The genus *Vitex*: A review

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ABSTRACT

The review includes 161 references on the genus *Vitex*, and comprises ethnopharmacology, morphology and microscopy, phytoconstituents, pharmacological reports, clinical studies, and toxicology of the prominent species of *Vitex*. Essential oils, flavonoids, iridoid glycosides, diterpenoides and ligans constitute major classes of phytoconstituents of the genus. A few species of this genus have medicinal value, among these, leaves and fruits of *V. agnus-castus* Linn. (*Verbenaceae*) has been traditionally used in treatment of women complaints. *V. agnus-castus* has also been included in herbal remedies, which are in clinical use to regulate the menstrual cycle, reduce premenstrual symptom tension and anxiety, treat some menopausal symptoms as well as to treat hormonally induced acne. Despite a long tradition of use of some species, the genus has not been explored properly. In the concluding part, the future scope of *Vitex* species has been emphasized with a view to establish their multifarious biological activities and mode of action.

Key words: Diterpenoides, essential oils, flavonoids, iridoid glycosides, *vitex agnus-castus*

INTRODUCTION

This review emphasizes the traditional uses and clinical potential of *Vitex* species. Through this review, authors intend to highlight the unexplored potential of the *Vitex* species. This genus needs to be investigated systematically so that potential species can be exploited as therapeutic agents.

The available information on *Vitex* has been divided into six sections, i.e., ethnopharmacology, morphology and microscopy, phytoconstituents, pharmacological reports, clinical studies and toxicology. The ethnopharmacological section has been further subdivided into two sections: Traditional uses and alternative and complementary medicinal uses. The reports in which *Vitex* species have been used as a folk medicine for the treatment of various ailments have been discussed under traditional uses. The subhead "Alternative and complementary medicinal uses" highlights *Vitex* species as medicine prescribed by medical practitioners for the treatment of various disorders. It also mentions uses for which *Vitex* species or their preparations that are available in the market. Under every section, *Vitex* species have been arranged in alphabetical order.

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The genus *vitex*

Vitex is the largest genus in the family *Verbenaceae* which comprises 250 species distributed all over the world.[1] The *Vitex* species are deciduous shrubs. The species used in medicine are *V. agnus-castus* Linn. and *V. negundo* Linn. *V. agnus-castus* (chaste tree) is widespread on riverbanks and on shores in the Mediterranean region, Southern Europe and in Central Asia.[2] *V. negundo* chiefly occurs in Pakistan, India, and Sri Lanka.[3] *V. rotundifolia* Linn. is distributed in the Mediterranean region, Central Asia, and along the seacoast from South to North of China.[4] *V. trifolia* occurs in Asian countries and in Vietnam.[5]

Traditional uses

Fruits of *V. agnus-castus* have been used in the treatment of many female conditions, including menstrual disorders (amenorrhoea, dysmenorrhoea), premenstrual dysphoric disorder (PMDD), corpus luteum insufficiency, hyperprolactinaemia, infertility, acne, menopause, disrupted lactation, cyclic breast pain, cyclical mastalgia and inflammatory conditions, diarrhea and flatulence.[2,6-9] Also, in Iranian traditional medicine its leaves and fruits are used for increasing milk.[10]

Leaves of *V. negundo* are considered as tonic, vermifuge and are given along with long pepper in caterrhal fever.[3,11-16]

The fruits of *V. rotundifolia* have been used as a folk medicine for the treatment of headache, cold, migraine, eye pain, female hormonal disorders, asthma, chronic bronchitis, and gastrointestinal infections such as bacterial dysentery and diarrhea.[4,17-19]

V. trifolia has been used as an anti-inflammatory and sedative for headache, rheumatism and for common cold and as anti-trypanosomal in Asian countries.[5,20] The plant is a Chinese folk medicine for the treatment of cancers.[21,22]

Alternative and complementary medicinal uses

V. agnus-castus has been included in a number of herbal preparations, which are in clinical use. Clinical studies demonstrated that extract of *V. agnus-castus* dried fruits are beneficial in the treatment of premenstrual syndrome, abnormal menstrual cycle, amenorrhea, mastodynia, and hyperprolactinemia, which are all due to increased level of prolactin.[7] *V. agnus-castus* is prepared either as a fluid extracts or a dried extract in pill form. Clinical trials have used a variety of doses.[7-9] Fluid extract: 1-2.5 ml of extract daily. Dried fruit: 1.5-3 mg daily as decoction. Dried extracts in pill or capsule form: 2-500 mg twice daily.[23] The German Commission E monograph recommends a daily intake 30-40 mg of the dried herb in capsules or in liquid preparations. *V. agnus-castus* is typically taken once in the morning with liquid for several months consecutively. For premenstrual syndrome, frequent or heavy periods, the plant can be used continuously for 4-6 months. Infertile women with amenorrhea can remain on *V. agnus-castus* for 12-18 months unless pregnancy occurs during treatment.[24]

