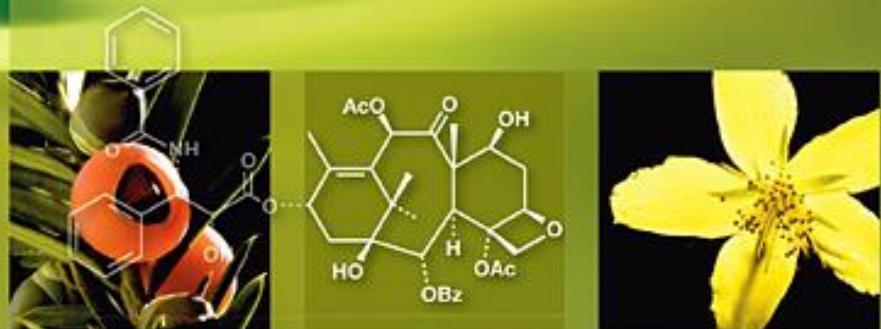




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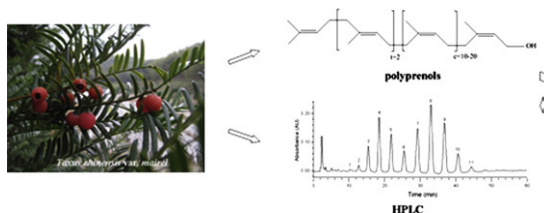


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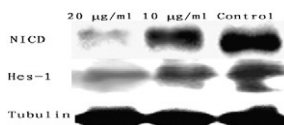
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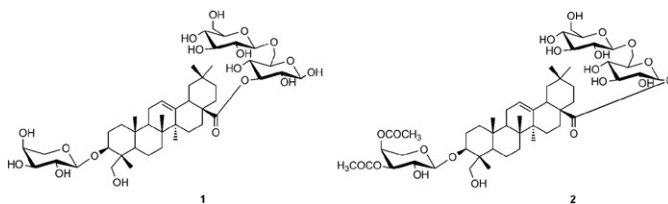
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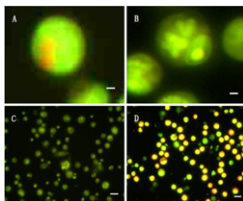


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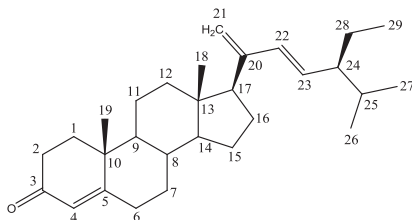
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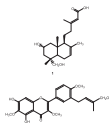


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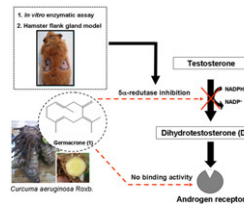
A new labdane diterpenoid, 2,18-dihydroxylabda-7,13(*E*)-dien-15-oic acid (**1**), and a new flavone, 5,7-dihydroxy-3,6,4'-trimethoxy-3'-(4-hydroxy-3-methylbut-2-enyl)flavone (**2**) with two known labdane diterpenes and three flavones were isolated from *Dodonaea viscosa*. Their structures were determined by extensive analysis of spectroscopic data and by comparison with literature data. The anti-inflammatory activity of some of the compounds was evaluated with a flow cytometry TNF- α secretion assay on human Thp-1 cell line.



