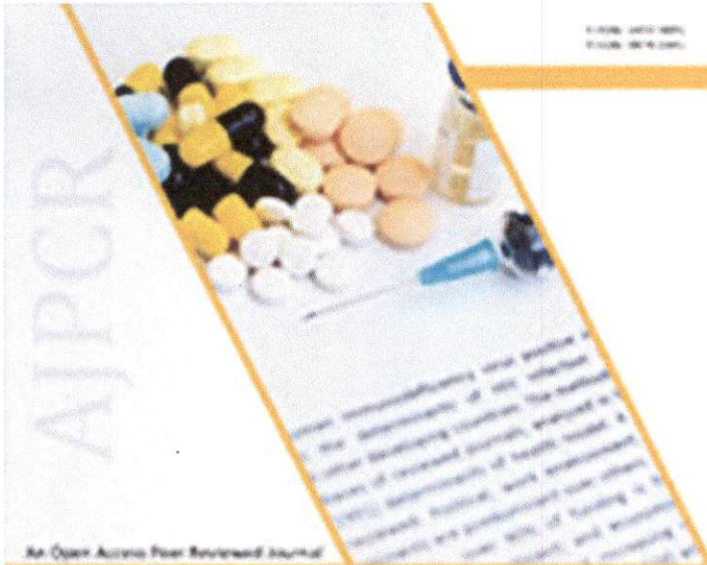


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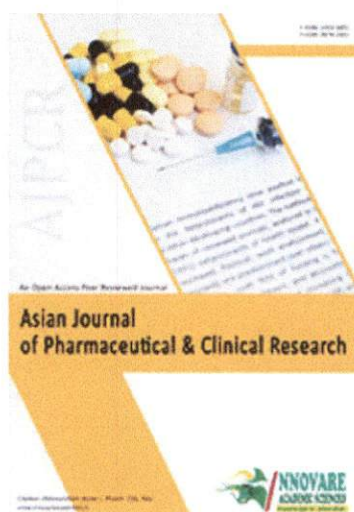
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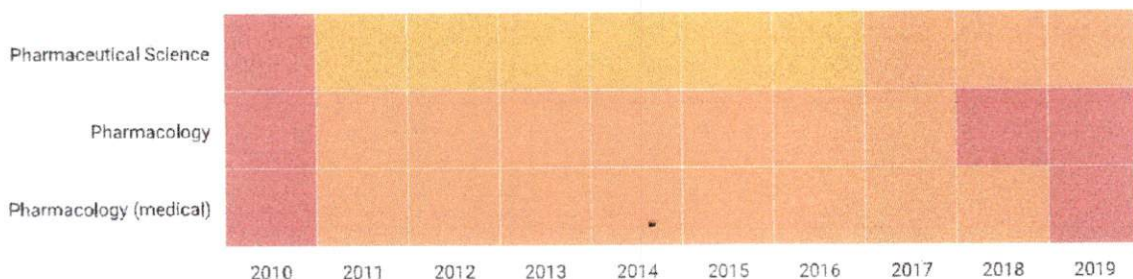
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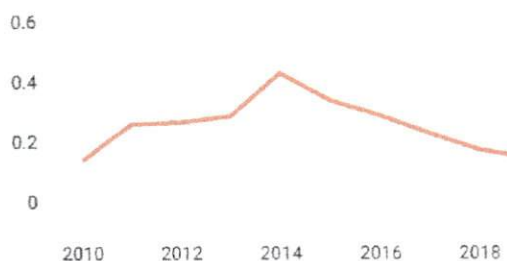
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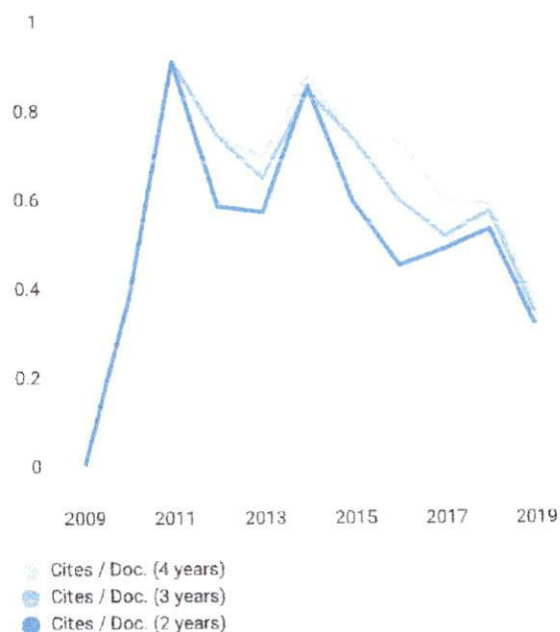
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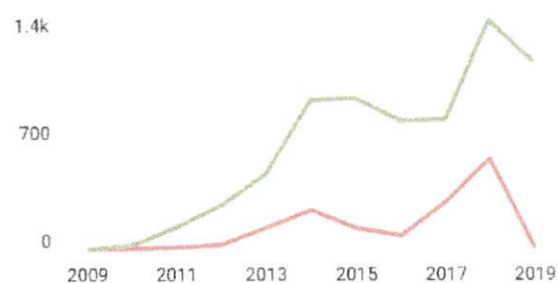
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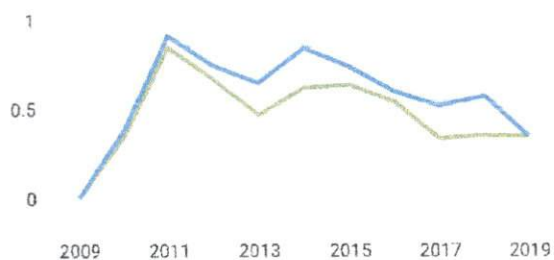
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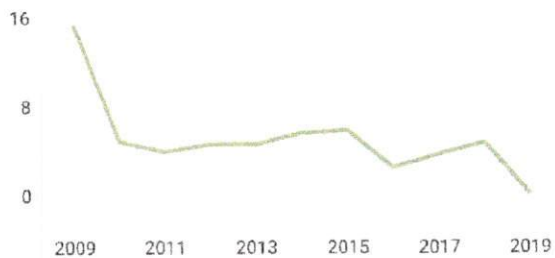
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THE COMBINATION THERAPY MODEL OF *ANDROGRAPHIS PANICULATA* EXTRACT AND CHLOROQUINE ON *PLASMODIUM BERGHEI* INFECTED MICEACHMAD FUAD HAFID^{1,3*}, DINI RETNOWATI², ATY WIDYAWARUYANTI^{1,3}

