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### REVIEW

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# Traditional uses, phytochemistry, and pharmacology of genus *Vitex* (Lamiaceae)

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Niranjan Das, Department of Chemistry, Iswar Chandra Vidyasagar College, Belonia 799155, Tripura, India. Email: ndnsmu@gmail.com Vitex, the genus of the family Lamiaceae, comprises of about 230 species mostly distributed in the warm regions of Europe and temperate regions of Asia. Several Vitex species have been used as folk medicine in different countries for the treatment of various kinds of diseases and ailments. The main aim of this review is to collect and analyze the scientific information available about the Vitex species regarding their chemical constituents and pharmacological activities. The phytochemical investigation of various Vitex species has resulted in the isolation of about 556 chemical constituents belong to various chemical category viz. iridoids, diterpenoids, triterpenoids, flavonoids, lignans, sesquiterpenoids, monoterpenoids, ecdysteroids, and others. The crude extracts of different Vitex species as well as pure phytochemicals exhibited a wide spectrum of in-vitro and in-vivo pharmacological activities. In the present review, the scientific literature data on the ethnopharmacological, phytochemical, and pharmacological investigations on the genus Vitex are summarized. More attention should be given in future research to evaluate the pharmacological potential with detailed mechanism of actions for the pure compounds, extracts of plants from this genus. Moreover, their clinical study is needed to justify their use in modern medicine and to further exploring this genus for new drug discovery.

#### KEYWORDS

Vitex, ethnobotany, phytochemistry, pharmacology, Vitex negundo

### 1 | INTRODUCTION

The genus Vitex, consisting of ca. 230 species, belongs to the Lamiaceae family. Its species are mostly distributed in the warm regions of Europe and temperate regions of Asia. The majority of the species are either trees or aromatic shrubs. A number of Vitex species have been used as traditional medicine in different countries for the treatment of various diseases and ailments. In India, mainly Vitex agnus-castus L., Vitex negundo, Vitex peduncularis Wall. ex Schauer, Vitex pubescens Vhal, and Vitex trifolia L. are found throughout the country (Chopra et al. 1992). The fruits and leaves of V. agnus-castus have been used mainly in traditional medicine. The fruits are given to

the females to treat diseases like menstrual disorders, premenstrual dysphoric disorder, hyperprolactinemia infertility, acne, menopause, disrupted lactation, breast pain, cyclical mastalgia and inflammatory conditions, diarrhea, and flatulence, and leaves are used for increasing milk (Azadbakht, Baheddini, Shorideh, & Naserzadeh, 2005; Odenthal, 1998). The leaves and fruits of V. *negundo* L. have been used in folk medicine for the treatment of asthma, chronic bronchitis, cold, headache, migraine, gastrointestinal infections, catarrhal fever, dysmenorrhea, and as an anthelmintic (Tirtha, 1998; Liu, Tseng, & Yang, 2004). The infusions of leaves, root bark, or young stem bark of V. *peduncularis* Wall. ex Schauer are useful in malarial and black water fever (Chopra et al., 1992). The Vitex rotundifolia

L.f. is widely used as folk medicine in Japan for headache, colds, migraine, eye pain, etc (Kimura & Kimura, 1980). The V. *trifolia* L. has been used as an anti-inflammatory and sedative agent for the treatment of headache, rheumatism, and the common cold in Asian countries (Kimura, 1996). The Iridoids, diterpenoids, triterpenoids, flavonoids, and lignans are the major bioactive principles of the *Vitex* species.

Previously, a collection of 108 references on the genus Vitex and its phytochemistry, ethnopharmacology, morphology, pharmacological reports, clinical studies, and toxicology were reviewed in 2013 by Rani and their co-workers (Rani & Sharma, 2013). In this present review, we have summarized systematically the literature data on the phytochemical, ethnopharmacological, and pharmacological investigations on the genus Vitex up to December 2020.

#### 2 | METHODOLOGY

The main literature search was conducted via SciFinder (http://cas. org/products/scifinder/index.html) covering period up to December 2020. Additional information was collected from PubMed (http:// www.ncbi.nlm.nih.gov/pubmed), Science Direct, Google Scholar, and different journals and books. The keywords like genus *Vitex*, ethnobotany of *Vitex*, phytochemistry of *Vitex*, pharmacology of *Vitex*, etc., have been used while searching using the database.

### 3 | TRADITIONAL USES OF PLANTS BELONGING TO GENUS VITEX

*Vitex* genus comprises about 230 species distributed all over the world (Mabberley, 1997). Several species of *Vitex* have long been used in traditional medicines in different countries. The photographs of few species are given in Figure 1.

In Iranian traditional medicine, the leaves and fruits of *V. agnuscastus* are used by women for increasing breast milk (Azadbakht et al., 2005). The fruits (Chaste berry) of this plant have been used as a dietary supplement in many countries of the Mediterranean region and Southern Europe for the treatment of hormonal imbalance syndrome in women. The fruits either as a fluid extract or dried fruits have been used in pills for 4–6 months for the treatment of many disorders including corpus luteum insufficiency, hyperprolactinemia, infertility, menstrual disorders, premenstrual dysphoric disorder, menopause,

disrupted lactation, and cyclical mastalgia (Dugoua, Seely, Perri, et al., 2008; Atmaca, Kumru, & Tezcan, 2003). The bark, fruits, and leaves of Vitex diversifolia Kurz are used in Andaman and India for the treatment of skin diseases, intestinal troubles, and amoebiasis (Bibi, Thangamani, & Venkatesalu, 2016). In Burkina Faso, the raw fruits of Vitex doniana Sweet are consumed to suppress the appetite (Pare, Hilou, Ouedraogo, & Guenne, 2016), In India, the Kani tribes of Kerala have been using the decoction or juice of V. trifolia L. for the treatment of wounds and ulcers (Xavier, Kannan, Lija, et al., 2014). In India, the decoction or tincture of the roots of V. negundo L. is used in dyspepsia, colic pain, dysentery, asthma, bronchitis and other respiratory disorders, and skin diseases (Ross, 2005) (Muthu, Ayyanar, Raja, & Ignacimuthu, 2006) (Rajadurai, Vidhya, Ramya, & Bhaskar, 2009), stem decoction is used in burns (Ladda & Magdum, 2012), the decoction of flowers is used in cholera and liver disorders (Pattanaik, Sudhakar Reddy, & Murthy, 2008), and leaf decoction is used in wounds, ulcers, and as a diuretic (Kirtikar & Basu, 1984). In Malaysia, the leaf and shoot juice are used in gynaecological disorders and as galactogogne (Tandon, Khajuria, Kapoor, et al., 2008). In Sri Lanka, the powdered root, tincture from root and bark, and fresh leaf juice of V. negundo are used in rheumatism (Kirtikar & Basu, 1984). In China, fresh leaf juice of V. negundo, is used to treat gout (Woradulavapinii, Soonthornchareonnon, & Wiwat, 2005). In Pakistan, the leaves are used as antiallergic (Zabihullah, Rasheed, & Akhtar, 2006). In Bangladesh, the roots and whole plant are used to treat malaria, and leaf decoction along with long pepper is used to treat catarrhal fever (Khan & Manzoor Rashid, 2006). In Philippines, the stem-bearing flowers are used in cancer (Graham, Quinn, Fabricant, & Farnsworth, 2000). In Maldives, the decoction of the leaf is used for the treatment of febrile, catarrhal, and rheumatic problems (Sujanapal & Sankaran, 2016). In Guimaras Island, Philippines, the decoction of leaves of V. trifolia subsp. litoralis stems is drunk for treatment of cough with phlegm and postpartum recovery (Ong & Kim, 2014). In Japan and China, the fruits of V. trifolia are used for colds and headaches, migraines, eye pain, and inflammation (Kimura & Kimura, 1980). In Tonga, an infusion of leaves is given to infants to treat mouth infections and stomachache (Whistler, 1992). In Bangladesh, the flowers of V. trifolia are prescribed to treat fevers accompanied with vomiting. In Fiji, the leaves of V. trifolia are used to treat coughs, gonorrhea, stomach pain, and wounds (Weiner, 1983). In Madagascar, the infusion of V. trifolia stems and leaves is used before meals to relieve stomach pain (Boiteau & Allorge-Boiteau, 2000). In Thailand, the decoction of V. trifolia L. flowers is used as a tea to alleviate asthma (Panthong,



Vitex negundo

Vitex trifolia

Vitex cannabifolia

FIGURE 1 Photographs of some Vitex species flowers

Kanjanapothi, & Taylor, 1986). In Futuna, South Pacific Island, V. trifolia leaves are chewed with leaves of Citrus sinensis (orange tree) to relieve pain in sore tooth (Whistler, 1992). In Hawaii, the crushed leaves of V. rotundifolia are used as an antiitch remedy and heal rashes (Whistler, 1992). A decoction of seeds and fruits of V. rotundifolia L.f. is taken orally in Korea, Japan, and China for colds, headaches, migraine, sore eyes, night blindness, myalgia, and neuralgia (But, 1996; Shin, Kim, Lim, et al., 2000). In India, the bark of V. peduncularis Wall. ex Schauer is used topically on the chest to alleviate chest pain (Kirtikar & Basu, 1984). Both bark and fruit of Vitex polygama Cham. are used in Brazil as emmenagogues and diuretics (Correa, 1926). The infusions from the boiled leaves of Vitex lucens are used by the Maori of New Zealand to treat sprains, backaches, sore throats, and ulcers (Brooker, Cambie, & Cooper, 1987). In Mexico, the Vitex mollis Kunth is used to treat dysentery, scorpion stings, diarrhea, and stomachaches (Argneta, Cano, & Rodarte, 1994).

#### 4 | PHYTOCHEMISTRY

The genus *Vitex* is comprehensively studied for its chemical constituents, and till date 556, chemical compounds belonging to different chemical classes from various species have been reported. These phytochemicals mainly include iridoids, diterpenoids, triterpenoids, flavonoids, lignans, sesquiterpenoids, monoterpenoids, ecdysteroids, and miscellaneous compounds. Out of the reported 556 compounds, 37 are iridoids (1-37) (Table 1), 143 are diterpenoids (SI. No. 38-181) (Table 2), 71 are triterpenoids (182-252) (Table 3), 99 are flavonoids (253-351) (Table 4), 75 are lignans (352-426) (Table 5), 26 are sesquiterpenoids (427-452) (Table 6), 16 are monoterpenoids (453-468) (Table 7), 27 are ecdysteroids (469-495) (Table 8), and 61 belong to other classes of compounds (496-556) (Table 9). Many of the isolated compounds were evaluated for their biological activities.

With respect to the isolated phytochemicals of the genus Vitex, the leaves, fruits, and seeds were the most common targets of investigation of the plants for isolation of bioactive principles and most of these compounds are reported from V. negundo, V. agnus-castus., V. trifolia L., V. cannabifolia Siebold & Zucc., and V. rotundifolia L.f. Iridoids, diterpenoids, triterpenoids, flavonoids, and lignans are the major bioactive principles of the Vitex species. Different species studied for their chemical constituents were the following: V. negundo L., V. agnus-castus., V. trifolia L., V. cannabifolia Siebold & Zucc., V. rotundifolia L.f., V. altissima L., V. leptobotrys Hallier f., V. peduncularis Wall. ex Schauer, V. polygama Cham., V. cienkowskii Kotschy & Peyr., V. quinata F.N.Williams, V. limonifolia Wall. ex C.B. Clarke, V. cymosa Bertero ex Spreng., V. cauliflora Moldenke, V. pinnata L., V. doniana Sweet, V. scabra Wall. ex Schauer, V. vestita Wall. ex Schauer, V. simplicifolia Oliv., V. strickeri Vatke & Hildebr., V. canescens Kurz, V. rivularis Gürke, V. pseudo-negundo var. pseudonegundo Hausskn (synonym of Vitex agnus-castus L.), V. cofassus Reinw. ex Blume, V. rehmannii Gürke, V. mollis Kunth, V. rotundiforia,

V. glabrata R.Br., V. kwangsiensia C. Pei, V. pubescens Vahl, and V. gardneriana Schauer.

#### 5 | PHARMACOLOGICAL ACTIVITIES

The pharmacological activities of crude extracts/pure isolates from several species of *Vitex* have been reported. Here, some of the important pharmacological activities are discussed in following sections.

#### 5.1 | In-vitro experiments

#### 5.1.1 | Anti-inflammatory activity

The iridoid agnuside (3) isolated from the *n*-BuOH extract of V. *peduncularis* stem bark showed significant anti-inflammatory activity by inhibiting the activity of proinflammatory enzymes, COX-2 with  $IC_{50}$  value of 0.026 ± 0.015 mg/ml, while it showed mild inhibitory effects on COX-1 (Suksamrarn, Kumpun, Kirtikara, et al., 2002a).

The flavonoid casticin (**292**) also known as vitexicarpin isolated from V. *rotundifolia* showed anti-inflammatory activity by preventing TNF- $\alpha$ -induced vascular inflammatory process in human umbilical vein endothelial cells (HUVEC) model (S. M. Lee et al., 2012).

The diterpene, viterotulin A (**47**), and the neolignan viterolignan A (**380**) isolated from V. *rotundifolia* showed anti-inflammatory activity by inhibiting NO production in LPS-induced RAW 264.7 macrophages with  $IC_{50}$  values of 16.4 and 21.1  $\mu$ M, respectively (C. Lee et al., 2013).

A lignan, negundin B (**367**) isolated from V. *negundo* roots exhibited potent anti-inflammatory activity by inhibiting the activity of soybean lipoxygenase and butyryl-cholinesterase (BChE) with IC<sub>50</sub> of 6.25 ± 0.5 and 194 ± 4.4  $\mu$ M, respectively. While another isolated lignan, vitrofolal E (**365**) isolated from the same plant showed moderate activity against BChE with IC<sub>50</sub> of 35.0 ± 105  $\mu$ M (Azadbakht et al., 2005).

The labdane diterpenes, negundoin C (69) and E (71) isolated from V. *negundo* seeds showed anti-inflammatory effects by inhibiting NO production by LPS-stimulated RAW 264.7 macrophages, with IC<sub>50</sub> values of 0.12 and 0.23  $\mu$ M, respectively. Further studies revealed that these compounds at 5  $\mu$ M concentration significantly reduced the levels of iNOS proteins to 0.40 ± 0.13% and 41.01 ± 6.02%, respectively, and Cox-2 protein to 2.06 ± 0.53% and 26.40 ± 7.43%, respectively (Zheng, Huang, Wang, et al., 2010).

A significant *in-vitro* anti-inflammatory activity against neutrophil elastase was presented by hexane extracts from V. *mollis* (leaf IC<sub>50</sub> = 235 µg/ml and stem IC<sub>50</sub> 446 = µg/ml) (Morales-Del-Rio, Gutiérrez-Lomelí, Robles-García, et al., 2015). Negundoin G, a terpene, isolated from seeds of V. *negundo* L. var. *heterophylla* significantly reduced the nitric oxide production (IC<sub>50</sub> 0.71 ± 0.16 µM) in murine microglial BV-2 cells induced by lipopolysaccharide (Hu et al., 2016).

The flavonoid vitexin (264) reduces neutrophil migration to inflammatory focus by down-regulating proinflammatory mediators

TABLE 1 List of iridoids reported from different species of Vitex and their biological activities

TABLE 1	List of iridoids reported from different species of Vitex and their biological activities					
Compound No.	Compound name	Plant source	Plant part/extraction solvent/fraction	Biological activity	References	
1	Nishindaside	V. negundo	Leaves/EtOH extract, n-BuOH fraction		(Dutta, Chowdhury, Chakravarty, et al., 1983)	
		V. cannabifolia	Fruit/MeOH extract	Free radical scavenging activity.	(Yamasaki, Kawabata, Masuoka, et al., 2008)	
	но		Leaves/MeOH extract, n-BuOH fraction		(Iwagawa, Nakahara, & Nakatani, 1993)	
	но но	V. rotundifolia	Fruit/EtOH extract/ EtOAc fraction		(Wu, Zhang, & Yin, 2010)	
2	Isonisindaside HO $H$ $HO$ $H$ $HO$ $HO$ $HO$ $HO$ $H$	V. cannabifolia	Leaves/MeOH extract, n-BuOH fraction		(lwagawa et al., 1993)	
3	Agnuside OH	V. agnus-castus	Fruit/MeOH extract		(Görler, Öhlke, & Soicke, 1985)	
			Leaves Leaves/MeOH extract		(Winde & Hänsel, 1960) (Kouno, Inoue, Onizuka, et al., 1988)	
	но Ого	V. rotundifolia	Fruit/MeOH extract		(Ono, ITO, Kubo, & Nohara, 1997)	
	HO		Fruit/EtOH extract/ EtOAc fraction		(Wu et al., 2010)	
	но́ но	V. agnus-castus	Flowering stems/ MeoH extract		(Kuruüzüm-Uz, Ströch, Demirezer, & Zeeck, 2003)	
		V. altissima	Leaves/EtOAc extract		(Sridhar, Subbaraju, Venkateswarlu, & Venugopal, 2004)	
			Plant/MeOH extract		(Ramírez-Cisneros, Rios, Aguilar-Guadarrama, et al., 2015)	
		V. mollis	Seeds/95% EtOH extract		(Arai, Fujimatsu, Uchida, et al., 2013)	
		V. negundo	Whole plant/MeOH extract/EtOAc fraction Leaves/EtOH extract		(Sathiamoorthy, Gupta, Kumar, et al., 2007)	
		V. trifolia	Leaves/MeOH extract, n-BuOH fraction		(Tiwari, Thakur, Saikia, et al., 2013)	
4	Eurostoside	V. rotundifolia	Leaves/MeOH extract		(Kouno et al., 1988)	
5	Hổ HO Viteoid II HO H HO O	V. rotundifolia	Fruit/MeOH extract		(Ono et al., 1997)	

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TABLE 1	(Continued)				
Compound No.	Compound name	Plant source	Plant part/extraction solvent/fraction	Biological activity	References
6	Aucubin HO HO HO HO HO HO HO HO	V. agnus-castus	Flowering stems/ MeOH extract Fruit/n-hexane extract		(Kuruüzüm-Uz et al., 2003) (S. Li, Qiu, Yao, et al., 2013)
7	10-O-Vanilloyl aucubin $H \rightarrow H \rightarrow$	V. cannabifolia V. rotundifolia	Fruit/MeOH extract Fruit/EtOH extract/ EtOAc fraction		(Yamasaki et al., 2008) (Wu et al., 2010)
8	2'-O-p-Hydroxybenzoyl-6'-O- trans-caffeoyl-8-epiloganic acid HO HO HO HO HO HO HO HO HO HO HO HO HO	V. altissima	Leaves/EtOAc extract	Potent antioxidant activity as measured using superoxide (NBT riboflavin photoreduction) free-radical- scavenging method with IC <sub>50</sub> value 31.9 $\mu$ M and DPPH- radical-scavenging method with IC <sub>50</sub> value 11.4 $\mu$ M.	(Sridhar et al., 2004)
9	2'-O-p-Hydroxybenzoyl-8-epi-loganic acid HO - + + + + + + + + + + + + + + + + + +	V. altissima	Leaves/EtOAc extract		(Sridhar et al., 2004)
10	Agnucastoside C	V. agnus-castus	Flowering stem/MeOH extract		(Kuruüzüm-Uz et al., 2003)

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$ \begin{array}{c c c c c } & \text{extract} & \text{extract} \\ & \downarrow &$		(00.1111202)				
$ \begin{array}{c c c c c } & \text{extract} & \text{extract} \\ & \downarrow &$	-	•				References
He OH extract $He OH extract$ $He OH extrac$	11		V. agnus-castus	-		(Kuruüzüm-Uz et al., 2003)
$ \begin{array}{c c} & & & \\ $	12		V. agnus-castus			(Kuruüzüm-Uz et al., 2003)
$15 \qquad Negundoside (2'-p-Hydroxybenzoyl K. negundo  COOH K. Method K. $	13	HO HO OH	V. altissima	Leaves/EtOAc extract		(Sridhar et al., 2004)
mussaenosidic acid) against T.	14	HO HO OH	V. altissima	Leaves/EtOAc extract	activity as measured using superoxide (NBT riboflavin photoreduction) free-radical- scavenging method with $IC_{50}$ value 24.3 $\mu$ M and DPPH- radical-scavenging method with $IC_{50}$	(Sridhar et al., 2004)
C. neoformans with MIC 6.25 μg/ml HO H V. altissima (Sathiamoorthy et al., 200 V. trifolia Leaves/EtOH extract (Sridhar et al., 2004) (Seh Taneja, Dhar, et al., 194	15	mussaenosidic acid) HOHHO HOHHO HO	V. altissima	Leaves/EtOH extract Leaves/MeOH extract,	against T. mentagrophytes and C. neoformans with	(Arai et al., 2013) (Sathiamoorthy et al., 2007) (Sridhar et al., 2004) (Sehgal, Taneja, Dhar, et al., 1982) (Tiwari, Thakur, et al., 2013)

### TABLE 1 (Continued)

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TABLE 1	(Continued)				
Compound No.	Compound name	Plant source	Plant part/extraction solvent/fraction	Biological activity	References
16	Mussaenosidic acid COOH	V. agnus-castus	flowering stems/ MeOH extract		(Kuruüzüm-Uz et al., 2003)
		V. trifolia	Leaves/MeOH extract, n-BuOH fraction		(Tiwari, Thakur, et al., 2013)
17	6'-O-p-Hydroxybenzoylmussaenosidic acid	V. agnus-castus	Flowering stems/ MeOH extract		(Kuruüzüm-Uz et al., 2003)
	н Соон	V. negundo	Leaves/EtOH extract		(Sehgal, Taneja, Dhar, et al., 1983)
	но н	V. trifolia	Leaves/MeOH extract, n-BuOH fraction		(Tiwari, Thakur, Saikia, et al., 2013)
18	Agnusoside	V. agnus-castus	Flowers/MeOH extract, H <sub>2</sub> O fraction		(Kırmızıbekmez & Demir, 2016)
19	Pedunculariside HO HO HO HO HO HO HO HO HO HO	V. peduncularis	Stem bark/n-BuOH		(Suksamrarn, Kumpun, Kirtikara, et al., 2002a)
20	Limoniside H <sub>3</sub> CO H <sub>3</sub> CO HO HO HO HO	V. limonifolia	Bark/EtOH extract		(Suksamrarn, Kumcharoen, & Suksamrarn, 1999)
21	Geniposide COOCH <sub>3</sub> HO HO HO HO HO HO HO	V. cannabifolia	Fruit/MeOH extract	DPPH free radical scavenging activity	(Yamasaki et al., 2008)

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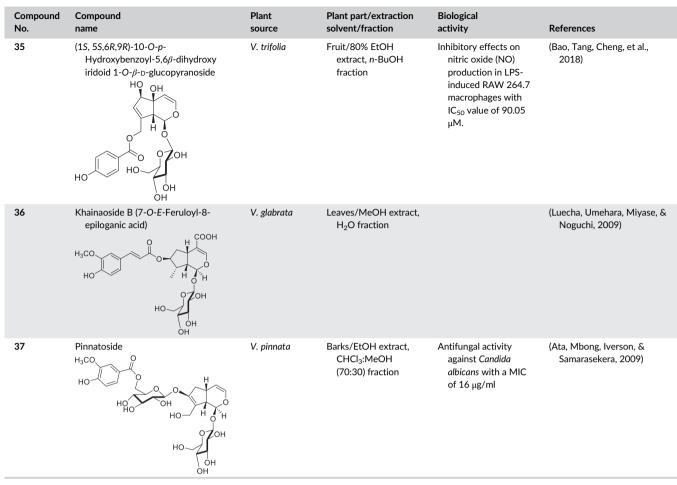
TABLE 1	(Continued)				
Compound No.	Compound name	Plant source	Plant part/extraction solvent/fraction	Biological activity	References
22	2'-O-p-Hydroxybenzoyl gardoside	V. altissima	Leaves/EtOAc extract		(Sridhar et al., 2004)
23	Viteoid I OH OH	V. rotundifolia	Fruit/MeOH extract		(Ono et al., 1997)
24	10-p-Hdroxybenzoyl-6 $\beta$ -hydroxybiridoid 1-O- $\beta$ -D-(6'-O-p-hydroxybenzoyl)- glucopyranoside HO HO HO HO HO HO HO	V. negundo	Leaves/70% EtOH extract		(Qiu, Tong, Yuan, et al., 2016)
25	Harpagide HO HO HO HO HO HO HO	V. agnus-castus	Leaves/EtOH extract		(Ramazanov, 2004)
26	8-O-Acetylharpagide HO OH $H_3COCO HO$ HO HO HO HO	V. agnus-castus	Leaves/EtOH extract		(Ramazanov, 2004)
27	2'-O-p-Hdroxybenzoyl-6'-O-trans- caffeoylgardoside $HO \rightarrow HO \rightarrow$	V. altissima	Leaves/EtOAc extract	Potent antioxidant activity as measured using superoxide (NBT riboflavin photoreduction) free-radical- scavenging method with IC <sub>50</sub> value 32.0 $\mu$ M and DPPH- radical-scavenging method with IC <sub>50</sub> value 10.9 $\mu$ M.	(Sridhar et al., 2004)

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TABLE 1	(Continued)				
Compound No.	Compound name	Plant source	Plant part/extraction solvent/fraction	Biological activity	References
28	1,4a,5,7a-Tetrahydro-1- $\beta$ -D-glucosyl-7- (3',4'-dihydroxybenzoyloxymethyl)- 5-ketocyclopenta[c]pyran-4- carboxylic acid HO $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$	V. negundo	Leaves/MeOH, petroleum ether extract		(Sharma, Prabhakar, Dhar, & Sachar, 2009)
29	Vitexnegheteroin K HO	V. negundo	Leaves/ 95% EtOH/ EtOAc extract	Moderate inhibitory effects on $\alpha$ - glucosidase (IC <sub>50</sub> , 1.30 ± 0.01 $\mu$ M) and weaker antioxidant effects {DPPH assay (IC <sub>50</sub> , 100> $\mu$ M); ABTS assay (IC <sub>50</sub> , 85.55 ± 5.52 $\mu$ M)}	(Hu, Li, Jia, et al., 2017)
30	Vitexnegheteroin L H H HO HO HO HO HO HO HO HO	V. negundo	Leaves/ 95% EtOH/ EtOAc extract	Moderate inhibitory effects on $\alpha$ - glucosidase (IC <sub>50</sub> , 7.42 ± 0.03 $\mu$ M) and weaker antioxidant effects {DPPH assay (IC <sub>50</sub> , 100> $\mu$ M); ABTS assay (IC <sub>50</sub> , 67.13 ± 4.27 $\mu$ M)}.	(Hu et al., 2017)
31	Eucommiol HO H OH HO	V. rotandifolia	Fruit/MeOH extract		(Ono et al., 1997)
32	HO H H	V. rotandifolia	Fruit/MeOH extract		(Ono et al., 1997)
33	Pedicularis-lactone	V. rotandifolia	Fruit/MeOH extract		(Ono et al., 1997)
34	1-oxo-Eucommiol HOHOH HOOH	V. rotandifolia	Fruit/MeOH extract		(Ono et al., 1997)

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#### **TABLE 1** (Continued)



via inhibition of p38, ERK1/2, and JNK pathway (Rosa, Rios-Santos, Balogun, & Martins, 2016).

