ASSESSMENT OF SOME INFLAMMATORY BIOMARKERS IN *PLASMODIUM BERGHEI* INFECTED MICE TREATED WITH ETHANOL EXTRACT OF *MUSA PARADIACA*

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ABSTRACT

Background: *Musa paradisiaca* possess certain medicinal properties as such have respective medicinal applications

Aim: The research aimed to assess the effect of a locally formulated herbal antimalarial therapy using dry plantain leaf extract (*Musa paradisiaca*) on some inflammatory biomarkers in mice infected with *Plasmodium berghei*

Methodology: Five groups of ten mice each namely control, *P. berghei* treated, artesunate treated *P. berghei* infected mice orally administered with curative, suppressive and prophylactic models 250, and 1000mg/kg *Musa paradisiaca leaf* extract for 5 days. Blood smears were evaluated for parasitaemia on the 10th day and the mice sacrificed. The animals were sacrificed and serum obtained from blood samples collected through cardiac puncture was used for Xyclogenase, interleukin 6 and Lipogenase analysis using immuno assay methods. The data obtained from the experiment was analyzed using SPSS version 21.

Results: The Interleukine 6 (pg/ml) was 123.85±5.43, 817.40±6-01, 235.11±5.19, 287.35±0.48, 286.70±0.59, 247.07±0.59, 381.70±0.11, 394.07±0.11, 711.06±7.47, 776.12±0.96 and 672.21±5.87 in control, *P.berghei,* Artesunate, 250, 1000 mg Curative, Artesunate, 250 mg and 1000 mg Suppressive, 250 mg and 1000 mg prophylactic respectively. The Xyclogenase (µ/l) was 8.19±0.00, 26.64±5.8, 18.03±0.95, 5.05±0.21, 3.69±0.49, 13.93±1.72, 4.04±0.62, 1.68±0.37, 5.33±1.42, 2.44±0.02 and 3.24±0.05 in control, *P.berghei,* Artesunate, 250, 1000 mg Curative, Artesunate, 250 mg and 1000 mg Suppressive, 250 mg and 1000 mg prophylactic respectively. The Lipogenase (µ/L) was 7.56±0.38, 24.00±0.53, 12.48±1.67, 31.62±35.93, 7.69±0.53, 15.84±0.51, 13.45±0.49, 24.15±0.53, 21.20±0.69, 17.81±1.26 and 10.28±0.47 in control, *P.berghei,* Artesunate, 250, 1000 mg Curative, Artesunate, 250 mg and 1000 mg Suppressive, 250 mg and 1000 mg prophylactic respectively.

Conclusion: The study showed that ethanol leaf extract of *Musa paradisiaca* reversed the induction of inflammatory markers such as 1L-6, xylclogenase, and lipogenase that was induced by *plasmodium berghie.*

Keywords: Interleukine 6, Xyclogenase, Lipogenase**,** *Plasmodium berghei, Musa paradisiaca*

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INTRODUCTION

Inflammation is the immune system's response to harmful stimuli, such as pathogens, damaged cells, toxic compounds, or irradiation and acts by removing injurious stimuli and initiating the healing process. Inflammation is therefore a defense mechanism that is vital to health (Nathan and Ding, 2010). Usually, during acute inflammatory responses, cellular and molecular events and interactions efficiently minimize impending injury or infection. This mitigation process contributes to restoration of tissue homeostasis and resolution of the acute inflammation. However, uncontrolled acute inflammation may become chronic, contributing to a variety of chronic inflammatory diseases (Zhou *et al.,* 2016). At the tissue level, inflammation is characterized by redness, swelling, heat, pain, and loss of tissue function, which result from local immune, vascular and inflammatory cell responses to infection or injury. Important microcirculatory events that occur during the inflammatory process include vascular permeability changes, leukocyte recruitment and accumulation and inflammatory mediator release (Takeuchi and Akira, 2016).

The etiologies of inflammation can be infectious or non-infectious (Medzhitov, 2010). Stimuli activate inflammatory cells, such as macrophages and adipocytes and induce production of inflammatory cytokines, such as IL-1β, IL-6, TNF-α and inflammatory proteins and enzymes. These molecules can potentially serve as biomarkers for diseases diagnosis, prognosis, and therapeutic decision making (Machowska *et al.,* 2016).

