







Suppressive and curative antiplasmodial properties of *Nauclea latifolia* root extract and fractions against erythrocytic stage of mice-infective chloroquine-sensitive *Plasmodium berghei* NK-65

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Background: Malaria remains a devastating disease, particularly in the tropics, where it is the highest killer of pregnant women and children under the age of 5 years. Significant efforts and resources have been vested in malaria control and eradication programmes, but the unavailability of malaria vaccine and the emergence of resistance of malaria parasite to existing antimalarial drugs have continued to hamper attempts at controlling or eradicating the disease. This warrants the development of new antimalarial drugs. *Nauclea latifolia* root is widely applied for malaria treatment in Nigeria.

Aim: This study investigated the antimalarial property of *N. latifolia* roots.

Setting: *N. latifolia* roots were collected from Ikwuano, Umuahia, Abia State, Nigeria.

Methods: To extract the bioactive constituents, an aqueous infusion of the plant was prepared and fractionated by solvent-solvent extraction with *n*-hexane, ethyl acetate and butanol, respectively. Antimalarial property was evaluated using suppressive and curative assays in mice infected with chloroquine-sensitive *Plasmodium berghei* NK-65 strain.

Results: The extract and fractions produced significant suppressive and curative antiplasmodial activities ($p < 0.05$). The aqueous extract and *n*-hexane and butanol fractions gave 85.22%, 84.52% and 91.32% chemosuppression, respectively, which were comparable to that of chloroquine used as positive control. The extract and fractions gave considerable curative effects in the range 52.23% – 77.00%.

Conclusion: These findings indicate that *N. latifolia* roots possess antimalarial property and reflect its ethnomedicinal use for malaria treatment. Thus, *N. latifolia* roots may be exploited for development of herbal formulations and isolation of novel bioactive compounds for malaria treatment.

Keywords: antimalarial; antiplasmodial; suppressive activity; curative activity; *Plasmodium berghei*; *Nauclea latifolia*.

Introduction

Malaria is a debilitating disease that remains a global health burden despite tremendous efforts towards its control and eradication. The malaria disease continues to wreak havoc to human lives especially in tropical and subtropical regions – particularly in sub-Saharan Africa. World Health Organization (WHO) (2016) reported that in 2015, the global tally of malaria reached 212 million cases and 429 000 deaths – about 90% of these cases and deaths were found in African countries. The disease burden is very alarming in children; malaria, being a major killer of children, takes the life of a child every 2 minutes, which accounts for about 70% of global malaria deaths (WHO 2016).

Tremendous resources are continuously committed to malaria management, control and eradication. These include chemotherapeutic and environmental interventions such as the use of antimalarial medications, insecticide-treated mosquito nets (ITNs) and indoor residual spraying (IRS). Efforts have also been brought to bear on the development of malaria vaccine. RTS,S/AS01, a recombinant protein-based malaria vaccine, was approved in 2015, by European regulators, as the world's first licensed malaria vaccine and is undergoing pilot trials in chosen countries (Walsh 2015). However, progress in malaria control is repeatedly threatened by the rapid development

and spread of resistance by plasmodium parasites to currently available antimalarial drugs and by malaria vector to a wide range of insecticides. This has prompted WHO to make a clarion call for the development of novel and more effective antimalarial medicines (WHO 2016).

In this respect, the use of medicinal plants as alternative medicines and sources for the discovery of novel bioactive compounds for drug development has been ongoing for centuries. In fact, some antimalarial drugs in use today were either isolated from plants or developed using the chemical structure of plant's isolates as templates. Two of such drugs are quinine, an alkaloid isolated from a cinchona tree, and artemisinin (qinghaosu), an endoperoxide sesquiterpene lactone isolated from *Artemisia annua*. These two drugs are now the mainstay of the treatment of severe malaria worldwide (WHO 2012).

