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Original Research Article

Telfairia occidentalis Seed Extracts Attenuated Oxidative Stress And Liver Injury In *Plasmodium berghei*-Infected Mice

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ABSTRACT

*Telfairiaoccidentalis*Hooke. F. (Cucurbitaceae) is a vegetable used medicinally in the treatment of malaria. The seed crude and gradient extracts of *T. occidentalis*(138 -553 mg/kg) obtained by cold extraction were investigated for antioxidative stress, haematological and hepatoprotective effects in *Plasmodium berghei*-infected mice using standard curative test. Hematological parameters, oxidative stress markers levels, liver function indices were determined and histopathology of livers of the treated infected mice. Characterisation of the active extract was done using GCMS. The crude and gradient extracts (138-553 mg/kg, p.o.) exerted significant ($p<0.05–0.001$) antimalarial activity against *P. berghei* infection with methanol gradient extract having the highest activity. Hematological parameters of the infected treated mice were altered. The extracts treatment significantly ($p<0.05$) lowered liver enzymes (ALT, AST and ALP), total and conjugated bilirubin and also decreased significantly ($p<0.05$) total protein and albumin levels of the treated mice relative to control. The seed extracts further improved ($p<0.05$) the levels of antioxidant enzymes and molecules (CAT, GPx, GST,SOD) of the treated infected mice. The MDA levels of the treated infected mice were reduced ($p<0.05$) relative to control. Histology of liver sections revealed absence or reductions in pathological features in infected mice treated with crude extract (276 mg/kg), DCM and ethyl acetate gradient extracts compared to untreated infected mice. GCMS analysis of the active gradient extract revealed the presence of polyunsaturated fatty acids and monoterpenes in the active methanol extract. These results suggest that the seed extract possess antimalarial, antioxidative stress and hepatoprotective activities due to it phytochemical constituents

Keywords: Telfairia occidentalis, Anti-plasmodial, Oxidative stress, Liver injury, Medicinal plant

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Introduction

Malaria continues to be one of the major health challenges globally. In 2023, four African countries were reported to account for more than 50% of all global malaria deaths (569 000 deaths). These include; Nigeria (30.9%), Democratic Republic of Congo (11.3%), Niger (5.9%) and Tanzania (4.3%), with 39.3% of all global malaria deaths in children aged younger than 5 years occurring in Nigeria alone.[1] In 2024, the World Health Organization, WHO,presented the 2023 fact sheet and found that WHO African Region recorded the highest number of malaria cases and death during the period.[2]

Enormous progress has been made over the past few years in the treatment and management of malaria. Advances have been made in high throughput screening, phenotypic assays and whole-genome target identification. Novel antimalarial molecules have been discovered and utilised and their mechanism of actions evaluated. The use of artemisinin-based combination therapies (ACTs) has been closely monitored and documented by the World Health Organization.[1, 2]

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In spite of the progress in the management of malaria over the past years, the above WHO 2023 malaria data show that malaria is yet to be eradicated and seriously threatening lives in Africa, especially in Nigeria. The emerging drug resistance, high costs of the existing antimalarial drugs and acute side effects of some of the existing drugs continue to pose challenges for African users. Therefore, spurring investigation into safe and low-cost treatments on medicinal plants which serve as reservoirs for active molecules against malaria is necessary. A number of plants of Nigerian origin have been investigated previously for *in vitro* and *in vivo* antimalarial activities by our group [3,4,5,6,7]for the discovery of solution to malaria. To add to the achieves of solutions, we intend in this study to evaluate the antimalarial activity of *T. occidentalis* seed extract on the liver oxidative stress markers as well as liver function parameters and histology in *Plasmodium berghei*-infected mice.

Telfairia occidentalis Hook is a fluted pumpkin of the *Cucurbitaceae* family widely consumed as food in Nigeria.[8] It is a popular vegetable all over Nigeria, especially in the Niger-Delta region and the Eastern part of the country; varieties of meals are prepared from the leaves, stem and seeds of the plant. [9] The seeds are very nutritious and are eaten roasted or boiled. The seed has history of being effective in the treatment and prevention of prostate disorders. The seed extract has been reported to exert antidiabetic,[10] cellular antioxidant, immunodulatory, anticancer, anti-inflammatory,[11]antiplasmodial,[8] antioxidant,[12] analgesic, [12,13]genotoxic ,[14] in vivo inhibitory effect on alpha amylase and alpha glucosidase, [15] antiulcer,[16] and antiprostatic[17] activities. Phytochemical studies of the seed extract have shown the presence of alkaloid, flavonoid, tannins, terpenes, saponin, and cardiac glycosides. [18]Okokon*et al*.[12] have reported the presence of esters and aromatic acids such as pentadecanoic acid, hexadecanoic acid; 16-octadecenoic acid methyl ester; 9, 12-octadecadienoyl chloride (Z,Z);

9- octadecadienoic acid (Z)-, 2, 3-dihydroxypropyl ester; octadecanoic acid; hexadecanoic acid,2,3-is[(trimethylsilyl)oxy] propyl ester, 2,4-heptadien-6-ynal,(E,E); benzoic acid; dodecanoic acid; linoleic acidethyl ester; hexadecanoic acid, methyl ester; α-phellandrene; α-campholene aldehyde;terpinen-4-ol; trans-β-ocimene; borneoland stigmastan-3-ol, in the seed extract.

The present study was therefore designed to evaluate the effect of seed extract and fractions of *T.occidentalis*on liver oxidative stress markers as well as liver function parameters and histology in *Plasmodium berghei*-infected mice

Materials and Methods

Plant collection and extraction

Fresh seeds of *Telfairia occidentalis* were purchased from Itam market in Itu Local Government Area, Akwa Ibom State, Nigeria, in June, 2023. The seeds were previously identified and authenticated by a taxonomist in the Department of Botany, University of Uyo, Uyo, Nigeria. Herbarium specimens (UUPH 1(b)) were deposited at Department of Pharmacognosy and Natural Medicine Herbarium, University of Uyo.The fresh seeds of the plant were dried on laboratory table for 2 weeks and reduced to powder. The seeds powder (1 kg) was macerated in 50% ethanol (5000 mL) for 72 hours, while the remaining part (2 kg) was gradiently macerated for 72 hours in each of, *n*-hexane, dichloromethane, ethyl acetate and methanol respectively, which is along their increasing polarity to give the corresponding gradient extract. The liquid filtrate of crude extract and solvent fractions were concentrated and evaporated to dryness *in vacuo* 40^0C using a rotary evaporator. The various yields were calculated and the extract and fractions were stored in a deep freezer at -4^0C, until used for the proposed experiments.

