

Phytochemical screening and in vivo antimalarial activity of extracts from three medicinal plants used in malaria treatment in Nigeria

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Abstract The use of plant to meet health-care needs has greatly increased worldwide in the recent times. The search for new plant-derived bioactive agents that can be explored for the treatment of drug-resistant malaria infection is urgently needed. Thus, we evaluated the antimalarial activity of three medicinal plants used in Nigerian folklore for the treatment of malaria infection. A modified Peter's 4-day suppressive test was used to evaluate the antimalarial activity of the plant extracts in a mouse model of chloroquine-resistant *Plasmodium berghei* ANKA strain. Animals were treated with 250, 500, or 800 mg/kg of aqueous extract. It was observed that of all the three plants studied, *Markhamia tomentosa* showed the highest chemosuppression of parasites of 73 % followed by *Polyalthia longifolia* (53 %) at day 4. All the doses tested were well tolerated. Percentage suppression of parasite growth on day 4 post-infection ranged from 1 to 73 % in mice infected with *P. berghei* and treated with extracts when compared with chloroquine diphosphate, the standard reference drug which had a chemosuppression of 90 %. The percentage survival of mice that received extract ranged from 0 to 60 % (increased as the dose increases to 800 mg/kg). Phytochemical analysis revealed the presence of tannins, saponins, and phenolic compounds in all the three plants tested.

Keywords *Markhamia tomentosa* · *Plasmodium berghei* · *Polyalthia longifolia* · *Trichilia heudelotii*

Introduction

There is an increasing rate of death associated with malaria disease and over one million people are affected, majority are children below 5 years (Tabuti 2008; Akanbi et al. 2012). Like other developing countries of the world, a similar condition has been observed in Nigeria. Also, the recent resistance of malaria parasites to the synthetic drugs like chloroquine which is resistant to *Plasmodium falciparum* has call for concern (Trape 2002). Due to limited availability and affordability of orthodox medicine in many tropical countries, the majority of the populations depend on traditional medical remedies (WHO 2002; Zirihi et al. 2005), mainly from plants which has been discovered to be a rich source of new drugs. Majority of the antimalarial drugs such as quinine and artemisinin that is widely used has also been developed from plants, and some were developed chemically using plant-derived compounds as pattern (Basco et al. 1994; Chiyaka et al. 2009). The World Health Organization supports the use of medicinal plants provided they are proven to be efficacious and safe (WHO 1985). The most important of these bioactive constituents of plants are alkaloids, tannins, flavonoids, and phenolic compounds.

According to an ethnobotanical survey in Nigeria (Adebayo and Krettli 2011), some 98 species from different families are used in traditional medicine singly or in combination to treat malaria and/or fever. These plants used for malaria treatment and control represent more than half of the Nigeria medicinal species. To date, there has been no literature cited to show that many of these plants have been

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scientifically investigated to establish whether or not they have antimalarial properties *in vivo*.

This paper evaluates the antimalarial activity of the extracts from three medicinal plants in the southern part of Nigeria and also investigates the qualitative and quantitative analysis of the major bioactive constituents of the three plants. The extracts were obtained from three Nigerian medicinal plants namely *Markhamia tomentosa* Benth. K. Schum. Ex Engl., *Polyalthia longifolia* Sonn. Thwaites, *Trichilia heudelotii* Planch. ex Oliv., belonging to three families, Bignoniaceae, Annonaceae, and Meliaceae, respectively. These three plants (Fig. 1) are locally used in traditional medicine to cure many diseases including malaria and fevers. (Burkill 1985; Abbiw 1990; Burkill 1997; Subramanion et al. 2013).

M. tomentosa is a shrub or tree of about 15-m high and is distributed in the Savannah forests in Africa. The tree possesses large yellow flowers in long terminal racemes. The leaves and stem bark are used to treat various diseases such as oedema, rheumatoid arthritis, gout, and muscular pain in Nigeria (Bouquets and Debray 1974; Burkill 1985; Arbonier 2002). Ethnopharmacological studies revealed that the leaves and stem bark of *M. tomentosa* possess antimicrobial, antiplasmodial, antioxidant, antiulcer, and analgesic properties (Aladesanmi et al. 2007; Tantangmo et al. 2010; Temdie et al. 2012; Shofidiya et al. 2014). The phytochemical screening and foliar epidermal studies of the leaves have also been carried out (Ugbabe and Ayodele 2008; Borokini and Omotayo 2012).

