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Antiplasmodial Activity and Phytochemical Evaluation of the Stems of *Albizia coriaria* and *Ficus sur*

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Malaria continues to cause havoc on various populations because of the high mortality and economic burden associated with the disease. Progress made in the therapeutics of the disease is threatened by the emerging parasite resistance to currently used first line treatment drugs. This has prompted the search for new, effective, and safe antimalarial agents. The use of traditional medicine in the treatment of various types of diseases including malaria is a regular practice seen with many cultures in Ghana. The stems of *Albizia coriaria* Welw ex. Oliver and *Ficus sur* Forssk are such plants used with little evidence about their *in vivo* efficacy.
Aim: This study therefore aimed to assess the *in vivo* antiplasmodial potential, and the acute toxicity of the hydroethanolic stem extract of *Albizia coriaria* and *Ficus sur*.

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Method: Qualitative phytochemical screening was done on the powdered plant material using standard methods. Acute toxicity was carried out according to OECD guidelines using the Limit test. *In vivo* antiplasmodial activity of the hydroethanolic extract was assessed using the Peter's 4-day suppressive and Rane's curative test.
Results: The 70% ethanol extract was safe with the lethal dose above 3000 mg/kg. All the extracts significantly ($P < 0.05$) suppressed parasitaemia in the Peter's suppressive and Rane's curative test with *Albizia coriaria* producing the highest chemotherapeutic activity of 68.89 and 61.46% in the suppressive and curative test respectively. That of *F. sur* was less than 50% in both assays. Artesunate reference drug recorded over 80% suppression in the curative test but lesser activity in the suppression assay compared to *A. coriaria*. Several plant metabolites including terpenoids, flavonoids and coumarins were found in both plant samples.
Conclusion: *Albizia coriaria* and *Ficus sur* 70% ethanol extract showed considerable antiplasmoidal activity and were found to be non-toxic in acute toxicity study, thus justifying their safe use in the treatment of malaria as suggested by folklore medicine.

Keywords: Antimalaria; suppressive test; phytochemicals; acute toxicity; plasmodium parasite.

1. INTRODUCTION

The use of plants in the treatment of diseases across various civilizations is well embedded in history [1]. Herbs and herbal products are being used extensively in all parts of the world, not only in traditional medicine, but also as a source of valuable substances useful as food, pharmaceuticals and cosmetics [2]. Only a small fraction of the over 350000 species of plants in the world have been evaluated pharmacologically and phytochemically. Phytochemical investigations of medicinal plants have revealed various phytoconstituents with varying pharmacological actions, some of which are used clinically. Hence, the plant kingdom can be said to have a massive storehouse of compounds of pharmacological significance that needs to be explored [3]. In most cases, information on the potential pharmacological activity is obtained through ethnobotanical survey. One disease, for which ethnobotanical information afforded clinically important drugs for its mitigation is malaria [4,5].

Malaria remains one of the most devastating diseases in the world, especially in developing countries, despite the global efforts targeted at eradicating or controlling the disease. The disease impacts over 500 million people internationally and causes mortality between 1 to 2.5 million people every year, with the most vulnerable groups being pregnant women and children under the age of 5" [1]. "Different ethnobotanical surveys have identified several plants used in traditional medicine for the treatment of malaria" [6]. Some of these plants were explored to produce natural, semi-synthetic and synthetic antimalarial drugs for clinical use. For example, from the aminoquinoline alkaloid quinine, isolated from the stem bark of Cinchona species, several antimalarial medications including chloroquine and amodiaquine were produced. Similarly, the leaves of the Chinese plant *Artemisia annua*, yielded several artemisinin derivatives including dihydroartemisinin, artesunate and artemether as antimalarials. The discovery of these agents, using natural products as template for their design, brought malaria on it knees averting needless deaths especially, in sub-Saharan Africa where the impact of the disease is most felt. However, due to the development of resistance by the plasmodium parasite, the efficacy of these antimalarials is on the wane. Chloroquine, for example, was abandoned as first line treatment of malaria about two decades ago upon recommendation by the world health organisation due to tangible proofs of resistance and therapeutic failure [7]. Artemisinin-based combination therapies were introduced to mitigate this threat but there are worrying signs of the development of resistance to this first line treatments. To date, however, resistance to quinine is not widespread [8], the first antimalaria compound discovered from plant. Thus, exploration of the efficacy of medicinal plants used in folklore medicine for the treatment of malaria is a rational research approach since majority of secondary metabolites in plants remain underexploited [9].

