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Changes Associated with Treatment of *Plasmodium berghei* Infected Mice with *Momordica charantia*, *Xylopia aethiopica* and *Entandrophragma angolense* Leaf Extract

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Authors' contributions

This work was carried out in collaboration among all authors. Authors FAK, OJO and MAA designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors FAK, MAA and OBO managed the analyses of the study. Authors OBO, SFA and AOO managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aim: Leaves of plants have been useful in the treatment of various diseases and infections. The study aims at determining the nephrotoxicity, hepatotoxicity, and hematological effect of *Momordica charantia*, *Xylopia aethiopica*, and *Entandrophragma angolense* on the *Plasmodium berghei* infected mice.

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Study Design: The plants' leaves were air-dried and extracted. Forty-two Swiss male mice, 18 to 25 g, were grouped into six of seven mice each. Group I was uninfected but were administered with normal saline for four days, Group II to VI were all infected with *P. berghei* and administered with normal saline, 300 mg/b.w. of *M. charantia* leaf extract, 300 mg/b.w. of *E. angolense* leaf extract, 300 mg/b.w. of *X. aethiopica* leaf extract and 40 mg/b.w. of chloroquine injection for four days, respectively.
Results: The treatment groups showed a lower level of toxicity when compared with chloroquine treatment. *X. aethiopica* has the greatest positive impact on the PCV level of the experimental animals of its treated group compared with other groups.
Conclusion: Our findings confirmed the antimalarial potential of *X. aethiopica* and thus can be used to treat malaria without anemia as a side effect.

Keywords: Momordica charantia; xylopia aethiopica; entandrophragma angolense; plasmodium berghei, malaria.

1. INTRODUCTION

Malaria is an infectious disease that continues to be associated with considerable morbidity and mortality and significant social and economic impact in developing countries. Malaria is largely caused by *Plasmodium falciparum* while the malaria caused by *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae* is generally a milder disease that is rarely fatal [1]. *Plasmodium knowlesi* is a zoonosis that causes malaria in macaques which can also infect humans [2,3].

Malaria infection develops serious systemic complications such as hematological abnormalities, splenomegaly, hepatitis, and hepatic dysfunction [4]. Changes in hematological indices result in diverse degree of anemia. The infection of red blood cells by malaria parasites may lead to structural, biochemical, and physiological modifications of the red blood cells therefore, resulting in some life-threatening symptoms of malaria. Moreover, malaria parasites attack the red blood cell thereby causing their lyses which may result in reduced hemoglobin level and packed cell volume [5]. The rapid drop in hemoglobin during acute infection and the slower decline in chronic infection appear to be due to increased extravascular hemolysis of red blood cell (RBCs) with a concomitant failure of the bone marrow to increase red cell production to compensate for these losses [6].

Another species of Plasmodium is *Plasmodium berghei* parasite often used in predicting the treatment outcomes of any suspected antimalaria agent due to its high sensitivity to chloroquine thereby making it an appropriate parasite for this study [7]. *Plasmodium berghei* have been used in studying the activity of potential antimalarials in mice because it produces diseases like those of human plasmodium infection [8,9].

Despite all efforts by various scientists in the prevention and treatment of malaria, the recent widespread resistance of *Plasmodium falciparum* to the currently available anti-malarial drugs like chloroquine and ACT; the resistance of the mosquito vectors to the current conventional insecticides; the serious setback in the development of malaria vaccines and the rampant adverse reactions of some conventional anti-malarial drugs poses some challenges to the breakthrough. Plants have always been a possible alternative and rich source of new drugs because of its availability and affordability as the search for malaria remedies with plants and improved interest in plant drugs by many communities staying in endemic area are on the increase.

Momordica charantia, commonly known as bitter melon or bitter gourd is tropical and subtropical climber of the family *Cucurbitaceae*. All parts of the plant, including the fruit taste very bitter, as it contains a bitter compound called momordicin that is believed to have a stomachic effect [10].

Xylopia aethiopica or Ethiopian pepper as it is usually called, is an angiosperm belonging to the family Annonaceae and is among the species that thrive in the evergreen rain forests of tropical and subtropical Africa. *Xylopia aethiopica* has a wide spectrum of biological activities and have played a crucial role in traditional medicines because of their valuable physiological and pharmacological properties [11].

