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Research Article

Effect of ethanol extract of *Hedyotis corymbosa* (L.) Lamk against parasitemia and hepatomegaly in *Plasmodium berghei* ANKA-infected mice

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ABSTRACT

Malaria is a parasitic infectious disease that remains one of the focuses of world health problems. The ethanol extract of *Hedyotis corymbosa* has biochemical compounds potentially become a new anti-malarial drug. This study aimed to analyze the effect of this extract on parasitemia and hepatomegaly in mice infected with *Plasmodium berghei* ANKA. Twenty five BALB/c mice were infected with *P. berghei* ANKA and grouped into 5 groups. Group 1-3 were treated with 250 mg/Kg BW (HC250), 300 mg/Kg BW (HC300), and 350 mg/Kg BW (HC350) of ethanol extract of *H. corymbosa* (EEHC), respectively. Group 4 was a positive control (POS) which was given dihydroartemisisnin-piperaquin (DHP) and Group 5 was a negative control (NEG) which was only given CMC Na 1%. Treatments were given orally once a day for four consecutive days. Parasitemia was observed daily on Giemsa-stained tail blood smear. On day 5 the mice were sacrificed, blood were collected by cardiac punctured, the livers were removed and the length, width, and weight were measured. There was no significant difference on parasitemia between Group 1, 2, 3 and NEG. However, the highest inhibition of parasite s growth was found in Group 3 (61.4%. Observation on hepatomegaly, showed that a significant difference on the length of the liver was found between Group 3 and NEG.

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INTRODUCTION

Malaria is a parasitic infectious disease caused by *Plasmodium spp*. that is spread through the bite of a female *Anopheles* mosquito as a vector. *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae*, and *Plasmodium knowles*i are the five *Plasmodium* species that cause malaria in humans. *P. falciparum* is the species that most frequently causes severe and fatal malaria among the five *Plasmodium* species. Malaria patients might have liver enlargement or hepatomegaly (Kementerian Kesehatan RI, 2019). Hepatomegaly is caused by hepatocyte inflammation, which causes an immunological response (Wilson *et al*., 2009). Malaria is still a concern to public health across the world, particularly in malaria-endemic areas. According to the World Health Organization, there were at least 229 million malaria infections and an estimated 409,000 malaria deaths in 2019 (Nyunt et al., 2017)(WHO, 2022). In 2020, the total number of malaria cases in Indonesia was 226,364 (Kementerian Kesehatan RI, 2021).

One of the particular targets of the global commitments mentioned in the Sustainable Development Goals (SDGs) is to eradicate malaria by 2030 (Pusat Data dan Informasi Kemenkes RI, 2016). The comprehensive treatment of malaria is one of the eradication efforts in Indonesia. However, the effectiveness of several anti-malarial medications has decreased or even become resistant, such as chloroquine (Kementerian Kesehatan RI, 2019). Parasite resistance to Sulfadoxine-Pyrimethamine, Halofantrine, Quinine, and Mefloquine has also been reported (Bloland & World Health Organization, 2001). Artemisinin resistance has been found in Cambodia, Laos, and Vietnam (WHO, 2019). To counteract the rise of anti-malarial resistance, new anti-malarial medicines must be provided.

Indonesia has been acknowledged as a country that is rich in natural resources, especially medicinal plants. Some medicinal plants in Indonesia, such as H. *corymbosa,* may be used and developed as novel anti-malarial drugs. The community has used this plant as a traditional treatment, such as fever reducer (antipyretic), anti-inflammatory, antibacterial, diuretic, detoxifying, anticancer, dysentery medicine, a gastric ulcer medicine, blood circulation, postpartum medicine, and medicine for digestion disorders (Soemardji, Anisa, & Damayanti, 2015). The plant *H. corymbosa* has been proven to have significant hepatoprotective effects. This is evidenced by a reduction in the serum level of hepatic enzymes, *serum* glutamic oxaloacetic transaminase (SGOT) and glutamic pyruvic transaminase (SGPT), as well as serum level of bilirubin, and an essentially normal liver histological image following treatment of *H. corymbosa* extract to wistar rats who had suffered liver injury due to paracetamol overdose (Sadasivan *et al*., 2006). Bioactive compounds such as alkaloids, flavonoids, tannins, glycosides, terpenoids, and steroids are contained in the ethanol extract of *H. corymbosa* (Selvan, Vellavan, & Sakunthala, 2015), and includes ursolic acid, a hepatoprotective molecule (Sadasivan *et al*., 2006). The alkaloid has anti-inflammatory and anti-malarial effects by reducing the function of heme polymerase, resulting in heme buildup, which is toxic to parasites and causes parasite death (Louisa, 2016). In addition to alkaloids, flavonoid compounds exert anti-malarial effects by reducing the entrance of L-glutamine and myoinositol into infected erythrocytes and decreasing *Plasmodium* fatty acid biosynthesis (FAS II), hence interrupting *Plasmodium* development and causing *Plasmodium* mortality (Ntie-Kang *et al.*, 2014). This aimed

