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Antimalarial Activity of Brown Alga Extract *Sargassum sp* on Liver Cell of Mouse (*Mus musculus*) Infected with *Plasmodium berghei*

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Abstract

Sargassum sp is rich in steroid, alkaloid, phenol, flavonoid, saponin, and tannin components, which have anti-malarial and immunomodulatory properties. This study aimed to assess the anti-malarial effects of an extract from brown algae *Sargassum sp* on liver cells in *Plasmodium berghei*-infected house mouse (*Mus musculus*). Twenty to thirty-gramme house mice were infected with *Plasmodium berghei* at a dosage of 0.1 ml per tail and monitored until the parasitemia level reached 1-5%. Subsequently, house mice (*Mus musculus*) were administered methanol extract of brown algae *Sargassum sp* at 10, 100, and 200 mg/g BW doses for four consecutive days, from day 0 to day 6. On day 6, surgery was performed to extract the liver organ and prepare histological preparations. The findings demonstrated that applying *Sargassum sp* extract effectively improved the restoration of liver damage in house mice infected with *Plasmodium berghei*.

Keywords: liver cells, Plasmodium berghei, Sargassum sp

Introduction

Indonesia has a significant prevalence of malaria, with approximately 35% of its people residing in locations where malaria is common (Kakisina dan Ukratalo, 2011; Elyazar *et al.*, 2011; Ipa *et al.*, 2020). Provinces in Eastern Indonesia, including Maluku, North Maluku, Papua, West Papua, and East Nusa Tenggara (NTT), have the highest malaria rates (Guntur *et al.*, 2021; Tobing *et al.*, 2024). The prevalence of malaria in the region is 5 cases per 1,000 persons. *Malaria* is an illness that occurs when a person becomes infected with parasites from the Plasmodium genus, which are transmitted through Anopheles mosquitoes. Many species of

Plasmodium typically cause malaria (Pertuak et al., 2023). The clinical symptoms of malaria are directly linked to one of its pathogenic mechanisms, known as sequestration. Sequestration is believed to have a substantial impact on the pathophysiology of severe malaria. Typically, the brain has the highest level of sequestration, followed by the liver and kidneys (Balaji *et al.,* 2020).

Malaria-induced liver problems remain a substantial health issue in tropical nations, resulting in a mortality rate of one million fatalities annually (Brown *et al.,* 2020). According to Wilson *et al.* (2009), splenomegaly is a symptom observed in malaria cases that might lead to liver damage. This occurs due to sporozoites entering the bloodstream and infiltrating the liver, where they develop into schizonts. These schizonts eventually burst in the liver, releasing merozoites that proceed to invade more liver cells. Certain merozoites that persist in the liver will undergo continual development, prompting the liver to release a substantial quantity of erythrocytes that will become infected with parasites (Anoosha, 2019). This will lead to a reduction in haemoglobin levels in the blood, as well as blood vessel thrombosis and liver necrosis. Circulation abnormalities will result in reduced blood flow to the liver (McCormick *et al.,* 2000).

The current therapy for malaria, per the guidelines set by the World Health Organisation (WHO), involves a combination of Artesunate and Piperaquin (also known as dehydro artemisinin piperaquin/DHP or arterakin) (Pasaribu *et al.,* 2013). Reports of parasite resistance to frequently used anti-malarial have been consistently documented worldwide since 1973. To address the issue of resistance and decrease the occurrence of illness and death caused by malaria, the World Health Organisation (WHO) has mandated the discontinuation of all single-drug treatments and instead implemented Arterimycinin Combination Therapy (ACT) for treatment. The quest for novel chemicals, including anti-malarial medicines and malaria inhibitors, is ongoing, utilizing natural and synthetic materials (Eyasu, 2015; Nasir *et al.,* 2020).

