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EFFECTIVENESS OF ETHANOL EXTRACT OF PURPLE EGGPLANT SKIN AS AN ANTIMALARIAL ON LIVER SIZE IN MICE INDUCED WITH *Plasmodium berghei*

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ABSTRAK

Malaria disebabkan oleh protozoa Plasmodium melalui gigitan nyamuk Anopheles, dengan salah satu gejalanya pembesaran hati. Penelitian ini bertujuan menguji efektivitas ekstrak etanol kulit terung ungu (Solanum melongena L.) terhadap ukuran hati mencit (Mus musculus) yang diinduksi Plasmodium berghei. Ekstraksi dilakukan dengan maserasi menggunakan etanol 70%. Mencit dibagi dalam kelompok perlakuan (dosis ekstrak 0,075 mg/20 gBB, 0,15 mg/20 gBB, dan 0,3 mg/20 gBB), kontrol positif (DHP 3,744 mg/20 gBB), kontrol negatif (akuades), dan kontrol normal. Pengamatan meliputi tingkat parasitemia serta berat, volume, dan indeks hati. Hasil menunjukkan bahwa dosis ekstrak memengaruhi ukuran hati mencit. Tidak ada korelasi signifikan antara parasitemia dengan berat (p=0,073) dan volume hati (p=0,133), namun terdapat korelasi signifikan dengan indeks hati (p=0,002). Penelitian ini merekomendasikan studi lanjutan mengenai potensi senyawa aktif terung ungu sebagai agen hepatoprotektor dan antimalaria.

ABSTRACT

Effectiveness of Ethanol Extract of Purple Eggplant Skin as an Antimalarial on Liver Size in Mice Induced with Plasmodium berghei. Malaria is caused by the protozoa Plasmodium through the bite of the Anopheles mosquito, with one of the symptoms being an enlarged liver. This study aims to test the effectiveness of ethanol extract of purple eggplant (Solanum melongena L.) skin on the liver size of mice (Mus musculus) induced by Plasmodium berghei. Extraction was carried out by maceration using 70% ethanol. Mice were divided into treatment groups (extract doses of 0.075 mg/20 gBW, 0.15 mg/20 gBW, and 0.3 mg/20 gBW), positive control (DHP 3.744 mg/20 gBW), negative control (aquades), and normal control. Observations included parasitemia levels as well as liver weight, volume, and index. The results showed that the extract dose affected the liver size of mice. There was no significant correlation between parasitemia and liver weight (p=0.073) and volume (p=0.133), but there was a significant correlation with liver index (p=0.002). This study recommends further studies on the potential of active compounds in purple eggplant as hepatoprotective and antimalarial agents.

INTRODUCTION

Malaria is a disease caused by protozoa of the genus Plasmodium through the bite of female Anopheles mosquitoes, and one of the symptoms is an enlarged spleen and liver.[1,2] Based on data from the World Malaria Report 2023, global data in 2022 estimated that there were 249 million cases of malaria in 85 countries and malaria-endemic areas. Based on the Annual Parasite Incidence (API) indicator from 2015-2021, the malaria morbidity rate was below 1 per 1,000 population and increased above 1, namely 1.1 in 2021. In 2021, there were 304.607 malaria cases in Indonesia, with the highest number in Papua at 275,243 cases, followed by East Nusa Tenggara (NTT) with 9,419 cases, and West Papua with 7,628 cases, where the eastern region of Indonesia remains highly endemic. Malaria in West Kalimantan has decreased in several areas (0.13), but it was noted that there was an outbreak in 2009.[3,4]

Patients infected with *Plasmodium* sp. may show specific symptoms, one of which is hepatomegaly (enlargement of the liver).[5,6] Platelets are phagocytosed by macrophages due to aggregation disturbances on the platelet membrane by IgG antibodies. This destruction activates the liver and spleen's Macrophage-Colony Stimulating Factor (M-CSF). Host cells and the liver produce oxidative stress as a defense against malaria infection; however, platelet membranes are less resistant to oxidative stress, leading to lysis.[6,7]

Dihydroartemisinin - piperaquine (DHP) is an active metabolite of artemisinin, which can rapidly eliminate parasites in patients and improve hemoglobin levels, while piperaquine has a half-life of around 23 days. DHP was used following clinical trials conducted by the Research and Development Agency in Timika, Papua, from 2004-2007. This drug was only administered to patients with chloroquine-resistant cases, such as in Papua. The malaria control program 2009 recommended artemisinin-based combination therapy, namely Artemisinin-based Combination Therapy (ACT) and DHP. However, issues arose with both drugs, causing reduced drug effectiveness and hindering the achievement of elimination goals, leading to drug resistance in patients.[8,9]