Microorganism

Chloroquine-sensitive strain of *Plasmodium berghei*ANKA strain was obtained from the National Institute of Medical Research (NIMR), Yaba Lagos, Nigeria and maintained by subpassage of blood from infected to healthy mouse once every 7-8 days.

Parasite inoculation

Each mouse used in the experiment was inoculated intraperitoneally with 0.2 mL of infected blood containing about 1 x 10^7*P. berghei*parasitized erythrocytes collected from an infected mouse with 20-30% parasitaemia. The inoculum consisted of 5 x 10^7 *P. berghei* infected erythrocytes per milliliter prepared by determining both the percentage parasitemia and the erythrocytes count of the donor mouse and diluting the blood with isotonic saline in proportions indicated by both determinations. [19,20]Parasitemia was monitored by standard methods; thin blood smears were made on glass slides, fixed using methanol, and stained using Giemsa stain, and parasitemia was counted using a microscope and was calculated as a percentage of infected red blood cells (RBCs) relative to the total number of cells in a microscopic field at ×100 magnification according to the formula [19] given below:

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

Experimental animals

Swiss albino mice (18-25 g), male and female, used in the study were obtained from the University of Uyo's animal house. They were kept in standard plastic cages in a well ventilated room and left to acclimatized for a period of 10 days before the experiments. The mice were fed on standard pelleted diet and water *ad libitum*. The care and use of animals were conducted in accordance with the National Institute of Health Guide for the Care and Use of laboratory Animals. Approval for the study was obtained from the University of Uyo's Animal Ethics Committee.

Drug administration

The extract, fractions, chloroquine and pyrimethamine that were used in the study were administered orally with the aid of a stainless metallic feeding cannula.

Evaluation of in vivo antimalarial activities of crude and gradient extracts of Telfairia occidentalis seed on P. berghei infected mce

This test was used to evaluate the schizontocidal activity of the crude extract, gradient extracts and chloroquine in established plasmodial infection. This was conducted according to the methods previously described.[21, 22]*P. berghei* was injected intraperitoneally into ninety (90) mice on the first day (D_0). Seventy-two hours later (D_3), the mice were divided into nine groups of ten mice per group. Groups 1-3 were given different doses of crude extract, 138, 276 and 553 mg/kg respectively, groups 4-7 were given 276 mg/kg of *n*-hexane, ethyl acetate, dichloromethane, and methanol gradient extracts respectively, group 8 was given 5 mg/kg chloroquine (positive control) and group 9 was given 10 mL/kg distilled water (negative control). The crude and gradient extracts as well as chloroquine were administered once daily for 5 days. Giemsa-stained thin smears were prepared from tail blood samples collected on each day of treatment to monitor the parasitemia level. The mean survival time (MST) of the mice in each group was determined over a period of 29 days (D_0-D_{28}). The average suppression of parasitemia was calculated according to the formula [19]as follows: (average % parasitemia positive control – average % parasitemia negative control) / (average % parasitemia negative control).On the sixth day, five mice were sacrificed from each group under diethyl ether vapour. Blood samples were collected into EDTA-bottles for hematological study and also into plain centrifuge tubes which were centrifuged after one hour at 2500 rpm for 15 mins to separate the serum at room temperature. These sera samples were stored at -20^{o}C until used for biochemical determinations. Liver from each mouse was surgically removed, weighed and divided into two parts. One part was fixed in 10% formaldehyde for histological process and the other part stored in ice cold normal saline.

Statement of ethical approval

This study was approved and ethically cleared by College of Health Sciences Animal Ethics Committee, University of Uyo (UU/CHS/IHREC/2025/VOL.1/16).

Haematological Analysis

Blood samples in different EDTA-coated sample bottles were analysed for haematological indices (RBC, HGB, PCV, WBC total and differentials – neutrophils, eosinophils, basophils, lymphocytes and monocytes) using automated Haematology analyser according to manufacturer's protocols (SysmexHaematology-Coagulation Systems®, Model KX-21N, Sysmex Incorporation, Kobe, Japan)[23] at the University of Uyo Teaching Hospital.

Effect of seed crude and gradient extracts on liver function parameters of P. berghei infected mice

ThisLiver function parameters such as total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), conjugated and total bilirubin were determined in the stored sera samples collected from the sacrificed mice spectrophotometrically using Randox analytical kits according to standard procedures of manufacturer's protocols.[24]

Effect of seed crude and gradient extracts on liver antioxidative stress markers of P. berghei infected mice

The excised livers were stored and washed with ice cold 0.9% NaCl. Homogenates were made in a ratio of 1 g of wet tissue to 9 ml of 1.25% KCl by using motor driven Teflon-pestle. The homogenates were centrifuged at 7000 rpm for 10 min at 4˚C and the supernatants were used for the assays of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx),reduced glutathione (GSH), and malondialdehyde (MDA). [25]

Effect of the seed crude and gradient extracts on Lipid Profile
Serum cholesterol, triglyceride and high-density lipoprotein (HDL) levels of the treated infected mice were measured using Chemistry Autoanalyzer by manufacturers' kits (SpetrumLab kits, Spectra Group Diagnostics, Egypt). Low and very low-density lipoprotein (LDL and VLDL) were estimated from the formula of Friedwald*et al.*[26]

Effect of the seed crude and gradient extracts on liver histology of P. berghei infected mice
The part of liver that was fixed in buffered formalin were processed and stained with haematotoxylin and eosin (H&E) for liver study according to standard procedures at Department of Chemical Pathology, University of Uyo Teaching Hospital, Uyo. Morphological changes observed and recorded in the excised organ of the sacrificed mice. Histologic pictures were taken as micrographs.

