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Contributed Paper

Wedelia trilobata L.: A Phytochemical and Pharmacological Review

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ABSTRACT

Studies on the traditional use of medicines are recognized as a way to learn about potential future medicines. *Wedelia* is an extensive genus of the family Asteraceae, comprising about 60 different species. *Wedelia trilobata* Linn. has long been used as traditional herbal medicine in South America, China, Japan, India and for the treatment of a variety of ailments. The aim of this review was to collect all available scientific literature published and combine it into this review. The present review comprises the ethnopharmacological, phytochemical and therapeutic potential of *W. trilobata*. An exhaustive survey of literature revealed that tannin, saponins, flavonoids, phenol, terpenoids constitute major classes of phytoconstituents of this plant. Pharmacological reports revealed that this plant has antioxidant, analgesic, anti-inflammatory, antimicrobial, wound healing, larvicidal, trypanocidal, uterine contraction, antitumor, hepatoprotective, and in the treatment of diabetes, menstrual pain and reproductive problems in women. *W. trilobata* seems to hold great potential for in-depth investigation for various biological activities, especially their effects on inflammation, bacterial infections, and reproductive system. Through this review, the authors hope to attract the attention of natural product researchers throughout the world to focus on the unexplored potential of *W. trilobata*, and it may be useful in developing new formulations with more therapeutic value.

Keywords: *Wedelia trilobata* (L.), ethnopharmacological use, phytochemistry, pharmacological activity

1. INTRODUCTION

The manufacture and clinical evaluation of herbal remedies and/or their constituents have made it possible to transform traditional medicine into a modern industry capable of making a significant contribution to the delivery of healthcare [1]. Many medicinal plants contain large amounts of antimicrobial and antioxidant compounds such as phenols and flavonoids. Phenolic compounds are a

group of plant metabolites that have numerous beneficial activities such as anti-inflammatory, anti- bacterial, anti-mutagenic, anti-viral and antioxidant properties [2]. This revival of interest in plant derived drugs is mainly due to the current widespread belief that "green medicine" is safe, and clinically effective, better tolerated by patients, less expensive and globally competitive [3,4]. Use of medicinal plants is becoming popular in United States and Europe [5] and in most of the developing world, plants or herbal products have forever played important roles in the treatment of wounds, intestinal problems, coughs and sneezes, general torpor etc [6].

Traditional knowledge about medicinal plants has without doubt served as an example for developing new drugs. Over the past decades, it has been shown that *Wedelia trilobata* L. contains high amount of diterpene, eudesmanolide lactones and luteolin with a variety of biological activities. This review assesses the scientific information on *W. trilobata* and focuses on the evidence available on its therapeutic benefits.

Wedelia, known officially by the scientific name, *Sphagneticola trilobata* (L.) Pruski, but still commonly referred to by its former name, *W. trilobata* (L.) Hitchc is a member of the family Asteraceae (formerly Compositae), the sunflower or daisy family. *W. trilobata* is a soil creeper and forms a thick carpet. The genus *Wedelia*, named in honor of Georg Wolfgang Wedel (1645-1721), Professor of Botany at Jena, Germany, has about 70 species of tropical and subtropical regions. *W. trilobata* is a very attractive plant because of its nearly constant and prolific blooming [7].

2. DESCRIPTION

2.1 Habitat

A weed of urban bushland, closed forests, forest margins, open woodlands, waterways, lake margins, wetlands, roadsides, disturbed sites, waste areas, vacant lots, and coastal sand dunes in tropical and sub-tropical regions. It may also encroach into lawns, footpaths and parks from nearby gardens [7, 8].

2.2 Geographical Distribution

Native to Mexico, Central America (i.e. Belize, Costa Rica, Guatemala, Honduras, Nicaragua and Panama), the and throughout the Caribbean, where it is noted as a weed in Trinidad, Puerto Rico, the Dominican Republic, Jamaica, Panama, and tropical South America (i.e. French Guiana, Guyana, Surinam, Venezuela, Brazil, Bolivia, Colombia, Ecuador and Peru). Naturalized in South Africa, Florida, Louisiana, Hawaii, Puerto Rico, and the Virgin Islands. Escaped in many tropical regions of the world, including Australia (South-eastern Queensland and north-eastern New South Wales), the Pacific Islands (i.e. American Samoa, the Cook Islands, Fiji, French Polynesia, Guam, Kiribati, the Marshall Islands, Nauru, Niue, New Caledonia, Palau, Western Samoa, Tonga and Hawaii), Malaysia, Indonesia, Thailand, India, Papua New Guinea [9, 10].

2.3 Scientific Classification

Kingdom: Plantae – Plants; Subkingdom: Tracheobionta – Vascular plants; Superdivision: Spermatophyta – Seed plants; Division: Magnoliophyta – Flowering plants; Class: Magnoliopsida – Dicotyledons; Subclass: Asteridae; Order: Asterales; Family: Asteraceae – Aster family; Genus: *Sphagneticola* O. Hoffmann – creeping-oxeye; Species: *Sphagneticola trilobata* (L.) Pruski – Bay Biscayne creeping-oxeye [9].