Sargassum sp is a variety of seaweed belonging to the Phaeophyceae class. It possesses antioxidant properties as it can impede the peroxidation of fats and the activity of free radicals (Catarino *et al.,* 2023). According to Vinodkumar & Packirisamy (2024), *Sargassum myriocystum*, derived from the southern coast of Tamil Nadu, India, is rich in steroid compounds, alkaloids, phenols, flavonoids, saponins, and tannins. Several studies have demonstrated the efficacy of flavonoid compounds in suppressing the proliferation of malaria parasites in several medicinal plants with anti-malarial properties (Kakisina dan Ukratalo, 2024). In addition, these compounds also function as antioxidants. Because the brown alga *Sargassum sp* contains natural antioxidants, this alga plays a crucial role in inhibiting the growth of *Plasmodium berghei* and preventing liver cell damage in mice (Tulashie et al., 2024). Antioxidants can also inhibit oxidation reactions by binding to free radicals and highly reactive molecules, thus preventing cellular damage.

This study aims to assess the effectiveness of an extract from brown algae *Sargassum sp* in treating malaria. Specifically, we will examine its impact on the condition of liver cells in house mice (*Mus musculus*) infected with *Plasmodium berghei*.

Literature Review

Malaria, caused by the *Plasmodium* parasite, is a serious infectious disease that significantly challenges global public health, especially in tropical and subtropical regions. Malaria is often treated with synthetic antimalarial drugs; however, resistance to these drugs is increasing, prompting the search for alternative therapies from natural sources. One promising source is the brown alga *Sargassum sp.*, which is known to contain bioactive compounds such as steroids, alkaloids, phenols, flavonoids, saponins, and tannins, all of which have potential antimalarial activity. Research by Rahma *et al*. (2015) has shown that *Sargassum sp.* extract can increase the number of erythrocytes and lymphocytes. In addition to its antimalarial effects, *Sargassum sp.* extract can potentially protect vital organs, such as the liver, which are often damaged due to malaria infection. *Plasmodium* infection can cause histological changes in liver cells, such as immune cell infiltration, necrosis, and tissue damage (Sobuj et al., 2024). These findings suggest that *Sargassum sp.* extract is effective in combating malaria and provides valuable hepatoprotective effects, making it a promising candidate for developing safer and more effective natural-based antimalarial therapies.

Research Method

Research Type

This study is a laboratory experimental research that follows a post-test-only controlled group design. A post-test-only controlled group design employs two groups: an experimental group that receives treatment and a control group that does not.

Research Design

This study had a completely randomized design (CRD) with four treatments and three replications. The study conducted by Tanduwinata et al. categorized the groups as follows: K (+) - house mouse infected with *Plasmodium berghei* without receiving any medication, P1 - house mouse infected with *Plasmodium berghei* and treated with *Sargassum sp* extract at a dose of 10 mg/g BW, P2 - house mouse infected with *Plasmodium berghei* and treated with *Sargassum sp* extract at a dose of 100 mg/g BW, and P3 - house mouse infected with *Plasmodium berghei* and treated with *Sargassum sp* extract at a dose of 200 mg/g BW.

Research Tools and Materials

The equipment utilized included measuring cups, Whatman 02 filter paper, a collection of glassware, electronic scales, knives, blenders (for homogenisation), a rotavapor, containers for housing house mice, an analytical balance, syringes, glass objects, scratch slides, centrifuge tubes, heparing tools, sonde tools, volumetric pipettes, spatulas, hand counters, satay grills, digital cameras, Olympus microscopes, centrifuge tubes, heparing tools, sonde tools, volumetric pipettes, a vaporising cup, and a spectrophotometer. The materials utilized include *Sargassum sp*, methanol, *Plasmodium berghei* culture, male house mouse, aluminum foil, tissue, cotton, immersion oil, detergent, 4% formalin, distilled water, paraffin, alcohol concentrations of 30%, 50%, 70%, 80%, 90%, and 100%, Xylol, and HE staining.

Working Procedure

Extraction

Specimens of *Sargassum sp* were collected from the waters of Liang Village, then transported to the laboratory, cleansed, and fragmented into smaller segments, followed by dehydration. Once the sample was dried, it was pulverized with a blender to extract the simplisia from *Sargassum sp*. Subsequently, the maceration method was employed to extract the sample using a methanol solvent. The extraction products were condensed using a rotary evaporator until the concentrated extract of *Sargassum sp* was obtained.

