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A REVIEW ON *UNANI* TRADITIONAL USES OF *SAMBHALU* IN FEMALES AS WELL AS PHYTOCHEMICAL AND PHARMACOLOGICAL PROPERTIES

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ABSTRACT: Herbal medicine, rather than merely curing a particular disease, aims at returning the body back to its natural state of health. *Vitex negundo* Linn. known as *Sambhalu* in *Unani* medicine belongs to family Verbenaceae. It is a large aromatic shrub distributed throughout India. It has been used since ancient times as a female remedy in *Unani* medicine. It is a well known plant because of its two main properties i.e. its use in female disorders specially disorders linked with female reproductive system and decreasing sexual desire. It is also used in other problems like roots and leaves used in eczema, ringworm and other skin diseases, liver disorders, spleen enlargement, rheumatic pain, gout, abscess, backache; seeds used as vermicide. It is also used to control population. This review is an attempt to highlight its therapeutic uses especially in females mentioned in *Unani* medicine as well as phytochemical and pharmacological properties.

INTRODUCTION: Natural products are a type of alternative medicine that originates from plants and plant extracts used to heal illness and disease and were the precursors to modern medicine. They are obtained from wide variety of natural resources including plant leaves, barks, berries, flowers and roots. [1] Plants used in traditional medicine contain a vast array of substances that can be used to treat chronic and even infectious diseases. The demand for more and more drugs from plant sources is continuously increasing. [2] The word Vitex is derived from the Latin 'vieo' (meaning to tie or bind) because of the flexible nature of its stems and twigs. Of the 270 known species of the genus, about 18 are in cultivation and are referred to as 'chaste tree', or simply Vitex.

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The genus was established by Linnaeus in 1753 with four species: Vitex agnus-castus, *V. negundo*, *V. pinnata*, and *V. trifolia* in the family Verbenaceae. [3] The *Vitex negundo* linn. commonly known as five leaved chaste tree, Nirgundi etc.[1, 4] It is distributed throughout the greater part of India up to an altitude of 1500 meter in the Himalayas. The shrub is very common in many part of the country and often occurs gregariously. It is abundant along the banks, rivers in moist situations, and open waste lands. It is widely planted as hedge plant along the roads and between fields.[5]

It is a well known plant because of its two main properties i.e. its use in female disorders specially disorders linked with female reproductive system and decreasing sexual desire. This plant is widely found in Mediterranean countries as well as central Asia. In past two main herbalists Pliny and Dioscorides have done great work on it and they mentioned its use as antipyretic and its property to stimulate perspiration, urination and many more. [4] Traditionally, various parts of the plant is used to

treat jaundice, urticaria, cellulitis, abcesses, carbuncles and eczema. The leaves of *Vitex negundo* has been reported for its anti-inflammatory, analgesic and antihistaminic property, snake venom neutralizing capacity, hepatoprotective and CNS depressant activities by various scientific studies.[6] This review is an attempt to highlight the medicinal potential of *Vitex negundo* especially in females as well as phytochemical and pharmacological properties.

Taxonomical classification:

Kingdom: Plantae- Plants

Subkingdom: Tracheobionta – Vascular plants

Super division: Spermatophyte – Seed plants

Division: Magnoliophyta – Flowering plants

Class: Magnoliopsida – Dicotyledons

Subclass: Asteridae

Order: Lamiales

Family: Verbenaceae

Genus: Vitex Linn.

Species: *Vitex negundo* Linn. [7]

TABLE1: VERNACULARS [8, 9]

Arabic	Aslag, Fanjangasht, Zukhamsateasabea, Zukhamsatilourag
Bengali	Nirgundi, Nishinda, Nisinda, Samalu
Bombay	Katri, Lingur, Nargunda, Nirgundi, Nirgur, Nisinda
Burma	Kiyowbhanbin, Kiyubanbin
Chinese	Houang Kin, Mu Ching
Deccan	Shamalu, Shambali
Gujerati	Nagaol, Nagda, Nagoda, Nagodz, Nigod, Nirgiri
Malaya	Ching tzu, Huang ching, Kheng chee, Man ching
Malayalam	Indrani, Nochi, Vellanochi
Marathi	Lingur, Nirguda, Nirgunda, Nirgundi, Nirgur
Nepal	Sewali
Persian	Banjangasht, Panjangusht
Sanskrit	Indrani, Nilapushpa, Nilanirgundi, Nirgundi, Shephali, Sinduvara
Tamil	Nirkkundi, Nochi, Sinduvaram, Vennochi
Telugu	Nallavavili, Sinduvaramu, Vavili, Vayila
Uriya	Begundia, Indrani