#### 5.1.2 | Antimicrobial activity

Compounds,4',5,7-Trihydroxy-3'-O- $\beta$ -D-glucuronic acid-6"-methyl ester (263) and negundoside (15) isolated from V. *negundo* leaves exhibited significant antifungal activity against *Trichophyton mentagrophytes* and *Cryptococous neoformans* with MIC value of 6.25 µg/ml. Flucanazole was used as a standard drug (Sathiamoorthy et al., 2007).

Supercritical fluid extract of V. negundo leaves exhibited strong antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus* and mild activity against *Escherichia coli*, *Pseudomonas aeruginosa* and yeast, *Candida albicans* in disc diffusion assay (Nagarsekar, Nagarsenker, & Kulkarni, 2010).

Vitex negundo leaf and bark methanolic extract, fresh leaf, as well as leaf aqueous extracts were shown to have significant antimicrobial activity against bacteria and fungal strains, for example, Bacillus cereus, Staphylococcus aureus, Escherichia coli, Salmonella typhimurium, Shigella sonnei, Klebsiella pneumoniae, Shigella dysentriae, K. pneumonia, Vibrio cholera, Candida albicans, Candida tropicalis, etc. (Devi, Kokilavani, & Poongothai, 2008) (Panda, Mohanta, Padhi, et al., 2016) (Prakash, Ramasubburayan, Ramkumar, et al., 2016).

Ethanol crude extract of leaf of V. doniana displayed in-vitro antibacterial activity with minimum inhibitory concentration (MIC) value of 93.75  $\mu$ g/ml against S. aureus and B. subtilis in a 96 well plate resazurin-based broth microdilution method with the antimicrobial drugs ampicillin and nystatin used as positive control (Abiodun, Sood, Osiyemi, et al., 2015).

The lignans, vitrofolals C (**362**), and D (**361**) and detetrahydroconidendrin (**353**) isolated from V. *rotundifolia* aerial parts showed significant antibacterial activity against various methicillinresistant *S. aureus* (MRSA) strains with MIC values in the range of 4– 64  $\mu$ g/ml in broth dilution method (Kawazoe et al., 2001).

The essential oils obtained by hydrodistillation from the aerial parts of V. *rivularis* showed antifungal activity against yeasts and dermatophyte strains with MIC and minimum lethal concentration (MLC) values ranging from 0.16 to 0.64  $\mu$ l/ml and 0.32 to 2.5  $\mu$ l/ml, respectively (Cabral et al., 2009).

Vitelignin A (**377**) isolated from V. *negundo* seeds showed moderate antifungal activity against C. *albicans*, *Cryptococcus neoformans*, and *Trichophyton rubrum* with MIC values of 32, 64, and 32 µg/ml, respectively (Zheng et al., 2011).

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TABLE 2	2 List of diterpenoids reported from different species of Vitex and their pharmacological activities				
Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
38	(rel 5S, 6R, 8R, 9R, 10S)-6-Acetoxy- 9-hydroxy-13(14)-labden-	V. rotundifolia	Fruit/MeOH extract		(Ono, Yamamoto, Yanaka, et al., 2001)
	16,15-olide O //	V. trifolia	Fruit/acetone		(Kiuchi, Matsuo, Ito, et al., 2004)
			Fruit/H <sub>2</sub> O:acetone (7:3) extract	Exhibited inhibition of Hela cell proliferation in MTT assay with $IC_{50}$ value in the range of 16.2 $\pm$ 0.9 $\mu$ M.	(Wu, Zhou, Zhang, et al., 2009)
39	9αHydroxy-13(14)-labden- 16,15-amide	V. agnus-castus	Dried fruit/70% EtOH extract, CHCl <sub>3</sub> fraction	Cytotoxicity activity against chronic myelogenous leukemia (K562) cell lines with IC <sub>50</sub> value of 0.70 μg/ml	(Pal, Li, Tewari, & Sun, 2013)
40	(rel 55, 65, 8R, 9R, 105)-6-Acetoxy- 9-hydroxy-13(14)-labden-16, 15-olide	V. rotundifolia	Fruit/MeOH extract		(Ono, Yamamoto, et al., 2001)
41	(rel 55, 6R, 8R, 9R, 105)-6-Acetoxy- 9-hydroxy-15-methoxy-13(14)- labden-16, 15-olide	V. rotundifolia	Fruit/MeOH extract		(Ono, Yamamoto, et al., 2001)
42	Vitexilactone	V. rotundifolia V. trifolia	Fruit/MeOH extract Fruit/MeOH extract Plant/MeOH extract		(Ono, Yamamoto, et al., 2001) (Wang, Zhang, Zheng, et al., 2014) (Kim, Kim, Oh, & Seo, 2013) (Kiuchi et al., 2004)
	OAc	ν. τησια	Fruit/acetone extract Fruit/hot aq. EtOH	Cytotoxicity against four human cancer cell lines (A549, HCT116, HL-60, and ZR-75-30), but did not show any activity (IC <sub>50</sub> < 5 µg/ml).	(Zheng, Zhu, Yu, et al., 2013) (J. Wu et al., 2009)
			Fruit/H <sub>2</sub> O:acetone (7:3)	Exhibited inhibition of Hela cell proliferation in MTT assay with $IC_{50}$ value in the range of 9.5 ± 0.8 $\mu$ M.	(Ono, Eguchi, Konoshita, et al., 2011)

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### TABLE 2 (Continued)

IABLE 2	(Continued)				
Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
		V. agnus-castus	Fruit/acetone extract		(Pal et al., 2013)
			Fruit/70% EtOH, CHCl₃ fraction	Cytotoxicity activity against chronic myelogenous leukemia (K562) cell lines with IC <sub>50</sub> value of 2.73 μg/ml	(Hu et al., 2016)
		V. negundo	Seeds/95% EtOH extract Leaves/70% EtOH		(Qiu et al., 2016)
			extract		
43	Vitexilactone B	V. trifolia	Fruit/hot aq. EtOH extract		(Zheng et al., 2013)
	AcO H	V. negundo	Seeds/aq. EtOH extract		(Zheng, Huang, Wu, et al., 2010)
44	Viteagnuside A	V. agnus-castus	Fruit/acetone extrac		(Ono et al., 2011)
	GlcO	V. negundo	Leaves/70% EtOH		(Qiu et al., 2016)
45	Viteoside A	V. rotundifolia	Fruit/MeOH extract		(Ono, Ito, & Nohara, 1998)
46	(+) Polyalthic acid	V. rotundiforia	Plant/MeOH extract, DCM fraction		(Miyazawa, Shimamura, Nakamura, & Kameoka, 1995)
	т. Н СООН	V. negundo	Fruit/40% EtOH extract	Significant inhibitory effects against A- 549 cell line with IC <sub>50</sub> value 20.3 µM.	(Huang, Qing, Zeng, et al., 2013)
47	Viterotulin A	V. rotundifolia	Fruit/MeOH extract, DCM fraction	Inhibitory activities on LPS-induced nitric oxide production in RAW264.7 cells with IC <sub>50</sub> value 16.4 μM	(Lee, Lee, Jin, et al., 2013)

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#### TADIE 2 (Continued)

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TABLE 2	(Continued)				
Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
48	Viterotulin B	V. rotundifolia	Fruit/MeOH extract, DCM fraction	Inhibitory effects on LPS-induced nitric oxide production in RAW264.7 cells with IC <sub>50</sub> value 49.1 μM	(Lee et al., 2013)
49	Vitexilactone C	V. negundu	Aerial part/EtOH seeds/95% EtOH extract	Inhibitory effect on nitric oxide (NO) production in murine microglial BV-2 cell line by the Griess reaction with IC <sub>50</sub> value 10.79 $\pm$ 1.16 $\mu$ M.	(Chen, Li, Ling, et al., 2012) (Hu et al., 2016)
50	9-Hydroxy-13(14)-labden-15,16-olide	V. trifolia	Leaves/MeOH, hexane fraction	Antitubercular activity (MIC = 100 μg/ml) against Mycobacterium tuberculosis H37Rv in BACTEC-460 assay	(Tiwari, Thakur, et al., 2013)
51	Viteagnusin I HO	V. agnus-castus	Fruit/MeOH extract		(Chen, Friesen, Webster, et al., 2011)
	,OH OAc	V. trifolia	Fruit/hot aq. EtOH (80%) extract, DCM fraction	Cytotoxicity against four human cancer cell lines (A549, HCT116, HL-60, and ZR-75-30), but did not show any activity (IC <sub>50</sub> < 5 µg/ml)	(Zheng et al., 2013)
52	Vitexlactam A	V. agnus-castus	Fruit/n-hexane extract		(Li, Zhang, Qiu, et al., 2002)
	NH NH OAc	V. rotundifolia	Fruit/n-hexane extract Fruit/MeOH, CHCl <sub>3</sub> fraction		(Li et al., 2013) (Wang et al., 2014)
53	Vitexlactam B	V. agnus-castus	fruit/n-hexane extract		(Li et al., 2013)
54	Vitexlactam C	V. agnus-castus	Fruit/n-hexane extract	Induced flavoenzyme NADP(H):quinine oxidoreductase type 1 (QR1), toxic to Hepa 1c1c7 cells.	(Li et al., 2013)

IADLE 2	(Continued)				
Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
55	(rel 55,6R,8R,9R,105,135,165)- 6-Acetoxy-9,13-epoxy-16-methoxy labdan-15,16-olide MeO H O O H O Ac	V. rotundifoli V. agnus-castus	Fruit/MeOH extract Fruit/acetone extract		(Ono, Yamamoto, et al., 2001) (Ono et al., 2011)
56	(rel 55,6R,8R,9R,105,13R,165)- 6-Acetoxy-9,13-epoxy-16-methoxy	V. rotundifolia	Fruit/MeOH extract		(Ono, Yamamoto, et al., 2001)
	labdan-15,16-olide	V. agnus-castus	Fruit/acetone extract		(Ono et al., 2011)
57	(rel 55,6R,8R,9R,105,135)-6-Acetoxy- 9,13-epoxy-15-methoxy labdan-	V. rotundifolia	Fruit/MeOH extract		(Ono, Yamamoto, et al., 2001)
	16,15-olide	V. agnus-castus	Fruit/acetone extract		(Ono et al., 2011)
58	(rel 55,6R, 8R, 9R, 10S, 13R)-6-Acetoxy- 9,13-epoxy-15-methoxy labdan-16,	V. rotundifolia	Fruit/MeOH extract		(Ono, Yamamoto, et al., 2001)
	15-olide MeO MeO MeO MeO MeO MeO MeO	V. agnus-castus	Fruit/acetone extract Fruit/hexane extract		(Ono et al., 2011) (Ono, Yamasaki, Konoshita, et al., 2008)
59	(rel 5S,8R,9R,10S,13S,15S,16R)- 9,13;15,16-Diepoxy- 15,16-dimethoxylabdane MeO	V. rotundifolia	Fruit/MeOH extract		(Ono, Yamamoto, et al., 2001)

### TABLE 2 (Continued)

TABLE 2	(Continued)				
Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
60	(rel 55,88,9R,105,135,15 <i>R</i> ,165)-9, 13; 15, 16-Diepoxy-15, 16-dimethoxylabdane MeO OMe	V. rotundifolia	Fruit/MeOH extract		(Ono, Yamamoto, et al., 2001)
61	(rel 55,88,9R,105,135,15R,16R)- 9,13;15,16-Diepoxy-15, 16-dimethoxylabdane MeO OMe	V. rotundifolia	Fruit/MeOH extract		(Ono, Yamamoto, et al., 2001)
62	Previtexilactone	V. trifolia	Fruit/acetone extract Fruit/H <sub>2</sub> O:acetone (7:3) extract Fruit/hot 80% EtOH	Exhibited inhibition of Hela cell proliferation in MTT assay with IC <sub>50</sub> value in the range of 19.4 ± 1.4 μM	(Kiuchi et al., 2004) (Wu et al., 2009) (Zheng et al., 2013)
			extract, DCM fraction		
63	Viteagnusin E	V. agnus-castus	Fruit/hexane extract		(Ono et al., 2008)
64	Viteagnusin I OMe	V. agnus-castus	Fruit/acetone extract		(Ono et al., 2011)
65	Viteagnusin J	V. agnus-castus	Fruit/acetone extract		(Ono et al., 2011)

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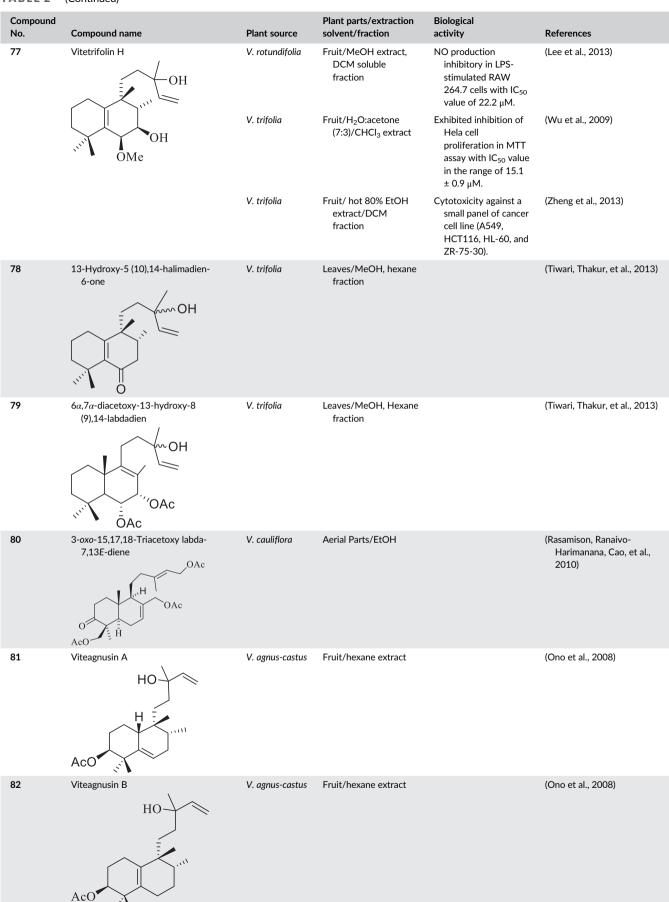
TABLE 2	(Continued)				
Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
66	Negundoal H CHO ACO	V. negundo	Seeds/aq. EtOH 80% extract	Cytotoxicity against human lung carcinoma (A549) cell line having IC <sub>50</sub> value >100 $\mu$ g/ml; colon carcinoma (HCT116) cell line having IC <sub>50</sub> value 24.59±2.24 $\mu$ g/ml; blood cancer (HL-60) cell line having IC <sub>50</sub> value 11.23±1.01 $\mu$ g/ml; and breast carcinoma (ZR- 75-30) cell line having IC <sub>50</sub> 20.04± 3.15 $\mu$ g/ml	(Zheng, Pu, Zhang, et al., 2012)
67	Negundoin A MeOOC	V. negundo	Seeds/EtOH 80% extract, DCM fraction	NO production inhibitory in LPS- stimulated RAW 264.7 cells with IC <sub>50</sub> value of 9.83 μM.	(Zheng, Huang, Wang, et al., 2010)
68	Negundoin B HOOC	V. negundo	Seeds/EtOH 80% extract, DCM fraction	NO production inhibitory in LPS- stimulated RAW 264.7 cells with IC <sub>50</sub> value of 23.43 μM.	(Zheng, Huang, Wang, et al., 2010)
69	Negundoin C OHC	V. negundo V. trifolia	Fruits/MeOH extract, EtOAc fraction, Seeds/DCM fraction Leaves/95% EtOH	NO production inhibitory in LPS- stimulated RAW 264.7 cells with $IC_{50}$ value of 0.12 $\mu$ M.	(Zheng, Huang, Wang, et al., 2010) (Fang, Kong, & Yan, 2016b) (Luo, Yu, Liu, et al., 2017)
	AcO	v. trijona	extract, EtOAc fraction		(200, 10, 20, 2027)
70	Negundoin D MeO	V. negundo	Seeds/EtOH 80% extract, DCM fraction	NO production inhibitory in LPS- stimulated RAW 264.7 cells with IC <sub>50</sub> value of 4.39 μM.	(Zheng, Huang, Wang, et al., 2010)
	Aco		Leaves/70% EtOH extract		(Qiu et al., 2016)
71	Negundoin E HO,,,,O ,,IO ACO	V. negundo	Seeds/EtOH 80% extract, DCM fraction	NO production inhibitory in LPS- stimulated RAW 264.7 cells with IC <sub>50</sub> value of 0.23 μM.	(Zheng, Huang, Wang, et al., 2010)

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TABLE 2	(Continued)				
Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
72	HO	V. negundo	Seeds/EtOH 80% extract, DCM fraction	NO production inhibitory in LPS-stimulated RAW 264.7 cells with IC <sub>50</sub> value of 0.30 $\mu$ M.	(Zheng, Huang, Wang, et al., 2010)
	NUT OH		Seeds/95% EtOH extract, DCM fraction	NO production inhibitory in LPS- stimulated RAW 264.7 cells with IC <sub>50</sub> value of 0.71 $\pm$ 0.16 $\mu$ M.	(Hu et al., 2016)
73	Vitetrifolin D	V. trifolia	Fruit/acetone extract		(Ono, Ito, & Nohara, 2001)
	OAc		Fruit/H₂O:acetone (7:3) extract	Exhibited inhibition of Hela cell proliferation in MTT assay with IC <sub>50</sub> value in the range of 15.0 $\pm$ 1.7 $\mu$ M	(Wu et al., 2009)
	S OAc		Leaves/95% EtOH extract, EtOAc fraction		(Luo et al., 2017)
		V. rotundifolia	Whole plant/DCM/ MeOH		(Kim et al., 2013)
			Fruit/MeOH extract		(Ono, Yanaka, Yamamoto, et al., 2002)
		V. agnus-castus	Fruit/acetone extract		(Ono et al., 2011)
			Fruit/70% EtOH extract, CHCl <sub>3</sub> fraction	Cytotoxicity activity against chronic myelogenous leukemia (K562) cell lines with IC <sub>50</sub> value 6.72 µg/ml	(Pal et al., 2013)
		V. negundo.	Whole plant/MeOH extract, EtOAc fraction	Exhibited cytotoxicity against cancer cell lines and Hedgehog (Hh) signaling pathway inhibitor.	(Arai et al., 2013)
			Seeds/Aq. EtOH extract		(Zheng, Lan, Bin, et al., 2011)
74	Vitetrifolin E (= Vitexifolin E)	V. trifolia	Fruit/acetone extract		(Ono, Ito, & Nohara, 2001)
	HOwn		Fruit/H <sub>2</sub> O:acetone (7:3) extract		(Wu et al., 2009)
	OAc	V. rotundifolia	Whole plant/MeOH extract, DCM fraction		(Kim et al., 2013)
75	Vitetrifolin F (=Vitexifolin F)	V. trifolia	Fruit/acetone extract		(Ono, Ito, & Nohara, 2001)
	How OH		Fruit/H <sub>2</sub> O:acetone (7:3)		(Wu et al., 2009)
	OAc	V. rotundifolia	Whole plant/MeOH extract, DCM fraction		(Kim et al., 2013)
76	Vitetrifolin G	V. trifolia	Fruit/acetone extract		(Ono, Ito, & Nohara, 2001)

TABLE 2 (Continued)



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т	ABLE 2	(Continued)				
	Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
	83	Viteagnusin C HO HO HO HO HO HO HO H	V. agnus-castus V. negundo	Fruit/hexane extract Seeds/80% aq. EtOH		(Ono et al., 2008)) (Zheng, Huang, Wang, et al., 2010)
	84	Viteagnusin D HO UNOH	V. agnus-castus	Fruit/Hexane extract		(Ono et al., 2008)
	85	Cembrene	V. agnus-castus	Seed/essential oil		(Asdadi, Hamdouch, Oukacha, et al., 2015)
	86	Sclareol HO OH H	V. agnus-castus	Seed/essential oil		(Asdadi et al., 2015)
	87	8-epi-sclareol HOII OH	V. agnus-castus V. negundo V. negundo	Fruit/hexane Whole plant/MeOH Seeds/80% Aq. EtOH	Hedgehog (Hh) signaling pathway inhibitor.	(Ono et al., 2011) (Arai et al., 2013) (Zheng, Huang, Wang, et al., 2010)
	88	Vitexifolin A HO wh	V. rotundifolia	Fruit/MeOH extract		(Ono et al., 2002)
						(Continues)

TABLE 2	(Continued)				
Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
89	Vitexifolin B HO HO HO	V. rotundifolia	Fruit/MeOH extract		(Ono et al., 2002)
90	Norditerpene aldehyde 1 H O H H	V. trifolia	Fruit/acetone extract	In-vitro minimum lethal concentration against epimastigotes of Trypanosoma cruzi 11µM.	(Kiuchi et al., 2004)
91	Norditerpene aldehyde 2 H O H O Ac	V. trifolia	Fruit/Acetone extract	In-vitro minimum lethal concentration against epimastigotes of Trypanosoma cruzi 36 μM.	(Kiuchi et al., 2004)
92	Vitetrifolin B	V. trifolia	Fruit/acetone extract		(Ono, Sawamura, Ito, et al., 2000)
93	Vitetrifolin C	V. trifolia	Fruit/acetone extract		(Ono et al., 2000)
94	Rotundifuran	V. rotundifolia V. trifolia V. trifolia V. agnus-castus	Leaves/light petroleum extract Fruit/acetone extract Fruit/hot 80% EtOH extract/DCM fraction Seeds/70% EtOH extract		(Asaka, Kamikawa, & Kubota, 1973) (Ono et al., 2000) (Zheng et al., 2013) (Jarry, Spengler, Wuttke, & Christoffel, 2006)
			Fruit/80% MeOH extract Fruit/70% EtOH extract, CHCl <sub>3</sub> fraction	Affinity to the dopamine-D <sub>2</sub> - receptor Cytotoxicity activity against chronic myelogenous leukemia (K562) cell lines with IC <sub>50</sub> value 2.91 μg/ml	(Hoberg, Orjala, Meier, & Sticher, 1999) (Pal et al., 2013)

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Compound No.

### TABLE 2 (Co

(Continued)				
Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
Dihydrosolidagenone	V. trifolia	Fruit/acetone extract		(Ono et al., 2000)
Vitedoin B	V. negundo	Seeds/DCM extract Seeds/MeOH		(Zheng, Huang, Wang, et al., 2010) (Ono, Nishida, Masuoka,
Aco H		extract		et al., 2004)
Vitexifolin D O O H Č Ac	V. rotundifolia	Fruit/MeOH extract		(Ono et al., 2002)
Trisnor-y-lactone	V. rotundifolia	Fruit/MeOH extract		(Ono et al., 2002)
iso-Ambreinolide	V. rotundifolia	Fruit/MeOH extract		(Ono et al., 2002)
Vitexifolin E O O H OAc	V. rotundifolia	Fruit/MeOH extract		(Ono et al., 2002)
Vitexifolin C	V. rotundifolia	Fruit/MeOH extract		(Ono et al., 2002)

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TABLE 2	(Continued)							
Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References			
102	Abietatrien-3 $\beta$ -ol	V. trifolia V. rotundifolia	Fruit/acetone extract Fruit/MeOH extract		(Ono et al., 2000) Ono, Yamamoto, Masuoka,			
	HO	v. rotanajona	Hulpheonexuae		et al. (1999)			
103	Vitetrifolin A	V. trifolia	Fruit/acetone extract		(Ono et al., 2000)			
104	HO	V. negundo	Seeds/80% EtOH extract, DCM fraction	NO production inhibitory in LPS- stimulated RAW 264.7 cells with IC <sub>50</sub> value of 1.16 μM.	(Zheng, Huang, Wang, et al., 2010)			
105	16-Hydroxy-pentandralactone	V. cofassus	Leaves/MeOH extract	Potent antiproliferative activity against five human tumor cell lines, namely lung carcinoma (A549), epidermoid carcinoma (KB), vincristine-resistant KB subline (KB-VIN), triple-negative breast cancer (MDA- MB-231), and estrogen receptor- positive breast cancer (MCF-7) with IC <sub>50</sub> values ranged from 6.4 to 11.4 µM.	(Rasyid, Fukuyoshi, Ando, et al., 2017)			
106	12-Epivitexolide A	V. vestita	Leaves/DCM extract	Cytotoxic activities against human colon cancer carcinoma HCT-116 cell line (1 < $ C_{50}s < 10 \ \mu$ M) and on a human fetal lung fibroblast MRC5 cell line (1 < $ C_{50}s < 10 \ \mu$ M).	(Corlay, Lecsö-Bornet, Leborgne, et al., 2015)			
107	Vitexolide B O O O O H O H	V. vestita	Leaves/DCM extract	Cytotoxic activity against human colon cancer carcinoma HCT-116 cell line (1 < IC <sub>50</sub> s < 10 μM).	(Corlay et al., 2015)			

### TABLE 2 (Continued)

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TABLE 2	(Continued)				
Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
108	Vitexolide C O O O O O H H O H O H O H O H O H H	V. vestita	Leaves/DCM extract	Cytotoxic activity against human colon cancer carcinoma HCT-116 cell line (1 < IC <sub>50</sub> s < 10 µM).	(Corlay et al., 2015)
109	Vitexolide E O O O O O O O O O O O O O O O O O O O	V. vestita	Leaves/DCM extract	Cytotoxic activities against human colon cancer carcinoma HCT-116 cell line (1 $< IC_{50}S < 10 \mu$ M) and on a human fetal lung fibroblast MRC5 cell line (1 $< IC_{50}S < 10 \mu$ M).	(Corlay et al., 2015)
110	Vitexolin A O O H O H	V. vestita	Leaves/DCM extract		(Corlay et al., 2015)
111	Vitexolin B O O O H O O O H	V. vestita	Leaves/DCM extract	Cytotoxic activity against human colon cancer carcinoma HCT-116 cell line (1 < IC <sub>50</sub> s < 10 µM).	(Corlay et al., 2015)
112	Vitexolide A	V. vestita	Leaves/DCM extract	Potent antibacterial activity with MIC ranging from 6 to 96 $\mu$ M and also cytotoxic activities against human colon cancer carcinoma HCT-116 cell line (1 < IC <sub>50</sub> S < 10 $\mu$ M) and on a human fetal lung fibroblast MRC5 cell line (1 < IC <sub>50</sub> S < 10 $\mu$ M).	(Corlay et al., 2015)

