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Triterpenoids From *Swietenia mahagoni* L Jacq. and Their Cytotoxic Activity against MCF-7 Breast Cancer and CV-1 Normal Kidney Cell Lines

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ABSTRACT. Triterpenoid is a group of natural products with various remarkable activities, including cytotoxic. One of the sources for this type of compounds is *Swietenia* genus belong to Meliaceae family. This genus known to contains various secondary metabolites including limonoids, flavonoids, and triterpenoids. Especially for triterpenoid, there is limited report on isolation as well as biological activity from *Swietenia* genus, such as *Swietenia mahagoni*. In this research, three triterpenoid compounds have been successively isolated and identified from *n*-hexane extract, namely, (-)-leucophyllone (**1**), toonaciliatavarin E (**2**), and moronic acid (**3**). All isolated were assed against MCF-7 breast cancer and CV-1 normal kidney cell lines. The result showed that only moronic acid (**3**) performed moderate activity against two cells with IC_{50} of 63.10 and 48.04 µM, respectively. The other isolated compounds (**1** and **2**) showed weak cytotoxicity with IC_{50} > 500 µM. Based on preliminary structure activity relationship, revealed that pentacyclic triterpenoid (moronic acid, **3**) showed stronger cytotoxicity compare with tetracyclic triterpenoids (-)-leucophyllone (**1**) and toonaciliatavarin E (**2**).

Keyword: Cytotoxicity, MCF-7 and CV-1, *Switennia mahagoni*, Triterpenoids

INTRODUCTION

Triterpenoids is a member of terpenoid compounds based on biosynthesis point of view, derived from the combination of six isoprene units to form a C30 skeleton of acyclic squalene (Ludwiczuk et al., 2017). Triterpenoids is a unique member of terpenoid which showed high structure complexity (mostly in cyclic form), most being functionalized with either hydroxyl, ether, aldehydes or carboxylic acids (Hill and Connolly, 2020). Related with its unique structure, triterpenoid showed many potential pharmacological activities such as antiplasmodial (Ma et al., 2015), topoisomerase II inhibitory activity (Wang et al., 2015), anti-inflammatory (Janakiram et al., 2015), angiogenic inhibitor (Yang et al., 2015), antibacterial (Zhu et al., 2015), insecticidal activity (Rao et al., 2015), immunosuppressive activity (Ren et al., 2015), anti tobacco mosaic virus (Yan et al., 2015), antiproliferative (Meng et al., 2015), and cytotoxic activity (Li et al., 2015; Hidayat et al., 2017).

Triterpenoids can be found in many plants species through the different of enzyme used in biosynthesis of triterpenoids (Cárdenas et al., 2019). One of the main source of triterpenoids with various chemical structure and bioactivity is Meliaceae family, including *Swietenia* genus (Sukardiman & Ervina, 2020). *Swietenia* is genus in Meliaceae family consist of four species, namely, *S. macrophylla*, *S. humilis*, and *S. aubrevilleana* (Mootoo et al., 1999). *Swietenia* has been widely exploited to produce a great variety of wood products, including furniture, boats, wooden floors, panelling, and musical instruments (Anderson 2015). This genus natively spread in tropical and sub-tropical region of America, from Florida in North America to Bolivia in South America. However, because of the high quality of its wood, this plant also cultivates in many plantations in Asian country such as Indonesia, India, and Bangladesh (Heyne, 1987). The plant from this genus known traditionally utilized for the treatment of high blood pressure, type II diabetes,

