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Short Communication

Effect of moringa extract on parasitemia, monocyte activation and organomegaly among *Mus musculus* infected by *Plasmodium berghei* ANKA

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Abstract

In Indonesia, malaria remains a problem, with 94,610 active cases in 2021 and its current therapy includes chloroquine and artemisinin; however, resistance has been commonly reported. To overcome this problem, studies about potential medicinal plants that can be used as antimalaria, such as moringa (*Moringa oleifera*) started to receive more attention. The aim of this study was to investigate the effects of moringa in parasitemia, monocyte activation, and organomegaly on animal model malaria. This experimental study used male *Mus musculus,* infected by *Plasmodium berghei* ANKA, as an animal malaria model. The extract was made by maceration of dry moringa leaves, which were then divided into three concentrations: 25%, 50%, and 75%. Dihydroartemisinin-piperazine was used as a positive control treatment, and distilled water as a negative control treatment. The animals were observed for six days to assess the parasitemia count and the number of monocyte activation. On day 7, the animals were terminated, and the liver, spleen, and kidney were weighed. The results showed that the effective concentrations in reducing parasitemia and inducing monocyte activation were 50% and 25% of moringa leaf extract, respectively. The smallest liver and spleen enlargement was observed among animals within the group treated with a 50% concentration of *M. oleifera* extract. In contrast, the smallest kidney enlargement was observed in the group treated with 25% of *M. oleifera* extract. Further analysis is recommended to isolate compounds with antimalarial properties in moringa leaves.

Keywords: Malaria, antimalaria, moringa, parasitemia, sequestration

Introduction

In Indonesia, malaria has become a significant problem in recent decades and become 10 most infectious diseases targeted to be eliminated in 2030 [1]. According to data from the Ministry of Health of the Republic of Indonesia, there were 402.488 positive cases of malaria, of which 361.508 cases were treated with standard treatment, and 157 deaths in 2023 [2]. The highest positive case distributions were in Papua Province, West Papua Province, and East Nusa Tenggara province [3]. Resistance to chloroquine and artemisinin treatment has been reported; however, limited options were available for malaria treatment [4]. In addition to the resistance, patient compliance to the malaria treatment was decreased due to the side effects such as nausea and vomiting, headache, myalgia, chest pain, and breathlessness [5].

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Medicinal plants have been used to treat various diseases since ancient times and are favored due to their minimum cost, fewer side effects and readily available. Moringa (*Moringa oleifera*) was frequently studied for antimalaria due to its use in traditional communities [6]. *M. oleifera* is widely distributed in Africa, Madagascar, the Arabian Peninsula, India and Indonesia. This plant has high antioxidant activity due to the high content of flavonoids [6]. *M. oleifera* has improved lactation for breastfeeding mothers in Indonesia [6]. Anti-inflammatory, anti-viral, anti-toxicity, and antioxidant properties [7]. Phytochemical analysis revealed that moringa contains flavonoids such as apigenin, kaempferol, rutin, and quercetin, which are promising antimalarial compounds [8]. Therefore, this study aimed to investigate the effect of *M. oleifera* on parasitemia, monocyte activation, and organomegaly in malaria using an animal model.

Methods

Study design and setting

An in vivo experimental study with a post-test-only control group design was conducted at the Research Laboratory, Faculty of Medicine and Health Sciences, Universitas Warmadewa, Denpasar, Indonesia. Male mice were obtained from the Bikul Bali Experimental Animal store. *P. berghei* isolates were obtained from the Department of Parasitology, Universitas Udayana, Bali, Indonesia. Observation of parasitemia, organomegaly and monocyte activation was conducted in the Research Laboratory, Faculty of Medicine and Health Sciences, Universitas Warmadewa.

