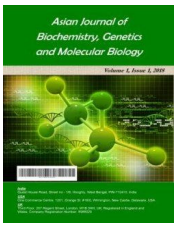

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Evaluation of Antimalarial Properties of *Ficus platyphylla* Del Leaf Extract in Mice

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Authors' contributions

This work was carried out in collaboration among authors. Author JO carried out the study, performed the statistical analysis and wrote the first draft of the manuscript. Author AEA did the editing of the manuscript while author AYK design the experiment. All authors read and approved the final manuscript.

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ABSTRACT

Aim: This study was aim at investigating the effect of crude petroleum ether leaf extract of *Ficus platyphylla* Del on *Plasmodium berghei* infected mice.
Place and Duration of Study: This research was carried out at the department of biochemistry, Federal university of technology minna, Niger state Nigeria in 2014.
Methodology: The crude plant extract of *F. platyphylla* was administered 72 hours at different doses post and pre infection for both the curative and prophylactic study respectively against residual infection. Mice were divided into 5 groups of 5 mice each, 3 of the groups where administered crude plants extract of *F. platyphaylla* at different doses (200, 400 and 600 mg/kg body weight) while the other two serve as negative and positive control group and were administered 0.5 ml and 50 mg/kg body weight respectively.

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Results: The extract at all doses produced significant (P<0.05) dose dependent chemo-suppressive activity with % inhibition of 38%, 61%, 74% and 81.8% for curative studies and 36.0%, 38.5%, 49.5% and 63.4% for prophylactic studies against the parasites at doses of 200 mg/kgbw, 400 mg/kgbw, 600 mg/kgbw of the extract and 50 mg/kgbw of Artesunate. All doses of the extract increased the survival time of the infected mice compared to the negative control group that was administered 0.5 ml normal saline. The variation in the values of Packed Cell Volume (PCV) for treated group before and after extract administration was not significant at (P<0.05). The phytochemical screening of the plant extract showed the presence of tannin, saponin, flavonoids, terpenoids, steroids, anthroquinone and phenol.
Conclusion: The result of this study shows that *F. Platyphylla* leaf extract exhibited some antiplasmodial activity that could be exploited for safe, effective and affordable antimalaria regimen.

Keywords: Malaria; Ficus platyphylla; Plasmodium berghei; anti-malarial; suppressive.

1. INTRODUCTION

Despite efforts put in by government and non-governmental organization all over the world towards the eradication of malaria; the causative pathogen has thrived over the years, spreading far beyond their evolutionary origins in Africa and Southern Asia. Malaria still remains a leading cause of death in most developing countries, especially in Africa. There are estimated to be 300-500 million clinical cases of malaria annually [1] and it is estimated to cause more than one million deaths annually, majority of which are children [2]. The parasite exhibits its activity by cleaving the erythrocytes of its host immediately after the release of the merozoites into the system. It achieves this with the aid of the protease enzyme whose major function is to catalyze the breakdown of other proteins by hydrolyzing their peptide bonds. Hence, clinical symptoms and signs of malaria occur shortly before or at the time of red blood cells lysis. The associated fever is caused by the release of merozoites, malaria pigment, parasites proteins and cellular debris. Chills or rigor followed by high fever are observed normally in a cyclical pattern [3].

Medicinal plants material remains an important source to combats serious disease in the world, being a store house to thousands of therapeutic phytochemicals [4]. It has been instrumental in traditional medicines to treat different disease from time immemorial in various part of the world [5,6]. In this regard, the first antimalarial was discovered by accident from the barks extracts of *Cinchona* (Rubiaceae) species.

Ficus platyphylla Del Holl (Moraceae) is a deciduous plant locally known as 'Gamji'' among the Hausa tribes in Nigeria, West Africa. It is widely distributed throughout the savannah region of West African Coast. The leaves and stem bark of the plant are used traditionally to treat malaria and anaemia [7]. Methanolic extracts of *F. platyphylla* barks have been previously shown to possess significant anti-inflammatory effects [8]. A study has also shown that the extract contains physoactive metabolites with potentials as an anti-epileptic agent [9].

It is in view of these, that this study is aimed at evaluating the antimalaria properties of crude leaf extract of *F. platyphylla* Del in mice.

2. MATERIALS AND METHODS

2.1 Plant Materials

Fresh leaves of the plants were collected from Lokoja, North Central Nigeria and were identified at the Department of Biological Science Ahmadu Bello University Zaria, Nigeria where a voucher specimen was deposited at the departmental herbarium.

2.2 Rodent Parasite (*Plasmodium berghei)*

The rodent parasite *Plasmodium berghei berghei* NK 65 used for the study was obtained from National Institute for Pharmaceutical Research and Development (NIPRD), Abuja, Nigeria and kept alive by continuous intra peritoneal passage in mice every four days at the Department of Biochemistry Federal University of Technology Minna, Nigeria [10].