¹Department of Pharmacognosy and Phytochemistry, Faculty of Pharmacy, Universitas Airlangga, Jalan Dharmawangsa Dalam, Surabaya 60286, Indonesia. ²Department of Pharmaceutical Technology, Faculty of Pharmacy, Universitas Airlangga, Jalan Dharmawangsa Dalam, Surabaya 60286, Indonesia. ³Division of Natural Product Medicine Research and Development, Institute of Tropical Disease, Universitas Airlangga, Kampus C Universitas Airlangga Mulyorejo, Surabaya - 60115, Indonesia. Email: achmadfuad@unair.ac.id

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ABSTRACT

Objective: The aim was to determine the antimalarial drug effectiveness of the combination therapy model of 80% ethanolic extract of sambiloto (EES) and chloroquine on *Plasmodium berghei* infected mice.

Methods: Five groups of *P. berghei* infected mice were used in this study, divided by three combinations therapy models of EES and chloroquine groups (Model A, B, C), one monotherapy of EES group (Model D) and one untreated group (Model E) as a control. EES and chloroquine were used at a dose of 100 mg/kg mice body weight and 0.15 mg/kg mice body weight, respectively. Only for Model C, chloroquine was used at a dose of 10 mg/kg mice body weight. Three combinations therapy models consisted of Model A: Infected mice treated by EES and chloroquine for 4 days; Model B: treated by EES for 4 days and chloroquine for 1 day at 1st day; Model C: treated by EES for 4 days and chloroquine for 1 day at 4th day. Meanwhile, Model D and E were treated by EES and vehicle each for 4 days, respectively. Blood smear of all mice was prepared with Giemsa stain. Antimalarial activity was determined by the difference between the mean value of parasitemia of control (Model E, taken as 100%) and those of the experimental group (Model A, B, C and D).