Inflammation is a biological response of the immune system that can be triggered by a variety of factors, including pathogens, damaged cells and toxic compounds. These factors may induce acute and/or chronic inflammatory responses in the heart, pancreas, liver, kidney, lung, brain, intestinal tract and reproductive system, potentially leading to tissue damage or disease. Both infectious and non-infectious agents and cell damage activate inflammatory cells and trigger inflammatory signaling pathways, most commonly the NF-κB, MAPK, and JAK-STAT pathways.

Plantain is an early cultivated plant and a major component of economy for various countries (Thompson, 2011). Plantain belongs to the species *Musa paradisiaca* of the family Musaceae and offer many healthy benefits. They act as a rich source of Vitamins, potassium, calcium, phosphorus and magnesium among others (Kumar *et al.,* 2012). All the parts of a Plantain plant possess certain medicinal properties, thus have respective medicinal applications. The fruit of *Musa paradisiaca* is an exceptional fruit offering different forms of nutrition. It is an excellent source of potassium and a single banana is said to provide 23% of potassium on daily basis. The flowers are useful in bronchitis, dysentery, and ulcers, whereas cooked flowers are given to people with diabetes. The fruit and leaves of Plantain are useful in treating burns and wounds (Rajesh, 2017). The fruit has a mild laxative property where as the plant sap is an astringent which is used in cases of hysteria, epilepsy, leprosy, fevers, hemorrhages, dysentery and diarrhoea. The unripe fruits have been evaluated for its antihyperglycemic, antioxidant, wound healing, hypolipidemic, hair growth promoter, cardioprotective and against thyroid dysfunction (Yakubu *et al.,* 2015). Plantain is also considered to be a rich source of antioxidants (Thompson, 2011). Bioactive compounds in Plantain leave include, phenolic compounds, carotenoids, biogenic amines, phytosterols.

Plasmodium berghei is found in the forests of Central Africa, where its natural cyclic hosts are the thicket rat (*Grammomys surdaster*) and the mosquito (*Anopheles dureni*).This species was first described by Vincke and Lips (1948) in the Belgian Congo. *Plasmodium berghei* was first identified in the thicket rat (*Grammomys surdaster*). It has also been described in *Leggada bella*, *Praomys jacksoni* and *Thamnomys surdaster.* In research laboratories, various rodents can be infected, such as mice, rats and gerbils (*Meriones unguiculatus*) (Junaid *et al.,* 2017).

In *P. berghei* infection, mice are found to have an accumulation of immune cells in brain blood vessels (Craig *et al.,* 2012).

The aim of this study is to assess Xyclogenase, interleukin 6 and Lipogenase in *Plasmodium berghei* infected Mice treated with ethanol extract of *Musa paradiaca.*

MATERIALS AND METHODS

Animal

A total of 106 healthy albino mice of about 2-3 months old weighing between 13-36g obtained from animal house of the Federal University of Technology, Owerri, Nigeria were used for the study. They were kept in the animal house of Madonna University, Elele campus and were housed in aluminum cages at room temperature and under light/darkness cycles. The mice were supplied with clean drinking water and fed *ad libitum* with standard commercial pelleted starter feed (vital feed) and were acclimatized for two weeks before administration. They were maintained in accordance with their commendations of the guide for the care and use of laboratory animals and experimental protocol was approved by the institution.

Extraction and preparation of plant materials

The leaves of *Musa paradisiaca* were obtained from a plantain plantation in Elele, Rivers State, Nigeria. They were cut into pieces, washed and dried. The dried pieces were grounded into fine powder using a manual grinder 10kg of the grounded powder was soaked in 10litres of 80% ethanol for 72 hours with intermittent stirring of the solution. The mixture was subsequently filtered through Whatman filter paper (125mm). The extract was concentrated using a rotary evaporator at 45°C and then dried with a water bath at 39°C to yield 40g of dark semi-solid extract and kept at 0-4°C until needed for use.