Entandrophragma angolense or commonly known as Tiama Mahogany is a tropical,

deciduous buttressed tree growing up to 50 m in height with 5 m trunk diameter. The bark of the tree is used to make decoction to treat fever [12]. The bark is harvested from the wild for local medicinal use. The bark is also used, usually in external applications, as an anodyne against stomach-ache and peptic ulcers, earache, and kidney, rheumatic, or arthritic pains [12].

This study aims to provide scientific data that will substantiate the effect of the three plants extract on kidney and liver functioning enzymes as well as the hematological parameter of malaria infected mice.

2. MATERIALS AND METHODS

2.1 Drugs, Animal and Diet

Chloroquine injection was product of Bliss GVS Pharma Limited, India. Forty-two Swiss mice of male sex weighing between 18-25 g were obtained from the animal house of IMRAT, College of Medicine, University of Ibadan, Oyo State, Nigeria. The mice were fed with standard mice pellets (Top Feed Nigeria Ltd., Ibadan, Nigeria) and water and were acclimatized in improvised cages for fourteen days at the animal house of IMRAT, College of Medicine, University of Ibadan, Oyo State.

2.2 Acute Toxicity (LD_{50}) of the Methanol Extract

The acute toxicity of the methanol extracts of was determined according to Lorke's method [13].

2.3 Collection and Extraction of Plant Sample

The three-plant samples were collected from a botanical garden at Ode Remo, Ogun State, Nigeria. The *Momordica charantia, Xylopia aethiopica,* and *Entandrophragma angolense, Plasmodium berghei* samples were identified and authenticated and voucher numbers GP/MC/19/001, GP/XA/19/002 and GP/EA/ 19/003 were assigned, respectively. It was air dried and ground into powder form. Five grams of each grounded material were extracted using 250 ml of methanol using Soxhlet extractor. The resulting crude extract obtained was concentrated at 40°C in a rotary evaporator. It was later dissolved again in distilled water (w/v) for its dose preparation.

2.4 Parasites

Samples of chloroquine sensitive *Plasmodium berghei* were obtained from IMRAT, College of Medicine, University of Ibadan, Oyo, Nigeria, maintained by sub-passage and used for the infection of malaria in mice under study.

2.5 Experimental Design Pellets

The mice were randomly divided into six groups of seven male mice each. The animals were weighed and fed with and water ad-libitum throughout the study.

Group I (CTRL) was administered with normal saline; Group II (IF) were induced with the chloroquine-resistant strain of *P. berghei* NK-65 and subsequently administered with normal saline throughout the period of the research; Groups III-VI were induced with the chloroquine-resistant strain of *P. berghei* NK-65. Group III (MCIF) were subsequently intraperitoneal administered with 300 mg/kg body weight of *Momordica charantia* extract for four days; Group IV (ECIF) were subsequently intraperitoneal administered with 300 mg/kg body weight of *Entandrophragma angolense* extract for four days; Group V (XAIF) were subsequently intraperitoneal administered with 300 mg/kg body weight of *Xylopia aethiopica* extract for four days; and Group VI (CQIF) were subsequently intraperitoneal administered with 40 mg/kg body weight of chloroquine injection for four days.

Twenty-four hours after the last administration, the animals were anaesthetized. Blood samples were collected by cardiac puncture and then centrifuged while the plasma was kept clean in a specimen bottle stored frozen. The animals were dissected to surgically remove the liver and kidney rinsed in iced cold 0.9% normal saline, blotted dry, homogenized, and later centrifuged. The supernatants were kept in a clean bottle and stored frozen.

2.6 Nephrotoxicity Determination

Creatinine concentration was determined by Jaffe kinetic assay [14]. Urea concentration was checked by Berthelot's reaction [14]. Total protein and Serum albumin were determined by Biuret method [15] and Doumas et al. [16] method, respectively.

2.7 Hepatotoxicity Determination

Alkaline phosphate was assayed by the phenolphthalein method as previously described [17,18]. Aspartate amino transferase was measured by monitoring the concentration of oxaloacetate hydrazine formed with 2,4 dinitrophenyl hydrazine according to the method of Obianime and Aprioku [19] and Reitman and Frankel [20] Alaline amino transferase was measured as described by Osonuga, et al. [21].

2.8 Hematological Tests

The blood samples were assayed for the packed cell volume (PCV), hemoglobin (HB), red blood count (RBC), white blood count (WBC) using the method used by Dacie and Lewis [22].

