64. Activities of andrographis paniculata

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Original Article

Activities of *Andrographis paniculata* (AS201-01) Tablet on Cox-2 and Prostaglandin Expression of Placental of *Plasmodium berghei* Infected Mice

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Abstract

Background: Placental malaria has ability to upregulate prostaglandin synthesis by increasing cyclooxygenase-2 (Cox-2) enzyme activity. Cox-2 and prostaglandin have a role in causing uterine contraction and therefore can cause abortion or preterm labor. Tablet AS201-01 containing the ethyl acetate fraction of *Andrographis paniculata* was tested in vivo on pregnant mice infected with *Plasmodium berghei*. AS201-01 inhibited the growth of *P. berghei*, increased TGF-β expression, decreased TLR-4 expression and apoptosis index of placental tissue in *P. berghei* infected pregnant mice and thus prevented placental malaria complications. These effects were correlated with the decrease of Cox-2 and prostaglandin expression.

Methods: Twenty-four pregnant mice (Balb/c) were divided into 4 groups (n=6). Mice were maintained at Animal Laboratory of Institute of Tropical Disease, Universitas Airlangga, Surabaya, Indonesia in 2016. G1 were uninfected pregnant mice, G2 untreated infected pregnant mice, G3 infected pregnant mice treated with AS201-01, and G4 infected pregnant mice treated with DHP tablet. All infection groups (G2-G4) were inoculated with $1x10^6$ of *P. berghei* parasite on day 9 of gestation and treated on day 11. All mice were terminated at day 15 of gestation, and placental tissue was collected. Cytokine expression of Cox-2 and prostaglandin were evaluated using immunohistochemistry.

Results: G3 was found to have lower Cox-2 and prostaglandin expression compared to G4 and G2, but higher compared to G1. Cox-2 and prostaglandin expression was significantly different among groups (P<0.001).

Conclusion: This study demonstrates the ability AS201-01 tablets have to decrease Cox-2 and prostaglandin expression on placental of *P. berghei* infected mice and therefore eliminates the adverse effects of placental malaria.

Introduction

Malaria cases are continuing to increase worldwide. WHO reported that around 228 million malaria cases were occurred worldwide and 405.000 deaths in 2018. Children aged under 5 yr and pregnant women are the most vulnerable group affected by malaria. The 11 million pregnant women exposed to malaria infections in 2018 delivered about 872 000 children with low birth weight (1). Pregnant women are particularly susceptible to malaria infection because of immunological changes occuring during pregnancy. During pregnancy, the causal parasite of malaria, *Plasmodium falciparum,* avoids detection by the maternal immune system by occupying blood spaces of the placenta (2).

The WHO recomended artemisinin-based combination therapy for all women in the second or third trimester of pregnancy who have uncomplicated *P. falciparum* malaria. However, information on the safety, efficacy and pharmacokinetics of artemisinin-based combination therapies in pregnant women is limited (3). Therefore, an alternative drug for malaria that is safe for pregnant women is urgently needed.

Andrographis paniculata has been used in various traditional medication systems. It has been found to have a wide range of pharmacological applications including anti-inflammatory, antioxidant and antimalarial properties among others (4-6). *A. paniculata* contains several active constituents include flavonoids, flavonoid glycosides, lactones and diterpenes. Four lactones consists of andrographolide, neoandrographolide, deoxyandrographolide and 14-deoxy-11, 12-didehydroandrographolide were isolated from the aerial parts of *A.paniculata* (7). Andrographolide has been found to be one of the major active compounds found in *A. paniculata*. Andrographolide and its derivatives have anti-inflammatory effects in experimental models asthma, stroke, and arthritis (8). They have been shown to significantly inhibit the expression of iNOS, Cox-2, mRNA, protein, enzyme activity in RAW 264.7 macrophages that are involved in anti-inflammatory activity (9). Andrographolide also reported to have antimalarial activity with IC_{50} value of 9.1 µM (10). The anti-malarial properties of *A. paniculata* have since been developed into an antimalarial tablet named AS201-01.

