Isolation, Characterization, Modification of Artocarpin Compound from Pudau Plant (Artocarpus kemando Miq.) and Bioactivity Antibacterial Assay of Artocarpin Compound and Their Modification Result

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Isolation, Characterization, Modification of Artocarpin Compound from Pudau Plant (*Artocarpus kemando* Miq.) and Bioactivity Antibacterial Assay of Artocarpin Compound and Their Modification Result

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Abstract: Artocarpus kemando Miq. is a species from the family Moraceae in Indonesia known as the Pudau plant. The purpose of this study is to isolate, characterize, modify and test the antibacterial activity of artocarpin compounds isolated from pudding plants. Stages of research include sample preparation, extraction, isolation, and purification of compounds using chromatographic techniques (TLC, VLC, and CC), characterization of compounds using spectroscopy. The isolated compound was obtained as a yellow crystal with a melting point of 185-187 °C. Based on the results of spectroscopic analysis, showed that the prenylated flavonoids had been successfully isolated, artocarpin in an amount of 35.2 mg. Modification of artocarpin with acetic anhydride produces artocarpin acetate as a yellow crystal. Artocarpin and modified compounds showed antibacterial activity against Bacillus subtilis and Escherichia coli.

1. Introduction

Indonesia is known as a country that have a large biodiversity, some of plants are consumed as food and the others have a potential to be developed as medicines. Based on this, the scientists continue to develop the potential of these plants as raw material for medicines to overcome various diseases. One he family of medicinal plants is Moraceae which consists of 60 genus including 1400 species [1]. One of the main genus of the Moraceae family is *Artocarpus*.

Artocarpus consists about 50 species, this genus is widely distributed in tropical and subtropical regions, including Indonesia [2]. The bark, leaves, seeds, fruits and roots of some species are reported have medicinal properties and used for the treatment of diseases such as diarrhea, fever, cirrhosis, hypertension, inflammation, malaria, ulcers, sores and for tapeworm infections [3,4,5] One of the species of Artocarpus which is an endemic plant in Indonesia is Artocarpus kemando Miq. can produce many prenylated flavonoid compound by means of isolation and some compounds obtained show interesting biological activity [6,7,8]. One of the compound contained in A. kemando Miq. is artocarpin [9].

Artocarpin is a prenylated flavon compound which has three hydroxyl groups. Two of them are in an metha position, so that the group is easily to oxidized. In order to avoid oxidation reactions, it is necessary to modaly with esterification [10]. In this study, artocarpin was isolated from A. kemando Miq. This plant was obtained from Karang Anyar, Klaten Village, Penengahan, South Lampung,

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Lampung, Indonesia. After that artocarpin esterified with acetic anhydride using pyridine catalyst, the ester compound were characterized by speroscopy methods and then tested for antibacterial bioactivity against the bacteria *B. subtilis* and *E. coli*.

2. Methods

2.1. General

The melting point was determined by the MP-10 Stuart melting point. The UV-vis and IR spectra were measured with Agilent Cary 100 and 21 Shimadzu Prestige FT-IR spectrophotometer 12 he ¹H and ¹³C NMR spectra were obtained with an Agilent spectrometer with DD2 console system at 570 MHz and 125 MHz, respectively. Vacuum liquid chromatography (VLC) was performed using a Merck Si-gel 60, and thin layer chromatography (TLC) analysis was Si-gel plates (Merck Kieselgel 60 F254, 0.25 mm).

2.2. Sample Preparation

Root wood of A. kemando Miq. obtained from Karang Anyar, Klaten village, Penengahan, South Lampur 21 Lampung, in March 2019 and identified at Bogoriense Herbarium, Research Biology Center, Indonesia, Institute of Sciences Bogor, Indonesia.

