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Prenylated Flavonols from the Leaves of *Macaranga gigantea* (Rchb.f. & Zoll.)

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ABSTRACT

*The genus Macaranga comes from the family of Euphorbiaceae and it is the only genus in the subtribe Macaranginae that have a large genus with 300 species of which 27 species were found in Peninsular Malaysia. This plant grows as shrubs or trees that can grow up to 15 m tall and known for their mutual associations with ants. Fresh or dried leaves of some Macaranga species were used by traditional healers to treat swellings, cuts, sores, boils and bruises. The isolation of chemical constituent from this genus has been shown to produce numerous results of phenolic compounds, such as flavonoids and stilbenoids. In this paper, we report the isolation of a prenylated flavonol, glyasperin A (**1**), together with a simple flavone apigenin (**2**) from the methanolic extract of the leaves of Macaranga gigantea. The structure of both compounds has been elucidated based on its spectroscopic data, including mass spectroscopy (MS), infrared (IR), ultraviolet-visible (UV-Vis), 1D and 2D nuclear magnetic resonance (NMR) spectra and comparison with the previous literature.*

Keywords: *Euphorbiaceae, Macaranga gigantea, flavonoid, glyasperin A, apigenin*

INTRODUCTION

Euphorbiaceae is the largest family of flowering plant with 300 genera and 7500 species, and *Macaranga* is the largest genera in this family [1]. This genus is the most diverse in South-East Asia, Africa, Madagascar and Australia [2]. Forty seven species were found in Borneo and 27 species in Peninsular Malaysia [3]. The species from this genus can be found in village-thickets, wastelands and swampy forests (Corner, 1988) [4]. The stem is covered by epicuticle wax crystals causing the surface to become very slippery for most insects, but in Asia, most species of this genus are known for their symbiotic relation between the tree and ant [5, 6]. The isolated chemical constituents from this genus showed that this genus is rich with secondary metabolites such as geranylated and farnesylated flavonoids, stilbenes, terpenes, tannins and coumarins which are the major classes of compounds reported from this plant [7-9]. About 190 compounds had been isolated, purified and characterized from the *Macaranga* species [10]. In earlier times, fresh or dried leaves of some *Macaranga* species was used by traditional healers to treat swellings, cuts, sores, boils, and bruises [11]. *M. gigantea* can be used to treat fungal infection and stomachaches [12]. Genus *Macaranga* was reported to show an interesting activities such as antitumor [13-15], antioxidant [16-18], antimicrobial [9, 19] and anti-inflammatory [8].

METHODOLOGY

Plant Material

The leaves of *M. gigantea* were collected from the forest area at Universiti Teknologi MARA, Puncak Alam. A voucher specimen (UKMB40430) was identified by a botanist from Universiti Kebangsaan Malaysia (UKM) and deposited in UKM Herbarium.

Instrumentations

Structures of the isolated compounds were elucidated by means of IR, UV-Vis, NMR and MS. The IR spectrum was recorded on Perkin Elmer spectrum one FT-IR spectrometer and UV-Vis spectrum was measured in methanol from Shimadzu UV-Vis 160i. The ^{1}H NMR and ^{13}C NMR were analysed in acetone-d on Bruker 600 Ultrashield NMR spectroscopy measured at 600MHz and 150MHz respectively. The MS data was recorded on High-Resolution Electrospray Time-of-Flight Mass spectrometry (HR-ESI-ToF-MS).

Chromatographic Method

Aluminum supported silica gel 60 F254 was used for thin layer chromatography (TLC) and supported silica gel 60 F254 (MERCK 1.07747) was used for preparative thin layer chromatography technique (pTLC). The vacuum liquid chromatography (VLC) and column chromatography (CC) technique used the Silica gel 60, 70-230 ASTM (MERCK 1.07747). The radial chromatography technique (RC) used the Si-gel 60 PF (Merck catalog 254 number: 1.07749). The TLC plates were spotted using a fine glass capillary tube and developed in a chromatographic chamber with various solvent systems at room temperature. The spots were then visualised under UV light (254 nm and 356 nm). The solvent used were industrial grade solvents such as n-hexane, chloroform, ethyl acetate, methanol, and acetone that were distilled for further isolation.