2.4 Synonyms

Complaya trilobata (L.) Strother, *Silphium trilobatum* L., *Thelechitonia trilobata* (L.) H.Rob. & Cuatrec., *Wedelia carnosa* Rich., *Wedelia paludosa* DC., *Wedelia trilobata* (L.) A.S. Hitchc., *Wedelia triloba* (Rich.) Bello [9].

2.5 Common Names

Atiat (Puluwat), Bay Biscayne creeping oxeye, creeping daisy, creeping wedelia, rabbit's paw, Singapore daisy, gold cup, yellow dots, trailing daisy, water zinnia and wild marigold (English), hansenfuss (Germany), America hama-guruma (Japan), di jin hua (China), kra dum tong (Thailand), wedelia kuning (Malaysia), Singapore-madeliefie (Africa), ampelkrage (Sweden), ut telia (Marshall Islands), and arnica-do-mato, pseudo-arnica, vedelia (Brazil) [10].

2.6 Botanical Description

It is a long lived (perennial) herb with a creeping or climbing habit. This mat-forming herb often creates a dense ground cover (usually 15-30 cm tall but occasionally upto 70 cm tall) that crowd out the growth of other species. It may also climb a short distance up trees or over other vegetation. The stems are rounded, green or reddish in color, and may be coarsely hairy. They grow up to 2 m long and regularly develop roots (adventitious roots) at their nodes. Short, semi-upright (ascending), flowering branches are produced of these creeping stems. The leaves are attractive, bright shiny green, somewhat fleshy oppositely arranged and simple, the blade obovate to elliptic or ovate and are stalkless (sessile) or borne on short stalks (petioles). These leaves 2-9 cm long and 2-5 cm wide, acute at the apex and winged and sessile at the base usually have three lobes (hence the name *trilobata*) and irregularly toothed (serrated) margins. They are glossy in appearance, mostly hairless (glabrous), and slightly fleshy (succulent) in nature. The single attractive bright-yellow flower heads are daisy-like in appearance and are borne on the end of terminal and axillary stalks (peduncles) 2 to 9 cm long, with 2 to 4 series of bracts forming the involucre at the base of the flower. Each flower-head has 8-13 yellowish 'petals' (ray florets) that are 6-15 mm long with 1- to 3 finely toothed tips and are pistillate. In the centre of these flower-heads there are numerous tiny yellow tubular disc florets 4-5 mm long, and mixed with chaffy bracts. The ray and disc florets are both yellow. The base of each flower-head (capitulum) is enclosed in a row (involucre) of narrow (lanceolate) green bracts (about 1 cm long). Flowering occurs throughout the year, but is most common from spring to autumn. The fruit is a 2 to 4-angled achene, with short, narrow pappus scales on the top [11]. The 'seeds' (i.e. achenes), when present, are 4-5 mm long and topped with a crown of short fringed scales. They are elongated in shape, brown in colour and have a rough surface texture. However, very few seeds reach maturity in cultivated or naturalised plants in Australia [12].

Figure 1. Photograph of *Wedelia trilobata* Linn.

2.7 Ethnopharmacological Uses

The aerial parts of this plant are used in traditional medicine in the Caribbean and Central America against bronchitis, colds, abdominal pains, dysmenorrheal [13], and even as a fertility enhancer [14]. In folk medicine, it is employed to treat backache, muscle cramps, rheumatism, stubborn wounds, sores and swellings, and arthritic painful joints [15]. The Miskito Indians of eastern Nicaragua use leaves for treatment of kidney dysfunctioning, cold, stingray wounds, snakebite, purge and amenorrhea [16,17]. Coe and Anderson (1996) reported that fruits, leaves and stem are used in childbirth and in the treatment of bites and stings, fever and infection [14]. *W. trilobata*, was utilized in Hong Kong as a substitute for *W. chinensis*, a traditional Chinese medicine used for the treatment of the common cold, hepatitis, indigestion and infections [18]. In Trinidad and Tobago, used for reproductive problems, amenorrhea, dysmenorrheal [19]. It is used for the treatment of fever and malaria in Vietnam [20].

Unpublished reports indicate that aqueous infusion has been employed locally and empirically in Southern part of Brazil in the management of diabetes. In fact, it is popularly referred to as *insulina* due to its observed antidiabetic properties [20]. Flowers and leaf part of the plant were used in the ladies for the purpose of amenorrhea, childbirth, abortion and to clear the placenta after birth [21,22]. The literature review reveals that the fresh entire plant is used as molluscicidal activity, antibacterial and antimycobacterial activity [21].

Suriname's traditional medicine uses the stem, leaves, and flower boiled in water for hepatitis, indigestion due to sluggish liver, white stools, burning in the urine and stopping of urine and for infections. Boiled fresh stems and leaves were used for bathe those suffering from backache, muscle cramps, rheumatism, or swellings. Used for painful joints of arthritis, fresh leaves and stems are mashed and spread on a cloth and applied to area, wrapped securely with a warm covering in South America. Wedelia species is used in lower Thailand for headache and fever [22].