Results: Three combination therapy models (Model A, B, C) and one monotherapy (Model D) were showed antimalarial activities against parasite with inhibition of parasite growth by 85.61%, 69.31%, 73.64% and 65.14%, respectively.

Conclusion: Model A was showed as the most effective combination therapy model on mice infected by malaria. The results indicated that combination therapy model of EES and chloroquine were able to increase the antimalarial effectiveness by 85.61% inhibition of parasite growth and having smaller risk of resistance by using low dose of chloroquine (0.15 mg/kg mice body weight).

Keywords: Antimalarial combination therapy, *Andrographis paniculata*, Chloroquine.

INTRODUCTION

Malaria is a parasite disease caused by five species of parasites of the genus *Plasmodium* that affect humans (*Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae* and *Plasmodium knowlesi*). WHO estimated 3.3 billion people were at risk of malaria in 2011, with populations living in sub-saharan African having the highest risk of acquiring malaria [1].

During through years chloroquine has been used as an antimalarial therapy, and the next problems are caused by the resistance of *P. falciparum* to chloroquine. The resistance to the usage of this antimalarial drug is rapidly spread in some tropical areas, such as Thailand, Vietnam, and Indonesia. This resistance is caused by the ability of *Plasmodium* to adapt antimalaria therapy [2].

One of the alternative therapies to prevent malaria was the combination therapy as suggested by WHO in 2001. The intentions of this combination therapy were: (1) increased antimalarial drug effectiveness; (2) reduced drug toxicity; and (3) reduced the level of drug resistance [3].

Taylor (2001) conducted a hospital-based 28 days *in vivo* test comparing combination of chloroquine-doxycycline to chloroquine or doxycycline alone for treating *P. falciparum* and *P. vivax* malaria in Irian Jaya. The results showed that the combination of chloroquine-doxycycline cured 90.9% patients with *P. falciparum* malaria compared to chloroquine and doxycycline that cured 20% and 64.7% patients, respectively [4].

The biodiversities of Indonesia plants are very rich, which are an advantage for many plant researches applied for therapy. One of the Indonesian plants that traditionally used for antimalaria is sambiloto (*Andrographis paniculata*, Nees.). The previous research indicated that sambiloto extract have antimalarial activity by inhibiting the growth of *P. falciparum* *in vitro* [5]. *A. paniculata* showed antimalarial activity against *P. berghei* and having dose dependent inhibitory properties. No mortality and physical signs of toxicity during the treatment at a dose of 100 mg/kg mice body weight [6].

The aims of this study were to determine the antimalarial drug effectiveness of the combination therapy models of ethanolic extract of sambiloto (EES) and chloroquine against malaria infection using *in vivo* animal model of the disease.

The difference in the extraction process gave difference compounds consisting in extract. At this experiment, the extraction process of sambiloto was done by using the 60%, 70%, and 80% ethanol as a solvent. The activity of antimalarial from the three of (EES) has been tested, and extract that gave the best result will combine with chloroquine in various combination therapy model.

MATERIALS AND METHODS

Animals

Male mice BALB/C strain were obtained from Pusat Veterinaria Farma (Pusvetma), Surabaya. They were weighting between 20 g and 30 g and maintained on standard animal pellets and water *ad libitum* at Animal Laboratory of the Faculty of Pharmacy, Universitas

Airlangga. Permission and approval for animal studies were obtained from Faculty of Veterinary Medicine, Universitas Airlangga.

Rodent malaria parasite

P. berghei ANKA strain was originally obtained from Eijkman Institute for Molecular Biology, Jakarta. The parasite has been maintained at Faculty of Pharmacy, Universitas Airlangga by a combination of passage in male BALB/C mice and cryoscopic storage.

Chemicals and reagents

Chloroquine was purchased from Sigma-Aldrich Chemical Company. Giemsa stain and solvents were purchased from Merck Chemical Company.

Plant material and extraction

Sambiloto (*A. paniculata*) was obtained from Pacet, East Java. Identification and authentication were carried out at the Purwodadi Botanical Garden, East Java. The sambiloto extracts gained from the maceration method using 60%, 70%, and 80% ethanolic concentration. The solvent was removed by vacuum. The ethanol extracts were stored at dessicator until it is being used.