P. longifolia is an evergreen tree with a height of over 30 ft. It exhibits symmetrical pyramidal growth with willowy pendulous branches and long narrow lanceolate leaves. It originates from India and is introduced to many tropical countries around the world, Nigeria inclusive. This plant is used as an antipyretic agent in indigenous systems of medicine (Raghunathan and Mitra 1982). Ethnopharmacological studies revealed that the stem bark and leaves of this plant display effective antimicrobial activity (Faizi et al. 2003a, b, 2008), cytotoxic function (Chang et al. 2000, 2006), and hypotensive effects (Saleem et al. 2005).

T. heudelotii (Abbiw 1990) is a medium-sized tree up to about 20-m high and 0.4 m in girth (Irvine 1961). The plant is mostly common in the tropical rain forest in Africa. The bark

is used to treat diseases such as gastrointestinal disorder, cough, gonorrhoea, syphilis (Irvine 1961; Lemmens 2008), and skin ulcer (Abbiw 1990). The stem bark is also used as anthelmintic, aphrodisiac, abortifacient, and antiplasmodial (Abbiw 1990; Lemmens 2008). It also has anti-inflammatory and analgesic properties (Mshana et al. 2000; Lemmens 2008). Phytochemical screening shows the presence of tannins, saponins, glycosides, terpenes, and flavonoids.

Materials and methods

Plant collection and authentication

Fresh leaves of *M. tomentosa* (Benth.) K. Schum. Ex Engl. (Bignoniaceae), *P. longifolia* Sonn. Thwaites (PL). (Annonaceae) and stem bark of *T. heudelotii* Planch. ex Oliv. were collected from Oke-Igbo in Ondo State, Iddo, and Eruwa in Oyo State in Nigeria, respectively, in December 2012. Identification and authentication were carried out in the Herbarium of the Department of Botany where voucher specimens (LUH 3936, LUH 3562, and LUH 3494) were deposited.

Plant extraction

The leaves of *M. tomentosa* and *P. longifolia* and the stem bark of *T. heudelotii* were air-dried at room temperature (30 ± 0.5 °C) and pulverized to a coarse powder. The plant parts (1 kg) were extracted exhaustively by mixing with 4 l of distilled water and allowed to boil for 4 h. The resulting extract was left to cool and filtered. The filtrates were freeze-dried, and the resulting extracts were stored at 4 °C.

Experimental animals

Fifty-five Swiss albino mice weighing between 18–22 g of either sex and aged 6–8 weeks were kept in the Animal House of the Institute for Advanced Medical Research and



Fig. 1 a *Markhamia tomentosa* plant. b *Polyalthia longifolia* plant. c *Trichilia heudelotii* plant

Training, College of Medicine, University of Ibadan, Oyo State, Nigeria. The animals were maintained under standard laboratory conditions, as approved by the Experimentation Ethics Committee of the College of Medicine, University of Lagos (CM/COM/08/VOL.XXVI). The animals, acclimatized for 1 week, were fed on a rodent diet (Livestock Feeds PLC, Ibadan, Oyo State, Nigeria) and had free access to drinking water.

Malaria parasite

The chloroquine-resistant *Plasmodium berghei* (ANKA) clone was used. *P. berghei* was obtained from the Malaria Research Laboratories, Institute for Advanced Medical Research and Training, College of Medicine, University of Ibadan. The experimental animals were inoculated intravenously with 1×10^6 red blood cells infected with the CQ-resistant *P. berghei* ANKA strain. The day of inoculation was defined as day zero (D0). The infected animals were distributed randomly into five groups of five animals per cage and were treated once daily with the extract by oral route. The animals in group I received 250 mg/kg dose of the extract by oral route. Groups II and III received 500 and 800 mg/kg, respectively. Group IV was treated with chloroquine at a dose of 10 mg/kg. Group V served as negative control. The anti-malarial activity of the extracts was determined using the Peter's 4-day suppressive test (Peter and Anatoli 1998; David et al. 2004). Survival rate of animals were monitored till day 14. On day 4 of the experiment, the animals' tail tip was cut to prepare the blood smears. The air-dried films were fixed with methanol and stained with Giemsa solution. Parasitemia was determined by counting the number of parasitized erythrocytes among at least 1000 RBC. In this study, in vivo anti-malarial activity of the three plant extracts and the mouse survival were monitored over a period of 2 weeks

