EUROPEAN ACADEMIC RESEARCH
Vol. X, Issue 8/ November 2022

Impact Factor: 3.4546 (UIF)
DRJI Value: 5.9 (B+)

ISSN 2286-4822
www.euacademic.org

# Antiplasmodial Activity of Carica Papaya L. Leaf Ethanolic Extracts in Swiss Albino Mice Infected with Plasmodium berghei

SAKINA MUHAMMAD BABANGIDA
*Kano State College of Education and Preliminary Studies, Kano, Nigeria*
SALAMATU IBRAHIM ZAKARI
NURA SALISU
*Department of Biology, Ahmadu Bello University, Zaria, Nigeria*

**Abstract:**

*Malaria is a vector-borne illness that had become the primary cause of sickness and large-scale death in Nigeria. The effects of Carica papaya leaf ethanolic extracts on Swiss albino mice infected with Plasmodium berghei were therefore the subject of a study. For the study, 15 swiss albino mice of both sexes, weighing 140-260 g, were divided into five groups. C. papaya fresh leaves were air-dried at 28 $^{o}$C for three weeks before being ground into powder. The crushed powder was weighed using a balance before being placed in 150 ml of 95% ethanol for 72 hours. By utilizing a rotary evaporator, the powder was transformed into an ethanolic extract. For the investigation, 15 swiss albino mice were housed in typical settings. About 1x10$^{6}$ intraperitoneal injections of P. berghei-infected blood were given to the animals. After 48 hours of infection, animals in group 1 got 0.2 ml of normal saline, group 5 received 5 mg/kg of chloroquine diphosphate intraperitoneally, and groups 2, 3, and 4 received oral doses of 100, 200, and 400 mg/kg of ethanolic extracts from C. papaya leaf, respectively. Standard protocols were used to examine the haematological profiles of the infected mice before, during, and after treatment periods. To determine the impact of the plant extract on P. berghei in Swiss albino mice, a 4-day curative test was conducted. The data was examined using one-way analysis of variance, and Duncan's New Multiple Range Test was used to identify significant means. The findings demonstrated that as concentrations increased, the PCV, RBC, and WBC values significantly varied between treatment groups. To combat and overcome the parasitemia, the body produces more lymphocytes, neutrophils, monocytes, eosinophils, and basophils during the infection stage. The number of parasitized erythrocytes significantly (P≤0.05) decreased with increase in concentration. It was inferred that 400 mg/kg of C. papaya stem extracts could serve as alternative to chloroquine diphosphate in the treatment of malaria.*

**Keywords:** *Carica papaya*, Curative Test, Parasitemia, Albino Mice.

## 1. INTRODUCTION

In nations where malaria transmission is a frequent occurrence as well as regions where it has been mostly controlled or eradicated, malaria remains a serious public health concern (WHO, 2019). In Africa, it is the main factor contributing to incidence and death (Badmos *et al*., 2021). Every year, 300 million to 500 million illnesses and one to three million fatalities are caused by malaria (Verma *et al*., 2011). Pregnant women and youngsters below five are more vulnerable to malaria. Every two minutes a youngster with the illness dies (WHO, 2018). In 2016, Nigeria had 27% of the world's malaria cases and 24% of the deaths due to malaria (WHO, 2018). A protozoan of the species *Plasmodium falciparum*, *P. vivax*, and *P. berghei* is mostly responsible for the

sickness (Alebie *et al.,* 2017) transmitted via bites of female mosquito of the genus *Anopheles* (Waiganjo *et al*., 2020).

Several conventional drugs were used for the treatment of malaria over the years with no proper fruitful results attributed to the increasing rate of resistance conferred by the parasites to the conventional drugs (Nyandwaro *et al.,* 2020; Tajbakhsh *et al.,* 2021) and evolving resistance of the vector to insecticides (Uzor *et al*., 2020). Therefore, new creative strategies to manage and control malaria are required in light of recent reports of *P. falciparum* that are artemisinin-resistant (Cudjoe *et al*., 2020) .In Nigeria, various treatments are needed to treat malaria. In most parts of the world, plant-derived medications have long been used in traditional medicine and use it to treat microbial infections. Herbal therapy is widely accessible in our varied grasslands, affordable, and, most importantly, has the ability to innovate modern medicines (Akinyemi *et al*., 2005).

Several tropical plants were shown to have specific antimalarial potentials, according to ethnopharmacological research (Rasoanaivo *et al*., 2011). Despite the fact that the mechanism of action of *C. papaya L.* against the malarial parasites is not yet fully known, it has been utilized in Nigeria in traditional settings to cure malaria. Therefore, the objective of this work was to investigate the mechanism of action of *C. papaya* leaf ethanolic extracts against *P. berghei*-infected mice in order to shed some light on how they behave.

## 2. METHODOLOGY

### Plant samples collection

Fresh *C. papaya* leaf was taken from the Botanical garden, ABU Zaria, and transported to the Herbarium, Department of Botany, ABU Zaria for authentication; voucher number ABU01203 was given.

