Research Article

Effects of *Momordiaca charantia* methanolic leaf extract on hepatic and splenic histopathology and some biochemical indices in *Plasmodium berghei* infected mice

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**ABSTRACT**: Malaria is caused by *plasmodium* parasite is still one of the commonest and ravaging diseases in some tropical countries. Therefore the present study investigated the anti-plasmodial potential of the methanolic extract of *Momordiaca charantia* (MEMC) in mice. A total of forty (40) healthy adult mice with an average weight of 21 g were used for the study, and were divided into five (5) groups of eight (8) mice each. Group I mice served as control, and were not infected with *Plasmodium berghei* (PB). Groups II, III, and IV mice were infected with PG, but only groups III and IV were treated with 100 mg/kg MEMC and 5 mg/kg chloroquine, an antimalarial drug respectively, while group V mice were orally administered 100 mg/kg of MEMC. All treatments lasted for five (5) days. Parasitemia, packed cell volume (PCV), plasma aminotransferase activities, as well as concentrations of bilirubin, albumin and electrolytes were determined. PCV increased in the treated groups as malaria parasites reduced. Histological examination of the liver and spleen revealed hypoplasia of the lymphoid nodules, presence of haemosiderin in the spleen of all the groups infected with the malaria parasite while haemosiderosis, vaculation and kupffer cells hyperplasia was observed in the hepatocytes of all infected groups, although, these conditions were more severe in the infected untreated group. The electrolytes determined were not significantly different at p< 0.05 from the control group, however, K⁺ and Na⁺ levels were increased in the uninfected treated with MEMC and the infected not treated groups respectively. Bilirubin level was significantly increased in all infected groups while albumin level was observed to reduce significantly in the malaria control group. Based on the findings of the study, MEMC showed ameliorative potentials on *P. berghei*-induced malaria infection. However, the plant extract may not have prompt effects on tissue repair in the animals.

**KEYWORDS**: Malaria, *Plasmodium berghei*, liver, spleen, electrolytes, aminotransferases, haematology

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INTRODUCTION

Malaria is a vector-borne infectious disease caused by protozan parasites. It is widespread in tropical and subtropical regions, including parts of the Americas, Asia, and Africa. Each year, there are approximately 515 million cases of malaria, killing between one and three million people, the majority of whom are young children in Sub-Saharan Africa (Dapper et al., 2007; Lothar et al., 2008), highest among under 5 years old and pregnant women (Dapper et al., 2007).

Malaria infection is caused by parasites entering the blood stream, the malaria parasite genus plasmodium is a unicellular eukaryote which in the course of its complex life style invades the erythrocytes of its vertebrate host. It is this intra erythrocytic phase of the parasite life cycle that gives rise to all the symptoms of malaria. Four species of plasmodium which are Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, and Plasmodium ovale are infectious to humans, but only malaria caused by Plasmodium falciparum is responsible for the vast majority of deaths from malaria (Lothar et al., 2008). The death is mainly as a result of two major complications which are cerebral malaria and anaemia (Lothar et al., 2008; Mohapatra, 2001). Other symptoms include fever, chills, nausea and flu-like illness. Splenomegaly, severe headache, hepatomegaly, hemoglobinuria with renal failure may also occur (Trampuz et al., 2003).

Momordica charantia (MC) (bitter melon) is a vine with green leaves and yellow flowers. It has a green oblong-shaped fruit similar to cucumber (Basch et al., 2003). It is used primarily as an alternative therapy for diabetes (Shahadat et al., 2008; Abascal and Yarnell, 2005), and in folk medicine to treat malaria infection.

So far there are many drugs and herbs available for the treatment of malaria, however most of which have posed some toxicity especially on the vital organs of the body. Hence, this study investigated the antimalarial potentials of MC and its protection on vital organs which are directly affected by the parasite in its host.

MATERIALS AND METHODS

Test material

Plasmodium berghei NK65 strain used for the induction of malaria in mice was obtained from Nigerian Institute of Medical Research (NIMER), Lagos, Nigeria.

