SEBHA UNIVERSITY JOURNAL OF PURE & APPLIED SCIENCES VOL.23 NO. 2 2024
DOI: 10.51984/JOPAS.V23I2.3085

مجلة جامعة سبها للعلوم البحتة والتطبيقية
Sebha University Journal of Pure & Applied Sciences

Journal homepage: www.sebhau.edu.ly/journal/jopas

In Silico Medicinal and Pharmacological Evaluation of Phytochemical Constituents from the Root Bark Extract of *Enantia Chlorantha* as Potential Antimalarial Drugs

*Sulyman Ibrahim[a], Halimat Lukman[b], Yusuf Ayipo[c], Halimah Babamale[a], Fatimah Abdulkadir[a], Abdulmumeen Hamid[b,d], Marili Zubair[a], Olubunmi Atolani[b]

[a]Department of Industrial Chemistry, Faculty of Physical Sciences, University of Ilorin, Ilorin, Nigeria
[b]Department of Chemical Sciences, College of Natural and Applied Sciences, Summit University, Offa, Nigeria.
[c]Department of Chemistry and Industrial Chemistry, Kwara State University, P M B, 1530 Malete Ilorin, Nigeria
[d]Department of Chemistry, Faculty of Physical Sciences, University of Ilorin, Ilorin, Nigeria

Keywords:
Plasmodium Falciparum
Drug-Likeness
Enantia Chlorantha
Enzyme
Ethnomedicine

ABSTRACT

Enantia chlorantha is a preferred medicinal plant among local healthcare providers in Nigeria for the treatment of malaria. While numerous studies have validated its potency, this updated report investigates the mechanistic and synergistic phytochemicals of the plant responsible for its antimalarial properties. The chemical composition of the methanol root bark extract was analyzed using Gas Chromatography-Mass Spectroscopy (GC-MS). The in silico pharmacological and toxicological profiles were determined using SwissADME and Protox II online servers. The simulation modeled the interaction between phytochemicals and Plasmodium falciparum dihydrofolate reductase-thymidylate synthase enzymes implicated in the pathogenic process of malaria via molecular docking. Docking was performed using PyRx-0.8 software coupled with AutoDock Vina. The findings indicate that N-[2-(2-Hydroxy-1-naphthylmethyleneamino)-4-methoxyphenyl] (-9.4 kcal/mol), squalene (-8.6 kcal/mol), curlone (-7.7 kcal/mol), tumerone (-7.8 kcal/mol), and ar-tumerone (-7.9 kcal/mol) demonstrated stronger binding affinities to the target protein compared to standard antimalarial medications such as artemether (-7.6 kcal/mol) and lumefantrine (-6.6 kcal/mol). These results were further confirmed by the phytochemicals' binding free energy ΛG_{Bind} (MMGBSA) values: N-[2-(2-Hydroxy-1-naphthylmethyleneamino)-4-methoxyphenyl] acetamide (-64.14 kcal/mol), squalene (-63.74 kcal/mol), and tumerone (-41.78 kcal/mol), compared to artemether (-23.39 kcal/mol) and lumefantrine (-43.01 kcal/mol). The toxicological profile suggests that the phytochemicals from E. chlorantha demonstrated reasonably low toxicity, comparable to standard drugs.

في التقييم الطبي والصيدلاني للمكونات الكيميائية لمستخلص لحاء جذر *Enantia* كلورانثا كأدوية محتملة مضادة للملاريا

*سليمان إبراهيم[a]، حليمة لقمان[b]، يوسف أيبو[c]، حليمة باباماليّ[a]، فاطمة عبد القادر[a]، عبد المؤمن حميد[b,d]، ماريلي زوبير[1]، أولوبونمي أتولاني [2]

