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# *In vivo* antimalarial activity of *Ipomoea involucrata* P. Beauv. in *Plasmodium berghei* infected mice

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## ABSTRACT

**Background:** Malaria is one of the most important tropical diseases which affects majorly populations in developing countries. Increased resistance of Plasmodium sp. to major antimalarial drugs is a major challenge to malaria control programs as well as to national health systems in endemic countries.
**Objectives:** To determine antimalarial property of Ipomoea involucrata extract in mice and ascertain the folkloric use in antimalarial recipe.
**Methods:** The antimalarial activity of Ipomoea involucrata extract and fractions were evaluated in the 4-day chemo-suppressive test in infected Plasmodium berghei NK 65 mice. Doses of extract and fractions (100 mg/kg, 200 mg/kg, 400mg/kg and 800 mg/kg) were administered orally to different groups while the positive control received 10 mg/kg Chloroquine (CQ). Pack cell volume (%PCV), bodyweight change and survival time were monitored.
**Results:** The extract exerted a dose- dependent effect on parasitaemia, with the 800 mg/kg hexane fraction group expressing the highest suppression of parasite growth of 96.3% when compared to CQ, the reference antimalarial drug with 96.2%.
**Conclusions:** The result indicated that Ipomoea involucrata extract has antiplasmodial properties that could be exploited as alternative therapy for malaria, hence the usage in antimalarial recipe is thus justified.

**Keywords**: *Ipomoea involucrata*, *Plasmodium berghei*, Malaria, Convolvulaceae, Phytomedicine

## INTRODUCTION

The increasing rate of death associated with malaria disease and associated morbidity has been the trend in malaria-endemic regions where the majority of children below 5 years are mostly affected (WHO, 2022). The African regions and poor or developing countries of the world accounts for the greater percentage of the infection and deaths (WHO 2011; CDC, 2021). The continual increase in the global prevalence of malaria is a result of the increasing resistance of malaria parasites to available drugs like chloroquine and this poses a great challenge to malaria control programmes (White, 2004; Menard & Dondorp, 2017). In addition to this, the high cost of malaria treatment and non-availability of drugs in developing countries makes it unaffordable to the common people. Nigeria is a major susceptible zone because *Plasmodium falciparum*, the most virulent species is predominantly found here because the development of the parasite is highly favoured by stable environmental conditions. The recent development of the malaria vaccine was disadvantaged. The malaria vaccine RTS,S/AS01 has a relatively low efficacy of 18–36% against severe malaria and short-term protection in users as immunity appears to quickly diminish (RTS,S CTP, 2015; Okombo & Chibale, 2018) thus limiting its use. The lack of an effective malaria vaccine necessitates the need for the discovery and development of new effective and safe drugs with novel modes of action to complement the drugs currently in use.

Many populations of tropical countries depend on traditional medical remedies which rely solely on plants which have been

Figure 1: *Ipomoea involucrata* plant

discovered to be a rich source of new drugs. The two most important antimalarial drugs, quinine and artemisinin that are widely used have been developed from plants while some others were developed chemically using plant derived-compounds as a pattern (Basco et al. 1994; Chiyaka et al. 2009). Over the years, plants have been important sources of new drugs and several medicinal plants continue to provide easily accessible alternatives to widely used antimalarials. Plants have always been considered to be a possible alternative and rich source of new drugs and remain the main source of many phytochemical compounds with antiplasmodial activity.

Nigeria biome is endowed with plants used for malaria treatment and control. These represent more than half of the Nigerian medicinal species. To date, there has been scanty literature on the investigation on antimalarial activities of many of these plants.

*Ipomoeas involucrata* is a slender but vigorous, sprawling or twining annual or perennial herb, of grassland, secondary scrub and forest, widespread throughout tropical Africa. The plant by virtue of its active growth has been found suitable as a natural forestry cover for plantations in S. Nigeria, and W. Cameroons. Several folkloric usages include, infusion drink as a stimulant, or preventative of fever, antiprotozoal (filarial infection), antibiotics for gonorrhea, antiasthma, aqueous decoction is taken by women for dysmenorrhea, and at child-birth to hasten expulsion of the after-birth; and a compress of pounded up stems is used for headache (Burkill, 1985). The whole plant parts are used in the treatment of convulsion in Nigeria (Okafor, 2013) while the stems and leaves are used for treating anaemia in Ghana (Okudaira et al., 2005).

