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Antagonistic effects of some commonly used herbs on the efficacy of Artemisinin derivatives in the treatment of malaria in experimental mice

O. A. Idowu¹, A. S. Babalola^{1*}  and J. Olukunle²

Abstract

Background: The use of herbs in combination with drugs in treatment of malaria is increasing, and this necessitated research on the possible antagonistic, additive, potentiation or synergistic properties of commonly used plants with standard drugs in treatment of malaria. In this study, extracts of *Morindamorindiodes* (Mm) root, *Morindalucida* (ML) leaf and *Vernonia amygdalina* (Va) leaf were combined with artesunate (Ar) and assessed for anti-malarial activities against established *Plasmodium berghei* NK65 infection in 45 experimental mice randomly distributed into 9 groups and treated at a graded dose of 100 mg/kg for the herbs and herbs–drugs combination, while chloroquine and artesunate was administered at 10 mg/kg

Results: At the end the sixth day, Mm root extract, ML and Va leaf extract reduced parasitaemia by 86.83%, 84.20% and 48.10%, respectively ($p < 0.05$). A total parasite clearance (100% chemosuppression) was observed in the group treated with artesunate and chloroquine. However, the combination of each extracts of *M. lucida*, *M. morindiodes* and *V. amygdalina* with artesunate significantly reduced the chemosuppression to 89.93%, 89.43% and 86.93%, respectively.

Conclusion: This study showed that though the extracts of *Morinda morindiodes* and *Morinda lucida* possess convincing antiplasmodial effect when administered singly, the combination of these extracts with artesunate could not produce total parasite clearance. There is need to enlighten the public on the possible setback associated with combined use of antimalarial plants with antimalaria drugs.

Keywords: Malaria, Treatment, Plasmodium, Herbs, Artesunate, Antagonist

Background

Malaria, a parasitic disease caused by protozoans of the genus *Plasmodium*, remains the world most devastating human parasitic infection (WHO 2013, 2020). Anti-malaria drugs have been utilized in diverse ways to prevent or treat malaria infections in malaria endemic areas for many years. The issue of resistance of malaria

parasite to anti-malaria drugs has been a lot of concern recently (WHO 2015; Ouji et al. 2018). As a result, researches are ongoing with aims of discovering more effective agents against the parasites. Currently, there are reports of parasite resistance to the currently developed Artemisinin combination therapy in some regions of Sub-Saharan Africa (WHO 2015; Ouji et al. 2018).

In recent times, natural products of plant sources have been given a lot of consideration as the main source of new, safer and more effective bioactive compounds with medicinal properties (Dike et al. 2012; Afolabi and Abejide 2020). Studies have documented over 1200

*Correspondence: ayodelebabalola2011@gmail.com

¹ Malaria Research Unit, Department of Pure and Applied Zoology, Federal University of Agriculture, Abeokuta, Nigeria
Full list of author information is available at the end of the article

plant species from 160 families used in the treatment of malaria or fever (Wilcox and Bodeker 2001). In fact, it is believed strongly that malaria would have destroyed Africa, if the herbs used to treat malaria by our ancestors were not effective. In Nigeria, malaria has become a household name, and the use of herbs to treat its symptoms is well established. A study revealed that different tribes in Nigeria maintain some sort of traditional medicine practitioner for treatment of various diseases including malaria (Ezekwesili and Okaka 2019). Furthermore, surveys conducted in different parts of Nigeria revealed many plants that had been identified by users to be potent against malaria (Nwachukwu et al. 2010; Idowu et al. 2010; Oludele and Olufunso 2018).

Vernonia amygdalina (bitter-leaf commonly found in West and Central African countries and *Morinda lucida* commonly found in northern and southern Nigeria, Fernadopo and over the Congo basin (Keay 1989) have been proven to have anti-plasmodial or anti-malarial activities against drug sensitive *Plasmodium berghei* in mice (Abosi and Raseroke 2003; Bello et al. 2009; Ebiloma et al. 2011; Paula et al. 2011; Lawal et al. 2012; Afolabi and Abejide 2020). A recent study has demonstrated that *Morinda lucida* possesses antimalarial properties attributed to anthraquinones (Idowu et al. 2010). The stem bark extract as well as the aqueous leaf extract of *M. lucida* has been reported to have chemosuppression properties ranging between 70% to 96.4%, respectively (Obih et al. 1985; Ebiloma et al. 2011; Afolabi and Abejide 2020) in *P. berghei* infected mice.

