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Research paper

Isolation of Four Flavanones from the Leaves of *Macaranga Hypoleuca (Rchb.f. & Zoll.)* Müll.Arg

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Abstract

Macaranga is a large genus belongs to Euphorbiaceae family which commonly distributed in the tropical region of Africa, South-East Asia, China, and India. The plant of this genus contain flavonoids and stilbenes bearing various terpenyl groups including prenyl, geranyl and farnesyl groups. The leaves of *M. hypoleuca* were collected from reserved forest UiTM Jengka Pahang, Malaysia, and the dried powdered leaves were macerated in methanol at room temperature. The crude methanol extract was subjected to liquid-liquid partition using *n*-hexane and ethyl acetate to obtain hexane, ethyl acetate and aqueous fractions. The ethyl acetate fraction was semi purified using vacuum liquid chromatography (VLC) to give nine major fractions (MHL1-MHL9). Fraction MHL3 was further purified by column chromatography (CC) and preparative thin layer chromatography (p-TLC) to give two pure compounds, 8-prenylnaringenin (**1**) and sakuranetin (5,4'-dihydroxy-7-methoxyflavanone) (**3**). Meanwhile, fraction MHL6 was purified using column chromatography (CC) and p-TLC to yield another two pure compounds, 6-(3-hydroxy-3-methyl)naringenin (**2**) and 7-O-methyleriodictyol (**4**). The chemical structure of these isolated compounds were determined based on their 1D and 2D NMR, UV, and IR data. From this study, four flavanones were isolated from the leaves of *M. hypoleuca*.

Keywords: *Euphorbiaceae; flavonoid; flavanone; Macaranga hypoleuca; phenolic compound*

1. Introduction

Euphorbiaceae is among the largest family of angiosperms flowering plant composed of over 300 genera [1], with *Macaranga* as the major genus consisting approximately 300 species [2]. Out of 280 *Macaranga* species worldwide, 27 species are broadly distributed in Malaysia where the plants usually grow in a place with a lot of sunlight in secondary or damaged forest as well as in village area, wastelands and swampy forests [3], [4]. Many plant parts of *Macaranga* species are widely used in traditional medicine, for example the dried root of *M. tanarius* was used as emetic agent, meanwhile the decoction of the root was used as an antipyretic as well as an antitussive in Malaysian and Thailand medicinal remedies. In addition, the leaves part of this species was used as anti-inflammatory for wound healing [5]–[7]. This genus is known to be rich source of prenylated flavonoids and stilbenoids which regarded as the major constituent possessed a wide range of biological activities. This includes anticancer [8], antioxidant [5], [9], antimicrobial [6], anti-inflammatory [10] and other different types of bioactivities.

2. Material and method

2.1. Characterization

The characterization of pure compounds (**1-4**) was done by using infrared (IR), ultraviolet-visible (UV-Vis), one and two dimensional nuclear magnetic resonance (1D and 2D NMR) spectroscopy. The NMR experiment was done in acetone-d_6 and chemical shift values are reported in ppm and shown as δ scale.

2.2 Plant material

The leaves and stem bark of *Macaranga hypoleuca* were collected from Hutan Simpan UiTM Jengka, Pahang and identified by a botanist from Universiti Teknologi MARA (UiTM) Shah Alam.

2.3 Extraction and isolation

The ground, air-dried leave of *M. hypoleuca* (2.5 kg) was macerated in methanol (10 L) for 24 hours and repeated for three times. The crude methanol extract was then subjected to liquid-liquid partition using n-hexane and ethyl acetate successively. The ethyl acetate fraction (370 g) was fractionated using vacuum liquid chromatography (VLC) eluted with the mixtures of n-hexane and EtOAc with increasing polarity to give eight major fractions (HL1-HL8). 444 mg of HL3 was further fractionated using column chromatography (CC) over Sephadex-LH20 gel with solvent system $CHCl_3$: MeOH (50: 50) yielded six subfractions (HL31-HL36). HL35 (100.4 mg) was subjected to column chromatography (CC) over silica gel and eluted with mixture of Hex: EtOAc, followed by EtOAc: MeOH to yield eight fractions (HL351–HL358). Further purification of fraction HL355 (17.3 mg) and HL354 (25.1 mg) using preparative thin layer chromatography (p-TLC) with solvent system Hex: Acetone yielded (**1**) (7 mg) and (**3**) (10 mg).