Purple eggplant (*Solanum melongena* L.) contains flavonoids, saponins, tannins, alkaloids, and polyphenols when using its skin extract. Research by R.U. Hamzah in 2016 stated that eggplant skin extract has hepatoprotective functions, which can reduce liver damage.[10] The researcher chose *Plasmodium berghei* because it has molecular similarities to *Plasmodium falciparum*, and its intermediary host is mice. The researcher is interested in conducting research titled: "The Antimalarial Effectiveness of Ethanol Extract of Purple Eggplant (*Solanum melongena* L.) Skin on the Liver Size of Mice (*Mus musculus*) Induced by *Plasmodium berghei*.

METHODS

The study was conducted using a true experimental in vivo design with a completely randomized design (CRD). The observations for data analysis focused on parasitemia levels on the 5th day, along with liver weight, volume, and liver index. The data were first subjected to the Shapiro-Wilk test to assess normality. The Kruskal-Wallis test was used as a non-parametric analysis for non-normal and homogeneous data. The Mann-Whitney test for further pairwise comparisons followed this. Finally, a correlation analysis was performed using Spearman's correlation. The

research data were processed using IBM SPSS Statistics version 25 and presented in the form of tables, graphs, and narrative descriptions.

Preparation of the Ethanol Extract of Purple Eggplant Skin

The preparation and extraction of purple eggplant skin had already been conducted in a previous study. Therefore, this research utilized the purple eggplant skin extract obtained from the earlier researcher as a stored biological material. The extract was sourced from the Chemistry Laboratory of the Faculty of Mathematics and Natural Sciences at Tanjungpura University.[11]

Grouping of Experimental Animals

The mice will be treated in the laboratory after being acclimatized for one week. Each mouse will be divided into six groups, with five per group. The test groups will be infected with *Plasmodium berghei* and administered the purple eggplant skin extract. Group 1 will receive a dose of 0.075 mg/20 g body weight, group 2 will receive a dose of 0.15 mg/20 g, and group 3 will receive a dose of 0.3 mg/20 g. Group 4 will be infected with *Plasmodium berghei* and treated with dihydroartemisinin-piperaquine (DHP) at a dose of 3.744 mg/20 g body weight as the positive control. Group 5 will be infected with *Plasmodium berghei* and given distilled water as the negative control, while group 6 will remain uninfected and untreated, serving as the normal control.

Inoculation of *Plasmodium berghei* in Test Mice

Inoculation of *Plasmodium berghei* is performed via the intraperitoneal route. When the parasitemia level of a donor mouse exceeds 10%, 2 mL of blood is drawn and mixed with 200 µL of 1% EDTA solution, then resuspended in 1.8 mL of Phosphate Buffered Saline (PBS). The two solutions are mixed thoroughly, and 0.2 mL of the inoculum is injected into the test mice. If parasitemia reaches over 2% for two consecutive 24-hour periods, treatment with antimalarial drugs and the ethanol extract of purple eggplant skin is administered from day one to day five. Subsequently, observations are made on the percentage of parasitemia over the five-day period.

Liver Organ Measurement

Mice will be terminated first, which is the euthanasia method for animals weighing <125 grams.[13] The liver can be removed after the mouse has died, followed by an abdominal wall dissection using tweezers and scissors until the peritoneal sac is opened. The liver organ is cut at the base to prevent leakage. The liver is cleaned from the accompanying connective tissue using a NaCl solution. The cleaned mouse liver will be weighed using an ohaus scale to determine its weight. Then, the volume is measured by calculating the difference between the amount of NaCl in a Pyrex measuring cylinder before and after the liver is placed inside.

The liver index of the mice can be measured using the following formula:[14]

$$\frac{\text{Liver Weight of Mice}}{\text{Body Weight of Mice}} \text{ X } 100\%$$

RESULT

The parasitemia level was first observed by examining *Plasmodium berghei*–infected erythrocytes within 1,000 erythrocytes. The count was conducted every 24 hours for 5 days after treatment was administered to test groups 1, 2, 3, the positive control group given DHP, and the negative control group given distilled water simultaneously. The results of the parasitemia degree calculations for each group can be seen in Table 1 below.

