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ANTI-PLASMODIAL ACTIVITY OF *BLIGHIA SAPIDA* LEAF EXTRACTS IN *PLASMODIUM BERGHEI* INFECTED MICE

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Keywords:

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ABSTRACT: *Blighia sapida* a tropical evergreen plant with a dense crown, is commonly called ackee apple. Traditionally, the stem backs and leaves of the plant are used in the treatment of high fever, strokes, malaria, headache and some eye ailments. This study examined the antiplasmodial activity of *Blighia sapida* leaf extracts in comparison with the standard antimalarial drug Artemether-Lumefantrine combination, with a view to determining the changes in the parasitemia level in mice infected with *Plasmodium berghei*. The results showed a significant decrease in parasitemia level over six days period for mice treated with Artemether-Lumefantrine, ethanolic, and aqueous leaf extracts of *B. sapida*, whereas the controls showed a continuous increase. The parasitemia level was significantly reduced ($P<0.05$) in mice treated with 6.0mg/kg body weight of Artemether-Lumefantrine with 88% suppression; those treated with the ethanolic leaf extract at 50mg/kg and 30mg/kg body weight had parasitemia suppressed by 59% and 43.67% respectively. Parasitaemia count in mice treated with 50mg/kg and 30mg/kg body weight of aqueous leaf extract of *B. sapida* was suppressed by 43.83% and 40%respectively. This study reveals that ethanolic and aqueous leaf extracts of *Blighia sapida* have promising anti-malaria activity at the concentrations used, although these were not as effective as the Artemether-Lumefantrine combination. However, the results lend credence to the ethnobotanical use of the plant for the treatment of malaria.

INTRODUCTION: Malaria is the most devastating human disease on earth; nearly half of the world's population is at risk of malaria. According to the World Health Organization[1], in 2015, there were roughly 212 million malaria cases and an estimated 429,000 malaria deaths. Increased prevention and control measures have led to a 29% reduction in malaria mortality rates globally since 2010.

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Sub-Saharan Africa still carries a disproportionately high share of the global malaria burden. In 2015, the region was home to 90% of malaria cases and 92% of malaria deaths [1]. In 2010, about 3.3 billion people were exposed to malaria. The highest risk was for people living in Africa, where approximately 91% of the cases were recorded, while 86% of deaths globally occur among children under five years of age [2, 3].

In adults, its common symptoms are headaches, weakness, fever, aches and pains, high body temperature, and bitterness of the mouth with loss of appetite, while in children, in addition to the above-mentioned symptoms, it may also manifest with nausea and vomiting [4]. The high rate of deaths in Africa is traceable to several factors such as poor

economic standards, the high cost of synthetic medicines, the development of resistance by the causative protozoan parasite, and the side effects of existing orthodox drugs, which have made the choice of herbal remedies against these infections inevitable and more economical [5]. The severe long-term effects of malaria parasites have compelled continued pharmacological investigations into plants used for treating malaria disease in search of potent and cost-effective solutions to mitigate the effect of the disease.

Plasmodium berghei is a protozoan parasite that infects mammals other than humans. They are not of direct concern to man practically; man's interest in these parasites is that they are practical model organisms in the laboratory for the experimental study of human malaria [6]. Rodent malaria parasites are used in many Research Institutes for studies to develop new drugs or vaccines against malaria [7]. Like all malaria parasites of mammals, *P. berghei* is transmitted by the anopheles mosquito, and it infects the liver after being released into the bloodstream by a bite from an infected female mosquito [8].

From ancient times, plants and their extracts have been used in the treatment of diseases in Africa, Asia and North America. Traditional medicine has been the focus for wider coverage of primary health care delivery in Africa and the rest of the world [9]. It comprises therapeutic practices for hundreds of years before the development of modern scientific medicine. It is still in use today without much-documented evidence of adverse effects [10].

Several antimalarial drugs have been developed from plant-based materials, for example, the alkaloid (quinine) derived from the bark of *Cinchona spp.* (Rubiaceae) and lately, artemisinin derived from *Artemisia annua* (Asteraceae). Historically, the majority of antimalarial drugs are of plant origin [11]. Several plants with anti-plasmodial properties have been proved as sources of novel anti-plasmodial compounds. Because the continuous resistance of malaria parasites to synthetic drugs like chloroquine is a major cause for concern [12] and due to the limited availability and affordability of orthodox medicine in many tropical countries, most indigenous populations depend on traditional medical remedies [13], mainly from plants that have been discovered to be a rich source of novel drugs [14]. Botanicals have played a significant role in human societies throughout history and prehistory [14]. In the tropical regions of Asia, South America, and Africa, where malaria is endemic, there is still widespread use of medicinal plants to treat the disease. It has been reported that *B. sapida*, among other plants, is used in southwest Nigeria for malaria treatment [15].

