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SHORT COMMUNICATION

Comparative effects of parenteral antimalarials in Swiss albino mice after chronic exposure to *Plasmodium berghei*

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Abstract

Mice are considered to be a similar model to humans in the pathogenesis of malaria. This study evaluates the effect of parenteral antimalarials on the spleen and liver of Swiss albino mice after chronic exposure to *Plasmodium berghei*. After chronic exposure to *P. berghei* NK65 strain, the level of parasitemia was assessed. The mice were treated for 3 days using chloroquine (5 mg/kg), quinine (10 mg/kg), and artemether (2 mg/kg). The effect of chronic exposure and the pattern of recovery were evaluated. There was significant decrease in total body weight after chronic exposure to *P. berghei* ($P < 0.05$). An increase in total weight recovery was seen after day 15 of treatment with the antimalarials; this was more pronounced with artemether. A significant increase in liver and spleen weights due to *P. berghei* infection was seen. There was a recovery pattern due to decrease in liver and spleen weights following antimalarial administration, which was greatest with artemether ($P < 0.05$). Significant changes were more in parasitized, quinine and artemether groups ($P < 0.05$). There was a significant decrease in total spleen protein due to chloroquine but a decrease due to quinine and artemether ($P < 0.05$). No significant changes in liver and spleen albumin were observed after treatment. The highest parasite clearance was observed with artemether, followed by quinine. Five mice died after chronic exposure in all the groups prior to treatment. There was significant enlargement and discoloration of spleen and liver after chronic exposure. This study showed that artemether aided recovery of the liver and spleen better than quinine and chloroquine in albino mice after chronic exposure to *P. berghei*. This suggests there is potential for improvement in antimalarial therapy.

KEYWORDS
antimalarials, mice, *Plasmodium berghei*

1 | INTRODUCTION

Malaria is one of the most serious diseases that affect people in developing countries in the subtropic and tropical areas.[1] Four plasmodial species have been known to cause malaria in humans, namely *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, and *Plasmodium knowlesi*.[2] Of all human species, *P. falciparum* is most pathogenic, as is indicated by the type of

malaria associated with it (malignant tertian malaria). Experimental models, such as *P. berghei*, show that it is a protozoan parasite that causes malaria in certain rodents. Originally isolated from thicket rats in Central Africa; *P. berghei* is one of four plasmodium species that have been described in African murine rodents, others being *P. chabaudi*, *P. vinckei*, and *P. yoelii*. *P. chabaudi* invades normocytes and reticulocytes and is used to investigate mechanisms of drug resistance and immune invasion. *P. yoelii* is used to study liver stage malaria, and innate or acquired immunity against liver stage malaria. *P. chabaudi* and *P. vinckei* invade both immature and mature red blood cells, while *P. berghei* and *P. yoelii* both invade reticulocytes.[3] There are two strains of *P. berghei*; *P. berghei* NK 65 (NK for New-York/Katanga) was isolated from the invertebrate vector *Anopheles dureni millecampsi* captured in Katanga (near Lumbumbashi) in 1965. *P. berghei* ANKA (ANKA for Anvers/Kasapa) was isolated from the same host in Kasapa (Katanga), not far from the same site.[4] The multiplication of the parasite in the blood causes pathologies such as anemia and damage to essential organs of the host such as lungs, liver, spleen. *P. berghei* infections may also affect the brain and can be the cause of cerebral complications in laboratory mice. These symptoms are, to a certain degree, comparable to symptoms of cerebral malaria in patients infected with the human malaria parasite *P. falciparum*.[5] The rodent parasite *P. berghei* is a well-used model in malaria research, including analyses of the severe pathology associated with malaria infections, pregnancy associated with malaria and lung pathology. It is also used to investigate drug sensitivity. As mentioned, *P. berghei* preferentially invades recticulocytes.[3] Liver and spleen are essential organs that can play a role in malarial pathogenesis.[6-8] This study assessed the effect of parenteral antimalarials on liver and spleen after chronic exposure to *P. berghei*.

