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Volkameria inermis: An overview of its chemical constituents and pharmacological properties, notably the amelioration of motor tics

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ABSTRACT

This overview on *Volkameria inermis* (Lamiaceae) is the first in updating information on the chemical constituents and pharmacological properties of the species, notably on its unique ability in ameliorating motor tics. The information was procured from Google, Google Scholar, PubMed, PubMed Central, Science Direct, J-Stage, and PubChem. Previously named *Clerodendrum inerme* (Verbenaceae), *V. inermis* is a scrambling or scandent coastal shrub in the tropics and sub-tropics. From different parts of the plant, compounds such as flavonoids, diterpenes/diterpenoids, sterols, triterpenes/triterpenoids, iridoid glycosides, phenolic glycosides, phenylethanoid glycosides (PEGs), phenylpropanoid glycosides (PPGs), chalcones, and sesquiterpenes have been reported. Major pharmacological properties of *V. inermis* include anti-cancer, anti-inflammatory, antioxidant, hepatoprotective, analgesic, and antibacterial activities. Other properties include anti-tyrosinase, antifungal, neuroprotective, hypotensive, hypoglycemic, amyloid-β aggregation, wound healing, antipyretic, and larvicidal activities. A unique pharmacological property of *V. inermis* leaf extract, discovered by scientists from Taiwan, is the amelioration of motor tic disorders, a spectrum of Tourette syndrome. This property included a case report, three *in vivo* studies, and one patent. Areas of further research of *V. inermis* are suggested.

Implication for health policy/practice/research/medical education:
The prospects of further research on the phytochemistry and pharmacological properties of *V. inermis* are rewarding. New compounds are still being reported. Among the pharmacological properties of *V. inermis*, the amelioration of motor tic disorders warrants further research, notably on the compounds and mechanisms involved. Comparisons with other *Volkameria* species would be interesting.

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Introduction

The genus *Clerodendrum*, previously under the family Verbenaceae, now belongs to the family Lamiaceae. The genus is very large and diverse, comprising ~580 species of vines, shrubs, and herbs worldwide (1,2). In China, 34 species have been recorded (3). Among species of the genus, pharmacological properties such as anti-inflammatory and antinociceptive, anti-oxidant, anti-hypertensive, anti-cancer, antimicrobial, anti-diarrheal, hepatoprotective, hypoglycemic, hypolipidemic, memory enhancing, and neuroprotective have been reported (4,5). Chemical constituents consist of a wide range of compounds, including flavonoids diterpenoids, triterpenoids, flavonoids, phenylethanoids, phenylpropanoids, and steroids (5,6).

Volkameria inermis L. of the family Lamiaceae is now the accepted name for *Clerodendrum inerme*, which has now become a homotypic synonym of the former (7). Some morphological features distinguishing *Volkameria* from *Clerodendrum* are in the leaf, inflorescence, fruit

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calyx, and fruit (7,8). In *Volkameria*, the leaf blade is often less than 6 cm in length, the inflorescence is axillary, fruit calyx is rarely accrescent, and fruit is not brightly colored. In *Clerodendrum*, the leaf blade is more than 6 cm long, the inflorescence is terminal, fruit calyx is accrescent, and fruit is brightly colored.

Commonly known as wild jasmine, *V. inermis* is an erect, scrambling or scandent shrub that can grow up to 3 m in height (3,9,10). Branches and twigs are slender and pubescent. Leaves are opposite, ovate to elliptical, thinly fleshy, and smooth with a pointed or obtuse tip (9). Inflorescences are 3-flowered at the axils of branches. Flowers have a long and narrow corolla tube bearing five white or pale lilac petals and are fragrant (3,9,11). The four long reddish to purple stamens protrude ~3 cm from the flower and curve upwards. Fruits are a drupe, bright green when young and turning black when mature. Shrubs of *V. inermis* are found in coastal areas associated with mangroves (9). Geographically, the species occurs from South Asia through Southeast Asia to southern China, northern Australia, and Polynesia.

A study on the pollination biology of *V. inermis* reported nectar robbing by bees that reduces the nectar resource from the flowers (11). As a result, pollinating butterflies have to increase the number of nectar-foraging visits and shuttle between *V. inermis* populations. Such a foraging behavior by butterflies increases the rate of cross-pollination.

