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IN VITRO ANTIMALARIAL ACTIVITY OF CHALCONE AND ITS DERIVATIVES

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ABSTRACT

Object: to evaluate in vitro antimalarial activity of chalcone and its derivatives.

Method: The Chalcones were tested its anti plasmodial activity against *Plasmodium falciparum* (3D7 strain) by using candle jar method, introduced by Trager and Jensen (1976).

Result and Discussion: The tested compounds gave IC₅₀ (half maximal inhibitory concentration) ranged between 0.242 and > 100 µg/ml.

Conclusion: All compounds have lower antimalarial activity than commercially standard antimalarial drug, Chloroquine diphosphate.

Keywords: Chalcones, *In vitro*, Antimalarial activity, *Plasmodium falciparum*.

INTRODUCTION

Malaria is a major parasitic infectious disease in the world, caused by *Plasmodium falciparum*. It continues to be one of the major public health problems in many tropical countries leading to widespread morbidity and mortality [1,2]. According to the annual report of World Health Organization, the malaria incidence in Indonesia in 2010 is still fairly high, about 37% from 242.7 million people. It is a threat to over 2 billion people living in areas of high incidence [3,4]. The available medicines such as Chloroquine is no longer effective to treat malaria, due to the increasing of multi drug resistance [1,5]. Nowadays, Artemisinin and its derivatives have become the only available drugs to treat malaria. Resistance to these drugs have not been clinically encountered so far [1,6]. In fact, synthesis of those compounds are delicate and very expensive. Moreover, sooner or later, resistance of that medicine will be arising. Therefore, it is important to develop some alternative compounds which have better antiplasmodial activity.

Chalcones are precursor of numerous plant metabolites with distinctive scaffold owing exceptional biological properties [1,7]. Their main structure is 1,3-diphenyl-2-propene-1-ones, wherein two benzene rings are associated by highly electrophilic three carbon

α,β -unsaturated carbonyl configuration [10,12]. In past few years, it had been reported Morachalcone A (figure 1), a naturally occurring substance from *Artocarpus champeden* Spreng, belonging to the family Moraceae, is a native plant of Indonesia which significantly inhibited the in vitro growth of the human malaria parasite *Plasmodium falciparum* [8,15]. Due to its simple structure and effortless to synthesize clarify the substantial interest of chemist in this particular group of compounds. There are various methods for the syntheses of chalcones have been discovered, including Claisen-Schmidt condensation [11,12], photo-Fries rearrangement [13], Suzuki coupling reaction [13,14], Friedel-Craft acylation [13], and also green chemistry method via microwave irradiation [11,13].

In our previous work, we have been synthesized chalcone (**KTS 11**) and some derivatives via Claisen-Schmidt condensation, namely 3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (**KTS 12**), 3-(2-methoxyphenyl)-1-phenylprop-2-en-1-one (**KTS 13**) and 3-(3-hydroxyphenyl)-1-phenylprop-2-en-1-one (**KTS 16**) in a good yields (73 - 93%) [9,16]. Figure 1 shows structure of chalcone and its derivatives which have been used in this experiment. In this report, we evaluated in vitro antimalarial activity of chalcone and its derivatives against parasite *Plasmodium falciparum* 3D7 strain.