Extraction Method

About seven kilogram of leaves of *M. gigantea* was washed to remove dirt, and dried at room temperature for two weeks. The dried leaves were cut into small pieces and ground to produce three kilogram of dried powder. The solvent used for extraction was methanol. All three kilogram of the dried powder sample was macerated in 30 liters of methanol for 72 - hours at room temperature. The methanol extract was filtered and evaporated under reduced pressure at 50°C using a rotary evaporator to produce concentrated methanol extract (270 g). The extract was stored at 5°C until further use. The extract was monitored by TLC, using a suitable solvent

system (*n*-hexane: ethyl acetate) in the chromatographic tank before being subjected for fractionation.

Purification Method

About 100 g of crude methanol extract was fractionated by using VLC with solvent system n-hexane: ethyl acetate in 100 ml (100:0 to 50:50) four time for each solvent system to give six (6) major fractions 1-6. Fraction 4 (one gram) was separated by RC eluted with *n*-hexane: chloroform (70:30 to 100) to afford Compound **1**, Glyasperin A (2 mg). Meanwhile, fraction 6 showed three major spots were subjected to CC, using chloroform: ethyl acetate and further purification using washing technique yielded Compound **2**, apigenin, (3.7 mg).

Spectral Data of Isolated Compound

Compound 1 (Glyasperin A): A yellow powder. HR-ESI-ToF-MS: *m/z* $[M+H]^+$ 423.1838 (calculated for $C_{25}H_{26}O_6$), IR: 3343 cm^{-1}, 2921, 2854 cm^{-1}, 1647 cm^{-1}, 1602-1483 cm^{-1}. UV λ_{max} (Methanol) : 234, 256, 272, 341, 368 nm. ^{1}H-NMR (600 MHz, acetone-*d*): δ_H 6.60 (s, H-8), 8.05 (d, 2.1, H-2'), 7.02 (dd, 8.5, 3.8, H-5'), 7.96 (dd, 8.6,2.3, H-6'), 3.36 (d, 7.1, H-1"), 5.38 (t, 7.4, H-2"), 1.66 (s, H-4"), 1.79 (s, H-5"), 3.40 (d, 7.3, H-1"'), 5.28 (t, 7.3, H-2"'), 1.76 (s, H-4"'/5"'), 12.44 (s, 5-OH). ^{13}C-NMR (150 MHz, acetone-*d*): δ_C 135.6 (C-3), 176.0 C-4), 103.3 (C-4a), 158.0 (C-5), 111.1 (C-6), 162.1 (C-7), 92.9 (C-8), 155.0 (C-8a), 128.3 (C-1'), 130.7 (C-2'), 132.3 (C-3'), 157.9 (C-4'), 114.9 (C-5'), 127.9 (C-6'), 21.1 (C-1"), 122.4 (C-2"), 130.7 (C-3"), 24.9 (C-4"), 17.0 (C-5"), 28.2 (C-1"'), 122.3 (C-2"'), 130.7 (C-3"'), 24.9 (C-4"'), 16.9 (C-5"').

Compound 2 (Apigenin): A white powder. HR-ESI-ToF-MS: *m/z* $[M+H]^+$ 271.0598 (calculated for $C_{15}H_{10}O_5$), IR: 3329 cm^{-1}, 1651 cm^{-1}, 1614-1455 cm^{-1}. UV λ_{max} (Methanol): 241, 270, 338 nm, ^{1}H-NMR (600 MHz, acetone-*d*): δ_H 6.65 (s, H-3), 6.27 (d, 2.1, H-6), 6.56 (d, 2.1, H-8), 7.96 (dd, 8.4, 1.8, H-2'/6'), 7.05 (dd, 9, 1.8, H-3'/5'), 13.03 (s, 5-OH). ^{13}C-NMR (150 MHz, acetone-$_d$): δ_C 157.9 (C-2), 103.2 (C-3), 182.3 (C-4), 104.5 (C-4a), 164.0 (C-5), 98.8 (C-6), 164.2 (C-7), 93.8 (C-8), 161.0 (C-8a), 128.3 (C-2'/6'), 115.9 (C-3'/5').

RESULTS AND DISCUSSION

Phytochemical study on the leaves of *M. gigantea* lead to the isolation of two flavonols: glyasperin A and apigenin. Compound 1 was isolated as a yellow powder. The HR-ESI-ToF-MS of compound 1 exhibit a pseudo-molecular ion peak of flavonoid skeletal at *m/z* 423.1838 $[M+H]^+$ corresponding to the molecular formula $C_{25}H_{26}O_6$. The IR spectrum indicated absorption for hydroxyl (3343 cm^{-1}), C-H alkyl (2921 cm^{-1}, 2854 cm^{-1}), conjugated carbonyl (1647 cm^{-1}) and aromatic (1602-1483 cm^{-1}). The UV spectrum exhibited maxima typical for flavonol structure at 234 nm, 256 nm, 272 nm, 341 nm and 368 nm.

