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Activity of Cytotoxic Flavanoids against a P-388 Murine Leukemia Cell Line from the Stem Bark of *Aglaia elliptica* (Meliaceae)

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Abstract

Two mixtures of flavanoid compounds (**1** and **2**), a mixture of catechin (**1a**) and epicatechin (**1b**), and a mixture of gallocatechin (**2a**) and epigallocatechin (**2b**), were isolated from the active fraction of the stem bark of *Aglaia elliptica* methanol extract. The chemical structure of the compounds was identified with spectroscopic data, including UV, IR, NMR (^{1}H, ^{13}C, DEPT 135°, HMQC, HMBC, ^{1}H-^{1}H COSY), and MS, and additionally compared with previously reported spectral data. All compounds were evaluated for their cytotoxic effects against P-388 murine leukemia cells. Compound **2** showed cytotoxicity against the P-388 murine leukemia cell, with an IC_{50} value of 7.79 µg/mL, but compound **1** was found not to be active (more than 100 µg/mL).

Abstrak

Aktivitas Sitotoksik Senyawa Flavanoid Terhadap Sel Murine Leukemia P-388 dari Kulit Batang *Aglaia elliptica* (Meliaceae). Dua campuran senyawa flavanoid (1 dan 2), suatu campuran dari katekin (1a) dan epikatekin (1b) serta campuran dari gallokatekin (2a) dan epigallokatekin (2b) telah diisolasi dari kulit batang *Aglaia elliptica*. Struktur kimia senyawa tersebut diidentifikasi berdasarkan data spektroskopi, meliputi UV, IR, NMR (^{1}H, ^{13}C, DEPT 135°, HMQC, HMBC, ^{1}H-^{1}H COSY) dan MS, serta tambahan dengan perbandingan data spektra yang diperoleh sebelumnya. Semua senyawa dievaluasi aktivitas sitotoksiknya terhadap sel murin leukemia P-388. Senyawa 2 menunjukkan aktivitas sitotoksik terhadap sel murin leukemia P-388 dengan nilai IC_{50} 7,79 µg/mL, sedangkan senyawa 1 tidak memberikan aktivitas sitotoksik (IC_{50} lebih besar dari 100 µg/mL).

Keywords: Aglaia elliptica, cytotoxic activity, flavanoid, Meliaceae, sel murine leukemia P-388

Introduction

Aglaia is distributed mainly in tropical rainforests of the Indo-Malaysian region [1]. The genus *Aglaia* (Meliaceae) is the largest genus of the Meliaceae family, comprising more than 150 species, approximately 65 of which grow in Indonesia [1,2]. Extracts from the *Aglaia* genus have been used traditionally for treating certain diseases. In Thailand, *Aglaia odorata* is used to treat heart disease, bruises, traumatic injury, febrifuge, and toxins, by causing vomiting [3]. Previous phytochemical studies of this genus revealed the presence of a compound with interesting biological activity, including antifungal and antitumor sesquiter penoids [4,5], cytotoxic and anti-inflammatory diterpe noids [3,6], cytotoxic and anti-retroviral triterpenoids [7-10], cytotoxic steroids [4], cytotoxic and anti-inflammatory alkaloids [10,11,14], and cytotoxic rocaglamides [13,14].

A. elliptica is a tree, mainly distributed in the northern part of Sulawesi in Indonesia [15]. Previous phytochemical study of this plant reported the presence of diamide and cycloartane-type triterpenoid from the leaves [17] and novel cytotoxic 1*H*-cyclopenta[*b*]benzo furan from the fruits [16]. In the present paper, we elucidate the isolation and structure of the mixture of flavonoid compounds, catechin (**1a**), epicatechin (**1b**), gallocatechin (**2a**), and epigallocatechin (**2b**), together with their cytotoxic activity against murine leukemia cells.

Materials and Methods

Equipment. UV spectra were measured using a Shimadzu UV-160A ultraviolet-visible spectrometer, with MeOH (Kyoto, Japan). The IR spectra were recorded on a Perkin-Elmer 1760X FT-IR in KBr (Waltham, MA, USA). The mass spectra were recorded with a Synapt G2 mass spectrometer instrument (Waters, Milford, MA, USA). NMR data were recorded on a JEOL ECZ-600 spectrometer at 600 MHz for ^{1}H and 150 MHz for ^{13}C (Tokyo, Japan), using TMS as an internal standard. Column chromatography was conducted on silica gel 60 (Kanto Chemical Co., Inc., Japan). TLC plates were precoated with silica gel GF_{254} (Merck, 0.25 mm), and detection was achieved by spraying with 10% H_2SO_4 in EtOH, followed by heating.