Nauclea latifolia Smith (Rubiaceae) is an important medicinal plant that is widespread in the humid tropical rainforest or in savannah woodland zone of West and Central Africa. It is a spreading, evergreen, multi-stemmed shrub or small tree that grows up to an altitude of 200 m (Balogun et al. 2016). It bears an interesting flower, glabrous rounded ovate leaves and large red ball fruit with long projecting stamens (Duke 2008). *Nauclea latifolia* is commonly known as African peach or Pin cushion tree. It is called *Ubulu inu* among the Igbos in the Eastern part of Nigeria; *Tafashiya* or *Marga* or *Tabashiya* or *Tuwon biri* among the Hausas in the Northern part of Nigeria; *Egbesi* among the Yorubas in the Western part of Nigeria; *Mbom-ibong* and *Itu* among the Ibibios and the Itsekiris in the Southern part of Nigeria (Arise et al. 2012).

Nauclea latifolia has remarkable ethnomedicinal uses, and different parts of the plant are used for preparing remedies for the treatment of various ailments. Decoction of the leaf is used for treating fever, filariasis and chicken pox and for deworming animals (Adebowale et al. 1993). The stem bark is applied as a diuretic, antihelmintic, antipyretic and aphrodisiac (Ademola, Fagbemi & Idowu 2007). Concoctions, infusions and decoctions of the root are taken as tonic, antipyretic, antidepressant and analgesic and also for the treatment of respiratory illnesses such as tuberculosis, asthma, bronchitis, cough and cold (Abdullahi et al. 2007; Lamidi et al. 1995). The stem bark and roots are also applied for treating jaundice, stomach ache, diarrhoea, dysentery, infertility, hypertension and diabetes (Maitera, Khan & James 2011; Okwori et al. 2008). The fruit of the plant is used for treating piles, dysentery, colic, emetic and menstrual disorders (Nworgu, Owolabi & Atomah 2010). The plants have also been reported to be applied for the treatment of gastrointestinal ulcers, leprosy, gonorrhoea, debility, dyspepsia, enteritis, sleeping sickness, prolonged menstrual flow, dental caries and septic mouth (Alaribe et al. 2018; Elujoba 1995; Gidado, Ameh & Atawodi 2005).

Researches have attested some of the ethnomedicinal uses of *N. latifolia*. Pharmacological studies have reported

the anticonvulsant, anxiolytic and sedative properties of *N. latifolia* roots decoction (Ngo Bum et al. 2009). *Nauclea latifolia* has also been reported to have antihypertensive, laxative, antioxidant, antilipidemic, antidiabetic, antimicrobial, antipyretic, antinociceptive, antiinflammatory, antiulcerogenic, antisecretory, antiviral, antihelmintic, antitrypanosomal and antidiarrhoeal activities (Ademola et al. 2007; Ademola, Oluwafemi & Nicole 2014; Akpanabiatu et al. 2005; Alaribe et al. 2018; Arise et al. 2012; Bassey & Jude 2014; Benoit-Vical et al. 1998; Maikai & Kobo 2008; Okwori et al. 2008; Owolabi, Nworgu & Odushu 2010; Onu, Nwiyi & Erumaka 2015; Taiwe et al. 2011).

The different parts of *N. latifolia* have been documented to contain various chemical constituents. Phytochemical studies reported the presence of alkaloids, flavonoids, phenols, tannins, terpenes, saponins, anthraquinones, reducing sugars, glycosides and cardiac glycosides in decoction of the roots of *N. latifolia* (Bassey & Jude 2014; Ngo Bum et al. 2009; Okwori et al. 2008; Taiwe et al. 2011). Alkaloids, saponins, carbohydrate and resins have also been identified in the extracts of *N. latifolia* leaf (Okwori et al. 2008). Indole alkaloids have been found in the heartwood, trunk-bark, stem bark and root of the plant (Brown, Chapple & Lashford 1977). The presence of monoterpenes in the epicarp of the plant's fruit has also been reported (Abreu & Pereira 1998).

Aqueous extract of *N. latifolia* roots is widely taken as an alternative medicine for the treatment of malaria in different parts of Nigeria. This study was conducted to assess the veracity of the aforementioned traditional usage of *N. latifolia* roots. Thus, we investigated the suppressive and curative antiparasmodial effects of *N. latifolia* against erythrocytic stage of mice-infective chloroquine (CQ)-sensitive *Plasmodium berghei* NK-65.

