*Section A-Research paper*

# Secondary Metabolite Extract of *Streptomyces hygroscopicus* subsp Hygroscopicus Increases the Expression of VEGF on Trophoblastic Cells but does not Influenced the Fetal Weight of Pregnant Malaria Mice

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## ABSTRACT

**Introduction:** During pregnancy, pregnant women are susceptible to malaria, contributing significantly to maternal and infant mortality. Over the past 100 years, several treatments for malaria have been proposed, but have systematically failed, largely due to the emergence of drug resistance, in part due to exposure of the parasite to low doses of the drug. Moreover only few anti malaria drug can be used for pregnant malaria. *Streptomyces hygroscopicus* subsp Hygroscopicus is a potential source for bioactive molecules that produce secondary metabolites that could be served as antimalarial agents.
**Aim:** This research was conducted to study the effect of secondary metabolite extract of *Streptomyces hygroscopicus* subsp Hygroscopicus on fetal growth and placental cell VEGF expression in pregnant mice.
**Methods:** An experimental study had conducted using Swiss mice infected with *P. berghei* as a malaria pregnancy model. Samples were divided into 3 control groups, there were (i) normal mice without any treatment or K- group (ii) normal mice treated with *Streptomyces hygroscopicus* extract dose 2600 µg/kgBW or KP group (iii) infected mice with *P. berghei* or K+ group, and 5 treatment groups there were (iv) mice infected with *P. berghei* and treated intra-peritoneal with Artemisinin or PA group, and mice infected with *P. berghei* and treated with metabolite extract *of S. hygroscopicus* (v) dose of 1600 µg/kgBW or P1 group, (vi) dose of 2600 µg/kgBW or P2 group, (vii) dose of 3600 µg/kgBW or P3group and the last (vii) dose of 4600 µg/kgBW or P4 group for 5 days respectively. The degree of parasitemia was measured from the first day of malaria induction until the last treatment. On day 15$^{th}$ of post mating, all of the pregnant mice were sacrificed. Fetal weights were measured using analytic balance. Expression of VEGF expression in the placental tissue was measured using immunohistochemistry.
**Results:** Statistical analysis showed that the fetal weight among control group and treatment groups was not significant different (Anova; p=0,423). There was a significant difference on VEGF expression in the trophoblast cell among control groups and treatment groups (Anova; p= 0,000).
**Conclusion:** These findings indicate that secondary metabolite *Streptomyces hygroscopicus* Subsp Hygroscopicus could increases the expression of VEGF on Trophoblastic Cells without influence the fetal weight.
**Key words:** *Streptomyces hygroscopicus* subsp Hygroscopicus, malaria in pregnancy, fetal weight, VEGF

# 1. INTRODUCTION

Pregnancy is actually a semi-allogeneic transplant, a unique and interesting physiology in which a fetus that would normally be rejected by the mother's immune response is accepted until the fetus is born (Halperin *et al*., 2000; Mor *et al*., 2010; Malik *et al*., 2016). A failed pregnancy is actually a type of rejection. It can be caused by many factors such as genetics, chromosomal and anatomical defects, as well as certain infection diseases (Chua *et al*., 2021).

Malaria infection in pregnant women, especially those who have not been vaccinated, can cause various symptoms of infertility, including abortion, premature birth, preterm birth, stillbirth, congenital anomalies, intrauterine growth retardation/restriction (IUGR) and low birth weight (LBW). It depends on the stage of pregnancy at which the mother got the malarial infection and the severity of the malarial disease. Severe complications are more common during the first-time birth than during the parity (Saba *et al*., 2008).

It has been demonstrated that dysregulation of angiogenesis, imbalance in cytokine production, and disruption of complement activation pathways may play a role in placental injury (Ataide *et al*., 2015). In hypoxic tissues, HIF-1α protein is stabilized and can bind HIF-1β to form an active transcription factor that will alter the transcription of growth factor genes involved in regulation of angiogenesis (Wang *et al*., 2022). This research was done to reveal if secondary metabolite extract of *Streptomyces hygroscopicus* subsp Hygroscopicus can increase the fetal weight and VEGF expression in placenta mice infected with *Plasmodium berghei*.