"Malaria is very endemic in Ghana, accounting for 2% and 3% of global cases and deaths respectively" [2]. "Ghana is ranked among eleven other countries, as a high-burden country, accounting for >70% of the global malaria cases and deaths" [10]. Several Ghanaians use home-based herbal remedies containing for example *Cryptolepis sanguinolenta* root and *Azadirachta*

indica leaves, for the management of malaria [10]. For most of these homebased medications, there is no scientific data in support of their use and their bioactive ingredients have also not been explored. In this research two of such plants, stem bark of Ficus sur and whole stem of Albizia coriaria used in folklore medicine for the treatment of malaria, were evaluated for their antiplasmodial activities.

"Ficus sur is one of the 750 plant species belonging to the family Moraceae. It occurs from sea-level up to 2500 m altitude, on riverbanks and in riverine forest, but also in upland forest, woodland and wooded grassland. Locally known as 'Odoma' (Akan-Twi). A decoction of the bark is used in the treatment of malaria, pain, rheumatism, diarrhoea, oedema in children, infertility and as a galactagogue" [11]. "*Albizia coriaria* is one of about 150 species that belong to the Genus Albizia. This genus is pan tropical, occurring in Asia, Africa, Madagascar, North America and Australia. It is utilized traditionally in the treatment of tape worm infection, stomach trouble, amoebic dysentery and malaria" [12]. The use of the stem of *Albizia coriaria* and *Ficus sur* in the treatment of malaria has been documented traditional medicine. There is, however, lack of scientific data on the efficacy of the plant extracts. This study therefore aimed to investigate the antiplasmodial activity of the hydroethanolic extract of the two plants and investigate their phytochemical constitution.

2. METHODS

2.1 Plant Material Collection and Authentication

The stem bark of *Albizia coriaria* and *Ficus sur* were harvested from Kwahu Asakraka in the Eastern Region of Ghana. The plant materials were authenticated by Mr Clifford Asare of the Department of Herbal Medicine, Faculty of Pharmacy and Pharmaceutical Sciences, Kwame Nkrumah University of Sciences and Technology (KNUST). Herbarium specimens of *A. coriaria* and *Ficus sur* were kept in the herbarium of the Department of Herbal medicine with identification numbers KNUST/HM1 /2020/S051 and KNUST/HM1/ 2020/S054 respectively.