Khaya senegalensis and *Khaya grandifoliola* stem and bark have been extensively used as antimalarial remedies but with adverse effects [16]. *Alstoniaboonei* (Cheese wood) has been a highly valuable plant, especially in situations where affordable antimalarial drugs are found ineffective due to drug-resistant malaria parasites[17]. Several other natural products having antimalarial activities have been documented in Nigeria [18]. Before any plant can be recommended, there is a need for scrutiny because there are indications of deleterious effects of many phytochemicals on human health [19].

Apart from contemporary antimalarial drugs that have been used for years and the conventional traditional herbs, artemisinin-based combination therapy (artemether and lumefantrine) is very active[20, 21] in the treatment of malaria caused by *Plasmodium falciparum* that is resistant to chloroquine, with common side effects which may include muscle and joint pains, fever, loss of appetite and headaches [22].

The need for an alternative drug has initiated intensive efforts to develop new antimalarial drugs from indigenous plants. Various studies have been documented with over 1200 plant species from 160 families used to treat malaria or fever [23]. Research and investigations have been carried out in many African nations such as Ethiopia [24], Ghana [25], Cameroon [26] and Nigeria [27, 18, 28, 29].

Blighia sapida is indigenous to the forests of most West African countries, where the fruits are rarely eaten but are used for other purposes [30]. The fruit is edible when ripe but toxic when unripe due to hypoglycin A and hypoglycin B. Ackee arils have been reported to have a comparable proximate composition of moisture, ash, carbohydrate, crude protein and crude fiber to many known legumes

and oil seeds [31, 32]. In Ghana, several uses are recorded for *B. sapida*; the bark is one of the ingredients in a concoction administered for epilepsy. The leaf juice is used for washing or as drops for sore eyes, conjunctivitis, and trachoma [33]. The bark and leaf decoctions are administered to treat oedema, intercostal pain, dysentery, diarrhoea, chest pain [34], malaria [15] in South-Western Nigeria. The pulp of twiggy leaves is applied on the forehead to treat migraine/headache. The ash obtained from dried husks and seeds is used for soap making in West Africa and the fruits contain saponin, which lathers in water and is used for washing [35]. *B. sapida has* also been used by the Centre for Scientific Research into Plant Medicine (CSRPM), Ghana, for the treatment of diarrhoea for over twenty years [36]. The leaves and seeds of the plant have also been reported by the people of Itak Ikot Akap Community, in Ikono Local Government Area of Akwa Ibom State, Nigeria to possess piscicidal properties [37].

Phytochemical Screening of *Blighia sapida*: Alkaloids, saponins, tannins, phlobatannins, flavonoids, terpenes, cardiac glycosides, and combined anthraquinones were detected in the leaf of *B. sapida*, whereas only saponins, flavonoids, combined anthraquinones, and cardiac glycosides were detected in the stem bark [31]. It has also been reported that *B. sapida* tested positive for the presence of some groups of phytochemicals such as reducing sugars, phytosterols and Polyphenol [38].

Research Objectives: Despite the recent successes recorded with the development of a malaria vaccine 39, therapeutic interventions must be encouraged, and plants have presented a vast array of beneficial chemicals in the treatment of diseases. To this end, mankind must stay ahead of the malaria disease by presenting a wide array of interventions. Therefore, this study was conducted to assess the antimalarial property of Blighia sapida leaf extracts compared to Artemether-Lumefantrine, a standard antimalarial drug in continuation of the search for cheap and affordable treatments for malaria.

MATERIALS AND METHODS:

Collection and Preparation of the Plant Material: Leaves of *Blighia sapida* were obtained from a single tree identified in the Department of Plant Science and Biotechnology, Adekunle Ajasin University, Akungba-Akoko, Ondo State, Nigeria, and the herbarium specimen was deposited at the Herbarium Unit of the Department. The harvested leaves were washed thoroughly with tap water and air-dried at room temperature on the laboratory bench. The dried leaves were milled using an electric blender and stored in specimen bags.