2.9 Statistical Analysis

The data were analyzed using SPSS version 22.0 and the values were expressed as Mean ± SEM (Standard Error of Mean). GraphPad Prism Version 5.0 for Windows (GraphPad Software, San Diego, CA, USA) was used for plotting of the graphs. The means of the groups were compared using one-way ANOVA (Analysis of Variance) and level of significance was determined using Duncan Multiple Range Test (DMRT) AT $P<0.05$.

3. RESULTS AND DISCUSSION

3.1 Acute Toxicity (LD_{50}) of the Methanol Extract

The LD_{50} of the methanolic extracts of the plants were calculated a 300 mg/Kg body weight.

3.2 Effect of the Medicinal Plants on Body Weight

Malaria is one of the most devastating parasitic disease affecting all countries of the world especially African countries which has increase mortality rate in the region. Since no vaccine has yet to be discovered to eradicate malaria infections, research has been focused on plants as a source of medicine to cure malaria infection. Medicinal plants have been found to contain phytoconstituents of relevance to phytomedicine [11,22,23]. Plants have provided active ingredients of medicine for years and are still source of lead compounds in the development of new therapeutics [24]. This research studies the effect of *M. charantia, E. angolense, X. aethiopica* and chloroquine on the weight, kidney, and hematological parameters of *P. berghei* infected mice.

The control groups gain weight progressively till the end of the experimental day seven whereas a decrease was observed in all other groups of experimental animals that were infected with *Plasmodium berghei* (Fig. 1). The change in weight after treatment showed that malaria parasitemia was associated with weight loss. The weight loss in untreated mice is most probably due to the deleterious effects of malaria parasitemia and the appetite depressant action on mice, the disturbed metabolic function. This is in line with the observation of Fidock et al. [25] and Uraku [26].

3.3 Effect of the Medicinal Plants on Hematological Parameters

The result of this study showed an insignificant decrease in these parameters in the untreated group when compared with the treated and control groups. The result of this study showed a decrease in percentage PCV in group II compared to the Group I (Control Group). In comparing the effect of *M. charantia, E. angolense* and *X. aethiopica*; the *X. aethiopica* showed a marked increase ($P>0.05$) in the PCV level after treatment for four days. The increase in PCV observed with *X. aethiopica* can probably be associated with the presence of phytochemicals in the plant extract which have strong antihemolytic effects. The result of this research also showed that the methanolic extract of *X. aethiopica* is more effective in increasing the PCV level compared to chloroquine.

WBC as well as other cells are involved in the body's immune system and help to fight disease [27]. Though an increase in WBC has been demonstrated to be linked to severe malaria, the increase in the WBC can be attributed to the role it plays during infection. They play a vital role in the body's immune system which is the primary defense mechanism against invading bacteria, viruses, fungi, and parasites. White blood cells function mainly to fight infection, defend the body by phagocytosis against invasion by foreign organisms, and to produce, transport and distribute antibodies in the immune response.