A considerable reputation has been given to *M. morindiodes* (Rubiaceae) in traditional medicine in some African countries. Its use against malaria, diarrhoea, amoebiasis, gonorrhoea and rheumatic pains is regular (Kambu 1990; Bashir et al. 2015). The root extract of *M. morindiodes* has been reported to have antiplasmodial properties with 70% chemosuppression in *P. berghei* infected mice (Soniran et al. 2011).

The increasing use of the herbal medicine requires concern about interactions between herbs and conventional drugs and also the regulation of the herbal medicines (WHO 2013). Herbal usage is often combined with western pharmaceuticals without regards for any interaction between them. This could lead to decreased efficacy or increased toxicity (Cohen and Ernst 2010). The interaction between herbs and standard drugs may occur in many ways including; decrease or increase of the bio-availability of the drugs, antagonistic or synergistic with drugs, enhancement or inhibition of adverse effects etc. (Scott et al. 2014).

Herb–drug interactions occur but are under-researched. Based on these facts, there is a need to investigate the interactions between these plants and drugs.

These plants are among the most frequently used plants by healers and herbalists in Nigeria against malaria. Studying herb–drugs interactions in human is faced with ethical challenges; hence, animal models are used as substitutes to explain human related phenomena. Therefore, this study was conducted to determine the possible antagonistic effects of some commonly used herbs on the efficacy of Artemisinin derivatives in the treatment of malaria in experimental mice.

Methods

Plant collection, identification and extraction

Fresh leaves of *M. lucida*, *V. amygdalina* and roots of *M. morindiodes* were collected from locations around Odeda Local Government, Abeokuta. Permission to collect the plants was granted by the state Ministry of Forestry and later by the owners of land where the plants were located. Visual identification and authentication were carefully done by a plant taxonomist Dr. Ekundayo of the Forestry Research Institute of Nigeria (FRIN).

Preparation of crude extract

The plant parts were washed, dried at room temperature ($28 \pm 2^\circ\text{C}$) and then pulverized using plant grinder. These were soaked separately in distilled water for 24 h and later filtered. The filtrates were afterward evaporated to dryness over water bath at 35°C for further use (Idowu et al. 2014).

Parasites

Sample of *P. berghei* (NK-65), obtained from National Institute of Medical Research (NIMR), Lagos, Nigeria, was used for the research to evaluate the anti-malarial activity of the plant materials used in this study.

Source of animals

A total of 45 (sample size was determined according to the resource equation formulae by Charan and Kantharriamale 2013) BALB/c mice (each weighing between 23.0 and 23.2 g) with mean weight of 23.2 ± 0.2 g and same physiological age commercially obtained from Nigerian Institute of Medical Research (NIMR), Yaba, were used for this study. The mice were free of pathogens and have not been used for any initial experiment.

Animal housing and husbandry

The mice were kept in plastic cages which contained dried wood shavings as beddings at room temperature ($28 \pm 2^\circ\text{C}$) and were fed with standard ration (Vital Feeds Limited, Ibadan) and clean water in the animal house. The mice were kept at 12 h light and dark cycle.

Experimental design

A total of 45 mice (each weighing between 23.0 and 23.2 g) were randomly divided into 9 groups. Six out of the nine groups were treated with the extracts (single and in combination with artesunate) using oral administration with a single dose per day. A dosage of 100 mg/kg body weight was administered to each mouse for treatment with single plant extract. The untreated group served as the negative control, while the group treated with artesunate and chloroquine at a dose of 10 mg/kg body weight served as the positive control for the experiment. Groups 1–3 were treated with the plant extracts at 100 mg/kg, while groups 4–6 were treated with combination of the plant extracts and artesunate. The treatment continued daily for six consecutive days. The experimental groups are presented in Table 1. At the end of experiment, the mice were kept for further studies.

Inoculation of experimental mice

Malaria parasite inoculums were prepared by collecting blood samples from donor mouse. The blood

Treatment of infected mice

Leaves extracts of *M. lucida* (Leaves), *M. morindiodes* (Root) and *V. amygdalina* (Leaves) and their various combinations with artesunates were administered to the mice orally with the aid of an oral cannula at 100 mg/kg bodyweight. Single administration with chloroquine and artesunate was administered at 10 mg/kg bodyweight, respectively.