Parasite innoculation

A chloroquine sensitive strain of *Plasmodium berghei* (NK 65 strain) parasite used in this study was obtained from the Department of Pharmacology and Toxicology, Faculty of Basic Clinical Sciences, University of Port Harcourt, Rivers State, Nigeria. The *Plasmodium berghei* was sustained by constant re-infestation of parasitized erythrocytes which were sourced from a donor-infected mouse by the tail via a heparinized syringe and made up to 20ml with normal saline. The animals were inoculated with 0.2ml of infected blood suspension. The donor mice were monitored for signs of infection which include; lethargy, anorexia, shivering and heat-seeking environment. Parasitemia was monitored daily by microscopic examination of Giesma stained thick film and viewed at ×100 objective. Furthermore, malaria parasite infection was detected by thin film stained with Leishman stain by parasite count using the formula:

Parasite density =Number of parasites counted × 100white blood cells/Number of white blood cells counted.

Acute toxicity study (LD_{50})

The crude extract of *Musa paradisiaca* leaf was evaluated for their toxicity in *P. berghei* non infected Swiss albino mice aged 2 months weighing 18-20g using, modified Locke's method of determining toxicity level of extract in mice (Guideline OO. 2001).

Experimental design

A total of 150 mice weighing 10-37g were assigned into 15 groups of ten mice each. The mice were then grouped into Curative, Suppressive and prophylactic groups and each treated as explained below.

Curative or Rane Test by evaluating Schizontocidal activity in Established Infection

The curative potential evaluation of the extract was done using a method of Ryley and Peter (1970). Standard inoculums of $1x10^{7}$ *P. berghei* infected erythrocytes were injected intraperitoneally on the mice except the control, on the first day (Day 0). Seventy-two hours later (day 3) the mice were divided into five groups of ten mice each. The groups were orally administered with *Musa paradisiaca leaf* extract (250 and 1000mg/kg/day), 50mg/kg artesunate to the artesunate group, normal food and water to the *P. berghei* while a 250ml volume of distilled water and food adlibitum were given to control group.

The drug extract was given orally once daily for 5days. Thin films stained with 10% Giemsa at pH 7.2 for 10 min and parasitaemia examined microscopically on each day of treatment to monitor parasiteamia level (Peters and Robinson 1992).

Evaluation of Blood Schizontocidal Activity on Early Infection (Suppressive Test)

Schizontocidal activity of the extract fraction and artesunate against early *P. berghei* infection was evaluated using the method of Knight and Peters (1980). Each mouse was inoculated on the first day (Day 0), intraperitoneally, with 0.2ml of infected blood containing about 1 X 10^7*Plasmodium berghei* parasitized erythrocytes except the control group. The animals were divided into five groups of ten mice each and orally administered shortly after inoculation with 250, and 1000 mg/kg/day doses of the *Musa paradisiaca* leaf extract, artesunate 50 mg/kg/day and a 250ml volume of distilled water to the control for five consecutive days, (day 0 to day 4) while the last group was fed food and water. On the 5th day (day 5), thin films were made from the tail blood of each mouse and smear on to a microscope slide to make a film. The blood films were fixed with methanol, stained with 10% Giemsa at pH 7.2 for 10 minutes and parasitaemia examined microscopically and the parasitaemia level was determined by counting the number of parasitized erythrocytes out of 200 erythrocytes in random fields of the microscope (Peters and Robinson 1992).

Average percentage chemo suppression was calculated as: 100[(A−B)/A], where A is the average percentage parasitaemia in the negative control group and B is the average parasitaemia in the test/standard group (Peters and Robinson 1992).

Evaluation of prophylactic activity (Repository test)

The method of Peters (1967) was adopted in the evaluation of the prophylactic potential of *M. paradisiaca*. In this method, Fifty mice randomly divided into five groups of 10 mice was assigned to control group, artesunate treated, *P. berghei* infected and the experimental groups of 250 and 1000mg/kg/day body weight *Musa paradisiaca* leaf extract. The control were administered diet and water *ad libitum*, the artesunate treated was given 50 mg artesunate per kg body weight intraperitoneally while the experimental groups were administered with 250, and 1000mg/kg/day body weight *Musa paradisiaca* leaf extract and the last group was infected with *P. berghei*. Treatments were initiated on day 0 and continued until day 4; the mice were all infected with the parasite except the control. Blood smears were then made from each mouse 72 hours after treatment (Abatan, and Makinde 1986) while the increase or decrease in parasitaemia was then determined by determining the number of parasites present per high power microscope field using a thin film and the red blood cell count.