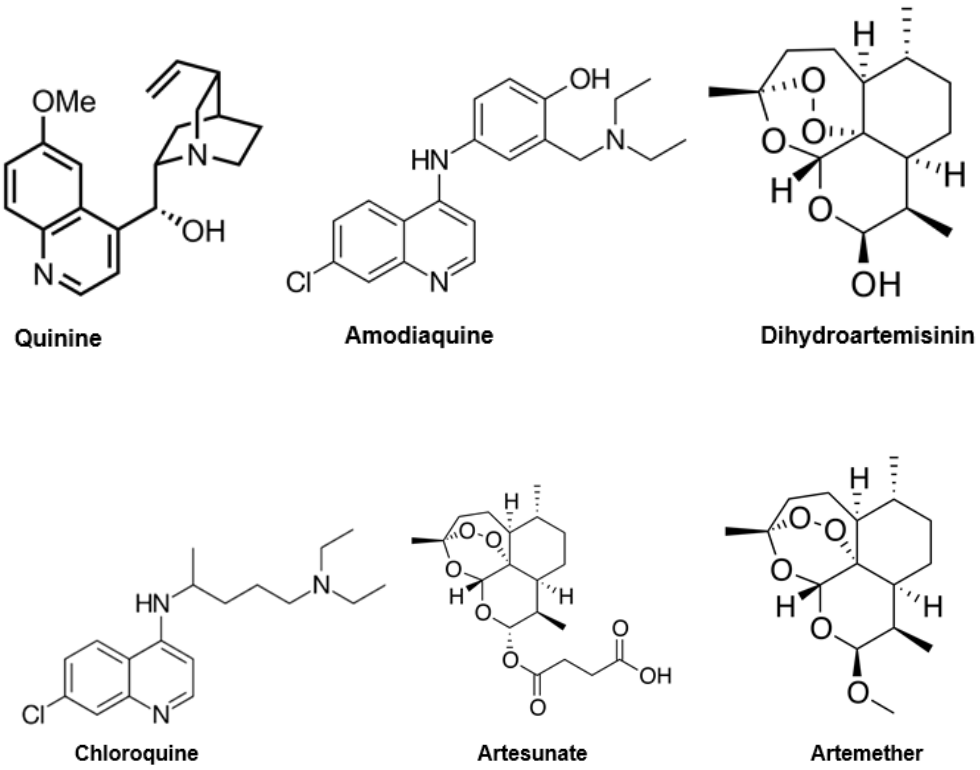

Plate 1. Chemical structure of different plant derived antimalarial compounds

2.2 Processing of Plant Materials and Extraction

The harvested plant materials were washed under running tap water, chopped into smaller pieces and air dried under shade and ambient temperature (28-35^{o}C) for 14 days. Each dried plant material was coarsely powdered using a mechanical grinder and packed into brown paper bags and kept at the laboratory until required for use. Five hundred grams each of the coarsely powdered stem bark of *Albizia coriaria* and *Ficus sur* were Soxhlet extracted with 70% ethanol. They were concentrated at 50 °C under reduced pressure using the rotary evaporator and subsequently kept in a desiccator [13].

2.3 Bioassays

2.3.1 Acute toxicity

Albizia coriaria and *Ficus sur* have a long history of use in traditional medicine as antimalarial plants without demonstrable toxicity hence the limit test at the single dose of 3000 mg/kg body weight was adopted [14]. Swiss albino rats were put into three [3] groups of three [3]. Two groups as test groups for each extract with the last group designated as the control group. Animals were starved overnight and given water *ad libitum*. Following the starvation period, rats were weighed and dosed with 3000 mg/kg bodyweight of extract using a gastric tube. Feeding was delayed for another 3 hours after drug administration, during which the rats were individually monitored at 30-minute intervals for the first 1 hour and then on occasionally for the following 24 hours, with specific attention paid to the first 4 hours. Thereafter, observation was made daily for the next 13 days for indicators of toxicity including gross physical and behavioural changes.

2.3.2 Experimental animals

Swiss albino mice and rats were obtained from the Noguchi Memorial Institute for Medical Research (NMIMR), University of Ghana, Legon, Accra. Animals were housed at the animal house of the Department of Pharmacology, KNUST. They were exposed to a 12:12 hours dark-to-light cycle with free access to clean drinking water and pellet diet. All the animals were allowed a week of acclimatization before the experiment [15]. All experiments were conducted with regards to the internationally accepted laboratory animal use, care and guidelines.

2.3.3 Parasite inoculation

The ANKA strain of *Plasmodium berghei* was obtained from the KNUST School of Medical Sciences. Healthy mice were infected with the Plasmodium parasite by intraperitoneal injection of 0.2 mL of inoculum (infected blood with the parasitaemia level: 1×10^7 parasitized erythrocytes) as described by Baah et al., [16].

2.3.4 Four-day suppressive antimalarial test

“This test was used to evaluate the schizonticide activity of the hydroethanolic extracts against *P. berghei* infected mice” [17]. Swiss Albino mice were inoculated on the first day (Day 0), intraperitoneally, with 0.2 ml of infected blood. The mice were then divided randomly into eight groups of five mice per group. Six groups (I, II, III, IV, V and VI) were assigned as test groups for the two extracts whereas groups (VII & VIII) were used as control (negative and positive). Three hours after infection 30, 100 and 300 mg/kg/day of hydroalcoholic crude extract of *A. coriaria* and *Ficus sur* were administered to the test groups. Artesunate at the dose of 4 mg/kg/day and an equivalent volume of vehicle (0.2 ml 7% tween 80 solution) were administered to the positive and negative control groups respectively, for four consecutive days (Day 0–3). On the fifth day, (96 h post-infection), thin blood smears were made from the tail of each mouse, fixed with methanol and stained with 10% Giemsa. Parasitaemia was determined by counting the number of parasitized red blood cells out of total red blood cells in five randomly chosen fields of the slide using a light microscope (Leica DM750, Wetzlar-Germany). Percentage parasitaemia was determined as described by Baah et al., [16].

