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Original Article

Constituents from leaves of *Macaranga hemsleyana*

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ABSTRACT

Objective: To study constituents of the leaves of *Macaranga hemsleyana*, and evaluate their inhibitory effects against NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome activation, and antiproliferative activity.

Methods: The constituents were isolated and purified by column chromatography on MCI gel CHP20P/P120, silica gel, Sephadex LH-20, and HPLC. The structures of compounds were determined by 1D, 2D NMR, and HR-ESI-MS data. The inhibitory effect of compounds on inflammasome activation was determined by lactate dehydrogenase (LDH) procedure. The antiproliferative activity was evaluated using MTT assay.

Results: The study led to the isolation of 23 compounds, including one new compound, identified as (2*Z*)-3-[4-(*β*-*D*-glucopyranosyloxy)-2′-hydroxy-5′-methoxyphenyl]-2-propenoic acid (**1**), together with 22 known compounds recognized as 1,4-dihydro-4-oxo-3-pyridinecarbonitrile (**2**), methyl 4-methoxynicotinate (**3**), 4-methoxynicotinonitrile (**4**), 1-(3-*O*-*β*-*D*-glucopyranosyl-4,5-dihydroxyphenyl)-ethanone (**5**), neoisoastilbin (**6**), isoastilbin (**7**), aromadendrin (**8**), neoastilbin (**9**), astilbin (**10**), quercitrin (**11**), neoschaftoside (**12**), apigenin 6,8-bis-*C*-*α*-*L*-arabinoside (**13**), vitexin (**14**), bergenin (**15**), scopoletin (**16**), glucopyranoside salicyl (**17**), koaburside (**18**), benzyl *β*-*D*-glucoside (**19**), icariside B5 (**20**), roseoside (**21**), loliolide (**22**), and adenosine (**23**). The tested compounds did not show LDH inhibition nor antiproliferative activity.

Conclusion: Compound **1** was a new glycoside. Compounds **2** and **3** were obtained for the first time from natural source. The 22 known compounds constituted of alkaloids (**2**–**4**, **23**), phenolics (**5**, **15**, **17**, **18**), flavonoids (**6**–**14**), coumarin (**16**), benzyl glycoside (**19**), and norsesquiterpenes (**20**–**22**). All the compounds, **1**–**23**, were revealed from *M. hemsleyana* for the first time. This is the initial uncovering of molecules **1**–**10**, **12**, **13**, **17**–**19**, and **23** from the genus *Macaranga*. The isolated compounds, **11**, **14**–**16**, and **20**–**22** established taxonomic classification of *M. hemsleyana* in Euphorbiaceae family. Flavonoids were outstanding as chemosystematic markers of *Macaranga* genus.

1. Introduction

The genus *Macaranga* Thou., consisting of about 300 species native to the tropics of Asia, Africa, Australia and the Pacific territories, is the largest in Euphorbiaceae family (Magadula, 2014; Ngoumfo et al., 2008; Tanjung, Mujahidin, Hakim, Darmawan, & Syah, 2010, 2017). Traditionally, some medicinal species of this genus have been utilized to manage boils, bruises cuts, sores and swellings (Magadula, 2014). Previous phytochemical studies showed that at least 26 *Macaranga* spp. reported about 200 compounds, including flavonoids, stilbenes, alkaloids, terpenoids, coumarins, and tannins, and some of which have indicated anti-inflammatory, antitumor, antioxidant, antiplasmodial and antimicrobial activities (Magadula, 2014; Peresse et al., 2017; Tanjung et al., 2010; Wang et al., 2008, 2009Wang, Huang, Zhao, Chen, & Chen, 2010; Zakaria, Ahmat, Jaafar, & Widyawaruyanti, 2012).

Macaranga hemsleyana Pax et Hoffm. is distributed mainly in Hainan, Guangxi, Yunnan, China (Plant Encyclopedia, 2019). Previous chemical studies on this plant led to the isolation of eight compounds, comprising *β*-sitosterol, stigmast-4-en-3-one,

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canophyllol, stigmast-4-en-3,6-dione, acetylaleuritolic acid, diisobutyl phthalate, dibutyl phthalate, and friedelin, from its leaves and branches (Wang, Liu, Hua, Li, & Chen, 2008, 2010).