malaria, epilepsy, and diarrhoea (Sukardiman & Ervina, 2020). Furthermore, some bioactivity had been reported, including insecticide (Jimenez et al., 1998), antidiabetic (Ovalle-magalenes et al., 2015), antiinflammation (Chen et al., 2010), antibacterial and antifungal (Dharmalingam et al., 2012), cytotoxic (Naveen et al., 2014), and anti-HIV (Tan et al., 2009). Compound in *Swietenia* genus have been revealed as limonoid, flavonoid, coumarin, and other phenolic compounds (Sukardiman & Ervina, 2020). Until now, only five triterpenoids have been found in genus *Swietenia*, namely, cyclomahagenol (Chakraborty et al., 1971), melianone (Basak et al., 1970), cycloswietenol and 30-norcycloswietenol (Lakshminarayana et al., 1981), and swietesenin (Sun et al., 2018a). Only swietesein which showed cytotoxic activity against SW480 and HL-60 cancer cell lines (Sun et al., 2018a). One of the member of *Swietenia* genus is *Swietenia mahagoni*. *Swietenia mahagoni* known for its high quality of woods. However, some parts of *S. mahagoni* tree has been explored its chemical constituent. Until 2018, researchers have been successively isolated 175 compounds, including 160 limonoids, three diterpenoids, three steroids, four phenolic, and five triterpenoids (Sun et al., 2018b). This previous study revealed that there are limited number of isolated triterpenoids, thus, the exploration of triterpenoid compounds is necessary. Herein, three triterpenoid compounds, (-)-leucophyllone (**1**), toonaciliatavarin E (**2**), and moronic acid (**3**) (Figure 1) have been isolated and elucidated for the first time in this species using chromatographic techniques as well as crystallization. Furthermore, cytotoxicity testing was done on both normal and cancer cells.

EXPERIMENTAL SECTION

General Experiment Procedure

Tetrametilsilan (TMS) was used as an internal standard while measuring the NMR spectra using a JEOL NMR spectrometer at 500 MHz for the ^{1}H spectrum and 125 MHz for the ^{13}C spectrum. The Waters Q-TOF Xevo mass spectrometer was used to obtain the mass spectra. For purification using column chromatography (CC), silica gel (70-230 mesh and 230-400 mesh, Merck) was utilized. GF_{254} silica gel plates (Merck, 0.25 mm) were used for TLC. By heating after sprinkling 10% H_2SO_4 in ethanol, the TLC is visualized.

Plant Material

S. mahagoni stembark was acquired in Cagar Alam Pangandaran, Indonesia. The plant was identified by the faculty of the Biology Department in the Faculty of Mathematics and Natural Sciences at Universitas Padjadjaran in Jatinangor, Indonesia, and was placed under the voucher number 13/HB/07/2021.

Extraction and Isolation

The dried powder stembark of *S. mahagoni* (6.8 kg) was macerated with ethanol for 6 days (6 x 10L). After filtration, the ethanol extract was evaporated on reduced pressure in rotary evaporator to give 3 kg of brown thick ethanol extract. Concentrated ethanol extract was partitioned with *n*-hexane, ethyl acetate, and *n*-buthanol. After evaporated in reduced pressure, *n*-hexane (90 g), ethyl acetate (1.02 kg), and *n*-buthanol (1.2 kg) were obtained.

Eight fractions (A–H) were produced from the *n*-hexane extract using vacuum liquid chromatography (VLC) on silica gel 60 employing a gradient elution system utilizing 10% *n*-hexane, ethyl acetate, and methanol. Fraction B (2.8 g) was divided into 9 fractions (B1-B9) by using column chromatography on silica gel (70-230 mesh) with a 2.5% gradient of *n*-hexane-ethyl acetate. With the assistance of column chromatography on silica gel (70-230 mesh) using *n*-hexane-ethyl acetate gradient of 1%, fraction B3 (190 mg) was split into 4 fractions (B3a-B3d). By crystallizing B3b, compound **1** (6 mg) was emerged. Five fractions (B9a-B9e) were generated when fraction B9 (1.0 g) was separated using column chromatography on silica gel (70-230 mesh) using an isocratic of *n*-hexane:ethyl acetate ratio of 8:2. Compound **2** (5 mg) was crystallized from fraction B9e. Applying column chromatography and an isocratic *n*-hexane:ethyl acetate ratio of 9:1, fraction B8 (300 mg) was separated into 5 fractions (B8a-B8e). Compound **3** (6 mg) was produced by further crystallization of fraction B8c.