2 | MATERIALS AND METHODS

2.1 | Animals

Albino mice weighing 21.40 ± 0.46 g (mean ± SEM) were purchased and acclimatized in the Animal House of the Department of Pharmacology and Toxicology, University of Benin, Benin City, Nigeria. Four donor mice, already inoculated with *P. berghei* (strain NK65), were obtained from the Nigerian Institute of Pharmaceutical Research and Development, Abuja, Nigeria. The animals were fed throughout with pelletized grower's mash and allowed access to drinking water ad libatum. The selected and grouped mice were infected with parasites *P. berghei* by obtaining parasitized blood from the cut tail of a donor mouse (3-4 drops) and diluted in 0.9 mL normal saline. The mice were inoculated intraperitoneally with 0.1 mL parasitized suspension according to previous reports.[9-11] Parasitemia was assessed by thin blood film made by collecting blood from the cut tip of the tail and this was stained using standard procedures.[12] The animals were left untreated for 14 days after inoculation to achieve chronic exposure. The level of parasitemia was assessed after staining the prepared slides according to past protocol.[13]

2.2 | Drugs and chemicals

Chloroquine phosphate (64.5 mg/mL), artemether (80 mg/mL), and quinine dihydrochloride (600 mg/2 mL) were purchased from registered pharmaceutical shop in Benin City, Nigeria. Serial dilution with water was carried out on the drugs to obtain individual concentrations. The drugs were administered intraperitonially in milligram per kilogram body weight.

The mice were grouped as (n = 5/group) for unparasitized control, parasitized control, and parasitized for chloroquine, artemether and quinine.

The drugs were administered intraperitoneally for 3 days on the fifteenth day of exposure. Routine checks on the level of parasitemia were made microscopically. On the nineteenth day, the mice were sacrificed using chloroform anesthesia. The spleens and livers of all animals sacrificed were collected and weighed, and some sections were used for biochemical analysis.

2.3 | Organ/body weight ratio

The weight of the spleens and liver were used to determine the organ/body weight ratio. The relative organ/body weight ratio was determined using the standard formula:[14]

$$\frac{\textit{Weight of organ}(g)}{\textit{Weight of animal on day of sacrifice }(g)} \times 100\%$$

2.4 | Preparation of tissue homogenate

The liver and spleen were homogenized in 5 mL of normal saline. The samples were centrifuged at 4000 rpm for 15 minutes, and then the supernatant layer was withdrawn and introduced into sterile tubes for biochemical investigation.

2.5 | Data analysis

The results were presented as means ± SEM (standard error of mean). Inferential analysis was carried out using one-way analysis of variance with Turkey's *post hoc* test (GraphPad software Inc., UK). A value of $P < 0.05$ indicates a statistically significant difference between compared data.

3 | RESULTS AND DISCUSSION

Numerous approaches to understanding the disease pathology of malaria have been carried in animal models. Severe infection with *P. falciparum* in humans involves multisystem disorders, presenting as multiple clinical features, not least of which is weight loss. Results obtained from this study showed that mice were susceptible to *P. berghei* infection (Figures 1 and 2). Rapid onset of malaria occurred a day after inoculation with parasites. The high level of parasitemia suggests a high degree of infection when the mice were left untreated for several days. This led to paleness due to massive loss

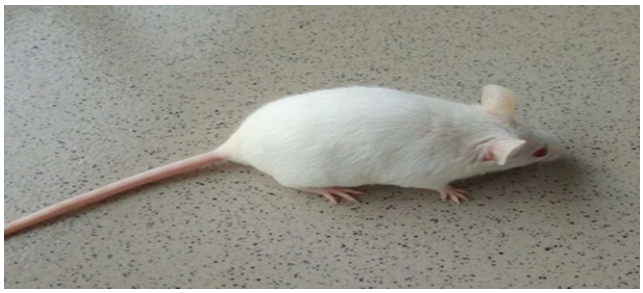

FIGURE 1 Mouse infected with *Plasmodium berghei* before chronic exposure

FIGURE 2 Mouse infected with *P. berghei* after chronic exposure

of red blood cells (RBCs), which is a characteristic sign of anemia (Figure 2). The pathogenesis of severe anemia during malaria infection is complex and involves multiple processes relating to both destruction and decreased production of erythrocytes.[15] During *P. falciparum* infection, reticulocyte levels are low,[14] indicating the suppression of erythropoietin synthesis. Increased RBC destruction also occurs through the rupture of parasitized red blood cells and the phagocytosis of the parasitized and unparasitized RBCs by hyperactive macrophages in the reticuloendothelial system.[16,17]