Plant material. The stem bark of *A. elliptica* was collected in Bogor Botanical Garden, Bogor, West Java Province, Indonesia, in June 2015. The plant was identified by the staff of the Bogoriense Herbarium, Bogor, and a voucher specimen (No. Bo-1294562) was deposited at the Herbarium.

Plant extraction. Dried ground stem bark (2.3 kg) of *A. elliptica* was extracted with methanol (12 L) at room temperature for 3 days. After removal of the solvent under vacuum, the viscous concentrate of MeOH extract (321.5 g) was first suspended in H_2O and then partitioned successively with *n*-hexane, EtOAc, and *n*-butanol. Evaporation resulted in the crude extracts of *n*-hexane (22.6 g), EtOAc (31.4 g), and *n*-butanol (34.5 g), respectively. The *n*-hexane, EtOAc, and *n*-butanol extracts exhibited cytotoxic activity against P-388 murine leukemia cells, with IC_{50} values of 67.72, 32.69, and >100 µg/mL, respectively. The EtOAc soluble fraction (20 g) was fractionated by column chromatography on silica gel using a gradient *n*-hexane and EtOAc to give fractions A–E, combined according to the TLC results. Fraction D (1.73 g) was subjected to column chromatography over silica gel, using a gradient mixture of $CHCl_3$:Me_2CO (10:0–1:1) as eluting solvents to afford six subfractions (D1–D6). Subfraction D4 (460 mg) was chromatographed on a column of silica gel, eluted with $CHCl_3$–MeOH (10:0–4:1), to give five subfractions (D4A–D4E). Subfraction D4D was chromatographed on preparative TLC, eluted with $CHCl_3$–MeOH (8.5:1.5), to give compound **1** (47.5 mg). Subfraction D5 (600 mg) was chromatographed on a column of silica gel, eluted with $CHCl_3$–MeOH (10:0–7:3), to give five subfractions (D5A–D5E). Subfraction D5D was chromatographed on a column of silica gel, eluted with $CHCl_3$–MeOH (10:0–1:1), to give compound **2** (127 mg).

Determination of cytotoxic activities [8,11,20]. The P-388 cells were seeded into 96-well plates at an initial cell density of approximately 3 x 10^4 cells cm^{-3}. After 24 h of incubation for cell attachment and growth, varying concentrations of samples were added. The compounds added were first dissolved in DMSO at the required concentration. Six subsequent desirable concentrations were prepared using phosphoric buffer solution (PBS, pH=7.30–7.65). Control wells received only DMSO. The assay was terminated after a 48 h incubation period by adding MTT reagent (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide, also named thiazol blue), and the incubation was continued for another 4 h, in which the MTT-stop solution containing sodium dodecyl sulphate (SDS) was added, and another 24 h incubation was conducted. Optical density was read using a micro plate reader at 550 nm. IC_{50} values were taken from the plotted graph of the percentage of live cells compared to control (%) receiving only PBS and DMSO, versus the tested concentration of compounds (μM). The IC_{50} value is the concentration required for 50% growth inhibition. Each assay and analysis was run in triplicate and averaged.

Results and Discussion

The stem bark of *A. elliptica* was ground and successively extracted with MeOH and partitioned with *n*-hexane, ethyl acetate, and *n*-butanol. All the extracts were evaluated for cytotoxic activity against P-388 murine leukemia cells. The ethyl acetate extracts exhibited the strongest cytotoxic activity against P-388 murine leukemia cells, with IC_{50} values of 32.69 µg/mL. Subsequent phytochemical analysis was therefore focused on the EtOAc extract of *A. elliptica*. The EtOAc extract was chromatographed over a column packed with silica gel 60 by gradient elution. The fractions were repeatedly subjected to normal-phase column chromatography to afford flavonoid compounds **1** and **2** (Figure 1).

