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Medicinal Properties of Ant Nest Plant (*Myrmecodia* Genus): A Comprehensive Review

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Abstract

BACKGROUND: The *Myrmecodia* genus belongs to the *Rubiaceae* family, which has the characteristic of an epiphytic plant. This genus spread from Malaysia, through the Philippines, Sumatra, Borneo, Java, New Guinea (Papua), Cape York to the Solomon Islands and Pacific region. It has been empirically proven to treat gout, inflammation, muscle pain relief, strengthen the body's immunity, and cancer treatment.

AIM: This article reviewed the scientific work about the *Myrmecodia* genus concerning their traditional uses, phytochemical compounds, and pharmacological activities of *Myrmecodia*.

METHODS: The sources were from the scientific literature online database, including Science Direct, PubMed, and Google Scholar between 1978 and 2021. Furthermore, 112 articles were collected, while 61 full-text were assessed for eligibility.

RESULTS: The *Myrmecodia* extract has many pharmacological activities, namely antioxidant, antibacterial, cytotoxic, and anticancer.

CONCLUSION: Moreover, this review may be used as scientific literature for the next investigations on the genus *Myrmecodia*, especially regarding pharmacological properties such as *in vitro* and *in vivo* studies and isolation of the active compounds.

Introduction

Natural therapy has been utilized since long ago, where the knowledge is obtained through generations so that it is known as traditional medicine in the community for local wisdom [1]. Nowadays, most of the world's population still relies on traditional medicines for healthcare purposes. Plants, in particular, are always used as herbal medicine, as they contain have a wide range of therapeutics for the treatment of diseases. Indonesia, a country in Southeast Asia, has a diverse flora that potential as medicinal plants from nature. One of the selected plants is the ant nest plant (*sarang semut* locally name). The ant nest plant *Myrmecodia* is an epiphytic plant of the Rubiaceae family [2]. Five known genera are belonging this family with hypocotyl and epiphytic plants such as *Myrmecodia*, *Hydrophytum*, *Anthorrhiza*, *Myrmephytum*, and *Squamellaria*. Only two of them are associated with ants, *Myrmecodia* and *Hydrophytum*. The *Myrmecodia* genus is the second most divine species in the world, after the genera *Hydrophytum*. The number of species of *Myrmecodia* genera is known 26 species. *Myrmecodia* is distributed from Malaysia through the Philippines, Sumatera, Borneo, Java, New Guinea (Papua), Cape York to the Solomon Islands, the Pacific region. The greatest diversity of *Myrmecodia* species is found on the island of Papua-Indonesia and Papua New Guinea [3]. Sarang semut (*Ant nest*) were used as folk medicine by local people in Indonesia, especially in the Papua region, to treat various diseases empirically [4]. This study is a comprehensive review, using and collecting the scientific literature online database on Science Direct, PubMed, and Google Scholar of *Myrmecodia* genus which is basically based on some criteria. The search keywords included "Myrmecodia," "Myrmecodia for anticancer," "Myrmecodia and phytochemical," and "Myrmecodia and pharmacological activity." Based on ethnomedicinal properties, only several species of the *Myrmecodia* genus are evaluated from scientific evidence-based medicine. In this articles, 112 articles were collected and identified from the scientific literature online database, between 1978 and 2021, while 61 full-text were included. This comprehensive review aims to determine the scientific evidenced base medicine of *Myrmecodia*

species in ethnopharmacological use and analyze phytochemical constituents and biological activities for the drug discovery from Indonesian medicinal plants.

