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Effect of Methanol Stem Bark Extract of *Ficus Trigonata* on Lipid Profile and Liver Function Indices in Mice Infected with *Plasmodium Berghei*

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Abstract

Antioxidant activity of methanol extract of Ficus trigonata stem bark and its effect on serum lipid profile and liver function parameters in Plasmodium berghei infected mice were investigated. In-vitro antioxidant activity of the methanol stem bark extract of the plant was determined using Ferric Reducing Antioxidant Power (FRAP) assay. Thirty (30) adult mice were separated into six (6) groups, each containing five (5) mice. Group I is the naive group, given only water and normal feed, Group II is the negative control, infected and untreated, Group III is the standard control, infected and treated with standard drug (chloroquine) while Group IV, V and VI, infected and treated with the methanol extract of Ficus trigonata stem bark for a duration of 5 days. Determination of lipid profile and liver enzyme markers were performed by standard procedures. The results clearly revealed that, the extract had good antioxidant activity with an IC_{50} of 2.31 mg/ml even though significantly less than that of ascorbic acid at P<0.05. The elevated serum Triacylglyceride (TAG), Total Cholesterol (TC), Low-Density Lipoprotein (LDL), Alanine Transaminase (ALT), Aspartate Transaminase (AST), Alkaline Phosphatase (ALP), Total Protein and Total bilirubin levels observed were significantly (P<0.05) decreased by the extract compared to infected and untreated group. However, the decreased serum High-Density Lipoprotein (HDL) and Albumin levels observed were significantly (P<0.05) elevated by the extract compared to infected and untreated group. Conclusively, the plant extract clearly revealed the potentials to restore a stable lipid profile and liver function markers in mice infected with Plasmodium berghei.

Keywords: Antioxidant, Ficus trigonata, Lipid, Liver and Stem bark

INTRODUCTION

Malaria poses a significant global public health concern, with a widespread impact on numerous countries worldwide. Annually, there are more than 200 million reported cases of malaria, resulting in over 420,000 fatalities (Laryea and Borquaye, 2019). This disease is prevalent in over 90 countries, placing approximately 40% of the global population either at risk of infection or directly affected by it. In sub-Saharan Africa, where a staggering 90% of all cases and fatalities from malaria are reported, the majority of the disease's morbidity and mortality are concentrated. Within this region, the pregnant women and children under the age of five are the group that are most vulnerable (Laryea and Borquaye, 2019).

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Upon being bitten by female anopheles mosquitoes, Plasmodium parasites embark on a voyage through the bloodstream, maturing before initiating reproduction within the liver. This complex life cycle ultimately culminates in the onset of characteristic malaria symptoms, which encompass manifestations such as headaches, pain, nausea, fever, weakness, abdominal discomfort, and profuse perspiration. When left untreated or inadequately managed over an extended period, malaria can give rise to severe complications, including but not limited to brain tissue damage, pulmonary edema, kidney failure, severe anemia and jaundice, characterized by yellow discoloration of the skin (Erhirhie *et al*., 2021).

A unicellular parasite (protozoan) that affects animals besides humans is called *Plasmodium berghei*. It is one of the four species of plasmodium that have been identified in African murine rodents. The other three species are *Plasmodium vinckei, Plasmodium chabaudi* and *Plasmodium yoelii,* and none of them directly affect domestic animals or humans. These parasites are of importance because they are useful model organisms for studying human malaria experimentally in the laboratory (Howick *et al.,* 2019).

Due to an increase in reactive oxygen species (ROS) production, both the host and the parasite experience oxidative stress during a malaria episode. Reactive oxygen species (ROS) may result in beneficial or detrimental effects on malaria, depending on production site and amount. It is well known that ROS may damage tissue by promoting lipid peroxidation and breaking down macromolecules (Loha *et al.,* 2019). ROS stimulates inflammation because it modifies cytokines and other mediators of the inflammatory process. Given the correlation between reactive oxygen species (ROS) and inflammation in malaria, substances or extracts that target parasite cells rather than host cells while absorbing ROS may have potential benefits (Adeniyi *et al.,* 2018).