Preparation of *M. oleifera* leaves extract

Fresh *M. oleifera* leaves were bought in a traditional market. The moringa leaves were identified in the Research Laboratory, Faculty of Medicine and Health Sciences, Universitas Warmadewa, Denpasar, Indonesia, with voucher code number MO 320. *M. oleifera* extract was prepared by drying and crushing the fresh moringa leaves. The powder of *M. oleifera* leaves was mixed with 70% ethanol in a ratio of 1:1 and allowed to stand for 3×24 hours. Then, the liquid extract was filtered using filter paper and the crude extract was concentrated using a rotary evaporator at 40°C [9].

Experimental animals, study groups, and treatment

Forty male healthy mice (*Mus musculus*) aged ±7 weeks old with weight of ±25 grams were used. The animals were acclimatized to the laboratory conditions for seven days and maintained under 12 hours dark and 12 hours light. The mice were kept in a 40×50 cm cage containing four mice per cage at 25°C with free access to standard mouse pellet and water *ad libitum*. After acclimatization, the mice were infected with 0.2 mL of blood containing *P. berghei* on the seventh day using intraperitoneal injection, as reported elsewhere [10]. This intraperitoneal injection was angled 10° from the abdomen with a position slightly away from the midline and in an area that is not too high to avoid infecting the bladder and liver [11].

The mice were divided into five groups with an equal number randomly assigned according to Federer's formula [12]. Group 1, or positive control, was given dihydroartemisinin-piperaquine (DHP) at a dose of 187.2 mg/kg body weight. Group 2 was treated with 25% moringa extract; group 3 with 50% moringa extract, and group 4 was given 75% moringa extract. The administration of extracts in each group was calculated as a dose of 1000 mg/kg body weight of moringa leaf extract in 0.5 mL water for every 25 g of body weight. Group 5, or negative control, was given distilled water at a dose of 0.5 mL/kg body weight [13]. The Moringa extract was given orally once a day (24-hour intervals), from H0 or the day of infection (2 hours after being infected) until H4 as recommended [14].

Study outcomes

The outcomes assessed in this study were parasitemia, monocyte activation, and organomegaly. Data on parasitemia were collected daily from day 1 until day 6. Every morning, the parasitemia was counted by performing a peripheral blood smear, followed by 10% Giemsa staining and observed under the microscope. The number of infected erythrocytes in the 5-field view was calculated and divided by 1000, then multiplied by 100% to get percent of parasitemia.

Parasitemia was also calculated to determine the severity of infection per 1000 erythrocytes. The examination was carried out by taking mice's blood in tails before therapy from day 1 until day 6 [15]. On H6, the animals were terminated by sedation using ketamine xylocaine. The mice's organs (liver, spleen, and kidney) were weighed using digital scales.

Data analysis

The data were presented as mean ± standard deviation (SD). To compare the effect of the extracts on the study outcome, the data were analyzed using the one-way analysis of variance (ANOVA) and Levene tests with a confidence level of $p<0.05$.

Results

Effects of *Moringa oleifera* extract on parasitemia

Forty mice were used as a malaria animal model divided into five groups of eight mice. Two mice died in groups 1, 2, and 5 during the experiment. These mice were excluded from the data analysis. Initial parasitemia was evaluated on day 1 after the intervention (**Table 1**). The highest level of parasitemia was observed in the negative control group (14.6%), followed by the moringa 75% group (8.6%), DHP group (7.7%), and moringa 25% group (7.3%). The lowest parasitemia was observed in the positive control group (6.2%) (**Table 1**).

Table 1. Effects of *Moringa oleifera* extract on parasitemia of *Mus musculus* infected by *Plasmodium berghei* ANKA from day 1 to day 6