Compound **1** was isolated as white amorphous powder. IR (KBr) υ_{max} 3427, 2972, 2858, 1705, 1461, 1372, 1077 cm^{-1}; ^{1}H-NMR and ^{13}C-NMR see **Table 1**. HR-TOF-MS *m/z* 477.3708 $[M+Na]^+$ (Calcd. $C_{31}H_{50}O_2Na^+$, *m/z* 477.3709). Compound **2** was obtained as white amorphous powder. IR (KBr) υ_{max} 3453, 2927,1654,1093 cm^{-1}; ^{1}H-NMR and ^{13}C-NMR see **Table 1**. HR-TOF-MS *m/z* 489.3583 $[M-H]^+$ (Calcd. $C_{30}H_{49}O_5^+$, *m/z* 489.3580). Compound **3** was obtained as white amorphous powder. IR (KBr) υ_{max} 3245, 2946, 2946, 1707, 1453, 1385, 1375, 1203 cm^{-1}; ^{1}H-NMR and ^{13}C-NMR ($CDCl_3$, 125 MHz), see Table 1. HRTOF-MS *m/z* 477.3311 $[M+Na]^+$, (Calcd. $C_{30}H_{46}O_3Na^+$, *m/z* 477.3345).

Determination of Cytotoxic Activity

The PrestoBlue assay was used to conduct the cytotoxic biological assay. Additionally, Thermo Fisher Scientific, Uppsala, Sweden's Presto Blue reagent was utilized to quickly assess a variety of resazurin-based cells by measuring cell viability. The ability to reduce live cells allowed for a quantitative determination of the samples' rate of proliferation. The results showed that healthy cells maintained a smaller habitat in their cytoplasm. As a viability indicator, resazurin reduction (blue), which reduced resorufin (purple), produced

results of absorbance or fluorescence. The conversion was inversely correlated with the number of cells that were metabolically active. Up to 70% confluence of MCF-7 and CV-1 cell lines were grown before being removed, hemocytometer-counted, and diluted with full culture RPMI media. In 96-well plates with 170,000 cells per well, the samples were put. The samples were treated to compounds **1-3** in PBS with 2% DMSO as the co-solvent at increasing concentrations (3.91, 7.81, 15.63, 31.25, 62.50, 125, 250, and 5,000 µg/mL) following an overnight phase of growth. All samples were incubated for 24 hours at 37 °C with 5% CO_2 as the positive control. After incubation, the medium was quickly changed to 10 µL of PrestoBlue reagent in 90 µL of RPMI medium. The colour of the plates changed from blue to purple after an extra hour or two of incubation when resorufin began to form. The IC_{50} value was calculated by measuring absorbance at 570 nm and 600 nm with a microplate reader to determine the quantity required to inhibit growth by 50%. The concentration was calculated using a plot of cytotoxicity against sample concentrations, and the outcome revealed 50% cytotoxicity (IC_{50}). The results of each test and analysis were averaged after being performed twice.

RESULTS AND DISCUSSION

The several steps separation using chromatographic methods, including vacuum liquid chromatography (VLC) and open column chromatography give three triterpenoid compounds (**1-3**, **Figure 1**). Structure elucidation was carried out by extensive spectroscopy method, including 1D NMR and 2D NMR.

