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In vitro antiplasmodiale activity and neurotoxicity of *Entandrophragma angolense*, *Griffonia simplifica*, *Uapaca guineensis*, three traditional plants used against malaria

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Abstract
Malaria remains a global health challenge, with increasing interest in plant-based therapies as potential alternatives to synthetic antimalarial drugs. *Entandrophragma angolense*, *Griffonia simplifica*, *Uapaca guineensis* are traditionally used for malaria treatment in West Africa. While their antimalarial properties have been documented, their potential neurotoxic effects have not been fully investigated. This study evaluates the *in vitro* antiplasmodial activity and neurotoxicity of extracts from these plants using neuronal cell lines and biochemical assays to assess cell viability. *Entandrophragma angolense* showed the best antiplasmodial activity. The findings highlight a concentration-dependent effect on neuronal viability, with *Griffonia simplifica* demonstrating the lowest neurotoxic potential. These results emphasize the need for further investigations to optimize the therapeutic index of these plant-based remedies.

Keywords: Antimalarial drug, antiplasmodial, cell lines, malaria, neurotoxicity

Introduction
Malaria is currently the deadliest parasitic disease in the world, especially in developing countries (Kofi *et al.*, 2012) [1]. This disease is transmitted by the female of an anophele mosquito and caused by a protozoan of genus *Plasmodium*.
Of the five plasmodial species, only *P. falciparum*, the most widespread in Côte d'Ivoire, is responsible for the deaths of thousands of people, mostly children (Schlitzer, 2008) [2].
The increasing resistance of *Plasmodium* to conventional antimalarial drugs has intensified the search for alternative therapies, particularly from medicinal plants with historical use in traditional medicine. Among these, *Entandrophragma angolense*, *Griffonia simplifica*, *Uapaca guineensis* have garnered attention due to their antimalarial efficacy and availability in endemic regions (Offoumou *et al.*, 2018) [3]. However, the safety profile of these plants, particularly their effects on the nervous system, is poorly understood. Neurotoxicity is a critical concern, as many plant-derived compounds can cross the blood-brain barrier and potentially disrupt neuronal functions (Amara *et al.*, 2018; Sülsen *et al.*, 2021) [4, 5]. This study aims to assess the *in vitro* neurotoxicity of these plants to inform their safe use in malaria therapy.

Materials and Methods
Plant materials
Hydro-ethanolic extracts of *Entandrophragma angolense*, *Griffonia simplifica*, *Uapaca guineensis* were prepared from dried barks collected in malaria-endemic region (Agboville). Samples were authenticated at the National Herbarium (CNF) and stored under standardized conditions.

Cell culture
Human neuroblastoma cells (SH-SY5Y) were used as a model for neuronal toxicity.

Vegetable material and preparation of extracts
Vegetable material consisted of stem back of *Entandrophragma angolense*, *Griffonia simplifica*, *Uapaca guineensis.* The plants were collected from Agboville department and were

identified by Floristic Center of Félix Houphouet-Boigny University. The plant samples were then dried in shade left over for 20 days and powdered with the help of grinder. Powder was extracted according to Zihiri and Kra (3003) [6] as follows: One hundred grams of powder were macerated in ethanol 70% during 48 hours. The obtained homogenate was filtered successively on cotton then on Whatman paper 3 mm. The filtrate is first reduced using a rotary evaporator BÜCHI type at 50 °C, then collected brown paste is lyophilized. We obtained ethanolic extract.

In vitro antiplasmodial assay on *P. falciparum*

For *in vitro* culture of *P. falciparum*, we used the isotopic alternative of the microphone-test (plate of 96 wells) of Reichmann adopted by WHO (Rieckmann *et al.*, 1978) [7]. This technique measure and quantify the capacity of drug to inhibit the growth of *P. falciparum* at the trophozoites stage.

In this technique, the strains are incubated at 37 °C in an impoverished in oxygen and enriched with carbon dioxide with 95% of humidity. After 24 h, plates were removed and added tritiated hypoxanthine (0.5 µCi by well). The plates were again returned to incubator for 24 h. After the incubation, the plates were frozen and thawed. Freezing and thawing of plates free plasmodial DNA radiolabeled by hypoxanthine. The DNA is recovered after washing on a filter paper in a rectangular fiberglass tape with a cell collector. Once the collection is complete, the paper was removed and dried. The radioactivity was measured using a Wallac Micro Beta counter. All results were expressed on a listing.