### Plant ethanolic extraction

The procedure goes with the recommendations made by Sasidharan *et al.* (2011). Gathered samples were properly cleaned before being air-dried for three weeks at room temperature (28 $^{o}$C) in the shade. Using a mortar and pestle, the dried leaves was pounded into a fine powder, which was then kept in dry containers until needed. To make the ethanolic extracts, 100 g for each powder were soaked in 150 ml of 95 per cent ethanol and then agitated in an orbital shaker at 120 rpm.After being unfiltered for another 24 hours, the mixture was run through gauze and Whatman No. 1 filter paper. Three distinct concentrations of 100, 200, and 400 mg/kg were prepared from the stem extract stock solution.

### Phytochemical analysis

According to the procedures outlined by Adegoke *et al*. (2010), the phytochemical screening of the ethanolic extract of *C. papaya* was done to ascertain the existence of active ingredients in the plant stem. The tests include: Wagner's test for alkaloids, Molisch's test for carbohydrates, and the lead subacetate test for tannins. the frothing/foaming test for saponins, the Keller-Killiani's test for the detection of cardiac glycosides, Triterpene and steroid identification by the Libermann-Burchard test, alkaline test for flavonoid detection, ferric chloride test for phenol detection, copper

acetate test for the detection of diterpenoids, Xanthoproteic assay for protein detection and Borntrager's test for anthraquinones detection.

**Experimental animals**

The Agaric ministry, Kano State approved the transaction ethically. The approach followed the guidelines for good laboratory practice (GLP) as set forth by the World Health Organization. Fifteen (15) healthy white swiss albino mice of both sexes weighing between 140 and 260 g were obtained from ABU Zaria. The mice were housed in metal cages in ventilated rooms with a 12-hour cycle of darkness and light. They were given regular feed pellets and unlimited access to water. Before beginning the investigation, the animals underwent a two-week acclimatization period.

**Animal inoculation**

A Swiss albino mouse was intraperitoneally injected with *P. berghei* at the Department of Parasitology and Entomology, Faculty of Veterinary Medicine, Ahmadu Bello University, Zaria, at maximal parasitemia and the parasite was allowed to attained a 40-50% parasitemia.A myocardial puncture was performed on the donor mouse after it was sacrificed, and 0.1 ml of acid citrate dextrose was poured into the syringe. The inoculum used to infect the test animals was created by diluting the blood with isotonic saline. The experimental mice were given 0.2 ml of diluted parasitized red blood cells with 109 parasites per ml as an inoculation. A 0.2 mL intraperitoneal injection of infected blood solution containing 1x106 red blood cells parasitized by P. berghei was given to each experimental mouse.

**Determination of extracts toxicity**

According to the Lorke method (1983), the lethal dose ($LD_{50}$) of the extracts was calculated to estimate the acute toxicity of the *C. papay*a extracts. The procedure involved giving three groups of swiss albino mice various doses (100, 200, and 400 mg/kg) of the extracts intraperitoneally. Following that, the occurrence of physical symptoms and mortality in mice for potential toxicity was observed.

**Curative test**

According to the method outlined by Iyiola *et al.*(2011) the chemotherapeutic activity of *C. papaya* leaf ethanolic extracts was tested in established infection . The albino mice were given 0.2 ml standard inocula of $1x10^6$-infected erythrocytes intraperitoneally on the first day (Day 0). Mice were put into three test groups (II, III, and IV) of three mice each 72 hours later (Day 3). As negative and positive controls, respectively, Groups I and V were allocated. The test groups were then given doses of the extract equal to 100, 200, or 400 mg/kg/day. Positive and negative controls each received 0.2 ml of saline and 25 mg/kg/day of chloroquine orally via cannula. 24 hours after the parasite inoculation, the parasitemia was first monitored. Each experimental mouse had their tail severed, from which blood was drawn to make thick and thin smears. The thick and thin films were both stained with 10% Giemsa stain for 15 minutes after the smear had dried and the thin smear had been fixed with 100% methanol. The compound microscope's oil immersion resolutions were used to see the slides (Vickers Instruments). Each slide was examined, and both the parasitized and non-parasitic red blood cells (RBCs) were noted.

**Packed Cell Volume Determination (PVC)**

PCV was estimated using the microhaematocrit technique described by Cole (1986) . In a nutshell, capillary activity filled blood samples into heparinized capillary tubes to a depth of 75% (34) of their length. The outside of the tubes was gently dried with gauze while the other end of the tubes was being sealed with flame. The tubes were then mounted on a microhematocrit centrifuge and spun at 3000 rpm for ten minutes.

**Haematological parameters evaluation**

The sum of Erythrocytes count was assessed using Cole's (1986) method. Blood samples were carefully aspirated using the pipette's 0.5 mark before being transferred into a clean cuvette containing diluent (0.9% normal saline). The diluted blood was released into the haemocytometer counting chamber and allowed to settle after being thoroughly mixed with a different pipette's dilution fluid. The total number of erythrocytes per microliter (L) was determined.The automated hematology analyzer technique illustrated by Asangha *et al.*(2017) was used to do the rest of the haematological measurements, like the counts of white blood cells (WBCs), monocytes (MON), neutrophils (NEU), lymphocytes (LYM), basophils (BAS) and eosinophils (EOS). Before the infection, during the infection, and after the completion of treatment, the haematological data were gathered.

**Statistical analyses**

ANOVA was employed to analyse the data, and Duncan's New Multiple Range Test was used to separate the means that were significant at the 5% level (DMRT). To calculate the extracts' lethal dose ($LD_{50}$), probit analysis was utilized.

