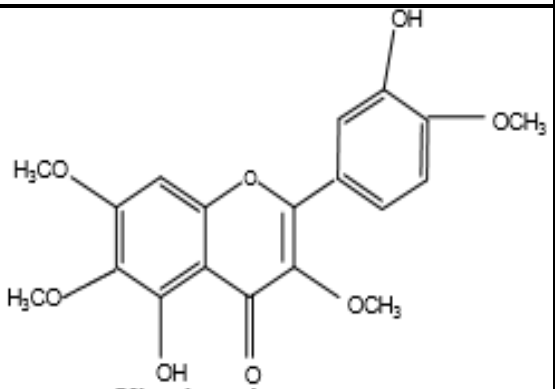
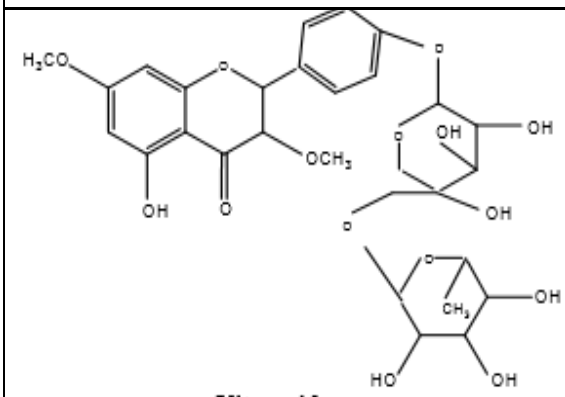