2.8 Phytochemical Reports

The main secondary metabolites from this plant mainly consist of terpenoids, flavonoids and polyacetylenes as well as steroids [20, 23-25]. The leaves and stem contains eudesmanolide lactones, luteolin and kaurenoic acid [26,27]. It has following different classes of phytoconstituents. Sesquiterpenoids, triterpenoid and diterpenoid: from the aerial part [18,20, 23-25, 28-34] and the flower of *W. trilobata*, [18,20, 23-25, 28-35], sterols: [23,25,31], flavonoids: [25], Benzene derivatives: [25, 31].

Wedelolactone was reported for hepatoprotective activity, antibacterial, anti hemorrhagic and antiepileptic activity [36-38]. These necessitate estimation of wedelolactone in *Wedelia* species for exploring its bioactivity. Wedelolactone was estimated by high performance thin layer chromatographic technique. The standard wedelolactone showed retention factor (Rf) value of 0.56 and this constituent was found to be present in the tested ethanolic extract of *W. trilobata*. The Rf values obtained for wedelolactone in the extracts was found to be 0.56. The amount of wedelolactone was estimated by comparing the peak area of standard and that present in the ethanolic extract. The content of wedelolactone present in the extract was found to be 0.084% w/w [21].

Essential oils are valuable plant products generally of complex composition comprising the volatile principles contained in the plant and more or less modified during the preparation process. Most constituents of oil belong to the large group of terpenes. The essential oil obtained from the leaves of *W. trilobata* was analyzed by GC/MS. α- pinene (above 30%), α-phellandrene (17.4%) and limonene (16.3%) were the major components [39].

The fourteen volatile components were identified from the essential oils of *W. trilobat*a leaves, stem and flowers. The essential oil was characterized by a high percentage of hydrocarbon sesquiterpenes (HS) (25.5-86.4%), hydrocarbon monoterpenes (HM) (22.9-72.3%) and low levels of oxygenated sesquiterpenes (OS) (0.0- 7.4%). The major components of volatile oils were germacrene D (11.9-35.8%), α-phellandrene (1.4-28.5%), α-pinene (7.3-23.8%), *E*-caryophyllene (4.6-19.0%), bicyclogermacrene (6.0-17.0%), limonene (1.8-15.1%) and α-humulene (4.0-11.6%). The content of the monoterpenes α-pinene, α-phellandrene and limonene increased from the mid-rainy season until the middle of the next dry season [40]. Table 1 shows the chemical structures of phytoconstituent present in *W. trilobata*.

2.9 Pharmacological Activities

Table 2 summarizes the pharmacological activity of *W. trilobata*.

Antidiabetic Activity

Male albino rats with diabetes induced by the administration of streptozotocin (45 mg/kg, i.v.) were treated with oral administration of *W. trilobata* (50 mg/kg). It was found to reduce blood glucose levels and improved weight gained which was accompanied by a marked restoration of decreased vitamin C and reduced glutathione in liver and kidney tissues of STZ-treated rats. *In vitro* data revealed that *W. trilobata* caused an inhibition of lipid peroxidation under Fe^{2+} or sodium nitroprusside assaults. Conversely, *W. trilobata* also caused a reduction in the high levels of thiobarbituric acid reactive substances (TBARS) observed in the liver, kidney, and testes as well as high serum triglyceride, ALT and AST of diabetic rats [41]. Rungprom *et al*. (2010) demonstrated that the methanolic extract of *W. trilobata* was found to be the potent α-glucosidase inhibitor comparable to the authentic drug, Acarbose® [42].

Table 1. Secondary metabolites of *Wedelia trilobata* (L.)

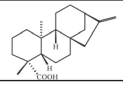
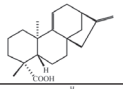
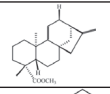
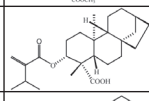
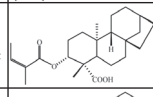
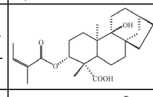
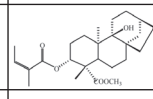
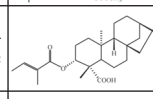
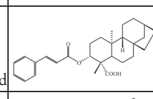
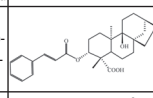
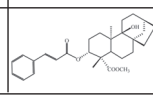
Compound name	Structure	Plant part	References
Diterpenes *ent*-kaur-16-en-19 oic acid (Kaurenoic acid)		Aerial part	25, 32-35
ent-kaura-9(11), 16-dien-19 oic acid (Grandiflorenic acid)		Aerial part leaves	25, 31, 33 35
ent-kaura-9(11), 16-dien-19 oic acid methyl ester		Aerial part	25
3α- (senecioyloxy)-*ent*-kaur-16-en-19 oic acid		Aerial part	32
(3α)-3-(angeloyloxy)-*ent*-kaur-16-en-19 oic acid		Aerial part	23-25, 32
3α-(angeloyloxy) 9β-hydroxy-*ent*-kaur-16-en-19 oic acid		Aerial part	23
Methyl-3α-(angeloyloxy) 9β-hydroxy-*ent*-kaurenoate		Aerial part	23
(3α)-3-(tiglinoyloxy)-*ent*-kaur-16-en-19 oic acid		Aerial part	23-25
(3α)-3-(cinnamoyloxy)-*ent*-kaur-16-en-19 oic acid		Aerial part	23-25, 32
(3α)- (cinnamoyloxy)-9β-hydroxy-*ent*-kaur-16-en-19 oic acid		Aerial part	23
Methyl-3α-(cinnamoyloxy)-9β-hydroxy-*ent*-kaurenoate		Aerial part	23

Table 1. Continued.

