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COLLEGE OF POSTGRADUATE STUDIES
2022/2023 PhD Thesis Abstract

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RT: **Biochemical Studies of Animalarial Leaf Fraction of *Urena lobata* Linn, and *in Silico* Analysis of the Bioactive Compounds on Anti-Plasmodial Target**

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AB: Malaria is a deadly disease caused by *Plasmodium* spp. that is transmitted by female *Anopheles* mosquitoes. The emergence of multidrug-resistant *P. falciparum* rendered current therapeutic approaches less effective, leading to a quest for novel anti-malarial agents. *Urena lobata* is a plant traditionally used to treat malaria in Enugu State, Nigeria. Therefore, this research focused on the biochemical studies of the antimalarial leaf fraction of *U. lobata*, and *in silico* analysis of the bioactive compounds on anti-plasmodial targets.

Crude methanol extract of *U. lobata* leaves was partitioned into hexane, ethyl acetate, butanol and aqueous fractions with successive solvent partition techniques. The most active anti-malarial fraction was determined using parasite density measurement. *In vitro* antioxidant activity was performed using total antioxidant capacity (TAC), 1, 1-diphenyl, 2-picrylhydrazyl (DPPH) and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assays. Subsequently, the most active fraction, *U. lobata* butanol leaf fraction (ULBLF) effects on parasitemia count in prophylactic, suppressive and curative experiments were investigated using 105 male Swiss albino mice. Mice were randomly divided into 7 groups of 5 mice per group. Group I: 0.2 mL distilled water; Group II: untreated; Group III: 10 mg/kg body weight (bwt) chloroquine; Group IV: 10 mg/kg bwt artesunate; Group V: 90 mg/kg bwt ULBLF; Group VI: 180 mg/kg bwt ULBLF and Group VII: 360 mg/kg bwt ULBLF. Groups II-VII were inoculated with *P. berghei*. Blood samples were collected for parasitemia count, *in vivo* antioxidant assays and haematological analysis. The ULBLF compounds were identified using gas chromatography-mass spectrometry (GC-MS) analytical method. Molecular docking of ULBLF compounds on selected anti-plasmodial druggable targets (*Pf*Hsp70, *Pf*LDH, *Pf*HT*1*, *Pf*Actin*1*, *Pf*Plasmepsin*2*, *Pf*Dihydroorotate dehydrogenase and *Pf*ATPase6), physicochemical and pharmacokinetic parameters were evaluated *in silico*. Data were analyzed using GraphPad Prism® 6.0. Multiple comparisons were done using one-way analysis of variance followed by Tukey-Kramer post hoc analysis. Data was considered statistically significant at $p < 0.05$.

Mice treated with ULBLF had a significantly reduced parasite density compared with other fractions. The ULBLF exhibited significantly high TAC and scavenging activities for DPPH

and ABTS compared with other fractions. Furthermore, ULBLF-treated mice in Groups III to VII had significantly reduced parasitemia count, GSH level, superoxide dismutase and catalase activities, while selected hematological indices were elevated when compared with Group II in all models. The GC-MS analysis identified 15 compounds. Molecular docking analysis showed that 9(1H)-phenanthrone-2,3,4,4a,4b,5,6,7,8,8a-decahydro- (PNTD) exhibited high ligand binding affinity against anti-plasmodial targets compared with other compounds. Physicochemical properties of PNTD did not violate Lipinski, Ghose, Egan and Verber rules. Pharmacokinetic predictive analysis indicated PNTD possesses high gastrointestinal absorption, blood-brain barrier permeability and no inhibitory effect on cytochrome P450s.

The ULBLF possesses substantial anti-malarial activity. The antimalarial mechanistic action was proposed to be through alteration of parasitized-red blood cell antioxidants, modulation of hematological indices and inhibition of anti-plasmodial targets attributable to its bioactive compounds. It is recommended that ULBLF be channeled towards formulating herbal anti-malarial drugs. In addition, PNTD could be considered in lead optimization for the development of anti-malarial drugs.

Keywords: Antioxidant, Bioactive compounds, Malaria, Molecular docking, Parasite protein, Plasmodium, *Urena lobata*

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Abbreviations: RFN: Researcher's Full Name, RD: Researcher's Department, RS: Researcher's School, RE: Researcher's Email, RAE: Researcher's Alternate Email, RP: Researcher's Phone Contact, RT: Registered Title, MS: Main Supervisor, ME: Main Supervisor's E-mail Address, SP: Main Supervisor's Phone Contact, CS: Co-Supervisor, CE: Co-Supervisor's E-mail Address, CP: Co-Supervisor's Phone Contact, AB: Abstract

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