Chemicals

All chemicals used in the study were of analytical grade. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, albumin, magnesium (Mg$^{2+}$), calcium (Ca$^{2+}$), sodium (Na$^+$), and potassium (K$^+$) kits were products of Randox Laboratory Ltd, UK.

Plant material

Fresh leaves of MC were harvested from a farm in Obantoko area of Abeokuta, Ogun state, Nigeria. They were autentificated by a Taxonomist at the Federal University of Agriculture Abeokuta, Abeokuta, Nigeria. Methanolic extract of the plant was prepared as described by Ashidi et al. (2007). Briefly, fresh leaves of MC were air dried in the shade at room temperature and milled to fine powder using an electric blender. About 200g of the powdered leaves was soaked in 1L of absolute methanol for 72 hours. The extract was then filtered using whatmann filter paper. The filtrate was poured into a beaker and concentrated at room temperature to give a yield of 4.6% w/w. Reconstituted extract of MC was administered orally to the mice daily after an overnight fast for five consecutive days.

Infection of mice with PB

Infection of mice was done as described by Peter and Anatoli (1998). Plasmodium berghei-infected red blood cells obtained from the tail vein of infected mice was diluted with phosphate buffered saline (PBS) so that each 0.2 mL that was subsequently injected contained approximately $10^5$ infected red cells (parasite) per kilogram of body weight.

Experimental design

A total of 40 male adult albino mice weighing between 20–22 g were obtained from Nigerian Institute of Medical Research, Lagos. The mice were allowed to acclimatize for 2 weeks to laboratory conditions and were kept in plastic cages at room temperature ($27\pm2^\circ$C) and humidity (55±5%) and a 12 hours cycle of light and dark. They were given free access to commercial animal pelleted diet and water. They were randomly divided into five (5) groups of eight (8) mice each. Group I represents the uninfected normal control. Groups II, III and IV were inoculated with the malaria parasite. Group II served as the infected untreated control, groups III and IV received oral daily doses of 100 mg/kg body weight of MEMC and 5 mg/kg body weight of chloroquine, while group V received oral daily dose of 100 mg/kg body weight of M. charantia. Parasitemia level and the packed cell volume (PCV) were monitored before treatments each day. Animals were treated for 5 days and sacrificed twenty four (24) hours after.
Sample collections
Blood was collected by cardiac puncture into clean heparinized tubes, and was centrifuged immediately at 3000 rpm for 10 minutes. The supernatant, which is plasma, was then aliquoted in clean eppendorf tubes for biochemical analysis. Liver and spleen were also harvested, washed in ice-cold saline, blotted dry, and were weighed immediately. Sections of these organs were cut and fixed in 10% formal saline for histopathological examinations.

Estimation of biochemical parameters
Heamatological indices such as PCV, haemoglobin count (Hb), red blood cell count (RBC), mean cell haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), and mean corpuscular volume (MCV) were determined using Automated Heamatological Analyzer, SYSMEX Corporation, Japan.

Plasma activities of ALT, AST, bilirubin, albumin, and the electrolytes were estimated as described in Randox kits, UK. Briefly, pyruvate and oxaloacetate respectively react with α-ketoglutarate to yield NADH from NAD⁺, which is directly proportional to the activities of the enzymes (ALT and AST) was measured spectrophotometrically.

Bilirubin in the presence of sulphanilic acid diazonium salt forms a red coloured azobilirubin in alkaline solution. The intensity of the colour formed is proportional to the bilirubin concentration in the sample. Albumin determination was based on its ability to bind an indicator bromocresol green (BCG), and the complex formed, which is directly proportional to albumin concentration was measured spectrophotometrically.

Na⁺ in the plasma was precipitated as a triple salt, the excess uranium was then reacted with ferrocyanide to produce a chromophore whose absorbance varies inversely with the concentration of Na⁺ in the plasma. Plasma K⁺ was determined after precipitation of the proteins, by using sodium tetraphenylboron in an alkaline medium to produce a colloidal suspension. The turbidity formed is proportional to K⁺ concentration in the sample, and was measured spectrophotometrically.