The powdery white amorphous form of compound **1** was obtained. Compound **1** established chemical composition is as follows $C_{30}H_{51}O_3$ according to HR-TOFMS with ion peak at *m/z* 477.3708 $[M+Na]^+$ (calcd. for $C_{31}H_{50}O_2Na^+$, *m/z* 477.3709). The FTIR spectra revealed the existances of C-H *sp²* (2972 cm^{-1}), carbonyl (1705 cm^{-1}), *gem*-dimethyl (1461 and 1372 cm^{-1}), and ether (1077 cm^{-1}) groups. The ^1H NMR spectra (**Table 1**) observed the appearance of Resonating seven tertiary methyls (δ_H 0.81, 0.99, 0.99, 1.03, 1.10, 1.24, and 1.24, each 3H), one methoxy at δ_H 3.13 (3H, s), one secondary methyl at δ_H 0.86 (3H, d, *J*=6.0 Hz), three methines *sp²* at δ_H 5.29 (1H, d, *J*=3.0 Hz), 5.51 (1H, dd, *J*=16.0, 8.0 Hz), and 5.38 (1H, d, *J*=16.0 Hz). The number of methyl groups indicating the characteristic of triterpenoid compounds (Farabi et al., 2022). The total 31 signal were resonating in ^{13}C NMR spectra (**Table 1**). The type of carbon also clarified by the DEPT experiment as nine methyls (including one methoxy at δ_C 50.4), eight methylenes, seven methines (including three *sp²* methines at δ_C 117.9, 128.7, and 136.7), and seven quaternary carbons (including one ketone at δ_C 217.9, one *sp²* quaternary carbon at δ_C 145.9, and one oxygenated quaternary carbon at δ_C 74.9). Three of the seven levels of unsaturation were accounted, while the rest of the levels came from a tetracyclic tirucallane-type triterpenoid core. The position of each functional group including its main skeleton of compound **1** were deduced based on HMBC and ^1H-^1H COSY correlations (**Figure 2**). The HMBC of each methyl group to corresponding neighbour carbons clarified the main core of tirucallane-type triterpenoid structure. Correlations of H-28 and H-29 to C-3, C-4, and C-5 and correlations of H-1 to C-3 confirmed the position of ketone at C-3. The position of double bond at C-7/C-8 was deduced based on correlations of H-30 and H-6 to C-7 and C-8. Correlations of H-22, H-26, and H-27 to C-23 and C-24 gave valuable information about the position of double bond at C-23/C-24. The ^1H-^1H COSY also confirmed the position of double bond at C-23/C-24 from the cross peak of H-21/H-20/H-22/H-23/H-24. The position of methoxy group at C-25 unambiguously determined by the correlations of H-1' to C-25. The compound **1** and (-)-leucophyllone, a compound isolated from the stembark of *Aglaia leucophylla* (Benosman et al., 1995), were found to be similar by comparison of the NMR data. Thus, compound **1** identified as (-)-leucophyllone which first time isolated from *S. mahagoni*.

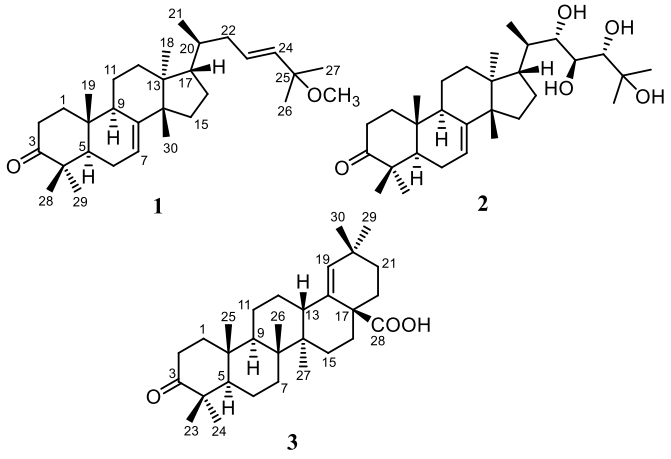

Figure 1. Chemical structure of compounds **1-3**.