Studies have reported the antimicrobial activity (Ezeabara & Vincent, 2021); anticonvulsant potencies (David-Oku et al., 2017), antisickling properties and potential to reduce stress in sickle cell patients, haematopoietic effect (Koffuor et al., 2012), antinociceptive and anti-inflammatory activities of *Ipomoea involucrata.* (Uche et al., 2011) It is also used for the management of complications associated with diabetes mellitus

In continuation of our investigation into the activities of Nigeria medicinal plants as potential antimalarial agents (Ojo et al. 2013; Fadare et al. 2013), we present our investigation of the *in vivo* antiplasmodial activity of extract and fractions obtained from *Ipomoea involucrata* in mice which is a constituent in an antimalarial recipe.

## Materials and Methods

Plant collection, authentication, and extract preparation

Fresh *Ipomoea involucrata* whole plant was collected from within the University of Ibadan, Nigeria and identified in the herbarium of the Forest Research Institute, Nigeria. Air dried sample was milled and extracted into methanol by maceration for 72 h and filtered. The filtrate was dried with a rotary evaporator. The residue was collected and stored prior to use at $4^0$C.

## Phytochemical analysis

Methanol extract of *Ipomoea involucrata* was screened to determine the phytochemical constituents using standard procedures (Harborne, 1983).

**Solvents- solvent partitioning of crude methanol extract of *Ipomoea involucrata***

Crude methanol extract of *I. involucrata* was partitioned into several solvents of different polarities ranging from non-polar to moderately polar solvent. The extract was redissolved in water: methanol (1:3). This was extracted into hexane and separated using a separating funnel. The procedure was repeated three times with new hexane. The filtrate was combined and evaporated with rotary evaporator to give hexane fraction. This was repeated using dichloromethane and ethyl aceteate which affords dichloromethane and ethyl acetate fractions respectively. The left over extract is regarded as water extract. (Sakar & Nahar, 2012)

**In vivo chemo-suppressive antimalarial assay**

The antimalarial activity of *Ipomoea involucrata* methanol extract and fractions were evaluated using a 4-day chemo-suppressive test (Peters, 1975).

**Animals**

Adult Swiss male and female albino mice weighing between 18-22 g were used to evaluate the antimalarial activity. They were housed at the Institute of Advanced Medical Research and Training (IAMRAT), University College Hospital, Ibadan, Nigeria. The mice were randomly distributed into six (6) groups of five (5) animals per cage.

**Suppressive test (4-day test)**

Animals were used according to Institutional Animal Care and Use Committee (IACUC) standards for the study. Each mouse was inoculated with 0.2 mL of infected blood containing about $1 \times 10^7$ doses of *P. berghei berghei* collected by cardiac puncture from a donor mouse.

The 4-day suppressive test was conducted according to the method of Peters (1975). For each extract/fraction, 30 mice distributed into 6 groups of 5 mice each were infected. Animals in group 1-4 received 100, 200, 400, and 800 mg/kg of methanol extract /fractions of *I. involucrata*, whereas those in group 5 (positive control) received 10 mg/kg of the standard drug chloroquine while 6 (negative control) received normal saline as placebo *ad libitum.* Treatment was administered orally and continued daily for the next 3 days for the group that received chloroquine or 4 consecutive days for the extract-treated groups. On day 4, blood samples were collected from the caudal vein and stained with 10% Giemsa stain. Thereafter, the number of parasitized cells was estimated under the microscope using the ×100 objective. The numbers of infected erythrocytes were counted until 1000 erythrocytes were achieved. The average percentage suppression of parasitemia was calculated in comparison with controls as follows:

% suppression = ((% parasitemia in negative control−% parasitemia in test group)/(% parasitemia in negative control))×100.

The mice were placed under further surveillance to ascertain the mean survival time (days) of the animals across each group. The animals in each group were daily monitored for mortality from D0, this was continued after the treatment period till the mortality of all the animals.

**Packed cell volume measurement**

Blood samples were collected with heparinized sealed capillary tubes from the tail of each mouse. The tubes were then placed in a micro-haematocrit centrifuge with the sealed end outwards and centrifuged for 5 min at 11,000 rpm and PCV was determined using a standard Micro-Hematocrit reader. The PCV is a measure of the proportion of RBCs to plasma and was measured before inoculating the parasite and after treatment.

