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Research Article

Bioassay-Guided Isolation of Antiplasmodial Compounds from *Hypericum lanceolatum* Lam. (Hypericaceae) and Their Cytotoxicity and Molecular Docking

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In Cameroon, malaria is still the cause of several deaths yearly and leading to the continued search for new potent leads to fight against *Plasmodium falciparum*. Medicinal plants like *Hypericum lanceolatum* Lam. are introduced in local preparations for the treatment of affected people. The bioassay-guided fractionation of the crude extract of the twigs and stem bark of *H. lanceolatum* Lam. led to the identification of the dichloromethane-soluble fraction as the most active (with 32.6% of the parasite *P. falciparum* 3D7 survival) which was further purified by successive column chromatography to obtain four compounds identified by their spectrometric data as two xanthones 1,6-dihydroxyxanthone (**1**) and norathyriol (**2**) and two triterpenes betulinic acid (**3**) and ursolic acid (**4**). In the antiplasmodial assay against *P. falciparum* 3D7, the triterpenoids **3** and **4** displayed the most significant potencies with IC_{50} values of $2.8 \pm 0.8\,\mu g/mL$ and $11.8 \pm 3.2\,\mu g/mL$, respectively. Furthermore, both compounds were also the most cytotoxic against P388 cell lines with IC_{50} values of $6.8 \pm 2.2\,\mu g/mL$ and $2.5 \pm 0.6\,\mu g/mL$, respectively. Further insights on the inhibition method of the bioactive compounds and their drug-likeness were obtained from their molecular docking and ADMET studies. The results obtained help in identifying additional antiplasmodial agents from *H. lanceolatum* and support its use in folk medicine for the treatment of malaria. The plant might be considered as a promising source of new antiplasmodial candidates in new drug discovery.

1. Introduction

For several centuries, malaria remains a significant threat to public health around the world and especially in developing countries which are still struggling to control and eradicate it [1]. *Plasmodium falciparum* is one of the parasites that cause the most severe forms of disease around the world [2]. The observed resistance of *P. falciparum* to prescribed antimalarial drugs is the main challenge that causes the increased incidence of malaria around the globe [3, 4]. However, the literature survey indicated that several compounds with antimalarial potential have been isolated from natural sources including plants, mushrooms, or microbes [2, 5, 6]. In malaria-endemic countries like Cameroon, the local population refers to medicinal plants for their treatment, and an important number of plants from Cameroonian flora have been reported as promising sources of antiplasmodial compounds [7–12].

Hypericaceae is a large family of plants comprising eleven genera and almost 584 accepted species [13]. The genera *Hypericum*, *Harungana*, *Vismia*, and *Psorospermum* are amongst the most encountered and widely used by the traditional healers and local population for the management

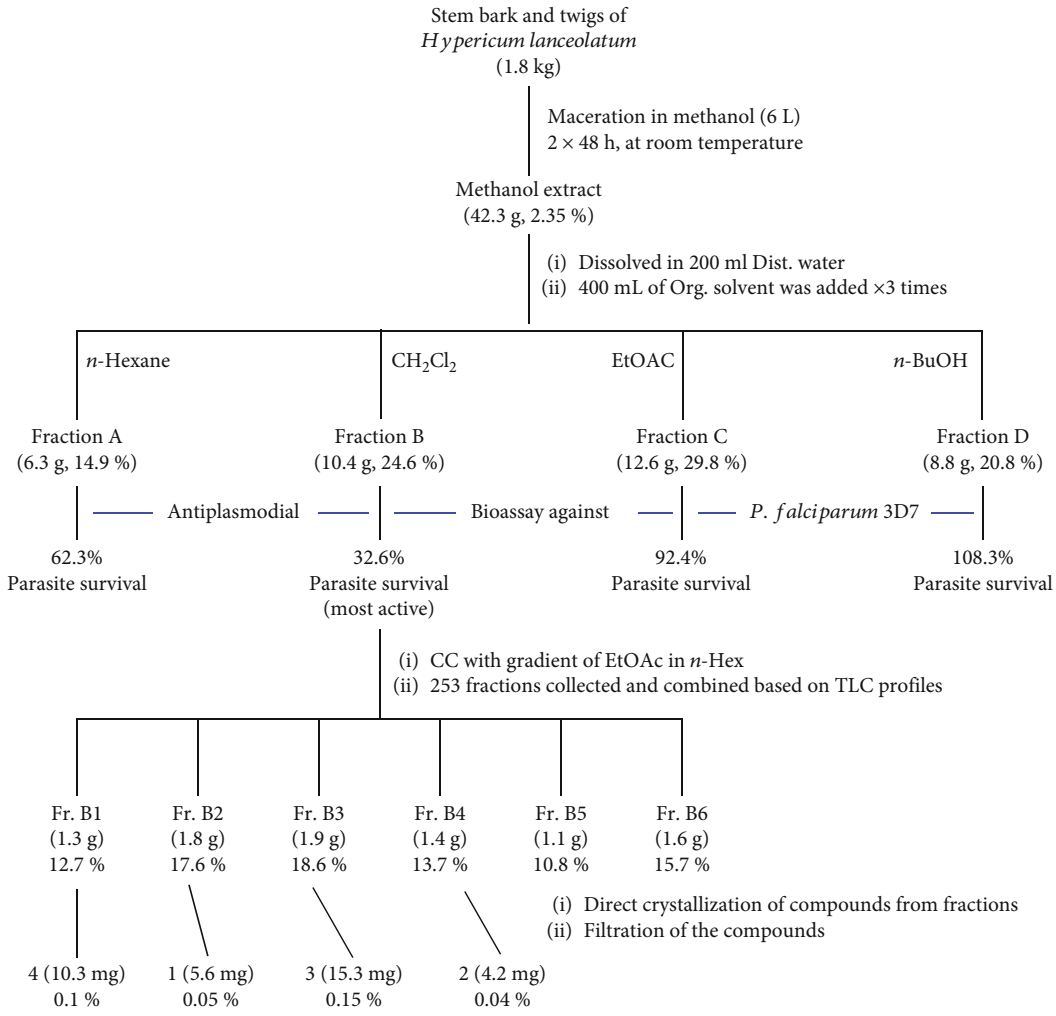


Figure 1: Flowchart of the isolation of bioactive compounds from *H. lanceolatum*.

