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Bioassay Guided Isolation of Artoindonesianin C with Antidiabetic Activity from *Artocarpus elasticus* Reinw. Ex. Blume Bark

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Abstract. *Artocarpus elasticus* Reinw. ex Blume is a member of the Moraceae tribe, which contains prenylated phenolic compounds, especially flavonoids with different structural variations such as flavanones, flavones, xanthones, chalcone, and stilbene. This research aims to isolate, identify, and evaluate their antidiabetic activity from *A. elasticus* Reinw. ex Blume bark. The research method consisted of isolation by column chromatography based on bioassay-guided fractionation, characterization of isolate using UV-Vis, FTIR, LC-MS, and NMR spectroscopy and *in vitro* antidiabetic activity assay against α-glucosidase enzyme. This study obtained artoindonesianin C with the molecular formula of $C_{26}H_{22}O_8$. Antidiabetic activity against α- glucosidase inhibitor showed significant activity with IC_{50} value of 31.88 µg/mL.

Keywords: *Artocarpus elasticus Reinw.* ex Blume, antidiabetic activity, artoindonesianin C, α-glucosidase enzyme

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia associated with abnormalities of carbohydrate, fat, and protein metabolism caused by decreased insulin secretion or decreased insulin sensitivity, or both and causes chronic and neuropathic complications [1]. The cause of diabetes mellitus is a lack of insulin, which functions to allow glucose to enter cells to be metabolized (burned) and thus utilized as an energy source. As a result, glucose builds up in the blood (hyperglycemia) and is eventually excreted in the urine without being used (glycosuria). Another cause is the decreased sensitivity of cell receptors to insulin (insulin resistance) caused by overeating and obesity [2].

Recently, some herbal medicines have been useful to treat diabetes and have been used empirically as antidiabetic remedies. One of the plant families known to have many benefits is Moraceae, a fairly large plant family consisting of 1180 species and 38 genera [3]. One of the genera belonging to the family Moraceae is Artocarpus. This plant is widely distributed throughout the archipelago, and several species are endemic to South Sulawesi. Artocarpus contains prenylated phenolic compounds, especially flavonoids with various structural variations such as flavanones, flavones, xanthones, chalcones, and stilbenes. The prenyl group on the flavonoid is in the C-3 position and the oxygenated B ring at the C-4' or C-2', C-4' or C-2', C-4', C-5' position. In addition, prenylation can also occur at positions C-6, C-8, and C3' [4,5,6]. *A. elasticus* also has a unique structure of flavonoids and produces broad pharmacological effects such as artonin E, artobiloxanthone, cycloartobiloxanthone, artoindonesian W, artoindonesianin P, and artoflavone B as α-glucosidase inhibitors [7, 8]. Therefore, the purpose of this study was to isolate α-glucosidase inhibitory compounds

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from *A. elasticus* barks using bioassay-guided fractionation techniques and identify the isolate using spectroscopic methods.

MATERIALS AND METHODS

Materials

General

UV/Vis analysis was recorded on Agilent Technology, Cary 60, and FTIR spectrum was measured with Shimadzu-Prestige 21. 1D and 2D NMR spectra were recorded with JEOL ECZR500 operating at 500 MHz using CD as a solvent. Molecular weight was obtained from LCMS data with ESI system (Mariner Biospectrometry). Column chromatography was performed on silica (60-230 mesh, Merck) and sephadex LH-20 (Sigma Aldrich). Preparative TLC and TLC was analysis on GF_{254} plates (Merck). α-Glucosidase was obtained from yeast *Saccharomyces cerevisiae* (EC 3.2.1.20).

Plant material

The barks of *Artocarpus elasticus were* collected from Mengga Forest, South East Sulawesi, Indonesia and identified by a botanist from Research Center for Biology LIPI. A voucher specimen was deposited in the herbarium with voucher specimen UHA46.

Methods

Extraction and Fractionation

The dried bark of *A. elasticus* was extracted by maceration. A portion of 800 grams powder was macerated with methanol solvent with ratio 1: 3 (simplicia : solvent) for 3 x 24 hours. The combined methanol extracts were evaporated to dryness with a rotary evaporator at a temperature of 40-50°C to give methanol extract (47.67 g). Furthermore, about 33 grams methanol extracts were fractionated by solvent extraction method in a ratio of 1:1 using a separating funnel with n-hexane, ethyl acetate and n-butanol for 3 times, then each fraction was evaporated under reduce pressure to yield n-hexane (7.57 g), ethyl acetate (9.72 g), *n*-butanol (3.01 g) and residue (water, 3.04 g) fractions.

