

Effect of Andrographis paniculata tablet (AS201-01) on Transforming Growth Factor Beta (TGF- β) expression and parasite inhibition in mice placenta infected with Plasmodium berghei

by Aty Widyawaruyanti

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Effect of *Andrographis paniculata* tablet (AS201-01) on Transforming Growth Factor Beta (TGF- β) expression and parasite inhibition in mice placenta infected with *Plasmodium berghei*



Aty Widyawaruyanti,^{1,2*} Jatmiko Rachmat,³ Nurya Viandika,⁴ Hilkatul Ilimi,² Lidya Tumewu,² Budi Prasetyo⁵

ABSTRACT

Background: Transforming Growth Factor β (TGF- β) is a cytokine regulator of inflammation that important in inhibited parasite growth and preventing inflammation. *Andrographis paniculata* was empirically used as traditional medicine in Indonesia to cure malaria by activating TGF- β . Preliminary studies showed that AS201-01 tablets containing the ethyl acetate fraction of *A. paniculata* had been shown to inhibit the growth of *Plasmodium berghei*.

Aims: This study aims to determine the effect of the AS201-01 tablet on parasite inhibition and TGF- β expression in *P.berghei* infected mice placenta.

Methods: About 24 pregnant mice were divided into 4 groups: healthy pregnant mice (normal) (G1), untreated infected pregnant mice (negative control) (G2), infected pregnant mice treated by AS201-01 tablets (G3), and infected pregnant mice treated with Dihydroartemisinin-

piperaquine (positive control) (G4). About 1×10^6 parasitemia were infected on the 9th day of pregnancy, while therapy was administered on the 11th day of pregnancy. The placenta was collected at the 15th day of pregnancy. The parasite inhibition and TGF- β expression were evaluated using Hematoxylin-Eosin (HE) and immunohistochemistry assay.

Results: The results showed that the parasite still found in the placenta of G2, G3, and G4 still, but parasite of placental in G2 was higher than G3 and G4. There was a significant difference in the parasite inhibition between G2 with G3 and G4 ($p < 0.05$). In addition, the immunohistochemistry assay found that there was a significant difference in TGF- β expression between G2 with G3, G4, and G1 ($p < 0.05$).

Conclusion: Administration of the AS201-01 tablets inhibit parasite *P.berghei* and increase TGF- β expression on the placenta of infected mice.

Keywords: *Andrographis paniculata*, AS201-01 tablet, parasite inhibition, TGF- β expression pregnant mice, *Plasmodium berghei*

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INTRODUCTION

Malaria in pregnancy is an immense public health problem with at least 50 million pregnant women living in the endemic malaria area.¹ In the endemic malaria areas, pregnant women are more susceptible to malaria parasites than non-pregnant women and become heavier in primigravida rather than multigravida, due to the decline in the immune system during pregnancy. However, the low transmission area for malaria in pregnancy results in low birth weight infant, spontaneous abortion, neonatal death, preeclampsia, maternal anemia, and maternal mortality. In high transmission areas, malaria is usually asymptomatic and impairs fetal growth.^{2,3}

The sequestration of infected erythrocytes in the placenta can activate inflammatory cytokines, resulting in the leading to impaired maternal-fetal exchange and damage to the placenta.^{4,5} This condition can be prevented by the activation of cytokine regulator of inflammation, i.e., Transforming Growth Factor β (TGF- β). TGF- β appears to play a pivotal role in downregulating the production of potentially

pathogenic pro-inflammatory cytokines and the clearance of parasite infected.⁶ Activation of TGF- β may inhibit parasite growth and prevent inflammation that has an adverse effect on mother and fetus.

