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Original Article

Antiplasmodial Activity of *Aidia genipiflora* and its Oleanane Triterpenoid, Oleanonic Acid

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ABSTRACT

Background: The emergence of resistance to frontline antimalarial therapies continues to undermine global malaria control efforts, especially in sub-Saharan Africa. The search for novel scaffolds from endemic medicinal plants remains a crucial strategy. **Objectives:** This study evaluated the antiplasmodial activity of *Aidia genipiflora* stem bark extract and its pentacyclic triterpenoid, oleanonic acid. **Materials and Methods:** The *in vitro* antiplasmodial activity of the methanolic extract and oleanonic acid was determined against chloroquine-resistant *Plasmodium falciparum* Dd2 were assessed using the SYBR Green I fluorescence assay. *In vivo* efficacy was investigated using the *Plasmodium berghei* ANKA in mice. Cytotoxicity of oleanonic acid was tested on human Red Blood Cells (RBCs) and HepG2 liver cells. Dihydroartemisinin (0.5-8 mg/kg) and saline served as positive and negative controls, respectively. **Results:** The extract and oleanonic acid exhibited notable *in vitro* activity with IC_{50} values of 6.28 µg/mL and 8.67 µg/mL, respectively. Oleanonic acid was non-toxic to RBCs (IC_{50}>100 µg/mL) but showed moderate toxicity to HepG2 cells (IC_{50}= 5.01 µg/mL), with selectivity indices of >11.53 and 0.59, respectively. *In vivo*, both extract and compound significantly (p<0.05) suppressed parasitaemia, with ED_{50} values of 14.76 mg/kg for the compound and 3.96 mg/kg for dihydroartemisinin. **Conclusion:** While oleanonic acid has been previously reported with antiplasmodial effects, this study provides the first evidence of its *in vivo* efficacy when isolated from *A. genipiflora*, highlighting this species as a novel source of antiplasmodial triterpenoids. The findings justify further mechanistic, pharmacokinetic, and structure-activity studies to optimize safety and efficacy.

Keywords: *Aidia genipiflora*, oleanonic acid, antiplasmodial, *Plasmodium falciparum*, *Plasmodium berghei*, triterpenoid, malaria.

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INTRODUCTION

Malaria remains a life-threatening infectious disease caused by protozoan parasites of the genus Plasmodium. It is characterized by fever, anemia, and splenomegaly due to intraerythrocytic invasion and destruction.[1] In 2022, there were an estimated 249 million cases globally, with the WHO African Region accounting for 94% of cases and 95% of deaths.[1] Ghana is among the top 15 high-burden countries, contributing significantly to morbidity and mortality despite ongoing interventions such as insecticide-treated nets, indoor residual spraying, and artemisinin-based combination Therapies (ACTs).[2]

The effectiveness of ACTs is increasingly threatened by resistance. Resistance to dihydroartemisinin-piperaquine has been reported in Southeast Asia, accompanied by delayed clearance after artesunate treatment.[3,4] Worryingly, recent reports of ACT failures in travellers returning from Africa suggest the early emergence of resistance on the continent.[5,6] These developments highlight the need to identify and optimize new antimalarial scaffolds.

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Natural products remain indispensable in antimalarial drug discovery, with quinine and artemisinin serving as classical examples.[7] Plant-derived secondary metabolites often possess diverse structures and bioactivities, making them attractive leads against resistant parasites.[9] Within this context, the Rubiaceae plant *Aidia genipiflora* (Hook.f.) Dandy has gained increasing pharmacological interest due to its bioactive constituents, including oleanonic acid, a pentacyclic oleanane-type triterpenoid.[9]

Oleanonic acid has been reported to exhibit antibacterial, resistance-modulatory, and anti-inflammatory activities.[10,11] Its immunomodulatory potential is relevant because inflammation and elevated cytokines are critical in malaria pathogenesis.[12] While Irungu *et al*[13] demonstrated antiplasmodial activity of oleanonic acid from *Ekebergia capensis*, no study has yet established its *in vivo* efficacy when isolated from *A. genipiflora*. This presents both a phytochemical novelty, introducing *A. genipiflora* as a new source, and a pharmacological contribution by validating its *in vivo* antimalarial potential.