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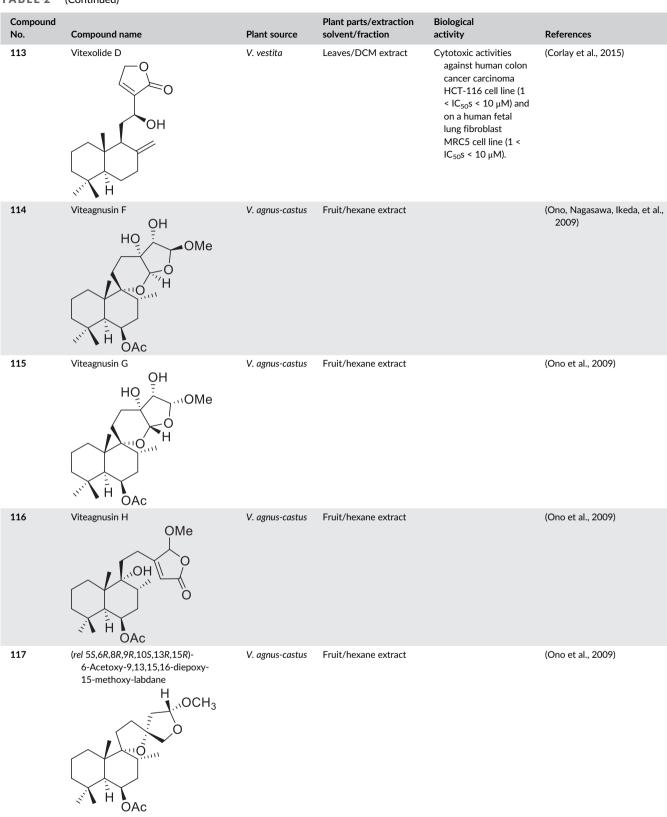


TABLE 2	(Continued)				
Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
118	(rel 55,6R,8R,9R,105,13R,155)- 6-Acetoxy-9,13,15,16-diepoxy- 15-methoxy-labdane H <sub>3</sub> CO	V. agnus-castus V. rotundifolia	Fruit/hexane extract Fruit/MeOH extract		(Ono et al., 2009) (Ono et al., 1999)
119	(rel 55,6R,8R,9R,105,135,155)- 6-Acetoxy-9,13,15,16-diepoxy- 15-methoxy-labdane HOCH <sub>3</sub>	V. agnus-castus V. rotundifolia	Fruit/hexane extract Fruit/MeOH extract		(Ono et al., 2009) (Ono et al., 1999)
120	( <i>rel</i> 55,6R,8R,9R,105,135,15R)- 6-Acetoxy-9,13,15,16-diepoxy- 15-methoxy-labdane OCH <sub>3</sub> H OAc	V. agnus-castus V. rotundifolia	Fruit/MeOH extract		(Ono et al., 2009) (Ono et al., 1999)
121	Iso-ambreinolide	V. agnus-castus	Fruit/hexane part		(Ono et al., 2009)
122	(rel 35,55,8R,9R,105)-3,9-dihydroxy-13 (14)-labden-16,15-olide	V. rotundifolia	Fruit/MeOH extract, DCM soluble fraction		(Lee et al., 2013)
123	9,13-Epoxy-16-norlabda-13E-en-15-al	V. rotundifolia	Fruit/MeOH extract, DCM soluble fraction	NO production inhibitory in LPS- stimulated RAW 264.7 cells with IC <sub>50</sub> value of 41.8 μM.	(Lee et al., 2013)

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TABLE 2	(Continued)				
Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
124	Isolophanthin A	V. rotundifolia	Fruit/MeOH extract, DCM soluble fraction		(Lee et al., 2013)
125	13-epi-2-Oxokolavelool	V. rotundifolia	Fruit/MeOH extract, DCM soluble fraction		(Lee et al., 2013)
126	Vitextrifolin A MeO, O, OMe H AcO	V. trifolia	Fruit/hot aq. EtOH (80%) extract, DCM fraction		(Zheng et al., 2013)
127	Vitextrifolin B MeO, O, H OMe AcO	V. trifolia	Fruit/hot aq. EtOH (80%) extract, DCM fraction		(Zheng et al., 2013)
128	Vitextrifolin C	V. trifolia	Fruit/hot aq. EtOH (80%) extract, DCM fraction		(Zheng et al., 2013)
129	Vitextrifolin D O (,,)OH	V. trifolia	Fruit/hot aq. EtOH (80%) extract, DCM fraction		(Zheng et al., 2013)

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TABLE 2	(Continued)				
Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
130	Vitextrifolin E	V. trifolia	Fruit/hot aq. EtOH (80%) extract, DCM fraction		(Zheng et al., 2013)
131	Vitextrifolin F	V. trifolia	Fruit/hot aq. EtOH (80%) extract, DCM fraction		(Zheng et al., 2013)
132	Vitextrifolin G	V. trifolia	Fruit/hot aq. EtOH (80%) extract, DCM fraction		(Zheng et al., 2013)
133	Deacetylvitexilactone	V. trifolia	Fruit/hot aq. EtOH (80%) extract, DCM fraction		(Zheng et al., 2013)
134	Negundol HO シーの	V. trifolia	Fruit/hot aq. EtOH (80%) extract, DCM fraction		(Zheng et al., 2013)
		V. negundo.	Fruits/80% EtOH extract	Antifungal activity with MIC <sub>80</sub> values in the range of 16–64 μg/ml	(Zheng, Lan, Wang, et al., 2012)
	Aco T		Fruit/EtOAc fraction of the MeOH extract		(Fang et al. 2016b)
135	125,165/R-Dihydroxy-ent-labda- 7,13-dien-15,16-olide OH OH	V. rahmannii	Aerial part/MeOH	Antioxidant, antimicrobial and cytotoxicity activity.	(Nyiligira, Viljoen, Van Heerden, et al., 2008)
					10 11

TABLE 2	(Continued)				
Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
136	Prerotundifuran	V. rotundifolia	Seeds/Light petroleum extract		(Asaka et al., 1973)
137	6-Acetoxy-9,13;15,16-diepoxy- 15-methoxylabdane	V. trifolia	Fruits/H <sub>2</sub> O: acetone -7:3(v/v), CHCl <sub>3</sub> extract	Inhibition of HeLa cell proliferation.	(Wu et al., 2009)
138	Vitetrifolin I OH OH	V. trifolia	Fruits/H <sub>2</sub> O: Acetone 7:3 (v/v), CHCl <sub>3</sub> extract	Cytotoxic activity, inhibition of HeLa cell proliferation, induced cell cycle G0/G1 phase arrest and apoptosis of HeLa cells.	(Wu et al., 2009)
139	Nishindanol HO	V. negundo	Whole plant/MeOH extract, EtOAc fraction	Exhibited cytotoxicity against cancer cell lines and Hedgehog (Hh) signaling pathway inhibitor.	(Arai et al., 2013)
140	Acuminolide	V. vestita	Leaves/DCM extract	Cytotoxicity against human colon cancer carcinoma HCT-116 cell line $(1 < IC_{50}s$ $< 10 \mu$ M) and on a human fetal lung fibroblast MRC5 cell line $(1 < IC_{50}s < 10 \mu$ M).	(Corlay et al., 2015)
	U H OH	V. cofassus	Leaves/MeOH extract	Potent antiproliferative activity against five human tumor cell lines, namely lung carcinoma (A549), epidermoid carcinoma (KB), vincristine-resistant KB subline (KB-VIN), triple-negative breast cancer (MDA- MB-231), and estrogen receptor- positive breast cancer (MCF-7) with IC <sub>50</sub> values ranged from 5.4 to 8.9 µM.	(Rasyid et al., 2017)

TABLE 2	(Continued)				
Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
141	8,13-Dihydroxy-14-labdene HO <sup>V</sup> OH	V. agnus-castus	Seeds/70% ethanol (v/v), hexane extract		(Jarry et al., 2006)
142	8-epi-Manoyl oxide	V. agnus-castus	Fruit/n-hexane Fruit/ 70% EtOH extract, CHCl <sub>3</sub> fraction Fruit/defatted MeOH extract	Weak cytotoxicity activity against chronic myelogenous leukemia (K562) cell lines with IC <sub>50</sub> value of 4.56 µg/ml	(Li et al., 2013) (Pal et al., 2013) (Chen et al., 2011)
143	Vitrifolin B	V. rotundifolia	Fruit/MeOH extract/ CHCl <sub>3</sub> fraction		(Wang et al., 2014)
144	6 <i>β</i> ,7 <i>β</i> -Diacetoxy-13-hydroxylabda- 8,14-diene HO OAc	V. agnus-castus	Fruit/hexane 100% Vitex agnus-castus extract BNO 1095 [extract of finely ground seeds with aq. ethanol 70% (v/v)]-n hexane fraction	Showed dopamine-D <sub>2</sub> - receptor affinity. Affinity to the dopamine-D <sub>2</sub> - receptor.	(Hoberg et al., 1999) (Jarry et al., 2006)
145	Limonidilactone	V. limonifolia	Leaves/n-hexane		(Aphaijitt, Nimgirawath, Suksamrarn, et al., 1995)
146	(rel 55,6R,8R,9R,105,135,155, 16R)- 6-Acetoxy-9,13;15,16-diepoxy- 15,16-dimethoxylabdane H OCH <sub>3</sub> H OCH <sub>3</sub> H OCH <sub>3</sub> H OCH <sub>3</sub>	V. rotundifolia	Fruit/MeOH extract		(Ono et al., 1999)

	ADLE 2	(Continued)				
	Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
	147	(rel 55,6R,8R,9R,10S,13S,15R, 16R)- 6-Acetoxy-9,13,15,16-diepoxy- 15,16-dimethoxylabdane H OCH <sub>3</sub> H OCH <sub>3</sub> OCH <sub>3</sub> OCH <sub>3</sub>	V. rotundifolia	Fruit/MeOH extract	DPPH free radical scavenging activity.	(Ono et al., 1999)
	148	(rel 55, 6R, 8R, 9R, 105, 135, 155, 165)- 6-Acetoxy-9,13,15,16-diepoxy- 15,16-dimethoxylabdane H <sub>3</sub> CO H <sub>3</sub> CO H H OAc	V. rotundifolia	Fruit/MeOH extract		(Ono et al., 1999)
	149	(rel 55, 6R, 8R, 9R, 105, 135, 15R, 16S)- 6-Acetoxy-9,13,15,16-diepoxy- 15,16-dimethoxylabdane H <sub>3</sub> CO H <sub>3</sub> CO H <sub>4</sub> OCH <sub>3</sub> OCH <sub>3</sub>	V. rotundifolia	Fruit/MeOH extract		(Ono et al., 1999)
	150	Vitrifolin A OH OH OAc	V. trifolia	Fruit/MeOH extract	NO production inhibitory in LPS- stimulated RAW 264.7 cells with $IC_{50}$ value of 22.3 $\mu$ M.	(Zhang, Zhang, Xie, & Row, 2013)
	151	Ferruginol OH	V. rotundifolia	Fruit/MeOH extract	In-vitro strong DPPH radical scavenging activity.	(Ono et al., 1999)
	152	5β-Hydro-8,11,13-abietatrien-6α-ol	V. negundo	Seeds/CHCl <sub>3</sub> extract		(Chawla, Sharma, Handa, et al., 1991)

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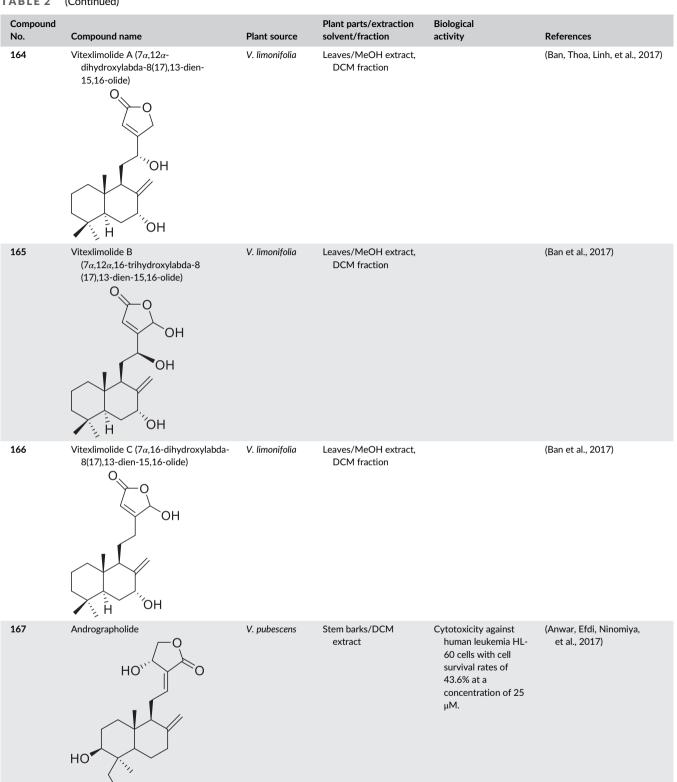
TABLE 2	(Continued)				
Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
153	3β-Hydroxy-abieta-8,11,13-trien- 7-one	V. negundo	Seeds/DCM fraction		(Zheng, Huang, Wang, et al., 2010)
154	Abieta-9 (11), 12-diene	V. rotundifolia	Fruit		(Sakurai, Okamoto, Kokubo, & Chida, 1999)
155	Abietane 9(11):12(13)-di- $\alpha$ -epoxide	V. rotundifolia	Fruit		(Sakurai et al., 1999)
156	Cleroda-7,14-dien-13-ol H <sub>3</sub> C HO H H CH <sub>3</sub>	V. agnus-castus	Seeds/70% ethanol (v/v), hexane extract	High dopaminergic activity.	(Jarry et al., 2006)
157	Cleroda-1,3,14-trien-13-ol H <sub>3</sub> C H H H H CH <sub>3</sub>	V. agnus-castus	Seeds/70% ethanol (v/v), hexane extract	High dopaminergic activity.	(Jarry et al., 2006)
158	(55,6R, 8R,9R,10S)-6-acetoxy-9, 16-dihydroxy-13,(14)-labden- 16,15-olide OH	V. rotundifolia	CH <sub>2</sub> Cl <sub>2</sub> soluble fraction of MeOH extract of whole plant		(Kim et al., 2013)

	(continued)				
Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
159	3β- hydroxyanticopalic acid O OH HO	V. vestita	Leaves/DCM fraction		(Corlay et al., 2015)
160	8α-Hydroxyanticopalic acid O OH	V. vestita	Leaves/DCM fraction		(Corlay et al., 2015)
161	6α-Hydroxyanticopalic acid O OH	V. vestita	Leaves/DCM fraction		(Corlay et al., 2015)
162	Isoambreinolide	V. trifolia	Leaves/MeOH extract/ hexane fraction	Antitubercular activity against Mycobacterium tuberculosis H37Rv in BACTEC-460 assay with MIC value 25 µg/ml	(Tiwari, Thakur, et al., 2013)
163	Nakamurol C	V. kwangsiensia	Fruits/MeOH extract, CHCl₃ fraction		(Shen, Wang, Zhu, et al., 2019)

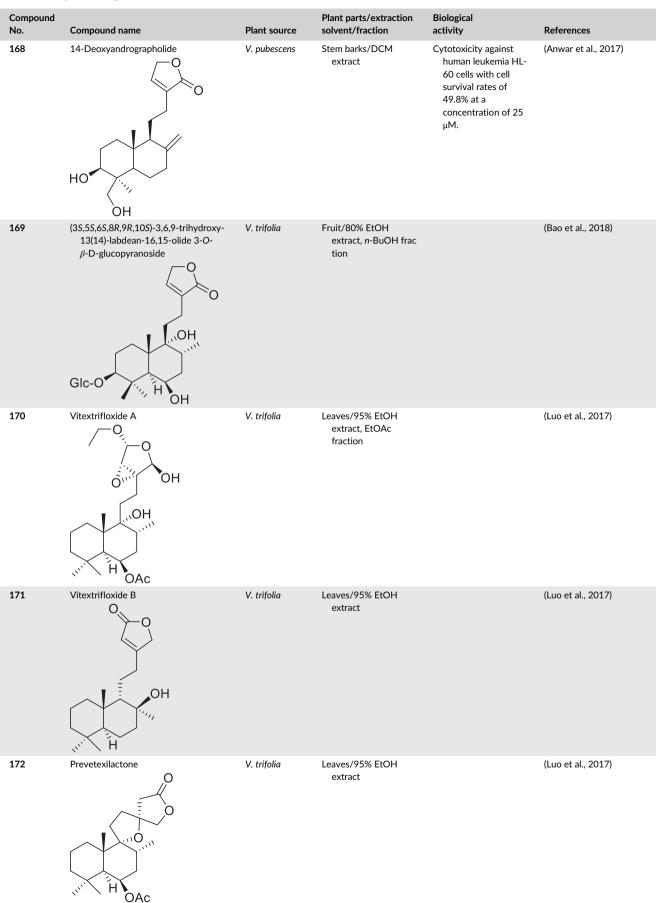
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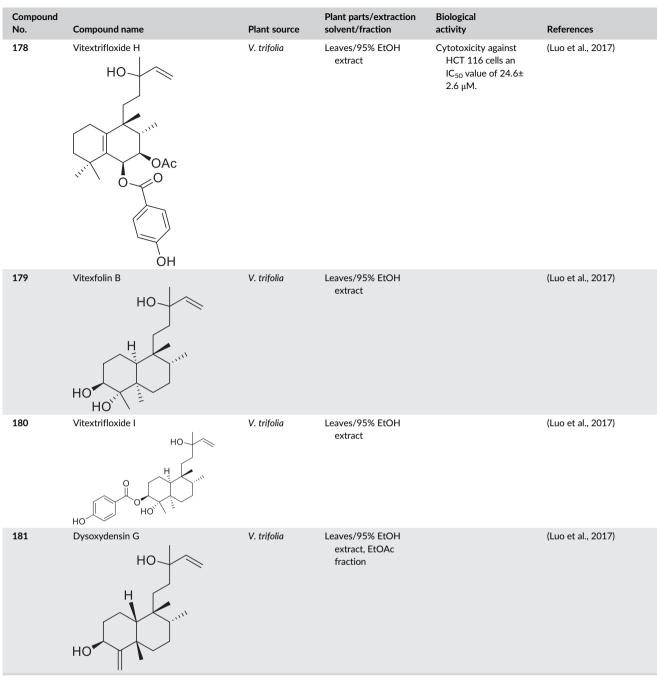
TABLE 2	(Continued)				
Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
173	Vitextrifloxide C	V. trifolia	Leaves/95% EtOH extract		(Luo et al., 2017)
174	Vitextrifloxide D	V. trifolia	Leaves/95% EtOH extract		(Luo et al., 2017)
175	Vitextrifloxide E	V. trifolia	Leaves/95% EtOH extract		(Luo et al., 2017)
176	Vitextrifloxide F HO  OMe	V. trifolia	Leaves/95% EtOH extract		(Luo et al., 2017)
177	Vitextrifloxide G HO ,	V. trifolia	Leaves/95% EtOH extract	Cytotoxicity against HCT 116 cells an IC <sub>50</sub> value of 20.3± 2.6 μM.	(Luo et al., 2017)

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#### TABLE 2 (Continued)



Ambika and Sundrarajan (2015a, 2015b) on studying synthesis of zinc oxide nanoparticles (ZnO NPs) with V. *negundo* extract found a significant antibacterial activity against *S. aureus* and *E. coli*. In addition, the authors discussed the capacity of Vitex nanoparticles to bind to human albumin serum. Moreover, *Candida* species were susceptible to the essential oil from V. *agnus-castus* seeds in doses ranging between 0.13 and 2.13 mg/ml (Asdadi et al., 2015).

The labdane diterpenes, 9-hydroxy-13 (14)-labden-15,16-olide (50), and isoambreinolide (162) isolated from V. *trifolia* leaves exhibited antitubercular activity against *Mycobacterium tuberculosis* 

H37Rv in BACTEC-460 assay with MIC value of 100 and 25  $\mu$ g/ml, respectively (Tiwari, Thakur, et al., 2013).

Nowadays, resistance to currently available antimicrobials represents a serious problem. Therefore, to develop the newer classes of antimicrobials is an urgent requirement for the humans and other domesticated animals. Extracts from the different parts of V. *doniana*, V. *rivularis*, V. *agnus-castus*, V. *rotundifolia*, and V. *negundo* were identified, and various compounds were also isolated to have their antimicrobial activity against a wide range of bacteria and fungi. Among different *vitex* mentioned here either for their antibacterial or

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Compound No.	l Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
182	Ursolic acid	V. negundo	Defatted leaf powder/ MeOH extract		(Chandramu, Manohar, Krupadanam, & Dashavantha, 2003)
	Н соон		Leaves/95% EtOH extract/EtOAc fraction		(Li, Su, Sun, et al., 2014)
			Powdered seeds/aqueous ethanol (80% v/v) extract, DCM fraction		(Zheng, Huang, Wu, et al., 2010)
			Powdered fruit/MeOH extract, EtOAc fraction	Brine shrimp lethality with $LC_{50}$ value 7.7 $\mu M$ .	(Fang et al. 2016b)
		V. trifolia	Leaves/MeOH extract/n- hexane fraction		(Tiwari, Thakur, et al., 2013)
		V. peduncularis	Leaves/acetone extract		(Sahu, Roy, & Mahato, 1984)
		V. altissima	Leaves/EtOAc extract	Exhibited moderate 5-lipoxygenase enzyme inhibitory activity (70%) at a dose of 500 µM.	(Sridhar, Rao, & Subbaraju, 2005)
183	2,3-dihydroxy-12-ursen-28-oic acid	V. agnus-castus	Fruit/acetone extract		(Ono et al., 2011)
184	$2\alpha$ -Hydroxy-ursolic acid	V. agnus-castus	Fruit/acetone extract		(Ono et al., 2011)
		V. peduncularis	Leaves/acetone extract		(Sahu et al., 1984)
		V. negundo	Leaves/MeOH, CHCl <sub>3</sub>		(Rudrapaul, Sarma, Das,
			fraction Leaves/95% EtOH, EtOAc fraction		et al., 2014) (Li et al., 2014)
185	Salvin A	V. cienkowskii	Stem bark/DCM-MeOH	Vasorelaxant properties.	(Dongmo, Azebaze, Donfack,
	HO,,, HO		and MeOH fraction		et al., 2011)
186	2α,3α-Dihydroxyurs-12, 20 (30)-dien- 28-oic acid	V. negundo	Leaves/95% EtOH, EtOAc fraction	NO production inhibitory activity in LPS-induced RAW 264.7 macrophages with IC <sub>50</sub> value 26.1 ± 3.6 μM.	(Li et al., 2014)
	HO,,, H HO''' H HO''' H			vaiue 20.1 ± 3.0 μm.	
187	$2\alpha$ , $3\alpha$ , $19\alpha$ -Trihydroxyurs-12-en-28-oic	V. negundo	Leaves/95% EtOH extract/		(Li et al., 2014)
	acid		EtOAc fraction		
	HO <sub>1/2</sub> HO <sub>1/2</sub>		Fruits/MeOH, EtOAc fraction		(Fang et al. 2016b)
	HO				

#### TABLE 3 List of triterpenoids reported from different species of Vitex and their biological activities

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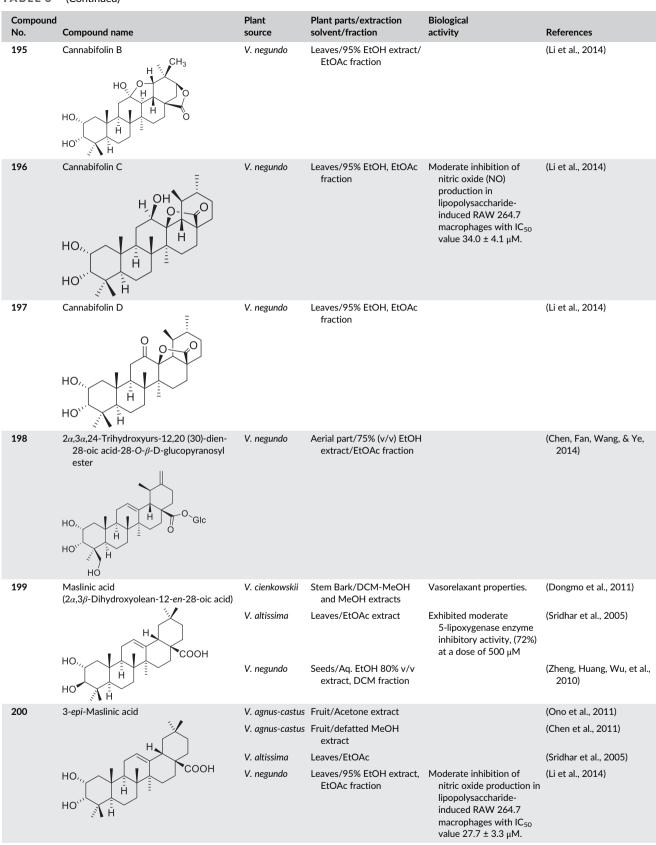
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TABLE 3	(Continued)				
Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
188	2 <i>a</i> ,3 <i>a</i> -Dihydroxyurs-12- <i>en</i> - 28-oic acid HO,, HO,, HO,, H	V. negundo	Leaves/95% EtOH, EtOAc fraction Fruits/MeOH extract/ EtOAc fraction	Brine shrimp lethality with LC <sub>50</sub> value 14.8 μM.	(Li et al., 2014) (Fang et al. 2016b)
189	$2\alpha,3\beta$ -Dihydroxyurs-12-en-28-oic acid HO,,, HO,,, HO,,, HO,,, HO,,, HO,,, HO,,,, HO,,,, HO,,,,, HO,,,,,,,,	V. trifolia	Leaves and twigs/MeOH extract		(Huang et al., 2013)
190	2 <i>α</i> -Hydroxyursolic acid	V. negundo	Seeds/95% EtOH, DCM fraction	$\begin{array}{l} \mbox{Moderate cytotoxic activity}\\ \mbox{against HepG2 cell line}\\ \mbox{with IC}_{50} \mbox{value 29.41}\\ \mbox{$\mu$M$, HCT116 cell line}\\ \mbox{with IC}_{50} \mbox{value 25.00}\\ \mbox{$\mu$M$, A2780 cell lines}\\ \mbox{with IC}_{50} \mbox{value}\\ \mbox{13.67}\mbox{$\mu$M$, and mild}\\ \mbox{inhibitory effects on}\\ \mbox{$LPS$-stimulated NO}\\ \mbox{$production with IC}_{50}\\ \mbox{$value > 3$$$$\mu$M}. \end{array}$	(Hu et al., 2016)
191	Tormentic acid HO,,, HO,,, HO,,,	V. negundo V. peduncularis	Leaves/95% EtOH extact/ EtOAc fraction	Moderate inhibition of nitric oxide (NO) production in lipopolysaccharide induced RAW 264.7 macrophages with IC <sub>50</sub> value 24.9 $\pm$ 4.6 $\mu$ M.	(M. M. Li et al., 2014) (Rudrapaul et al., 2014)
192	HO HO HO HO HO HO HO HO HO HO HO HO HO H	V. negundo	CHCl <sub>3</sub> fraction Seeds/aq. EtOH 80% (v/v)	Strongly cytotoxic against ZR-75-30 cell line with $IC_{50}$ value of 0.56 $\pm$ 0.19 $\mu$ g/ml and moderate cytotoxic to HCT116, HL-60 cell lines with $IC_{50}$ values of 14.95 $\pm$ 3.17, 9.11 $\pm$ 2.63 $\mu$ g/ml, respectively.	(Zheng, Pu, et al., 2012)
193	Negundonorin B HO <sub>1</sub> , HO <sup>1</sup> , HO <sup>1</sup> , H	V. negundo	Seeds/aq. EtOH 80% (v/v)	Moderate cytotoxicity against HL-60 cell line having $IC_{50}$ value 17.52 $\pm$ 3.85 µg/ml and ZR- 75-30 cell line having $IC_{50}$ value 39.26 $\pm$ 4.15µg/ml	(Zheng, Pu, et al., 2012)
194	Cannabifolin A H0, H H0, H H0, H H0, H H	V. negundo	Leaves/95% EtOH/EtOAc fraction		(Li et al., 2014)