Table 1. Degree of Parisitemia

Day -	Test 1 Mean±SD	Test 2 Mean±SD	Test 3 Mean±SD	Positive Control Mean±SD	Negative Control Mean±SD	Statistic *Kruskal- Wallis*
1	15,74 ± 3,88	13,88 ± 2,55	15,22 ± 3,5	3,6 ± 1,83	12,64 ± 2,24	
2	13,72 ± 4,21	11,48 ± 3,72	13,76 ± 3,19	2,9 ± 2,1	15,36 ± 3,09	
3	12,1 ± 4,56	8,52 ± 1,61	11,48 ± 0,52	2,22 ± 1,18	16,04 ± 5,09	*p* =0,01
4	8,28 ± 5,75	5,9 ± 1,96	8,62 ± 2,28	1,14 ± 0,60	20 ± 5,51	
5	4,06 ± 1,55	4,22 ± 1,4	4,90 ± 0,81	3,80 ± 0,41	20,74 ± 5,39	

(Source: Primary Data 2019)

The results in Table 1 utilized the Kruskal-Wallis test because the data being tested were not homogeneous, showing a significant difference in the degree of *Plasmodium berghei* parasitemia among the five groups (p=0.01).

The statistical analysis results of the degree of parasitemia on day 5, using the Mann-Whitney test in Table 2, indicate that the degree of parasitemia in test group 1 did not show a significant difference compared to test groups 2 and 3. In contrast, the positive and negative control groups showed a significant difference (p=0.009). The statistical analysis of the degree of parasitemia on day 5 with the Mann-Whitney test can be seen in Table 2 below.

Table 2. Statistical Analysis of the Degree of Parasitemia on Day 5 using the Mann-Whitney Test

*If (*p<0,05)* or *(p=0,00)* then there is a significant difference

Groups	Test 2	Test 3	Positive Control	Negative Control
Test 1	*p*= 0,753	*p*=0,462	*p*= 0,009*	*p* =0,009*
Test 2		*p*= 0,462	*p*=0,009*	*p* =0,009*
Test 3			*p*= 0,009*	*p* =0,009*
Positive Control				*p* =0,009*

The average liver weight of the mice in Table 3 shows that the negative control group has the highest average compared to the other groups. Test groups 1, 2, and 3 have lower average liver weights. In contrast, the average of the positive control group (1.27) is still lower and even approaches the average liver weight of the normal control group (1.06).

Table 3. Average Liver Weight of Mice

Mice	Test 1	Test 2	Test 3	Positive Control	Negative Control	Normal Control	*Oneway ANOVA*
1	1,41	1,41	1,41	1,46	2,01	1,10	
2	1,93	1,48	1,48	1,15	1,90	1,09	
3	1,35	1,48	1,48	1,20	1,27	1,03	*p=0,000**
4	2,38	1,52	1,52	1,25	2,30	1,05	
5	1,66	1,40	1,40	1,30	2,01	1,06	
Mean±SD	1,74±0,42	1,45±0,053	1,55±0,266	1,27±0,11	1,89±0,38	1,06±0,02	

*If (*p<0,05)* or *(p=0,00)*, then there is significant difference

The results of the statistical analysis regarding the liver weight of mice on day 5, using the post-hoc LSD test in Table 4 below, indicate that test group 2 and the positive control group have a significant difference compared to the negative control group, while test group 2 does not show a significant difference from the positive control group.

Table 4. Statistical Analysis of Liver Weight of Mice on Day 5 Using the Post-Hoc LSD Test

Group	Test 2	Test 3	Positive Control	Negative Control	Normal Control
Test 1	*p*=0,097	*p*=0,269	*p*=0,009	*p*=0,369	*p*=0,000*
Test 2	-	*p*=0,556	*p*=0,270	*p*=0,015*	*p*=0,027*
Test 3	-	-	*p*=0,097	*p*=0,051	*p*=0,007*
Positive Control	-	-	-	*p*=0,001*	*p*=0,229
Negative Control	-	-	-	-	*p*=0,000*

*If (*p<0,05)* or *(p=0,00)*, then there is significant difference

The volume of the mouse liver was measured after the administration of purple eggplant skin extract at doses of 1, 2, 3, DHP, and distilled water using a PYREX measuring cylinder in milliliters (ml). The results show that the negative control group has the highest average compared to all other groups. Test group 2 (1.61), test group 3 (1.58), and the positive control group (1.30) also had lower average results compared to the negative control group. The average liver volume of the mice is shown in Table 5 below.