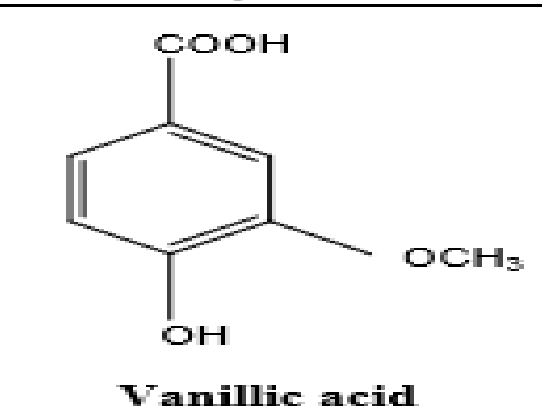
Luteolin



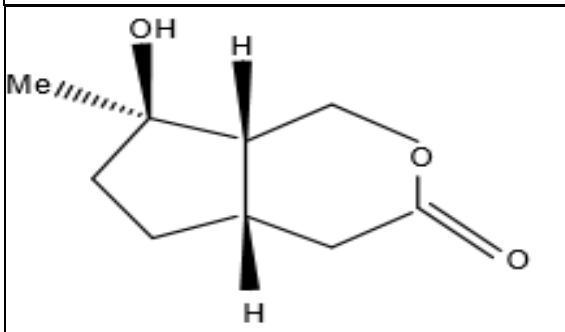
Vitexicarpin



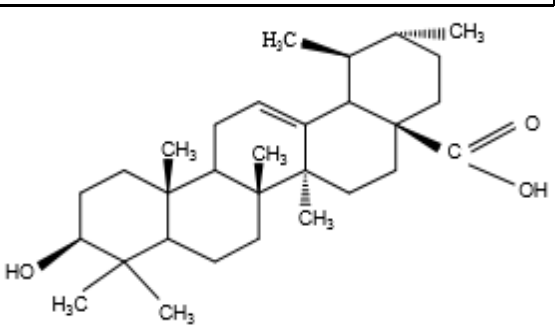
Vitexoside



Vanillic acid



Lagundinin



Ursolic Acid

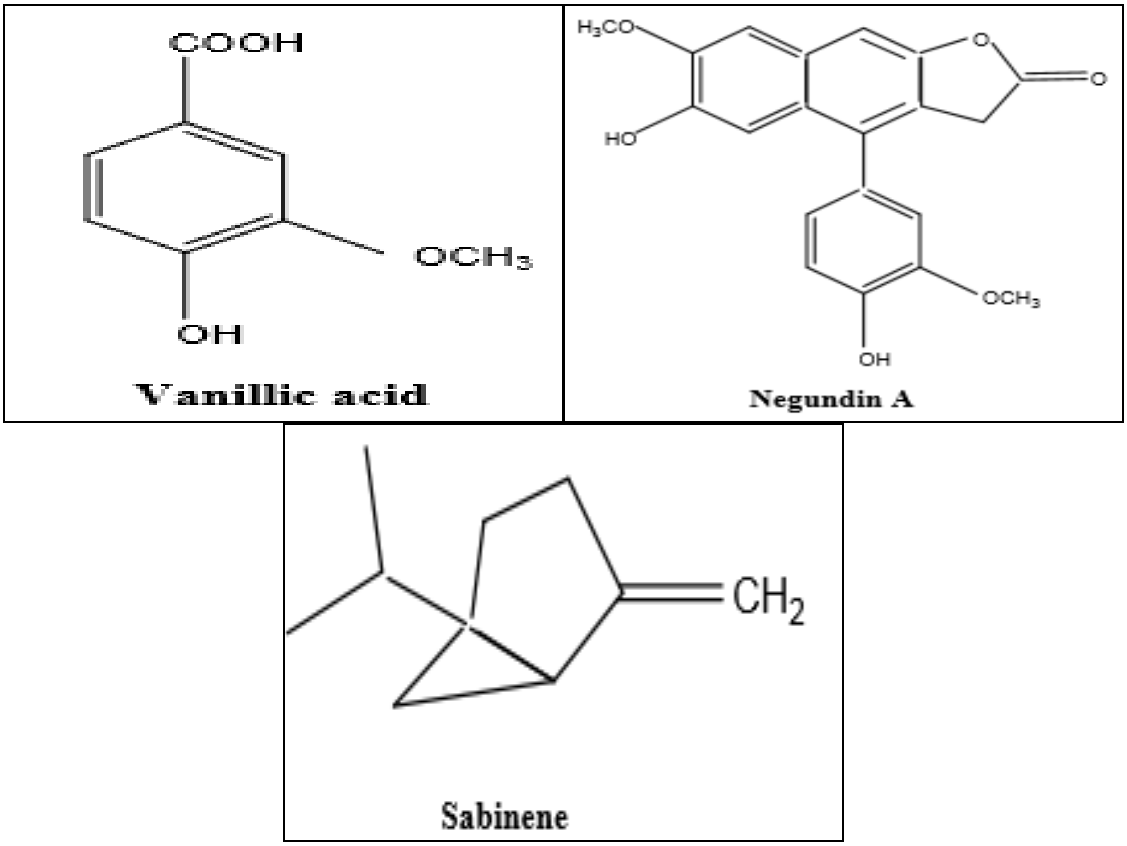


Fig 2: Phytochemical constituents

Leaves : The various chemical constituents present in leaves of *Vitex negundo* Linn are Friedelin, carotene, casticin, artemetin [7], terpinen-4-ol, α-terpineol, sabenine, globulol, spathulenol, β- farnesene, farnesol, bis (1,1dimethyl) methylphenol, α-pinene, β-pinene, linalool, terpinyl acetate, caryophyllene epoxide, caryophyllenol, vitexicarpin, viridiflorol [8-11], 4,4″- dimethoxy-trans-stilbene, 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) [12-15], terpinen-4-ol, αcopaene, β-caryophyllene, β-elemene, camphene, α-thujene, α-pinene, sebinene, linalool, stearic acid and behenic acid [16], α-elemene, δ- elemene, β-elemene, β-eudesmol, camphor, camphene, careen, 1,8- cineol, 1-oceten-3-ol, γterpinine, α-phellendrene, β-phellendrene, α- guaiene, abieta-7,13-diene, neral, geranial, bornyl acetate, nerolidol, βbisabolol, cedrol [17-21], 2′-p-hydroxybenzoyl mussaenosidic acid, agnuside, lagundinin, aucubin and nishindaside [22], 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-7glucoside, isoorientin [23], 3′-benzoyloxylhydroxy-3,6,7,4- tetramethoxyflavone, 5,3′-dibenzoyloxy-3,6,7,4teramethoxyflavone, 5,3′-Dipropanyloxy-3,6,7,4′- tetramethoxyflavone, 5,3-Dibutanoyloxy3,6,7,4tetramethoxyflavone,5,3′-Dipenty4enoyloxy-3,6,7,4′ tetramethoxyflavone, 5,3-Dihexanoyl 3,6,7,4 tetramethoxyflavone [24], betulinic acid, ursolic acid [25], dimethoxyflavonone, 5,3′-dihydroxy-7,8,4′trimethoxyflavonone, 7,8-Dimehylherbacetin-3-rhamnoside, vitegnoside [26], 1,4a,5,7a tetrahydro 1βDglucosyl (3′,4′dihydroxybenzoyloxymethyl)-5-ketocyclopenta[c] pyran-4-carboxylic acid, luteolin-7-O-β-D-glucosid [27],6′p-hydroxy benzoylmussaenosidic acid [28].

