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Isolation, Characterisation and Assessment of Antimalarial Properties of *Khaya senegalensis* (Stem back) extract

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ABSTRACT
In active malaria transmission areas, the disease is responsible for the death of many children less than five years of age and expecting mothers. Locals in underdeveloped African nations relied heavily on traditional herbal formulations to treat a number of ailments including malaria.In this study, the antimalarial potential of the stem back of African Mahogany (*K. senegalensis*) popularly known as Mad'aciinmost parts ofHausa land in Northern Nigeriawas further assessed with a view to substantiate traditional claim and revalidate already existing studies. The study also demonstrates the efficacies of crude *Khaya senegalensis* (Stem back) extracts on *P. falciparum* (3D7) *in vitro.* Secondary metabolites such as Alkaloids and Flavonoids were identified in all solvent extracts, the presence of which, might be indicative of the antimalarial activities observed. Similarly,suppression of parasite growth was observed to be dependenton the dosage used for all solvent extracts. Suppression of parasite growth was observed to be 52.97% for the highest concentrations (50 µg/mL) of hexane and methanolic extracts and 64.43% for the aqueous extracts. For the lowest concentrations (6.25 µg/mL) of each crude extract (Hexane = 41.32%, Methanol = 24.57% and Aqueous = 46.00%) respectively, suppression of growth of parasites was relatively lower compared to other dose levels. Further fractionation of crude extracts and assessment of antimalarial activities in other strains of*P. falciparum* as well as curative and repository activities of the extracts and fractions on other malaria parasites in experimental animal models are required to substantiate the antimalarial efficacies of *Khaya senegalensis.*

Keywords:
Malaria,
Antimalarial,
Phytochemicals,
Khaya senegalensis,
Medicinal plant.

INTRODUCTION

The protozoan parasitesof the genus *Plasmodium*, of which; *Plasmodium falciparum*, *P. vivax*, *P. ovale* and *P. malariae were responsible for malaria in human.*Similarly, another species of *Plasmodium* parasite known to infect macaque monkeys, *P. knowlesi*, were reportedlyseen to infect humans as zoonotic malaria (Sabbatani *et al.,* 2010).Of these five species infecting human,*P. falciparum*has been reported to be responsible for most of the deaths due to malaria (Flannery *et al.,* 2013).In active malaria transmission areas especially the sub-Saharan Africa, malaria is most frequently the leading cause of fever (White *et al.,* 2014).

Adebayo and Krettli (2011) revealed that in endemic areas, one in every five malaria patients use plant materials to treat the disease.Despite the availability of orthodox medicines, traditional medicines are popularly used due to their cheaper costs and for historical and cultural reasons (Lawal *et al.,* 2015). In Nigeria for example, a good number of plant species were recognized by locals for their antimalarial potentials. The antimalarial activities of the stem bark, root bark and leaves of *Morinda lucida* and the stem bark of *Alstonia boonei* have been documented (Bello *et al.,* 2009). In South Western Nigeria, a combination of either *A. boonei* (bark), *Magnifera indica* (bark, leaves), *Psidium guajava* (leaves), *Carica papaya* (leaves); *Enantia chlorantha* (bark), *A. boonei* (bark), *Diospyros mespiliformis* (bark); or *Ocimum gratissimum* (Leaves), *Anarcadium occidentale* (foliage leaves), *Lecaniodiscus cupanioides* (foliage leaves), *Curcuma longa* (foliage leaves) and *Citrus aurantifolia* (foliage leaves) are used as prophylaxis against malaria (Odugbemi *et al.,* 2007; Idowu *et al.,* 2010; Idowu *et al.,* 2015). In the South-southern part of the country, root decoction of *Zea mays* is taken as warm tea for the treatment of malaria in Ibibio traditional medicine (Okokon *et al.,* 2016). In the Northern part of Nigeria however, leaves of *Moringa oleifera* are reportedly used for the treatment of malaria