Gas Chromatography-Mass Spectrometry Analysis
Gas chromatography-mass spectrometry (GC-MS) data of the active gradient extract (methanol) were recorded on an Agilent 7890A gas chromatograph connected with an Agilent MS model 5975C MSD detector (Agilent Technologies, USA). A HP5-MS column 5% phenyl-methylpolysiloxane, 30m × 0.25mm × 0.25µm was used with a helium gas flow under a pressure of 10 psi. The injector temperature was set at 280°C. The oven temperature started from 150°C for 3min, and increased to 300°C at 10°C/min, and held for 5 min at 300°C. The mass spectrometer was operated using the electron ionization mode at 70eV. The gradient extract was directly injected in *n*-hexane as described previously.[28]The phytochemicals were identified by comparison of spectra in the NIST 2011 database.

Statistical analysis
Data collected were analyzed using one way analysis of variance (ANOVA) followed by Tukey's multiple comparison post-test GraphpadInstat 3 (Graph pad prism software Inc. La Jolla, CA, USA). Values were expressed as mean ± SEM and significance relative to control were considered at $p<0.001$ and $p<0.05$.

Result and Discussion

Yields of crude and gradient extracts
The percentage yields of the crude extract and gradient extracts were; crude-21.03%, n-hexane-1.6%, DCM-2.82%, ethyl acetate-1.04%, methanol-2.1%.

Antiplasmodial effect of crude and gradient extracts of T. occidentalison established infection
There were progressive dose-dependent reductions of parasitaemia in all the extracts-treated groups relative to control. These reductions were statistically significant relative to the control ($p<0.001$). The methanol gradient extract had the highest activity with chemosuppressive effect of 77.48 % on day 7, this was lower compared with that of the standard, chloroquine, 93.17%. The seed extracts demonstrated significant ($p<0.001$) protective potentials on the mice as was seen in the mean survival time of the animals. The groups treated with methanol gradient extract had a longer mean survival time, 18.00 ± 1.15 days followed by those of crude extract (553 mg/kg) treated mice, 15.66 ± 1.45 days. These were less than that of the standard drug, chloroquine (29.83 ± 0.16 days; Table 1).

Table 1: Curative Activity and Mean Survival Time of Mice Treated With Crude Extract and Gradient Extracts of *T. occidentalis* Seed During Established *Plasmodium berghei* Infection

Treatment	Dose (mg/kg)	Parasitaemia Day 7	Chemosupression	MST
Control	10ml/kg	35.76±1.24	-	8.33±1.24
Crude Extract	138	25.23±0.34[c]	29.44	10.33±2.96
	276	21.39±0.33[c]	40.18	13.33±3.93[b]
	553	10.22±1.34[c]	71.42	15.66±1.45[b]
n-hexane	276	22.29±0.67[c]	37.66	11.66±1.45[a]
Dichloromethane	276	20.32±1.38[c]	43.17	12.66±1.33[b]
Ethyl acetate	276	28.26±0.14	20.97	10.00±1.15
Methanol	276	8.05±0.24[c]	77.48	18.00±1.15
Chloroquine	5	2.44±0.28[c]	93.17	29.83±0.16[b]

Values are expressed as mean ± SEM. Significant relative to control. [a]$p<0.01$; [b]$p<0.001$.n = 5.

Effect of crude and gradient extracts of Telfairia occidentalis seed on haematological indices of Plasmodium berghei-infected mice.
Administration of crude and gradient extracts of *Telfairia occidentalis* seed to *P. berghei*-infected mice did not cause any significant ($p>0.05$) effect on RBC counts, hemoglobin concentration, PCV, neutrophils, monocytes, basophils and eosinophils percentages when compared to control. However, WBC counts were reduced significantly ($p<0.001$) in all the treatment groups except the highest dose of the extract (553 mg/kg). Platelet counts of the infected mice were significantly ($p<0.05$) increased only at the middle dose (276 mg/kg) of the crude extract and ethyl acetate gradient extract treated groups (Table 2).

Effect of crude and gradient extracts of Telfairia occidentalis seed on liver function parameters of Plasmodium berghei-infected mice.
The levels of liver function indices (AST, ALT, ALP, total cholesterol, total protein, albumin, total and conjugated bilirubin) were found to be elevated in untreated *P. berghei* -infected mice. However, treatment of *P. berghei* infected mice with crude and gradient extractsof *T. occidentalis* seed produced dose-dependent and significant ($p<0.05$-0.001) reductions in the levels of AST, ALT, ALP,total and conjugated bilirubin with the crude extract and methanol gradient extract treated groups having the most significant ($p<0.05$-0.001) reduction relative to control. Some of the effects were better than those of chloroquine-treated group (Table 3). The total protein and albumin levels of the treated infected mice were similarly reduced dose-dependently and significantly by the crude and gradient extractstreatments with crude extract and methanol gradient extract-treated groups having the highest significant effect ($p<0.001$) (Table 3).

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Table 2: Effect of Crude Extract and Gradient Extracts of *T. occidentalis* Seed on Haematological Parameters of *P. berghei*-Infected Mice