Ca²⁺ reacts with Arsenazo 11{1, 8-Dihydroxy-3,6-disulpho-2,7-naphthalene-bis (azo)-dibenzenearsonic acid} at neutral pH, to yield a blue coloured complex whose intensity is proportional to the Ca²⁺ concentration in the sample, while magnesium (Mg²⁺) forms a purple coloured complex when treated with calmagite in alkaline solution. The intensity of the purple colour is proportional to the Mg²⁺ concentration in the sample.

Histopathology
The formal-saline fixed tissues were paraffin embedded, sectioned and layered onto glass slide, and then stained with haematoxylin–eosin dye and finally read under a microscope by a pathologist.

Statistical analysis
Values are expressed as mean ± standard error of mean. The data were statistically analyzed using analysis of variance (ANOVA) and Duncan Multiple Range test. Data from the test groups were compared with the control group and p < 0.05 were considered to be statistically significant.

RESULTS
Parasitemia levels
There was a reduction in parasitemia level following treatment with 100 mg/kg MEMC after day 3, and was consistent beyond (Table 1). However, unlike the extract, 5 mg/kg body weight of chloroquine phosphate reduced parasitemia level after treatment on day 1 from 7.44 ± 1.16 to 6.29 ± 1.26 and gradually to 1.43 ± 0.36 that was observed on the day the animals were sacrificed. The positive control group (infected untreated) had increased parasitemia level from 7.27 ± 1.06 to 27.73 ± 3.70 all through the experiment (Table 1).

Effects of infection and treatments on organ weight
There was a significant (p < 0.05) increase in the weights of all groups infected with the parasite compared to the normal control group with an average of about 50 % increase and over 200 % increase in the spleen. However the group III treated with 100 mg/kg of MEMC was observed to have the highest increase in size of the spleen (Table 2).

Hematological results
Packed cell volume (PCV) was observed to increase in the chloroquine-administered group (IV) throughout the period of treatment. The haemoglobin levels were also increased significantly in MEMC and chloroquine treated (p<0.05) groups (Table 3).

Activities of AST and ALT
Activities of AST and ALT were increased significantly (p < 0.05) in the infected untreated group. However, the infected mice treated with the standard drug had the highest activity of AST. Total bilirubin also was increased in all infected groups (Table 4).
Effects on electrolyte concentrations

Potassium (K⁺) and magnesium (Mg²⁺) levels in the group not infected but treated with MEMC (V) were elevated, and were significant (p < 0.05) when compared to the normal group (Table 5). All infected groups had slightly lower levels, but were not significant compared to normal control group (I). Na⁺ level was significantly elevated in the malaria control group (II), while all the other groups had concentrations that were not significantly (p > 0.05) different from the control group. Also, the concentration of Ca²⁺ significantly increased (p < 0.05) by 40% only in the infected mice treated with MEMC (Table 5).

Histopathology results

Our results on histopathology (Figure 1) reveal normal appearance of hepatocytes in normal control (I) group, haemosiderosis, vacuolation and kupffer cells hyperplasia in malaria control group (II), mild diffuse kupffer cell proliferation and presence of hemosiderin in malaria infected treated with MEMC (III), mild hemosiderosis in malaria infected and treated with 5 mg/kg bwt of chloroquine (IV), while no visible lesions were seen in group V (MEMC only). For the spleen (Figure 2), no visible lesions were seen in the normal control mice (I), hypoplasia of the lymphoid nodules and presence of hemosiderin were seen in infected not treated mice (II), mild...
Table 3. Effects of MEMC and chloroquine treatments on haematological parameters in *P. berghei* infected mice