In an effort to further unravel the constituents of this plant, the methanolic extract of its leaves was studied, enabling the isolation of one new compound (**1**), and 22 known compounds (**2**–**23**), (Fig. 1). Taking into account the folklore application of *Macaranga* species to manage inflammation, and the antitumor activity displayed by previously isolated compounds (Magadula, 2014; Tanjung et al., 2010), we endeavored to evaluate the anti-inflammatory and anti-tumor effects of selected constituents (**1**–**8**). However, all the tested compounds didn't show considerable activity.

2. Materials and methods

2.1. General

The instruments for recording optical rotations, IR, NMR, ESIMS, HRESI, and the chromatographic equipment and materials, were the same as reported previously (Pu et al., 2020). Optical rotation was measured on a Jasco P-1020 polarimeter (Jasco Corporation, Tokyo, Japan). IR spectrum was measured on a Tenor-27 spectrometer (Thermo Fisher Scientific, Waltham, USA) and UV Spectrum was obtained with the Shimadzu UV2401PC spectrometer (Shimadzu Corporation, Tokyo, Japan). HR-ESI-MS was performed on an Agilent 1100 HPLC/TOF spectrophotometer (Agilent Technologies, Santa Clara, USA). The NMR spectra were recorded on Bruker AM-400 (Bruker Corporation, Switzerland), operating at 400 MHz for ^{1}H and at 100 MHz for ^{13}C, respectively. Coupling constants are expressed in hertz, and chemical shifts are given on a δ (parts per million, $\times 10^{-6}$) scale with tetramethylsilane (TMS) as an internal standard. Semipreparative HPLC was performed on an Agilent 1260 liquid chromatography system equipped with a Zorbax SB-C_{18} column (9.4 mm × 250 mm, 5 μm). Column chromatography (CC) was run on silica gel (200–300 mesh; Qingdao Marine Chemical Factory, Qingdao, China), 75–100 μm MCI-gel CHP20P (Mitsubishi Chemical Co., Ltd., Tokyo, Japan), and Sephadex LH-20 (Pharmacia Biotech, Uppsala, Sweden). TLC was performed on silica gel GF254 (SiO_2; Qingdao Haiyang Chemical Factory, Qingdao, China), and spots were visualized by heating silica gel plates sprayed with 10% H_2SO_4 in EtOH. All solvents (Kunming Teng Branch Technology Co., Ltd., Kunming, China) used for isolation were of analytical grade.

2.2. Plant materials

The leaves of *M. hemsleyana* were collected from Honghe County (Latitude: 23° 09′ 32.30″ N; Longitude: 102° 44′ 41.46″ E), Yunnan Province, and identified by Prof. Xiwen Li of Kunming Institute of Botany, Chinese Academy of Sciences. The materials (Voucher number XWL201303) were kept at the Key Laboratory of Medicinal Chemistry for Natural Resource, Ministry of Education, Yunnan Research & Development Center for Natural Products, School of Chemical Science and Technology, Yunnan University, Kunming, China.

2.3. Extraction and isolation

The air-dried powdered leaves (1.5 kg) of *M. hemsleyana* were refluxed in MeOH (3 × 48 h, each). The MeOH extract was evaporated under reduced pressure to produce a residue (356 g) which was suspended in water then partitioned with petroleum ether, EtOAc, and BuOH. The BuOH extract (75 g) was subjected to MCI gel (5.4 cm × 40 cm) CC, eluted with H_2O/MeOH (10:90–90:10, volume percent) to produce five fractions, Frs. A–E.

