JURNAL KIMIA VALENSI
p-ISSN: 2460-6065; e-ISSN: 2548-3013
Journal homepage: https://journal.uinjkt.ac.id/index.php/valensi
Research Article

Sesquiterpenoids from the stem bark of *Aglaia pachyphylla* Miq (Meliaceae) and cytotoxic activity against MCF-7 Cancer Cell Line

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Article Info
Received: June 11, 2023
Revised: June 17, 2023
Accepted: Sept 27, 2023
Online: November 30, 2023

Citation:
afriansyah, W., Abdullah, F. F., Juliansyah, E., Farabi, K., Harizon, Kuncoro, H., Nurlelasari, Maharani, R., Taib, M. N. A. M., Supratman, U., & Harneti, D. (2023). Sesquiterpenoids from the stem bark of *Aglaia pachyphylla* Miq (Meliaceae) and cytotoxic activity against MCF-7 Cancer Cell Line. *Jurnal Kimia Valensi*, 9(2), 300-305.

Doi: 10.15408/jkv.v9i2.32782

Abstract

Sesquiterpenoids are terpenoid-derived compounds formed from three isoprene units with diverse pharmacological activities. Sesquiterpenoids can be obtained from higher plants, such as the genus *Aglaia* from the Meliaceae family. This study aims to isolate and characterize the structure of sesquiterpenoidsfrom the *n*-hexane extract of *Aglaia pachyphylla* Miq stem bark and to determine their cytotoxic activity against MCF-7 breast cancer cells. The *n*-hexane extract was separated and purified by various chromatography techniques such as vacuum liquid chromatography, normal-phase chromatography, and reversed-phase chromatography to obtain three sesquiterpenoids. The chemical structures of sesquiterpenoids were identified by various spectroscopic analyses such as IR, MS, 1D-NMR, and 2D-NMR and compared with previously reported spectrum data. Three sesquiterpenoids were identified as β-caryophyllene oxide (**1**), 1β-Hydroxy-4(15),5-eudesmadiene (**2**), and spathulenol (**3**). The three compounds were tested against MCF-7 breast cancer cells using the PrestoBlue method. Compound **2** showed the highest cytotoxic activity with an IC_{50} value of 262,25 µM.

Keywords: *Aglaia pachyphylla*, cytotoxic activity, MCF-7, sesquiterpenoid.

1. INTRODUCTION

Meliaceae is a family of plants in the Sapindales order, consisting of trees and shrubs with pinnate leaves that are widely distributed from Southeast Asia to South America [1]. Ethnobotanical studies show all parts of plants from the meliaceae family including stem barks, roots, and leaves are often used as traditional medicine to treat wounds, constipation, dysentery, rheumatism, viral respiratory diseases, and skin diseases [2–6]. Plants from this family have also been scientifically proven for their pharmacological activities such as antiplasmodial, insecticidal, antioxidant, anticancer, antimicrobial, and anti-inflammatory with diverse chemical constituents [7–9]. Terpenoids and limonoids are major compounds produced from this family with cytotoxic activity that has been widely studied and also includes antiviral, antiplasmodial, antifeedant, antimicrobial, anti-inflammatory, and antioxidant [10]. *Aglaia* is the largest genus of this family, with 65 of the 150 species distributed in Indonesia [11]. In addition, the *Aglaia* genus is one of the producers of terpenoid with a percentage of 43%, including sesquiterpenoid, diterpenoid and triterpenoid, especially sesquiterpenoid isolated from variety of species such as *A. grandis*, *A. simplicifolia*, *A. leucophylla*, *A. foveolata*, *A. harmsiana*, *A. forbesii*, *A. silvetris*, *A. minahassae*, *A. odorata* var. microphyllina, *A. perviridis* [12–19]. *Aglaia*

pachyphylla Miq is distributed in Southeast Asia, including Thailand, Malaysia, and Indonesia, on the island of Borneo and the forests of Weh Island [20,21]. Until now, there has been no research on isolated compounds and their biological activities from this species. Therefore, this study described the structural elucidation of isolated compounds **1-3** from *A. pachyphylla* Miq and their cytotoxic activity against MCF-7 breast cancer cells.