Sample collection and analysis

At the end of 10days of treatment, the blood samples were collected with a sterile syringe and needle and was put in plain tubes. The samples were centrifuged at 1500rpm (revolution per minute) for 10 minutes. After centrifugation, the serum obtained was used for the analysis.

Determination of interleukin 6

Principle: This ELISA kit uses the Sandwich-ELISA principle. The micro ELISA plate provided in this kit has been pre-coated with an antibody specific to Rat IL-6. Standards or samples are added to the micro ELISA plate wells and combined with the specific antibody. Then a biotinylated detection antibody specific for Rat IL-6 and Avidin-Horseradish Peroxidase (HRP) conjugate are added successively to each micro plate well and incubated. Free components are washed away. The substrate solution was added to each well. Only those wells that contain Rat IL-6, biotinylated detection antibody and Avidin-HRP conjugate change to blue in color. The enzyme-substrate reaction was terminated by the addition of stop solution and the color turns yellow.

The optical density (OD) was measured spectrophotometrically at a wavelength of 450 nm ± 2 nm. The OD value is proportional to the concentration of Rat IL-6. The concentration of Rat IL-6 in the samples were determined from the standard curve.

Procedure: One hundred microliter (100uL) of the Standard working solution was added to the first two columns in duplicate. One hundred microliter (100uL) of the samples was added to the sample wells. The plate was covered with the sealer and Incubated for 90 minutes at 37°C. The solutions were added to the bottom of the micro ELISA plate well, The liquid was removed out of each well and Immediately 100 µL of Biotinylated Detection Ab working solution was added to each well. It was covered with the plate sealer, gently mixed up and incubated for 1 hour at 37°C. The solution was decanted from each well, and washed thrice using 350 uL of wash buffer each time. The solution was decanted from each well and patted using clean absorbent paper. One hundred microliter (100uL) of HRP conjugate working solution was added to each well, covered and incubated for 30 minutes at 37°C. The solution was washed five times using 350 uL of wash buffer each time. Ninety microliter (90 µL) of substrate reagent was added to each well and covered and incubated for 15 minutes at 37°C with the plate protected from light. Fifty microliter (50 µL) of stop solution was added to each well in the same order as the substrate solution. The optical density (OD value) of each well was determined at once with a micro-plate reader set to 450Assay procedure (Chen *et al.,* 2016).

Determination of xyclogenase

Principle of Assay: The COX activity kit uses a specific chemiluminescent substrate to detect the peroxidative activity of COX enzymes. After inhibition by NSAIDs, the direct residual activity of COX is measured by addition of a proprietary luminescent substrate and arachidonic acid. Light emission starts immediately and is directly proportional to the COX activity in the sample. The chemiluminescent signals measured over 5 seconds. One Unit of COX activity is defined as the amount of enzyme needed to consume 1 nmole of oxygen per minute at 37°C.

Procedure: All sampling were done in duplicate. All samples were allowed to warm to room temperature and all activity measurements were done at room temperature. Fifty microliter (50 µL) of the Tris-phenol buffer was added into all wells. Fifty microliter (50 µL) of the hematin solution was added into all wells followed by Fifty microliter (50 µL).COX-I or COX-II preparations to all wells, except for the Blank and Zero Activity wells. The wells were pre-incubated at room temperature for 5 minutes. Twenty Five microliter (25 µL) of NSAID inhibitor solution was added to appropriate wells and incubated at room temperature for 120 minutes (dependent on inhibitor). The microtiter plate was placed in luminometer for the chemiluminescent measurement. Fifty microliter (50 µL) of cold COX Chemiluminescent Substrate was injcted followed by 50 µL of diluted cold arachidonic acid solution. The contents of the wells were read immediately in a luminometer for 5 seconds. The integrated light output for the 5 second read time in Relative Light Units (RLU) was determined while the average net Relative Light Units (RLU) for each standard and sample was determined by subtracting the average blank RLU from the average RLU for the standards and samples: $Average\ Net\ RLU = Average\ RLU – Average\ Blank\ RLU$ (Glover *et al.,* 2011).