The present study, therefore, investigated the *in vitro* and *in vivo* antiplasmodial activities of *A. genipiflora* stem bark extract and oleanonic acid, alongside cytotoxicity evaluation, to provide preclinical evidence supporting its potential as a lead compound in malaria drug discovery.

MATERIALS AND METHODS

Plant Material Collection and Authentication

Fresh stem bark of *Aidia genipiflora* (Hook.f.) Dandy was collected from the wild in the Central Region of Ghana (06°36.704′N, 000°42.659′W). The plant was authenticated by comparison with herbarium specimens deposited at the Faculty of Pharmacy and Pharmaceutical Sciences, Kwame Nkrumah University of Science and Technology (KNUST), Kumasi. A voucher specimen (UCC/PHM/AG/2023/SB01) was deposited at the Department of Pharmacognosy and Herbal Medicine, University of Cape Coast, for future reference.[9]

Extraction, Isolation, and Characterization of Oleanonic Acid

Air-dried and pulverized stem bark (3 kg) was Soxhlet-extracted with chloroform-methanol (1:4 v/v). The concentrated extract (AG extract) was fractionated over silica gel (70-230 mesh) using gradient elution with petroleum ether, ethyl acetate, and methanol. Fractions were pooled based on TLC profiles, and the ethyl acetate fraction was subjected to further purification to afford oleanonic acid. Structural elucidation was confirmed by 1D/2D NMR and MS data compared with literature.[9,13]

Parasite Strains and Animals

Plasmodium falciparum strains (chloroquine-sensitive 3D7 and chloroquine-resistant Dd2) and *Plasmodium berghei ANKA* strain were obtained from Noguchi Memorial Institute for Medical Research (NMIMR), Ghana. Healthy ICR mice (18-22 g) were housed under standard conditions with free access to food and water. All experimental protocols were approved by the Institutional Animal Care and Use Committee (IACUC), University of Cape Coast (Approval No. UCC/IACUC/2023/AG01).

In vitro Antiplasmodial Assay

Synchronized *P. falciparum* parasites were cultured in O^+ human red blood cells at 2% haematocrit using RPMI 1640 supplemented with 25 mM HEPES, 0.5% AlbuMAX II, 0.2% sodium bicarbonate, and 50 µg/mL hypoxanthine, under a mixed gas atmosphere (90% N_2, 5% CO_2, 5% O_2) at 37°C.[14,15]

Antiplasmodial activity was assessed using the SYBR Green I fluorescence assay, which measures parasite DNA content as a proxy for viability.[16,17] Briefly, parasites at 1% parasitaemia and 2% haematocrit were incubated with serial dilutions of AG extract or oleanonic acid (0.39-100 µg/mL) for 72 hr in 96-well plates. Artesunate and dihydroartemisinin served as positive controls, and 0.5% DMSO as vehicle control. Fluorescence was read at 485 nm excitation and 530 nm emission.

In vivo Antiplasmodial Assay

The 4-day suppressive test was performed following standard.[18,19] Mice were inoculated intraperitoneally with 1.2×10^6 *P. berghei*-infected RBCs. After 72 hr, they were randomized into groups ($n = 5$) and treated orally for four days with AG extract (50-800 mg/kg), oleanonic acid (3-150 mg/kg), or vehicle (10% Tween-80 in saline). Dihydroartemisinin (0.5-8 mg/kg) was used as a positive control.