Table 5. Average Liver Volume of Mice

Mice	Test 1	Test 2	Test 3	Positive Control	Negative Control	Normal Control	*Oneway ANOVA*
1	1,40	1,45	1,46	1,25	2,00	1,40	
2	1,75	1,70	1,40	1,44	1,80	1,75	
3	1,25	1,65	1,50	1,10	1,20	1,25	*p=0,003**
4	2,50	1,50	1,75	1,36	2,50	2,50	
5	1,60	1,75	1,80	1,37	2,00	1,60	
Mean±SD	1,70±0,48	1,61±0,12	1,58±0,18	1,30±0,13	1,90±0,46	1,07±0,11	

*If (*p<0,05)* or *(p=0,00)*, then there is significant difference

The results of the statistical analysis regarding the liver volume of mice on day 5, using the post-hoc LSD test, indicate that there is a significant difference in the normal control group compared to test groups 1, 2, 3, and the negative control group; however, there is no significant difference with the positive control group. The negative control group shows a significant difference compared to the positive control and normal control groups (LSD > 0.005) and does not have a significant difference with test groups 1, 2, and 3 (LSD < 0.005). The statistical analysis of the liver volume of mice on day 5 using the Post Hoc Least Significant Difference (LSD) test can be seen in Table 6 below.

Table 6. Statistical Analysis of Liver Volume of Mice on Day 5 Using the Post Hoc LSD Test

Groups	Testi 2	Test 3	Positive Control	Negative Control	Normal Control
Test 1	*p*=0,638	*p*=0,538	*p*=0,047*	*p*=0,300	*p*=0,003*
Test 2	-	*p*=0,883	*p*=0,118	*p*=0,138	*p*=0,009*
Test 3	-	-	*p*=0,154	*p*=0,105	*p*=0,013*
Positive Control	-	-	-	*p*=0,004*	*p*=0,239
Negative Control	-	-	-	-	*p*=0,000*

*If (*p<0,05)* or *(p=0,00)*, then there is significant difference

The liver index of the mice was measured after the administration of purple eggplant skin extract at doses 1, 2, 3, DHP, and distilled water. It was calculated using the formula: the weight of the mouse liver in milligrams divided by the body weight of the mouse in milligrams, then multiplied by 100%. The results in Table 7 show that the negative control group has the highest average liver index compared to all groups. The positive control group, given a dose of DHP (Dihydroartemisinin-Piperaquine), had an average liver index of 5.18, which is lower than that of the test groups and approaches the average value in the normal control group. The average liver index of the mice can be seen in Table 7 below.

Table 7. Average Liver Index of Mice

Mice	Test 1	Test 2	Test 3	Positive Control	Negative Control	Normal Control	*Oneway ANOVA*
1	5,67	6,40	7,24	5,48	7,86	4,07	
2	8,06	6,58	6,02	5,50	9,11	4,95	
3	6,61	7,15	6,47	4,48	7,50	5,15	*p=0,000**
4	8,55	6,79	5,59	4,54	7,88	4,20	
5	7,28	5,49	7,02	5,94	8,03	5,25	
Mean±SD	7,23±1,14	6,48±0,61	6,46±0,68	5,18±0,64	8,07±0,61	4,72±0,55	

*If (p<0.05) or (p=0.00), then there is a significant difference

The results of the statistical analysis using the Post-Hoc Least Significant Difference (LSD) test on the liver index of mice on day 5, shown in Table 8, indicate that test group 1 has a significant difference compared to the positive control and normal control groups. In contrast, it does not show a significant difference from test groups 2, 3, and the negative control group.

Table 8. Statistical Analysis of Liver Index in Mice on Day 5 Using the Post-hoc LSD Test

Group	Test 2	Test 3	Positive Control	Negative Control	Normal Control
Test 1	*p*=0,119	*p*=0,114	*p*=0,000*	*p*=0,084	*p*=0,000*
Test 2	-	*p*=0,980	*p*=0,011*	*p*=0,002*	*p*=0,001*
Test 3	-	-	*p*=0,011*	*p*=0,002*	*p*=0,001*
Positive Control	-	-	-	*p*=0,000*	*p*=0,329
Negative Control	-	-	-	-	*p*=0,000*

