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Evaluation of Antiplasmodial Activity of Ethanolic Leaf Extract of *Lannaeacida* on *Plasmodium berghei* Infected Albino Mice

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Abstract: This study evaluated the antiplasmodial activity of ethanolic extract of *Lannae acida* leaves and its effect on haematological and biochemical parameters of *Plasmodium berghei* infected mice. Malaria is a parasitic disease of global economic importance caused by protozoon of the genus plasmodium. Acute toxicity study of the extract was determined using the method of Lorke 1983. The antiplasmodial activity was evaluated using albino mice infected with plasmodium berghei and treated with graded doses (100mg/kg, 200mg/kg and 400mg/kg body weight) of the extract. Haematological parameters (PCV, RBC, Haemoglobin concentration) as well as Biochemical parameters (serum ALT and AST) were determined using standard methods. LD50 of the extract was calculated to be 2154mg/kg body weight of the extract. The extract exhibited a dose dependent antiplasmodial activity. % RBC, PCV and Hb decreased significantly ($p<0.05$) in the infected and untreated group compared to every other groups. Serum AST and ALT levels were significantly higher ($p<0.05$) in the infected and untreated group but within the same range in other groups. The extract of *Lannaeacida* leaves proved to be a good candidate for antimalarial drug development.

Key words: Antiplasmodial · Extract · Lannae Acida · Activity · Haematological · Biochemical · Plasmodium

INTRODUCTION

Malaria parasites are intracellular obligate parasites, which target and reside in the host erythrocytes and alter these cells to deliver optimally for their own needs [1]. Infection is caused by a parasite of genus *Plasmodium* which is transmitted to human beings by infected female anopheles mosquitos. *Plasmodium falciparum* is the most prevalent malaria parasite in the WHO African Region, accounting for 99.7% of estimated malaria cases in 2017, as well as in the WHO regions of South-East Asia (62.8%), the Eastern Mediterranean (69%) and the Western Pacific (71.9%). *P. vivax*is the predominant parasite in the WHO Region of the Americas, representing 74.1% of malaria cases [2].

Malaria continues to play a critical role in the global infectious disease burden with significant morbidity and mortality, especially in sub-Saharan Africa. International travelers are at risk in more than 90 countries worldwide, mainly in Africa, Asia and the Americas [3].

Fifteen countries in sub-Saharan Africa and India carried almost 80% of the global malaria burden. Five countries accounted for nearly half of all malaria cases worldwide: Nigeria (25%), Democratic Republic of the Congo (11%), Mozambique (5%), India (4%) and Uganda (4%) [4]. It is obvious from the above report that effort is needed to be intensified in Africa especially in Nigeria towards search for affordable and efficient malarial treatment so as to stem the havoc of the disease that has wrecked in Nigeria.

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Severity of disease is determined by multiple factors, including parasite species and timing of anti-malarial treatment [5]. Malaria can be transmitted by three known ways; vector transmission, blood transmission and congenital transmission. Also, the malaria parasite interferes with three major organs in the body, namely: the brain, kidney and liver [6].

Malaria pathogenesis is based mainly on extensive changes in biochemical and hematological parameters [7]. Cytoadherence of infected red blood cells to the vascular endothelial cells of different host organs, including the kidneys, is reported to alter microcirculation of these organs which ultimately disrupt their physiological functions [8].

The attitude of people in the community and lack of basic infrastructural facilities may be responsible for the rampant prevalence of malaria infections [9]. Despite significant progress in the treatment of malaria, this disease has staged a huge comeback in large areas of the world, due to development of drug-resistant parasites [10]. Research into the identification and production of more effective, cheaper and potentially less toxic remedies for the treatment of malaria would therefore continue to be relevant [11].

Different parts of plants species including leaves, stem barks and roots are frequently used to prepare infusion, concoction, or decoction for the prophylactic and treatment purposes [12], where they are administered orally, in bath or steam inhalation for 3 to 6 days, or more often until parasites clearance or not [13].

Lanneaacida (syn. *Odinaacida*) (Anacardiaceae), commonly called “faruhi” in Fulani-Fulfulde (Nigeria), “fa`ar´u” in Hausa, “Mipadi” in Giziga, or “Timbiya” in Moundang in Cameroun [14], grows in Sub-Saharan Africa. Barks of *L. acida*are traditionally used in Nigeria as antiabortifacient, vermifuge and to treat anal hemorrhoids, diarrhoea, dysentery, malnutrition and debility [15] and in Cameroon to treat dysmenorrhea, amenorrhea and infertility, while the leaves treat rheumatism [16]. It is a tree of up to 14 meters in height that is relatively common in West African savannas and along forest edges. Female trees produce small (~ 10 mm long), single seeded, ellipsoid drupes which appear green to the human eye when unripe and dark purple when ripe. Several dozen are clustered in infructescences. Fruiting starts at the end of the dry season/beginning of the wet season and lasts one to two months [17].