2.3. Extraction and Isolation

A.kemando Miq. root wood powder (3 kg) macerated with methanol as a solvent for 3x24 hours. Then to remove the solvent, evaporated with a rotary evaporator to obtained a crude extract (41 g). The extract was fractionated with hexane solvent to obtained a methanol fraction (29.8 g). the methanol fraction in vacuum liquid chromatography was eluted with EtOAc / n-hexane in a ratio of 0-100%, to produce five main fractions (A - E). Fraction C 1.2455 g was then chromatographed with silica gel adsorbent and acetone / hexane eluent at a ratio of 20:80%. (10 pmatography results obtained yellow crystals from the C8 fraction (140 mg), then purified further by column chromatography using silica gel adsorbents and hexane / acetone eluents in a ratio of 20:80%, producing yellow crystals from the C8f fraction as much as 35.2 mg, expressed as compound (1). The purity of the crystals obtained was determine 20 by measuring the melting point and TLC chromatograms were made with three eluent systems. The structure of the compound (1) was determined by UV-Vis, IR, and NMR spectroscopy.

2.4. Modification of Artocarpin Compound

Modification of artocarpin compounds by using acetic anhydride and pyridine catalyst. 10 mg of artocarpin compound was mixed with 0.1 mL of pyridine catalyst, then added 0.24 mL of acetic anhydride reagent and put into a closed reaction flask. The mixture is allowed to stand for up to 3 x 24 hours and spotted with TLC every 24 hours. After that, the mixture with aquades, filtered and vacuum so that yellow precipitate is obtained. The modified results were recrystallized with ether/hexane solvent to produce 6.6 mg yellow crystal. Expressed as compound (2) and analyzed by determining the melting point and TLC with three eluent systems. The success of the esterification was determined using UV-Vis and IR spectroscopy.

2.5. Antibacterial Bioactivity Test

In the antibacterial bioactivity test, the paper disc diffusion method was used [11]. Antibacterial test using Nutrient Agar (NA) media. 4.2 grams of NA were dissolved in 150 mL aquades and then heated until homogeneous 5 prtocarpin compound and modified compound were made variations in three concentrations: 0.5 mg/disk; 0.4 mg/disk and 0.3 mg/disk. 1.5 mg compound (1) are dissolved in 150 μ L, then taken 50 μ L; 40 μ L; and 30 μ L to be bottled into a 170 r disk.

In the antibacterial test against *B. subtilis* a amoxicillin was used as a positive control, while the antibacterial test on *E. coli* used chloramphenicol as a positive control. After the media solidifies, inserted NA added with aquades containing 1 ose of bacteria. Then the paper disk containing the sample, positive control and negative control is inserted into the NA that has been made. Petri dishes are covered with paper and plastic wrap and then put in an incubator for 1x24 hours.

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3. Results And Discussion

3.1. Isolation of compounds from A. Kemando Miq.

To determine the purity of compound (1), the sample was spotted in TLC together with standard artocarpin using three different eluent systems and obtained the same Rf results (Figure 1). From the TLC results it is estimated that the compound (1) is an artocarpin compound. Melting point of compound (1) 185-187 °C.

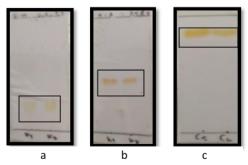


Figure 1. Comparison chromatograms of compound (1) (left) and standard artocarpin (right), using three eluent systems (a) ethyl acetate: n-hexane 75% Rf = 0.20, (b) acetone: n-hexane 65% Rf = 0.34, (c) ethyl acetate: dichloromethane 60% Rf = 0.85.

3.2. Modification of Artocarpin Compound

The purity of compound (2) was determined, the melting point of compound (2) 150-152 °C and at TLC together with compound (1) using three eluent systems, Rf of compound (2) was higher than that of compound (1). This shows that compound (2) is more nonpolar compared to compound (1), because the hydroxyl group in compound (1) is thought to have been esterified (Figure 2).

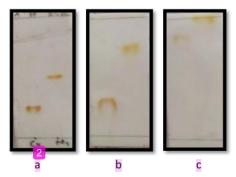


Figure 2. Comparison chromatogram of compound (1) (left) and compound (2) (right) using three eluent systems (a) acetone: n-hexane 75% Rf = 0.20; 0.42, (b) ethyl acetate: n-hexane 75% Rf = 0.26; 0.71, (c) ethyl acetate: dichloromethane 85% Rf = 0.82; 1.00.