Habitat: Bengal, Southern India and Burma. [9]

Morphological Description: A large shrub or sometimes a small slender tree; bark thin, grey; branchlets quadrangular, whitish with a white tomentum. Leaves 3-5 foliolate; leaflets lanceolate, acute, the terminal leaflet 5-10 by 1.6-3.2 cm. with a petiolule 1-1.3 cm long, the lateral leaflets smaller with a very short petiolule, all nearly glabrous above, covered with a fine white tomentum beneath, base acute; common petioles 2.5-3.8 cm long. Flowers in pedunculated branched tomentose cymes, opposite along the quadrangular tomentose rhachis of a large terminal often compound pyramidal panicle; bracts 1.5-2.5 mm long, lanceolate, caduceus. Calyx 3 mm long, white-tomentose; teeth triangular, 0.8-1 mm long. Corolla 1 cm long, bluish purple, tomentose outside, hairy inside at the insertion of the stamens. Filaments hairy at the very base. Ovary glabrous; stigma forked. Drupe less than 6 mm. diam., black when ripe.[8]

Mahiyat (Description in Unani Medicine)

Parts used: seeds, [10, 11, 12] root, [11] leaves, [11, 12] fruit, [12] bark.[10]

Af'al (actions): *Jali* (detergent), *Musakkine dard* (alangesic),[10, 13] *Muhallile waram* (anti-inflammatory),[10, 12, 13] *Mujaffif, Daf'e taffun* (antiseptic),[10, 13] *Mundamile qurooh* (wound healing), *Mufatteh sudad* (Deobstruent),[10, 12] *Mulattif,*[12, 13] *Kasire riyah* (Carminative),[13] *Daf'e humma* (Antipyretic), *Mushtahi* (appetizer), *Mukhrije deedan, Qatile deedan* (Anthelmintic), *Muqawwie baah* (Aphrodisiac).[11]

***Mizaj* (temperament):** Hot 2° and Dry 2° [10, 13]

***Miqdare khurak* (dose):** seed-2 to 5g [10]

***Muzir* (adverse effect):** for Kidney, [13] *Mujaffif mani* [10]

***Musleh* (correctives):** Babool gum, [10, 12, 13] *Kateera*, [12, 13]

***Badal* (substitute):** *Shahdana* [10, 13]

***Murakkab* (compound formulations):** *Safoofe fanjkusht*, *Roghane haft berg*. [13]

Therapeutic uses mentioned in *Unani* medicine:
It is used in females to treat different ailments (**Table2**). Local application of pounded leaves is helpful in fissure in ano. [12] Local application of warm leaves is beneficial in resolving *warme barid* (cold swelling) and flatulance. [11, 12] Juice of green leaves dropped into eyes to improve the vision. Gargling with decoction of leaves is helpful to treat mouth ulcers and throat pain. Sitz bath in its decoction is helpful in *warme maqaad* (proctitis). Pounded leaves cooked in oil is applied locally to treat putrefied ulcers and also to resolve hard swellings. Seeds are used orally along with *sikanjabeen* to resolve hard swellings of spleen. Seeds soaked in vinegar are used as hot fomentation in case of flatulence. [13] It cures cough and boils. It is beneficial in leprosy, asthma and rectal prolapse. Leaves soaked in cold water whole night and are used as gargle to treat toothache, gingivitis, bleeding gums, halitosis and excessive salivation. Oral use of decoction of leaves helpful in cold, corrhyza and headache. Pillow stuffed with its leaves is used to reduce headache. Oral use of pounded leaves is helpful in relapsing fever. Oral use of powdered fruit in the form of tablet reduces arthralgia. Powdered dry fruit is used orally to reduce backache and headache. Juice of leaves is used locally to treat skin diseases and swellings. Dried leaves are used in *hukka* which is beneficial in cold and headache. Its root and leaves act as a diaphoretic and diaphoresis. Grind together its leaves along with garlic, rice and jaggery and used orally to get wormicidal effect. [11]