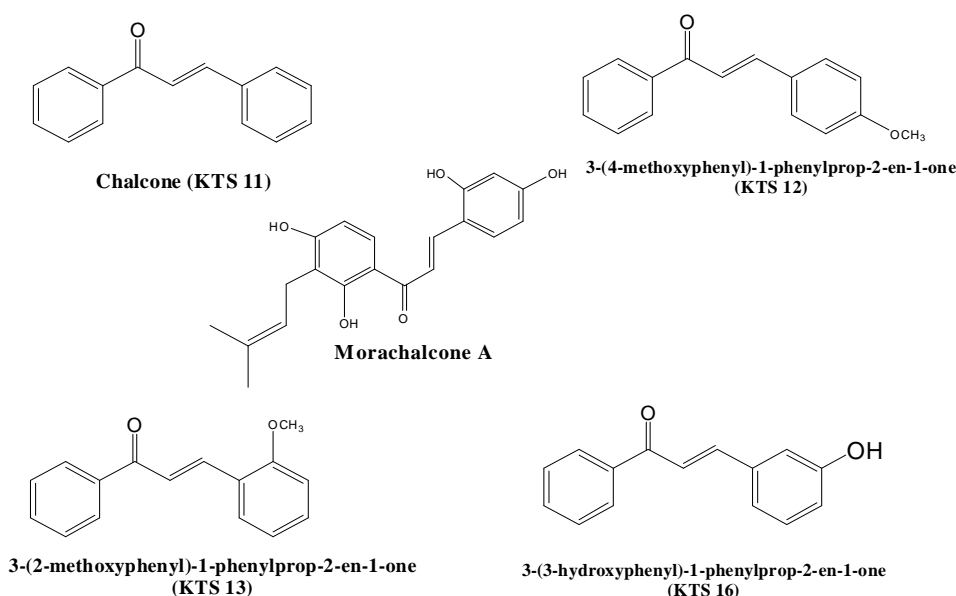


Fig. 1: Chalcone and Its Derivatives

MATERIALS AND METHODS

Antiplasmodial activity of chalcones was basically conducted by using candle jar method of Trager and Jensen [17]. Briefly, Stock solution of tested compounds were arranged in DMSO and diluted with complete medium, which consist of RPMI 1640 supplemented with 10% human plasma, 25 mM HEPES and 25 mM NaHCO₃, to the required concentrations of samples in culture plate wells were 100; 10; 1; 0.1; and 0.01 µg/ml. The final DMSO concentration in the culture media had no effect on parasite growth.

Asexual blood stage parasite of *Plasmodium falciparum* (3D7 strain) were tested to graded concentration of each compound in 24-well culture plates in duplicates for 48 h at 37 °C. Growth of the parasite was observed by preparing a blood smear fixed with methanol and stained with Giemsa stain. The antimalarial activity of each compound was stated as an IC₅₀ value, defined as the concentration of the compound causing 50% inhibition of parasite growth relative to untreated control. Concentration versus response curve was set up to figure out IC₅₀ value of each compound [1,2].

RESULTS AND DISCUSSION

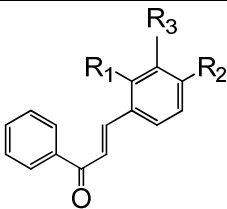
Plasmodium is an intracellular parasite for most part of its life cycle in the vertebrate host. The intraerythrocytic parasite grows and reproduces asexually by converting the toxic heme molecules into nontoxic hemozoin. Inhibition of hemoglobin degradation process proves fatal for the parasite. It is envisaged that malarial aspartic proteases and cysteine protease mediate the haemoglobin degradation to release amino acids that are entailed for intraerythrocytic parasite growth and multiplication [18,19]. Structure-based studies expected antimalarial of chalcone derivatives inhibition on trophozoite cysteine protease as most likely mode of action [20, 21]. Availability of continues cultivation of

human malaria parasite, *Plasmodium falciparum* [17] affords an interesting in vitro system for preliminary screening to recognize antiparasitic action of compounds in the absence of immune substances [18].