The difference between the mean values of the control group (defined as 100 %) and those of the experimental groups was calculated and expressed as percent suppression of parasite growth using the method of Li et al. (2003) and Devi et al. (2001) as shown in the equation below

Suppression of parasite

$$= 100 - \frac{\text{Mean parasitaemia of treated animals}}{\text{Mean parasitaemia of control}} \times 100$$

Statistical analysis

Mean parasitemia was determined in the control and treated groups. The mean parasitemia was compared using the Student's *t* test. Percent suppression of parasite growth of the treated and control groups were compared using one-way ANOVA and two-tailed Student's *t* test (GraphPad Prism

4.0, GraphPad Software, San Diego, USA), with $P < 0.05$ being considered significant.

Phytochemical analysis

Chemical tests for the screening and identification of bioactive chemical constituents of the three medicinal plants were carried out in aqueous extracts using the standard procedures as described by Sofowora (1993); Trease and Evans (2002) and Harborne (1973).

Quantitative analysis of phytochemical constituents

Test for tannins About 0.5 g of each plant extract was stirred with about 10 ml of distilled water and then filtered. Few drops of 1 % ferric chloride solution were added to 2 ml of the filtrate, and occurrence of a blue-black, green, or blue-green precipitate indicates the presence of tannins.

Test for steroids In about 0.2 g of each plant extract, 2 ml of acetic acid was added, and the solution was cooled well in ice followed by the addition of concentrated H_2SO_4 carefully. Color development from violet to blue or bluish green indicated the presence of a steroidal ring, i.e., aglycone portion of cardiac glycoside.

Test for terpenoids A little of each plant extract was dissolved in ethanol. To it, 1 ml of acetic anhydride was added followed by the addition of concentrated H_2SO_4 . A change in color from pink to violet showed the presence of terpenoids.

Test for saponins One gram of each portion was boiled with 5 ml of distilled water, filtered. To the filtrate, about 3 ml of distilled water was further added and shaken vigorously for about 5 min. Frothing which persisted on warming shows the presence of saponins.

Test for flavonoids About 0.5 g of each plant extract was dissolved in ethanol, and it was warmed and then filtered. Three pieces of magnesium chips were then added to the filtrate followed by few drops of concentrated HCl. A pink, orange, or red which changed to purple color indicates the presence of flavonoids.

Ferric chloride test for flavonoids About 0.5 g of each plant extract was boiled with distilled water and then filtered. To 2 ml of the filtrate, few drops of 10 % ferric chloride solution were then added. A green-blue or violet coloration indicated the presence of a phenolic hydroxyl group.

Glycosides One milliliter of concentrated H_2SO_4 is prepared in a test tube, and 5 ml of aqueous extract from each plant sample is mixed with 2 ml of glacial $\text{CH}_3\text{CO}_2\text{H}$ containing 1

drop of FeCl_3 . The above mixture is carefully added to 1 ml of concentrated H_2SO_4 so that the concentrated H_2SO_4 is underneath the mixture. A brown ring will appear indicating if cardiac glycoside is present.

Test for alkaloids About 0.2 g of the each plant extract was stirred with 5 ml of 1 % aqueous HCl on water bath and then filtered. From the filtrate, 1 ml was taken individually into two test tubes. To the first portion, few drops of Dragendorff's reagent were added; occurrence of orange-red precipitate was taken as positive. To the second 1 ml, Mayer's reagent was added and appearance of buff-colored precipitate will be an indication for the presence of alkaloids.

Cardiac glycosides (Keller-Killani test) Five milliliters of each plant extracts was treated with 2 ml of glacial acetic acid containing one drop of ferric chloride solution. One milliliter of concentrated sulphuric acid was added. A brown ring of the interface indicated a deoxysugar characteristic of cardenolides.

A violet ring may appear below the brown ring, while in the acetic acid layer, a greenish ring may form just gradually throughout a thin layer

Anthraquinone Borntrager's test About 0.5 g of the plant extract was shaken with benzene layer separated and half of its own volume of 10 % ammonia solution added. A pink, red, or violet coloration in the ammoniacal phase indicated the presence of anthraquinone.