Morphology

V. agnus-castus, commonly known as chaste tree or sage tree, is a beautiful little deciduous tree or large shrub with a showy summertime flower display. *V. agnus-castus* is a sprawling plant that grows 3-6 m and about as wide. The leaves are 7.6-10 cm in diameter and are palmately compound with 5-7 fingerlike leaflets. The foliage is aromatic and is typically grey-green to dark green above and lighter on the undersides. Branched flower clusters are produced on new wood in late spring and early summer and bloom sporadically until early fall. It is also fragrant and attracts pollinating bees and hummingbirds. Flowers are followed by a fleshy fruit that contains four seeds that are sometimes used as seasoning, similar to black pepper (monk's pepper is another of these species common names). Flower color ranges from violet to blue to deep purple.[25]

V. negundo are large and erect aromatic shrubs, which grow to a height of 2-5 m. The leaves have five leaflets in a palmately arrangement, an acute terminal leaflets (16-32 mm) with petiolate having 1-1.3 cm long, lanceolate, 4-10 cm long, hairy beneath and pointed at both ends. The bluish purple flowers are numerous. The fruit is succulent, black when ripe, rounded and about 4 mm in diameter.[15]

V. rotundifolia is a sprawling shrub 6-8 feet in diameter and 6 inches to 2 feet tall. The round leaves are gray-green to silvery and 1-2 inches long. The foliage has a spicy fragrance. The 1 inch flowers are bluish purple and are produced in small clusters at the ends of the branches throughout the year.[26]

V. trifolia is a fast-growing shrub, is popular for its variegated foliage and pretty blue flowers and grows to a height of 10-12 feet. The trifoliate evergreen leaves are gray-green with white marginal variegation. These soft leaves have grayish pubescence on their underside and smell pungent when crushed. Attractive blue or lavender flowers with white spots appear in terminal clusters during the summertime.[27]

Pharmacological reports

The available literature reveals that among 36 species of *Vitex*, only 16 species, i.e., *V. agnus-castus*, *V. negundo*, *V. rotundifolia*, *V. trifolia*, *V. gardneriana*, *V. ferrugenia*, *V. cannabifolia*, *V. doniana*, *V. polygama*, *V. leucoxylon*, *V. pinnata*, *V. scabra*, *V. mollis*, *V. altissima*, *V. glabrata*, *V. megapotamica*, *V quinata* have been evaluated for their pharmacological activities. This study gave us a clue that bicyclic terpenes isolated from *V. agnus-castus* fruits are used for the treatment of movement disorders.[28] Flavonoids and diterpenoids, isolated from ethyl acetate extract of *V. agnus-castus* fruits, have been reported to exhibit antioxidant activity and n-hexane extract did not show any effect.[29] Essential oils, isolated from *V. agnus-castus*, showed a significant antibacterial activity.[30] Caffeic and chlorogenic acids, extracted from leaves and fruits of *V. agnus-castus*, exhibited potent antioxidant activity.[31] Ethanolic extracts of *V. agnus-castus* fruits, exhibited estrogenic activity at two dose levels 0.6 and 1.2 g/kg per body wt. (b.w.) when studied by the vaginal smear and uterine weight methods for normal and ovariectomized female rats.[32] Cell culture experiments showed that flavonoid apigenin, isolated from *V. agnus-castus* exhibited estrogenic acivity.[33]

The chloroform extracts of *V. negundo* (40 mg/kg/body wt. and 135 mg/kg), exhibited broad cytotoxicity in a human cancer cell line panel.[34] Two pentacyclic triterpenoids, isolated from *V. negundo* leaves have been reported to exhibit antifeedant activity against the larvae of an agricultural pest, the castor semilooper (*Achoea janata*), and also possess antibacterial activity against *Bacillus subtilis* and *Escherichia coli*, when tested by the paper disk method.[35-36] It has been reported that flavone glycoside, isolated from ethanolic extract of *V. negundo* leaves, exhibits significant antifungal activity against *Trichophyton mentagrophytes* and *Cryptococcus neoformans* at Minimum inhibitory concentration MIC 6.25 μg/mL.[37] Lignans, isolated from *V. negundo* exhibited potent inhibitory activity against lipoxygenase enzyme, while moderate activity against butyryl-cholinesterase.[3] This study showed that lignans isolated from *V. negundo* roots, were found to be active against α-chymotrypsin (Ki values 31.75-47.11 μM).[38] Tris (2,4-di-tert-butylphenyl)

phosphate (TDTBPP) was isolated from the leaves of *V. negundo* and the acute anti-inflammatory activity of TDTBPP was assessed by carrageenan-induced rat paw odema. TDTBPP reduced the raw paw odema volume significantly at the tested doses of 50 mg/kg and 70 mg/kg body weight.[39] Cataract was induced by single subcutaneous injection of sodium selenite (4 mg/kg body weight) and methanolic extract of leaves of *V. negundo* (1 mg/Kg bodyweight) was administered i.p., (intraperitoneal) It showed modulated selenite induced cataractogensis in rat pups by preventing loss of chaperone property.[40] The anti-hyperglycemic effect of iridoid glucoside from the leaves of *V. negundo* (50 mg/kg b.w) was comparable with glibenclamide. It also possesses the significant productive effect on glycoprotein metabolism in addition to its antidiabetic effect.[41]