Fr. C (14 g) was chromatographed over silica gel (200–300 mesh), eluted with $CHCl_3$/MeOH/H_2O (95:5:0, 90:10:0, 90:10:1, 85:15:1, 80:20:2, 75:25:2, 70:30:5, volume percent), to give five fractions Frs. C1−C5. Fr. C3 (0.95 g) was further purified by preparative HPLC with an isocratic mobile phase system of CH_3CN/H_2O (30:70, volume percent) to afford **11** (t_R = 27 min, 13.8 mg). Fr. C5 (6 g) was applied to MCI gel CHP20P to give rise to four fractions, Frs. C5a–C5d. Frs. C5a (3 g), C5b (1 g) and C5c (1.2 g) were separately purified by preparative HPLC as described above using CH_3CN/H_2O to furnish **18** (t_R = 39 min, 12 mg), **19** (t_R = 44 min, 10 mg), **20** (t_R = 50 min, 7 mg), and **21** (t_R = 52 min, 5 mg) from Fr. C5a (13:87, volume percent), **12** (t_R = 69 min, 16 mg) and **13** (t_R = 73 min, 14 mg) from Fr. C5b (14:86, volume percent), **3** (t_R = 22 min, 3 mg) from Fr. C5c (3:97, volume percent).

Fr. D (22 g) was subjected to Sephadex LH-20 CC (4.5 cm × 130 cm), eluted with $CHCl_3$/MeOH (1:1, volume percent) to yield seven sub-fractions, Frs. D1–D7. Fr. D6 (12 g) was applied to MCI column, eluted as mentioned above to afford two sub-fractions Fr. D6a and Fr. D6b. Fr. D6a (4 g) was chromatographed over silica gel (200–300 mesh), eluted as aforementioned to bring forth Fr. D6a1 (430 mg) and Fr. D6a2 (2 g). Fr. D6a1 (430 mg) and D6a2 (2 g) were purified by HPLC with an isocratic mobile phase system of CH_3CN/H_2O to afford **15** (t_R = 37 min, 15.6 mg) from Fr. D6a1 (10:90, volume percent), **5** (t_R = 41 min, 15.6 mg), **2** (t_R = 15 min, 98.6 mg), **23** (t_R = 24 min, 6 mg), **17** (t_R = 37 min, 5 mg), and **1** (t_R = 44 min, 15.6 mg) from Fr. D6a2 (3:97, volume percent).

Fr. D6b (6 g) was chromatographed over silica gel (200–300 mesh), eluted as presented above to furnish three sub-fractions, Frs. D6b1–D6b3. Fr. D6b2 (1.8 g) was purified by preparative HPLC with an isocratic mobile phase system of CH_3CN/H_2O (16:84, volume percent) to afford **14** (t_R = 74 min, 22.7 mg).

The EtOAc extract (50 g) was applied to silica gel (200–00 mesh), eluted with PE/EtOAc/ $(CH_3)_2CO$ (100:0:0, 90:10:0, 0:100:0, 0:0:100, volume percent), to give three fractions, Frs. K–M. Fr. K (1.7 g) was applied to silica gel (200–300 mesh), eluted with PE/$(CH_3)_2CO$ (20:1, 0:1, volume percent), to afford three fractions, Frs. K1–K3. Fr. K3 (1.9 g) was purified by preparative HPLC as aforementioned; CH_3CN/H_2O (25:75, volume percent) to afford **4** (t_R = 20 min, 20.2 mg), **16** (t_R = 30 min, 15.4 mg) and **22** (t_R = 35 min, 9.0 mg).

Fr. L (8 g) was applied to silica gel (200–300 mesh), eluted with PE/$(CH_3)_2CO$ (20:1, 0:1, volume percent), to afford four fractions, Frs. L1–L4. Fr. L4 (3.9 g) was purified by preparative HPLC with an isocratic mobile phase system of CH_3CN/H_2O (25:75, volume percent) to afford **9** (t_R = 31 min, 16.0 mg), **10** (t_R = 39 min, 37.1 mg), **6** (t_R = 41 min, 26.8 mg), **7** (t_R = 43 min, 9.0 mg) and **8** (t_R = 47 min, 132.6 mg).

