

Antiplasmodial Activity of Stigmastane Steroids from Dryobalanops oblongifolia Stem Bark

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Research Article

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Abstract: Three stigmastane steroids: 6-hydroxystigmast-4-en-3-one (1), stigmast-4-en-3-one (2), and 3-hydroxystigmast-5-en-7-one (3) were successfully isolated from the acetone extract of *Dryobalanops oblongifolia* stem bark. The structural determination of isolated compounds was carried out on the basis of data analysis of NMR and MS spectra. In order to identify the antiplasmodial activity, the isolated compound was put to test against *Plasmodium falciparum* 3D7. Antiplasmodial activity of the isolated compounds showed that the IC_{50} values of 6-hydroxystigmast-4-en-3-one were 37.29 $\mu\text{g}/\text{mL}$ while the IC_{50} values of stigmast-4-en-3-one were 43.54 $\mu\text{g}/\text{mL}$ and the IC_{50} values of 3-hydroxystigmast-5-en-7-one were 13.34 $\mu\text{g}/\text{mL}$ (chloroquine phosphate was used as a positive control, IC_{50} 0.006 $\mu\text{g}/\text{mL}$). Judging from the results, the isolated compounds were proven to demonstrate mediocre antiplasmodial activity. Compound (3) indicated a better antimalarial activity than compound (1) and (2), even though there was no satisfactory activity that indicated its ability to combat chloroquine. Therefore, it might not be developed as an antimalarial drug.

Keywords: Antiplasmodial; *Dryobalanops oblongifolia*; *Plasmodium falciparum*; Stigmastane steroid.

1 Introduction

Malaria is one of the infectious diseases that has become a major problem of health. It is found in nearly most of all tropics, particularly developing and poor countries. *Plasmodium*, a parasitic protozoa genus, is what causes malaria in humans. The parasite that derived from the genus namely *Plasmodium falciparum* is the lethal part that causes acute infection worldwide with an annual death toll of 1-2 million people [1, 2].

Quinine which isolated from cinchona tree has been widely used to cure malaria, yet it is still powerless to comprehensively break the life cycle of *Plasmodium* parasites [3]. Artemisinin, a sesquiterpene lactone, is reported as a potential antimalarial drug and have the ability to kill all phases of the parasites' life cycle through interaction with heme, yet animal experiment shows neurotoxic and cardiotoxic effect [4]. Development of synthesized drugs, such as chloroquin, pyrimethamine, cycloguanil, and sulfadoxine, have indicated the decline of effectivity caused by the resistance of *Plasmodium* [3,5,6,7]. Therefore, it is crucial to develop alternative medicines from plants by constituent exploration as potential antimalarial drugs.

Dryobalanops oblongifolia belongs to the family of Dipterocarpaceae and is widely found in Indonesia and Malaysia [8]. The phytochemical screening of fruit of *D. oblongifolia* revealed the presence of steroids compounds in this species [9]. *Dryobalanops* is known to produce oligostilbene constituents with various interesting activity such as antibacterial, antioxidant, antimalarial and cytotoxic [10, 11, 12, 13, 14]. In continuation for searching bioactive compounds from Indonesia's plants, a study towards *D. oblongifolia* was conducted by isolating the agents and examining the antiplasmodial activity against *Plasmodium falciparum* 3D7. Based on our knowledge this three stigmastane steroids (1-3) were first report from family Dipterocarpaceae and these isolated metabolites expressed only moderate antiplasmodial activity.

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2 Experimental section

2.1 General procedures

Firstly, CDCl_3 was used to dissolve ^1H and ^{13}C NMR and 2D NMR of stigmastane steroids spectra. While using TMS as the internal standard, JEOL J-500 spectrometer was used to record and it was utilized in CDCl_3 at 125 MHz (^{13}C) and 500 MHz (^1H). On a TSQ Quantum Access MAX Triple Quadrupole Mass Spectrometer, mass spectrometry was analyzed. Gravitation column chromatography (GCC) was conducted with Merck Si gel 60 (700-200 mesh). Vacuum liquid chromatography (VLC) and radial chromatography were conducted using Si gel 60 PF₂₅₄ and Si gel 60 GF₂₅₄. The analysis of Thin Layer Chromatography (TLC) was done on Merck kieselgel 60 GF₂₅₄, precoated Si gel plates, with a thickness of 0.25 mm. This research used already distilled analytical and technical grade solvents.