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to determine the effect of ethanol extract of *H. corymbosa* on parasitemia and hepatomegaly in mice infected with *Plasmodium berghei* ANKA.

METHODS

Ethical approval

The study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Airlangga as stated on the certificate number 35/EC/KEPK/FKUA/2022

Preparation of the ethanol extract of *H. corymbosa* (EEHC)

The EEHC was prepared by maceration of simplicia in 70% ethanol solvent in the Laboratory of Herbal Materia Medika, Batu City, East Java Province, Indonesia. The EEPG was then used to prepare a doses of 250 mg/kgBW, 300 mg/kgBW, and 350 mg/kgBW in 1% CMCNa (Yuliandra, Armenia, Salasa, & Ismed, 2015)

Research Design

This study was an experimental laboratory study that employed the post-test-only control group design approach. Twenty-five female BALB/c mice were injected intraperitoneally with 200 µl of *P. berghei*-infected blood from donor mice which was equal with $1x10^6$ infected erythrocytes. Infected mice were then divided randomly grouped into 5 groups. Group 1-3 were treated with 250 mg/kgBW (HC250), 300 mg/kgBW (HC300) and 350 mg/Kg BW (HC350) of ethanol extract of *H. corymbosa* (EEHC), respectively. Group 4 was a positive control (POS) which was given 187,2 mg/kg body weight dihydroartemisisnin-piperaquin (DHP) and Group 5 was a negative control (NEG) which was only given sterile water. Treatments were given orally once a day for four consecutive days. Parasitemia was observed daily on Giemsa-stained tail blood smear. On day five all mice were sacrificed, blood was collected by cardiac punctured, and the livers were removed to evaluate the effect of the EEHC administration.

Observation of parasitemia in mice was carried out. The percentage of parasitemia was calculated by counting the infected erythrocytes within 1000 erythrocytes. The percentage inhibition of parasitemia was calculated using the following formula:

$$\% \text{ Inhibition} = \frac{\text{Mean\% parasitemia in NEG- Mean \% parasitemia in TG}}{\text{Mean \% parasitemia in NEG}} \times 100$$

TG: tested group
NEG: Negative control group

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On day five, mice were sacrificed after being anesthetized using chloroform inhalation. Livers were removed to measure the length, width, and weight to assess hepatomegaly. The length and width of livers were measured using a ruler and stated in millimeters (mm) (Arwati *et al*., 2021). The weight of the liver was measured using an analytical scale (Maslachah, Sugihartuti, & Wahyuni, 2019).

Data analysis

Parasitemia data were statistically analyzed One Way Anova (analysis of variance), while the weight, length, and width of the liver were analyzed using Mann-Whitney and Kruskal Wallis analysis in SPSS.

RESULTS

Parasitemia and inhibition of parasitemia

Observation of parasitemia resulted in the average percentage of parasitemia, as shown in Figure 1. Parasitemia in the POS group was completely zero from day 2 to day 4 post-treatment, while in the NEG group, it was increased from day 1 to day 4. The administration of EEHC in the groups caused a decrease of parasitemia since day 2. The percentage inhibition of parasitemia in mice by EEHC 250 mg/Kg BW was the lowest (48.40%). Meanwhile, the highest percentage of parasitemia inhibition was found in the group treated with 350 mg/Kg BW, which was 61.40%.