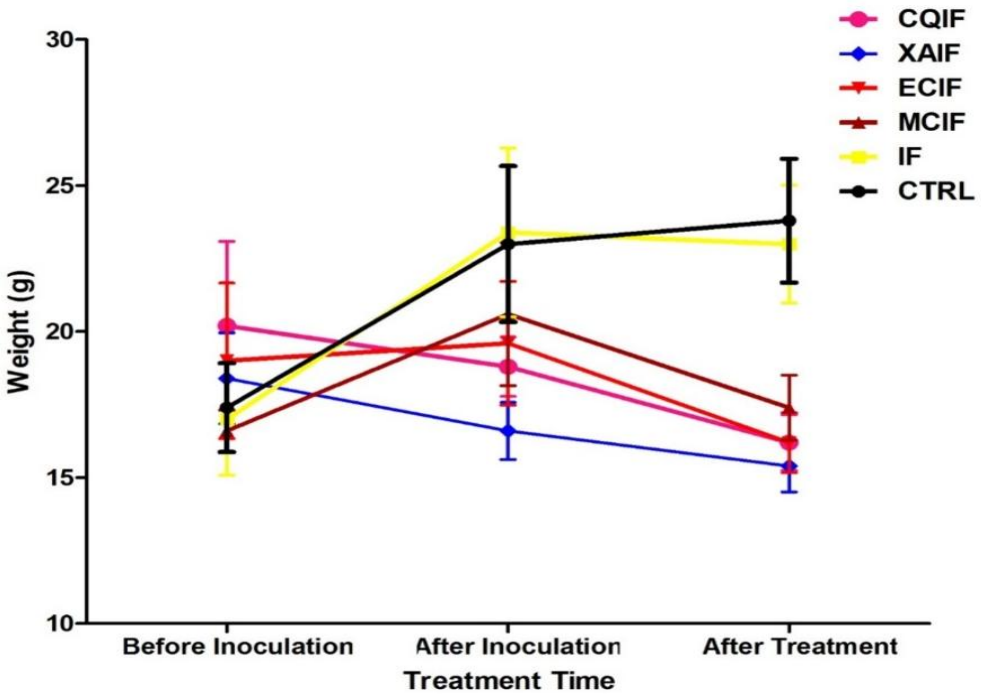


Fig. 1. Weight of experimental animals before and after inoculation and after treatment

The observation of a significant increase in the level of Hemoglobin (HB) in the mice treated with extracts as reported in this research suggest the absence of trauma in animals administered with the extract. This is in accordance with previous work [3]. Increase in hemoglobin may be due to anabolic effects brought about by their high testosterone level.

There was a significant increase in the white blood count in the infected animal and this count was restored in all the treatment groups (Fig. 2). Whereas there was no significant difference in the white blood count of the experimental animals.

3.4 Effect of the Medicinal Plants on Kidney Function Parameters

A significant decrease ($P < 0.05$) was observed in the serum creatinine, urea, and albumin level in the treated mice when compared with the control group (Fig. 3). The decrease in creatinine and urea concentration agreed to the report by Akanbi [27] that there exists a reduction in creatinine and urea during acute malaria infection. The decrease in albumin may be due to increase in plasma volume, loss of albumin from the body in urine. When albumin level reduces, toxic effect may develop from an unbound system. There is a significant increase in total protein ($P>0.05$) of the groups treated with leaves extract while that of the chloroquine group decreases which is similar to the previous study that reported hyperproteinemia in infected rabbits [28].

3.5 Effect of the Medicinal Plants on Liver Function Parameters

After treatment with the plants extract, there is no significant difference ($P<0.05$) in the AST level (Fig. 4). This may be due to some of the phytochemical constituents of the plant which affects the nutritional ability of the experimental animals as this was discovered during the experiment, that the weight of the experimental animals reduced, and restlessness was also displayed by the animals.

There is an increase in the activities of alanine aminotransferase (ALT) when the animals were being infected with the plasmodium parasite but after treatment with the plants extracts the activities of ALT were being normalize (Fig. 4). An increase in the ALT value in the liver may be due to glucose intolerance. Elevated ALT level is discovered in those with impaired glucose metabolism [29]. ALT is a more specific indicator

of liver inflammation than AST. Increase in ALT has been reported to be seen in any condition involving necrosis of hepatocytes, myocardial cells, erythrocytes, or skeletal muscle cells [30]. In this study, ALT activities increased in infected group. Although, the extract decreased the activities of the enzymes, they were not significant compared to infected only mice.

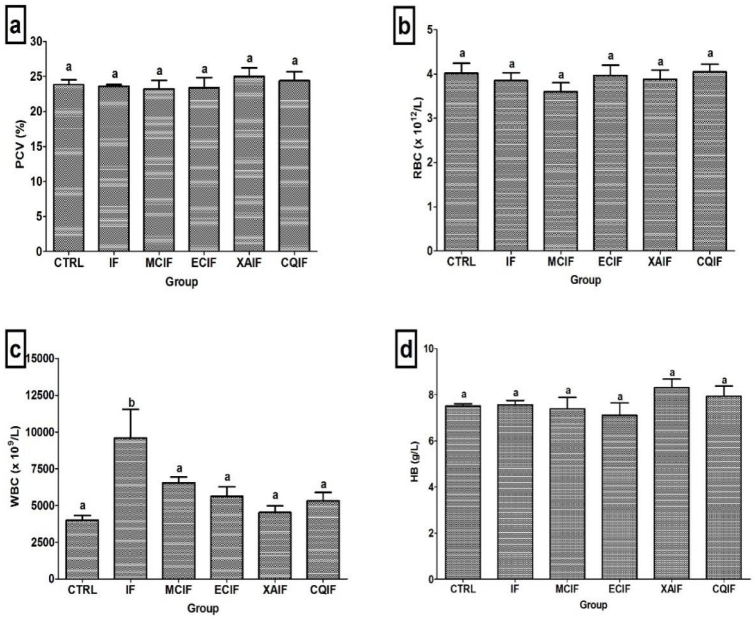


Fig. 2. Hematology parameter determination. (a) Packed cell volume in percentage, (b) red blood cell in x10^{12}/L, (c) white blood cell in x10^{9}/L and (d) hemoglobin in g/L. Different letters on the bar indicates significance difference at *P*<0.05