## 3. RESULT

Table 1 lists the findings for the phytochemical components of *C. papaya* leaf ethanolic extract. Eight (8) active compounds were found in the extract, including carbohydrates, saponins, proteins, anthraquinones, phenols, flavonoids, terpenoids/steriods, and alkaloids.

**Table 1: Phytochemical constituents in *Carica papaya* leaf ethanolic extract**

| Extract | Constituent | Test | Result |
|---|---|---|---|
| *Carica papaya* | Flavonoids | Alkaline | + |
| | Phenols | Ferric chloride | + |
| | Proteins | Xanthoproteic | + |
| | Alkaloids | Wagner's | + |
| | Anthraquinones | Borntrager's | + |
| | Saponins | Frothing/Foami | + |
| | Tannins | Lead subacetate | - |
| | Terpenoids/Steriods | Libermann-Burchard's | + |
| | Diterpenoids | Copper Acetate's | - |
| | Cardiac glycosides | Keller-Killiani's | - |
| | Carbohydrates | Molisch's | + |

**KEY: + = PRESENT -= ABSENT**

The outcome of the extracts' acute toxicity tests showed that there was absence of mortality in the dose range from 100 to 400 mg/kg in either the first 24 or the next 72 hours. This indicates that the doses used were appropriate. There were no overtly toxic physical or behavioral abnormalities, like a decreased motor activity, body or limb tone,

writhing, breathing issues, or death. The results show that the extract's $LD_{50}$ exceeds 1000 mg/kg.

The effects *of C. papaya* ethanolic extracts on the haematological profile of *P. berghei*-infected mice are illustrated in Table 2. The results revealed a difference in the effects of various extract concentrations on the blood parameters of infected mice that was statistically significant (P 0.05). (except for basophils). During the periods of infection, the extracts significantly lower PCV values by a range of 50.5 to 43.7%. The WBC counts rise from $9.7x10^3$ to 10.6 $x10^3$/L during the infection period. Following treatment, these values decreased from 10.9x $10^3$ to $11.6x10^3$/L, similar to how RBC counts rise during an infection and following extract therapy. The outcome also demonstrated that the extracts had a substantial impact on neutrophils and lymphocytes. During the infection phase, the neutrophils were reported to decline from 49.00 to 53.00% with a drop in concentration. However, following therapy, neutrophil levels drop from 46.2 to 45.3% with a reduction in concentration. A similar pattern was observed in the lymphocyte count. Furthermore, the extracts revealed that Eosinophil and Basophil numbers rose during the infection phase.

**Table 2: Effect of *C. papaya* extracts on blood parameters in mice infected with *P. berghei***

| Sample (mg/kg) | PCV (%) | WBCx$10^3$ | RBCx$10^6$ | MON | NEU | LYM | EOS | BAS |
|---|---|---|---|---|---|---|---|---|
| $Saline_{BI}$ | 47.5±2.6$^a$ | 11.3±0.6$^a$ | 11.5±0.6$^a$ | 1.7±0.8$^a$ | 49.0±1.8$^a$ | 45.0±1.4$^a$ | 3.2±1.2$^a$ | 1.2±0.4$^a$ |
| $Saline_{DI}$ | 44.7±3.1$^a$ | 10.2±0.6$^a$ | 12.6±2.7$^a$ | 1.5±0.6$^a$ | 44.8±19.3$^b$ | 39.5±4.6$^b$ | 2.7±1.0$^a$ | 2.3±1.4$^a$ |
| $Saline_{AT}$ | 40.5±3.5$^{ab}$ | 11.0±0.3$^a$ | 12.1±0.6$^a$ | 1.8±0.6$^a$ | 52.8±4.9$^a$ | 40.2±4.9$^b$ | 2.0±1.0$^a$ | 3.2±0.8$^a$ |
| $100_{BI}$ | 49.5±2.5$^a$ | 11.3±0.5$^a$ | 11.9±0.5$^a$ | 2.2±1.3$^a$ | 50.8±6.8$^a$ | 42.3±7.2$^b$ | 2.5±0.6$^a$ | 2.2±0.4$^a$ |
| $100_{DI}$ | 47.2±2.4$^b$ | 10.4±0.8$^b$ | 11.7±0.5$^a$ | 1.6±0.8$^c$ | 50.8±4.9$^a$ | 42.7±4.9$^b$ | 2.7±1.6$^a$ | 2.3±1.0$^a$ |
| $100_{AT}$ | 46.2 ± 1.9$^c$ | 11.4±0.8$^a$ | 11.2±0.4$^b$ | 1.8±0.8$^b$ | 46.2±1.5$^b$ | 46.7±2.3$^a$ | 2.3±1.0$^a$ | 3.0±1.1$^a$ |
| $200_{BI}$ | 46.8±1.9$^a$ | 10.9±0.4$^a$ | 11.1±0.3$^b$ | 1.3±0.5$^b$ | 51.0±5.4$^a$ | 42.8±5.6$^b$ | 3.2±0.8$^a$ | 1.5±1.2$^a$ |
| $200_{DI}$ | 43.8±2.5$^b$ | 9.7±0.2$^b$ | 11.8±0.6$^a$ | 2.0±0.8$^a$ | 48.5±2.3$^b$ | 44.2±2.3$^a$ | 2.3±0.5$^b$ | 3.0±0.9$^a$ |
| $200_{AT}$ | 43.7±2.9$^b$ | 10.9±0.4$^a$ | 11.9±0.4$^a$ | 1.2±0.4$^c$ | 48.2±2.8$^b$ | 44.8±1.9$^a$ | 2.5±0.5$^b$ | 3.3±0.8$^a$ |
| $400_{BI}$ | 50.5±1.6$^a$ | 11.4±0.2$^a$ | 12.0±0.5$^a$ | 2.8±1.2$^a$ | 53.0±6.4$^a$ | 40.7±5.3$^c$ | 1.7±0.8$^c$ | 1.8±0.8$^a$ |
| $400_{DI}$ | 48.0±1.0$^b$ | 10.6±0.5$^b$ | 12.0±0.2$^a$ | 1.5±0.5$^c$ | 48.7±1.5$^b$ | 44.2±1.9$^b$ | 2.7±1.0$^b$ | 2.7±0.8$^a$ |
| $400_{AT}$ | 46.0±1.7$^c$ | 11.6±0.3$^a$ | 10.7±4.1$^b$ | 1.7±0.8$^b$ | 45.3±1.8$^c$ | 46.8±1.6$^a$ | 3.2±1.5$^a$ | 3.0±1.0$^a$ |
| $Chl_{BI}$ | 47.5±1.8$^a$ | 10.5±0.2$^a$ | 11.4±0.7$^b$ | 2.8±1.2$^a$ | 47.7±2.1$^a$ | 46.5±2.9$^b$ | 2.8±1.2$^b$ | 1.7±0.8$^a$ |
| $Chl_{DI}$ | 44.2±1.2$^b$ | 10.1±0.5$^b$ | 11.8±0.7$^b$ | 1.5± 0.5$^c$ | 44.2±1.5$^b$ | 49.1±1.4$^a$ | 2.7±0.8$^b$ | 2.7±1.0$^a$ |
| $Chl_{AT}$ | 47.2±1.7$^a$ | 10.9±0.8$^a$ | 12.0±0.5$^a$ | 1.7±0.8$^b$ | 43.8±1.9$^c$ | 49.7±1.2$^a$ | 3.2±0.8$^a$ | 2.0± 1.1$^a$ |