Neurotoxicity essay

Differentiation of SH-SY5Y cells to SH-SY5Y-neurons

SH-SY5Y cells were maintained in continuous culture for at least one week. For differentiation, the old SH-SY5Y cell culture media was removed and replaced with a new MEM media containing 10 µM retinoic acid. Maintenance of the culture by half media change every alternate day (media containing retinoic acid) was done for six days to obtain mature neurons (Azmi *et al.*, 2013) [8].

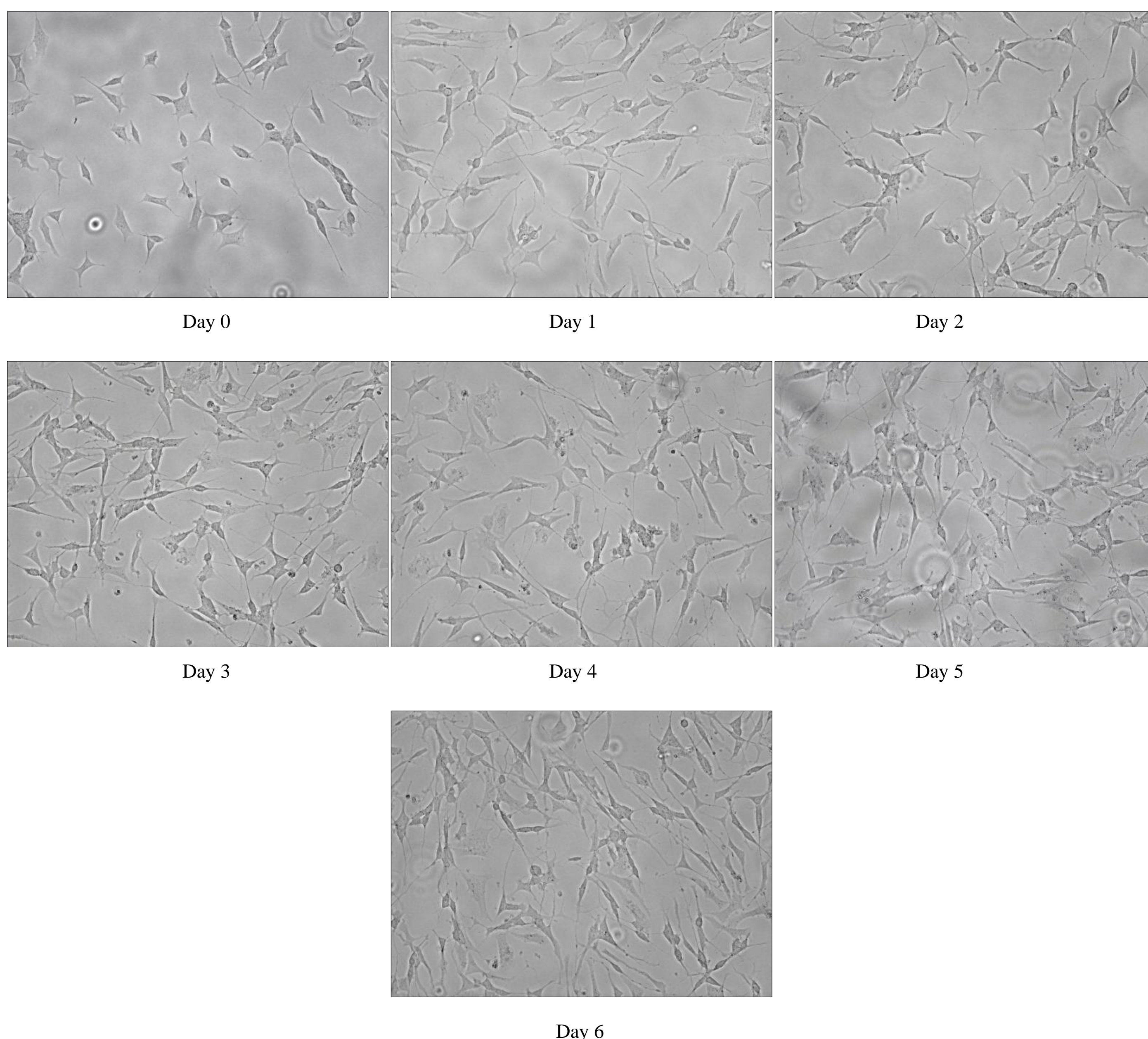

Fig 1: Differentiation SH-SY5Y to SH-SY5Y-neurons

Treatments

Human SHSY-5Y neurons were cultured in 96-well culture plates at a density of 15,000 cells/well, and incubated at 37 °C for 24 h. When Cells were approximately 80% confluent, media was removed and replaced by the different concentrations of plant extracts: 800 - 400 - 200 - 100 - 50 - 25 - 12.5 - 6.25 - 3.125 µg/mL (100 µL per well). Plate was incubated for 48 h at 37 °C.

MTT assay for assessing cell viability

After appropriate time intervals, the media was removed and replaced by 100 µL growth medium with 0.5 mg/mL MTT, and the plates were incubated for an additional 3 h at 37°C. Subsequently, the supernatant was removed and replaced by 100 µL of solubilization solution (50% DMF and 20% SDS) to dissolve the formazan crystals. The optical density (OD) was measured at 570 nm using a 96-well multiscanner autoreader. The results were presented as a percentage of viable cells as compared to the control.

Results

The results of the *in vitro* antiplasmodial activity on Plasmodium falciparum of extracts are presented in table 1.

The antimalarial activity of extracts was defined according to the IC_{50} values obtained. An extract showing an IC_{50} value ≤ 5 µg/mL was classified as highly activity. Extracts with IC_{50} values ≥ 5 µg/mL and ≤ 15 µg/mL were considered as promising activity. Extracts with IC_{50} values ≥ 15 µg/mL and ≤ 50 µg/mL were considered as moderately activity and those with IC_{50} values > 50 µg/mL inactive (Bero *et al*., 2009; Usman *et al*., 2012) [9, 10]. According the Selectivity Index (SI), all extracts are not toxic.

Table 1: Antiplasmodial and cytotoxicity activities

	IC^{50} (µg/mL)		
	SHSY-5Y Neurons	***P. falciparum* (K1 strain)**	**Selectivity Index (SI)**