Day	Group	Frequency (%)	Number of parasites Mean±SD	Parasitemia (%)	*p*-value
1	DHP	6 (17.4)	62.3±13.0	6.2	<0.001
	Moringa (25%)	6 (17.4)	77.6±31.0	7.7	
	Moringa (50%)	8 (23.5)	73.3±15.3	7.3	
	Moringa (75%)	8 (23.5)	86.0±12.4	8.6	
	Distilled water	6 (17.4)	146.8±13.8	14.6	
2	DHP	6 (17.4)	80.0±15.4	8.0	<0.001
	Moringa (25%)	6 (17.4)	157.0±19.9	15.7	
	Moringa (50%)	8 (23.5)	130.0±22.9	13.0	
	Moringa (75%)	8 (23.5)	71.5±12.4	7.1	
	Distilled water	6 (17.4)	170.2±55.4	17.0	
3	DHP	6 (17.4)	65.5±19.1	6.5	<0.001
	Moringa (25%)	6 (17.4)	153.0± 21.0	15.3	
	Moringa (50%)	8 (23.5)	130.1±5.1	13.0	
	Moringa (75%)	8 (23.5)	131.6±12.7	13.1	
	Distilled water	6 (17.4)	227.2±26.7	22.7	
4	DHP	6 (17.4)	60.1±11.3	6.0	<0.001
	Moringa (25%)	6 (17.4)	144.0±4.5	14.4	
	Moringa (50%)	8 (23.5)	113.0±37.5	11.3	
	Moringa (75%)	8 (23.5)	119.0±18.8	11.9	
	Distilled water	6 (17.4)	243.0±36.5	24.3	
5	DHP	6 (17.4)	43.0±12.7	4.3	<0.001
	Moringa (25%)	6 (17.4)	104.0±4.7	10.4	
	Moringa (50%)	8 (23.5)	86.1±9.4	8.6	
	Moringa (75%)	8 (23.5)	112.0±25.1	11.2	
	Distilled water	6 (17.4)	257.0±44.3	25.7	
6	DHP	6 (17.4)	37.5±4.9	3.7	<0.001
	Moringa (25%)	6 (17.4)	102.0±4.5	10.2	
	Moringa (50%)	8 (23.5)	72.8±8.3	7.2	
	Moringa (75%)	8 (23.5)	96.0±24.4	9.6	
	Distilled water	6 (17.4)	346.0±41.3	34.6	

The parasitemia levels in all groups increased on day 2, except for the moringa 75% group, which decreased from 86.0±12.4 to 71.57±12.4. Overall, the moringa 50% group has the highest parasitemia decrease after day 2, from 130.0±22.9 to 72.8±8.3. In contrast, the parasitemia level of the moringa 75% group increased from 71.5±12.4 on day 2 to 96.0±24.4 on day 6 (**Table 1**).

Effects of *Moringa oleifera* extract on monocyte activation

The highest monocyte activation on day 1 was observed in the moringa 75% group (7.37±2.32, $p<0.05$) (**Table 2**). However, during the treatment from day 1 to day 6, the highest increase of monocyte activation was observed in group 2 (1.0 on day 1), which increased to 7.00 on day 6 (**Table 2**).

Table 2. Effects of *Moringa oleifera* extract on monocyte activation of *Mus musculus* infected by *Plasmodium berghei* ANKA from day 1 to day 6

Day	Group	Frequency (%)	Number of monocytes (Mean±SD)	*p*-value
Day 1	DHP	6 (17.4)	1.0±Na	0.002*
	Moringa (25%)	6 (17.4)	1.0±Na	
	Moringa (50%)	8 (23.5)	7.0±1.0	
	Moringa (75%)	8 (23.5)	7.3±2.3	
	Distilled water	6 (17.4)	2.2±0.5	
Day 2	DHP	6 (17.4)	6.4±0.5	0.001*
	Moringa (25%)	6 (17.4)	4.5±0.5	
	Moringa (50%)	8 (23.5)	6.2±0.9	
	Moringa (75%)	8 (23.5)	1.0±Na	
	Distilled water	6 (17.4)	3.0±Na	
Day 3	DHP	6 (17.4)	1.0±Na	0.001*
	Moringa (25%)	6 (17.4)	5.0±Na	
	Moringa (50%)	8 (23.5)	5.0±1.0	
	Moringa (75%)	8 (23.5)	1.0±Na	
	Distilled water	6 (17.4)	1.8±0.7	
Day 4	DHP	6 (17.4)	5.0±Na	0.002*
	Moringa (25%)	6 (17.4)	4.0±1.4	
	Moringa (50%)	8 (23.5)	6.7±0.9	
	Moringa (75%)	8 (23.5)	1.0±Na	
	Distilled water	6 (17.4)	2.6±0.8	
Day 5	DHP	6 (17.4)	4.6±3.7	0.510
	Moringa (25%)	6 (17.4)	6.0±Na	
	Moringa (50%)	8 (23.5)	4.0±1.6	
	Moringa (75%)	8 (23.5)	3.6±1.7	
	Distilled water	6 (17.4)	2.5±0.5	
Day 6	DHP	6 (17.4)	5.5±6.3	0.240
	Moringa (25%)	6 (17.4)	7.0±Na	
	Moringa (50%)	8 (23.5)	9.0±1.4	
	Moringa (75%)	8 (23.5)	8.5±2.0	
	Distilled water	6 (17.4)	2.0±1.4	