# 2. METHODS

## *Study Design*

This study was an experimental study. Forty four pregnant Swiss mice resulting from synchronized mating were divided into 3 control groups (i) normal mice without any treatment or K- group (ii) normal mice treated with *Streptomyces hygroscopicus* extract dose 2 or KP group (ii) infected mice with *P. berghei* or K+ group and 5 treatment groups, there were (iv) mice infected with *P. berghei* and treated intra-peritoneal with Artemisinin or PA group, and mice infected with *P. berghei* and treated with metabolite extract *of S. hygroscopicus* (v) dose of 1600 µg/kgBW or P1 group, (vi) dose of 2600 µg/kgBW or P2 group, (vii) dose of 3600 µg/kgBW or P3group and the last (vii) dose of 4600 µg/kgBW or P4 group for 5 days respectively. The degree of parasitemia was measured from the first day of malaria induction until the last treatment. Pregnant mice were infected with 0.2 mL liquid containing $5x10^6$ *Plasmodium berghei* (ANKA- strain) intraperitoneally. Pregnant mice were infected in $1^{st}$ day of post mating. On day $15^{th}$ of post mating, all of the pregnant mice were scarified, the litters were weight individually using analytic balance (Mettler AE 50). Measuring of angiogenesis was done by immunohistochemistry using monoclonal antibody to VEGF (Santa Cruz Biotechnology's VEGF (VG-1). VEGF expression was calculated in the trophoblast of immunohistochemical staining preparations.

## *Synchronization of estrus and mating*

Female mice were separated from male mice for 2-3 weeks. The female mice were in a condition of un-estrus state (Leeboot effect). They were then exposed to odors of males in order to restart the estrus cycle (Pheromone effect). The female mice were simultaneously in

estrus condition for about 72 hr after being exposed to male odor (Whitten effect). Finally they were simultaneously mated in pair (1:1) within 1 night

## *Inoculation of Mice*

Inoculation was done by intraperitoneally injection of as much as $10^6$ per mL of *Plasmodium berghei* ANKA strain on the day 1st post mating or in the second period of pregnancy.

## *Measurement of parasitemia*

To observe the degree of parasitemia, 10 µL of blood was isolated from the end of the tail of the mice and smeared as a thin smear and dried. Then, the smear was fixed with absolute methanol until it was well distributed and dried. The slides were stained with Giemsa solution (a mixture of Giemsa stain (Merck, HX612241) and Giemsa buffer (Bioanalitika, Indonesia) at a ratio of 1:9 for 30 min, rinsed with water and dried. The degree of parasitemia was determined by examining a blood smear under a microscope at a magnification of 1000×. The percentage of parasitemia was computed based on the number of erythrocytes infected with malaria parasites per 1000 erythrocytes.

## *Preparation of secondary metabolite extract*

The fermented *Streptomyces hygroscopicus* subsp. hygroscopicus was mixed with ethyl acetate 1:5 (v/v), shaken for 1 hour and placed in a separate funnel for 4 hours. The aqueous phase was then discarded and the solvent phase (ethyl acetate) was removed. It was evaporated in a water bath at 80-90°C (Sharma *et al*., 2010).

## *Measurement of Angiogenesis*

Angiogenesis is measured by measuring VEGF expression. VEGF was measured using placental tissue preparations that had been initialized through immunohistochemical methods using mouse VEGF monoclonal antibodies (Fitri *et al*., 2015; Meng *et al*., 2016). Placental tissue slides were depharafinize and washed using PBS pH 7.4. $H_2O_2$ was added 3% (in methanol) and then incubated for 15 minutes. Slides were washed with PBS 3 times and added with unspecific blocking protein (Triton added blocking buffer) continue with incubated for 1 hour at room temperature. After washing with PBS 3 times, slides were added with primary antibody (VEGF) and then incubated overnight at $4^0$C. Slides then were washed with PBS 3 times and added with secondary antibody then incubated for 1 hour at room temperature. Slides were washed with PBS 3 times and added with SA-HRP and then incubated for 40 minutes at room temperature. Slides then were washed using PBS pH 7.4 and added using a substrate for Peroxidase (DAB-Diamino Benzidine) for 20 minutes at room temperature. Finally slides were washed with $H_2O$ and Counterstain with Mayer hematoxilen for 10 minutes, rinsed with tap water then left to dry, mounting the entanglement and covered with a cover glass then observed under a light microscope with 1000x magnification. The brown color of the cell shows VEGF expression.