TABLE 2: THERAPEUTIC USES IN SPECIFIC FEMALES PROBLEMS

Diseases	Uses
Dysmenorrhoea	Oral use of powdered seeds helpful in reducing pain during menses.[11]
Amenorrhoea	Oral use of powdered seeds act as emmenogogue.[11] Fumigation with its leaves and fruit along with *pudina sehrai* act as emmenogogue.[12]
Oligomenorrhoea	Oral use of powdered seeds helpful in regularising the menstrual cycle.[11]
Infammatory condition of uterus	Sitz bath with decoction of leaves of *Vitex negundo* or boiled leaves can be applied locally to reduce inflammation.[13]
Infammatory condition of ovaries	Sitz bath with decoction of leaves of *Vitex negundo*.[13]
Augumentation of labour	Application of pounded root over umbilical region or over the vulvae causes easy delivery of the baby.[11]
Oligogalactorrhoea	Powdered seeds are used orally in case of poor laction.[13]
Use in Puerperium	Tablet formed with pounded leaves in the dose of 3gm and cooked in ghee is used for one week in puerperium with benefit.[12]

Phytochemical properties:

Leaves:
Phytochemical analysis of V. negundo by *Sahayaraj et al* (2008) showed the presence of compounds such as phenols, saponins, xathoproteins, triterpenoids, tannins and flavonoids. The major compounds identified in V. negundo are 1H-indene, cyclododecanol, patchoulane, 1,2-dihexylcyclopropene-3-carboxylic acid, 2-heptenoic acid, (+) -aromadendrene, trans-caryophyllene, 7-oxabicyclo [4.1.0] heptane, cyclohexane, farnesol, pentadecane and 1-octanol. [14] The phytochemical screening by *Nirmalkumar* (2007) revealed the presence of phlobatannins, carbohydrates, tannins, glycosides, volatile oils, resins, balsams, flavonoids and saponins, while terpenes, sterols, anthorquinones and phenols were absent. [15] The Phytochemical Screening by *Aditya & Kumar* (2014) shows presence of Alkaloids, flavanoids, carbohydrates, glycosides and tannins in *Vitex negundo* leaves. [16]

Root: Six phenylnaphthlene-type (1, 3~7) and a spirocycloyclohexadienone-type (8) neolignans, a dihydronaphthalene dione (2), and a sesquiterpenoid derivative (9) were isolated from the bioactive fraction of the roots of *Vitex negundo* L by *Young-Ji et al* (2011). [17]

Pharmacological properties:
1. Antimicrobial activity: Study was carried to investigate the antimicrobial properties of the essential oil of leaves of *Vitex negundo*. The essential oil from leaves of *Vitex negundo* was tested against pathogenic microorganisms; *S.*

aureus, E.coli, K. pneumoniae, B. subtilis, M. luteus and *Candida albicans*. The oil tested exhibited good antimicrobial activity against all the clinical isolates when compared with standard. [18] Flavonoids from leaf extracts of Pongamia pinnata and leaf and seeds extracts of *Vitex negundo* were screened against *Bacillus cereus, Escherichia coli, Mycobacterium smegmatis, Proteus vulgaris, Pseudomonas aeruginosa, Salmonella typhimurium, Staphylococcus aureus, S. epidermidis, Candida albicans* and *Trichoderma viride* adopting disc diffusion method. Results were compared with the zone of inhibition produced by commercially available standard antibiotics. Maximum activity was observed in flavonoid extract of V. negundo leaves. [19]

The methanol crude extract of *Vitex negundo* was fractionated with kupchan method and pet-ether and carbon tetrachloride were made for screening the antimicrobial and antitumor potentials using disc diffusion method and brine shrimp lethality bioassay respectively. An established antibiotic (Kanamycin, 30µg/disc) and cytotoxic agent (Vincristine sulphate) were used to compare the results. All the fractions showed most prominent zone of inhibition against a number of bacterial and fungal strains. Especially in comparison to the standard kanamycin, all fractions gave prominent zone of inhibition against *Bacillus subtilis, Bacillus megaterium, Salmonella typhi, Vibrio mimicus* and *a fungal strain, Aspergillus niger*. [2]