Measurement of experimental outcomes

Estimation of percentage chemosuppression

Each day, blood samples were taken from the caudal vein of each mouse on a clean glass slide; thin films were prepared and stained with 10% Giemsa solution. The parasitaemia was estimated by careful examination of the well-stained thin blood film. Parasitaemia was determined by dividing the number of parasitized red blood by the total number of red blood cells and then multiplied by 100 to express it as a percentage.

Percentage malaria parasitaemia (%) and Day 6 chemosuppression (%) were determined using the formula below:

$$\text{Percentage malaria parasitaemia (\%)} = \frac{\text{Number of parasitized RBC}}{\text{Total number of RBC counted}} \times 100$$

$$\text{Day 6 Malaria chemosuppression} = \frac{\text{MP of untreated at day 6} - \text{MP of treated at day 6}}{\text{MP of untreated at day 6}} \times 100$$

collected from the donor mouse was then diluted with normal saline such that 0.1 ml contained 10⁴ of the parasite.

Forty-five (45) mice were divided into nine (9) groups of five mice each; all the mice were infected with the parasites by inoculating them intraperitoneally with 0.1 ml of the prepared blood solution.

where MP is the percentage malaria parasitaemia.

Statistical analysis

Raw data obtained from the laboratory were analysed using one-way analysis of variance (ANOVA) to compare means across groups using Statistical Product and Service Solution (SPSS), version 21.0 (Chicago, IL). The data

Table 1 Experimental plans for test animals and control

Groups	Experimental plan	Remarks
1, 2, 3	Were infected with <i>Plasmodium berghei</i> and administered with 100 mg/kg body weight of <i>Morinda lucida</i> , <i>Morinda morindiodes</i> and <i>Vernonia amygdalina</i> plant extracts, respectively, for 6 consecutive days	Treatment
4, 5, 6	Were infected with <i>Plasmodium berghei</i> and administered with 100 mg/kg body weight of combination of <i>Morinda lucida</i> , <i>Morinda morindiodes</i> and <i>Vernonia amygdalina</i> plant extracts with artesunate, respectively, for 6 consecutive days	Herb–drug combined treatment
7, 8	Were infected with <i>Plasmodium berghei</i> and administered with 10 mg/kg body weight of artesunate and chloroquine for 6 consecutive days	Drug treatment control
9	Were infected but not Treated	Untreated control

Table 2 Mean percentage parasitaemia of mice treated with single therapy

Treatment Grps	Day1	Day2	Day3	Day4	Day5	Day6
<i>M. morindiodes</i>	23.25 ± 0.29 ^a	21.83 ± 0.29 ^c	20.38 ± 0.29 ^c	11.72 ± 0.13 ^c	10.25 ± 0.04 ^b	4.21 ± 0.11 ^b
<i>M. lucida</i>	27.73 ± 0.04 ^d	26.73 ± 0.04 ^d	24.98 ± 0.04 ^d	18.18 ± 0.11 ^d	10.99 ± 0.56 ^b	6.99 ± 0.02 ^c
<i>V. amygdalina</i>	29.07 ± 0.02 ^e	28.20 ± 0.18 ^e	23.81 ± 0.33 ^d	19.15 ± 0.60 ^e	18.34 ± 0.67 ^c	17.38 ± 0.60 ^d
Artesunate	26.38 ± 0.13 ^c	20.76 ± 0.13 ^b	10.05 ± 0.13 ^b	3.26 ± 0.07 ^b	0.00 ± 0.00 ^a	0.00 ± 0.00 ^a
Chloroquine	25.75 ± 0.13 ^b	17.48 ± 0.13 ^a	8.56 ± 0.13 ^a	2.5 ± 0.07 ^a	0.00 ± 0.00 ^a	0.00 ± 0.00 ^a
Untreated	29.88 ± 0.13 ^f	30.43 ± 0.13 ^f	30.71 ± 0.13 ^e	31.14 ± 0.00 ^f	33.05 ± 0.00 ^d	32.67 ± 0.07 ^e