Table 3 displays the findings of how *C. papaya* extracts affected *P. berghei* parasitemia. With an increase in concentration, the number of infected RBCs significantly decreased, falling from $2.1x10^6$/L to as low as $0.9x10^6$ /L. Additionally, there is a considerable increase in the percentage parasitemia cure with increasing concentration; 400 mg/kg exhibited high curative effect from36.1-71.7% with increase in concentration.

**Table 3: Impact of *C. papaya* extracts in lowering parasitemias in mice infected with *P. berghei***

| Sample (mg/kg) | Total RBC | Infected RBC | Average Parasitemia | % Curative |
|---|---|---|---|---|
| $Saline_{DI}$ | 544.4 | 2.1 | 21.9 | - |
| $Saline_{AT}$ | 534.4 | 1.4 | 20.3 | - |
| $100_{DI}$ | 470.8 | 1.9 | 20.1 | 8.2 |
| $100_{AT}$ | 431.7 | 1.1 | 14.0 | 36.1 |
| $200_{DI}$ | 472.6 | 1.8 | 17.7 | 19.2 |
| $200_{AT}$ | 433.9 | 1.25 | 9.5 | 56.6 |
| $400_{DI}$ | 438.6 | 1.85 | 19.9 | 9.1 |
| $400_{AT}$ | 563.4 | 0.9 | 6.2 | 71.7 |
| $Chl_{DI}$ | 472.5 | 1.9 | 17.3 | 5.8 |
| $Chl_{AT}$ | 603.1 | 0.7 | 3.5 | 84.0 |

## 4. DISCUSSION

The leaves of *C. papaya* contained eight active compounds that most likely played a big part in reducing *P. berghei* parasitemia. There is evidence that alkaloids, saponins,

tannins, flavonoids, and steroids are biological activity (Nethathe and Ndip, 2011). These phytochemicals may be responsible for the extracts' antiplasmodial efficacy, as this study found (Abdulelah and Zainal-Abidin, 2007). The quinine, which is an antimalarial, is among the alkaloids reported by Baskaran *et al.* (2012) to be of high antiplasmodial efficacy. Earlier studies (Kayano *et al.*, 2011) have linked the presence of flavonoids, tannins, and triterpenes to the antimalarial activities of plants. The observed antimalarial activity of these chemicals may be the result of their individual or combined action. The non-toxic effects of the *C. papaya* extracts according to this study agrees to the outcome of Jayasinghe *et al.* (2008) who reported non-toxicity of a plant extract as the primary concern of indigenous therapeutic medicines used to treat malaria fever that meet the CDER's (1996) criterion for lack of acute toxicity .To assess the efficiency of the extracts in avoiding haemolysis brought on by an increasing parasitemia level, PCV was assessed. The current investigation found that treatment with *C. papaya* extracts decreased PCV readings. This outcome is in agreement with that of Bantie *et al.* (2014), Nardos and Makonnen (2017) who individually reported malaria parasites caused the PCV to decline 48 hours after infection, on average. When mice are infected with *P. berghei*, their erythrocytes are destroyed either by the parasite's growth or by the activity of reticuloendothelial cells in the spleen, which are stimulated to create an abundance of phagocytes when there are a lot of aberrant erythrocytes present (Chinchilla *et al.*, 1998). These mechanisms are responsible to treat mice and people with malaria-induced anemia (Lamikanra *et al.*, 2007).