During pregnancy, the possibility of massive sequestration by the plasmodium parasite on the placenta can cause endothelial dysfunction that affect Parasiticed Red Blood Cells (PRBCs). The attachment results in a local immune response by activating macrophages (11). Decreased endothelial function results in reduced fetal supply of nutrients and oxygen. Plasmodium during pregnancy also results in local or systemic responses, such as maternal production of cytokines for an inflammatory response (12). Cytokines play a key role in the pathological mechanism of malaria. They are a Tumor Necrosis Factor (TNF) that is produced by macrophages. TNF-α triggers Interferon gamma (IFN-γ) to produce other cytokines and increase prostaglandin synthesis. Increased prostaglandin along with an increase TNF-α concentration in placental, is thought to cause premature abortion and labor (13).

The Nuclear transcription factor-kappa B (NF-ϰB) also plays an important role in the regulation of proteins associated with labor such as Cox-2. Cox enzymes can produce prostaglandin and thromboxane from arachidonic acid. This enzyme has 2 isoform units, namely Cox-1 and Cox-2, and Cox-3 variants. Cox-1 is present in several cells, and can stimulate prostaglandin and thromboxane production. Whereas Cox-2, is expressed in cells related to inflammatory processes, such as macrophages and mast cells, if these cells are stimulated by proinflammatory cytokines

or bacterial lipo-polysaccharides/LPS. Cox-2 can stimulate large quantities of prostaglandin production (14).

Transforming Growth Factor β (TGF-β) also has an important role in embryo development (15). TGF-β is a powerful immunosuppressant by suppressing the proliferation and maturation of T, B, NK cells, macrophage activity and as an anti-cytokine which is a signal to stop the immune response and inflammatory response (16). TGF-β regulates the immune response because it inhibits the production of Interferon gamma (IFN-γ) and regulates Interleukin 10 (IL-10). At the beginning of infection, TGF-β promotes T-Helper (Th-1) which controls parasite growth, then downregulates Th-1 as a response to limiting inflammatory reactions (17).

Previous studies showed that AS201-01 tablet which contain ethyl acetate fraction of *A. paniculata* was inhibited parasite *P. berghei* growth and increased TGF-β expression (18). The activation of TGF-β in placenta was clearing the parasites and prevent the occurence of inflammation and pathology that cause adverse effects on mother and fetus (18). TGF-β inhibits IFN- γ production and further inhibits the synthesis of prostaglandin meaning that AS201-01 tablet possibly able to decrease prostaglandin in accordance with its ability to increase TGF-β expression. *A. paniculata* extract and andrographolide was also known to have effects on inhibition of the NF-κB (19). The inhibition of NF-κB will decrease the regulation of Cox-2 and thus decrease prostaglandin.

AS201-01 has ability to decrease Toll-Like Receptor-4 (TLR-4) expression and apoptosis index of placental tissue on *P.berghei* infected pregnant mice (20). Placental malaria may cause the increase of TLR-4 expressions and apoptosis index beyond normal. Barbosa et al, reported in vitro studies with transfected cells that showed *P. berghei* NK65 iRBCs could activate TLR-2, TLR-4, and TLR-9, leading to NF-κB activation. It was identified that stimulation of the TLR-4 pathway by the parasite triggers the innate immune system, causing a local production of TNF-α (21).

The decline of TLR-4 and apoptosis index implies that AS201-01 could inhibit NF-κB activation and production of TNF-α and thus inhibits Cox-2 and prostaglandin production. Therefore, this study aimed to determine the impact of AS201-01 tablets on placental Cox-2 and prostaglandin expression in *P. berghei* infected pregnant mice.

Materials and Methods

Materials

A. paniculata tablet (AS201-01) containing ethyl acetate fraction equivalent to 35 mg of andrographolide was made at Institute of Tropical Disease, Universitas Airlangga, Surabaya Indonesia. D-ARTEPP™ tablet (DHP tablet) containing Dihydroartemisinin and Piperaquine phosphatase 40 mg/320 mg was produced by Guilin Pharmaceutical Co., Ltd, Guangxi, China.

Ethical approval

Permission and approval for animal studies were obtained from Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, Indonesia with ethical clearance No: 560-KE/2016.

