Special Conference Edition, April, 2022
http://dx.doi.org/10.4314/bajopas.v13i1.25S

Bayero Journal of Pure and Applied Sciences, 13(1): 142 - 148
ISSN 2006 – 6996

ANTIMALARIAL ACTIVITIES OF THE METHANOL LEAF EXTRACT OF *Senna itilaca* MILL. IN *Plasmodium berghei* INFECTED MICE

***Olorukooba, A.B., [1] Khan, F. [1], Budaye, P.P.[1], Tikau, B.[1], Hamza, A.N.[2] and Musa, A. O.[3]**

[1]Department of Pharmacology and Therapeutics, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, Kaduna State-Nigeria

[2]Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, Kaduna State-Nigeria

[3]Department of Botany, Faculty of Life Sciences, Ahmadu Bello University, Zaria, Kaduna State-Nigeria

***Corresponding Author:** aolorukooba@gmail.com, +2348057665703

ABSTRACT

Malaria constitutes a major public health threat, particularly in the tropical and subtropical countries of the world. Senna italica has been traditionally used for the management of many ailments, including stomach disorders, fever, jaundice, and malaria. The present study investigated the antimalarial activity of the methanol leaf extract of Senna italica. Preliminary phytochemical screening and acute oral toxicity tests were carried out using standard protocols. Antimalarial activity was investigated using suppressive, curative, and prophylactic models in Plasmodium berghei-infected mice. Phytochemical screening showed the presence of tannins, saponins, carbohydrates, anthraquinones, alkaloids, flavonoids, glycosides, and steroids. The oral median lethal dose was estimated to be greater than 5000 mg/kg. The extract at doses of 250, 500 and 1000 mg/kg produced a significant ($p<0.05$) dose-dependent reduction in parasitemia levels in the suppressive, curative, and prophylactic tests. In addition, administration of the extract prolonged the mean survival time of the mice in all models compared to the controls (chloroquine 5 mg/kg and pyrimethamine 1.2 mg/kg). The results from this study suggest that the methanol leaf extract of Senna italica possesses antimalarial activity, thus providing a scientific basis for its use in traditional medicine for the treatment of malaria.

Keywords: Senna italica, Malaria, Parasitemia, Antimalarial, Mean Survival Time

INTRODUCTION

Malaria is a life-threatening parasitic disease caused by the parasite Plasmodium (WHO, 2020). Five species of Plasmodium including *P. vivax*, *P. falciparum*, *P. malariae*, *P. ovale*, and *P. knowlesi,* have been identified to cause malaria in humans, with falciparum and vivax being the most drug-resistant species (Sato, 2021). Recent reports have shown an increase in the number of malaria cases associated with interruptions in the provision of malaria prevention, diagnosis, and treatment during the COVID-19 pandemic (WHO, 2021). The socioeconomic impact of malaria on individuals and the government is also enormous (El-Houderi et al., 2019). In addition, with increasing resistance to mainstream drugs, including artemisinin-based combinations, there is an urgent need to fast-track the discovery and development of newer more efficacious antimalarial drug regimens (Tajbakhsh et al., 2021).

Senna italica is a deciduous and perennial herb or small shrub and grows about 50 to 75 cm in height with herbaceous branches from woodystock (Vijaya et al., 2018). It belongs to the family Fabaceae and is widely distributed in African countries, Iran, Iraq, Pakistan and from India to Sri Lanka. Phytochemical constituents, including anthraquinones, tannins, saponins, flavonoids and steroids, have been isolated from various parts of the plant (Yagi et al., 2013; Gololo et al., 2018). Pharmacological studies have shown that *Senna italica* possesses antioxidant, antibacterial and antiproliferative activities (Masoko et al., 2009); antiobesity and hypoglycaemic effects (Malematja et al., 2018); anti-tick activity (Magono et al*.,* 2008); antibacterial activity (Dabai et al*.,* 2012); antioxidant and anticancer activities (Omar et al., 2018) and antihelminthic activity (Mahmuda et al., 2020).

The present study thus aimed to evaluate the antimalarial effects of the methanol leaf extract of *Senna italica* in *Plasmodium berghei*-infected mice to provide a scientific rationale for its use in the management of malaria.