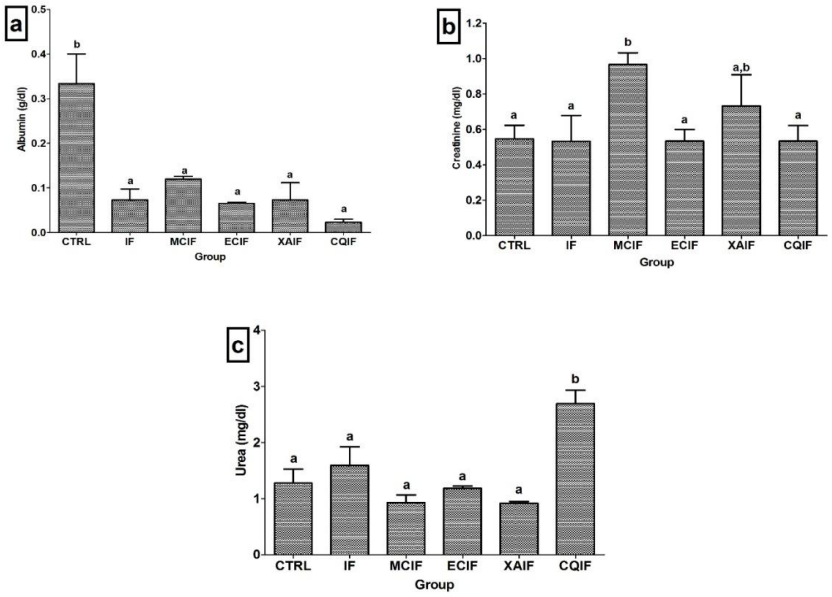


Fig. 3. Kidney function parameters determination. (a) Albumin (g/dl), (b) creatinine (mg/dl) and (c) urea (mg/dl). Different letters on the bar indicates significance difference at *P*<0.05

There is reduction in the activities of ALP when the animals were being infected with the plasmodium parasite but after treatment with the methanolic extracts of the activities of ALP were being elevated (Fig. 4). The reduction in the enzyme activity in the liver suggest that the integrity of the plasma membrane of the hepatocytes in the infected untreated mice has been compromised. ALP activities, at the administered dosage of the extract was not significantly changed in liver, suggesting the extract may not interfere with plasma membrane integrity of the hepatocytes and other metabolic activities mediated by ALP in the liver. The lack of change in liver ALP activity also suggests that the extract does not cause hepatobiliary obstruction [31].

Laboratory liver tests help to elucidate the alteration of markers which reflect the liver disease. The assessment of enzyme abnormalities like the predominant pattern of enzyme alteration, the magnitude of enzyme alteration in the case of aminotransferases, isolated elevation or in conjugation with some other parameter helps in the diagnosis of the disease.[29] Administration of the methanolic extract of *Momordica charantia* and chloroquine caused a decrease in the activities of aspartate aminotransferase (AST), alanine aminotransferase (ALT) but there is an increase in the activities of alkaline phosphate (ALP). Momoh [32] and Momoh [33] showed clearly that increase in level of ALP is associated with liver damage.

3.6 Effect of the Medicinal Plants on Total Protein and Antioxidants Levels

There is equilibrium between levels of intracellular ROS and the endogenous antioxidant system under normal physiological conditions. The endogenous antioxidant system is composed of enzymes such as the superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione (GSH). Production of ROS beyond the antioxidant capacity of the physiological system leads to oxidative stress, while excessive oxidative stress leads to the liberation of free radicals which leads to the oxidation of vital body molecules such as nucleic acids, lipids, glucosides, and proteins, by causing cellular lesions that could lead to necrosis and apoptosis [34]. The plasmodium parasite specifically targets the RBCs of its host, leading to complex and harmful pathophysiology [35]. Once the parasites enter into the RBC, it metabolizes the host's hemoglobin in its acidic food vacuole as a source of amino acids and to regulate the osmotic pressure necessary for its growth [36]. This leads to generation of ROS [37]. Degradation of hemoglobin similarly increase intracellular iron levels which in turn further increase the levels of H_2O_2 and $OH^{\cdot}$ that may cause molecular and cellular damage [38]. The results showed significant reduction in the activity of catalase and this was evident in the level of total proteins (Fig. 5). Although, there was no difference in the level of glutathione (Fig. 5).