MATERIALS AND METHODS

Plant Collection: The plant samples were collected from Ndiechi Onuebonyi village in Izzi Local Government Area of Ebonyi State, Nigeria and identified by Dr. Mrs. Nnamani, C. V a plant Taxonomist in Applied Biology Department of Ebonyi State University, Abakaliki, Nigeria.

Preparation and Extraction of Plant Materials: The plant samples were sorted to eliminate dead matter and other unwanted particles, dried under room temperature for two weeks, grinded into powder using electric mill and subsequently sieved. 200g of powdered *L. acida* (leaves) was extracted with the aid of a Soxhlet extractor using 600 ml of 99 % ethanol for 72 h, concentrated to dryness using a rotary evaporator and the residue was stored in a freezer at 4°C, this process was repeated until enough quantity was collected. Prior to use, the extracts were dissolved in normal saline so that the doses required were prepared by necessary dilutions and given according to weight of the animals.

Animals: Both male and female albino mice (25-30 g) obtained from the animal house of the Department of Veterinary Medicine, University of Nigeria, Nsukka, were acclimatized for 7 days before commencing the study. The mice were conveniently housed under standard environmental conditions at 22-25°C. All mice had ad libitum access to commercial feed pellets and clean water throughout the study. All the animals were treated in compliance with the National Institute of Health Guide for care and use of laboratory animals.

Drug: An artemisinin combination drug P - ALAXIN (consisting of dihydroartemisin 40 mg and Piperaquine phosphate 320 mg), manufactured by Bliss GVS Pharmaceutical LTD, India was obtained from Godal Pharmacy in Abakalikiand diluted in distilled water to final doses of 5 mg/kg body weight.

Acute Toxicity Study: The acute toxicity study was performed following the method described by Ihekwereme *et al.* [18].

Inoculation: A strain of chloroquine resistant *P. berghei* was obtained from the Department of Veterinary Medicine, University of Nigeria Nsukka and maintained in the laboratory by serial blood passage from mouse to mouse.

Parasitaemia Determination: The animals used in this study were divided into 6 groups of five mice each. All the groups except 1 (Uninfected and untreated) were infected intraperitoneally with 0.2ml of infected blood containing about $1x10^7$ of *P. berghei*-aparasitized erythrocyte per ml on Day 0. Group 2 was treated with 100mg/kg body weight of the extract, Group 3 was administered 200mg/kg body weight, Group 4 was treated with 400mg/kg b.w of the extract, Group 5 received 5mg/kg b.w of ACT while Group 6 was Infectedand Untreated. The parasite counts of the different groups were determined after 72 h before the commencement of treatment which actually confirmed that the micewere down with malaria by making thin smears which were fixed in methanol and stained with Giemsa stain from the tail blood of each mice, examined microscopically under oil immersion lens and the percentage of parasitaemia was determined by counting the parasitized erythrocytes out of 1000 erythrocytes in 10 different fields [19].

Hematological Parameters: Determination of hematological parameters such as: Packed Cell Volume (% PCV), Hemoglobin concentration and Red blood cell (RBC) were carried out according to the methods described by Jarike *et al*, [20].

Biochemical Parameters: Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) were determined by (Reitman and Frankel, 1957) using assay kits (Randox Laboratories Ltd, UK).

Statistical Analysis: The results were expressed as mean ± standard deviation (SD). Parameters in the groups were compared by one-way (ANOVA) using the computer software Statistical Package for Social Sciences (SPSS) Version 20.0. All data was analyzed at 95% confidence interval and values were considered statistically significant at $p \leq 0.05$.

RESULTS

Acute Toxicity: The acute toxicity study showed that the extract doses up to 1600mg/kg b.w of *Lannaeacida*gave no sign of toxicity in the mice but 2900 mg/kg and 5000 mg/kg body weight produced mortality within 24hrs of administration. The oral Mean Lethal Dose (LD_{50}) was therefore calculated to be 2154mg/kg body weight of the extract.

