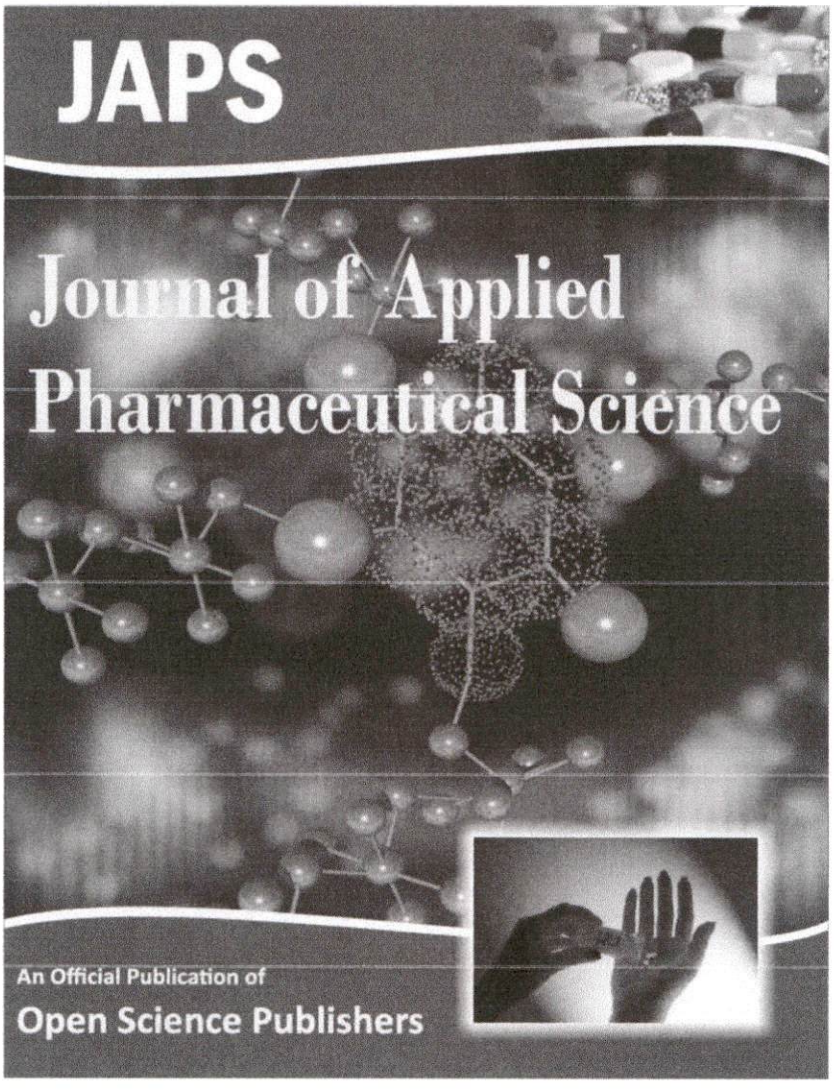
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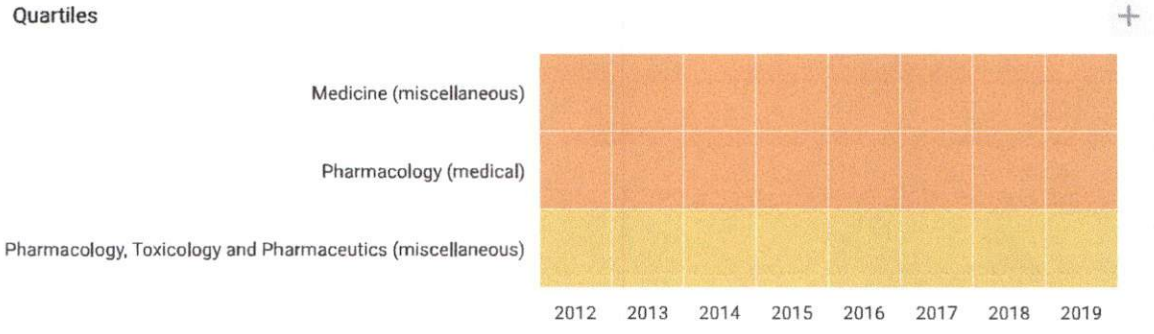