Values were expressed as mean ± standard deviation (SD). Values with different superscripts (Alphabets) in a column are significantly different ($p < 0.05$) from each other. This implies that for each day, values with superscript a are the least value, followed by b then c, d e to f (highest). For example, at day 1, the lowest values for percentage parasitaemia were recorded in mice treated with *M. morindiodes* followed by that of chloroquine, while the highest parasitaemia was in untreated mice. These differences are statistically significant (all the values did not have similar superscript). At days 5 and 6, mice treated with artesunate and chloroquine have the least values for parasitaemia and both the same superscripts (a). This means they are not significantly different from one another

Mean values were from five mice observed in each group

were first checked for normality of distribution using normality Kolmogorov–Smirnov and Shapiro–Wilk tests. The results were presented as mean ± standard deviation (SD) in tables. Mean values with $p < 0.05$ were considered significant.

Results

A steady and consistent reduction in parasitaemia was observed in mice treated with all plant extracts from day 1 to 6. However, the level of chemosuppression varies with each plant extracts (Table 2).

The root extract of *M. morindiodes* was observed to produce a high reduction in parasitaemia (Table 2) with chemosuppression of 86.83% on day 6 (Fig. 1). Furthermore, the root extract of *M. morindiodes* recorded a significantly higher day 1 ($p < 0.05$) chemosuppression than the positive control (artesunate) (Fig. 1). There was

a close margin between the chemosuppression demonstrated by *M. morindiodes* and artesunate even at day 2 of treatment. Though chemosuppression increased significantly in groups treated with *M. morindiodes* in the subsequent days, a wide gap in chemosuppression was observed between the artesunate group and *M. morindiodes* group (Fig. 1).

Chemosuppression of *Morinda lucida* on day 1 was 6.87% compared with 21.45% recorded in *Morinda morindiodes* ($p < 0.05$). The wide gap in chemosuppression between *M. morindiodes* and *M. lucida* continued for 4 days. As at the 5th day of treatment, there was no significant difference between the chemosuppression demonstrated by both plants (Fig. 1).

Vernonia amygdalina produced a significantly ($p < 0.05$) lower chemosuppression than *M. morindiodes* and *M. lucida* on day 6 of the experiment. The

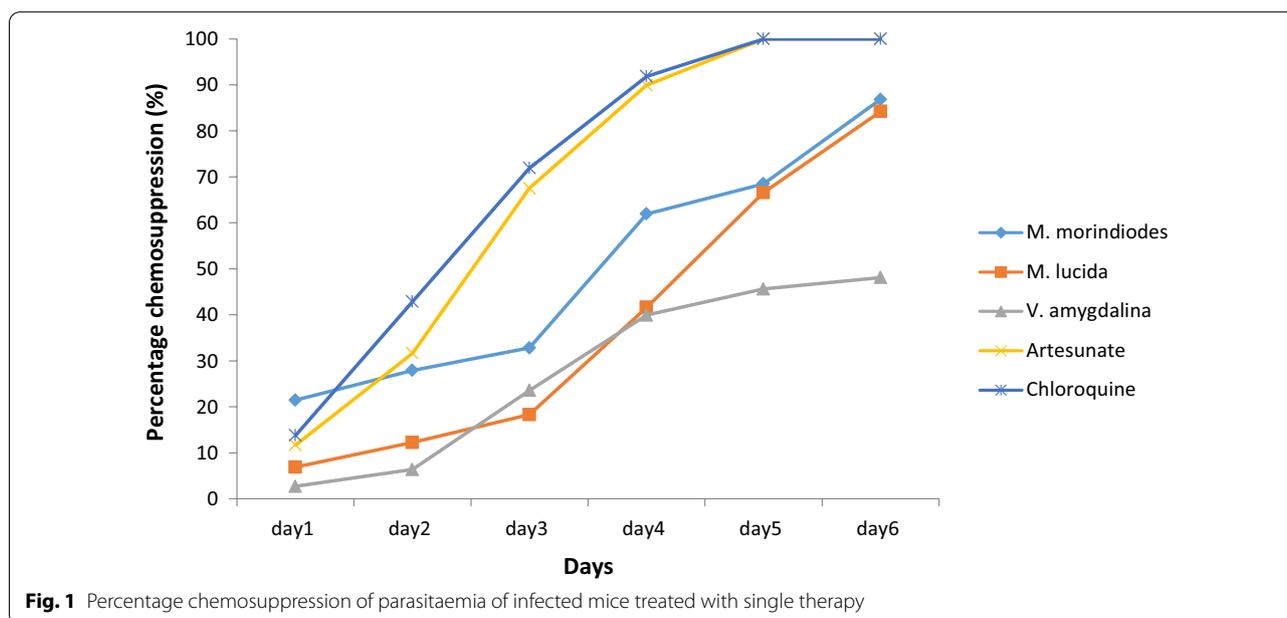


Fig. 1 Percentage chemosuppression of parasitaemia of infected mice treated with single therapy

