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Research Article

Isolation and activity test of antioxidant, antibacterial, and cytotoxic compounds from the stem bark of *Aglaia foveolata* Pannell

Anselmania Kartini Dhey[1], Eka Rasuna Andriani[1], Berliana Mardawati[1], Bunga Nur Annisa[2], Rhesi Kristiana[3], Vera Permatasari[2], Gian Primahana[2], Muhammad Eka Prastya[2], Puspa Dewi Narrij Lotulung[2], Tjandrawati Mozef[2], Akhmad Darmawan[2], Sofa Fajriah[2], Chairil Anwar[1], Winarto Haryadi[1]

1 *Department of Chemistry, Faculty of Mathematics and Natural Science, Gadjah Mada University, Yogyakarta 55281, Indonesia*

2 *Research Center for Pharmaceutical Ingredients and Traditional Medicine, National Research and Innovation Agency (BRIN), South Tangerang 15314, Indonesia*

3 *Indonesian Marine Education and Research Organization (MERO) Foundation, Br. Muntig Department, Karangasem, Bali 80853, Indonesia*

Corresponding author: Winarto Haryadi (wnrt_haryadi@mail.ugm.ac.id)

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Abstract

Aglaia foveolata Pannell (*A. foveolata*) is a type of plant that has many benefits, including the skin, leaves, roots, and seeds as medicinal ingredients. The potential of this plant is inseparable from the content of various bioactive compounds. This study aims to isolate, characterize the active compound from the stem bark of *A. foveolata* and test its activity as an antioxidant with the ABTS method, cytotoxic (MCF-7 cancer cells) with the MTT method, and antibacterial (bacterial strains ATCC and MDR) with the MIC. There are four isolated compounds obtained, namely (1) 17,24-epoxy-25-hydroxybaccharan-3-one, (2) β-stigmasterol glucoside, (3) Eichlerianic acid, and (4) 17,24-epoxy-25 -hydroxy-3- oxobaccharan-21-oic acid, which is a class of triterpenoid and steroid compounds. The best activity as an antioxidant was compound 3 (25.68 µg/mL); cytotoxic activity against MCF-7 cells namely compound 4 (94.59 µg/mL); antibacterial activity against ATCC strains: (1) *P. aeruginosa* namely compound 3 (29.4 µg/mL), (2) *E. coli*, (3) *S. aureus*, (4) *B. subtilis* for compounds 1, 2, and 4 have the same activity (62.5 µg/mL) while compound 3 was not active; MDR bacterial strains: (1) *P. aeruginosa* namely compound 4 (62.5 µg/mL), (2) *E. coli* namely compound 3 (62.5 µg/mL), (3) *S. aureus* namely compound 4 (62 .5 µg/mL), (4) *B. subtilis* namely compound 4 (62.5 µg/mL) and (5) *K. pneumoniae* namely compound 1 (125 µg/mL).

Keywords

Aglaia foveolata, triterpenoid, antioxidant, cytotoxic, antibacterial

Introduction

Indonesia, a megabiodiversity country, has the second biggest biodiversity in the world (Elfahmi et al. 2014; Gurning et al. 2021). About 80% of tropical forest area is covered by native medicinal plants, hence it is promisingly for pharmaceutical research especially in the discovery of natural product drug (Gurning and Haryadi 2022).

However, there has not been much exploration of these plants until now, one of them is *Aglaia*. *Aglaia* is the largest genus belonging to the family Meliaceae, comprising over 130 species distributed mainly in tropical forest and more than 65 grow in Indonesia (Bueno Pérez et al. 2014). Decoction and powders of this genus has been used as herbal medicine in Indonesia for wound, cough, fever and skin diseases. Various phytochemicals of this genus have been reported with fascinating bioactivities including several rocaglate derivatives, triterpenoids, and steroids (Harneti and Supratman 2021). These metabolites have been described to exhibit cytotoxic (Awang et al. 2012), insecticide (Brader et al. 1998), anti-inflammatory, and antitumor activities (Huang et al. 2022). Silvestrol, a rocaglate derivatives, has been extensively studied for its role as anti-tumor and anti-virus. It more toxic against various cancer cell (e.g MCF-7, LNCaP, Lu1 and HT-29) (Schulz et al. 2021).