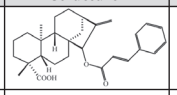
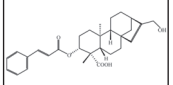
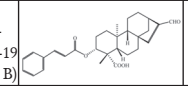
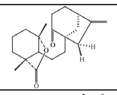
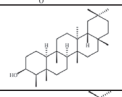
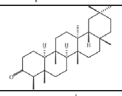
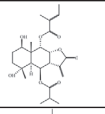
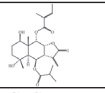
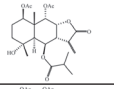
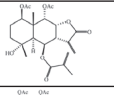
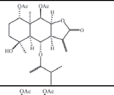
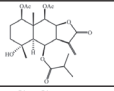
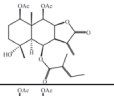
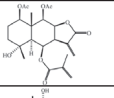
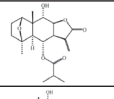
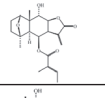
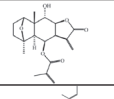
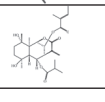
Compound name	Structure	Plant part	References
15α-(cinnamoyloxy)-*ent*-kaur-16-en-19 oic acid		Aerial part	32
(3α)-3-(cinnamoyloxy)-17-hydroxy-*ent*-kaur-15-en-19 oic acid (Wedelidin A)		Aerial part	25
(3α)-3-(cinnamoyloxy)-17-oxo-*ent*-kaur-15-en-19 oic acid (Wedelidin B)		Aerial part	25
Wedelia-seco-kaurenolide		Aerial part	23, 24
Triterpenes Friedelinol		Aerial part	25
Friedelin		Aerial part	25
Sesquiterpenes 1β, 4α-dihydroxy-6β-isobutyryloxy-9α-(tigloyloxy) prostatolide		Aerial part	29
9α-(angeloyloxy)-1β, 4α-dihydroxy-6 β-isobutyryloxy prostatolide		Whole plant	29
1β, 9α-diacetoxy-4α-hydroxy-6 β-isobutyryloxy prostatolide		Whole plant	29
1β, 9α-diacetoxy-4α-hydroxy-6 β-methacryloxy prostatolide		Whole plant	29
Wedeliatrilolactone B		Aerial part	25
Trilobolide 6-*O*-isobutyrate		Flower Leaves Whole plant	23 28, 29 18, 20,30
Trilobolide 6-*O*-angelate		leaves	23
Trilobolide 6-*O*-methacrylate		leaves	20, 23
Oxidoisotrilobolide 6-*O*-isobutyrate		leaves	23, 30
Oxidoisotrilobolide 6-*O*-angelate		leaves	23
Oxidoisotrilobolide 6-*O*-methacrylate		leaves	23
Wedelolide A		Leaves	20

Table 1. Continued.

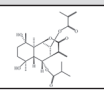
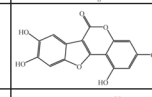
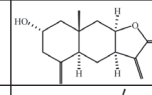
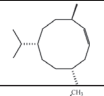
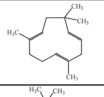
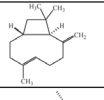
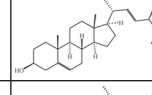
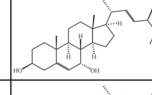
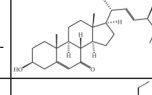
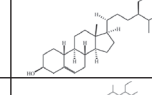
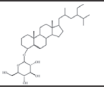
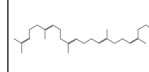
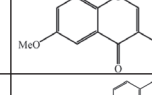
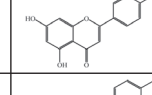
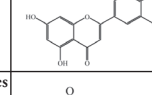
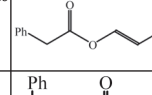
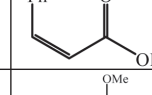
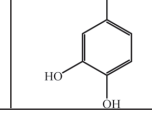
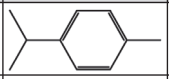
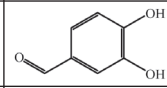
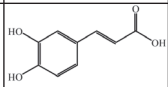
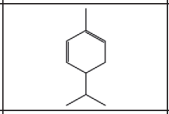
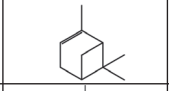
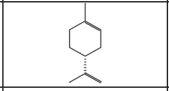
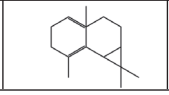
Compound name	Structure	Plant part	References
Wedelolide B		Leaves	20
Wedelolactone		Entire plant	21
Ivalin		Aerial part	25
Germacrene D		Aerial part	23
α-humulene		Aerial part	23, 40
Caryophyllene		Aerial part	23, 40
Steroids Stigmasterol		Aerial part	25
(7α)-7-hydroxystigmasterol		Aerial part	25
(3β)-3-hydroxy stigmasta-5, 22-dien-7-one		Aerial part	25
Sitosterol		Aerial part	23, 40
Daucosterol		Aerial part	31
Squalene		Aerial part	23, 40
Flavonoids 3-hydroxy-6-methoxychromen-4-one		Aerial part	25
Apigenin		Aerial part	25
Diosmentin		Aerial part	25
Benzene derivatives Benzeneacetic acid 2-phenylethenyl ester		Aerial part	25
Isocinnamic acid		Aerial part	25
4-methoxy catechol		Aerial part	25