2.4. Acidic hydrolysis of compound *1* and GC-analysis

Compound **1** was subjected to acidic hydrolysis according to a procedure outlined previously (Kaunda & Zhang, 2020). The compound (2 mg) was dissolved in 5% HCl (1 mL) and heated (90 °C) for 2 h. HCl was then removed by evaporation in vacuum. The reaction mixture was diluted with H_2O and extracted with EtOAc. The aqueous layer was neutralized with 0.1 mol/L NaOH and essentially dried to give the monosaccharide. The sugar-pyridine (2 mL) solution was added into *L*-cysteine methyl ester hydrochloride (about 1.5 mg) and the reaction mixture kept at 60 °C for 1 h before addition of trimethylsilylimidazole (2 mL). The reaction mixture was further kept at 60 °C for 1 h, before stopping the reaction and immediately submitting it for GC analysis, run on Hewlett Packard (HP) 5890 series II gas chromatography equipped with flame ionization detector (FID) and thermal conductivity detector

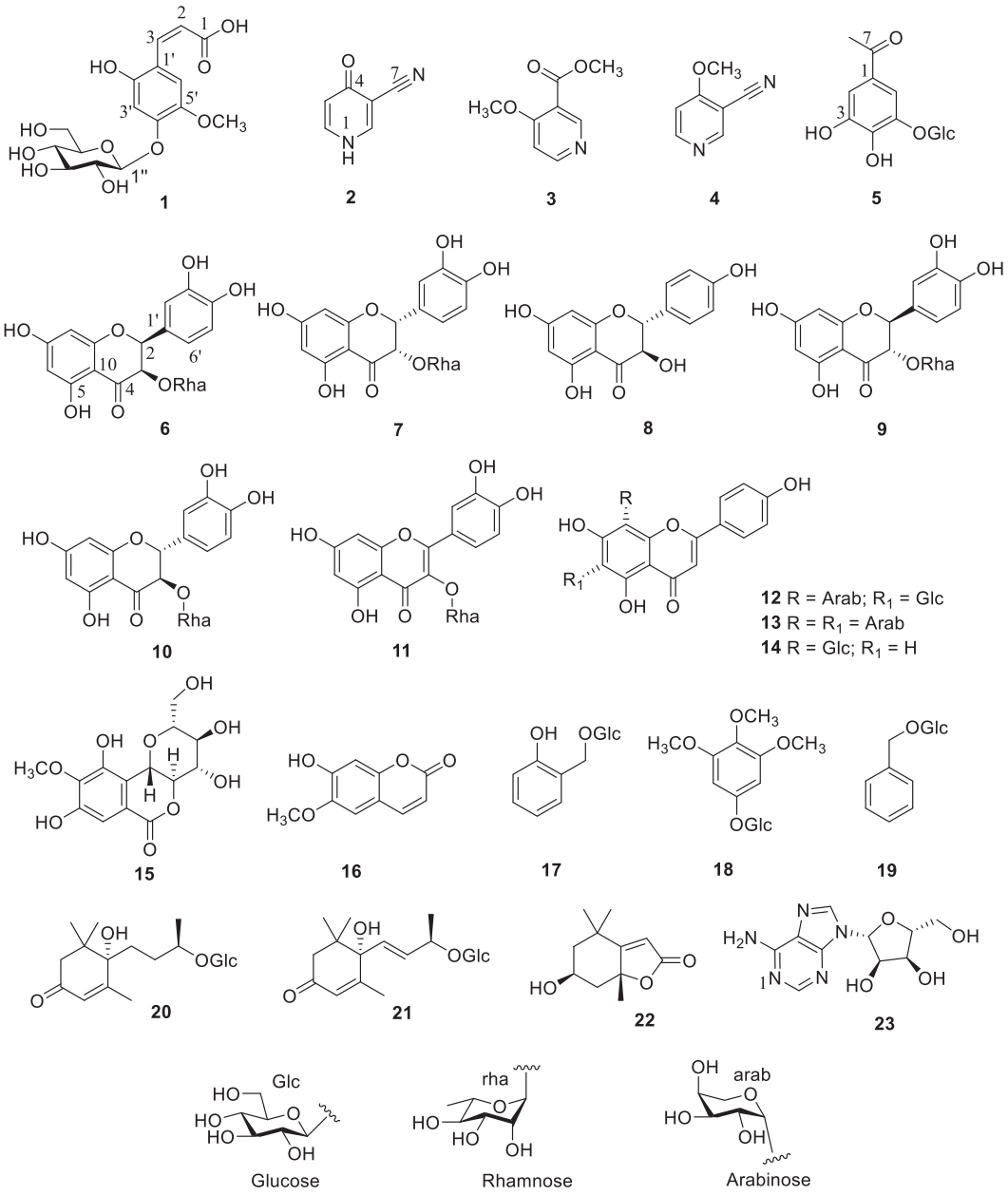

Fig. 1. Chemical structures of compounds **1**–**23** isolated from leaves of *M. hemsleyana*.

(TCD). The column was HP-5, column temperature: 280 °C, increasing at the rate of 3 °C/min; carrier gas: N_2 (1.5 mL/min); injector and detector temperature: 250 °C; injection volume: 1.0 L; and split ratio: 1/100. The retention time of the sample was compared with that of the derivative of authentic sugar, under the same condition. The sugar moiety was determined to be *D*-glucose (t_R = 28.092 min) by matching with the standard, *D*-glucose (t_R = 29.198 min).

2.5. NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome activation assay