2.3.5 Rane’s curative test

The curative potential of the hydroethanolic stem extracts of the plants were evaluated as described by Nardos *et al* [18]. “Seventy-two (72) hours following parasite inoculation, mice were randomly divided into eight groups after the establishment of parasitaemia. Mice were dosed with 30, 100 and 300 mg/kg/day of extract, 4 mg/kg/day of artesunate and 2 ml/day of the vehicle for 4 consecutive days. Thin blood smears were prepared from the tail vein of the mice before treatment and 24 hours following the last treatments to assess parasitaemia. Body weights were taken prior to the start of treatment and on day 7 post-infection. Animals were monitored for survival over 30 days post-infection” [19].

2.4 Phytochemical Screening

The dried powdered stem bark of *Albizia coriaria* and *Ficus sur* were subjected to general qualitative phytochemical screening using standard methods [20].

3. RESULTS

3.1 Acute Oral Toxicity

Administration of the 70% ethanol extract of the stem bark of *Albizia coriaria* and *Ficus sur* at 3000 mg/kg caused no observable physical and behavioural changes for 24 hours. Additionally, no mortality was seen within the 2-week observation period. Hence the LD_{50} of the extracts were estimated to be above 3000 mg/kg. The acute toxicity test suggests a good margin of safety.

3.2 Peter's Suppressive Test

In antimalarial research, *in vivo* models are used due to their possible prodrug influence and equipping the body's defences in getting rid of the pathogen [21]. *Albizia coriaria* extract demonstrated a significant ($P < 0.05$) dose-dependent suppression with the highest activity (68.89%) recorded for the 300 mg/kg dose. The suppressive effect of *A. Coriaria* at 300 mg/kg body weight was higher than that of artesunate (4 mg/kg). The hydroethanolic extract of *Ficus sur,* however, showed the highest suppression of 44.00% at 100 mg/kg with the highest dose of 300 mg/kg having considerably lower activity (35.11%) (Table 1). At all doses of the two extracts, the survival time of mice in the treatment groups were prolonged, with the 300 mg/kg dose of *A. coriaria* producing the greatest survival time (Table 1).

3.3 Effect of the Extracts on Bodyweight in the Suppressive Test

Treatment with *Albizia coriaria* and *Ficus sur* prevented significant decrease in the weight of the mice in the treated groups relative to the vehicle treated group (NC) which showed a reduction (Fig. 1). Similarly, there was no significant weight decline in the artesunate-treated group. All the tested extracts prevented the weight loss associated with the infection.

Table 1. Effect of the extracts on parasitaemia and survival time of the *P. berghei*-infected mice in the Suppressive test

Dose (mg/kg)		% Parasitaemia (mean ± SEM)	% Suppression	MST
NC		45.00 ± 5.21	-	9.25±2.87
Ficus	300	29.20 ± 0.86[a2]	35.11	23.19±4.10
	100	25.20 ± 1.66[a4]	44.00	25.65±2.86
	30	29.80 ± 1.46[a2]	33.78	17.71±3.25
Albizia	300	14.00 ± 0.71[a4]	68.89	28.07±2.14
	100	30.95 ± 5.08[a1]	31.22	20.42±4.65
	30	33.22 ± 0.57[a1]	26.18	18.30±5.68
ART	4	16.29 ± 2.67[a4]	63.80	26.22±2.42

Values are presented as Mean±SEM, N = 5, NC = vehicle-treated group, ART = Artesunate. Values are significantly different at [1]P < 0.05, [2]P < 0.01, [4]P < 0.0001, [a]compared to the vehicle-treated group (NC), MST = Mean Survival Time.

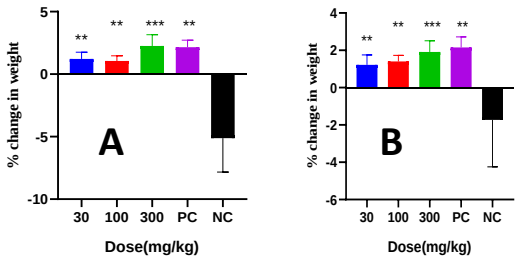

Fig. 1. Percentage change in weight of mice infected with *P. berghei* on day 0 and day 4 in the 4-day suppressive assay in *Albizia coriaria* (B), and *Ficus sur* (A)