*If (p<0.05) or (p=0.00), then there is a significant difference

The hypothesis correlation test used was the Spearman correlation test for non-normally distributed data. The Spearman correlation test results indicated that the parasitemia levels and liver weight of *Mus musculus* induced by *Plasmodium berghei* did not correlate, with a correlation coefficient of p=0.365 and a significance value of sig=0.073. Similarly, liver volume also showed no correlation, with a correlation coefficient of p=0.309 and sig=0.133. However, there was a correlation between parasitemia levels and the liver index, with a correlation coefficient of p=0.595 and sig=0.002. The points on the graph represent the parasitemia values for each group, which were then plotted. The graphs showing the relationship between parasitemia levels and liver weight, liver volume, and liver index in mice can be seen in Figures 1, 2, and 3 below:

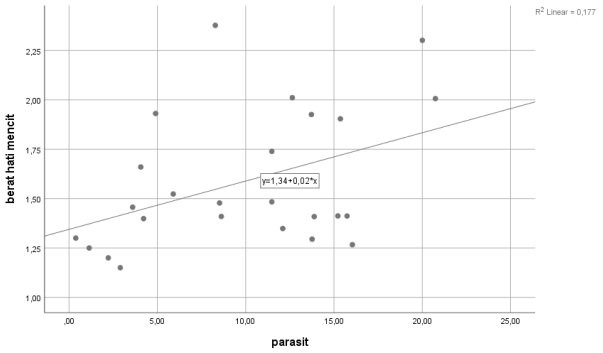

Figure 1. The Relationship Between Parasitemia Levels and Liver Weight

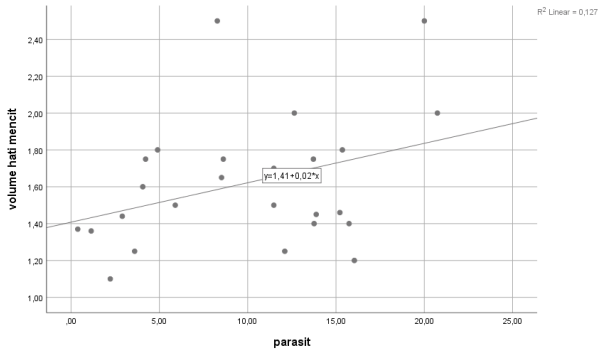

Figure 2. The Relationship Between Parasitemia Levels and Liver Volume

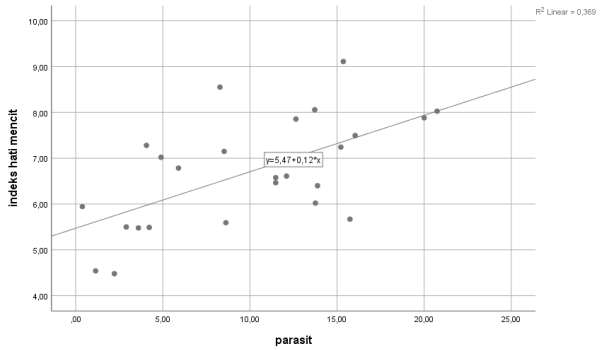

Figure 3. The Relationship Between Parasitemia Levels and Liver Index

DISCUSSION

The liver is a target organ that plays a crucial role in the malaria cycle, serving as the site where the parasite operates and where the host's immune system functions. The liver contains hepatocytes responsible for assisting metabolic processes within the body and performing cell regeneration. Physiologically, liver cells can undergo apoptosis, and macrophages phagocytose these apoptotic cells. This process triggers the activation of specific enzymes involved in signal transduction and exudation, synthesizing new macromolecules.[6,15]

Liver cells exposed to *Plasmodium* lead to an inflammatory process, resulting in necrosis of the surrounding cells. Cytokines assist T lymphocytes in activating phagocytic cells. CD8+ cytotoxic T lymphocytes, directly and indirectly, damage the hepatocytes infected by the parasite through the action of cytokines.[7,1]

The spleen and liver enlargement is due to the accumulation of infected erythrocytes, lymphocytes, and macrophages. *Plasmodium* has a pre-erythrocytic phase where sporozoites interact with Kupffer cells, and if successful, they continue to invade hepatocytes, where sporozoites develop into merozoites. The high number of sporozoites in the liver increases reactive oxygen species (ROS); however, hepatocytes do not undergo immediate cell death until the sporozoites mature into merozoites. Once the merozoites mature, hepatocytes will experience cell death, allowing the merozoites to continue their life cycle by invading erythrocytes. This increase in ROS can have a parasiticidal effect; however, if excessive, it may damage the surrounding tissues.[6,7,16]