Previous phytochemical studies of the species *Aglaia foveolata* reported some variety of compounds from leaves, bark and stem bark including flavaglines (e.g. silvestrol, bisamides, and rocaglamides) and dammarane-type triterpenoid (Roux et al. 1998; Salim et al. 2007; Pan et al. 2013). These metabolites have been evaluated for their cytotoxic activities. Antioxidant activity of compounds or extracts from other species of *Aglaia* has been described previously (Sianturi et al. 2016; Permatasari et al. 2023), but no information is available on the antioxidant activity of triterpenoid from the species of *A. foveolata*. In addition, methanol extract of stem bark *A. foveolata* showed antimicrobial activity (Dalimunthe et al. 2022), however, there are still limited reports regarding antibacterial activity of this species. Therefore, the present study aimed to isolate other triterpenoid compounds of *A. foveolata* and evaluate their antioxidant activity (ABTS), antibacterial activities against several normal and multidrug-resistant strains, and cytotoxic against MCF-7 human breast cancer.

Materials and methods

Plant materials

The bark of *A. foveolata* was collected from Mekongga forest, Southeast Sulawesi, Indonesia. The sample was identified by a botanist at Herbarium Bogoriense (collection number SR-IS-22).

Extraction and isolation

2.8 kg of dried samples of dried stem bark of *A. foveolata* were extracted by maceration method using 70% ethanol at room temperature for 3 days. The EtOH extract was concentrated in vacuum at ± 40 °C and 150 g crude extract was obtained. The crude extract was suspended in H_2O: MeOH (7: 3, 300 mL) to give an aqueous solution. The extract was continued by partitioning using the same volume of *n*-hexane solvent, then concentrated, followed by ethyl acetate (EtOAc), and *n*-butanol (BuOH). Evaporation produced crude extracts of *n*-hexane (63.36 g), EtOAc (61.83 g), n-BuOH (24.6 g), and residue H_2O (0.21 g). The cytotoxic activity of all extracts was evaluated against MCF-7 breast cancer cells, and the EtOAc extract showed the strongest cytotoxic activity. Therefore, the phytochemical analysis was focused on the EtOAc extract.

The EtOAc extract (48.7 g) was separated by column chromatography using silica gel (stationary phase) and the eluent (mobile phase) of a mixture of *n*-hexane:EtOAc (10:0–0:10), so that 75 fractions (F_1–F_{75}) were obtained. The TLC profiles of the fractions monitored by LC produced F_2, F_{15}, F_{17}, and F_{21}. This fraction was tested for cytotoxic activity, and fractions F_{15} and F_{21} showed the strongest activity, so further purification was carried out. The F_8 and F_{38} fractions were identified based on the spectroscopic method as pure compounds, yielding 17,24-epoxy-25-hydroxy-baccharan-3-one (1) (0.3 g) and stigmast-5,22-dien-3β-ol- 3-O-β-D-glucopyranoside (2) (0.1 g).

The F_{15} fraction was subjected to CC on a silica gel using a gradient elution mixture of *n*-hexane: EtOAc (10:0–0:10) to produce the subfractions (A–J). Subfraction J (60 mg) was chromatographed on a preparative RP-18 column (SupelcosilTM PLC 18 column (25 cm × 21.2 mm, 12 µm)), using isocratic conditions (CH_3CN-H_2O, 30:70) resulting in the purification of the eichlerianic acid compound (3) (12.2 mg, t_R 9.97 minutes). Similarly, the compound 17,24-epoxy-25-hydroxy-3-oxobaccharan-21-oic acid (4) (10.1 mg, t_R 8.05 minutes) was obtained from the F21 fraction (20 mg) using a SupelcosilTM PLC 18 column (25 cm × 21.2 mm, 12 µm); CH_3CN-H_2O, 55:45).