Table 1. Continued.

Compound name	Structure	Plant part	References
p-cymene		Aerial part	23, 40
Protocatechualdehyde		Aerial part	31
Caffeic acid		Aerial part	31
Cyclic terpenes α-phellandrene		leaves	39, 40
α-pinene		leaves	40
d-limonene		leaves	39, 40
Bicyclogermacrene		leaves	40

Antileishmaniasis activity

Kaurenic acid (ent-kaur-16-in-19-oic), isolated from the Venezuelan plant *W. trilobata* was evaluated on *Leishmania* (V) *braziliensis* both *in vivo* and *in vitro*. The compound had a lethal effect on axenic amastigotes and promastigotes with LD_{50} of 0.25 and 0.78 μg/ml, respectively, in 24 h. Additionally, a 70% reduction was observed in the size of the skin lesions in Balb/c mice with no evident toxic effect. The results indicated that this compound has a potent leishmanicidal effect on *L.* (V.) *braziliensis* [34].

Table 2. Biological and pharmacological activities (*in vitro* and *in vivo*) of *W. trilobata*.

Extract/compound	Pharmacological activity	Reference
	ANTIBACTERIAL ACTIVITY	
N-hexane extract of aerial part without flower	Inhibitory effect on Gram positive bacteria, *Bacillus cereus*, *Bacillus subtilis*, *Mycobacterium megmatis*, *Staphylococcus aureus*, *Staphylococcus epidermidis* and Gram negative bacteria, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Salmonella* group *C*, *Salmonella paratyphi*, *Shigella sonnei*	44
Ethyl acetate extract of aerial part without flower	Inhibitory effect on Gram negative bacteria, *Salmonella* group *C*	44
Ethanol extract of stem	Inhibitory effect on *Bacillus subtilis*, *Pseudomonas fluorescens*, *Clavibacter michiganensis* sub sp. *michiganensis*, *Xanthomonas oryzae* pv. *oryzae*, *Xanthomonas axanopodis* pv. *malvacearum* and strains of *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa* and *Klebsiella pneumonia*	27
Ethanol extract of leaves	Strong inhibitory effect on *P. aeruginosa, K. pneumoniae, P. fluorescens*, *X. oryzae* pv. *oryzae*, *X. axanopodis* pv. *malvacearum*, moderately inhibited the *E.coli*, *C. michiganensis* sub sp. *michiganensis* but less activity was observed on *S. aureus*.	27
Ethanol extract of flower	Strong inhibitory effect on *Staphylococcus aureus*, *X. oryzae* pv. *oryzae* moderately inhibited the *K.pneumoniae, P. fluorescens*, *X. axanopodis* pv. *malvacearum* but less activity was observed on *E.coli*, *P. aeruginosa*, *Clavibacter michiganensis* sub sp. *Michiganensis*	27

Table 2. Continued.

Extract/compound	Pharmacological activity	Reference
Methanol extract of flower	Moderate inhibitory activity against *Bacillus cereus*, *Bacillus subtilis*, *Escherichia coli*, *Klebsiella pneumonia*, *Staphylococcus aureus* and *Shigella flexneri*	46
Ethanol extract of stem, leaves and flower	**ANTIFUNGAL ACTIVITY** Weak inhibition against *Aspergillus flavus* *A. niger, A. nidulans, A. Flaviceps, Fusarium solani, F. oxysporum, F. verticilloides*	27
Ethanol extract of leaf, stem and flower	**ANTIOXIDANT ACTIVITY** DPPH radical scavenging activity was more for leaves than stem and flower	27
Ethyl acetate fraction of *Wedelia trilobata*	DPPH radical scavenging activity	40
Methanol extract of flower	DPPH radical scavenging activity	46
Ethanol extract of leaf, stem and flower	**ANTIINFLAMMATORY ACTIVITY** All the three extract was effective in inhibiting heat induced albumin denaturation**.** Maximum inhibition 87.14% was observed from leaf extract followed by stem (86.76%) and flower (61.63%).	27
	The extracts inhibited the heat induced hemolysis of RBCs to varying degree. The maximum inhibitions 78.11% from leaf extract followed by stem (74.17%) and flower (58.74%).	27
	The ethanolic extract exhibited significant antiproteinase activity from different parts. The maximum inhibition was observed from leaf ethanolic extract (84.19%), in decreasing order was stem (81.84%) and flower ethanolic extract (67.17%).	27
Ethyl acetate (WEA) and chloroform:methanol (50:50) (WCM) fractions from ethanolic extract of *W. trilobata* leaves	**WOUND HEALING ACTIVITY** The WEA displayed antibacterial and fibroblast stimulatory activities while WCM exhibited antioxidant activity	47
ent-kaura-9(11), 16-dien-19-oic acid isolated from *W. trilobata* leaves	Offered wound healing activity due to a combination of antimicrobial, stimulation of fibroblast growth	35
The petroleum ether, chloroform, ethyl acetate and methanol extract of leaves	**CNS DEPRESSANT ACTIVITY** The petroleum ether extract represented good CNS depressant activity	43
n-hexane and ethyl alcohol extracts	**CYTOTOXIC ACTIVITY** The ethyl alcohol extracts of flower had good anti-migration and anti-invasion ability especially on 80 μg/mL dose	45