of numerous affections including malaria, typhoid fever, wounds, inflammatory diseases, or microbial infections [14–16]. A recent paper has reported the *Hypericum* genus as a significant source of natural bioactive compounds with a large range of traditional use for the treatment of illnesses like fever, jaundice, pain, lung abscesses, poisoning from venomous animal bites, hepatic disorders, and dysentery [16]. Likewise, the plant *Harungana madagascariensis*, the sole species of the genus *Harungana*, is commonly used for the treatment of malaria in Cameroonian folk medicine, and its use is further supported by the antiprotozoal activities of its extracts reported in literature [17, 18]. In their recent review, Tepa et al. have compiled an updated list of Cameroonian medicinal plants introduced in local preparations of medicines for malaria-affected persons as well as their in vitro potency against *P. falciparum* strains [19]. From their meta-analysis, they concluded that the plant *Dacryodes edulis* (African pear) (Burseraceae) represents a significant opportunity to be considered in the treatment of uncomplicated malaria affection; furthermore, plants like *Entandrophragma congoënse* (Meliaceae), *Xylopia africana* (Annonaceae), *Vernonia guineensis* (Asteraceae), or *Strychnos icaja* (Loganiaceae) displayed interesting active compounds with promising activities in the fight against *P. falciparum* [19].

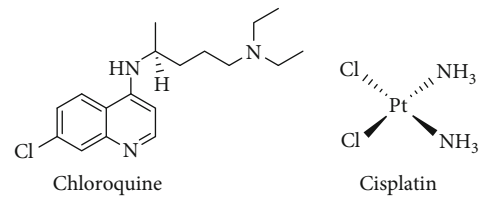


Figure 2: Structures of reference drugs used in this study.

Hypericum lanceolatum Lam. (Hypericaceae) is a rare species found in the mountainous region of West Cameroon [20]. The plant is widely used in traditional medicine by the local population for the treatment of malaria and several other ailments [21, 22]. Briefly, it is reported that the solution obtained from the maceration of its leaves with palm wine can help for the treatment of skin infections and epilepsies while its roots can be boiled in water and taken for the treatment of microbial infections like dysentery, venereal diseases, and gastrointestinal disorders [21, 22].

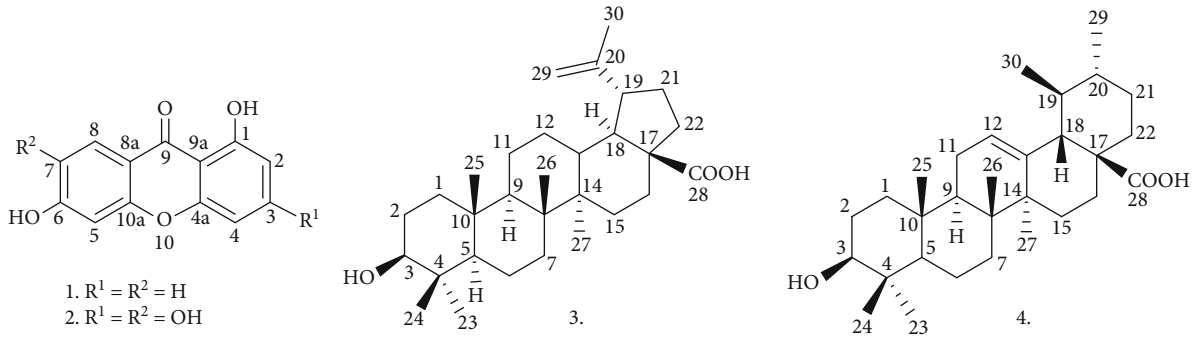


Figure 3: Chemical structures of compounds (**1**–**4**) isolated from *H. lanceolatum*.

Considering the few number of reports on phytochemical and biological investigations of the plant which is very rare and is important in traditional medicine, we have carried out further investigations of the twigs and stem bark of *H. lanceolatum* as continuity of our ongoing project on the identification of antiplasmodial lead compounds from Cameroonian medicinal plants [7–9]. The methanolic crude extract was partitioned using four organic solvents and tested against *P. falciparum* 3D7. The results showed that the dichloromethane-soluble fraction showed the lowest rate of parasite survival (most active) and was further investigated. We report herein the isolation and characterization of the bioactive compounds from the active fraction as well as their cytotoxicity, molecular docking, and ADMET analyses.

2. Materials and Methods

2.1. Plant Material. The twigs and stem bark of *H. lanceolatum* Lam. were harvested in February 2021 at Balatachi (5° 37′ 42″ N, 10° 12′ 03″ E, 1580 m), Bamboutos Subdivision, West Region, Cameroon. Its identification was done by a botanist at the National Herbarium of Cameroon by morphological comparison of the collected plant material with the previous one available in the database of the herbarium under voucher number 32356/HNC.