17,24-epoxy-25-hydroxybaccharan-3-one (1): forms a colorless needle pattern; UV (MeOH) λ_{max} (log ε) 205 nm; IR (KBr) ν_{max}: 3501, 1697, 1453, 1377, 1082, 895 cm^{-1}; 1H and 13C NMR (500/126 MHz, chloroform-*d*), see Table 1; HR-ESIMS m/z 459.386 $[M + H]^+$ (calculated for $C_{30}H_{51}O_3$, 459.725 g/mol).

Stigmast-5,22-dien-3β-ol-3-O-β-D-glucopyranoside (2): colorless needles; UV (MeOH) λ_{max} (log ε) 205 nm; IR (KBr) ν_{max} 3381, 1459, 1370, 1018 cm^{-1}; ^1H and ^{13}C NMR (500/126 MHz, dmso-d_6), see Table 1; HR-ESIMS m/z 512.343 [M + betainyl]$^+$ (calculated for $C_{29}H_{47}OOC$-$CH_2N^+(CH_3)_3$, 512.831 g/mol).

Eichlerianic acid (3): oily needles; UV (MeOH) λ_{max} (log ε) 205 (4.297) nm; IR (KBr) ν_{max} 3509, 1699, 1451, 1379, 1029 cm^{-1}; ^1H and ^{13}C NMR (500/126 MHz, methanol-d_4), see Table 1, HR-ESIMS m/z 497.358 $[M + Na]^+$ (calculated for $C_{30}H_{50}O_4Na$, 497.705 g/mol).

17,24-epoxy-25-hydroxy-3-oxobaccharan-21-oic acid (4): amorphous solid; UV (MeOH) λ_{max} (log ε) 205 nm; IR (KBr) ν_{max} 3508, 1749, 1696, 1448, 1334, 1031 cm^{-1}.; ^1H and ^{13}C NMR (500/126 MHz, chloroform-*d*), see Table 1; HR-ESIMS m/z 511.471 $[M + Na]^+$ (calculated for $C_{30}H_{48}O_5Na$, 511.690 g/mol).

Antioxidant assay (ABTS radical scavenging activity)

The radical scavenging activity of the isolated compounds was determined using the modified ABTS (2,2'-azinobis-3-ethylbenzothiazoline-6-sulfonic acid) decolorization method using a 96-well plate (Gomes et al. 2018). µL sample to produce final concentrations of 15.63, 3.91, 0.98, 0.244, and 0.061 µg/mL. After being incubated at room temperature for 20 minutes, the absorbance was read at a wavelength of 734 nm using a microplate reader (Benchmark). Trolox was used as a positive control. The percentage of free radical inhibition using the ABTS method is calculated using the formula given below:

$$ABTS^{\bullet+} \text{ scavenging activity} = [(A_{control} - A_{sample}) / A_{control}] \times 100\%$$

Antioxidant activity data were presented as IC_{50} values and obtained through a linear regression curve.

Cytotoxic assay

The isolated compounds were tested against breast cancer cells (MCF-7) using the MTT method (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) in 96-well microplates. Briefly, cells were maintained in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% (v/v) Fetal Bovine Serum (FBS) and Antibiotic-antimycotic. After 24 h of incubation, cells were treated with different concentrations of all compounds (6.25, 12.50, 25, 50, and 100 µg/mL), and doxorubicin (Sigma, St. Louis, MO) was used as a positive control. The test was stopped after an incubation period of 48 hours by adding 10 µL of MTT reagent and then incubated for 4 hours at 37 °C. The medium was carefully removed, and the cells were dissolved in 100 µL DMSO as a reaction stop. Absorbance was read with a microplate reader at a wavelength of 570 nm. The IC_{50} value was calculated using the linear regression method using Microsoft Excel software.