Isolation and Purification

The amount of 7 grams ethyl acetate fraction (the active fraction) was further purified using VLC (Vacuum Liquid Chromatography) with gradient elution (*n*-hexane-ethyl acetate-methanol) to obtain nine main fractions. Fraction 4 was subjected to a silica gel (Kieselgel 60, 60-230 mesh) column chromatography eluted with gradient elution (*n*-hexane-ethyl acetate-methanol) to afford nine sub-fractions (SF1-SF9). Sub-fraction SF5 further was purified using sephadex LH-20 eluted with dichloromethane-methanol (1:1) to give 8 sub-fractions ($SF_{5.1} - SF_{5.8}$). Furthermore, $SF_{5.5}$ was purified using preparative TLC with *n*-hexane:ethyl acetate (9:1) as mobile phase to afford a pure compound **1** (8 mg). Compound **1** was characterized with UV/Vis, FTIR, LCMS and FT-NMR spectrometers, and its α-glucosidase inhibitory activity assay was examined.

α-Glucosidase Inhibitory Activity Assay

The α-glucosidase inhibitory activity assay was evaluated according to the previous method with minor modifications [9, 10]. A total of 5 µL sample dissolved in DMSO at various concentrations was added with 495 µL of phosphate buffer pH 7.0 and p-nitrophenyl-α-D-glucopyranoside (PNPG) solution of 5 mM as much as 250 µL, then incubated for 5 minutes at 37°C. The reaction was started by adding 250 µL of enzyme solution to the sample, followed by incubation for 15 minutes at 37°C. After the incubation period was completed, the reaction was stopped by adding 1000 µL Na_2CO_3. The absorbance of the sample was measured using a UV-Vis spectrophotometer at a

wavelength of 400 nm. Furthermore, blanks were prepared to correct background absorbance where the enzyme was replaced with 250 µL of phosphate buffer. The percent inhibition of α-glucosidase inhibitory activity was calculated using the following formula: % Inhibition= (A - B)/A x 100, where A was the absorbance of the control reaction and B was the absorbance in the presence of the sample. The value of IC_{50} was calculated from the main inhibitory values by applying linear regression analysis. Quercetin and α-mangostin were used as reference standard.

RESULTS AND DISCUSSION

The extraction process of the dried barks of *A. elasticus* yielded 5.96% of methanol extract. This extract exhibited high activity as an α-glucosidase inhibitor with IC_{50} 1.95 µg/mL. Furthermore, the fractionation process of methanol extract yielded 25.25% of *n*-hexane fraction, 32.41% of ethyl acetate fraction, 10.05% *n*-butanol fraction, and 13.12% residue (water) fraction. These fractions were further assayed their α-glucosidase inhibitory activity, and all had a strong activity with IC_{50} 8.67, 8.67, 1.24, 9.30 µg/mL with quercetin as the positive control (IC_{50} 9.30 µg/mL). Further studies were conducted on ethyl acetate fraction. This fraction was purified using a gravity chromatography column with silica gel 60 GF_{254} as the stationary phase with gradient elution using solvents with different polarities ranging from 100% non-polar solvents to 100% polar solvents (*n*-hexane, ethyl acetate, and methanol). All subfractions obtained were identified by Thin Layer Chromatography (TLC), and the spots were observed under UV light at λ 254 nm and 365 nm afforded nine sub-fractions (SF1-SF9). These subfractions were analyses for their α-glucosidase inhibitory activity shown in Table 1. Since SF5 showed the highest activity, it was selected for the next purification process. This subfraction further was subjected to Sephadex LH-20 column chromatography and by Preparative Thin Layer Chromatography and obtained the active compound **1** as a yellow powder (8 mg). The structure of **1** was determined by using UV-Vis spectrophotometry, FTIR, LC-MS, and NMR.

TABLE 1. α-Glucosidase Inhibitory Activity of extracts, fractions, and subfractions from *A. elasticus* barks

Sample	IC_{50} (µg/mL)	Sample	IC_{50} (µg/mL)	Sample	IC_{50} (µg/mL)
Quercetin (positive control)	9.30	Residue (water) fraction	9.30	SF5	1.38
Methanol Extract	1.95	SF1	132.95	SF6	1.42
n-hexane fraction	8.67	SF2	11.47	SF7	4.10
Ethyl acetate fraction	8.67	SF3	8.85	SF8	8.74
n-butanol fraction	1.24	SF4	1.39	SF9	8.08

The UV-Vis spectrophotometry analysis of compound **1** showed two absorption bands at the maximum wavelength (λmax) of 265 nm and 395 nm, and it was characteristic for xanthone derivative [11]. The FTIR spectrum also showed typical of hydroxyl, aliphatic, carbonyl and benzene groups at absorption λ 3437, 2862, 1641 and 1458 nm, respectively. The ESI-MS data showed that compound **1** has molecular weight *m/z* 462.47 with a molecular formula of $C_{26}H_{22}O_8$.

