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Hydroethanolic Extracts of *Senna alata* Leaves Possess Antimalarial Effects and Reverses Haematological and Biochemical Pertubation in *Plasmodium berghei*-infected Mice

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Abstract

The current work investigated the chemical profile, antimalarial potential and capacity of hydroethanolic *Senna alata* extract (SAE) to reverse hematological and biochemical pertubation in *Plasmodium berghei* infected mice. Results of the phytochemical analysis revealed the presence of alkaloids, flavonoids, phenolics, tannins, terpenoids, saponins, steroids and cardiac glycosides. Total phenolic and flavonoid content was estimated to be 45.29 ± 2.34 mg GAE/g and 25.22 ± 2.26 mg QE/g respectively. *In vitro* analysis of the extract also confirmed its antioxidant property. Results of the test for prophylaxis of *P. berghei* indicated that SAE suppressed parasitemia significantly in treated groups in a dose dependent manner when compared with negative control group. Similarly, SAE improved the mean survival time (MST) and packed cell volume (PCV) of infected mice. The test for curative effect showed that SAE significantly suppressed parasitemia to $4.50 \pm 1.05\%$ compared to untreated group $29.83 \pm 3.49\%$. Results of liver and kidney functions indices of treated animals indicated that whereas infection with *P. berghei* caused increase in the levels of AST, ALT, ALP, urea and creatinine, treatment with SAE significantly reversed the perturbation. Similarly, infected mice were dyslipidemic with concomitant increased activity of HMG CoA reductase and decreased activity of antioxidant enzymes with increase in lipid peroxides levels. However, these alterations were significantly reversed by administration of SAE. Results of this study shows that *Senna alata* possess antimalarial activity and therefore justify the traditional use of plant for the treatment of malaria.

Keywords

malaria, plasmodium, *Senna alata*, lipid metabolism, parasitemia

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Introduction

Malaria is a major health challenge with high mortality rates in Africa. About 92% of malaria infections happen in sub-Saharan Africa.[1] Female Anopheles mosquitoes transmit plasmodium into humans which results in malaria. Pregnant women and children (0-5 years) are the most vulnerable groups affected by malarial infections.[2] Malaria continues to be a major health challenge due to inadequate preventive measures and growing resistance to several common antimalarial drugs, such as chloroquine, piperaquine, artemisinin derivatives, quinine, primaquine, amodiaquine, and

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lumefantrine.[3] After several years of intensive research efforts, there is still no commercially available malaria vaccine.

The World Health Organization advocates the use of natural products and finds it to be a successful method for the conquest of infectious diseases. Around 80% of people in the world use herbal medicine for their health need.[4] The dependence on herbal medicines is primarily due to their affordability, cost-effectiveness, and accessibility. A rich reservoir of bioactive metabolites is found in natural products and hence possible sources of new antimalarial products.[5] For instance, You-You-Tu discovered Artemisinin, an anti-malarial drug in China in the early 70's from *Artemisia annua* L.[6]

Senna alata also referred to as *Cassia alata*, is an abundant herb and a flowering shrub generally referred to as candle bush, ringworm plant, ringworm bush, craw-craw plant, or acapulo in the Leguminosae family. It is about 1-4 m tall, flourishing in sunshine and wetlands, both annually and sometimes biannually.[7] In Egypt, India, Ghana, Brazil, Australia, Sri Lanka, Somalia, and throughout Africa, *S. alata* is widely spread. Diverse clinical activities in disease prevention have been demonstrated by *S. alata* in African, Chinese, and Ayurvedic traditional medicine. In the Northern part of Nigeria, *S. alata* is used in the treatment of skin, diarrhea, wound, inflammation, constipation, and burns.[8] The leaf decoction is also used to counteract stress, toothache, body, and abdominal pain in the South-Western region.[9] It also cures dermal diseases, epilepsy, acts as a bowel stimulant, lowers colon water absorption to stop constipation. In Cameroon, it was recorded that the leaves, bark, and stem were used to treat ringworm, hepatitis, and gastroenteritis.[10]