differences observed in chemosuppression of *M. morindiodes* and *M. lucida* was observed to be statistically ($p < 0.05$) significant throughout the experiments. All the plant extracts show significant differences ($p < 0.05$) when compared with the untreated group (Table 2).

Combined treatment (Herb vs. artesunate)

A total parasite clearance was observed in mice treated among the mice treated with chloroquine and artesunate alone (Table 3). However, the combination of each extracts of *M. lucida*, *Morinda morindiodes* and *V.*

amygdalina with artesunate significantly reduced the chemosuppression to 89.93%, 89.43% and 86.93%, respectively ($p < 0.05$) when compared with the control groups treated with artesunate and chloroquine alone (Fig. 2).

The group treated with combination of artesunate with *V. amygdalina* (*Ar + Va*) recorded the lowest day 1 chemosuppression when compared with other combinations ($p < 0.05$). However, high increase in chemosuppression was observed during the subsequent days of treatment. As at the 5th day of treatment, there was a close gap in chemosuppression between all the combined treatment groups (Fig. 2).

Table 3 Mean percentage parasitaemia of mice treated with combined therapy

Treatment Grps	Day1	Day2	Day3	Day4	Day5	Day6
Artesunate + Va	29.18 ± 0.13 ^e	29.01 ± 0.13 ^e	26.9 ± 0.17 ^e	11.35 ± 0.07 ^e	5.35 ± 0.7 ^d	4.19 ± 0.07 ^d
Artesunate + Mm	25.91 ± 0.13 ^c	26.03 ± 0.13 ^d	17.33 ± 0.13 ^d	9.36 ± 0.07 ^d	3.81 ± 0.07 ^b	3.59 ± 0.07 ^c
Artesunate + Ml	23.13 ± 0.13 ^a	23.53 ± 0.13 ^c	13.78 ± 0.13 ^c	8.03 ± 0.07 ^c	4.44 ± 0.07 ^c	3.37 ± 0.07 ^b
Artesunate	26.38 ± 0.13 ^d	20.76 ± 0.13 ^b	10.05 ± 0.13 ^b	3.26 ± 0.07 ^b	0.00 ± 0.00 ^a	0.00 ± 0.00 ^a
Chloroquine	25.75 ± 0.13 ^b	17.48 ± 0.13 ^a	8.56 ± 0.13 ^a	2.5 ± 0.07 ^a	0.00 ± 0.00 ^a	0.00 ± 0.00 ^a
Untreated	29.88 ± 0.13 ^f	30.43 ± 0.13 ^f	30.71 ± 0.13 ^f	31.14 ± 0.00 ^f	33.05 ± 0.00 ^e	32.67 ± 0.03 ^e

Values were expressed as mean ± standard deviation (SD). Values with different superscripts (Alphabets) in a column are significantly different ($p < 0.05$) from each other. This implies that for each day, values with superscript (a) are the least value, followed by b then c, d e to f (highest). For example, at day 1, the lowest values for percentage parasitaemia were recorded in mice treated with artesunate + Ml followed by that of chloroquine while the highest parasitaemia was in untreated mice. These differences are statistically significant (all the values did not have similar superscript). At days 5 and 6, mice treated with artesunate and chloroquine have the least values for parasitaemia and both the same superscripts (a). This means they are not significantly different from one another. The opposite goes for mice treated with (artesunate + Mm) and (artesunate + Ml) at day 6. The former was significantly higher than the latter ($p < 0.05$) due to the fact that the two values share different superscripts (b and c)

