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Phytochemistry and Pharmacology of *Guettarda speciosa* L.

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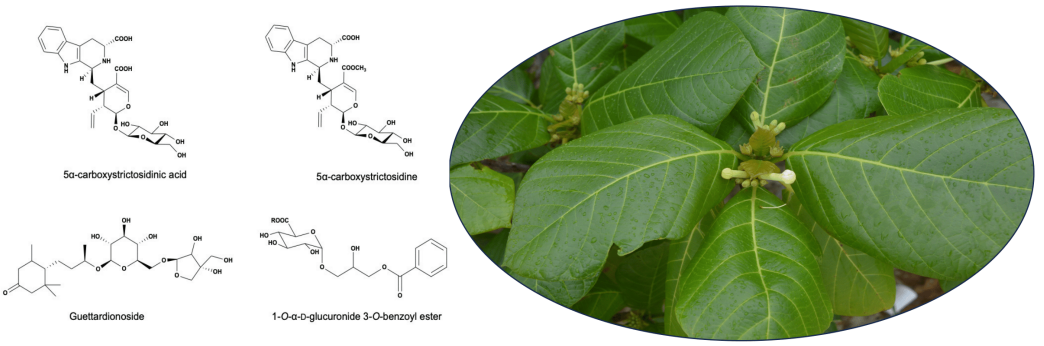
Graphical Abstract



Abstract

Guettarda speciosa L. (Rubiaceae), commonly known as zebra wood or sea randa, is a shrub mainly found on coastal areas of tropical countries. Its leaves, stem, and bark are extracted using various solvents and used as anticholinergic and as treatments for inflammations, colds, cough, wounds, epilepsy, and postpartum infection. This review paper highlights the phytochemical constituents and biological activities of *G. speciosa*.

Keywords: *Guettarda speciosa*; Rubiaceae; medicinal plant; ethnomedicinal plant; phytochemical; pharmacological activity

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Introduction

Plants serve as food, ornaments, and habitats for many living things and are also used as treatment for ailments and diseases. However, some also contain toxic substances. Plants play a prominent role in the scientific field, especially in pharmaceutical sciences where drug discovery and development hugely utilize plant materials. Ayurveda, an Indian practice where plants are used in traditional medicine, posed certain drawbacks such as lack of literature sources in different languages and insufficient knowledge on the foundation of this traditional system that led to hindrance of its development [1].

Guettarda speciosa L. (Rubiaceae) is widely distributed in East and South Africa, Eastern Madagascar, India, Southeast Asia, the South Pacific, Eastern Australia, and the Southeastern coast of North America. It thrives along sea cliffs, beach thickets, tropical and sub-tropical areas, as well as land forests [2-4]. *G. speciosa* is one of the approximately 150 species from the genus *Guettarda* of the Rubiaceae family and it is the only *Guettarda* species that can be found in the Philippines [5-6].

G. speciosa grows up to a height of 12-25 m, its trunk reaches a diameter of 50 cm to 1 m, and its leaves measure about 5-20 cm long [7]. With its high cellulosic content and high maximum degradation temperature of 353.37 °C, these natural cellulose fibers can be used as alternative material to fabricate thermosetting polymer composites in the manufacturing and automobile industries [7].

Utilization of the root, bark, leaves, and flowers of *G. speciosa* can serve as treatments to various diseases like coughs, colds, seizures, wounds, and others. The tree is commonly grown as an ornamental plant and its flowers are used for extracting essential oils used in perfume preparations [8-9]. A recent study shows that *G. speciosa* has high salt tolerance ability in which it can be used for vegetation construction and ecological restoration of tropical islands [10].

To date, this is the first review paper that is organized systematically for both the phytochemical constituents and the corresponding structures from *G. speciosa*, as well as the pharmacological activities of the different plant parts and solvent extracts of *G. speciosa*. This review paper can serve as a basis for future research on *G. speciosa*.