2.2 Plant Material

Mount Mali was the place where *D. oblongifolia* Dyer stem bark was originally collected. The mount is located in Tempunak, Sintang, West Kalimantan of Indonesia. The researchers then proceeded to the identification step by sending the plant specimen to the Biological Research Center of LIPI in Bogor, Indonesia. A voucher specimen was put in safekeeping at the herbarium.

2.3 Extraction and Isolation

At room temperature, as much as 5 kg of *D. oblongifolia* stem bark powder was pulped twice in acetone. It is meant to afford the extraction of brownish gummy after the process of vacuum evaporation. The extract was subsequently separated into 2 fractions: 1 fraction is able to be dissolved in acetone – diethyl ether while the other fraction is insoluble. As much as 48 g of the soluble fraction was divided into fractions using vacuum liquid chromatography (VLC) (*n*-hexane – ethyl acetate, enhancing polarity) to give four main fractions which are fraction A-D. By using radial chromatography techniques and Gravitation Column Chromatography (GCC), as much as 1.7 g of Fraction B was separated and purified. The process led to the production of compound 1 with a total of 6.5 mg and compound 2 with a total of 3 mg. In order to isolate both compounds and enhance the polarity, *n*-hexane and ethyl acetate mixtures were used. As

much as 1.6 g of Fraction C was separated and refined by using the same chromatography techniques and solvent mixtures, resulting in the production of compound 3 with a total of 3.4 mg.

2.3.1 In Vitro Antiplasmodial Assays

The antiplasmodial activity of compound 1-3 was determined in the Tropical Disease Institute of Universitas Airlangga, which is located in Surabaya, Indonesia. In this part, the method used was equivalent with the former method described by Widyawaruyanti et al. [15]. The dissolution of these samples was conducted in DMSO and they were stored at -20°C until use. A culture plate with 24 wells was used to cultivate the *P. falciparum* clone. The concentration range of each compound was 100, 10, 1, 0.1, and 0.01 $\mu\text{g/mL}$. As a positive control, a drug with antimalarial characteristics namely Chloroquine phosphate was used. The antiplasmodial activity measurement of compound 1-3 and chloroquine phosphate was calculated in replica. The monitoring process of parasitaemia was conducted when 48 hours had passed by firstly making a blood test fixed with MeOH and spattered with Geimsa (Merck). With the aim to determine the parasitaemia average ratio and average inhibition, the researchers calculated the total number of infected erythrocytes from originally 1000 healthy erythrocytes. The researchers used IC_{50} value to state the antiplasmodial activity of compound 1-3. IC_{50} value is the concentration of compounds that causes 50% inhibition of the parasite growth. The IC_{50} value was obtained by using probit analysis processed by the SPSS program.

Ethical approval: The conducted research is not related to either human or animal use.

3 Result and Discussion

The acetone extracted from *D. oblongifolia* stem bark was fractionated and purified using radial chromatography, gravitation column chromatography, and vacuum liquid chromatography. It was intended to produce three stigmastane steroid compounds, specifically 6-hydroxystigmast-4-en-3-one (1), stigmast-4-en-3-one (2), and 3-hydroxystigmast-5-en-7-one (3). The isolated compound structures were identified on the basis of ^1H - and ^{13}C -NMR spectral data, and 2D NMR experimentations and contrast with the reported data and MS spectral data.

Table 1: Average Inhibition of isolated compounds (1-3) and Chloroquine phosphate against *P. falciparum* 3D7.