The pharmacological actions of the plant include antioxidant,[11] wound healing,[12] anti-inflammatory,[13] antihelmintic,[14] antimicrobial,[15] anti-tumor,[16] anti-diabetic,[17] and anti-malarial.[7] In a detailed review by Oladeji et al,[7] it was reported that quinones and terpenes isolated from *Senna alata* significantly displayed *in vitro* antiplasmodial activity. Similarly, justification for the ethnobotanical use of the plant in the treatment of malaria was provided by the ability of aqueous leaf extract of the plant to inhibit 3D7 *P. falciparum* in mice.[7] These pharmacological activities are attributed to the presence of array of chemical compounds that are bioactive such as Phenolics (kaempferol, glycosides, rhein, aloe-emodin), steroids, terpenoids, anthraquinones, and fatty acids (linoleic acids, oleic, and palmitic).[7] The objective of the current study was to evaluate the chemical profile and the *in vivo* antimalarial activity of *S. alata* in mice infected with *P. berghei*.

Materials and Methods

Plant Material

Leaves of *Senna alata* were collected from the campus of Anyigba town, Nigeria. It was identified by a Botanist and assigned Voucher no. PT-271. Shade dried leaves were pulverized and extracted with 50% ethanol (H_2O/Ethanol) for 48 h. The suspension was filtered and the filtrate was evaporated to dryness using a rotary evaporator.

Phytochemical Analysis

Qualitative phytochemical analysis of the crude extract was carried out according to the methods Trease and Evans,[18] and Harbone.[19] Total phenolic content was determined according to the method of Singleton and Rossi[20] while total flavonoid was determined by the method reported by Arogba.[21]

In Vitro Antioxidant Activity

Antioxidant activity of the hydroethanolic extract of *S. alata* was determined using established protocols. Total antioxidant power was estimated according to the method described by Sharifia et al[22] The reducing power assay was performed according to the method described by Yen et al[23] based on the ability of the extract to reduce potassium ferricyanide. Free radical scavenging activity of the extract was determined based on the extracts ability to scavenge stable DPPH radical.[24]

Experimental Animals and Malaria Parasite

All protocols for animal experiments were approved by the first authors' institution based on established policies of animal care as well as the ARRIVE guidelines for animal based experiments. Healthy male albino mice were purchased from the animal care facility of Ahmadu Bello University, Zaria, Nigeria. The mice were acclimatized for 14 days prior to experiments. Animals were kept in well aerated cages and fed with animal chow and water ad libitum. *Plasmodium berghei* NK65 was obtained from the Department of Parasitology, National Institute for Medical Research, Yaba, Lagos, Nigeria. Mice host was used to maintain the strain. Passages were routinely done from mice with high parasitemia to naïve mice. Induction of parasitemia was done via intraperitoneal injection of blood (20-30% parasitemia). Parasitemia was monitored by examination of blood smears under a light microscope.

$$\text{Parasitemia}\,(\%) = \frac{\text{Total number of parasitized RBCs}}{\text{Total number of RBCs}} \times 100$$

In Vivo Antimalarial Activity Test

Antimalarial activity was determined by two independent tests namely: Peter's four days chemosuppresive test and curative test. The chemosuppresive test was done on mice challenged with *Plasmodium berghei* infection for 3 h followed by treatment with varied concentration of *Senna alata* extract (SAE) for four (4) days. Thirty six mice were allocated to six groups for the experiment as given below:

Group I: Normal control
Group II: Negative control (malaria control)
Group III: 25 mg/kg/day Chloroquine (CQ)
Group IV: 100 mg/kg/day SAE
Group V: 200 mg/kg/day SAE
Group VI: 400 mg/kg/day SAE

Similarly, the curative test was done by challenging mice with *Plasmodium berghei* infection for 72 h prior to commencement of treatment with 200 mg/kg bw for four (4) days. Twenty four mice were allocated to four groups and treated as shown below:

Group I: Normal control
Group II: Negative control (malaria control)
Group III: 25 mg/kg/day Chloroquine (CQ)
Group IV: 200 mg/kg/day SAE

Percentage suppression of parasitemia was calculated as:

$$\text{Percent Suppression} = \frac{\text{Parasitemia in negative control} - \text{Parasitemia in treated group}}{\text{Parasitemia in negative control}} \times 100$$

Mice were observed for 29 days post infection and the mean survival time (MST) was calculated as follows:

$$\text{Mean Survival Time (MST)} = \frac{\text{Sum of survival days of all mice in a group}}{\text{Total number of mice in the group}}$$

Table 1. Phytochemical Profile and Antioxidant Activity of *Senna alata*.

