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The Effect of Ethanol Extract of Noni (Leaves *Morinda citrifolia*) on Parasitemia in Balb/c Mice infected with *Plasmodium berghei*

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***Abstract*—Malaria fever is a disease that is still a problem in developing countries. *Plasmodium berghei* is a facultative intracellular parasite, the immune system that plays a role in the cellular system. *Morinda citrifolia* is a traditional medicinal plant that contains many active compounds that can reduce the number of malaria Parasitemia. Objective: To prove the effect of ethanol extract *morinda citrifolia* on the decrease of malaria parasitemia of Balb/c mice infected by *Plasmodium berghei*. Methods: This type of research was experimental with the design of *the post test only control group design* in experimental animals, balb/c mice consisting of 24 male mice, divided into 4 groups. (K) was a control group infected with *Plasmodium berghei*, and the treatment group (P1, P2, P3) were given extract *morinda citrifolia* with multilevel doses (0.32 mg /kgBW/day, 0.64 mg/kgBW / day, 1,28 mg/kg BW/day) for 3 days after being infected with *Plasmodium berghei* as much as 0.1 ml $x10^6$. During 4 days given a multilevel dose of noni leaf extract and the 7th day intravenous blood isolation was carried out followed by parasitemia examination. Data were obtained from the calculation of the number of malaria parasitemia decreases in each field of view. Results: The mean decrease in malaria control paristemia was higher than the treatment group (22.17 x 10^6) ± (16.65 x 10^6) with (p =0.0001). Conclusion: Administration of ethanol extract of *Morinda citrifolia* can reduce malaria parasitemia in Balb/c mice.**

Keywords*—Paravitemia, Morinda citrifolia, Plasmodium berghei

1. INTRODUCTION

Malaria is a disease caused by the parasite protozoa *Plasmodium berghei* which is characterized by symptoms of fever, sweating cold, hemolytic anemia, and splenomegaly (1).

Data *World Health Organization* in 2015 occurred 214 million cases of malaria and 438,000 deaths. As many as 88% of cases and 90% of deaths occur in Africa, taking the life of a child under 5 years every 2 minutes.(2).

Indonesia has a high risk of malaria from 2005-2015 as many as 82% of cases originating from Papua, West Papua, Maluku and North Maluku . *Anopheles are* found all over the world except in Antarctica, and of 430 species only 30-40 species transmit malaria in nature . Malaria infection in humans and animals is caused by the Plasmodium parasite which is transmitted by the Anopheles mosquito (transmits malaria also to humans) and infects the liver after being injected into the bloodstream with the bite of an infected female mosquito. Plasmodium has the ability to cause malaria in animals, including mice (mice). Plasmodium berghei infection also affects the brain and can cause cerebral complications in laboratory mice (5). Many approaches have been developed to control the threat of mosquitoes. One such approach to preventing mosquitoes borne by disease is to kill mosquitoes at the larval stage. Larvasida is a successful way to reduce mosquito populations in places they breed before they emerge into adulthood. Prevention of breeding mosquitoes through the use of larvicides is the most effective way to fight with the *importunation* of these mosquitoes.

Malaria cases in Bengkulu Province in 2015 based on laboratory examinations as many as 33,814 without blood preparations and 28,333 examinations with blood preparations, found 2,631 tested positive for malaria, as many as 1.874,944 residents in Bengkulu Province were at risk of malaria with female and male sex. (Dinas Kesehatan Provinsi Bengkulu, 2015).

Morinda citrifolia (Noni) is one of the many herbal medicines used extensively in the past 2000 years (4). Noni leaf is a plant that is widely found in Indonesia which has properties capable of curing diseases, with chemical compounds found in noni leaves, namely tannins, saponins, and alkaloids (5). Noni leaf doses used in this study were divided into three stratified doses of 0.32 mg / kgBW / day orally, 0.64 mg / kg BW / day orally and 1.28 mg / kg BW / day of mice. The selection of multilevel doses is based on a dose of the use of noni leaves in the community as much as 10-100 gram which is used for the treatment of malaria.

Leaf extract *Morinda citrifolia* has major components such as anthrax-quinones, flavones, glycosides, trisaccharide. American fatty acid esters, proteins, acetyl, bio-ligands, and sterol derivatives (6). The pre-erythrocyte and blood parasite stages show important antigens that have been considered as targets for malaria vaccines. At present, the RTS recombinant vaccine, which is composed by

antigens from hepatitis B and P. falciparum circum sporozoite (PfCSP), has moderate effectiveness which decreases with the time of vaccination (7), and is largely determined by 3 factors of transmission chain, the host , agent and environment. (8).