10.6 g of HL6 was fractionated using VLC and eluted with the mixture of Hex: EtOAc and followed by EtOAc: MeOH to give eight fractions (HL61-HL68). Fraction HL65 was further fractionated and isolated by Sephadex-LH20 gel column (twice), column chromatography (CC) over silica gel ($CHCl_3$: EtOAc), radial chromatography ($CHCl_3$: MeOH) and p-TLC ($CHCl_3$: MeOH) to yield (**2**) (6.5 mg). Compound (**4**) (2 mg) was obtained from the separation of HL64 (2.05 g) using Sephadex-LH20 gel column (MeOH), column chromatography (CC) over silica gel (Hex: Acetone) and p-TLC (Hex: EtOAc).

8-prenylnaringenin (**1**). Yellow sticky solid. UV (MeOH) λ_{max} nm: 226.4, 242, 293.2, 340.4; ATR-IR ν_{max} cm^{-1}: 3313 (OH), 1635 (C=O), 1612 (C=C), 1077; ^{1}H-NMR (Acetone-d_6, 600 MHz) δ ppm : 12.16 (1H, s, OH-5), 7.43 (2H, d, J = 8.4 Hz, H-2'/H-6'), 6.93 (2H, d, J = 8.4 Hz, H-3'/H-5'), 6.05 (1H, s, H-6), 5.46 (1H, dd, J= 13.2, 3 Hz, H-2), 3.16 (1H, dd, J= 12.8, 16.8 Hz, H-3b), 2.76 (1H, dd, J= 16.8, 3 Hz, H-3a), 5.21 (1H, d, J = 7.2 Hz, H-2''), 3.23 (2H, d, J = 7.2 Hz, H-1''), 1.62 (6H, s, H-4''/H-5''); ^{13}C-NMR (Acetone-d_6, 150 MHz) δ ppm: 79.71 (C-2), 43.41 (C-3), 197.55 (C-4), 162.94 (C-5), 96.41 (C-6), 165.47 (C-7), 108.35 (C-8), 161.03 (C-9), 103.13 (C-10), 130.89 (C-1'), 128.78 (C-2'/C-6'), 116.18 (C-3'/C-5'), 158.76 (C-4'), 22.25 (C-1''), 123.78 (C-2''), 131.13 (C-3''), 17.86 (C-4''), 25.88 (C-5'') [11].

6-(3-hydroxy-3-methyl)naringenin (**2**). Brown sticky solid. UV (MeOH) λ_{max} nm: 224.4, 293.2, 339.5; IR ν_{max} cm^{-1}: 3214 (OH), 1629 (C=O), 1610 (C=C), 1076; ^{1}H-NMR (Acetone-d_6, 600 MHz) δ ppm : 12.13 (1H, s, OH-5), 7.37 (2H, d, J = 9 Hz, H-2'/H-6'), 6.84 (2H, d, J = 9 Hz, H-3'/H-5'), 5.95 (1H, s, H-8), 5.37 (1H, dd, J= 12.6, 2.4 Hz, H-2), 3.08 (1H, dd, J= 16.8, 12.6 Hz, H-3b), 2.76 (1H, dd, J= 17.4, 3 Hz, H-3a), 1.63 (2H, m, H-2''), 2.59 (2H, d, J = 7.2 Hz, H-1''), 1.19 (6H, s, H-4''/H-5'') [12]; ^{13}C-NMR (Acetone-d_6, 150 MHz) δ ppm: 78.56 (C-2), 42.53 (C-3), 196.69 (C-4), 161.97 (C-5), 108.66 (C-6), 164.27 (C-7), 95.73 (C-8), 160.17 (C-9), 102.46 (C-10), 130.26 (C-1'), 127.781(C-2'/C-6'), 115.25 (C-3'/C-5'), 157.60 (C-4'), 17.36 (C-1''), 42.93 (C-2''), 69.67 (C-3''), 28.56 (C-4''/C-5'').