Table 2. Continued.

Extract/compound	Pharmacological activity	Reference
	ANALGESIC ACTIVITY	
Ethanol extracts	Blocked the writhing response by 49.17%	48
Kaurenoic acid, a diterpene obtained from *Wedelia trilobata*	Exhibited analgesic effect by inhibiting cytokine production and activation of the NO-cyclic GMP-protein kinase G-ATP sensitive potassium channel signaling pathway.	49
	ANTILEISHMANIASIS ACTIVITY	
Kaurenoic acid (ent-kaur-16-in-19-oic), isolated from the Venezuelan plant *W. trilobata*	Potent leishmanicidal effect on *L.* (V.) *braziliensis*	34
	ANTIDIABETIC ACTIVITY	
Aqueous extract of leaves	Reduction in blood glucose level in streptozotocin induced diabetes	41
Methanolic extract of aerial parts	α-glucosidase inhibitor	42

Central nervous system (CNS) depressant activity

The petroleum ether, chloroform, ethyl acetate and methanol extract of leaves of *W. trilobata* (30 mg/kg, i.p.) were evaluated for CNS depressant activity using pentobarbitone-induced sleeping time, and locomotor activity in mice. The petroleum ether extract potentiated pentobarbitone sodium induced sleeping time in mice than other extracts. The animal treated with petroleum ether extract showed reduction in the locomotor activity scores was significantly higher than that of standard drug diazepam and other extract. The petroleum ether extract represented good CNS depressant activity [43].

Antimicrobial activity

A biological screening of activity against Gram-positive and Gram-negative bacteria, yeasts, and fungi of crude extracts from *W. trilobata* (10 μg/ml) was reported. The *N*-hexane extract showed antibacterial activity against *Bacillus subtilis*, *Mycobacterium smegmatis*, *Staphylococcus aureus*, and *Staphylococcus epidermidis* (Gram-positive bacteria); along with *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Salmonella* group C, *Salmonella paratyphi*, and *Shigella sonnei* (Gram-negative bacteria). The ethyl acetate extract was active only against *Salmonella* group C; and the aqueous extract was inactive against the tested bacteria. None of the tested extracts showed biological activity against the yeasts *(Candida albicans, Candida tropicalis, Rhodotorula rubra)* or the fungi *(Aspergillus flavus, Aspergillus niger, Mucor* sp., *Trichophyton rubrum)* [44].

Ethanol extract of leaf, stem and flower of *W. trilobata* (10 μg/ml) was assessed for its antimicrobial efficacy using disc method against different fungi (*A. flavus*, *A. niger*, *A. nidulans*, *A. flaviceps*, *Alternaria carthami*, *Alternaria helianthi*, *Cercospora carthami*, *Fusarium solani*, *Fusarium oxysporum*, *Fusarium verticilloides* and *Nigrospora oryzae*)

and bacteria (*B. subtilis*, *Pseudomonas fluorescens*, *Clavibacter michiganensis* sub sp. *michiganensis*, *Xanthomonas oryzae* pv. *oryzae*, *Xanthomonas axanopodis* pv. *malvacearum* and strains of *S. aureus, E. coli, P. aeruginosa* and *K. pneumonia*e). The ethanolic stem extract significantly inhibited the growth of almost all the bacteria isolates but did not show any significant effect on fungal isolates. The leaf extract showed more potent against *P. aeruginosa, K. pneumoniae, P. fluorescens*, *X. oryzae* pv. *oryzae*, *X. axanopodis* pv. *Malvacearum* [27].

W. trilobata flowers, leaves and stems were extracted with ten times of ethyl alcohol. The extract was then partitioned by *N*-hexane, ethyl acetate, *N*-butyl alcohol and water to evaluate its antimicrobial activity. The result showed that most extracts had antimicrobial activities except the water extracts from flower. The ethyl acetate extract was the most effective among all the extracts [45].

The methanolic flower extract of *W. trilobata* was screened for antibacterial activity by disc diffusion method against *Bacillus cereus*, *Bacillus subtilis*, *Escherichia coli*, *Klebsiella pneumonia*, *Staphylococcus aureus* and *Shigella flexneri*. The extract showed a moderate inhibitory activity against all bacterial species with zones of inhibition of 10-16 mm in comparison with chloramphenicol which showed zones of inhibition 12-24 mm [46].