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TABLE 3	(Continued)				
Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
201	Acetyloleanolic acid (oleanolic acid acetate)	V. negundo	Roots/ DCM:MeOH (1:1)	<i>In vitro</i> hepatoprotective activity.	(Mishra, Pani, Rout, et al., 2014)
202	3β-Acetoxyolean-12- <i>en</i> - 27-oic acid	V. negundo V. negundo	Defatted seeds/CHCl <sub>3</sub> Whole plant/acetone		(Chawla, Sharma, Handa, & Dhar, 1992) (Verma, Siddiqui, & Aslam, 2011)
203	2 <i>a</i> ,3 <i>a</i> -Dihydroxyolean-5, 12- dien-28-oic acid	V. negundo	Defatted seeds/CHCl <sub>3</sub> Roots/MeOH	Mild anti-inflammatory activity.	(Chawla, Sharma, Handa, & Dhar, 1992) (Srinivas, Rao, Rao, & Raju, 2001)
204	2α,3α-dihydroxyolean-12- <i>en</i> -28-oic acid HO,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	V. negundo	Fruits/MeOH, EtOAc fraction Calli/80% Ethanol, EtOAc fraction	Brine shrimp lethality with $LC_{50}$ value 29.4 $\mu$ M.	(Fang et al. 2016b) (Noel & Dayrit, 2005)
205	2β,3α-Diacetoxyoleana-5,12-dien-28-oic acid	V. negundo	Defatted seeds/CHCl <sub>3,</sub> Roots/MeOH		(Chawla, Sharma, Handa, & Dhar, 1992) (Srinivas et al., 2001)
206	2 <i>a</i> ,3 <i>β</i> -Diacetoxy-18-hydroxyoleana- 5,12-dien-28-oic acid HO AcO, AcO	V. negundo V. negundo	Defatted seeds/CHCl <sub>3,</sub> Roots/MeOH		(Chawla, Sharma, Handa, & Dhar, 1992) (Srinivas et al., 2001)
	2a,3a,24-trihydroxyolean-12- <i>en</i> -28-oic acid HO <sub>1</sub> , HO <sub>1</sub> , HO <sub>1</sub> , HO	V. negundo	Leaves/95% EtOH extract/ EtOAc fraction	Moderate inhibition of nitric oxide (NO) production in lipopolysaccharide- induced RAW 264.7 macrophages with IC <sub>50</sub> value 40.5 ± 4.9 µM.	(Li et al., 2014)

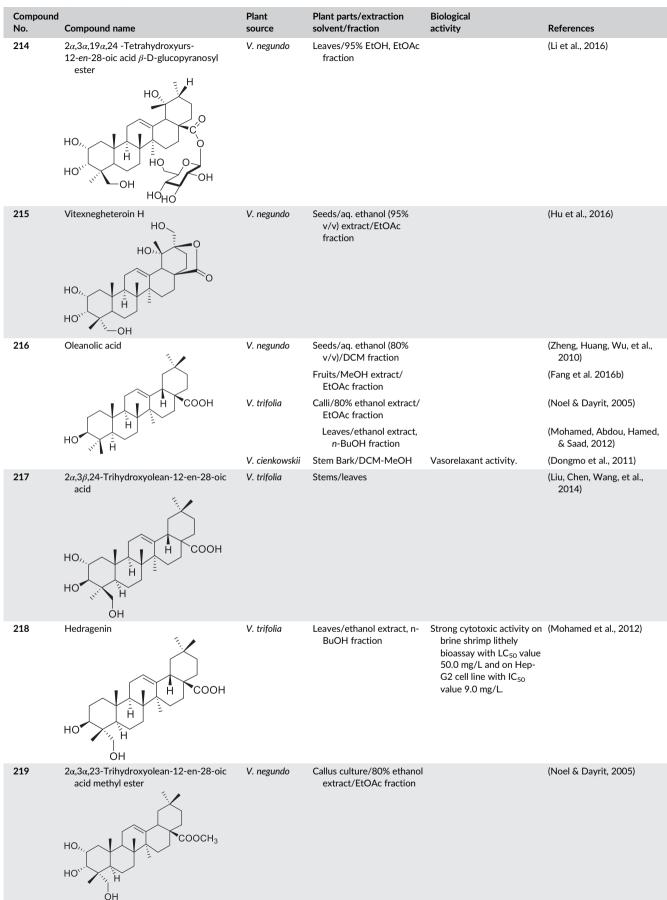
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	Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
	208	Cannabifolin E HO,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	V. negundo	Leaves/95% EtOH extract/ EtOAc fraction		(Li et al., 2014)
	209	Cannabifolin F HOr, HO <sup>11</sup>	V. negundo	Leaves/95% EtOH extract/ EtOAc fraction		(Li et al., 2014)
	210	Betulinic acid	V. negundo	Defatted leaf powder/ MeOH extract		(Chandramu et al., 2003)
				Seeds/Aq. EtOH 80% v/v, DCM fraction		(Zheng, Huang, Wu, et al., 2010)
		но Л н	V. trifolia	Leaves and twigs/MeOH, EtOAc fraction		(Huang, Zhong, Xie, et al., 2013)
	211	$3\beta$ -Hydroxy-11-oxours-12-ene	V. negundo	Leaves/70% EtOH		(Qiu et al., 2016)
	212	Vulgarsaponin A	V. negundo	Aerial part/75% (v/v) EtOH extract/EtOAc fraction		(Chen et al., 2014)
				Leaves/95% EtOH extract/ EtOAc fraction		(Li, Li, SunJ, et al., 2016)
	213	2a,3a,19a,24-Tetrahydroxyolea-12-en- 28-oic acid $\beta$ -D-glucopyranosyl ester HO, HO, HO, HO, HO, HO, HO, HO, HO, HO,	V. negundo	Leaves/95% EtOH, EtOAc fraction		(Li et al., 2016)
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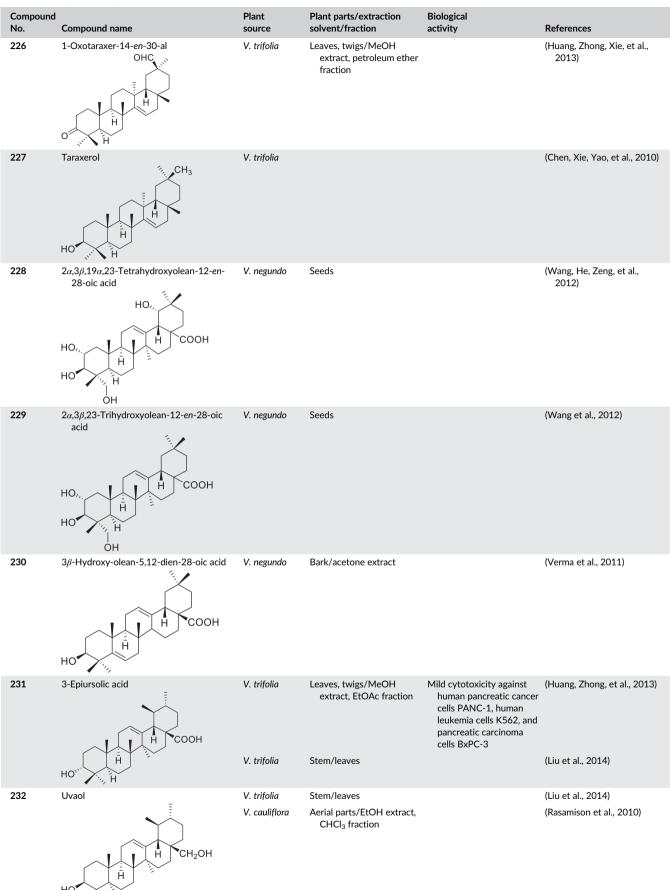


Dens Not Compound namePlant SourcePlant participationBiological activity220 $2nd_{2}2-Tinp(recorption (12 m - 20 m))$ andV. regardsCalls caller (100 minute) straC/EOAC fraction(Neel 4, Dayrit, 2005)221 $\beta$ AmyrinV. trifolio $\psi_{ij}$ $\psi_{ij}$ Loss (callers callers ca	TABLE 3	(Continued)				
$ \begin{array}{c c c c c c } \mbox{add} & \mbox{etacl}, \mbox{function} & \mbox{etacl}, \mbox{function} & \mbox{function}, \mbox{function} & \mbox{function}, funct$	-	Compound name				References
$ \begin{array}{ c c c c } \hline & & & & & & & & & & & & & & & & & & $		acid HO,, HO <sup>V</sup> , H	V. negundo			(Noel & Dayrit, 2005)
$ \begin{array}{ c c c c } & & & & & & & & & & & & & & & & & & &$		HO		BuOH fraction Callus culture/80% ethanol		
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	222		V. trifolia			(Mohamed et al., 2012)
$12 - en - 28 - oic acid O - a - L- rhamnopyranosyl-(1''' - 4'') - O - \beta - D- glucopyranosyl-(1'' - 6') - O - \beta - D- glucopyranoside ester  + \int_{H} + \int_$	223	$(1''' \rightarrow 4'')$ -O-[ $\beta$ -D-(E-6'''-O-Caffeoyl)- glucopyranoside]-oxy-olean-12- <i>en</i> -	V. trifolia		brine shrimp lithely bioassay with LC <sub>50</sub> value 41.0 mg/L and on Hep- G2 cell line with IC <sub>50</sub>	(Mohamed et al., 2012)
extract, petroleum ether 2013)		12- <i>en</i> -28-oic acid O-α-L- rhamnopyranosyl-(1 <sup><i>m</i></sup> →4 <sup><i>m</i></sup> )-O-β-D- glucopyranosyl-(1 <sup><i>m</i></sup> →6 <sup><i>m</i></sup> )-O-β-D- glucopyranoside ester HO <sub>3</sub> SO H H C <sup><i>n</i></sup> O OH HO OH OH HO HO OH OH HO	V. trifolia			(Mohamed et al., 2012)
	225		V. trifolia	extract, petroleum ether		

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#### TABLE 3 (Continued)



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1	ABLE 3	(Continued)				
	Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
	233	α-Amyrin HO HO HO HO	V. trifolia	Leaves/MeOH extract, hexane fraction		(Tiwari, Thakur, et al., 2013)
	234	Corosolic acid	V. trifolia	Leaves/MeOH extract, <i>n</i> - BuOH fraction		(Tiwari, Thakur, et al., 2013)
			V. negundo	Aerial part/75% (v/v) EtOH extract, EtOAc fraction		(J. Chen et al., 2014)
		но,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	V. negundo	Powdered fruit/MeOH, EtOAc fraction		(Fang et al. 2016b)
		HO	V. altissima	Leaves/ethyl acetate	Exhibited moderate 5-lipoxygenase enzyme inhibitory activity (80%) at a dose of 500 µM	(Sridhar et al., 2005)
	235	3-epi-Corosolic acid	V. altissima	Leaves/ethyl acetate	Exhibited moderate 5-lipoxygenase enzyme inhibitory activity (79%) at a dose of 500 µM	(Sridhar et al., 2005)
		HOM HOM H	V. negundo	Seeds/ 80% EtOH(v/v), CH <sub>2</sub> Cl <sub>2</sub> fraction	$\begin{array}{l} \mbox{Modest cytotoxicity} \\ \mbox{against HL-60 cell line} \\ \mbox{with IC}_{50} \mbox{value 21.30} \\ \mbox{\pm}2.20 \ \mbox{µg/ml} \mbox{ and ZR-} \\ \mbox{75-30 human cancer cell} \\ \mbox{line with IC}_{50} \mbox{ value} \\ \mbox{28.41 \pm 5.31 \ \mbox{µg/ml}} \end{array}$	(Zheng, Pu, et al., 2012)
	236	Ursolic acid acetate	V. trifolia	Leaves/ethanolic extract		(Jangwan, Aquino, Mencherini, et al., 2013)
	237	Lupeol HO HO HO HO	V. trifolia	Leaves and twigs/MeOH, Pet. ether extract		(Huang, Zhong, et al., 2013)
	238	Platanic acid H H H COOH	V. trifolia	Leaves/ethanolic extract		(Jangwan et al., 2013)
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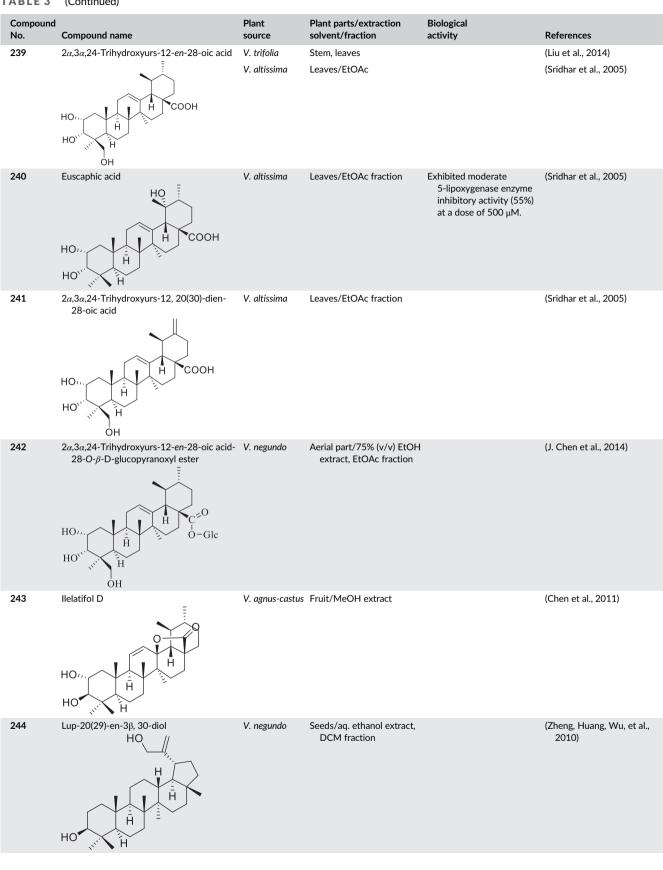
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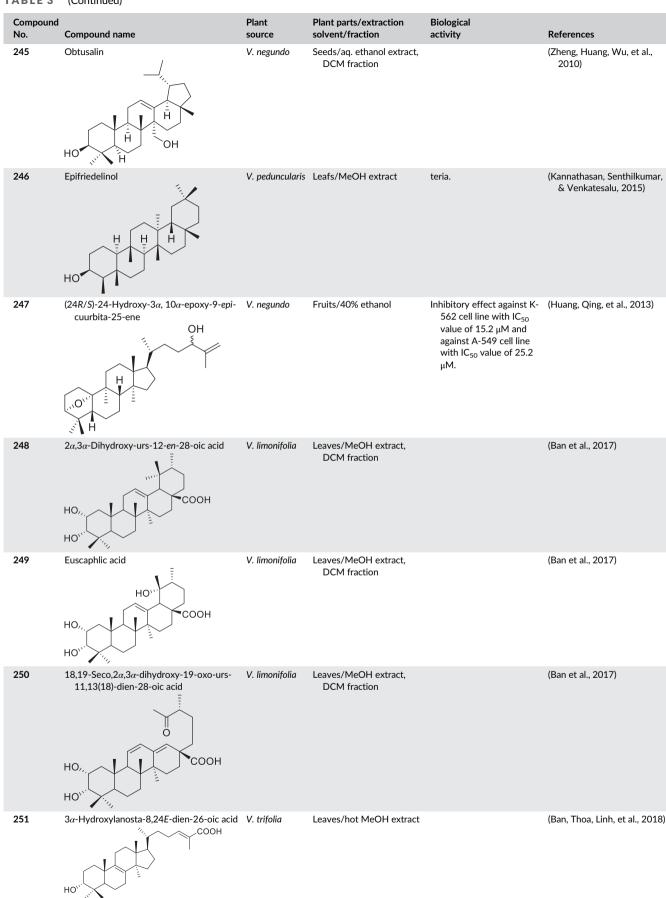
#### TABLE 3 (Continued)

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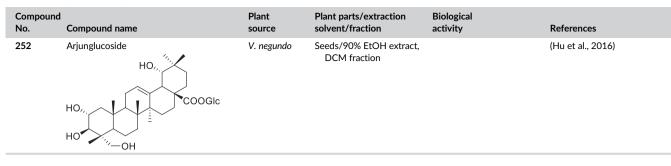


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antifungal activity V. *negundo* is one with both the antibacterial and antifungal activities. This particular medicinal plant may take place in the pharma industry as an important source of antimicrobial agent in the coming days.

#### 5.1.3 | Anticancer activity

The flavonoid casticin (**292**) isolated from the fruits of *V. rotundifolia* showed significant cytotoxicity against human lung cancer cells (PC-12) and human colon cancer cells (HCT 116) with  $GI_{50}$  values of 114 and 119 ng/ml, respectively, in MTT assay. The standard drug cisplatin showed  $GI_{50}$  of 111 and 794 ng/ml, against PC-12 and HCT 116 cells, respectively (Ono et al., 2002). Casticin (**292**) also significantly inhibited gallbladder cancer cell proliferation in a dose- and time-dependent manner (Ling, Jiao, Feng, et al., 2017).

Vitexicarpin (also known as casticin) (**292**) isolated from the leaves of V. *negundo* showed antiproliferative activity against KB, LNCaP, and Lul (human lung) cancer cells with  $ED_{50}$  values of 0.5, 0.5, and 0.7 µg/ml, respectively (Díaz et al., 2003).

Negundonorin A (**192**) isolated from V. *negundo* seeds showed strong cytotoxicity against breast cancer (ZR-75-30) cells with IC<sub>50</sub> value of 0.56  $\pm$  0.19 µg/ml, while negunfurol (**430**) isolated from the same plant exhibited potent cytotoxicity against HL-60 cells with IC<sub>50</sub> of 0.94  $\pm$  0.26 µg/ml (Zheng, Pu, et al., 2012). The compound (6-hydroxy-4-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-3,4-dihydro-2-naphthaldehyde) (**371**) was isolated from V. *negundo* seeds and exhibited cytotoxic activity against HepG2 comparable to positive control (Hu et al., 2016). A clerodane-type diterpene named acuminolide (**140**) isolated from V. *cofassus* Reinw. ex Blume exhibited antiproliferative activity against human tumor cells (lung carcinoma, breast cancer strains, and epidermoid carcinoma lines) with IC<sub>50</sub> values ranging from 6.4 to 11.4 µM (Rasyid et al., 2017).

Methanolic extract of V. *negundo* showed lethal concentration  $(LC_{50})$  of (660.85 ± 74.86 mg/ml) for 50% mortality of brine shrimp A. *salina* in Artemia nauplii cytotoxicity assay (Prakash et al., 2016).

Ethanolic extract from V. *trifolia* shows significant anticarcinogenic effect *in-vitro* by rendering 85% protection to hepatic microsomes against the degranulatory attack by the carcinogen 3,8-diamino-5-ethyl-6-phenylphenanthridinium bromide (EB) in rat hepatic microsomal degranulation method (Mathankumar, Tamizhselvi, Manickam, & Purohit, 2015).

Vitexicarpin (**292**) isolated from the fruits of V. *rotundifolia* showed significant *in-vitro* antiangiogenic activity by inhibiting vascular-endothelial growth factor (VEGF)-induced endothelial cell (EC) proliferation, migration, and capillary-like tube formation on matrigel in a dose-dependent manner (0.1–5.0  $\mu$ M) (Zhang, Liu, Zhao, et al., 2013).

#### 5.1.4 | Antioxidant activity

6'-O-trans-caffeoylnegundoside (14), 2'-O-p-hydroxybenzoylgardoside (22) and 2'-O-p-hydroxybenzoyl-6'-O-trans-caffeoyl-8-epiloganic acid (8) isolated from V. altissima leaves exhibited potent antioxidant activity, both in superoxide free-radical scavenging assay (using NBT method) (IC<sub>50</sub>, 24.3, 32.0, and 31.9 μM, respectively) and in DPPH radical scavenging assay (IC<sub>50</sub>, 15.2, 10.9, and 11.4 μM, respectively) in comparison to the known antioxidants, BHT, and α-tocopherol, having IC<sub>50</sub> values 381 and 19 μM, respectively (Sridhar et al., 2004).

Lignans isolated from the seeds of V. *negundo* showed antioxidant activity both in lipid peroxidation and DPPH methods. The antioxidant activity was higher with the DPPH method. Among the tested lignans, vitedoamine A (**356**), 6-hydroxy-4-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-3,4-dihydro-2-naphthaldehyde (**371**), and vitrofolal F (**366**) showed radical scavenging activity similar to  $\alpha$ -tocopherol (standard antioxidant) in the DPPH assay (Ono et al., 2004).

The lignans, vitecannasides A (**374**) and B (**375**) and the flavonoids, isoorientin (**267**), and orientin (**269**) isolated from the fruits of *V. cannabifolia* showed stronger antioxidant activity than that of Lcysteine in the DPPH assay. The activity of iso-orientin (**267**) and orientin (**269**) was more than that of  $\alpha$ -tocopherol (standard antioxidant) in the same assay (Yamasaki et al., 2008).

Vitex honey obtained from V. negundo var. heterophylla showed a strong scavenger action of the DPPH radical with IC<sub>50</sub> values ranging from 44.18 to 55.21 mg ml<sup>-1</sup> and also demonstrated a ferric reducing antioxidant power and ferrous ion-chelating activity (Wang, Li, Cheng, et al., 2015). Methanolic extract from V. doniana Sweet fruit pulp (1.0 mg/ml) demonstrated significant antioxidant activity on the DPPH radical, superoxide ion, hydrogen peroxide, and hydroxyl radical, with

TABLE 4	List of flavonoids reported from differ	ent species of	Vitex and their biological	activities	
Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
253	Apigenin	V. pinnata	Leaves		(Kamal, Clements, Gray, & Ebel, 2011)
	но	V. agnus-castus	Fruits/MeOH	Dose-dependent receptor binding to delta and mu opioid receptors.	(SN. Chen et al., 2011)
	он о		Finely ground seed/aqueous ethanol 70% (v/v)-BNO 1095	Specific ligands for the ERβ.	(Jarry et al., 2006)
254	Apigenin-7-glucoside Glc-0 OH OH OH	V. negundo	Leaves, seeds, roots		(Mingqing Huang, Zhang, Xu, et al., 2015)
255	3-C-Glucopyranosylapigenin HO O OH Glc OH O	V. negundo	Seeds/ 95% EtOH extract, DCM fraction	Moderate inhibitory effects on $\alpha$ -glucosidase (IC <sub>50</sub> , 49.91 ± 4.42 $\mu$ M); strong ABTS radical scavenging activity (IC <sub>50</sub> , 2.37 ± 0.04 $\mu$ M) and weaker DPPH scavenging activity (DPPH assay (IC <sub>50</sub> , 100> $\mu$ M)	(Hu et al., 2017)
	Chrysoplenol D $H_3CO$ $O$ $OH$ $OH$ $H_3CO$ $OCH_3$ $OH$ $OH$ $OH$	V. trifolia	Leaves/MeOH extract, CHCl <sub>3</sub> fraction		(Tiwari, Thakur, et al., 2013)
257	Retusin H <sub>3</sub> CO O O O O O CH <sub>3</sub> O CH <sub>3</sub> O C CH <sub>3</sub> O C CH <sub>3</sub> O C CH <sub>3</sub> O C CH <sub>3</sub> O C CH <sub>3</sub> O C C C C C C C C C C C C C C C C C C	V. pinnata	Leaves/hexane	Antibacterial activity against Microbacterium marinum.	(Kamal et al., 2011)
258	Kaemferol trimetyl ether MeO U U U U U U U U U U U U U U U U U U U	V. pinnata	Leaves		(Kamal et al., 2011)
259	Rhamnocitrin H <sub>3</sub> CO OH OH OH	V. quinata	Leaves/MeOH extract, EtOAc fraction		(Kamal et al., 2011)
260	Eupatorin H <sub>3</sub> CO H <sub>3</sub> CO OH OH	V. agnus-castus	Seeds/70% Aq. EtOH		(Jarry et al., 2006)

#### TABLE 4 List of flavonoids reported from different species of Vitex and their biological activities

(Continues)

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TABLE 4	(Continued)				
Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
261	6-C-Glucosyl-5-O-rhamnopyranosyl- trimethoxy- wogonin OCH <sub>3</sub> HO HO HO Glc OGlc O	V. negundo	Stem Bark/EtOAc		(Subramanian & Misra, 1979)
262	Luteolin OH	V. pinnata	Leaves Leaves/MeOH, EtOAc fraction		(Kamal et al., 2011) (Rudrapaul et al., 2014)
	HO	V. negundo	Leaves/EtOH extract, <i>n</i> - BuOH fraction	Moderate antifungal activity with MIC 25 µg/ml.	(Sathiamoorthy et al., 2007)
	OH O		Leaves/95% EtOH extract, EtOAc fraction	Strong radical scavenging activity {DPPH assay (IC <sub>50</sub> , $3.51 \pm 0.09 \mu$ M), ABTS assay (IC <sub>50</sub> , $0.86 \pm 0.01 \mu$ M)} and moderate a-glucosidase inhibitory effect (IC <sub>50</sub> , $1.62 \pm 0.13 \mu$ M).	(Hu et al., 2017)
			Whole plant/MeOH extract, EtOAc fraction	Exhibited cytotoxicity against cancer cell lines and Hedgehog (Hh) signaling pathway inhibitor.	(Arai et al., 2013)
		V. agnus-castus	Fruit/MeOH	Dose-dependent receptor binding to delta and mu opioid receptors.	(SN. Chen et al., 2011)
		V. trifolia	Leaves and twigs/MeOH	Cytotoxicity against human pancreatic cancer cells PANC-1, human leukemia cells K562, and pancreatic carcinoma cells BxPC-3.	(Ming-Yu Huang et al., 2013)
		V. rotundifolia	Fruit/EtOH extract, EtOAc fraction		(Wu et al., 2010)
263	4',5,7-Trihydroxy-3'-O-β-D-glucuronic acid-6"-methyl Ester O(6"-methylGlcA) HO OH	V. negundo	Leaves/ethanol extract, <i>n</i> -BuOH fraction	Antifungal activity against Trichophyton mentagrophytes and Cryptococcus neoformans at MIC 6.25 µg/ml	(Sathiamoorthy et al., 2007)
264	Vitexin		Leaves/90% EtOH extract Leaves/MeOH extract,		(Sahu et al., 1984) (Rudrapaul et al., 2014)
		V. negundo	EtOAC fraction Roots/MeOH extract		(Srinivas et al., 2001)
		V. trifolia	Leaves/MeOH extract, BuOH fraction		(Tiwari, Thakur, et al., 2013)
	ОН О	V. altissima	Leaves/EtOAc extract	Moderate antioxidant activity, both in NBT ( $IC_{50}$ , 62 µg/ml) and DPPH ( $IC_{50}$ , 43 µg/ml) free radical scavenging tests.	(Sridhar et al., 2005)