Mean values were from five mice observed in each group

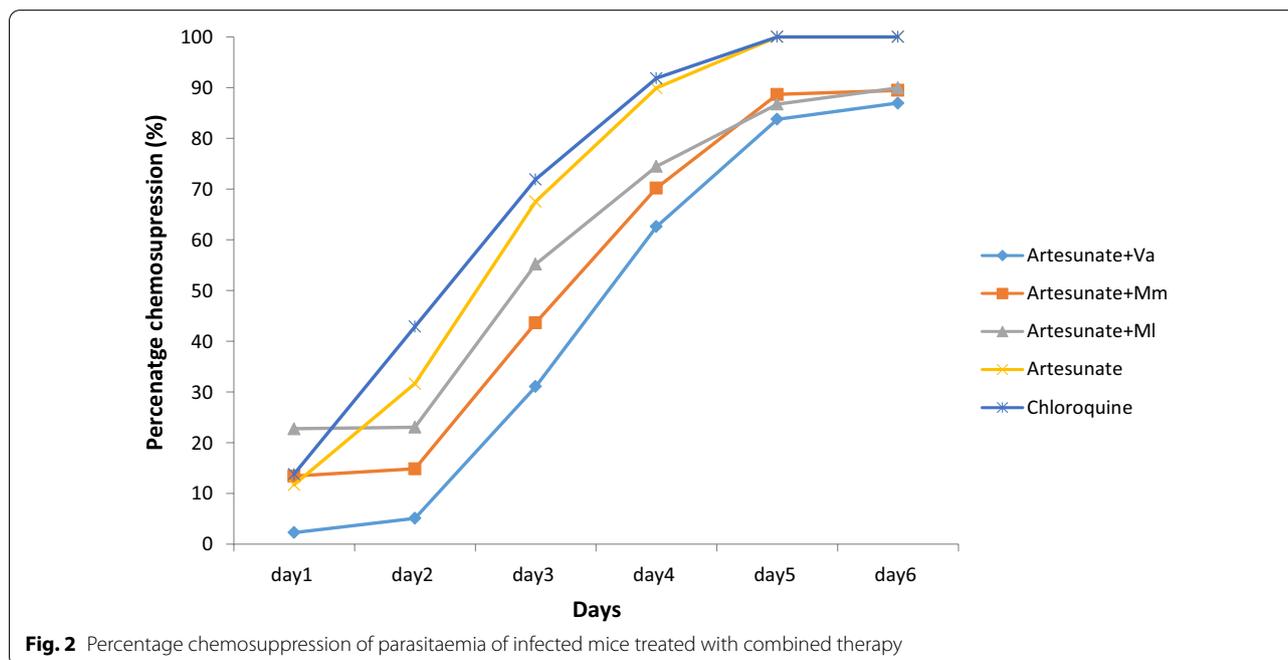


Fig. 2 Percentage chemosuppression of parasitaemia of infected mice treated with combined therapy

Though the combination of *M. lucida* plant extracts and artesunate produced the highest day 1 chemosuppression compared with the positive control (artesunate) (Fig. 2), its combination with artesunate reduced the efficacy of artesunate during this study.

Discussion

In this study, the anti-plasmodial effects of three plant extracts in both single therapy and combined therapy (herb–drugs) was observed in a six day treatment of *P. berghei* infected mice.

Morinda morindiodes initiated a very early chemosuppression than artesunate and other plant extracts when administered singly. (It recorded a significantly higher chemosuppression than artesunate on the first day of treatment.) However, it could not maintain the property when combined with artesunate. Studies have shown that *M. morindiodes* is able to act faster as an anti-plasmodial agent when administered singly (Idowu et al. 2014). This finding is in conformity with other report from Nigeria that recorded similar performance in water extract of the root of *Morindamorindiodes* in which a significant decrease in parasitaemia (70%) was reported in comparison with the activities of other plant parts in *P. berghei* infected mice (Soniran et al. 2011).

Leaf extract of *M. lucida* in this study demonstrated a chemosuppression of 84.2% in a six-day treatment. This is in keep with the findings of Ebiloma et al. (2011), who reported up to 85.05% chemosuppression in vivo anti-plasmodial activity of aqueous leaf extract of *M. lucida* carried out in *P. berghei* NK-65 parasitized mice.

A more recent study on antiplasmodial effect of crude extract of *M. lucida* root showed a chemosuppression of 56.3% (Maimuna et al. 2013). The disparity observed with this current study could be as a result of the plant parts used. This could suggest that Leaf *M. lucida* may possess more antiplasmodial properties compared with other parts.