MATERIALS AND METHODS

Chemicals and Drugs

Chemicals and drugs used for the study were of analytical grade and included Dragendorff's reagent, Haematoxylin stain, Lead sub-acetate, Meyer's reagent, Molisch' s reagent, Sulphuric acid, Wagner's reagent (BDH Ltd. Poole, UK), 0.9% Normal saline solution (Dana Pharmaceuticals Ltd, Nigeria) Distilled water, Geimsa powder (Philip Harris Ltd., England), Chloroquine (Sigma-Aldrich, USA), Pyrimethamine (SKG Pharma Ltd) purchased from reliable manufacturers.

Plant Collection and Identification

Parts of the plant *Senna italica* were collected from Nguru local government, Yobe State Nigeria in April 2021. The plant was identified in the Herbarium Section of the Department of Botany, Ahmadu Bello University Zaria, Nigeria by a botanist and compared with an existing specimen with voucher number ABU03106.

Experimental Animals

One hundred (100) Swiss albino mice of either sex weighing between 20-25 g were obtained from the Animal House, Department of Pharmacology and Therapeutics, Ahmadu Bello University, Zaria Nigeria. They were maintained under standard conditions and were given rodent feed with water *ad libitum*. All experiments performed on the laboratory animals were in accordance with the criteria outlined in the Guide for the Care and Use of Laboratory Animals by the National Institute of Health (Publication No. 80-23, 2011).

Plasmodium parasite

Plasmodium berghei NK65 was obtained from the Nigerian Institute of Medical Research (NIMR), Yaba, Lagos. The parasite was maintained by continuous reinfestation intraperitoneally in mice every 4 days (Adzu et al., 2007).

Each mouse used in the experiment was inoculated with 0.2 mL of infected blood containing approximately $1x10^7$ *P. berghei* parasitized red blood cells. This was prepared by determining both the percentage parasitemia and the erythrocyte count of the donor mouse and diluting them with normal saline in proportion indicated by both determinations (Okonkon and Nwafor, 2010).

Plant Extraction

The leaves of *Senna italica* plants were air dried in the shade and ground using a mortar and pestle to obtain a powder. The powdered leaves (600 g) were subjected to cold maceration with 70% v/v methanol for 72 hours with intermittent shaking. The extract was filtered with the aid of filter paper (Whatman No. 3), and the filtrate was concentrated using a rotary evaporator and evaporated to dryness over a water bath. The dried extract was stored in an airtight container placed in a desiccator for further use. The extract was labelled as the methanol leaf extract of *Senna italica* (MLSE).

Preliminary Phytochemical Screening

MLSE was subjected to preliminary phytochemical test to detect the presence or absence of phytochemical constituents, including alkaloids, saponins, steroids, triterpenes, tannins, flavonoids, carbohydrates, glycosides and anthraquinones. Screening procedures were carried out according to the method of Evans (2009).

Acute Toxicity Study

An oral acute toxicity study was conducted on the leaf extract according to the Organization for Economic Cooperation and Development test guideline 425 in mice (OECD, 2001). Three mice were administered 5000 mg/kg body weight of MLSE, while one mouse served as a control. The mice were observed individually during the first 30 mins and 4 hours post-dosing and thereafter 24 hours for a period of 14 days for signs of toxicity and death.

Suppressive Test

The *in vivo* antimalarial activity of *Senna italica* extract was evaluated using a 4-day suppressive test in *P. berghei*-infected mice (Peters, 1965). Swiss albino mice were inoculated with 0.2 mL of blood containing approximately 1×10^7 *P. berghei* parasites using the intraperitoneal route. The animals were randomly divided into five groups of five mice each, three test groups and two control groups. Groups 1 and 5 were administered distilled water (10 ml/kg) and chloroquine (5 mg/kg). Groups 2, 3 and 4 were administered the extract at doses of 250 mg/kg, 500 mg/kg, and 1000 mg/kg respectively. Each drug was administered as a single daily dose. All the extracts and the drug were given orally using a standard orogastric tube to ensure safe ingestion of the extracts and the drug. Treatment commenced 3 hours post-infection on day 0 and was continued daily for four days (i.e., from day 0 to day 3). On the fifth day (D4), blood samples were collected from the tail of each mouse. Thin smears were prepared and stained with Giemsa solution. Then, each stained slide was examined under the microscope with an oil immersion objective of 100x magnification power. The parasitemia level was determined by counting the number of parasitized red blood

cells out of 100 erythrocytes in 4 fields of the microscope. Percentage chemosuppression was calculated using the formula below. Animals were kept for 28 days to calculate the mean survival time.