In this study, the body weights of the mice were measured to monitor the effects of infection and the subsequent parenteral antimalarial treatments on factors such as food and water intake and metabolism. A decrease in body weight of infected mice was clearly evident in this study due to prolonged exposure (Figure 3). This might also be due to disturbed metabolic function and hypoglycemia, which has been reported to be associated with malaria infection.[18] An increase in weight after treatment with the parenteral antimalarial drugs was observed after a few days. The weight reduction effect of *P. berghei* and weight recovery after parenteral antimalarials support an earlier report of an increase in body weight after oral administration of artemether/lumefantrine in rats.[19] An increase in body weight after oral administration of dihydroartemisinin (an artemisinin derivative) has also been reported.[20] In contrast, other studies[21,22] showed that artesunate administration had no significant effect on body weight. The significant changes in body weight seen in some of these studies may be due to long-term plasmodial exposure.

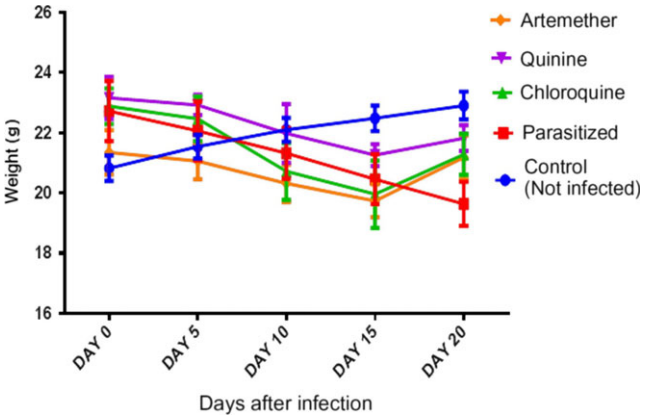

FIGURE 3 Effect of parenteral antimalarial drugs on the body weight of Swiss albino mice. Day 0 indicates the day of commencement of infection. After chronic exposure to *P. berghei* for 15 days, treatment was initiated for 3 days. There was a decrease in weight of the parasitized mice until day 15 and an increase in weight after parenteral antimalarials were administered ($P < 0.05$). Five mice died due to the chronic exposure to *P. berghei*

However, in our study, the increase in total body weight after day 15 indicates recovery of the mice after antimalarial intervention (Figure 3).

3.1 | Effect of parenteral antimalarials on the liver weight

Generally in toxicological studies, relative organ body weight changes are often associated with treatment-related effects.[23] Liver weight elevation is associated with potent hepatic enzyme-inducing compounds. There were a significant differences between the parasitized group ($^{**}P < 0.01$) vs control group, quinine group ($^{*}P < 0.05$) vs chloroquine and artemether groups. Artemether group ($^{\#*}P < 0.01$) vs parasitized group (Figures 4 and 5). The results showed that artemether has greater impact in reversing hepatomegaly. There was also an increase in the weight of the mice in the artemether group after treatment with the antimalarial drug. Analysis of organ weight in toxicology studies has been an important endpoint for identification of potentially harmful effects of chemicals. Differences in organ weight between treatment groups are often accompanied by differences in body weight between these groups, making interpretation of organ weight differences more difficult. Analysis of organ/body weight index is predictive for evaluating the condition of the liver.[24] A significant decrease in relative liver and body weights in the quinine and artemether groups was observed when compared to the parasitized group. This supports report of significant decrease in the relative liver/body weight in parasitized mice and rats. Quinine-treated group had more prominent decrease than in infected control group. This suggests that quinine and artemether (an artemisinin derivative) are potentially better in reducing the risk of liver toxicity in infection-related damage due to chronic exposure to *P. berghei* (Figures 4 and 5). Malaria may

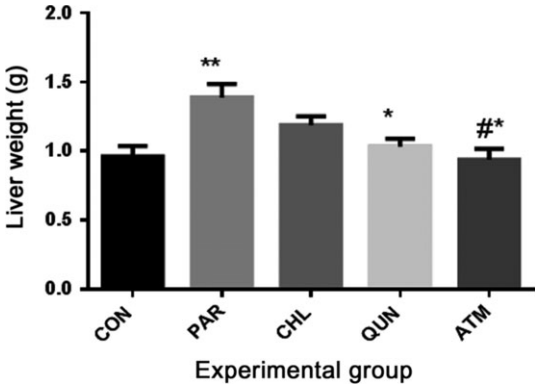

FIGURE 4 Effect of parenteral antimalarials on liver weight of mice after chronic exposure to *P. berghei*. $^{**}P < 0.01$ vs control group. $^{*}P < 0.05$ vs chloroquine and artemether groups. $^{\#*}P < 0.01$ vs parasitized group. n = 5. CON: control, PAR: parasitized, CHL: chloroquine, QUN: quinine, ATM: artemether

result in hepatomegaly, that is, enlargement of the liver, as seen in this study. This could be the reason for the increase in the weight of the liver of these groups infected with malaria. The decrease in the weight of the liver following treatment was less significant with chloroquine.