Seeds: The seeds of *Vitex negundo* Linn have chemical constituents such as n-Tritriacontane, n-hentriacontanol, nhentricontane, n-pentatricontane, n-nonacosane, β-sitosterol, phydroxybenzoic acid and 5-oxyisophthalic acid, 3, 4dihydroxybenzoic acid [29-31], artemetin [32], 3β-acetoxyolean-12-en-27-oic acid, 5β-hydro-8,11,13-abietatrien6α-ol, 2α,3α-dihydroxyoleana-5,12-dien-28-oicacid, 2β,3α-diacetoxyoleana-5,12-dien-28-oicacid and 2α,3βdiacetoxy-18-hydroxyoleana-5,12-dien-28-oic acid [33-34], vitedoin A, vitedoamine A, vitedoin B [35-36], 5,7,3′trihydroxy 6,8,4′-trimethoxy [37], 6-hydroxy-4-(4-hydroxy-3- methoxy-phenyl)-3-hydroxymethyl-7-methoxy-3, 4dihydro-2-naphthaldehyde [38].

Stem and bark: The various chemical constituents present in the stem and bark are vitexin cafeate, 4′-O-methyl myricetin-3-O-[4′-O-β-D-galactosyl]-β-D-galactopyranoside [39], βamyrin, epifriedelinol and oleanolic acid [40], Hepta methyl-phenyl-cyclotetra siloxane, Cyclo heptasiloxane,tetra decamethyl Nona methyl, phenyl-cyclopenta siloxane, Cyclo octa siloxane,hexadeca methyl, Borazine, 2,4,6- tripheny-l1, 3, 5-tryophl, Nonamethyl, phenyl-cyclopenta siloxane, Tetracosamethylcyclododeca siloxane, penta methyl phenyl-Disilane, Heptasiloxane, 3a,3a′-Dichloro-2α,3α ethano-3β-methyl-cholestan-2a-one, Octadecamethyl, cyclonona siloxanes Cyclo octa siloxane, hexadeca methyl [41], p-hydroxy benzoic acid, β-sitosterol [42], 5-hydroxy-3,6,7,3′4′-pentamethoxy flavone, 5-hydroxy-3′dihydroxy7,8,4′-trimethoxy flavanone,3β-acetoxy-olean-12-en-27-oic acid, 3β-hydroxy-olean-5, 12-dien-28-oic acid [43].

Roots: Vitexoside, agnuside, R-dalbergiphenol [44-45], negundin A, negundin B, 6-hydroxy-4-(4-hydroxy-3-methoxy)-3hydroxymethyl-7-methoxy-3,4-dihydro-2-naphthaledehyde, vitrofolal E, (+)-lyoniresinol, (+)-lyoniresinol-3α-O-βd-glucoside, (+)-(−)-pinoresinol, and (+)-diasyringaresinol [46], 2β,3α-diacetoxyoleana-5,12-dien-28-oic acid; 2α,3α-dihydroxyoleana-5,12-dien-28-oic acid, 2α,3β -diacetoxy-18-hydroxyoleana-5,12-dien-28-oic acid, vitexin and isovitexin [47], acetyl oleanolic acid, sitosterol, 3-formyl-4.5-dimethyl-8-oxo-5H-6,7-dihydronaphtho (2,3-b) furan (a new furanoeremophilane) [48].

Pharmacological Activity

Anti-inflammatory activity

Anti-inflammatory activity of chloroform extract of seeds of *Vitex negundo* in Sprague-Dawley male rats in carrageenan induced rat paw edema using Ibuprofen as standard drug [49]. Anti-inflammatory activity of bark, seeds, seed oil and essential oil of *Vitex negundo* [50-53], U. Jana *et al.* reported preliminary anti-inflammatory activity of *Vitex negundo* in albino rats along with *Zingiber officianale* and *Tinospora cordifolia* [54]. Anti-inflammatory activity from the aqueous extract of *Vitex negundo* leaves in Wistar rats (male) using carrageenan-induced & formaldehyde-induced rat paw edema using indomethacin as standard. The early phase of carrageenan-induced rat paw edema was significantly suppressed in an inversely dose-dependent manner [55]. R.K. Gupta *et al.* reported anti-inflammatory activity from the ethanolic extract of *Vitex negundo* leaves in albino rats (of either sex) using carrageenan-induced rat paw edema and cotton pellet granuloma models using phenylbutazone (10-100 mg) and ibuprofen (10-200 mg) as standards [56]. Pradeep Singh *et al.* reported anti-inflammatory activity of ethanolic extract of roots [57].