## *Ethical approval*

The experiments were performed in accordance with the guidelines and approval (No.255/ EC/ KEPK/ 09/ 2019) of the Institutional Animal Care and Use Committee of Brawijaya University

## Statistical analysis

The data of the research results were analyzed with SPSS software program calculations

## 3. RESULTS

The degree of parasitemia in the K+ group increased on the 3rd day and continued to increase until the 6th day. The degree of parasitemia in the PA group increased on day 3 and then decreased until the end of the study. This group experienced the largest decrease of all treatment groups. The degree of parasitemia in the P1, P2, and P3 groups experienced almost the same pattern of increase. Their parasitemia increased on day 3, then increased slightly, but the increase was not as big as compared to the K+ group. The degree of parasitemia in the P4 group increased on day 3 and then slightly increased until day 6. However, the increasing was less than those of groups P1, P2, and P3. The treatment group of *Streptomyces hygroscopicus* subs Hygroscopicus extract (P1, P2, P3, and P4) was able to reduce the degree of parasitemia according to the treatment dose (data not shown)

The effect of *Streptomyces hygroscopicus* subs Hygroscopicus extract on fetal weight was analyzed with the One Way ANOVA test. Based on the results of the analysis using ANOVA, a p-value of 0.423 was obtained, which means that there was no significant difference among groups in this study.

Placental angiogenesis in mice was identified by measuring the presence of VEGF in placental tissue. Placental tissue that had been placed in formalin was treated according to the angiogenesis measurement method by immunohistochemical method using a VEGF monoclonal antibody (Santa Cruz Biotechnology's VEGF/VG-1).

**Table 1 Average of VEGF expression in placental tissue**

| Groups | Average of VEGF expression |
|---|---|
| K- | 108 ± 6.56 |
| KP | 103 ± 4.36 |
| PA | 94 ± 2.65 |
| P1 | 36 ± 3.61 |
| P2 | 58 ± 4.36 |
| P3 | 78 ± 6.24 |
| P4 | 93 ± 6.43 |

(Remarks: group K- (normal mice without any treatment), group KP (normal mice treated with *Streptomyces hygroscopicus* extract dose 2), K+ not identified because all mice died, group PA (infected mice treated with Artemisinin), group P1 (infected mice treated with extract dose 1600 µg/kgBW), group P2 (infected mice treated with extract dose 2600 µg/kgBW), group P3 (infected mice treated with extract dose 3600 µg/kgBW), and group P4 (infected mice treated with extract dose 4600 µg/kgBW).

All pregnant mice were dissected, and the placenta was collected, and then paraffinized for immunohistochemical staining. Next, VEGF expression in the placenta was observed. Observations were made with a magnification of 1000x.

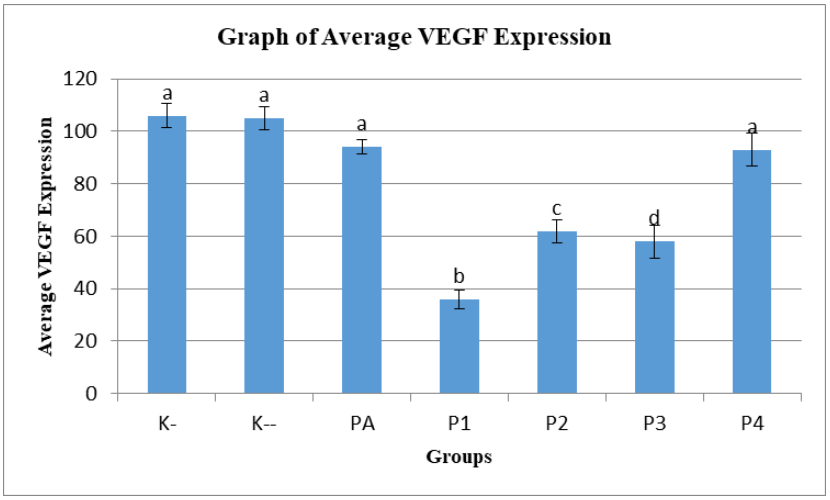


**Figure 1: Graph of VEGF expression in placental tissue. Different notation means significant difference between group.** Remarks: group K- (normal mice without any treatment), group KP (normal mice treated with *Streptomyces hygroscopicus* extract dose 2), K+ not identified because all mice died, group PA (infected mice treated with Artemisinin), group P1 (infected mice treated with extract dose 1600 µg/kgBW), group P2 (infected mice treated with extract dose 2600 µg/kgBW), group P3 (infected mice treated with extract dose 3600 µg/kgBW), and group P4 (infected mice treated with extract dose 4600 µg/kgBW.