Alkaloids and flavonoid have been identified as the predominant secondary metabolite from the phytochemical screening of the aqueous leaf extract of *M. lucida* (Ebiloma et al. 2011). The high alkaloid and flavonoid contents could be linked to the observed antimalarial activity in the group treated with *M. lucida*. Previous works have also shown the antimalaria activity of alkaloids and flavonoids in plants (Balogun et al. 2009; Okokon et al. 2005).

Leaf extract of *V. amygdalina* demonstrated a percentage chemosuppression of 48.1% in a six-days treatment. Leaf extract of *V. amygdalina* assessed against *P. berghei* by Abosi and Raseroke (2003) produced 67% suppression of parasitaemia. The huge difference in suppression rate observed in the mice treated with *V. amygdalina* in this

study could be attributed to the dose-dependent nature of its crude extract (Abosi and Raseroke 2003; Njan et al. 2008; Paula et al. 2011). Majority of the studies that reported high suppression administered the plant extract at higher dose (>200 mg/kg compared with 0.1 mg/g employed in this study).

The production of varieties of flavonoids and bitter sesquiterpene lactones has contributed to the bio activities of *V. amygdalina* (Favi et al. 2008). However, the taxonomy of *V. amygdalina* from different geographical area could be different, hence, possessing variable bio activities (Austin 2000). Thus, the low suppression of parasitaemia observed in the mice treated with *Vernonia amygdalina* compared with some other studies (Abosi and Raseroke 2003; Njan et al. 2008) could also be attributed to difference in geographical locations in which the plants were collected.

Viewing from the angle of herb–drug relationship, all the plant extracts reduce the efficacy of artesunate, implying a sort of an antagonistic effect. The standard drug (artesunate) produced the highest efficacy, when compared with the activities of the plant extracts. One reason is the fact that the plant extracts are in their crude forms with the active components not isolated and developed into active drugs (Adzu and Haruna 2007; Ebiloma et al. 2011; Idowu et al. 2014). On the other hand, this might be an indication that there is some level of antagonistic relationship between the plant extracts and artesunate in this study. This could be as a result of possible reduction in the bio-availability of artesunate in the host blood (Brinker et al. 1998) or the stimulation of enzyme activities to degrade the drug. The reduction in the efficacy of artesunate recorded in this study has implication for development of drug resistance (Watkins and Wosobo 1993). It has been reported that combination of herbs with western pharmaceuticals without regards for any interaction between them is a common phenomenon in malaria endemic areas (Idowu and Mafiana 2007; Uzor et al. 2020). One major limitation of this study is that the bio-availability of the drug was not accessed in the experimental mice. Hence, our future studies will be tailored toward that direction.

Conclusion

This study showed that though the extracts of *Morinda morindiodes* and *Morinda lucida* possess convincing antiplasmodial effect when administered singly, the combination of these extracts with artesunate could not produce total parasite clearance. There is need to enlighten the public on the possible setback associated with combined use of antimalarial plants with antimalaria drugs.

Abbreviations

Mm: *Morinda morindiodes*; Ml: *Morinda lucida*; Va: *Vernonia amygdalina*; M. lucida: *Morinda lucida*; V. amygdalina: *Vernonia amygdalina*; M. morindiodes: *Morinda morindiodes*; MP: Malaria parasitaemia; NIMR: Nigeria Institute of Medical Research.

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Authors' contributions

Author IOA conceptualized this research. Authors BAS and IOA designed the research protocol and methodology. Authors BAS and IOA carried out the field work. Author OJ provided studies and other technical inputs. Author BAS did the statistical analysis and developed the manuscript. All the authors read, corrected and approved the final manuscript.

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Availability of data and materials

The datasets generated during and/or analysed during the current study are not publicly available due [General agreement among the authors] but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Nigeria Institute of Medical Research gave approval to use the animals for this study. The ethics and consent concerning the use of mice for this research were approved by the Department of Biological Sciences, University of Agriculture, Abeokuta, Nigeria, with Reference number UG/2007/0920. Experiments were performed in accordance with the Guide of the Care and Use of Laboratory Animals of the National Institutes of Health.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹ Malaria Research Unit, Department of Pure and Applied Zoology, Federal University of Agriculture, Abeokuta, Nigeria. ² Pharmacology Research Unit, Department of Veterinary Physiology and Pharmacology, Federal University of Agriculture, Abeokuta, Nigeria.

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