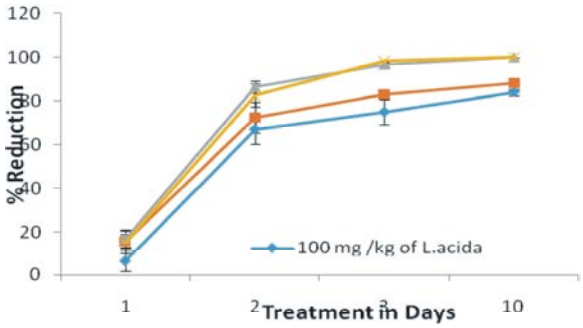

Fig. 1: Percentage of parasitaemia reducti

Perasitaemia Suppression: The percentage reduction in parasite load of the different experimental groups is shown in Fig. 1 indicates that the group treated with 400mg/kg body weight of the extract produced the highest parasite surpression in day one which was significantly different ($p<0.05$) from that of the group treated with 100mg/kg b.w but not significantly different ($p>0.05$) when compared to the effect of the groups treated the ACT and 200mg/kg b.w. On day 2, the 400mg/kg bw group also gave an increased antiplasmodial activity above ACT but not significantly different ($p>0.05$). This effect when compared to the other treatment groups showed remarkable increase ($p<0.05$). In Day 3 the ACT group had higher parasite surpression than 400mg/kg group but within a very close range. On day 10, ACT group and the group treated with 400mg/kg body weight both produced 99.98 % parasitaemia suppression.

Red Blood Cell (RBC) Count: Fig.2 shows that the percentage of red blood cell (RBC) count of the infected and untreated group decreased significantly ($p<0.05$) in relation to the treated groups. It also indicates comparable effect on RBC count of the groups treated with different doses of extract as well as the group administered standard drug with no significant change ($p>0.05$).

Packed Cell Volume (PCV): The impact of the extract on packed cell volume can be described as a dose dependent one.Figure 3 shows that the percentage PCV of the groups treated with extract increased with increasing dose of the plant extract without a significant change ($p>0.05$) among them. The group treated with ACT though produced the highest percentage PCV but not significantly different ($p>0.05$) from those of plant extract. Percentage PCV value of the infected and untreated group decreased significantly ($p<0.05$) in comparison with every other treatment group.

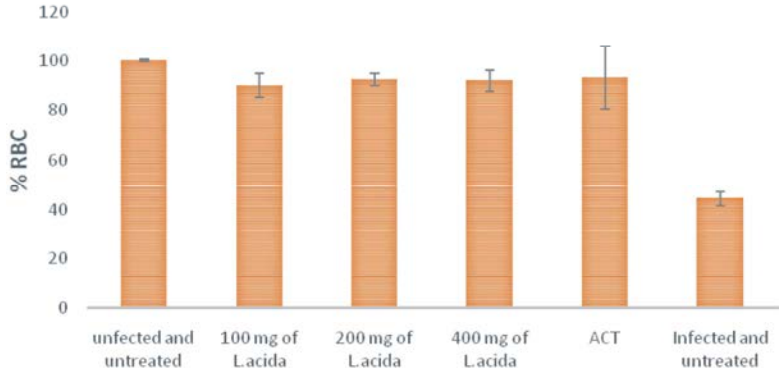

Fig. 2: Effect of treatment on Red blood cell count.

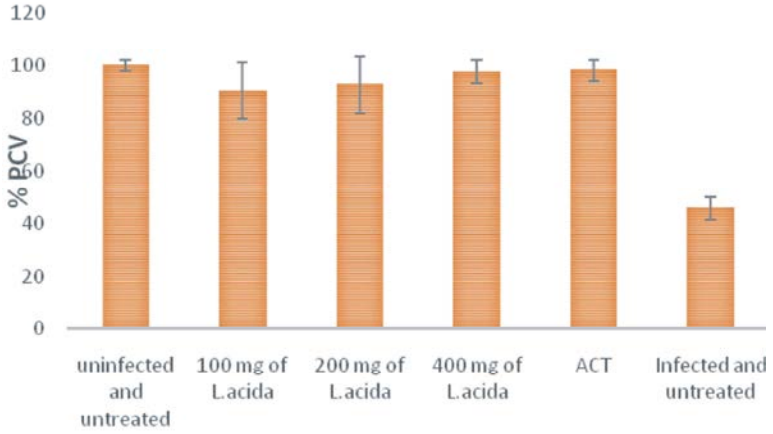

Fig. 3: Effect of treatment on packed cell volume (PCV).