The difficulty of malaria therapy in pregnancy is more often caused by the selection of safe antimalarial drugs for mothers and fetuses because most of the available antimalarial drugs provide side effects for mother and fetus. A variety of medications has been established as safe and effective in pregnancy, including chloroquine, quinine, sulfadoxine pyrimethamine, mefloquine, chlorproguanil, dapsone, and amodiaquine. However, increasing resistance to these agents has led to a need for more effective malaria treatments especially for women pregnancy.⁷ The World Health Organization (WHO) recommends artemisinin-based combination therapy (ACT) as first-line treatment of *P. falciparum* malaria.⁸ Limited information regarding the safety and embryotoxicity effect of ACT if given in 1st trimester is a new problem in the treatment of pregnancy malaria.^{9,10}

¹Department of Pharmacognosy and Phytochemistry at Faculty of Pharmacy Universitas Airlangga, Surabaya

²Institute of Tropical Disease, Universitas Airlangga, Mulyorejo, Surabaya

³Resident of Obstetrics and Gynecology at Faculty of Medicine Universitas Airlangga, Mayjen. Prof. Dr. Moestopo 6-8, Surabaya

⁴Postgraduate student of Health Reproduction Program at Faculty of Medicine, Universitas Airlangga, Surabaya

⁵Department of Obstetrics and Gynecology at Faculty of Medicine, Universitas Airlangga, Mayjen. Prof. Dr. Moestopo 6-8, Surabaya

*Correspondence to:

Aty Widyawaruyanti, Department of Pharmacognosy and Phytochemistry at Faculty of Pharmacy Universitas Airlangga, Surabaya, Institute of Tropical Disease, Universitas Airlangga, Mulyorejo, Surabaya
aty_w@yahoo.com,
aty-w@ff.unair.ac.id

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The use of plants in antimalarial drug discovery efforts has been widely practiced, particularly from herbs traditionally used by communities to treat malaria. The ethnopharmacological approach can be a promising avenue for finding the effective and safe of novel antimalarial candidates.^{11,12} Based on Yeung et al. (2008) study, the antimalarial drugs of natural ingredients are more stable and have lesser side effects compared to synthetic materials.¹³ This suggests that potential crops as a source of new and effective antimalarial drug discovery are safe.¹⁴

Andrographis paniculata belongs to the family Acanthaceae is one of the most popular medicinal plants used traditionally for the treatment of an array of diseases such as cancer, diabetes, high blood pressure, ulcer, leprosy, bronchitis, and malaria for centuries in Asia, America and Africa continents.¹⁴ In Indonesia, this plant is used as a traditional medicine to cure malaria. The previous study showed that Three phytopharmaceutical products of *A. paniculata* (Tablet I: wet granulated formula of AP fraction A; Tablet II: wet granulated formula of AP fraction B; Tablet III: solid dispersion formula of AP fraction B) were inhibited parasite's growth with inhibition range of 70.15% to 80.35%.¹⁵ Ethyl acetate fraction of *A. paniculata* (namely AS201-01) also known to inhibit *P. berghei* with ED₅₀ value of 6.75 mg/kg BW. It was significantly able to increase the survival time of infected mice compared to the untreated group.¹⁶ Currently, ethyl acetate fraction has been developed into phytopharmaceutical products in tablet form (namely AS201-01). Research to determine the effectiveness and safety of tablets to treat malaria in pregnancy has never been done. This study aimed to determine the effect of AS201-01 tablet on parasite inhibition and TGF- β expression in the *P.berghei* infected mice placenta.

MATERIALS AND METHODS

Materials

Andrographis paniculata tablet (AS201-01) contained ethyl acetate fraction which equals to 35 mg of andrographolide per tablet. The tablet was produced at Faculty of Pharmacy, Airlangga University. Dihydroartemisinin and Piperaquine phosphatase (DHP) tablet which contains Dihydroartemisinin 40 mg/ Piperaquine phosphatase 320 mg (D-ARTEPP™) was produced by Guilin Pharmaceutical Co., Ltd, Guangxi, China.