2.2. Extraction and Bioassay-Guided Fractionation. The extraction and isolation of the bioactive compounds were carried out following the chart in Figure 1. Briefly, the collected stem bark and twigs of *H. lanceolatum* were cut, air-dried, and ground to afford almost 1.8 kg of powder which were macerated twice in 6 L of methanol at room temperature for 48 h, each. After filtration and removal of the solvent under reduced pressure, we obtain 42.3 g of crude extract which was dissolved in 200 mL of distilled water and partitioned with *n*-hexane, dichloromethane, ethyl acetate, and *n*-butanol (three times each using 400 mL of organic solvent) to afford four main fractions A (6.3 g), B (10.4 g), C (12.6), and D (8.8 g), respectively. The four major fractions A–D were subjected to antiplasmodial assay, in which fraction B (dichloromethane-soluble fraction) was found to be the most active with 32.6% of parasite survival.

Further purification of fraction B (10.2 g) with silica gel column chromatography eluting with a gradient of ethyl acetate in *n*-hexane from the proportion 4 : 1 to 2 : 3 led to the collection of 253 fractions of 100 mL each, which were combined into six subfractions B1–B6. Four pure compounds (**1**–**4**) were filtered after their precipitation in four subfractions. For instance, ursolic acid (**4**, 10.3 mg) was obtained as a white powder in B1 (1.3 g, *n*-hexane/ethyl acetate 3 : 1), while an orange solid 1,6-dihydroxyxanthone (**1**, 5.6 mg) was precipitated in B2 (1.8 g, *n*-hexane/ethyl acetate 7 : 3). Likewise, another white powder identified as betulinic acid (**3**, 15.3 mg) was formed in B3 (1.9 g, *n*-hexane/ethyl acetate 13 : 7), and norathyriol (**2**, 4.2 mg) was a brown deposit in B4 (1.4 g, *n*-hexane/ethyl acetate 11 : 9).

Table 1: Yield of isolated bioactive compounds in the active fraction.

Compounds	Yield
1	0.05%
2	0.04%
3	0.15%
4	0.10%

2.3. Identification of Isolated Compounds. The four isolated compounds have been identified using their NMR data. Briefly, their ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker Advance III 500 MHz NMR spectrometer (Bruker, Rheinstetten, Germany) equipped with a 5 mm cryogenic DCH ($^{1}H/^{13}C$) probe. Chemical shifts are reported in parts per million (δ) using tetramethylsilane (TMS) (Sigma-Aldrich, Munich, Germany) as the internal standard, while coupling constants (J) were measured in hertz. Column chromatography was carried out on silica gel 230-400 mesh (Merck, Darmstadt, Germany) and silica gel 70-230 mesh (Merck).

2.4. Antiplasmodial Assay. The antiplasmodial evaluation of the fractions and pure compounds has been done following the protocol described in our recent publication [7].

2.4.1. Culture of the Parasite. Plasmodium falciparum 3D7 strain (chloroquine-sensitive) was obtained from the Biodefense and Emerging Infections (BEI) Research Resources (Manassas, VA) and were cultured in fresh O^{+} human red blood cells at 3% (v/v) hematocrit in RPMI 1640 culture media containing glutamax and $NaHCO_3$ (Gibco, UK), supplemented with 25 mM HEPES (Gibco, UK), 1x hypoxanthine

Table 2: Antiplasmodial and cytotoxicity activities of extracts and isolated compounds.

Compounds	Antiplasmodial (*Pf* 3D7)		Cytotoxicity (P388)	SI
	Parasite survival	IC_{50} (μg/mL)	IC_{50} (μg/mL)	
F1	62.3%	—	—	—
F2	32.6%	—	—	—
F3	92.4%	—	—	—
F4	108.3%	—	—	—
1	—	33.6 ± 0.1	17.6 ± 0.7	0.5
2	—	52.2 ± 4.6	21.8 ± 0.3	0.4
3	—	2.8 ± 0.8	6.8 ± 2.2	2.4
4	—	11.8 ± 3.2	2.5 ± 0.6	0.2
Chloroquine	—	0.07 ± 0.01	—	—
Cisplatin	—	—	0.5 ± 0.2	—

% parasite survival at 10 μg/mL. F1: hexane-soluble fraction; F2: CH_2Cl_2-soluble fraction; F3: EtOAC-soluble fraction; F4: *n*-butanol-soluble fraction; SI: selectivity index.

(Gibco, USA), 20 μg/mL gentamicin (Gibco, China), and 0.5% Albumax II (Gibco, USA). The obtained parasitic cultures were treated with 5% D-sorbitol to obtain only ring-stage parasitized cells, and 1% ring-stage of parasitemia was maintained for antimalarial assay.

2.4.2. In Vitro Antiplasmodial Assay. The fractions obtained from the partition of the crude extracts as well as the compounds isolated from the most active fraction were all tested *in vitro* for their antiplasmodial activities using the schizont maturation inhibition assay method. Briefly, the samples to be tested were dissolved into dimethyl sulfoxide (DMSO) to obtain the stock solutions (10 mM) which were subsequently diluted in triplicate with an RPMI medium which have been introduced in the prepared tested samples and parasite cultures (1% parasitemia and 1.5% hematocrit). After the successive dilution process and the mixture of samples with parasite cultures, the final concentration of DMSO per 100 μL culture per well was 0.1% while chloroquine (Figure 2) was used as the reference drug at a range of 1–0.0078 μM each and dimethyl sulfoxide (0.1%) was used as the negative control. All the prepared solutions were incubated for 72 h at 37°C and 5% CO_2-humidified atmosphere. Upon incubation, plates were checked under a microscope for the presence of trophozoite stage through evaluation of Giemsa-stained smears. The schizont inhibition (%) of each concentration of prepared samples was evaluated to determine the level of parasitemia using the formulae: schizont inhibition (%) = no.of schizonts (control) − no.of schizonts (test)/no.of schizonts (control) × 100. Subsequently, the concentration that inhibits 50% of parasite growth (IC_{50}) was determined and given as mean ± SD ($n = 3$).