In Thai traditional medicine, *V. inermis* is used to treat skin diseases (12). A tincture or decoction from these leaves is used in the traditional Indian or Ayurvedic medicine for the treatment of fever, cough, skin rashes, and boils (13,14). In Vietnamese folk medicine, this plant is used to treat various diseases, such as rheumatism, neuralgia, backache, stomach ache, cold, fever, malaria, and hepatitis (15). In Indian tribal medicine, leaves of *V. inermis* are used for treating fever, cough, skin rashes and boils, used in conjunction with other plant leaves (13).

This overview begins with an introduction to plants of the genus *Clerodendrum*, their species diversity, pharmacological properties and chemical constituents, followed by a brief description of the botany, biology, and traditional uses of *V. inermis*. After the introduction, information on the classes and names of compounds of *V. inermis* is updated. The pharmacological properties of the extracts and compounds of *V. inermis* are categorized based on bioactivities, effects, and mechanisms. The amelioration of motor tic disorders is given special mention.

Chemical constituents

Information on the chemical constituents of *V. inermis* (16) has been updated in this overview. The aerial part, leaf, stem, and root of the *V. inermis* plant (Figure 1) contain flavonoids (15), diterpenes/diterpenoids (12), sterols (10), triterpenes/triterpenoids (10), iridoid glycosides (9), phenolic glycosides (6), phenylethanoid glycosides (PEGs) (6), phenylpropanoid glycosides (PPGs) (4), and sesquiterpenes (2) (Table 1). There is only one phytochemical study on the flower of *V. inermis*. Two new chalcones, namely, 3-hydroxy-3',4'-dimethoxychalcone and 3,2'-dihydroxy-3',4'-dimethoxychalcone have been isolated from the flower along with two known flavones, 7-*O*-methylwogonin and eucalyptin (17).

Figure 1. Flower, bud, and leaves of *Volkameria inermis*.

Among the diterpenes/diterpenoids (Table 1) from the aerial parts or leaf of *V. inermis*, crolerodendrum A ($C_{20}H_{20}O_6$) and crolerodendrum B ($C_{20}H_{19}O_6$) have been isolated (15). Crolerodendrum A is new to the species while crolerodendrum B is new to science. They are abietane diterpenes with hydroxyl (–OH) groups at C11, C12, C14, and C16 of ring C. Crolerodendrum A ($C_{20}H_{20}O_6$) has a carbonyl (C=O) group at C2 of ring A and another at C7 of ring B. The C=O group at C2 is absent in crolerodendrum B ($C_{20}H_{19}O_6$). Cleroinermin ($C_{20}H_{28}O_4$) is a neo-clerodane diterpenoid that has a bicyclic ring decalin moiety and a six-carbon side chain including a furan skeleton and a C=O group (6,23). The furan skeleton is a five-membered aromatic ring with four carbons to one oxygen.

Inerme A ($C_{52}H_{74}O_{19}$) and inerme B ($C_{53}H_{76}O_{20}$) are dimeric neo-clerodane diterpenoids with their two hexahydrofurofuran rings joined by an ethereal linkage at C15 and C15' (24). Inerme B, with a methoxy ($-OCH_3$) group at C1, is a methoxylated derivative of inerme A (6). The chemical structures of crolerodendrums A & B, and cleroinermin are shown in Figure 2.

PPGs are found in *V. inermis*. They are characterized by having a caffeoyl moiety and a hydroxyphenylethyl moiety that are linked to a glucose moiety by ester and glycosidic linkages, respectively (44). Other sugars such as rhamnose, xylose, or arabinose may be attached to the glucosyl residue. PPGs are also called phenethyl glycosides, PEGs, or caffeoyl PEGs. Acteoside or verbascoside ($C_{29}H_{36}O_{15}$) is the most reported compound in *V. inermis* (Figure 2). The PPG consists of four moieties i.e., caffeic acid, glucose, rhamnose, and hydroxytyrosol (45,46). Caffeic acid and hydroxytyrosol are linked to the glucose moiety *via* ester and glycosidic bonds, respectively.