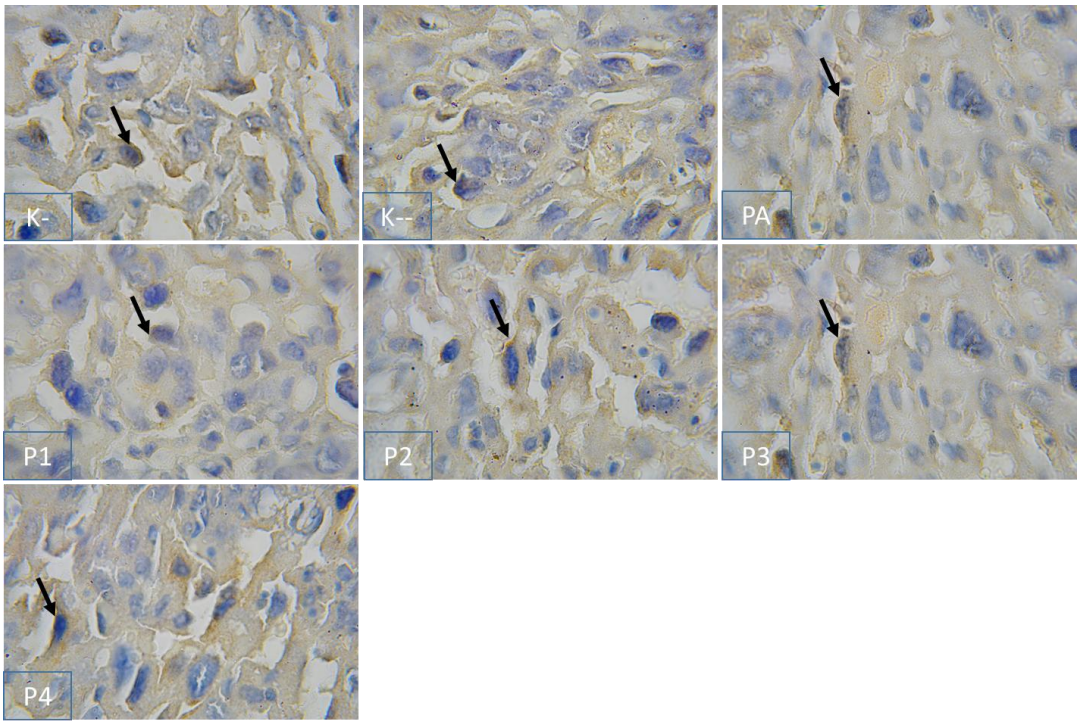


**Figure 2. VEGF expression in placental of each groups** Arrows indicate VEGF-expressing regions Remarks: group K- (normal mice without any treatment), group KP (normal mice treated with *Streptomyces hygroscopicus* extract dose 2), K+ not identified because all mice died, group PA (infected mice treated with Artemisinin), group P1 (infected mice treated with extract dose 1600 µg/kgBW), group P2 (infected mice treated with extract dose 2600 µg/kgBW), group P3 (infected mice treated with extract dose 3600 µg/kgBW), and group P4 (infected mice treated with extract dose 4600 µg/kgBW). Light microscope magnifications 1000X.

## 4. DISCUSSION

The physiology of pregnancy and the pathology of malaria synergistically influence the course and determine the specificity and severity of malaria disease. Pregnant women tend to

prefer their type 2 cytokines, making them more susceptible to diseases such as malaria, which require type 1 cytokines to protect pregnant women. In malaria-infected pregnant women, a transition from TH2 to TH1 occurs, resulting in an imbalance of the local placental immune system. This is reflected in a decrease in IL-10 and an increase in her IFN-, IL-2 and TNF-2. (Malik *et al*., 2016; Kane *et al*., 2011). Recent studies have revealed the involvement of IL-17 produced by TH17 and IL-10 secreted by T regulators. High placental IL-17 levels correlated with low fetal weight, and interestingly, low fetal weight was caused by decreased placental IL-10 (Fitri *et al.*, 2015).