Mixture of catechin and epicatechin (**1**), yellow amorphous powder, m.p. 176–177 °C, UV (MeOH) λ_{max} nm (log ε) 275 (3.93), IR (KBr) ν_{maks} (cm^{-1}) 3330 (O-H stretch), 1572 (C=C ring stretch), 1146 (asymmetric C-O-C stretch), 1051 (symmetric C-O-C stretch), 827 (substituted benzene ring). ^{1}H-NMR (CD_3OD, 600 MHz), see Table 1; ^{13}C-NMR (CD_3OD, 125 MHz), see Table 1; HR-TOFMS (positive ion mode) *m/z* 291.0878 $[M+H]^+$ (calcd. for $C_{15}H_{14}O_6$, *m/z* 290.0790).

Mixture of gallocatechin and epigallocatechin (**2**), brown amorphous powder, m.p. 198-202 °C, UV (MeOH) λ_{max} nm (log ε) 277 (4.07), IR (KBr) ν_{maks} (cm^{-1}) 3325 (O-H stretch), 1577 (C=C ring stretch), 1144 (asymmetric C-O-C stretch), 1062 (symmetric C-O-C stretch), 829 (substituted benzene ring). ^{1}H-NMR (CD_3OD, 600 MHz), see Table 1; ^{13}C-NMR (CD_3OD,

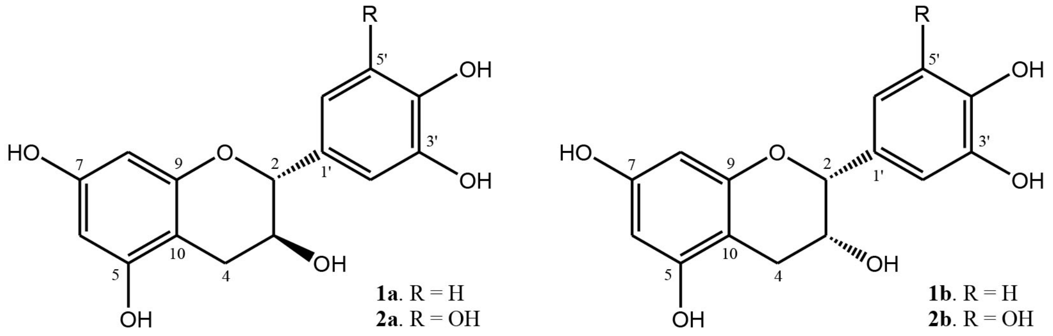

Figure 1. Structures of Compounds 1 and 2

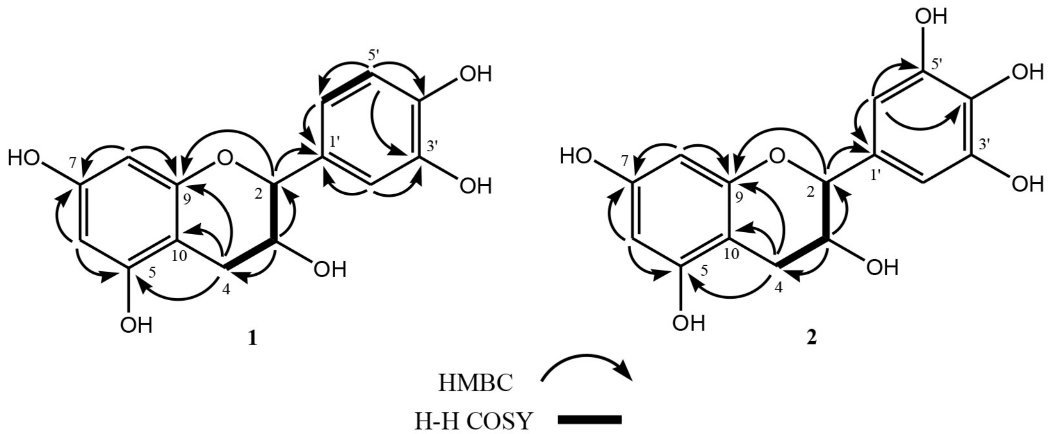

Figure 2. Selected HMBC and ^{1}H-^{1}H COSY Correlations for Compounds 1 and 2

125 MHz), see Table 1; HR-TOFMS (positive ion mode) *m/z* 307.0825 $[M+H]^+$ (calcd. for $C_{15}H_{14}O_7$, *m/z* 306.0740).