Parasitaemia was determined from Giemsa-stained thin smears prepared on day 8. Percent parasitaemia and chemosuppression were calculated relative to controls:[20]

$$\text{Percentage chemosuppression} = \left[\frac{\text{Parasitaemia in control} - \text{Parasitaemia in treated}}{\text{Parasitaemia in contro}}\right] x\ 100$$

Cytotoxicity Assays

Cytotoxicity of oleanonic acid was evaluated on human RBCs (for haemolysis) and HepG2 liver cells using the MTT assay.[21,22] RBC haemolysis was quantified spectrophotometrically at 540 nm after 48 hr incubation, and HepG2 viability was measured after 72 hr exposure to serial dilutions of the compound. The Selectivity Index (SI) was calculated as:

$$SI = \frac{CC50\ (\text{mammalian cells})}{IC50\ (\text{parasites})}$$

Data Analysis

IC_{50} and CC_{50} values were obtained by non-linear regression of concentration-response curves (GraphPad Prism v9.1.5). Results were expressed as Mean±SEM of at least three independent

experiments. Statistical significance was determined by one-way ANOVA followed by Tukey's *post hoc* test, with $p \leq 0.05$ considered significant.

RESULTS AND DISCUSSION

In vitro Antiplasmodial Activity of Oleanonic Acid

Oleanonic acid (Figure 1), a pentacyclic triterpenoid isolated from *Aidia genipiflora*, demonstrated concentration-dependent inhibitory effects against the chloroquine-resistant *Plasmodium falciparum* Dd2 strain. Using the SYBR Green I fluorescence assay, the compound yielded IC_{50} values of 10.00 µg/mL and 7.34 µg/mL in two independent experiments, giving a mean IC_{50} of 8.67 µg/mL. In comparison, the reference drug artesunate exhibited markedly higher potency, with IC_{50} values of 2.75 ng/mL and 0.64 ng/mL, giving a mean IC_{50} of 1.70 ng/mL (Figure 2 and Table 1).

In vivo Antiplasmodial Activity

Effect of Aidia genipiflora Stem Bark Extract

Administration of the methanolic extract of *A. genipiflora* significantly suppressed parasitaemia in *Plasmodium berghei*-infected mice in a dose-dependent manner. Suppression ranged from 17.5% at 50 mg/kg to 94.2% at 800 mg/kg when compared with the vehicle-treated group (Table 2). These findings demonstrate the potent *in vivo* efficacy of the crude extract.

Effect of Oleanonic Acid

Oleanonic acid (3-150 mg/kg) produced significant, dose-dependent suppression of parasitaemia in *P. berghei*-infected mice $p<0.0001$). The compound exhibited an ED_{50} of 14.76 mg/kg, while dihydroartemisinin (DHA), used as a reference drug, was more potent with an ED_{50} of 3.96 mg/kg (Figures 3A and 3B).

On day 8, endpoint analysis showed that oleanonic acid induced a clear dose-dependent chemosuppression, though consistently lower than DHA at equivalent doses (Figures 4A and 4B)

These results reinforce the *in vivo* efficacy of both the extract and its constituent, suggesting possible additive or synergistic effects of triterpenoids, flavonoids, and alkaloids found in the crude extract.[9] These findings also indicate that oleanonic acid is effective in suppressing parasite multiplication *in vivo* and supports its potential as a scaffold for developing antimalarial agents, particularly in combination therapies.

Cytotoxicity and Selectivity Index

To assess safety, cytotoxicity of oleanonic acid was evaluated in human Red Blood Cells (RBCs) and HepG2 liver cells using the MTT assay. Oleanonic acid showed no toxicity to RBCs (CC_{50}>100 µg/mL), but moderate toxicity to HepG2 cells with a CC_{50} of 5.08 µg/mL (Table 3). These results correspond to a high selectivity index (SI>11.53) for RBCs and a low SI of 0.59 for HepG2 cells. According to the Medicines for Malaria Venture

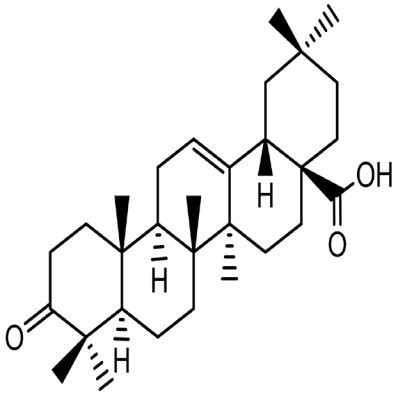

Figure 1: Chemical structure of oleanonic acid ($C_{30}H_{46}O_3$; molecular weight 454.7 g/mol).