Treatment	WBC ($x10^9$/L)	LYM ($x10^9$/L)	NEUT ($x10^9$/L)	RBC ($x10^{12}$/L)	HGB (g/dL)	PCV (%)	MONO (%)	EOSINO (%)	BASO (%)	PLT ($x10^9$/L)
Control	37.25±1.50	59.66±12.52	35.86±14.06	3.12±0.33	5.26±0.41	21.13±1.28	6.00±1.85	0.76±0.38	1.03±0.14	272.0±32.39
Extract(138 mg/kg)	7.86±3.73^c	44.83±6.07	47.86±4.36	3.54±0.17	5.06±0.35	18.46±1.63	2.66±0.40	0.73±0.06	1.33±0.28	199.0±55.53
Extract(276 mg/kg)	19.33±1.02^c	47.40±4.15	21.83±8.45	1.94±0.48	3.30±0.55	12.90±2.10	8.03±2.80	0.26±0.08	1.20±0.30	406.33±25.26^a
Extract (553 mg/kg)	27.84±4.17	68.66±7.76	20.30±6.47	2.77±0.40	4.66±0.52	19.73±2.32	3.70±0.40	0.26±0.03	0.76±0.12	147.30±27.51
Hexane extract	16.90±3.79^c	74.96±6.09^a	20.90±4.77	3.56±1.07	5.53±1.57	21.70±5.89	4.40±1.29	0.46±0.08	1.30±0.53	174.66±51.85
DCM extract	7.36±3.64^c	66.30±1.80	39.46±8.13	6.43±3.94	6.20±1.89	23.00±7.68	5.13±0.96	0.83±0.28	1.56±0.31	119.60±54.87
Ethyl acetate extract	14.32±1.85^c	53.96±18.30	26.63±3.54	3.27±0.52	5.10±0.72	19.46±2.54	3.90±0.86	0.40±0.15	0.66±0.14^c	591.66±35.26^a
Methanol extract	10.47±3.03^c	72.93±4.32^a	29.83±7.33	4.57±0.39	6.93±0.66	25.80±2.95	8.36±3.41	0.60±0.05	1.30±0.32	118.33±39.02
Chloroquine	5.39±0.31^c	44.83±5.07^a	48.76±9.79^a	6.53±0.76	9.53±0.68^a	40.40±3.72^b	8.06±2.33	1.10±0.55	0.56±0.17^c	129.33±22.57

All values are presented as mean±S.E.M. for 5 rats in each group compared with control group ^{a}p<0.05, ^{b}p<0.01, ^{c}p<0.00. WBC-white blood cell, NEUT-Neutrophils,RBC- Red blood cell, LYM-Lymphocytes, MONO-Monocytes, ESINO-Esinophils, BASO- Basophils, HGB-Hemoglobin, PCV- Packed cell volume, PLT-Platelet

Table 3: Effect of Crude and Gradient Extracts of *T. occidentalis* Seed on Liver Function Parameters of Mice Infected With *Plasmodium berghei*

Treatment	Dose (mg/kg)	LIVER FUNCTION PARAMETERS							
		AST (IU/L)	ALT(IU/L)	ALP(IU/L)	Total Cholesterol	Total protein (g/L)	Albumin (g/L)	Total bilirubin(µmol/mL)	Conjugated bilirubin(µmol/mL)
Control	-	33.42±1.34	23.01±0.11	35.86±2.02	4.22±0.37	76.66±0.35	44.26±0.53	6.33±0.43	4.48±0.18
Crude Extract	138	23.22±1.21^b	18.01±1.32^a	27.10±0.36^c	3.18±0.10	62.46±0.66	42.00±1.15	5.14±0.14	3.76±0.14
	276	21.33±0.54^b	17.33±0.25^b	24.02±0.66^c	2.20±0.12	61.83±1.18^c	41.30±1.38	4.42±0.66	3.38±0.33^b
	553	20.51±0.45^b	14.02±0.56^c	21.33±0.57^c	2.14±0.19	60.47±1.38^c	39.33±1.85^a	4.20±0.22^a	2.86±0.24^c
n-hexane	276	22.33±1.38^b	17.66±0.22^b	28.25±0.33^c	2.88±0.02	62.34±0.89^c	42.66±1.45	5.10±0.26	3.56±0.66
Dichloromethane	276	21.02±1.26^b	15.34±1.02^a	20.12±0.22^c	2.36±0.15	61.53±1.56^c	37.58±1.15^b	4.20±0.44^a	3.27±0.16^b
Ethyl acetate	276	22.10±0.44^b	17.55±0.18^c	21.18±0.38^c	2.33±0.33^a	63.00±0.66^c	41.33±2.30^a	4.68±0.15^a	3.57±0.44^c
Methanol	276	20.12±0.26^b	14.03±0.78^b	19.02±0.44^c	2.10±0.05	60.12±2.89^a	35.38±0.33^c	4.14±0.66	2.66±0.78^c
Chloroquine	5	20.33±1.29^b	16.88±1.26^a	19.26±0.16^c	2.20±0.36^b	61.89±1.65^c	38.26±0.56^c	4.10±0.66^b	3.12±0.87^a

Values are expressed as mean ± SEM. Significant relative to control. ^{a}p<0.05; ^{b}p<0.01; ^{c}p<0.001. n = 6.AST- Aspartate aminotransferase,ALT- Alanine aminotransferase, ALP- Alkaline phosphatase

Effect of crude and gradient extracts of Telfairia occidentalis seed on liver oxidative stress markers of Plasmodium berghei-infected mice

The non-enzymatic and enzymatic endogenous antioxidants (GSH, SOD, CAT, GPx, and GST) were found to be reduced in the untreated *Plasmodium berghei*-infected mice. However, treatment of *Plasmodium berghei*-infected mice with crude and gradient extracts of *Telfairia occidentalis* seed caused dose-dependent and significant ($p<0.05$-0.001) increases in the levels of these enzymatic and non-enzymatic antioxidants when compared to control. The highest dose of the crude extract (553 mg/kg) and methanol gradient extract produced the most significant ($p<0.001$) increases in these antioxidants levels relative to control. The MDA level which was elevated in the untreated infected mice was decreased by crude and gradient extractstreatment and the decrease was significant ($p<0.05$-0.001) when compared to control (Table 4).

Table 4: Effect of Crude and Gradient Extracts of *T. occidentalis* Seed on Liver Antioxidant Enzymes of Mice Infected with *Plasmodium berghei*