The leucocytes (WBCs) counts were reported to increase in the treated groups with increase in dose. This complies with the report of Ihedioha *et al.*(2012) who observed that the blood profile of albino mice had an increased amount of distinct WBCs over the normal range. The rise in the variety of WBCs can likely be ascribed to the extracts' immunostimulatory effects on blood that has been parasitized by *P. berghe*i. This result is consistent with that of Silitonga (2017), who found that rats given BCG plus *Plectranthus amboinicus* leaf extract had higher leucocyte counts in their hematological profiles. According to the current study, *C. papaya* extracts alter the immune system by raising the number of lymphocytes, monocytes, and neutrophils in the blood of infected mice to fight *P. berghei* parasitemia.

Ethanolic extracts of *C. papaya* leaves greatly reduced parasitemia as compared to the controls, demonstrating their efficacy in the treatment of malaria.Similar to this, Francois *et al.*(1996) discovered that *Neutolaena lobata* leaf extracts had a greater than 50% cure . Furthermore, earlier studies have suggested that *C. papaya* may have antimalarial properties both *in vitro* and *in vivo*. Ali *et al.*(2002) also reported on the inhibitory effectiveness of *Salvadora persica* methanolic and chloroform extracts against *P. berghei* proliferation.

## 5. CONCLUSION

The ethanolic extracts of *C. papaya* leaves have been found to have antiplasmodial potentials. They cause immune-stimulating reactions by greatly increasing the amounts of various WBCs, like neutrophils, eosinophils, lymphocytes, basophils and monocytes. In comparison to the control groups, the treated groups have more lymphocytes, neutrophils, and monocytes. With *C. papaya* having the biggest impact, high quantities of the extracts considerably decreased the generation of *P. berghei* parasitemia. The extract from *C. papaya* may have antiplasmodial properties because of its active

phytochemicals. Because it shows no host toxicity, we advised 400 mg/kg of *C. papaya* extract against malarial infections brought on by *Plasmodium spp*.