Table 1. Classes and names of compounds from *Volkameria inermis*

Compound class	Compound name	Plant part	Reference
Aliphatic	(*Z*)-3-Hexenyl-β-glucopyranoside	Aerial part	(12)
glucosides	Pentadecanoic acid β-D-glucoside	Aerial part	(18)
Aliphatic ketones	6-Nonacosanone	Aerial part	(19)
	11-Pentacosanone*	Aerial part	(19)
Alkane	n-Octacosane	Leaf	(20)
Benzyl alcohol	Benzyl alcohol β-glucopyranoside	Aerial part	(12)
glucosides	Benzyl alcohol β-(2'-*O*-β-xylopyranosyl) glucopyranoside	Aerial part	(12)
Chalcones	3,2'-Dihydroxy-3',4'-dimethoxychalcone*	Flower	(17)
	3-Hydroxy-3',4'-dimethoxychalcone*	Flower	(17)
Diterpenes/	Clerodendrins A & B	Leaf	(21)
Diterpenoids	Clerodermic acid*	Aerial part	(19,22)
		Leaf	(10)
	Cleroinermin*	Aerial part	(23)
	Crolerodendrums A & B*	Leaf	(15)
	14,15-Dihydro-15-hydroxy-3-epicaryoptin (mixture)	Leaf	(24)
	14,15-Dihydro-15β-methoxy-3-epicaryoptin*	Leaf	(15,24,25)
	Harwickiic acid	Leaf	(15)
	Inermes A & B	Leaf	(24)
	Methyl vouacapenata	Leaf	(26)
	Uncinatone	Leaf	(15)
Fatty acid	Linolenic acid methyl ester	Leaf	(27)
Flavonoids	Acacetin	Leaf	(15,22,28)
		Leaf & root	(29)
	Apigenin	Leaf	(10,22)
		Aerial part	(23)
	Diosmetin	Leaf	(28)
	Eucalyptin	Flower	(17)
	Galangustin	Leaf & root	(29)
	Hispidulin	Leaf	(10,28,30,31)
	5-Hydroxy-7,4'-dimethoxyflavone	Leaf	(22)
	7-Hydroxyflavone	Leaf	(26)
	5-Hydroxy-6,7,4'-trimethoxyflavone•	Aerial part	(32)
	Kaempferol	Leaf	(33)
	Kaempferol 3,7,4'-trimethyl ether	Leaf	(15)
	4'-Methylscutellarein	Leaf	(34)
	7-*O*-Methylwogonin	Flower	(17)
	Pectolinarigenin	Leaf	(34)
		Leaf & root	(29)
	Quercetin	Leaf	(33)
	Salvigenin	Leaf	(22)
	Scutellarin	Leaf	(10)
Hydroquinone	2,6-Dimethoxy-*p*-hydroquinone 1-*O*-β-glucopyranoside	Aerial part	(12)
glycosides	Seguinoside K	Aerial part	(12)
Iridoid glycosides	Inerminosides A*, A1*, B*, C* & D*	Leaf	(35,36)
	Inerminoside A1	Aerial part	(37)
	Melittoside	Aerial part	(12,37)
	Monomelittoside	Aerial part	(12,37)
	Sammangaoside C*	Aerial part	(12)
Lignan &	Dehydrodiconiferyl alcohol-4-*O*-β-D-glucopyranoside	Stem	(38)
lignan glucosides	Icariol A_2	Stem	(38)
	Lariciresinol-4-*O*-β-D-glucopyranoside	Stem	(38)
	Syringaresinol-4-*O*-β-glucopyranoside	Stem	(38)