Statistical analysis of the parasitemia percentage data of mice on day 5 using the OneWay ANOVA test showed a significant difference of parasitemia among EEHC-treated groups ($p<0.05$). Post hoc Games Howell test showed no significant difference in parasitemia between the treatment groups ($p>0.05$), and all EEHC-treated groups were significantly different from the POS (DHP) group. The POS group differed significantly from the NEG group ($p<005$).

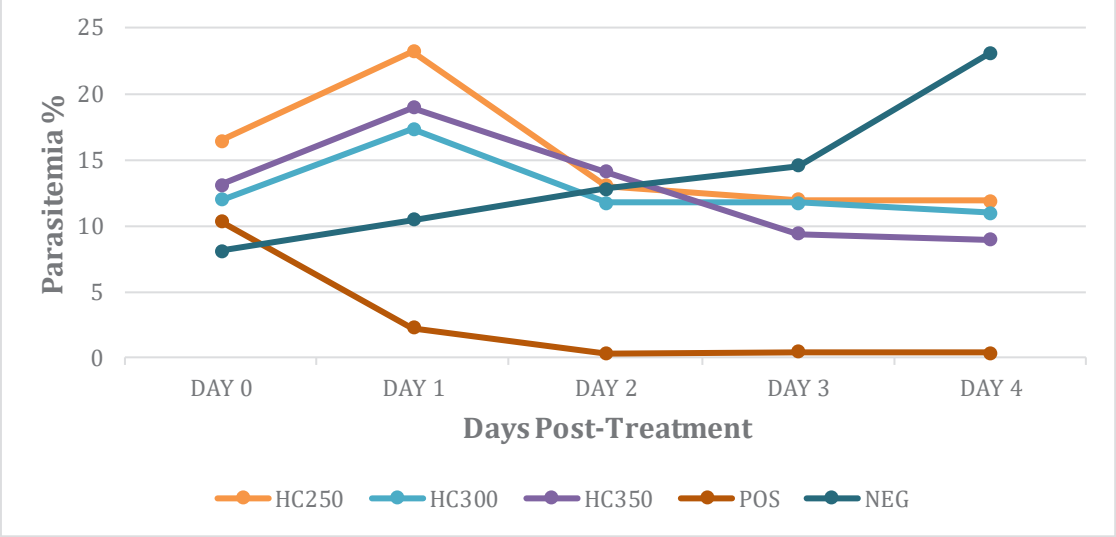

Figure 1. Percentage parasitemia in BALB/c mice infected with *P. berghei* ANKA treated with ethanol extract of *H. corymbosa*

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Table 1. Parasitemia at day five post treatment with EEHC and inhibition of EEHC on parasitemia

Group	Parasitemia (%)	Inhibition (%)
HC250	11.9	48.40
HC300	10.98	52.39
HC350	8.9	61.40
POS	0.36*	98.44

*Parasitemia in EEHC treated groups and NEG were different significantly with POS group ($p<0.05$) by Posthoc Games Howell analysis