2.5. In Vitro Cytotoxicity Assay on P388 Cell Line. The *in vitro* study of the cytotoxicity potency of the isolated compounds was performed using the P388 (mouse leukaemia) cell line which was obtained from the American Type Culture Collection (ATCC) (Rockville, MD, USA). The cells were arranged in 96-well plates at a density of 10^4 cells per well containing 100 mL of culture medium and then cultured for 24 h in the opti-MEM medium supplemented with 2 mM

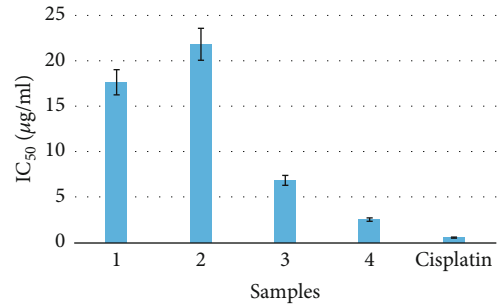


Figure 4: Cytotoxicity of tested compounds (**1**–**4**) and cisplatin against P388 cell lines.

Table 3: Binding energy to the antiplasmodium (5TBO) receptor.

Compounds	Binding energy (ΔG) kcal/mol
1	-8.4
2	-8.2
3	-2.6
4	-0.8
Chloroquine	-7.0

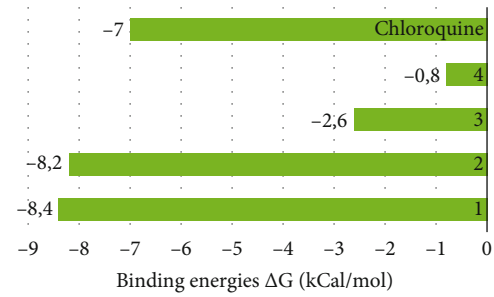


Figure 5: Binding affinity score of *H. lanceolatum* extracts against 5TBO receptor.

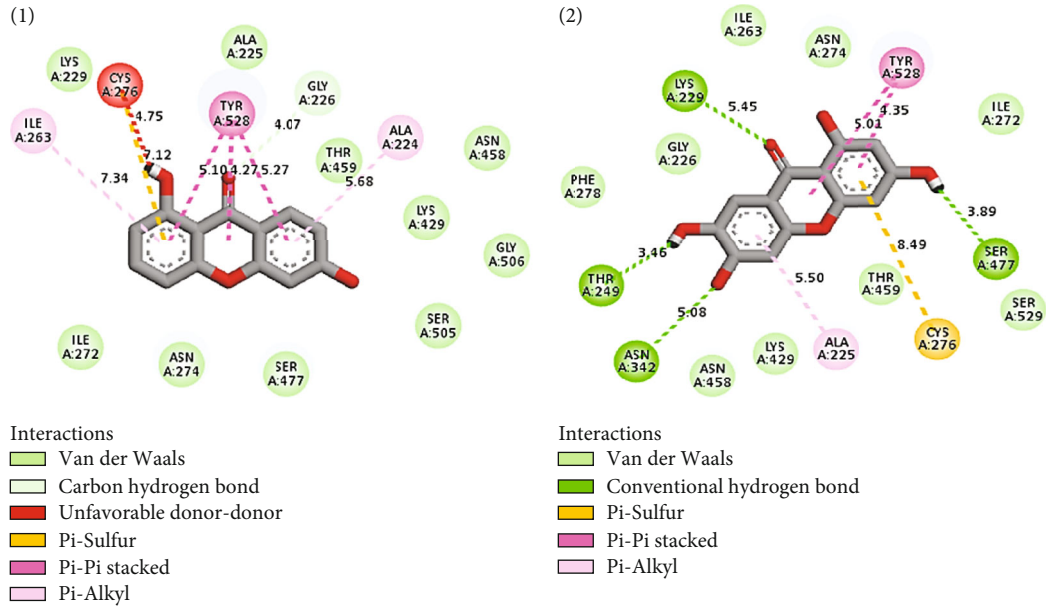


Figure 6: Interactions of compounds **1** and **2** with 5TBO receptor in its binding site.

glutamine (Gibco, Grand Island, NY, USA), streptomycin (50 μg/mL), penicillin (50 U/mL), and 5% fetal calf serum (Gibco). After the cell cultures were maintained at 37°C in an atmosphere saturated with 5% CO_2, the four tested compounds prepared at the concentration of 1 mg/mL by dissolving in the mixture DMSO/culture medium (1 : 9) were diluted in cell culture to reach the required concentrations (ranging from 1 to 100 μg/mL). The *in vitro* cytotoxic activity of the tested compounds was evaluated using the MTT assay for leukaemia cells. Cisplatin (Figure 2) was used as the positive control, the experiment was done in triplicate, and the results (IC_{50}) were expressed as mean ± SD ($n = 3$).

2.6. Statistical Analysis. The data from biological activities were treated using one-way ANOVA and SigmaPlot 12.5 software. The level of significance in all statistical tests was $p < 0.05$.

2.7. Selectivity Index (SI). The selectivity index (SI) was calculated to access the selectivity of the compounds to *P. falciparum* and is expressed as the ratio between the cytotoxic and antiparasitic activity (IC_{50}) of each tested sample.

2.8. Computational Methodology

2.8.1. Ligand Preparations. Four compounds that were isolated from *H. lanceolatum* were drawn with the ChemDraw® Ultra software [23] and optimized using the Avogadro® software [24] at the Molecular Mechanics Force Field '99 (MMFF99) level. Then, ligands were recorded in *.pdb* format with a specified hydrogen state. Chloroquine® was the standard used for this study.

2.8.2. Receptor Preparations. The selected target for the *in silico* investigation is the malaria *P. falciparum* receptor (5TBO.pdb).

The receptor was retrieved from the RCSB database at http://www.rcsb.org.