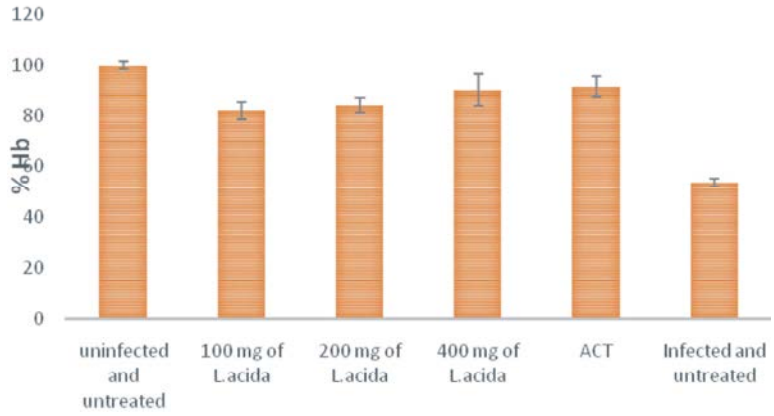

Fig. 4: Effect of treatment on haemoglobin concentration (Hb)

Hemoglobin Concentration (Hb): Percentage of hemoglobin concentration of the infected and untreated group depreciated significantly ($p<0.05$) with respect to all the treatment groups as well as the uninfected and untreated group. No significant difference in PCV is noticeable when the uninfected-untreated group is compared with all the treatment groups (Figure 4).

Serum Alanine Aminotransferase Activity: Figure 5 shows that the serum alanine aminotransferase activity of the infected and untreated group increased significantly ($p<0.05$) when compared to all the treatment groups, the uninfected and untreated group inclusive. ALT activity of the uninfected and untreated group is within the same range as those of the treatment groups with no remarkable difference.

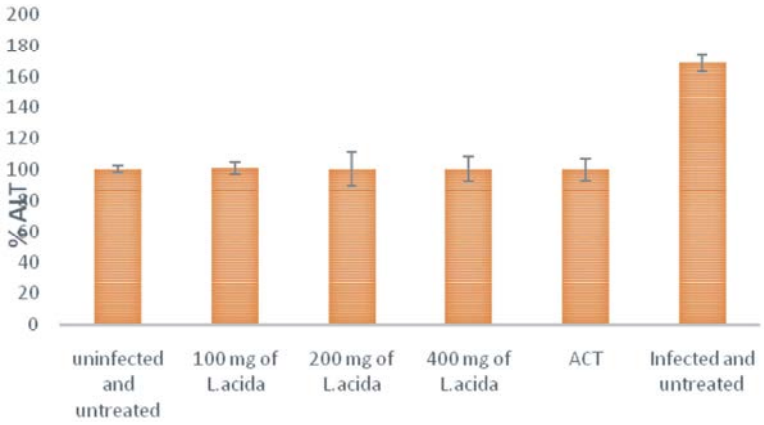

Fig. 5: Effect of treatment on alanine aminotransferase (ALT).

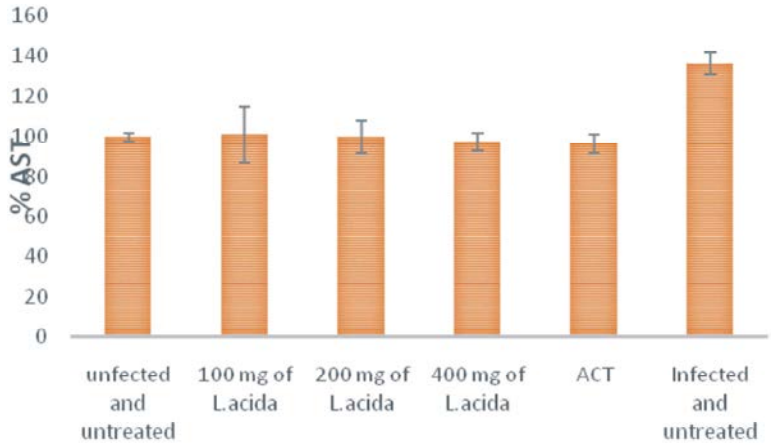

Fig. 6: Effect of treatment on aspartate aminotransferase (AST) activity.

Serum Aspartate aminotransferase (AST) Activity: Fig. 6 shows that Serum AST activity in the infected-untreated group increased significantly ($p<0.05$) above all other groups whereas the group treated with ACT (Standarddrug) showed the least activity but not significantly different ($p>0.05$) from rest of the groups.

DISCUSSION

Acute Toxicity: The major and overriding criterion in the selection of herbal medicines for use in health services is safety [21]. The LD_{50} of the ethanolic leaf extract of *Lannaeacida* was determined to be 2154mg/kg body weight of the extract. Plant extracts should not only be efficacious but safe for consumption. Thus the need that while screening plants' extracts for their antimalarial activities, their toxic potentials [22] should also be investigated. This high mean lethal dose value is a scientific confirmation of the safe use of the plant for malaria treatment in certain communities in Nigeria.