The inhibitory effects of compounds **1**–**8** against NLRP3 inflammasome activation was carried out according to a procedure hitherto reported by our research group (Pu et al., 2020). J774A.1 cells were primed with 50 ng/mL lipopolysaccharide (LPS) for 3 h, pretreated with the test compounds or MCC950, and eventually activated by the NLRP3 stimulus nigericin (10 μmol/L) for 1 h or ATP (2.5 mmol/L) for 45 min. The supernatant was collected for lactate dehydrogenase (LDH) release and IL-1β identification. The LDH release level was determined according to the manufacturer's instructions (Beyotime Biotechnology, Shanghai, China). The IL-1β levels were detected by a mouse IL-1β/IL-1F2 DuoSet ELISA kit (R&D Incorporation, USA) following the manufacturer's instructions. Western blot assays were used to detect the supernatant IL-1β and Casp-1 levels and the RIPA-treated lysates, as well as NLRP3, pro-Casp-1, pro-IL-1β, ASC, and β-actin.

2.6. Anti-tumor activity

The antitumor activity of compounds **1**–**5** was carried out as formerly divulged by our research group (Pu et al., 2018). Human colon adenocarcinoma cell line HCT-116, and breast cancer cell line MCF-7, were purchased from the American Type Culture Collection

(ATCC). Both the HCT-116 and MCF-7 cells were cultured in Dulbecco's modified eagle medium (high glucose media), supplemented with 10% FBS, 10 mg/mL streptomycin and 100 U/mL penicillin (complete medium) in a humidified atmosphere at 37 °C and 5% CO_2. To explore the anti-tumor effect of the compounds in cancer cells, HCT-116 and MCF-7 cells were seeded at (1×10^4) per well in 96-well plates, grown overnight, and then different compounds (0, 4, 8, 16, 32 and 64 μmol/L) were added into each well for 24 h. After that, 10 μL of CCK-8 solution was added to each well, and the plates were incubated for 1.5 h. The absorbance was finally determined at 450 nm by a microplate reader. The IC_{50} values were calculated from concentration–response curves using Graphpad Prism software.