Methodology

Collection of plant materials

Fresh roots of *N. latifolia* were collected from Ikwuano, Umuahia, Abia State. The plant material was identified and authenticated (voucher no.: LH 4016) by Mr Odewo at the Herbarium of the Department of Botany, University of Lagos. The roots were air dried under shade and then ground into fine powder.

Extraction and fractionation

The powdered material (615 g) was extracted by maceration with 2.5 L of distilled water for 48 hours at room temperature. The plant extract was lyophilised to obtain a solid mass herein referred to as aqueous root extract of *N. latifolia* (ARNL). A portion (15 g) of ARNL was fractionated by solvent-solvent extraction with *n*-hexane, ethyl acetate and butanol in succession. The fractions were concentrated *in vacuo* at 40 °C to afford *n*-hexane root fraction of *N. latifolia* (HRNL), ethyl acetate root fraction of *N. latifolia* (ERNL) and butanol root fraction of *N. latifolia* (BLNL).

Animals and rodent parasite

Sixty adult Swiss albino mice (18 g – 25 g) were obtained from Animal Facility Centre of College of Medicine of the University of Lagos, Nigeria, and used for this study. The animals were acclimatised in experimental animal house for 2 weeks and were fed with standard mice pellet diet and water *ad libitum*. The experiment was conducted in strict compliance with the internationally accepted principles for laboratory animal use and care as contained in the Health Research Ethics Committee of College of Medicine, University of Lagos guidelines on animal use.

Chloroquine-sensitive *P. berghei berghei* (NK65 Strain) was sourced from Malaria Drug Research Laboratory, Institute for Advanced Medical Research and Training (IMRAT), College of Medicine, University of Ibadan, Nigeria. The parasites were kept alive by continuous intraperitoneal passage in mice every 4 days (Adzu & Haruna 2007).

Antiplasmodial studies

Evaluation of suppressive activity (4-day suppressive test)

Evaluation of suppressive potentials of *N. latifolia* roots was performed according to the method described by Knight and Peters (1980). The mice were inoculated, intraperitoneally, with standard inoculums of *P. berghei* with 1×10^7 infected erythrocytes on day 0 (D0). After parasite inoculum was confirmed, the animals were randomly divided into six groups (groups 1–6) of five mice each. Groups 1–4 were orally administered 100 mg/kg ARNL, HRNL, ERNL and butanol root fraction of *N. latifolia* (BRNL), respectively. Two control groups were maintained: positive control, group 5, was treated with 5 mg/kg CQ, while the negative control, group 6, received equivalent amount of distilled water orally. Subsequently, on days 1–3, all the animals were treated accordingly (with the same dose and same route) as on day 0.

On day 4 of the experiment (D4), blood was collected from the tail vein of each mouse and smeared on to a microscope slide in order to make a thin film (Saidu et al. 2000). The slides were then fixed with methanol, stained with 10% Giemsa at pH 7.2 for 10 min to reveal parasitised erythrocytes. Parasitaemia was determined microscopically by counting at least a total of 1000 uninfected and infected erythrocytes from random fields. The percentage parasitaemia was determined as follows:

$$\text{Percentage parasitaemia} = \frac{\text{No. of infected erythrocytes}}{\text{Total no. of erythrocytes}} \quad [\text{Eqn 1}]$$

The percentage suppression of parasitaemia was expressed as mean chemosuppression and this was calculated for each test sample by comparing the parasitaemia in infected (negative) control with those of treated mice. The average percentage suppression was calculated from the following expression:

$$\text{Average \% suppression} = \frac{A - B}{A} \times 100 \quad [\text{Eqn 2}]$$

where *A* is the average percentage parasitaemia in negative control group and *B* is the average percentage parasitaemia in test group.