Table 1. Continued

Compound class	Compound name	Plant part	Reference
Megastigmane	Sammangaosides A* & B*	Aerial part	(12)
glucosides			
Neolignan	(7*S*,8*R*)-Dehydrodiconiferyl alcohol 4-*O*-β-glucopyranoside	Aerial part	(12)
glucosides	(7*S*,8*R*)-Dehydrodiconiferyl alcohol 9-*O*-β-glucopyranoside	Aerial part	(12)
Phenolic	Cistanoside D•	Stem	(39)
glycosides	Clerodenoside A	Stem	(39)
	Leonuriside A	Stem	(38)
	Markhamioside F•	Aerial part	(40)
	Purpureaside B•	Aerial part	(40)
	Seguinoside K	Stem	(39)
Phenylethanoid	Cistanoside E•	Aerial part	(40)
glycosides	Darendoside B	Aerial part	(12)
	Decaffeoylverbascoside	Aerial part	(12,40)
	Isocistanoside F•	Aerial part	(40)
	2-(3-Methoxy-4-hydroxylphenyl)-ethyl-*O*-2'',3''-diacetyl-α-L-rhamnopyranosyl-(1→3)-4-*O*-(*E*)-feruloyl-β-D-glucopyranoside*	Aerial part	(37)
	Salidroside	Aerial part	(12)
Phenylpropanoid	Campneoside I•	Aerial part	(37,40)
glycosides	Isoverbascoside	Aerial part	(12,37,40)
		Stem	(39)
	Leucosceptoside A	Aerial part	(12)
	Acteoside (Verbascoside)	Aerial part	(12,37,40)
		Stem	(39)
		Root	(41)
Sesquiterpenes	Reynosin	Leaf	(26)
	Tumerone	Leaf	(26)
Sterols	4-Androstenediol	Leaf	(26)
	24,24-Dimethyl-25-dehydrolophenol*	Aerial part	(42)
	5α,8α-Epidioxyergosta-6,22-diene-3β-ol	Leaf	(15)
	24β-Ethyl-cholesta-5,9(11),22-*E*-trien-3β-ol*	Aerial part	(19,43)
	Gramisterol	Aerial part	(42)
	4α-Methyl-24β-ethyl-5α-cholesta-14,25-dien-3β-ol*	Aerial part	(19,43)
	Obtusifoliol	Aerial part	(42)
	β-Sitosterol	Aerial part	(32)
	Stigmasta-5,22,25-trien-3-β-ol	Aerial part	(32)
		Leaf & root	(29)
	Stigmasta-5,22,25-trien-3-yl-*O*-D-glucopyranoside	Leaf & root	(29)
Triterpenes/	β-Amyrin	Leaf	(20)
Triterpenoids	β-Amyrin palmitate	Leaf & root	(29)
	Betulin 3-acetate	Leaf & root	(29)
	Betulinic acid•	Aerial part	(32)
		Leaf & root	(29)
	Friedelin	Leaf	(20,22)
	B-Friedoolean-5-ene-3-β-ol•	Aerial part	(32)
	Lup-1,5,20(29)-trien-3-*O*-β-D-glucopyranoside*	Leaf	(20)
	Lupeol laurate	Leaf & root	(29)
	Oleanolic acid	Leaf	(10)
	Squalene	Leaf	(27)

* Compound new to science, • Compound new to *V. inermis*.

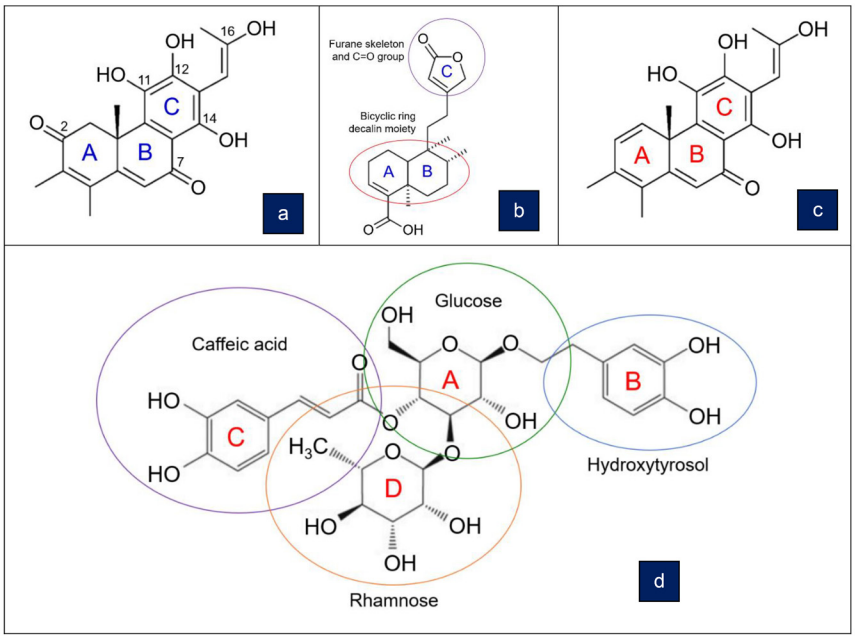

Figure 2. Chemical structures of crolerodendrum A (a), cleroinermin (b), crolerodendrum B (c), and verbascoside or acteoside (d).