and typhoid fever (Stevens *et al.,* 2013). Furthermore, the stem back, leaves and root of *M. oleifera*, stem backof *Khaya senegalensis*, leaves and stem back of *Prosopis africana,* stem back of *Ficus platyphylla, F. thonningii* and *Afzelia africana* as well as leaves of *Cissus populnea* were reported to be used as remedies for fever in the North East (Adebayo and Krettli, 2011). In the North central part of the country, the bark and leaves of *Azadirachta indica*, leaves of *Vernonia amygdalina*, leaves and fruits of *Carica papaya*, bulb of *Allium sativum*, bark of *Khaya grandifoliola*, roots and leaves of *M. lucida* and roots of *Rauwolfia vomitoria* are the most frequently used traditional antimalarial remedies (Kunle *et al.,* 2013).

To achieve the goal of discovering new antimalarial drugs, certain strategies; use of combined therpies with available drugs in clinical use, determining markers that may reverse drug resistance, drug reprofiling, synthesizing analogues of drugs in clinical use and the discovery of antimalarials from natural products had been reported (Oliveira *et al.,* 2009; Matthews *et al.,* 2013).

*K. senegalensis*is a deciduous evergreen tree, with a height ranging between 15-30 meters, and a diameter of up to 1 meter. The tree has a stem of 8-16 meters, a dark grey bark, with small/thin reddish-tinged scales (Orwa *et al.,* 2009). The tree is a native of riverine forests and is scattered within the higher-rainfall savannah woodlands. *K. senegalensis*belongs to the family Meliaceae (Kolawole *et al.,* 2011) Plate I. In addition to *K. senegalensis*, four more species of the genus *Khaya*which include *K. anthoteca*, *K. senegalensis*, *K. ivoriensis* and *K. grandifoliola* (Ibrahim *et al.,* 2006) exist in Africa. According to Orwa *et al.* (2009), *K. senegalensis* is a native of Cameroon, Central African Republic, Chad, Cote d'Ivoire, Equatorial Guinea, Gambia, Ghana, Guinea, Guinea-Bissau, Mali, Niger, Nigeria, Senegal, Sierra Leone, Sudan, Togo, and Uganda.