***Values are significantly different at P < 0.05, ***Values are significantly different at P < 0.001, compared to the negative control group (NC)*

3.4 Rane's Curative Test

The 70% ethanol stem extracts of *Albizia coriaria* and *Ficus sur* caused a significant ($P < 0.001$) decrease in parasitaemia levels on day 7 relative to day 3 at all tested doses. A dose dependent parasitaemia suppression was observed with all the extracts with the highest suppression seen at the highest dose for both extracts. *A. coriaria* produced the highest percentage suppression of 61.46 followed by *F. sur*. Artesunate (25 mg/kg/day) had a superior curative potential (85.25 %) than the extracts at all doses (Table 2). Survival time increased with increasing doses for all the tested extracts. The hydro ethanol extract of *Albizia coriaria* recorded the highest survival of 24.05 days but this was lower than that of Artesunate.

Table 2. Effect of the extracts on parasitaemia and survival time of the *P. berghei*-infected mice in the Curative test

Dose (mg/kg)		% Parasitaemia (mean ± SEM)		% Suppression	MST
		DAY 3	DAY 7		
NC		52.00±5.21	56.00±5.21[a]	NS	10.58±4.21
Ficus	300	56.21±3.14	28.26±4.25[a]*	49.54	19.55±7.45*
	100	51.05±5.47	34.28±6.25[a]*	38.79	15.36±4.31*
	30	48.21±6.50	39.24±5.10[a]*	29.93	14.70±6.29*
Albizia	300	53.59±4.35	21.58±3.65[a]*	61.46	24.05±5.33*
	100	55.36±2.15	26.19±2.50[a]*	53.23	20.46±6.10*
	30	49.10±4.88	36.57±7.22[a]*	34.70	17.28±4.36*
ART	25	54.47±3.78	8.26±0.52[a]*	85.25	30.00±0.00*

*Values are presented as mean ± SEM, N = 5, NC = vehicle-treated group, ART = Artesunate, NS = No Suppression. [a] Values are significantly different at P < 0.001 compared to Day 3, *compared to the vehicle-treated group at P < 0.05. MST = Mean Survival Time.*

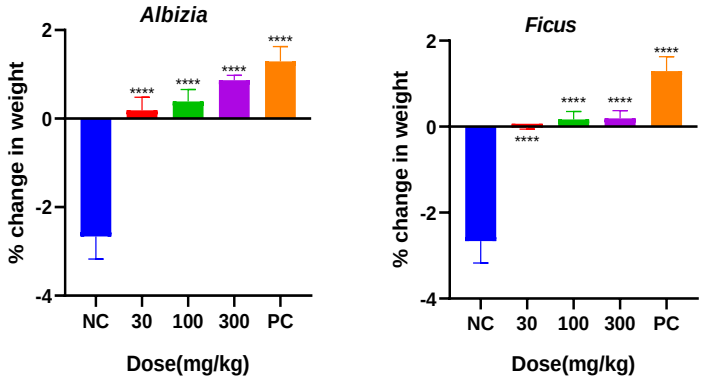

Fig. 2. Percentage change in weight of mice infected with *P. berghei* on day 0 and day 4 in the 4-day suppressive assay in *Albizia coriaria* and *Ficus sur*. ****Values are significantly different at *P* < 0.001 compared to the negative control group (NC)

Table 3. Phytochemical constituents of *Albizia coriaria,* and *Ficus sur*.

Phytochemical component	*Ficus sur*	*Albizia coriaria*
Coumarins	+	+
Flavonoids	+	+
Alkaloids	-	+
saponins	+	+
triterpenoids	+	+
phytosterols	+	-
tannins	+	+
Reducing sugars	+	+

3.5 Effect of the Extracts on Bodyweight in the Curative Study

All the extracts were able to prevent the decline in the bodyweight of the treated mice at all tested doses in the curative assay (Fig. 2) compared to the negative control group. The extracts also produced a dose dependent increase in the bodyweight of the mice. Even though the 30 mg/kg group of *Ficus sur* also recorded a decline in the percentage change in bodyweight, it was still significantly, $p<0.001$ different from the untreated group.

3.6 Preliminary Phytochemical Screening

The qualitative phytochemical screening of the powdered plant materials of *A. coriaria* and *F. sur* revealed the presence of all secondary metabolites tested except for alkaloids and phytosterols in the former and later respectively (Table 3).