[1]قسم الكيمياء الصناعية، كلية العلوم الفيزيائية، جامعة إيلورين، إيلورين، نيجيريا
[2] قسم العلوم الكيميائية، كلية العلوم الطبيعية والتطبيقية، جامعة ساميت، أوفا، نيجيريا.
[3]قسم الكيمياء والكيمياء الصناعية، جامعة ولاية كوارا،PMB ، 1530 ماليت إيلورين، نيجيريا
[4]قسم الكيمياء، كلية العلوم الفيزيائية، جامعة إيلورين، إيلورين، نيجيريا

الكلمات المفتاحية:
المتصورة المنجلية
التشابه الدوائي
إنانتيا كلورانثا
إنزيم
الطب العرقي

الملخص

إن نبات *Enantia Chlorantha* هو نبات طبي مفضل بين العديد من مقدمي الرعاية الصحية المحليين في نيجيريا لعلاج الملاريا .وفي حين أثبتت العديد من الدراسات فاعليته، فإن هذا التقرير الشامل المحدث الذي يبحث في المواد الكيميائية النباتية الميكانيكية والتآزرية للنبات المسؤول عن الادعاء بأنه مضاد للملاريا .تم تحليل التركيب الكيميائي لمستخلص لحاء جذر الميثانول باستخدام كروماتوغرافيا الغاز - مطيافية الكتلة (GC-MS).تم تحديد الملف الدوائي والسمية الحاسوبية باستخدام خادم ADME السويسري و Protox II

*Corresponding author.
E-mail addresses: ibrahim.sio@unilorin.edu.ng ,(H. Y. Lukman) lukman.halimat@summituniversity.edu.ng ,(Y. O. Ayipo), yusuf.ayipo@kwasu.edu.ng , (H. Fu. Babamale) babamale.hf@unilorin.edu.ng , (F. R. Abdulkadir) abdulkadir.fr@unilorin.edu.ng, (A. A. Hamid) hamid.aa@unilorin.edu.ng, (M. F. Zubair) marilizub@unilorin.edu.ng, (O. Atolani) atolani.o@unilorin.edu.ng

Article History: Received 24 March 2024 - Received in revised form 18 December 2024 - Accepted 22 December 2024

عبر الإنترنت .تحاكي المحاكاة الحالية التفاعل بين المواد الكيميائية النباتية وإنزيمات ثنائي هيدروفولات ريدوكتاز-ثيميديلات سينثاز في بلازموديوم فالسيباروم، والتي تورطت في العملية المرضية لعدوى الملاريا من خلال الالتحام الجزيئي .تم تنفيذ عملية الالتحام باستخدام برنامجPyRx-0.8 ، إلى جانب .AutoDock Vina تشير النتائج إلى أن(9.4-) [N-[2-(2-Hydroxy-1-naphthylmethyleneamino)-4-methoxyphenyl ، و(8.6-) squalene، و(7.7-) curlon، و(7.8-) tumerone، و(7.9-) ar-tumerone، لديها أقوى تقارب للبروتين مقارنة بأدوية مكافحة الملاريا القياسية، (7.6-) artemether و .(6.6-) lumefantrineوقد تم تأكيد ذلك من خلال قيم الطاقة الحرة الملزمة (MMGBSA) ΛGBind للمواد الكيميائية النباتية-2)-N[-2 .هيدروكسي-1-نفثيلميثيلينامينو-4-(ميثوكسيفينيل [أسيتاميد 64.14-) كيلو كالوري/مول(، سكوالين 63.74-) كيلو كالوري/مول (وتوميرون 41.78-) كيلو كالوري/مول (في حين أن الأدوية الضابطة أرتيميثير 23.39-) كيلو كالوري/مول (تظهر طاقة ارتباط أقل، ويظهر لومفرانتين 43.01-) كيلو كالوري/مول (طاقة ارتباط مماثلة للسكوالين 63.74-) كيلو كالوري/مول .(يشير الملف السبي للمواد الكيميائية النباتية إلى أن مركبات .E chlorantha أظهرت سمية منخفضة بشكل معقول والتي يمكن مقارنتها بالأدوية القياسية المستخدمة كدواء ضابط .تشير النتائج إلى أن المواد الكيميائية النباتية الموجودة في .E chlorantha يمكن أن تعمل كأدوية فعالة مضادة للملاريا.