Evaluation of schizontocidal activity on established infection (curative or Rane test)

Evaluation of curative potentials of *N. latifolia* roots was carried out according to the method described by Ryley and Peters (1970). The mice were inoculated, intraperitoneally, with standard inoculums of *P. berghei* with 1×10^7 infected erythrocytes on day 0 (D0). Seventy-two hours later, after the parasite inoculum was confirmed, the animals were randomly divided into six groups (groups 1–6) of five mice each. Groups 1–4 were orally administered 100 mg/kg ARNL, HRNL, ERNL and BRNL, respectively. Two control groups were maintained: positive control, group 5, was treated with 5 mg/kg CQ, while the negative control, group 6, received equivalent amount of distilled water orally. The treatment was carried out once daily for 5 days (D0–D4). Thin blood smears stained with 10% Giemsa at pH 7.2 for 10 min were prepared from tail blood of each mouse daily for the 5 days to monitor the parasitaemia level.

Statistical analysis

All values are expressed as mean \pm standard error of mean (SEM). The significance of difference in means between control and treated animals for different parameters was determined by using one-way analysis of variance (ANOVA) and Student's *t*-test on Microsoft Excel 2010® Data Analysis tools. A *p*-value of <0.05 was considered statistically significant.

Ethical consideration

Ethical clearance was obtained from the Health Research Ethics Committee, College of Medicine, University of Lagos (CMUL/HREC/03/18/341, 26 March 2018).

Results

Results of evaluation of suppressive activity (4-day suppressive test)

The results of evaluation of suppressive potentials of *N. latifolia* roots are presented in Table 1, which shows the percentage parasitaemia and percentage suppression of

TABLE 1: Suppressive activity of *Nauclea latifolia* roots extract and fractions against *Plasmodium berghei*-infected mice (4-day test).

| Treatment | Dose (mg/kg) | % Parasitaemia | % Suppression |
|------------------|--------------|------------------|---------------|
| Negative control | - | 15.90 \pm 0.36 | - |
| ARNL | 100 | 2.35 \pm 0.21* | 85.22 |
| HRNL | 100 | 1.38 \pm 0.80* | 91.32 |
| ERNL | 100 | 5.48 \pm 0.44* | 65.53** |
| BRNL | 100 | 2.46 \pm 0.10* | 84.52 |
| CQ | 5 | 0* | 100.00 |

ARNL, aqueous root extract of *N. latifolia*; HRNL, *n*-hexane root fraction of *N. latifolia*; ERNL, ethyl acetate root fraction of *N. latifolia*; BRNL, butanol root fraction of *N. latifolia*; CQ, chloroquine.

Values are mean \pm SEM (*n* = 5).

*, Significantly different (*p* < 0.05) from negative control.

**, Significantly different (*p* < 0.05) from CQ.

TABLE 2: Curative activity of *Nauclea latifolia* roots extract and fractions against *Plasmodium berghei*-infected mice (Rane test).

| Treatment | Dose (mg/kg) | % Parasitaemia | | | | | | % Cure at day 4 |
|------------------|--------------|------------------|--------------|---------------|---------------|---------------|---------------|-----------------|
| | | Before treatment | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | |
| Negative control | - | 14.33 ± 0.06 | 14.65 ± 0.16 | 15.75 ± 0.58 | 19.15 ± 0.22 | 21.19 ± 0.64 | 23.34 ± 0.95 | 0.00 |
| ARNL | 100 | 15.21 ± 0.56 | 14.30 ± 0.56 | 11.98 ± 0.38* | 10.25 ± 0.16* | 7.60 ± 0.24* | 5.37 ± 0.25* | 77.00* |
| HRNL | 100 | 14.61 ± 0.01 | 14.23 ± 0.30 | 12.20 ± 0.48* | 11.10 ± 0.39* | 8.91 ± 0.28* | 7.71 ± 0.21* | 67.00* |
| ERNL | 100 | 14.87 ± 0.45 | 14.53 ± 0.81 | 13.51 ± 0.29* | 13.13 ± 0.39* | 11.81 ± 0.45* | 10.45 ± 0.20* | 52.23* |
| BRNL | 100 | 14.88 ± 0.91 | 14.30 ± 0.27 | 12.42 ± 0.23* | 11.06 ± 0.48* | 9.34 ± 0.43* | 8.43 ± 0.25* | 63.88* |
| CQ | 5 | 15.31 ± 0.71 | 14.21 ± 0.45 | 9.41 ± 0.18* | 1.83 ± 0.93* | -ve | -ve | 100.00* |

ARNL, aqueous root extract of *N. latifolia*; HRNL, *n*-hexane root fraction of *N. latifolia*; ERNL, ethyl acetate root fraction of *N. latifolia*; BRNL, butanol root fraction of *N. latifolia*; CQ, chloroquine. Values are mean ± SEM (*n* = 3).