3.2 | Effect of parenteral antimalarials on spleen weight

A significant increase in the weight of spleens in the chloroquine, quinine, artemether and parasitized groups was observed compared to the control group. Infections by malaria parasites induce a dramatic, albeit variable splenic response mostly characterized by splenomegaly. In fact, spleen size has been used as a tool to determine the intensity of malaria transmission in endemic regions.[6] Significant increase was also found in the spleen weight index of the chloroquine, quinine,

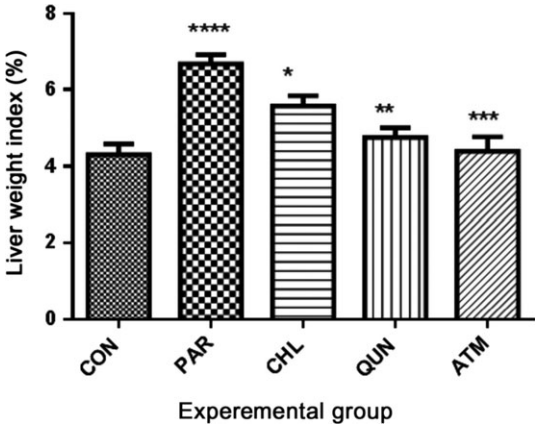

FIGURE 5 Effect of parenteral antimalarials on the liver weight index. $^{****}P < 0.0001$ vs chloroquine, quinine, and artemether groups. $^{*}P < 0.05$ vs quinine and artemether groups. $^{**}P < 0.01$ vs chloroquine and artemether groups. $^{***}P < 0.001$ vs parasitized, chloroquine, and quinine groups. n = 5. CON: control, PAR: parasitized, CHL: chloroquine, QUN: quinine, ATM: artemether

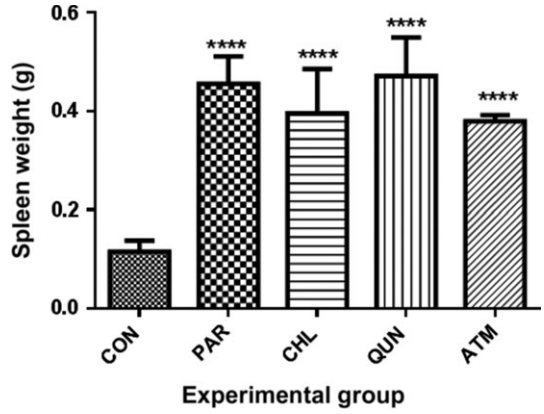

FIGURE 6 Effect of parenteral antimalarials on the spleen weight of mice. Significant changes were observed in parasitized, chloroquine, quinine, and artemether groups. $^{****}P < 0.0001$ vs control. n = 5. CON: control, PAR: parasitized, CHL: chloroquine, QUN: quinine, ATM: artemether

artemether and parasitized groups compared to the control group, with changes greater chloroquine, quinine and parasitized groups. This result further supports the aforementioned report of the effects of quinine and artesunate on parasitized rats and mice[25] showing significant increases in quinine and parasitized groups compared to the control group. Quinine showed greater significant increase than artesunate and control groups. Splenomegaly, like hepatomegaly, which is a common indicator during malaria, is a result of the organs being congested and thus swollen from the accumulation of the malarial pigment hemozoin, which leads to discoloration.[26] The mice in our study were generally pale, showing a high level of anemia. The spleen, changed to dark color. Treatment with antimalarial drugs that "mop-up" the parasites should lead to recovery and therefore a reversal of the harm done by the parasites. Figures 6 and 7 show that artemether was most effective at reversing splenomegaly, followed by chloroquine and then quinine, which were least effective.