Antioxidant activity

Ethanol extract of leaf, stem and flower (0.5 mg/ml) of *W. trilobata* was evaluated for its antioxidant activity by measuring the scavenging activity of 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical and the ferric reducing antioxidant power (FRAP) assay. It was observed that ethanol extract of the leaf of *W. trilobata* offered higher activity than that of stem and flower. At a concentration of 0.1 mg/ml, the scavenging activity of ethanol extract of the stem and flower and leaves reached 82.64, 55.41 and 86.17% respectively but less than those of ascorbic acid (98%) and BHT (97.8%) at 0.1 mg/ml, the study showed that the extracts have the proton donating ability and could serve as free radical inhibitors or scavenging, acting possibly as primary antioxidants. The FRAP values for the ethanol extract of leaf and stem were significantly lower than that of ascorbic acid but higher than that of BHT [27].

The methanolic extract of *W. trilobata* flower showed good antioxidant activity (IC_{50} = 90 μg/ml) in DPPH method. Reference standard ascorbic acid showed IC_{50} of 60 μg/ml. The extract of *W. trilobata* flower exhibited higher ABTS (2,2'-azino-bis (3- ethylbenzothiazoline-6- sulphonic acid) radical scavenging activity with IC_{50} of 80 μg/ml whereas gallic acid showed IC_{50} of 30 μg/ml [46].

Anti-inflammatory activity

Ethanol extract of leaf, stem and flower (0.5 mg/ml) of *W. trilobata* was evaluated for its *in vitro* anti-inflammatory using albumin denaturation, membrane stabilization assay and proteinase inhibitory assay. All the three extracts were effective in inhibiting heat induced albumin denaturation. Maximum inhibition 87.14% was observed from leaf extract followed by stem (86.76%) and flower (61.63%). All the extracts were effective in inhibiting the heat induced hemolysis. The extracts inhibited the heat induced hemolysis of RBCs to varying degree. The maximum inhibitions 78.11% from the leaf extract followed by the stem (74.17%) and flower (58.74%). The *W. trilobata* ethanolic extract exhibited significant antiproteinase activity from

different parts. The maximum inhibition was observed from leaf ethanolic extract (84.19%), in decreasing order was stem (81.84%) and flower ethanolic extract (67.17%) [27].

The ethyl alcohol and water extracts of *W. trilobata* flowers were used to treat RAW 264.7 macrophage, which induced inflammation by LPS. In the nitric oxide assay, the extracts of *W. trilobata* flower had better inhibitory ability against LPS induced inflammation [45].

Wound healing activity

An ethanolic extract of *W. trilobata* leaves was subjected to column chromatography. Hexane, ethyl acetate (WEA) and chloroform:methanol (50:50) (WCM) fractions were obtained. The fractions were tested using relevant *in vitro* wound healing assays. WEA (3 μg/mL) promoted fibroblast L929 viability up to more than 90% before and more than 85% after hydrogen peroxide induced oxidative stress. WEA (3 μg/mL) induced a 70% migration rate in the *in vitro* scratch assay and the collagen content was increased to 261 μg/mL compared to the control (57.5 μg/mL) [47].

The ent-kaura-9(11), 16-dien-19-oic acid isolated from *W. trilobata* leaves offered wound healing activity due to a combination of antimicrobial, stimulation of fibroblast growth and protection of the cells from hydrogen peroxide-induced injury, all of which could play some role in its effect on tissue repair. It showed promising antibacterial activity with MIC value of 15.62 μg/mL against *S. aureus* and 7.81 μg/mL against *S. epidermidis*. The ent-kaura-9(11), 16-dien-19-oic acid (2.5-0.08 μg/mL) produced an increase in the percentage viability of mouse fibroblast L929 cells from 97-117% and protection of the fibroblast L929 cells against oxidative stress induced by hydrogen peroxide (94-80%) [35].

Cytotoxic activity

In transient transfection assay the *N*-hexane and ethyl alcohol extracts of *W. trilobata* flower could activate PPARα. In MTT assay of SK-Hep-1, extract of *W. trilobata* flower had the best inhibitory ability. The ethyl alcohol extract of *W. trilobata* had the best ability to diminish the expression of matrix metalloproteinase (MMP)-9 and MMP-2. The ethyl alcohol extracts of flower had good anti-migration and anti-invasion ability especially on 80 μg/mL dose [45].

Analgesic activity

Comparative study in mice on the analgesic activity of the ethanol extracts of *W. trilobata*, *W. biflora* and *E. alba* was evaluated by acetic acid induced writhing method. It was found that *W. trilobata* extract showed dose-dependent blocking of writhing response. Dose of 500 mg/kg of *W. trilobata* extract and aspirin (500 mg/kg) block the writhing response by 49.17% and 68.68% [48].

Kaurenoic acid (10 mg/kg) obtained from *Wedelia trilobata* kaurenoic acid inhibited overt nociception like behavior induced by phenyl-p-benzoquinone, complete Freund's adjuvant (CFA) and formalin. Kaurenoic acid (1-10 mg/kg p.o.) also inhibited acute carrageenin and PGE_2 induced and chronic CFA induced mechanical hyperalgesia. [49].