Determination of Lipogenase

Principle: In the Lipoxygenase Activity Assay Kit, lipoxygenase converts the LOX substrate to an intermediate that reacts with the probe, generating a fluorescent product. The increase in fluorescent signal can be measured at λEx = 500 nm/λEm = 536 nm and is directly proportional to LOX activity. A lipoxygenase inhibitor that completely inhibits lipoxygenase activity is also included in order to calculate the specific activity of LOX in biological samples.

Procedure: Enough working reagents for the number of assays to be performed was mixed. Seventy microliter (70 uL) of Reaction Mix was prepared for each Sample (S) and Sample plus Inhibitor (SI) well and Mixed well while 70 uL of. Background Control was prepared for each Sample Background Control (BC) well and mixed well. The plate reader was set on kinetic mode set to record fluorescence every 30 seconds at λEx = 500 nm/ λEm = 536 nm. One hundred microliter (100ul) of Sample (S) and Sample plus Inhibitor (SI) was dispensed into the Sample (S), Sample plus Inhibitor (SI) and Positive Control wells respectively Seventy microliter (70 uL) of Reaction Mix was dispensed into each Sample (S), Sample plus Inhibitor (SI) and Positive Control wells of a 96-well white plate (pre-chilled on ice) containing the samples and positive control while 70 uL of. Background Control was dispensed into each Sample Background Control (BC) well. Measurement were started immediately at 30 second intervals for 30-40 minutes at room temperature by recording fluorescence (RFU).The total incubation time depends on the LOX activity in samples hence enzymatic activity of the samples were taken at two time points (T1 and T2) in the linear range. The oxidized probe Standard Curve was prepared and read in endpoint mode (i.e., at the end of the incubation time). The standard curve was obtained by Subtracting the Standard Background (zero Oxidized Probe) RFU reading from all other Standard RFU readings and the corrected Standard RFU readings was plotted against the Standard Oxidized Probe concentration. Also the Sample Background Control (BC) RFU values were subtracted from the corresponding Sample (S) RFU values and the amount of oxidized probe in each Sample reaction was estimated using the standard curve. The Change in amount of oxidized probe between time T1 and T2 was calculated while LOX activity was calculated in sample (nmol/ (min × mL) or mU/mL) = $\Delta M \times DF\ \Delta T \times V$, where ΔM = Change in amount of oxidized probe between time T1 and T2 ΔT = T2 – T1 (minutes) V = Sample protein content added to well (mg) DF = Dilution factor of Sample It should be noted that Specific lipoxygenase activity in sample = Detected activity in Sample – Detected activity in Sample plus Inhibitor. One unit of lipoxygenase is the amount of enzyme that will cause oxidation of 1 μmol of the LOX probe per minute at pH 7.4 at room temperature (Nishikimi *et al.*, 2022).

Statistical analysis

Data obtained were subjected to statistical analysis using statistical package for social science version 21 using statistical tools such as t-test and analysis of variance (ANOVA). Results were expressed as Mean ± Standard Deviation (X±SD).The values of $P<0.05$ was considered significant.

RESULT

INTERLEUKINE 6, XYCLOGENAGE AND LIPOGENASE CONCENTRATIONS IN P.BERGHEI INFECTED MICE TREATED WITH CURATIVE ETHANOL LEAF EXTRACT OF MUSA PARADISIACA

The Interleukine 6 (pg/ml) of 123.85±5.43 in control was increased by *P. berghei* to 817.40±6-01. The Interleukine 6 (pg/ml) was 235.11±5.19, 287.35±0.48 and 286.70±0.59 in Artesunate, 250 mg and 1000 mg curative respectively. The Xyclogenase (µ/l) activity of 8.19±0.00 in control was increased by *P. berghei* to 26.64±5.8 while administration of artesunate, 250 and 1000 extract reduced it to 18.03±0.95, 5.05±0.21 and 3.69±0.49. The Lipogenase (µ/L) of 7.56±0.38 in control was increased by *P. berghei* to 24.00±0.53 while administration of artesunate, 250 and 1000 extract increased it to 12.48±1.67, 31.62±35.93 and 7.69±0.53 respectively.