1. Introduction

Malaria is a significant public health challenge, particularly in developing nations. The infection is caused by *Plasmodium* parasites, transmitted through the bites of infected female *Anopheles* mosquitoes. Among the *Plasmodium* species, *P. vivax* and *P. falciparum* pose the greatest threats, with *P. falciparum* responsible for the highest mortality rates. The efficacy of existing antimalarial drugs is diminishing due to the emergence of drug resistance, underscoring the urgent need for novel therapeutic agents [1–3].

Medicinal plants have been used for millennia to treat a variety of illnesses. Many malaria treatments have botanical origins, such as quinine, derived from *Cinchona* bark, which was widely used for decades. Recent research highlights the potential of botanically derived antimalarial agents [4]. For instance, an investigation into the therapeutic properties of *Prabchompo othaweep* identified 13 out of 48 crude extracts as effective against the K1 strain of *P. falciparum* [5]. Similarly, the aqueous fruit extract of *Terminalia arjuna* has shown antimalarial activity against *Plasmodium* parasites in both humans and animals [6].

In recent decades, artemisinin combination therapies (ACTs) have been pivotal in the treatment of uncomplicated malaria. While artemisinin derivatives remain highly effective against *P. falciparum* in most malaria-endemic regions, resistance to these drugs is emerging. Notably, artemisinin resistance is often accompanied by resistance to its partner drugs in ACTs, though these therapies remain effective against *P. vivax* and other malaria species [7–9].

Current priorities in malaria management include ensuring access to accurate diagnostics, effective treatments, and strategies to combat the emergence of resistance in *P. falciparum*. Without significant interventions, malaria prevalence is projected to remain high in the coming decades. This highlights the ongoing need for the discovery and development of new antimalarial agents [10].

Medicinal plants play a crucial role in the management of various illnesses. *Enantia chlorantha*, a medicinal plant widely used in Nigeria, is renowned for its biological and pharmacological properties, particularly its efficacy in treating uncomplicated malaria. Previous studies have demonstrated its significant antimalarial activity through in vitro and in vivo experiments using crude extracts [11–13]. This study seeks to evaluate the bioactivity of phytochemicals from the root bark of *E. chlorantha* for their potential to inhibit malaria-related proteins. The ultimate goal is to identify novel candidates for further development as antimalarial drugs.

2. Materials and Methods

2.1 Sample Collection and Preparation

The bark of *Enantia chlorantha* was collected from the Basin in Ilorin South Local Government Area, Kwara State, Nigeria. The plant was identified and authenticated at the Herbarium of the Department of Plant Biology, University of Ilorin, Nigeria. The collected plant materials were air-dried for two weeks, pulverized using a mortar and pestle, and stored in cellophane bags in a cool environment until further use.

2.2 Medicinal Plant Extracts.

The air-dried, crushed bark of *E. chlorantha* was subjected to cold methanol extraction for three days. The extract was filtered using Whatman No. 1 filter paper, and the solvent was evaporated using a rotary evaporator until a dry residue was obtained. The crude extract was stored in screw-cap glass vials and kept in a refrigerator at a temperature below 10 °C for subsequent analysis [15].

2.3 Phytochemical Identification

Preliminary phytochemical screening was performed to identify the chemical constituents of the bark extract. Established methods were used to test for alkaloids, tannins, phenols, flavonoids, quinone derivatives, saponins, cyanogenic compounds, and coumarins [15].

2.4 Gas Chromatography-Mass Spectroscopy Characterization of extract

The methanol extract of *E. chlorantha* bark was analyzed using GC-MS on an Agilent 19091S-433 system. The experimental conditions followed those previously described by [16].