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>PCV (%) Day 2</th>
<th>PCV (%) Day 4</th>
<th>PCV (%) Day 6</th>
<th>Hb (g/dL)</th>
<th>RBC (×10⁶/μL)</th>
<th>MCH (pg/cell)</th>
<th>MCHC (g/dL)</th>
<th>MCV (x 10⁹/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (Uninfected Control)</td>
<td>45.40±1.88³</td>
<td>45.55±2.04³</td>
<td>51.25±0.63³</td>
<td>19.12±1.17³</td>
<td>9.15±0.51³</td>
<td>20.97±1.15³</td>
<td>0.37±0.02³</td>
<td>5.68±0.33³</td>
</tr>
<tr>
<td>Group II (Infected, Untreated)</td>
<td>15.97±1.37³</td>
<td>13.72±1.18³</td>
<td>11.75±0.75³</td>
<td>5.15±0.29³</td>
<td>2.17±0.32³</td>
<td>24.95±2.99³</td>
<td>0.38±0.01³</td>
<td>6.53±0.87³</td>
</tr>
<tr>
<td>Group III (Infected; MEMC, 100 mg/Kg)</td>
<td>27.50±2.20³</td>
<td>29.20±2.58³</td>
<td>31.00±1.08³</td>
<td>12.00±0.83³</td>
<td>6.10±0.20³</td>
<td>19.63±0.94³</td>
<td>0.38±0.02³</td>
<td>5.20±0.32³</td>
</tr>
<tr>
<td>Group IV (Infected; Chloroquine, 5 mg/Kg)</td>
<td>25.67±0.02³</td>
<td>31.20±3.03³</td>
<td>46.75±0.25³</td>
<td>18.67±0.75³</td>
<td>7.42±0.23³</td>
<td>25.16±0.77³</td>
<td>0.39±0.02³</td>
<td>6.36±0.19³</td>
</tr>
<tr>
<td>Group V (Uninfected; MEMC, 100 mg/Kg)</td>
<td>33.10±1.85³</td>
<td>33.46±0.97³</td>
<td>50.33±0.88³</td>
<td>19.60±2.03³</td>
<td>7.37±1.17³</td>
<td>20.88±1.28³</td>
<td>0.35±0.01³</td>
<td>7.09±1.08³</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± S.E.M; n=8. Values within a column having different superscripts are significantly different (p<0.05).

Table 4: Effects of MEMC and chloroquine treatments on plasma aminotransferase activities, concentrations of bilirubin and albumin in *P. berghei* infected mice

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>ALT (U/L)</th>
<th>AST (U/L)</th>
<th>Total Bilirubin (mg/dL)</th>
<th>Direct Bilirubin (mg/dL)</th>
<th>Albumin (g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (Uninfected Control)</td>
<td>3.13±0.67³</td>
<td>2.24±0.03³</td>
<td>0.14±0.03³</td>
<td>0.10±0.03³</td>
<td>0.88±0.11³</td>
</tr>
<tr>
<td>Group II (Infected, Untreated)</td>
<td>6.88±0.46³</td>
<td>6.12±1.03³</td>
<td>0.39±0.01³</td>
<td>0.28±0.01³</td>
<td>0.55±0.14³</td>
</tr>
<tr>
<td>Group III (Infected; MEMC, 100 mg/Kg)</td>
<td>4.31±1.50³</td>
<td>3.70±0.12³</td>
<td>0.23±0.10³</td>
<td>0.13±0.09³</td>
<td>0.98±0.11³</td>
</tr>
<tr>
<td>Group IV (Infected; Chloroquine, 5 mg/Kg)</td>
<td>4.13±1.64³</td>
<td>8.75±2.13³</td>
<td>0.30±0.17³</td>
<td>1.30±0.15³</td>
<td>1.30±0.15³</td>
</tr>
<tr>
<td>Group V (Uninfected; MEMC, 100 mg/Kg)</td>
<td>3.38±1.50³</td>
<td>3.79±0.13³</td>
<td>0.18±0.17³</td>
<td>0.14±0.08³</td>
<td>0.97±0.26³</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± S.E.M; n=8. Values within a column having different superscripts are significantly different (p<0.05).
vacoulation of the lymphoid nodules and hemosiderosis were seen in infected mice treated with MEMC (III), vacoulation of the lymphoid nodules and presence of hemosiderin in infected mice treated with chloroquine (IV), while spleen appears normal in MEMC treatment only.

**DISCUSSION**

Malaria is still the most dangerous parasitic infectious disease which causes millions of deaths every year (WHO, 2008; Inga et al., 2002). In many countries where malaria is endemic, the traditional medical methods hold a strong part in the public health care system. For safety reasons phytochemical investigations on medicinal plants traditionally used as antimalarials are urgently needed (Inga et al., 2002).