It has been reported that methanol extract of *V. rotundifolia* fruits, exhibits antioxidative activity with the references to α-tocopherol and Butylated hydroxyanisole BHA using ferric thiocyanate method.[18] Diterpenoid (ferruginol), isolated from the fruit of *V. rotundifolia* also exhibited a stronger antioxidative activity.[42] Casticin, a flavonoid isolated from fruits of *V. rotundifolia* exhibited considerable growth inhibitory activity against human lung cancer cells (PC-12) and human colon cancer cells (HCT116) using the 3-(4,5-dimethythiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) MTT assay.[43] These results suggested that rotundifuran isolated from the fruit of *V. rotundifolia*, may be used as a potential chemopreventive and chemotherapeutic agent.[44] Polymethoxyflavonoids, isolated from the fruit of *V. rotundifolia*, exhibited antiproliferative activity in human myeloid leukemia HL-60 cells.[45] *V. rotundifolia* fruit extract inhibits cholesterol acyltransferase, thus can be used in prevention and treatment of cardiovascular disease caused by hypercholesterolemia.[46] It has been reported that Casticin exhibits antimitotic activity on the growth of KB cells at 0.23 μM.[47] Polyphenol, trans-resveratrol isolated from *V. rotundifolia* exhibited highly potent tyrosinase inhibition effect, thus inferring its importance in cosmetic industries as anti aging and skin-whitening agent.[48] The results showed that essential oil isolated from the fruits of *V. rotundifolia* exhibits estrogenic activity on proliferation of MCF-7 cells by proliferation assay method.[4]

V. trifolia exhibited anticancer activity on the proliferation of mammalian cancer cells, evaluated by sulforhodamine B, which is widely used in Chinese folk medicine.[21,49] The fruit extracts of *V. trifolia* exhibited antipyretic, analgesic, and anti-inflammatory activity.[50] Flavonoids, isolated from methanolic extract of *V. trifolia* exhibited bacteriostasis activity.[51] Vitetrifoline E, isolated from *V. trifolia* leaves has been reported to exhibit tracheospasmolytic activity by blocking spontaneous contraction of male guinea pig trachea induced by histamine at the doses 1.3×10^{-5} M.[52] *V. trifolia* exhibited antimalarial activity in the range of $10\text{-}100 \times 10^{-6}$ g/mL against *Plasmodium falciparum* (K1, multidrug resistant strain) *in vitro*.[53] Aqueous and ethanolic extracts of leaves of *V. trifolia* were investigated for hepatoprotective activity against carbon tetrachloride (CCl_4) induced liver damage. Results showed significant reduction in total bilirubin and serum marker enzymes, increase in total protein at dose level of 20 and 30 mg/kg/day p.o. Silymarin was used as standard at a dose of 100 mg/kg/day p.o. (oral route).[54]

A study reported that extracts of *V. leucoxylon* exhibited hypoglycemic, anti-inflammatory, and antipyretic activity.[55-56]

Iridoid glucosides, isolated from the ethyl acetate extracts of *V. altissima* leaves showed potent antioxidant activity by both the superoxide nitro blue tetrazolium (NBT) riboflavin photoreduction, free-radical-scavenging and 2,2-diphenyl-1-picryl-hydrazyl (DPPH) radical scavenging methods.[57] Ethyl acetate extract of *V. altissima* leaves exhibited significant anti-inflammatory activity in rat paw edema model.[58]

Pinnatoside iridoid glucoside, isolated from of *V. pinnata* bark, exhibited modest antifungal activity against *Candida albicans*.[59]

Hydroalcoholic extracts of *V. polygama* leaves showed potent anti-inflammatory, antinociceptive and antioxidant activity. It is also used in folk medicine to prevent kidney stone and inflammation.[60]

The oils from glandular trichomes of *V. ferruginea* exhibited significant antifungal activity against dermatophyte strains with MIC between 0.16 and 0.64 μL/mL.[61]

Organic extracts of *V. mollis* leaves showed insecticidal and insect growth regulatory activity on fall armyworm neonate larvae (*Spodoptera frugiperda*), an important insect pest of corn.[62]

A study suggested that aqueous extract of *V. doniana* fruit exhibits antidiarrheal activity at doses of 150-650 mg/kg.[63] The ethanol and distilled water extracts of *V. doniana* showed DPPH scavenging activity in CCl_4 treated albino rats. Vitamin C was used as the standard antioxidant. The water extracts produced a significant decrease ($P < 0.05$) in liver malondialdehyde, while the levels of superoxide dismutase and catalase (CAT) significantly increased ($P < 0.05$) relative to the positive control.[64]

Ecdysteroids, isolated from *V. scabra* stem bark exhibited very low moulting activity in the Musca bioassay.[65]

It has been reported that ethyl acetate as well as n-butanol extracts of *V. megapotamica* leaves showed the hypoglycemic effect in diabetic rats, but ethyl acetate fraction produced the maximum hypoglycemic effects at the doses of 400 and