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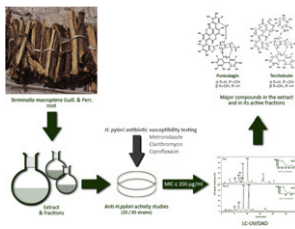
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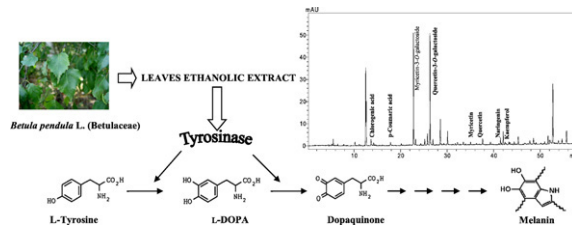
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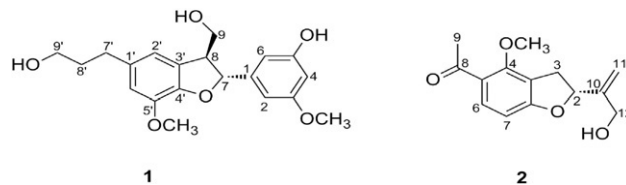
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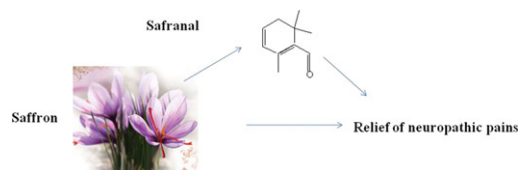
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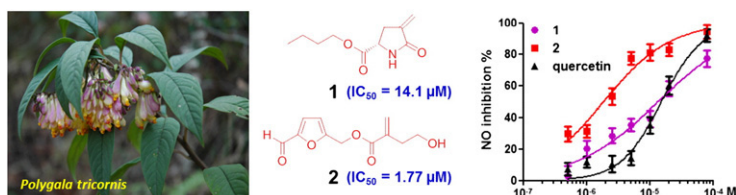
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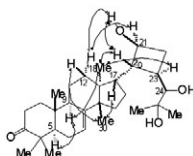
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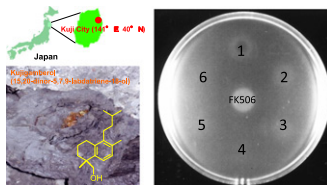
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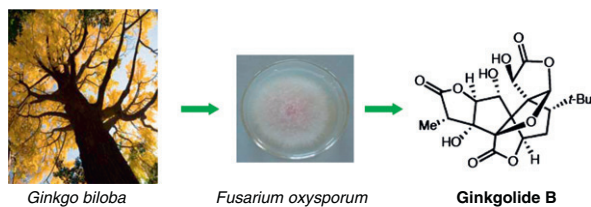
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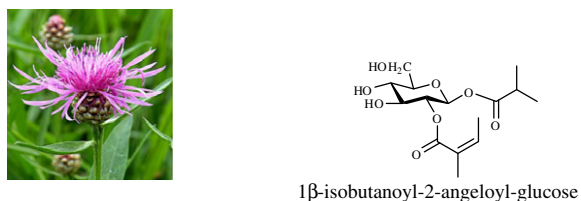
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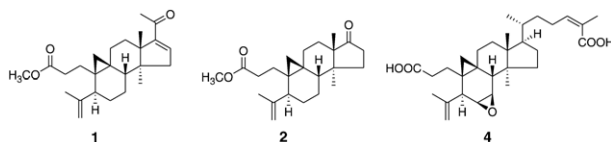


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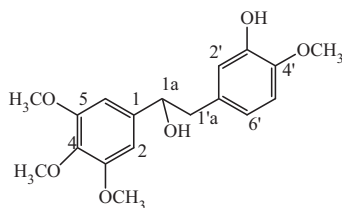
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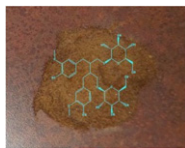


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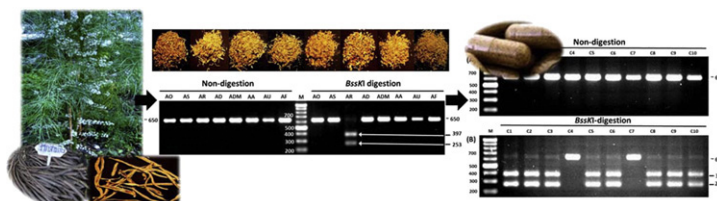
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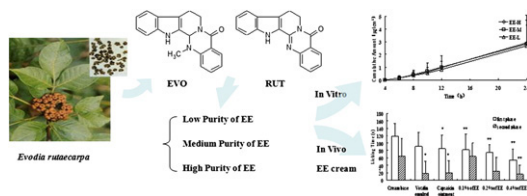
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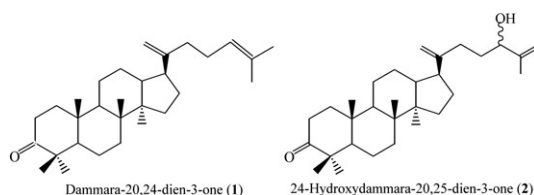
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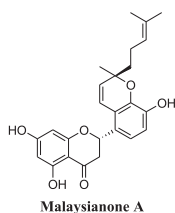
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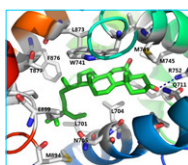
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Steroids with inhibitory activities against the prostate cancer cells were isolated from *Tydemania expeditionis*. Molecular docking revealed the important role of carbonyl group in the interactions with androgen receptor.