Methodology

The databases such as PubMed, PubChem, ScienceDirect, Mendeley, ResearchGate, Google Scholar, SciFinder, and SpringerLink were used in obtaining data and information on *G. speciosa*. The structures were drawn using ChemDraw Professional 16.0 software. The keywords used in obtaining the references were "*Guettarda speciosa,*" "phytochemicals," and "pharmacological activities." Some of the referenced articles were written in foreign languages such as French, Malaysian, and Indian, but English versions of publications were available and were utilized instead.

Table 1. Phytochemical constituents of *Guettarda speciosa*.

Isolated Compound	Plant Part	Reference
Alkaloids		
5α-carboxystrictosidine	Root Bark	[17]
5α-carboxystrictosidinic acid	Root Bark	
Sickingine	Leaf	[16]
Cadambine	Leaf	
Ester		
1-*O*-α-D-glucuronide 3-*O*-benzoyl ester	Leaf	[16]
Glycosides		
Sweroside	Leaf	[16]
Quinovic glycoside C		
Iridoids		
Secologanin	Leaf	[17]
Loganic acid		
Morroniside		[16]
Megastigmane glycoside		
Guettardionoside	Leaf	[16]
Sterol		
Ecdysone	Leaf	[16]
Sugar		
D-glucuronic acid	Leaf	[16]
Phenolic compounds		
5-*O*-caffeoylquinic acid	Leaf	[17]
4,5-di-*O*-caffeoylquinic acid		
3-*O*-caffeoylquinic acid		[17; 23]
Icariside D1		[16]
3,4-di-*O*-caffeoylquinic acid		
Isoquercetin		[23]
Quercetin 3-*O*-glucoside		
Flavonoids		
Quercetin rutinoside		
Quercetin 3-*O*-galactoside	Leaf	[23]
Apigenin 7-*O*-glucuronide		

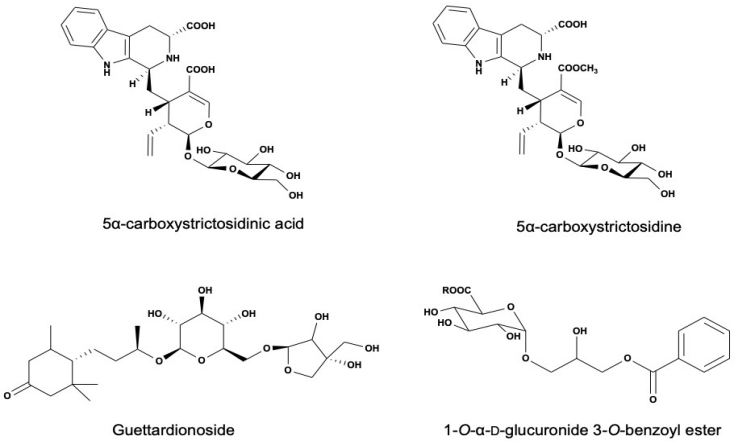

Figure 1. Four isolated novel compounds of *Guettarda speciosa*.