$$\% \text{ suppression} = \frac{\text{parasitemia in negative control} - \text{parasitemia in treated group}}{\text{parasitemia in negative control}} \times 100\%$$

$$\text{mean survival time} = \frac{\text{sum of survival time of all mice in group(days)}}{\text{total number of mice in that group}}$$

Curative Test

Rane's test, which evaluates the curative potential of an extract or compound, was carried out according to the method described by Ryley and Peters (1970). Twenty-five (25) mice of both sexes were infected through the intraperitoneal route with 0.2 mL of blood containing approximately 1×10^7 *P. berghei*-infected erythrocytes on the first day (Day 0). After 72 h (day 3), the animals were randomly assigned to five groups of five mice each. The animals were then treated for four days; groups 1 and 5 received distilled water (negative control - 10 ml/kg) and chloroquine (positive control - 5 mg/kg. Groups 2, 3 and 4 were administered the extract at doses of 250, 500, and 1000 mg/kg. All extracts and drugs were given by the orogastric route. Blood samples were collected from the tail vein of each mouse and examined under a microscope as described in the suppressive test to determine the parasitemia count. Thereafter, the mice were followed for 28 days, and the mean survival time was determined using equation ii as shown previously.

Prophylactic Test

Evaluation of the prophylactic activity of the extract was carried out according to the method described by Peters (1965). Twenty-five (25) mice were randomly distributed into five groups of five mice each and treated as described earlier under the suppressive model except that the positive control used was pyrimethamine (1.2 mg/kg). The test animals received treatment for three days prior to infection. Following the completion of treatment, animals were inoculated with 0.2 ml of blood containing approximately 1×10^7 *P. berghei*-infected erythrocytes, and this day was assigned as day zero (D0). The animals were kept for 72 hours, after which blood smears were prepared from the tail vein of each mouse, and the parasitemia level was determined. Finally, the animals were followed for 28 days to record the mean survival time.

RESULTS

Phytochemical Screening of the Methanol Leaf Extract of *Senna italica*

The preliminary phytochemical screening of the methanol leaf extract of *Senna italica* showed the presence of tannins, saponins, carbohydrates, anthraquinones, alkaloids, flavonoids, glycosides, and steriods (Table 1).

Table 1: Phytochemical Constituents Present in the Methanol Leaf Extract of *Senna italica*

Phytochemical constituents	Inference
Carbohydrates	+
Steroids	+
Flavonoids	+
Tannins	+
Anthraquinones	-
Saponins	+
Cardiac glycosides	+
Alkaloids	+

Key; + = present, - = absent

Acute Toxicity Studies

Oral administration of the extract did not cause mortality, nor were there any signs or symptoms of behavioral or neurological toxicity observed within the first 24 hours or during the 14-day follow-up period. This indicates that the median lethal dose (LD_{50}) is more than 5000 mg/kg.

Suppressive Activity of the Methanol Leaf Extract of *Senna italica*

A significant ($p<0.05$) dose-dependent reduction in parasitemia levels was observed following the administration of the extract, with the highest percentage suppression observed to be 67.6% at the dose of 1000 mg/kg. The standard drug (chloroquine, 5 mg/kg), however produced a percentage suppression of 85.8% (Table 2).

Administration of the methanol leaf extract of *Senna italica* prolonged the mean survival time in treated animals compared to the negative control (Table 3).