Hepatocellular dysfunction due to malaria is indicated by elevated blood levels of aminotransferases and bilirubin that surpass the upper limit of normal ranges by three times. Malarial hepatopathy is linked with an increased risk of shock, acute renal damage, cerebral malaria and acute respiratory distress syndrome (ARDS). Patients of all ages can experience it, however adults experience it more frequently. One potential cause of malarial hepatopathy is activation of the liver macrophages that digest hemoglobin or infested erythrocytes. In every malarial nodule, cholestasis, granulomatous lesions and focal hepatocyte necrosis have been reported. Histopathological alterations such as hepatocyte destruction, hepatic cell congestion, inflammatory infiltrates, hemoglobin accumulation, and cholestasis have been shown in malaria patients exhibiting jaundice (Scaccabarozzi *et al*., 2018).

Individuals infected with malaria have a variety of metabolic disturbances, such as changes to their serum lipid composition. As it multiplies inside the liver cells, Plasmodium has the ability to "salvage cholesterol" from the host cells. Hepatocellular damage caused by malaria parasites results in anomalous hepatic lipid management, making the liver incapable of preserving the lipid and lipoprotein metabolism equilibrium. Derangements in the plasma lipid profile result from this effect of the hepatocellular damage (Warjri *et al.,* 2016). A recent meta-analysis research on malaria has demonstrated that alterations in serum lipid levels are a defining hallmark of the illness. Individuals suffering with malaria exhibit hypocholesterolemia, reduced levels of HDL and LDL cholesterol, and elevated amount of very low-density lipoproteins (VLDL) and triglycerides in conjunction with these changes. These temporary lipid abnormalities can occur in both complex and non-complicated Plasmodium cases, including the most common species (Dias *et al.,* 2016).

Plants serve as a valuable repository of bioactive secondary metabolites, often referred to as natural products. Notably, certain essential anti-malarial drugs, such as quinine and artemisinin (AT), have botanical origins (Pinheiro *et al*, 2019). They are typically used in the creation of treatments for inflammation, fever, and malaria. Remarkably, more than 80% of the indigenous populace in many tropical areas, including communities in Africa, still rely on medicinal plants to cure a variety of ailments, including malaria. Despite the fact that standard malaria medications are widely accessible in both rural and urban settings, this dependency continues (Okello and Kang, 2019).

The *Ficus trigonata* (L.), a remarkable evergreen tree, known by various local names such as banyan, black fig, and jaguey blanco, holds a special place in Northern Nigeria, where it is referred to as "cediya" (Wael *et al*., 2014). This botanical treasure, the Black Fig, has been at the center of traditional and pharmacognosy practices. Extensive historical usage has credited its bark, leaves, seeds, fruits, roots, and latex with curative properties, spanning the treatment of amnesia, gonorrhea, inflammation, ulcers, and a host of other conditions (Reddy and Vadde, 2021). Beyond folklore, scientific investigations have unveiled the multifaceted potential of Black Fig, with reports indicating its anti-HIV, acetylcholinesterase inhibitory, anti-lipid peroxidative, and anti-diabetic activities. The bark extract exhibits exceptional qualities by inhibiting the entry and production of the herpes simplex virus type 2 while protecting the liver against hepatotoxicity and promoting wound healing. The root extracts of *Ficus religiosa,* a close relative, have shown a dose-dependent ability to protect against seizures from various causes, making it a promising candidate for neurological disorders (Reddy and Vadde, 2021). Based on the available information no scientific evidence reported on the effect of the *Ficus trigonata* stembark on lipid profile and liver function parameters in *Plasmodium berghei* infected mice, hence the need for this study. By examining the extract's antioxidant activities, its impact on lipid profiles and liver function indices, this research seeks to shed light on potential therapeutic applications and insights for addressing the health challenges posed by malaria.

MATERIALS AND METHODS

Study Area

The study was conducted in the Laboratory of the Department of Biochemistry, Faculty of Life Sciences, Modibbo Adama University, Yola, Adamawa state, Nigeria.

Collection of Plant material

Ficus trigonata stem bark was obtained from Song Local Government in Adamawa State, Nigeria. An identification of the specimen was made by a botanist from Plant science Department, Modibbo Adama University, Yola, Adamawa state, Nigeria.

Experimental animals

Five to six weeks old mice, thirty (30) in number, were acquired from the National Veterinary Research Institute, Vom, Plateau State. They were placed in plastic cages with bedding made of softwood shavings and chips. They were provided with clean drinking water and feed. The working setting was gradually introduced to all animals one week prior to the start of the experiment.

Parasite Strain

Malaria induction was carried out in experimental mice using *Plasmodium berghei* (NK-65) strain (chloroquine-sensitive), purchased from the National Institute of Medical Research (NIMR), Yaba Lagos, Nigeria. The donors were mice that had already contracted *P. berghei*.