Phenolic compounds The extract (500 mg) was dissolved in 5 ml of distilled water. To this, few drops of neutral 5 % ferric chloride solution were added. A dark green color indicated the presence of phenolic compounds.

Quantitative determination of phytochemicals

Preparation of fat-free sample Two grams of the sample were defatted with 100 ml of diethyl ether using a Soxhlet apparatus for 2 h.

Determination of total phenols by spectrophotometric method The fat-free sample was boiled with 50 ml of ether for the extraction of the phenolic component for 15 min. Five milliliters of the extract was pipetted into a 50-ml flask, then 10 ml of distilled water was added. Two milliliters of ammonium hydroxide solution and 5 ml of concentrated amyl alcohol were also added. The samples were made up to mark and left to react for 30 min for color development. This was measured at 505 nm.

Alkaloid determination using Harborne (1973) method Five grams of the sample was weighed into a 250-ml beaker, and 200 ml of 10 % acetic acid in ethanol was added and covered and allowed to stand for 4 h. This was filtered, and the extract was concentrated on a water bath to one quarter of the original volume. Concentrated ammonium hydroxide was added dropwise to the extract until the precipitation was complete. The whole solution was allowed to settle, and the precipitate was collected and washed with dilute ammonium

Table 1 Response to treatment in Swiss albino mice infected with CQR *P. berghei* to aqueous extract of three medicinal plants at day 4

Dose of plant extracts (mg/kg)	Parasitemia±SEM (%)	Parasite suppression±SEM (%)	% survival till day 14
<i>Markhamia tomentosa</i> (l)			
250	6.85±0.65	46	20
500	7.15±0.36	43	40
800	4.96±0.73	73	60
<i>Polyalthia longifolia</i> (l)			
250	12.56±1.80	1	0
500	9.95±0.95	21	40
800	5.94±1.29	53	40
<i>Trichilia heudelotii</i> (sb)			
250	19.05±4.29	0	0
500	9.95±1.67	21	40
800	7.63±0.47	40	40
Chloroquine (CQ)			
10	1.33±0.56	90	60
Untreated control (NT)	12.66±1.07		0

Values are parasite density±standard deviation (PD±SEM)

CQ Chloroquine diphosphate (10 mg/kg/day), NT untreated control, l leaf, sb stem bark

Table 2 Qualitative phytochemical screening of the medicinal plants studied

Secondary metabolites	<i>Markhamia tomentosa</i>	<i>Polyalthia longifolia</i>	<i>Trichilia heudelotii</i>
Alkaloids	+	+	–
Tannins	+	+	+
Saponins	+	+	+
Flavonoids	+	+	–
Cardiac glycosides	–	–	+
Anthraquinones	–	–	+
Phlobatannins	–	–	+
Phenolic compounds	+	+	+
Proteins	+	+	+
Terpenes	+	–	+
Steroids	–	–	–

hydroxide and then filtered. The residue is the alkaloid, which was dried and weighed.

Flavonoid determination by the method of Bohm and Kocipai-Abyazan (1994) Ten grams of the plant sample was extracted repeatedly with 100 ml of 80 % aqueous methanol at room temperature. The whole solution was filtered through Whatman filter paper No. 42 (125 mm). The filtrate was later transferred into a crucible and evaporated into dryness over a water bath and weighed to a constant weight.

Saponin determination Twenty grams of plant sample was dispersed in 200 ml of 20 % ethanol. The suspension was heated over a hot water bath for 4 h with continuous stirring at about 55 °C. The mixture was filtered and the residue re-extracted with another 200 ml of 20 % ethanol. The combined extracts were reduced to 40 ml over water bath at about 90 °C. The concentrate was transferred into a 250-ml separating funnel, and 20 ml of diethyl ether was added and shaken vigorously. The aqueous layer was recovered while the ether layer was discarded. The purification process was repeated. Sixty milliliter of normal butanol extracts were washed twice with 10 ml of 5 % aqueous sodium chloride. The remaining solution was heated in a water bath. After evaporation, the sample was dried in the oven into a constant weight. The saponin

content was calculated in percentage (Nahapetian and Bassiri 1975).