Antibacterial assay

Evaluation of antibacterial activity using ATCC bacteria and clinically isolated MDR bacterial strains, including two gram-positive bacteria (*Staphylococcus aureus* (*S. aureus*) ATCC 6538 and *Bacillus subtilis* (*B. subtilis*) ATCC 19659) and two gram-negative bacteria (*Escherichia coli* (*E. coli*) ATCC 8739 and *Pseudomonas aeruginosa* (*P. aeruginosa*) ATCC 15442), and multiresistant isolates from *S. aureus*, *B. subtilis* strain M18, *P. aeruginosa* strain M19, *E. coli* strain M4, and *Klebsiella pneumoniae* (*K. pneumoniae*) strain M19. This bacterium was isolated from the Central General Hospital (RSUP), Doctor Kariadi, Semarang, Central Java (R. Kristiana Collection, MERO Foundation, Bali). The Minimum Inhibitory Concentration (MIC) value of the isolated compound was measured using a standard microdilution test with slight modifications (Farabi et al. 2017; Saptarini et al. 2022). A double dilution of the sample solution (100 µl) was added to a 96-well sterile microplate containing 100 µL Mueller-Hinton broth medium (MHB). Next, each bacterial inoculum was incubated in sterile normal saline to give 1×10^8 CFU mL^{-1} and smeared into each well. These plates were then incubated at 37 °C for 24 hours. The MIC value was determined as the lowest sample concentration capable of preventing bacterial growth observed with clear well media. Tetracycline (Sigma-Aldrich) was used as a positive control.

Results and discussion

Ethyl acetate fraction of the stem bark of *A. foveolata* afforded three known triterpenes and steroid including 17,24-epoxy-25-hydroxybaccharan-3-one (**1**) (Joycharat et al. 2008), stigmast-5,22-dien-3*β*-ol-3-O-*β*-D-glucopyranoside (**2**, *β*-stigmasterol glucoside) (Setha et al. 2013) , 20S,24S-epoxy-25-hydroxy-3,4-secodammar-4(28)-en-3-oic acid (**3**, eichlerianic acid) (Schulz et al. 2021; Saptarini et al. 2022), and 17,24-epoxy-25-hydroxy-3-oxobaccharan-21-oic acid (**4**) (Dalimunthe et al. 2022) (Fig. 1). These four known compounds were identified by comparison of their spectroscopic data (IR, NMR, and mass spectrometry) with the data in the literature. The NMR spectroscopic data for compounds **1–4** were tabulated in Table 1.

These compounds were evaluated for their cytotoxic activity against the MCF-7 human breast cancer, antioxidant (Table 2), and antibacterial (Tables 3, 4). In this study, in vitro methods, ABTS used to investigate the antioxidant properties of *A. foveolata*.

The relative antioxidant ability to scavenge the radical $ABTS^{\bullet+}$ has been compared to positive control Trolox and is an outstanding method for determining the antioxidant activity of hydrogen-donating antioxidants. As shown in Table 1, all the compounds showed antioxidant activity but less than the standard. Eichlerianic acid showed the strongest antioxidant activity, 17,24-epoxy-25-hydroxy-3-oxobaccharan-21-oic acid, and *β*-stigmasterol glucoside showed strong activity, whereas 17,24-epoxy-25-hydroxybaccharan-3-one showed weak activity (Hidayat et al. 2018).

The cytotoxic effect on the MCF-7 breast cancer line was measured using a standard MTT assay compared to Doxorubicin as positive control. Among the four compounds, 17,24-epoxy-25-hydroxybaccharan-3-on (**1**) and 17,24-epoxy-25-hydroxy-3-oxobaccharan-21-oic acid (**4**) showed moderate activity, whereas *β*-stigmasterol glucoside (**2**) and eichlerianic acid (**3**) showed weak or no activity. This indicated that the presence of sugar moiety may decrease cytotoxic activity (Farabi et al. 2017). Cytotoxic of dammarane-type triterpenoids influenced by closed A-ring and opened side ring. Dammarane which has an opened A-ring and closed side ring like eichlerianic acid showed weak activity (Purwantiningsih et al. 2020).