Extraction of Plant material

The stem bark of *Ficus trigonata* was dried for two weeks, and the dried plant material was ground into fine powder. Eighty (80) grams of the powder was soaked in methanol (250 mL) and placed in an orbital shaker for 72 hours. The methanol extract was filtered with a muslin cloth, and the filtrate was evaporated to dryness in a temperature-regulated water bath preset at 40◦C.

Determination of *in vitro* Antioxidant Activity

Ferric Reducing Antioxidant Power (FRAP)

The Ferric reducing antioxidant power (FRAP Assay) was determined according to the procedure of Banerjee *et al*., (2008) with slight modification. In a separate test tube, at different concentrations of precisely 1 mL of the test sample extract was combined with 1 mL of the 2M sodium phosphate buffer (pH 6.6) and 1 mL of the 1% potassium ferric cyanide. After 20 minutes of incubation at 50^0C in a temperature-controlled water bath, 1 mL of 10% trichloroacetic acid was added to the reaction. After that, the mixture was centrifuged at room temperature for ten minutes. Exactly, 1 mL of deionized water and 200 mL of 0.1% $FeCl_3$ were mixed and added to the 1 mL of supernatant that had been produced. The preparation of the blank was identical to that of the sample, with the exception that distilled water was used in place of the 1% potassium ferricyanide. At 700 nm, the reaction mixture's absorbance was measured.

FRAP radical scavenging (%) = [Absorbance (control) – Absorbance (sample) / Absorbance control] x 100

Parasite Inoculation

Through cardiac plexus puncture, parasitized erythrocytes were obtained from donor mice and diluted with trisodium citrate. On day 0, mice received an intraperitoneal injection of 0.2 ml of blood solution containing 10^6–10^7 parasitized erythrocytes.

Animal Grouping

Adult mice, thirty (30) in number, used for the study were separated into six (6) groups, each containing five (5) mice. Group I is the naive group, given only water and normal feed, Group II is the negative control, infected with *Plasmodium berghei* and untreated, Group III is the standard control, infected and treated with standard drug (chloroquine) while Group IV, V and VI, infected and treated with the methanol extract of *Ficus trigonata* stem bark at concentrations of 100 mg, 200 mg, and 300 mg of extract/kg BWT respectively for a duration of 5 days. After treatment and observation, the mice were fasted overnight and on day 6, they were anaesthetized using diethyl ether before they were sacrificed.

Blood Sample Collection

After a cardiac puncture, blood was collected, allowed to clot and centrifuged for five minutes at 3000 rpm and 4°C to separate the serum for lipid profile and liver enzyme markers analysis.

Determination of Lipid profile and Liver function Indices

Triglyceride was measured with a Randox Kit and Spectrophotometer. Enzymatic colorimetric technique was used to measure cholesterol following the report of National Cholesterol Education Program study. The sample was treated with phosphotungstic acid and magnesium ions to precipitate low-density lipoproteins (LDL). Only the high-density lipoproteins (HDL) remained in the supernatant after centrifugation; their total cholesterol content was determined (Li *et al*., 2015). The alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and direct and total bilirubin were

measured in accordance with the instructions provided by the manufacturers of the test kits. The procedure described by Doumas *et al.* (1971) was used to measure the serum total protein content and albumin level (Tietz, 1995).

Data Analysis

Students' package for social sciences (SPSS) version 20 computer software was used for the analysis of data, values were reported as Mean + SEM, subjected to analysis of variance (ANOVA) and statistically regarded as significant at $P < 0.05$.

RESULTS

Antioxidant Activity of the Methanol Stem Bark Extract of *Ficus trigonata*

All of the extract's concentrations 0.2, 0.4, 0.6, 0.8, and 1.0 milliliters had significantly less antioxidant activity than ascorbic acid at $P<0.05$. However, as the concentration increases so also the antioxidant activity of the extract. The IC_{50} obtained is 2.313 mg/ml as presented in table 1.