Infected species of malaria parasites and increased knowledge of the molecular biology of *Plasmodium berghei* increase the value of this particular rodent model to investigate many aspects of the biological aspects of Plasmodium (9). One of the pathological reactions that are characteristic of malaria infections is the enlargement of the spleen and liver organs caused by the number of infected erythrocytes, lymphocytes, and macrophage cells deposited in both organs.(10)

II. METHODS

This study was an experimental laboratory study with the design of *The Post Test-Only Control Group* that used animal experiments in Balb/c mice as the object of research. The treatment is the administration of ethanol extract of *Morinda citrifolia* with the output is a decrease in parasitemia in the blood of Balb/c mice.

The material used in this study was aquadest, Plasmodium berghei parasite was obtained from the Mitochondrial Laboratory and Infectious Disease Research Institute, Eijkman, Central Jakarta, Noni (Morinda Citrifolia), 96% ethanol, balb / c mice, Giemsa Color. The sample used is the leaf part of the noni plant which was taken in the Curup area of Rejang Lebong Regency, Bengkulu Province.

The processing of samples of noni leaves is then dried and pollinated until they are ready to extract the maceration method. The noni leaf powder was macerated with 96% ethanol for 2 x 24 hours. Simplicia which has been macerated with ethanol solution is filtered to obtain filtrate. The solvent filtrate was evaporated with a rotary evaporator so that the dried extract of noni leaves was produced, the experimental animals were grouped into 4 groups and each group consisted of 6 male mice. Group I as a negative control of mice was given aquadest, group II was given noni leaf extract with a dose of 0.32 mg/KgBW. Group III was given a dose of 0.64 mg / KgBW, and Group IV was given a dose of 1.28 mg / KgBW.

On day 1 of the mice injected intraperitoneally, plasmodium berghei 0.1 ml, day 2 and 3, we see the development of the parasite, then the 4th to 7th day the mice were given noni leaf extract and the control was given orally aquadest conducted at the SBIH Ruyani Laboratory, Faculty of Mathematics and Natural Sciences, University of Bengkulu. Analysis test using statistical test *One Way Anova* followed by *Post Hoc Test* or Test *Bonferroni*.

III. RESULTS

Maintenance and research were carried out from the beginning of October to the beginning of November 2017 at the SBIH Ruyuni Laboratory, Faculty of Mathematics and Natural Sciences, University of Bengkulu. The study used 4 treatment groups with the number of 24 mice, which infected *Plasmodium berghei* with the output (*outcome*) in the form of a decrease in malaria parasitemia, but at the end of the study there were 21 mice, because there were 3 mice that died in the implementation of the study.

Table 1 Results of analysis of the mean number of parasitemia decreases after treatment of multilevel dose of noni leaf extract (Morinda Citrifolia)

Group	N	Mean ± SD	P
K	6	22.17 ± 16.65	
P1	6	18.50 ± 16.65	0.0001
P2	6	10 , 79 ± 9.31	
P3	3	8.33 ± 6.69	

Table 1 known the average number of parasitemia decreases in the treatment group (P1, P2, P3) was lower than the control group. The highest mean decrease in parasitemia was in the control group (22.17 ± 16.65) while the lowest average was in the P3 group (8.33 ± 6.69). Results Statistical analysis with the ANOVA test shows that there are differences between the various groups at p <0.05.

Table 2 Analysis *Post Hoc Test* Number of decrease in Parasitemia

Group	K	P1	P2	P3
K		0.402	0.017	0.011
P1	0.402		0.070	0.020
P2	0.017	0.070		0.130
P3	0.011	0.020	0.130	

The Balb/c mice used in this study was obtained from the Biology Laboratory of the Faculty of Mathematics and Natural Sciences, University of Bengkulu. The number of mice used was 24, where each group was divided into 6 heads. Mice were then adapted for 7 days at the SBIH Ruyani Laboratory, University of Bengkulu.

Adapted mice were fed and drank after being adapted for 7 days before being treated, previously calculated the mean weight of mice. Administration of ethanol extract of noni leaves (*Morinda citrifolia*) with a dose of P1; 0.32 mg / kgBW / day, P2; 0.64 mg / kgBW / day, P3; 1.28 mg / kgBW / day given for 4 days, as well as the control group given aquadest, after mice were infected with *Plasmodium berghei*.