The antibacterial activities of the isolated compounds were evaluated against normal ATCC and MDR bacterial

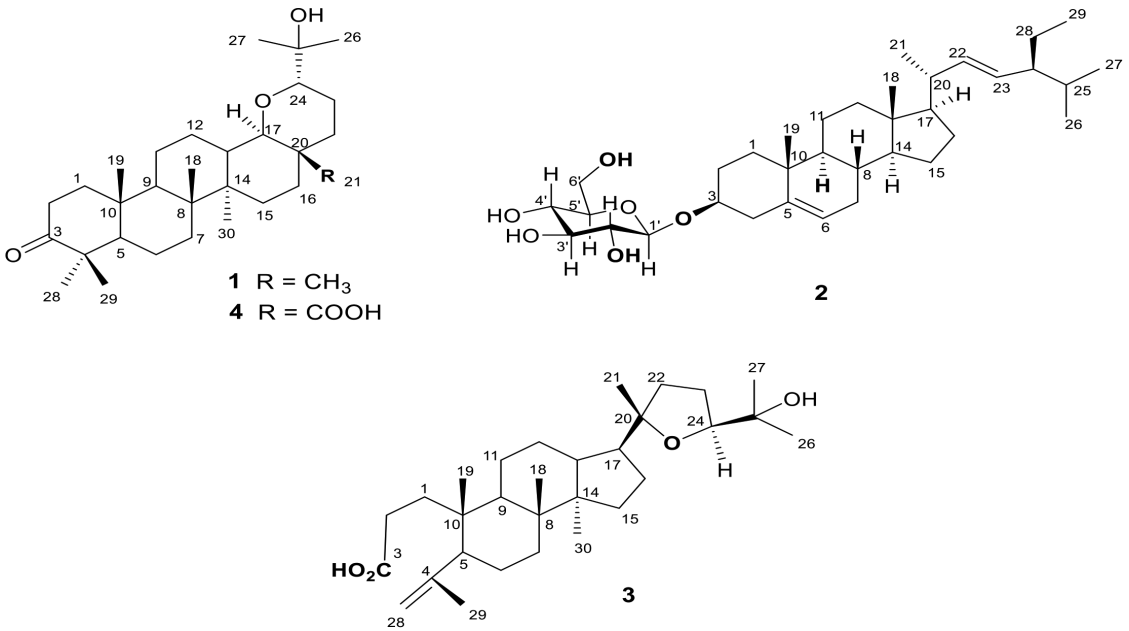

Figure 1. Structures of isolated compounds **1–4**.

Table 1. ^{1}H-NMR and ^{13}C-NMR (500/126 MHz) Data for **1–4**.

Position	1[a]		2[b]		3[c]		4[a]	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	1.44, 1.93	39.9	1.93	33.4	1.39, 1.95	35.8	1.39, 1.95	39.9
2	2.44, 2.51	34.2	2.34, 2.90	31.4	2.33, 2.14	30.0	2.41, 2.51	34.3
3	-	218.4	3.12	76.9	-	178.9	-	218.2
4	-	71.3	3.05	38.4	-	149.1	-	47.5
5	1.33	50.2	-	140.5	2.07	51.7	1.37	55.2
6	1.47, 1.79	22.1	5.32 *s*	121.3	1.72, 1.84	26.1	1.49, 1.53	19.7
7	1.40	31.3	1.80	29.3	-	35.3	1.43	33.0
8	-	40.4	1.64	31.5	-	41.4	-	42.7
9	1.43	50.0	1.09	49.7	1.29, 1.37	42.5	1.47	50.0
10	-	36.9	-	36.3	-	40.3	-	37.1
11	1.31, 1.53	25.9	1.46	22.7	-	23.6	1.36, 1.62	21.0
12	1.11, 1.96	26.1	1.36	36.9	-	28.3	1.16, 2.04	24.1
13	1.74	43.1	-	41.9	1.58, 1.71	44.4	1.83	40.4
14	-	47.5	1.15	56.2	-	52.0	-	40.9
15	0.97, 1.64	27.1	1.50	25.4	-	32.7	1.25, 1.52	28.3
16	1.34	34.7	1.62	27.9	1.57, 1.69	27.0	1.12, 2.22	30.8
17	3.64 *t*	55.4	1.20	55.5	-	51.3	4.04	76.1
18	1.08 *s*	16.1	0.64 *s*	11.9	0.88 *s*	17.0	0.96 *s*	15.7
19	0.93 *s*	16.2	0.95 *s*	19.8	0.95 *s*	21.0	0.93 *s*	16.0
20	-	-	1.40	35.6	-	88.0	-	47.3
21	0.99 *s*	21.1	1.00	19.0	1.15 *s*	26.3	-	176.8
22	1.38, 1.52	37.7	4.92	138.1	1.83, 1.90	36.3	1.78, 1.99	32.1
23	1.45, 1.75	19.8	5.16	128.9	-	27.9	1.89, 2.01	20.4
24	3.76 *t*	84.6	1.13	45.2	3.68 *t*	87.9	3.71 *t*	79.6
25	-	86.6	1.60	28.7	-	72.2	-	75.5
26	1.14 *s*	24.4	0.81	19.2	1.16 *s*	27.6	1.30 *s*	27.3
27	1.20 *s*	27.8	0.80	18.7	1.13 *s*	25.8	1.21 *s*	28.1
28	1.10 *s*	26.2	1.26	23.9	4.70, 4.85	114.1	1.05 *s*	26.7
29	1.03 *s*	21.8	0.90 *d*	12.2	1.76 *s*	24.0	1.01 *s*	21.2
30	0.87 *s*	15.3			1.07 *s*	16.0	0.95 *s*	15.3
Glc								
1′			4.89	100.8				
2′			3.65	73.5				
3′			3.52	76.8				
4′			3.48	70.1				
5′			4.22	76.8				
6′			4.47 *t*	61.1 *t*				