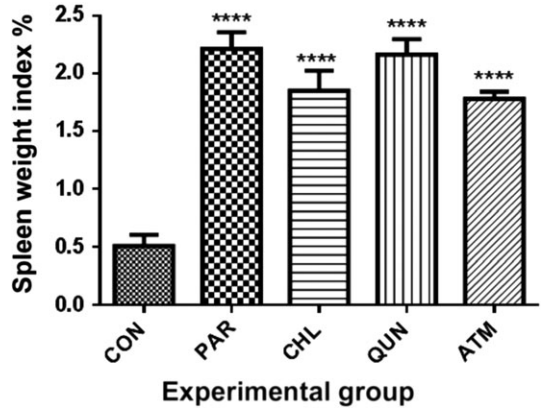

FIGURE 7 Effect of parenteral antimalarials on spleen weight index. Significant changes were observed in parasitized, chloroquine, quinine, and artemether groups. $^{****}P < 0.0001$ vs control. n = 5. CON: control, PAR: parasitized, CHL: chloroquine, QUN: quinine, ATM: artemether

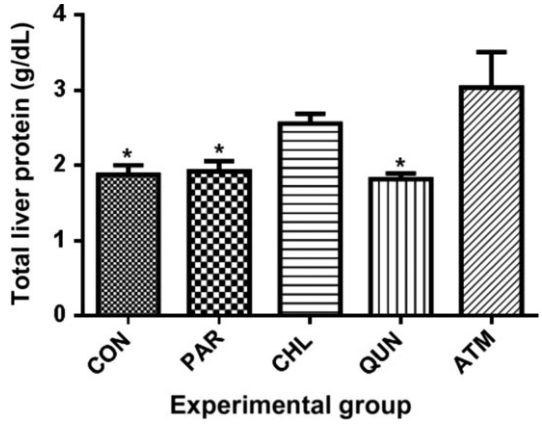

FIGURE 8 Effect on parenteral antimalarials on liver total protein. Significant changes were observed in control, parasitized, and quinine groups. *$P < 0.0001$ vs artemether. n = 5. CON: control, PAR: parasitized, CHL: chloroquine, QUN: quinine, ATM: artemether

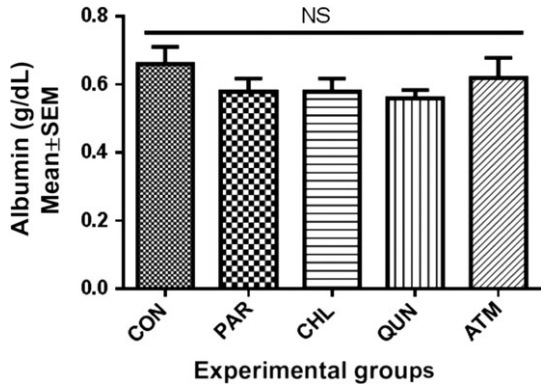

FIGURE 9 Effect of parenteral antimalarials on serum albumin in the liver of mice after chronic exposure to *P. berghei*. There was no significant difference in albumin levels between the experimental groups. n = 5. CON: control, PAR: parasitized, CHL: chloroquine, QUN: quinine, ATM: artemether

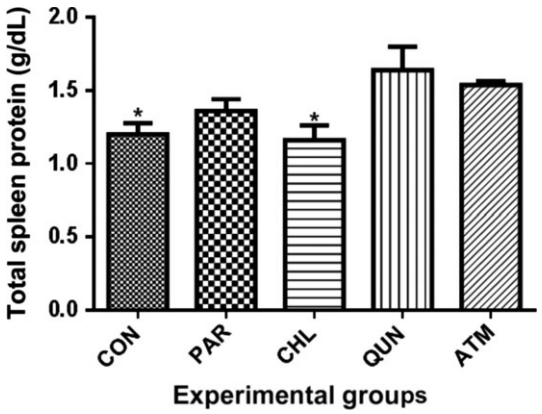

FIGURE 10 Effect on parenteral antimalarials on the total spleen protein after chronic exposure to *P. berghei*. There were significant changes in the control and chloroquine groups (*$P < 0.05$) vs parasitized, quinine, and artemether groups. n = 5. CON: control, PAR: parasitized, CHL: chloroquine, QUN: quinine, ATM: artemether