In the ^1H NMR spectrum, 13 signals representing 26 hydrogens were observed. A signal of chelated hydrogen at δ_H 12.46 (5-OH) showed that there is an interaction of hydrogen bond between hydroyl group with carbonyl group, which cause it to be more deshielded. One singlet signal at δ_H 6.60 (s, H-8) represented one hydrogen attached at ring A of the flavonol skeletal. Signals of ABD system can be observed by the presence of a pair of doublet-doublet δ_H 7.02 (dd, 8.5,3.8, H-5'), δ_H 7.96 (dd, 8.6,2.3, H-6') and doublet-*meta* at δ_H 8.05 (d, 2.1, H-2') at ring B. This signal indicated that there are two substituents attached at both rings. The isoprenylated chain was deduced by the presence of four methyl at δ_H 1.66 (H-4"), δH 1.79 (H-5") and δ_H 1.76 (H-4"'/5"'), two methylene at δ_H 5.38 (H-2"), δ_H 5.28 (H-2"') and two methine vinyl signal at δH 3.36 (H-1") and δ_H 3.40 (H-1"').

The ^{13}C NMR signal, showed the presence of 21 carbon signals representing 25 carbon atoms. Four carbon signals at δ_C 162.1 (C-7), δ_C 158.0 (C-5), δ_C 157.9 (C-4'), and δ_C 155.0 (C-8a) showed the charactheristic of oxyaryl group at which indicated that this structure is a derivative of kaempferol. Based on the spectroscopic data analysis of Compound **1**, the structure was confirmed as 6,3'-diisopropylkaempferol or Glyasperin A. This compound was previously obtained from the root bark of Formosan *Broussonetia Papyrifera* [20]. Glyasperin A was tested for its radical scavenging activity against 2,2-diphenyl-1-picrylhydrazyl (DPPH) which showed IC50 125.10 µM, indicated that it is more active than standard ascorbic acid (329.01 µM) [21].

Table 1: Comparison of ^{1}H NMR and ^{13}C NMR Spectroscopic Data of Compound 1 with Literature

Position	Compound **1**		Glyasperin A*	
	δ_H (mult, J Hz)	δ_C	δH (mult, J Hz)	δ_C
2	-	-	-	147.0
3	-	135.6	-	136.4
4	-	176.0	-	176.4
4a	-	103.3	-	103.8
5	-	158.0	-	158.7
6	-	111.1	-	111.6
7	-	162.1	-	162.9
8	6.60 (s)	92.9	6.56 (s)	93.7
8a	-	155.0	-	155.5
1’	-	128.3	-	128.9
2’	8.05 (d, 2.1)	130.7	8.00 (d,2.5)	130.1
3’	-	132.3	-	132.9
4’	-	157.9	-	157.9
5’	7.02 (dd, 8.5, 3.8)	114.9	6.97 (d,8.5)	115.6
6’	7.96 (dd, 8.6, 2.3)	127.9	7.91 (dd, 8.5, 2.5)	127.8
1”	3.36 (d, 7.1)	21.1	3.30 (d,7.4)	21.8
2”	5.38 (t, 7.4)	122.4	5.23 (tm,7.4)	123.2
3”	-	130.7	-	131.5
4”	1.66 (s)	24.9	1.77 (s)	25.8
5”	1.79 (s)	17.0	1.64 (s)	18.0
1”’	3.40 (d, 7.3)	28.2	3.34 (d, 7.3)	29.9
2”’	5.28 (t, 7.3)	122.3	5.33 (tm, 7.3)	123.1
3”’	-	130.7	-	131.5
4”’	1.76 (s)	24.9	1.74 (s)	25.8
5”’	1.76 (s)	16.9	1.74 (s)	17.8
5-OH	12.44 (br s)	-	12.41 (br s)	-

Compound **1** NMR Spectra recorded at 600 MHz (^{1}H) and 150 MHz (^{13}C-APT) in acetone-*d*

*Glyasperin A NMR Spectra recorded at 500 MHz (^{1}H) and 125 MHz (^{13}C-APT) in acetone-*d*

Compound 2 was obtained as a white powder. The HR-ESI-ToF-MS of compound 2 exhibit a pseudo-molecular ion peak at *m/z* 271.0598 $[M+H]^+$ corresponding to the molecular formula $C_{15}H_{10}O_5$. The IR spectrum indicated absorption for hydroxyl (3329 cm^{-1}), conjugated carbonyl (1651 cm^{-1}), and aromatic (1614-1455 cm^{-1}) group. The UV spectrum exhibited maxima typical for flavone structure at λ_{max} 241, 270, 338 nm.