Treatment	Dose (mg/kg)	ANTIOXIDANT PARAMETERS					
		GSH (µg/mL)	SOD (µg/mL)	CAT (µg/mL)	GPX (µm/mL)	MDA (µmol/mL)	Liver weight (g)
Control	-	0.22±0.001	2.18± 0.12	0.025±0.001	1.28±0.01	0.56±0.01	2.31±0.16
Crude Extract	138	0.22±0.01	4.28±0.15^{c}	0.038±0.001^{c}	1.74± 0.01^{b}	0.42±0.02^{a}	2.16±0.01
	276	0.35±0.03^{a}	4.88± 0.23^{c}	0.041±0.001	1.90± 0.02	0.31±0.01^{c}	2.24±0.20
	553	0.38±0.01^{b}	6.04±0.14^{c}	0.043±0.002^{c}	2.23± 0.02^{c}	0.26±0.05^{b}	2.32±0.16
n-hexane	276	0.25±0.01^{c}	5.39± 0.66^{c}	0.039±0.004^{c}	1.88± 0.05^{b}	0.40±0.02^{b}	2.14±0.18
Dichloromethane	276	0.30±0.02	5.73±0.58^{c}	0.044±0.002^{c}	2.00± 0.01^{a}	0.38± 0.02^{b}	2.14±0.05
Ethyl acetate	276	0.24±0.02^{c}	4.87±0.65^{c}	0.038±0.0003^{c}	1.81± 0.01^{a}	0.42± 0.01^{a}	2.29±0.13
Methanol	276	0.33±0.02^{b}	5.81±0.56^{c}	0.045±0.0001^{c}	2.30±0.02^{c}	0.29±0.01^{b}	2.21±0.22
Chloroquine	5	0.35±0.03^{c}	4.78± 0.33^{c}	0.042±0.0020^{c}	1.99± 0.05^{b}	0.40±0.01^{a}	2.28±0.12

Values are expressed as mean ± SEM. Significant relative to control. $^{a}p<0.05$; $^{b}p<0.01$; $^{c}p<0.001$. n = 6. SOD- superoxide dismutase, CAT-catalase, GPx- glutathione peroxidase, MDA- malondialdehydeand GSH-reduced glutathione.

Effect of crude and gradient extracts of Telfairia occidentalis seed on lipid profile of Plasmodium berghei-infected mice

Treatment of *Plasmodium berghei*-infected mice withcrude and gradient extracts of *Telfairia occidentalis* seed (138 - 553 mg/kg) did not cause any significant ($p>0.05$) effect on the lipid profile parameters (total cholesterol, triglycerides, HDL, LDL, and VLDL) when compared to control. Although there were slight decreases in the levels of these indices in the respective treatments, these decreases were not significantly different ($p>0.05$) when compared with that of the control (Table 5).

Table 5: Effect of crude and gradient extracts of *Telfairia occidentalis* on lipid profile of mice infected with *Plasmodium berghei*

Treatment	Dose mg/kg	Total cholesterol (mMol/L)	Triglyceride (mMol/L)	HDL-C (mMol/L)	LDL-C (mMol/L)	VLDL (mMol/L)
Control	10 mL/kg	4.36± 0.31	1.56± 0.14	1.43± 0.08	2.43± 0.29	0.70± 0.02
Crude extract	138	3.26±0.32	1.38± 0.08	1.50± 0.03	2.33± 0.14	0.66± 0.03
	276	3.16± 0.12	1.34± 0.02	1.50± 0.06	2.45± 0.10	0.61± 0.01
	553	3.04± 0.66	1.23± 0.03	1.40± 0.09	2.42± 0.19	0.52± 0.04
n-hexane	276	3.20± 0.11	1.29± 0.06	1.54± 0.04	2.86± 0.28	0.58± 0.01
Dichloromethane	276	3.23± 0.26	1.43± 0.05	1.67± 0.03	2.34± 0.34	0.64± 0.02
Ethyl acetate	276	3.76± 0.26	1.33± 0.13	1.54± 0.04	2.35± 0.12	0.60± 04
Methanol	276	3.13± 0.31	1.20± 0.03	1.54± 0.13	2.28± 0.13	0.65± 0.02
Chloroquine	5	3.50± 0.11	1.42± 0.04	1.50± 0.04	2.29± 0.09	0.64± 0.04

Data are expressed as MEAN ± SEM. (n=5).

Effect of crude and gradient extracts on the histology of liver of Plasmodium berghei-infected mice.

Histological sections of livers of infected mice receiving various treatments at magnification (x100) stained with H&E method revealed that untreated infected mice in group 1(control) given distilled water (10 mL/kg) had liver tissue demonstrating a severely altered hepato-architecture with areas of degenerated hepatic cells, inter-hepatic fibrosis, increased degenerating and vacoulated hepatocytes, widespread micro-vesicular steatosis, and shrinked ductal cells within the hepatic portal area. Infected mice in group 2 treated with low dose of the crude extract (138 mg/kg) had liver tissue showing a less protected and moderately altered hepato-architecture with increased degenerating and vacoulated hepatocytes, increasing spread of micro-vesicular steatosis within the hepatic lobules and fibrosis of the interstitial connective tissues area surrounding the portal triad. Group 3 infected mice treated with the middle dose of the crude extract (276 mg/kg) had liver tissue showing a protected hepatic architecture with well-presented portal vein, and hepatic artery, within the portal area, well-protected hepatocytes, and widespread presence of proliferated Kupfer cells within the sinusoids of the hepatic lobules. Liver section of mice treated with high dose of the crude extract (553 mg/kg) showed a less protected and moderately altered hepato-architecture

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with increased degenerating and vacoulated hepatocytes, increasing spread of micro-vesicular steatosis within the hepatic lobules and fibrosis of the interstitial connective tissues area surrounding the portal triad. Liver tissues of infected mice in group 5 treated with n-hexane gradient extract showed a non protected and severely altered hepato-architecture with increased degenerating and vacoulated hepatocytes. Group 6 infected mice treated with DCM gradient extract had liver tissue showing a protected hepatic architecture with well-presented portal vein, and hepatic artery, within the portal area, well-protected hepatocytes, and widespread presence of proliferated Kupfer cells within the sinusoids of the hepatic lobules. Ethyl acetate gradient extract treated infected mice in group 7 had liver tissue demonstrating a protected and mildly altered hepato-architecture with sparse degenerating and vacoulated hepatocytes, and widespread presence of proliferated Kupfer cells within the sinusoids of the hepatic lobules. Methanol gradient extract treated mice in group 8 had liver tissue demonstrating a less protected and moderately altered hepato-architecture with degenerated hepatocytes and vacoulated hepatocytes, increasing spread of micro-vesicular steatosis within the hepatic lobules and fibrosis of the interstitial connective tissues area surrounding the portal triad. Chloroquine treated mice had liver tissue demonstrating a protected hepatic architecture with well-presented portal vein, and hepatic artery, within the portal area, well-protected hepatocytes, presence of Kupfer cells, and sinusoids within the hepatic lobules (Figure 1).