Sakuranetin (5,4'-dihydroxy-7-methoxyflavanone) (**3**). White solid. UV (MeOH) λmax nm: 230, 286, 331; IR νmax cm-1: 3346 (OH), 1639 (C=O), 1616 (C=C), 1156; ^{1}H-NMR (Acetone-d6, 600 MHz) δ ppm: 12.16 (1H, s, 5-OH), 5.51 (1H, dd, J= 13.2, 3 Hz, H-2), 2.79 (1H, dd, J= 16.8, 3 Hz, H-3a), 3.24 (1H, dd, J= 16.8, 13.2 Hz, H-3b), 6.06 (1H, d, J= 2.4 Hz, H-6), 6.07 (1H, d, J= 2.4 Hz, H-8), 7.42 (2H, d, J= 8.4 Hz, H-2'/H-6'), 6.92 (2H, d, J= 9 Hz, H-3'/H-5'), 3.86 (3H, s, OCH_3); ^{13}C-NMR (Acetone-d6, 150 MHz) δ ppm: 80.05 (C-2), 43.52 (C-3), 197.59 (C-4), 165.03 (C-5), 95.49 (C-6), 168.91 (C-7), 94.58 (C-8), 164.22 (C-9), 103.79 (C-10), 130.69 (C-1'), 128.96 (C-2'/C-6'), 116.22 (C-3'/C-5'), 158.78 (C-4'), 56.21 (C-OCH_3) [13].

7-O-methyleriodictyol (**4**). Dark yellow sticky solid. UV (MeOH) λmax nm: 230, 287, 332; ^{1}H-NMR (Acetone-d6, 600 MHz) δ ppm: 12.16 (1H, s, OH-5), 5.45 (1H, dd, J= 12.6, 3 Hz, H-2), 3.19 (1H, dd, J= 12.8, 16.8 Hz, H-3a), 2.76 (1H, dd, J= 16.8, 3 Hz, H-3b), 6.05 (1H, d, J= 2.4 Hz, H-6), 6.07 (1H, d, J= 2.4 Hz, H-8), 7.05 (1H, s, H-2'), 6.88 (2H, s, H-5'/H-6'), 3.86 (3H, s, OCH_3) [14]; ^{13}C-NMR (Acetone-d6, 150 MHz) δ ppm: 79.20 (C-2), 42.68 (C-3), 196.74 (C-4), 164.10 (C-5), 94.53 (C-6), 167.97 (C-7), 93.66 (C-8), 163.30 (C-9), 102.88 (C-10), 130.49 (C-1'), 113.92 (C-2'), 145.29 (C-3'), 145.68 (C-4'), 115.22 (C-5'), 118.28 (C-6'), 55.32 (C-OCH_3)