Parameter	
Alkaloids	+
Flavonoid	+
Phenolics	+
Tannins	+
Terpenoids	+
Saponins	+
Steroids	+
Anthraquinones	−
Cardiac glycosides	+
Extraction yield (%)	17.73 ± 0.42
Total Phenolics (mg GAE/g)	45.29 ± 2.34
Total Flavonoid (mg QE/g)	25.22 ± 2.26
Total Antioxidant Power of extract (EC_{50} µg/ml)	48.50
Total Antioxidant Power of Vitamin C (EC_{50} µg/ml)	22.53
Total Reducing Power of extract (EC_{50} µg/ml)	20.37
Total Reducing Power of Vitamin C (EC_{50} µg/ml)	19.03
DPPH radical scavenging activity of extract (IC_{50} µg/ml)	100.16
DPPH radical scavenging activity of Quercetin (IC_{50} µg/ml)	60.62

Animal Sacrifice and Biochemical Assays

Animals were anesthetized using Chloroform before collecting blood via cardiac puncture. Whole blood was used for determination of Packed Cell Volume (PCV) using the capillary method. PCV was thus calculated:

$$\text{PCV} = \frac{\text{Erythrocyte volume}}{\text{Total blood volume}} \times 100$$

Biochemical assay was performed on serum derived from clotted blood using Diagnotic kits for Liver function (AST, ALT, ALP), Kidney function (Urea, Creatinine), Oxidative stress markers (lipid peroxidation, catalase, superoxide dismutase, glutathione peroxidase) and Lipid profile (HDL, TG, Total Cholesterol (TC)), HMG-CoA reductase according to Diagnostic kits manufacturer's protocols.

Statistical Analysis

InStat Graphad software was used for Analysis of variance (ANOVA) to ascertain significant differences between means. Differences were considered statistically significant at $P < .05$.

Results and Discussion

Malaria has become a leading infectious disease in sub-saharan Africa. A major obstacle in combating malaria presently is the resistance to approved antimalarial drugs.[3] Therefore, researchers are challenged with the enormous task of finding new drugs that are safe and combat resistant strains of malaria. Quite commonly, medicinal plants have been researched in order to source antimalarial bioactive compounds with some good level of success. One of such celebrated successes is the discovery of Artemisinin from *Artemisia annua* which is now used for conventional treatment of malaria.[2]

In the present study, qualitative phytochemical screening of hydroethanolic leaves extracts of *Senna alata* revealed the presence of phenolics, flavonoid, alkaloids, tannins, terpenoids, saponins, steroids, and cardiac glycosides (Table 1). The phenolic compounds such as benzoic and cinnamic acid derivatives are known to be responsible for most of the antioxidant activity of plants. Therefore, the total phenolic and flavonoid content of *S. alata* was quantified. From the results presented in Table 1, the total phenolic content was 45.29 ± 2.34 mg GAE/g while the total flavonoid content was 25.22 ± 2.26 mg GAE/g. As expected, the plant extracts demonstrated antioxidant potential based on measured total antioxidant power (EC_{50} 48.50 µg/ml), total reducing power (EC_{50} 20.37 µg/ml), and capacity to scavenge DPPH radical (IC_{50} 100.16 µg/ml). The antioxidant activities and reported pharmacological properties of the plant may be due primarily to the abundance of phenolics and flavonoids.

Measurement of parasitemia (number of parasitized cells present in blood) is the most common experimental protocol for quantifying malaria infection as well as assessing efficacy of antimalarials. Decreased parasitemia expressed as percentage

chemosuppression is important for recovery from symptomatic malaria.[25,26] In this study, *P. berghei* infected mice treated with the plant extract had reduced parasitemia comparable to the values obtained for the standard drug chloroquine (Table 2). The plant extract exerted chemosuppression in dose dependent manner; the highest chemosuppression of 84.36% was recorded at 400 mg/kg/day *S. alata* extract. Therefore, the extracts of *S. alata* is rich in compounds with antimalarial activity. Similarly high degree of chemosuppression has been reported for *Artemisia abyssinica* which showed 90.48% chemosuppression.[27]