33. Spectroscopic analyses

The UV-Vis spectrum of compound (1) in the MeOH solvent produces absorption at λ max 321 and 279 nm which is a typical spectrum of flavones. Band I which shows the characteristics of the B and C rings of the flavon structure as sinamoil chromophore. Maximum peak at λ max 279 nm is a typical absorption of flavones in band II that shows the characteristics of benzoyl chromophore. UV-Vis spectrum of compound (2) in the MeOH solvent obtained λ max: 280 and 300 nm The maximum absorption in the ultraviolet region at λ max 300 nm represents the spectrum in band I and the maximum absorption at λ max 280 nm is the spectrum in band II. Based on this data it can be seen

that band 1 for compound (2) has decreased wavelength (hypsochromic effect) when compared to compound (1) by 21 nm. This shows that there has been a substitution of a hydroxy group in compound (1) into an ester in compound (2) (Figure 3).

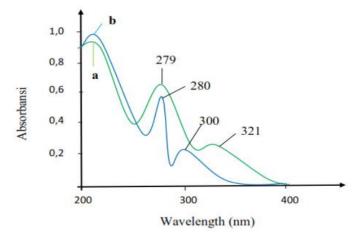


Figure 3. UV-vis spectrum of (a) compound (1) and (b) compound (2) (in methanol).

The results of the IR spectrum analysis of compound (1) are equivalent to artocarpin (KBr) Vmax.: 3390, 2955 22866, 1680, 1481, 1471, 1352, 1259, 1205, 1149,1097 and 979 cm⁻¹ (Figure 42 The absorption peak at 3390 cm⁻¹ is a stretching vibration from hidroxy group, 2958 cm⁻¹ dan 2866 cm⁻¹ is C-H alifatik, 1620 cm⁻¹ is carbonyl group (C=O) conjugated with C=C, 1205 cm⁻¹ is bond C-O alcohol, 1481 cm⁻¹ provide inf 9 mation about the presence of aromatic ring which is strengthened by the absorption C-H at 900-600 cm⁻¹.

In the IR spectrum of compound (2) data are obtained (KBr) Vmax.: 3510, 3093, 2956, 2866, 1772, 1647, 1587, 1485, 1450, 1354, 1301, 1201, 1145, 1099, 1041, 1012, 974 cm⁻¹ (Figure 4). Absorption at wave numbers 3200-3500 cm⁻¹ is absorption from O-H stretching vibration [12]. The compound (2) there is still visible absorption of 3510 cm⁻¹ but the intensity is smaller than the compound (1). In addition, there was also a change in the absorption of the wave number of the carbonyl group (C = O) seen at 1772 cm⁻¹ with a greater intensity compared to the compound (1). This shows that compound (1) has undergone a change in the hydroxyl group into an ester group due to the esterification reaction.

The ¹H-NMR spectrum of compound (1) 3 ows that there is a singlet proton at C sp3 at δ 1.56 ppm (3H, 6) and at δ 1.43 ppm (3H, s). The peak at δ 182 ppm (1H, d, J = 7.0 Hz) shows to the correlation with the proton at δ 3.12 ppm. The proton C sp³ at a chemical shift of δ 1.09 ppm (6H, d, J = 6.7 Hz) indicates a double peak, at δ 2.43 ppm (1H, m) which shows the peq2 of the multiplet because the proton is coupled by the proton at δ 6.73, 1.08, and 1.09 ppm. Protons at δ 6.57 ppm (1H, d, J = 13 Hz) is an alkene proton is coupled by a protons at δ 6.73 15 m.

The aromatic protons found at δ 6.61 (1H, s) are protons in ring A, while δ 6.51 ppm (1H, d, J = 13 Hz) the possibility of protons on ring B coupled by protons at δ 6.52 ppm (1H, dd, J = 8.4 Hz a 12 2.3 Hz) are coupled by protons at δ 7,20 (1H, d, J = 8.6 Hz). In addition, there is a proton C sp3 at δ 3.96 ppm (3H, s) which appears as the peak of the singlet which is likely 23 riginate from the proton methoxy group (Figure 5).