Animals and pregnancy monitoring

Eight to twelve week-old Balb/c mice were bred and maintained on standard animal pellets and water *ad libitum* at Animal Laboratory of Institute of Tropical Disease, Universitas Airlangga, Surabaya, Indonesia in 2016. Female mice were injected with 5 IU PG600 hormone and continued injection of 5 IU Human Chorionic Gonadotropin (HCG) hormone at 48 h post PG600 injection. The female mice were then mated with male mice in monogamous pairs. All female mice were weighed before mating and then daily to con-

firm successful pregnancy. The first observation of vaginal plug was considered as Gestation day 0 (GD 0) of pregnancy. Vaginal plugs and weight gain after mating are considered true markers for successful pregnancy (22).

Rodent malaria parasite

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

Experimental design

Twenty four pregnant mice (Balb/c) were divided into 4 groups, G1-G4 (n = 6). G1 were uninfected pregnant mice. G2 were untreated infected pregnant mice. G3 were infected pregnant mice treated with AS201-01 at a dose equal to 25 mg andrographolide/kg body weight, twice daily for 4 days. G4 were infected pregnant mice and treated by DHP tablet at a dose equal to 1.25 mg dihydroartemisinin and 9.98 mg piperaquine phosphate/kg body weight, once a day for 3 days. Infected groups were inoculated with $1x10^6$ of *P. berghei* parasite on day 9 of gestation (GD 9) intraperitoneally and were given treatments on day 11 of gestation (GD 11). Mice were terminated on day 15 of gestation (GD 15). Placental material was collected in 10% formalin.

Determination of Cox-2 and Prostaglandin

Placental material made prepared for use with immunohistochemical methods antibody Cox-2 and antibody prostaglandin. The parafin blocks were stained with immunohistochemical kit using mAb-anti Cox-2 NOVUS NBP1-49796 to determine Cox-2 expression and Rb mAb to prostaglandin D ab182141 to determine prostaglandin expression.

Cox-2 and prostaglandin expression were calculated semi-quantitatively according to the modified method Remmele (23), 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 1). Data of each sample is the average value of IRS, which observed in different 10 felds of view at 400× magnification.

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%	

Data analysis

Data analysis was performed using GraphPad Prism 7.0 software (GraphPad Co. Ltd., San Diego, CA, USA). The significance of mean difference between independent groups was determined by using one-way analysis of variance (ANOVA) followed by Post hoc Dunnett's test. The differences were considered to be significant at the $P<0.05$ level.

Result

Immunohistochemistry examination of Cox-2 and prostaglandin expression was showed by yellowish to brown chromogen in immunore-

active cells (Fig. 1 and 2). There were significant differences between the four groups in Cox-2 and prostaglandin expression (P<0.001). G2, the untreated infected group had the most immunoreactive cells of any group. G3, the AS201-01 treated group and G4, the DHP treated group showed less Cox-2 and prostaglandin immunoreactive cells than G2.

The mean Cox-2 expression of G3 (1.60 ± 0.55) was lower than G4 (2.90 ± 1.29) and G2 (4.83 ± 1.11) however, G1 (1.23 ± 0.39) had the lowest Cox-2 expression (Fig. 3). There were significant difference of Cox-2 expression G1 compared to G2 (P<0.001), G1 compared to G4 with P value of 0.005, G2 compared to G3 with P value of 0.000, G2 compared to G4 with P value of 0.002 and G3 compared to G4 with P value of 0.023. There was no significant difference between G1 compared to G3 with P value of 0.496. The analysis results showed that Cox-2 expression of healthy group was not different with infected group treated with AS201-01 tablet.

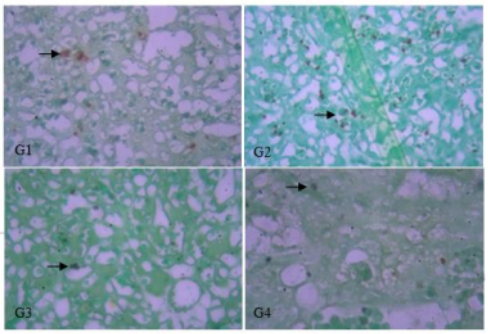

Fig. 1: Cox-2 expression of all groups. Groups were uninfected pregnant mice (G1); untreated infected pregnant mice (G2), infected pregnant mice treated with AS201-01 (G3), and infected pregnant mice treated with DHP tablet (G4). Positive immunoreactive cells marked with yellowish to brown chromogen (→); magnification 400x; Nikon microscope