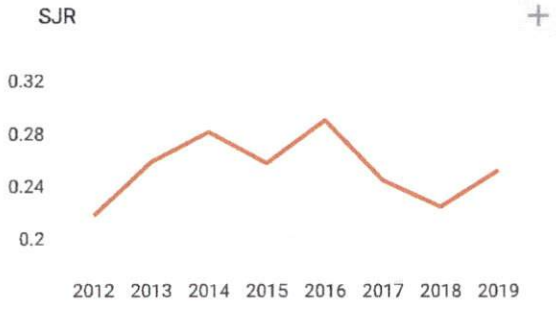


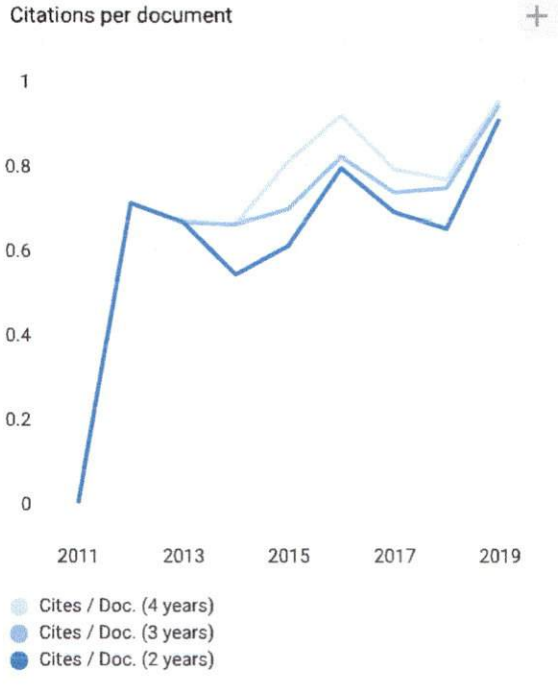


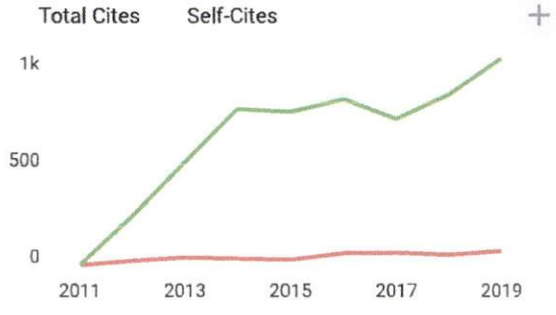


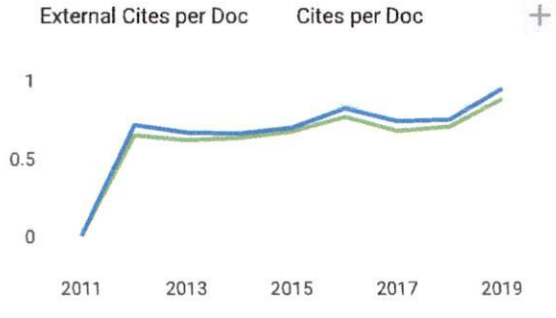


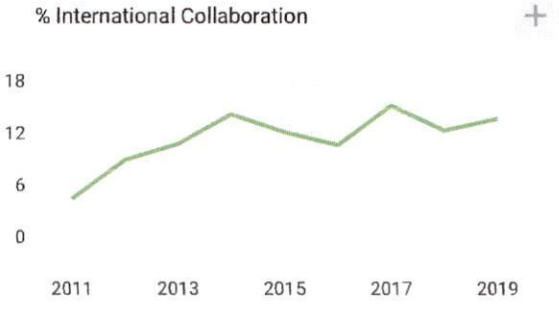



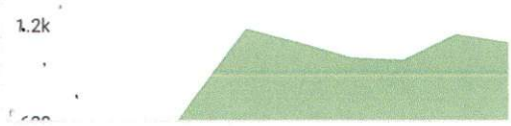




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# Treated *Plasmodium berghei* infected pregnant mice by *Andrographis paniculata* tablet (AS201-01) decreasing the TLR-4 expression and apoptosis index of placental tissue

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TLR-4 expression, Apoptosis index, *Plasmodium berghei*, in vivo assay, *Andrographis paniculata* tablet (AS201-01).