*Significance level at $p=0.05$
Na: cannot be analyzed

Effects of *Moringa oleifera* extract on organomegaly

The mean of organ weight varied between groups after treated with moringa extracts (**Table 3**). The difference in liver weight was not statistically significant between the positive, negative and treated groups. On the other hand, the spleen weight in the negative control group was significantly different to those of positive control and treated groups ($p<0.001$). The smallest liver and spleen enlargement were observed in the moringa 50% group, which was given 50% concentration of *M. oleifera* extract. However, the smallest kidney enlargement was observed in the moringa 25% group (**Table 3**).

Table 3. Effects of *M. oleifera* extract on organomegaly of *Mus musculus* infected by *Plasmodium berghei* ANKA

Variable	Group	Frequency (%)	Organ weight Mean±SD, gram	*p*-value
Liver weight	DHP	6 (17.4)	2.20±0.84	
	Moringa (25%)	6 (17.4)	2.00±Na	
	Moringa (50%)	8 (23.5)	1.92±0.22	
	Moringa (75%)	8 (23.5)	2.01±0.27	
	Distilled water	6 (17.4)	2.06±0.35	0.88
Spleen weight	DHP	6 (17.4)	1.15±0.07	
	Moringa (25%)	6 (17.4)	0.70±Na	
	Moringa (50%)	8 (23.5)	0.55±0.09	

Variable	Group	Frequency (%)	Organ weight Mean±SD, gram	*p*-value
Right kidney weight	Moringa (75%)	8 (23.5)	0.78±0.32	
	Distilled water	6 (17.4)	6.00±1.22	0.001*
	DHP	6 (17.4)	1.05±0.07	
	Moringa (25%)	6 (17.4)	0.50±Na	
	Moringa (50%)	8 (23.5)	0.57±0.04	
	Moringa (75%)	8 (23.5)	0.65±0.16	
Left kidney weight	Distilled water	6 (17.4)	6.20±0.83	0.001*
	DHP	6 (17.4)	0.95±0.21	
	Moringa (25%)	6 (17.4)	0.50±Na	
	Moringa (50%)	8 (23.5)	0.57±0.07	
	Moringa (75%)	8 (23.5)	0.58±0.07	
	Distilled water	6 (17.4)	6.20±1.30	0.001*

*Significance level at p=0.05
Na: cannot be analyzed

Discussion

Our study showed that moringa extract effectively reduced parasitemia in mice compared with negative control. Moringa extract was previously proven to contain active compounds such as flavonoids, saponins, tannins, catechol, tannins, anthraquinones, and alkaloids [15]. Its potential properties include antioxidant, anti-plasmodial, anti-aging, anti-microbial, disinfectant, excellent carrier oil, and hepato-protective agent [14]. Moringa extract kills the parasite, repairs injured cells, and promotes the regeneration of infected cells [3]. A previous study reported that Moringa extract possessed significant anti-plasmodial activity, as displayed by its ability to suppress *P. berghei* infection in mice [16]. A total of 46 flavonoids were identified in the leaves and seeds of *M. oleifera* extract, contributing to its anti-plasmodial activity [8]. Not only from leaves, but the ethanol extract of *M. oleifera* seeds also demonstrated a high anti-plasmodial activity against *P. berghei* in albino rats [17].