[a]$CDCl_3$; [b]dmso-d_6; [c]methanol-d_4.

Table 2. Antioxidant and Cytotoxic Activity (IC_{50} values) of Compounds **1–4**.

Compound	ABTS	MCF-7	
	IC_{50} (µg/mL)	Inhibition (%)	IC_{50} (µg/mL)
1	187.18	34.73 ± 2.79	175.11
2	62.87	10.13 ± 4.22	446.87
3	25.68	7.92 ± 4.32	535.11
4	54.50	44.77 ± 7.30	94.59
Doxorubicin	-	91.56 ± 0.18	-
Trolox	18.02	-	-

Table 3. MIC values of the isolated compound against ATCC strains.

Sample	Bacterial tested			
	P. aeruginosa	*E. coli*	*S. aureus*	*B. subtilis*
	MIC (µg/mL)			
1	125	62.5	125	125
2	62.5	62.5	125	125
3	29.4	-	-	-
4	62.5	62.5	62.5	62.5
Tetracycline (Control)	3.90625	3.90625	3.90625	3.90625

Table 4. MIC values of the isolated compound against MDR strains.

Sample	Bacterial tested				
	P. aeruginosa	*E. coli*	*S. aureus*	*B. subtilis*	*K. pneumoniae*
	MIC (µg/mL)				
1	250	250	250	250	125
2	250	250	250	250	250
3	-	62.5	125	125	250
4	62.5	125	62.5	62.5	250
Tetracycline (Control)	3.90625	3.90625	3.90625	3.90625	3.90625

strains (Tables 2, 3). Hence, eichlerianic acid (**3**) was highly active (MIC 29.4 µg/mL) against *P. aeruginosa* and was not active to inhibit other normal bacterial strains. This activity suggests that the contribution of electron withdrawing groups (-COOH) (Purwantiningsih et al. 2020). However,

this compound was not active against *P. aeruginosa*-MDR strains, but significantly active against others MDR-bacterial. The other compounds including 17,24-epoxy-25-hydroxybaccharan-3-on (**1**), *β*-stigmasterol glucoside (**2**), and 17,24-epoxy-25-hydroxy-3-oxobaccharan-21-oic acid (**4**) were significantly active with MIC values 62.5–250 µg/mL against normal and MDR bacterial strains.

Conclusion

Dammarane and baccharane-type triterpenoids and stigmasterol-glucoside were isolated from the stems bark of *A. foveolata*. Compound **3** showed the strongest ABTS radical cation scavenging activities, and compound **2–4** exhibited strong activity. For cytotoxic activity, baccharanes compound **1** and **4** showed moderate activity against MCF-7. In addition, antibacterial assay showed all the compounds exhibited strong activity against normal and MDR bacterial strains, while compound **3** showed strongest activity against *P. aeruginosa*-normal strains. To the best our knowledge, this is the first report of triterpenoid of *A. foveolata* as antioxidants and antibacterial.

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