Results and discussion

The in vivo antimalarial activity of aqueous extracts of the leaves of *M. tomentosa* and *P. longifolia* and stem bark of *T. heudelotii* in chloroquine-resistant *P. berghei* (ANKA) strain was evaluated. The leaves of *P. longifolia* showed minimal suppression (53 %) of parasite multiplication at the highest dose (800 mg/kg), but the extract of *T. heudelotii* had poor suppression of parasites growth. The mean percentage parasitemia in the untreated control group ranged from 1 to 73 % on day 4 post-infections. The mice treated with chloroquine (10 mg/kg) resulted in 90 % suppression of parasite growth.

The several comparison tests indicated that the mice treated with *M. tomentosa* and *P. longifolia* extracts resulted in reduced parasite load as compared to their respective negative control groups. From the aqueous extract of *M. tomentosa* showed statistically significant ($P < 0.05$) chemosuppression against *P. berghei* in mice tested at all dose levels compared to the mice in the untreated group on day 4. In the group of animals treated with the varying doses of *T. heudelotii*, there was no suppression of parasitemia in all the days of treatment. This result however does not support the report of (Atindehou et al. 2004) that the *T. heudelotii* possesses good antimalarial activity. In the group of animals that received 800 mg/kg body weight of *M. tomentosa* and *P. longifolia*, parasite growth suppression ranged between 73 and 53 %, respectively. Moreover, the animals treated with the 800 mg/kg of *M. tomentosa* extract survived longer than the animals in the corresponding negative control groups. While in the group of animals that received 250 and 500 mg/kg of *M. tomentosa* and *P. longifolia*, parasitemia was minimally suppressed from 37 to 58 %. The animals treated with chloroquine (10 mg/kg) recorded 69 % suppression till day 7 post-infection.

In this study, remarkable suppression of parasitemia by plant extracts translated into a longer mouse survival. The survival rate of the animals after treatment with various doses of the three plant extracts was assessed. The rate of survival of the animals treated with CQ are presented in Table 1. However, the animals treated with 800 mg/kg of

Table 3 Quantitative phytochemical screening of the medicinal plants studied

Extract	Tannins mg/100 g	Alkaloids mg/100 g	Phenols mg/100 g	Flavonoids mg/100 g	C. glycosides mg/100 g	Saponin mg/100 g	Anthraquinones mg/100 g
<i>Markhamia tomentosa</i>	29.24±0.08	6.48±0.18	22.73±0.16	4.41±0.06	0.00±0.00	8.99±0.23	0.00±0.00
<i>Polyalthia longifolia</i>	0.00±0.00	5.52±0.18	0.00±0.00	5.22±0.19	2.65±0.13	10.64±0.15	0.00±0.00
<i>Trichilia heudelotii</i>	46.93±1.16	1.43±0.18	41.41±0.22	13.08±0.26	3.05±0.19	8.46±0.23	9.57±0.19

M. tomentosa and CQ showed the same survival rate of 60 % till day 14, while the untreated group did not survive till day 14. Survival time increases as the dose increases

Larvicidal activity of *M. tomentosa* has been reported (Adebajo et al. 2012). In addition, the ethyl acetate fraction of the stem bark of *M. tomentosa* has been found to possess good in vitro antimalarial activity (Tantangmo et al. 2010).

In the qualitative and quantitative analysis of the three plants studied, some of these secondary metabolites were present and some were absent. The presence of tannins and saponins was observed in all the three plants. However, *M. tomentosa* have the highest contents of alkaloids (6.48 ± 0.18) as compared to *P. longifolia* (5.52 ± 0.18) and *T. heudelotii* (1.43 ± 0.18). The high content of alkaloids in *M. tomentosa* could be attributed to the higher antimalarial properties observed in the plant. The result in this study is similar to the result of Borokini and Omotayo (2012) who had earlier reported the presence of alkaloids in *M. tomentosa*. Alkaloids are important phytochemicals, that are said to be pharmacologically active (Trease and Evans 1989). Quinine, an alkaloid, is popular for its antimalarial activity against the malaria parasite (Iwu and Klayman 1992) (Tables 2 and 3).

The result obtained in this study demonstrated that the aqueous leaf extract of *M. tomentosa* possesses the best potent antimalarial activity than the other two plants. This appears to be the first report of antimalarial properties of aqueous leaf extract of *M. tomentosa* in vivo. The result of this study support the traditional claim of the plant in the use for malaria treatment, and effort are currently underway to identify the bioactive component(s) of the plant and toxicological effects in animals.

Conflict of interest The authors declare that they have no competing interest.

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