Table 2: Effect of the Methanol Leaf Extract of *Senna italica* on Suppressive Activity in *Plasmodium berghei*-Infected Mice

Treatment Group	Dose (mg/kg)	Average Parasitemia	Average percentage chemosuppression (%)
DW	10 ml/kg	20.47 ± 1.62	-
MLES	250	13.15 ± 1.85*	35.7
MLES	500	13.13 ± 0.81*	35.8
MLES	1000	6.63 ± 0.88*	67.6
CQ	5	2.90 ± 0.59*	85.8

Values are presented as the mean ± SEM; data analyzed by one-way ANOVA followed by Dunnett's post-hoc test; n=6; * = $p<0.05$ versus control; DW = distilled water; MLES = methanol leaf extract of *Senna italica*; CQ = chloroquine; route of administration = oral

Table 3: Effect of Methanol Leaf Extract of *Senna italica* on Mean Survival Time in Mice in the Suppressive Test

Treatment Group	Dose (mg/kg)	MST (days)
DW	10 ml/kg	8.67 ± 0.67
MLES	250	18.4 ± 4.06*
MLES	500	22.8 ± 2.44*
MLES	1000	24.2 ± 2.37*
CQ	5	25.2 ± 2.80*

Values are presented as the mean ± SEM; data were analyzed by one-way ANOVA followed by Dunnett's post-hoc test; n=6; * = $p<0.05$ versus control; DW = distilled water; MLES = methanol extract of *Senna italica*; CQ = chloroquine; MST = mean survival time; route of administration = oral

Curative Activity of the Methanol Leaf Extract of *Senna italica*

The methanol leaf extract of *Senna italica* at doses of 250 mg/kg, 500 mg/kg and 1000 mg/kg produced a significant ($p < 0.05$) dose-dependent reduction in parasitemia levels, producing percent chemosuppression of 50%, 59% and 69%, respectively. The standard drug (chloroquine, 5 mg/kg), however produced chemosuppression of 92.6% (Table 4).

Analysis of mean survival time showed that groups that took the higher two doses (500 mg/kg and 1000 mg/kg) significantly outlived ($p < 0.05$) the animals in the negative control. The positive control also significantly increased the mean survival time compared to the negative control ($p < 0.05$), as shown in the tables below (Table 5).

Table 4: Effect of Methanol Leaf Extract of *Senna italica* on Curative Activity in *Plasmodium berghei*-Infected Mice

Treatment Group	Dose (mg/kg)	Average Parasitemia	Average percentage chemosuppression (%)
DW	10 ml/kg	28.47 ± 0.95	-
MLES	250	14.23 ± 1.25*	50.0
MLES	500	11.67 ±1.19*	59.0
MLES	1000	8.57 ± 0.57*	69.9
CQ	5	2.10 ± 0.24*	92.6

Values are presented as the mean ± SEM; data were analyzed by one-way ANOVA followed by Dunnett's post-hoc test; n=6; * = $p<0.05$ versus control; DW = distilled water; MLES = methanol leaf extract of *Senna italica*; CQ = chloroquine; route of administration = oral

Table 5: Effect of Methanol Leaf Extract of *Senna italica* on Mean Survival Time in Mice in the Curative Test

Treatment Group	Dose (mg/kg)	MST (days)
DW	10 ml/kg	9.50 ± 2.10
MLES	250	18.4 ± 3.82*
MLES	500	24.2 ± 2.46*
MLES	1000	26.4 ± 1.60*
CQ	5	22.0 ± 2.80*

Values are presented as the mean ± SEM; data were analyzed by one-way ANOVA followed by Dunnett's post-hoc test; n=6; * = p<0.05 versus control; DW = distilled water; MLES = methanol extract of *Senna italica*; CQ = chloroquine; MST = mean survival time; route of administration = oral

Prophylactic Activity of the Methanol Leaf Extract of *Senna italica*

In comparison to the negative control, there was significantly lower parasitemia in all extract-treated groups (p < 0.05). The standard drug (pyrimethamine, 1.2 mg/kg) showed better parasite suppressive activity (p < 0.05) than both the negative control and extract (Table 6).

The results from the mean survival time revealed that the extract-treated mice lived longer than the negative control, and the two higher doses of the extract (500 mg/kg and 1000 mg/kg) showed longer survival times than the standard drug (Table 7).