**ABSTRACT**

**Objective**: This study aimed to evaluate the effect of *Andrographis paniculata* tablet (AS201-01) in decreasing expression of Toll-Like Receptor-4 (TLR-4) and apoptosis index of placental tissue of *Plasmodium berghei* infected pregnant mice. **Material and methods**: A total of 24 pregnant mice were divided into 4 groups, G1 was uninfected pregnant mice group, G2 was untreated *Plasmodium berghei* infected pregnant mice, G3 was *P. berghei* infected pregnant mice treated with AS201-01 tablet and G4 was *P. berghei* infected pregnant mice treated with dihydropiperaquine-phosphate (DHP) tablets. All mice were sacrifice at day 15th of pregnancy and the placenta was collected. The TLR-4 expression and apoptosis index were evaluated using immunohistochemistry assay. **Results**: The TLR-4 expression and apoptosis index on G3 was lower than G2 and showed a statistically significant difference (P = 0.00). The TLR-4 expression and apoptosis index of placental tissue in *P. berghei* infected pregnant mice which treated with AS201-01 tablet were decreased compared to untreated group and DHP tablet treated group as well. **Conclusion**: AS201-01 tablet containing ethyl acetate fraction of *A. paniculata* could decrease TLR-4 expression and apoptosis index of placental tissue in *P. berghei* infected pregnant mice.

## INTRODUCTION

Malaria is a tropical disease caused by *Plasmodium* infection. Pregnant women and fetus are subjects at high risk of malaria infection. *Plasmodium* which infected pregnant women will accumulate in placenta. Pregnancy is a unique condition as there is a changing in antibodies and immune system. These systems causing a special bond between *Plasmodium* proteins with receptors on the surface membrane of syncitiotrophoblast cell that lead to placental malaria (Eriksson *et al.*, 2013).

In the patient's body, *Plasmodium*-infected erythrocytes will stimulate the immune response Th-1 to produce INF-γ in high quantities and increase the number of potential receptors such as CD36, TLR-4, and TLR-9, on the syncitiotrophoblast cell surface (Rogerson *et al.*, 2007). In addition, infected erythrocytes will express a *Plasmodium* parasite antigen protein known as Glycophosphatidyl Inositol (GPI) *Plasmodium*. This GPI *Plasmodium* protein will act as ligand parasite by identification receptors such as TLR-4, which present on the surface membranes of syncitiotrophoblast cell (Kyes *et al.*, 2001). The binding between GPI *Plasmodium* and TLR-4 stimulates proinflammatory cytokines through the Myeloid Differentiation Factor 88 (MyD88) and NF-κB signaling pathways and then activates pro-apoptotic proteins (Brabin *et al.*, 2004). *Plasmodium* infections may also induce the formation of Reactive Oxygen Species (ROS) which also lead to increase apoptosis via intrinsic pathways (Wang *et al.*, 2015; Mutabingwa *et al.*, 2005; Sharma *et al.*, 2012).

Placental malaria may cause the increase of TLR-4 expressions and apoptosis index beyond normal thus increasing fetus complications such as abortion, low birth

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weight, intrauterine fetal growth restriction, and consequently, intrauterine fetal death (Allaire *et al.*, 2000; Houmsou *et al.*, 2010; Steketee *et al.*, 2001).

One of the antimalarial drugs being developed is *Andrographis paniculata* which traditionally used as an antimalarial drug in Indonesia. Ethyl acetate fraction of *A. paniculata* was found to have antimalarial effect as reported in the previous study (Widyawaruyanti *et al.*, 2014). Further study is to develop ethyl acetate fraction of *A. paniculata* which was formulated in tablet dosage form called AS202-01. The tablet was reported to inhibit the growth of *Plasmodium berghei* in nonpregnant mice (Widyawaruyanti *et al.*, 2017). Our recent study resulted in another formulation of ethyl acetate fraction of *A. paniculata* as a tablet dosage form (called AS201-01 tablet) as well. The tablet was a potential alternative to an antimalarial drug. The effect of the tablet on *P. berghei* infected pregnant mice was unknown, in particular, the effect on TLR-4 expression and apoptosis index. Possibly along with its antimalarial activity, the tablet may also decrease TLR-4 expression and apoptosis index in *P. berghei* infected pregnant mice.

It is hoped, *P. berghei* infected pregnant mice which were treated with an AS201-01 tablet would decrease TLR-4 expression and apoptosis index so that could prevent placental malaria complication and worsening of the fetus. Therefore, this study is aimed to evaluate the effect of the AS201-01 tablet in decreasing of TLR-4 expression and apoptosis index of placental tissue in *Plasmodium*-infected pregnant mice.