2.5 Procedure for ADME Evaluation

The SwissADME tool was used to estimate the physicochemical properties, ADME parameters, and drug-likeness of the phytochemicals. Properties such as lipophilicity, water solubility, pharmacokinetics, and drug-like potential were predicted and compared to Momordicin I [17]. Canonical SMILES formulas for the phytochemicals were generated using ChemDraw software. These SMILES formulas were input into SwissADME (http://www.swissadme.ch/index.php) to determine the ADME properties.

2.6 Prediction of Toxicity using Protox II In-silico tool

The Toxicities profile was done using the Canonical SMILES formula via Protox II database available on this site https://tox-new.charite.de/protox_II/index.php?site=compound_input.

2.7 Computational Study

2.7.1 In Silico Molecular Docking

Proteins Retrieval, Prepping, and Active Site Identification

Artemether, an FDA-approved antimalarial drug was searched on chEMBL at (https://www.ebi.ac.uk/chembl/) to know its mechanism of action. Artemether, an inhibitor of *Plasmodium falciparum* dihydrofolate reductase-thymidylate synthase protein, was adopted as a standard protocol. The antimalarial properties of the phytochemical root bark extracts of E. chlorantha, which were already screened using Lipinski rules for drug development, were predicted by studying molecular interactions between the compounds and enzymes relevant to malaria. The protein data bank provided the crystal structures of the human Plasmodium falciparum dihydrofolate reductase-thymidylate synthase protein [PDB ID: 7F3Z]. The protein

structures were generated by removing water molecules and leftover ligands, except for the most active (control) ligand. The non-standard naming and connection of protein residues were also eliminated [18, 19].

The proteins were cleaned and chain A was used for molecular docking respectively. The binding site coordinates for the enzymes were obtained by determining the binding site attributes of the co-crystalized inhibitors using Discovery Studio Visualizer 20.0. Docking was done using AutoDock Vina 1.1.2, and each complex's best pose was documented [20].

2.7.2 Ligand Procurement

FDA-approved antimalaria drug Artemether and all phytochemical substances derived from the GC-MS methanolic extract of E. chlorantha root bark were obtained and stored in SDF format from the PubChem database (www.pubchem.com).

2.7.3 Docking and Post-Docking Analysis

The docking process was conducted using PyRx-0.8 software in conjunction with AutoDock Vina. Phytochemicals in the 7methanolic fraction of *E. chlorantha* were subjected to docking analysis to determine their interaction with the active site of Plasmodium falciparum dihydrofolate reductase-thymidylate synthase proteins. This was achieved by selecting the binding pocket of the phytoconstituents in a 2D structure of a co-crystallized protein obtained from the protein data bank. The binding pose with the greatest binding affinity was stored in the Protein Data Bank (PDB) format. Subsequently, the ligand-protein interactions were analyzed in Discovery Studio [21]. The binding free energies of the selected ligands in complexes Plasmodium falciparum dihydrofolate reductase-thymidylate synthase proteins were calculated using the MM-GBSA approach according to the procedure described by [22]

3. Results and Discussion:

The initial phytochemical screening of the methanolic extract of *Enantia chlorantha* root bark, as shown in Table 1, reveals the presence of alkaloids, tannins, terpenoids, saponins, phenolics, flavonoids, carbohydrates, and steroids. Glycosides, however, were not detected. These findings align with previous studies suggesting that the antimalarial properties of *E. chlorantha* are attributable to its phytochemical composition [23–25].

Gas Chromatography-Mass Spectroscopy (GC-MS) analysis identified 47 chemical compounds in the methanolic extract, with key phytoconstituents including ar-tumerone, tumerone, curlone, conessine, Z-(13,14-epoxy)tetradec-11-en-1-ol, and lup-20(29)-en-3-ol (Table 2). Among these, eight phytochemicals with druggable properties were selected for virtual screening to evaluate their antimalarial potential against artemether and lumefantrine, two FDA-approved antimalarial drugs.