Traditional Uses

The *Myrmecodia* genus has been traditionally used as folk medicine throughout Southeast Asia to treat ulcer, swelling, headache, hemorrhoid, nosebleed, backache, skin rashes, allergy, uric acid disorder, renal problems, tuberculosis, tumor, coronary artery disease, hepatitis, rheumatism, and diarrhea [5], [6], [7], [8]. Based on an ethnopharmacology study from some selected regions in Indonesia, the genus of *Myrmecodia* has been used as traditional medicine by the community in East Indonesia, especially in Papua, to treat inflammation, muscle pain relief, and strengthen the body's immunity [9]. Rural people in the Papua community use the tuber (hypocotyl) powder of the *Myrmecodia* plant as a brewed drink like tea with decoction method [10], [11]. In the Papua region, *Myrmecodia pendens* Merr. and Perry can treat severe diseases, such as nausea, breast cancer, and immunomodulator [12], [13]. Meanwhile, in Belu Regency, East Nusa Tenggara, people used this plant as a traditional medicine to treat blood circulation and gout [14]. People in Borneo Island used *M. pendens* as an antibacterial [15]. *Myrmecodia tuberosa* Jack. is generally used in the West Papua region-Indonesia to natural healing remedies and treat cancer [16]. In Wamena-Papua, this plant was applied to enhance body immunity for a long time [17]. Meanwhile, people in Mindanao-Philippines used fresh tubers of this species to treat several diseases such as goiter, stomachache, and fever [18]. In Vietnam, *M. tuberosa* was used as a folk medicine to treat hepatitis [19]. Another species of *Myrmecodia* genus *Myrmecodia platytyrea* Becc. is believed to have medicinal value, commonly used for cancer treatment, keeping blood glucose and cholesterol at normal levels [20], [21], [22]. *Myrmecodia beccarii* Hook.f. and *Myrmecodia rumphii* Becc. A resident in Merauke Regency, Papua, used as herbal medicine for gout and immunostimulant [23], [24]. The usages of *Myrmecodia* species as traditional medicine can be found in Table 1.

Table 1: Traditional uses of the tuber of *Myrmecodia* species

Species	Region	Traditional uses
M. pendens Merr. and Perry	Wamena-Papua	to treat ulcer, hemorrhoid, nosebleed, backache, allergy, uric acid disorder, stroke, rheumatism and diarrhea [4]
	Bintuni-West Papua	to treat nausea and complementary medicine for breast cancer [5]
	Belu-NTT	for treatment of blood circulation and gout [14]
M. tuberosa Jack.	West Papua	natural healing remedies for tumor [16]
	Lamdong-Vietnam	to treat hepatitis and stomachache [19]
	Indonesia and Malaysia	treatment for cancer and tumor and to reduce the glucose level in the blood [25]
M. platytyrea Becc.	Throughout Southeast Asia	complementary medicine for the treatment cancer [20]
	Papua	for cancer treatments, and prevent and cure diarrhea [21]
M. beccarii Hook.f.	Merauke-Papua	strengthening immunity and treatment for gout [23]
M. rumphii Becc.		treatment for rheumatic and tumor [24]

Phytochemistry

The widespread use of the *Myrmecodia* genus has resulted in the phytochemical constituent analysis of different species. Based on a phytochemical screening test, generally, the hypocotyl of the *Myrmecodia* genus contained flavonoid, tannin, saponin, glycoside, carbohydrates, and quinone [4], alkaloids [18], iridoid [19], [25], steroid/triterpenoid [26], diterpenoid [27], phenolics [28], and polyphenolics [29], [30]. The phytochemical screening showed the major compounds of *Myrmecodia* species are phenolic and flavonoid (Figure 1). Several species of them have been successfully identified, *M. pendens* contained kaempferol, luteolin, rutin, quercetin and apigenin, rosmarinic acid, procyanidin B1, the polymer of procyanidin B1, gallic acid, (+)-catechin, caffeic acid, p-coumaric acid, and ferulic acid [7], [31], [32]. Some researchers reported that phenolic glycoside with aliphatic moiety [13], dibenzo-p-dioxin-2,8-dicarboxylic acid [33], guaiacol, 1,4-di-tert-butoxybenzene, 4-methylcatechol and 2,6-dimethoxy-phenol [34], anthocyanin [35] and biflavonoid [36] have been isolated from *M. pendens*. Other isolates of flavonoid and phenolic compounds were found in *M. platytyrea* such as, acylated flavanone, flavanone (liquiritigenin or isoliquiritigenin), O-methylated isoflavone (calycosin) and 2-(2-methylbutyryl) phloroglucinol glucoside [37]. Some iridoid compounds were found in *M. tuberosa*, namely, myrmecodoide A, myrmecodoide B, asperulosidic acid, deacetylasperulosidic acid, premnosidic acid, asperuloside [19], and morindolide in *M. platytyrea* [37]. Stigmasterol was identified from *M. platytyrea* [21], [29], [30], [37] and the other terpenoid compounds have been isolated from *M. pendens* such as, diterpenoid type labdane [27], stigmast-4-ene-3-one, pomolic acid, 6'-O-tridecanoyl-3-O-β-D glucosyl-sitosterol, phloroglucinol sesquiterpene, and betulin [33].