*, Significantly different (*p* < 0.05) from negative control.

ARNL, HRNL, ERNL, BRNL and CQ, used as positive control. The percentages of chemosuppression of *N. latifolia* root extract and fractions were in the range of 65.53% – 91.32%. These were statistically significant (*p* < 0.05) compared to the negative control group and comparable to that of standard drug CQ with a percentage suppression of 100%.

Results of evaluation of schizontocidal activity on established infection (curative test)

The results of evaluation of curative effects of *N. latifolia* roots are presented in Table 2, which shows the percentage parasitaemia and percentage cure of ARNL, HRNL, ERNL, BRNL and CQ on the different days of treatment. These results were similar to those obtained for the suppressive test. The percentages of curative effect produced by *N. latifolia* root extract and fractions were in the range of 52.23% – 77.00%, which were statistically significant (*p* < 0.05) compared to the negative control group, which showed a daily increase in parasitaemia level.

Discussion

Malaria management, control and eradication clearly remain challenging and difficult tasks. This problem has widely been attributed to the unavailability of malaria vaccine, emergence of resistance of malaria parasite to existing antimalarial drugs and lack of newer drugs. Thus, there is need for novel, effective and safe antimalarial drugs. Natural products have contributed immensely to human healthcare. They have served and remain a rich source of novel bioactive compounds for the management of different human ailments. *Nauclea latifolia* is an important medicinal plant that has tremendous ethnomedicinal uses and pharmacological properties. The aqueous infusion of the roots of the plant is widely taken as an alternative medicine for the treatment of malaria in different parts of Nigeria. Thus, in this study, the antimalarial property of *N. latifolia* roots was evaluated.

To simulate the ethnomedicinal preparation for malarial remedy, the pulverised *N. latifolia* roots material was extracted with water to obtain ARNL, which was fractionated with solvents of increasing polarity to obtain *n*-hexane (HRNL), ethyl acetate (ERNL) and butanol (BRNL) root fractions of *N. latifolia* as previously described. To evaluate the

antimalarial property of the various extract and fractions, the *in vivo* suppressive and curative antiplasmodial effects against established erythrocytic stage of mice-infective CQ-sensitive *P. berghei* NK-65 were investigated. *In vivo* models are often used in antimalarial studies because they take into consideration the possible prodrug effect and probable involvement of the immune system in combatting the parasite (Waako et al. 2005). The rodent parasite, *P. berghei*, is widely used in antimalarial drug discovery and was applied in the development of some conventional antimalarial drugs such as quinine, CQ, halofantrine, mefloquine and recently the artemisinin derivatives (Thomas et al. 1998; Nutham et al. 2015; Somsak, Polwiang & Chachiyo 2016).

The results of the evaluation of suppressive property of *N. latifolia* roots are as presented in Table 1. During the 4-day early infection study, the extract and fractions of *N. latifolia* roots exerted significant suppressive antiplasmodial activities. The *n*-hexane fraction (RHNL) gave the highest activity, a 91.32% chemosuppression. The suppressive activities of the extract and fractions, which save ERNL (65.53% chemosuppression), were comparable to that of CQ with a percentage suppression of 100%. The highest parasitaemia (15.90%) was recorded in the negative control group, while no parasitaemia (0%) was recorded in the positive control group, treated with CQ. The parasitaemia for the groups treated with the extract and fractions were 2.35%, 1.38%, 5.48% and 2.46% for ARNL, HRNL, ERNL and BRNL, respectively, which were greatly lower than that in the negative control group. The decrease in parasitaemia level in the treatment groups shows that the animals responded to the treatment given and indicates that the treatments had an effect on the multiplication and erythrocyte infectivity of *P. berghei* parasites in mice. According to Deharo et al. (2001), *in vivo* antiplasmodial activity could be classified as moderate, good and very good if an extract showed percentage parasitaemia suppression equal to or greater than 50% at a dose of 500 mg/kg, 250 mg/kg and 100 mg/kg per day, respectively, suggesting therefore that the extract and fractions of *N. latifolia* root have very good activities.