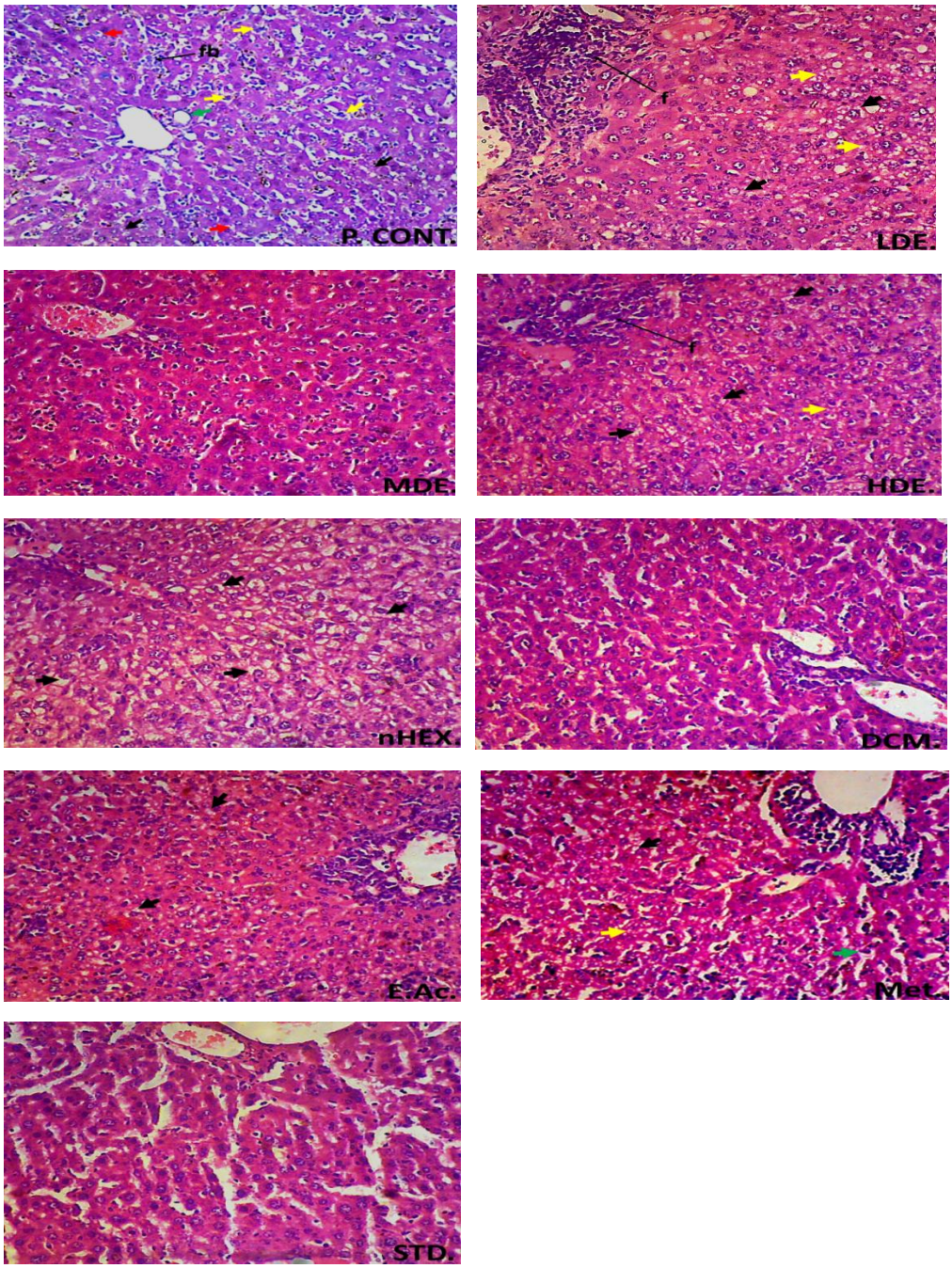

Figure 1: Histologic liver sections of *Plasmodium berghei*-infected mice treated with normal saline (CONT), seed extract of *T. occidentalis*, 138 mg/kg (LDE), 276 mg/kg (MDE), 553 mg/kg (HDE), n-hexane fraction(n-HEX), DCM fraction (DCM), ethyl acetate fraction (E.AC), methanol fraction MET) and chloroquine, 5 mg/kg (CHQ) at magnification X400. Keys:degenerated hepatic cells (yellow arrow) increased degenerating and vacoulated hepatocytes (red arrow), widespread micro-vesicular steatosis (black arrow), fibrosis of connective tissues (fb),shrinked ductal cells (green arrow) and organic deposits (Od) inter-hepatic fibrosis (fb).

GC-MS analysis

GC-MS analysis of methanol fraction indicated that it contains unsaturated fatty acids such as acetic acid, 1,1-dimethylethyl ester, butanoic acid, 1,1-dimethylethyl ester, propanoic acid, hexanoic acid, 5,6-dibromo-6-[p-chlorophenyl]-2,4-dioxo-, ethyl ester,octanoic acid, palmitic acid, 9-hexadecenyl ester, (Z)-,oleic acid, 2-(1-octadecenyloxy)ethyl ester, (E)-,9,12-Octadecadienoic acid (Z,Z)-, 2-[(trimethylsilyl)oxy]-1-[[(trimethylsilyl)oxy]methyl]ethyl ester, α-Carotene,7,8-dihydro-3,3',19-trihydroxy-8-oxo-, triacetate,pentaethylene glycol monododecyl ether, eicosanoic acid, eicosanoic acid, octadecyl ester, octanoic acid, 2-hexenyl ester, (E), 1,3-Dioxolane-2-pentanoic acid, 2-methyl-, ethyl ester, 9,12-Octadecadienal, 1-dodecyne, 13-Tetradece-11-yn-1-ol, cyclopropanecarboxylic acid, dodec-9-ynyl ester (Figure 2).