2. RESEARCH METHODS

General Experimental Procedures

Infrared spectra were measured by a Perkin-Elmer spectrum-100 FT-IR in the plate of KBr (Waltham, Massachusetts, USA). High-resolution mass spectra were measured by Waters Q-TOF-HRTOFMS-XEV^{otm} mass spectrometer (Milford, MA, USA). Meanwhile, the NMR spectra of **1** and **2** were also recorded by JEOL JNM-ECZ500R/S1 spectrometer at 500 MHz for ^{1}H and 125 MHz for ^{13}C, whereas **3** was measured by Bruker Av-500 spectrometer (Bruker, Karlsruhe, Germany) at 500 MHz for ^{1}H and 125 MHz for ^{13}C, using $CDCl_3$ as a solvent and tetramethyl silane (TMS) as an internal standard. Vacuum liquid chromatography (VLC) and Column chromatography was carried out on silica gel 60 (Merck, 70-230 and 230-400 mesh) and octadecyl silane (ODS, Fuji Sylisia Chemical LTD., Chromatorex® C_{18} DM1020 M, 100–200 mesh). Thin layer chromatography (TLC) was performed using silica gel 60 GF_{254} (Merck) and RP-18 F_{254}s plates (Merck) with a variety of solvent systems. Detection of the TLC plate was monitored under UV light at 254 and 365 nm before spraying with 10 % H_2SO_4 in ethanol.

Plant Materials

The stem bark of *A. pachyphylla* Miq was collected from Forest Areas with Special Purposes, Samboja Research Forest, Kutai Kartanegara, East Kalimantan, Indonesia, in December 2020. The plant was determined at the Herbarium Wanariset (WAN), Balikpapan (collection No. FF 11.20), and stored at the Faculty of Forestry, Mulawarman University.

Extraction and Isolation

A 4.8 kg stem bark of *A. pachyphylla* Miq was constantly macerated using ethanol 70%, filtered and concentrated under vacuum to remove the solvent to give concentrated ethanol extract (685 g). The ethanol extract was suspended in water: ethanol (1:1), extracted successively with *n*-hexane, ethyl acetate (EtOAc), and *n*-butanol. The *n*-hexane soluble fraction (26 g) was fractionated by VLC using 10% gradient eluent system of *n*-hexane: EtOAc (100:0 – 0:100) and EtOAc: MeOH (100:0 – 80:20) on silica gel to give nine fractions (A-I). Combined according to TLC results, fraction B (5.1 g) was subjected to column chromatography (CC) silica gel (70-230 mesh) with 10% gradient of *n*-hexane: CH_2Cl_2 gained five subfractions (B1-B5). Subfraction B3 (458.3 mg) was chromatographed on a column of silica gel, eluting with *n*-hexane: EtOAc (20:1) to obtain nine subfractions (B3a-B3i). Then B3a and B3i were recrystallization with MeOH to give compounds **1** (8.4 mg) and **2** (20.1 mg). Meanwhile, subfraction B4 was purified on a silica gel column,eluting with *n*-hexane: EtOAc (15:1) obtained B4a-B4c. B4b (30.5 mg) was separated on the C-18 column and eluted using 8:2 of MeOH : water to yield compound **3** (5.8 mg).