Antioxidant activity

The antioxidant potency of *Vitex negundo* Linn. was investigated by all the fractions of *Vitex negundo* Linn. exhibited a potent scavenging activity for (2, 2′-azino-bis 3-ethyl benzothiazoline-6-sulfuric acid) ABTS radical cations in a concentration dependent manner, showing a direct role in trapping free radicals. The polar fractions of *Vitex negundo* Linn. possess potent antioxidant properties. Tandon and Gupta have also reported similar antioxidant properties of *Vitex negundo* Linn. in rats, by using ethanol induced oxidative stress model [58-59]. The extracts also possess the ability to combat oxidative stress by reducing lipid peroxidation owing to the presence of flavones, vitamin C and carotene. Rooban *et al.* evaluated the antioxidant and therapeutic potential of *Vitex negundo* Linn. flavonoids in modulating solenoid-induced cataract and found it to be effective [60-61].

CNS depressant activity

A methanolic extract of the leaves of *Vitex negundo* was found to significantly potentiate the sleeping time induced by pentobarbitone sodium, diazepam and chlorpromazine in mice [62].

Antifungal activity

Sathiamoorthy *et al.* isolated six compounds from the powdered leaf extracts of *Vitex negundo.* The isolated compounds were evaluated for antifungal and anti-bacterial activity. From the isolated compounds two possess potent anti-fungal activities and very active when compared to other isolated compounds. Significant antifungal activity in ethanolic extract against Cryptococcus neoformans and Trichophyton mentagrophytes was offered by two compounds isolated from the leaf extract of *Vitex negundo* [63].

Hepatoprotective activity

The ethanolic extract of *Vitex negundo* at 250 and 500 mg/kg doses significantly decrease Serum Bilirubin, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline Phosphates (ALP) and Total Protein (TP) levels against hepatotoxicity (HT) produced by administering a combination of three antitubercular drugs isoniazide (7.5 mg/kg), rifampin (10 mg/kg) and pyrazinamide (35 mg/kg). Alcoholic extract of the seeds of *Vitex negundo* Linn. showed the hepatoprotective action against carbon tetrachloride induced liver damage. The extract was found to be effective in preventing liver damage which was evident by morphological, biochemical and functional parameters [64]. Nirgundi exerts a protective effect on CYP2E1dependent CCl4 toxicity via inhibition of lipid peroxidation, followed by an improved intracellular calcium homeostasis and inhibition of Ca2+ dependent proteases [65-66].

Hypoglycemic activity

Villasenor and Lamadrid have provided an account of the anti hyperglycemic activity of *Vitex negundo* Linn. leaf extracts[67].

Effect on oxidative stress

Leaf extracts of *Vitex negundo* were determined to possess anti-oxidant potential by [68]. The extracts were useful in decreasing levels of superoxide dismutase, catalase and glutathione peroxidase in Freund's adjuvant induced arthritic-rats [69]. The extracts also possess the ability to combat oxidative stress by reducing lipid peroxidation owing to the presence of flavones, vitamin C and carotene [70]. Rooban *et al.* [71] evaluated the antioxidant and therapeutic potential of *Vitex negundo* flavonoids in modulating solenoid-induced cataract and found it to be effective.

Enzyme-inhibitory activity

Root extracts of *Vitex negundo* showed inhibitory activity against enzymes such as lipoxygenase and butyryl-cholinesterase [72]; α-chymotrypsin [73]; xanthine-oxidase [74] and tyrosinase [75]. Woradulayapinij *et al.* [76] reported the HIV type 1 reverse transcriptase inhibitory activity of the water extract of the aerial parts of *Vitex negundo*.

Effect on reproductive potential

The flavonoid rich fraction of seeds of *Vitex negundo* caused disruption of the latter stages of spermatogenesis in dogs [77] and interfered with male reproductive function in rats [78]. It must however be noted that these findings are in sharp contrast with the traditional use of *Vitex negundo* as aphrodisiac [79]. Hu *et al.* [80] determined that ethanolic extracts of *Vitex negundo* showed estrogen-like activity and propounded its use in hormone replacement therapy.

Antipyretic activity

The literature reveals that the leaf extract of *Vitex negundo* causes a significant antipyretic effect in yeast provoked

elevation of body temperature. In the cases, the methanol extract caused a significant lowering of body temperature, with the effect being comparable to that of paracetamol. Thus the present pharmacological evidence provides support for the folklore claim as an antipyretic agent. Flavonoids are known to target prostaglandins which are involved in the late phase of acute inflammation, pyrexia and pain perception. Flavonoids reduce lipid peroxidation by preventing or slowing the onset of cell necrosis and by increasing the vascularity. Hence the presence of flavonoids in the methanol extract of *Vitex negundo* may be contributory to its antipyretic activity [81].