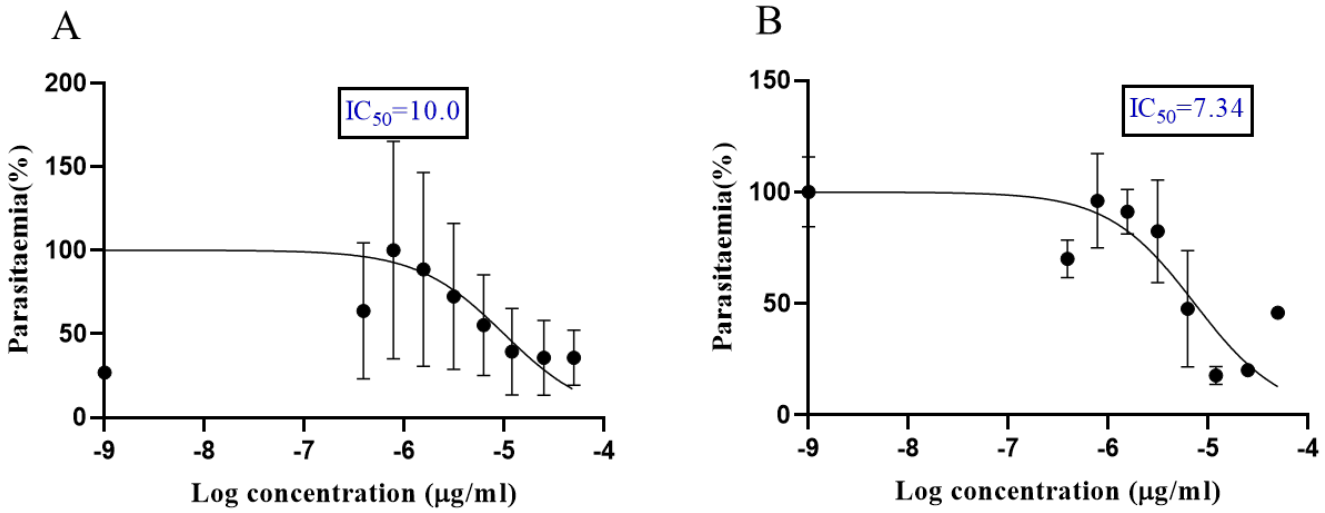

Figure 2: Dose-response inhibition curve showing percent parasitaemia after oleanonic acid treatment in initial experiment (A) and a repeated experiment (B).

Table 1: IC_{50} **values of artesunate and oleanonic acid against *P. falciparum* Dd2.**

Compound	IC_{50} (Trial 1)	IC_{50} (Trial 2)	Mean IC_{50}
Artesunate	2.75 ng/mL	0.64 ng/mL	1.70 ng/mL
Oleanonic acid	10.00 µg/mL	7.34 µg/mL	8.67 µg/mL