β-Caryophyllene oxide (**1**). Colorless oil, IR (KBr plate) ν_{max} cm^{-1}: 2927; 1743; 1460; 1381; 1167 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ_H 1.75 (1H, t, 9.5, H-1), 1.65 (1H, m, H-2a), 1.60 (1H, m, H-2b), 2.05 (1H, m, H-3a), 2.09 (1H, m, H-3b), 2.87 (1H, dd, 5.0 Hz, 11.0 Hz, H-5), 2.08 (1H, m, H-6a), 2.12 (1H, m, H-6b), 2.21 (1H, m, H-7a), 2.28 (1H, m, H-7b), 2.60 (1H, q, 10.0, H-9), 1.68 (1H, m, H-10a), 1.59 (1H, m, H-10b), 1.19 (3H, s, CH_3-12), 4.96 (1H, s, H-13a), 4.83 (1H, s, H-13b), 0.99 (3H, s, CH_3-14), 0.97 (3H, s, CH_3-15); ^{13}C-NMR ($CDCl_3$, 125 MHz), see Table 1; HR-TOF MS (positive ion mode) *m/z* 221.1905 $[M+H]^+$ (calculated for $C_{15}H_{25}O$, *m/z* 221.1905).

1β-Hydroxy-4(15),5-eudesmadiene (**2**). Pale yellow oil, IR (KBr plate) ν_{max} cm^{-1}: 3400; 2931; 1712; 1463; 1379; 1041 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ_H 3.43 (1H, dd, 11.0, 4.0 Hz, H-1), 1.82 (1H, m, H-2a), 1.67 (1H, m, H-2b), 2.17 (1H, m, H-3a), 2.35 (1H, m, H-3b), 5.54 (1H, s, H-6), 2.01 (1H, m, H-7a), 1.60 (1H, m, H-8a), 1.33 (1H, m, H-8b), 1.34 (1H, m, H-9a), 1.89 (1H, m, H-9b), 1.63 (1H, m, H-11), 0.91 (3H, d, 7.0 Hz, CH_3-12), 0.89 (3H, d, 6.6 Hz, CH_3-13), 0.91 (3H, s, CH_3-14), 4.61 (1H, t, 2.0 Hz, H-15a), 4.79 (1H, t, 2.0 Hz, H-15b); ^{13}C-NMR ($CDCl_3$, 125 MHz), see Table 1; HR-TOF MS (positive ion mode) *m/z* 243.1729 $[M+Na]^+$ (calculated for $C_{15}H_{24}ONa$, *m/z* 243.1725).

Table 1. Comparison of ^{13}C-NMR data of compound **1-3** ($CDCl_3$, 125 MHz) and literatures

Carbon Position	Compounds					
	1	β-caryophyllene oxide *	**2**	1β-Hydroxy-4(15),5-eudesmadiene **	**3**	Spathulenol*** *
	δ_C (mult.)	δ_C (mult.)	δ_C (mult.)	δ_C (mult.)	δ_C (mult.)	δ_C (mult.)
1	50.7 (d)	50.7 (d)	79.0 (d)	78.9 (d)	53.5 (d)	53.5 (d)
2	27.3 (t)	27.3 (t)	30.2 (t)	30.2 (t)	26.8 (t)	26.8 (t)
3	39.2 (t)	39.2 (t)	32.4 (t)	32.3 (t)	41.8 (t)	41.8 (t)
4	59.9 (s)	59.7 (s)	148.0 (s)	147.9 (s)	81.1 (s)	81.1 (s)
5	63.9 (d)	63.9 (d)	144.3 (s)	144.3 (s)	54.4 (d)	54.5 (d)
6	29.8 (t)	29.8 (t)	126.6 (d)	126.6 (d)	29.9 (d)	29.9 (d)
7	30.3 (t)	30.3 (t)	42.2 (d)	42.2 (d)	27.5 (d)	27.5 (d)
8	151.9 (s)	151.9 (s)	20.9 (t)	20.9 (t)	24.8 (t)	24.8 (t)
9	48.8 (d)	48.8 (d)	35.1 (t)	35.1 (t)	38.9 (t)	38.9 (t)
10	39.8 (t)	39.8 (t)	40.4 (s)	40.4 (s)	153.5 (s)	153.5 (s)
11	34.1 (s)	34.1 (s)	32.2 (d)	32.1 (d)	20.4 (s)	20.4 (s)
12	17.1 (q)	17.1 (q)	19.5 (q)	19.5 (q)	16.4 (q)	16.4 (q)
13	112.9 (t)	112.9 (t)	19.1 (q)	19.0 (q)	28.7 (q)	28.7 (q)
14	21.7 (q)	21.7 (q)	17.4 (q)	17.3 (q)	106.3 (t)	106.4 (t)
15	29.9 (q)	29.9 (q)	109.6 (t)	109.5 (t)	26.2 (q)	26.2 (q)