**Data analysis**

Chemosuppression of parasite growth and survival of animals were expressed as mean ± SEM. Statistical significance of means of different variables was analysed using Student's t test and one-way analysis of variance between groups (ANOVA) was used to compare the difference in percentage inhibition of parasite growth. For all statistical tests, P statistical significance was set at $P<0.05$.

**Results and Discussion**

Table 1 showed the result of the preliminary phytochemical screening of *I. involucrata*. Secondary metabolites detected were majorly alkaloids, tannins, saponins and flavonoids. This is in accordance with the findings of Essiett & Ukpong (Essiett & Ukpong, 2014). The *in vivo* antimalarial activity of the methanol extract, hexane,

dichloromethane, ethyl acetate and aqueous fractions of *I. involucrata* against *P. berghei* NK 65 strain in Swiss albino mice is presented in Table 2. Mean parasitaemia on day 4 in the untreated control animals was 7.25%, while mean parasitaemia in animals treated with selected doses (100–800 mg/kg) of *I. involucrata* extracts ranged from 0.48% to 7.20%. A dose-dependent chemosuppression of parasite growth was observed in animals treated with the extract and fractions of *I. involucrata*. At 800 mg/kg of the hexane extract of *I. involucrata* tested, there was a significant percentage inhibition of parasiteamia compared to the untreated control group ($P \leq 0.05$), with the longest survival time of 24 days. Methanol extract showed significant suppression of parasite growth (93.4%) and was partitioned into hexane, dichloromethane and ethyl acetate. Of all the fractions, hexane fraction of *I. involucrata* produced the highest chemosuppression of 90.7% at a dose of 800 mg/kg, while Chloroquine had parasitaemia suppression of 96.2% on D4. All the doses of the aqueous fraction of *I. involucrata* tested did not produce any significant chemosuppression of parasitaemia. However, 800 mg/kg of the ethyl acetate fraction of *I. involucrata*, produced a moderate chemosuppression of parasitaemia of 61.4%. It was also observed that animals that were treated with selected doses of the extract/fractions survived longer than the control untreated animals.

In spite of the numerous efforts to control malaria, the disease remains a global threat of enormous proportion and significantly contributes to the health and economic imbalances in endemic countries (Dhimam, 2019). Hence, the need of finding appropriate, effective, and cheap alternatives against the infection. The possibility of synthesizing new antimalarials from plants has become a major goal in the control programs, which is becoming more urgent, in light of the limited number of antimalarial currently in development. Natural products have played a major role in the discovery of leads for the development of drugs to treat human diseases, especially malaria, indicating that new antimalarial leads may certainly continue to emerge from tropical plant sources, We demonstrate that *I. involucrata* investigated in this study possesses antimalarial properties that deserve further analysis and could become a cheap, readily available source of antimalaria agents in developing countries.

Members of the Genus Ipomoea have been found to possess antiplasmodial activities (Tia et al., 2022). The result from the phytochemical study of the methanol extract of *I. involucrata* showed the presence of several secondary metabolites including; alkaloids, flavonoids, saponins, terpenoids and tannin which have been reported previously to possess antiplasmodial activity (Christensen & Karazmi (2001); Chierrito et al., 2014; Alli et al., 2011; Afolabi et al, 2016).

In this study, *I. involucrata* methanol extract exhibited a dose related chemosuppressive activity against the rodent malaria parasite (*P. berghei*). It was observed that there was a continuous significant increase in the parasite count in untreated mice from day to day when compared to animals treated with 800mg/kg of extract (Figure 2). The crude methanol extract significantly suppressed the parasite growth. It had percentage chemosuppression of 93.4%. The activity was retained after the methanol extract was partitioned into hexane, dichloromethane and ethyl acetate. Of all the fractions tested *Ipomoea involucrata* hexane fraction had the greatest chemosuppressive effect, with the highest dose of 800 mg/kg eliciting the highest suppressive activity (90.7%) this was followed by the dichloromethane fraction with 75.8%. The ethyl acetate fraction showed a moderate chemosuppression activity while the lowest activity was demonstrated by the aqueous fraction. *I. involucrata* possess antioxidant activity which could enhance the antimalarial effect demonstrated by the plant (Opene et al., 2018).