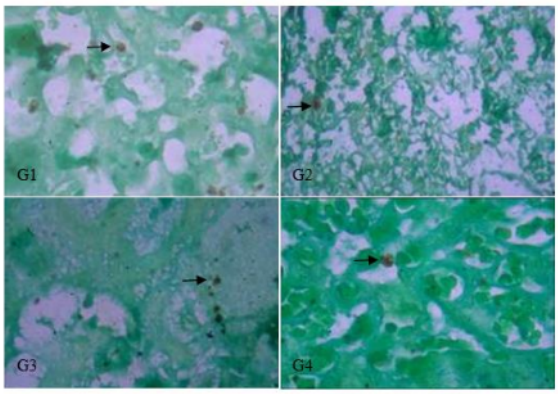

Fig. 2: Prostaglandin expression in all groups. Groups were uninfected pregnant mice (G1); untreated infected pregnant mice (G2), infected pregnant mice treated with AS201-01 (G3), and infected pregnant mice treated with DHP tablet (G4). Positive immunoreactive cells marked with yellowish to brown chromogen (→); magnification of 400x; Nikon microscope

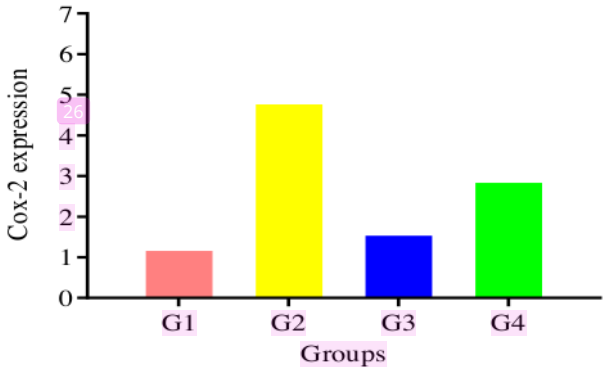

Fig. 3: Mean of Cox-2 expressions of placental *P. berghei* pregnant mice in all groups. Groups were uninfected pregnant mice (G1); untreated infected pregnant mice (G2), infected pregnant mice treated with AS201-01 (G3), and infected pregnant mice treated with DHP tablet (G4). Data are reported as Mean ± SD

The average of prostaglandin expression on group treated with AS201-01 tablet (G3 8.5±0.11) was lower than group treated with DHP tablet (G4 15.83±0.69) and untreated group (G2 21.17±1.93). Meanwhile, prostaglandin expression on G4 was lower than G2 and G1 had lowest prostaglandin expression among others (Fig. 4). There were significant differences of prostaglandin expression data analysis on G1 compared to G2 with *P* value of 0.004, G1 compared to G3 with *P* value of 0.046, G1 compared to G4 with *P* value of 0.004, G2 compared to G3 with *P* value of 0.003 and G2 compared to G4 with *P* value of 0.009, G3 compared to G4 with *P* value of 0.008.

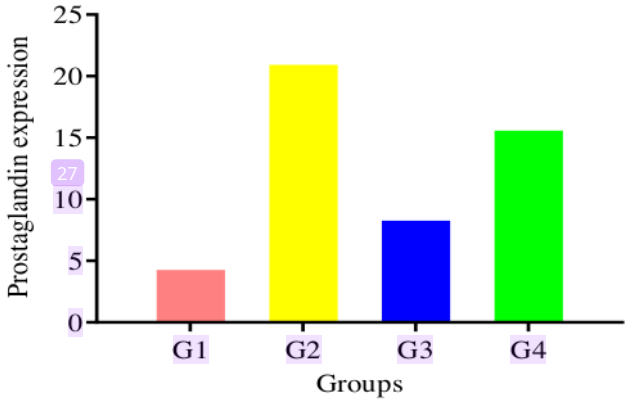

Fig. 4: Mean of prostaglandin expressions of placental *P. berghei* pregnant mice in all groups. Groups were uninfected pregnant mice (G1); untreated infected pregnant mice (G2), infected pregnant mice treated with AS201-01 (G3), and infected pregnant mice treated with DHP tablet (G4). Data are reported as Mean ± SD