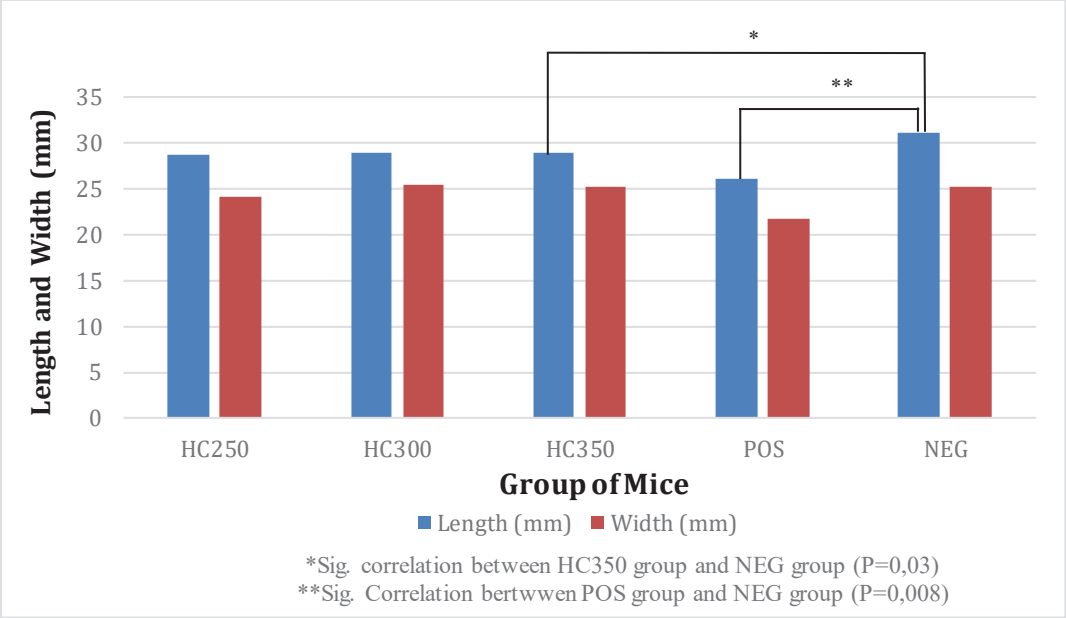

Figure 2. The mean of liver length and width in mice infected with *P. berghei* ANKA treated with EEHC

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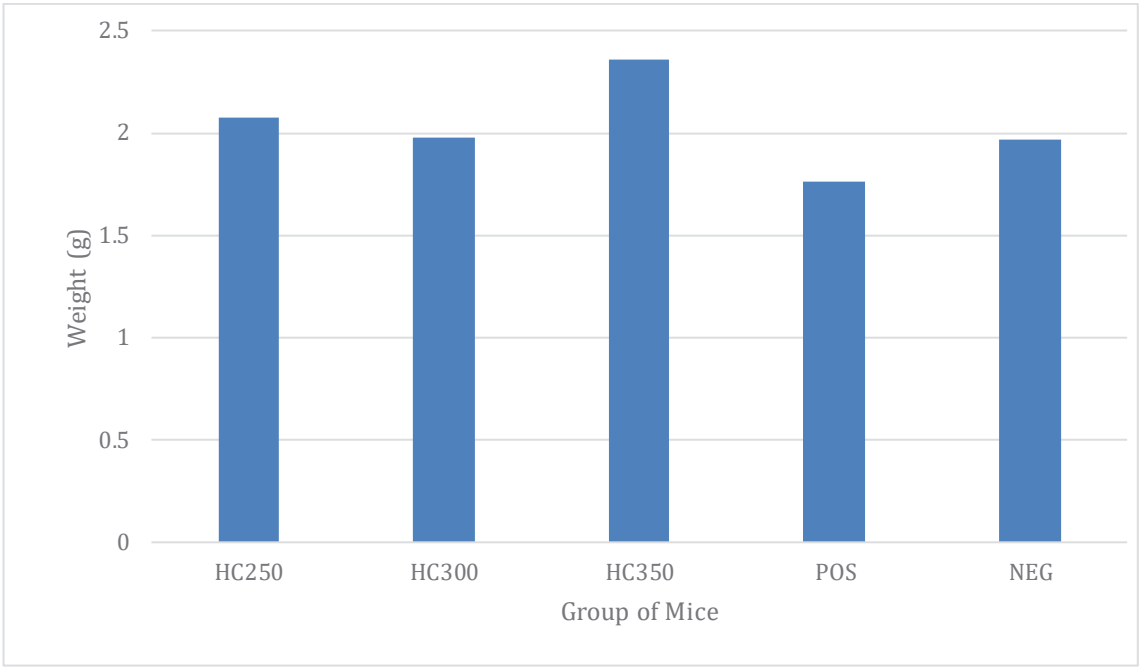

Figure 3. The mean of liver weight in mice infected with *P. berghei* ANKA treated with EEHC