4. DISCUSSION

The present study focused on validating the anti-plasmodial activity of two medicinal plants used in the management of malaria for which scientific credence of their biological activity is not widespread. *Albizia coriaria* showed higher activities in both the suppressive and curative test (Tables 1 and 2). The Peter's 4-day suppressive assay is the preliminary model for assessing the antimalarial activity of potential agents against Plasmodium parasite [22]. *Albizia coriaria* reduced parasitaemia in a dose dependent manner and at a level (68.89%) considered as having good antiplasmodial activity against *Plasmodium berghei* according to the classification by Muñoz et al., [23]. *A. coriaria* extract produced superior activity at the highest dose in the suppressive assay (Table 1) suggesting that it could be suited for treating the disease at the early stages of infection.

The curative test evaluates the potential of an agent to clear the parasites in an established infection [24]. This is relevant as it mimic the state in which people in endemic areas use these plant medicines in the treatment of malaria. Both extracts demonstrated a dose dependent parasite clearance with *A. coriaria* superior to F. sur, but both were lower than artesunate used as positive control (Table 2). This corroborates earlier reports by Muthaura et al., [24] where the methanol extracts of *A. coriaria* stem bark demonstrated promising *in vitro* antiplasmodial activity. Similarly, the dichloromethane extract of the plant showed *in vitro* antipalsmodial activities against chloroquine sensitive and resistant strains of *P. falciparum* (25). Thus, the results of the present study and those reported elsewhere highlight the antimalarial potential of *A. coriaria* and justifies it use in traditional medicine.

Weight loss in malaria infection can lead to exacerbation of the pathology which can lead to the eventual death of the organism [26]. Therefore, the extracts' ability to prevent the weight loss may be contributing to the significant levels of survival by the experimental animals compared to the animals in the negative control group. The increase in the survival time of the mice corroborates the decline of the parasitaemia's degenerative consequences in the treated groups. At all the doses tested, the plant extracts significantly improved the mice's duration of survival compared to the negative control. The mean survival time *A. coriaria* was comparable to the reference drug artesunate used as positive control. Considering the significant activity recorded by *A. coriaria*, future research should target it purification or fractionation as this could lead to fractions of compounds with much potent antiplasmodial effect than the crude extract.

The diverse array of secondary metabolites in plants are responsible for their therapeutic indications in several diseases [20]. The only metabolite absent from *A. coriaria* was phytosterols whereas alkaloids were not detected in *F. sur*. The absence of alkaloids in the latter does not support earlier reports by Ishola et al., [27] where alkaloids were detected in the stem bark. Also, the absence of phytosterols does not corroborate earlier reports by Omara et al., [28]. This could be attributed to plant related factors such as geographical location, season and time of harvesting. These metabolites detected have been reported to show chemo suppressive effect in plants [29–31]. The most active plant, *A. coriara* was found to contain considerable amount of alkaloids (Table 3). The alkaloids have well established antimalarial activity as evidenced by drugs such as quinine, the alkaloidal drug derived from cinchona bark, and its structural analogues. The chemotherapeutic action of several plant metabolites against plasmodium parasite have been attributed indirectly to strengthening of the immune system and inhibition of parasite lactate dehydrogenase (reference) as well as other pathways and

targets that have not yet been completely understood [32].

In the acute toxicity test, both extracts caused no visible signs of acute toxicity as evidenced by the gross behavioral and physical changes of the experimental mice. The acute toxicity test suggests a good margin of safety. This also supports its long-standing usage in traditional medicine in the treatment of many disorders without evidence of toxicity. It thus corroborates findings from the cytotoxicity assay of Albizia coriaria reported by [33] where the extract was found to be safe.

5. CONCLUSION

The stem of *Albizia coriaria* and *Ficus sur* demonstrated good antiplasmodial activities in the suppressive assay. This study has provided a basis for the traditional use of the stem of *Albizia coriaria,* and *Ficus sur* in the treatment of malaria.

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CONSENT

It is not applicable.

ETHICAL APPROVAL

Animal experimental techniques were carried out after the study received ethical permission from the Committee on Animal Ethics and Research, Department of Pharmacology, Kwame Nkrumah University of Science and Technology (KNUST/Cology/034). Furthermore, guidelines for the Helsinki Declaration for the care of experimental animals were meticulously observed [13].

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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