## MATERIAL AND METHODS

### Materials

The AS201-01 tablet contains ethyl acetate fractions of *A. paniculata*, equivalent to 35 mg of andrographolide per tablet. The tablet was produced at Faculty of Pharmacy, University Airlangga, Surabaya, Indonesia. DHP tablet contains dihydroartemisinin 40 mg and piperaquine phosphatase/320 mg (D-ARTEPP™) was produced by Guilin Pharmaceutical Co., Ltd., Guangxi, China.

### Parasite

*P. berghei* ANKA strain was obtained from Eijkman Institute for Molecular Biology, Jakarta. On the 9th day post mating, mice were injected with *P. berghei* ANKA strain per 0.2 ml of blood intraperitoneally. This parasite has been maintained at the Institute of Tropical Disease, Universitas Airlangga, Surabaya, Indonesia.

### Animals

This study used female and male mice Balb/c strain at 16 to 18 weeks of age which were obtained from the Animal Experimental Development Unit - Gajah Mada University (Yogyakarta, Indonesia). They were maintained at Animal Laboratory of Institute of Tropical Disease, Universitas Airlangga. Permission and approval for animal studies were obtained from Faculty of Veterinary Medicine, Universitas Airlangga, with ethical clearance No: 560-KE/2016.

### Experimental design

Eighteen of pregnant mice were infected with $1 \times 10^6$ of *P. berghei* parasite on day 9th of gestation (GD 9). These infected mice then divided into 3 groups which were G2, G3, and G4 (n = 6). Administered therapy was begun on day 11th of gestation (GD 11). G2 was an untreated group. G3 was treated by AS201-01 tablet, at a dose equal to 25 mg andrographolide/Kg body weight, twice daily for 4 days. Meanwhile, G4 was treated by Dihydroartemisinin Piperquine-Phosphate (DHP) tablet, once a day for 3 days. Additionally, G1 was uninfected pregnant mice (n = 6). All mice were then terminated on the 15th day of gestation (GD 15) and placenta collected in formalin 10% for further analysis.

### Measuring TLR-4 expression and apoptosis index

Placenta samples in paraffin blocks were stained with immunohistochemical KIT using monoclonal anti-rat TLR-4 (NBP 2-45710) Nuvosbio for measuring TLR-4 expressions and TACS-XL in situ apoptosis detection KIT (4828-30-DK) for measuring apoptosis index.

### Evaluation of TLR-4 expression and apoptosis index

Observation and counting the number of TLR-4 expression and apoptosis index in placenta tissue under microscope H600L Nikon (10 × 100) were done in five fields of view. TLR-4 expression and apoptosis index was calculated used Immunoreactive Score (IRS) that referred to the result of multiplying the score of percentage immunoreactive cells with a score of color intensity on the cell immunoreactive with Tunnel assay staining. Placenta tissue that consists of syncytiotrophoblast cells undergoing DNA fragmentation will be labeled as brown chromogen.

### Statistical analysis

Data was analyzed by statistical software SPSS version 17. The normality data distribution was determined by Kolmogorov-Smirnov test. The significance of the mean difference between independent groups for normal distribution data was determined by using one-way analysis of variance (ANOVA). Meanwhile, for nonnormal distributed data was determined by using nonparametric Kruskal-Wallis test. Significance different of groups was analyzed by using Post Hoc Tukey's HSD test. A p-value <0.05 was considered significant.

## RESULTS AND DISCUSSION

Studies to determine the effect of administration of AS201-01 tablets against TLR-4 expression and apoptosis index of placental tissue of plasmodium-infected pregnant mice were performed. Figure 1 showed the placenta TLR-4 expression in all groups. The highest TLR-4 expression was shown in G2 and the lowest in G1. The result of the statistical analysis showed that there was a significant difference (P = 0.00) on TLR-4 expression between group G2 with G1, G3, and G4. Meanwhile, figure 3 showed means of apoptosis index in all groups. The highest apoptosis index was in G2 and the lowest in G1. The statistic analysis result using one way ANOVA showed a significant difference between G2 and G1 (P = 0.00) and also between G2 and G3 (P = 0.00). There was no significant difference in apoptosis index between G1 dan G3 (P = 0.15).