Table 1: Phytoconstituents of various species of *vitex*

Species	Phytoconstituents
V. agnus castus Linn.	Essential oil constituents[30,76] 1,8-cineole, β-phellandrene, α-terpinyl acetate, trans-β-farnesene, β-caryophyllene and bicyclogermacrene; iridoid glycosides[77] 6'-O-foliamenthoyl mussaenosidic acid [agnucastoside A],[1] 6'-O-[6,7-dihydrofoliamenthoyl] mussaenosidic acid [agnucastoside B] 7-O-trans-p-coumaroyl-6'-O-trans-caffeoyl-8-epiloganic acid [agnucastoside C], aucubin, agnuside, mussaenosidic acid, 6'-O-p-hydroxybenzoylmussaenosidic acid] and myzodendrone; flavonoids luteolin 6-C-[4"-methyl-6"-O-trans-caffeoylglucoside], luteolin 6-C-[6"-O-trans-caffeoylglucoside], luteolin 6-C-[2"-O-methoxyflavone; diterpenes[2,78-79] 6β,7β-diacetoxy-13-hydroxylabda-8,14-diene,[2] rotundifuran, vitexilactone, halimane-type viteagnusins A-B, labdane-typeviteagnusins C-E, vitexlactam A;[3] essential fatty acids;[80] tannins; alkaloid[15]
V. negundo Linn.	Essential oils[81-86] δ-elemene, β-eudesmol, carene, β-caryophyllene, caryophyllene oxide, 1-oceten-3-ol, α-pinene, terpinyl acetate, 4-terpineol, γ-terpinene, bicyclogermacrene, viridiflorol and β-eudesmol; iridoid glycosides[15] 6'-p-hydroxybenzoyl mussaenosidic acid with derivatives 2-p-hydroxylbenzylmussaenosidic acid,[4] 6-p-hydroxybenzoylmussaenosidicacid,[5] p-hydroxybenzoyl ester of mussaenosidicacid,[6] p-hydroxybenzoylmethyl ester of mussaenosidic acid,[7] agnuside,[8] lagundinin and nedundoside;[9] flavonoids[34,37,87] casticin, chryso-splenol, vitexin, vitexicarpin,[10] 5,3'-dihydroxy-3,6,7,4'-tetramethoxyllavone, hydroxy-3,6,7,3',4'-pentamethoxy flavones, 5 hydroxy-7,4'-dimethoxy flavone,[11] 5-hydroxy-3,6,7,3',4'-pentamethoxy flavones,[12] 5,7-dihydroxy-6,4'-dimethoxyflavanone,[13] 5,3'-dihydroxy-7,8,4'-trimethoxyflavanone,[14] 7,8-dimethyl herbacetin 3-rhamnoside,[15] Vitexoside, sakuranetin 4'-O[6''-O-α-l-rhamnopyranosyl]-β-d-glucopyranoside,[16] 3-[3-methoxy-4-hydroxyphenyl] Prhexatetracontanoate,[17] agnoside, 5-hydroxy-1,3-benzenodicarboxylic acid and R-dalbergiphenol; ligans[15,88-89] vitedoin A,[18] vitedoamine A,[19] vitedoin B,[20] 6-hydroxy-4-[4-hydroxy-3-methoxy-phenyl]-3-hydroxymethyl-7-methoxy-3,4-dihydro-2napthaldehyde;[21] triterpenoids[15,35] betulinicacid[22] and ursolic acid;[23] alkaloid[15,90] vitrafalal;[24] diterpene[31] vitedoin
V. gardneriana Schauer	Flavonoids; terpenoids/steroids; saponins; reducing sugars; phenylpropanoglycosides, iridoid glycoside aucubine;[91] ecdysteroid[92] 20-hydroxy-ecdysone
V. altissima Linn.	Tetrahydrofuranoid lignin[57,58] altissinone,[25] flavone C-glucoside, 2''-O-p-hydroxybenzoylorientin;[26] iridoid glucosides[57] 6'-O-trans-feruloylnegundoside, 6'-O-trans-caffeoylnegundoside, 2'-O-p-hydroxybenzoyl-6'-O-trans-caffeoylgardoside, 2'-O-p-hydroxybenzoyl-6'-O-trans-caffeoyl-8-epiloganic acid, 2'-O-p-hydroxybenzoyl gardoside, 2'-O-p-hydroxybenzoyl-8-epiloganic acid, agnuside and negundoside
V. scabra	Ecdysteroids[65] 24-epi-pinnatasterone,[27] scabrasterone, calonysterone, pterosterone, 24-epi-makisterone A, polypodine B, 20-hydroxyecdysone, ajugasterone C, pinnatasterone, turkesterone 11α-hydroxyecdysone, 20,26-dihydroxyecdysone and 24-epi-abutasterone
Vitex cymosa	Iridoid[93] tarumal,[28] viteoid and agnuside
Vitex leptobotrys	Chalcones 2',4'-dihydroxy-4,6'-dimethoxychalcone, 4'-hydroxy-4,2',6'-trimethoxychalcone, 2',4,4', β-tetrahydroxy-6'-methoxy-α,β-dihydrochalcone; alkaloid[94] N-trans-feruloyltyramine; ecdysteroid ecdysterone, 24[28]-dehydromakisterone A, makisterone A, 24-epi-makisterone A, ajugasterone C, deoxycrustecdysterone and pinnatasterone
V. canescens	Ecdysteroids[95] [24R]-11α,20,24-trihydroxyecdysone [29; R1 = β-OH, R2=Me], 11α,20,26-trihydroxyecdysone [30; R1=H; R2=CH2OH], 24-epi-abutasterone, 20-hydroxyecdysone, 24-epi-makisterone A, shidasterone, calonysterone, and turkesteron
Vitex pinnata	Iridoid glucoside[59] pinnatoside, viscioside, apigenin, and luteolin
V. cannabifolia	Lignans vitecannasides A and B; iridoid glucosides; flavonoids; phenylbutanone Glucoside[96]
V. lucens	Flavonoid vitexin and saponaretin; glycoflavonoid vitexin, isovitexin, orientin, iso-orientin, vicenins and lucenins
V. limonifolia	Iridoids limoniside [agnuside 4''-O-Me ether] and agnuside
V. trifolia Linn.	Benzofuran-type lignan[97] vitrifol A; alkaloid vitricin; glucoside agnuside; diterpenes halimane-type[23] vitetrifolins D-G; abietane-type[98] vitetrifolin A,[31] labdane-type[98] vitetrifolins B and C, norditerpenoids[5,99] aldehydes[32] vitexifolin E, vitexifolin F, vitexilactone, 6-acetoxy-9-hydroxy-13[14]-labden-16,15-olide and previtexilactone; essential oils;[42] flavonoid[51] casticin, 3',5-dihydroxy-3,4',7-trimethoxyflavone, 4',5-dihydroxy-3,6,7-trimethoxy flavone, vitexinand kaemferol-3-O-β-d-glucopyranoside
V. rotundifolia Linn.	Lignans[100] vitrofolal D,[33] arylnaphthalene norlignansvitrofolals A, vitrofolals B-C;[34] diterpenes[20,21,43] labdane-type viteoside A, vitexifolin A[36] vitexilactone, abietane-type abieta-9,[11] 12-diene[35] and abietane 9[11]:12[13]-di-α-epoxide, clerodane-type vitexifolin B, abeoabietane-type vitexifolin C, norlabdane-typevitexifolin D and vitexifolin E, halimane-type vitetrifolin D, norlabdane-type trisnor-γ-lactone and iso-ambreinolide; phenolic compoundsthreo-guaiacyl glycerol, erythro-guaiacyl glycerol, taxifolin, ddiconiferyl alc., dihydrodehydrodiconiferyl alc.-9-O-β-d-ihydrodehydroglucoside and dihydrodehydrodiconiferyl alc.-[4→8]-erythro-guaiacylglycerol ether; iridoids viteoids, eucommiol, iridolactone, pedicularis-lactone, agnuside, VR-I and 1-oxo-eucommiol; flavonoids[43] casticin, artemetin, 5,3'-dihydroxy-6,7,4'-trimethoxyflavanone, vitexicarpin; essential oils[101]
V. peduncularis	Iridoid[13] peduncullariside, aguside; flavones[102] vitexin
V. diversifolia Bak.	Essential oils[103]
V. quinata	β-Sitosterol, vitexin, 20-hydroxyecdysone 20,22-monoacetonide, 3,5-O-dicaffeoyl quinic acid and daucosterol[104]