DISCUSSION

The novelty of this study is that the antimalaria activity of EEHC and the effect of EEHC on hepatomegaly have not been reported. In this current report, the antimalaria activity of EEHC has been proven against parasitemia in mice infected with *P. berghei* ANKA. Parasitemia is the result of calculating the number of parasites in a thousand erythrocytes and is used to determine the pathology severity of malaria infection. The percentage of parasitemia in the treated mice showed anti-malarial activity of ethanol extract of *H. corymbosa* against *P. berghei* ANKA infection. In this study, the parasitemia percentage of mice in the group given ethanol extract of *H. corymbosa* was lower than NEG but still higher than the treatment group given DHP, although not significant. The percentage of parasitemia between groups of doses of ethanol extract of *H. corymbosa* was also not significantly different. However, on the inhibition percentage, it was found that the larger the extract dose, the greater the percentage of inhibition of parasitemia. The highest percentage of inhibition was indicated by treatment with ethanol extract of *H. corymbosa* at a dose of 350 mg/Kg BW, which was 61.4%. That showed that the ethanol extract of *H. corymbosa* at a dose of 350 mg/Kg BW has anti-malarial activity inhibiting malaria parasite growth by 61.4%.

The ethanol extract of *H. corymbosa* used in this study contains alkaloids and flavonoids, which have been proven in phytochemical tests. Other study have also proven that the ethanol extract of *H. corymbosa* contains secondary metabolites such as alkaloids, flavonoids, serpentine, terpenoids, quercetin, and other bioactive compounds such as glycosides, steroids, and tannins (Selvan *et al*., 2015). The alkaloid compound indirectly kill parasites by activating the expression of the transcription factor PPARγ (peroxisome proliferator-activated receptor), which has an impact on suppressing TNF-α (Margono, Suhartono, &

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Arwati, 2016). Furthermore, TNF-α production is related to the parasitic load (Leão *et al.*, 2020). In addition, the alkaloid compound has anti-inflammatory and anti-malarial effects by suppressing heme polymerase activity in *Plasmodium's* food vacuoles (Louisa, 2016). As a result, *Plasmodium* parasites die due to the accumulation of heme which is toxic to the parasite.

Other phytochemical compounds contained in *H. corymbosa* extract, such as flavonoids, are also known to have anti-malarial activity. A study proved that the flavonoid compounds contained in *Dasymaschalon acuminatum* leaves have antiplasmodial solid activity against *Plasmodium falciparum* (Chokchaisiri, Chaichompoo, Chalermglin, & Suksamrarn, 2015). Another study reported that flavonoid derivatives obtained from the ethanolic extract of *Macaranga gigantea* leaves had potent antiplasmodial activity against *Plasmodium* berghei ANKA (Muhaimin *et al*., 2019).

As antiplasmodial, flavonoids work through their ability to suppress the biosynthesis of parasitic cell membrane fatty acids, enzymes, proteins, or even DNA that is vital for parasites. Polyphenolic flavonoids have phenolic OH groups capable of causing tissue damage or oxidative damage to parasite cellular components if converted to stable phenoxy anions under cellular oxidative stress in vivo. Flavonoids are one of the phytochemical compounds that can modulate strong immunity. Flavonoids induce TNF-α and other anti-inflammatory agents by inhibiting reactive oxygen or nitrogen compounds. In addition, flavonoids can also modify intracellular signaling pathways in immune cells (Afolayan, Adegbolagun, Mwikwabe, Orwa, & Anumudu, 2020). Another research also revealed that the alkaloid and flavonoid compounds contained in the ethanol extract of *Morinda citrifolia* were the main compounds that acted as antiplasmodials against mice infected with *P. berghei* ANKA (Rahayu, Hernaningsih, & Arwati, 2021).

This study found that the liver of mice in the group treated with the highest ethanol extract of *H. corymbosa*, which was 350 mg/Kg BW (HC350), had a significantly smaller effect on liver length when compared to the negative control group. Meanwhile, at other doses of ethanol extract of *H. corymbosa*, namely 250 mg/KgBW (HC250) and 300 mg/KgBW (HC300), there was no significant difference in liver length against the NEG. On the width and weight of the liver of mice, all treatment groups with ethanol extract of *H. corymbosa* dose had no significant difference with the negative control group. That indicated that the ethanol extract of *H. corymbosa* at a dose of 350 mg/Kg BW had a minor effect on hepatomegaly in *P. berghei* infection due to the shorter liver length.