Using the BIOVIA® DS version 2021 software [25], the receptor was processed by removing water molecules and adding polar hydrogens as well as polar charges. Following that, the files were stored in a *.pdbqt* format.

2.8.3. Docking Protocol. The *.pdb* binding site for the receptor was consulted from the Computed Atlas of Surface Topography of Proteins (CASTp) webserver [26]. The binding sites revealed a catalytic triad of residues, A:249, A:342, and A:429.

2.8.4. Molecular Docking. Vina/PyRx® software tools were used to simulate molecular docking [27, 28]. We measured the receptor-binding affinities of isolated metabolites from *H. lanceolatum*.

2.8.5. Graphical Illustrations. The ligand interaction graphics from the Vina score were taken from the BIOVIA® DS version 2021 software [25], on an 8-core Debian 10 machine while the R statistical programming language's ggplot2 package [29] was used to create all graphical plots.

2.8.6. ADMET Property Prediction. The SMILES index formula of each isolated molecule in the ADMETLab 2.0 [30] web server allowed for the prediction of the absorption, distribution, metabolism, excretion, and toxicity properties.

3. Results and Discussion

3.1. Phytochemical Study. The antiplasmodial bioassay-guided investigation of *H. lanceolatum* twigs and stem bark methanolic extract led to the identification of the dichloromethane-soluble fraction as the most active one from which four distinct compounds (Figure 3) have been isolated as major leads with significant yields in the range

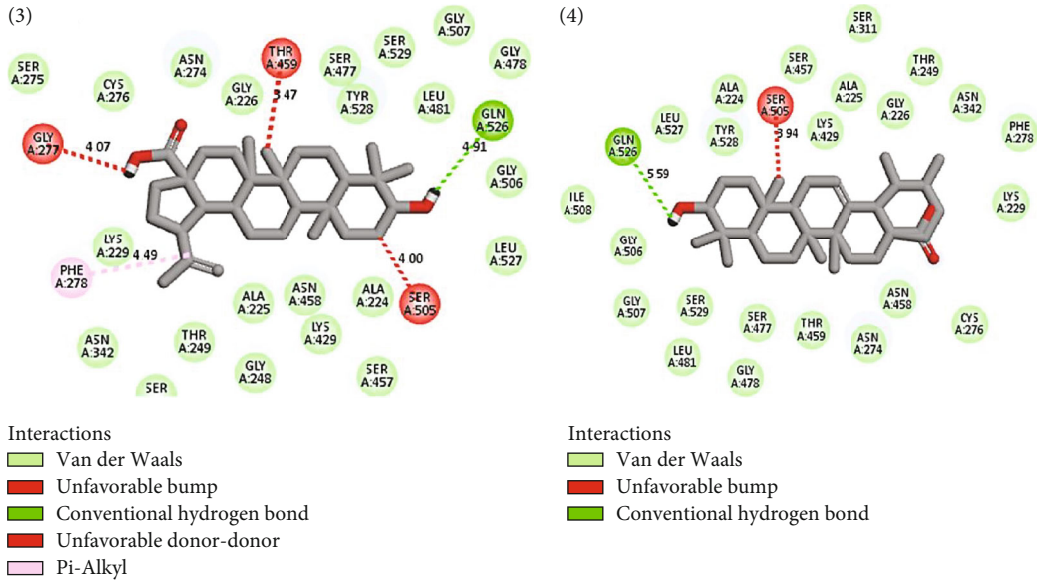


Figure 7: Interactions of compounds **3** and **4** with 5TBO receptor in its binding site.

of 0.05–0.15% of the dichloromethane active subextract (Table 1). The structure elucidation of the isolated compounds was conducted by exploration of their spectral data (see Figures S1–S8 on supplementary data) which allow their characterization as two xanthones including 1,6-dihydroxyxanthone (**1**) [31] and norathyriol (**2**) [32] as well as two triterpenes, namely, betulinic acid (**3**) [14, 33] and ursolic acid (**4**) [34].

Xanthones represent one of the main classes of compounds reported from the family Hypericaceae [15]. Unsurprisingly, two xanthones (**1** and **2**) have been obtained from the most active fraction. Although both compounds **1** and **2** are reported for the first time from the genus *Hypericum*, ten xanthones and derivatives have been reported from the previous phytochemical investigations of *H. lanceolatum* [21].

3.2. Antiplasmodial Activity. The major compound betulinic acid (**3**) obtained with the highest yield of 0.15% (Table 1) was also found to be the most active compound in the fraction with an IC_{50} value of $2.8 \pm 0.8\,\mu$g/mL against *P. falciparum* 3D7 and SI of 2.4 (Table 2). The compound has been previously described in *H. lanceolatum* [21] and also reported as one of its antimalarial agents with potency evaluated against the strains W2mef and SHF4 of *P. falciparum* [22].

The second triterpene ursolic acid (**4**) was obtained from the active fraction with a yield of 0.1% and a potency in terms of IC_{50} equal to $11.8 \pm 3.2\,\mu$g/mL and the lowest SI of 0.2. Our recent report on the investigations of Cameroonian medicinal plants for their antiplasmodial metabolites indicated that ursolic acid (**4**) possessed a weak antiplasmodial potency and inhibited the *Plasmodium* parasite through interactions with *Plasmodium* dihydroorotate dehydrogenase indicating important residue-hydrogen bond interactions with ASN274 (3.07), CYS276 (3.00), and GLY277 (2.32) [7].