No	Compound	% Average Inhibition (µg/mL)					IC ₅₀ µg/mL	IC ₅₀ µM
		100	10	1	0,1	0,01		
1	6-hydroxystigmast-4-en-3-one	60.78	35.14	18.40	10.26	1.36	37.29	86.91
2	Stigmast-4-en-3-one	58.06	34.76	20.28	11.17	1.51	43.54	105.36
3	3-hydroxystigmast-5-en-7-one	72.40	42.08	26.09	12.07	1.51	13.34	31.08
4	Chloroquine phosphate	99.13	89.38	82.01	65.73	58.55	0.006	0.01

* The IC₅₀ value was obtained by using probit analysis of SPSS program.

Compound 1 was isolated as an achromatic formless powder. C₂₉H₄₈O₂ was established as the molecular formula by means of ESI-MS ([M+H]⁺ ion at *m/z* 429.076). There were a total of 6 methyl groups that were found to be present according to the ¹H-NMR spectrum. They were 2 groups of tertiary methyl [δ_{H} 0.74 (H-18) and 1.38 (H-19)], 3 groups of secondary methyl [δ_{H} 0.92 (H-21), 0.81 (H-26), and 0.84 (H-27)], and 1 group of primary methyl δ_{H} 0.85 (H-29). Furthermore, 1 oxygenated methine proton was seen at δ_{H} 4.35 (H-6), while 1 sp² methine was seen at δ_{H} 5.81(H-4). Meanwhile, it appeared that there was an overlap in the proton peaks of methylene and methine groups. There were 29 carbon signals revealed by the ¹³C-NMR spectrum that contained an oxygenated secondary carbon at δ_{C} 73.3 (C-6), a carbonyl carbon at δ_{C} 200.4 (C-3), and 2 olefinic carbons [δ_{C} 126.3 (C-4) and 168.5 (C-5)]. There was an indication that the carbon signals that were present at δ_{C} 126.3, 168.5, and 200.4 signified an α,β -unsaturated carbonyl system that was present in compound 1. It indicated a suggestion that **compound 1** was stigmastane steroid, especially when looking at the data of ¹H-NMR and ¹³C-NMR. There were many correlations that have been pointed out by the spectra of compound 1 Heteronuclear Multiple Bond Correlation (HMBC) particularly between H-21/C-17, H-21/C-20, and H-21/C-22; H-22/C-23; H-25/C-23, H-25/C-24, H-25/C-27, and H-25/C-28; H-26/C-24, H-26/C-25, and H-26/C-27; H-27/C-25 and H-27/C-26; H-29/C-28. The structure of side chain was established by these correlations. The presence of pentenoperhydrophenanthrene nucleus was indicated by the correlations between H-18/C-12, H-18/C-13, and H-18/C-14; H-19/C-1, H-19/C-5, H-19/C-9, and H-19/C-10, they signified the tetracyclic. In addition, there were indications showed by the HMBC links between H-4 / C-2, H-4 / C-6, H-4 / C-10, and H-6 / C-4, H-6 / C-8, H-6 / C-10 that there are 2 different locations for the α,β -unsaturated carbonyl system and the hydroxyl group. The location of the former is in ring A, while the latter in ring B (Table 1). Aside from the analysis of the HMBC spectrum, the determination of hydroxyl group location can also be

achieved by doing a TOCSY test. Compound 1 structure was indicated as 6-hydroxystigmast-4-en-3-one (Figure 1) [16].

Compound 2 was isolated as an achromatic formless powder with a [M+H]⁺ ion at *m/z* 413.244. It was isolated during ESI-MS analysis and it corresponded to C₂₉H₄₈O molecular formula. Compound 2 was discovered by the NMR data as a steroid with stigmastane skeleton. Although compound 2 has a high resemblance with compound 1 in terms of ¹H-NMR and ¹³C-NMR spectrum chemical shifts, compound 2 does not possess any hydroxyl group (Table 1). Compound 2 structure was indicated as stigmast-4-en-3-one (Figure 1) [17, 18].