3. Results

3.1. Structure elucidation

Phytochemical investigation of *M. hemsleyana* led to the isolation of one new glycoside, (2*Z*)-3-[4-(*β*-*D*-glucopyranosyloxy)-2′-hydroxy-5′-methoxyphenyl]-2-propenoic acid (**1**), together with twenty-two known compounds (**2**–**23**). The structure of **1** was elucidated by detailed spectroscopic analysis and chemical derivations. The known compounds (Fig. 1) were identified as 1,4-dihydro-4-oxo-3-pyridinecarbonitrile (**2**) (Boschelli & Gomes, 2009), methyl 4-methoxynicotinate (**3**) (Ross, 1966), 4-methoxynicotinonitrile (**4**) (Yakushijin Sugiyama, & Murata, 1980), 1-(3-*O*-*β*-*D*-glucopyranosyl-4,5-dihydroxyphenyl)-etha none (**5**) (Xiao, Xuan, Xu, Bai, & Zhong, 2002), neoisoastilbin (**6**), isoastilbin (**7**) (Kasai Hirono, Chou, Tanaka, & Chen, 1988), aromadendrin (**8**) (Costa et al., 2021), neoastilbin (**9**), astilbin (**10**), quercitrin (**11**) (Kasai Hirono, Chou, Tanaka, & Chen, 1988), neoschaftoside (**12**) (Batista & Gomes, 1993), apigenin 6,8-bis-*C*-α-*L*-arabinoside (**13**) (Wang, Zhang, Li, Wang, & Ma, 2019), vitexin (**14**) (Vu et al., 2021), bergenin (**15**) (Ramaiah et al., 1972), scopoletin (**16**) (Yang et al., 2014), glucopyranoside salicyl (**17**) (Cho, Yang, Kim, Kim, & Sung, 2014), koaburside (**18**) (Sahakitpichan et al., 2014), benzyl *β*-*D*-glucoside (**19**) (Elshamy et al., 2021), icariside B5 (**20**) (Matsunami et al., 2009), roseoside (**21**) (Vu et al., 2021), loliolide (**22**) (Jang et al., 2004), adenosine (**23**) (Jamie, David, Mathew, Keth, & Colin, 2014), by comparing their 1D NMR data with those reported in literature (Tables S1–S6).

Macahemsloside A (**1**): Yellow amorphous powder; [α]28 D – 30.1 (*c* 0.1, MeOH); UV (MeOH) λ_{max} (log ε) 220 (0.26), 267 (0.08), 308 (0.08), 198 (0.58), 225 (0.27), 288 (0.11), 335 (0.11) nm; IR (KBr) ν_{max} 3 748, 3 711, 3 399, 2 925, 2 260, 2 128, 1 713, 1 651, 1 566, 1 514, 1 453, 1 425, 1 386, 1 280, 1 171, 1 160, 1 074, 1 046, 1 024, 930 cm^{-1}; ECD (MeOH) λ_{max} (Δε) 203 (−1.23), 269 (+0.57); ^1H and ^{13}C NMR (400/100 MHz, CD_3OD) data, see Table 1; HRESIMS *m*/*z*: 371.0987 $[M - H]^-$ (calcd. for $C_{16}H_{19}O_{10}$, 371.098 4). It was furnished as a yellowish amorphous powder, with a molecular formula $C_{16}H_{20}O_{10}$, according to a deprotonated molecule peak at *m*/*z* 371.098 7 $[M - H]^-$ (calcd. for $C_{16}H_{19}O_{10}$, 371.098 4). The IR spectrum of **1** expressed the presence of hydroxy (3 399 cm^{-1}) and alkene (1 651 cm^{-1}) functionalities. Its ^1H NMR spectrum (Table 1) displayed two-singlet aromatic protons at δ_H 7.31 (1H, s) and 7.16 (1H, s), two olefinic protons at δ_H 7.97 (1H, d, *J* = 9.5 Hz) and 6.33 (1H, d, *J* = 9.5 Hz), one methoxyl at δ_H 3.82 (1H, s), indicating the presence of a feruloyl moiety possessing a *cis* configuration (*J* value being 9.5 Hz) (Park & Tomohiko, 2011), and one anomeric proton signal at δ_H 5.09 (1H, d, *J* = 6.4 Hz), denoting the existence of a sugar moiety whose chemical shift and coupling constant suggested a *β*-configuration for the anomeric carbon (Roslund, Taehtinen, Niemitz, & Sjoeholm, 2008). The ^{13}C and DEPT NMR spectra of **1** (Table 1) showed a total of 16 signals, including one carboxylic group (δ_C 161.0), two olefinics (δ_C 144.7 and 113.8), two methines (δ_C 110.1 and 103.4), four quaternary carbons [δ_C 112.7, three *O*-bearing ones (δ_C 150.3, 149.4 and 146.4)], one methoxyl (δ_C 56.5), and 6 signals (δ_C 100.0, 73.4, 77.1, 70.0, 77.5, 61.9), belonging to a hexosyl sugar unit, determined to be a *D*-glucosyl moiety according to acidic hydrolysis, followed by GC analysis of the corresponding trimethylsilylated *L*-cysteine adduct. The ^1H–^1H COSY of δ_H 6.33 (H-2)/7.97 (H-3) in tandem with their HMBC correlations with δ_C 161.0 (C-1), revealed the presence of a propenoic acid moiety linked to the aromatic ring on the basis of HMBC correlations from δ_H 6.33 to δ_C 112.7 (C-1′), and δ_H 7.97 to δ_C 112.7, 149.4 (C-2′) and 110.1 (C-6′) (Fig. 2). The methoxyl at δ_H 3.82 was attached to δ_C 146.4 (C-5′) owing to the HMBC cross peaks observed from δ_H 3.82 to δ_C 146.4; This was further corroborated by the ROESY correlations of δ_H 3.82/7.31 (H-6′). Finally, the C-4′ glucosylation was determined based on the HMBC correlation from H-1″ (δ_H 5.09) to C-4′ (δ_C 150.3), and this was substantiated by the ROESY correlation of H-1″ (δ_H 5.09)/H-3′ (δ_H 7.16). According to the above pieces of evidence, compound **1** was elucidated as (2*Z*)-3-[4-(*β*-*D*-glucopyranosyloxy)-2′-hydroxy-5′-methoxyphenyl]-2-propenoic acid.