In vivo antimalarial activity test

In vivo antimalarial activity was performed based on Peter's test (The 4-days suppressive test) [7]. All sambiloto extracts were tested on mice infected by *P. berghei* at a dose of 100 mg/kg mice body weight. Sambiloto extracts suspension were given orally for 4 days (D₀-D₃) and the percentage of parasite growth were observed every day. Blood samples were taken to determine parasitemia level for 7 days (D0-D6). The result examined by making thin blood smear from mice's tail with giemsa stain on object glass. The sambiloto extract, which has the highest antimalarial activity will be used and combined with chloroquine. Antimalarial activity was determined by the difference between the mean value of parasitemia of negative control and those of the experimental group that was expressed as inhibition percentage. Inhibition percentage was calculated using the following formula:

$$100\% - \left(\frac{Xe}{Xk} \times 100\% \right)$$

Xe: % parasitemia growth of experimental group

Xk: % parasitemia growth of negative control

Various combination therapy models done at this research were as follows:

1. Model A: Combination therapy of ethanolic extract of sambiloto EES at a dose of 100 mg/kg body weight and chloroquine at a dose of 0.15 mg/kg body weight given for 4 days (D₀-D₃). Positive control for Model A (K [+]) were given chloroquine at a dose of 0.15 mg/kg body weight given for 4 days (D₀-D₃).
2. Model B: Combination therapy of EES at a dose of 100 mg/kg body weight given for 4 days (D0-D3) and chloroquine at a dose of 0.15 mg/kg body weight given for 1 day at 1st day (D₀). Positive control for Model B (K [+]) were given chloroquine at a dose of 0.15 mg/kg body weight given for 1 day at 1st day (D₀).
3. Model C: Combination therapy of EES at a dose of 100 mg/kg body weight given in 4 days (D₀-D₃) and chloroquine at a dose of 10 mg/kg body weight given for 1 day at 4th day (D₃). Positive control for Model C (K [+]) were given chloroquine at a dose of 10 mg/kg body weight given for 1 day at 4th day (D₃).
4. Model D: The monotherapy of EES at a dose of 100 mg/kg mice body weight given for 4 days (D₀-D₃).
5. Model E (as a negative control): Given with vehicle for 4 days (D₀-D₃).

Statistical analysis

Statistical analysis of data obtained from this research was performed by one-way ANOVA and Tukey HSD Test.

RESULTS AND DISCUSSION

The present study assessed the antimalarial drug effectiveness of ethanolic extract of *A. paniculata* in combination with chloroquine. *A. paniculata* was selected based on its ethnomedicinal use. Previous study shows that *A. paniculata* has potential antibacterial and antimalarial activity, such as bacteria, viruses and parasites [8,9]. Misra *et al.* studied antimalarial activity of *A. paniculata* against *P. berghei* NK65 in *Mastomys natalensis*. The results showed that a crude ethanol extract and fractions reduced the level of parasitemia in a dose-dependent manner [10]. Methanolic extract of *A. paniculata* also revealed antimalarial effect. Combination with methanolic extract of *Hedyotis corymbosa* showed substantial enhancement in the antimalarial activity. In addition, combination with curcumin showed synergism effect, increased *in vivo* potency and did not showed any *in vivo* toxicity [11]. Andrographolide was also found synergic with curcumin and additively interactive with artesunate [12]. The results of these studies encourage the idea that combination treatment can produce better antimalarial effect. There was a suggestion that antimalarial drugs should not be used alone in the treatment, but always in combination. Simultaneous use of two or more antimalarial with different modes of action and which do not share the same resistance mechanism will reduce the risk of resistance [13].

This study had the results that from the previous test of antimalarial activities of the three sambiloto ethanolic extracts at a dose of 100 mg/kg mice body weight dose, ethanolic extract 80% sambiloto gave the highest antimalarial activity, which inhibit the parasite's growth by 65.14%. Therefore, this extract will be applied in various combination therapies model with chloroquine. The result can be shown in Table 1.

In subsequent study, combination therapies consist of 4 models, which are Model A, B, C, and D. Except for Model D, the three other models were combination of EES and chloroquine. The result of antimalarial activities all models will be shown in Table 2.