Plasmodium berghei Infection in Donation House Mouse

The donation house mice were intraperitoneally infected with frozen *Plasmodium berghei*, with a volume of up to 200 µl injected into their bodies. In addition, parasitemia was observed daily until it exceeded >20%. A surgical procedure was performed to extract blood from the hearts of infected house mice, which was then transferred into blood tubes containing heparin, resulting in a parasitemia percentage of 5%. Each mouse received an intraperitoneal injection of 0.1 ml (Ukratalo *et al.,* 2023).

Anti-malarial activity testing

House mice infected with *Plasmodium berghei* were then monitored for levels of parasitemia by collecting blood from the house mouse's tail tip (± 1 mm) and then transferring it onto a glass surface. Before generating a thin blood smear, the blood can spread horizontally towards the object glass's left and right sides. Next, the objective lens is moved forward across the surface of the thin blood layer on the preparation and then left to dry at room temperature. After drying, the blood preparations were treated with 100% methanol for 3 minutes to fix them. Giemsa solution was used to stain the blood preparations. The preparations were wholly immersed in the solution and allowed to sit for 45 minutes. Subsequently, it was delicately rinsed under a stream of water at a 40-degree angle and then dried. The preparations were scrutinized using a microscope after being treated with immersion oil (10 x 100 magnification). Analysis of the blood smear slides will reveal the presence of malaria parasites, indicating an infection in the blood (Kakisina and Ukratalo, 2011).

Upon reaching a parasitemia level of 1%, the anti-malarial effectiveness of *Sargassum sp*. was seen. The house mice were divided into groups P1, P2, and P3, and the extract was administered for four consecutive days. On the sixth day, a surgical procedure was conducted to extract the livers of house mice.

Preparation of Histological

The liver cell preparation was conducted with Hematoxylin Eosin (HE) staining (Kaihena *et a.,* 2023). The collected samples were fixed in 10% NBF solution for a period of 24 hours. Subsequently, they underwent a dehydration process using a series of graded alcohol solutions, starting from 70% and gradually progressing to 80% and 96%. After dehydration, the samples were cleared using xylol and then subjected to the impregnation stage, being soaked in liquid paraffin for 12 hours. Tissues were cleaned with xylene and embedded in

paraffin. Using a rotary microtome, sections were cut at a nominal thickness of 5–6 µm and stained with hematoxylin and eosin to observe microscopic histopathological alterations and their severity. Histopathological observations of the liver were performed after staining using Hematoxylin and Eosin staining (HE staining) by taking 400x and 1000x magnification photos under a microscope Olympus.

Data Analysis

The histology of liver cells will be studied through a descriptive examination of sinusoids and hepatocytes in liver histology images (Kaihena *et a.,* 2023).

Result

Figures 1, 2, 3, and 4 demonstrate histological images of liver cells from house mice in the positive control group, *Plasmodium berghei*-infected house mice treated with a methanol extract of brown algae *Sargassum sp.*