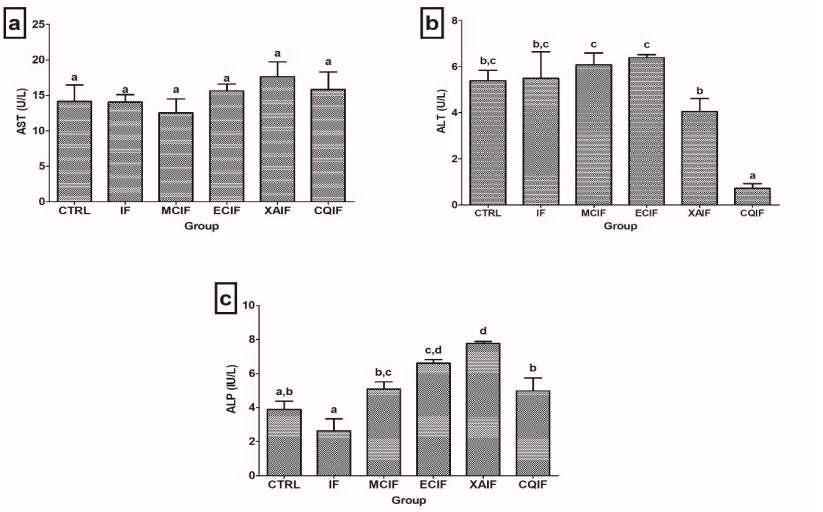


Fig. 4. Liver parameters determination. (a) AST (U/l), (b) ALT (U/l), and (c) ALP (U/l). Different letters on the bar indicates significance difference at P<0.05

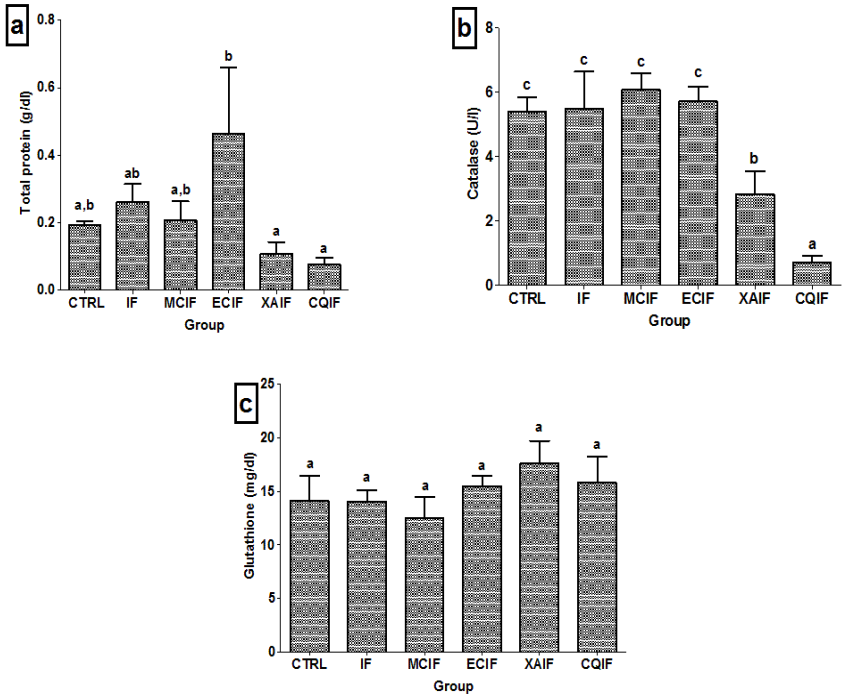


Fig. 5. Total protein and antioxidants determination. (a) Total protein (g/dl), (b) catalase (U/l), and (c) glutathione (mg/dl). Different letters on the bar indicates significance difference at *P*<0.05

4. CONCLUSION

In this study, the effect of *Plasmodium berghei* on the experimental animals was greatly reduced by the plants' extract used in this study. The extracts provide a better antiplasmodial effect and show low level of toxicity when compared to the chloroquine groups. It can therefore be concluded that, methanolic extract of *Momordica charantia, Xylopia aethiopica* and *Entandrophragma angolense* had a significant inhibitory activity to chloroquine sensitive *P. berghei* in mice.

CONSENT

Not applicable.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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