IV. DISCUSSION

Calculation of mice parasitemia rates is a method commonly used in malaria research. The function of this calculatson is to determine whether or not a mice is positive after being infected with intraperitoneal red blood cells that

have been infected with *berghei P*. The control group mice in the fifth day of study died after being infected with *Plasmodium berghei*, there were several possibilities for the mice to die in the study. First, it can be caused by stress that can reduce the immune system, the body through stimulation of cortisol and adrenaline secretion and affect the release of noradrenaline and sympathetic prostaglandins nerve terminals in blood vessels and lymphoid organs. The systemic effects of glucocorticoids and catecholamines affect cytokines so that a decrease in cytokine production is needed in response to bacterial infections through cellular immune responses.

Mice in the group (P3) died during the study on the sixth day after treatment of the number of deaths of 3 mice. The death of mice in the treatment (P3) should be carried out research on their organs, such as the liver and kidneys to determine the right mechanism of death. However, the alleged cause of death is due to the resin content contained in the ethanol extract of Noni leaves (*Morinda citrifolia*). The content of this resin compound when consumed continuously in high doses will result in accumulation of resin toxins in the body which will cause side effects on the nervous system which can cause death.

Immunity to *Plasmodium berghei* involves *cell mediated immunity components* such as lymphocytes. Secondary lymphoid organs such as the spleen function to effectively capture and collect antigens, for proliferation and differentiation of lymphocytes that have been desensitized (*committed lymphocyte antigens*). Lymphocytes recirculate from one lymphoid organ to another, lymph and blood flow, so that during an infection many lymphocytes are exposed to the infecting germ antigen. The ability to recognize the antigen is caused by the presence of receptors on the surface of the lymphocyte cell. Lymphocytes that have been stimulated by specific antigens will immediately divide and will express new receptors that allow them to respond to cytokines from other cells which are signals of proliferation.

Lymphocytes will also secrete their own cytokines and under the influence of these cytokines they will experience a number of cleavage cycles before differentiating into mature effector cells. Proliferation will reduce cells *clonal selection*.

Macrophage Fagocytosis Index

The results of this study were that between the control group with treatment P1, the treatment of P2 and treatment P3 found a significant difference. In addition, in the K, P1, P2 and P3 groups showed an increase in phagocytic activity of macrophages according to the increase in dose, namely K <P1 <P2 <P3.

infection *Berghei's Plasmodium* activates the cellular immune system. Macrophages as professional phagocytes, function as effectors, after cells are activated by microbes, cytokines and other stimuli. The administration of ethanol extract *Morinda Citrifolia is* able to activate macrophages.

The role of macrophages activated in the cellular immune response is 3 (1) phagocytes and killing intracellular microbes through the production of microbicidal molecules (2) stimulating local acute inflammation (3) cleaning dead tissue due to bacterial infection and tissue repair.

Pheophorbide Phypolesper in a plant can modulate various immune systems, Pheophorbide Phypolesper is also lipophilic which can damage microbial membranes. Pheophorbide Phypolesper can increase IL-2 activity and lymphocyte proliferation. Activated Th1 cells will affect SMAF, namely molecules including IFNγ which can activate macrophages, so that macrophages experience metabolic enhancement, motility and phagocytic activity quickly and more efficiently in killing pathogenic bacteria or microorganisms.

The effect of giving ethanol extract of noni leaf (*Morinda citrifolia*) in this study can reduce the number of parasitemia compared to controls with a significant difference, with the group given a dose of 0.32 mg (P1), 0.64 mg (P2), and 1.28 mg (P3), although between treatment doses (P1, P2, P3) there was no significant difference but the treatment group which was given ethanol of noni leaf (*Morinda citrifolia*) decreased parasitemia compared to controls. This is due to the stimulation of compounds *Morinda citrifolia*, which are flavonoids against parasitemia.

The highest mean decrease in parasitemia was in the control group (22.17 ± 16.65) while the lowest average was in the P3 group (8.33 ± 6.69). Results Statistical analysis with the Anova test showed that there were significant differences between various groups at $p < 0.05$ in accordance with the research conducted by J M Makinde et.al. (11)

V. CONCLUSION

Decrease in malaria parasitemia in the group receiving noni leaf extract (*Morinda citrifolia*) with multilevel doses (0.32 mg/kgBW/day, 0.64 mg/kgBW/day, 1.28 mg/kgBW/ day) compared to the group that did not get the extract Noni leaves (*Morinda citrifolia*). Further research is needed to determine the dose of toxin of ethanol extract of noni leaves (*Morinda citrifolia*) and examination of the nervous system, kidney and liver organs to determine the mechanism of death mice in each treatment group.

Mean phagocytosis of macrophages in all four groups showed phagocytic activity of macrophages which increased with increasing doses.

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