In addition to suppression of parasitemia, the plant extracts also fostered survival of parasitized mice measured as MST. MST is a parameter used to check how long animals survive with a disease or after a certain treatment. Plant materials that can prolong the survival time of infected experimental animals compared to the negative controls are considered as effective antimalarials that possibly modulate pertubations in metabolic pathways.[28] In this study, *P. berghei* infected mice treated with *S. alata* extracts had MST that was significantly higher than untreated mice but significantly lower than the chloroquine treated group. However, the effect of the extracts on MST was dose dependent but was not significantly different across the different doses of the extract. The current finding correlates with the report on the effect of *Dodonaea angustifolia* seed on MST of parasitized animals.[29] Although the extracts of *S. alata* were chemosuppressive and improved MST, it did not completely ameliorate weight loss with exception of 200 mg/kg/day of the extract (Table 3). The reason for this dose-specific effect is not clear however, the weight loss in other groups of mice could be as a result of the depressing effect of the extract on appetite or feed intake.[30]

PCV is measured to access the possible hemolysis and anemia which characterizes malaria infection. The effect of *S. alata* extracts on PCV is indicated in Table 3. As expected, PCV significantly decreased in the untreated group but in the *S. alata* treated and chloroquine groups, the PCV was stabilized to near normal. Again the group administered 200 mg/kg/day of the extract has the highest evidence of recovery with change in PCV of −0.47%. Many factors could be responsible for decreased PCV for example, the malaria parasite is known to cause cells to produce free radicals which compromise the red blood cell membrane. Therefore, the ability of the extract to stabilize PCV in infected mice could be as a result of antioxidant compounds of the plant extracts. Also, it is conceivable that the extract has a high iron content which may have contributed to synthesis of red blood cells. Similar results have been reported in literature.[31] The plant extracts also showed high chemosuppression in the curative model of malaria treatment (Table 4). The cure by the extracts is evidenced by decreased parasitemia and high chemosuppression not significantly different from chloroquine treatment.

Table 2. Chemosuppresive Antimalarial Activity of *Senna alata*.

Treatments	Parasitaemia (%)	Chemosuppression (%)	Mean survival time (days)
Normal control	—	—	29.00 ± 0.00
Negative control	26.67 ± 1.51	0.00	9.50 ± 2.17
25 mg/kg/day CQ	0.5 ± 0.14^{a}	98.13	27.83 ± 1.33^{a}
100 mg/kg/day SAE	$5.17 \pm 0.75^{a,b}$	80.61	$21.00 \pm 2.00^{a,b}$
200 mg/kg/day SAE	$4.33 \pm 0.52^{a,b}$	83.76	$21.67 \pm 1.21^{a,b}$
400 mg/kg/day SAE	$4.17 \pm 0.75^{a.b}$	84.36	$23.33 \pm 2.66^{a,b*}$

Values are presented as mean ± SD of six(6) determinations.
a < 0.001 compared with negative control.
b* < 0.01 compared to CQ group.

Literature is overflowing with evidence of metabolic derangements in parasitized animals. These derangements range from nephropathy, hepatotoxicity, dyslipidemia to oxidative stress. Therefore, in this study, we aimed to investigate the possible effect of the *S. alata extracts* on the above listed indices. Liver function was tested by assaying three enzymes namely, aspartate amino transferase (AST), alanine amino transferase (ALT), and alkaline phosphatase (ALP). Infection with *P. berghei* significantly increased the levels of these enzymes in untreated mice. Treatment with *S. alata extracts* significantly decreased the concentrations of the liver enzymes when compared to the untreated group ($P < .05$). More so, the extracts were more effective at restoring the levels of AST and ALP than chloroquine (Table 4). This result agrees with the study of Onyemakonor et al[32] which showed that *P. falciparum* malarial infection significantly elevates the serum ALT, AST, and ALP activities in a way that correlates with the parasites' density and concluded that malarial infection confers a measure of hepatic compromise. Aminotransferase enzyme activities are usually elevated in the blood in many disorders related to the liver; hence, they are used in the assessment of liver-cell injury or damage.[33] The pathogenesis of malaria infection involves the liver sporozoic stage and erythrocyte merozoic stage, which ultimately leads to the destruction of infected red blood cells.[34] Since both hepatic cells and the erythrocytes are rich sources of these enzymes, the activities of the invading malaria parasites in these tissues can lead to the damage of their membranes and the consequent release of AST and ALT into the serum. Thus, resulting in the observed increase in the serum activities of these enzymes and a corresponding decrease in their activities in the affected tissue or organ. Alkaline phosphatase (ALP) on the other hand is a marker enzyme often used to access the plasma membrane integrity. Alterations in the activity of the enzyme would indicate likely damage to the plasma membranes.[35]

The kidney function parameters (Creatinine and Urea) of *P. berghei* infected mice administered with curative doses of *Senna alata* showed no significant differences in the urea level compared to the negative control. The level of creatinine was significantly reduced when compared to the negative control and 25 mg/kg/day CQ. Mild to chronic renal dysfunction is common during malaria infection.[36] The parasite

Table 3. Effect of Hydroethanolic Plant Extracts on Body Weight and Packed Cell Volume (PCV) of Plasmodium Berghei Infected Mice.