Ar-tumerone, one of the druggable phytochemicals in *E. chlorantha*, has been reported to inhibit cancer cells in a dose-dependent manner, with IC_{50} values ranging from 11.0 to 41.81 mg/L. Similarly, tumerone, another abundant compound in the root bark, has demonstrated significant antioxidant and anti-inflammatory activities in previous studies [26, 27]. Curlone, accounting for 9.06% of the phytochemicals in *E. chlorantha*, also exhibits notable antioxidant and anti-inflammatory effects [28, 29]. Furthermore, conessine has been shown to reduce efflux pump activity in *Klebsiella pneumoniae* by a statistically significant margin (p-value < 0.001), indicating the pharmacological potential of *E. chlorantha*'s phytochemicals.

Medicinal plants have been integral to human history, offering a reservoir of lead compounds that contribute to the development of new drugs. These compounds are often highly effective, have fewer adverse effects, and are cost-efficient [30]. Examining the pharmacological basis of traditional medicinal plants and identifying their active phytochemicals is essential for modern drug development [31, 32].

The Swiss ADME tool facilitates the calculation of physicochemical descriptors and predicts ADME parameters, pharmacokinetic properties, drug-likeness, and medicinal chemistry compatibility of small compounds. This tool is instrumental in modern drug discovery [33].

Although prior studies have explored the *in vivo* and *in vitro* antimalarial potential of *E. chlorantha* [23–25], the specific phytochemicals responsible for these activities remain unclear. Tables 4 and 5 summarize the physicochemical parameters and lipophilicity traits of the phytochemicals in *E. chlorantha*.

Molecular weight is a critical factor in drug development, influencing processes such as intestinal absorption, blood-brain barrier penetration, elimination rates, and interactions with molecular targets [34]. Lipophilicity, often measured through partition coefficients (logP) or distribution coefficients (logD), is another key parameter in drug discovery. Higher lipophilicity, indicated by greater logP values, is associated with improved drug properties and efficacy [35]. Lup-20(29)-en-3-ol has the maximum molecular weight of 426.72 gmol-1, while Prop-2-ynyl has the lowest molecular weight of 39.06 gmol-1. All the compounds satisfied the physicochemical criteria. The phytochemicals have a number of hydrogen bond donors and acceptors that lies within the proposed range for both possible new and commercially available generic pharmaceuticals. The Lipinski, Gbose, Veber, Egan, and Mueller rule of five is a guideline for determining oral bioavailability. It states that a chemical should have a molecular weight below 500 gmol-1, a logP value below 5, and no more than 5 hydrogen bond donors and 10 hydrogen bond acceptors [36].

The higher consensus logP (ClogP) is also highly influential in all disciplines' molecular discovery endeavors (Table 5). Except for Stearic acid (5.93), Oleic acid (5.65), Lup-20(29)-en-3-ol (7.27), Clionasterol (7.24), Oleoyl chloride (6.42), and Octadecanal (6.17), all of the other phytochemicals had a ClogP value in the range of 6.98 - 7.24.

A molecule is solubility significantly depends on the choice of solvent, as well as the ambient temperature and pressure. The solubility breadth is defined as the saturation concentration, which is the point at which further addition of solute does not increase its concentration in the solution [16]. A medicine is classified as very soluble if the maximum dose strength can dissolve in 250 mL or less of water-based solution throughout a pH range of 1 to 7.5. Swiss ADME incorporates two topological methods for predicting water solubility. The first method involves using the ESOL model, which categorizes solubility on a logarithmic scale ranging from insoluble (<-10) to highly soluble (>0). The second method is based on Ali et al, 2012 work and categorizes solubility on the same logarithmic scale.