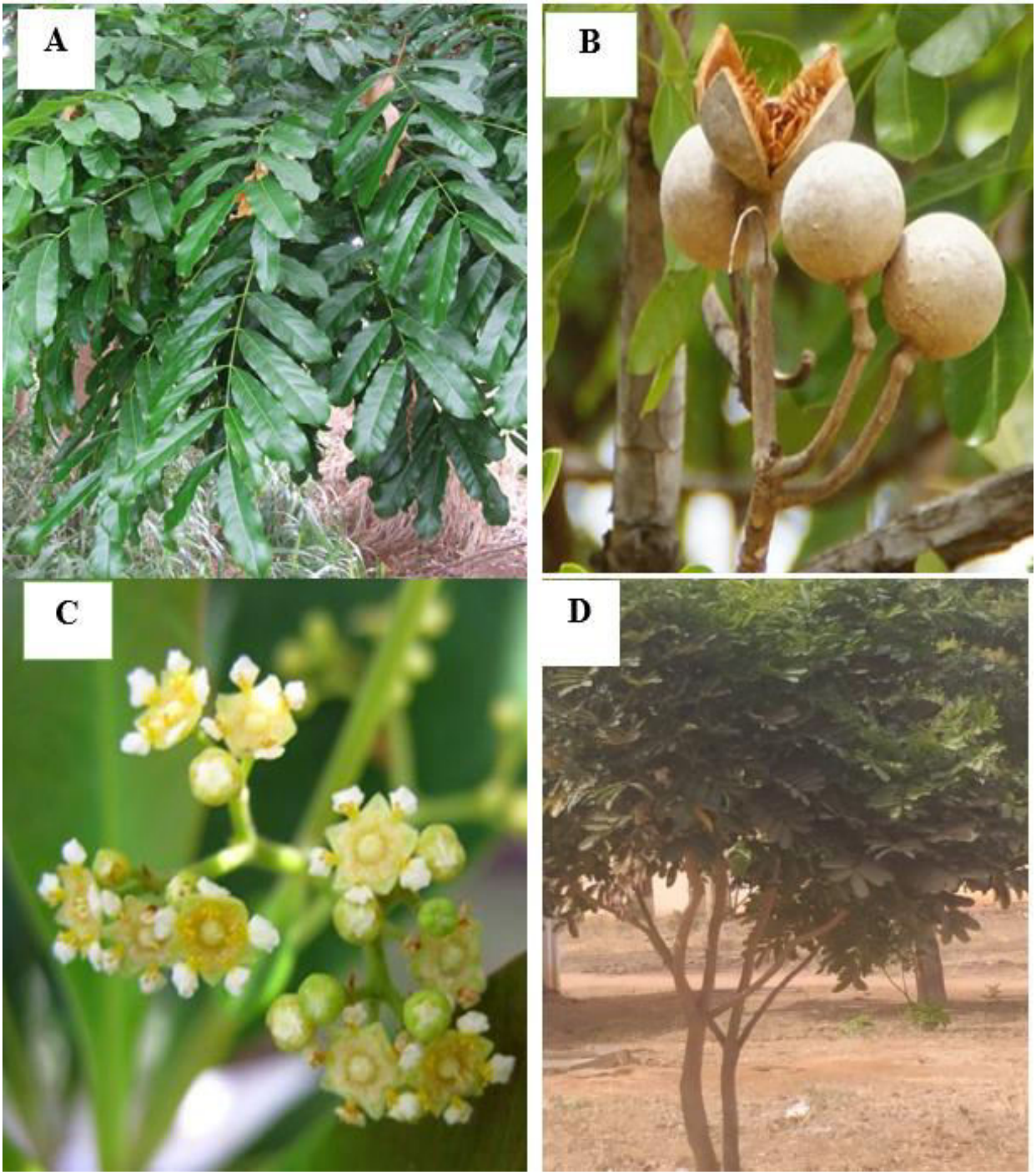

Plate I: Parts of *K. senegalensis* used as ethnomedicines showing (a) the leaves (b) seed pods (c) flowers and (d) whole plant.

Medicinal values of K. senegalensis

In Nigeria, *K. senegalensis* commonly referred to as madaci by the predominant Hausa speaking communities of the North, is a **medicinal plant** that is widely used to treat various diseases. A decoction of the stem bark of *K. senegalensis* is widely used to treat fever. This may not be unconnected with its traditional use as an antimalarial herbal remedy (Kankia and Zainab, 2015). Additionally, a decoction of the stem back is used to treat jaundice, dermatoses, malaria, other forms of fever, mucous diarrhea, and venereal diseases as well as for hookworm infection and a taeniacide remedy (Adebayo *et al.* 2003; Onu *et al.,* 2013). Similarly, an ethno pharmacological survey revealed the traditional use of *K. senegalensis*

root, leaves and stem back in the treatment of diabetes, malaria, anaemia, diarrhea, gastrointestinal diseases and fever amongst others (Ibrahim *et al.,* 2014). Kankia and Zainab, (2015) further reported its use in the treatment of catarrh, epilepsy, hysteria, rheumatism, hemorrhoids, painful menstruation, skin-ulcerations, burns and wounds. In an experimental animal study, a prolonged administration of ethanol extract of the plant was proved to produce a significant reduction in the alkaline phosphatase activities of the kidney (Adebayo *et al.*, 2003). Similar laboratory studies reported the efficacy of this plant on biochemical, haematological, and histopathological parameters of Rats (Onu *et al.,* 2013), antioxidant activity (Ibrahim *et al.,* 2014), antimalarial (Shayoub *et al.,* 2016), **free radical** scavenging as well as antimicrobial activity (Alain *et al.,* 2014) were reported.