Packed cell volume (PCV) is a measure to determine the effectiveness of drug/extract in preventing hemolysis resulting from increasing parasitemia associated with malaria. In developing countries malaria is one of the main causes of anaemia. Hematological indices are the major determinant of the effect of parasite multiplication in malaria as they involve the blood and the blood-forming system (Omarine Nlinwe & Nange, 2020). A general reduction in PCV across the group was observed in the study. *P. berghei*- infected mice suffer from anaemia because of the destruction of

red blood cells (Tangteerawatana et al., 2007). There was no significant difference in the reduction of PCV values of the groups treated with *I. involucrata* extract and fractions when compared with the group treated with chloroquine, the standard reference drug. Administration of extract and fractions of *I. involucrata* prevented significant PCV reduction. There was a significant reduction in PCV of the infected untreated group due to the progressive increase in parasitemia.

All the extract and fractions prevented the reduction in body weight of the mice at all doses except for lower doses (100mg/kg and 200 mg/kg) of the aqueous fraction. Chloroquine also had a preventive effect against loss in mice body weight, while the control group mice had a significant reduction in body weight. The remarkable decrease in body weight of control mice may be due to the effect of the untreated *Plasmodium* infection, since the decrease in body weight is part of its clinical signs. *Plasmodium* parasite will increase in mice if not treated leading to destruction of the red blood cells causing the death of the animals in a lower time span (short survival time). Effective antimalarial drugs are expected to extend the survival time of *P. berghei*-infected mice, to more than 12 days from the day of inoculation (Salawu et al, 2010). This was observed in the treated animals which had longer survival time. The mean survival time showed a comparable result in the survival time of the methanol extract and fractions of the *I. involucrata* to that of the standard drug (chloroquine). In untreated animals, it was observed that there was increase in parasitized red blood cells from day to day.

## Conclusion

The result of this study showed that the methanol extracts and fractions of the whole plant of *I. involucrata* possess parasite suppressive effects in *P. berghei* infected Swiss albino mice in a dose and time-dependent manner. *I. involucrata* possesses potent antimalarial effects which suggests that it could be an alternative potential drug lead for the development of a safe, effective, and affordable antimalarial agent. The study also provided justification for the traditional therapeutic use of the plant in the treatment of malaria

## Compliance with ethical standards

The study was carried out in accordance with international, national guidelines for the care and use of animals.

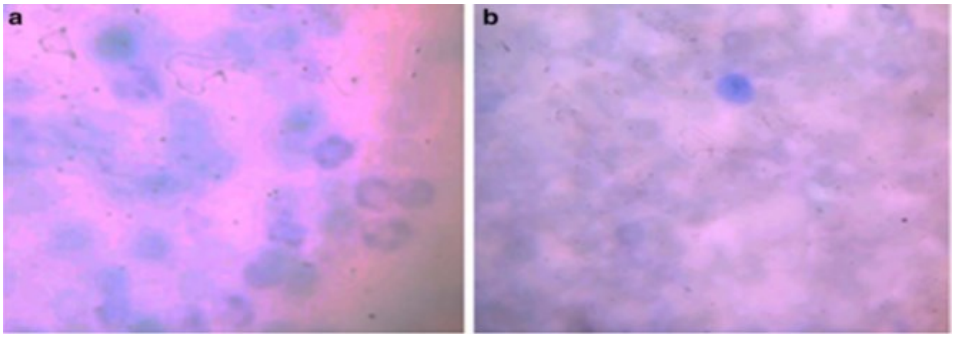


Fig.2: (a) Blood smear showing parasitized RBC in untreated mouse; b Blood smear of treated mouse with 800 mg/kg of plant extract. Magnification ×100, oil immersion

**Table 1:** Phytochemicals

| **Alkaloids** | **+++** |
|---|---|
| Cardiac glycosides | _ |
| Flavonoids | +++ |
| Quinones | + |
| Steroids | + |
| Terpenoids | ++ |
| Saponins | +++ |
| Tannins | +++ |