Extraction of Plant Materials: A decoction was made by placing 100g of the milled sample in 2 liters of boiling water. The supernatant was collected and concentrated, and the filtrate was lyophilized in the laboratory. The dry extract was collected and stored in a moisture-free container for use. Another portion of the milled leaves weighing 100g was also measured into 2 liters of absolute ethanol, stirred continuously, and left for 72 h. The filtrate was separated using Whatman filter paper (18cm diameter and 0.1 µm pore diameter). The filtrate was then dried in an oven at 40°C and stored in a vial at 4°C in a refrigerator.

Experimental Animals and Malaria Parasite: Eight-week-old Swiss albino mice used for this study were obtained from the Animal Unit of the Institute for Advanced Medical Research and Training (IAMRAT), College of Medicine, University of Ibadan, Nigeria. The animals were kept in well-aerated wired cages, fed with standard mouse feed (Top Feeds Ltd, Nigeria), and allowed to drink water freely for one week before they were infected with *Plasmodium berghei* NK 65, donated by the Institute for Advanced Medical Research and Training (IAMRAT), College of Medicine, University of Ibadan, Nigeria. The animals were infected by the serial passage of blood collected from a donor mouse to the naïve recipients. This study was undertaken in line with the internationally accepted laboratory animal use and care guideline [40].

***In-vivo* Antimalarial Assay:** The animals were infected intraperitoneally with an aliquot of 0.2ml of standard inoculums (1×10^7 *Plasmodium berghei* strain NK 65 parasitized erythrocytes). The infected blood was obtained from a donor mouse with a parasitemia of 35 to 40% by heart puncture into a test tube having anticoagulant (0.5% trisodium citrate). The blood was then diluted with normal saline (0.9% NaCl). Thirty Mice weighing between 28g to 34g were distributed evenly into six

groups. Group 1 (control) was not given any antimalarial treatment. Group 2 was treated with 6.0mg/kg body weight of Artemether-Lumefantrine, Groups 3 and 4 were treated with 50 mg/kg body weight of ethanolic and aqueous leaf extract of *B. sapida*, respectively. Groups 5 and 6 were treated with 30 mg/kg body weight of ethanolic and aqueous leaf extract of *B. sapida*, respectively. All the treatments were administered once daily by gavages using an intubator for five consecutive days. Observation for changes in parasitaemia level began twenty-four hours after parasitising the animals and ended twenty-four after the last treatment. Blood was taken daily from the tail vein of the mice for six days.

Drugs and Reagents: Artemether 80mg - Lumefantrine 480mg (GETZ Pharma PVT Ltd. Pakistan), Giemsa (BioLab Diagnostics Ltd., India), Ethanol (Nosak Distilleries Limited, Nigeria), Trisodium citrate (Annexe Chem Private Limited, India) and normal saline (Biomedical Limited, Nigeria) were used. All reagents were analytically graded and procured from legal pharmaceutical suppliers.

Parasitological Study: Blood films were prepared from blood collected from each mouse over six days. The slides were screened for malaria parasites using 10% Giemsa's stain at pH 7.2. The number of parasites counted per 200 white blood cells was recorded and used to calculate parasite density based on 8000 assumed leucocytes/µl of blood as previously described [41].

Statistical Analysis: The one-way Analysis of Variance (ANOVA) was used to analyze the differences at $P<0.05$ among the treatments (SPSS 23.0, SPSS Inc., Chicago, Illinois, USA). The results were expressed as mean ± Standard Error (SE).

RESULTS AND DISCUSSION: Treatment of *Plasmodium berghei* infected mice elicited a change in parasitaemia. A reduction was regarded as an indicator of the antimalarial properties of any compound. Results obtained in this study **Fig. 1** and **2** indicated a reduction in parasitaemia induced by *B. sapida* extracts. The mean±SE for parasitaemia count in mice treated with 6.0mg/kg body weight of Artemether-Lumefantrine significantly reduced from 528±44.54 to 60±8.94 over six days' observation and treatment period. Mice treated with the ethanolic leaf extract of *B. sapida* at 50mg/kg and 30mg/kg body weight had parasitaemia suppressed from 608±23.32 to 248±14.97 and 536±27.13 to 320±28.2 respectively, while the mean±SE value of parasitaemia count in the group treated with 50mg/kg and 30mg/kg body weight of Aqueous leaf extract of *B. sapida* was suppressed from 584±20.40 to 328±14.97 and 560±52.15 to 336±24.00 respectively. This indicates that Artemether-Lumefantrine significantly expressed an effect on the red blood cell count/parasitaemia count [42].