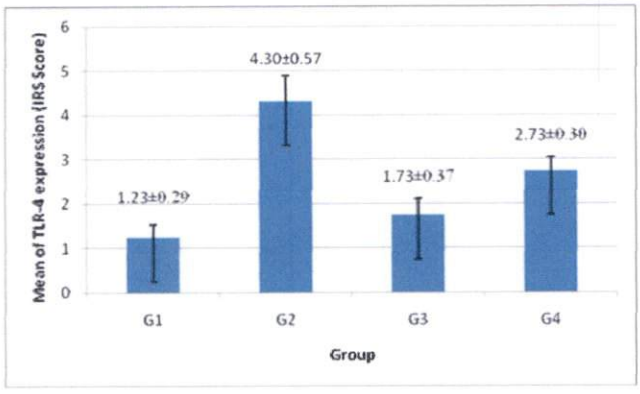


**Fig. 1**: Mean of placenta TLR-4 expression in all groups (G1: normal group. G2: infected untreated pregnant mice group. G3: infected pregnant mice and treated with AS201-01 tablet group, G4: infected pregnant mice and treated with DHP tablet group).

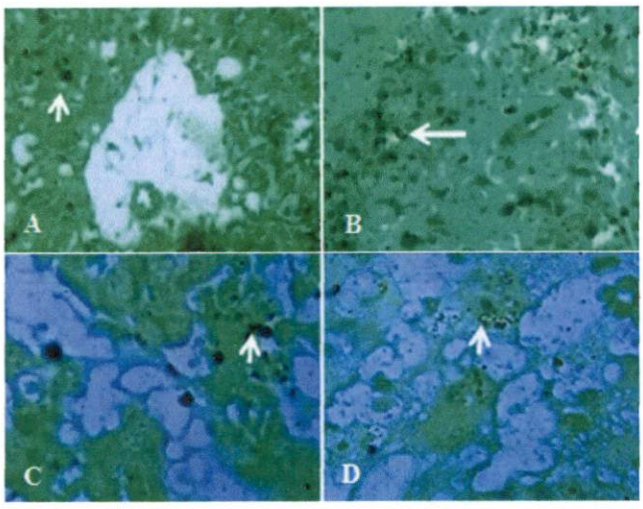


**Fig. 2**: TLR-4 expression in: A. normal group (G1), B. infected untreated pregnant mice group (G2), C. infected pregnant mice and treated with AS201-01 tablet group (G3), D. infected pregnant mice and treated with DHP tablet group (G4). The arrows show the TLR expression on cell membrane surface. The sample was observed under a light microscope with 100x objective magnification.

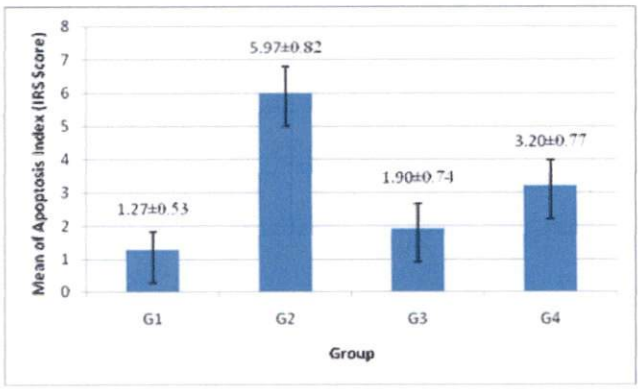


**Fig. 3**: Mean of placental apoptosis index in all groups (G1: normal group, G2: infected untreated pregnant mice group, G3: infected pregnant mice and treated with AS201-01 tablet group, G4: infected pregnant mice and treated with DHP tablet Group).