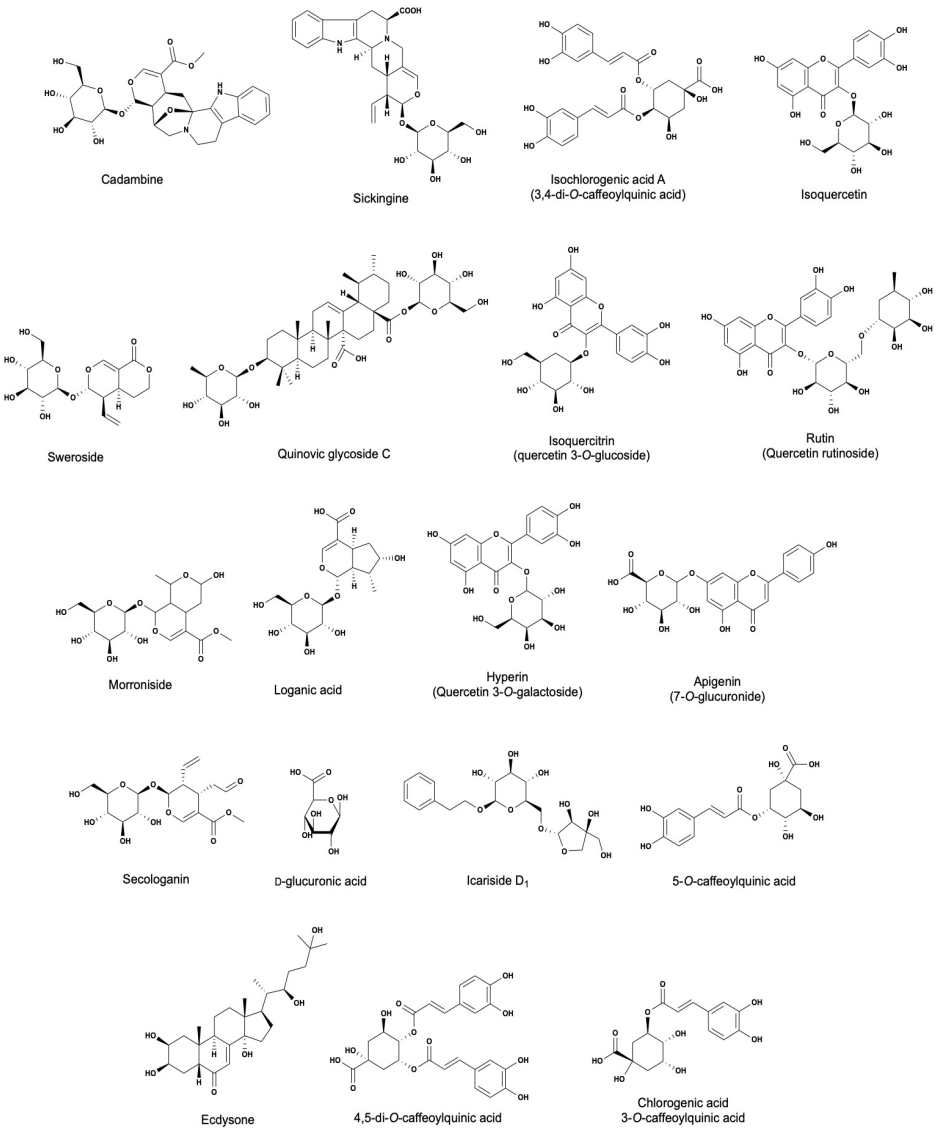

Figure 2. Identified and isolated compounds from *Guettarda speciosa*.

Ethnomedical Uses. *G. speciosa* is used as a traditional folk medicine in Southeast Asia, East Africa, and the South Pacific as anticholinergic, secondary amenorrhea treatments, and as remedies for inflammation, cough, fever, diarrhea, and maternal postpartum infection [2-3, 11-12]. In addition, *G. speciosa* has been utilized for the promotion of menstruation in traditional Fijian practices [12]. Traditional medical Indian practitioners use the ethanolic extract of the inner bark of *G. speciosa* to treat epilepsy [13]. The decoction of the leaves is used to treat coughs, colds, and sore throats [3]. In Tirunelveli District, India, the inner bark is being utilized as a traditional treatment of epilepsy [14]. The stem, bark, latex, flowers, fruits, and the whole plant are used to treat wounds in some countries. In Tahiti, the plant is used as antidiarrhoeic, febrifugal, and anticholinergic. In Tonga, the inner bark of the plant is used to treat epilepsy and conjunctivitis, and the same plant part is used to treat dysentery in New Guinea. The sap of the leaves is used to treat skin rashes in Micronesian practices. Ulcerated sores of the anus are treated with oil-washed shoots. The liquid gathered from the bark is consumed to treat edema [12]. Aside from being utilized in perfume preparations, the plant's wood, flowers, and leaves are also used to treat acne and allergies [9].

Phytochemistry of Guettarda speciosa

Identified phytochemical constituents of Guettarda speciosa. There are 23 isolated and identified compounds in *G. speciosa*. Among these compounds, four new phytochemical constituents were identified (Figure 1). The isolated compounds from different parts of *G. speciosa* (Table 1 and Figure 2) include alkaloids, an ester, glycosides, iridoids, a megastigmane glycoside, a sterol, phenolic compounds, and flavonoids.