The tested compounds were evaluated its antimalarial activity against *Plasmodium falciparum* (3D7 strain). Chalcone gave IC₅₀ 0.242 µg/ml, while compound with methoxy group on *para* position of 3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one gave IC₅₀ value 54.316 µg/ml. The presence methoxy group on *ortho* position of 3-(2-methoxyphenyl)-1-phenylprop-2-en-1-one gave undesired result with IC₅₀ value >100 µg/ml, which means it has no antimalarial activity. Other chalcone derivative with hydroxyl group on *meta* position, 3-(3-hydroxyphenyl)-1-phenylprop-2-en-1-one gave IC₅₀ value 14.136 µg/ml. Figure 2 shows the graph of concentration versus response of chalcone and its derivatives against blood stages of *Plasmodium falciparum* (3D7 strain). In this experiment, the standard antimalarial drug, Chloroquine diphosphate was also examined and gave IC₅₀ value 0.006 µg/ml. From this result, it can be concluded that chalcone which has no substituent at its both ring gave the greatest IC₅₀ value among the tested compounds. And also they all have lower antimalarial activity than commercially available antimalarial medicine, Chloroquine. The table 1 shows IC₅₀ values of the Chalcones as described below:

From literature, it was reported that the IC₅₀ value of Morachalcone A, that isolated from *Artocarpus champeden* Spreng was 0.002 µg/ml [8]. The absence of isoprenyl group and multi-hydroxyl group of chalcone-skeleton is decreasing its ability to inhibit parasite growth. Therefore, it needs to be designed furthermore to develop innovative strategies to synthesis other new chalcone derivatives, which have better antimalarial potency.

Table 1: Antimalarial activity of Chalcone and its derivatives (IC₅₀ value)

Structure	Compound	IC ₅₀ (µg/ml)	Substituent		
			R ₁	R ₂	R ₃
	KTS 11	0.242	H	H	H
	KTS 12	54.316	H	OCH ₃	H
	KTS 13	> 100	OCH ₃	H	H
	KTS 16	14.136	H	H	OH
	Standard-antimalarial agent	Chloroquin diphosphate	0.006	-	-

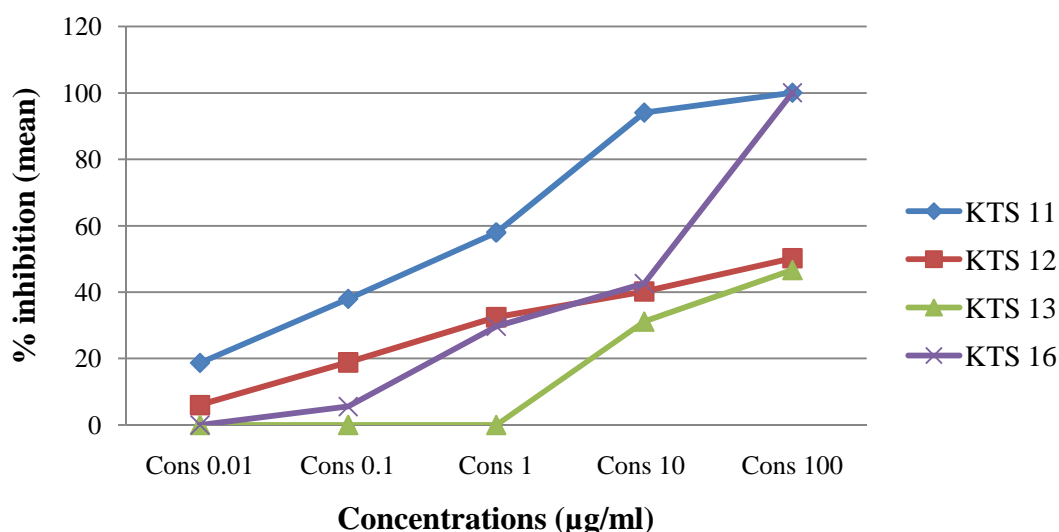


Fig. 2: Concentrations-Response Curve of the Chalcones

CONCLUSIONS

Chalcone and its derivatives have been tested for its antimalarial activity against *Plasmodium falciparum* (3D7 strain). All the tested compounds have lower antimalarial activity than commercially available antimalarial drug, Chloroquine, with IC₅₀ value range from >100 to 0.242 µg/mL.