Moringa also has an immunomodulator effect that significantly increases the level of CD4+ in mice infected by *P. berghei* [3]. Our study indicated that the number of activated monocytes was increased after treatment with *M. oleifera* extract, with the highest increase of activated monocytes observed in group 2 (treated with 25% moringa extract). Monocytes are precursor cells in the innate immune system made in the bone marrow and travel through the blood to tissues in the body, where they become macrophages or dendritic cells. Macrophages surround and kill microorganisms, ingest foreign material, remove dead cells, and boost immune responses, phagocytes, the infected red blood cells in malaria infection. The role of Moringa as an immunomodulatory agent was also proven in a previous study that stated *M. oleifera* treatment increases Tbet expression in CD4+ T cells and remediates immune defects of malnutrition in *P. chabaudi*-infected mice [18].

The liver and spleen are the main organs that contribute to protection against malaria infection [19]. The liver is the first site where sporozoites invade tissue for further development, proliferate to become schizonts, and mature schizonts rupture to release merozoite [16]. Merozoite will invade healthy red blood cells and trigger changes in the morphology of red blood cells, such as membrane modification, formation of malarial pigment, and change of cytoplasmic configuration. The development of malarial parasites starts at immature trophozoite, mature or growing trophozoite, differentiation into gametocyte, somehow becoming hypnozoite or dormant schizont in the hepatocyte. *M. oleifera* had a hepatoprotective role in preventing damage to hepatocytes by reducing pro-inflammatory reactions by stimulating the production of Treg [5]. The spleen also has a vital role in eliminating infected red blood cells by *Plasmodium* sp. Infected red blood cells are killed by macrophages. Destructed RBC also released hemozoin or malaria pigment that accumulated in severe malaria [20]. In malaria, splenomegaly happens due to the obstruction of the blood vessel by erythroid precursors, which might cause the closing of the circulation and secretion of soluble factors by blood vessel macrophages [21]. The change in erythrocyte morphologies is a significant determinant of their trapping and removal of parasites by the spleen [22]. Moringa extract has an anti-inflammatory effect that prevents fluid accumulation in tissue, which prevents organ enlargement [11].

Renal enlargement can be caused by obstruction of blood circulation in glomerular, tubular necrosis and hydronephrosis [22,23] and is linked to the localization of host monocytes in the kidney as well as sequestration of parasitized erythrocyte [23]. Malaria-associated acute kidney injury is characterized by elevated levels of acute kidney injury (AKI) biomarkers, including urinary neutrophil gelatinase-associated lipocalin, serum cystatin C, and blood urea nitrogen [24-25]. Deposit of malarial pigment in the glomerular area also contributes to worsening renal destruction and results in renal failure in severe malaria infection [23,25]. Sequestration by *Plasmodium* infection disturbed the microcirculation and blood filtration of waste products [24,26]

Conclusion

M. oleifera extract effectively decreased parasitemia, increased monocyte activation, and reduced organomegaly in mice infected by *P. berghei*. The effective concentrations in reducing parasitemia and inducing monocyte activation were 50% and 25% of moringa leaves extract, respectively. The smallest liver and spleen enlargement was observed in the group treated with 50% concentration of *M. oleifera* extract. In contrast, the smallest kidney enlargement was observed in group 2 treated with 25% of *M. oleifera* extract. Further research is recommended to explore specific mechanisms of active compounds in inhibiting parasite proliferation.

Ethics approval

This research was approved by the Ethical Committee of Health Research, Faculty of Medicine and Health Sciences Warmadewa University, by ethic number 320/Unwar/FKIK/EC-KEPK/IV/2023, dated April 3, 2023.

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

How to cite

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