3. Results and Discussion

Compound **1-4** (**Figure 1**) were successfully isolated from the methanolic leaves extract of *M. hypoleuca* and compound **2-4** were first time isolated from genus *Macaranga*. Compound (**1**) was obtained as yellowish sticky solid. The UV spectrum of this compound displayed maximum absorption at λ_{max} 226, 242, 293 and 340 nm and IR spectrum showed absorption bands at 3313 cm^{-1} (broad, OH), 1635 cm^{-1} (C=O carboxylate), 1612 cm^{-1} (C=C) and 1077 cm^{-1} (C-O). The ^{1}H NMR spectrum of (**1**) displayed a typical characteristic for a flavanone by the presence of methylene proton signals at δ_H 3.16 (1H, dd, J= 12.8, 16.8 Hz, H-3b), δ_H 2.76 (1H, dd, J= 16.8, 3 Hz, H-3a) and one oxymethine proton at δ_H 5.46 (1H, dd, J= 13.2, 3 Hz, H-2). One singlet proton signal observed at δ_H 6.05 (1H) which belongs to H-6 indicated that ring A is a pentasubstituted ring system. The appearance of an aliphatic methylene proton at δ_H 3.23 (2H, d, J = 7.2 Hz, H-1''), one vinyl proton at δ_H 5.21 (1H, d, J = 7.2 Hz, H-2'') and two olefinic methyl groups at δ_H 1.62 (6H, s, H-4''/H-5'') showed the presence of prenyl group. At ring B, two set of *ortho*-coupled aromatic methine protons at δ_H 7.43 (2H, d, J = 8.4 Hz, H-2'/H-6') and δ_H 6.93 (2H, d, J = 8.4 Hz, H-3'/H-5') indicated the presence of AABB spin system. In addition, the signal for a chelated OH observed at a very downfield region at δ_H 12.16 (1H, s, OH-5) is due to hydrogen bonding between hydroxyl group at C-5 and carbonyl group at C-4. The ^{13}C NMR APT displayed 18 carbon signals which represent a total of 20 carbons. One aliphatic methylene carbon appeared at δ_C 43.41 (C-3) and one oxymethine carbon at δ_C 79.71 (C-2) showed that (**1**) is a flavanone. Other signals are four oxyaryl carbons (δ_C 158.76-165.47), three aromatic quartenary carbons (δ_C 103.13, 108.35, 130.89), five methine carbons (δ_C 96.41, 116.18, 128.78) and carbonyl carbon (δ_C 197.55). In addition, carbon signals for prenyl group appeared at δ_C 17.86 (C-4"), 22.25 (C-1"), 25.88 (C-5"), 123.78 (C-2") and 131.13 (C-3"). Based on spectral data and comparison with literature data, compound **1** was assigned as 8-prenylnaringenin.

Previously, 8-prenylnaringenin was isolated from *M. kurzii* and was evaluated against human lung carcinoma (A-549) and human-hepatocellular (Hep G2) cell lines by MTTmethod. The results showed that 8-prenylnaringenin inhibited the proliferation of A-549 cell line with IC50 values of 9.76 µg/mL [15].

Compound (**2**) was isolated as brownish sticky solid. The UV spectrum of this compound displayed maximum absorption at λ_{max} 224, 293 and 339 nm and IR spectrum showed absorption bands at 3214 cm^{-1} (broad, OH), 1629 cm^{-1} (C=O carboxylate), 1610 cm^{-1} (C=C) and 1076 cm^{-1} (C-O). The ^{1}H NMR spectrum of (**2**) exhibited similar signal pattern to that of compound (**1**) in the presence of methylene proton at δ_H 3.08 (1H, dd, J= 12.6, 16.8 Hz, H-3b), δ_H 2.76 (1H, dd, J= 17.4, 3 Hz, H-3a) and one oxymethine proton at δ_H 5.37 (1H, dd, J= 12.6, 2.4 Hz, H-2) as key characteristic for flavanone. The difference between the ^{1}H NMR spectrum of **2** and **1** can be observed in ring A where the prenyl group occupied the C-6 of compound **2** instead of at C-8 in compound **1**. However, the prenyl group that attached to C-6 is a hydroxylated prenyl group which can be seen by the presence of methylene proton signal at δ_H 1.63 (2H, m, H-2'') instead of vinyl proton at δ_H 5.21 (1H, d, J = 7.2 Hz, H-2'') in compound **1**. Two set of *ortho*-coupled aromatic methine protons at δ_H 7.37 (2H, d, J = 9 Hz, H-2'/H-6') and δ_H 6.84 (2H, d, J = 9 Hz, H-3'/H-5') indicated the presence of AABB spin system at ring B. One singlet signal located at a very downfield region at δ_H 12.13 (1H, s, OH-5) indicated the chelated OH at C-5 due to hydrogen bonding between hydrogen and oxygen atom of carbonyl group at C-4. The ^{13}C NMR APT displayed 17 carbon signals which represent a total of 20 carbons. One aliphatic methylene carbon appeared at δ_C 42.53 (C-3) and one oxymethine carbon at δ_C 78.56 (C-2) showed that (**2**) is a flavanone. Other signals are four oxyaryl carbons (δ_C 157.60-164.27), three aromatic quartenary carbons (δ_C 102.46, 108.66, 130.26), five methine carbons (δ_C 95.73, 115.25, 127.70) and carbonyl carbon (δ_C 196.69). In addition, carbon signals for prenyl group appeared at δ_C 17.36 (C-1"), 28.56 (C-4"/C-5"), 42.93 (C-2") and 69.67 (C-3"). Based on spectral data and comparison with previous reported data, compound **2** was determined as 6-(3-hydroxy-3-methyl)naringenin and was first time been isolated from plant.