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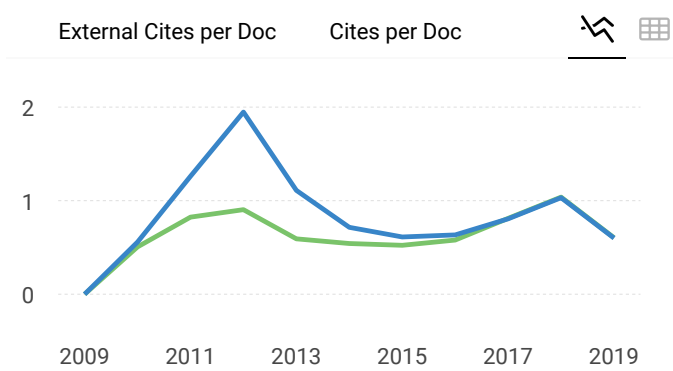
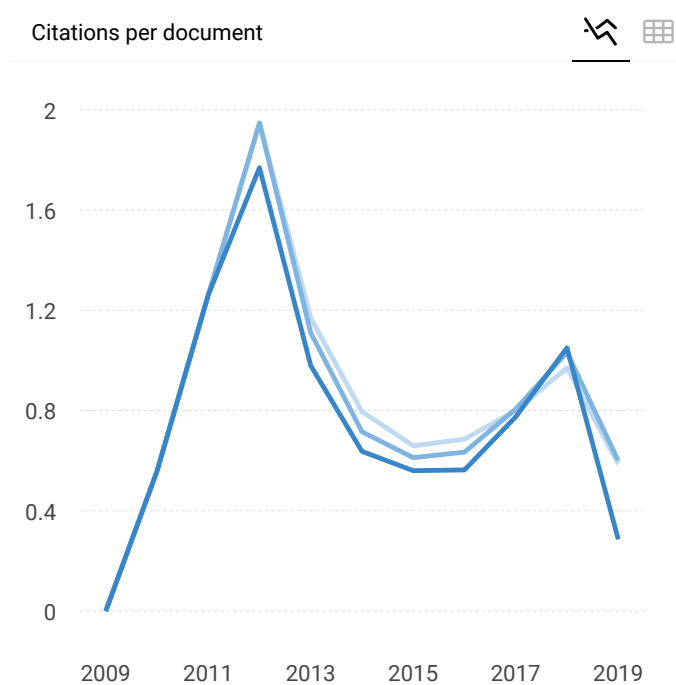
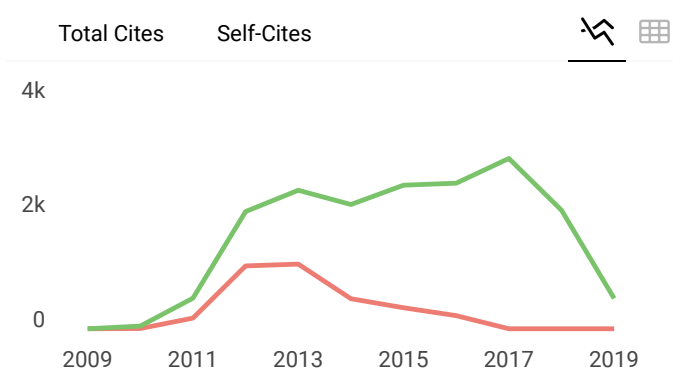
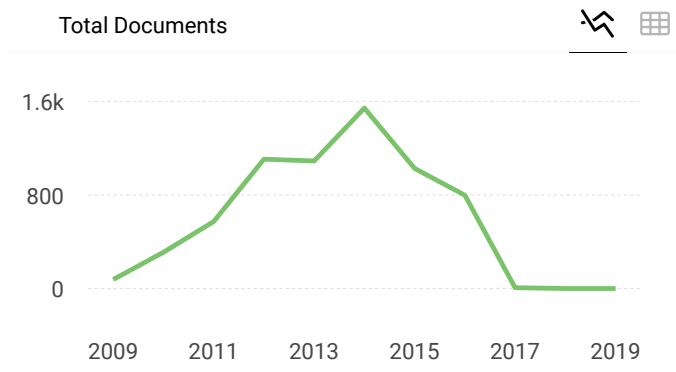
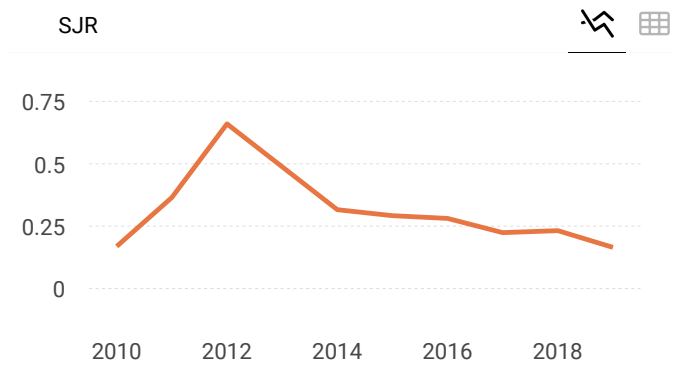
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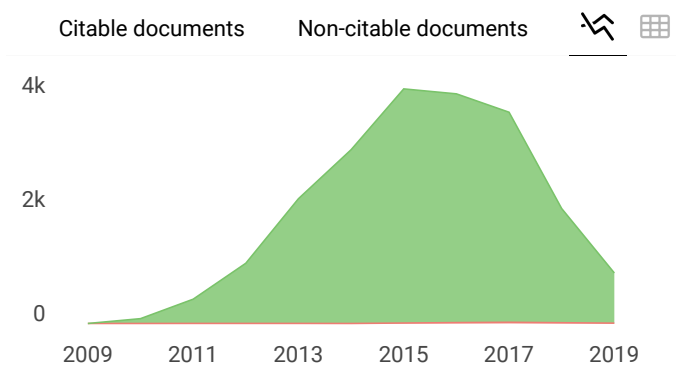