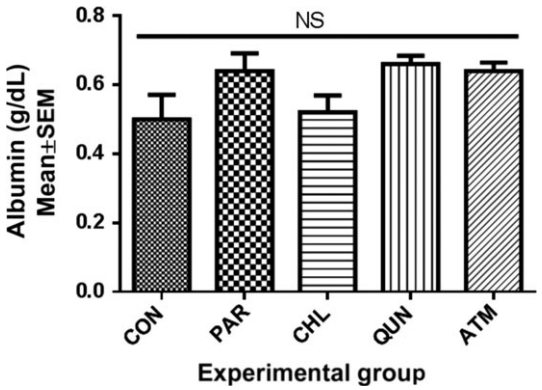

FIGURE 11 Effect of parenteral antimalarials at standard doses on serum albumin in the spleen of mice after chronic exposure to *P. berghei*. There were no significant changes in all the groups. n = 5. CON: control, PAR: parasitized, CHL: chloroquine, QUN: quinine, ATM: artemether

3.3 | Effect of parenteral antimalarial drugs on liver serum proteins

An effect of antimalarial drugs on liver serum proteins is expected, as the liver serves as the major conduit for drug metabolism.[27] In this study, there was a significant increase in total protein (*$P < 0.05$) in the artemether group compared with the control group. There was a slight increase in the chloroquine group and a decrease in the quinine group compared to the control group. There was no statistically significant difference in liver serum albumin between the groups (Figure 9), but a slight decrease in the albumin level was observed in the infected groups. A previous study[28] reported a transient decrease in serum concentrations of total protein and albumin in malaria patients treated with artemether, suggesting that the drug may have an effect on the liver, and that the altered circulating concentration of albumin in the human study may be due to the side-effects of artemether on liver cells.[29] Protein synthesis in the liver may be affected by any chemical with either moderate or extensive hepatotoxic effects, such as those produced by plasmodium or antimalarials. Most drugs bind to albumin and globulins.[30] Our results (Figures 8 and 9), showing a significant difference in total protein but no significant decrease in albumin concentration, suggest a mild adverse effect of artemether.

3.4 | Effect of parenteral antimalarial drugs on serum proteins of spleen

There was a significant increase in total spleen protein in the quinine group compared with the control group (Figure 10), but no statistically significant difference between the artemether and chloroquine groups compared to the control group, with the artemether group being slightly higher and the chloroquine group slightly lower than the control group. A significant difference in the level of parasitemia was observed with chloroquine, quinine and artemether. Albumin in the liver and spleen did not change significantly, even after

TABLE 1 Clearance of parasites following treatment

	Mean values ± SEM of level of parasitemia (%)		
Group	Day 0	Day 1	Day 2
Chloroquine	29.95 ± 1.15	20.275 ± 1.355	14.36 ± 2.56**
Quinine	27.675 ± 2.605	21.275 ± 2.185	13.44 ± 1.06***
Artemether	21.47 ± 0.79	13.765 ± 0.435	8.335 ± 1.635***
Parasitized	29.155 ± 2.045	35.88 ± 1.62	41.6 ± 0.8
Control	0	0	0

There were significant changes in level of parasitemia following treatment with parenteral antimalarial drugs.
Chloroquine: $^{**}P < 0.05$, Qunine: $^{***}P < 0.05$, Artemether: $^{***}P < 0.05$.

TABLE 2 Post-mortem observations on the liver and spleens in malaria-infected mice

Organ	Post-mortem observation
Liver	Enlargement of the size (Hepatomegaly); Discolouration of liver
Spleen	Enlargement of the size (splenomegally); Discolouration of spleen

The assessed organs showed pathological changes in color and size.

treatment with the antimalarials (Figures 9 and 11). The highest clearance of parasites was observed in the artemether group, followed by quinine and chloroquine groups (Table 1). This result further proves that there was better parasite clearance with artemether. Five mice infected with *P. berghei* did not survive the course of the experiment, which reflects the high mortality due to chronic exposure. There was significant enlargement and discoloration of spleen and liver after chronic exposure (Table 2).

In conclusion, this study has shown that artemether promoted recovery of the liver and spleen better than quinine and chloroquine in albino mice after chronic exposure to *P. berghei*. This suggests better potential therapies for resolving the pathogenesis of malaria infection.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

The authors have agreed to publish this work. The protocol was designed by the corresponding author. The work was carried out by the two authors in the Department of Pharmacology and Toxicology, University of Benin, Nigeria.

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