Compounds **1a** and **1b** were isolated as a mixture, which was obtained as a yellow powder. On the basis of their ^{1}H NMR and ^{13}C NMR spectra, the ratio of compounds **1a** and **1b** was deduced as 3:5 in the mixture. Most of the signals were well-resolved for both compounds. The HR-TOFMS spectrum showed $[M+H]^+$ *m/z* 291.0878 (calcd. *m/z* 290.0790), which corresponded to the molecular formula of $C_{15}H_{14}O_6$ and thus required nine degrees of unsaturation, originating from six C *sp*^{2}, and the remaining tricyclic flavanoids. UV spectra in MeOH showed the presence of a flavan-3-ol skeleton [18]. The IR spectra showed absorption peaks at 3330, 1572, 1146, 1051, and 827 cm^{-1}, suggesting the presence of hydroxyl groups, C=C olefin rings, symmetric and asymmetric C-O-C, and a substituted benzene ring, respectively. The ^{1}H-NMR of the **1a** (CD_3OD 600 MHz) spectrum showed the presence of five olefinic methine groups, resonating at δ_H 5.77, 5.76 (each 1H, d, J = 2.1 Hz, H-6, H-8), 6.83 (1H, d, J = 1.7, H-2), 6.61 (1H, d, J = 8.6 Hz, H-5), and 6.65 (1H, dd, J = 1.7, 8.6 Hz, H-6), two oxymethine groups at δ_H 4.41 (1H, d, J = 7.8 Hz, H-2) and 3.83 (1H, m, H-3), and one methylene group at δ_H 2.70 (1H, dd, J = 8.3, 16.3 Hz, H-4a) and 2.37 (1H, dd, J = 5.5, 16.3 Hz, H-4b). Two *meta*-protons at ring A, evidenced by J constant coupling of H-6 and H-8 (2.1 Hz) and HMBC correlations between H-6 and C-5, H-7 and C-9 (Figure 2). Benzene trisubstitution in ring B was observed at δ_H 6.83 (1H, d, J = 1.7, H-2), 6.61 (1H, d, J = 8.6 Hz, H-5), and 6.65 (1H, dd, J = 1.7, 8.6 Hz, H-6), and ^{1}H-^{1}H COSY cross peak H-5 /H-6 (Figure 2). The flavan-3-ol skeleton in ring C was evidenced by ^{1}H-^{1}H COSY cross peak H-2/H-3/H-4 also from the HMBC correlation from H-2 to C-9 and C-1 , H-3 to C-2 and C-4, and H-4 to C-5, C-9, and C-10. The ^{13}C NMR of **1a** (CD_3OD 150 MHz) and DEPT 135^0 spectra showed the presence of five olefinic methines and seven quaternary olefinic carbons (12 *sp*^{2} carbons), two oxymethines, and one methylene. These functionalities accounted for six of the total nine degrees of unsaturation, and the remaining three degrees of unsaturation were consistent with the flavan-3-ol structure. The ^{1}H NMR and ^{13}C NMR chemical shifts of **1a** and **1b** were similar, the main difference being the conformation of C-3. In **1a**, the coupling constant between H-2/H-3 (^3J) was 7.8 Hz, indicating that the

Table 1. NMR data (600 MHz for ^{1}H and 150 MHz for ^{13}C, in CD_3OD) for Compounds 1 and 2