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Compound No. 265

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	(Continued)				
ł	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
	Isovitexin	V. negundo	Roots/MeOH		(Srinivas et al., 2001)
	HO Glc OH O		Leaves/95% EtOH, n- BuOH fraction	$\begin{array}{l} \mbox{Moderate radical} \\ \mbox{scavenging {DPPH assay}} \\ \mbox{(IC}_{50}, 50.63 \pm 1.51 \ \mu M) \\ \mbox{ABTS assay (IC}_{50}, 1.70 \\ \pm 0.03 \ \mu M) \\ \mbox{and} \\ \mbox{$\alpha$-glucosidase inhibitory} \\ \mbox{effect (IC}_{50}, 4.60 \pm 0.05 \\ \ \mu M). \\ \end{array}$	(Hu et al., 2017)
		V. peduncularis	Leaves/MeOH extract, EtOAC fraction		(Rudrapaul et al., 2014)
		V. agnus-castus	Seeds/aqueous ethanol 70% extract (v/v)		(Jarry et al., 2006)
	Vitexin 2"-rhamnoside Glc <sup>2</sup> -Rha HO OH OH	V. negundo	Whole plant		(Mingqing Huang et al., 2015)
	Iso-orientin OH	V. cannabifolia	Fruit/MeOH	DPPH radical scavenging activiity.	(Yamasaki et al., 2008)
	но	V. negundo	Leaves/ethanol extract, n- BuOH fraction	Antifungal activity against Trichophyton mentagrophytes at 2 µg/ml concentration.	(Sathiamoorthy et al., 2007)
	Glc OH O	V. negundo	Seeds/ 95% EtOH, DCM fraction	Stronger DPPH radical scavenging activity.	(Hu et al., 2017)
		V. polygama	Leaves/hydroalcoholic extract, <i>n</i> -BuOH fraction		(Gallo, Vieira, Fernandes, et al., 2008)
		V. agnus-castus	Seeds/ aqueous ethanol 70% (v/v)		(Jarry et al., 2006)
	Isoorientin-6"-O-caffeate HO OH (6"-caffeoyl)Glc OH O	V. negundo	Seeds/ 95% EtOH, DCM fraction	Potent antioxidant {DPPH assay (IC <sub>50</sub> , 3.38 $\pm$ 0.21 $\mu$ M), ABTS assay (IC <sub>50</sub> , 0.75 $\pm$ 0.01 $\mu$ M)} and $\alpha$ -glucosidase inhibitory effects (IC <sub>50</sub> , 0.24 $\pm$ 0.02 $\mu$ M).	(Hu et al., 2017)
	Orientin OH	V. cannabifolia	Fruit/MeOH	Free radical scavenging activity	(Yamasaki et al., 2008)
	Glc OH	V. polygama	Leaves/hydroalcoholic extract, BuOH fraction		(Gallo et al., 2008)
	он о	V. negundo	Seeds/ 95% EtOH extract, DCM fraction	Strong antioxidant activity {DPPH assay (IC <sub>50</sub> , 12.30 $\pm$ 0.54 $\mu$ M), ABTS assay (IC <sub>50</sub> , 0.86 $\pm$ 0.03 $\mu$ M)} and weaker $\alpha$ -glucosidase inhibitory effects (IC <sub>21</sub> , 10.47	(Hu et al., 2017)

Leaves/EtOAc extract

effects (IC<sub>50</sub>, 10.47 ± 0.31 μM)

270 2"-O-p-Hydroxybenzoyl orientin 2"-p-hydroxybenzyl-Glc HO.  $\cap$ 

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V. altissima

,OH

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(Sridhar et al., 2005)

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### TABLE 4 (Continued)

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TABLE 4	(Continued)						
Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References		
271	Luteolin-7-methyl ether H <sub>3</sub> CO OH OH OH	V. agnus-castus	Aerial parts/EtOH:H <sub>2</sub> O (7:3, v/v) extract, EtOAC fraction		(Aissaoui, Algabr, Mezhoud, et al., 2016)		
272	Schaftoside HO O OH Glc OH O	V. polygama V. negundo	Leaves/hydroalcoholic extract, <i>n</i> -BuOH fraction Roots/70% methanol- water (v/v)		(Gallo et al., 2008) (Mingqing Huang et al., 2015)		
273	Isoschaftoside	V. polygama	Leaves/hydroalcoholic extract, <i>n</i> -BuOH fraction		(Gallo et al., 2008)		
	Glc HO Ara OH O	V. negundo	Roots/70% methanol- water (v/v)		(Mingqing Huang et al., 2015)		
274	Flavosativaside Glc <sup>2</sup> -Glc HO OH OH	V. negundo	Roots/70% methanol- water (v/v)		(Mingqing Huang et al., 2015)		
275	Hyperoside HO O O-Glc	V. negundo	Roots/70% methanol- water (v/v)		(Mingqing Huang et al., 2015)		
276	Luteoloside Glc- O O O O O O O O O O O O O O O O O O O	V. negundo	Roots/70% methanol- water (v/v)		(Mingqing Huang et al., 2015)		
277	Kaempferol-3-O-rutinoside HO OH O ORha <sup>1</sup> - <sup>6</sup> Glc	V. negundo	Roots/70% methanol- water (v/v)		(Mingqing Huang et al., 2015)		
278	Kaempferol 3-(6"-malonyl)glucoside 6"-malonyl-Glc HO OH OH	V. negundo	Roots/70% methanol- water (v/v)		(Mingqing Huang et al., 2015)		
279	3-O-Methylkaempferol HO O OH OH O OCH <sub>3</sub>	V. agnus-castus	Fruit/MeOH (90%) extract	Dose-dependent delta and mu opioid receptor binding.	(SN. Chen et al., 2011)		

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TABLE 4	(Continued)				
Compoun No.	d Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
280	Kaempferol HO OH OH OH	V. agnus-castus V. rotundifolia	Fruit/MeOH (90%) extract Fruit/EtOH extract, EtOAc fraction		(SN. Chen et al., 2011) (Wu et al., 2010)
281	Carlinoside OH HO Glc OH OH	V. polygama	Leaves/hydroalcoholic extract, <i>n</i> -BuOH fraction		(Gallo et al., 2008)
282	Isocarlinoside OH HO HO Ara OH OH OH	V. polygama	Leaves/hydroalcoholic extract, <i>n</i> -BuOH fraction		(Gallo et al., 2008)
283	Quercetin HO HO OH OH	V. negundo	Leaves/95% EtOH extract, EtOAc fraction	Strong antioxidant activity {DPPH assay (IC <sub>50</sub> , >100 $\mu$ M), ABTS assay (IC <sub>50</sub> , 2.08 ± 0.10 $\mu$ M)} and moderate $\alpha$ -glucosidase inhibitory effect (IC <sub>50</sub> , 4.27 ± 0.05 $\mu$ M).	(Hu et al., 2017)
	ОН О	V. rotundifolia	Fruit/EtOH extract/ EtOAc fraction		(Wu et al., 2010)
284	3,7-Dimethylquercetin $H_3CO$ $OH$ $OH$ $H_3CO$ $OH$ $OH$ $H_3CO$ $OH$ $OH$	V. agnus-castus	Fruit/MeOH (90%) extract		(SN. Chen et al., 2011)
285	3-Methyl quercetin HO HO OH OCH <sub>3</sub>	V. agnus-castus	Fruit/MeOH (90%) extract		(SN. Chen et al., 2011)
286	3,4'-Dimethoxy quercetin 7-O- glucopyranoside Glc-O OH OH OH OH	V. trifolia	Leaves/EtOH extract, EtOAc fraction	Strong antioxidant capacity with SC <sub>50</sub> value 13.19 ± 0.20 μg/ml.	(Mohamed et al., 2012)
287	3,6,4'-Trimethoxy quercetin 7-O- glucopyuranoside $Glc-O \rightarrow OH \rightarrow OH$ $H_3CO \rightarrow OH \rightarrow OCH_3$	V. trifolia	Leaves/EtOH extract, EtOAc fraction		(Mohamed et al., 2012)

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## TABLE 4 (Continued)

1	ABLE 4	(Continued)				
	Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
	288	Quercetin 7-O-neohespridoside neohespridoside $Rha^2 Glo + OH + O$	V. trifolia	Leaves/EtOH extract, EtOAc fraction	Strong antioxidant capacity with SC <sub>50</sub> value 29.48 $\pm$ 0.47 µg/ml	(Mohamed et al., 2012)
	289	Peduncularisin (5,4'-dihydroxy- 3,6-dimethoxy flavone) OH MeO OH OMe	V. peduncularis	Leaves/acetone extract		(Sahu et al., 1984)
	290	Pachypodol (5,4'-dihydroxy-3,7,3'- trimethoxy flavone) MeO OH OH OH	V. peduncularis	Leaves/acetone extract		(Sahu et al., 1984)
	291	Penduletin	V. agnus-castus	Seeds/aqueous ethanol 70% (v/v)	Specific ligand for the estrogen Receptor $\beta$ .	(Jarry et al., 2006)
		MeO O OMe MeO OH O	V. negundo V. simplicifolia	Fruit/defatted MeOH extract Aerial parts/EtOH extract Leaves/MeOH extract	Exhibited promising	Chen et al., 2011) (Y. J. Chen et al., 2012) (Nwodo, Okoye, Lai, et al.,
					trypanocidal activity with IC <sub>50</sub> value 13.8 μg/ml and cytotoxicity 14.0 μg/ml.	2015)
	292	Casticin (Vitexicarpin) OH OMe	V. agnus-castus	Fruit/acetone	Mild Antioxidative activity. Dose-dependent delta and mu opioid receptor binding.	(Ono et al., 2011)
		MeO		Fruit/defatted MeOH extract		(SN. Chen et al., 2011)
		MeO´ Ý Ý ÔMe OH O		Fruit/MeOH extract, EtOAC fraction		(S. Li et al., 2013)
				Seeds/aqueous ethanol 70% (v/v)		(Jarry et al., 2006)
			V. rotundifolia	Fruit/MeOH extract/n- hexan fraction	Significantly reduced vascular inflammation through inhibition of ROS-NF-κB pathway in vascular endothelial cells.	(Lee, Lee, Kim, et al., 2012)
				Fruit/MeOH extract	Growth inhibitory activity against human lung cancer cells (PC-12) and human colon cancer cells (HCT116) using the MTT assay.	(Ono et al., 2002)
				Fruit/EtOH extract/ EtOAc fraction		(Wu et al., 2010)
				Fruit/MeOH extract	Potential angiogenesis inhibitor.	(Zhang, Liu, Zhao, et al., 2013)

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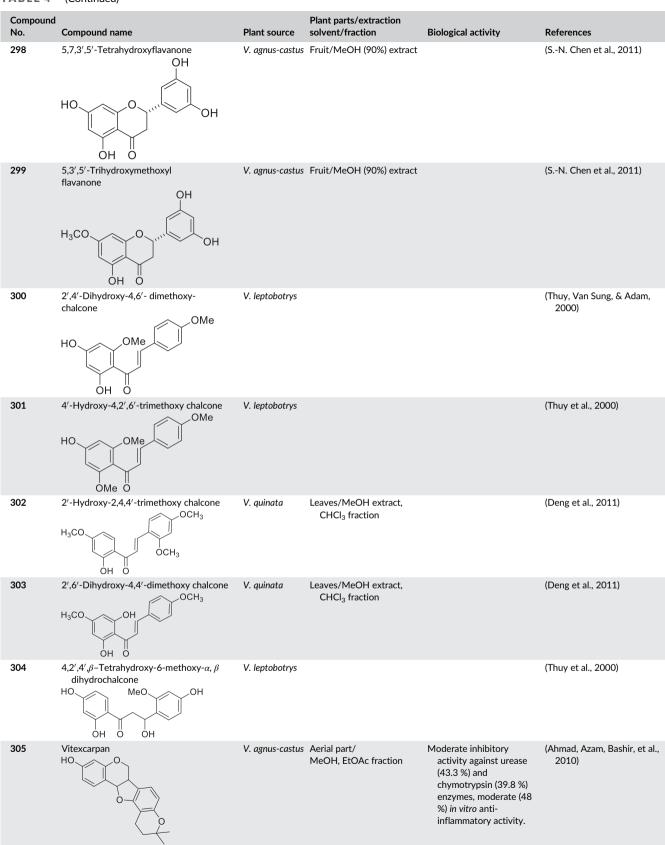
TABLE 4	(Continued)				
Compound No.	d Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
		V. negundo	Leaves/CHCl <sub>3</sub> fraction	Exhibited broad cytotoxicity in a human cancer cell line panel.	(Díaz, Chávez, Lee, et al., 2003)
		V. fructus	Purchased from Chromadex Inc. (Irvine, CA, USA)	Ameliorated cigarette smoke-induced acute lung inflammatory response in a murine model.	(H. Lee, Jung, Lee, et al., 2015)
		V. trifolia	Leaves/MeOH, CHCl <sub>3</sub> fraction		(Tiwari, Thakur, et al., 2013)
		V. trifolia	Leaves and twigs/MeOH extract, EtOAc fraction	Exhibited cytotoxicity against PANC-1, K562, and BxPC-3 cancer cell lines with IC <sub>50</sub> values of 4.67, 0.72, and 4.01 μg/ml, respectively.	(Ming-Yu Huang et al., 2013)
293	Artemetin	V. rotundifolia	Fruit/MeOH extract		(Ono et al., 2002)
	OMe	V. agnus-castus	Seeds /aqueous ethanol 70% extract (v/v)		(Jarry et al., 2006)
	MeO O		Fruit/n-hexane		(S. Li et al., 2013)
	MeO OH O	V. trifolia	Leaves and twigs/MeOH extract, EtOAc fraction		(Huang, Zhong, et al., 2013)
294	5,4'-Dihydroxy-3,6,7,8,3'- pentamethoxyflavone	V. cannabifolia	Fruit/MeOH	DPPH radical scavenging activity.	(Yamasaki et al., 2008)
	OMe MeO MeO OMe	V. negundo	Seeds/95% EtOH, DCM fraction	Moderate $\alpha$ -glucosidase inhibitory effect, cytotoxicity against human HepG2 and rat C6 cell lines.	(Fang et al. 2016b)
	MeO´ Y Y OMe OH O	V. negundo	Seeds/ 95% EtOH, DCM fraction	Moderate antioxidant activity {DPPH assay (IC <sub>50</sub> , >100 $\mu$ M) ABTS assay (IC <sub>50</sub> , 2.94 $\pm$ 0.03 $\mu$ M)} and $\alpha$ -glucosidase inhibitory effect (IC <sub>50</sub> , 2.70 $\pm$ 0.12 $\mu$ M).	(Hu et al., 2017)
295	5,3'-Dihydroxy-7,8,4'- Trimethoxy flavanone	V. negundo	Leaves/CHCl <sub>3</sub>		(Achari, Chowdhury, Dutta, & Pakrashi, 1984)
	OMe MeO		Bark/acetone		(Verma et al., 2011)
	он о				
296	5,3'-Dihydroxy-6,7,4'-trimethoxy flavanone	V. negundo	Leaves/CHCl <sub>3</sub>		(Achari et al., 1984)
	OH	V. rotundifolia	Fruit/MeOH		(Ono et al., 2002)
	OMe	V. agnus-castus	Seeds/aqueous ethanol 70% extract (v/v)		(Jarry et al., 2006)
	MeO				
	MeO OH O				
297	(S) -5-Hydroxy-7,4'-dimethoxy flavanone	V. quinata	Leaves/MeOH extract, CHCl <sub>3</sub> fraction	Cytotoxicity with ED <sub>50</sub> values of 6.7, 4.7 and 1.1 $\mu$ M, respectively against	(Deng, Chin, Chai, et al., 2011)
	MeO OH O			a panel of three human cancer cells.	

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### TABLE 4 (Continued)

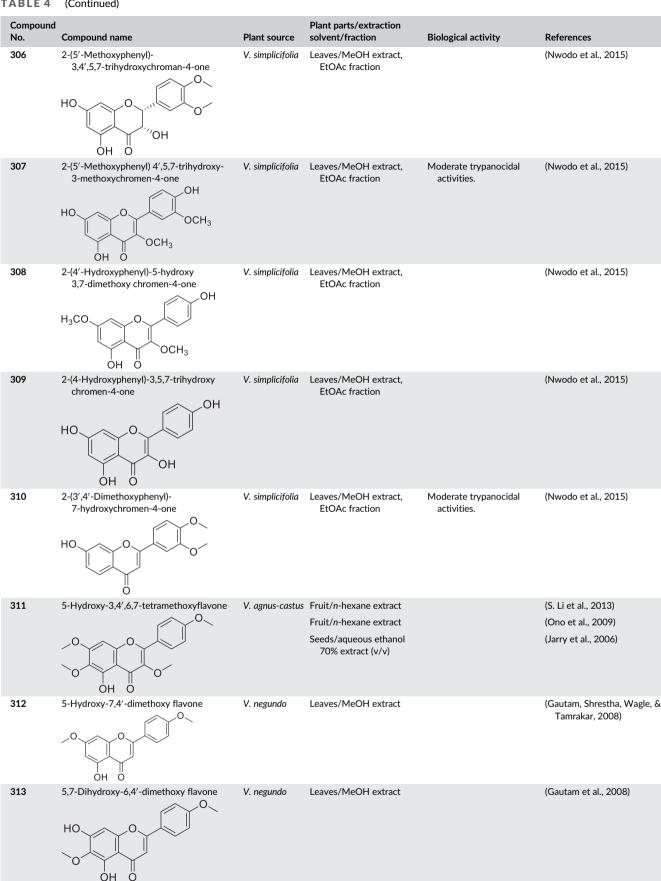
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#### DAS ET AL.

## TABLE 4 (Continued)

	TABLE 4	(Continued)				
	Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
	314	7,8-Dimethyl herbacetin-3-rhamnoside OMe MeO OH ORha OH	V. negundo	Leaves/MeOH extract		(Gautam et al., 2008)
	315	5-Hydroxy-3',4',3,6,7-pentamethoxy flavone MeO MeO OMe OMe OMe OMe	V. negundo	Leaves/MeOH extract Leaves/petroleum ether extract		(Gautam et al., 2008) (A. Banerji, Chadha, & Malshet, 1969)
	316	5-Hydroxy-3',4',3,6,7-pentamethoxy flavone MeO MeO MeO OMe OMe OMe OMe	V. negundo	Leaves/ethanol extract, n- BuOH fraction	Antifungal activity against <i>Cryptococcus neoformans</i> with MIC 12.5 µg/ml	(Sathiamoorthy et al., 2007)
	317	5,4'-Dihydroxy-3,6,7-trimethoxy flavone H <sub>3</sub> CO $O$ $OH$ H <sub>3</sub> CO $OH$ $OCH_3$ $OH$ $OH$ $OH$ $OH$ $OH$ $OH$ $OH$ $OH$	V. negundo	Seeds/95% EtOH extract, DCM extract	Strong antioxidant activity.	(Hu et al., 2017)
	318	5,4'-Dihydroxy-3,6,7,8- tetramethoxy flavone $H_3CO$ $OCH_3$ $OH$ $H_3CO$ $OCH_3$ $OH$ $H_3CO$ $OCH_3$	V. negundo	Fruits, seeds/ 95% EtOH, DCM extract		(Fang et al. 2016b)
	319	5,6,3',4'-Tetrahydroxy-3,7-dimethoxy flavone $H_{3}CO$ $O$ $OH$ $OH$ $H_{3}CO$ $OH$ $OH$ $HO$ $OCH_{3}$ $OH$ $OH$ $OH$	V. negundo	Leaves/95% EtOH, EtOAc extract	Strong antioxidant activity {DPPH assay (IC <sub>50</sub> , 3.67 $\pm$ 0.12 µM), ABTS assay (IC <sub>50</sub> , 1.23 $\pm$ 0.06 µM)} and moderate $\alpha$ -glucosidase inhibitory effect (IC <sub>50</sub> , 2.11 $\pm$ 0.06 µM).	(Hu et al., 2017)
	320	5,4'-Dihydroxy-3,7,3'-trimethoxy flavone OCH <sub>3</sub> H <sub>3</sub> CO OH OH OCH <sub>3</sub>	V. negundo	Seeds/95% EtOH, DCM extract	Strong antioxidant activity {DPPH assay (IC <sub>50</sub> , >100 $\mu$ M), ABTS assay (IC <sub>50</sub> , 7.57 ± 0.05 $\mu$ M) and weaker $\alpha$ -glucosidase inhibitory effect (IC <sub>50</sub> , 18.66 ± 0.84 $\mu$ M).	(Hu et al., 2017)
	321	5,4'-Dihydroxy-6,7,3'-trimethoxy flavone OCH <sub>3</sub> H <sub>3</sub> CO H <sub>3</sub> CO H <sub>3</sub> CO OH OH	V. negundo	Seeds/95% EtOH, DCM extract	Strong antioxidant activity {DPPH assay (IC <sub>50</sub> , >100 $\mu$ M), ABTS assay (IC <sub>50</sub> , 5.12 ± 0.05 $\mu$ M) and weaker $\alpha$ -glucosidase inhibitory effect (IC <sub>50</sub> , 9.96 ± 0.53 $\mu$ M).	(Hu et al., 2017)

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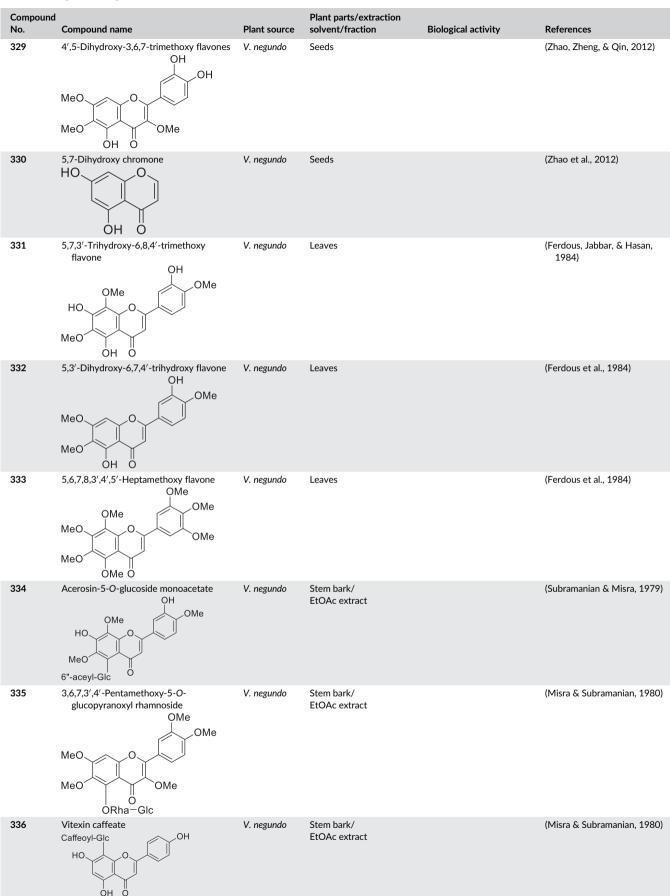
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BLE 4	(Continued)				
Compound Io.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
22	5,4'-Dihydroxy-3,6,7,3'-tetra flavone H <sub>3</sub> CO	methoxy V. <i>negundo</i> CH <sub>3</sub> OH	Seeds/95% EtOH extract, DCM fraction	Strong antioxidant activity {DPPH assay ( $IC_{50}$ , >100 $\mu$ M) ABTS assay ( $IC_{50}$ , 2.95 $\pm$ 0.03 $\mu$ M)} and moderate $\alpha$ -glucosidase inhibitory effect ( $IC_{50}$ , 3.51 $\pm$ 0.14 $\mu$ M).	(Hu et al., 2017)
	H <sub>3</sub> CO OCH <sub>3</sub> OH O		Fruit/MeOH extract, EtOAc fraction	Weak cytotoxicity against human HepG2 and rat C6 cell lines.	(Fang et al. 2016b)
23	5-Hydroxy-3,6,7,8,3',4'-hexa flavone OCH <sub>3</sub> H <sub>3</sub> CO	nmethoxy V. <i>negundo</i> CH <sub>3</sub> JOCH <sub>3</sub>	Seeds/95% EtOH, DCM fraction	Strong antioxidant activity {DPPH assay ( $IC_{50}$ , >100 $\mu$ M), ABTS assay ( $IC_{50}$ , 2.85 ± 0.06 $\mu$ M)} and weaker $\alpha$ -glucosidase inhibitory effect ( $IC_{50}$ , 10.28 ± 1.19 $\mu$ M).	(Hu et al., 2017)
	H₃CO ОН О	<sub>3</sub> V. negundo	Fruit/MeOH extract, EtOAc fraction	Moderate cytotoxicity against human HepG2 and rat C6 cell lines.	(Fang et al. 2016b)
24	Diosmetin-7-O-β-D-glucopy OF GlcO OH OH	-	Seeds/95% EtOH extract, DCM fraction	Moderate antioxidant activity {DPPH assay (IC <sub>50</sub> , >100 $\mu$ M) ABTS assay (IC <sub>50</sub> , 9.37 $\pm$ 0.10 $\mu$ M)} and weaker $\alpha$ -glucosidase inhibitory effect (IC <sub>50</sub> , 35.90 $\pm$ 0.36 $\mu$ M).	(Hu et al., 2017)
25	5-Hydroxy-3,7,4'-trimethoxy MeO O OMe OH O	OMe	Stem barks/EtOH extract		(Vale, Gonçalves, Teixeira, et al., 2017)
26	Luteolin-7-Ο-β-D-glucoside	V. negundo H OH	Leaves/petroleum ether, MeOH extract Seeds/95% EtOH extract,		(Sharma et al., 2009) (Hu et al., 2017)
	Gico O OH O		DCM fraction		
27	Chrysoplenetin	V. negundo Ne OH	Fruit/MeOH	Cytotoxicity activity against PANC-1 human pancreatic cancer and a host of other human	(Awale, Linn, Li, et al., 2011
	MeO MeO OH OH	<u> </u>		cancer cells.	
28	Chrysosplenol D	V. negundo DH OH	Fruit/MeOH	Cytotoxicity activity against PANC-1 human pancreatic cancer cells.	(Awale et al., 2011)
	MeO O MeO OM		Whole plant/MeOH extract, EtOAc fraction		(Arai et al., 2013)

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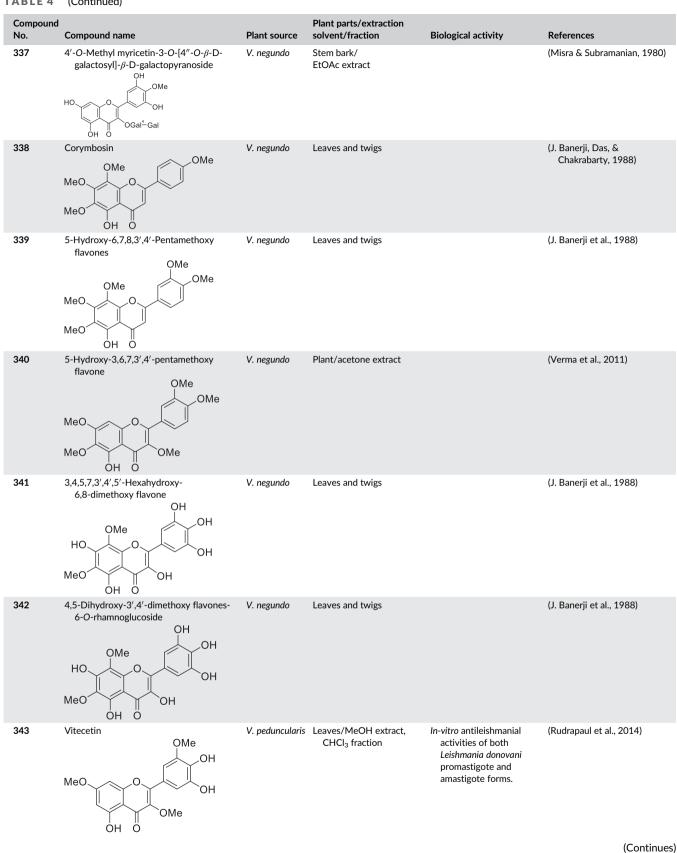
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#### TABLE 4 (Continued)