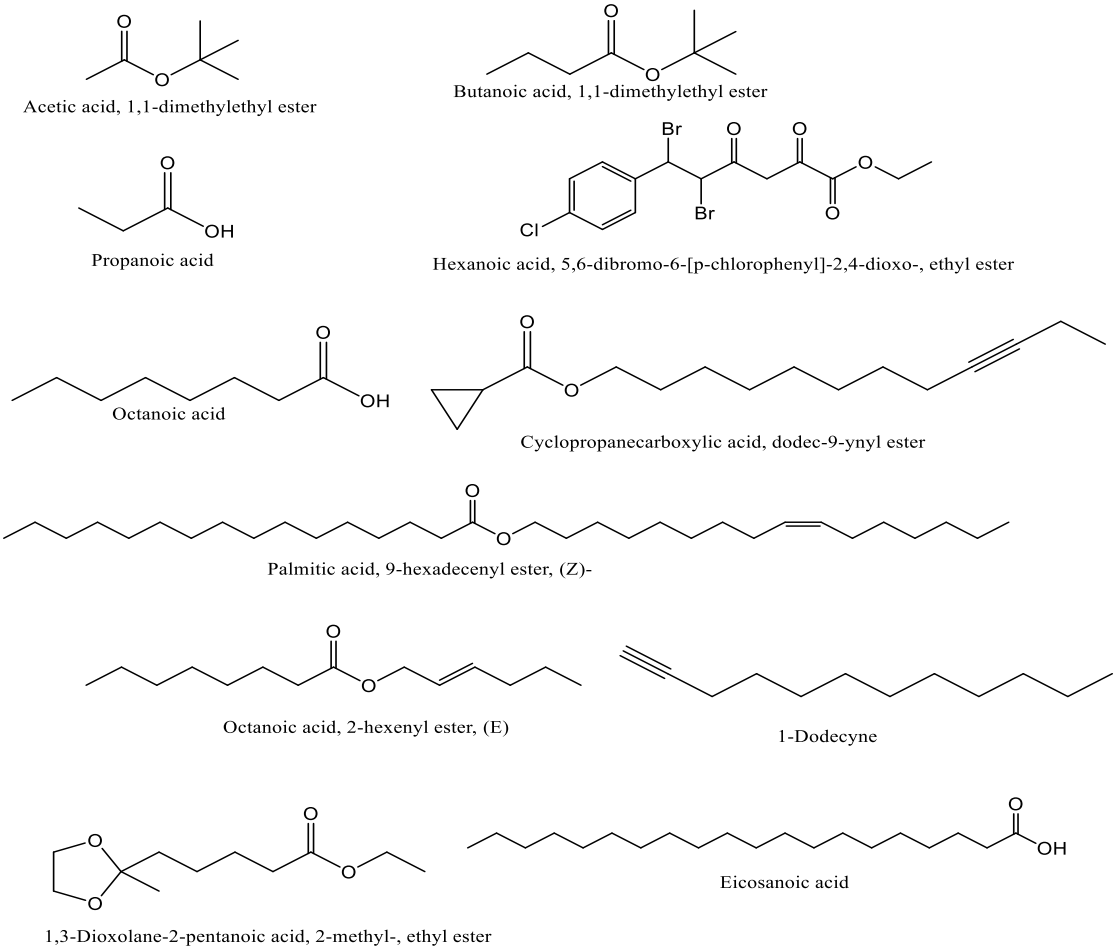

Figure 2: Phytochemical constituents of methanol fraction of seed extract

The seeds of *T. occidentalis* are used locally as food and also to treat various diseases such as malaria, diabetes, fever, inflammatory diseases and pain among others. The seed crude and gradient extracts of *T.occidentalis* were investigated for antimalarial activity against rodent malaria parasite, *P. berghei* infection in mice using standard *in vivo* models. It was found that the extracts significantly reduced the parasitaemia in a dose-dependent fashion with methanol gradient extract exerting the highest suppression, confirming the antimalarial potential of the seed extract.

Prolonged MST of the extracts' treated infected mice was also observed suggesting a considerable protection by the extracts. The extracts may have exhibited plasmodicidal or plasmodistatic activity in this regard which further confirms and validates the use of the seed decoctions as malarial remedy. The observed slight variations in the activities of the extracts may have resulted immunostimulating potentials of some constituents of these extracts. Tannins and fatty acids such as linoleic acids have been reported to possess immune-stimulating properties. [19]

The strong activities of the extracts on the progression of *Plasmodium berghe i*parasitaemia as observed in the study, suggest their effect on the erythrocytic stages of the parasite.[29] The incomplete protection of the infected mice in most cases by the extracts could have resulted from low doses (138 - 553 mg/kg) used, short half-life/duration of action of the extracts due to rapid biotransformation processes and subsequent elimination.[29]However, these results corroborate with previous reports on antimalarial activities of the leaf, seed and root extracts of *T. occidentalis*.[9,30] These results validate the use of the seed of *T. occidentalis* decoctions as malarial remedy.

Okokon *et al*. [12] had previously reported the presence of pharmacological active compounds such as fatty acids esters, aromatic esters, aldehydes and stigmasterols in the seed extract. Also, the GC-MS analysis of active methanol fraction indicated the presence of unsaturated fatty acids such as hexanoic acid, 5,6-dibromo-6-[p-chlorophenyl]-2,4-dioxo-, ethyl ester,octanoic acid, palmitic acid, 9-hexadecenyl ester, (Z)-,oleic acid, 2-(1-octadecenyloxy)ethyl ester, (E)-,9,12-Octadecadienoic acid (Z,Z)-, 2-[(trimethylsilyl)oxy]-1-[[(trimethylsilyl)oxy]methyl]ethyl ester, α-Carotene, 7,8-dihydro-3,3',19-trihydroxy-8-oxo-, triacetate, and eicosanoic acid, octadecyl ester among others. A recent study reported that HPLC characterisation of the seed extract and fractions showed eleven flavonoids; kaempferol, catechin, epicatechin, anthocyanidin, narigenin, flavonones, flavones, narigenin, rutin, naringin, and resveratol in the seed extract and fractions.[16]. Some alkaloids such as ribalinidine, ammodendrine, spartein and lunamarin were also confirmed in the seed extract. [16] In their study, the polar fraction (butanol) had significantly high flavonoid and alkaloid levels compared to others. This outcome in part, supported our findings of high antiplasmodial activities in the methanol gradient extract.