Table 1: Interleukine 6, xyclogenage and lipogenase concentrations in *P. berghei* infected mice treated with curative ethanol leaf extract of *Musa paradisiaca*

Group	Interleukine 6 (pg/ml)	Xyclogenase (µ/l)	Lipogenase (µ/L)
Control	123.85±5.43	8.19±0.00	7.56±0.38
P bergei	817.40±6-01*	26.64±5.80*	24.00±0.53*
Artesunate	235.11±5.19*,**	18.03±0.95*,**	12.48±1.67*,**
250 mg curative	287.35±0.48*,**	5.05±0.21**	31.62±35.93*,**
1000 mg curative	286.70±0.59*,**	3.69±0.49*,**	7.69±0.53**

*= Compare with the control
**= Compare with the *P.berghei* treated

The Interleukine 6 (pg/ml) of 123.85±5.43 in control was increased by *P. berghei* to 817.40±6-01. The Interleukine 6 (pg/ml) was 247.07±0.59, 381.70±0.11 and 394.07±0.11 in Artesunate, 250 mg and 1000 mg Suppressive respectively. The Xyclogenase (µ/l) activity of 8.19±0.00 in control was increased by *P. berghei* to 26.64±5.8 while administration of artesunate, 250 and 1000 extract reduced it to 13.93±1.72, 4.04±0.62 and 1.68±0.37. The Lipogenase (µ/L) of 7.56±0.38 in control was increased by *P. berghei* to 24.00±0.53 while administration of artesunate, 250 and 1000 extract increased it to 15.84±0.51, 13.45±0.49 and 24.15±0.53 respectively.

Table 2: Interleukine 6, xyclogenage and lipogenase concentrations in *P. berghei* infected mice treated with suppresive ethanol leaf extract of *Musa paradisiaca*

Group	Interleukine 6 (pg/ml)	Xyclogenase (µ/l)	Lipogenase (µ/L)
Control	123.85±5.43	8.19±0.00	7.56±0.38
P bergei	817.40±6-01*	26.64±5.80*	24.00±0.53*
Artesunate	247.07±0.59*,**	13.93±1.72*,**	15.84±0.51*,**
250 mg Suppressive	381.70±0.11*,**	4.04±0.62*,**	13.45±0.49*,**
1000 mg Suppressive	394.07±0.11*,**	1.68±0.37*,**	24.15±0.53*

*= Compare with the control
**= Compare with the *P.berghei* treated

The Interleukine 6 (pg/ml) of 123.85±5.43 in control was increased by *P. berghei* to 817.40±6-01. The Interleukine 6 (pg/ml) was 711.06±7.47, 776.12±0.96 and 672.21±5.87 in Artesunate, 250 mg and 1000 mg prophylactic respectively. The Xyclogenase (µ/l) activity of 8.19±0.00 in control was increased by *P. berghei* to 26.64±5.8 while administration of artesunate 250 and 1000 extract reduced it to 5.33±1.42, 2.44±0.02 and 3.24±0.05. The Lipogenase (µ/L) of 7.56±0.38 in control was increased by *P. berghei* to 24.00±0.53 while administration of artesunate, 250 and 1000 extract increased it to 21.20±0.69, 17.81±1.26 and 10.28±0.47 respectively.

Table 3: Interleukine 6, xyclogenage and lipogenase concentrations in *P.berghei* infected mice treated with prophylactic ethanol leaf extract of *Musa paradisiaca*

Group	Interleukine 6 (pg/ml)	Xyclogenase (µ/l)	Lipogenase (µ/L)
Control	123.85±5.43	8.19±0.00	7.56±0.38
P bergei	817.40±6-01*	26.64±5.80*	24.00±0.53*
Artesunate	711.06±7.47*	5.33±1.42**	21.20±0.69*
250 mg prophylactic	776.12±0.96*	2.44±0.02*,**	17.81±1.26*,**
1000 mg	672.21±5.87 *,**	3.24±0.05*,**	10.28±0.47**

*= Compare with the control
**= Compare with the *P.berghei* treated

DISCUSSION

Musa paradisiacal is a major staple food to major parts of African and the world. Its fruit and leaves are used in treatment of wound, burn, hysteria, epilepsy, and leprosy (Rajesh, 2017).The study was done to evaluate the serum interleukin 6(1L-6), xyclogenase, and lipogenase in mice infected with *plasmodium berghie* that have been treated with curative, suppressive and prophylactic ethanol leaf extract of *Musa paradisiaca.*