Antihelmintic activity

Ethanolic extracts of Moringa oleifera and *Vitex negundo* were taken for anthelmintic activity against Indian earthworm Pheritima posthuma. Various concentrations of both extracts were tested and results were expressed in terms of time for paralysis and time for death of worms. Piperazine citrate (10 mg/ml) was used as a reference standard and distilled water as a control group. Dose dependent activity was observed in both plant extracts but *Moringa oleifera* shows more activity as compared to *Vitex negundo* [82].

Anti-eosinophilic activity

Egg albumin induced asthma in guinea pig model was used to study the anti eosinophilic activity of the *Vitex negundo* Linn. The effects of various fractions such as aqueous subfraction, acetone subfraction, chloroform subfraction of the leaves of *Vitex negundo* Linn on the bronchial hyper responsiveness and serum bicarbonate level was evaluated. Aqueous subfraction of the leaves of *Vitex negundo* Linn possessed anti eosiniphilic activity [83].

Antiestrogenic activity

The various fractions of *Vitex negundo* leaf extract (n-hexane, chloroform, n-butanol, remnant fraction) was administered to female swiss albino mice to evaluate the anti implantation potential. Mice uterus was used to estimate the lipid peroxidation and assay of superoxide dismutase (SOD) activity. In comparison to control n-hexane fraction treated mice altered the level of superoxide anion radical and superoxide dimutase activity [84].

Anti-HIV activity

The anti-HIV activity of ethanolic leaf extract of *Vitex negundo* Linn was studied against HIV-1 reverse transcriptase. Using a non radioactive HIV-RT colorimetric ELISA kit and with recombinant HIV-1 enzyme it was evaluated in vitro. The study concluded that the ethanolic extract exhibits anti HIV activity and the flavonoids as anti-viral agents [85].

Larvicidal activity

The larvicidal activity of flavonoid extract of different parts of *Vitex negundo* and *Andrographis paniculata* is performed against the late III or IV instar larvae of Aedes aegypti and Anopheles stephensi and the two plants showed good larvicidal activity and can be used to synthesis eco- friendly insecticide [86].

Anti snake venom activity

Snake venom neutralization by the methanolic roots extracts of *Vitex negundo* Linn and *Emblica officinalis* was performed against the Vipera russelli and Naja kauthia venom induced lethal activity both in vivo and invitro and since no precipitating bands were found between the plants extract and snake venom which revealed that these plants extracts posses potent anti snake venom activity [87].

Mosquito repellent activity

P.K. Amancharla tested mosquito repellent activity of aqueous extract of *Vitex negundo* leaves. A new chemical 'rotundial' was tested for the said activity [88].

Anti-androgenic activity

S.K. Bhargava reported antiandrogenic activity of various flavonoids from the seeds of *Vitex negundo*. The flavonoids which shows estrogenic properties as well as anti-implantation activities are 5, 7, 3'-trihydroxy and 6, 8, 4'trihydroxy flavones [89].

Anticonvulsant activity

The plant has been studied for its anticonvulsant activity. The petroleum and butanol leaf extracts have shown protection, whereas, none of root extract has shown protection against maximal electro shock (MES) seizures. Petroleum root extract could only provide protection against Leptazole induced convulsios whereas methanolic leaf extract showed significant protection against Strychnine and Leptazole induced convulsions. Gupta and Tandon not only suggested anticonvulsant activity of ethanolic leaf extract of this plant but also indicated that it can potentiate the effects of standard anticonvulsanta, which may help to reduce dose and dose related side effects of standard anticonvulsants [90].

Anti-arthritic activity

Freund's complete adjuvant model (FCA) was used to study the anti-arthritic effect of ethanolic extract of *Vitex negundo* Linn leaf. FCA induced the arthritis and liver function test and radio logical examinations where performed for the analysis anti arthritic activity of leaf extract [91].

Conclusions

According to the thorough study of the available literature it is quite obvious that the importance of *Vitex negundo* in traditional system of medicine is of utmost significance. Almost all parts of the plant are use in preparing herbal medicines. The plant is known to possess anti-inflammatory, anti-rheumatic, antipyretic, hepatoprotective, antioxidant, and snake venom neutralization, mosquito repellent and anti-allergic activities. Phytochemical studies on *Vitex negundo* revealed the presence of volatile oil, triterpenes, diterpenes, sesquiterpenes, lignan, flavonoids, flavones, glycosides derivative.

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