Previous research reported that the methanol extract of *H. corymbosa* possess hepatoprotective properties due to its ursolic acid content. This is evidenced by the histopathological picture of the liver of wistar rats induced by paracetamol overdose, which is close to normal in the group treated with doses of methanol extract of *H. corymbosa* (Sadasivan et al., 2006). This hepatoprotective property is also due to quercetin compounds in ethanol extract of *H. corymbosa*. Quercetin (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4-Hchromen-4-one) is a derivative of flavonoid phytochemical compound classified as flavonols (David, Arulmoli, & Parasuraman, 2016). Furthermore, quercetin might be a compound with hepatoprotective properties through their research which revealed the ability of quercetin to treat rat hepatocytes that suffered oxidative damage due to ethanol induction (Liu *et al.*, 2012).

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Besides having hepatoprotective properties, quercetin also has anti-inflammatory properties. In vitro, several studies have shown that quercetin can inhibit the development of lipopolysaccharide (LPS) mediated by TNF-α (Li *et al*., 2016). Quercetin can also suppress TNF-α and Interleukin (IL)-1α mRNA levels triggered by LPS and reduce apoptotic neuronal cell death (Bureau, Longpré, & Martinoli, 2008). Another study showed that quercetin could inhibit the emergence of pro-inflammatory inflammatory responses such as IL-1ß, IL-6, IFN-γ, TNF-α, and IL-12p70 (Michalski *et al*., 2020). Numerous biological effects of quercetin have been reported; however, the report on side effects of quercetin is very few. Rare cases have been observed in some patients to have headaches and tingling nerve sensation after quercetin consumption. An in vivo study in mice reported the potential toxicity of quercetin is the repression of mitochondrial copy number via decreased POLG expression and excessive TFAM expression in irradiated murine bone marrow.

Hepatomegaly in human malaria infection occurs due to an inflammatory reaction in the liver caused by parasites that develop and replicate in liver cells. One of the solid triggers for the inflammatory response, IL-12p70, is thought to arise as a result from chronic malaria infection that triggers a pro-inflammatory response. The pro-inflammatory response IL-12p70 is known to correlate with the occurrence of hepatomegaly (Wilson *et al*., 2009). It has been demonstrated that children chronically exposed to malaria have an increased in number and size of Kuppfer cells (Walters & McGregor, 1960), and if activated, are a potential source of TNF-α. As levels of TNF-α RII, a neutralizer of TNF- α which releases from human cell lines is triggered by TNF-α itself, were found to be correlated with Pfs-IgG3, it suggests that the immune system is mounting a reaction to restrict inflammation (Higuchi & Aggarwal, 1994; Van Zee *et al*., 1992). sTNF-RII levels were likewise related with the presence of hepatomegaly. Control of TNF-α production during malaria infections is partially controlled by IL-10 and levels of circulating IL-10 were substantially linked with Pfs-IgG3 levels and the presence of hepatomegaly (Ho et al., 1998, 1995). The statements above may indicate that the quercetin content in the ethanol extract of *H. corymbosa* may play a role in hepatomegaly in malaria infection by suppressing inflammation in the liver.

The limitation of this study is the lack of information regarding the anti-malarial activity of EEHC, resulting in minimal details on the mechanism of action of EEHC against malaria parasites, changes in host immunity as well as pathological changes. Therefore, further research regarding the EEHC on malaria still needs to be done. Other examinations, such as histopathology of the liver and other organs such as the kidney and spleen, need to be carried out to determine the effect of EEHC on the histopathological changes of these organs in malaria infection microscopically before the antimalaria drug development.

CONCLUSION

Ethanol extract of *H. corymbosa* did not significantly affect the percentage of parasitemia in mice infected with *P. berghei* ANKA. However, EEHC was able to inhibit the growth of parasites up to 61.4% at a dose of 350 mg/Kg BW. In addition, ethanol extract of *H. corymbosa* at the same dose also affected hepatomegaly, especially the liver length in mice infected with *P. berghei* ANKA.

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