2. Antibacterial activity:

The leaf extracts of *Vitex negundo* solvented by ethanol, showed the spectrum of inhibition on salmonella paratyphi. Most of the bacterial pathogens like *salmonella paratyphi, klebsiella pneumonia, vibrio cholera, streptococcus mutans* and *E.coli* were found to be susceptible in leaf extracts of the *Vitex negundo*. Petroleum ether leaf extract of *Vitex negundo* showed good activity against Salmonella paratyphi and entrobactor. [20] In another study an attempt was made to determine the *in vitro* antibacterial activity of sequentially extracted different solvent (dichloromethane, ethyl acetate, ethanol, methanol and water) extracts of leaf, flower and fruit of *Vitex negundo* L. and bulb of *Allium sativum* L. (Garlic) against phytopathogens namely *Pseudomonas solanacearum* and *Xanthomonas axonopodis* pv. Citri. All the test samples showed inhibitory effect on both of the test pathogens and the diameter of inhibition zone ranged from 9.9 ± 0.5 mm to 48.5 ± 1.3 mm. [21] Antimicrobial assay of the different solvent extracts such as petroleum ether, chloroform, ethyl acetate, methanol and water were screened to show the presence of phytochemicals like alkaloids, steroids, tannins, phenolic compounds and terpenoids. The antimicrobial screening by disc diffusion method on different test pathogen showed potent inhibitory against *Bacillus cereus, B. subtilis* and *Pseudomonas alimenta* with the zone of inhibition ranging from 7- 25mm. [22]

The antibacterial activity of the ethanolic extracts of *Vitex negundo* L. (EEVN), *Fragaria vesca* L. (EEFV), *Terminalia arjuna* (EETA) and Citrus maxima (EECM) was evaluated on *Staphylococcus aureus, Escherichia coli* and *Pseudomonas aeruginosa*. The ethanolic extracts of *Vitex negundo* (EEVN), *Fragaria vesca* (EEFV) and *Terminalia arjuna* (EETA) showed significant activity against *Staphylococcus aureus*. Ethanolic extract of *Citrus maxima* (EECM) and EEFV showed zones of inhibition for *Pseudomonas aeruginosa*. *Staphylococcus aureus* was maximally inhibited by EEVN. *Escherichia coli* were maximally inhibited by EEFV. Maximum zone of inhibition for *Pseudomonas aeruginosa* was shown by EECM. EEVN and EETA showed no antibacterial effect against *Pseudomonas aeruginosa*. EECM showed no antibacterial activity for *Staphylococcus aureus*. [6]

Penta Methoxy Flavone from leaves of *Vitex negundo* have exhibit satisfactory antioxidant ,antibacterial activity and anticancerous activity that may be use for the development of antioxidants and antibiotics for effective protection of free radicals and various bacterial causing diseases and for the inhibition of cancerous cells. [1] Evaluation of methanol leaf extract of *Vitex negundo* L. (Verbenaceae) for antibacterial activities was done using agar disc diffusion method. The methanol leaf extract showed growth inhibitory potency against all of the studied bacteria (*Bacillus subtilis, Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli* and *Salmonella typhi*). The minimum inhibitory concentrations ranged from

0.312 mg/ml to 1.25 mg/ml. The least MIC value was recorded against S. *aureus* and *P. aeruginosa*. [23] The antibacterial activity of the leaves of *Vitex negundo* was tested against three bacteria Viz., *Staphylococcus aureus Escherichia coli* and *Klebsiella Peumoniae*, The fresh aqueous, heated aqueous extract, chloroform and methanolic extract of leaves were used for screening their antibacterial potential. The fresh and aqueous extracts of leaves in various dilutions were found to have antibacterial activity against the three bacteria. [24] Antimicrobial properties of different parts of *Vitex negundo* were evaluated on bacterial strains viz, *Bacillus cereus* ATCC 11778, *Bacillus subtilis* ATCC 6633, *Staphylococcus epidermidis* ATCC 12228, *Enterobacter aerogenes* ATCC 13046, *Escherichia coli* ATCC 25922, *Klebsiella Pneumoniae* NCIM 2719, *Proteus vulgaris* NCTC 8313, *Pseudomonas aeruginosa* ATCC 27853, *Psuedomonas putida* ATCC 12842, *Salmonella typhimurium* ATCC 23564.