Based on ^{1}H-NMR data ($CDCl_3$, 500 MHz), it showed the presence of an intramolecular hydroxyl group (OH) at chemical shift δ_H 12.60 ppm (1H, s, OH-1). A 2,2-dimethylchromene was shown with the presence of two methyl groups at chemical shift δ_H 1.50 and 1.49 (6H, s, Me-14 and Me-15) and two olefinic protons at δ_H 7.04 (1H, d, J= 10 Hz, H-11) and 5.70 (1H, d, J = 10 Hz, H -12). Isoprenyl group was showed with the presence of methyl group at δ_H 2.13 (3H, s, Me-20) and a terminal methylene protons at δ_H 4.86 & 5.28 (2H, s, H-21). Sharp singlets at δ_H 6.31 (1H, s, H-2), and 8.26 ppm (1H, s, H-8) indicated two aromatic protons in ring B and D. Signals of a hydroxyl group also showed at δ_H 7.06 (1H, OH-18), an isolated methylene group at δ_H 4.86 and 5.28 (2H, s, H-21). A methoxy group was showed at δ_H 3.74 (3H, s, - OCH_3), 7.04 (1H, d, J= 10 Hz, H-11) $\delta_{H\,7}$ one singlet proton at the H-8 position with a chemical shift of H 8.26 one singlet proton at the hydroxyl position (-OH) with a chemical shift of 7.06 (1H, s, OH-18), one singlet protons at position H-2 with a shift of 6.31 two singlet protons at position H-21 with a chemical shift of 4.86 and 5.28 (2H, s, H-21), three singlet protons at the methoxy position with a chemical shift of 3.74 (3H, s, 23-OCH_3).

The ^{13}C-NMR ($CDCl_3$, 125 MHz) of compound **1** contained 26 carbons, consists of 4 methyl (-CH_3), 4 methine (-CH), 2 methylene (-CH_2), 13 quaternary carbons and 3 carbonyl (C=O). The methyl groups consist of a typical methoxy group (O-CH_3) at a chemical shift δ_C 52.1 ppm, methyl sp3 at δ_C 25.4 ppm (C-20) and methyl at C-14 and C-15 with δ_C C 28.7 ppm. The methylene groups (-CH_2) were presented at δ_C 54.0 (C-17) and δ_C 117.7 ppm (C-21).

The methine (-CH) group were showed in δ_C 100.1 (C-2), 132.9 (C-8), 115.0 (C-11), and 128.1 (C -12). Quaternary carbons showed at δ_C 161.8 (C-1), 160.0 (C-3), 100.2 (C-4), 150.9 (C-4a), 125.6 (C-5), C 156.7 (C-6), 141.9 (C-7), 121.9 (C-8a), 104.1 (C-9a) , 151.4 (C-10a), 79.1 (C-13), 76.9 (C-18), and 138.1 ppm (C-19). The carbonyl groups (C=O) showed at δ_C 179.4 ppm (C-9), C 197.0 ppm (C-16) and C 174.5 ppm (C-22).

TABLE 2. ^{1}H, ^{13}C, HMQC and HMBC data of compound **1**

Position	HMQC		Artoindonesianin C [11]	HMBC
	δ_H (ppm, multiplisitas, J(Hz))	δc (ppm)	δc (ppm)	δc (ppm)
1	-	161.8	162.1	
2	6.31 (*s*)	100.1	99.1	C-9a
3		160.0	160.6	
4		100.2	101.1	
4a		150.9	150.9	
5		125.6	124.3	
6		156.7	158.6	
7		141.9	141.0	
8	8.26 (*s*)	132.9	131.3	C-6, C-9, C-10a
8a		121.9	120.7	
9		179.4	178.9	
9a		104.1	103..5	
10a		151.4	150.1	
11	7.04 (*d*, *J* = 10)	115.0	113.8	C-13
12	5.70 (*d*, *J* = 10)	128.1	128.4	C-2
13		79.1	78.9	
14	1.50 (*s*)	28.7	28.0	-
15	1.49 (*s*)	28.7	28.0	-
16		197.0	198.0	
17	3.20 (*d*, *J* = 18)	54.0	52.6	C-16, C-18
18	7.06 (*s*)	76.9	76.3	-
19		138.1	137.6	
20	2.13 (*s*)	25.4	24.5	C-8, C-19, C-21
21	4.86 (*s*); 5,28 (*s*)	117.7	117.5	C-19, C-20
22		174.5	172.6	
23	3.74 (*s*)	52.1	52.4	174.5