In this study, the antimalarial potential of *K. senegalensis* was further elucidated with a view to substantiate traditional claim and revalidate already existing studies. The study also demonstrates the efficacies of crude *Khaya senegalensis* (Stem back) extracts on *P. falciparum* (3D7) *in vitro.*

MATERIALS AND METHODS

Processing plant samples

The stem back of *Khaya senegalensis*was also collected from live trees, washed in clean tap water and dried under shade at ambient temperature (28-37ºC). Dried sample was then ground to powder using grinding machine (IKA WERKE, M 20). Powdered plant sample wasthen stored at room temperature in a screw cap sample container, until further use.

Phytochemical extraction

Phytochemical extraction of powdered plant sample was performed by successive extraction (cold) procedures with n-hexane, Methanol, and distilled water (in order of increasing polarity) respectively as described by Mojarrab *et al*. (2014). Briefly, powdered sample was weighed (100 g), transferred into a screw cap, wide mouth, clear sample bottles and macerated in 500 ml each of organic solvent (i.e. 1:5 w/v) as previously described (Bukar *et al.,* 2009; Senguttuvan *et al.,* 2014; Yusuf *et al.,* 2014). The suspension was stirred, screw capped and shake for 24 hours in a shaker (IKA WERKE, HS 501) at room temperature. This was filtered using muslin cloth and the residue was air dried for further extraction with a different solvent. Consequently, filtrates from n-hexane and methanolic extractions were concentrated at 40ºC using a rotary evaporator (Stuart, RE300DB) (Bukar *et al.,* 2009; Pandey *et al.,* 2014; Senguttuvan *et al.,* 2014; Yusuf *et al.,* 2014) and solvents recovered, while aqueos extracts were freezed at -20ºC and lyophilized in a freeze drier (FDL-10N-50-TD-MM).

Powdered extracts were stored at 4ºC in a screw cap container until needed for use (Bukar *et al.,* 2009; Pandey *et al.,* 2014). Subsequent to extraction of phytochemicals, each extract was weighed and the percentage yield calculated using the following formula

$$\text{Percent (\%) yield} = \frac{\text{Weight of extract (g)}}{\text{Weight of Powdered Material (g)}} \times 100$$

Phytochemical screening

After the extraction of phytochemicals from plant powder, extracts were screened with a view to determining the presence or otherwise of some active metabolites. These analysis was performed in accordance with the protocol described by Kumar *et al.* (2013).

Parasite culture

For malaria parasite culture, blood (group O+) required for parasite invasion was obtained from a voluntary donor whose consent was sought. Complete culture medium was prepared in accordance with Daskum *et al.* (2019) and blood sample (group O +) for parasite cultures was processed as per the recommendation and protocol previously described (Orman *et al.,* 2015; Amir, 2016). Finally, cryopreserved malaria parasites, *P. falciparum* (3D7) was maintained in continuous culture as previously described (Trager and Jensen, 1976). To ensure that parasitaemia is maintained within the minimum threshold, cultures were checked on daily basis, culture medium replenished and a required volume of blood is added (D'Alessandro *et al.,* 2013).

Preparation of crude plant extracts for *in vitro* growth suppression assay

A stock, 100mg/ml of each extract was freshly prepared according to the methods of Donkor *et al.* (2015). Briefly, 0.1g of each extract was weighed and dissolved in 1ml dimethylsulfoxide (DMSO) to ensure total dissolution. To make the reaction mixture, an aliquot, 10 µL from each stock was reconstituted in 990 µL of complete culture medium (RPMI 1640) initially prepared, to attain a concentration of 1000µg/ml. This was mixed thoroughly using a vortex mixer and subjected to further serial dilutions to obtain various concentrations (500, 250, and 125 µg/ml) respectively. In each working solution, the concentration of DMSO ranges between 1 to 0.025% and 0.5 to 0.0625 in the respective wells, hence does not affect parasite growth.