The most susceptible gram positive bacteria was Bacillus cereus, while the most susceptible gram negative bacteria were *Klebsiella pneumonia, Pseudomonas aeruginosa, Pseudomonas putida*. The extracts of root and bark have shown moderate antimicrobial activity when compared with flower and leaves. Among these bacteria *Proteus vulgaris* is resistant against all extracts of leaves and flowers. [25]

3. Antifungal activity:

In vitro antifungal activity of fruits of *Vitexs negundo* Linn., was examined against 5 common fungal strains, *Candida albicans, Candida glabrata, Aspergillus flavus, Microsporum canis* and *Fusarium solani*. Ethanol extract of fruit seeds showed significant activity against *Fusarium solani* and moderate response against Microsporum canis with no effect on *Candida albicans*. [26] Ethanolic extracts of the mature leaves of *Piper betle* L., leaves and roots of *Vitex negundo* L. and leaves of *Jasminum grandiflorum* Laterial were prepared and their anticandidal activity against standard cultures of *Candida albicans*, *Candida glabrata*, *Candida krusei*, *Candida parapsilosis* and *Candida tropicalis* was investigated by the agar well diffusion bioassay. Extracts which gave a zone of inhibition of 3 mm radius were reckoned to be significantly active. [27] The methanolic leafs extract of *Vitex negundo* and *Adhatoda vasica* were analyzed for anti-typhoid activity against *Salmonella typhi*. The leaves of both plants inhibited the growth of *Salmonella typhi*. The antibacterial activity of both leaf extracts were compared with gentamycin. The results show that leaf extracts of *Vitex negundo* and *Adhatoda vasica* confer anti-typhoid activity against Salmonella typhi. [28]

4. Miticidal activity:

One study was designed to determine the miticidal effect of methanolic extract from *Vitex negundo* Lam. at the rate of 10 and 20% concentrations through topical application on scabies affected skin of camel, buffalo, goat, dog and man. The ivermectin was used as reference compound and100% methyl alcohol as control group. The topical application of the treatment groups on scabies affected buffalos gave 43, 73 ,81 and 0%, on camels 46, 75, 84 and 0% on dogs 42, 77, 83 and 0%, on goats 42, 69, 81 and 0% and on man 61, 78, 84 and 0% protection, respectively, after 5th weeks of application. [29]

5. Anthelmintic 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*.[30]

6. Anti-HIV activity:

One study was aimed to determine the activity of ethanolic leaf extract of *Vitex negundo* L. against HIV-1 Reverse Transcriptase (RT) and to identify and quantify the flavonoids present. The effects of ethanolic (85%) leaf extract of *Vitex negundo* L. on RT activity in vitro were evaluated with recombinant HIV-1 enzyme, using a non-radioactive HIV-RT colorimetric ELISA kit. The plant *Vitex negundo* L. ethanolic leaf extract

exhibited the most notable activity of 92.8% against HIV-1 RT at 200 µg/ml concentration. [31]

7. Larvicidal activity:

Larvicidal activity of flavonoid extracts of different parts of *Vitex negundo* (Linnaeus) and *Andrographis paniculata* (Nees) have been studied against the late III or early IV instar larvae of Aedes aegypti and Anopheles stephensi (Liston). Flavonoid extract of whole aerial part of A. paniculata was found to be inactive against the selected larvae of Ae. aegypti even at the concentration of 600 ppm, whereas it caused 70% mortality in An. stephensi at the concentration of 200 ppm. Flavonoid extract of flower-buds produced highest mortality (100%) at the concentration of 600 ppm for the late III or early IV instar larvae of Ae. aegypti and at the concentration of 200 ppm for the larvae of An. stephensi. GC-MS analysis of the most active flavonoid extract from flower-buds of Vitex showed 81 peaks. Phenol (26.83% area), naphthalene (4.95% area), 2,3-dihydrobenzofuran (6.79% area), Phenol-2,4-Bis (1,1-dimethyl) (4.49% area), flavones 4'-OH,5-OH,7-di-O-glucoside (0.25% area) and 5-hydroxy-3,6,7,3',4'-pentamethoxy flavones (0.80% area) were present in major amount. [32]