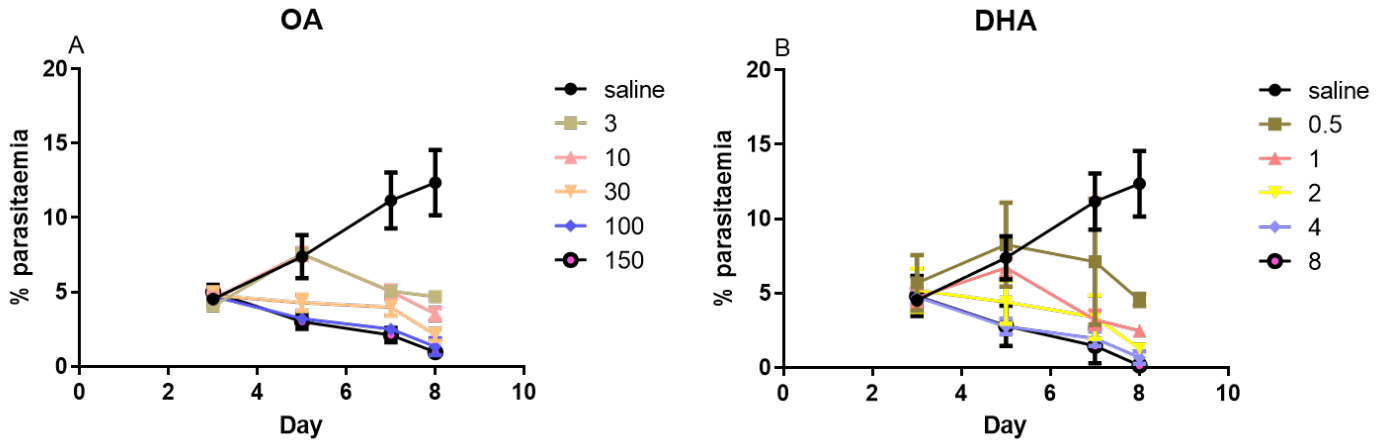

Figure 3: Daily parasitaemia curves in oleanonic acid-treated mice (A) and in DHA-treated mice (B) compared with vehicle control.

(MMV) criteria, an SI≥10 is desirable for lead compounds.[25] Although the HepG2 result indicates moderate cytotoxicity, the strong selectivity for RBCs suggests preferential activity toward parasitized erythrocytes, making oleanonic acid a promising, albeit partially selective, antiplasmodial candidate.

DISCUSSION

This study demonstrates that both the crude stem bark extract of *Aidia genipiflora* and the isolated triterpenoid oleanonic acid possess antiplasmodial activity. Although oleanonic acid exhibited only moderate *in vitro* potency (IC_{50} = 8.67 µg/mL) compared with artesunate, it produced significant *in vivo* efficacy *in Plasmodium berghei*-infected mice (ED_{50} = 14.76 mg/kg), with dose-dependent chemosuppression. Such differences between *in vitro* and *in vivo* activity are frequently observed in natural product pharmacology and may be attributed to improved bioavailability, host-immune interactions, or metabolism *in vivo*.[23,24]

The crude extract showed stronger parasitaemia suppression at higher doses, suggesting that multiple phytoconstituents contribute additively or synergistically to the overall activity. This aligns with the traditional use of multi-component plant remedies and underscores the therapeutic potential of *A. genipiflora* as a source of structurally diverse secondary metabolites.[7,25] Such synergism is of particular interest in malaria therapy, where combination effects can help delay or overcome resistance development.

The cytotoxicity results provide important lead-optimization insights. Oleanonic acid showed no toxicity toward RBCs (CC_{50}>100 µg/mL; SI>11.5), indicating good selectivity for

Table 2: Dose-dependent chemosuppression of AG extract against *P. berghei ANKA*.

Dose (mg/kg)	Parasitaemia (%)	Chemosuppression (%)
50	11.89	17.45 ± 8.49
100	6.40	55.56 ±1.40
200	3.28	77.26 ±1.69
400	2.10	85.42 ±1.69
800	0.83	94.18 ±1.51
Vehicle	14.40	-

parasitized erythrocytes-a desirable property for antimalarial agents.[26,27] However, the moderate toxicity observed against HepG2 cells (CC_{50} = 5.08 µg/mL; SI = 0.59) suggests possible hepatotoxic risk. While this raises caution, it does not invalidate the compound's potential; rather, it highlights the need for structure-activity relationship (SAR) studies, semi-synthetic analogues, and detailed toxicity profiling to expand its therapeutic window. Importantly, many frontline antimalarials, including artemisinin derivatives, also required optimization to balance efficacy and safety before clinical use.[28,29]