ANOVA analysis showed that there was significantly different between models therapy (F value 5.26; α 0.05), this indicated that each

Table 1: Growth and inhibition percentage of parasitemia in infected mice that treated with ethanolic extract 60%, 70%, and 80% of sambiloto

Ethanolic concentration (%)	Growth (%)	Inhibition (%)
60	2.84	45.90
70	2.52	52.00
80	1.83	65.14
K(+)	0	100
K(-)	5.25	-

Table 2: Growth and inhibition percentage of parasitemia in mice that treated with combination ethanolic extract 80% sambiloto and chloroquine

Model	Growth (%)	Inhibition (%)
A		
Treatment	0.65	85.61
K(+ A)	2.37	48.02
B		
Treatment	1.39	69.31
K(+ B)	3.10	31.64
C		
Treatment	1.20	73.64
K(+ C)	0	100
D	1.83	65.14
K(-)	4.54	-

model has different antimalarial effectiveness. Tukey's HSD analysis (*post-hoc* test) indicated that Model A gave the greatest differentiation for antimalarial therapy model.

Parasite's growth profile of each combination therapy model will be shown in the graphic below:

Fig. 1 shows that in Model A, the parasite has grown slightly from D₀ to D₄ and gave degradation until D₆ after drug administration was stopped. Compared to the negative (-▲-) and positive control (-■-), the treatment group (-◆-) gave a better result according to the ability of this model to inhibit the parasite's growth.

Model B inhibited parasite's growth by 69.31% (Table 2), and Fig. 2 showed the ability from this model to produce inhibition compared to the negative (-▲-) and positive control (-■-). Even though the parasitemia level slightly increased until D₆, this showed that the combination therapy act from the beginning of treatment and the increase of parasitemia might be caused by short half-life of ethanolic extract 80% sambiloto. Andrographolide is one of the major compounds that contain in *A. paniculata* extract. Study of pharmacokinetic and oral bioavailability of Andrographolide from *A. paniculata* extract revealed that Andrographolide was quickly and almost completely absorbed into the blood following the oral administration of extract at a dose of 20 mg/kg body weight. A large part (55%) of Andrographolide is bound to plasma proteins and only limited amount can enter the cells. The half-life of andrographolide is approximately 6.6 hrs [14].

Model C profile as in Fig. 3 showed the degradation of parasite after the administration of chloroquine in D₃ until the last day of observation (D₆). This result was similar to the Model A, but there was a large difference in

the dose of chloroquine used. At Model A, the chloroquine dose applied approximately 1/100 times than in Model C (0.15 mg/kg body weight out of 10 mg/kg body weight) but could produce similar antimalarial activity. In Model, C was indicated that the dose of chloroquine used yield no inhibition up to 100%. The accumulation rate of chloroquine in blood is required to give a therapeutic effect. In addition, this could increase the resistance of chloroquine, which is also supported with the long half-life of chloroquine and the long duration usage. Chloroquine has the elimination half-life for 99.3 hrs in malaria infected mice [15]. With a small dose used, but could produce great activity, this expected to be able to suppress the resistance risk of chloroquine.

The treatment of ethanolic extract 80% sambiloto (-◆-) for 4 days (D₀-D₃) only could inhibit parasite to 65.14% (Table 2). Fig. 4 shows that after the administration stopped in D₃, the increase of parasitemia level is occurred. It was possibly happened because the short half-life of ethanolic extract 80% sambiloto. When the treatment was stopped, then the increasing of parasitemia level was quite sharp. Compared to Model A, since the beginning of treatment the parasite growth profile was not too high, and with the existence of a combination therapy proved that the combination therapy gave better antimalarial activity compared to monotherapy.