*($CDCl_3$, 150 MHz); **($CDCl_3$, 100 MHz); ***($CDCl_3$, 125 MHz)

Spathulenol (**3**). Colorless oil, IR (KBr plate) ν_{max} cm$^{-1:}$ 3388; 2928; 1635; 1454; 1375; 1128 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): 1.30 (1H, m, H-1), 1.89 (1H, dd, 6.0, 12.0 Hz, H-2a), 1.62 (1H, dd, 6.0, 12.0 Hz, H-2b), 1.75 (1H, m, H-3a), 1.55 (1H, m, H-3b), 1.30 (1H, m, H-5), 0.46 (1H, t, 5.0 Hz, H-6), 0.71 (1H, m, H-7), 1.96 (2H, m, H-8), 2.42 (1H, dd, 6.0, 13.5 Hz, H-9), 1.03 (3H, s, CH_3-12), 1.05 (3H, s, CH_3-13), 4.66 (1H, s, H-14a), 4.69 (1H, s, H-14b), 1.28 (3H, s, CH_3-15); ^{13}C-NMR ($CDCl_3$, 125 MHz), see Table 1; HR-TOF MS (positive ion mode) *m/z* 221.1918 $[M+H]^+$ (calculated for $C_{15}H_{25}O$, *m/z* 221.1905).

Determination of Cytotoxic Activity

Compounds **1-3** were determined for their cytotoxic activities against MCF-7 human breast cancer cells using PrestoBlue cells viability assay [22]. The cells were maintained in a Roswell Park Memorial Institute (RPMI) medium supplemented with 10% (v/v) Fetal Bovine Serum (FBS) and 1 µL/mL penicillin type antibiotic (Sigma Aldrich P4333). Cultures were incubated at 37°C in a humidified atmosphere of 5% CO_2. The cells were seeded in 96-well microliter plates at 1.7×10^4 cells per well. After 24 h, compounds **1-3** were separately added to the wells. After 96 h, cell viability was determined by measuring the metabolic conversion of resazurin substrate into pink fluorescent resorufin product resulting from reduced viable cells. The PrestoBlue assay results were read using a multimode reader at 570 nm. IC_{50} values were taken from the plotted graph of the percentage of living cells compared to control (%), receiving DMSO, versus the tested concentration of compounds (µg/mL). The IC_{50} values mean concentration required for 50% growth inhibition.

3. RESULTS AND DISCUSSION

The ethanolic extract from the dried stem bark of *A. pachyphylla* Miq was macerated and extracted consecutively with *n*-hexane, ethyl acetate, and *n*-butanol. The *n*-hexane extract of *A. pachyphylla* Miq was separated by a combination of normal phase and reversed-phase column chromatography to give compounds **1-3**.