Compound (**3**) was obtained as white solid. The UV spectrum of this compound displayed maximum absorption at λmax 230, 286 and 331 nm and IR spectrum showed absorption bands at 3346 cm^{-1} (broad, OH), 1639 cm^{-1} (C=O carboxylate), 1616 cm^{-1} (C=C)

and 1156 cm^{-1} (C-O). The ^1H NMR spectrum of (**3**) displayed a typical characteristic for a flavanone by the presence of methylene proton signals at δ_H 2.79 (1H, dd, J= 16.8, 3 Hz, H-3a), 3.24 (1H, dd, J= 16.8, 13.2 Hz, H-3b) and one oxymethine proton at δ_H 5.51 (1H, dd, J= 13.2, 3 Hz, H-2). Two *meta* coupled aromatic protons was spotted at δ_H 6.06 (1H, d, J= 2.4 Hz) and 6.07 (1H, d, J= 2.4 Hz) belongs to H-6 and H-8 of a *di*-substituted (at C-5 and C-7) ring A. The ^1H NMR spectrum displayed the appearance of an AABB spin system at δ_H 7.42 (2H, d, J= 8.4 Hz, H-2'/H-6') and 6.92 (2H, d, J= 9 Hz, H-3'/H-5') consistent with 4'-substituted ring B. Furthermore, one signal was observed at δ_H 3.86 (3H, s) which was assigned to methoxyl group located at C-7 as established from HMBC spectrum, which showed correlation between methoxyl proton at δ_H 3.86 with C-7 (δ_C 56.21). In addition, the ^1H spectrum also displayed the presence of chelated OH at a very downfield region at δ_H 12.16 (1H, s, OH-5) which was due to hydrogen bonding between hydroxyl group at C-5 and carbonyl group at C-4. The ^{13}C NMR APT displayed 14 carbon signals which represent a total of 16 carbons. One aliphatic methylene carbon appeared at δ_C 43.41 (C-3) and one oxymethine carbon at δ_C 79.71 (C-2) showed that (**3**) is a flavanone. Other signals are four oxyaryl carbons (δ_C 158.78-168.90), two aromatic quartenary carbons (δ_C 103.79 and 130.69), six methine carbons (δ_C 94.58, 95.49, 116.22, 128.98) and carbonyl carbon (δ_C 197.59). In addition, carbon signals for methoxyl group appeared at δ_C 56.21 (C-OCH_3). Based on spectral data and comparison with literature data, compound **3** was assigned as Sakuranetin (5,4'-dihydroxy-7-methoxyflavanone) [13].

Sakuranetin was previously isolated from the leaves of *Dodonaea angustifolia* from Ngong forest and was reported to possessed good antifungal activity against *S. cerevisiae* with an MIC < 7.8 µg/well, probably due to it lipophilic nature [16]. Besides that, sakuranetin isolated from *Hebe cupressoides* showed moderate antifungal activity against *Trichophyton mentagrophytes* where 60 µg/disk of sakuranetin gave 3 mm zone of inhibition of *T. mentagrophytes*, but no inhibition of *Candida albicans* [13].