Putative phytochemicals of Guettarda speciosa. There are 48 putative compounds using the ethanolic leaf extract that were identified in *G. speciosa* using gas chromatography-mass spectrometry (GC-MS) (Table 2) [15]. The putative compounds belong to the following classes: alkaloids, phenolic compounds, fatty acids, flavonoids, glyceride, iridoid, terpenes, hydrocarbons, steroids, sterol, and esters. There are nine putative compounds identified in the leaf of *G. speciosa* (Table 3) using liquid chromatography-mass spectrometry (LC-MS). However, sweroside and sickingine were already confirmed using chromatographic analysis of the root, bark and leaves of *G. speciosa* [16-17].

Pharmacological Activities Associated with Guettarda speciosa. Several biological studies involving crude polar solvent extracts of *G. speciosa* were conducted using its flowers, roots, leaves, and inner bark. The plant has been reported to have wound healing activity, antibacterial, antifungal, antiseizure and antiepileptic, hepatoprotective, antidiarrheal, anti-inflammatory, anti-neurodegenerative, anti-amyloidogenic, anti-ulcer, and antioxidant activities (Table 4).

The leaf ethanolic extract exhibited wound healing activity on a dose dependent manner with 10% w/w proving to have significant results [12]. Both the chloroform and ethanolic extracts of the inner bark of *G. speciosa* showed antifungal and antibacterial activities [18]. The ethanol extract of the inner bark also showed antiseizure and antidiarrheal activity in in vivo studies [2, 13-14, 19].

Table 2. Putative compounds from the leaves of *Guettarda speciosa* using GC-MS.

Compound Class	Putative Compounds
Alkaloids	Curan-17-oic acid, 19, 20-dihydroxy-, methyl ester, (19S)-
	3-Phenyl-5-t-butylpyridazine
	2-Acetyl-3-(2-cinnamido)ethyl-7-methoxyindole
Phenolic Compounds	Lucenin 2
	Phenol, 2,4-bis(1,1-dimethyl ethyl)
	4H-1-Benzopyran-4-one, 2-(3,4-dimethoxyphenyl)-5,7-dihydroxy-
Fatty Acids	Doconexent
	Octadecanoic acid
	Pentadecanoic acid
	1-Eicosanol
	1-Heptatriacotanol
	2-Hexadecanol
Flavonoids	5-Hydroxy-7,8,2',6'-tetramethoxyflavone
	Quercetin 7,3',4'-Trimethoxy
Glyceride	Docosanoic acid, 1,2,3-propanetriyl ester
Iridoid	Isochiapin B
Terpenes	Squalene
	Quassin
	Duvatrienediol
	Cladosporide A
	7,8-Epoxylanostan-11-ol, 3-acetoxy
Hydrocarbons	Nonacosane
	Undecane
	Dodecane
	Tetradecene
	Dotriacontane
	Hexadecane
	2,6-Diisopropylnaphthalene
	10-Ethyl-1,8-diphenyl-anthracene
	Hexacosane
	Rhodopin
	1-Hexadecanol,2-methyl-
Steroids	2-Methylcortisol
	Ethyl iso-allocholate
	Stigmasterol
	Campesterol
Sterol	6,7-Diaza-5á-cholesterol
Esters	n-Butyl cinnamate
	Fumaric acid, dodecyl 3-heptyl ester
	2-Myristynoyl pantetheine
	Hexadecanoic acid,1-(hydroxymethyl)-1,2- ethanediyl ester
	Octadecanoic acid, 2,3-dihydroxypropyl ester
	Hexadecanoic acid, ethyl ester
	Oleic acid, eicosyl ester
	Oxiranepentanoic acid, 3-undecyl-, methyl ester, cis-
	8-hydroxysclerodin methyl ether
	1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester
	Phytol, acetate

Table 3. Putative compounds identified in *Guettarda speciosa* using LC-MS.

Putative compound	Plant Part	Reference
Strictosidine	Leaf	[3]
Loganin		
β-Sitosterol		
5-Caffeoylquinic acid		
Rotundic acid		
4,5-Dicaffeoylquinic acid		
Quinovic acid		
Sickingine		
Sweroside		

Table 4. Pharmacological activities of *Guettarda speciosa*.