*M. charantia* has been known for its hypoglycemic effect (Shahadat et al., 2008; Abascal and Yarnell, 2005; Muhammad et al., 1981). Parasitemia was established in the mice when their tail blood was viewed under the microscope five days after infected with PB. All treated groups had their parasitemia level decreased significantly. It was observed that the parasitemia in the positive control groups increased all through the course of the experiment.

The tendency for 100 mg/kg body weight of *M. charantia* to reduce parasitemia in the mice was observed on day 4 of treatment, and this may be attributed to its anti-malarial potentials, which agrees with previous works of Inga et al. (2002) and Monuz et al. (2000). Also, the standard drug reduced the level of parasitemia on day 2 of the treatment. It has been reported by Inga et al. (2002) that the fraction of *M. charantia* that had antimalarial effect contains flavones. Also, Miliken (1997) and Okokon et al. (2005) reported that antimalarial activities depend on the presence of alkaloids and phenolic compounds in plants. Our previous work on *M. charantia* showed the presence of these phytochemicals (Balogun et al., 2012) and this could explain the antimalarial effects as marked by the reduction in the parasitemia level of infected mice following treatments with the extract.

All the groups that were infected had increased relative spleen and liver weights compared to normal control group. These findings suggested that infection with *P. berghei* may have led to spleenomegaly and hepatomegaly in all infected groups as supported by Suh et al. (2004). The liver is the site for pre- and exo-erythrocytic stages for the multiplication of the parasite while the spleen has been shown to be involved in the excretion of destroyed red blood cells and this could be an explanation for the increase in size of these two organs.

### Table 5: Effects of MEMC and chloroquine treatments on plasma electrolytes

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Mg$^{2+}$ (mg/L)</th>
<th>Ca$^{2+}$ (mg/L)</th>
<th>K$^+$ (mmol/L)</th>
<th>Na$^+$ (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (Uninfected Control)</td>
<td>6.78±0.16$^a$</td>
<td>5.45±1.82$^{ab}$</td>
<td>4.40±0.24$^{a}$</td>
<td>35.13±1.08$^{ab}$</td>
</tr>
<tr>
<td>Group II (Infected, Untreated)</td>
<td>7.10±0.18$^a$</td>
<td>5.85±0.89$^{ab}$</td>
<td>2.60±0.17$^a$</td>
<td>43.25±1.18$^{b}$</td>
</tr>
<tr>
<td>Group III (Infected; MEMC, 100 mg/Kg)</td>
<td>6.95±0.19$^a$</td>
<td>7.15±0.72$^{abc}$</td>
<td>3.23±0.12$^a$</td>
<td>36.55±4.42$^{ab}$</td>
</tr>
<tr>
<td>Group IV (Infected; Chloroquine, 5 mg/Kg)</td>
<td>7.18±0.09$^a$</td>
<td>6.10±0.85$^{ab}$</td>
<td>2.08±0.09$^a$</td>
<td>36.20±3.68$^{ab}$</td>
</tr>
<tr>
<td>Group V (Uninfected; MEMC, 100 mg/Kg)</td>
<td>11.67±2.58$^a$</td>
<td>5.03±1.07$^a$</td>
<td>13.52±5.50$^a$</td>
<td>35.67±2.03$^{ab}$</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± S.E.M; n=8. Values within a column having different superscripts are significantly different (p<0.05).
Chotivanich *et al.* (2002) reported that the spleen plays a pivotal role in policing the circulating RBC population, removing RBCs that are coated with antibody or have reduced deformability and extracting intracytoplasmic particulate material, such as nuclear remnants (Howell Jolly bodies) or oxidized hemoglobin (Heinz bodies). The spleen is an organ where worn out red blood cells are broken down and this could be one of the possible reasons for hemosiderosis observed in the spleen of infected groups revealed in the histology results (Figure 2).

Splenomegaly observed in this study in the infected mice agrees with the results of Chotivanich *et al.* (2002) who reported that fever and splenomegaly are the most frequent physical findings on examination of infected subjects.