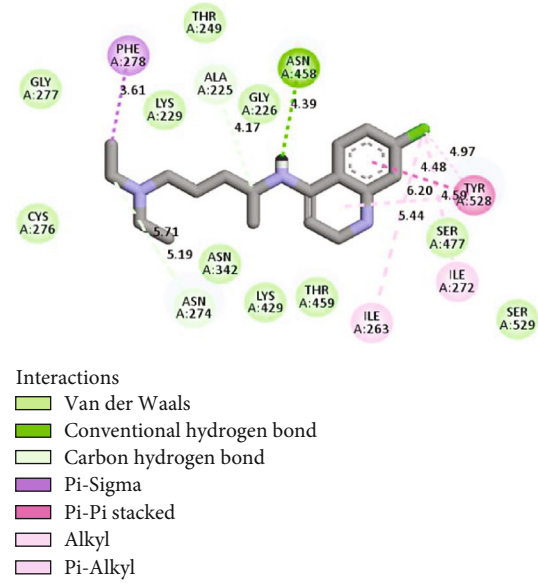


Figure 8: Interactions of chloroquine with 5TBO receptor in its binding site.

Compounds **1** and **2** were obtained with the lowest yields and were also the less active compounds from the fraction. That observation indicated that the potency of the fraction is supported by the activity of its major compounds identified as the two triterpenes here. Therefore, a synergistic action might be associated with their action mechanism in inhibiting the parasite *P. falciparum* 3D7.

3.3. Cytotoxicity Assay. The cytotoxicity test using the MTT assay method against P388 murine leukaemia cells (Table 2 and Figure 4) showed strong cytotoxic activity with IC_{50} values ranging from $2.5\,\mu$g/mL for compound **4** to $21.8\,\mu$g/mL for compound **2**. It is important to indicate that the two most active compounds **3** and **4** displayed the highest

Table 4: ADMET prediction results of isolated compounds of *H. lanceolatum* extract.

Absorption and distribution	1	2	3	4	Chloroquine
BBB (±)	++	+	+	—	+
GIA (±)	Good	Very good	Very poor	Very good	Good
Log S	–6.44	–4.9	–7.06	–4.94	-1.65
CYP450 2C19 inhibitor	No	No	No	No	No
CYP450 1A2 inhibitor	No	No	No	No	No
CYP450 3A4 inhibitor	No	No	No	No	No
CYP450 2C9 inhibitor	No	No	No	No	No
CYP450 2D6 inhibitor	No	No	No	No	No
Toxicity					
AMES mutagenesis	No	No	No	No	No
Acute oral/toxicity rating	Low	Low	Low	Low	Low
hERG toxicity	None	None	None	None	None
Carcinogenicity	Very low	Very low	Very low	Very low	Very low
Lipinski violation?	No	No	No	Yes	Yes

cytotoxicity and the SI values of 2.4 and 0.2, respectively, which obviously represented the highest and lowest SI values of this study.

However, even if the antiplasmodial test showed some promising results in searching for new antiplasmodial agents, it is important to notice that the high cytotoxicity of the active compounds against this tumour cell line might limit their use as a potential treatment. This observation can be linked to the low SI values of tested compounds (<10) which indicate an unfavourable safety window between the effective concentration against the parasite and the toxic concentration to the cell line [35]. Therefore, further investigations are required to increase the potency of the potent candidates isolated within this study and also to reduce their toxicity for the safe development of new potent antiplasmodial drugs.

3.4. Molecular Docking. Further insights on the antiplasmodial potency of the isolated compounds and evaluation of their drug-likeness have been provided by their *in silico* inhibition of the *P. falciparum* dihydroorotate dehydrogenase (PDB code: 5TBO) which is an important target enzyme associated to *P. falciparum* 3D7 used in this study for *in vitro* tests of isolated compounds [36].

Table 3 and Figure 5 describe the binding actions of the analyzed compounds with the binding energy associated with them. The result infers that the xanthones **1** and **2** (-8.4 kcal/mol and -8.2 kcal/mol, respectively) performed better than the standard Chloroquine® with the binding energy of -7.0 kcal/mol, but their *in vitro* potencies were lower than those of triterpenoids **3** and **4** (Table 2). This might be explained by the nature of the interactions of the compounds in the binding site of the receptor which is mostly π–π stacked bonds for the xanthones and conventional hydrogen bonds for the triterpenoids. Figures 6–8 better illustrate the standing of the isolated bioactive compounds performing better in binding activity than Chloroquine®, the standard drug used in this study.

From those results, we can suggest that the interactions of ligands with GLN526 (4.91 and 5.59), THR249 (3.46), SER477 (3.89), and ASN342 (5.08) through conventional hydrogen bonds in the binding site of *P. falciparum* dihydroorotate dehydrogenase might play an important role in the inhibitory mechanism of *P. falciparum* 3D7 (Figures 6 and 7).

3.5. ADMET Studies. The drug-likeness of the bioactive compounds isolated from *H. lanceolatum* was evaluated, and the results are compiled in Table 4 describing their adsorption, distribution, metabolism, excretion, and toxicity (ADMET) properties. The results show that the xanthones **1** and **2** have good absorptions properties with excellent water solubilities as advised by Falade et al. [37] that a potential drug should have water solubility within the range of 7 to 3 g/dm^3. Likewise, compounds **1**–**4** are reported to possess a noncompetitive drug metabolic mechanism as they are seen to not inhibit any of the cytochrome P450 enzymes. Based on their computational validation, compounds **1**–**4** are very less toxic if used as an antimalarial drug as the standard drug Chloroquine® (Table 4).

These results as for the *in vitro* cytotoxicity studies showed that the compounds deserve further investigations on further (tumour and normal) cell lines before a further conclusion on their safe use.