PEGs are another class of compounds isolated from the aerial part of *V. inermis*. PEGs are characterized by having cinnamic acid and hydroxytyrosol moieties attached to glucopyranose *via* ester and glycosidic linkages, respectively, with rhamnose, xylose, or apiose attached to a glucose moiety, forming the core of the molecule (47). 2-(3-Methoxy-4-hydroxylphenyl)-ethyl-*O*-2",3"-diacetyl-α-L-rhamnopyranosyl-(1→3)-4-*O*-(*E*)-feruloyl-β-D-glucopyranoside, a PEG with two glucose moieties, is new to science (37). New compounds to *V. inermis* are cistanoside E and isocistanoside F (40).

A study on the chemical composition of essential oils from different parts of V. inermis reported that the dominant components were 2-hydroxy-benzoic acid, phenylmethyl ester (34.2%), and dibutyl phthalate (31.5%) in the twig, dibutyl phthalate (59.3%) and bis(2-ethylhexyl) phthalate (17.3%) in the leaf, and dibutyl phthalate (44.3%) and ferruginol (30.7%) in the root (48).

Pharmacological properties

Information on the pharmacological properties of *V. inermis* (16,49) is updated in this review. Major pharmacological properties of *V. inermis* include anti-cancer (10), anti-inflammatory (5), antioxidant (5), hepatoprotective (4), analgesic (3), and antibacterial (3) activities (Table 2). Minor properties represented by single studies are those on antifungal, amyloid-β aggregation, anti-pyretic, anti-tyrosinase, neuroprotective, hypotensive, hypoglycemic, wound healing, and larvicidal activities.

Most studies on the pharmacological properties of *V. inermis* are based on extracts. There are few studies on the bioactive compounds. They included one anti-cancer study on hardwickiic acid (15), two anti-inflammatory studies on hispidulin, acacetin, and diosmetin (28), one study on the antioxidant activity of crolerodendrum B, uncinatone, and hardwickiic acid (15), one study on antibacterial activity of squalene and linolenic acid methyl ester (27), and one study on the neuroprotective activity of acacetin (70).

Although acteoside or verbascoside is the most reported compound in studies on the phytochemistry of *V. inermis* (Table 1), there are no reports on its pharmacological properties in the literature. This is probably because of its extremely low content in *V. inermis*. From other species, acteoside has been reported to possess diverse bioactivities such as antioxidant, antibacterial, anti-viral, anti-tyrosinase, anti-cancer, anti-inflammatory, anti-diabetic, anti-nephritic, hepatoprotective, neuroprotective, osteoprotective, skin-protective, wound healing, immunomodulatory, and vasorelaxant properties (46,75,76).

To date, there are no reports on the anti-cancer properties of acacetin from *V. inermis,* although the anti-cancer properties of acacetin from other plant species have been reported (77). Cell lines susceptible to acacetin included lung, liver, gastric, prostate, breast, squamous, and colon cancer cells including leukaemia, pharyngeal carcinoma, and glioblastoma.

Compounds from *V. inermis* with pharmacological properties include acacetin and hispidulin (Table 2). Acacetin has the ability to inhibit amyloid-β aggregation, a hallmark of Alzheimer's disease (29), and possesses neuroprotective properties by inhibiting glutamate release (70). Hispidulin possesses anti-inflammatory properties (28). Acacetin is a flavonoid with two –OH groups at ring A and one $-OCH_3$ group at ring B (Figure 3). Hispidulin is another flavonoid with three –OH groups (two at ring

Table 2. Pharmacological properties of extracts and compounds of *Volkameria inermis*