Table 1: Antioxidant activity of methanol extract of *Ficus trigonata* stem bark

Concentration (ml)	*Ficus trigonata* (%)	Ascorbic acid (%)
0.2	42.837±0.75 [a]	99.757±1.27
0.4	45.923±1.05 [a]	99.544±0.40
0.6	47.482±0.48[a]	99.350±0.92
0.8	64.066±1.07 [a]	99.170±0.64
1.0	84.542±0.83 [a]	97.180±0.75

IC_{50} = 2.313 mg/ml

Values were expressed as Mean + SEM, n=3

Values found in the same column with [a] superscript were significantly lower than Ascorbic acid at $P< 0.05$

Effect of Methanol Extract of *Ficus trigonata* Stem Bark on Lipid Profile of *Plasmodium berghei* Infected Mice.

As presented in Figure 1, the findings made revealed that, the increased levels of LDL, TC and TAG observed in the negative control were significantly decreased at $P<0.05$, following the treatment with the extract at different concentrations. The higher concentration of the extract, 300mg/kgBW gave better effect compare to others. However, the decreased HDL level observed was significantly ($P<0.05$) elevated by the extract with higher concentration (300mg/kgBW) giving a better effect compare to others.

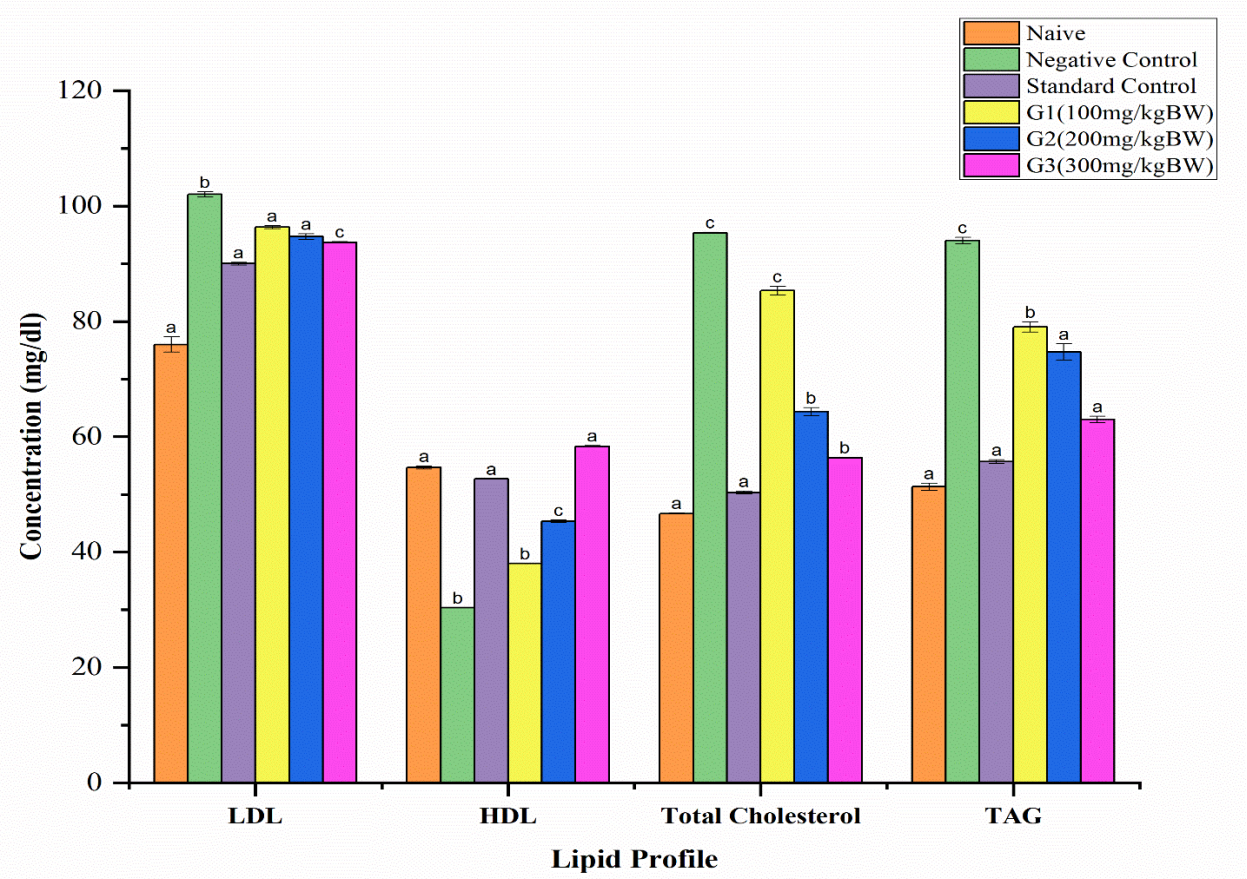

Figure 1: Effect of methanol extract of *Ficus trigonata* stem bark on the lipid profile in *Plasmodium berghei* infected mice.