Limited availability and affordability of orthodox medicine in many tropical countries have left much of the population depending on traditional medical remedies [13]. Of the many diseases that afflict tropical countries where the greater majority of the world's poor reside, malaria remains a major global health problem with high mortality and morbidity than any other infection [2].

This is further exacerbated by its high degree of transmissibility. A concerted international effort has been put into obtaining a cure for this deadly disease culminating in the recent breakthrough in vaccine therapy [39]. This, however, does not prevent the need for further chemotherapeutic interventions [43]. There has been a remarkable help in administering several compounds, but progress has been challenging due to the resilience of the causative parasite in developing resistance to available medications [44]. Chloroquine had been the drug of choice for several years until widespread resistance demanded the search for more potent formulations [45].

Therefore, the race is on to identify natural remedies for the treatment of malaria. Currently, the standard drug is the Artemether-Lumefantrine combination which was formulated from artemisinin extracted from *Artemisia annua* [46] a member of the Asteraceae family. *Blighia sapida*, has been identified as one of the local plants commonly used in southwest Nigeria for malaria treatment [15]. It is imperative to seek comparison with the standard treatment in use if the effects are to be measured appropriately.

This is why this study focused on the comparative effects of leaf extracts of *B. sapida*, with the standard Artemether-Lumefantrine combination. Although the results obtained in **Fig. 1** show that leaf extracts of *Blighia sapida*, as well as the Artemether-Lumefantrine combination, effectively reduced the *P. berghei* parasite level, the leaf extracts of *Blighia sapida* were not as efficacious as the Artemether-Lumefantrine combination.

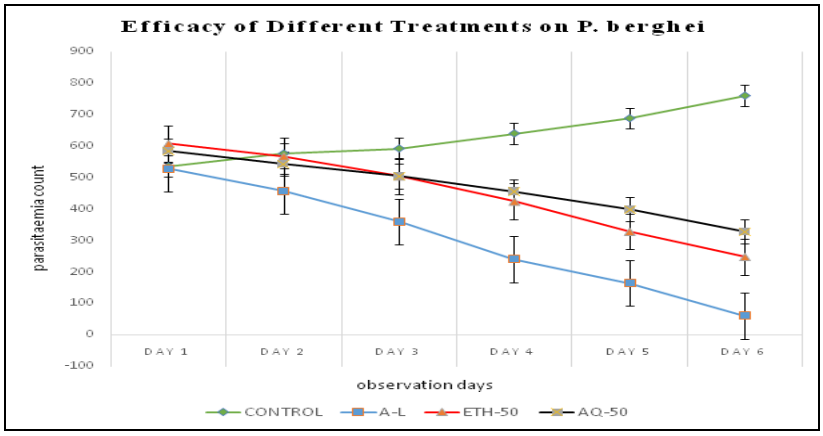

FIG. 1: COMPARISON BETWEEN THE EFFICACY OF THE 50MG/KG PLANT EXTRACT TREATMENTS AND THE STANDARD DRUG ON *P. BERGHEI*. The graph compares the mean value and standard error difference for all treatment groups. The effects of ethanolic and aqueous leaves extract at 50mg/kg body weight compared to 6mg/kg body weight of Artemether-Lumefantrine (Standard) and the control group. Control = control group, A-L = group treated with Artemether-Lumefantrine, ETH-50 = group treated with 50mg/kg body weight of ethanolic extract, AQ-50 = group treated with 50mg/kg body weight of aqueous extract.