From the 1 H-NMR spectrum of compound (1) it is estimated that the chemical shift of the proton is in the carbon position number: δ 1, 08 and 1.09 (H-17 and H-18), 2.43 (H-16), 6.73 (H-15), 6.57 (H-14), 1.43 (H-13), 1.56 (H-12), 5.12 (H-10), 3.12 (D-9), 6.61 (H-8), 3.96 (H-OCH3), 6.51 (H-3'), δ 6.52 (H-5'), and δ 7.20 ppm (D-6').

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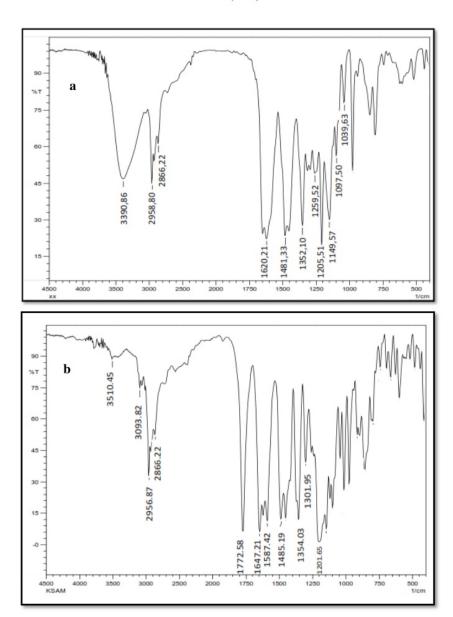
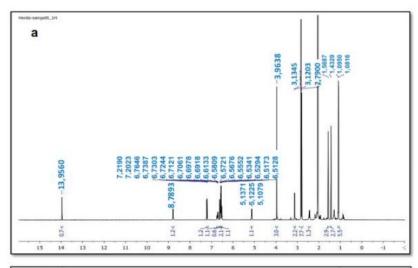


Figure 4. IR spectrum of (a) compound (1) and (b) compound (2).

The 13 C-NMR spectrum of the compound (1) shows 26 carbon, including oxygenated aromatic carbon at δ 157.4; 159.8; 163.8; 142.3; 142.3; and 132.3 ppm. The chemical shift at δ 183.3 ppm indicates a carbonyl group. Carbon atoms from the methoxy group appear at δ 56.6 ppm, while C sp3 at δ 34.3; 25.8; 24.3; 23.1 and 17.6 ppm. Aromatic and aliphatic C sp2 at δ 105.6; 108.1; 109.8; 117 and 121.9 pm (Figure 5).

Based on ¹³C-NMR spectrum data compared with the literature [13] (Table 1) and also the TLC chromatogram shows that the compound (1) is an artocarpin compound.



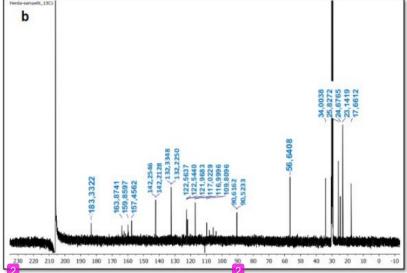


Figure 5. NMR spectrum of compounds (1) (a) ¹H-NMR and (b) ¹³C-NMR (1).

3.4. Antibacterial Bioactivity Test

In the antibacterial bioactivity test with variations in three concentrations, that is 0.3 mg/disk, 0.4 mg/disk, and 0.5 mg/disk. In the antibacterial bioactivity test, the isolated artocarpin compound (1) against *E. coli* bacteria was obtained by inhibiting zones of 9 mm, 10 mm, and 12 mm, respectively (0.3; 0.4; 0.5 mg/disk). These results indicate that compound (1) can inhibit bacteria in the medium category. In the antibacterial bioactivity test the modified artocarpin compound (2) produces inhibition zones of 5, 6, and 7 mm (0.3; 0.4; 0.5 mg/disk), so these results indicate that the antibacterial bioactivity of the compound (2) also included in the medium category (Table 2).