Compound (**4**) was isolated as dark yellow sticky solid. The UV spectrum of this compound displayed maximum absorption at λ_{max} 230, 287 and 332 nm. The ^1H NMR spectrum of (**4**) displayed similar signal pattern to that of compound (**3**) in the presence of methylene proton at δ_H 3.19 (1H, dd, J= 12.8, 16.8 Hz, H-3b), 2.76 (1H, dd, J= 16.8, 3 Hz, H-3a) and one oxymethine proton at δ_H 5.45 (1H, dd, J= 12.6, 3 Hz, H-2) as the characteristic signals for flavanone. The difference between the ^1H NMR spectrum of **4** and **3** can be observed in ring B where the signal of AABB spin system in **3** has been replaced by the signals of ABD spin system appeared at δ_H 6.88 (2H, s, H-5'/H-6') and δ_H 7.05 (1H, s, H-2'), due to the presence of another hydroxyl group at C-3'. The ABD spin system of this compound gave out only two signals as the proton at C-5' and C-6' appeared at the same chemical shift as singlet. Lastly, one singlet signal located at a very downfield region at δ_H 12.16 (1H, s, OH-5) indicated a chelated OH at C-5 due to hydrogen bonding between hydrogen atom of hydroxyl group and oxygen atom of carbonyl group at C-4. The ^{13}C NMR APT displayed 16 carbon signals which correspond the structure of compound **4** with a total of 16 carbons. One aliphatic methylene carbon appeared at δ_C 42.68 (C-3) and one oxymethine carbon at δ_C 79.20 (C-2) proved that (**4**) is a flavanone. The spectrum showed the presence of one methoxy group at δ_C 55.32. Other signals were attributed to five oxyaryl carbons (δ_C 145.29-167.97), two aromatic quartenary carbons (δ_C 102.88 and 130.49), five methine carbons (δ_C 93.66, 94.53, 113.92, 115.22 and 118.28) and carbonyl carbon (δ_C 196.69). Based on all data and previous reported data, compound **4** was assigned as 7-O-methyleriodictyol [14].

From the previous study, 7-O-methyleriodictyol has been isolated from the resinous exudates of the plant *Heliotropium sinuatum* (Heliotropiaceae) and evaluated *in vitro* and *in vivo* antiviral activity against infectious salmon anemia virus (ISAV). The result showed that this compound was able to inhibit the infectivity of ISAV *in vitro* assay with EC_{50} of 0.2 µg/ml. While the *in vivo* study showed that this compound was able to 100% protect the fish infected with ISAV and keeping 100% fish viability despite the cytotoxicity of the compound displayed as CC_{50} of 12.80 µg/ml [17].

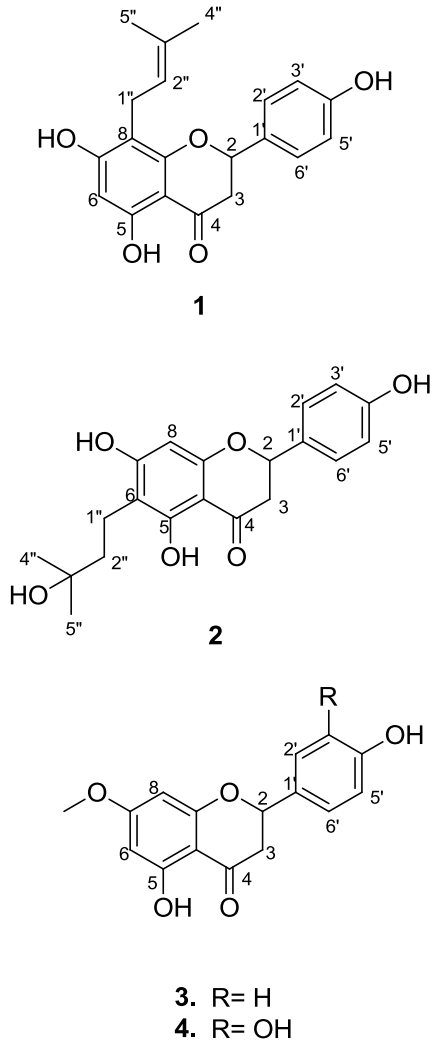

Figure 1: 8-prenylnaringenin (**1**), 6-(3-hydroxy-3-methyl)naringenin (**2**), sakuranetin (**3**) and 7-O-methyleriodictyol (**4**)

4. Conclusion

Phytochemical study of the leaves of *M. hypoleuca* resulted in the isolation of four flavanones, which upon further elucidation by using modern spectroscopic techniques such as UV, IR NMR and MS confirmed that the flavanones are 8-prenylnaringenin (**1**), 6-(3-hydroxy-3-methyl)naringenin (**2**), sakuranetin (**3**) and 7-O-methyleriodictyol (**4**).

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