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Table 1: Contd...

Species	Phytoconstituents
V. doniana Sweet	Phytin, phytin-phosphorus and tannin[105]
V. glabrata R.Br.	Ecdysteroid 20-hydroxyecdysone[106]
V. pooara, V. rehmanii, V. obavata and *V. zeyheri*	Essential oils,[107] labdane diterpene[108]

800 mg/kg.[66]

Ethanol extracts of *V. glabrata* (EEVG) was evaluated for the anti-inflammatory activity using carrageenan-induced paw edema and cotton pellet induced granuloma formation in rat models. EEVG showed significant anti-inflammatory activity in rats at a dose of 400 mg/kg, p.o. and was comparable ($P < 0.05$) to that of diclofenac sodium (standard, 50 mg/kg, p.o.).[67] EEVG was also evaluated for the antioxidant and hepatoprotective effects in a CCl_4-induced liver damage model in rats. Hepatoprotective activity was evaluated by changes in the levels of the serum enzymes, i.e., AST, ALT, ALP and total bilirubin, and further by histopathological examinations of liver tissues. Antioxidant activity was measured in terms of superoxide dismutase, glutathione, lipid peroxidation, CAT and peroxidase levels in liver homogenate.[68]

A phytochemical investigation of the leaves of *V. quinata* (Lour.) guided by the MCF-7 human breast cancer cell line, led to the isolation of a new δ-truxinate derivative[1] and a new phytonoic acid derivative,[2] together with 12 known compounds. The structures of the new compounds were determined by spectroscopic methods as dimethyl 3,4,3',4'-tetrahydroxy-δ-truxinate[1] and methyl 10R-methoxy-12-oxo-9-16E-phytodienoate,[2] respectively. In a cytotoxicity assay, S-5-hydroxy-7,4'-dimethoxyflavanone[3] was found to be the sole active principle, with ED_{50} values of 1.1-6.7 μM, respectively, when tested against a panel of three human cancer cells. Methyl-3,4,5-O-tricaffeoyl quinate[4] showed activity in an enzyme-based Enzyme-linked immunosorbent assay (ELISA) NF-κB p65 assay, with an ED (50) value of 10.3 μM.[69]