## REFERENCES


1. Abdillah, S., Risma, M.T., Yunahara, F., Ni Made, D.S. and Rita, M.D. 2015.Phytochemicalscreening and antimalarial activity of some plants traditionally used in Indonesia. *Asian Pacific Journal of Tropical Disease*, 5(6): 454–57.
2. Abdulelah, H. and Zainal-Abidin, B. 2007. *In vivo* anti-malarial tests of *Nigella sativa* (black seed) diferent extracts, *American Journal of Pharmacology and Toxicology*, 2(2): 46–50.
3. Adebayo, J.O. and Krettli, A.U. 2011. Potential antimalarials from Nigerian plants: A Review. *Journal of Ethnopharmacology*, 133(2): 289–302.
4. Adegoke, A.A., Iberi, P.A., Akinpelu, D.A., Aiyegoro, O.A., and Mboto, C.I. 2010. Studies On phytochemical screening and antimicrobial potentials of *Phyllanthus amarus* against multiple antibiotic resistant bacteria. *International Journal of Applied Research in Natural Products,* 3(3): 6-12.
5. Aherne, S.A., Daly, T., O'Connor, T. and O'Brien, N.M. 2007. Immunomodulatory effects of ß-sitosterol on human Jurkat T cells. *Planta Medica*, 73(09): 797–1034.
6. Airaodion, A.I., Airaodion, E.O., Ekenjoku, J.A., Ogbuagu, E.O. and Ogbuagu, U. 2019.Antiplasmodial potency of ethanolic leaf extract of *Carica papaya* against *Plasmodium berghei* in Infected Swiss Albino Mice. *Asian Journal of Medical Principles and Clinical Practice,* 2(2): 1-8.
7. Aiyegoro, O.A, Akinpelu, D.A. and Okoh, A.I. 2007. *In Vitro* antibacterial potentials of the stem bark of Redwater Tree (*Erythrophleum suaveolena*). *Journal of Biological Sciences*, 7(7): 1233-1238.
8. Ajaiyeoba, E., Falade, M., Ogbole, O., Okpako, L. and Akinboye, D. (2006). *In vivo* antimalarial and cytotoxic properties of *Annona senegalensis* extract. *African Journal of Traditional, Complementary and Alternative Medicine,* 3:137–41.
9. Ajayi, A.O. and Akintola, T.A. 2010. Evaluation of antibacterial activity of some medicinal plants on common enteric food-borne pathogens. *African Journal of Microbiology Research,* 4(4): 314-316.
10. Akinyemi, K.O., Smith, S.I., Oyefolu, A.O. and Coker, A.O. 2005. Multidrug resistance in *Salmonella enterica* serovar typhi isolated from patients with typhoid fever complications in Lagos, Nigeria. *Public Health*, 119: 321-327.
11. Akuodor, G.C., Idris-Usman, M., Ugwu, T.C., Akpan, J.L., Ghasi, S.I., and Osunkwo, U.A. 2010. *In vivo* schizontal activity of ethanolic leaf extract of *Gongronema latifolium* on *Plasmodium berghei berghei* in mice. *Afr. J. Biotech*., 10;9(5): 2316–2321-227.
12. Akuodor, G.C., David-Oku, E., Nkorroh, J.A., Essien, A.D., Nkanor, E.E., Ezeunala, M.N.and Chilaka, K.C. 2017. Antiplasmodial activity of the ethanolic root bark extract of *Icacina senegalensis* in mice infected by *Plasmodium berghei*. *J Basic Clin Physiol Pharmacol.,* 28(2): 181–184.
13. Alebie, G., Befikadu, U. and Amha, W. 2017. Systematic review on traditional medicinal plants used for the treatment of malaria in Ethiopia: Trends and perspectives. *Malaria Journal*, 1–13pp.
14. Ali, H., Konig, G., Khalid, S., Wright, A. and Kaminsky, R. 2002. Evaluation of selected Sudanese medicinal plants for their *in vitro* activity against hemofagellates, selected bacteria, HIV-1- RT and tyrosine kinase inhibitory, and for cytotoxicity. *Journal of Ethnopharmacology,* 83(3): 219–228.
15. Ali, A.J., Akanya, H.O. and Dauda, B.E.N. 2010. Polygalloyltannin isolated from the roots of *Acacia nilotica* Del. (Leguminoseae) is effective against *Plasmodium berghei* in mice, *J. Med. Plants. Res.*, 4(12): 1169-1175.
16. Alorkpa, E.J., Boadi, N.O., Badu, M. and Saah, S.A. 2016. Phytochemical screening, antimicrobial and antioxidant properties of assorted *Carica papaya* leaves in Ghana. *Journal of Medicinal Plants Studies*, 4(6): 193-198.
17. Anwar, F., Latif, S., Ashara, M. and Gilani, A.H. 2007. *Moringa oleifera*: A food plant with Multiple medicinal uses. *Journal of Phytotherapy Research*, 21: 17-25
18. Asangha, E.E., Igile, G.O., Iwara, I.A., Ebong, P.E. and Eseyin, O.A. 2017. Hematological indices of *Plasmodium berghei* infected mice treated with ethanol extract and fractions of *Nauclea latifolia* roots. *International Journal of Current Microbiology and Applied Sciences,* 6: 2546-2556.
19. Asres, K., Bucar, F., Knauder, E., Yardley, V., Kendrick, H. and Crof, S.L. 2001. *In vitro* antiprotozoal activity of extract and compounds from the stem bark of *Combretum molle*. *Phytotherapy Research*, 15(7): 613–617.
20. Atanu, F.O., Idih, F.M., Nwonuma, C.O., Hetta, H.F., Alamery, S. and Batiha, G.E. 2021.Evaluation of antimalarial potential of extracts from *Alstonia boonei* and *Carica papaya* in *Plasmodium berghei*-Infected Mice. *Hindawi Evidence-Based Complementary and Alternative Medicine*, 2021, Article ID 2599191:1-11 .
21. Baskaran, C., Ratha, V., Velu, S. and Kumaran, K. 2012. The efficacy of *Carica papaya* leaf extract on some bacterial and a fungal strain by well diffusion method. *Asian Pacific Journal of Tropical Disease*, 658-662.
22. Builder, M.I., Wannang, N.N., Ajoku, G.A., Builder, P.F., Orisadipe, A. and Aguiyi, J.C. 2011. Evaluation of the antimalarial potential of *Vernonia ambigua* Kotschy and Peyr (Asteraceae). *Int J Pharmacol.,* 7:238–47.