Bioactivity	Effect and mechanism	Reference
Anti-cancer	Hardwickiic acid from the methanol leaf extract showed strong cytotoxicity against HCT116 colon cancer cells with IC_{50} value of 3.5 µM.	(15)
	The petroleum ether leaf extract inhibited Ehrlich ascites carcinoma with IC_{50} value of 60 µg/mL.	(33)
	The aqueous leaf extract inhibited DMBA-induced buccal pouch tumor by 80%, exerted potent lipid peroxidation inhibitory effects, and improved the antioxidant defense system in hamsters.	(50)
	Oral intake of the ethanol leaf extract reduced tumor incidence, volume, and burden, as well as inhibited lipid peroxidation in DMBA-induced skin carcinogenic mice.	(51)
	Oral intake of the ethanol leaf extract reduced tumor formation as well as restored the status of glycoconjugates and the osmotic fragility of red blood cells in DMBA-induced skin carcinogenic mice.	(52)
	Against A549 lung cancer cells, the ethanol leaf extract exhibited cytotoxicity with an IC_{50} value of 16 µg/mL.	(53)
	The aqueous methanol aerial part extract was weakly cytotoxic against A549 lung cancer cells with an IC_{50} value of 260 µg/mL, compared to 88 µg/mL of doxorubicin, the positive control.	(54)
	Against Burkitt's lymphoma cells, the aqueous methanol aerial part extract was weakly cytotoxic with an IC_{50} value of 213 µg/ml, compared to 62 µg/mL of doxorubicin.	(55)
	At 300 µg/mL, the ethyl acetate fraction inhibited MCF-7 breast and HepG2 liver cancer cells with 68% and 53% cytotoxicity, respectively.	(56)
	The methanol leaf extract inhibited the migration, invasion, and adhesion of A549 lung cancer cells, but cytotoxicity was not detectable with IC_{20} and IC_{50} values exceeding 400 µg/mL.	(57)
Anti-inflammatory	Hispidulin, acacetin, and diosmetin from the leaf exhibited potent inhibition of NO production in RAW264.7 macrophages with IC_{50} values of 44, 43, and 57 µM, respectively.	(28)
	Hispidulin from the leaf inhibited PGE2 production including inducible iNOS and COX-2 expressions by inhibiting NF-κB and the JNK pathways.	(28)
	The methanol aerial part extract (200 mg/kg) exhibited stronger anti-inflammatory activity than indomethacin using the formalin-induced hind-paw oedema method.	(32)
	Using the cotton pellet granuloma assay, the methanol leaf extract displayed significant and dose-related inhibition of granulator phases of inflammation.	(58)
	The ethanol aerial part extract showed a significant and dose-dependent inhibitory effect on ear oedema formation in mice, using the xylene-induced inflammation assay.	(59)
Antioxidant	Depending on the solvents used, TPC and TFC of stem extracts were 0.9−1.9 mg/100 g GAE and 3.2−5.7 mg/100 g CE, while DPPH radical scavenging IC_{50} and inhibition of linoleic acid peroxidation were 24−81 µg/mL and 41−72%, respectively.	(14)
	Crolerodendrum B, uncinatone, and hardwickiic acid from the methanol leaf extract exhibited strong DPPH radical-scavenging activity with ED_{50} values of 18, 10, and 11 µM, respectively.	(15)
	The methanol aerial part extract and 5-hydroxy-6,7,4'-trimethoxyflavone showed maximum radical scavenging activity of 62% (100 µg/mL) and 37% (20 µM), respectively, using the DPPH assay.	(32)
	The DPPH radical scavenging activity of methanol leaf extract (88%) was comparable to or greater than that of ascorbic acid (89%), BHA (83%), and α-tocopherol (67%).	(60)
	Out of six solvents used, the methanol leaf extract displayed the strongest DPPH (28 µg/mL) and ABTS (70 µg/mL) radical scavenging activity.	(61)
Hepatoprotective	Rats treated with ethanol leaf extract showed significant decrease in the levels of markers such as enzymes AST, ALT, and ALP, as well as cholesterol and triglyceride content.	(62)
	The ethanol leaf extract exhibited protective activity against CCl_4-induced liver damage in rats by significantly decreasing serum enzymes ALP, ALT, and AST, including triglycerides and total cholesterol, and significantly increasing glutathione level.	(63)
	The ethanol leaf extract at 200 mg/kg exerted protective activity against paracetamol-induced hepatic injury in rats by lowering serum levels of GOT, GPT, ALP, and total bilirubin.	(64)
	The methanol leaf extract protected against CCl_4-induced hepatic damage in mice by significantly inhibiting CAT, GSH, and SOD activity.	(65)
Analgesic	The methanol leaf extract (500 mg/kg) displayed significant analgesic activity against acetic acid-induced writhing in mice, comparable to diclofenac sodium (10 mg/kg), the standard drug.	(58)
	The ethanol aerial part extract attenuated acetic acid-induced writhing with strongest activity at 500 mg/kg (46%) comparable to that of diclofenac sodium (58%).	(59)
	The aqueous leaf extract showed significant analgesic effects in rats using hot-plate, tail-flick, and tail-immersion methods.	(66)
Antibacterial	Squalene and linolenic acid methyl ester from the methanol leaf extract displayed stronger antibacterial activity towards *Bacillus subtilis* and *Staphylococcus aureus* (Gram-negative) than *Escherichia coli* and *Pseudomonas aeruginosa* (Gram-positive).	(27)