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Flavonoids with antiplasmodial and cytotoxic activities of *Macaranga triloba*

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ABSTRACT

A new flavanone derivative, malaysianone A (**1**), four prenylated flavanones, 6-prenyl-3'-methoxyeriodictyol (**2**), nymphaeol B (**3**), nymphaeol C (**4**) and 6-farnesyl-3',4',5,7-tetrahydroxyflavanone (**5**), and two coumarins, 5,7-dihydroxycoumarin (**6**) and scopoletin (**7**), were isolated from the dichloromethane extract of the inflorescences of *Macaranga triloba*. The structures of these compounds were elucidated based on spectroscopic methods including nuclear magnetic resonance (NMR-1D and 2D), UV, IR and mass spectrometry. The cytotoxic activity of the compounds was tested against several cell lines, with **5** inhibiting very strongly the growth of HeLa and HL-60 cells (IC₅₀: 1.3 µg/ml and 3.3 µg/ml, respectively). Compound **5** also showed strong antiplasmodial activity (IC₅₀: 0.06 µM).

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1. Introduction

Macaranga triloba, locally known as “Mahang merah”, is a tree endemic to Southeast Asia found at forest margins. Its water extract was used as pain relief for stomach trouble in Java [1]. Previous investigation on the chemistry and pharmacology of this genus showed that its crude extracts displayed an interesting bioactivity profile, possessing various bioactivities including antioxidant [2,3], cyclooxygenase-I and II-inhibitory [4], antibacterial [5], antitumor and antimicrobial [6], and cytotoxic effects [7–9]. The genus *Macaranga*, one of the largest genera of the Euphorbiaceae family has approximately 280 species [10]. This genus is known for a wide range of mutualistic associations with ants, ranging from facultative to strictly obligate relationships [11,12]. In Malaysia, there are approximately 40 species, growing mostly in secondary forests [13]. *Macaranga* has been reported as a plant rich in prenylated flavonoids, especially geranyl flavonoids [14–17]. This paper reports the structure elucidation of **1** and the bioactivities of the isolated flavonoids from the inflorescences of *M. triloba*.

2. Experimental

2.1. General experimental procedures

¹H and ¹³C NMR were recorded in CDCl₃ on a Bruker 300 Ultrashield NMR spectrometer measured at 300 and 75 MHz, respectively. Chemical shifts (δ) are reported in ppm and coupling constants (J) are reported in Hz. CD spectra were recorded on a JASCO J-720WI spectropolarimeter. HRESI-MS were obtained with an Agilent TOF/MS G6224A mass spectrometer. Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum One FTIR spectrometer. Ultraviolet (UV) spectra were recorded on Shimadzu UV-vis 160i spectrophotometer. The following adsorbents were used for purification: VLC used Silica gel 60, 70–230 mesh ASTM (Merck cat no. 1.07747), radial chromatography used Si-gel 60 PF₂₅₄ (Merck cat. no. 1.07749) and TLC analysis with Merck Kieselgel 60 F254 0.25 mm (cat. no. 1.05554). Distilled technical and analytical grade solvents were used in this study.

2.2. Plant material

The inflorescences of *M. triloba* were collected from Pasir Raja, Hulu Terengganu, Malaysia and identified by Dr. Shamsul

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E-mail address: noriz118@salam.uitm.edu.my (N. Ahmat).

Khamis, Institute of Bioscience, Universiti Putra Malaysia. A voucher specimen (UiTM17/09) was deposited at the Herbarium of Universiti Teknologi MARA, Malaysia.