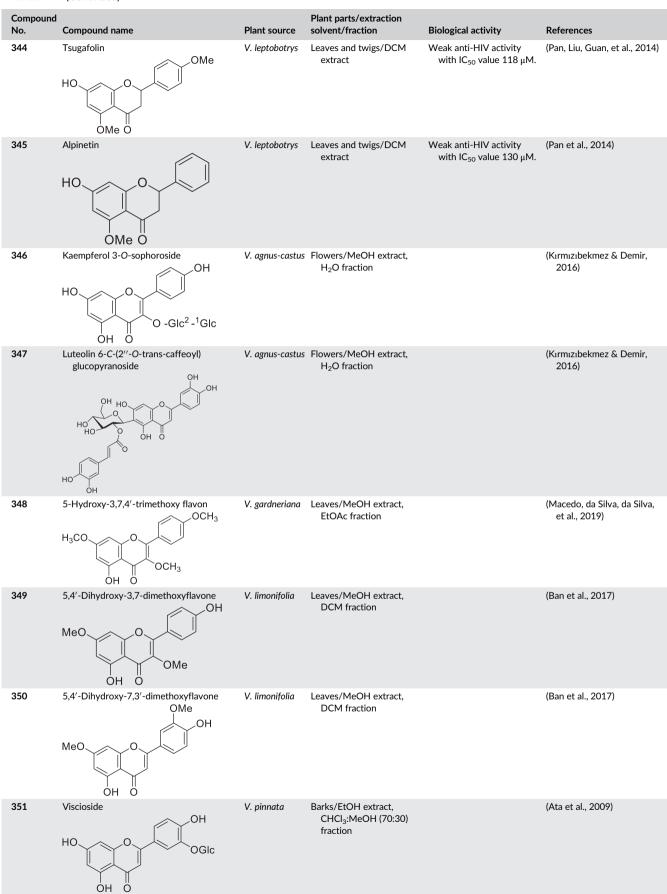
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#### TABLE 4 (Continued)



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#### Plant parts/ Compound No. Compound name Plant source fraction **Biological activity** References 352 Negundin A V. negundo Roots/MeOH Inhibitory activity against (Haq, Malik, Anis, et al., lipoxygenase enzyme, 2004) MeO acetyl-cholinesterase, butyryl-cholinesterase. HO OMe ÓН 353 Detetrahydroconidendrin V. negundo Seeds/MeOH extract DPPH free radical (Ono et al., 2004) scavenging activity C MeO Fruit/MeOH, EtOAc (Fang et al. 2016b) extract V. cannabifolia Fruit/MeOH extract (Yamasaki et al., 2008) HO V. rotundifolia Subterranean part/MeOH Antibacterial activity (Kawazoe, Yutani, extract, EtOAc fraction against methicillin-Tamemoto, et al., 2001) resistant Staphylococcus aureus (MRSA) strains. OMe ÓН 354 4-(3,4-Dimethoxyphenyl)-6-hydroxy-Subterranean part/MeOH (Kawazoe et al., 2001) V. rotundifolia 5-methoxynaphtho[2,3-c]furan-1(3H)extract, EtOAc fraction one HO **ÓMe** OMe OMe 355 4-(3,4-Dimethoxyphenyl)-6-hydroxy-V. rotundifolia Subterranean part/MeOH (Kawazoe et al., 2001) 7-methoxynaphtho[2,3-c]furan-1(3H)extract, EtOAc fraction one MeO HO OMe ÓМе 356 Vitedoamine A Seeds/MeOH extract, DPPH free radical (Ono et al., 2004) V. negundo C scavenging activity. MeO. Seeds/aq. EtOH (80%) (Zheng, Tang, Huang, et al., extract 2009) HO Aerial part/EtOH-H<sub>2</sub>O (7:3, (Nie, Yu, Tao, et al., 2016) v/v) extract OMe

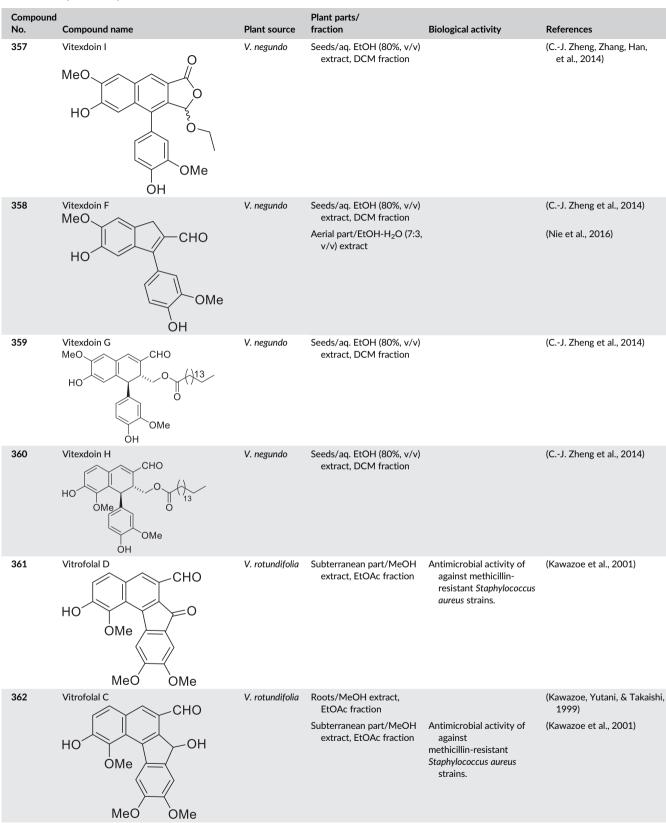
#### TABLE 5 List of lignans reported from different species of Vitex and their biological activities

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#### TABLE 5 (Continued)



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Т	ABLE 5	(Continued)				
	Compound No.	Compound name	Plant source	Plant parts/ fraction	Biological activity	References
	363	Vitrofolal A	V. rotundifolia	Roots/MeOH extract, EtOAc fraction		(Kawazoe et al., 1999)
		HO OMe OMe OMe		Subterranean part/ MeOH extract, EtOAc fraction		(Kawazoe et al., 2001)
	364	Vitrofolal B	V. rotundifolia	Roots/MeOH extract, EtOAc fraction		(Kawazoe et al., 1999)
		HO OH OMe OMe		Subterranean part/ MeOH extract, EtOAc fraction		(Kawazoe et al., 2001)
	365	Vitrofolal E MeO	V. negundo	Seeds/MeOH extract	DPPH free radical scavenging activity.	(Ono et al., 2004)
		но		Roots/MeOH extract, CHCl <sub>3</sub> fraction	In-vitro moderate activity against butyryl- cholinesterase.	(Haq et al., 2004)
		OMe		Seeds/EtOH extract	Inhibitory activities on LPS- induced nitric oxide (NO) production in RAW264.7 cells with IC <sub>50</sub> value 0.50 $\mu$ M.	(Zheng, Huang, Han, et al., 2009)
			V. rotundifolia	Subterranean part/MeOH extract, EtOAc fraction		(Kawazoe et al., 2001)
			V. cannabifolia	Fruits/MeOH extract		Yamasaki et al., 2008)
		Vitrofolal F MeO CHO	V. negundo	Seeds/MeOH extract Roots/MeOH, CHCl <sub>3</sub>	DPPH free radical scavenging activity.	(Ono et al., 2004) (Haq et al., 2004)
		но он		fraction Seeds/EtOH extract	Strong inhibitory activities	(Zheng, Huang, et al., 2009)
		OMe		Seeds/ LIOT Extract	on LPS-induced nitric oxide (NO) production in RAW264.7 cells with $IC_{50}$ value 0.11 $\mu$ M.	(Zheng, Fluang, et al., 2007)
			V. rotundifolia	Subterranean part/MeOH extract, EtOAc fraction		(Kawazoe et al., 2001)
			V. cannabifolia	Fruits/MeOH extract		(Yamasaki et al., 2008)
	367	Negundin B MeO HO HO H <sup>'</sup> CH <sub>2</sub> OH OMe	V. negundo	Roots/MeOH extract	Potent inhibitory activity against lipoxygenase enzyme.	(Haq et al., 2004)
	368	OH (+)-Lyoniresinol	V. negundo	Roots/MeOH extract		(Haq et al., 2004)
		MeO HO OMe MeO OMe	J			
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#### TABLE 5 (Continued)

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٦	ABLE 5	(Continued)				
	Compound No.	Compound name	Plant source	Plant parts/ fraction	Biological activity	References
	369	(+)-Lyoniresinol-3 <i>a</i> -O-β-D- glucopyranoside MeO OH HO OH MeO OMe OH	V. negundo	Aerial part/ EtOH extract		(Nie et al., 2016)
	370	(–)-Lyoniresinol-3 <i>a</i> -O-β-D- glucopyranoside MeO HO OMe OMe OMe OH	V. negundo	Aerial Part/ EtOH extract		(Nie et al., 2016)
	371	6-Hydroxy-4(4-hydroxy- 3-methoxyphenyl)-3-hydroxymethyl-	V. negundo	Seeds/MeOH extract	DPPH free radical scavenging activity.	(Ono et al., 2004)
		3-methoxy-3,4-dihydro- 2-naphthaldehyde $MeO \rightarrow G \rightarrow $		Defatted Seeds/CHCl <sub>3</sub> extract Whole plant/MeOH	Antiedema activity.	(Chawla, Sharma, Handa, et al., 1992) (Arai et al., 2013)
				extract, EtOAc fraction Seeds/95% EtOH extract, EtOAc fraction	Cytotoxicity against human liver carcinoma (HepG2 with IC <sub>50</sub> , 8.24 $\mu$ M), colon carcinoma (HCT116 with IC <sub>50</sub> , 57.52 $\mu$ M), and ovarian carcinoma (A2780 with IC <sub>50</sub> , 77.85 $\mu$ M) cell lines, inhibitory activity on nitric oxide (NO) production with an IC <sub>50</sub> value >1 $\mu$ M and antioxidant activity in ABTS assay with IC <sub>50</sub> = 1.71 ± 0.22 $\mu$ M.	(Hu et al., 2016)
				Seeds/80% EtOH extract, EtOAc fraction	Inhibitory activities on LPS- induced nitric oxide (NO) production in RAW264.7 cells with IC <sub>50</sub> value 3.54 $\mu$ M.	(Zheng, Huang, et al., 2009)
				Seeds/80% EtOH extract, EtOAc fraction	Analgesic, antiinflammatory, and antinociceptive effect.	(Zheng, Tang, et al., 2009)
			V. cannabifolia	Aerial part/EtOH extract Fruit/MeOH extract		(Nie et al., 2016) (Yamasaki et al., 2008)
	372	6-Hydroxy-4-(4-hydroxy- 3-methoxyphenyl)-3-acetoxymethyl- 7-methoxy-3,4-dihydro- 2-naphthaldehyde MeO CHO HO OAc OMe	V. negundo	Fruit/MeOH extract, EtOAc fraction		(Fang et al. 2016b)

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1	ABLE 5	(Continued)				
	Compound No.	Compound name	Plant source	Plant parts/ fraction	Biological activity	References
l	373	Vitedoin A	V. negundo	Seeds/MeOH extract	Free radical (DPPH) scavenging activity.	(Ono et al., 2004)
		HO OMe OMe OMe OMe		Seeds/95% EtOH extract, EtOAc fraction	Moderate cytotoxic activity against HCT116 cell line (IC <sub>50</sub> , 10.18 $\mu$ M), inhibitory effects on LPS-stimulated nitric oxide (NO) production (IC <sub>50</sub> , >3 $\mu$ M) and significant antioxidant activity in ABTS assay (IC <sub>50</sub> , 1.63 $\pm$ 0.08 $\mu$ M).	(Hu et al., 2016)
			V. cannabifolia	Fruit/MeOH extract, EtOAc fraction		(Fang et al. 2016b)
				Aerial Part/EtOH extract		(Nie et al., 2016)
	074		Maria a la falla	Fruit/MeOH extract		(Yamasaki et al., 2008)
	374	Vitecannaside A CHO HO OMe OMe OMe OMe	V. cannabifolia	Fruit/MeOH extract	DPPH free radical scavenging activity.	(Yamasaki et al., 2008)
	375	Vitecannaside B MeO	V. cannabifolia	Fruit/MeOH extract	DPPH free radical scavenging activity.	(Yamasaki et al., 2008)
		HO OGIC	V. negundo	Seeds/95% EtOH extract, EtOAc fraction	Inhibitory effects on LPS- stimulated NO production (IC <sub>50</sub> , 19.01 $\pm$ 2.49 $\mu$ M) and strong ABTS radical scavenging activity (IC <sub>50</sub> , 3.20 $\pm$ 0.14 $\mu$ M).	(Hu et al., 2016)
		ÓН		Aerial part/EtOH extract		(Nie et al., 2016)
	376	Pinoresinol OMe	V. cannabifolia	Fruit/MeOH extract Fruit/MeOH extract,		(Yamasaki et al., 2008)
		MeO HO	V. negundo	EtOAc fraction		(Fang et al. 2016b)
	377	Vitelignin A O	V. negundo	Seeds	Antifungal activity against Candida albicans (MIC 32	(Zheng et al., 2011)
					μg/ml), Cryptococcus neoformans (MIC 64 μg/ml), and Trichophyton rubrum (MIC 32 μg/ml)	
	378	Altissinone	V. altissima	Leaves/EtOAc extract		(Sridhar et al., 2005)

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1	TABLE 5	(Continued)				
	Compound No.	Compound name	Plant source	Plant parts/ fraction	Biological activity	References
	379	$2\alpha, 3\beta$ -7-O-Methylcedrusin MeO HO HO OH OH OH OH	V. negundo	Seeds/ MeOH		(Ono et al., 2004)
	380	Viterolignan A MeO HO HO OH OMe	V. rotundifolia	Fruit/MeOH extract, DCM soluble fraction	Inhibitory activities on LPS- induced NO production in RAW264.7 cells with IC <sub>50</sub> value 21.1 $\mu$ M.	(C. Lee et al., 2013)
	381	Viterolignan B HO HO OMe	V. rotundifolia	Fruit/MeOH extract, DCM soluble fraction	Inhibitory activities on LPS- induced NO production in RAW264.7 cells with $IC_{50}$ value 42.8 $\mu$ M.	(C. Lee et al., 2013)
	382	Vitexnegheteroin E HO HO H HO H H OCH <sub>3</sub>	V. negundo	Seeds/95% EtOH extract, n-BuOH fraction	Inhibitory effect on nitric oxide (NO) production in murine microglial BV-2 cell line by the Griess reaction with IC <sub>50</sub> value $17.27 \pm 6.10 \ \mu\text{M}$ and strong ABTS radical scavenging activity with IC <sub>50</sub> value $3.20 \pm 0.14 \ \mu\text{M}$ .	(Hu et al., 2016)
	383	Vitexnegheteroin F MeO HO HO OMe OMe OMe OH	V. negundo	Seeds/95% EtOH extract, EtOAc fraction	Weaker cytotoxic activity against three human cancer cell lines namely HepG2 (IC <sub>50</sub> , 55.48 $\mu$ M), HCT116 (IC <sub>50</sub> , >100 $\mu$ M) and A2780 (IC <sub>50</sub> , >100 $\mu$ M) and strong ABTS radical scavenging activity with IC <sub>50</sub> value 3.20 $\pm$ 0.14 $\mu$ M.	(Hu et al., 2016)
	384	Vitexnegheteroin G H <sub>3</sub> CO HO HO HO OH	V. negundo	Seeds/95% EtOH extract, EtOAc fraction	Inhibitory effect on nitric oxide (NO) production in murine microglial BV-2 cell line by the Griess reaction with IC <sub>50</sub> value >30 $\mu$ M and strong ABTS radical scavenging activity with IC <sub>50</sub> value 3.20 $\pm$ 0.14 $\mu$ M.	(Hu et al., 2016)
	385	(3R,4S)-6-Hydroxy-4-(4-hydroxy- 3-methoxyphenyl)-5,7-dimethoxy- 3,4-dihydro-2-naphthaldehyde-3 <i>a</i> -O- $\beta$ -D-glucopyranoside, [Vitecannaside C] H <sub>3</sub> CO H <sub>3</sub> CO HO HO HO HO HO HO HO H	V. negundo	Aerial parts/EtOH-H <sub>2</sub> O (7:3, v/v), EtOAc extract		(Nie et al., 2016)

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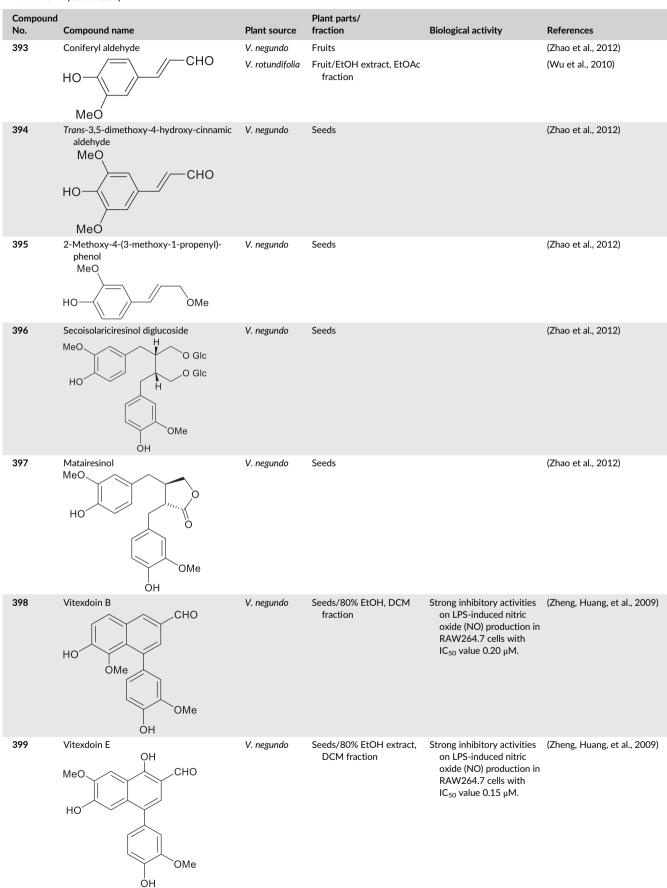
TABLE 5	(Continued)				
Compound No.	Compound name	Plant source	Plant parts/ fraction	Biological activity	References
386	6.7,4'-Trihydroxy-3'-methoxy -2,3-cycloligna-1,4-dien-2 <i>a</i> ,3 <i>a</i> -olide [Vitexdoin G] HO HO HO HO OCH <sub>3</sub> OH	V. negundo	Aerial parts/EtOH-H <sub>2</sub> O (7:3, v/v) extract, EtOAc fraction		(Nie et al., 2016)
387	Cannabilignin	V. negundo	Leaves/95% EtOH extract		(Li et al., 2016)
388	Isocannabilignin	V. negundo	Leaves/95% EtOH extract		(Li et al., 2016)
389	9R-Hydroxy-d-sesamin HOmeration	V. negundo	Leaves/95% EtOH extract	Weak nitric oxide production inhibitory activity in lipopolysaccharide stimulated BV-2 microglial cells with IC <sub>50</sub> value of 69.1 $\pm$ 5.8 $\mu$ M.	(Li et al., 2016)
390	cis-Dihydro-dehydro-diconiferyl alcohol- 9-Ο-β-D-glucoside HO Glc-O OMe MeO	V. agnus-castus	Fruit/hexane and MeOH extract		(S. Li et al., 2013)
391	(+)-Diasyringaresinol MeO HO HO HO HO HO HO HO HO HO HO HO HO HO	V. negundo	Roots/MeOH extract		(Haq et al., 2004)
392	Vitedoamine B MeO HO HO O HO O CH <sub>3</sub>	V. negundo	Seeds/80% EtOH extract, DCM fraction	Inhibitory activities on LPS- induced nitric oxide (NO) production in RAW264.7 cells with IC <sub>50</sub> value 0.87 μM.	(Zheng, Huang, et al., 2009) (Continues)

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#### TABLE 5 (Continued)

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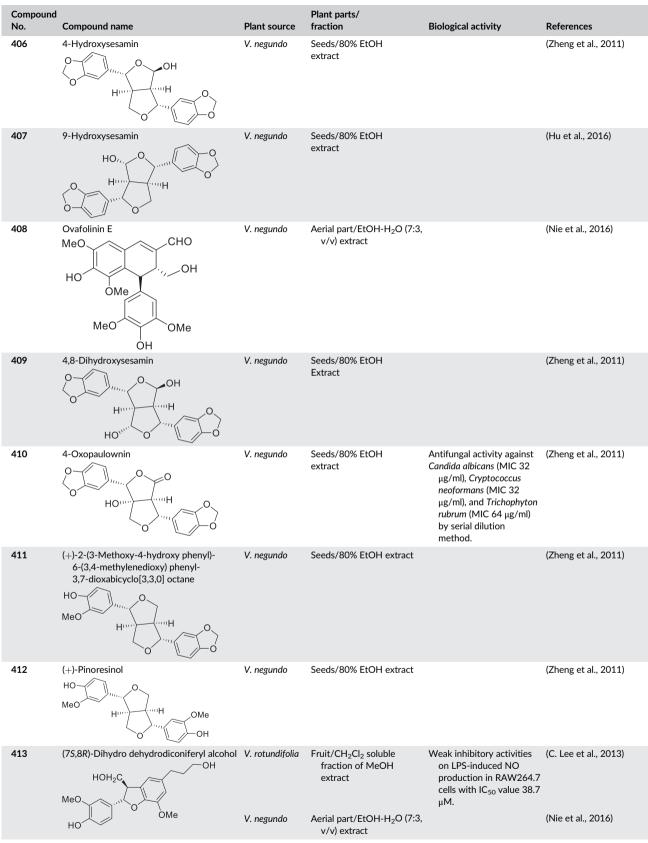
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TABLE 5	(Continued)				
Compound No.	Compound name	Plant source	Plant parts/ fraction	Biological activity	References
400	Vitexdoin C MeO HO CHO OMe OH	V. negundo	Seeds/80% EtOH extract, DCM fraction	Inhibitory activities on LPS- induced nitric oxide (NO) production in RAW264.7 cells with IC <sub>50</sub> value 0.57 $\mu$ M.	(Zheng, Huang, et al., 2009)
401	Vitexdoin D MeO HO CHO OMe OH	V. negundo	Seeds/80% EtOH extract, DCM fraction	Strong inhibitory activities on LPS-induced nitric oxide (NO) production in RAW264.7 cells with IC <sub>50</sub> value 0.13 μM.	(Zheng, Huang, et al., 2009)
402	Vitexdoin A HO HO	V. negundo	Seeds/80% EtOH extract, DCM fraction	Strong inhibitory activities on LPS-induced nitric oxide (NO) production in RAW264.7 cells with IC <sub>50</sub> value 0.38 μM.	(Zheng, Huang, et al., 2009)
	OMe		Seeds/95% EtOH extract, EtOAc fraction	$\label{eq:linear} \begin{array}{l} \mbox{Inhibitory effect on nitric} \\ \mbox{oxide (NO) production in} \\ \mbox{murine microglial BV-2} \\ \mbox{cell line by the Griess} \\ \mbox{reaction with IC}_{50} \mbox{value} \\ \mbox{>}30 \mbox{ $\mu$M} \mbox{ and significant} \\ \mbox{ABTS radical scavenging} \\ \mbox{activity (IC}_{50} \mbox{ value 1.43} \\ \mbox{$\pm$ 0.03 \mbox{$\mu$M})}. \end{array}$	(Hu et al., 2016)
		V. cannabifolia	Aerial part/EtOH-H <sub>2</sub> O (7:3, v/v) extract Fruit/MeOH, EtOAc fraction		(Nie et al., 2016) (Fang et al. 2016b)
403	4-Oxosesamin H H H H H H H H	V. negundo	Seeds/80% EtOH (v/v) extract, DCM fraction	Aantifungal activity against Candida albicans (MIC 64 µg/ml), Cryptococcus neoformans (MIC 16 µg/ml), and Trichophyton rubrum (MIC 64 µg/ml) by serial dilution method.	(Zheng et al., 2011)
404	(+)-Sesamin	V. negundo	Seeds/80% EtOH (v/v) extract, DCM fraction		(Zheng et al., 2011)
405	(+)-Paulownin	V. negundo	Seeds/80% EtOH (v/v) extract, DCM fraction		(Zheng et al., 2011)
	HOME		Fruits/40% EtOH extract	Cytotoxic effects against A-549 cell line with IC_{50} value 22.6 $\mu$ M.	(Huang, Qing, et al., 2013)
	0 00		Fruits/MeOH extract, EtOAC fraction		(Fang et al. 2016b)

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#### TABLE 5 (Continued)



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TABLE 5	(Continued)				
Compound No.	Compound name	Plant source	Plant parts/ fraction	Biological activity	References
414	Ficusal	V. rotundifolia	Fruit/CH <sub>2</sub> Cl <sub>2</sub> soluble fraction of MeOH extract		(C. Lee et al., 2013)
	HOH <sub>2</sub> C MeO HO OMe	V. agnus-castus	Fruit/MeOH		(SN. Chen et al., 2011)
415	(+)-Lariciresinol OH HO HO OMe	V. rotundifolia	Fruit/CH <sub>2</sub> Cl <sub>2</sub> soluble fraction of MeOH extract		(C. Lee et al., 2013)
416	Fiscusesquiligan A Meo HO HO HO HO HO HO HO HO HO HO	V. rotundifolia	Fruit/CH <sub>2</sub> Cl <sub>2</sub> soluble fraction of MeOH extract		(C. Lee et al., 2013)
417	Vitexkarinol	V. leptobotrys	Leaves and twigs/DCM extract		(Pan et al., 2014)
418	Neopaulownin OHU UNH	V. leptobotrys	Leaves and twigs/DCM extract		(Pan et al., 2014)
419	Balanophonin OCH3 OHC HO	V. agnus-castus	Fruit/MeOH extract		(SN. Chen et al., 2011)
420	Vladirol F	V. agnus-castus	Fruit/MeOH extract		(SN. Chen et al., 2011)
421	Vitekwangin A MeO HO HO HO OMe	V. kwangsiensia	Fruits/MeOH extract, CHCl <sub>3</sub> fraction		(Shen et al., 2019)

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# TABLE 5 (Continued)

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Compound No.	Compound name	Plant source	Plant parts/ fraction	Biological activity	References
422	6-Hydroxy-4-(3,4-dimethoxyphenyl)- 3-hydroxymethyl-5-methoxy- 3,4-dihydro-2-napthaldehyde	V. kwangsiensia	Fruits/MeOH extract, CHCl <sub>3</sub> fraction		(Shen et al., 2019)
423	6-Hydroxy-4-(4-hydroxy- 3-methoxyphenyl)-3-hydroxymethyl- 7-methoxy-3,4-dihydro- 2-naphthaldehyde MeO HO HO HO HO HO HO HO	V. kwangsiensia	Fruits/MeOH extract, CHCl <sub>3</sub> fraction		(Shen et al., 2019)
424	Matairesinol 4'-O-β-D glucopyranoside GlcO	V. trifolia	Leaves/hot MeOH extract		(Ban et al., 2018)
425	Verrucosin MeO HO HO OH	V. limonifolia	Leaves/MeOH extract, DCM fraction Leaves/MeOH extract, DCM fraction		(Thoa, Ban, Trang, et al., 2018) (Ban et al., 2017)
426	Khainaoside A (3,4-methylenedioxyprinsepiol 3'-O- $\beta$ -D-glucopyranoside) $(H_{HO}^{OH} \rightarrow (H_{HO}^{OH}) \rightarrow (H_{HO}^{OH}) \rightarrow (H_{HO}^{OH})$	V. glabrata	Leaves/MeOH extract, $H_2O$ fraction		(Luecha et al., 2009)

scavenging percentage ranging between 72 and 86%; moreover it showed a significant ferric ion reducing power (Ajiboye, 2015). Meanwhile, essential oil from, *V. agnus-castus* demonstrated a low antioxidant activity in the DPPH assay with IC<sub>50</sub> of 1.072 mg/ml (Asdadi et al., 2015). Antioxidant properties were also reported for *V. mollis* Kunth methanolic extract using ABTS<sup>+</sup> and DPPH<sup>+</sup> radicals. Al-Wajeeh, Halabi, Hajrezaie, et al. (2016) investigated *V. pubescens* Vahl leaf extract and found a potent reduction of ferric with high FRAP value at 723.0 ± 0.03 µmol Fe (II)/g and DPPH IC<sub>50</sub> value of 38.3 ± 0.1 µg/ml.