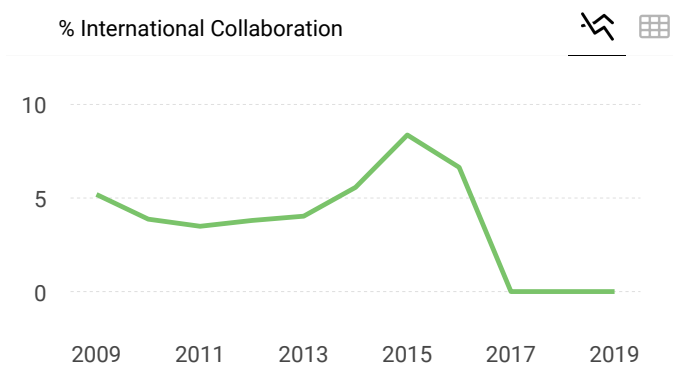
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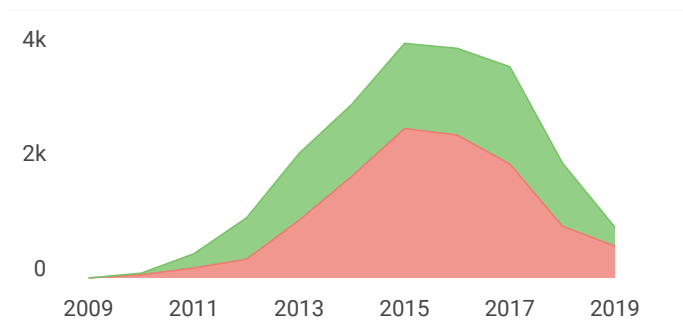
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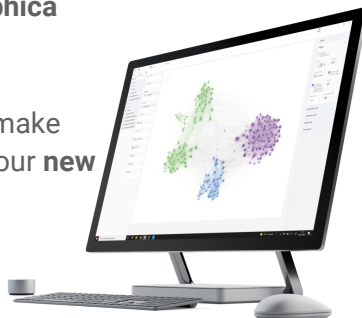
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