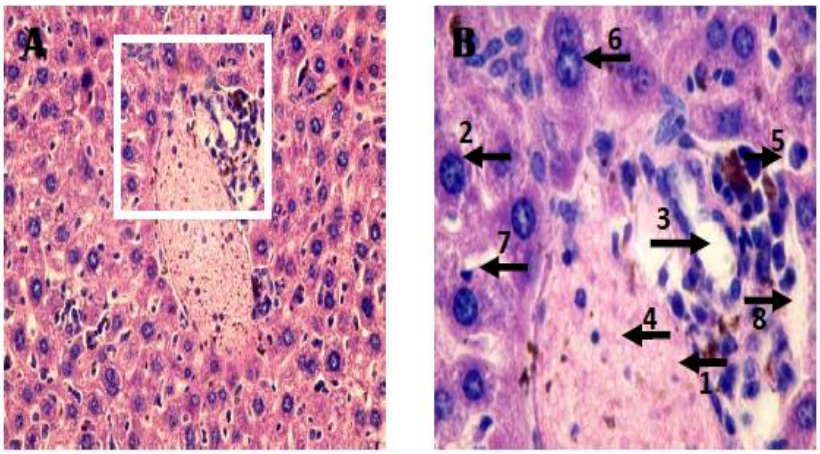

Figure 1. Liver cell histology of *Plasmodium berghei* infected house mouse (K+). (A) 400x magnification and (B) 1000x magnification. Notes: 1. Central vein, 2. Hepatocytes, 3. Sinusoids, 4. Inflammation of the central vein, 5. Hydrophic degeneration, 6. Necrosis, 7. Fatty degeneration, 8. Dilation of sinusoids

Based on observations in the positive control group injected with *Plasmodium berghei*, however, not given brown algae extract, the liver cells are damaged, namely (4) inflammation of the ventral vein, (5) hydrophilic degeneration, (6) necrosis, (7) fatty degeneration, and (8) sinusoid dilation.

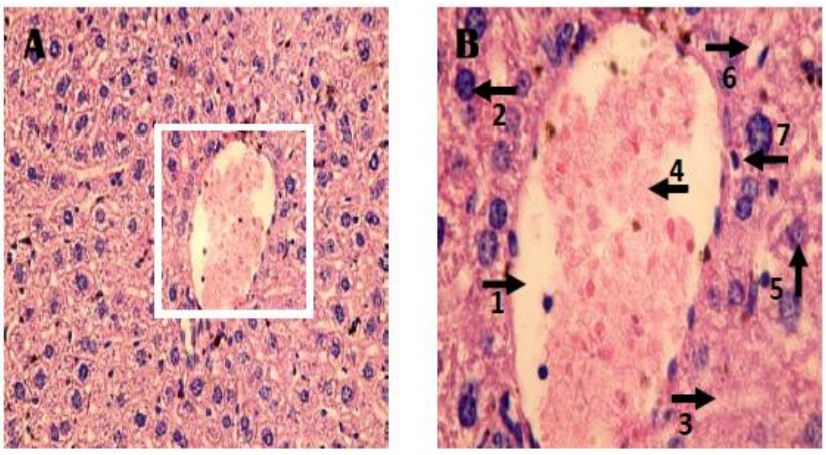

Figure 2. Liver cell histology of house mouse infected with *Plasmodium berghei* and treated with methanol extract of brown algae *Sargassum sp* at 10 mg/g BW. (A) 400x magnification and (B) 1000x magnification. Notes: 1. Central vein, 2. Hepatocytes, 3. Sinusoids, 4. Inflammation of central vein, 5. Necrosis, 6. Fatty degeneration, 7. Hydropic degeneration

Figure 2. demonstrates that the liver cells of house mice infected with *Plasmodium berghei* treated with methanol extract of brown algae *Sargassum sp* at a dose of 10 mg/g BW are still damaged. The presence of damage such as (4) inflammation of the ventral vein, (5) necrosis, (6) fatty degeneration and (7) hydrophic degeneration.