The body will experience increased oxidative stress when levels become excessive, ultimately leading to platelet lysis and thrombocytopenia. The ethanol extract of purple eggplant

skin possesses antioxidant properties that can slow down or prevent the formation of free radical oxidation, thereby reducing liver damage caused by the parasite.[6,10]

This study found that the negative control group receiving distilled water exhibited higher liver weight, volume, and index than those treated with the ethanol extract of purple eggplant skin and dihydroartemisinin-piperaquine (DHP). An excessive amount of water in the body can also lead to protein damage within the cells, resulting in reduced organ density. This phenomenon is due to osmosis, where water moves from a hypotonic environment to a hypertonic one, leading to cell lysis. Water influences organ density, meaning that the more water that enters the cellular structure, the more protein is damaged, ultimately decreasing the organ's density and increasing its weight.[17, 18]

In this study, it was found that there was a correlation between the level of parasitemia and the liver index of mice, where the liver index in the negative group was higher than all groups because the group was infected with Plasmodium without being given treatment so that damage to infected liver cells occurred. This study is in line with the research of Putri et al., where the largest organ index was found in the negative control group, and the smallest organ index was found in the DHP group, which was not significantly different from the normal control group.[19]

Dihydroartemisinin-Piperaquine is a combination of the active metabolites of artemisinin and piperaquine, where artemisinin acts quickly to eliminate parasites in the body, and piperaquine has a long half-life of approximately 23 days (ranging from 19 to 28 days). The positive control group receiving DHP did not match the average of the normal control group because DHP was administered for only 5 days, while the recommended duration for antimalarial medications is 14 days. Test groups 1, 2, and 3 exhibited antimalarial effectiveness, with lighter liver weight, volume, and index compared to the negative control group; however, they still could not compete with the positive control group receiving DHP.[8,9,17]

Alkaloids in purple eggplant are metabolized in the liver into dimethyl xanthine, which is then converted into methyl uric acid, aided by the CytP450 oxygenase enzyme system. This methyl uric acid in the liver can stimulate the expression of tumor necrosis factor (TNF), modulating the immune system. Tannins can react with proteins to form water-soluble compounds, effectively killing microorganisms by disrupting their cell membranes.[17,18] This aligns with previous research indicating that the methanol extract of purple eggplant acts as a hepatoprotective agent in Swiss albino mice induced with CCl4.[6, 9]

A significant increase in the activity of SGPT, SGOT, bilirubin, creatinine, and urea is experienced by malaria patients. In some cases, complications like jaundice can occur, leading to elevated Serum Glutamic Oxaloacetic Transaminase (SGOT) activity. This enzyme, primarily found in liver parenchymal cells, is released into the bloodstream when liver cells are damaged due to the entry of sporozoites. As a result, there is an increase in aminotransferase enzymes in the blood. In severe malaria cases, both SGPT and SGOT levels rise, serving as indicators of liver damage, which can lead to hepatomegaly (enlarged liver).[17,18,22,23]

An ultrastructural study conducted by Prommano et al. found a correlation between a high burden of parasitized red blood cells (PRBC) in the liver of malaria patients and the occurrence of jaundice, hepatomegaly, and elevated liver enzymes. However, this study's findings do not align with those of Prommano et al. In the current study, no correlation was found between parasitemia levels and liver weight or volume, although a correlation was observed with the liver index of the

mice.[24] The study on the correlation between parasitemia and liver index in mice is also influenced by body weight and the physical condition of the mice. This is consistent with the research conducted by Putri et al., which found that the size of the liver index is related to the level of parasitemia.[25] The study conducted by Darlina et al. reported that liver enlargement occurs 7 days post-*Plasmodium berghei* infection without any intervention. In contrast, this study administered treatment for only 5 days, which may explain the limited liver damage observed, as the duration may not have been long enough for significant liver injury to occur.[29]

CONCLUSION

The ethanol extract of purple eggplant skin (*Solanum melongena L.*) effectively affects the liver size, liver weight, liver volume, and liver index in mice (*Mus musculus*) induced with *Plasmodium berghei*. The level of parasitemia with liver weight and liver volume of mice (Mus musculus) induced by Plasmodium berghei has no correlation, but a correlation was found between the level of parasitemia and the liver index of mice.

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