The study involved 24 of 8 to 12 weeks old, 25-30 g in weight and healthy female mice Balb/c. The animals were maintained at the Animal Laboratory of Institute of Tropical Disease, Airlangga University. Permission and approval for animal studies were obtained from Faculty

of Veterinary Medicine, Airlangga University, Surabaya, Indonesia, with ethical clearance No: 560-KE/2016.

Plasmodium berghei ANKA strain was originally obtained from Eijkman Institute for Molecular Biology, Jakarta. The parasite has been maintained at Institute of Tropical Disease, Airlangga University by a combination of passage in male Balb/c mice and cryoscopic storage.

METHODS

Gestation timing and pregnancy monitoring

For pregnancy study, female mice were injected with 5 IU pregnant mare serum gonadotropin (PMSG, foligon) and 5 IU human chorionic gonadotropin (hCG, Chorulon) 48 h after PMSG. The female mice were then mated with male mice in monomating. All female mice were weighed before mating and then daily observed to confirm successful pregnancy. First observation of vaginal plug was considered as Gestation day 0 (GD 0) of pregnancy. Vaginal plugs and weight gain after mating were regarded as true markers for a successful pregnancy.

Experimental design

All mice, except for normal group, were infected by 1×10^6 of *P. berghei* parasite on day 9 of gestation (GD 9) and were given therapy on day 11 of gestation (GD 11). Twenty-four pregnancy mice (Balb/c) then were divided into 4 groups (n = 6). Group 1 (G1) was healthy pregnant mice (Normal). Group 2 (G2) was untreated infected pregnant mice (negative control). Group 3 (G3) was given by *A. paniculata* tablet (AS201-01) which equal to 25 mg/kg body weight of andrographolide, twice daily for 4 days. Group 4 (G4) was given by DHP tablet equivalent to 1.25 mg Dihydroartemisinin and 9.98 mg Piperaquine phosphate/kg body weight, once a day for 3 days (positive control). All mice were sacrificed at day 15th of pregnancy. The placenta was collected in formalin 10%. The parasite inhibition and TGF- β expression were evaluated using Hematoxylin-Eosin (HE) and immunohistochemistry assay.

Examination of parasite inhibition

The slide observed under microscope H600L Nikon (10x100). Criteria of parasite accumulation in placenta as described in Table 1 (Supplement). Classification of placental malaria was performed based on the Bulmer et al. (1993) category to clarify the results of placental parasite accumulation examination.¹⁷ Bulmer category was shown in Table 2 (Supplement).

Table 1 Criteria of parasite accumulation in placenta

Score	Description
0	There are no microscopic parasites per field of view
+ (1)	1-10 asexual stage parasites per 100 microscopic field of view
++ (2)	11-100 asexual stage parasites per 100 microscopic field of view
+++ (3)	1-10 asexual stage parasites per one microscopic field of view
++++ (4)	11-100 asexual stage parasites per one microscopic field of view

Table 2 Classification of placental malaria based on the Bulmer category

Score	Description
0	No infection.
1	Active infection. Parasites found in maternal blood erythrocytes in the intervillous space and found pigments in erythrocytes and monocytes.
2	Chronic active infection. As in Category 1, however, pigment is also found in fibrin or cells in fibrin and or found pigment in syncytiotrophoblast cells.
3	Post-chronic infection. No parasites are found, pigments are limited in fibrin or cells in fibrin.

Table 3 Semiquantitative scale of IRS

A	B
Score 0: No positive cells score	Score 0: No reaction color
Score 1: Positive cells less than 10%	Score 1: The color intensity mild
Score 2: Positive cells between from 11% - 50%	Score 2: The color intensity moderate
Score 3: Positive cells between from 51% - 80%	Score 3: The color intensity strong
Score 4: Positive cells between from more than 80%	