Compound **1** was isolated as a colorless oil, with a molecular formula $C_{15}H_{24}O$ based on HR-TOFMS of the positive ion peak *m*/*z* 221.1905 $[M+H]^+$ calcd. (221.1905) with four degrees of unsaturation. IR spectra show absorption bands that indicate the presence of aliphatic CH sp^3 (2927 cm^{-1}), C=C olefinic (1743 cm^{-1}), *gem*-dimethyl (1460 and 1381 cm^{-1}), and ether group (1167 cm^{-1}), The ^{1}H-NMR spectra showed proton resonance related to three methyl singlets at δ_H 0.97 (3H, s, CH_3-15), 0.99 (3H, s, CH_3-14), and 1.19 (3H, s, CH_3-12). In addition, it was observed at δ_H 4.83 (1H, s, H-13a) and 4.96 (1H, s, H-13b) as one olefinic methylene group. Analysis of ^{13}C-NMR and DEPT 135° spectra of compound **1** shows that there are 15 carbons consisting of three methyls [δ_C

17.1 (C-12), 21.7 (C-14), 29.9 (C-15)], five methylenes [δ_C 27.3 (C-2), 29.8 (C-6), 30.3 (C-7), 39.2 (C-3), 39.8 (C-10)], three methines [δ_C 48.8 (C-9), 50.7 (C-1), 63.9 (C-5)], two quaternary carbons δ_C 34.1 (C-11) and 59.9 (C-4), one olefinic methylene δ_C 112.9 (C-13) as well as one olefinic quaternary δ_C 151.9 (C-8). The ^{13}C-NMR and DEPT suggested one disubstituted double bond has been identified as olefinic methylene ($C=CH_2$) which calculated for one unsaturated degree. Meanwhile, the three remaining unsaturated degrees corresponded to the tricyclic sesquiterpenoid, one cyclic came from epoxide cyclic it is supported by a typical shift in ^{1}H-NMR for epoxide ring at δ_H 2.87 and from ^{13}C-NMR it can observed from chemical shift at δ_C 63.9 (C-5) for methine and 59.9 (C-4) for carbon quaternary, two unsaturated degrees for two cylices. Based on analysis ^{1}H-NMR, ^{13}C-NMR, and DEPT 135°, compound **1** indicate caryophyllene type [13], it is supported by three methyl singlets δ_H 0.97 (3H, s, CH_3-15), 0.99 (3H, s, CH_3-14), and 1.19 (3H, s, CH_3-12), two methyls δ_H 0.97 (3H, s, H-15) and 0.99 (3H, s, H-14) as *gem*-dimethyl suggested at C-14/C-15 based on biosynthetic of caryophyllene [23]. The comparison of the NMR data of compound **1** with the data for β-caryophyllene oxide isolated from *A. harmsiana* [13] was similar. Therefore, the structure of compound **1** was identified as β-caryophyllene oxide. Compound **1** was isolated for the first time from this species.