2.3. Extraction and isolation

The inflorescences (1.5 kg) of *M. triloba* were air dried, ground and soaked successively with *n*-hexane, dichloromethane and methanol (3 × 16 L, 24 h each). The dichloromethane extract (44.41 g), a dark brown gum, was subjected to vacuum liquid chromatography (VLC) on silica gel using a gradient elution system of *n*-hexane/EtOAc 10:0, 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9 and 0:10. Twenty-five fractions were obtained and spotted on TLC using the same solvent system. Similar TLC profiles were grouped to yield 6 fractions (F₁–F₆). Fraction F₃ was subjected to column chromatography (CC) using gradient elution system of *n*-hexane/CHCl₃ 1:9 and *n*-hexane/EtOAc 10:0, 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9 and 0:10 to yield 47 fractions, which were pooled based on TLC profiling, to yield 15 fractions (F₁–F₁₅). Fraction F₁₃ was subjected to preparative thin-layer chromatography (PTLC) to obtain **6** (5.0 mg) using solvent system CH₂Cl₂/acetone 95:5 (1 mm thickness). Fraction F₁₅ was subjected to medium pressure liquid chromatography (MPLC) using gradient elution system of H₂O/MeCN 8:2, 7:3, 6:4, 5:5, 4:6 and 3:7 to yield 27 fractions (F₂₁–F₂₇). Fractions (F₂₁–F₂₆) were combined and subjected to radial chromatography (RC) to yield **2** (21.1 mg) using CHCl₃/acetone 9:1 (2 mm thickness). Fraction F₁₆ was further chromatographed on reverse-phased column chromatography (RPCC) to yield 26 fractions (F₃₁–F₃₆) using H₂O/MeCN 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9 and 0:10. Fractions F₃₂–F₃₁₁ were combined and subjected to RC using CHCl₃/EtOAc 9.5:0.5 (2 mm thickness) yielding **3** (326.7 mg). Fractions F₃₁₄–F₃₁₉ were pooled and subjected to RC using CHCl₃/EtOAc 9:1 (1 mm thickness) to yield **4** (20.6 mg). Compound **5** (58.1 mg) was obtained from the first RPCC H₂O/MeCN 3:7 from fraction F₃₂₁. Fraction F₃₂₂–F₃₂₃ was subjected to RC using CHCl₃/acetone 9.8:0.2 (2 mm thickness) to yield 20 fractions (F₄₁–F₄₀). Subfractions F₄₁–F₄₆ were combined and chromatographed on RC using *n*-hexane/EtOAc/MeOH 8:1.9:0.1 (1 mm thickness) to yield 21 fractions (F₅₁–F₅₂₁). Subfractions F₅₁₁–F₅₁₅ were combined to obtain **1** (6.0 mg). Fraction F₄ from VLC was subjected to CC using CH₂Cl₂/acetone 10:0, 9:1, 8:2, 7:3, 6:4 and 5:5 to yield 10 fractions (F₆₁–F₆₁₀). Fractions F₆₁–F₆₅ were combined and subjected to RC to obtain **7** (6.0 mg) using CH₂Cl₂/acetone 9.8:0.2 (0.5 mm thickness).

2.4. Antiplasmodial activity

The antiplasmodial activity of the dichloromethane extract and the isolated compounds was determined by methods previously described by Widyawaruyanti [18]. The samples were dissolved in DMSO and kept at –20 °C until use. The malarial parasite *Plasmodium falciparum* (3D7) clone was propagated in a 24-well culture plate in the presence of 10, 1, 0.1, 0.01 and 0.001 µg/ml range of concentrations of each compound. Chloroquine diphosphate was used as positive control. The growth of the parasite was monitored by making a blood smear fixed with MeOH and stained with Geimsa (Merck). The antiplasmodial activity of each compound was expressed as an IC₅₀ value, defined as the

concentration of the compound causing 50% inhibition of parasite growth relative to an untreated control.

2.5. Cytotoxicity assay

Cytotoxicity was quantitatively estimated by non-radioactive, colorimetric assay system using tetrazolium salt, MTT (Sigma, USA) as reported by Mosmann [19]. MTT was dissolved in phosphate buffered saline at 5 mg/ml and filter sterilized to eliminate a small quantity of insoluble residue present in some batches of MTT. The MTT stock solution was added directly to all appropriate microtitre-plate well (20 per 100 µl medium) containing cells. The plate was incubated for 4 h at 37 °C to allow MTT metabolism to formazan. The supernatant was aspirated and 100 µl of acid-isopropanol (0.04 M HCl in propan-2-ol) was added and mixed thoroughly to dissolve the dark blue formazan crystals. The optical density (OD) was measured on an automated spectrophotometric EL 340 multiplet/microelisa reader (Bio-Tek Instruments Inc.) using test and reference wavelength of 570 and 630 nm respectively. The cytotoxic dose that killed cell was determined from the compound's concentration that reduces the mean absorbance at 570 nm to 50% (IC₅₀) of those in the untreated control cells [20].