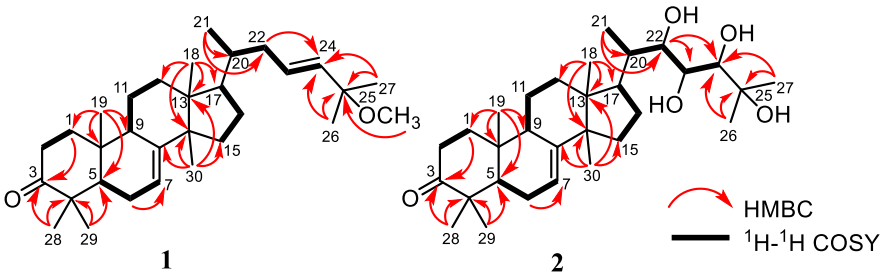

Figure 2. Selected HMBC and ^{1}H–^{1}H COSY correlations for compounds **1**-**2**.

Table 1. NMR data of compounds **1**-**3** (in $CDCl_3$).

No.	**1**		**2**		**3**	
	^{13}C NMR δc (mult.)	^{1}H NMR δ_H (∑H, mult., *J*=Hz)	^{13}C NMR δc (mult.)	^{1}H NMR δ_H (∑H, mult., *J*=Hz)	^{13}C NMR δc (mult.)	^{1}H NMR δ_H (∑H, mult, *J*=Hz)
1	38.6 (t)	1.96; 2.10 (2H, m)	38.6 (t)	1.44, 2.00 (2H, m)	39.8 (t)	1.95 (2H, m)
2	35.0 (t)	2.50 (2H, m)	35.0 (t)	2.26, 2.75 (2H, m)	33.8 (t)	2.46 (2H, m)
3	217.9 (s)	-	217.0 (s)	-	218.3 (s)	-
4	48.9 (s)	-	47.9 (s)	-	47.3 (s)	-
5	52.4 (d)	1.71 (1H, t, 6.0)	52.4 (d)	1.70 (1H, dd, 11.0, 6.0)	54.8 (d)	1.37 (1H, m)
6	24.4 (t)	2.08 (2H, m)	24.4 (t)	2.08 (2H, m)	19.6 (t)	1.46 (2H, m)
7	117.9 (d)	5.29 (1H, d, 3.0)	117.8 (d)	5.29 (1H, d, 3.0)	34.0 (t)	1.48 (2H, m)
8	145.9 (s)	-	146.0 (s)	-	40.5 (s)	-
9	48.5 (d)	2.26 (1H, m)	48.6 (d)	2.25 (1H, m)	50.4 (d)	1.39 (1H, m)
10	35.1 (s)	-	35.1 (s)	-	36.9 (s)	-
11	18.3 (t)	1.55 (2H, m)	18.4 (t)	1.55 (2H, m)	21.4 (t)	1.33 (2H, m)
12	34.1(t)	1.46 (2H, m)	33.5 (t)	1.87 (2H, m)	26.0 (t)	1.64 (2H, m)
13	43.6 (s)	-	43.6 (s)	-	41.5 (d)	1.60 (1H, m)
14	51.3 (s)	-	51.3 (s)	-	42.6 (s)	-
15	33.6 (t)	1.76 (2H, m)	34.1 (t)	1.48 (2H, m)	29.3 (t)	1.63 (2H, m)
16	28.2 (t)	1.96 (2H, m)	27.9 (t)	1.40 (2H, m)	33.3 (t)	1.65 (2H, m)
17	52.7 (d)	1.46 (1H, m)	49.4 (d)	1.80 (1H, m)	47.9 (s)	-
18	22.1 (q)	0.81 (3H, s)	12.8 (q)	0.99 (3H, s)	136.6 (s)	-
19	12.9 (q)	0.99 (3H, s)	21.9 (q)	0.80 (3H, s)	133.3 (d)	5.16 (1H, s)
20	36.4 (d)	1.45 (1H, m)	37.6 (d)	1.67 (1H, m)	32.0 (s)	-
21	18.6 (q)	0.86 (3H, d, 6.0)	12.5 (q)	0.83 (3H, d, 6.0)	33.4 (t)	2.16 (2H, t, 12.0)
22	39.2 (t)	2.19 (2H, m)	83.8 (d)	3.81 (1H, d, 8.5)	33.5 (t)	2.25 (2H, t, 12.0)
23	128.7 (d)	5.51 (1H, dd, 16.0, 8.0)	77.4 (d)	3.65 (1H, dd, 8.5, 7.5)	20.9 (q)	1.01 (3H, s)
24	136.7 (d)	5.38 (1H, d, 16.0)	73.0 (d)	3.96 (1H, d, 7.5)	26.8 (q)	1.06 (3H, s)
25	74.9 (s)	-	81.0 (s)	-	15.8 (q)	0.78 (3H, s)
26	25.8 (q)	1.24 (3H, s)	21.4 (q)	1.20 (3H, s)	16.5 (q)	0.94 (3H, s)
27	26.3 (q)	1.24 (3H, s)	27.9 (q)	1.21 (3H, s)	14.8 (q)	0.99 (3H, s)
28	24.6 (q)	1.03 (3H, s)	24.4 (q)	1.03 (3H, s)	181.2 (s)	-
29	21.7 (q)	1.10 (3H, s)	21.7 (q)	1.10 (3H, s)	30.3 (q)	1.00 (3H, s)
30	27.5 (q)	0.99 (3H, s)	27.8 (q)	1.02 (3H, s)	29.0 (q)	0.97 (3H, s)
1′	50.4 (q)	3.13 (3H, s)				