23. CDER 1996. Guidance for industry single dose acute toxicity testing for chemical and *Crossopteryx febrifuga* (Rubiaceae) on mice *in vivo*. *Journal of Ethnopharmacology*, 93: 167–171.
24. Chandra, P. and Arbor, A. 2016. Order in the Warez Scene–Explaining an underground virtual community with the CPR framework. Online Behaviors, San Jose, CA, USA. 372-383 pp.
25. Coles, E.H. 1986. *Veterinary Clinical Pathology.* 4th edition, W.B Saunder, Philadelphia,London, 1-42.
26. Cudjoe, E., Donu, D., Okonu, R.E., Amponsah, J.A. and Amoah, L.E. 2020. The *In Vitro* antiplasmodial activities of aqueous extracts of selected Ghanaian herbal plants. *Journal of Parasitology Research*, 2020, Article ID 5041919, 1-8.
27. Ene, A.C., Atawodi, S.E., Ameh, D.A., Ndukwe, G.I. and Kwanashie, H.O. 2009. Bioassay -guided fractionation and *in vivo* antiplasmodial effect of fractions of chloroform extract of *Artemisia maciverae* Linn. *Acta Trop*., 112: 288-94.
28. Fatmawaty, F. and Astuti, H. 2013. Antimalarial activity of *Delonix regia* on mice with *Plasmodium berghei*. *Journal of Natural Products,* 6: 61-66.
29. Fatmawaty, R., Amanda, A., Innayah, S. and Vivitri D.P. 2017. Antimalarial effect of flamboyant (*Delonix regia*) bark and papaya (*Carica papaya* L) leaf ethanolic extracts against *Plasmodium berghei* in mice. *Biomedical and Pharmacology Journal,* 10(3): 1081-1089.
30. Francois, G., Passreiter, C., Woerdenbag, H. and van Looveren, M. 1996. Antiplasmodial activities and cytotoxic effects of aqueous extracts and sesquiterpene lactones from *Neutolaena lobata*. *Planta Med.,* 62:126–129.
31. Gebrehiwot, S., Shumbahri, M. Eyado, A. and Yohannes, T. 2019. Traditionally used medicinal plants of Afar region, Ethiopia, against *Plasmodium berghei* in swiss albino mice. *Journal of Parasitology Research*, 2019(1): 1-8.
32. Ghaleb, M.A., Bassam, A.A. and Kamel, M.A. 2009. *In Vitro* activity of certain drugs in combination with plant extracts against *Staphylococcus aureus* infections. *African Journal of Biotechnology*, 8 (17): 4239-4241.
33. Hilou, A., Nacoulma, O.G. and Guiguemde, T.R. 2006. *In vivo* antimalarial activities of extracts from *Amaranthus spinosus* and *Boerhaavia erecta* in mice. *Journal of Ethnopharmacology,* 103(2): 236–240.
34. Ibrahim, S., Ibrahim, M.A., Musa, A.M., Aliyu, A.B., Haruna, N.S. and Okafor, A.I. 2011. *Indigofera pulchra* leaves extracts contain antiplasmodium berghei agents. *Bangladesh J Pharmacol*., 6: 69-73.
35. Ihedioha, J.I., Ugwuja, J.I., Noel-Uneke, O.A., Udeani, I.J. and Daniel-Igwe, G. 2012. Reference values for the haematology profile of onventional grade outbred albino mice (*Mus musculus*) in Nsukka, Eastern Nigeria. *ARI.* 9(2):1601-1612.
36. Jahan, N., Afaque, S.H., Khan, N.A., Ahmad, G. and Ansari, A.A. 2008. Physico-chemical studies of the gum acacia. *Indian Journal of Natural Products and Resources*, 7(4): 335-337.
37. Jayasinghe, C.D., Udagama-Randeniya, P.V. and Ratnasooriya, W.D. 2008. *In vivo* antimalarial activity of aqueous root extract of *Barringtonia acutangula* in mice. *Pharmacognosy Magazine*, 4:51–58.
38. Kayano, A.C.A., Lopes, S.C.P., Bueno, F.G., Cabral, E.C., Souza-Neiras, W.C., Yamauchi, L.M., Foglio, M.A., Eberlin, M.N., Mello, J.C,P. and Costa, F.T.M. 2011. *In vitro* and *in vivo* assessment of the antimalarial activity of *Caesalpinia pluviosa*. *Malaria Journal*, 10: 112.
39. Koehn, F.E. and Carter, G.T. 2005. The evolving role of natural products in drug discovery. *Nat. Rev. Drug Discov*., 4: 206-20.
40. Krettli, A.U., Adebayo, J.O. and Krettli, L.G. 2009. Testing of natural products and synthetic molecules aiming at new antimalarials. *Current Drug Targets*, 10(3): 261–270.
41. Li, N., Xia, Q., Ruan, J., Fu, P.P. and Lin, G. 2011. Hepatotoxicity and tumorigenicity induced by metabolic activation of pyrrolizidine alkaloids in herbs. *Current Drug Metabolism*, 12(9):823-834.
42. Lorke, D. 1983. A new approach to practical acute toxicity testing. *Arch. Toxicol*., 54:275-287.
43. Malviya, S., Rawat, S., Kharia, A. and Verma, M. 2011. Medicinal attributes of *Acacia nilotica* Linn. A comprehensive review on ethnopharmacological claims. *International Journal of Pharmacy and Life Sciences*, 2(6): 830-837.
44. Mbah, C.C., Akuodor, G.C., Anyalewachi, N.A., Iwuanyanwu, T.C. and Osunkwo, U.A, 2012. *In vivo* antiplasmodial activities of aqueous extract of *Bridelia ferrogenea* stem bark against *Plasmodium berghei berghei* in mice. *Pharmaceutical Biology,* 50 (2):188-194.
45. Mohana, D.C, Satish, S. and Raveesha, K.A. (2008). Antibacterial evaluation of some plant extracts against some human pathogenic bacteria. *Advances in Biological Research*, 2(3-4): 49-55.
46. Musa, A.M., Sule, M.I., Ilyas, M., Iliya, I., Yaro, A.H., Magaji, M.G., Aliyu, A.B., Abdullahi, M.I. and Hassan, H.S. 2010. Analgesic and antiinflammatory studies of the methanol extract of *Indigofera pulchra*. *Res. J. Medicine Med. Sci.,* 5: 106-10.
47. Nethathe, B.B. and Ndip, R.N. 2011. Bioactivity of *Hydnora africana* on selected bacterial pathogens: Preliminary phytochemical screening. *African Journal of Microbiology Research*, 5 (18): 2820-2826.
48. Ohouko O.F.H., Koudouvo, K., Novidzro, K.M., Dougnon, T.V., Agbonon, A., Tozo, K.S., Dougnon, T.J. and Gbeassor, M. 2020. Phytochemical and toxicological studies of *Acacia nilotica* and *Faidherbia albida* used in West African traditional medicine. *International Journal of Recent Scientific Research*, 11(06B): 38906-38910.
49. Okokon, J.E., Ofodum, K.C., Ajibesin, K.K., Danladi, B. and Gamaniel, K.S. 2005.
50. Pharmacological screening and evaluation of antiplasmodial activity of *Croton zambesicus* against *P. berghei* infection in mice. *Indian Journal of Pharmacology*, 37(4): 243–246.