Table 1
^1H (400 MHz) and ^{13}C (100 MHz) NMR data of **1** in DMSO d_6 (δ in ppm).

Positions	δ_H (*J* in Hz)	δ_C (*J* in Hz)
1		161.0
2	6.33 (1H, d, 9.5)	113.8
3	7.97 (1H, d, 9.5)	144.7
1′		112.7
2′		149.4
3′	7.16 (1H, s)	103.4
4′		150.3
5′		146.4
6′	7.31 (1H, s)	110.1
1″	5.09 (1H, d, 6.4)	100.0
2″	3.29 [a]	73.4
3″	3.29 [a]	77.1
4″	3.16 (1H, m)	70.0
5″	3.44 [a]	77.5
6″	3.69 (1H, d, 9.9); 3.44 [a]	61.9
OCH_3	3.82 (1H, s)	56.5

[a] Signals overlapped.

3.2. Biological activity

In view of the traditional application of *Macaranga* species as anti-inflammatory agents (Magadula, 2014), as well as anti-tumor effects displayed by its previously isolated constituents (Tanjung et al., 2010), some selected compounds (**1**–**8**) were evaluated for their inhibitory effects against the NLRP3 inflammasome (Table S7), and **1**–**5** were further submitted for anti-tumor activity against breast cancer MCF-7 and human colon cancer HCT-116 cell lines (Table S8). All the tested compounds did not show NLRP3 inflammasome inhibition nor antiproliferative activity.

4. Discussion

The compounds isolated from *M. hemsleyana* leaves comprise phenolics (**1**, **15**, **17**, **18**), alkaloids (**2**–**4**, **23**), flavonoids [flavanones (**6**–**9**), flavonol (**11**), flavones (**12**–**14**)], coumarin (**16**), and norsesquiterpenes (**20**–**22**). All the compounds (**1**–**23**) were obtained from *M. hemsleyana* for the first time; Compounds **2**–**10**, **12**, **13**, **17**–**19**, and **23** were previously undescribed in the genus *Macaranga*. Interestingly, this is the first-time isolation of a new glycoside (**1**) from this genus.