The results of the evaluation of curative effects of *N. latifolia* roots are as presented in Table 2. Similar to their suppressive properties, the extract and fractions gave significant curative antiplasmodial activities. A daily increase in parasitaemia level was observed for the negative control group, while

marked reductions in parasitaemia level were observed for the groups treated with the extract or fractions and CQ from day 2 of treatment. After the final treatment, the percentage cure of the extract and fractions were 77.00%, 67.00%, 52.23% and 63.88% for ARNL, HRNL, ERNL and BRNL, respectively, which were relatively lower than that in the positive control group, treated with CQ, with percentage cure of 100%, indicating complete curative effect. The observed lower efficacy of the extract and fractions, when compared to CQ, is not uncommon with medicinal plants extracts and may in part be because of non-selectivity of the extract or slow absorption and poor bioavailability of the extracts (Adzu & Haruna 2007).

Determination of percentage inhibition of parasite growth is regarded as the most dependable parameter in antimalarial drug discovery (Bantie et al. 2014; Mojab 2012). The extract and fractions of *N. latifolia* roots exerted significant inhibitory effects in parasite growth in both suppressive and curative assays, which signify that the plant is endowed with antimalarial property. The results further show that the *n*-hexane and butanol fractions had comparable antiplasmodial property to the crude aqueous extract. In fact, the *n*-hexane fraction showed a relatively higher suppressive effect than the aqueous extract. However, the current evidence does not suffice to speculate if this is because of an antagonistic interaction among different antiplasmodial constituents in the crude extract. A similar pattern was observed in the antiplasmodial activities of ethanolic extract and fractions of stem bark of *N. latifolia* reported by Ettebong et al. (2015), where the aqueous fraction had a higher suppressive effect than the crude ethanolic extract. Our results corroborate the previous findings of Benoit-Vical et al. (1998), who reported the antiplasmodial property of aqueous stem and root *N. latifolia* extracts.

Previous studies have reported the phytochemical constituents of *N. latifolia* roots to include alkaloids, flavonoids, phenols, tannins, terpenes, saponins, anthraquinones, reducing sugars and glycosides (Bassey & Jude 2014; Ngo Bum et al. 2009; Okwori et al. 2008; Taiwe et al. 2011). The presence of these phytochemicals in *N. latifolia* roots could be responsible for its antimalarial activities. Although the mechanism of action of the extract and fractions used in this study has not been elucidated, they might have exerted their antiplasmodial activities either by causing red blood cell oxidation or by inhibiting protein synthesis or by other unknown mechanism. In addition, antioxidant substances have been reported to inhibit heme polymerisation (Vial 1996), a mechanistic action of the antiplasmodial activity of quinoline-containing antimalarial drugs such as CQ. Hence, the antiplasmodial property of *N. latifolia* root could be associated with its antioxidant activity as reported by Alabi et al. (2017).

Conclusion

Our results showed that the crude aqueous extract and *n*-hexane, ethyl acetate and butanol fractions of *N. latifolia*

roots demonstrated significant antimalarial activities. The activities of the aqueous, *n*-hexane and butanol infusions were comparable to that of CQ. These findings may validate the ethnomedicinal use of *N. latifolia* roots in the treatment of malaria and suggest that roots of *N. latifolia* present a source of promising phytochemicals for the development of novel antimalarial agents. Therefore, further studies to isolate, identify, elucidate and characterise the active constituents of *N. latifolia* roots extract and fractions are recommended.

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Competing interests

The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.

Author's contributions

C.S.A., A.R.O. and H.A.B.C. are responsible for manuscript design; C.S.A., M.O.N., I.N.J. and B.D.O. for execution; C.S.A., A.R.O., M.O.N., I.N.J. and B.D.O. for interpretation; C.S.A. and A.R.O. for writing of the manuscript.

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Data availability statement

The datasets generated during this study are available from the corresponding author on request.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the affiliated institution of the authors.

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