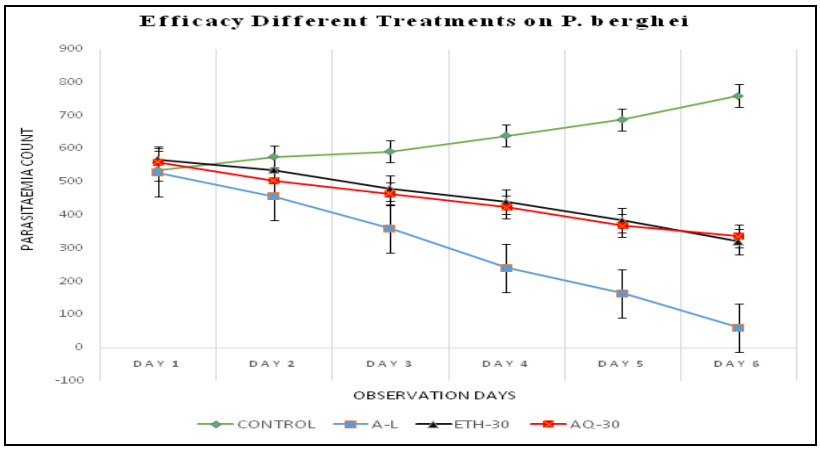

FIG. 2: COMPARISON BETWEEN THE EFFICACY OF THE 30MG/KG PLANT EXTRACT TREATMENTS AND THE STANDARD DRUG ON *P. BERGHEI*. The graph compares the mean value and standard error difference for all treatment groups. The effects of ethanolic and aqueous leaves extract at 30mg/kg body weight compared to 6mg/kg body weight of Artemether-Lumefantrine and the control group. CNTRL = control group, A-L = group treated with Artemether-Lumefantrine, ETH-30 = group treated with 30mg/kg body weight of ethanolic extract, AQ-30 = group treated with 30mg/kg body weight of aqueous extract.

TABLE 1: EFFECT OF THE TREATMENTS ON PARASITAEMIA IN FIVE-DAY SUPPRESSIVE TEST

Treatment	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
CNTRL	0	+7.4627	+10.4480	+19.4030	+28.3580	+41.7910
A-L	0	-13.6364	-31.8182	-54.5455	-68.9394	-88.6364
ETH-50	0	-6.5790	-17.1053	-30.2632	-46.0526	-59.2105
AQ-50	0	-6.8493	-13.6986	-21.9178	-31.5068	-43.8356
ETH-30	0	-5.6338	-15.4930	-22.5352	-32.3944	-43.6620
AQ-30	0	-10.0000	-17.1429	-24.2857	-34.2857	-40.0000

The table shows percentage (%) parasitaemia level change for all groups. CNTRL = control group, A-L = standard drug group treated with Artemether-Lumefantrine, ETH-50 = group treated with 50mg/kg body weight of ethanolic extract, AQ-50 = group treated with 50mg/kg body weight of aqueous extract, ETH-30 = group treated with 30mg/kg body weight of ethanolic extract, AQ-30 = group treated with 30mg/kg body weight of aqueous extract.

Percentage of parasitemia increase and decrease = initial – final parasitemia level / Initial parasitemia level × 100

The results in **Table 1** indicate that the effect of the extracts on *P. berghei* was concentration-dependent, although the threshold was not determined. The ethanolic extract exhibited greater effectiveness than the aqueous extract; this can be attributed to the solvent potency to extract more phytochemicals from medicinal plants than its aqueous counterpart [47, 48].

The percentage parasitemia count as shown in **Table 1** shows that the group of infected mice treated with 6.0mg/kg body weight of Artemether-Lumefantrine combination reflects a significant reduction of 88.63% in the parasitaemia level of the mice, which was significantly better than reduction obtained with the leaf extracts. Treatment with 50mg/kg body weight of ethanolic leaf extract of *B. sapida,* elicited a reduction of up to 59.21% in the parasitemia level which was better than the 43.84% reduction obtained from the aqueous leaf extract of *B. sapida.* At the lower dosage of 30mg/kg body weight, the ethanolic and aqueous extracts had comparable suppression levels of 43.66% and 40%, respectively, whereas the controls had a 41.79% increase in parasite density.

This agrees with previous study [49], which reported that parasitemia level increases progressively after inoculation until the point of death in the absence of suitable treatment. Although the results obtained were encouraging, this study indicates that leaf extracts of *Blighia sapida*, although efficacious in reducing parasitemia, did not show greater potency than the Artemether-Lumefantrine combination. However, there is a need for further studies to explore the use of other extracting solvents and to determine the response to increased levels of the extracts in concert with toxicological studies.

CONCLUSION: Based on the results, this study confirms that the ethanolic and aqueous leaf extracts of *Blighia sapida* have promising anti-malaria activity at the concentrations used. The results lend credence to the ethnobotanical use of the plant for the treatment of malaria. Further research using higher concentrations of the ethanolic and aqueous leaf extracts of the plant, and/or using other solvents can be employed to test the efficiency in treating malaria disease.

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Ethics Approval: Ethical clearance to experiment on mice was obtained from the Centre for Research and Development, Adekunle Ajasin University, Akungba-Akoko, Nigeria. The mice were handled in accordance with "The care and Use of Animals for Scientific purposes" guidelines of the Animal Use and Care Committee (AUCC) and the legal provisions captured in the constitution of the Federal Republic of Nigeria, Animal Diseases (Control) Act. Cap A17 LFN, 2004.

CONFLICT OF INTEREST: Nil

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