Compound 3 was isolated too as an achromatic formless powder that has C₂₉H₄₈O₂ molecular formula (ESI-MS, [M+H]⁺ ion at *m/z* : 429.227). Compound 3 has high resemblance with compound 1 and 2 in terms of NMR spectrum chemical shifts, exposing that compound 3 was a stigmastane steroid. There were 29 carbon signals displayed by ¹³C-NMR and DEPT spectra. These carbon signals consisted of 6 methyl carbons, 10 methylene carbons, 9 methine carbons, and 3 quaternary carbons, and carbonyl ketone. The HMBC spectra proved that 1 hydroxyl group and the α,β -unsaturated carbonyl system were present with links between H-4/C-2, H-4/C-3, H-4/C-5, H-4/C-6, H-4/C-10 ; H-6/C-4, H-6/C-8, and H-6/C-10 ; H-8/ C-7, H-8/C-9. There are indications initiated by the HMBC analysis that the hydroxyl group and the α,β -unsaturated carbonyl system was located on different positions. The location of the former was at the position of C-3 in ring A, while the location of the latter was in ring B (Table 1). Compound 3 structure was identified as 3-hydroxystigmast-5-en-7-one. The confirmation can be seen through a contrast with stigmast 3-hydroxy-5-en-7-one chemical shifts, which is similar to the previously published research (Figure 1) [19, 20].

The examination of antiplasmodial activity against *P. falciparum* 3D7 was carried out by in vitro to three stigmastane steroid compounds. The test results showed

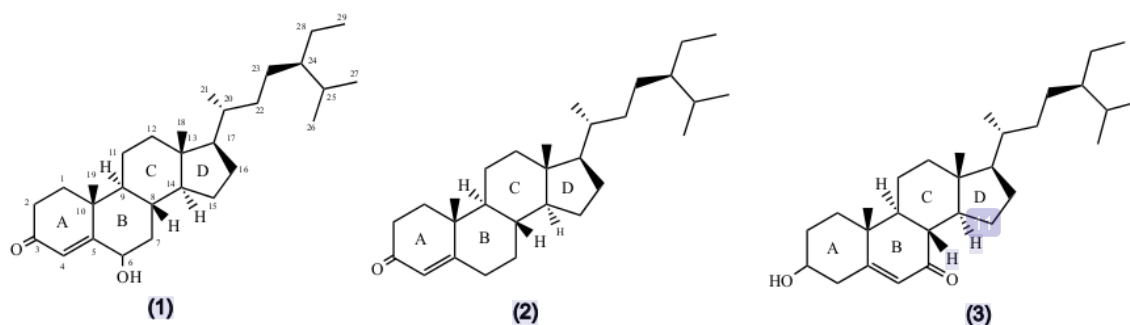


Figure 1: The structure of isolated compounds 1, 2 and 3 from *D. oblongifolia*.

6-hydroxystigmast-4-en-3-one (1)

Table 2: Antimalarial activity of 6-hydroxystigmast-4-en-3-one against *P. falciparum* 3D7.

Dose ($\mu\text{g/ml}$)	R	% Parasitaemia		% Growth	% Inhibition	% Average Inhibition
		0 jam	48 jam			
Kontrol (-)	1	1.17	4.49	3.32	-	-
	2	1.17	4.48	3.31	-	-
100	1	1.17	2.45	1.28	61.45	60.78
	2	1.17	2.49	1.32	60.12	
10	1	1.17	3.34	2.17	34.64	35.14
	2	1.17	3.30	2.13	35.65	
1	1	1.17	3.86	2.69	18.98	18.40
	2	1.17	3.89	2.72	17.82	
0.1	1	1.17	4.15	2.98	10.24	10.26
	2	1.17	4.14	2.97	10.27	
0.01	1	1.17	4.45	3.28	1.20	1.36
	2	1.17	4.43	3.26	1.51	
IC_{50}						37.29 $\mu\text{g/mL}$