Malaysianone A (**1**): Pale yellow amorphous solid; m.p. 92; [α]_D²⁵ +24.6 (c 0.92, CHCl₃); UV (MeOH) λ_{max} nm (log ε): 226 (4.82), 272 (4.45) and 285 (4.46); IR ν_{max} cm⁻¹ (KBr): 3365, 2945, 2830, 1688 and 1451; ¹H NMR (CDCl₃) see Table 1; ¹³C NMR (CDCl₃) see Table 1; and HRESI-MS *m/z*: [M+H]⁺ 422.4424 (calc. for C₂₅H₂₆O₆ 422.4444). CD (c=0.125 mM, MeOH): 232 [Δε=+8.3], 252 [+1.3], 255 [+1.6], 273 [–0.1], 291 [–2.0], 307 [0], 313 [+0.2], 316

Table 1
¹H NMR spectroscopy data of **1**.

No	δ _H (J in Hz)	δ _C	HMBC (¹ H ↔ ¹³ C)
2	5.52, dd, (J = 3.0 Hz, 13.2 Hz)	76.2	C-4
3	3.16, dd, (J = 13.2, 17.1 Hz, H-3a)	42.4	C-2, C-4
	2.74, dd, (J = 3.0, 17.1 Hz, H-3b)		C-4
4	–	196.2	–
5	12.07 (–OH, s)	164.4	C-5, C-6, C-8
6	6.01, d, (J _m = 2.1 Hz)	95.5	C-10
7	–	164.9	–
8	6.01, d, (J _m = 2.1 Hz)	96.8	C-6, C-7
9	–	163.3	–
10	–	103.1	–
1'	–	124.7	–
2'	–	118.9	–
3'	–	139.7	–
4'	–	145.1	–
5'	6.93, d, (J _o = 8.4 Hz)	114.6	C-1', C-3'
6'	6.86, d, (J _o = 8.4 Hz)	118.8	C-2, C-2', C-4'
1''	5.71, d, (J = 9.9 Hz)	118.8	C-1', C-2', C-3', C-3''
2''	6.63, d, (J = 9.9 Hz)	130.9	C-2', C-3'', C-4'', C-5''
3''	–	79.1	–
4''	1.44, d	26.1	C-2'', C-3'', C-5''
5''	1.77, m	40.7	C-3'', C-7'', C-8''
6''	2.11, m	22.8	–
7''	5.11, dt, (J = 1.2, 5.7 Hz)	123.7	–
8''	–	132.1	–
9''	1.60, s	17.7	C-10''
10''	1.69, s	25.7	C-9'', C-8'', C-7''

Measured in CDCl₃ at 300 MHz (¹H) and 75 MHz (¹³C).

[+0.1], 330 [+0.7], 338 [+0.6], 355 [0], 360 [0.3] and 365 [−0.1]nm.

3. Results and discussion

The chloroform extract of the inflorescences of *M. triloba* was fractionated using vacuum liquid chromatography (VLC) and purified by various chromatographic techniques. Seven compounds (1–7) were isolated (Fig. 1), including a new flavanone named malaysianone A (1). The structural elucidation was achieved through chemical and spectroscopic analysis, including HRMS, UV, ^1H , ^{13}C and 2D NMR (COSY, HMQC and HMBC), and by comparison with reported data.