Pharmacological Activities

Myrmecodia species have been screened for various pharmacological activities *in vitro* and *in vivo* using animal models.

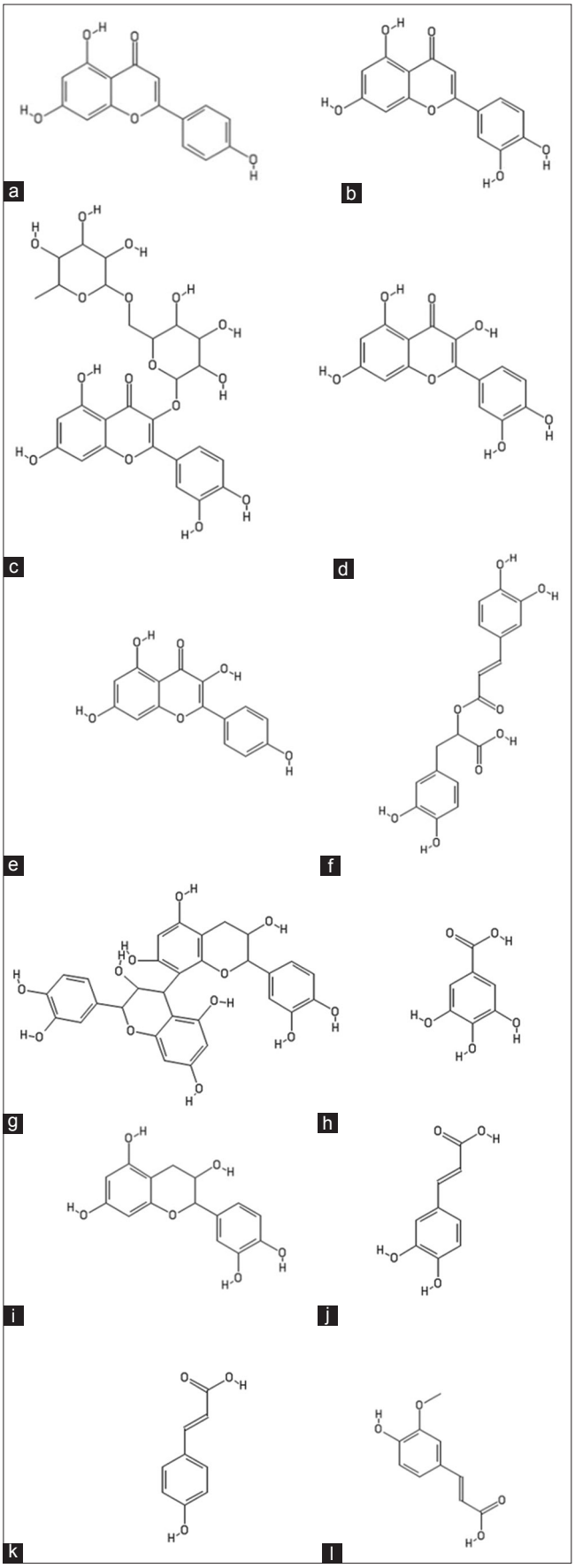

Figure 1: Some structures of phenolic compounds that have been identified from Myrmecodia Species. (a) kaempferol; (b) luteolin; (c) rutin; (d) quercetin; (e) apigenin; (f) rosmarinic acid; (g) procyanidin B1; (h) gallic acid; (i) +(−) catechin; (j) caffeic acid; (k) p-coumaric acid; (l) ferulic acid.