2.3 Animals

Healthy Swiss albino mice of both sex of about 6 weeks old weighing 20-25 g each was used for the experiments. The animals were fed *ad libitum* with standard feed and had free access to water. They were also maintained under standard

conditions of humidity, temperature and 12 hours light/darkness cycle. Experiment were conducted in strict compliance with internationally accepted principle for laboratory animal use and care as contained in the Canadian council on animal care guidelines and protocol review [11].

2.4 Methods

2.4.1 Parasite inoculation

The method described by Kabiru et al. [12] was used for the inoculation of parasite into experimental animals. The inoculums consisted of $5x10^7$ of *P. berghei berghei* parasitized erythrocytes per ml. This was carried out by determining both the percentage parasitaemia and erythrocytes count of the donor mouse and diluting the blood with phosphate buffer saline in proportions indicated by both determinations.

2.4.2 Preparation of crude extracts

Fifty (50) grams of powdered leaves of *F. platyphylla* was weighed and macerated in 250 ml of 100% petroleum ether, the extraction lasted for 2 hours, thereafter it was filtered hot using muslin cloth and solvents removed under reduced pressure using a water bath. Extract obtained was transferred into a sterile universal bottle and kept in the refrigerator at 4ºC until required for use [13].

2.4.3 Phytochemical screening

To elucidate the secondary metabolites present, the crude leave extract was subjected to qualitative phytochemical screening using the methods of Odebiyi and Soforowa [14].

2.4.4 Rane (Curative test)

Evaluation of curative potentials of *F. platyphylla* leaf extract (FLE) was carried out as described by Ryley and Peters, [15]. Twenty five mice were selected and intraperitoneally injected with 1 x 10^7 *P. berghei* infected erythrocytes. Seventy two hours after, the animals were divided into 5 groups of 5 animals each. Group 1 was administered normal saline (0.5 ml/kg body weight), groups 2, 3 and 4 received 200, 400 and 600 mg/kg body weight of FLE respectively while group 5 received 50 mg/kg body weight of artesunate. All administration of extracts, standard drug and normal saline were carried out daily through oral routes. Treatment continued until the seventh day and a thin film was prepared with blood collected from the tail of each mouse. The films were fixed with methanol, stained with Giemsa stain and parasitemia was ascertained by microscopic examination in five different fields.

2.4.5 Evaluation of prophylactic activity

The prophylactic activity of the extract was tested using the residual infection procedure described by Saidu et al. [16]. Adult mice of both sexes were weighed and randomized into 5 groups of 5 mice each. Mice in group 1 were administered 0.5ml normal saline/kg body weight. Groups II, III and IV were administered 200, 400 and 600 mg FLE/kg body weight orally while group V received 50 mg/kg body weight of artesunate orally daily for 5 days. On the fifth day, all the mice were inoculated with standard inoculum of 0.1 x 10^7 *P. berghei berghei* NK 65 infected erythrocytes. Thin film of blood smears were made from each mouse 72 h after inoculation [17] and examined microscopically for the level of parasitaemia.

2.5 Determination of Packed Cell Volume (PCV)

The packed cell volume was evaluated using the method of Daice and Lewis [18]. Blood sample was collected into a heparinized capillary tube from the tip of the tail of each mouse and sealed with a plastacin. The tube was then centrifuge using a micro hematocrite centrifuge at 11,000rpm, for 5minutes. PCV was read using the micro haematocrite reader.

2.6 Statistical Analysis

A completely randomized design was used throughout this study and data was subjected to one-way analysis of variance and mean comparison with Duncan's Multiple Range Test (significance level of $P < 0.05$) using Statistic Package for Social Sciences (SPSS 22.0 for Windows: SPSS Inc., Chicago, IL, USA.

3. RESULTS

3.1 Phytochemical Screening

The preliminary phytochemical test carried out on warm sample of petroleum ether leaf extracts of *F. platyphylla* is presented in Table 1. The analysis reviewed the presence of tannins, saponins, anthroquinones, flavonoids, and terpenoids while steriods, phenols, alkaloids and cardiac glycosides were not detected.

Table 1. Phytochemical constituents of petroleum ether leaf extract of *F. platyphylla*

Bioactive agent	Petroleum ether leaf extracts
Tannins	+++
Saponin	++
Flavonoids	+++
Terpenoids	++
Steriods	+
Anthroquinones	+++
Phenol	_
Alkaloids	_
Cardiac glycosides	_

Trace(+); Moderate (++); High (+++); Absent (-)

3.2 Rane (Curative Test)

FLE produced significant dose-dependent decrease in parasite counts at ($p<0.05$). The mean percentage inhibition of parasitemia of the extract treated groups on day 7 were 38.4, 61.6 and 74.8% for groups administered with 200, 400, and 600 mg/kg body weight of the extract respectively while that of the artesunate treated group was 81.8% (Table 2).