Compound 1 was obtained as a pale yellow amorphous solid. The UV spectrum showed maxima at 232 and 329 nm, suggestive of a flavanone moiety [21]. The IR spectrum displayed strong bands for hydroxyl (3365 cm^{-1}), conjugated carbonyl (1688 cm^{-1}), and alkene (1451 cm^{-1}) groups. The HREIMS mass spectrum revealed a $[\text{M} + \text{H}]^+$ ion at m/z 422.4424 corresponding to the molecular formula $\text{C}_{25}\text{H}_{26}\text{O}_6$. The ^1H NMR spectrum (Table 1), recorded in CDCl_3 , displayed a set of signals at δ_{H} 5.52 (^1H , dd , $J = 13.2, 3.0\text{ Hz}$), 2.74 (^1H , dd , $J = 17.1, 3.0\text{ Hz}$), and 3.16 (^1H , dd , $J = 17.1, 13.2\text{ Hz}$), diagnostic for H-2 and H-3 of a flavanone nucleus and a one-proton signal at δ_{H} 12.07 characteristic of the 5-OH. A doublet at δ_{H} 6.01 ($J_m = 2.1\text{ Hz}$) was assigned to a pair of *meta*-coupled protons at H-6 and H-8 of ring A. *Ortho*-coupled protons at δ_{H} 6.86 and 6.93 (d , $J_o = 8.4\text{ Hz}$ each) were attributed to H-6' and H-5' of the B ring. The presence of a pair of olefinic protons at δ_{H} 5.71 and 6.63 (d , $J = 9.9\text{ Hz}$ each) indicated that an oxygen atom at C-3' was cyclized with C-3'' to form a pyran ring. Comparison with tanariflavanone B (8) [22] confirmed this observation. The remaining signals were ascribed to the aliphatic protons of the pyran and prenyl groups [δ_{H} 1.44 (H-4''), δ_{H} 1.77 (H-5''), δ_{H} 2.11 (H-6''), δ_{H} 5.11 (H-7''), δ_{H} 1.60 (H-9'') and δ_{H} 1.69 (H-10'')]. The ^{13}C NMR spectrum of 1 showed 25 carbon resonances (Table 1) including a downfield carbonyl signal at δ_{C} 196.2 (C-4). Five oxyaryl carbons can be observed at δ_{C} 139.7, 145.1, 163.3, 164.4, and 164.9, four quaternary sp^2 carbons at δ_{C} 103.1, 118.9, 124.7 and 132.1, and seven methine sp^2 carbons at δ_{C} 95.5, 96.8, 114.6, 118.8 (2 C), 123.7 and 130.9. The flavanone

nucleus was evidenced from the sp^3 methylene and methine carbons at δ_{C} 42.4 and 76.2, respectively. The rest of the signals were accounted for six aliphatic carbons in the pyran and prenyl groups (δ_{C} 17.7, 22.8, 25.7, 26.1, 40.7 and 79.1).

The HMBC correlations of 1 are illustrated in Fig. 2 and tabulated in Table 1. The correlations between δ_{H} 6.93 with quaternary sp^2 carbon δ_{C} 124.7 and oxyaryl sp^2 carbon at δ_{C} 139.7 together with correlations showed by proton δ_{H} 6.86 with another oxyaryl sp^2 carbon at δ_{C} 145.1 confirmed the location of δ_{H} 6.93 and 6.86 at H-5' and H-6' of the B-ring, respectively. The olefinic proton at δ_{H} 5.71 gave 3J HMBC correlations to δ_{C} 124.7 (C-1') and quaternary sp^3 carbon δ_{C} 79.1, thus supporting its position at H-1'' while its COSY correlation with δ_{H} 6.63 established H-2''. The 2J and 3J HMBC correlations observed between the methyl proton at δ_{H} 1.44 with methine sp^2 carbon δ_{C} 130.9 (C-2''), δ_{C} 79.1 (C-3'') and methylene sp^3 carbon δ_{C} 40.7 (C-5'') indicated the methyl attachment to the pyran ring. Another set of HMBC correlations between the methylene protons at δ_{H} 1.77 with δ_{C} 79.1 (C-3'') and methine sp^2 carbon δ_{C} 123.7 supported its connectivity to the pyran and prenyl groups. Compound 1 has a positive Cotton effect at 338 nm ($\Delta\varepsilon + 0.6$) and a negative Cotton effect at 291 nm ($\Delta\varepsilon - 2.0$), thus confirming the stereochemistry of C-2 as *S* [23]. The distinct negative Cotton effect at 273 nm ($\Delta\varepsilon - 0.1$) enabled the assignment of the absolute stereochemistry of C-3'' as *R*. The structure of 1 was thus assigned as shown in Fig. 1. Based on these assignments, this new flavanone was established as malaysianone A.