Table 2. Continued

Bioactivity	Effect and mechanism	Reference
	Methanol, ethyl acetate, and aqueous aerial part extracts showed significant inhibition against 15 of the 18 bacterial species tested, including Gram-positive and Gram-negative bacteria.	(67)
	The methanol extracts of leaf and root displayed the strongest activity against *Staphylococcus aureus* with no activity by the aqueous extracts.	(68)
Antifungal	The ethyl acetate and hexane leaf and stem extracts (1 mg/mL) were effective against *Trichophyton mentagrophytes* and *T. rubrum*.	(13)
Amyloid-β aggregation	The dichloromethane leaf and root extracts (2 mg/mL) inhibited amyloid-β aggregation (~90%), and inhibition by acacetin was 29% at 20 μM.	(29)
Anti-pyretic	The aqueous leaf extract showed significant reduction in boiled milk-induced pyrexia in rabbits.	(66)
Anti-tyrosinase	The methanol leaf extract displayed 17% tyrosinase inhibitory activity.	(69)
Neuroprotective	Acacetin from the ethanol leaf extract inhibited glutamate release by attenuating voltage-dependent Ca^{2+} entry and preventing kainic acid-induced *in vivo* excitotoxicity.	(70)
Hypotensive	The aqueous leaf extract exerted hypotensive effects on the arterial pressure in rabbits, hypotension was light, progressive, and reversible at doses from 10^{-3} to 10 mg/mL.	(71)
Hypoglycemic	The ethanol leaf extract exerted hypoglycemic effects on STZ-induced diabetic mice by increasing glucose uptake and reducing plasma glucose level.	(72)
Wound healing	Using the scratch wound-healing assay, the aqueous leaf extract at 100 μg/mL enhanced the wound closure rate of HaCaT cells by 54%, compared to the control group of 31%.	(73)
Larvicidal	Against the fourth instar mosquito larvae of *Culex quinquefasciatus* and *Aedes aegypti*, the hexane leaf extract exhibited adult emergence inhibition with EI_{50} of 8.1 and 19.5 mg/L.	(74)

Abbreviations: ABTS, 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid); ALP, alkaline phosphatase; ALT, alanine amino transferase; AST, aspartate amino transferase; BHA, butylated hydroxyanisole; CAT, catalase; CCl_4, carbon tetrachloride; CE, catechin equivalent; COX-2, cyclooxygenase 2; DMBA, 7,12-dimethylbenz(a)anthracene; DPPH, 2,2-diphenyl-1-picrylhydrazyl; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; GSH, glutathione; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinase; MT, motor tics; NF-κB, nuclear factor kappa B; NO, nitric oxide; PGE_2, prostaglandin E2; SOD, superoxide dismutase; STZ, streptozotocin; TFC, total flavonoid content; and TPC, total phenolic content.

A and one at ring B), and one $-OCH_3$ group at ring A (78).

Other bioactivities of acacetin include anti-cancer, antimicrobial, antiviral, anti-diabetic, anti-inflammatory, anti-arthritic, anti-aging, anti-Alzheimer, neuroprotective, cardioprotective, and antinociceptive properties (77,79). Reviews on hispidulin have reported bioactivities such as antioxidant, antifungal, anti-cancer, anti-platelet, anti-convulsant, anti-osteoporotic, neuroprotective, anti-inflammatory, and hepatoprotective properties (78,80).

Motor tics

Tourette syndrome (TS) is a childhood neurological disorder characterized by the presence of motor and phonic tics (81). Tics are involuntary, sudden, rapid, repetitive, non-rhythmic, stereotyped movements or phonic productions (81,82). Those who suffer from motor or phonic tics for more than one year are diagnosed as chronic tic disorder.

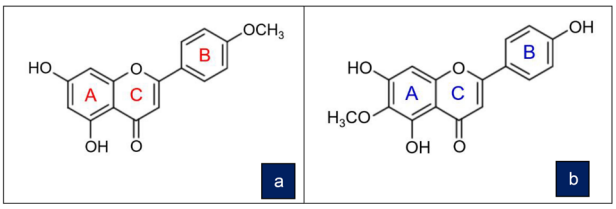

Figure 3. Chemical structures of acacetin (a) and hispidulin (b).