Clinical studies

In clinical trials, serotonin reuptake inhibitors, i.e. fluoxetine and the extract of *V. agnus-castus* were studied for the treatment of PMDD. In this study *V. agnus-castus* extract showed that fluoxetine was more effective for psychological symptoms while the extract diminishes the physical symptoms of premenstrual disorders.[70] Dopaminergic compounds present in extract of *V. agnus castus* fruits are widely used to treat premenstrual mastodynia (mastalgia) indicated by double-blind placebo-controlled studies.[71] This study suggested that at low doses *V. agnus-castus* increases milk production in lactating women and also used to modify libido.[72] Water extract of *V. negundo* in combination with matra basti as 500 mg tablets showed relief from signs and symptoms of sciatica [pain, weakness, numbness, and other discomforts along the path of the sciatic nerve often accompany low back pain, herniated disk, spinal stenosis, piriformis syndrome in clinical studies on 119 patients in the age group of 20-60 years.[73]

Toxicology

Adverse effects of *V. agnus-castus* were found to be mild and reversible.[26] The most frequent ones include: Nausea, mild gastrointestinal complaints, fatigue, menstrual disorders, dry mouth, acne, pruritus, and erythematous rash. In the case of lactation, theoretical and expert opinion conflict as to whether chaste tree increases or decreases lactation.[9,23,72,73]

Leaf extracts of *V. negundo* showed no histomorphological changes in the stomach of rats at any of the doses but causes gastric damage known to act by prostaglandin inhibition.[12,74]

The water extracts of *V. grandifolia* was administered at a dose of 0.5-2 g/kg body weight (b. wt.) in rats. It caused a significant increase in the serum electrolytes, creatinine, and liver function enzymes dose dependently compared with the control ($P \leq 0.001$). The architecture of liver, kidney and lungs was significantly altered in the treated groups compared with the control. Major clinical signs observed in the treated groups were polydipsia, polyuria, puffiness of hair and calmness, which were consistent with an increase in the dose of the extract. It shows that prolonged administration of the aqueous leaf extracts of *V. grandifolia* at the dose used in this study tends to be toxic to the rats. Its use in folkloric medicine should be with utmost care.[75]

CONCLUSION

About 250 species of the genus *Vitex* have reported in various floras. An exhaustive survey of literature revealed that sporadic information is available on 36 species. Among these eight species, most of ethnopharmacological reports are available on *V. agnus-castus* and *V. negundo*. Futher, only 24 species of *Vitex* [Table 1] have been investigated for their phytoconstituents.

A close scrutiny of literature on *Vitex* reveals that 16 species have been investigated pharmacologically. Pharmacological studies infer that *V. agnus-castus* exhibits antibacterial activity, for the treatment of movement disorders and also posses antioxidant activity; *V. negundo* shows antibacterial activity, antifeedant activity, potent inhibitory activity against lipoxygenase enzyme and potent antioxidative activity; *V.*