In the study, there was significant increase (P<0.05) in 1L-6, xyclogenase, and lipogenase concentrations in mice infected with *plasmodium berghie* compared with their respective controls (curative, suppressive and prophylactic models). This is similar to previous studies by Borges *et al*., (2017) and Wang *et al*., (2023). Borges *et al*., (2017) reported that the expression of eicosanoid-producing enzymes in mice sensitive to cerebral malaria increases the expression of cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX) in the vessels and brain tissue, followed by high levels of the transcriptional regulators of lipid metabolism, peroxisome proliferator-activated receptor gamma (PPAR-γ), which results in increased parasitemia, reduced survival, and less NO and H_2O_2 production in those animals while Wang *et al*., (2023) reported that Placenta malaria caused by *Plasmodium berghei* and *plasmodium falciparum* can upregulate prostaglandin synthesis by increasing COX-2 enzyme activity. This is suggestive that *plasmodium berghie* induce inflammatory markers such as 1L-6, xyclogenase, and lipogenase.

The administration of curative, ethanol leaf extract of *Musa paradisiaca* showed significant reduction in 1L-6, xylclogenase, and lipogenase concentrations suggestive that the extract reversed the induction of inflammatory markers. This agree with previous study by Widoyanti *et al*., (2023). Widoyanti *et al*., (2023) reported that the ethyl acetate leaf extract of *Musa paradisiaca* showed the strongest antioxidant capacity and anti-inflammatory activity, probably through the inhibition of inducible nitric oxide synthase (iNOS) and 15-lipoxygenase (15-LOX) and reported Positive correlations between the activities and the total phenolic/flavonoid content of banana byproducts. An in silico docking analysis demonstrated that flavonoid glycosides in banana byproducts, such as kaempferol-3-O-rutinoside and rutin, may bind to inducible iNOS, whereas omega-3-polyunsaturated fatty acids, such as eicosapentaenoic acid, may bind to 15-LOX and cyclooxygenase-2 (COX-2). The broad spectrum of bioactivities attributed to flavonoids in the human body such as antioxidant, anti-inflammatory, anti-mutagenic, and anti-viral make them favorable to be used in different dietary approaches (Rakhaa *et al.,* 2022). Kurnijasanti and Candrarisna (2019) reported that banana stem extract can decrease TNFα, IL-1ß and IL-6 expression along with the increased dose of banana stem extract.

The administration of suppressive ethanol leaf extract of *Musa paradisiaca* showed significant reduction in 1L-6, xylclogenase, and lipogenase concentrations. This is suggestive that the extract reversed the induction of inflammatory markers. The administration of prophylactic ethanol leaf extract of *Musa paradisiaca* also showed significant reduction in 1L-6, xylclogenase, and lipogenase concentrations except at 250mg of the leaf extract on 1L-6 suggestive that the extract reversed the induction of inflammatory markers at 1000mg of the leaf extract. Numerous plant-derived bioactive compounds, predominantly flavonoids may inhibit the inflammation by reducing the level of several cytokines (IL-6, IL-1β, and TNF-α) or otherwise suppressing its key mediators such as prostaglandin, COX-2, and ROS (Ginwala *et al*., 2019). Adegoke *et al* (2023) reported that *Musa paradisiaca* leaf extract protects brain of *Plasmodium berghei* infected mice from free radicals. George-Opuda *et al* (2023) reported that *P. berghei* elevated liver oxidation parameters while *Musa paradisiaca* leaf increased some antioxidants parameters, suggesting prophylasis and suppressive properties.

The study showed that ethanol leaf extract of *Musa paradisiaca* reversed the induction of inflammatory markers such as 1L-6, xylclogenase, and lipogenase that was induced by *plasmodium berghie.*

CONCLUSION

The result of this study showed that *plasmodium berghie* induced the inflammatory markers such as 1L-6, xylclogenase, and lipogenase while the administration of ethanol leaf extract of *Musa paradisiaca* reversed the induction.

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