A unique pharmacological property of *V. inermis* leaf extract is the amelioration of motor tic disorders as discovered by scientists from Taiwan *via* a case report and affirmed by subsequent studies. In 2009, a 13-year-old girl was admitted to the National Taiwan University Hospital in Taipei, Taiwan, due to motor tic disorder with intractable, rhythmic, and jerky movements of four limbs (83). The conscious movements lasted for hours, and she complained of dizziness, headache, and nausea. Her daily medications included haloperidol, alprazolam, biperiden, lamotrigine, and clonazepam. When she was 14 years old, her medications were discontinued, except for lamotrigine, and clonazepam. Her mother started to prescribe her an aqueous extract of ground *V. inermis* leaves. Her tics subsided dramatically an hour later after taking the extract. Her symptoms were suppressed after orally taking the extract twice a week. She took the extract once in 2-6 months when her tics recurred (83). After taking the extract for two years, her motor tics were markedly reduced, and examinations of her hemogram, liver and renal function, blood gas, and blood electrolyte were all normal.

Subsequently, an *in vivo* study was conducted by the same group of scientists in Taiwan to assess the effects of ethanol leaf extract of *V. inermis* on hyperlocomotion and pre-pulse inhibition (PPI) disruptions in mice, induced by methamphetamine (mAMP), and *N*-methyl-D-aspartate

(NMDA) channel blockers using ketamine and MK-801 (84). Results showed the *V. inermis* leaf extract relieved hyperlocomotion and PPI disruptions, and improved sensorimotor gating deficit, suggesting its therapeutic potential for treating TS and schizophrenia.

Subsequently, two more studies were undertaken on the effects of hispidulin from *V. inermis* on motor tic disorders. Hispidulin remitted motor tics and alleviated mAMP-induced hyperlocomotion (HL) in mice without motor impairment, suggesting its therapeutic potential towards hyper-dopaminergic disorders (30). In addition, hispidulin alleviated mAMP-induced HL in mice by acting on $GABA_A$ receptors in the cerebellum (31). Apomorphine-induced HL was however not affected.

Based on the findings of the case study (83), and subsequently the *in vivo* studies, a patent was filed by LC Chiou, PC Fan, and WJ Huang from Taipei, and SJ Wang from Sinjhuang as inventors, and the National Taiwan University, Taipei Medical University, and Fu Jen Catholic University as assignees (85). The United States Patent, number US 2011/0159129 A1 and dated June 2011, was entitled 'Use of *Clerodendrum* sp. for treating tic disorders or psychiatric disorders with sensor motor gating deficits.' The invention related to the use of a composition made from the leaves of *Clerodendrum inerme* for treating tic disorder or sensorimotor gating deficits.

Conclusion

Diverse chemical constituents have been reported in *V. inermis*. They include flavonoids, diterpenes/diterpenoids, sterols, triterpenes/triterpenoids, iridoid glycosides, phenolic glycosides, PEGs, PPGs, chalcones, and sesquiterpenes. Anti-cancer, anti-inflammatory, antioxidant, hepatoprotective, analgesic, and antibacterial activities are the major pharmacological properties of *V. inermis*, with anti-tyrosinase, antifungal, neuroprotective, hypotensive, hypoglycemic, amyloid-β aggregation, wound healing, antipyretic, and larvicidal activities as the minor properties. The prospects of research on the phytochemistry of *V. inermis* are rewarding as compounds new to science and new to the species are still being reported. There are no studies on the pharmacological properties of acteoside or verbascoside, the most reported compound from *V. inermis*. Among the pharmacological properties of *V. inermis*, the amelioration of motor tic disorders warrants further research, notably on the compounds and their mechanisms involved. Comparisons between *V. inermis* and other *Volkameria* species would be another interesting field of research.

Authors' contribution

EWCC conceived the idea. HTC and SKW collated articles from databases, analyzed their information, drafted the manuscript, and prepared the tables and figures. The manuscript was finalized by EWCC and HTC. EWCC, the lead and corresponding author, completed, submitted, and revised the manuscript, and paid the article processing charges.

Conflict of interests

The authors declare no conflict of interest.

Ethical considerations

All ethical issues have been carefully observed by the authors.

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