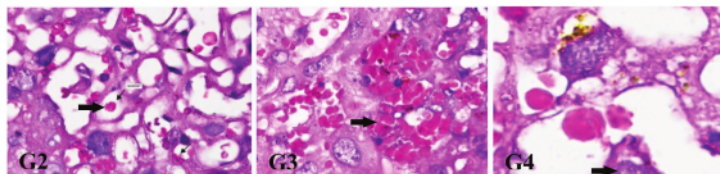


Figure 1 G2 showed an overview of Plasmodium parasite-infected placenta (arrows) and have not obtained pigment hemozoin. The arrow in the G3, and G4 indicated an infected erythrocytes (rosetting) and a schizont stage, respectively, (HE staining, magnification 1000x; H600L Nikon microscope; Fi2 300 megapixel camera DS)

Examination of the expression of TGF- β placenta

The immunohistochemical staining with methyl green for TGF- β expression examination was carried out on the last paraffin block of placental tissue. Cytokine expression was assessed semi-quantitatively according to the modified method Remmele, where the index scale of Remmele immunoreactive score (IRS) is the result of multiplying the percentage score and the color intensity scores of immunoreactive cells (Table 3) (Supplement). Data of each sample is the average value of IRS which observed in different 10 fields of view at 400 \times magnification.¹⁸

Statistical analysis

Data were analyzed by statistical software SPSS version 17. A non-parametric test was determined by using Kruskal-Wallis test, and the significance different of groups analysis was carried out by using the Mann-Whitney test. A p-value <0.05 was considered significant.

RESULTS

Parasite inhibition of placenta

The results showed that in G2, G3, and G4 still found parasite in placenta, but parasite of placental in G2 was higher than G3 and G4 (mean = 3.83) (Table 4 and Figure 1). It was indicated that AS201-01 tablets, besides DHP tablets, have antimalarial activity. Statistical analysis of the parasite inhibition showed that there was a significant difference in the parasite inhibition between G2 with G3 and G4 ($p < 0.05$, $p = 0.001$). It was indicated that AS201-01 tablets inhibited the *P. berghei* growth.

The classification of placental malaria according to modified Bulmer et al. (1993) indicated that in G2, all mice (6 mice) were included in an active infection. In G3 treated with AS201-01 tablets, there were 4 mice including active infection and 2 mice belonging to chronic infection. While in G4 treated with DHP tablets, there were 3 uninfected mice, 1 mice have active infection, and 2 mice have chronic infection (Table 5). These data suggest that administration of AS201-01 tablets may decrease the number of mice that have active infection, although the decrease is not as good as on the administration of DHP tablets.

TGF- β expression in placenta

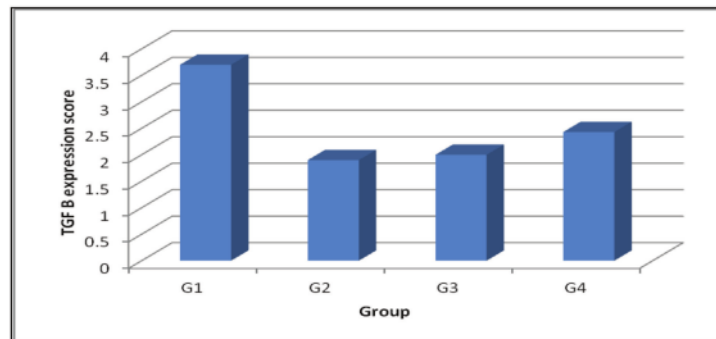
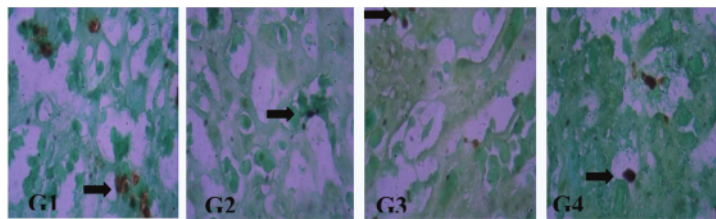
The immunohistochemistry examination of TGF- β expression was shown by the colors of light to dark brown in immunoreactive cells (Figure 2 and 3).