Parasitaemia Suppression: The use of medicinal plants in malaria therapy and also, in the therapy of many other diseases is common place at the primary healthcare level in many developing countries [23] of which Nigeria is one. The emergence of resistant strains necessitates the introduction of potent new drugs or drug combinations against malaria. Preferably, new drugs should have novel modes of action or be chemically different from the drugs in current use [24]. Parasitaemia suppression produced by the ethanolic leaf extract of *Lannaeacida* followed a dose dependent pattern, with 400mg/kg body weight which was the highest dose of the extract used showing no significant difference ($p>0.05$) with that of standard drug (ACT) throughout the study period. It could therefore be said to have shown an effect comparable to that of standard drug. This finding is in line with that of Mohammed, Erkoand Giday [25] who reported a significant dose dependency in the suppression of *P. berghei*in mice treated with *Croton macrostachyus* water and methanol extracts (200, 400 and 600 mg/kg).

Though ours wasn't significant all through the study. We have also reported similar finding previously [26] in which the antiplasmodial effect of S*arcocephaluslatifolius* ethanolic leaf extract showed direct proportionality with the dose of the extract administered such that the higher doses produced higher parasitaemia suppression.

The pharmacological activities of medicinal plants are believed to arise from their constituent phytochemicals [27]. The observed antiplasmodial activity of *Lannaeacida* could be traced to different phytochemical groups. Alkaloids, flavonoids and terpenes have been variously implicated in antiplasmodial activities of many plants [28]. These compounds have also been shown to exert antiplasmodial activity by elevating the red blood oxidation and inhibitingthe parasite's protein synthesis. This counteractsthe oxidative damage induced by the malaria parasite [29].

Haematological Parameters: The consideration of hematological indices in this study was informed by the fact that most pronounced changes related to malaria involve the blood and the blood-forming system [30]. There was a remarkable decline in the PCV of the Infected and untreated group in this studywith respect to other groups, this could be attributed to the progressive increase in parasitaemiadue to lack of treatment [31]. This is also supported by the report of [32] that lower PCV seen in children with malaria parasite infection has been attributed to severe premature erythrocyte destruction and ineffective erythropoiesis resulting in life threatening anemia seen in all forms of malaria infection especially in *Plasmodium falciparum* infections.

Percentage RBC Count and Haemoglobin concentration examined were also seen to have decreased in the Infected and untreated group significantly ($p<0.05$) when compared to all other groups. An indication of anemia was seen in malaria cases. Anaemia is usually appraised by evaluating the packed cell volume (PCV), haemoglobin (Hb) and red blood cell (RBC) count in malaria of infected people [33]. Reduced hemoglobin in malaria may be attributed to the increase in breakdown of red blood cells by the parasites [34].

The extract of *Lannaeacida* could therefore be said to have restored these shortfalls in hematological indices because their values showed no significant difference when those of the treated groups were compared with the uninfected and untreated group.

Biochemical Parameters: Liver enzymes AST, ALT increase in malaria parasite infection to level dependent on the degree ofparasitaemia and suggest that liver is involved in the pathophysiology of malaria [35]. Our findings showed (Fig. 5) that the serum alanine aminotransferase activity of the infected and untreated group increased significantly ($p<0.05$) when compared to all the treatment groups, the uninfected and untreated group is inclusive. AST activity (Figure 6) in the infected-untreated group also increased significantly ($p<0.05$) above all other groups, these may have resulted from the fact that the invasion of liver cells by malarial parasites causes organ congestion, sinusoidal blockage and cellular inflammation [36] which impacted the parenchymal (transaminases) and membranous (alkaline phosphatase) enzymes of the liver to leak into the circulatory system leading to increased enzyme activity [37].According to WHO [38], liver involvement in malaria is seemed common in patients with severe malaria and may manifest as jaundice, that is raised serum bilirubin, hepatomegaly, elevated liver enzymes like aspartateaminotransaminase and alanine transaminase.

Serum ALT and AST levels of the uninfected and untreated group observed in this study were within the same range as those of the treatment groups with no remarkable difference, which could be attributed to thehepatoprotective ability of the extract as well as its suppression of the malaria parasites**.**WHO [39] corroborated this finding in their report that the relative milder changes inthe specific ALP, ALT and AST activities observed in the group infected and treated with 600 mg/kg b.w methanol extract of *C. albidum*stem bark, suggest that the extract suppressed the build-up of parasites, in addition to enhanced immune response, in the mice and probably abrogated the hepatic phase of development of the protozoa.

CONCLUSIONS

The antiplasmodial activity observed from ethanolic leaf extract of *Lannaeacida* in this study at a high oral LD_{50} value lends credence to the safe use of the plant in treatment of malaria withincommunities in Nigerian.

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