8. Antifilarial activity:

Antifilarial effect of ethyl acetate extract of *Vitex negundo* (Verbenaceae) leaves was evaluated against Setaria cervi filarial parasite in vitro. In vitro screening was done by the method of motility inhibition and MTT reduction assay with concentrations of 0.03 to 1.00mg/mL for 2 to 24 hour incubation periods respectively. In motility assay, complete inhibition of motility was observed and in MTT reduction assay which gave >50% reduction for concentrations 0.20, 0.50 and 1.00mg/Ml at 10, 6, 2 hour incubation periods respectively in a dose dependant manner ($P<0.05$). [33] Antifilarial activity was assessed for Methanolic extract of *Vitex negundo* L. Leaves against Setaria cervi filarial parasite. Activity was assessed by the method of motility inhibition and MTT reduction assay with concentrations 0.3-0.006 mgmL-1 for 2 to 24 hrs incubation period respectively, by comparing with control. In motility assay, complete inhibition of motility was observed and in MTT reduction assay which gave >50% reduction for concentrations 0.06, 0.1and 0.3 mgmL-1 at 10, 6 and 2hrs incubation period respectively in a dose dependent manner ($p<0.05$). [34]

9. Anti-oxidant activity:

Antioxidant activity of *Vitex negundo* (VN) extract was studied using 1,1-diphenyl-2-picrylhydrazyl (DPPH) and Ferric reducing or antioxidant power (FRAP) assays. The antiproliferative activity of VN extract against WRL68 and HepG2 was investigated based on methylthiazol tetrazolium (MTT) spectrophotometric assay. VN extract showed 79.43% inhibition of DPPH stable radical with IC_{50} 13.31 ± 0.18 µg/ml. This inhibition was too closed to butylated hydroxyl toluene (BHT) 82.53% (IC_{50}13.8 ± 0.14) and gallic acid 89.51% (IC_{50} 3.1 ± 0.08). [35]

The antioxidant potential of six important Indian medicinal plants V. negundo, V. trifolia, T. bellerica, T. chebula, E. officinalis and A. racemosus were evaluated. Extracts of all the six medicinal plants exhibited antioxidant potential but T. bellerica , T. chebula, E. officinalis proved more active. The presence of antioxidant activity in the extracts showed that these plants have the potential to be an alternate source of natural antioxidants.[36] In another study antioxidant activity of the leaf extract of *Vitex negundo* was evaluated. Antioxidant activity was evaluated by DPPH method and the leaves of V. negundo showed 23.21 mg/100 of Ascorbic acid Equivalent Antioxidant Capacity (AEAC).[37] The methanolic extracts of Adhatoda vasica and *Vitex negundo* were analyzed for antioxidant and reducing power potentiality. Both plants showed strong antioxidant and reducing power ability. The strong antioxidant and reducing power ability of the plant underlines their use as antioxidant supplement against diseases such as typhoid during which antioxidant system fails; cardiovascular diseases which are caused due to accumulation of Reactive oxygen species; ageing related diseases, Alzheimer, Prkinson's disease, Amytrophic lateral sclerosis, cataractogenesis and other diseases. [38]

The methanolic leafs extract of *Vitex negundo* and *Adhatoda vasica* were analyzed for anti-typhoid activity against Salmonella typhi. The antioxidant activity was determined and compared with BHA

and reducing power was compared with Ascorbic acid. Both the samples had high antioxidant and reducing power activity. Several studies reported the loss of antioxidant system during infection of Salmonella typhi. The leaf extracts of *Adhatoda vasica* and *Vitex negundo* showed considerable antioxidant activity which can used as remedy against antioxidant system collapse and thus promises to be effective antioxidant supplement for typhoid patients. [28]

10. Antipyretic:

The antipyretic activity of leaf extracts of *Vitex negundo* linn Plant was evaluated by using yeast induced pyrexia model in Wistar Albino rats. The data obtained indicate that the Petroleum ether and Methanolic extracts of a leaves of plant *Vitex negundo* linn, at dose of 300 mg/kg body weight per oral route (P.O) showed the significant reduction in yeast provoked elevated temperature. The antipyretic effects of the extracts were compared with standard drug paracetamol. [39]

11. Antidiabetic activity:

Aqueous and ethanol leaf extract of *Vitex negundo* was studied for its antidiabetic activity using alloxan induced diabetic model in rats. The aqueous extract showed ($P<0.01$) significant activity than the ethanol extract at the tested dose level, which were comparable to glibenclamide, a standard antidiabetic drug.[5]