Methanolic crude extract of V. *negundo* showed good antiradical scavenging activity of  $87.02 \pm 0.215\%$  as quantified by the DPPH method (Prakash et al., 2016).

A lot of compounds and various extracts from different parts of V. *doniana*, V. *agnus-castus*, V. *pubescens*, V. *altissima*, V. *negundo*, and V. *mollis* were reported for their antioxidant activity on the DPPH radical, superoxide ion, hydrogen peroxide, and hydroxyl radical.

Among different chemical classes of compounds were reported from *Vitex* for their antioxident activity, flavonoids and lignans are the major ones. These two classes of compounds from *Vitex* were reported to have their anticancer activity also. Specially, a lignin, 6-hydroxy-4-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-3,4-dihydro-2-naphthal dehyde, from *Vitex* which is reported here to have both of its antioxidant and anticancer activity. But, natural antioxidants were already reported for their role in cancer (Asadi-Samani, Farkhad, Mahmoudian-Sani, & Shirzad, 2019; Valadez-Vega et al., 2013). Based on this correlation, we

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Plant parts/extraction Biological Compound No. Compound name Plant source solvent/fraction activity References 427 1,6-Dioxo-2(3),9(10)-V. negundo Stem bark/MeOH extract, (Tiwari, Yadav, Vasudev, dehydrofuranoeremophilane hexane fraction et al., 2013)  $\cap$ 428 Stem bark/MeOH extract, (Tiwari, Yadav, et al., 2013) 4,6-Dimethyl-11-dimethoxymethyl-V. negundo 1-oxo-4H,2,3-dihydronapthofuran hexane fraction  $\cap$ СНО 429 4,6-dimethyl-11-formyl-1-oxo-Stem bark/MeOH extract, (Tiwari, Yadav, et al., 2013) V. negundo 4H,2,3-dihydronaphthofuran hexane fraction  $\cap$ OMe MeO 430 Negunfurol Seeds/80% ethanol Cytotoxicity against human (Zheng, Pu, et al., 2012) V. negundo extract colon carcinoma (HCT116) cell line with IC<sub>50</sub> value 8.11 ± 1.40 HO µg/ml; blood cancer (HL-60) cell line with IC<sub>50</sub> value 0.94  $\pm$  0.26 µg/ml; and breast carcinoma (ZR-75-30) cell line having IC<sub>50</sub> 13.18 ± 3.05 µg/ml 431 Spathulenol V. agnus-castus Fruit/n-hexane (S. Li et al., 2013) Seed essential oil (Asdadi et al., 2015) Н V. poligama (Barbosa, Demuner, Leaves Howarth, et al., 1995) HO H H Me Mé Mé 432 s-Cadinol V. agnus-castus Seed essential oil (Asdadi et al., 2015) ŃΗ HO 433 Farnesyl acetate V. agnus-castus Seed essential oil (Asdadi et al., 2015)

TABLE 6	List of sesquiterpenoids reported	from different species of	Vitex and their biological activities
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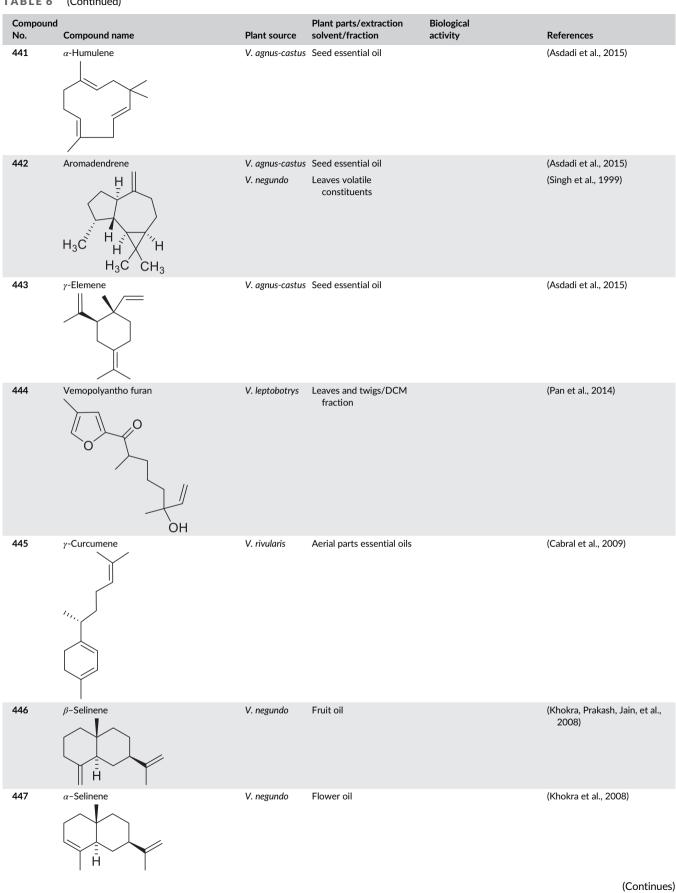
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	Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
	434	$\beta$ -Caryophyllene	V. negundo	Volatile constituents of leaves		(Singh, Dayal, & Bartley, 1999)
		+	V. agnus-castus	Seed essential oils		(Asdadi et al., 2015)
				Leaves essential oil		(Khalilzadeh, Saiah, Hasannejad, et al., 2015)
				Seed, leaves, and flowers essential oil		(Neves & Da Camara, 2016)
			V. rivularis	Aerial parts of essential oil		(Cabral, Gonçalves, Cavaleiro, et al., 2009)
			V. quinata	Leaves essential oil		(Dai, Thang, Ogunwande, et al., 2015)
	435	$\beta$ -Caryophylleneoxide	V. negundo	Leaves/diethylether		(Singh et al., 1999)
			V. agnus-castus	Seed essential oil		(Asdadi et al., 2015)
	436	α-Bergamotene	V. agnus-castus	Seed essential oil		(Asdadi et al., 2015)
		H				
	437	β-Farnesene	V. agnus-castus	Seed, leaves, fruit, flower essential oil		(Asdadi et al., 2015); (Khalilzadeh et al., 2015); (Neves & Da Camara, 2016)
	438	β-Bisabolene	V. agnus-castus	Seed essential oil		(Asdadi et al., 2015)
	439	Myristicin O O O	V. agnus-castus	Seed essential oil		(Asdadi et al., 2015)
	440	$\beta$ -Cadinene	V. agnus-castus	Seed essential oil		(Asdadi et al., 2015)

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Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
448	4α,10α- Dihydroxyaromadendrane HO HO HO H	V. agnus-castus	Fruit/Acetone Fruit/defatted MeOH extract		(Ono et al., 2011) (SN. Chen et al., 2011)
449	Germacrene D	V. rivularis	Aerial parts essential oil		(Cabral et al., 2009)
450	4β,10β-Dihydroxyaromadendrane	V. agnus-castus	Fruit/hexane extract		(Ono et al., 2009)
451	3-Formyl-4,5-dimethyl-8- <i>oxo-5H</i> - 6,7-dihydronaphtho[2,3- <i>b</i> ]furan	V. negundo	Seeds/hot aqueous ethanol (80% v/v), CH <sub>2</sub> Cl <sub>2</sub> extract	Evaluated <i>in-vitro</i> cytotoxicity against human lung carcinoma (A549) cell line having $IC_{50}$ value >100 µg/ml; colon carcinoma (HCT116) cell line having $IC_{50}$ value >100 µg/ml; blood cancer (HL-60) cell line having $IC_{50}$ value 29.15±2.37 µg/ml; and breast carcinoma (ZR- 75-30) cell line having $IC_{50}$ , >100 µg/ml	
452	Schensianol A	V. kwangsiensia	Fruits/MeOH extract, CHCl <sub>3</sub> fraction		(Shen et al., 2019), (Zheng, Pu, et al., 2012)

are very much optimistitic that *Vitex* will bring a novel lead for the treatmt of cancer in near future.

# 5.1.5 | Antiviral activity

According to (Tietjen, Gatonye, Ngwenya, et al., 2016), organic extract obtained from V. *doniana* L. inhibited HIV-1 replication *in-vitro* at  $25 \ \mu g/ml$ .

# 5.1.6 | Trypanocidal activity

Six diterpenoids, two nor-diterpene aldehydes 1 and 2 (90 and 91), vitexifolins E (74) and F (75), vitexilactone (42), and 6-acetoxy-

9-hydroxy-13(14)-labden-16,15-olide (**38**) isolated from the fruits of V. *trifolia* showed significant *in-vitro* trypanocidal activity against epimastigotes of *Trypanosoma cruzi* with MLCs of 11, 36, 34, 34, 66, and 66  $\mu$ M, respectively (Kiuchi et al., 2004; Wu et al., 2009).

# 5.1.7 | Antimutagenic activity

(+)-Polyalthic acid (**46**) isolated from MeOH extract of V. *rotundiforia* whole plant exhibited antimutagenic activity by suppressing the mutagenicity of Trp P-1 (3-amino-1,4-dimethyl-5H-pyrido [4,3b] indole) in Umu gene expression assay with ID<sub>50</sub> value of 0.29  $\mu$ M/ml (Miyazawa et al., 1995).

List of monoterpenoids reported from different species of Vitex and their biological activities Plant parts/extraction Compound Biological No. Compound name Plant source solvent/fraction activity References 453 Sabinene V. negundo Leaves/diethyl (Singh et al., 1999) ether 454 Vitexoid V. trifolia Fruits/H<sub>2</sub>O:acetone -7:3 Antiproliferative activity (J. Wu et al., 2009) (v/v) extract, CHCl<sub>3</sub> against HeLa cells with  $\sim$ IC<sub>50</sub> value 26.6 ± 1.8 fraction CH<sub>3</sub> H μMol/L. OF 455  $\alpha$ -Pinene V. agnus-castus Seed essential oil (Asdadi et al., 2015) V. negundo Essential oil (Khalilzadeh et al., 2015) V. pseudo-Leaves/ (Singh et al., 1999) negundo Essential oil Essential oil (Borzoui, Naseri, Abedi, & Karimi-Pormehr, 2016) 456  $\beta$ -Pinene Seed essential oil V. agnus-castus (Asdadi et al., 2015) Leaves (Singh et al., 1999) V. negundo Essential oil V. quinata Leaves (Dai et al., 2015) Essential oil 457 V. agnus-castus Seed essential oil (Asdadi et al., 2015)  $\beta$ -Myrcene 458 Seed essential oil (Asdadi et al., 2015) V. agnus-castus p-Cymene V. negundo Leaves (Singh et al., 1999) Essential oil (Asdadi et al., 2015) 459 Limonene V. agnus-castus Seed essential oil Essential oils (Khalilzadeh et al., 2015) Leave, Essential oil (Singh et al., 1999) V. negundo 460 1,8-Cineole Seed essential oil (Asdadi et al., 2015) V. agnus-castus (Neves & Da Camara, 2016) Leaves, fruit, and flower essential oil V. pseudo-negundo Essential oil (Borzoui et al., 2016)

# TABLE 7

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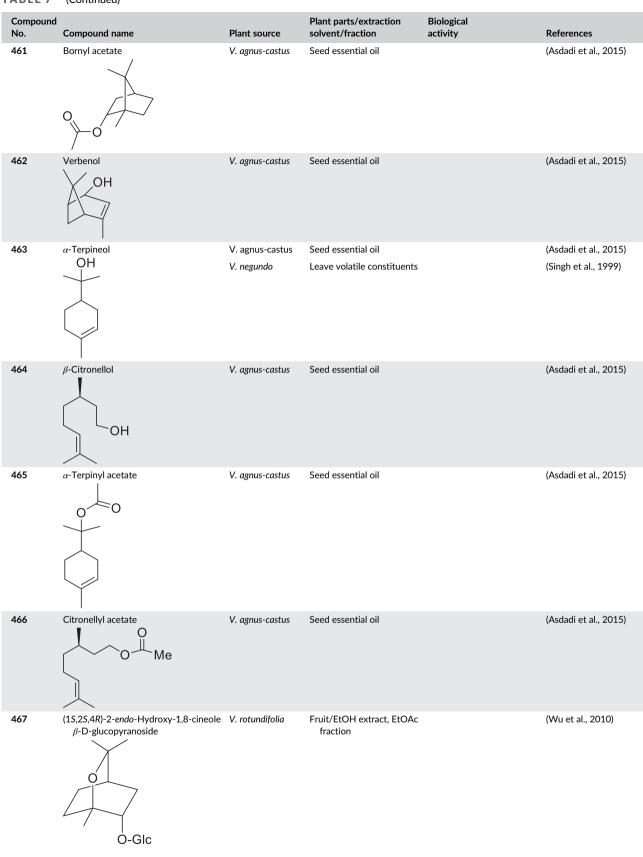
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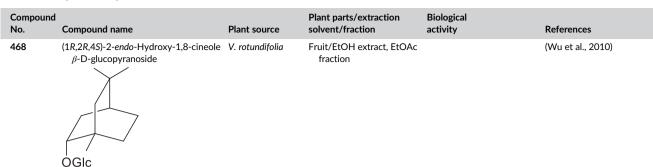
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# 5.1.8 | Antiosteoporotic activity

The lignan vitexdoin F (**358**) isolated from V. *negundo* seeds showed potent antiosteoporotic effect by inhibiting the proliferation and ALP activity of osteoblastic UMR106 cells at  $10^{-7}$ M concentration (C.-J. Zheng et al., 2014).

# 5.1.9 | Vasorelaxant activity

The CH<sub>2</sub>Cl<sub>2</sub>-MeOH (1:1) extract of V. *cienkowskii* stem bark showed significant endothelium-dependent vasorelaxant activity with EC<sub>50</sub> value of 12.12  $\mu$ g/ml in isolated rat aortic rings precontracted with noradrenaline (1  $\mu$ M). The isolated compounds, mixture of salvin A and maslinic acid, tanacetamide, and  $\beta$ -sitosterol glycoside from this bioactive fraction showed vasorelaxant effect in the same model with EC<sub>50</sub> values of 1.999, 4.256, and 1.178 mg/L, respectively (Dongmo et al., 2011).

Tetra-acetylajugasterone C (470) isolated from V. *cienkowskii* stem bark produced strong vasorelaxant activity in a concentrationdependent manner in rat artery rings precontracted with 1  $\mu$ M noradrenalin or 60 mM KCl with IC<sub>50</sub> values of 8.40 and 36.30  $\mu$ M, respectively (Dongmo et al., 2014).

## 5.2 | In-vivo experiments

# 5.2.1 | Anti-inflammatory activity

The EtOH extract of *Vitex glabrata* leaves exhibited significant antiinflammatory activity in carrageenan-induced paw edema and cotton pellet-induced granuloma formation in rat models. The extract showed significant anti-inflammatory activity in rats at a dose of 400 mg/kg bw, *p.o.*, and the activity was comparable to that of standard reference drug, diclofenac sodium (50 mg/kg *p.o.*) (Chouhan, Sridevi, Singh, & Singh, 2012). The EtOAc extract of *Vitex altissima* L. leaves also exhibited significant anti-inflammatory activity in rat paw edema model (Sridhar et al., 2004). The CHCl<sub>3</sub>, EtOAc, and *n*-BuOH fractions from methanolic extract of the stem-bark of *V. doniana* Sweet

exhibited significant anti-inflammatory activity on carrageenaninduced paw edema model in rats at a dose of 100 mg/kg bw, p.o. by inhibiting the paw edema volume by 68-72%, which effects were comparable to that of the reference drug, diclofenac (50 mg/kg p.o.), which was including having 81.94% inhibition. Seven ecdysteroids namely 21-hydroxyshidasterone (478), 11*β*-hydroxy-20-deoxyshidasterone (491). 24-hvdroxv (488). ecdysone 24-hydroxyecdysone-2,3-acetonide (487). shidasterone (477). ajugasterone C (469), and  $11\beta$ , 24-dihydroxy ecdysone (489) isolated from these fractions showed significant (p < .05) inhibitory effect (58– 71% inhibition after 6 hr) at 100 mg/kg, p.o. on rat paw edema development. The reference drug, diclofenac sodium, showed 70% inhibition after 6 hr (Ochieng et al., 2013).

Casticin (292) also protected against lipopolysaccharide (LPS)induced acute lung injury in mice by inhibiting inflammatory cytokines production through the inhibition of NF- $\kappa$ B and NLRP3 signaling pathways (Wang, Zeng, Zhang, et al., 2016).

The CHCl<sub>3</sub> extract of V. *negundo* seeds exhibited antiinflammatory activity in carrageenan-induced rat paw edema model. The extract at a dose of 500 mg/kg bw, *p.o.* showed 34.8% inhibition of paw edema volume after 3.5 hr of injection of carrageenan. The isolated triterpenoid,  $2\alpha$ , $3\alpha$ -dihydroxyoleana-5, 12-dien-28-oic acid (**203**) showed weak inhibition (18.7%) of paw edema volume at a dose of 50 mg/kg *p.o.* The standard drug, ibuprofen (50mg/kg, *p.o.*), showed 63.2% inhibition of paw edema volume (Chawla, Sharma, Handa, & Dhar, 1992).

The EtOAc extract and its isolate, 6'-O-trans-feruloyInegundoside (13) from V. *altissima* leaves exhibited moderate anti-inflammatory activity in the carrageenan-induced rat paw edema model by inhibiting 39 and 20% of the paw edema volume at a dose of 250 and 200 mg/kg after 3 hr, respectively (Sridhar et al., 2004).

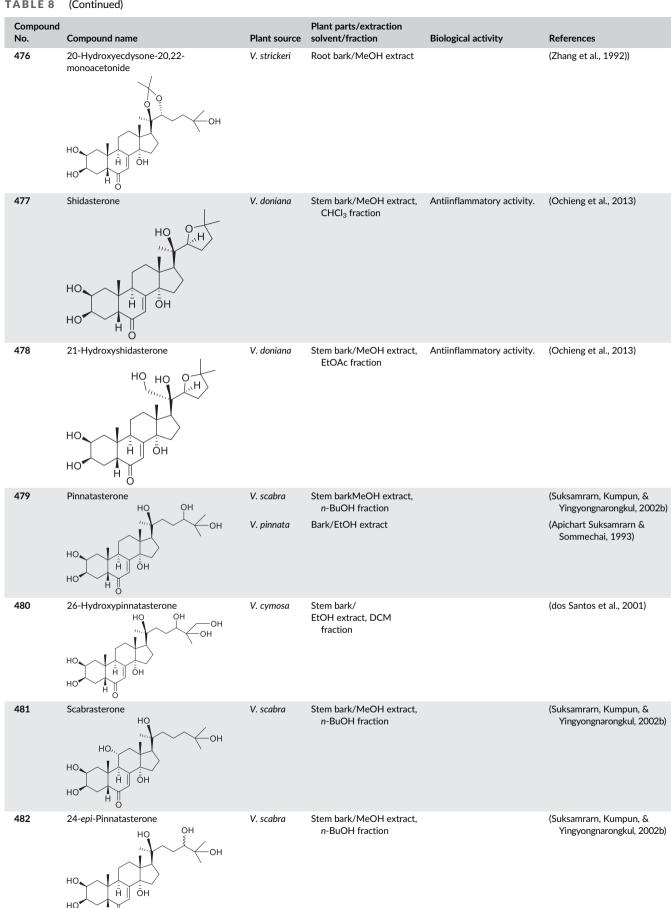
Ethanolic crude extract from V. *megapotamica* presented antiinflammatory effects in complete Freund's adjuvant (CFA)-induced chronic inflammation model at 10 mg/kg, without altering locomotor activity (Hamann, Zago, Rossato, et al., 2016). However, agnuside, an iridoid compound isolated from V. *mollis* Kunth, did not exhibit inhibitory activity against COX-1 and COX-2 *in-vitro* model (Ramírez-Cisneros et al., 2015). On the other hand, phenol glucoside 4-hydroxyphenethanol-3-O- $\beta$ -D-(6'-O-p-hydroxy benzoyl)-glucopyranoside (**517**) isolated from

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 TABLE 8
 List of ecdysteroids reported from different species of Vitex and their biological activities

TABLE 8	8 List of ecdysteroids reported from different species of Vitex and their biological activities					
Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References	
469	Ajugasterone C HO	V. polygama	Stem barks/EtOH extra		(dos Santos, Delle Monache, & Leitão, 2001)	
		V. strickeri V. doniana	Root bark/MeOH extract Stem bark/MeOH, EtOAc and <i>n</i> -BuOH fraction	Significant <i>in vivo</i> antiinflammatory activity.	(Zhang, Stout, & Kubo, 1992) (Ochieng, Ishola, Opiyo, et al., 2013)	
		V. scabra	Stem bark/MeOH extract, <i>n</i> -BuOH fraction		(Suksamrarn, Kumpun, & Yingyongnarongkul, 2002b)	
470	Tetra-acetylajugasterone C HO AcO AcO HO DAC	V. cienkowskii	Stem bark/DCM-MeOH and MeOH fraction	Vasorelaxant activity	(Dongmo, Nkeng-Efouet, Devkota, et al., 2014)	
471	Ajugasterone C-20,22- monoacetonide	V. polygama V. strickeri	Branches/EtOH extract Root bark/MeOH extract		(dos Santos et al., 2001) (Zhang, Stout, & Kubo, 1992)	
472	20-Hydroxyecdysone	V. cymosa	Stem bark/EtOH extract, DCM fraction		(dos Santos et al., 2001)	
		V. strickeri V. scabra V. canescens	Root bark/ MeOH extract Stem bark/MeOH extract, <i>n</i> -BuOH fraction Bark/EtOH		(Zhang et al., 1992) (Suksamrarn, Kumpun, & Yingyongnarongkul, 2002b) (Apichart Suksamrarn, Sommechai, Charulpong, & Chitkul, 1995)	
473	Turkesterone	V. polygama V. scabra	Branches/EtOH extract Stem bark/MeOH extract,		(dos Santos et al., 2001) (Suksamrarn, Kumpun, &	
	HO HO HO HO HO HO HO HO HO HO HO HO HO H	V. canescens	n-BuOH fraction Bark/EtOH extract		Yingyongnarongkul, 2002b) (Suksamrarn et al., 1995)	
474	Abutasterone	V. strickeri	Root bark/ MeOH extract		(Zhang et al., 1992))	
475	Canescensterone Canescensterone HO HO HO HO HO HO HO HO	V. canescens	Bark/EtOH extract		(Suksamrarn et al., 1995)	



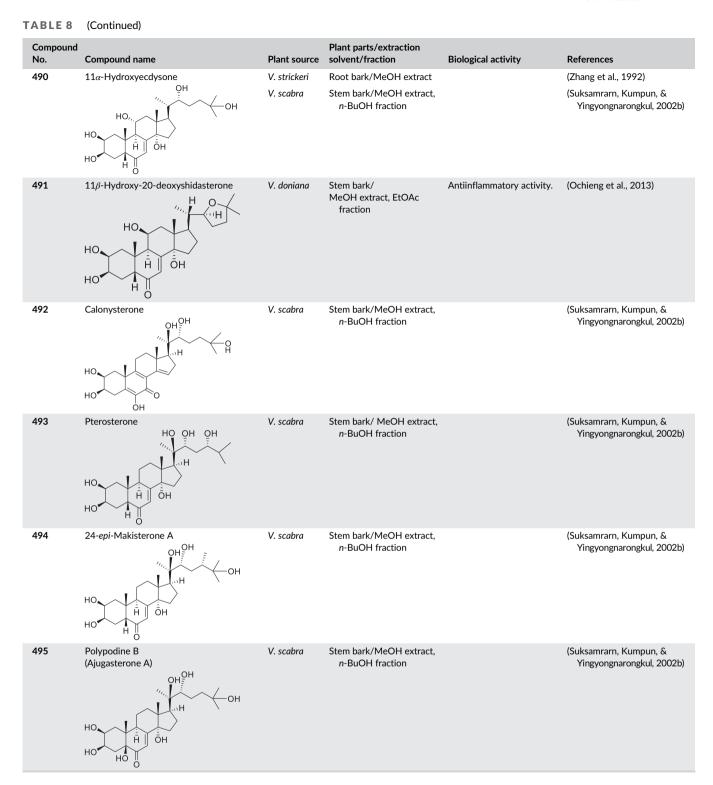
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# TABLE 8 (Continued)

TABLE	(continued)				
Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
483	24-epi-Abutasterone HO OH OH HO H OH HO H OH HO	V. scabra	Stem bark/MeOH extract, n-BuOH fraction		(Suksamrarn, Kumpun, & Yingyongnarongkul, 2002b)
484	(24 <i>R</i> )-11 $\alpha$ ,20,24-Trihydroxy-ecdysone HO OH OH HO, HO, OH HO, HO, OH HO, HO, OH HO, HO, HO HO, HO, HO HO, HO HO, HO HO, HO HO, HO HO, HO HO HO HO HO HO HO HO HO HO HO HO HO H	V. canescens	Root bark/EtOH extract, <i>n</i> -BuOH fraction		(A Suksamrarn, Promrangsan, & Jintasirikul, 2000)
485	11 <i>a</i> , 20, 26-Trihydroxy- -ecdysone and its C-25 epimer HO $HO_{HO}$ $HO$ $HO$ $HO$ $HO$ $HO$ $HO$ $HO$ $HO$	V. canescens	Root bark/EtOH extract, <i>n</i> -BuOH fraction		(A Suksamrarn et al., 2000)
486	20,26-Dihydroxyecdysone HO $OH$ HO $HO$ HO $HO$ HO $HO$ HO $HO$ HO $HO$ HO $OH$ HO	V. scabra	Stem bark/ MeOH extract, n-BuOH fraction		(Suksamrarn, Kumpun, & Yingyongnarongkul, 2002b)
487	24-Hydroxy-2,3-acetonide ecdysone	V. doniana	Stem bark/ MeOH extract, EtOAc fraction	Antiinflammatory activity.	(Ochieng et al., 2013)
488	24-Hydroxy ecdysone OH OH HO HO HO HO HO HO HO HO HO HO HO HO H	V. doniana	Stem bark/ MeOH extract, EtOAc fraction	Antiinflammatory activity.	(Ochieng et al., 2013)
489	11 $\beta$ ,24-Dihydroxy ecdysone OH OH HO	V. doniana	Stem bark/ MeOH extract, <i>n</i> -BuOH fraction	Antiinflammatory activity.	(Ochieng et al., 2013)



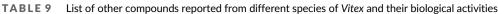
V. negundo L. var. heterophylla reduced 50% nitric oxide production on macrophage in concentrations at 30.76  $\mu$ M (Qiu et al., 2017).