Position	**1a**		**1b**		**2a**		**2b**	
	^{13}C NMR δc (mult.)	^{1}H NMR δH (Int., mult, J=Hz)	^{13}C NMR δc (mult.)	^{1}H NMR δH (Int., mult, J=Hz)	^{13}C NMR δc (mult.)	^{1}H NMR δH (Int., mult, J=Hz)	^{13}C NMR δc (mult.)	^{1}H NMR δH (Int., mult, J=Hz)
2	81.5 (d)	4.41 (1H, d, 7.8)	78.5 (d)	4.66 (1H, d, 1.6)	81.5 (d)	4.51 (1H, d, 7.4)	78.5 (d)	4.72 (1H, d, 1.7)
3	67.5 (d)	3.83 (1H, m)	66.1 (d)	4.03 (1H, dd, 3.2,	67.4 (d)	3.96 (1H, m)	66.2 (d)	4.14 (1H, dd, 3.5, 4.5)
4	27.2 (t)	2.70 (1H, dd, 8.3, 16.3)	27.9 (t)	4.6)	26.8 (t)	2.83 (1H, dd, 8.2, 16.1)	27.8 (t)	2.72 (1H, dd, 4.3, 16.6)
		2.37 (1H, dd, 5.5, 16.3)		2.68 (1H, dd, 4.5,		2.48 (1H, dd, 5.5, 16.1)		2.81 (1H, dd, 3.5, 16.6)
5	156.7 (s)	-	156.5 (s)	16.1)	156.7 (s)	-	156.5 (s)	-
6	94.9 (d)	5.77 (1H, d, 2.1)	95.0 (d)	2.61 (1H, dd, 2.8,	94.9 (d)	5.88 (1H, d, 2.1)	95.0 (d)	5.91 (1H, d, 2.1)
7	156.3 (s)	-	156.1 (s)	16.1)	156.3 (s)	-	156.1 (s)	-
8	94.2 (d)	5.76 (1H, d, 2.1)	94.6 (d)	-	94.3 (d)	5.73 (1H, d, 2.1)	94.5 (d)	5.74 (1H, d, 2.1)
9	156.0 (s)	-	156.0 (s)	5.78 (1H, d, 2.1)	155.9 (s)	-	155.3 (s)	-
10	99.5 (s)	-	98.7 (s)	-	99.4 (s)	-	98.7 (s)	-
1′	131.0 (s)	-	130.9 (s)	5.77 (1H, d, 2.1)	132.2 (s)	-	132.7 (s)	-
2′	114.8 (d)	6.83 (1H, d, 1.7)	114.6 (d)	-	105.8 (d)	6.46 (1H, d, 0.5)	105.6 (d)	6.57 (1H, d, 0.6)
3′	144.9 (s)	-	144.9 (s)	-	145.5 (s)	-	145.3 (s)	-
4′	144.4 (s)	-	144.6 (s)	-	130.2 (s)	-	130.2 (s)	-
5′	113.9 (d)	6.61 (1H, d, 8.6)	114.0 (d)	6.82 (1H, d, 1.8)	145.5 (s)	-	145.3 (s)	-
6′	118.7 (d)	6.65 (1H, dd, 1.7, 8.6)	118.1 (d)	-	105.8 (d)	6.46 (1H, d, 0.5)	105.6 (d)	6.57 (1H, d, 0.6)
				-				
				6.60 (1H, d, 8.4)				
				6.63 (1H, dd, 1.8, 8.4)				

conformations of C-2 and C-3 were axial–axial, respectively. Otherwise, in **1b**, ^3J of H-2/H-3 was 1.6 Hz, indicating that the conformations of C-2 and C-3 were axial–equatorial, respectively. A comparison of NMR data of **1a** and **1b** with data of catechin and epicatechin isolated from green tea (*Camellia sinensis*) [19] revealed that the structure of the compounds was very similar; therefore, compound **1** was identified as a mixture of compound catechin (**1a**) and epicatechin (**1b**), respectively. These compounds were isolated from *A. elliptica* for the first time.

Compounds **2a** and **2b** were isolated as a mixture, which was obtained as a dark brown powder. On the basis of their ^{1}H NMR and ^{13}C NMR spectra, the ratio of compounds **2a** and **2b** in the mixture was deduced as 2:3. Most of the signals were well-resolved for both compounds. The HR-TOFMS spectrum showed $[M+H]^+$ *m/z* 307.0825 (calcd. *m/z* 306.0740), which corresponded to the molecular formula of $C_{15}H_{14}O_7$ and thus required nine degrees of unsaturation, originating from six C sp^2, and the remaining tricyclic flavanoids. UV spectra in MeOH showed the presence of a flavan-3-ol skeleton [18]. The IR spectra showed absorption peaks at 3325, 1577, 1144, 1062, and 829 cm^{-1}, suggesting the presence of hydroxyl groups, C=C olefin rings, symmetric and asymmetric C-O-C, and a substituted benzene ring, respectively. The ^{1}H-NMR of the **2a** (CD_3OD 600 MHz) spectrum showed the presence of four olefinic methine groups, resonating at δ_H 5.88, 5.73 (each 1H, d, J = 2.1 Hz, H-6, H-8) and 6.46 (2H, d, J = 0.5, H-2 , H-6), two oxymethine groups at δ_H 4.51 (1H, d, J = 7.4 Hz, H-2) and 3.96 (1H, m, H-3), and one methylene group at δ_H 2.83 (1H, dd, J = 8.2, 16.1 Hz, H-4a) and 2.48 (1H, dd, J = 5.5, 16.1 Hz, H-4b). The ^{13}C NMR of the **2a** (CD_3OD 150 MHz) and DEPT 135^0 spectra showed the presence of six`olefinic methines, eight quaternary olefinic carbons (14 sp^2 carbons) and one methylene. The NMR chemical shift showed that compound **2a** is similar to **1a**, as catechin derivatives. The main difference was the presence of an additional hydroxy group at C-5 instead of an olefinic methine in **1a**, observed in the HMBC correlation of H-1 and H-6 to C-3 , C-4 , C-5 , C-1 . The NMR chemical shift of **2a** and **2b** was similar, the main difference being the conformation of C-3. In **2a**, the coupling constant between H-2/H-3 (^3J) was 7.4 Hz, indicating that conformations of C-2 and C-3 were axial–axial, respectively. Otherwise, in **2b**, ^3J of H-2/H-3 was 1.7 Hz, indicating that conformations of C-2 and C-3 were axial–equatorial, respectively. A comparison of NMR data of **2a** and **2b** with data of gallocatechin and epigallocatechin from green tea (*Camellia sinensis*) [19] revealed that the structure of the compounds was very similar; therefore, compound **2** was identified as a mixture of gallocatechin (**2a**) and epigallocatechin (**2b**), respectively. These compounds were isolated from *A. elliptica* for the first time.