Treatments	Body weight (g)			Change in PCV (%)
	Weight D_0	Weight D_4	Weight change (%)	
Normal control	22.00 ± 0.63	22.17 ± 0.75	0.77	0.65
Negative control	23.67 ± 0.82	21.33 ± 0.82	−9.89	−18.62
25 mg/kg/day CQ	22.67 ± 0.82	23.17 ± 1.17	2.21	0.99
100 mg/kg/day SAE	23.00 ± 1.10	22.83 ± 0.75	−0.74	−2.99
200 mg/kg/day SAE	23.17 ± 0.98	22.83 ± 0.75	2.85	−0.47
400 mg/kg/day SAE	23.33 ± 0.81	23.17 ± 0.75	−0.69	−3.27

Values are presented as mean ± SD of six(6) determinations.

Table 4. Liver and Kidney Function Parameters of *Plasmodium Berghei* Infected Mice Administered with Curative Doses of *Senna alata*.

Treatments	Parasitaemia (%)	Chemo-suppression (%)	Liver function parameters			Kidney function parameters	
			AST (UL^{-1})	ALT (UL^{-1})	ALP (UL^{-1})	Urea (mmol/L)	Creatinine (μmol/L)
Normal control	—	—	16.40 ± 1.34	18.73 ± 0.56	50.6 ± 2.85	3.50 ± 0.04	55.67 ± 1.70
Negative control	29.83 ± 3.49	0.00	33.86 ± 1.09	50.36 ± 0.61	124.20 ± 4.28	4.79 ± 0.98	102.76 ± 2.91
25 mg/kg/day CQ	1.17 ± 1.17[a]	96.08	17.98 ± 0.84[a]	22.16 ± 0.62[a]	60.26 ± 2.08[a]	4.04 ± 0.03	71.85 ± 1.38[a]
200 mg/kg/day SAE	4.50 ± 1.05[ab**]	84.91	15.79 ± 0.82[ab*]	22.53 ± 0.46[a]	43.24 ± 2.25[ab]	4.19 ± 0.03	67.97 ± 1.74[ab**]

Values are presented as mean ± SD of six(6) determinations.
a < 0.001 compared with negative control.
b < 0.001, b* < 0.01, b** < 0.05 compared to CQ group.

Table 5. Effect of Curative Doses of *Senna alata* Extracts on Lipid Metabolism in *Plasmodium Berghei* Infected Mice.

Treatments	TC (mmol/L)	HDL (mmol/L)	TG (mmol/L)	HMG CoA reductase (U/mg protein)
Normal control	2.48 ± 0.52	0.62 ± 0.05	1.47 ± 0.28	0.073 ± 0.013
Negative control	3.64 ± 0.96	0.36 ± 0.03	2.16 ± 0.19	0.126 ± 0.011
25 mg/kg/day Chloroquine phosphate (CQ)	2.59 ± 0.38[b**]	0.58 ± 0.02[a*]	2.05 ± 0.32	0.061 ± 0.027[a]
200 mg/kg/day SAE	2.67 ± 0.05[b**]	1.46 ± 0.14[ab]	1.33 ± 0.08[ab]	0.059 ± 0.011[a]

Values are presented as mean ± SD of six(6) determinations.
a < 0.001, a* < 0.01 compared with negative control.
b < 0.001, b** < 0.05 compared to CQ group.

sequestration into the renal microvasculature bed could lead to the increased creatinine and urea and eventually result in ischemia.[37] Severe cases of malaria-related renal problems can take the form of nephritis syndrome that progresses to renal failure. Severe proteinuria, increase in urea in blood, low specific urine severity, low urinary to blood urea ratio, hyperkalaemia and metabolic acidosis are the characteristics of this disease.[38]