12. Anticancer activity:

Aqueous and organic extracts of the leaves of VN were used to identify its cytotoxic effect on six types of cancer-origin and normal cells, namely hormone-dependent breast cancer cell line (MCF-7), non-hormone-dependent breast cancer cell line (MDA-MB-231), ovarian cancer cell line (Caov-3), cervical cancer cell line (HeLa), liver cancer cell line (HepG2) and human foreskin fibroblast cell line (Hs27). The anti-proliferation activities of these extracts were investigated by employing colorimetric MTT (3-(4,5-dimethylthiazol-2-yl)2,5 diphenyltetrazolium bromide) assay through time periods of 24, 48 and 72 h. Preliminary results showed that the methanol extracts had significant effects ($p<0.05$) on MDA-MB-231 with IC_{50} values 65.38 μg/mL. [40]

13. Antiflatulant:

The different essential oils and extracts of *Vitex negundo* Linn was studied for its antiflatulent activity. The standard drug used was simethicone (10 mg/10 g of flatulent diet, p.o.), which inhibited gas production up to 90 % as compared to control. Addition of test drugs (essential oils/ethanolic extracts) to the chickpea diet (5 %) decreased the amount of gas production significantly up to 69% by root and leaves extracts while dry fruit oil inhibited gas formation to 81%. The antiflatulent activity in this plant may due to combined effect of flavonoids a nd triterpenoids constituents. [41]

14. Antiepileptic activity:

One study was to evaluate antiepileptic activity of methanolic extract of *Vitex negundo* leaf on maximal electroshock (MES), Pentylenetetrazole, Strychnine, Picrotoxin and lithiumpilocarpine induced convulsions in mice. The extract protected animals against MES induced convulsions and showed potentiating effect against different chemical induced convulsions against standard drugs. Methanolic extract of *Vitex negundo* may be interfering with inhibiting Na+ Channels and interfering with gabanergic mechanism is due to the presence of flavanoids attributed to their activity in a dose dependant manner. Screening results indicate methanolic extract of *Vitex negundo* may be showing possible efficacy potential in the treatment of epilepsy. [42]

15. Anti-inflammatory activity:

The anti-inflammatory activity of the leaf extract of *Vitex negundo* was investigated on topical administration using the TPA (tetradecanoylphorbol acetate)-induced mouse ear inflammation model. The crude methanolic extract of *V. negundo* showed moderate inhibition (74%) at a dose of 2 mg per year. [43] A novel compound Tris(2,4-di-tert-butylphenyl) phosphate (TDTBPP) was isolated from the leaves of *Vitex negundo* and the crystal structure was reported recently. The acute anti-inflammatory activity of TDTBPP was assessed by Carrageenan-induced rat paw odema method. TDTBPP reduced the raw paw odema volume significantly at the tested doses of 50 mg/kg and 70 mg/kg body weight. [44] Another study was undertaken to assess the anti-inflammatory effect of ethanolic extract of *Vitex negundo* roots in

rats. The anti-inflammatory action was studied by Plethysmometer method. It is observed that the ethanolic extract of *Vitex negundo* roots shows considerable anti-inflammatory effect by using carrageenan induced rat paw edema method. The higher dose groups of *Vitex negundo* root extract (400 mg/kg) were revealed more activity than their corresponding lower dose. [45] The *Vitex negundo* and Murraya Koenigii leaves were studied for anti-inflammatory activity.

All animals were divided into five groups, six rats in each group. Group I was treated as toxicant control to observe swelling, group II was treated with Aspirin (10 mg/kg, p.o), group III and IV were treated with hydroalcoholic extract of leaves of *Vitex negundo* and Murraya Koenigii at two doses (100 mg/kg, p.o.) respectively. The anti-inflammatory activity was studied by using carrageenan induced paw edema in rats. The study showed that hydroalcoholic leaves extract of *Vitex negundo* and Murraya Koenigii significantly reduce paw edema when compared with group I (Toxicant control) rats and the result were dose dependent. [46]

The extract of *Vitex negundo* at different concentrations was incubated with egg albumin and bovine albumin in controlled experimental conditions and subjected to determination of absorbance to assess the anti-inflammatory property. Diclofenac sodium was used as the reference drug. Findings exhibited a concentration dependent inhibition of protein (albumin) denaturation by the *Vitex negundo*. The effect of diclofenac sodium was found to be less when compared with the *Vitex negundo* (1000 µg/ml). [47] Another study was done to evaluate the effect of *Vitex negundo* L. in experimentally induced inflammatory bowel disease (IBD). The ethanolic extract of leaves of *Vitex negundo* L. showed significant amelioration of experimentally induced colitis, which may be attributed to its anti-inflammatory and antioxidant property. [48]