The cytotoxicity effects of the two isolated compounds **1** and **2** against P-388 murine leukemia cells were investigated according to the method described in previous papers [8,11], and an artonin E (IC_{50} 0.3 µg/mL) was used as a positive control [20].

The cytotoxic activity of isolated compound **2** is not active, having an IC_{50} value of more than 100 µg/mL, whereas compound **2** is active, having an IC_{50} value of 7.79 µg/mL. The activity of **1** was stronger than that of **2**, indicating that an additional hydroxy group at C-5 in the aromatic ring can support their reactivity and corrosiveness. This hydroxy group at C-5 in **2** can also act as a hydrogen bond donor that increases the affinity of the compound in the active site of the enzyme or in the biological receptor [21].

Conclusions

Two mixtures of known flavanoids, here labeled compound **1** and compound **2**, were isolated from the stem bark of *Aglaia elliptica*. Compounds **1** and **2** were evaluated for their cytotoxic activity against P-388 murine leukemia cells, *in vitro*. It was found that compound **2** is active, indicating that the presence of a hydroxyl group in the aromatic ring can increase cytotoxic activity.

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Reference

[1] Pannell, C.M. 1992. Taxonomic monograph of the genus Aglaia lour (Meliaceae). Kew Bulletin Additional. Series XVI. Kew, Richmond, Surrey: HMSO; pp. 359-362.

[2] Wood, D.L., Silverstain, R.M., Nakajima, M. 1970. Control of Insects Behavior by Natural Product. Academic Press. New York.

[3] Yodsaoue, O., Sonprasit, J., Karalai, C., Ponglimanont, C., Tewtrakul, S., Chantrapromma, S. 2012. Diterpenoids and triterpenoids with potential anti-inflammatory activity from the leaves of *Aglaia odorata*. Phytochemistry. 76:83-91, doi: 10.1016/j. phytochem.2012.01.015.

[4] Joycharat, N., Plodpai, P., Panthong, K., Yingyongnarongkul, B., Voravuthikunchai, S.P. 2010. Terpenoid constituents and antifungal activity of *Aglaia forbesii* seed against phytopathogens. Can. J. Chem. 88:937-944, doi: https://doi.org/10.1139/ V10-085.

[5] Liu, S., Liu, S. B., Zuo, W., Guo, Z., Mei, W., Dai, H. 2014. New sesquiterpenoids from *Aglaia odorata* var. Microphyllina and their cytotoxic activity. Fitoterapia. 92:93-99, doi: 10.1016/j.fitote.2013. 10.013.

[6] Cai, X., Wang, Y., Zhao, P., Li, Y., Luo, X. 2010. Dolabellane diterpenoids from *Aglaia odorata*. Phytochemistry. 71:1020-1024, doi:10.1016/j.phy tochem. 2012.01.015.

[7] Yodsaoue, O., Sonprasit, J., Karalai, C., Ponglimanont, C., Tewtrakul, S., Chantrapromma, S. 2012. Diterpenoids and triterpenoids with potential anti-inflammatory activity from the leaves of *Aglaia odorata*. Phytochemistry. 76:83-91, doi:10.1016/ j.phytochem.2012.01.015.