Six other known compounds were identified as 6-prenyl-3'-methoxyeriodictyol (2) [24], nymphaeol B (3) [25], nymphaeol C (4) [26,27], 6-farnesyl-3',4',5,7-tetrahydroxyflavanone (5) [28], 5,7-dihydroxycoumarin (6) [29] and scopoletin (7) [30]. Compounds 2, 5, and 6 were found for the first time in the genus *Macaranga*.

Prenylated and geranylated flavanones have been reported to possess several biological activities. In this study, four major flavonoids (2–5) were subjected to antiplasmodial and cytotoxicity activities. Biological activity of 1 cannot be tested as it was obtained in small amounts. The dichloromethane crude extract of *M. triloba* was tested for its *in vitro* antiplasmodial activity against a chloroquine sensitive strain of *P. falciparum*

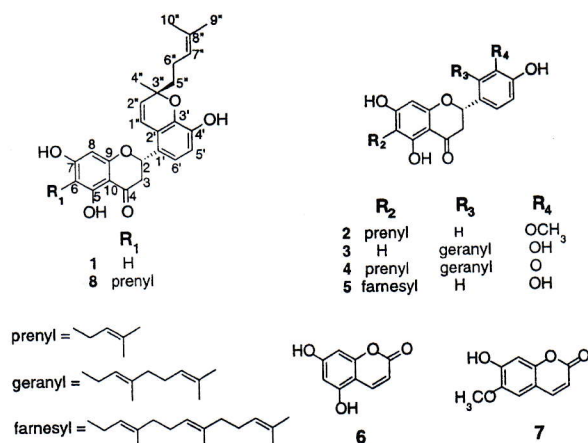


Fig. 1. Chemical constituents from the inflorescences of *Macaranga triloba*.

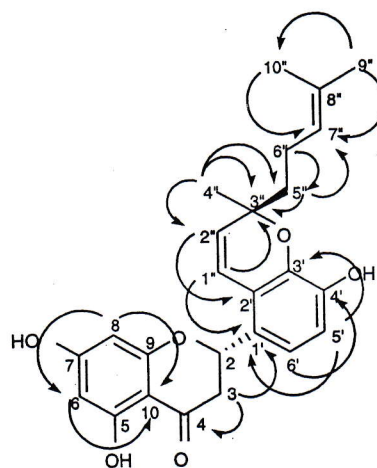


Fig. 2. Representative HMBC correlations for 1.

Table 2
Antimalarial activity of flavonoids of *M. triloba*.

Compounds	IC ₅₀ (μM)
2	n.a.
3	4.02 ± 0.9
4	2.04 ± 0.6
5	0.06 ± 0.8
Chloroquine diphosphate	0.0063 ± 0.5

Each sample was tested in triplicates; the IC₅₀ values were obtained from the average values of percent inhibition within a series of concentration; n.a. – no activity.

(3D7). The IC₅₀ value of the crude extract (IC₅₀ = 2.01 μg/ml) showed a concentration-dependent growth inhibition of the parasite *P. falciparum*, indicating the crude extract as a good potential as an antiplasmodial agent. Subsequently, the flavonoids isolated from the inflorescences of *M. triloba* were screened for their antiplasmodial activity (Table 2). Compound 5 displayed strong antiplasmodial activity with an IC₅₀ value of 0.06 μM, followed by a moderate activity of 4 and 3 with IC₅₀ 2.04 and 4.02 μM, respectively. Compound 2 however, showed no activity towards the *P. falciparum* strain. The presence of adjacent methoxyl and hydroxyl groups [31] or the absence of adjacent hydroxyl groups might contribute to the inactivity of compound 2. The substituents on the flavanone skeleton clearly influenced its antiplasmodial activity which warrants further investigation.