Compound **2** was observed as white amorphous powder. The chemical structure of compound **2** determined as $C_{30}H_{50}O_5$ based on HR-TOFMS with ion peak at m/z 489.3583 [M-H]- (calcd. for $C_{30}H_{49}O_5^-$, m/z 489.3580). The FTIR, 1H NMR and 13C NMR spectra (**Table 1**) of compound **2** showed high similarity with compound **1**. The main skeleton is identical as tirucallane-type triterpenoids. However, the main difference with compound **1** was observed in side chain of compound **2**. 1H NMR characteristic for oxygenated methine groups observed at δ_H 3.81 (1H, d, J=8.5 Hz), 3.65 (1H, dd, J=8.5, 7.5 Hz), and

3.96 (1H, d, J=7.5 Hz). In 13C NMR, resonated four oxygenated carbons including three oxygenated methines (δc 83.8, 77.4, and 73.0) and one oxygenated quaternary carbon (δc 81.0). All those additional of hydroxyl groups revealed that compound **2** was oxygenated derivatives of compound 1. The position of each four hydroxyl groups which attached in side chain unambiguously determined by 1H-1H COSY and HMBC experiments (**Figure 2**). The HMBC correlations of H-21 to C-20 and C-22 determined the hydroxyl group at C-22. Correlations of H-22 to C-23 and 24 confirmed the presence of hydroxyl group at C-23. A hydroxyl group also identified at C-24 and C-25 based on HMBC correlations of H-26 and H-27 to C-24 and C-25. The more pronounced correlation was observed in 1H-1H COSY correlations of H-21/H-20/H-22/H-23/H-24. Finally, compound **2**'s NMR data were compared to toonaciliatavarin E, which was isolated from Toona ciliata stembark (Zhang et al., 2012), it was discovered that the two compounds were identical. Thus, compound **2** identified as toonaciliatavarin E that was the first to isolate in S. mahagoni.

Table 2. ^{13}C NMR data comparison of compound **3** with moronic acid (125 MHz in $CDCl_3$) (Sari et al., 2020).