Compound **2** was isolated as a pale yellow oil with a molecular formula $C_{15}H_{24}O$ based on HR-TOFMS of the positive ion peak *m*/*z* 243.1729 $[M+Na]^+$ calcd (243.1725) with four degrees of unsaturation. IR spectra showed absorption bands that indicate the presence of hydroxyl (3400 cm^{-1}), aliphatic (C-H sp^3) (2931 cm^{-1}), olefinic (C=C) (1712 cm^{-1}), *gem*-dimethyl (1463 and 1379 cm^{-1}), and ether group (C-O) (1041 cm^{-1}). The ^{1}H-NMR spectra showed proton resonance related to one tertiary methyl δ_H 0.91 (3H, s, CH_3-14), two secondary methyls at δ_H 0.89 (3H, d, *J*= 7.0 Hz, CH_3-13) and 0.91 (3H, d, *J*= 7.0 Hz, CH_3-12), one oxymethine at δ_H 3.43 (1H, dd, *J*= 4.0, 11.0 Hz, H-1), one olefinic group at δ_H 5.54 (1H, s, H-6), and olefinic methylene group at δ_H 4.61 (1H, t, *J*= 2.0, H-15) and 4.79 (1H, t, *J*= 2.0, H-15). Analysis of ^{13}C-NMR and DEPT 135° spectra of compound **2** shows that there are 15 carbons consisting of three methyls [(δ_C 17.4 (C-14), 19.1 (C-13), 19.5 (C-12)], four methylenes [(δ_C 20.9 (C-8), 30.2 (C-2), 32.4 (C-3), 35.1 (C-9)], two aliphatic methines [(δ_C 32.2 (C-11), 42.2 (C-7)], one oxygenated methine δ_C 79.0 (C-1), one aliphatic quaternary carbon [(δ_C 40.4 (C-10)], two olefinic quaternary carbons [(δ_C 144.3 (C-5); 148.0 (C-4)], one olefinic methylene δ_C 109.6 (C-15) and one olefinic methine δ_C 126.6 (C-6). Based on ^{1}H-NMR, ^{13}C-NMR, and DEPT 135°, compound **2** has four unsaturated degrees, two unsaturated degrees from two double bonds such as terminal olefinic group ($C=CH_2$) and methine olefinic group (C=CH), two unassigned hydrogen deficiency indexes corresponded to the bicyclic sesquiterpenoid structure. Three methyls and quaternary carbon from compound **2** indicate the characteristic of eudesmane-type sesquiterpenoid. It is supported by the existence one tertiary methyl at δ_H 0.91 (3H, s, H-14) and one aliphatic quaternary carbon at (δ_C 40.4 (C-10), as well as the evidence of two secondary methyls with the same value of *J* coupling constant δ_H 0.89 (3H, d, *J*= 7.0 Hz, H-13) and 0.91 (3H, d, *J*= 7.0 Hz, H-12) as an isopropyl group in eudesmane skeleton. A comparison of the NMR data of compound **2** and 1β-Hydroxy-4(15),5-eudesmadiene isolated from *Artemisia annua* [24] showed that the structure of these two compounds is very similar, consequently, compound **2** was identified as a 1β-Hydroxy-4(15),5-eudesmadiene, the compound **2** was the first time isolated from the *Aglaia* genus and this species.

Compound **3** was isolated as a colorless oil, with a molecular formula $C_{15}H_{24}O$ based on HR-TOFMS of the positive ion peak *m*/*z* 221.1918 $[M+H]^+$ calcd. (221.1905) with four degrees of unsaturation. IR spectra showed absorption bands that indicate the presence of hydroxyl (3388 cm^{-1}), CH sp^3 aliphatic (2928 cm^{-1}), C=C olefinic (1635 cm^{-1}), *gem*-dimethyl (1454 and 1375 cm^{-1}), and ether group (1128 cm^{-1}). The ^{1}H-NMR spectra showed proton resonance related to three tertiary methyls at δ_H 1.03 (3H, s, CH_3-12), 1.05 (3H, s, CH_3-13), and 1.28 (3H, s, CH_3-15), olefinic methylene group at δ_H 4.66 (1H, t, *J*= 2.0 Hz, H-15) and 4.69 (1H, t, *J*= 2.0 Hz, H-15), and two methines at δ_H 0.46 (1H, t, *J*= 5.0 Hz, H-6) and 0.71 (1H, m, H-7). Analysis of ^{13}C-NMR and DEPT 135° spectra of compound **3** shows that there are 15 carbons consisting of three methyls at δ_C [16.4 (C-12), 26.2 (C-15), 28.7 (C-13)], one aliphatic quaternary carbon δ_C [20.4 (C-11)], four aliphatic methylenes δ_C [24.8 (C-8), 26.8 (C-2), 38.9 (C-9), 41.8 (C-3)], four aliphatic methylenes δ_C [27.5 (C-7), 29.9 (C-6), 53.5 (C-1), 54.4 (C-5)], one oxygenated quaternary carbon δ_C [81.1 (C-4)], one olefinic methylene δ_C [106.3 (C-14)], one olefinic quaternary carbon [153.5 (C-10)]. Based on ^{1}H-NMR, ^{13}C-NMR, and DEPT 135°, compound **3** has four unsaturated degrees. One unsaturated degree from terminal olefinic group ($C=CH_2$). Meanwhile, the remaining from tricyclics framework, the chemical shift from ^{1}H-NMR at δ_H 0.46 (1H, t, *J*= 5.0 Hz, H-6) and 0.71 (1H, m, H-7), suggested the