Harvesting for microscopic examination and parasite count

Following the 48 hour incubation of synchronized parasite cultures with different concentrations of crude plant extracts, parasites were harvested as previously described (Basco, 2007) for assessment of the antimalarial effects of the extracts. Briefly, ~170 µL of culture medium (supernatant) was carefully aspirated from each well and discarded leaving a small volume (~30 µL) to allow resuspension of settled erythrocytes by gentle pipetting. This was used to make thin smears

in grease free glass slide, and examined as per standard procedures (Huy Vu *et al.,* 2021).

RESULTS AND DISCUSSIONS

Results

Phytochemical extraction

Table 1: Yield of crude K. senegalensis (Stem back) extracts

Plant	Local/Hausa (English) Names	Part used	Extract	Yield (g)	Yield (%)
K. senegalensis	Mad'aci (African Mahogany)	Stem back	Hexane	77.46	15.49
			Methanol	65.43	13.09
			Aqueous	54.40	10.88

Yield of extract

The yield of *K. senegalensis* (Stem back), was in the range of 54.40–77.46 g. More yield 77.46 (15.49%) was obtained for hexane extract and the aqueous extract had the least yield 54.40 (10.88%) recorded the least (Table 1).

Phytochemical screening

Results obtained for phytochemical screening are summarized in Table 2. The presence of phenols, terpenoids, tanins, cardiac glycosides, Xanthoproteins, Alkaloids and flavonoids was observed in the hexane extract but not Resins and Anthraquinones. Similarly, all secondary metabolites seen in the hexane extract were also identified in the methanolic and aqueous extracts of both plants except Terpenoids, Tannins as well asCardiac glycosides which are absent in the methanolic and aqueous extracts of the plant. Although, similar metabolites were identified in hexane and methanolic extracts, compounds present could vary on the basis of their polarity.

Table 2: Phytochemical analysis of crude K. senegalensis (Stem back), extracts

Type of extract	Phenols	Terpenoids	Resins	Tannins	Cardiac glycosides	Anthraquinones	Xanthoproteins	Saponins	Alkaloids	Flavonoids
n-Hexane										
	+	+	-	+	+	-	+	+	+	+
Methanol										
	+	-	+	-	+	-	+	+	+	+
Aqueous										
	+	+	+	+	-	-	+	+	+	+

***In vitro* antimalarial effects of crude extracts against *P. falciparum* (3D7) culture**

To establish the antimalarial efficacy of crude *K. senegalensis* (Stem back) extracts against *P. falciparum* (3D7) culture *in vitro,* sensitivity tests were carried out as earlier described. Table 3 summarizes the percentage parasitaemia, percentage suppression of parasite growth and the IC_{50} of extracts investigated. Results of parasitaemia are presented as Mean ± Standard error of mean (M±SEM) except for the IC_{50} and confidence intervals (95%), while percentage suppression of parasite growth was calculated in accordance to standard formula (Chessed et al., 2023). Suppression of parasite growth was observed to be dependent on the concentration of extract used. Parasite growth suppression was observed to be 52.97% for the highest concentrations (50 µg/mL) of hexane and methanolic extracts and 64.43% for the aqueous extracts. A relatively lower suppression of parasite growth was observed for the lowest concentrations (6.25 µg/mL) of each crude extract (Hexane = 41.32%, Methanol = 24.57% and Aqueous = 46.00%) respectively. However, lower concentrations comparable to the lowest concentrations used in this study, are required to inhibit parasite growth and development by 50% (Hexane $IC5_0$= 3.882 µg/mL; methanol 8.462 µg/mL and Aqueous 4.349 µg/mL).

Table 3: *In vitro* Antimalarial activities of hexane, methanolic and aqueous *K. senegalensis* (stem back) extracts.