Euphorbiaceae family is characterized by alkaloids, flavonoids and terpenes, as the primary classes of chemical constituents

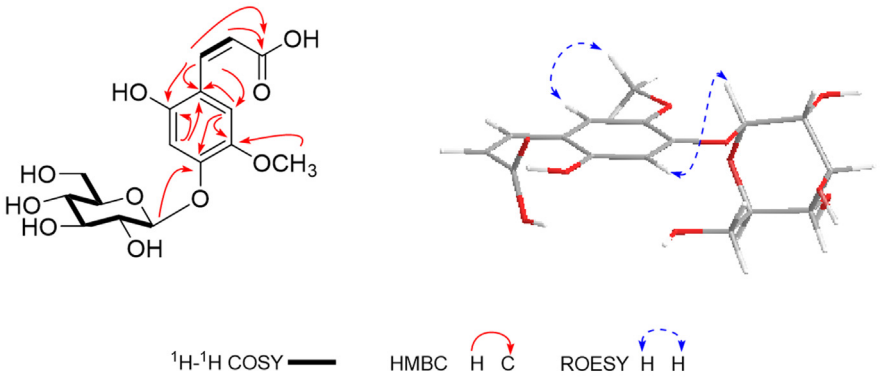

Fig. 2. Key HMBC, ^{1}H–^{1}H COSY and ROESY correlations of **1**.

(Magadula, 2014; Peresse et al., 2017). Thus, the alkaloids (**2**–**3**, **23**), flavonoids (**6**–**14**), and norsesquiterpenes (**20**–**22**) ratified the taxonomic classification of *M. hemsleyana* within Euphorbiaceae family.

As for compound **1**, there have been only two reports on feruloyl moieties from the family Euphorbiaceae, including *N-trans*-feruloyloctopamide from *Antidesma hainanensis* Merr., (Cuong et al., 2016) and *N-trans*-feruloyltyramine from *A. acidum* (Kaennakam, Sichaem, Siripong, & Santi, 2013). Therefore, the unveiling of a glycoside with a feruloyl moiety (**1**) in *Macaranga* genus is unprecedented and contributes to the taxonomic classification of *M. hemsleyana,* as well as *Macaranga* genus in Euphorbiaceae family.

Previously isolated compounds from *Macaranga* genus, notably quercitrin (**11**) (Huonga et al., 2019) and vitexin (**14**) from *M. indica* (Vu et al., 2021), bergenin (**15**) from *M. peltata* (Ramaiah et al., 1972), scopoletin (**16**) from *M. kurzii* (Yang et al., 2014), *M. gigantifolia* (Darmawan, Kosela, Kardono, & Syah, 2012), *M. barteri* (Ngoumfo et al., 2008), *M. triloba* (Jang et al., 2004), and *M. denticulata* (Sutthivaiyakit, Unganont, Sutthivaiyakit, & Suksamrarn, 2002), icariside B5 (**20**) from *M. tanarius* (Matsunami et al., 2009), roseoside (**21**) from *M. indica* (Vu et al., 2021) and *M. tanarius* (Matsunami et al., 2009), and loliolide (**22**) from *M. triloba* (Jang et al., 2004), hereupon confirm that *M. hemsleyana* possesses identical constituents as other species of this genus.

In view of the above enumerations, flavonoids represent key chemosystematic markers of the genus *Macaranga*.

5. Conclusion

From the methanolic extract of *M. hemsleyana* leaves, a total of 23 compounds, including one new glycoside (**1**) and 22 known compounds (**2**–**23**) were isolated. Compounds **1**–**8** were tested for their ability to inhibit NLRP3 inflammasome activation. Additionally, the anti-tumor potency of compounds **1**–**5** were investigated against MCF-7 and HCT-116 cancer cell lines. None of the compounds showed considerable activity. The isolated compounds, **11**, **14**–**16**, and **20**–**22** established the taxonomic classification of *M. hemsleyana* in Euphorbiaceae family. Consistently, flavonoids were outstandingly the predominant chemosystematic markers of the *Macaranga* genus.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chmed.2023.03.006.

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