Table 4 The accumulation parasite in placenta of pregnant mice infected with *P. berghei*

Groups	Score of accumulation parasite in placenta					Average
	0	1	2	3	4	
G2 (Untreated)	0	0	0	1	5	3.83
G3 (AS201-01 tablet)	0	3	1	1	1	2
G4 (DHP tablet)	4	1	0	0	1	0.83

Table 5 The classification of placental malaria according to Bulmer category

Groups	Classification of placental malaria Score			
	0	1	2	3
G2 (Untreated)	0	6	0	0
G3 (AS201-01 tablet)	0	4	2	0
G4 (DHP tablet)	3	1	2	0

**Figure 2** The average score of TGF-β expression in placenta**Figure 3** TGF-β expression in placenta, G1 (normal), G2 (negative control), G3 (AS201-01 tablet), G4 (positive control) (IHC staining, magnification 1000x; H600L Nikon microscope; Fi2 300 megapixel camera DS)

There was a significant difference in TGF-β expression between G2 with G3, G4, and G1 ($p < 0.05$, $p = 0.001$). It indicated that AS201-01 tablets were increased TGF-β expression.

DISCUSSION

In this study, we investigated the effect of *A. paniculata* tablet (AS201-01) on parasite inhibition in

the placenta of *P. berghei* infected pregnant mice. The use of pregnant mice infected by *P. berghei* to study pregnancy malaria has been widely practiced.¹⁹ *P. berghei* that infects pregnant mice may cause accumulation or sequestration in the placenta intervillous space; this condition is similar to the pregnant women who infected with malaria. In addition, the chondroitin sulfate A (CSA) and HA which known able to mediate adhesion of *P. falciparum* to human placenta were also found in *P. berghei* infection.²⁰ Based on this data, *P. berghei* infected pregnant mice is quite representative as a model of malaria pregnancy experiment.

The results showed that AS201-01 tablets were inhibited *P. berghei* growth in placenta and decrease the number of mice that have an active infection. The antimalarial effects of AS201-01 tablets are caused by the andrographolide compound as the primary components. This compound has been shown to be active as antimalarial in non-pregnant mice with ED_{50} value of 3.82 mg/kg body weight.²¹ The activity period of andrographolide was found in the ring stage of parasite apparently. In addition, the andrographolide in the parasite life cycle corresponds to the protein and nucleic acid synthesis.²²

The ability of AS201-01 tablet inhibiting *P. berghei* was suspected because the administrations of AS201-01 tablet can increase the TGF-β. This study results found that the administration of AS201-01 tablet (G3) dan DHP tablet (G4) could increase the TGF-β expression compared to the untreated group (G2). The levels of TGF-β in serum were found to be decreased in patients infected with *Plasmodium falciparum* but returned to the normal range after initiation of treatment.²³

TGF-β may inhibit the development of malarial pathology by direct effects on parasite sequestration with downregulating these adhesion molecules expression thus reducing the risk of placental malaria. TGF-β can protect against the severe pathology of *P. berghei* and *P. chabaudi* malaria, and play a pivotal role in controlling parasite growth, at least in the early stages of infection. The apparent ability of TGF-β to help control parasite growth may relate to the fact that, at the beginning of an immune response, low concentrations of TGF-β promote inflammation, recruit monocytes and macrophages to the site of injury, and activate them to become phagocytic.^{24,25} The activation of TGF-β expression in placenta, besides clearing the parasite can also prevent the occurrence of inflammation and pathology that cause adverse effects on the mother and fetus. The AS201-01 tablet was potential to be developed as a new antimalarial drug due to its ability to activate TGF-β. The further studies related to the combination of AS201-01 tablet with

standard antimalarial drugs are needed to obtain safe, effective and efficient combination drugs, particularly for the malarial pregnancy therapy.

In summary, the administration of AS201-01 tablets inhibits parasite *P. berghei* and increase the TGF- β expression of infected mice placenta. The AS201-01 tablet is expected to be used as a new antimalarial drug to treat malaria in pregnancy.

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