4. Conclusion

This paper deals with the antiplasmodial bioassay-guided investigations of the twigs and stem bark of *H. lanceolatum* from which four major active compounds identified as 1,6-dihydroxyxanthone (**1**), norathyriol (**2**), betulinic acid (**3**), and ursolic acid (**4**) have been isolated and displaying good to moderate antiplasmodial activity against the chloroquine-sensitive strain *P. falciparum* 3D7 as well as strong cytotoxicity against the P388 cell line. Furthermore, the *in silico* antiplasmodial evaluation of the isolated compounds was performed to provide further evidence of their action mechanism that

could support their potency, while the ADMET study of the isolated compounds showed that they displayed favourable drug-likeness parameters as leads. In addition to complementing the previous results reported, the results justify the use of the plant in folk medicine for the treatment of malaria and related symptoms indicating that the plant *H. lanceolatum* is a promising source of candidates requiring further pharmacological and pharmacokinetic investigations in the development of new potent drugs or phytomedicines for malaria.

Data Availability

The NMR data used to support the findings of this study are available on supplementary data.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Supplementary Materials

Figures S1 and S2 show the ^{1}H NMR and ^{13}C NMR spectra of compound **1**, respectively. Figures S3 and S4 display the ^{1}H NMR and ^{13}C NMR spectra of compound **2**, respectively. Similarly, Figures S5 and S6 show the ^{1}H NMR and ^{13}C NMR spectra of compound **3**, while Figures S7 and S8 show the ^{1}H NMR and ^{13}C NMR spectra of compound **4**, respectively. *(Supplementary Materials)*

References

[1] W. Amelo and E. Makonnen, "Efforts made to eliminate drug-resistant malaria and its challenges," *BioMed Research International*, vol. 2021, Article ID 5539544, 12 pages, 2021.

[2] G. M. Happi, P. K. Nangmo, L. C. Dzouemo, S. F. Kache, A. D. K. Kouam, and J. D. Wansi, "Contribution of Meliaceous plants in furnishing lead compounds for antiplasmodial and insecticidal drug development," *Journal of Ethnopharmacology*, vol. 285, article 114906, 2022.

[3] C. Rasmussen, P. Alonso, and P. Ringwald, "Current and emerging strategies to combat antimalarial resistance," *Expert Review of Anti-infective Therapy*, vol. 20, no. 3, pp. 353–372, 2022.

[4] M. Imwong, T. T. Hien, N. T. Thuy-Nhien, A. M. Dondorp, and N. J. White, "Spread of a single multidrug resistant malaria parasite lineage (*PfPailin*) to Vietnam," *The Lancet Infectious Diseases*, vol. 17, no. 10, pp. 1022-1023, 2017.

[5] G. M. Happi, L. Z. Meikeu, K. G. Sikam, L. C. Dzouemo, and J. D. Wansi, "Mushrooms (basidiomycetes) as a significant source of biologically active compounds for malaria control," *Natural Resources for Human Health*, vol. 2, no. 2, pp. 129–141, 2022.

[6] G. M. Happi, V. K. Ntabo, D. Soh, and J. D. Wansi, "Potential of *Streptomyces* in producing antiplasmodial lead compounds," *Natural Resources for Human Health*, vol. 3, no. 1, pp. 7–20, 2023.

[7] K. G. Sikam, G. M. Happi, S. A. Ahmed et al., "*In vitro* antiplasmodial, molecular docking and pharmacokinetics studies of specialized metabolites from *Tetrapleura tetraptera* (Fabaceae)," *South African Journal of Botany*, vol. 151, pp. 949–959, 2022.

[8] L. C. Dzouemo, G. M. Happi, S. A. Ahmed et al., "Chemical constituents of the bark of *Zanthoxylum gilletii* (Rutaceae) and their *in vitro* antiplasmodial and molecular docking studies," *Journal of Chemistry*, vol. 2022, Article ID 1111817, 10 pages, 2022.

[9] S. A. Ahmed, G. M. Happi, D. Soh, and S. Salau, "Molecular docling, pharmacokinetics and molecular dynamics simulation studies of some bioactive compounds isolated from *Entandrophragma congoënse* for antiplasmodial activity," *Asian Journal of Chemical Sciences*, vol. 12, no. 2, pp. 1–13, 2022.

[10] G. M. Happi, S. F. Kouam, F. M. Talontsi, S. Zühlke, M. Lamshöft, and M. Spiteller, "Minor secondary metabolites from the bark of *Entandrophragma congoënse* (Meliaceae)," *Fitoterapia*, vol. 102, pp. 35–40, 2015.

[11] G. M. Happi, B. T. Ngadjui, I. R. Green, and S. F. Kouam, "Phytochemistry and pharmacology of the genus *Entandrophragma* over the 50 years from 1967 to 2018: a 'golden' overview," *The Journal of Pharmacy and Pharmacology*, vol. 70, no. 11, pp. 1431–1460, 2018.

[12] G. M. Happi, F. M. Talontsi, H. Laatsch et al., "*seco*-Tiaminic acids B and C: identification of two 3,4-*seco*-tirucallane triterpenoids isolated from the root of *Entandrophragma congoënse* (Meliaceae)," *Fitoterapia*, vol. 124, pp. 17–22, 2018.

[13] Theplant list, 2022, March 2023, http://theplantlist.org/1.1/browse/A/Hypericaceae/.

[14] G. M. Happi, A. S. W. Mbobda, M. Frese et al., "A new phenylpropanoid glycoside from *Psorospermum tenuifolium* Kotschy (Hypericaceae)," *Trends in Phytochemical Research*, vol. 5, pp. 31–36, 2021.

[15] G. M. Happi, G. L. M. Tiani, B. Y. M. Gbetnkom et al., "Phytochemistry and pharmacology of *Harungana madagascariensis*: mini review," *Phytochemistry Letters*, vol. 35, pp. 103–112, 2020.

[16] G. I. Caldeira, L. P. Gouveia, R. Serrano, and O. D. Silva, "Hypericum genus as a natural source for biologically active compounds," *Plants*, vol. 11, no. 19, p. 2509, 2022.