51. Okpe, O., Habila, N., Ikwebe, J., Upev, V.A., Okoduwa, S.I.R. and Isaac, O.T. 2016. Antimalarial potential of *Carica papaya* and *Vernonia amygdalina* in mice infected with *Plasmodium berghei*, *Journal of Tropical Medicine*, 32.
52. Oluwakanyinsola, S.A., Adeniyi, T.Y., Akingbasote, J.A. *et al*. 2010. Acute and subacute toxicity study of ethanolic extract of the stem bark of *Faidherbia albida* (DEL) A. Chev (Mimosoidae) in rats. *African Journal of Biotechnology*. 9(8): 1218-1224.
53. Onaku, L.O., Attama, A.A., Okore, V.C., Tijani, A.Y., Ngene, A.A. and Esimone, C.O. (2011). Antagonistic antimalarial properties of pawpaw leaf aqueous extract in combination with artesunic acid in *Plasmodium berghei*-infected mice. *J. Vec. Borne. Dis.*, 48: 96-100
54. Oraebosi, M.I. and Good, G.M. 2021. *Carica papaya* augments anti-malarial efficacy of artesunate in *Plasmodium berghei* parasitized mice. *Annals of Parasitology*, 67(2): 295–303.
55. Rasoanaivo, P., Wright, C.E., Wilcox, M.L., and Gilbert, B. 2011. Whole plant extracts versus single compounds for the treatment of malaria: Synergy and positive interactions. *Malaria Journal*, 10 (Suppl 1): S4.
56. Salawu, O.A., Tijani, A.Y., Babayi, H. *et al*. 2010. Antimalarial activity of ethanolic stem bark extract of *Faidherbia albida* (Del) a. Chev (Mimosoidae) in mice. *Archives of Applied Science Research*. 2(5): 261–268.
57. Sasidharan, S., Chen, Y., Saravanan, D., Sundram, K. and Yoga Latha, L. 2011. Extraction, isolation and characterization of bioactive compounds from plants' extracts. *African Journal of Traditional Complementary and Alternative Medicine,* 8:1–10.
58. Saxena, S., Pant, N., Jain, D.C. and Bhakuni, R.S. 2003. Antimalarial agents from plant sources. *Current Science*, 85(9): 1314–1329.
59. Silitonga, M. and Silitonga, P.M. 2017. Haematological profile of rats (*Rattus norvegicus*) induced BCG and provided leaf extract of *Plectranthus amboinicus* (Lour Spreng). Proceedings of the 4th International Conference on Research, Implementation, and Education of Mathematics and Science (4th ICRIEMS) AIP Conf. Proc. 1868, 090008-1–090008-7.
60. Sofowara, A. 1993. *Medicinal plants and traditional medicine in Africa*. Ibadan, Nigeria.Spectrum Book LTD. 289 pp.
61. Tahir, A.E. Satti, G.M.H. and Khalid, S.A. 1999. Antiplasmodial activity of selected Sudanese medicinal plants with emphasis on *Acacia nilotica*. *Phytother. Res*., 13: 474–478.
62. Tamasi, A.A., Shoge, M.O., Adegboyega, T.T. and Chukwuma, E.C. 2021. Phytochemical analysis and in-vitro antimicrobial screening of the leaf extract of Senna occidentalis (Fabaceae). *Asian Journal of Natural Products Biochemistry*, 19(2): 57-64.
63. Thomas, T.G., Raghavendra, K., Lal, S. and Saxena, V.K. 2004. Mosquito larvicidal properties of latex from unripe fruits of *Carica papaya* Linn. (Caricaceae). *The Journal of Communicable Diseases,* 36: 290-292.
64. Tijani, A.Y., Uguru, M.O. and Salawu, O.A. 2008. Anti-pyretic, antiinflammatory and anti-diarrhoeal properties of *Faidherbia albida* in rats. *African Journal of Biotechnology*. 7:696-700.
65. Ukaegbu, C.O., Nnachi, A.U., Mawak, J.D. and Igwe, C.C. 2014. Incidence of concurrent malaria and typhoid fever infections in febrile patients in Jos, Plateau State Nigeria. *International Journal of Scientific and Technology Research*, 3(4): 157-161.
66. Usman, W.A., Mahmoud, S.J. and Ahmed, Z.H. 2013. Antimicrobial activity of stem bark of *Faidherbia albida*. *British Journal of Pharmaceutical Research*, 3:786–794.
67. Uzor, P.F., Prasasty, V.D. and Agubata, C.O. 2020. Natural products as sources of antimalarial drugs. *Evidence-Based Complementary and Alternative Medicine*, 2020, Article ID 9385125, 1-4.
68. Verma, G., Dua, V.K., Agarwai, D.D. and Atul, P.K. 2011. Anti-malarial activity of *Holarrhena antidysenterica* and *Viola canescens*, plants traditionally used against malaria in the Garhwal region of North-west Himalaya. *Malaria Journal,* 10: 20.
69. WHO 2018. World Malaria Day Ready to beat malaria. Switzerland. World Health Organization, 1-3 pp.
70. WHO 2019. Drug resistance in malaria, World Health Organization, Geneva,1-27 pp.