The flavonoids were tested for cytotoxic activity against three cancer cell lines, namely HL-60 (human leukemia), MCF-7 (human breast cancer), and HeLa (human cervical cancer), using 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) dye-reduction assay (Table 3). Compound 5 exhibited very strong activity against HeLa, HL-60 (IC₅₀ values of 1.3, 3.3 respectively) and strong inhibition against MCF-7 cells with IC₅₀ value 5.6 μg/ml. Compounds 2, 3 and 4 demonstrated moderate activity with IC₅₀ of 12.2, 17.0 and 18.2 μg/ml, respectively against HeLa cell lines and weak activity towards MCF-7 with IC₅₀ 22.8, 23.5 and 23.0 μg/ml, respectively. Compounds 2 and 4 were moderately active against HL-60 cell lines with IC₅₀ value of 15.1 and 11.6 μg/ml, respectively, while 3 weakly inhibited the growth of HL-60 cell line with IC₅₀ 21.3 μg/ml. Based on the observation displayed on the activity of compounds 2–5, we expect 1 to show similar biological activity as 3. This is due to the similar structural property of 1 and 3. Compound 5 which contained the farnesyl group located at C-6 was found to display strong antiplasmodial and cytotoxic activities. However, macagigantin, a farnesylated flavonol from *M. gigantea* merely showed moderate activity against P-388 cells (IC₅₀ value of 11.3 μM) [32]. This compound does not possess the adjacent hydroxyl groups on ring B as compound 5. This difference may contribute to the stronger activity displayed by compound 5. We can conclude that the structural criteria reported in this study, showed the importance of the presence of farnesyl (on ring A) and adjacent hydroxyl groups (on ring B) on the biological activity of flavonoids.

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Table 3
Cytotoxic activity of flavonoids of *M. triloba*.

Cell lines Compounds	IC ₅₀ value (μg/ml)		
	HL-60	MCF-7	HeLa
2	15.1 ± 3.5	22.8 ± 0.8	12.2 ± 2.6
3	21.3 ± 3.2	23.5 ± 3.6	17.0 ± 2.8
4	11.6 ± 1.5	23.0 ± 2.4	18.2 ± 1.0
5	3.3 ± 0.6	5.6 ± 0.4	1.3 ± 0.8

IC₅₀ activity (inhibition): very strong: <5 μg/ml; strong: <5–10 μg/ml; moderate: 10–20 μg/ml; weak: 20–100 μg/ml and not active > 100 μg/ml.

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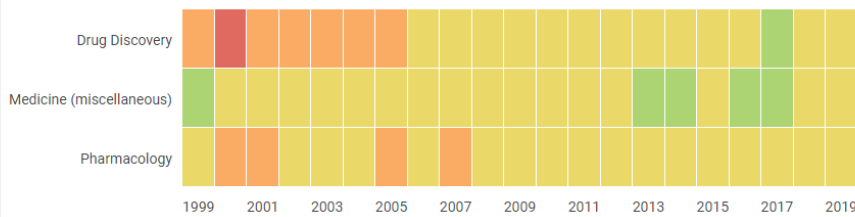
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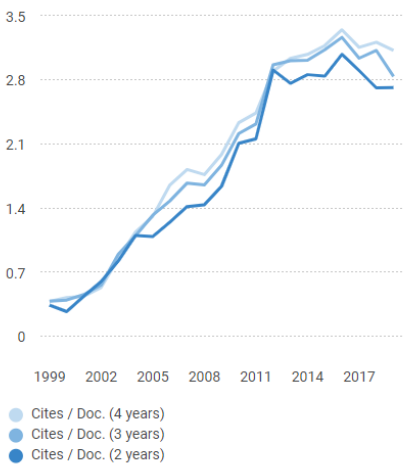
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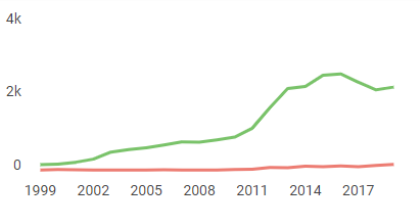
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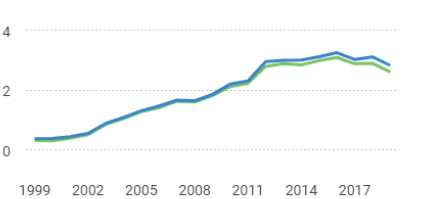
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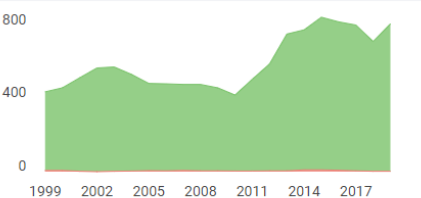
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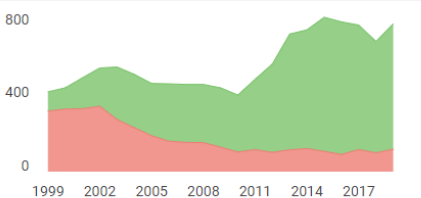
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