[17] F. Kengni, S. P. C. Fodouop, D. S. Tala, M. N. Djimeli, C. Fokunang, and D. Gatsing, "Antityphoid properties and toxicity evaluation of *Harungana madagascariensis* Lam (Hypericaceae) aqueous leaf extract," *Journal of Ethnopharmacology*, vol. 179, pp. 137–145, 2016.

[18] E. O. Iwalewa, N. O. Omisore, C. O. Adewunmi et al., "Antiprotozoan activities of *Harungana madagascariensis* stem bark extract on trichomonads and malaria," *Journal of Ethnopharmacology*, vol. 117, no. 3, pp. 507–511, 2008.

[19] A. G. N. Tepa, P. Ambassa, L. S. Ayong, P. C. B. Nya, and C. A. Pieme, "The antiplasmodial potential of medicinal plants used in the Cameroonian pharmacopoeia: an updated systematic review and meta-analysis," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 4661753, 18 pages, 2022.

[20] J. Hutchinson and J. M. Dalziel, *Flora of West Tropical Africa*, R. W. J. Keay, Ed., vol. 1, part 1, 1954, Whitefriars, London, 1954.

[21] H. K. Wabo, T. K. Kowa, A. H. N. Lonfouo et al., "Phenolic compounds and terpenoids from *Hypericum lanceolatum*," *Records of Natural Products*, vol. 6, pp. 94–100, 2012.

[22] D. Zofou, T. K. Kowa, H. K. Wabo, M. N. Ngemenya, P. Tane, and V. P. K. Titanji, "*Hypericum lanceolatum* (Hypericaceae) as a potential source of new anti-malarial agents: a bioassay-guided fractionation of the stem bark," *Malaria Journal*, vol. 10, no. 1, p. 167, 2011.

[23] N. Mills, *ChemDraw Ultra 10.0 CambridgeSoft, 100 Cambridge Park Drive, Cambridge, MA 02140. http://www.cambridgesoft.com. Commercial Price: 1910fordownload, 2150 for CD-ROM; Academic Price: 710 for download, 800 for CD-ROM*, ACS Publications, 2006.

[24] M. D. Hanwell, D. E. Curtis, D. C. Lonie, T. Vandermeersch, E. Zurek, and G. R. Hutchison, "Avogadro: an advanced semantic chemical editor, visualization, and analysis platform," *Journal of Cheminformatics*, vol. 4, no. 1, p. 17, 2012.

[25] D. S. Biovia, *BIOVIA Workbook, Release 2017; BIOVIA Pipeline Pilot, Release 2017*, Dassault Systèmes, San Diego, 2021.

[26] W. Tian, C. Chen, X. Lei, J. Zhao, and J. Liang, "CASTp 3.0: computed atlas of surface topography of proteins," *Nucleic Acids Research*, vol. 46, no. W1, pp. W363–W367, 2018.

[27] S. Dallakyan and A. J. Olson, "Small-molecule library screening by docking with PyRx," in *Chemical Biology*, pp. 243–250, Humana Press, New York, NY, 2015.

[28] O. Trott and A. J. Olson, "AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading," *Journal of Computational Chemistry*, vol. 31, no. 2, pp. 455–461, 2010.

[29] H. Wickham, W. Chang, and M. H. Wickham, "Package 'ggplot2.' Create elegant data visualisations using the grammar of graphics," *Version*, vol. 2, no. 1, pp. 1–189, 2016.

[30] G. Xiong, Z. Wu, J. Yi et al., "ADMETlab 2.0: an integrated online platform for accurate and comprehensive predictions of ADMET properties," *Nucleic Acids Research*, vol. 49, no. W1, pp. W5–14, 2021.

[31] T.-X. Shi, S. Wang, K.-W. Zeng, P.-F. Tu, and Y. Jiang, "Inhibitory constituents from the aerial parts of *Polygala tenuifolia* on LPS-induced NO production in BV2 microglia cells," *Bioorganic & Medicinal Chemistry Letters*, vol. 23, no. 21, pp. 5904–5908, 2013.

[32] H. D. Locksley and I. G. Murray, "Xanthones from the heartwood of *Ochrocarpos odoratus*," *Phytochemistry*, vol. 10, no. 12, pp. 3179–3183, 1971.

[33] G. M. Happi, M. T. Yimtchui, S. A. Ahmed et al., "Chemical constituents from *Uapaca guineensis* (Phyllanthaceae) and the computational validation of their antileishmanial and anti-inflammatory potencies," *Journal of Chemistry*, vol. 2022, Article ID 7087110, 21 pages, 2022.

[34] S. C. N. Wouamba, G. M. Happi, M. N. Pouofo et al., "Antibacterial flavonoids and other compounds from the aerial parts of *Vernonia guineensis* Benth. (Asteraceae)," *Chemistry and Biodiversity*, vol. 17, no. 9, article e2000296, 2020.

[35] G. E. de Souza, R. V. Bueno, J. O. de Souza et al., "Antiplasmodial profile of selected compounds from malaria box: in vitro evaluation, speed of action and drug combination studies," *Malaria Journal*, vol. 18, no. 1, p. 447, 2019.

[36] M. A. Phillips, K. L. White, S. Kokkonda et al., "A triazolopyrimidine-based dihydroorotate dehydrogenase inhibitor with improved drug-like properties for treatment and prevention of malaria," *ACS Infectious Diseases*, vol. 2, no. 12, pp. 945–957, 2016.

[37] V. A. Falade, T. I. Adelusi, I. O. Adedotun, M. Abdul-Hammed, T. A. Lawal, and S. A. Agboluaje, "*In silico* investigation of saponins and tannins as potential inhibitors of SARS-CoV-2 main protease (M^{pro})," *In Silico Pharmacology*, vol. 9, no. 1, p. 9, 2021.