Compound (1) and compound (2) were also tested for antibacterial bioactivity against *B. subtilis* bacteria. Compound (1) produces inhibition zones of 11, 15, and 17 mm (0.3; 0.4; 0.5 mg/disk). Whereas the compound (2) shows inhibition zones of 10, 11, and 14 mm (0.3; 0.4; 0.5 mg/disk). Based on these results, it can be stated that both compounds have antibacterial bioactivity against *B. subtillis* in the strong category [14] (Table 3).

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From the results of the antibacterial bioativity test, it is known that the size of the inhibition zone of compound (1) is greater than that of compound (2), both against *E. coli* bacteria and *B. subtilis* bacteria. This is because compound (1) has three hydroxyl groups which cause denaturation of proteins from bacteria through an adsorption process involving hydrogen bonds so that the antibacterial bioactivity of compound (1) is better than compound (2).

Table 1. Comparison of chemical shift ¹³C-NMR from artocarpin literature [13] and compounds (1).

No C	compounds (1)).			
No C Artocarpin [13] Combounds (1) 2 163.6 159.9 3 122.2 122.0 4 183.9 183.3 4a 106.0 105.6 5 159.7 142.3 6 110.4 109.8 7 164.3 163.9 8 90.7 90.5 8a 158.0 157.5 1' 113.2 116.2 2' 157.8 142.21 3' 103.7 90.6 4' 161.9 132.3 5' 108.0 108.1 6' 132.8 132.3 9 24.9 24.6 10 122.8 122.5 11 132.4 121.9 12 25.9 25.8 13 17,7 17,6 14 117.2 117.0 15 142.8 122.6 16 34.5 34.0		13 _{C-NN}	¹³ C-NMR (ppm)		
2 163,6 159,9 3 122,2 122,0 4 183,9 183,3 4a 106,0 105,6 5 159,7 142,3 6 110,4 109,8 7 164,3 163,9 8 90,7 90,5 8a 158,0 157,5 1' 113,2 116,2 2' 157,8 142,21 3' 103,7 90,6 4' 161,9 132,3 5' 108,0 108,1 6' 132,8 132,3 9 24,9 24,6 10 122,8 122,5 11 132,4 121,9 12 25,9 25,8 13 17,7 17,6 14 117,2 117,0 15 142,8 122,6 16 34,5 34,0 17 23,2 23,1	No C	Artocarpin [13]	Compounds (1)		
4 183,9 183,3 4a 106,0 105,6 5 159,7 142,3 6 110,4 109,8 7 164,3 163,9 8 90,7 90,5 8a 158,0 157,5 1' 113,2 116,2 2' 157,8 142,21 3' 103,7 90,6 4' 161,9 132,3 5' 108,0 108,1 6' 132,8 132,3 9 24,9 24,6 10 122,8 122,5 11 132,4 121,9 12 25,9 25,8 13 17,7 17,6 14 117,2 117,0 15 142,8 122,6 16 34,5 34,0 17 23,2 23,1	2		159,9		
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16 34,5 34,0 17 23,2 23,1	14	117,2	117,0		
17 23,2 23,1	15	142,8	122,6		
	16	34,5	34,0		
	17	23,2	23,1		
	18	23,2	23,1		
OCH ₃ 56,6 56,6			*		

Table 2. Inhibition zones from compound (1) and compound (2) against E. coli bacteria.

Concentration,	Inhibition Zone, mm				
mg/disk	Compound (1)	Compound (2)	Control +	Control -	
0.5	11	7	30	-	
0.4	9	6	30	-	
0.3	8	5	28	-	

Table 3. Inhibition zones from compound (1) and compound (2) against B. subtilis bacteria.

Concentration,	Inhibition Zone, mm			
mg/disk	Compound (1)	Compound (2)	Control +	Control -
0.5	17	14	29	-
0.4	15	11	28	-
0.3	11	10	28	-

4. Conclusions

Artocarpin has been successfully isolated from root wood *A. kemando* Miq. and has also been modified into ester using acetic anhydride to produce artocarpin acetate. The success in the esterification reaction has been shown by the comparison of melting point, TLC chromatogram, UV and IR spectra of both compounds. In the antibacterial test using *E. coli*, both compounds showed medium category, whereas against *B. subtillis* showed strong category activity.

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