Different extracts and compounds from V. doniana, V. altissima, V. glabrata, V. megapotamica, V. peduncularis, V. rotundifolia, V. negundo, and V. mollis were reported for their anti-inflammatory activity via inhibition of NF- $\kappa$ B and NLRP3 signaling pathways, via inhibition of the levels of the inflammatory cytokines TNF- $\alpha$ , IL-6, and IL-1 $\beta$  production, via suppression of LPS induced NO formation, via inhibition of COX proteins and iNOS proteins, and via inhibition of p38, ERK1/2, and JNK

pathways. Genus *Vitex* may be an important natural source for the development of novel anti-inflammatory molecule in future.

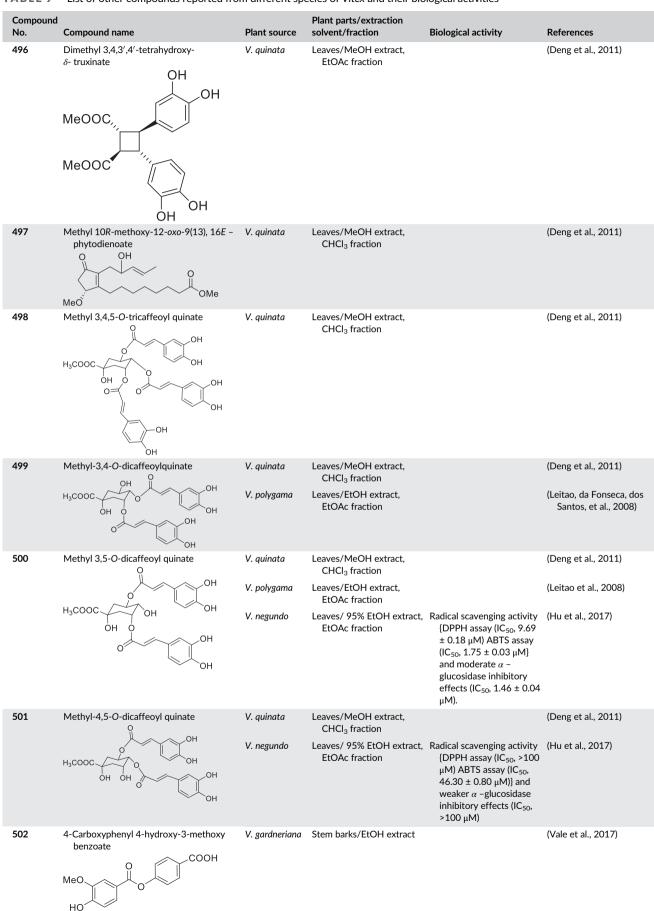
# 5.2.2 | Anticancer activity

Casticin (292) also inhibited tumor growth *in-vivo* experimented with xenografted tumors (Song et al., 2017). The antiproliferative activity of vitexicarpin (292) was also evaluated on *in-vivo* hollow



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1	ABLE 9	(Continued)				
	Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
	503	β-Sitosterol	V. negundo V. pinnata V. agnus-castus V. cienkowskii V. trifolia	Leaves/MeOH Leaves Seed essential oil Fruit/n-hexane extract Stem bark/DCM-MeOH Leaves and twigs/MeOH		(Chandramu et al., 2003) (Kamal et al., 2011) (Asdadi et al., 2015) (S. Li et al., 2013) (Dongmo et al., 2011) (Ming-Yu Huang et al., 2013)
	504	β-Sitosterol glucoside	V. cienkowskii V. trifolia	Stem bark/DCM-MeOH fraction Leaves and Twigs /MeOH extract	٧	(Dongmo et al., 2011) (Ming-Yu Huang et al., 2013)
	505	Stigmasterol	V. trifolia	Leaves/EtOH extract, EtOAc fraction		(Mohamed et al., 2012)
	506	Rotundial CHO H	V. rotundifolia	Volatile constituents of fresh leaves	Mosquito repellent activity.	(Watanabe, Takada, Matsuo, & Nishimura, 1995)
	507	Tanacetamide O HN HO HO HO OH	V. cienkowskii	Stem bark/DCM-MeOH and MeOH	Vasorelaxant activity	(Dongmo et al., 2011)
	508	p-Hydroxybenzoic acid COOH	V. negundo	Leaves/MeOH		(Chandramu et al., 2003)
			V. pinnata	Leaves/MeOH extract, EtOAC fraction		(Rudrapaul et al., 2014)
			V. agnus-castus	Leaves, seeds, roots/70% MeOH-water		(Mingqing Huang et al., 2015)
			V. trifolia	Fruit/MeOH extract, EtOAc fraction		(S. Li et al., 2013)
				Leaves and Twigs/MeOH, EtOAc fraction		(Ming-Yu Huang et al., 2013)
			V. rotundifolia	Fruit/EtOH extract/ EtOAc fraction		(Wu et al., 2010)
			V. gardneriana	Stem barks/EtOH extract		(Vale et al., 2017)
	509	Methyl-4-hydroxybenzoate	V. negundo	Dried fruit/40% EtOH extract		(Huang, Qing, et al., 2013)

(Continues)

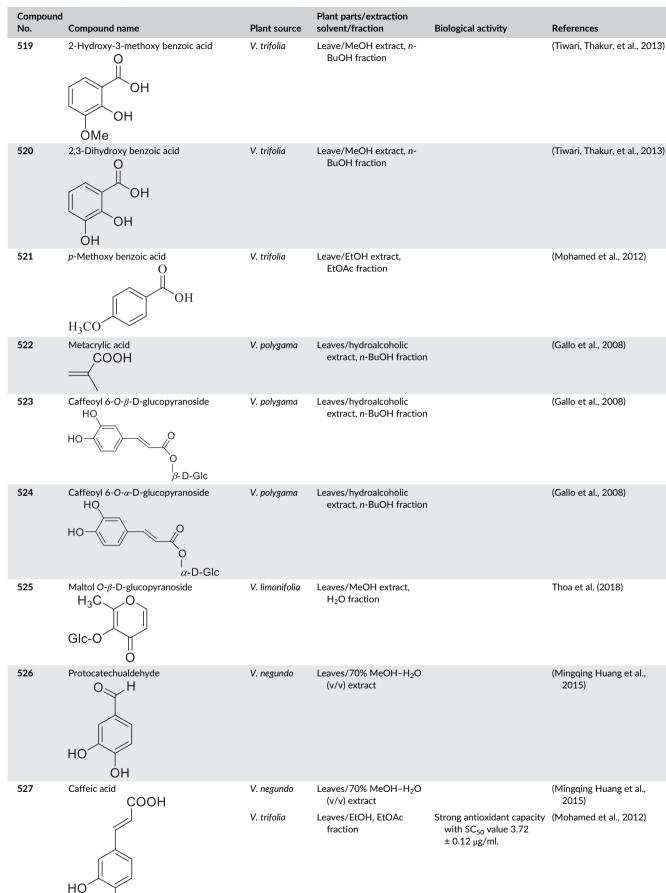
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ABLE 9	(Continued)				
Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
510	4-(3,4-Dihydroxyphenyl)-2-butanone HO HO	V. negundo	Leaves/70% EtOH, EtOAc fraction	Inhibitory effects on LPS- induced nitric oxide (NO) production in RAW264.7 macrophages and did not show any activity (IC <sub>50</sub> value >100 µM	(Qiu et al., 2016)
		V. negundo	Fruit/MeOH, EtOAc fraction		(Fang, et al., 2016b)
511	3-(4-hydroxyphenyl)- 1-(2,4,6-trimethoxyphenyl)-2-propen- 1-one OMe OMe OMe OMe	V. leptobotrys	Leaves and twigs/DCM extract	Inhibited HIV-1 replication by 77% at 15.9 μM.	(Pan et al., 2014)
512	HO HO HO	V. negundo	Leaves/70% EtOH extract	$\label{eq:link} \begin{array}{l} \mbox{Inhibitory effects on LPS-} \\ \mbox{induced nitric oxide (NO)} \\ \mbox{production in RAW264.7} \\ \mbox{macrophages with IC}_{50} \\ \mbox{value 64.89 \pm 4.77 } \mbox{\mu}M. \end{array}$	(Qiu et al., 2016)
513	4-(3',4'-dihydroxyphenyl)-butan-2-one-4'- <i>O-β</i> -D-glucoside	V. cannabifolia	Fruit/MeOH extract	DPPH radical scavenging activity.	(Yamasaki et al., 2008)
	GlcO	V. rotundifolia	Leaves/MeOH extract		(Kouno et al., 1988)
514	Methyl <i>p</i> -hydroxyphenylacetate	V. negundo	Leaves/70% EtOH extract	Inhibitory effects on nitric oxide (NO) production in RAW 264.7 macrophages with IC <sub>50</sub> value 74.10 $\pm$ 5.26 $\mu$ M.	(Qiu et al., 2016)
515	p-Methoxycinnamic acid MeO	V. negundo	Leaves/70% EtOH extract	Inhibitory effects on nitric oxide (NO) production in RAW 264.7 macrophages with IC <sub>50</sub> value 70.14±4.63 µM.	(Qiu et al., 2016)
516	4-Hydroxyphenethanol 3-O-β-D-(6'-O-p- hydroxybenzoyl)-glucopyranoside OH HO HO HO HO OH	V. negundo	Leaves/70% EtOH extract	Inhibitory effects on LPS- induced nitric oxide (NO) production in RAW264.7 macrophages with IC <sub>50</sub> value 30.76±2.21 µM.	(Qiu et al., 2016)
517	p-Hydroxybenzoic acid glucose ester	V. agnus-castus	Fruit/n-hexane and MeOH extract		(S. Li et al., 2013)
518	3,4-Dihydroxy benzoic acid (Protocatechuic acid)	V. pinnata	Leave/MeOH extract, EtOAc fraction		(Rudrapaul et al., 2014)
	0 	V. negundo	Leaves/70% MeOH-H <sub>2</sub> O (v/v) extract		(Mingqing Huang et al., 2015)
	ЮН	V. rotundifolia	Fruit/EtOH extract, EtOAc fraction		(Wu et al., 2010)
	но ү он	V. gardneriana	Stem barks/EtOH extract		(do Vale et al., 2017)

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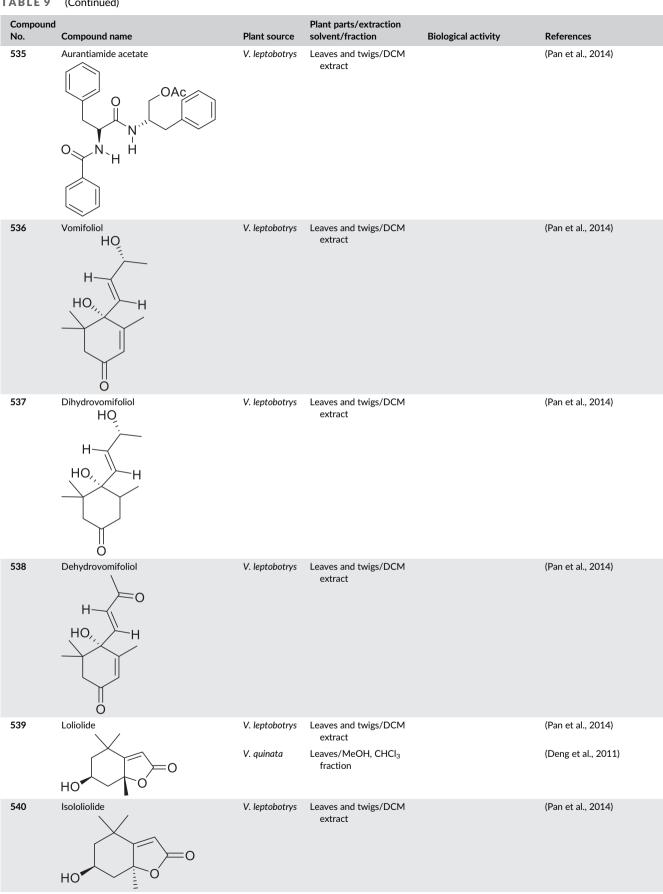
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# TABLE 9 (Continued)

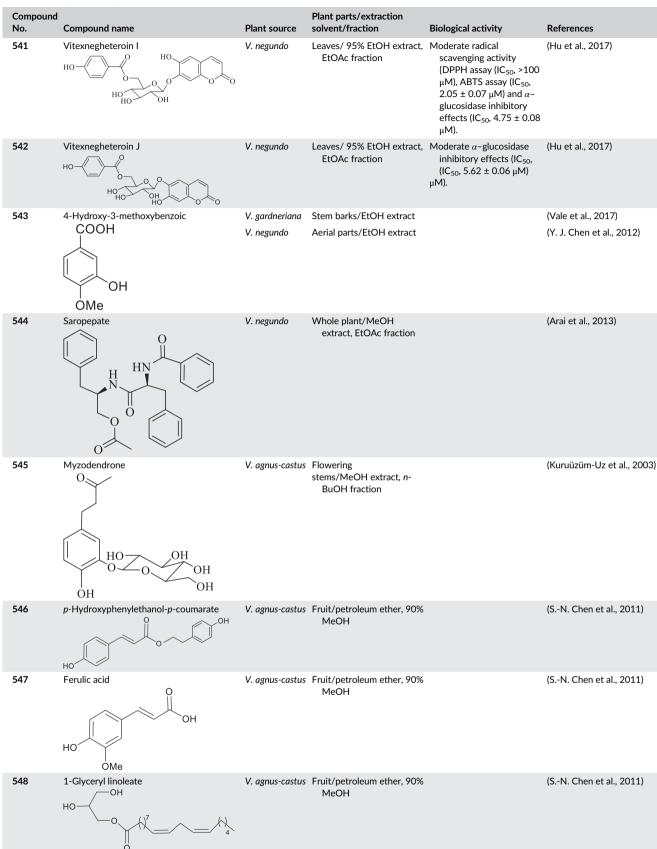
TABLE 9	(Continued)				
Compound No.	Compound name	Plant source	Plant parts/extraction solvent/fraction	Biological activity	References
528	Neochlorogenic acid OH HOOC OH OH OH OH OH OH	V. negundo	Leaves/70% MeOH-H <sub>2</sub> O (v/v) extract		(Mingqing Huang et al., 2015)
529	Chlorogenic acid O HOOC OH OH OH OH	V. negundo	Leaves/70% MeOH-H <sub>2</sub> O (v/v) extract		(Mingqing Huang et al., 2015)
530	Cryptochlorogenin acid OH HOOC OH OH OH OH OH	V. negundo	Leaves/70% MeOH-H <sub>2</sub> O (v/v) extract		(Mingqing Huang et al., 2015)
531	Isochlorogenic acid B	V. negundo	Leaves/70% MeOH-H <sub>2</sub> O (v/v) extract		(Mingqing Huang et al., 2015)
532	Isochlorogenic acid A (3,5-Di-O-caffeoylquinic acid) O HOOC OH OH OH OH OH OH OH OH OH	V. negundo V. cymosa	Leaves/70% MeOH-H <sub>2</sub> O (v/v) extract Fruits/EtOH extract, EtOAc fraction		(Mingqing Huang et al., 2015) (Leitao et al., 2008)
533	Isochlorogenic acid C $OH \rightarrow OH \rightarrow$	V. negundo	Leaves/70% MeOH-H <sub>2</sub> O (v/v) extract		(Mingqing Huang et al., 2015)
534	Aurantiamide	V. leptobotrys	Leaves and twigs/DCM extract		(Pan et al., 2014)



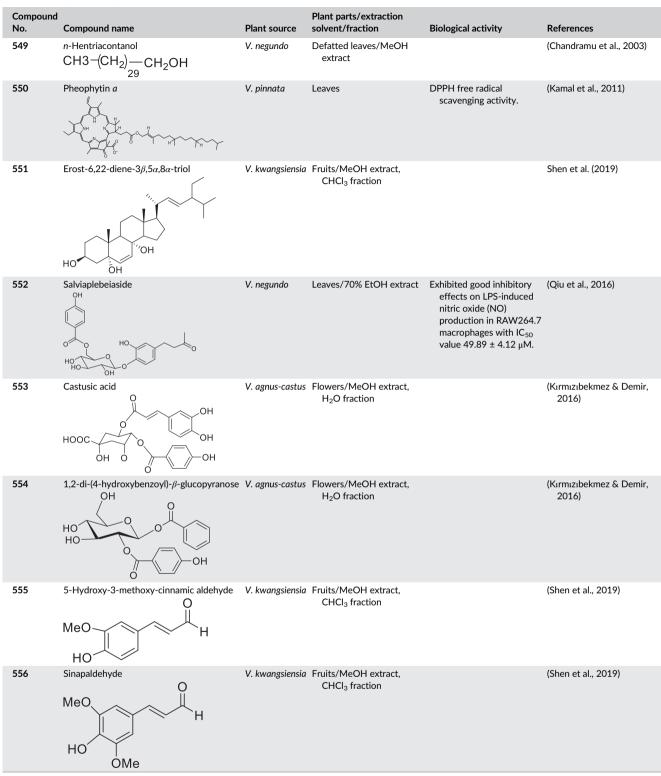


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fiber model in mice using the *K*B, LNCaP, and Lul cancer cells at doses of 10, 20, and 40 mg/kg. With LNCaP cells, the compound inhibited the growth by 0–7.2 % at the *ip* site and 0–2.4 % at the sc site. While with *K*B cells, it was ineffective at the *ip* site and inhibited the growth by 0–8.2 % at the *sc* site. The compound was also ineffective in *in-vivo* mouse P-388 leukemia model (135 mg/kg) (Díaz et al., 2003).

# 5.2.3 | Antinociceptive activity

Essential oil from V. *agnus-castus* leaves significantly decreased pain responses in both formalin and tail immersion tests. In addition, the study concluded that the opioidergic system and muscarinergic receptors of cholinergic system might be involved in the antinociceptive effect (Khalilzadeh et al., 2015).

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In another *in-vivo* study, V. *megapotamica* crude extract tested at 10 mg/kg dose exhibited a significant antinociceptive action in the complete Freund's adjuvant (CFA)-induced chronic inflammation model on rats (Hamann et al., 2016).

# 5.2.4 | Moulting hormone activity

24-*epi*-Pinnatasterone (**482**) and scabrasterone (**481**) isolated from the stem bark of *V. scabra* exhibited weak *in-vivo* moulting activity with  $EC_{50}$  values of  $5.2 \times 10^{-4}$  and  $1.0 \times 10^{-3}$  M, respectively based on the activity of positively control 20-hydroxyecdysone (**472**) ( $1.6 \times 10^{-5}$  M) in Musca assay. The low moulting activity of these ecdysteroids was possibly due to lacking of a 22R-hydroxyl group in their molecule (Suksamrarn, Kumpun, & Yingyongnarongkul, 2002b).

# 5.2.5 | Cardioprotective activity

Vitex negundo leaf ethanolic extract showed a cardioprotective action on isoproterenol-induced myocardial necrosis in Wistar rats. The results demonstrated that a pretreatment with V. negundo extract prevented the deleterious effects related to myocardial infarction. In addition, the extract normalized cardiac marker enzymes, antioxidant enzymes, and signaling molecules (Prasad, Mopuri, Islam, & Kodidhela, 2017).

# 5.2.6 | Memory improvement activity

In a study with ovariectomized Wistar rats, the animals were submitted to Step-through passive avoidance (STPA) test for the evaluation of learning and memory. The results showed that oral administration of *V. agnus-castus* ethanolic extract improved learning and memory performance significantly. These results may be related to an increase in estrogen receptor alpha (ER $\alpha$ ) gene expression in hippocampii of rat brain (Allahtavakoli, Honari, Pourabolli, et al., 2015).

# 5.2.7 | Hepatoprotective activity

The hydroalcoholic extract and *n*-butanolic fraction from fruit of *V. agnus-castus* L. displayed a significant protection on liver of rats with nonalcoholic fat liver disease (NAFLD) at 8.33 and 0.83 mg/kg concentrations, respectively (Moreno, Campos-Shimada, Da Costa, et al., 2015). Moreover, the protective effect of *Vitex* honey obtained from *V. negundo* was confirmed on paracetamol-induced liver injury in rats model. Results demonstrated a significant reduction in AST and ALT activities and MDA levels, while also enhancement was observed of the SOD and glutathione peroxidase activities at dose 20 g kg<sup>-1</sup> (Y. Wang et al., 2015). *V. doniana* methanolic extract from fresh fruit pulp demonstrated a hepatoprotective effect in mice induced by acetaminophen. The extract exhibited an increase of

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SOD, CAT, glutathione peroxidase, and glutathione reductase and a normalization of AST and ALT serum levels at 100 mg/kg dose (Ajiboye, 2015).

# 5.2.8 | Gastroprotective activity

Vitex pubescens Vahl ethanolic leaf extract at 500 mg/kg reduced significantly the ulcer area (79%) on ethanol-induced gastric hemorrhagic ulceration model using Sprague–Dawley rats. According to the authors, this gastroprotective activity might be related to increased antioxidant enzymes activities (CAT, SOD, and GSH), decreased lipid peroxidation upsurge of HSP70, and reduced expression of Bax proteins (Al-Wajeeh et al., 2016).

# 5.2.9 | Antiaging activity

The ethanolic extract from V. agnus-castus (600 mg/kg per day) was able to improve antioxidant defenses like superoxide dismutase (SOD) and catalase (CAT) to reduce malondialdehyde (MDA) levels and attenuate the aging effects caused by D-galactose in mice. The treatment with Vitex extract minimizes atrophy of the endometrium, degeneration of follicles, alterations in serum levels of LH and FSH. and reduces the decline in estrogen through antioxidant responses (Ahangarpour, Najimi, & Farbood, 2016). Other study investigating the aging effects included by D-galactose demonstrated that hydroalcoholic fruit extract from V. agnus-castus diminished body weight gain and the loss of kidney weight in female mice. Moreover, kidney histological analyses revealed that the extract tested was able to reduce vasodilation, brush border loss, tubular dilation, and cell swelling in proximal tubules (Oroojan, Ahangarpour, Khorsandi, & Najimi, 2016).

# 5.2.10 | Endocrine effects

Essential oil from V. *agnus-castus* possessed an endocrine effect on pituitary-thyroid and adrenocortical axes in middle-aged male rats. The essential oil of *Vitex* modulated the levels of triiodothyronine (TH) and adrenocorticotrophic hormone (ACTH) hormones, often involved in anxiety and depressive disorders (Šošić-Jurjević, Ajdžanović, Filipović, et al., 2016).

# 5.2.11 | Ischemic tissue injury protective activity

Aqueous extract of V. *doniana* leaves showed a significant protective effect on ischemic tissue injury in rats submitted to testicular torsion. Histology analyses of group treated with 200 mg of V. *doniana* Sweet demonstrate significant protection of seminiferous tubule diameter with reduction of the luminal size of germinal epithelium (Adelodun, Adewole, Bejide, et al., 2016).

# 6 | CONCLUSIONS AND FUTURE DIRECTIONS

The different species of Vitex are being used in traditional medicines in different parts of the world. The plants are scattered in many countries such as India, Iran, Malaysia, Sri Lanka, China, Pakistan, Bangladesh, Philippines, Maldives, Guimaras Island, Japan. Madagascar, Thailand, Futuna, South Pacific Island, Hawaii, Mexico, and New Zealand. The current review documented the up-to-date ethnobotanical, phytochemical, and pharmacological research data of the genus Vitex. The phytochemical studies on the various species of Vitex reported isolation and characterization of a total of 556 chemical compounds, and their structure was mentioned in the review. The volume of experimental records gives evidence of the presence of a rich variety of phytochemicals viz. iridoids, diterpenoids, triterpenoids, flavonoids, lignans, sesquiterpenoids, monoterpenoid, ecdysteroids, etc., with a wide range of bioactivities. Out of the reported 556 chemical compounds, 38 are iridoids, 144 are diterpenoids, 71 are triterpenoids, 99 are flavonoids, 75 are lignans, 26 are sesquiterpenoids, 16 are monoterpenoids, 27 are ecdysteroids, and 61 are other compounds. Many of the isolated compounds, crude extract and fractions were evaluated for their pharmacological activity. In addition, diterpenoids, flavonoids, lignans, triterpenoids, and Iridoids were found to be the major chemical constituents of the genus Vitex, and these constituents are known for their biological efficiency. Thus, these constituents should be explored for their different pharmacological activities. It is interesting to note that although there are many studies on the plants of the genus, most of them are limited to a few Vitex species viz. V. negundo L., V. agnus-castus L., V. rotundifolia L.f., V. trifolia L., V. cannabifolia Siebold & Zucc., etc. We speculate that this might be due to the extensive use of the species in traditional medicine systems and herbal supplements worldwide. It will be important that future research systematically study all yet unexplored as well as less explored multiple species of the genus for novel phytochemicals with varied useful bioactivities so that costeffective, prospective medicinal drug, and healthcare products can be developed at a large scale in the future. Moreover, very limited data are available for the toxicity profile of the genus Vitex. This specifies that detailed toxicity study is necessary to be carried out for different pharmacologically active fractions as well as pure phytochemicals of medicinally important species of the genus Vitex. This may open ways for discovery of new drugs for treating various health disorders and benefit of mankind.

# ACKNOWLEDGMENTS

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# CONFLICT OF INTEREST

The authors declared no conflict of interest.

# AUTHOR CONTRIBUTIONS

Niranjan Das conceived the study and wrote the first draft of the manuscript. Andréia C. F. Salgueiro, Debasish Roy Choudhury, Sudip Kumar Mandal, Rajan Logesh, Md Mahadi Hassan, and Hari Prasad Devkota supported the writing of the first draft of the manuscript and revised the manuscript. All of the authors made conceptual contributions to the content, have corrected and improved the first draft, and approved the final manuscript.

# DATA AVAILABILITY STATEMENT

No data were generated in this work.

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