*Plasmodium berghei* infection in pregnant mice causes placental malaria, indicated by the presence of parasite sequestration in the intervillous region of the placenta. *Plasmodium* sequestration induces vascular endothelial cells within the placenta. Induced endothelial cells may release proinflammatory mediators and reduce anti-inflammatory effects (Rogerson *et al*., 2018), thereby reducing VEGF expression and inhibiting angiogenesis. Sequestration of the malaria parasite is thought to lead to decreased angiogenesis, as evidenced by reduced VEGF expression in infected placental tissue from pregnant mice.

In our study, it could not be proven that in the *P.berghei* infection could decrease VEGF expression because all mice in the K+ group died. However, in all groups infected with *P.berghei* and treated with both Artemisinin and with *Streptomyces hygroscopicus*, VEGF expression was much lower than those in the normal mice group except in the highest dose group or P4 group which showed VEGF expression had achieved the same level as the negative control group. This also proves that administration of *Streptomyces hygroscopicus* extract can increase VEGF expression during malarial infection.

Angiogenesis involves the branching of new microvessels from larger vessels (Frater *et al*., 2008). Angiogenesis is a key process in villous vessel development and terminal chorion formation in the human placenta. Blood vessel growth within the placenta begins during the first stages of pregnancy and continues until delivery (Kaufmann *et al*., 2004; Nakagawa *et al*., 2004). Previous studies have shown that malaria during pregnancy is associated with placental pathology. There was a relationship between the amount of angiogenic factors in peripheral blood and the placenta, which plays an important role in the structure and function of the placenta. Angiopoietin-1 levels in women with malaria during pregnancy were associated with specific structure and function of the placenta (Vanessa *et al*., 2021)**.** Vascular endothelial growth factor (VEGF) has been identified as one of the positive regulators of the angiogenic process and the formation of new blood vessels. VEGF is predominantly expressed during the first trimester of embryonic and fetal development and is involved in trophoblast cell proliferation, migration and metabolic activity (Arroyo *et al*., 2009; Ahmed *et al*., 2000; Shiraishi *et al*., 1996). Therefore, parameters for measuring angiogenesis can be determined by measuring VEGF expression

In a previous study, pregnancy malaria due to *Plasmodium vivax* infection caused low birth weight due to an increase in HIF-1 alpha (Prasetyorini *et al*., 2022). Previous research on experimental animals also stated that HIF-1 alpha increased in pregnant mice infected with *Plasmodium berghei* (Rahmah *et al*., 2019). Hypoxia inducible factor-1alpha (HIF-1α) is an important transcriptional mediator of responses to hypoxic conditions associated with changes and imbalances of many chemical mediators including angiogenic factors, which cause fetal growth abnormalities (Prasetyorini *et al*., 2022).

The effects of intrauterine growth restriction on fetal and placental weights were studied in day 21 mice. Fetal weight and placental perfusion from days 19 to 21 of gestation decreased by approximately 10% and 50%, respectively, in 21 days of the treatment group compared with the control group. Severely reduced blood flow within the maternal placenta is believed to be the primary cause of intrauterine growth restriction (Gilbert et al., 1992).

During the course of malaria infection, the placenta is exposed to hypoxia. This causes apoptosis and fetal growth retardation (Endo *et al*., 2005; Bouef *et al*., 2008). Fetal growth retardation due to increased apoptosis of placental cells may be affected by sequestration of infected erythrocytes and accumulation of monocytes within the placenta, which induces free radical liberation. In our study, unfortunately we could not prove that *P.beghei* infection caused low birth weight due to the absence of the K+ group at the end of the study, however we could approve that administration of *Streptomyces hygroscopicus* extract did not have a significant effect on reducing the incidence of low birth weight according to the results of statistical analysis.

## 5. CONCLUSION

In conclusion, *Plasmodium berghei* infection in pregnant Swiss mice correlates with low VEGV expression and secondary metabolite extract of *Streptomyces hygroscopicus* subsp Hygroscopicus could increases the expression of VEGF on Trophoblastic Cells although does not influence the fetal weight.

**Author's Contribution**: L.E., S.W. and K.N. gave substantial contributions to the conception or design of the work in acquisition, analysis, or interpretation of data for the work. K.N. and L.E. had a part in article preparing for drafting or revising it critically for important intellectual content. L.E., S.W. and T.N. gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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