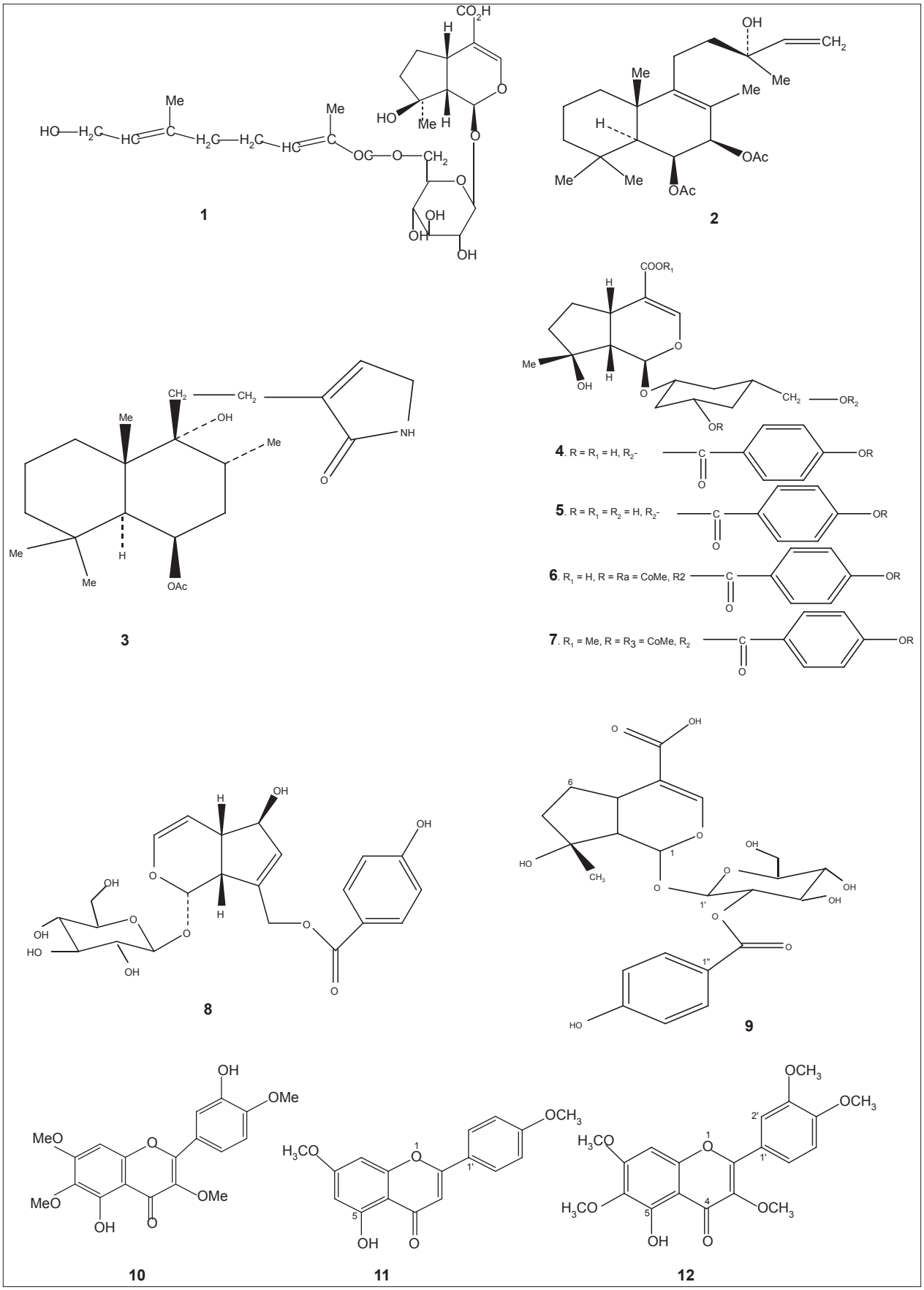

Figure 1: Structures of various phytoconstituents of *Vitex* species

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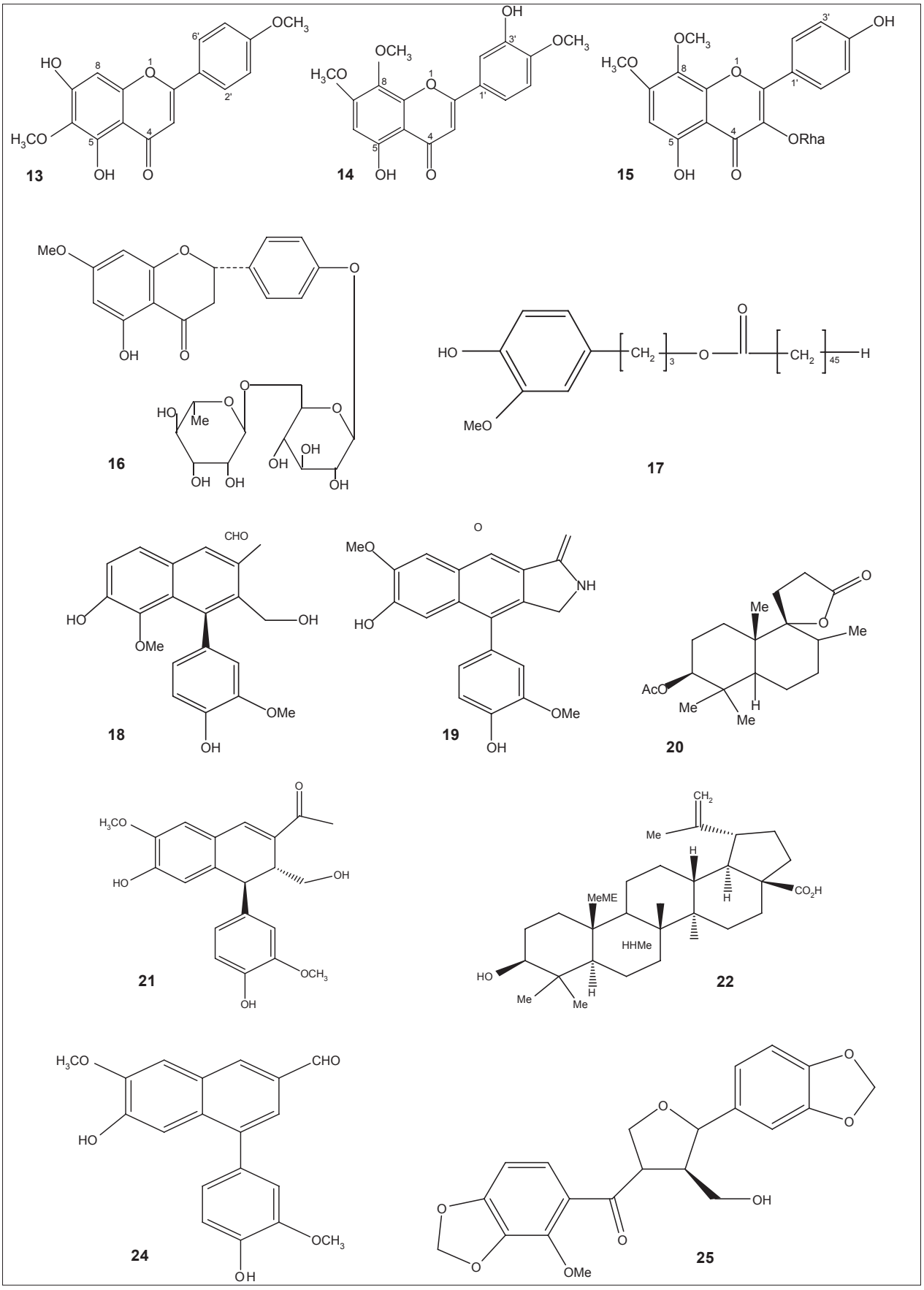