From a broader perspective, this work makes three key contributions. First, it provides the first *in vivo* evidence of the antiplasmodial efficacy of oleanonic acid when isolated from *A. genipiflora*, thereby adding species-specific pharmacological relevance. Second, it highlights the potential value of *A. genipiflora* as a source of antiplasmodial natural products. Third, it demonstrates that triterpenoids such as oleanonic acid, despite moderate *in vitro* activity, may possess favourable *in vivo* efficacy

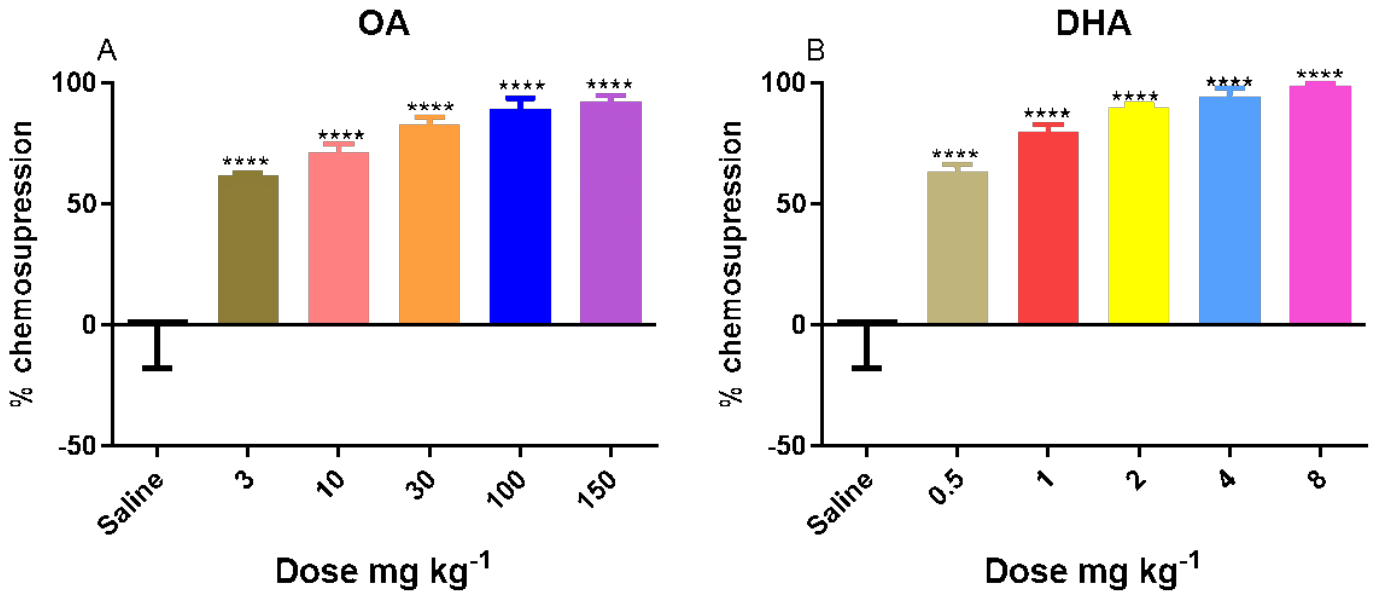

Figure 4: Percentage chemosuppression of oleanonic acid (3-150 mg/kg) (A) and DHA (0.5-8 mg/kg) (B).

Table 3: Cytotoxicity (CC_{50}) and Selectivity Index (SI) of oleanonic acid.

Cell type	Cell line	CC_{50} (µg/mL)	Parasite IC_{50} (µg/mL)	SI
Hepatic	HepG2	5.08	8.67	0.59
Erythrocytic	Human RBCs	>100	8.67	>11.53

profiles, making them worthy of further optimization within modern hit-to-lead frameworks.[30] Taken together, the results establish a scientific basis for further investigation of *A. genipiflora* and its constituents in antimalarial drug discovery. Oleanonic acid in particular represents a promising, though partially selective, scaffold that could be refined through medicinal chemistry approaches and tested in combination therapies to enhance efficacy and safety.