Phytoconstituents such as alkaloids, flavonoids and triterpenoids as well as polyunsaturated fatty acids (PUFAs) such as hexadecanoic acid, methyl ester, 9,12-octadecadienoic acid methyl ester (linoleic acid), 9,12,15-octadecatrienoic acid, methyl ester (linoleic acid), and 9-octadecenoic acid as found in the seed extracts in this study have been reported to exert antiplasmodial activity.[31]Monoterpenes such as limonene (trans-β-ocimene and α-pinene), found in organic materials have been implicated in endoperoxidation leading to plasmocidal activity.[32]

GC-MS analysis of the dichloromethane fraction have revealed the presence of hexadecanoic acid, monoterpenes like trans-β-ocimene and α-pinene and other compounds, which are active antioxidant compounds.[19] The compounds present in the seed extracts maybe responsible for the observed antiplasmodial activities. Antioxidant activities linked to flavonoids have been suggested to account for the antiplasmodial activity of many plants, [33] because raised free radical levels are common features of severe malaria complications. Reduction of these free radicals generation could be responsible for the activities of these extracts. These compounds present in these seed extracts may have contributed to the plasmodicidal activity of the extracts.

Raised transaminases levels and hyperbilirubinemia were observed in untreated infected animals. Malaria infection has been linked to hepatic dysfunction with prominent increased liver enzymes activities due to blood flow alteration, sinusoids blockage, intrahepatic blood flow obstruction and immune responses.[34] Liver excretory function impairment results in hyperbilirubinemia.[35] Administration of seed extracts of *T.occidentalis* to *P. berghei*-infected mice was found to decreased the elevated total protein, albumin, AST, ALT, ALP, direct and total bilirubin. The increases recorded in serum total protein, albumin, ALT, AST, ALP, direct and total bilirubin in the parasitized non-treated mice were suggested to have resulted from hyper-parasitemia responses.[36] Hepatic dysfunction may have been responsible for the increased serum AST, ALT, and ALP activities in *P. berghei*infected mice observed in this study [37,38] or hepatic damage as could be confirmed in the liver histology. The observed increase in activities of markers enzymes corroborated the report of Uzuegbu and Emeka.[39] However, administration of *T. occidentalis* seed extracts reduced and restore normal levels of total protein, albumin, direct and total protein and the activities of AST, ALT and ALP in the serum of infected treated mice. The result is indicative of hepatoprotective activity of the seed extracts and further supports the hepatoprotective potential of the *T. occidentalis* previously reported.[40] Besides, the histological analysis of liver from malaria infected mice showed a significant pathologic sign expressed by general architectural alteration of liver with areas of degenerated hepatic cells, inter-hepatic fibrosis, increased degenerating and vacoulated hepatocytes, widespread micro-vesicular steatosis, and shrinked ductal cells within the hepatic portal area suggestive of inflammatory reaction in the tissue. These were reduced or absent following extracts' treatments which further confirm the hepatoprotective activity of the seed extract due to the antioxidant activities of its phytochemical constituents as previously reported.

In this study, the activities of SOD, CAT, GPx and GSH level were found to decrease significantly, while MDA level was significantly increased in the untreated infected group. These results corroborate previous reports [41,42] The seed extracts exerted protective effect by increasing the activity of antioxidant enzymes and molecules as well as reducing the level of MDA significantly, thus lipid peroxidation. This activity can be explained by the presence of PUFAs, flavonoids and monoterpenes among others that have capacity to scavenge free radicals [31,43]. These phytochemicals among others with antioxidant activities are present in this seed extracts and maybe responsible for the antioxidant activity of *T. occidentalis* seed as previously reported.[12,13]

The seed extracts did not cause any significant change in the treated red blood cell indices, PCV and Hb concentration when compared to control in this study. However, significant decreases in basophil percentage, WBC and platelets counts were observed in this study compared to the control. Increase in WBC count of untreated infected mice has been reported previously by several researchers in malaria infection.[44] This can be attributed to the parasites and their pigment (hemozoin) playing a key role in malaria immunogenic effects.[45] The leucocytosis significantly decreased in correlation to the reduction of the parasitaemia after treatment with the seed extract portraying a significant antimalarial activity. The platelets count of the extracts-treated infected mice were not affected significantly when compared to that of untreated *P. berghei*-infected mice except significant increase observed in the groups treated with the high dose (553 mg/kg) of the crude extract and ethyl acetate extract. The thrombocytopenia in malaria infection could be associated to platelets consumption as a part of disseminated intravascular coagulation, an excessive removal of normal or immunologically deranged platelets by the hypertrophied reticuloendothelial system or as a result of splenic pooling of platelets and decrease in platelet life span.[46] The treatment of infected mice with the *T. occidentalis* extracts must have protected the infected mice, though not at all treatments, from the immune cells and platelets dysregulation, through the presence of phyochemicals that could have acted by detoxification of enzymes and modulating effect on the immune system.[47]

Besides, malaria infection also induced oxidative modification of lipoproteins thereby contributing to oxidative stress, progression and complications of malaria infections.[48] The alteration in lipid metabolism has been attributed to acute phase response to the infection.[49] However, treatment with *T. occidentalis* seed extracts did not cause any significant ($p>0.05$) effect on serum concentration of total cholesterol (TC), triglyceride (TG), LDL and very low-density lipoprotein (VLDL) and HDL in the parasitized treated mice. The results suggest that the plant may not possess hypolipidemic potential at the doses administered in this study may be due to its low doses used, moderate antiplasmodial effect and free radical scavenging potentials.

Conclusion

The results of this study show that the seed extract and fractions of *T. occidentalis* possess anti-malarial, antiplasmodial, anti-oxidative stress and hepatoprotective activities. These pharmacological effects are likely due to the phytochemical constituents that are present in both the extract and fractions.These results confirm and validate its use in traditional medicine for treatment of various conditions such as malaria, diabetes, fever, etc.

Conflict of interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby, declare that the work presented in this article are original and that any liability for claims relating to the content of this article will be borne by them.

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