Packed cell volume (PCV) which is a measure of the relative mass of cells present in a sample of blood increased in all the groups that were treated. The infected not treated group (II) had a reduction in the PCV of about 80% compared to the normal control group (I). This observation of anemic state has also been reported in *Plasmodium* infected mice that were untreated (Iyawe and Onigbinde, 2009; Adam *et al.*, 2005; Akpotuzor *et al.*, 2007). Anaemia is a condition marked by decrease in total cell mass of the blood, a state in which the blood index values of total haemoglobin is less than 12 g/dl.
(Uthman, 1994). Although, all the groups infected with the parasite were anemic, our findings revealed an increase in the Hb levels following treatments especially in the group treated with MEMC. This confirms the haemopoetic properties of this plant extract as reported by Dhar et al. (2007) and Sahadat et al., (2008).

The liver is the site for pre- and exo-erythrocytic stages for the multiplication of the parasite in vivo. In the hepatocytes, kupffer cell hyperplasia was observed in the treated groups (Fig. 1). This was more obvious in the group treated with the plant extract possibly due to the delay of clearance of the parasite which was observed on day 4. During tissue damage, some enzymes found in organ, find their way into the serum through leakage arising from altered permeability (Wills, 1985). AST is similar to ALT, in that both enzymes are associated with liver parenchymal cells. The difference is that ALT is found predominantly in the liver, with clinically negligible quantities found in the kidneys, heart, and skeletal muscle, while AST is found in the liver, heart (cardiac muscle), skeletal muscle, kidneys, brain, and red blood cells (Nalpas et al., 1986). As a result, 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 (Uthman, 1994). In this study, ALT and AST activities increased significantly in infected group (II). This is corroborated by the histopathology changes observed in the hepatocytes of the infected mice. Although, the extract decreased the activities of the enzymes, they were not significant compared to infected only mice. This may be attributed to the short duration of administration of the extract.

Achudume (2009) showed that there was no significant difference in AST and ALT activities in chloroquine treated wistar rats, while lyawe and Onigbinde (2009) reported an increase in ALT and AST activities in Plasmodium infected only group compared to the control. Biyani et al. (2003) reported a reduction in aminotransferases in groups treated with M. charantia and glibenclamide in a study conducted on diabetic rats suggesting the protective action of the extract.

Bilirubin is often raised due to haemolysis (Geofrey, 2006), but in severe disease can reflect liver damage (Geofrey, 2006; Uthman, 1994). From our findings, elevated levels of total and direct bilirubin was recorded in group infected with Plasmodium only compared to control. Treatment with MEMC significantly reduced their concentrations, thus, exerting better effects than chloroquine.

Increased in serum Na⁺ is usually associated with condition of water loss in excess of salt loss, an occurrence that is highly possible in conditions of profuse sweating, polyuria, hyperglycorticidism or mineralocorcidism or in condition of inadequate water intake (Uthman, 1994). Also, hyperkalemia has been linked to dehydration in children suffering from severe malaria. Our report showed electrolytes imbalance in the course of treatment. Potassium (K⁺) value was seen to reduce in infected animals while Na⁺ was elevated only in the malaria control group. The imbalance in these ions is confirmed by Suh et al. (2004) and Maitland et al. (2005) who reported that electrolytes imbalance during malaria infection depends on the duration of the infection as observed in children with severe malaria.

The results recorded in our histopathological examinations indicate direct adverse and toxic effects of the parasite on liver and spleen. This may be due to exo-erythrocytic phase in the liver whereby the parasite infects the hepatocytes and multiplies asexually, releasing merozoites that rupture the liver (Garnham, 1996; Soniran et al., 2012). The spleen being the site of eradication of affected red blood cells caused by parasite invasion may also explain the damaging effects recorded. This is supported by the findings of Chotivanich et al. (2002), who reported that the role of the spleen is increased in malaria infection, in other to clear the system of infected red blood cell, and extraction of intracytoplasmic particulate materials.

In conclusion, MEMC showed ameliorative potentials on Plasmodium berghei-induced malaria infection and possible biochemical complications, but may also have slow tissue recovery effects in mice. Further studies need to be done on the plant extract to check the ameliorative effects of long term administration on tissues.

REFERENCES