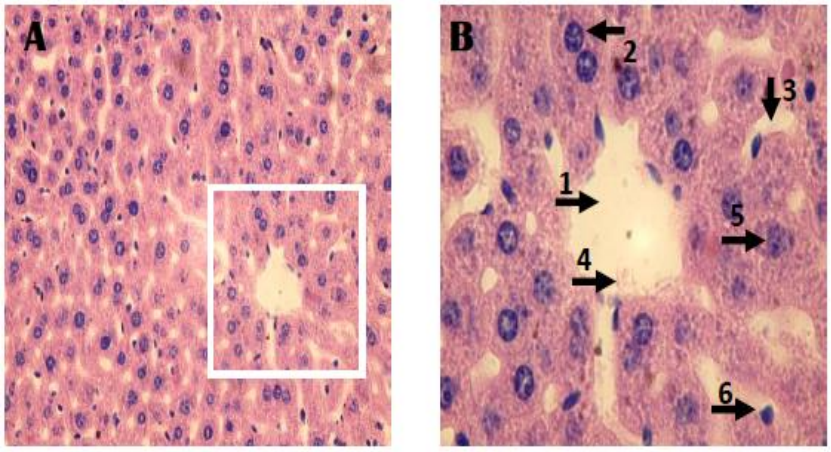

Figure 3. Liver cell histology of house mouse infected with *Plasmodium berghei* and treated with methanol extract of brown algae *Sargassum sp* at a dose of 100 mg/g BW. (A) 400x magnification and (B) 1000x magnification. Notes: 1. Central vein, 2. Hepatocyte, 3. Sinusoid, 4. Inflammation of central vein, 5. Necrosis, 6. Fat degeneration

In the group of house mice infected with Plasmodium bergei treated with methanol extract of brown algae Sargassum sp at a dose of 100 mg/g BW, liver cells improved. However, damage remained, such as (4) inflammation of the central vein, (5) necrosis, and (6) fatty degeneration.

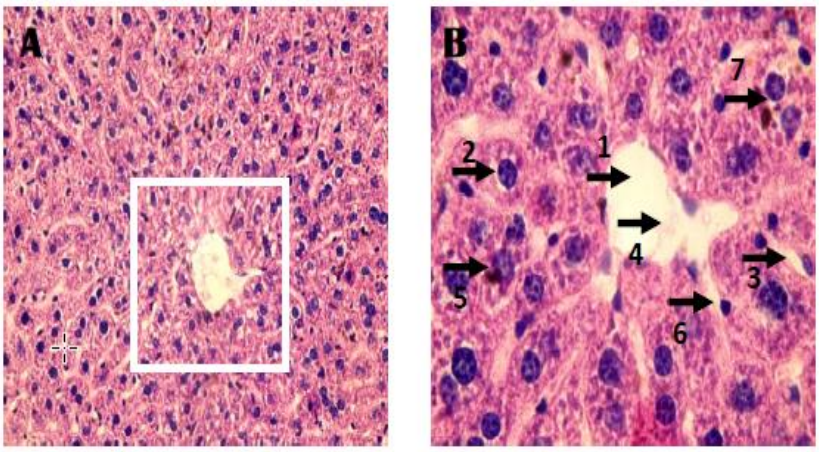

Figure 4. Histology of liver cells of house mouse infected with *Plasmodium berghei* and treated with methanol extract of brown algae *Sargassum sp* at a dose of 200 mg/g BW. (A) 400x magnification and (B) 1000x magnification. Notes: 1. Central vein, 2. Hepatocytes, 3. Sinusoids, 4. Inflammation of the central vein, 5. Necrosis, 6. Fatty degeneration, 7 Hydropic degeneration.

Figure 4. demonstrates that the hepatic cells in house mice are currently normal. The periphery of the central vein exhibits ongoing inflammation, accompanied by mild swelling and pycnosis in the hepatocyte nucleus.

Discussion

The infection of house mice with *Plasmodium berghei* leads to hepatic damage due to the parasite's initial development in the host's liver, followed by its entry into the bloodstream and subsequent onset of malaria. The investigation identified several types of damage, including inflammation of the central vein, hydrophic degeneration, necrosis, fatty degeneration, and dilatation of sinusoids. The onset of liver cell damage caused by *Plasmodium berghei* infection initiates at the cell membrane, as it is the primary point of contact with the external environment. Furthermore, the cell membrane serves as a conduit for transporting ions (namely sodium and potassium) and complex compounds. *Glutamate Pyruvate Isomerase* (GPI), a toxin found in malaria, can damage the cell membrane (Abd Majid, 2011). This damage can create an accumulation of sodium ions within the cell, leading to the movement of extracellular fluid into the cell. As a result, inflammation occurs in the ventral vein.