Where: a indicates values significantly greater than the naive control at P<0.05
b indicates values significantly less than the naive control at P<0.05
c indicates values significantly greater than the negative control at P<0.05
d indicates values significantly less than the negative control at P<0.05
LDL= low density lipoprotein, HDL=High density lipoprotein and TAG=Triglyceride

Effect of methanol extract of *Ficus trigonata* stem bark on Liver Function Indices in *Plasmodium berghei* infected mice.

The increase in ALT, AST, ALP, and TB levels observed in the negative control group after infection without treatment were significantly (P<0.05) lowered after treatment with the extract at different concentration. The higher concentration (300mg/kg BW) of the extract gave more effect than other concentration. However, the decreased albumin level observed was significantly (P<0.05) elevated with also higher concentration (300mg/kg BW) of the extract giving more effect when compared to other. These observations are presented in Figure 2.

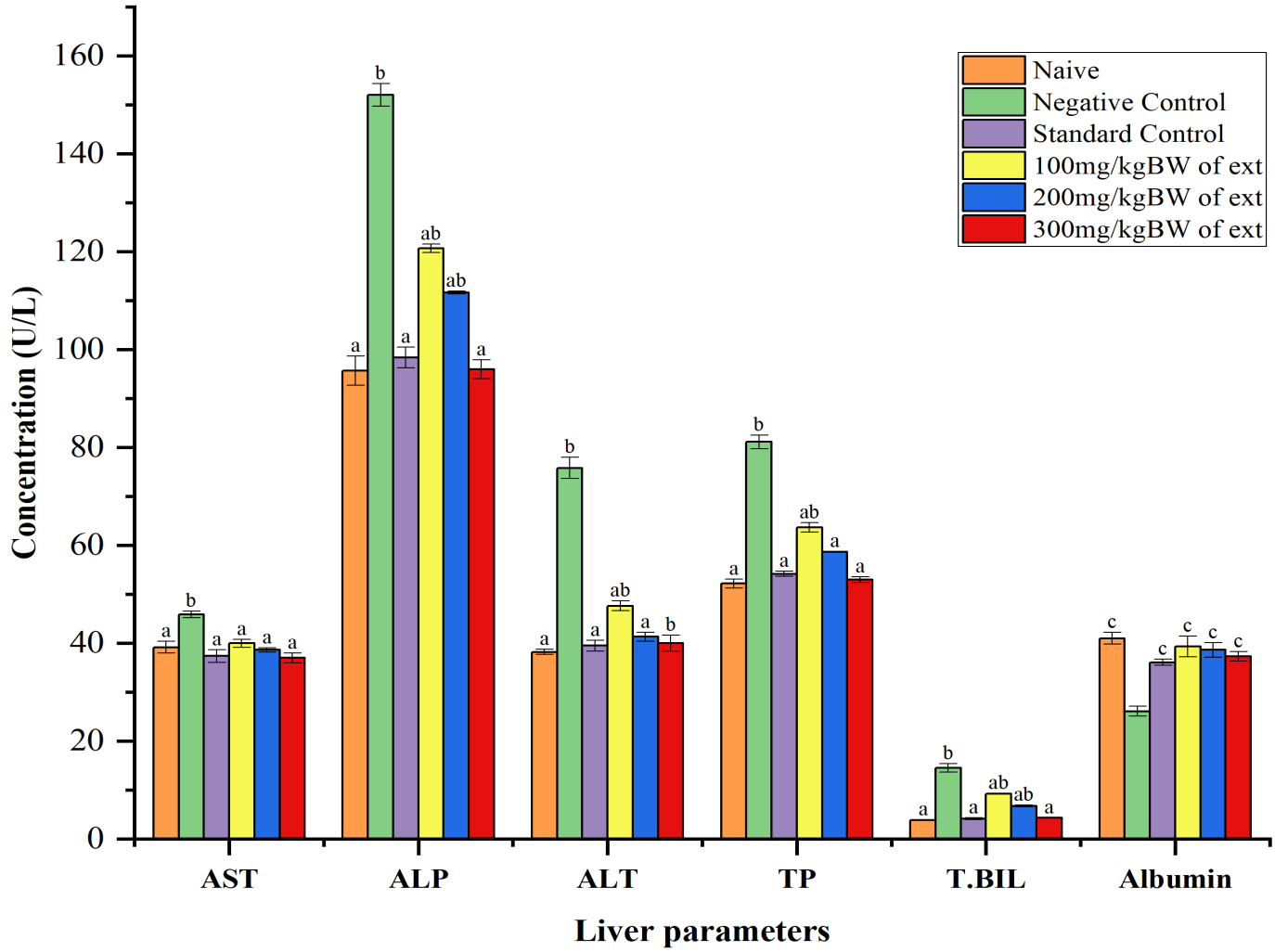

Figure 3: Effect of methanol stem bark extract of *Ficus trigonata* on Liver Function Indices in mice infected with *Plasmodium berghei*.

Where "a" indicates values significantly less than negative control at P<0.05
"b" indicates values significantly greater than normal (Naive) at P<0.05
"c" indicates values significantly greater than negative control at P<0.05
"ab" indicates values significantly greater than normal but less than negative control at P<0.05

DISCUSSION

Antioxidant potential of the methanol extract of *Ficus trigonata* stem bark was clearly established in this study. However, it is important to note that this plant extract's antioxidant activity is lower when compared to ascorbic acid, a well-known and potent antioxidant reference. The plant's effect on antioxidant activity is concentration-dependent, which is an impressive pattern that was noted. The antioxidant property of the plant extract increased along with its concentration. This implies that the plant extract's antioxidant capacity is probably dose-dependent, with larger concentrations perhaps producing better effectiveness. These observations are consistent with other studies on plant extracts having antioxidant capabilities. Similar concentration-dependent increase were found by Wael, *et al*. (2014). This might be related to the plant's phenolic chemicals, which Abdel-Hameed (2009) gave as reasons for the antioxidant activities of the plant.