Antioxidant activity

Many *Myrmecodia* species showed potential antioxidant activity with 2,2-diphenyl-1-picrylhydrazyl (DPPH) method. The free radical scavenging activity (antioxidant activity) of the ethanol extract of hypocotyl *M. pendens* was evaluated using DPPH radical and the IC_{50} value occurred at 96.21 μg/mL of extract and contained total phenol and flavonoid contents 330.61 mg GAE/g and 63.28 mg QE/g of dry extract, respectively. The extract was analyzed by High Performance Liquid Chromatography and five flavonoid compounds were identified and quantified, kaempferol (13.767 mg/g), luteolin (0.005 mg/g), rutin (0.003 mg/g), quercetin (0.030 mg/g), and apigenin (4.700 mg/g) of dry extract [31]. The ethyl acetate fraction of this extract contained procyanidin B1 dimer (3.236 mg/g dry sample) and rosmarinic acid (20.688 mg/g dry sample) showed significant free radical scavenging capacities with IC_{50} values of 27.59 μg/mL and 35.80 μg/mL, respectively [32]. Meanwhile, the antioxidant activities of the aqueous fractions of *M. pendens* were higher than chloroform fractions [15]. The new extraction method was successfully investigated, Supercritical Carbon dioxide (SC-CO_2) with DPPH-scavenging test showed antioxidant capacity of *M. pendens* with an IC_{50} level of 3.62 mg/mL [7] and The Microwave-Assisted Extraction (MAE) showed scavenging radical activity with IC_{50} 0.98 μg/mL [35]. Ethanolic extract of stem bark, leaves and tuber of *M. tuberosa* showed antioxidant activity with 95.17%, 94.55%, and 93.42% DPPH scavenging activities, respectively [25]. The previous study investigated ethyl acetate fractions of the hypocotyl of *M. platytyrea* showed antioxidant activity with IC_{50} 21.57 μg/mL [37]. Polyphenols and flavonoids of ethanol and ethyl acetate extracts expressed the highest antioxidant activity compared to dichloromethane and methanol extracts of *M. platytyrea* with High Performance Thin Layer Chromatography (HPTLC)-DPPH bioautographic methods [21], [29], [30]. The methanol extract of *M. beccarii* and *M. rumphii* showed antioxidant activity with IC_{50} 8.18 μg/mL [23] and 90.98% DPPH radical scavenging activity, respectively [24].

Antibacterial activity

Some of *Myrmecodia* species demonstrated significant antibacterial agents against various types of bacterial spectrum. *M. pendens* gave had antibacterial activity against *Escherichia coli*, *Salmonella* sp. and *Bacillus* sp. [15], *Candida albicans*, *Staphylococcus aureus* [38], *Streptococcus mutans* [39], *Shigella dysenteriae* [40], *Streptococcus sanguinis* [41], [42], [43], *Enterococcus faecalis* [34], [44], *Porphyromonas gingivalis* [45] and *Treponema denticola* [42].