Plant Name	Type of extract	Dose (µg/mL)	Parasitaemia (%)	Growth supression (%)	IC_{50} (µg/mL)
			Mean ± SEM		
K. senegalensis	Hexane	6.25	4.16 ± 0.04	41.32	3.882
		12.5	3.94 ±0.12	44.37	
		25	3.71 ±0.09	47.63	
		50	3.33 ± 0.28	52.97	
	Methanol	6.25	5.34 ± 0.16	24.57	8.462
		12.5	4.99 ± 0.43	29.62	
		25	4.05 ± 0.58	42.81	
		50	3.33 ± 0.05	52.97	
	Aqueous	6.25	3.83 ± 0.25	46.00	4.349
		12.5	3.34 ± 0.26	52.83	
		25	2.90 ± 0.24	59.03	
		50	2.52 ± 0.03	64.43	

SEM = Standard error of Mean; CI = Confidence Interval; IC_{50} = 50% Inhibitory concentration µg/mL = Microgram per mills concentration.

Discussions

In the present study, the metabolites (Flavonoid and alkaloids) were identified in hexane, methanolic and aqueous stem back extracts of *K. senegalensis*. This finding corroborate with the results of Kankia and Zainab, (2015); Aguoru *et al.* (2017) who reported the presence of Flavonoids and alkaloids in methanolic and ethanolic stem back extracts of *K. senegalensis* and attributed their presence to antioxidant, anthelmintic, antimicrobial, antifungal, and anticancer activities, respectively. Although these phytochemicals were identified by quantitative phytochemical analysis (Bello *et al.,* 2009; Kumar *et al.,* 2013), further fractionation and evaluation of antiplasmodial activities of individiual metabolite was not performed, due primarily to existing proof that crude plant extracts often have greater *in vitro* antiplasmodial activity than isolated constituents at an equivalent dose (Rasoanaivo *et al.,* 2011; Somsak *et al.,* 2016). The increased activity exerted by crude extracts may likely be as a result of synergistic effects caused by bioactive metabolites. Another reason for the use of crude extract in this research was the traditional use of crude herbal remedy in the treatment of diseases. Specific phytochemical, for example, Flavonoids have been attributed to a delay or total prevention of oxidation of cellular oxidizable substrates (Muhammad *et al.,* 2017).

The *in vitro* antimalarial activities of hexane, methanolic and aqueous stem back extracts of *K. senegalensis* on *P. falciparum*(3D7) strain revealed ~53% inhibition of parasite growth at the highest dose level (50 µg/mL). Tona *et al.* (1999) suggests that compounds/extracts suppressing parasite growth by ≥ 70% are considered more active, those that suppress parasite development by ≤ 50% to ~70% are classified as active while any suppression <50% is categorised as inactive. In view of the foregoing, results obtained for *in vitro* antimalarial screening of Hexane extract of *K. senegalensis* (stem back) at the highest dose level may be classified as active however, at much lower dose levels, the extract could be regarded as inactive. Although the concentration thought to cause 50% inhibition (IC_{50}) of parasite growth relative to the untreated control was observed to be 3.882 µg/mL, the pharmacological activity exerted by this extract is not as potent as expected. The methanolic extract of the same plant showed similar activity at the highest dose but with a varying IC_{50} of 8.46 µg/mL. This implies that, ≥8 µg/mL of the crude extract is required to cause at least 50% clearance of parasitaemia. A reasonably good activity was observed for all dose levels of the aqueous extract of this plant. At 12.5 µg/mL concentration, an inhibition of parasite growth (52.83%) comparable to the highest dose of both hexane and methanolic extract was observed. This activity increases as the dose increase showing potent biological activity (64.43% suppression of parasite growth) at the highest dose, (IC_{50} = 4.35 µg/mL). This outcome may justify the

traditional use of water in preparing the ethno medicine for the treatment of malaria suspected fever.

CONCLUSION

Phytochemicals with reported biological activities such as flavonoids and alkaloids were identified in crude extracts of all solvent extracts, the presence of which, might be indicative of the antimalarial activities observed. Moreover, a dose dependent suppression of plasmodial growth was observed for all solvent extracts on *P. falciparum* (3D7). Further fractionation of crude extracts and assessment of curative and repository activities of the extracts and fractions on other strains *P. falciparum*in experimental animal models are required to substantiate the antimalarial efficacies of *Khaya senegalensis.*

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