SwissADME utilizes topological and fragmental methods to forecast solubility (log S), categorizing values of -10 or below as insoluble and values of -4 or higher as soluble. Table 6 presents the water solubility properties of the phytochemicals found in *E. chlorantha*. The solubility of all phytochemicals suggests their capacity for bioabsorption, with the exception of Lup-20(29)-en-3-ol (-8.64), Clionasterol (-7.9), and Oleoyl chloride (-6.5), which exhibit low solubility.

The utilization of the P-gp substrate allows for the measurement of active efflux across biological membranes. The protein in question confers defense to the Central Nervous System (CNS) against deleterious agents and exhibits significant upregulation in malignant cells. Approximately 50% to 90% of drugs are metabolized by the five main isoforms, namely CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4. The inhibition of these particular types of enzymes is anticipated to be a prevalent factor in medication interactions related to the transportation and conversion of medicines throughout the body. The accumulation of medications or their byproducts might harm the processes of absorption, distribution, metabolism, and excretion (ADME) [16]. Except for sitosterol and stigmasterol, which exhibited low gastrointestinal (GI) absorption, the pharmacokinetics and drug similarity tests conducted using SwissADME showed that all other phytochemicals had high levels of GI absorption.

The blood-brain barrier (BBB) is a specialized network of blood vessels that regulates the transit of chemicals between the brain and blood inside the vascular central nervous system. Its main function is to prevent the circulation of medicines into the brain. Fourteen (14) of the enlisted compounds (29.79 %) are not permeable to the BBB while the remaining thirty-three (33) (70.21 %) are BBB permeant. Small molecule compounds may be able to cross this barrier provided their molecular weight is < 400 g/mol and hydrogen bond formation < 8 [37].

The localization of P-gp has a greater effect on restricting the

absorption of drugs from the bloodstream into the brain and from the intestinal lumen into epithelial cells, compared to its effect on aiding the excretion of drugs from hepatocytes and renal tubules into the adjacent luminal space. Due to its activation of the isoenzymes CYP2C19 and CYP2D6, there is a potential for aggregation or drug-drug interactions, resulting in possible toxicity [16]. Fortunately, most of the compounds are not P-gp substrate activator except N-[2-(2-Hydroxy-1-naphthylmethyleneamino)-4-methoxyphenyl] acetamide, Curlone and 10,11-dihydro-10-hydroxy-2,3dimethoxydibenz(b,f)oxepin.

Having a bioavailability score of 0.85, the drug-likeness parameter is deemed high as it satisfies the Lipinski, Verber, and Egan rule. The synthetic accessibility score of SwissADME is derived from the assumption that the presence of molecular fragments in readily attainable compounds is correlated with the ease of synthesis. The contribution of fragments to synthetic Accessibility is often advantageous for common chemical moieties, but detrimental for unusual ones.

The drug-likness and bioavailability score as well as medicinal chemistry properties result for the *E. chlorantha* compounds are displayed in Tables 8 and 9 respectively. The results show Ten compounds namely N-[2-(2-Hydroxy-1-naphthylmethyleneamino)-4-methoxyphenyl]acetamide, Dodecanoic acid, ar-Tumerone, Tumerone, Curlone, 4-((1E)-3-Hydroxy-1-propenyl)-2-methoxyphenol, Z-(13,14-Epoxy)tetradec-11-en-1-ol,10,11-dihydro-10-hydroxy-2,3dimethoxydibenz(b,f)oxepin, Conessine and Squalene obeyed the rules with only one violation at most indicating their greater feasibility as drug candidates. Results from medicinal chemistry are intended to enhance ongoing efforts in drug discovery. There is no need for concern regarding their Pan-Assay Interference Compounds (PAINS), indicating that they are highly specific compounds.