The packed cell volume of infected mice administered with FLE before and after extract administration is represented in Table 3, from the result it can be deduced that there were increase in the value obtained for PCV of mice in all treated groups but not in the negative control group which shows a reduction in the value of PCV throughout the study period.

The mean survival period in days were calculated to be 20.33± 0.67, 22.33±1.45, 27.00±2.08, 27.33±2.67 and 10.00±1.15 for 200, 400, 600 mg/kg body weight of the plant extract and the control groups (50 mg/kgbw Artesunate and 0.5 ml normal Saline) respectively (Table 4).

3.3 Prophylactic Test

FLE exhibited significant ($p<0.05$) dose dependent reduction in the level of parasiteamia; 36.7, 38.5, 49.5 and 63.4% at 200 mg/kgbw, 400 mg/kgbw, 600 mg/kgbw and 50 mg/kg body weight artesunate treated groups respectively (Table 5).

There was a slight increase in PCV value for all the treated groups after extract administration except for that of the negative control group in which no change in PCV value was observed. However PCV value for all the treated groups drops 72hours after infection with *p. berghei* (Table 6).

Table 7 shows mean survival periods in days calculated to be 20.67±3.17, 21.0± 3.29, 25.33 ± 4.67, 26.67 ± 3.33 and 10.0 ± 1.0 for 200, 400, 600 mg/kgbw of crude pet ether leaf extract of *F. platyphylla*, 50 mg/kg body weight of artesunate and the control group (0.5 ml of normal saline) respectively.

4. DISCUSSION

The present study was carried out to evaluate the antimalaria properties of *F. platyphylla* Del leave extract widely used in traditional treatment for malaria in some parts of Nigeria. Traditional remedies are common in regions where patients cannot afford to use chemically synthesized drugs. Poverty, traditional beliefs and moribund health centers have driven patients to use plants as the major source for treatment of various ailments [19].

The analytical result of qualitative phytochemical analysis of *F. platyphylla* showed the presence of tannins, saponins, flavonoids, terpenoids, steriods, anthroquinones and phenol, these findings agrees with the previous studies on the

Table 2. Curative effect of FLE on parasitaemia in mice

Treatment	Dose (mg/kgbw per day)	Day 2	Day 3	Day 4	Day 5	% inhibition
Normal saline	0.5 ml	9.6 ± 0.0^{c}	5.0 ± 0.20^{a}	9.33 ± 0.30^{bc}	10.6 ± 0.13^{d}	-
FLE	200	7.7 ± 0.10^{b}	7.9 ± 0.55^{a}	5.1 ± 0.30^{a}	5.6 ± 0.20^{c}	38.4
FLE	400	6.3 ± 0.30^{a}	6.0 ± 2.00^{a}	5.1 ± 0.50^{a}	3.7 ± 0.10^{b}	61.6
FLE	600	5.7 ± 0.10^{a}	5.5 ± 0.22^{a}	6.5 ± 0.10^{b}	2.3 ± 0.30^{a}	74.8
Artesunate	50	6.3 ± 0.10^{a}	5.8 ± 0.32^{a}	5.4 ± 0.0^{ab}	2.1 ± 0.10^{a}	81.8

Table 3. Effect of FLE on Packed Cell Volume (PCV) of mice infected with *Plasmodium berghei*

Treatment	Dose (mg/kgbw per day)	Mean PCV (Before treatment)	Mean PCV (After treatment)
Normal Saline	0.5 ml	54.0 ± 2.06[a]	51.0 ± 4.73[a]
FLE	200	55.7 ± 7.62[a]	54.33 ± 7.31[a]
FLE	400	55.7 ± 5.3[a]	56.33 ± 4.17[a]
FLE	600	57.0 ± 3.05[a]	58.67 ± 3.18[a]
Artesunate	50	54.0 ± 4.93[a]	56.0 ± 4.61[a]

Table 4. Effect of FLE on mean survival time of mice infected with *Plasmodium berghei*

Treatment	Dose (mg/kgbw per day)	Mean survival time
Normal Saline	0.5ml	10.00 ± 1.15[a]
FLE	200	20.33 ± 0.67[a]
FLE	400	22.33 ± 1.45[bc]
FLE	600	27.00 ± 2.08[c]
Artesunate	50	27.33 ± 2.67[c]

Table 5. Prophylactic effect of FLE on parasitaemia in mice

Treatment	Dose (mg/kgbw per day)	Day 2	Day 3	Day 4	Day 5	% inhibition
FLE	200	4.10±0.1[b]	3.9±0.61[a]	7.5±1.10[b]	8.10±0.5[a]	36.0
FLE	400	5.90±0.1[c]	5.5±1.0[ab]	5.0±0.20[a]	6.6 ±0.58[b]	38.5
FLE	600	2.90±0.9[c]	2.1±3.20[a]	6.8±0.20[b]	5.6±0.40[ab]	49.5
Artesunae	50	1.47±0.29[a]	1.43±0.3[a]	4.30±1.3[a]	4.73±1.7[a]	63.4
Normal saline	0.5 ml	8.4 ± 0.40	8.20±0.22[b]	9.3 ± 0.33	10.2±0.0[c]	Normal saline