Reproductive problems

Previous research has shown that Caribbean women and Creoles have always used bitter herbs to control their fertility. A study was conducted focused on the plants used for reproductive purposes in

Trinidad and Tobago. The plants used to address women's reproductive problems were used mainly for infertility, menstrual pain and childbirth. Results showed that *W. trilobata* was used for menstrual pain and for the female complaints. The non-experimental validation method can be used to advise the public on which plants are safe, effective and useful, and which are not; pending clinical trials. This is important since few clinical trials were conducted on Caribbean plants [19].

Other activity

The methanolic extract of *W. trilobata* flower was tested for pTZ57R/T plasmid DNA protection against hydroxyl radical, evidenced by fragmentation assay. The extract showed stronger protective effect against DNA damage by hydroxyl radical released by Fenton's reaction [46].

Toxicity studies

The ethanolic extract (25- 1.56 μg /ml), ethyl acetate fraction (6.25- 0.39 μg/ml) and chloroform: methanol fraction (22- 0.39 μg/ml) of leaves of *W. triolbata* were evaluated for cytotoxicity using L929 mouse fibroblast cell using MTT (3-(4,5-dimethylthiazolyl)-, 5 diphenyltetrazolium bromide) assay. At these concentrations extract as well as fractions produced cell survivability of more than 80%. However at higher concentrations of the above dose levels there was evidence of cytotoxicity [47].

The ent-kaura-9(11), 16-dien-19-oic acid at dose range of 10- 0.08 μg/ml produced cell viability of L929 mouse fibroblast in the range of 89-117%. Further increase in concentration above 10 μg/ml produced cellular damage resulting in cell death [35].

The J774-G8 macrophages were treated with kaurenoic acid isolated from W. trilobata at a concentration varying between 10- 250 μg/ml. The effect of the compound on cellular viability was evaluated using MTT assay Low toxicity was observed for J774-G8 macrophages with a LD_{50} of 25 μg/ml and high viability (70-92%), while a moderate viability was observed for infected macrophages (37-81%), with concentrations of 25 μg/ml or less [34].

3. DISCUSSION

The present review emphasizes the phytochemical, traditional, pharmacological and, clinical reports on *W. trilobata*. Tannin, saponins, flavonoids, phenolic, terpenoids constitute major classes of phytoconstituents of this plant. The plant contains a range of phytochemical substances credited with various pharmacological properties. Recent research carried out indicates its uses such as antioxidant, anti-inflammatory, antimicrobial, wound healing, antidiabetic activity. In recent years, the search for phytochemicals possessing antioxidant, antimicrobial and anti inflammatory properties have been on the rise due to their potential use in the therapy of various chronic and infectious diseases. Epidemiology and experimental studies have implicated oxidative cellular damage arising from an imbalance between free radical generating and scavenging systems as the primary cause of cardio-vascular, diseases, cancer, aging etc. Due to risk of adverse effects encountered with the use of synthetic antibiotics, medicinal plants may offer an alternative source for antimicrobial agent with significant activity against pathogenic and infective micro-organisms. In addition, a number of antibiotics have lost their effectiveness due to the development of resistant strains, mostly through the expression of resistance

genes. Strong antioxidants, antimicrobial and anti inflammatory activities specifically in the ethanolic leaf and stem extracts of *W. trilobata* were observed. These activities may be due to strong occurrence of polyphenolic compounds such as flavonoids, tannins, terpenoids, phenols and saponins [29]. The authors are involved in evaluating the wound healing effect of *W. trilobata* with a view to isolating bioactive phytoconstituent(s). One of the phytoconstituent isolated and evaluated for wound healing potential is grandiflorenic acid (ent- kaura-9(11)-dien-19-oic acid) [37, 55]. The presence of a wide range of chemical compounds indicates that the plant could lead the way for the development of novel agents having good biological activity. Exploration of the chemical compounds of the plant will provide the basis for developing such a lead. The phytomedicines can be developed as an alternative and are relatively inexpensive than modern drugs. One of the reasons is their use, preparation, and safety is already understood in traditional systems of medicines [57]. Many chemical compounds are present in the plant but isolation of active constituents can be carried out using different extraction methods such as microwave extraction, isolation and by using various appropriate chromatographic techniques. Despite a long tradition of use of *W. trilobata* for treatment of various ailments, it still remains unexplored pharmacologically to prove its traditional claims. Thus it can be considered as a valuable plant in both traditional and modern drug development areas for its versatile medicinal uses. Emphasis must be laid on the pharmacological activity of the phytoconstituent to unravel the hidden medicinal qualities of this plant as well as the local knowledge system should be globalize which would increase the benefits obtained to wider population. There are no clinical data available that would provide evidence of efficacy of *W. trilobata* in humans. Extracts and constituents of *W. trilobata* may have considerable clinical potential in humans and need to be studied further in in vivo models and ultimately in clinical studies.

DISCLOSURE STATEMENT

No competing financial interests exist.

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