Alibasyah *et al*. reported that biflavonoid and diterpenoid compounds were isolated from ethyl acetate extract of *M. pendens* exposed antibacterial

activity against *P. gingivalis* pathogen using Kirby-Bauer method with minimum inhibitory concentration (MIC) of 19.57 μg/mL and 39.06 μg/mL, respectively [36]. Six compounds phenolic and terpenoid group have been found in *M. pendens* and some of them gave antibacterial activity by Kirby-Bauer method with the inhibition zone of isolates at concentration of 5000 μg/mL, such as dibenzo-p-dioxin-2,8-dicarboxylic acid against *E. faecalis* (8.55 mm), stigmast-4-ene-3-one and pomolic acid against *S. mutans* were 9.00 mm and 10.24 mm respectively and phloroglucinol sesquiterpene against *P. gingivalis* (12.31 mm). Gartika *et al*. evaluated labdane diterpene isolate from ethyl acetate extract of *M. pendens* had antibacterial activity against *S. mutans* biofilm as 50 μg/mL, and the minimum biofilm eradication concentration value for one min induction time was 40% [27].

The extract of *M. tuberosa* was evaluated for antimicrobial activity test against *C. albicans*, *E. coli* and *S. aureus* by disc diffusion method with MIC value 0.8%, 0.8%, and 1.6% w/v, respectively, and minimum bactericidal concentration (MBC) value by microdilution assay were >6.4% w/v against *C. albicans*, 6.4% w/v against *E. coli* and 1.6% w/v against *S. aureus* [38]. Six iridoids have been isolated from methanol extract *M. tuberosa* had antibacterial activity against *S. aureus* with MIC value of 100.0 μg/mL [19], and phenolic compound of ethyl acetate fraction showed the potential antibacterial activity [28].

Kuswandani *et al.* figured that the combination of n-hexane and ethyl acetate fractions of *M. pendens* gave the best effect against *E. faecalis* using serial microdilution method with MIC 0.049 mg/mL and Mueller-Hnlton method with MBC 12.50 mg/mL [46].

Cytotoxic activity

Many assays have been used to evaluate the toxicity activities of *Myrmecodia* species that associated with the potential of anticancer activity. Some crude extracts and compounds showed the inhibitory activity against various *in vitro* cancer cell lines (Table 2) [48], [49], [50], [51], [52], [53], [54], [55], [56], [57], [58]. Besides, Suharyanto and Purwono reported that *M. pendens* had effective anticancer activity *in vivo* model series. The pre-clinical trials revealed the optimum dose 750 mg/kg body weight of *M. pendens* extract could use to treat lung cancer cell from necrosis [59].

Immunomodulatory activity

The hypocotyl of *M. tuberosa* ethanol extract (50 μg/mL) showed the highest macrophage phagocytic index and for the species *M. pendens* ethyl acetate fraction (50 μg/mL) presented the highest activity in lymphocytes proliferation assay. Both were potential candidate as immunomodulatory agents from herbal medicine [5]. Sumardi *et al.* reported that the active n-hexane fraction of *M. tuberosa* was administrated orally on doxorubicin-induced rats for 28 days, could maintain the number of TCD4+ cells, with ED_{50} value 24.24 mg/kg body weight [16].

Table 2: Cytotoxic activity of crude extract, fraction and isolate of Myrmecodia species