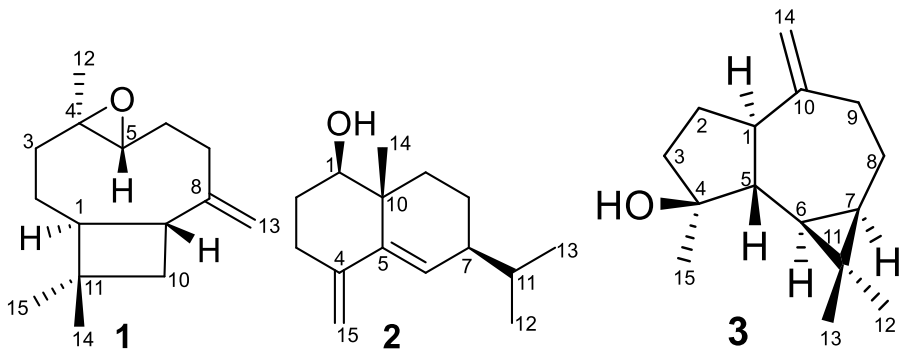

Figure 1. Structure of compound **1**-**3**

presence of cyclopropane moiety on a sesquiterpenoid aromadendrane type framework and it supported by the existence of upfield quaternary carbon at δ_C 20.4 (C-11) that verifies the cyclopropane ring on aromadendrane type [25]. Determination of the structure of compound **3** was compared with previously isolated aromadendrane-type sesquiterpenoid compounds from the *Aglaia* genus. These aromadendranes were spathulenol, 4β,10α-dihydroxyaromadendrane, 4α, 10α-dihydroxyaromadendrane, ledol, and viridiflorol [11]. The NMR data of spathulenol has similarities with compound **3**, based on a comparison of spectra data with spathulenol [14]. Therefore, compound **3** was determined as known compound, namely spathulenol. Compound **3** was isolated for the first time from this species.

Table 2. Cytotoxicity of compounds **1**-**3** against MCF-7 cancer cell line

Compounds	IC_{50} (µM)
	MCF-7
1	>500
2	262.25
3	340.20
Cisplatin (positive control)	53.0

The results of the cytotoxic activity test of compounds **1-3** against MCF-7 breast cancer cell line were summarized in Table 2. Cisplatin (53 µM) was used as a positive control. The evaluation of compounds **1-3** showed that compound **2** has the highest activity with an IC_{50} value of 262.25 µM, and compound **1** has the lowest cytotoxic activity value, which is > 500 µM, and is included in the inactive category. Compound **2** was first determined for cytotoxic activity, in previous study by Brown *et al.*, 2003 only showed the structure elucidation and not reported the cytotoxic activity. Compounds **1**&**3** were determined the cytotoxic activity for the first time from this species.

4. CONCLUSIONS

Three known sesquiterpenoids, one caryophyllene-type, β-caryophyllene oxide (**1**), one eudesmane-type, 1β-Hydroxy-4(15),5-eudesmadiene (**2**), and one aromadendrane-type, spathulenol (**3**) were isolated from *n*-hexane extract of the stem bark of *Aglaia pachphylla* Miq. Compound **2** was isolated for the first time from this genus with the highest cytotoxic activity against MCF-7 breast cancer cell 262.25 µM.

ACKNOWLEDGMENTS

The authors are grateful to Indonesian Ministry of Research, Technology, and Higher Education for Grant of Pendidikan Magister menuju Doktor untuk Sarjana Unggul (PMDSU) 2022-2023 (1318/UN6.3.1/PT.00/2022; 12 May 2022) Indonesia, Directorate of Research and Community Engagement Universitas Padjadjaran for publication funding, and to Universitas Padjadjaran for supporting with the study facilities.

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