[8] Harneti, D., Tjokronegoro, R., Safari, A., Supratman, U., Loong, X., Mukhtar, M.R., Mohamad, K., Awang, K., Hayashi, H. 2012. Cytotoxic triterpenoids from the bark of *Aglaia smithii* (Meliaceae). Phytochem. Lett. 5:496-499, doi:10.1016/j.phytol. 2012.04.013.

[9] Zhang, F., Wang, J., Gu, Y., Kong, Y. 2010. Triterpenoids from *Aglaia abbreviata* and their cytotoxic activities. J. Nat. Prod. 73:2042-2046, doi:10.1021/np100599g.

[10] Esimone, C.O., Eck, G., Nworu, C.S., Hoffmann, D., Uberla, K., Proksch, P. 2010. Dammarenolic acid, a secodammarane triterpenoid from *Aglaia sp.* shows potent anti-retroviral activity in vitro. Phytomedicine. 17:540-547, doi: 10.1016/j.phymed. 2009.10.015.

[11] Sianturi, J., Purnamasari, M., Darwati, Harneti, D., Mayanti, T., Supratman, U., Awang, K., Hayashi, H. 2015. New bisamide compounds from the bark of *Aglaia eximia* (Meliaceae). Phytochem. Lett. 13:297-301, doi:10.1016/j.phytol.2015.07.003.

[12] Wang, S., Cheng, Y., Duh, C. 2001. Cytotoxic constituents from leaves of *Aglaia elliptifolia*. J. Nat. Prod. 64:92-94, doi: 10.1021/np000341q.

[13] Chin, Y., Chae, H., Lee, J., Bach, T.T., Ahn, K., Lee, H., Joung, H., Oh, S. 2010. Bisamides from the twigs of *Aglaia perviridis* collected in Vietnam. Bull. Korean. Chem. Soc, 31(9):2665-2667, doi: 10.5012/bkcs.2010.31.9.2665.

[14] Pan, L., Kardono, L.B.S., Riswan, S., Chai, H., Blanco, E.J.C., Pannell, C.M., Soejarto, D.D., McCloud, T.G., Newman, D.J., Kinghorn, A.D. 2010. Isolation and characterization of minor analogues of silvestrol and other constituents from large-scale re-collection of *Aglaia foveolata*. J. Nat. Prod. 73:1873-1878, doi: 10.1021/np100503q.

[15] Wang, S., Cheng, Y., Duh, C. 2001. Cytotoxic constituents from leaves of *Aglaia elliptifolia*. J. Nat. Prod. 64:92-94, doi: 10.1021/np000341q.

[16] Muellner, A.N., Samuel, R., Chase, M.W., Pannell, C.M., Greger, H. 2005. Aglaia (Meliaceae): an evaluation of taxonomic concepts based on DNA

data and secondary metabolites. Amer. J. Bot. 92(3):534-543, doi: 10.3732/ajb.92.3.534.

[17] Cui, B., Chai, H., Santisuk, T., Reutrakul, V., Farnsworth, N.R., Cordell, G.A., Pezzuto, J. M., Kinghom, A.D. 1997. Novel cytotoxic lH-cyclopenta[*b*]benzofuran lignans from *Aglaia elliptica*. Tetrahedron. 53(52):17625-17632, doi:10.1016/ S0040-4020(97)10231-9.

[18] Andersen, O.M. Markham, K.R. 2006. Flavonoids: Chemistry, Biochemistry, and Applications. Taylor and Francis. New York.

[19] Davis, A.L., Cai, Y., Davies, A.P., Lewis, J.R. 1996. ^{1}H and ^{13}C NMR assignments of some green tea polyphenols. Mag. Res. Chem. 34:887-890, doi:10.1002/(SICI)1097-458X(199611)34:11<887: AID-OMR995>3.0.CO;2-U

[20] Hakim, E.H., Achmad, S.A., Juliawaty, L.D., Makmur, L., Syah, Y.M., Aimi, A., Kitajima, M., Takayama, H., Ghisalberti, E.L. 2007. Prenylated flavonoids and related compounds of the Indonesian Artocarpus (Moraceae). J. Nat. Med. 61(2): 229-236, doi:10.007/s11418-006-0048-0.

[21] Sianturi, J., Purnamasari, M., Mayanti, T., Harneti, D., Supratman, U., Awang, K., & Hayashi, H. 2015. Flavonoid compounds from the bark of *Aglaia eximia* (Meliaceae). Makara J. Sci. 19(1):7-12, doi:10.7454/ mss.v19i1.4476.