From this various combination therapy models of ethanolic extract 80% sambiloto and chloroquine, could be shown that every model has given different result, and from the observation until D₆, we could conclude that Model A gave the best potential success for antimalarial therapy compared to the other model. This caused by the ability of this model to produce high inhibition (85.61%, Table 2), the parasite's number

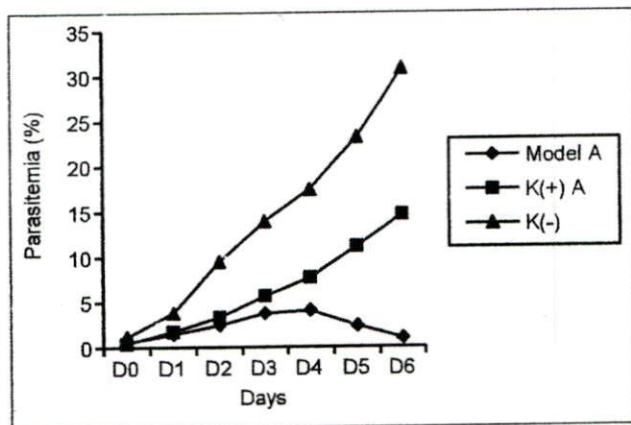


Fig. 1: Parasite's profile of Model A

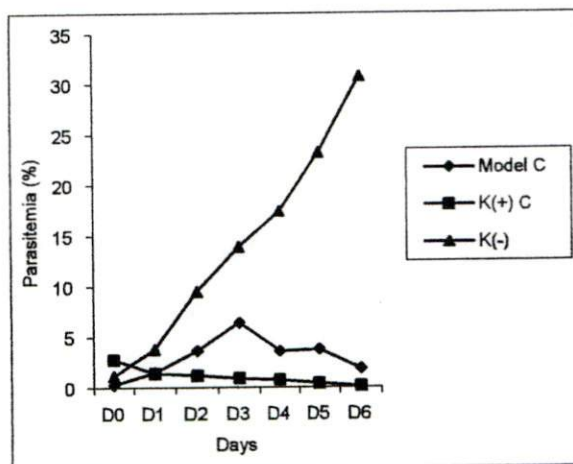


Fig. 3: Parasite's profile of Model C

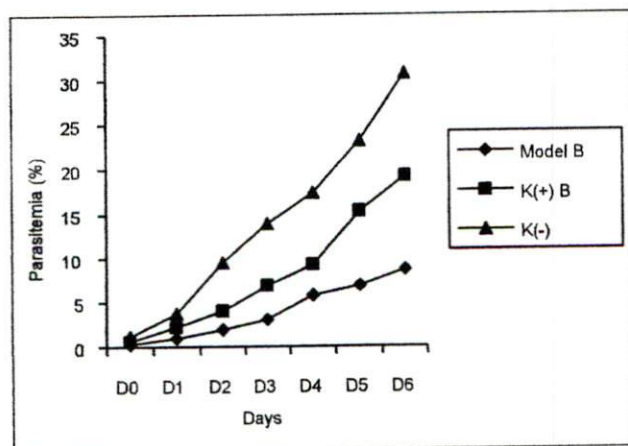


Fig. 2: Parasite's profile of Model B

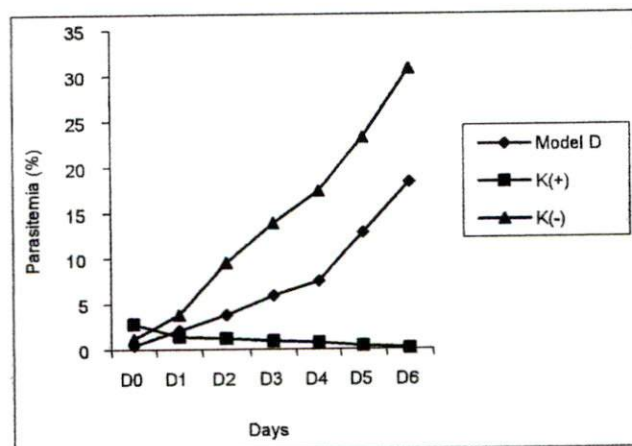


Fig. 4: Parasite's profile of Model D

downwards, as well as having smaller resistance risk because of the low dosage of chloroquine that was used (0.15 mg/kg body weight). However from various combination therapy models that already performed, there was no combination model resulted in 100% parasite inhibition. In the future, research for other combination therapies model needs to be done as the alternative improvement of antimalarial therapy.

CONCLUSION

Based on the activity of antimalarial and the parasite profile that was shown from each combination therapies model, the model gave the potential success therapy was the Model A which is combination therapy of ethanolic extract 80% sambiloto at a dose of 100 mg/kg body weight and chloroquine at a dose of 0.15 mg/kg body weight which given in 4 days (D₀-D₃).

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