that the IC_{50} value of 6-hydroxystigmast-4-en-3-one (1) was as much as 37.29 $\mu\text{g/mL}$. Meanwhile, for stigmast-4-en-3-one (2), the IC_{50} value was as much as 43.54 $\mu\text{g/mL}$, whereas the IC_{50} value of 3-hydroxystigmast-5-en-7-one (3) was as much as 13.34 $\mu\text{g/mL}$. Chloroquine phosphate was used a positive control with as much as 0.006 $\mu\text{g/mL}$ IC_{50} (Table 1). Judging from the results, mediocre antiplasmodial activity was found in the three stigmastane steroid compounds [21]. Compound 3 showed better antiplasmodial activity than the others. The structure of stigmastane steroids chemical compound revealed that the presence and position of hydroxyl group can influence their antiplasmodial activity. The location of hydroxyl group in compound 3 is easier to interact with extracellular and intracellular fluids so that

it can be easily carried to target molecule [22]. However, compound 3 is considered as lacking the ability to fight against the chloroquine so it may not be promoted as an antimalarial agent.

4 Conclusion

There were three stigmastane steroids that were successfully isolated from the acetone extract derived from the stem bark of *Dryobalanops oblongifolia*. The evaluation on antiplasmodial activity was performed to all of the isolated compounds, specifically 6-hydroxystigmast-4-en-3-one (1), stigmast-4-en-3-one (2), and 3-hydroxystigmast-

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Stigmast-4-en-3-one (2)**Table 3:** Antimalarial activity of sistigmast-4-en-3-one against *P. falciparum* 3D7.

Dose ($\mu\text{g/ml}$)	R	% Parasitaemia		% Growth	% Inhibition	% Average Inhibition
		0 jam	48 jam			
Kontrol (-)	1	1.00	4.65	3.65	-	-
	2	1.00	4.60	3.60	-	-
100	1	1.00	2.53	1.53	57.50	58.06
	2	1.00	2.49	1.49	58.61	
10	1	1.00	3.35	2.35	35.62	34.76
	2	1.00	3.38	2.38	33.89	
1	1	1.00	3.91	2.91	20.27	20,28
	2	1.00	3.87	2.87	20.28	
0.1	1	1.00	4.21	3.21	12.06	11.17
	2	1.00	4.23	3.23	10.28	
0.01	1	1.00	4.58	3.58	1.91	1.51
	2	1.00	4.56	3.56	1.11	
IC₅₀						43.54 $\mu\text{g/mL}$

3-hydroxystigmast-5-en-7-one (3)**Tabel 4:** Antimalarial activity of 3-hydroxystigmast-5-en-7-one against *P. falciparum* 3D7.

Dose ($\mu\text{g/ml}$)	R	% Parasitaemia		% Growth	% Inhibition	% Average Inhibition
		0 jam	48 jam			
Kontrol (-)	1	1.17	4.49	3.32	-	-
	2	1.17	4.48	3.31	-	-
100	1	1.17	2.09	0.92	72.29	72.40
	2	1.17	2.08	0.91	72.51	
10	1	1.17	3.08	1.91	42.47	42.08
	2	1.17	3.10	1.93	41.69	
1	1	1.17	3.64	2.47	25.60	26.09
	2	1.17	3.60	2.43	26.59	
0.1	1	1.17	4.10	2.93	11.75	12.07
	2	1.17	4.07	2.90	12.39	
0.01	1	1.17	4.44	3.27	1.51	151
	2	1.17	4.43	3.26	1.51	
IC₅₀						13.34 $\mu\text{g/mL}$

5-en-7-one (3). The antiplasmodial activity indicated that there was a total of 37.29 $\mu\text{g/mL}$ of IC₅₀ value in 6-hydroxystigmast-4-en-3-one. Meanwhile, the IC₅₀ value of stigmast-4-en-3-one was as much as 43.54 $\mu\text{g/mL}$ while as much as 13.34 $\mu\text{g/mL}$ of IC₅₀ value was found in 3-hydroxystigmast-5-en-7-one (chloroquine phosphate was

used as a positive control, IC₅₀ 0.006 $\mu\text{g/mL}$). Compound 3 was the most active isolated compounds although there was not enough activity to fight against chloroquine. As the consequence, compound 3 did not meet the standard of an antimalarial drug and may not be developed as a proper medication of the disease.

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Conflict of interest: Authors declare no conflict of interest.

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