Entandrophragma angolense	110	6	18
Griffonia simplifica	> 800	12.66	> 60
Uapaca guineensis	280	24.38	11

IC_{50}: Concentration of product that kill 50% of cells or P. falciparum

SI: corresponding to the ratio between the cytotoxic and antiparasitic activities of each sample tested. The values greater than 10 were considered indicative of lack of toxicity; however, the substances with values below 10 were considered toxic (Bézivin *et al*., 2003) [11].

Discussion

The main goal of this work was to investigate the potential antimalarial properties and cytotoxicity of some plants used in traditional medicine, against malaria and/or fever, and providing scientific validation for their use. Therefore, selection of plants was carried out based mainly on an ethnobotanical approach (Uddin *et al*., 2012) [12].

Ethanolic extract of *Entandrophragma angolense* and *Griffonia simplifica* have promising activity on K1 strains. These results justify the use of these plants in the treatment of malaria in traditional medicine. Ethanolic extract of *Uapaca guineensis* have moderately activity resistant strain K1.

However, it is important to note that *Uapaca guineensis* is frequently used to treat fever, generally associated to malaria. Therefore, an explanation for their lack of *in vitro* antimalarial inactivity could be that these plants may act as antipyretics or may enhance the immune system, rather than having direct antiparasitic activity (Bero and Quetin-Leclercq, 2011) [13].

The study of the cytotoxicity of these plants used in the traditional treatment of malaria has revealed that in addition to their antimalarial activity these plants are non-toxic to human neurons.

Conclusion

The search for new antimalarial drugs has become increasingly urgent due to plasmodial resistance to existing drugs. We have highlighted that plants are still a source of research to be exploited against infectious diseases such as malaria. *Entandrophragma angolense* and *G. simplicifolia* shows promise as a safer alternative.

These findings contribute to the development of plant-based antimalarial therapies with optimized therapeutic indices.

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