Table 6. Effect of FLE on Packed Cell Volume (PCV) of mice infected with *Plasmodium berghei* (Prophylactic test)

Groups	Dose (mg/kgbw per day)	PCV before treatment	PCV after treatment	PCV 72 hours after inoculation
FLE	200	55.7 ± 1.94[a]	56.33 ± 1.74[a]	53.3 ± 1.31[a]
FLE	400	62.67 ± 0.71[a]	63.0 ± 0.5[a]	61.33 ± 0.03[a]
FLE	600	61.67 ± 0.03[a]	63.67 ± 0.33[a]	62.0 ± 0.08[a]
Artesunate	50	60.0 ±1.15[a]	60.67 ± 1.85[a]	57.3 ± 1.45[a]
Normal saline	0.5 ml	61.0 ± 1.52[a]	61.0 ±1.51[a]	57.7 ± 1.45[a]

Table 7. Mean days of survival of mice infected with *P. berghei* and treated with FLE (Prophylactic test)

Treatment	Dose (mg/kgbw per day)	Mean survival time
FLE	200	20.67 ± 3.17[ab]
FLE	400	21.0 ± 3.79[ab]
FLE	600	25.33 ± 4.67[b]
Artesunate	50	26.67 ± 3.33[b]
Normal saline	0.5 ml	10.0 ± 1.0[a]

phytochemical constituents of *F. platyphylla* [20, 21]. The observed antimalaria activity of FLE in this study may be attributed to the presence of saponin. These compounds have been previously shown to be responsible for the antimalaria activities in many plants [22].

The determination of percentage inhibition of parasitemia has been noted to be a reliable parameter for assessment of antimalaria effect of a test compound [23]. With respect to the curative test, FLE exerted significantly suppressive effects in mice treated with 400

mg/kgbw and 600 mg/kgbw (Table 2). This effect was however lower in group that received a lower dose while we observed a daily increase in parasitemia in the negative control group on day 7. The observed significant suppressive effects of FLE against *P. berghei* in mice is a confirmation of an earlier report in which stem bark ethanolic extracts of *F. platyphylla* significantly inhibited *Plasmodium berghei*, *invitro,* in mice [24]. Only one of the mice in the group administered 600mg/kgbw of petroleum ether leaf extract survived up to 28 days, when compared with the experimental animal in the artesunate-treated group, where two (2) of the animals survived beyond 28 days.

PCV is a widely known index of anemia [25], FLE was able to prevent a drastic reduction in PCV in infected mice when compare to infected untreated experimental control, thus, showing its efficacy in ameliorating malaria-induced anemia. This was consistent with the marked decrease in parasite load observed in the cause of infection in the groups of mice treated with the 400 mg/kg body weight and 600 mg/kg body weight doses of FLE. The increase in PCV of extract-treated groups, as well as artesunate-treated groups, may be as a result of clearance of the parasite from circulation thereby enabling the cells to gradually divide and replenish the blood [26].

In the prophylactic study, FLE significantly at ($p<0.05$) exerted a dose dependent reduction in the parasitemia level in the extract-treated groups while the standard drug artesunate has the highest chemo-suppressive effect. Although the result from the antimalaria study of the crude petroleum ether extract of *F. platyphylla* suggest that the extract has more curative effect, than prophylactic effect as evident from the percentage prophylaxis (Table 5). This low activity may be due to rapid hepatic clearance of the active component of the plant extract and so parasite clearance may not be completely cleared from the blood stream.

The level of packed cell volume of the mice in FLE-treated groups and that of the untreated group drastically reduced 72 hours after inoculation of parasite, which may be as a result of short duration of action of the extract occasioned by rapid metabolism. As a result, *plasmodium* parasites which are usually localized in cell lyse the red blood cell and thus the percentage packed cell volume is affected. The survival rate of mice infected with *plasmodium berghei* and treated with crude pet ether leaf extract compares favourably with group treated with standard artesunate.

5. CONCLUSION

The result shows that *F. platyphylla* leaf extracts exhibited some antimalaria properties as claimed by local herbal traditionalist, thus justifying their long use in local malaria treatment. Hence, the plant could be exploited for safe, effective and affordable antimalaria regimen.

ETHICAL APPROVAL

The ethical clearance for this study was approved by Federal University of Technology, Minna/Nigeria ethical review board (CUERB) in accordance with international standard on the care and use of experimental animals.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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