Species	Extraction method	Extract/fraction	Extract/ fraction/ compound	Cancer cell line (IC_50 μg/mL)
M. pendens Merr. and Perry	Reflux	Gradient: EtOAc, BuOH, water	Water extract	Hela (29.36), MCM-B2 (74.20) [4]
			EtOAc	Hela (48.13), MCM-B2 (111.06) [4]
			BuOH	Hela (42.33), MCM-B2 (87.13) [4]
			Water fraction	Hela (27.61), MCM-B2 (64.57) [4]
			Doxorubicin	Hela (5), MCM-B2 (5.0) [4]
	Soxhlet	EtOH	EtOH	Hela (33.28) [47]
			Doxorubicin	Hela (5.56) [47]
	Maceration	Gradient: EtOH, n-hexane, EtOAc, water	EtOH	SP-C1 (937.562) [48], [49], [50]
			n-Hexane	SP-C1 (2691.535) [48], [49], [50]
			EtOAc	SP-C1 (452.059) [48], [49], [50]
			Water	SP-C1 (12302.69) [48], [49],[50]
	Maceration	EtOH	EtOH	B88 (471.79) [51]
	Soxhlet	Gradient: EtOAc, Methanol	Terpenoid	SKOV-3 (481.0) 48 hrs [52]
			Isolate	SKOV-3 (463.0) 72 hrs [52]
	Reflux	Water	Water	Fibroblast (<1000) [12]
		EtOH	EtOH	Fibroblast (<1000) [12]
	Maceration		Water	Fibroblast (<1000) [12]
			EtOH	Fibroblast (<1000) [12]
	Maceration	MeOH: partition n-Hexane, EtOAc	MeOH	Caco-2 (<100) [53]
			n-Hexane	Caco-2 (24), HCT-116 (33.0) [53]
			EtOAc	Caco-2 (<100) [53]
	Maceration	EtOAc	EtOAc	Burkitt's Lymphoma (<500) [54]
	Maceration	EtOAc: partition n-Hexane, EtOH, Water	EtOAc	Burkitt's Lymphoma (<1000) [55]
			n-Hexane	Burkitt's Lymphoma (<1000) [55]
			EtOH	Burkitt's Lymphoma (<1000) [55]
			Water	Burkitt's Lymphoma (<1000) [55]
	Decoction	Water	Water	HSC-3 (<5000) 24 h; (<3000) 48 h [56]
			Doxorubicin	HSC-3 (0.005 mg/ml) [56]
	Decoction	Water	Water	HSC-3 (<5000) 24 h; (<2500) 48 h [57]
			Doxorubicin HCl	HSC-3 (5000) [57]
M. platytyrea Becc.	Soxhlet	MeOH	MeOH[b]	HCC (<100) [20]
M. tuberosa Jack.	Maceration	EtOH	EtOH[a]	HT-29 (16.0) [25]
				Hela (14.0) [25]
			EtOH[c]	MCF-7 (6.0) [25]
	Maceration	EtOH	EtOH	KB (215.0) [17]
			Docetaxel	KB (12.5) [17]
	Decoction	Water	Water[a]	Brine Shrimp (132.6)* [18]
			Water[b]	Brine Shrimp (441.6)* [18]
	Maceration	EtOH	EtOH	Brine Shrimp (38.68)* [18]
			EtOH	Brine Shrimp (126.62)* [18]
	Maceration	EtOH; partition n-Hexane	Non hexane fraction (NHF)	Hela (0.54) [58]
				MCF-7 (0.22) [58]
				T47D (0.23) [58]

[a]*hypocotyl (tuber),* [b]*leaves,* [c]*bark,* *LC: Lethal Concentration.

Antidiabetic activity

The dichloromethane extract of *M. platytyrea* showed significant α-amylase inhibitory activity and correlated with stigmasterol compound present in this extract [29], [30]. The ethyl acetate extract of *M. tuberosa* tuber figured moderate level activity for inhibition of α-glucosidase enzyme [25].

Other pharmacological activities

Simanjuntak *et al*. expressed that a chemical compound was successfully isolated as xanthine oxidase inhibitor with IC_{50} 79.77% from n-butanol fraction of *M. pendens* extract [60] and the ethanol extract affected treating inflammation of dental pulp [61]. *M. platytyrea* water extract was able to lower LDL cholesterol concentration in blood and potential to remedy hypercholesterolemia related diseases, especially atherosclerosis [22].

Conclusion

The present comprehensive review discussed the traditional uses, pharmacological activities, and phytochemical properties of the *Myrmecodia* genus. A literature survey had been conducted that most of the species are used as folk medicine in Indonesia especially in the Papua region. According to evidence-based pharmacological activities, most of the *Myrmecodia* species were limited to the *in vitro* screening of biological activities and still limited *in vivo* model. Indeed, phytochemical research with guidance bioactivities of *Myrmecodia* species may be useful for searching active compounds from natural medicine.

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