CONCLUSION

The stem bark extract of *Aidia genipiflora* and its isolated triterpenoid oleanonic acid exhibited significant antiplasmodial activity. While oleanonic acid showed moderate *in vitro* potency, its strong *in vivo* efficacy provides the first evidence of antiplasmodial activity from this species. The compound was non-toxic to erythrocytes but moderately toxic to HepG2 cells, warranting further optimization. These findings position *A. genipiflora* as a promising source of antimalarial agents and justify future studies on mechanism, structure-activity relationships, and combination therapies.

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ABBREVIATIONS

ACTs: Artemisinin-based combination therapies; **AG extract:** *Aidia genipiflora* extract; **APCs:** Article processing charges; **CC_{50}:** 50% cytotoxic concentration; **DHA:** Dihydroartemisinin; **DMEM:** Dulbecco's Modified Eagle's Medium; **DMSO:** Dimethyl sulfoxide; **ED_{50}:** 50% effective dose; **GHS:** Ghana Health Service; **HepG2:** Human hepatocellular Carcinoma Cell Line; **IC_{50}:** 50% Inhibitory Concentration; **IACUC:** Institutional Animal Care and Use Committee; **MMV:** Medicines for Malaria Venture; **MS:** Mass spectrometry; **NCI:** National Cancer Institute; **NMR:** Nuclear Magnetic Resonance; **NMIMR:** Noguchi Memorial Institute for Medical Research; **PBS:** Phosphate-Buffered Saline; **RBCs:** Red blood Cells; **SAR:** Structure-activity relationship; **SEM:** Standard Error of mean; **SI:** Selectivity Index; **TLC:** Thin-Layer chromatography; **WHO:** World Health Organization.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FUNDING

This research was partially supported by the Directorate of Research, Innovation and Consultancy (DRIC), University of Cape Coast, Ghana. The funding body had no role in the design of the study, data collection, analysis, interpretation of results, or manuscript preparation.

AUTHOR CONTRIBUTION

Daniel Anokwah (DA), Ebenezer Gyamfi (EG) and Elvis Asamani (EA) conceived and designed the study. DA, EA, Mark Tetteh-Tsifoanya (MTT), Felix Kwame Zoiku (FKZ) Daniel Obeng Mensah (DOM), and Silas Acheampong Osei (SAO) performed the *in vitro* antiplasmodial and cytotoxicity studies. DA, EA, EG, Reinhard Isaac Nketia (RIN), Jonathan Asante (JA), and Ernest Obese (EO) carried out the *in vivo* experiments. DA, Robert Peter Biney (RPB), and Elvis Ofori Ameyaw (EOA) analysed the data and contributed to interpretation of the results. Evelyn Asante-Kwatia (EAK), Benjamin Kingsley Harley (BKH) and RIN assisted with chromatographic separations and structural elucidation of compounds. DA drafted the manuscript, and all authors critically revised, read, and approved the final version of the manuscript.

CONSENT

All experimental procedures involving animals were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Cape Coast (Approval No. UCC/IACUC/2023/AG01). Consent and permission were also obtained from the management of the Animal House, Department of Biomedical Sciences, University of Cape Coast, for the use of facilities.

SUMMARY

This study evaluated the antiplasmodial activity of *Aidia genipiflora* stem bark extract and its isolated triterpenoid, oleanonic acid. Using SYBR Green I assay, oleanonic acid showed moderate *in vitro* activity against *Plasmodium falciparum* (IC_{50} = 8.67 µg/mL). *In vivo*, both extract and compound produced significant, dose-dependent suppression of *Plasmodium berghei*, with oleanonic acid achieving an ED_{50} of 14.76 mg/kg. Cytotoxicity assays revealed high selectivity toward erythrocytes but moderate HepG2 toxicity. These findings provide the first *in vivo* evidence of oleanonic acid from *A. genipiflora*, supporting its potential as a scaffold for antimalarial drug development.

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