Increased LDL, total cholesterol and triglyceride and decreased HDL levels were noticed in this present study. These observations are in agreement with findings made in other studies (Joseph and Chukwudozie 2015; Rajyalakshmi *et al*. 2019; Kingsley *et al*. 2022). The alterations in lipid profile observed after infection with *P. berghei* in this study which were reversed after treatment with the extract may be attributed to the antioxidant properties of the plant. These antioxidants help in preventing lipid oxidation and oxidative damage. Numerous studies have reported the importance of antioxidant vitamins in impeding the progression of atherosclerosis, a condition associated with elevated lipid levels (Achuba, 2005). Moreover, there is substantial evidence suggesting that vitamin C and vitamin E have the potential to increase HDL-cholesterol levels and reduce total cholesterol in the blood. By doing so, they contribute to a decreased risk of cardiovascular disease (Egbung *et al*., 2011). The antioxidant-rich *Ficus trigonata* extract may have had a considerable impact on the lipid profile of the treated mice, according to the findings of this study, which makes sense given the context of the extract's antioxidant activity. This may suggest the extract's capacity to inhibit lipid peroxidation and oxidative damage, which in turn may have contributed to the observed ameliorative effects against the alterations brought on by dyslipidemia caused by malaria.

Increased levels of alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), total protein and total bilirubin after infection with *P. berghei* found in this present study may be attributed to cellular response to the parasitemia or hepatic dysfunction caused by the infection. This observation is in agreement with that reported by William *et al*., (2022) that, the elevated biochemical markers of infected mice but untreated may be due to hyper-parasitemia cellular response. Oh *et al*., (2017) also reported that, increased serum ALT and AST activities observed in infected mice might result from hepatic dysfunction or hepatic damage. In other findings, it was also reported that, patients with liver dysfunctions showed elevation in serum enzyme activities (Enemchukwu *et al*., 2014; Al-Salahy *et al*., 2016; Sidiki *et al*., 2023). The elevated levels of these liver function indices observed in this study were significantly restored after treatment with the extract. This observation might suggest the ability of the extract to help repair hepatic parenchyma and regeneration of hepatocytes as reported by William *et al*. (2022) that serum liver enzymes levels will be restored to normal after the repair of hepatic parenchyma and regeneration of hepatocytes.

CONCLUSION

The results of this investigation clearly demonstrated that, the methanol stem bark extract of *Ficus trigonata* has significant antioxidant characteristics and showed promise in reducing changes in the lipid profile and liver function indices in mice infected with *Plasmodium berghei*. These results provided a strong rationale for further exploration of this extract as a potential therapeutic agent for malaria-related complications.

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