No.	Compound **3** ^{13}C NMR δc (ppm)	Moronic acid ^{13}C NMR δc (ppm)
1	39.8	39.8
2	33.8	33.8
3	218.3	218.2
4	47.3	47.2
5	54.8	54.8
6	19.6	19.6
7	34.0	34.0
8	40.5	40.5
9	50.4	50.4
10	36.9	36.9
11	21.4	21.4
12	26.0	26.0
13	41.5	41.4
14	42.6	42.5
15	29.3	29.3
16	33.3	33.3
17	47.9	47.9
18	136.6	136.5
19	133.3	133.2
20	32.0	32.0
21	33.4	33.4
22	33.5	33.5
23	20.9	20.9
24	26.8	26.8
25	15.8	15.8
26	16.5	16.4
27	14.8	14.8
28	181.2	182.3
29	30.3	30.3
30	29.0	29.0

Table 3. Cytotoxic effects on the MCF-7 and CV-1 cell lines for compounds **1-3**.

Compounds	IC_{50} MCF-7 (μM)	IC_{50} CV-1 (μM)
(-)-leucophyllone (**1**)	> 500	>500
toonaciliatavarin E (**2**)	> 500	> 500
moronic acid (**3**)	63.10	48.04
cisplatin*	53.00	43.00

*positive control

The powdery white amorphous form of compound **3** was produced. The chemical structure of compound **3** confirmed as $C_{30}H_{46}O_3$ according to HR-TOFMS with ion peak at m/z 477.3311 $[M+Na]^+$ (calcd. for $C_{30}H_{46}O_3Na^+$, m/z 477.3345). The FTIR spectra revealed the presences of hydroxyl (3245 cm-1), C-H sp2 (2946 cm-1), carbonyl (1707 cm^{-1}), and gem-dimethyl (1453 and 1385 cm-1) groups. The 1H NMR spectra (**Table 1**) showed resonating of seven tertiary methyls (δ_H 1.06, 1.01, 1.00, 0.99, 0.97, 0.94, and 0.78, each 3H) and one methines sp2 at δ_H 5.16 (1H, s). The number of methyl groups indicating the characteristic of triterpenoid compounds (Farabi et al., 2022). The total 30 signal were occurred in 13C NMR spectra (Table 1). The type levels of unsaturation were come from a pentacyclic oleanane-type triterpenoid core. When compound 3's NMR data were compared to moronic acid purified from Chisocheton macrophyllus rind (**Table 2**) (Sari et al., 2020), it was discovered that the two compounds were similar. Thus, compound **3** elucidated as moronic acid which first time isolated from *S. mahagoni*.

All isolated triterpenoid compounds (1-3) were tested against MCF-7 breast cancer cell line and CV-1 normal kidney cell lines according to same methods previously reported by Farabi et al., (2022) and Cisplatin used as a positive control. The resulted of IC50 appears in **Table 3**. Compound 1 and 2 can be classified as inactive with IC50 value more than 500 μM (Wibowo et al., 2011). However, compound 3 showed moderate activity against those two cell indicating that pentacyclic triterpenoids showed better cytotoxic activity than tetracyclic triterpenoids. From the presence of each functional groups in compounds **1**-**3**, the significant difference is the presence of carboxylic acid in compound 3 which can be assume that this functional group will increase cytotoxic activity against those two cells. This results also supported by literature review (Chudzik et al., 2015) which showed that pentacyclic triterpenoids performed remarkable cytotoxic activity against several cancer cell lines, for example betulinic acid who also contain carboxylic acid group in their structure, demonstrated cytotoxic activity against lung cancer (A549), colorectal carcinoma (DLD-1), breast cancer (MCF-7) and prostate cancer (PC-3).

CONCLUSIONS

Three triterpenoids have been isolated from the stembark of *S. mahagoni*, identified as, (-)-leucophyllone (**1**), toonaciliatavarin E (**2**), and moronic acid (**3**) for the first time. Compound **3** showed strongest cytotoxic activity compare with compound **1** and **2**. Based on this study, pentacyclic triterpenoids gave better cytotoxicity than tetracyclic triterpenoid against MCF-7 breast cancer cell lines and CV-1 normal kidney cell lines. The presence of carboxylic acid moiety in compound **3** also suggested to increase cytotoxic activity.

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