16. Wound Healing Activity:

An aqueous extract was examined for its wound healing activity in the form of ointment in experimental wound models in albino rats. The studies included parameters like epithelization period, wound contraction, tensile strength of incision wounds. The results of the wound healing study with respect to the incision and excision wound models in rats revealed statistically significant wound healing activity ($p<0.05$) when compared to control and standard, which was evidenced by faster epithelization, increase in the tensile strength and hydroxyproline content. [49]

17. DPPH scavenging activity:

One study was done to assess the total phenolic compounds (TPC) and 1, 1-diphenyl-2-picrylhydrazyl (DPPH) scavenging activity in the flowers and leaves of *Clitoria ternatea* and *Vitex negundo* Linn. by using methanol and water extraction. leaves for both plants showed higher amount of TPC compared to the flowers. Methanol extracted *Vitex negundo* Linn. showed higher DPPH scavenging activity compared with *Clitoria ternatea*. In contrast, DPPH scavenging activity for water extracted *Clitoria ternatea* showed higher value in compare with water extracted *Vitex negundo* Linn. [50]

18. Improvement in learning and memory:

One study was done to demonstrate the improvement in learning and memory by hydroalcoholic extract of *Vitex negundo* Linn. leaves (HEVN). Effects of HEVN were evaluated in normal as well as in scopolamine- induced cognitive deficit mice paradigms using elevated plus maze (EPM) and object recognition test (ORT). Administration of HEVN (250 and 500 mg/kg/day, p.o.) for 8 days significantly increased inflexion ratio in EPM, discrimination index in ORT, and decreased brain Acetyl-cholinesterase level (AchE) in both paradigms and prolonged the onset of time of death in sodium nitrite induced respiratory arrest in mice. [51]

19. Gastroprotective Role:

The gastroprotective activity of aqueous extract of *Vitex negundo* (L) against the gastric mucosal damage induced by aspirin was studied in albino rats. Aspirin was administered intraperitoneally at a dose of 80mg/kg body weight to induce ulcer and the resultant elevated levels of lipid peroxide was taken as an index of oxidative stress. The gastroprotective effect of *V. negundo* (L) was observed at an oral dose of 200mg/kg body weight administered for 18 days before ulcer induction.[52]

20. Hepatoprotective activity:

Liver cells (HuH-7) were treated with CCl4, and the mechanism of the cytoprotective effect of negundoside (NG) was assessed. Silymarin, a known hepatoprotective drug, was used as control. NG protected HuH-7 cells against CCl4 toxicity and loss of viability without modulating CYP2E1 activity. Prevention of CCl_4 toxicity was associated with a reduction in oxidative damage as reflected by decreased generation of reactive oxygen species (ROS), a decrease in lipid peroxidation and accumulation of intracellular Ca^{2+} levels and maintenance of intracellular glutathione homeostasis.[53]

21. Cytotoxic Activies:

The hydroalcoholic extracts from the aerial parts of *Vitex negundo* was studied for its cytotoxic activity against Dalton's ascites lymphoma (DAL) and Ehrlich ascites carcinoma (EAC) cell lines. Results was carried out by trypan blue dye exclusion technique on cell counting in vitro cytotoxicity activity of Dalton's ascites lymphoma cell line 200 µg/ml. The higher cytotoxic activity was found in hydroalcoholic extract of *Vitex negundo*.[54]

22. Insect growth regulatory activity:

The methanolic leaf extracts of *Acalypha alnifolia* and *Vitex negundo* were studied for IGRs activity against *Aedes aegypti*. Effect of A. alnifolia showed (L1 to L4) prolonged larval duration and up to 8 days at 500 ppm. Whereas, in control complete larval development was completed in 4 days. Similarly, methonolic extract of V. negundo was prolonged larval (L1 to L4) duration up to 3 to 5 days at 500 ppm concentration than the control.[55.]

CONCLUSION: This review highlights the medicinal potential of *Vitex negundo* in specific female problems as well as other problems as mentioned in Unani classical texts. Studies reported justify the Unani traditional claims but there is lacking of studies to confirm its role in specific female problems. Future research should focus on its efficacy in female problems and the mechanisms by which *Vitex negundo* medically effected and understand its mechanism of bioactivity and diagnosing the active components that have medicinal effectiveness.

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