Two-dimensional NMR analysis was performed with HMQC and HMBC. The HMQC spectrum showed a direct correlation between protons and carbon ($^{1}J_{C,H}$). HMQC data showed a chemical shift at δ_H 8.26 ppm correlated with carbon at δ_C 132.9 ppm, δ_H 7.10 ppm to carbon at δ_C 115.0 ppm, δ_H 5.70 ppm to carbon at δ_C 128.1 ppm, δ_H 1.26 ppm to carbon at δ_C 28.7 ppm, δ_H 3.20 ppm to carbon at δ_C 52.1 ppm, δ_H 7.08 ppm to carbon at δ_C 76.9 ppm, δ_H 2.13 ppm to carbon at δ_C 25.4 ppm and δ_H 4.86 ppm for carbon at δ_C 117.7 ppm. HMQC correlation can be seen in Table 2.

The HMBC spectrum showed an indirect correlation between proton and nearby carbon with a distance of two to three bonds ($^{2,3}J_{CH}$). HMBC data showed that the methyl groups on Me-14 and Me-15 correlate with the quaternary carbons C-7 and C-19 and with the C-21 methylene group. The methoxy group (O-CH_3) at C-23 has a correlation with

the carbonyl group (C=O) at C-22. The H-8 position correlates with the carbonyl (C=O) at C-9 and two quaternary carbons at C-6 and C-10a. The H-21 position correlates with the methine group at C-8 and the methyl group at C-20. The methylene group at position H-17 has a correlation with the carbonyl group (C=O) at C-16 and the alcohol (C-OH) and ester (R-CO_2) groups at C-18. At the H-12 position has a correlation with methyl at C-14 and C-15 and quaternary carbon at C-4. The H-11 position correlates with the oxygenated quaternary carbon at the C-13 position. Besides, the H-2 position correlated with C-9a. HMBC correlation can be seen in Figure 1.

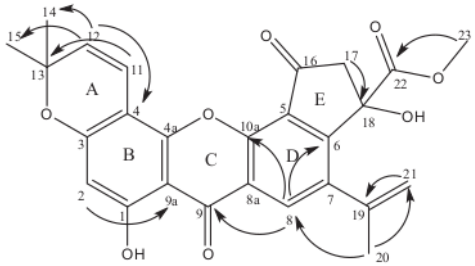

FIGURE 1. HMBC correlation of compound **1**

Based on the results of the analysis of ^{1}H-NMR, ^{13}C-NMR, HMQC and HMBC data as well as UV-VIS, FTIR and LC-MS spectrometer and supported with literature [11] it was concluded that compound **1** is a xanthone derivative, Artoindonesianin C. This compound was first report in *A. elasticus* and found in the species *A. teysmanii* Miq [11].

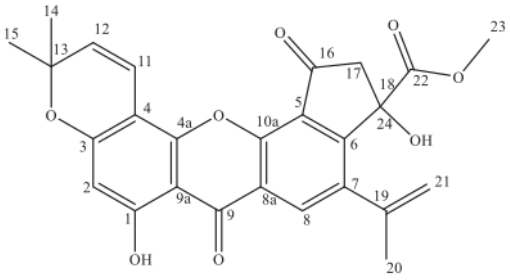

FIGURE 2. Artoindonesianin C isolated from *A. elasticus* barks.

The antidiabetic activity of artoindonesianin C was evaluated using α-glucosidase from the yeast *S. cerevisiae*. α-Glucosidase inhibitors might reduce a blood sugar level and lead to suppressed postprandial hyperglycaemia responsible for diabetes [7]. In this study, α-mangostin (IC_{50} 14.55 µg/mL) was used as positive control because it is a xanthone group and known to have α-glucosidase inhibitor activity [12]. The results showed that artoindonesianin C have potential to inhibit α-glucosidase enzyme with IC_{50} 31.88 µg/mL. The activity decreased compared to SF-5 since there was a synergistic activity between the compounds in the fraction level, therefore artoindonesianin C which is a pure compound has a lower ability to inhibit α-glucosidase enzyme.

CONCLUSIONS

The present study revealed that artoindonesianin C has been successfully isolated from *A. elasticus* barks and potential to be developed as an antidiabetic agent. Besides, the extracts and fractions from *A. elasticus* also have potential source as herbal medicine for antidiabetic type 2 remedies [7].

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