Discussion

This study showed that *A. paniculata* tablet significantly reduced Cox-2 and prostaglandin expression compared to the DHP tablet on placental of *P. berghei* infected pregnant mice. The result was in accordance with previously reported studies. Neoandrographolide which isolated from *A.paniculata* was significantly ($P<0.05$) inhibited the production of Nitric Oxide (NO) and Prostaglandin E2 (PGE2) in Lipopolysaccharide (LPS) stimulated macrophages without inducing toxicity at a concentration of 30-90μM (24). Furthermore, the study results indicated that the anti-inflammatory activity of neoandrographolide possibly result from the inhibition inducible NO synthase (iNOS) and Cox-2 expression through inhibiting p38 mitogen-activated protein kinase (MAPKs) activation (24). Meanwhile, andrographolide was suggested as a promising anti-inflammatory drug. Andrographolide was suppressed the production of NO and PGE2 as well as the mRNA abundance of iNOS, TNF-α, Cox-2 and IFN-β in a dose dependent manner in both LPS activated RAW264.7 cells and peritoneal macrophages. The novel molecular signaling pathway of andrographolide to supress inflammatory responses was identified at activator protein (AP-1) and interferon regulatory factor (IRF-3) pathways (25).

The decline of Cox-2 and prostaglandin could possibly prevent the premature abortion and labor in pregnancy malarial. Similar studies have found AS201-01 was able to increase TGF-β and decrease TLR-4 and apoptosis index along with its ability to inhibit *P. berghei* growth (18, 20).

Pregnant women are a high-risk group when considering malaria infections. Not only are they more susceptible to malaria, the disease can be more difficult diagnose the sequestration of the parasites in the placenta. Maternal erythrocytes during pregnancy are particularly susceptible to infection that can, in turn, cause chronic infection and inflammation of the placenta (26). The destructive effect of malaria infection during pregnancy has been correlated with immune activation in the placental tissue (21).

Accumulation of the parasite on placental tissue can lead to proinflammatory immune responses and tissue damage. Infected placenta has been shown to have an increase in inflammatory molecules such as TNF, IL-8 and IL-6 (27). Cytokine NF-kB activation decreases the antioxidant capacity. The presence of inflammation causes the cell membrane phospholipids to be changed by the phospholipase A2 and this will increase the arachidonate to be converted into prostaglandins by activation of high Cox-2. An increasing level of Cox-2 will also lead to functional withdrawal of progesterone through interaction with progesterone receptors, and this will increase prostaglandins (28).

Increased prostaglandin will activate the enzyme collagenase, dilation of blood vessels and uterine contractions. Increased activation of collagenase enzymes will lead to dilatation of the cervical canal (29). Increased activation of amnionic cytokines, decidua and khorion will lead to increased apoptosis resulting in rupture of membranes.

The presence of an external stimulant such as TNF-α, will increase the activation of NF-kB transcription. Due to the high activation of NF-kB there will be an increase in Cox-2 expression, which will convert arachidonic acid into prostaglandin. A high prostaglandin will lead to the breakdown of cervical collagen and an increase in estrogen and oxytocin resulting in uterine contractions and cervical dilatation.

The antimalarial activity of AS201-01 could possibly be due to andrographolide as one its major constituents. Andrographolide can induce reactive oxygen species (ROS)-dependent apoptotic cell death, including superoxide anions, hydroxyl radicals, oxigen singlets, peroxinitrite and nitric oxide. The mechanism was by downregulation of ROS

production via protein kinase-C (PKC) and by passing the synthesis of novo protein or decreasing protein stability in post-transcriptional. Andrographolide also causes significant increases in catalase, superoxide dismutase and gluthatione-s-transferase activity. 14-deoxyandrographolide and 14-deoxy 11, 12 didehydroandrographolide also perform antioxidant activity. It is possible that, an increased dose of *A. paniculata* extract turned an antioxidant effect into an antimalarial effect (30).

Conclusion

This study showed that *A. paniculata* tablets (AS201-01) decreased Cox-2 and prostaglandin placental expression in *P. berghei* infected pregnant mice. Therefore, AS201-01 could potentially use as an alternative drug for malaria during pregnancy.

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Conflict of interest

The authors declare that there is no conflict of interest.

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