+++ =Abundant, ++ = present, + = present in trace amount, – =not detected

Table 2: Effect of *Ipomoea involucrata* on parasite suppression, weight and PCV of *Plasmodium falciparum* infected mice

| Drug/ extract | Dose (mg/kg) | Mean % parasi-taemia | % chemosup-pression | Weight (g) | | Weight change (g) | PCV | | PCV Change | Survival time (days) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | $D_0$ | $D_7$ | | $D_0$ | $D_7$ | | |
| IIM | 100 | 2.45±0.25 | 61.4 | 19.12 | 20.17 | 1.05 | 42.16 | 39.42 | -2.74 | 14.8 |
| | 200 | 0.85±0.10 | 88.3 | 19.12 | 19.18 | 0.86 | 51.74 | 50.22 | -1.52 | 19.2 |
| | 400 | 0.65±0.12 | 91.0 | 20.10 | 21.13 | 1.03 | 54.00 | 50.78 | -3.22 | 20.4 |
| | 800 | 0.48±0.05 | 93.4 | 20.08 | 21.15 | 1.07 | 43.67 | 40.22 | -3.45 | 26.0 |
| IIH | 100 | 3.01±1.25 | 58.5 | 21.41 | 22.46 | 1.05 | 40.51 | 38.76 | -5.13 | 14.5 |
| | 200 | 2.66±0.36 | 63.3 | 18.86 | 19.63 | 0.77 | 47.64 | 43.51 | -4.13 | 14.2 |
| | 400 | 2.01±0.21 | 72.3 | 19.62 | 20.76 | 1.14 | 50.23 | 48.21 | -2.02 | 18.1 |
| | 800 | 0.50±0.04 | 90.7 | 20.12 | 21.63 | 1.51 | 48.25 | 47.01 | -1.24 | 22.0 |
| IIC | 100 | 7.01±1.36 | 3.5 | 19.01 | 18.98 | -0.03 | 46.98 | 42.32 | -4.66 | 8.3 |
| | 200 | 6.05±0.47 | 16.6 | 19.78 | 20.82 | 1.04 | 43.22 | 40.22 | -3.00 | 11.2 |
| | 400 | 2.58±0.51 | 64.3 | 20.24 | 21.46 | 1.02 | 45.67 | 40.22 | -5.45 | 18.5 |
| | 800 | 1.81±0.22 | 75.8 | 19.01 | 20.28 | 1.27 | 40.51 | 38.31 | -2.20 | 18.5 |
| IIE | 100 | 7.01 ±1.4 | 3.5 | 18.78 | 18.52 | -0.26 | 48.67 | 40.32 | -2.32 | 8.3 |
| | 200 | 6.05 ±0.8 | 16.6 | 20.02 | 20.38 | 0.36 | 47.64 | 43.22 | -4.42 | 11.2 |
| | 400 | 2.58 ±0.5 | 64.3 | 19.62 | 20.42 | 0.80 | 48.25 | 43.22 | -5.03 | 18.5 |
| | 800 | 2.45±0.25 | 61.4 | 18. 86 | 19.73 | 0.87 | 49.69 | 43.67 | -6.02 | 18.5 |
| IIA | 100 | 4.92 ±0.28 | 3.1 | 20.16 | 20.08 | -0.08 | 46.98 | 42.33 | -4.65 | 8.7 |
| | 200 | 4.29 ±0.3 | 16.3 | 20.84 | 20.78 | -0.06 | 40.51 | 38.21 | -2.30 | 10.2 |
| | 400 | 4.08 ±0.5 | 20.5 | 19.44 | 20.28 | 0.84 | 52.01 | 48.23 | -3.78 | 10.2 |
| | 800 | 4.06 ±0.5 | 22.5 | 19.92 | 20.21 | 0.29 | 50.71 | 47.65 | -3.06 | 11.5 |
| CQ | 10 | 0.30±0.20 | 96.2 | 20.95 | 22.48 | 1.53 | 49.93 | 47.67 | -2.26 | 23.5±12 |
| Untreated | | 7.25±0.25 | 0 | 19.82 | 18.60 | -1.22 | 49.34 | 31.62 | 17.72 | 9.5 ± 0.5 |

Values expressed as Mean ± SEM, n=6, IIM= *I. involucrata* methanol extract, IIH = *I. involucrata* hexane fraction, IIC= *I. involucrata* dichloro-methane fraction, IIE= *I. involucrata* Ethyl acetate fraction, IIA= *I. involucrata* aqueous fraction.


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