Upon reaching the liver, the *P. berghei* parasite invades hepatocytes, crucial liver cells. This infection can initiate a localized inflammatory reaction around the ventral vein, the primary drainage location from the liver (Figures 1, 2, 3, and 4). The inflammation can arise due to the immune system's reaction to the parasite and the cellular harm inflicted by the parasite. Infection with *P. berghei* can lead to hydrophic degeneration and liver cell injury, distinguished by fluid buildup within the cells (Figures 1, 2, 3, and 4). This can occur due to a biological reaction to the invasion of parasites, leading to alterations in the structure and function of liver cells. *P. berghei* parasites can directly invade and destroy liver cells, leading to necrosis or death of these cells. Necrosis occurs when cell organelles are directly damaged,

leading to an abnormal drop in cell quantity and alterations in cell morphology that range from the breakdown of cell proteins to the solidification of cell proteins.

Infection with *P. berghei* can also lead to hepatic steatosis, characterized by fat accumulation in liver cells. The presence of metabolic changes and stress caused by the infection, along with inflammatory responses and structural alterations in the liver, can account for this phenomenon. Sinusoids are small blood veins in the liver that facilitate the transfer of chemicals between the blood and hepatocytes. Infection with *P. berghei* can result in inflammation and structural alterations in the vicinity of the sinusoids, which can lead to dilatation or other pathological modifications, ultimately impacting blood circulation and liver functionality (Khovidhunkit *et al.*, 2004; Basir *et al.*, 2011; Mei *et al.*, 2020)

Figures 3 and 4 demonstrate that administering brown algae extracts at doses of 100 mg/g BW and 200 mg/g BW resulted in a significant reduction in cellular damage in the affected cells of the house mice, bringing the damage level close to the normal state. This phenomenon is believed to occur because T cells, functioning as regulators, stimulate cytotoxic T cells, macrophages, and other phagocytes through the T helper-1 (Th-1) cell subset. The Th-1 subset activates cellular immunity by secreting *Interferon* (IFN) and *Tumour Necrosis Factor* (TNF), stimulating the activity of macrophages, monocytes, and leukocytes. The phagocytes will generate reactive oxygen species, including NO, H2O2, singlet O2, and OH-, which will impede the growth and deterioration of parasites by inducing oxidative stress. Th-1 stimulates the activation of *Nature Killer* (NK) cells through the mechanism of *Antibody-Dependent Cellular Cytotoxicity* (ADCC). ADCC is a mechanism by which antibodies act against parasites facilitated by eosinophil cells (Tizard, 2000). Typically, these antibodies adhere to the parasite, facilitating its phagocytosis. The Th-1 subset will trigger targeted and non-targeted cellular immune responses to eliminate Plasmodium parasites within red blood cells (Pawłowska *et al.*, 2023).

Moreover, the presence of natural antioxidants, including flavonoids, saponins, tannins, and alkaloids, in brown algae, *Sargassum sp*, is crucial for suppressing the growth of *Plasmodium berghei* and safeguarding the integrity of house mouse liver cells. Flavonoid molecules are potent antioxidants that can act as scavengers of Reactive Oxygen Species (ROS). Antioxidants collaborate sequentially to facilitate redox processes. Flavonoids have demonstrated their capacity as antioxidants, antimutagenics, antineoplastics, and vasodilators. Flavonoids possess significant antioxidant properties that make them valuable for managing various diseases by mitigating oxidative damage.

Conclusion

Based on the results and discussion, it can be concluded that administering *Sargassum sp.* extract significantly improved liver cell damage in mice infected with *Plasmodium berghei*. This was evidenced by histopathological observations, which showed structural and functional improvements in liver cells after the extract administration, as indicated by the reduction in liver tissue damage. Given the ability of *Sargassum sp.* extracts to repair liver damage caused

by malaria infection, it can be considered a potentially effective natural therapy, which not only has the potential to reduce liver organ damage but also supports overall body health recovery.

Declaration of conflicting interest

The authors declare that there is no conflict of interest in the implementation and results of this research.

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