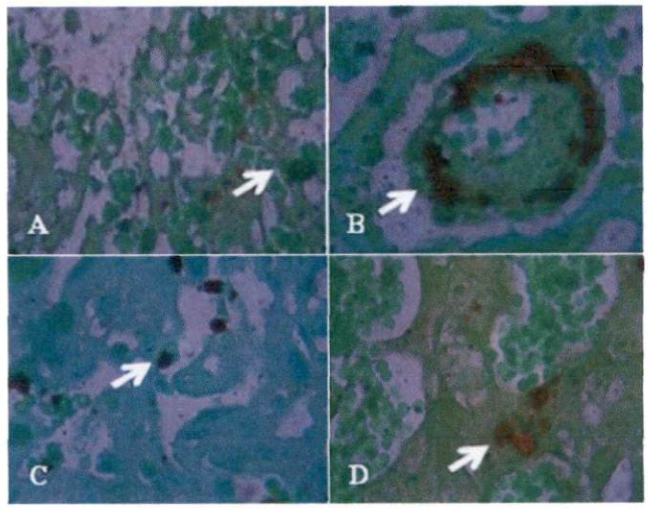


**Fig. 4**: Apoptosis index in: A. normal group (G1), B. infected untreated pregnant mice group (G2), C. infected pregnant mice and treated with AS201-01 tablet group (G3), D. infected pregnant mice and treated with DHP tablet group (G4). The arrows show the apoptosis on cell membrane surface. The sample was observed under a light microscope with 100x objective magnification.

The study results showed that TLR-4 expression and apoptosis index in uninfected group (G1) were low. This group was used as normal control. Meanwhile, the highest TLR-4 expression and apoptosis index was found in *P. berghei* infected untreated pregnant mice group (G2). This result was in accordance with previous report that found the apoptosis index of *P. berghei* infected pregnant mice was higher than in uninfected pregnant mice (Sharma *et al.*, 2012). *P. berghei* infected pregnant mice which treated with *A. paniculata* tablet AS201-01 (G3) were showed lower TLR-4 expression and apoptosis index compared to G2. This suggests that administration of AS201-01 tablets may decrease TLR-4 expression and apoptosis index. In the placenta, apoptosis normally occurs to maintain a pregnancy. An excessive increase in apoptosis may cause a disruption of blood flow to the placenta resulting in decreased fetal weight (Rogerson *et al.*, 2007; Allaire *et al.*, 2000).

**Table 1**: Semiquantitative IRS score. The result of multiplication percentage of the immunoreactive cell (A) with color intensity score (B).

| A | B |
|---|---|
| Score 0: no positive cell | Score 0: no color reaction |
| Score 1: positive cell less than 10% | Score 1: low color Intensity |
| Score 2: positive cell between 11–50% | Score 2: medium color Intensity |
| Score 3: positive cell between 51–80% | Score 3: high color Intensity |
| Score 4: positive cell more than 80% | |

The ability of AS20-01 tablets in decreasing the TLR-4 expression and apoptosis index because of the *A. paniculata* effect as an immunomodulator and antioxidant, which inhibit T lymphocyte cells in activating TLR-4 (Lin *et al.*, 2009; Qin *et al.*, 2006). This TLR-4 activation inhibition leads to activation inhibition of cytokine and pro-apoptosis proteins which may decrease apoptosis index of the placenta through extrinsic pathways (Rogerson *et al.*, 2007). It was also inhibited ROS formation thus

decreasing apoptosis via intrinsic pathway (Rogerson *et al.*, 2007; Brabin *et al.*, 2004; Lin *et al.*, 2009).

*A. paniculata* tablet has an antimalarial effect. The antimalarial effect is due to the andrographolide which is the major compound of this plant. The period of activity of andrographolide was found evidently on the ring stage of the parasite (Luo *et al.*, 2013). *A. paniculata* extract and andrographolide effects include inhibition of the nuclear transcription factor-kappa B (NF-κB). *Plasmodium*-infected erythrocytes have shown to induce NF-κB regulated inflammatory pathways in human cerebral endothelium. NF-κB is activated and translocated into the nucleus, where it binds to the DNA regulatory site to regulate specific gene expression, especially cell signaling for parasite growth and development. Therefore, the inhibition of transcription factor of *A. paniculata* extract against *P. berghei* ANKA might be a critical process to inhibit blood stage propagation of parasites in vivo (Luo *et al.*, 2013; Mishra *et al.*, 2009).

Tablets AS201-01 can be used as an alternative to treats malaria in pregnancy. Therapy with this tablet is expected to prevent the side effects of malaria in pregnancy, such as low birth weight, abortion, and fetal growth inhibited.

## CONCLUSION

In conclusion, *A. paniculata* tablet (AS201-01) which contain ethyl acetate fraction of *A. paniculata* could decrease the TLR-4 expression and apoptosis index of placental tissue in *P. berghei* infected pregnant mice.

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## CONFLICT OF INTEREST

There is no conflict of interest.

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