The effect of *S. alata* treatment on lipid metabolism of *P. berghei* infected mice is reported in Table 5. Infection with *P. berghei* caused an increase in levels of TC and triglycerides (TG) with concomitant reduction in high density lipoprotein (HDL) levels. However, mice administered 200 mg/kg/day *S. alata* extracts had a significant decrease in the levels of TC and triglycerides and significant increase in the HDL level when compared to the negative control group. Similarly, HMG-CoA reductase activity was significantly increased by infection with *P. berghei* but significantly decreased by the extracts compared to the negative control. The present study has revealed an increase in the HDL in the group treated with *S. alata* and shows that it tends to boost HDL levels in the body which tends to have an inverse pattern of parasitemia in Table 4. Malaria has been implicated to cause changes in the plasma lipid profile in man, with a typical rise in triglyceride concentration and reduction in HDL-cholesterol concentration.[39] It has been reported that the HDL level could be determined by the parasite load in an organism. Hence, the increase in HDL-cholesterol level could be result of the decrease in the parasite load in these groups, while the reduction in the HDL-cholesterol level in the negative control could be because of the high level of parasite load in this group.

Table 6. Effect of Curative Doses of *Senna alata* Extracts on Oxidative Stress Markers in *Plasmodium Berghei* Infected Mice.

Treatments	SOD (UI/L)	CAT (IU/L)	GPx (U/mg protein)	GSH (mg/dL)	Lipid peroxides (mg/dL)
Normal control	9.14 ± 0.12	0.69 ± 0.09	2.56 ± 0.21	4.46 ± 0.77	5.62 ± 1.01
Negative control	7.11 ± 0.45	0.34 ± 0.06	1.87 ± 0.39	1.22 ± 0.18	17.25 ± 3.53
25 mg/kg/day Chloroquine phosphate (CQ)	8.42 ± 1.09	0.42 ± 0.12	$2.39 \pm 0.15^{a*}$	3.81 ± 0.50^{a}	6.58 ± 0.65^{a}
200 mg/kg/day SAE	$10.62 \pm 1.13^{ab*}$	$0.55 \pm 0.15^{a**}$	3.33 ± 0.16^{ab}	$4.60 \pm 0.67^{ab**}$	6.86 ± 1.26^{a}

Values are presented as mean ± SD of six(6) determinations.
a < 0.001, a* < 0.01 compared with negative control.
b < 0.001, b* < 0.01, b** < 0.05 compared to CQ group.

Antioxidant enzyme and reduced glutathione levels decreased in *P. berghei* infected mice with a corresponding increase in the concentration of lipid peroxides (Table 6). However, administration of the curative doses of *S. alata* extracts is shown in Table 6 caused a significant ($P < .05$) increase in the activities of SOD, CAT, and GPx and increase the GSH level when compared to both the normal control and the negative control with a corresponding decrease in the lipid peroxides level. Oxidative stress as a result of anaemia is key factor in the pathogenesis of malaria.[40] The reaction of the host immune system to pathogens and the parasite's interaction with phagocytes also generate a pool of reactive oxygen species (ROS).[41,42] Lipid peroxidation may be caused by increased ROS in malaria. It can be inferred from the results in Table 6 that the plant extract enhance the antioxidant status of the infected animals. The mechanism for this is unclear and is a subject for further research. However, it could be inferred that the extract either induces the synthesis of the antioxidant enzymes or at least protect the integrity of same.

Conclusion

This study reveals that the *S. alata* extracts have antimalarial and antioxidant activities as well as the potential to reverse biochemcial pertubation in *Plasmodium berghei*-infected mice. Hence, it justifies the use of *S. alata* in malaria treatment in herbal medicines. The observable effect could be as a result of the pharmacologically active metabolites present in the extract which could exert the antimalarial activity by acting synergistically or singly.

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Author Contributions

FOA—conceptualization, funding acquisition, investigation, writing and supervision; DR—writing of draft, investigation, software analysis; OBI—editing, software analysis, writing and editing, funding acquisition; JSA—editing, writing and editing, funding acquisition; GEB—funding acquisition, resources, writing; PAI—editing, software analysis, writing and editing. All authors have read and agreed to the published version of the manuscript. All authors have read and agreed the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

All the reagents used in this study were prepared, used, and disposed of according to the set laboratory guidelines. Animal study was approved by the Institutional Review Board of the Department of Biochemistry, Faculty of Natural Sciences, Kogi State University, Nigeria.

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