Table 6: Effect of Methanol Leaf Extract of *Senna italica* on Prophylactic Activity in *Plasmodium berghei* Mice

Treatment Group	Dose (mg/kg)	Average Parasitemia	Average percentage chemosuppression (%)
DW	10 ml/kg	24.43 ± 1.62	-
MLES	250	16.07 ± 0.52*	34.2
MLES	500	10.00 ± 0.17*	59.1
MLES	1000	9.67 ± 0.52*	60.4
PYR	1.2	5.37 ± 0.33*	78.0

Values are presented as the mean ± SEM; data were analyzed by one-way ANOVA followed by Dunnett's post-hoc test; n=6; * = p<0.05 versus control; DW = distilled water; MLES = methanol leaf extract of *Senna italica*; PYR = pyrimethamine; route of administration = oral

Table 7: Effect of Methanol Leaf Extract of *Senna italica* on Mean Survival Time in Mice in the Prophylactic Test

Treatment Group	Dose (mg/kg)	MST (days)
DW	10 ml/kg	10.00 ± 0.67
MLES	250	23.00 ± 3.50*
MLES	500	26.40 ± 1.60*
MLES	1000	28.00 ± 0.00*
PYR	1.2	20.40 ± 4.75*

Values are presented as the mean ± SEM; data were analyzed by one-way ANOVA followed by Dunnett's post-hoc test; n=6; * = p<0.05 versus control; DW = distilled water; MLES = methanol extract of *Senna italica*; PYR = pyrimethamine; MST = mean survival time; route of administration = oral

DISCUSSION

Novel antimalarial drugs and potent vaccines are urgently needed to address the development of resistance to the commonly used antimalarial drugs and the resultant increase in morbidity and mortality. The plant *Senna italica* has been used in traditional medicinal to treat a plethora of illnesses including malaria. The acute toxicity and *in vivo* antimalarial activity of the methanol leaf extract of the plant were investigated in this study.

Phytochemical screening of the methanol leaf extract of *Senna italica* revealed the presence of phytochemicals, including tannins, saponins, carbohydrates, alkaloids, flavonoids, glycosides, and steriods, which have been previously reported (Sani et al., 2020). These phytochemical constituents have also been found to be present in other plants with reported

antimalarial activity (Sibhatu et al*.,* 2019). The antimalarial activity observed in this study may be due to the presence of these phytochemicals, which may act singly or in synergy with one another.

Acute toxicity studies are carried out to predict the short-term safety of exposure to a substance. The absence of changes in general behavior, body weight and mortality, which are critical for the evaluation of toxicity, suggests that the plant at a dose of 5000 mg/kg is relatively safe (Lorke, 1983).

Three models were used to test the antimalarial effect of MLSE. The four-day suppressive test evaluates the potential schizonticidal activity of test compounds (Peters et al*.,* 1975), and using this model, the methanol leaf extract of *Senna italica* had a maximum suppression of 67.6% at 1000 mg/kg. Compounds that reduce parasitemia load by 30% or more are considered to have schizonticidal activity against malaria (Krettli et al*.,* 2009). By this standard, the methanol extract of the plant can be considered to possess schizonticidal activity.

The curative test investigates the potential of a plant/compound to prevent further malaria attacks in an established malaria infection (Ryley and Peters, 1970). In this study, although there was no cure, there was a significant reduction in parasitemia with all the doses used. The level of parasitemia in the extract-treated groups was consistently lower than that in the negative control, indicating parasite clearance activity by the extract. The higher doses of the extract, compared to the negative control, resulted in significantly longer survival times. This relationship of dose-versus-survival time may be related to the higher degree of parasite suppression, which, hence, resulted in mitigation of its deleterious pathologic consequences (Tewolde et al*.,* 2020).

A prophylactic test was conducted to determine whether the extract can prevent parasitemia proliferation. In this test, the extract was able to hinder the growth of parasitemia at all doses used. The degree of suppression was, however, lower than that seen in the two previous models. This effect may have been related to the fact that the extract was administered prior to infection establishment and hence may have been rapidly metabolized and/or excreted (Okyere et al., 2020). Similar results, in which plants had better suppressive effects than prophylactic effects, were reported in other studies (Tewolde et al*.,* 2020).

CONCLUSION

The ability of MLSE to suppress parasitemia levels and increase mean survival times of *P. berghei* infected mice suggests that the extract possesses antimalarial activity, which could possibly be due to the presence of various phytochemicals.

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