Plant part	Activity	Extract	Assay/model	Reference
Inner bark	Antibacterial and antifungal	Chloroform and ethanol	In vitro disc diffusion method	[18]
Inner bark	Antiepileptic	Ethanol (95%)	In vivo Maximal Electroshock (MES) and Pentylenetetrazole (PTZ) using Wistar albino rats	[14]
Inner bark	Antiseizure	Ethanol (95%)	In vivo Maximal Electroshock (MES) and Pentylenetetrazole (PTZ) using Wistar albino rats	[13,19]
Inner bark	Antidiarrheal	Ethanol (90%)	In vivo castor oil-induced-diarrhea model using Wistar albino rats	[2]
Inner bark	Hepatoprotective	Methanol	In vivo CCl4-induced hepatotoxicity using Wistar albino rats	[20]
Leaf	Anti-inflammatory	Chloroform and methanol	In vitro Cyclooxygenase 1 (COX-1)	[3]
	Cytotoxicity		In vitro ATP luminescence assay using SH-SY5Y cells	
	Anti-amyloidogenic		In vitro Thioflavin T (ThT) assay	
Leaf	Wound healing	Ethanol	In vivo excision wound model using Wistar albino female rats	[12]
Leaf	Anti-ulcer	Ethanol	In vivo ethanol and pyloric ligation (PL) induced gastric ulcer model using Wistar albino rats	[21]
Leaf	Antioxidant	Aqueous	In vitro nitric oxide (NO) radical scavenging assay	[22]
Stem and leaves	Anti-inflammatory	Methanol	In vivo acute Lung Injury (ALI) mouse model using male C57BL/6 mice	[23]
Unspecified plant part	Anti-inflammatory	Methanol	In vitro LPS-induced murine macrophages RAW 264.7 cell model	[11]

The 95% ethanolic inner bark extract exhibited an increase in neurotransmitter (noradrenaline, dopamine, serotonin, and gamma-amino butyric acid) levels after induction of seizure via MES and PTZ model on Wistar albino rats [14]. The methanolic extract of the inner bark of the plant exhibited hepatoprotective activity against CCl4-induced hepatotoxicity [20]. The chloroform and methanol leaf extracts showed anti-inflammatory, cytotoxicity, and anti-amyloidogenic activities in in vitro assays. Moreover, the methanolic leaf extracts were safe up to 2000 mg/kg on Sprague-Dawley rats [3]. The methanol extract of unspecified plant part of *G. speciosa* exhibited anti-inflammatory activity in in vitro studies [11]. The ethanolic leaf extract of *G. speciosa* showed anti-ulcer activity in ethanolic and ligation gastric ulcer model [21]. The petroleum ether, chloroform, acetone, ethanol, and aqueous leaf extracts were tested for antioxidant activities. However, only the aqueous leaf extract showed antioxidant activity in in vitro nitric oxide scavenging assay [22]. The stem and leaf methanolic extracts exhibited anti-inflammatory activity in in vivo studies [23]. Concentrations of 50 µg/mL and 100 µg/mL of the methanolic extract of *G. speciosa* did not cause metabolic disarray or any significant reactive oxygen species (ROS) on RAW 264.7 cells [23].

Conclusion

G. speciosa has multiple uses ranging from industrial materials development, ornamental purposes and perfume, construction of vegetation and ecological restoration, and several treatments for diseases. The folkloric uses are consistent with the findings of several pharmacological studies of *G. speciosa*. All the references acquired for the pharmacological activities utilized polar solvent extracts. The leaves of *G. speciosa* exhibited the highest number of pharmacological activities. The flower part of *G. speciosa* is yet to be explored and future research could lead to interesting findings.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Conceptualization – MAT; Methodology – RKR. The original draft was prepared by Ryan Karlo Ramos. The writing, reviewing, and editing of the paper were done by Ryan Karlo Ramos, Jameson Eusebio, and Mario Tan. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement

Not applicable.

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