In the ^1H NMR spectrum, six signals representing eight protons were observed. A chelated hydrogen at δ_H 13.03 (s, 5-OH) showed the presence of hydroxyl group attached at C-5 of the flavone skeletal. Two proton signals, which is a pair of doublet for AA'BB' spin system at aromatic region δH 7.96 (dd, 8.4, 1.8, H-2'/6') and δ_H 7.05 (dd, 9, 1.8, H-3'/5') corresponding to the hydroxyphenyl group attached to C-4' at ring B. Two proton signals at the aromatic region of ring A showed a doublet at δ_H 6.27 (d, 2.1, H-6) and δ_H 6.56 (d, 2.1, H-8) which indicate two protons attached to the C-8 and C-6 at A ring.

The ^{13}C NMR signals showed the signals of 15 peaks representing, 15 carbons in the compound. Oxyaryl signals were observed at δ_C 164.0 (C-5), δ_C 164.2 (C-7), and δ_C 162.5 (C-4'). Signal at δ_C 128.3 (C-2'/6') and δC 115.9 (C-3'/5') represent the aromatic methine for B ring, while δC 93.8 (C-8) and δ_C 98.8 (C-6) for A ring. Based on the data collected, compound **2** was confirmed as 5,7,4'-trihydroxyflavone or apigenin [22]. This compound was also reported isolated from flowering herb *Erigeron Acris L*. [23] and was found most commonly isolated in from *Matricaria recutita* from the family of Asteraceae [24]. Apigenin has shown to be an anti-inflammatory [25], antioxidant and anticancer activities [26].

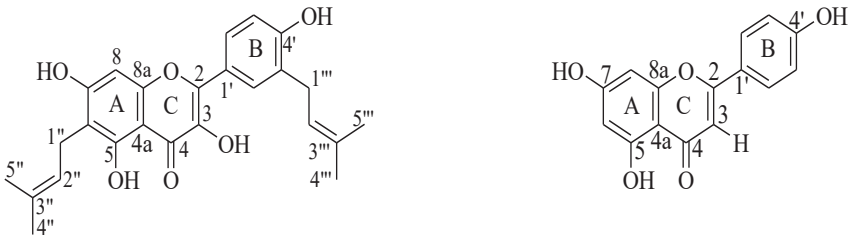
Table 2: Comparison of ^1H NMR and ^{13}C NMR Spectroscopic Data of Compound 2 with Literature

Position	Compound **2**		Apigenin*	
	δ_H (mult, J Hz)	δ_C	δ_H (mult, J Hz)	δ_C
2	-	157.9	-	163.93
3	6.65 (s)	103.2	6.77 (s)	103.06
4	-	182.3	-	181.94
4a	-	104.5	-	103.94
5	-	164.0	-	161.69

6	6.27 (d, 2.1)	98.8	6.22 (d, 2.1)	99.07
7	-	164.2	-	164.34
8	6.56 (d, 2.1)	93.8	6.50 (d, 2.1)	94.18
8a	-	161.0	-	157.48
2'/6'	7.96 (dd, 8.4, 1.8)	128.3	7.92 (d)	128.64
3'/5'	7.05 (dd, 9, 1.8)	115.9	6.95 (d)	116.17
5-OH	13.03 (s)	-	12.99 (s)	

Compound 2 NMR Spectra recorded at 600 MHz (^{1}H) and 150 MHz (^{13}C-APT) in acetone-*d*

*Apigenin NMR Spectra recorded at 200 MHz (^{1}H) and 50 MHz (^{13}C-APT) in dmso-d_6



(1) **(2)**

Figure 1: The Isolated Compound from *M. gigantea*

CONCLUSION

A prenylated flavonol, Glyasperin A (1) and a simple flavone, apigenin (2) was successfully isolated from the methanolic extract of the leaves of *M. gigantea* by using several chromatographic techniques and the structure was deduced from the spectroscopic data and comparison with the literature.

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