Figure 1: Structures of various phytoconstituents of *Vitex* species

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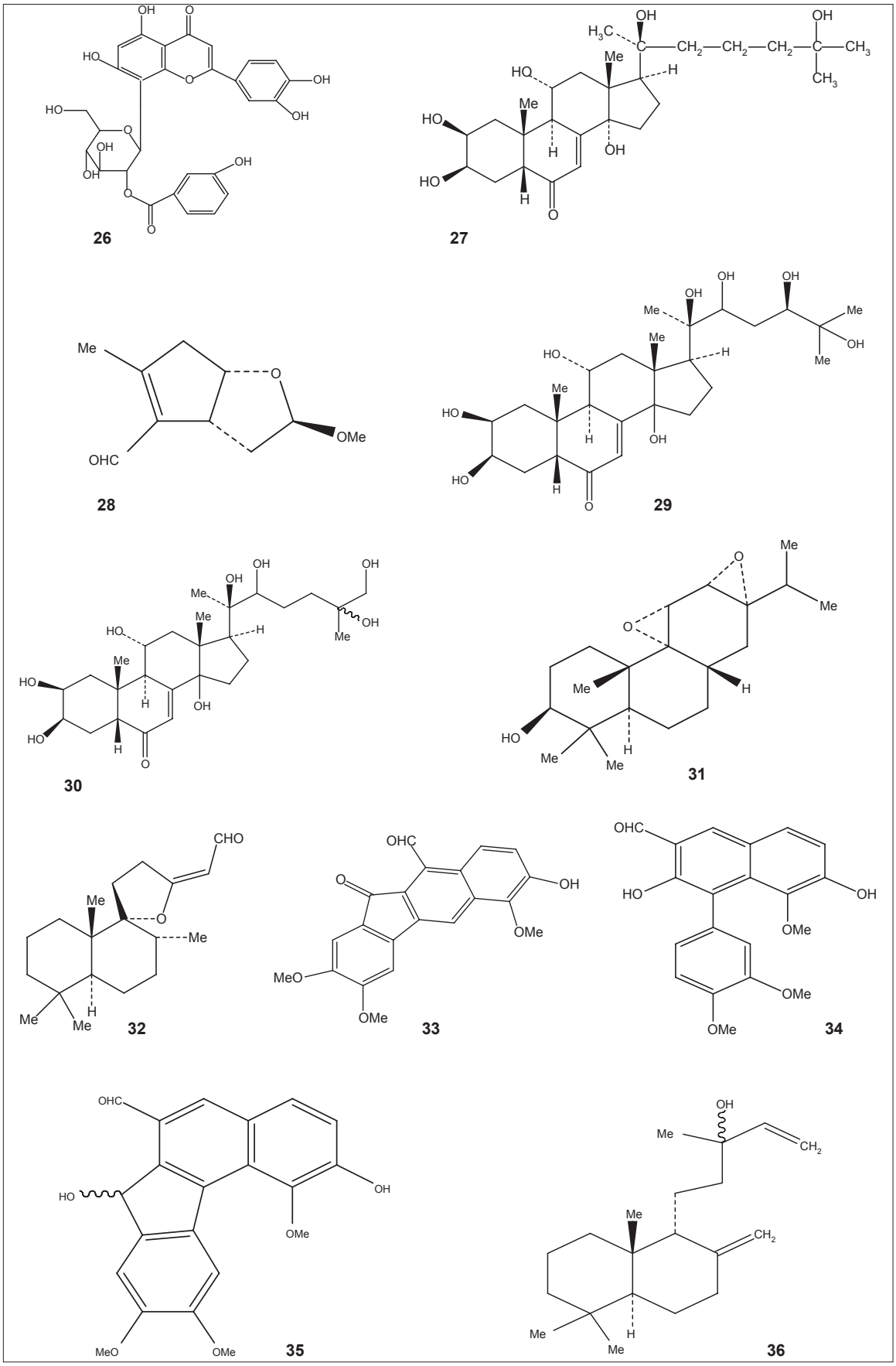

Figure 1: Structures of various phytoconstituents of *Vitex* species

rotundifolia possessed potent repelling activity, stronger antioxidative activity, antiproliferative activity, potential chemopreventive agents, antiaging and skin-whitening effects; *V. trifolia* exhibits antipyretic, analgesic, anti-inflammatory functions, bacteriostasis and antimalarial activity.

V. agnus-castus has been included in a number of herbal formulation, which is in clinical use for the treatment of various ailments. Tinctures of the plant are also available in Indian market and are frequently used for the treatment of premenstrual syndrome disorder, but no pharmacological work supports its efficacy in Central Nervous System (CNS) disorders. Keeping in view the traditional, alternative and complementary medicinal uses, sporadic phytochemical and pharmacological reports, low toxicity, and frequency of use in herbal formulations, *V. agnus-castus* seems to hold great potential for in-depth investigation for various biological activities, especially its effect on the central nervous system.

Few preliminary pharmacological reports support medicinal potential of some *Vitex* species. These species need to be investigated systematically with a view to establish their varied pharmacological activities and mode of actions.

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