The progress in computer research has enabled *in silico* methodologies to provide substantial advantages for regulatory demands, risk assessments, and the pharmaceutical business in evaluating the safety profile of a chemical. ProTox-II is a predictive model that combines molecular similarity, pharmacophores, fragment propensities, and machine-learning algorithms to forecast different types of toxicity, including acute toxicity, hepatotoxicity, cytotoxicity, carcinogenicity, mutagenicity, immunotoxicity, adverse outcomes pathways (Tox21), and toxicity targets [38].

The *in silico* toxicological evaluation of *E. chlorantha* phytochemicals is shown in Table 10.

The result showed that N-[2-(2-Hydroxy-1-naphthylmethyleneamino)-4-methoxyphenyl] acetamide with a lethal dosage of 1000mg/Kg has tendency to induce immunotoxicity at a prediction probability of 0.90, Carcinogenicity at a prediction probability of 0.57, and Mutagenicity with a prediction probability of 0.70. Of the ten phytochemicals that obey Lipinski rules of drugs, ar-Tumerone, Dodecanoic acid, Tumerone, Curlone, Squalene, shows no tendencies to induce immunotoxicity, carcinogenicity, mutagenicity or general toxicities. Compounds of *E. chlorantha* demonstrated reasonably low toxicity across the end point toxicities reported. Artemether and Lumefantrine show relatively high tendency of 0.92 and 0.99 probability of inducing immunotoxicity (Table 10). Seven of the Phytochemicals that passed the ADMET test were subjected to molecular docking and MMGBSA binding energies analysis.

Bond interactions, including electrostatic, hydrogen, and hydrophobic interactions enhance the binding affinity and biological activity of complex molecules. These interactions also contribute to stabilizing targeted drug complexes' biochemical environment. Additionally, ligand-protein interactions involving a higher number of hydrogen bonds tend to form stronger complexes with increased binding affinity [39].

The binding affinities of the *Plasmodium falciparum* protein with a particular ligand indicates the ability of the ligands to inhibit the interaction between the *Plasmodium falciparum* and dihydrofolate reductase-thymidylate synthase proteins. Any action that disrupts their interaction creates an unsustainable environment in which the *Plasmodium falciparum* could thrive. Table 11 shows the binding affinities and MMGBSA binding energies of selected phytochemicals from *Enantia chlorantha*, artemether, and lumefantrine control drugs. The results of the interaction in Figures 1 – 7. A greater negative number indicates superior binding affinities. Seven (7) phytochemicals exhibited favorable docking scores relative to the controls were selected for post-docking MMGBSA validation following the docking process.

The results indicates that N-[2-(2-Hydroxy-1-naphthylmethyleneamino)-4-methoxyphenyl] (-9.4 kcal/mol), squalene (-8.6 kcal/mol), curlone (-7.7 kcal/mol), tumerone (-7.8 kcal/mol), ar-tumerone (-7.9 kcal/mol) shows the best affinity towards the protein and established significant interactions more than approved antimalarial drugs artemether (-7.6) and lumefantrine (-6.6) (Table 11). The higher docking scores of the selected ligands compared to standard inhibitors signify enhanced binding affinities to the protein. The binding free energy values (ΔG_{Bind}, MMGBSA) of the phytochemicals were confirmed as follows: N-[2-(2-Hydroxy-1-naphthylmethyleneamino)-4-methoxyphenyl] acetamide (-64.14 kcal/mol), squalene (-63.74 kcal/mol), and tumerone (-41.78 kcal/mol). In contrast, the control drugs exhibited lower binding energy: artemether (-23.39 kcal/mol) and lumefantrine (-43.01 kcal/mol), the latter showing binding energy comparable to that of squalene (-63.74 kcal/mol). This suggests enhanced binding affinities and inhibitory potentials of the chosen phytochemicals, aligning with docking scores and supporting the traditional use of *E. chlorantha* in Nigeria as an effective antidote for malaria infection.

Table 1: Phytochemicals Screening Results of Methanol Extract of *Enantia chlorantha* bark extracts

Phytochemicals	Qualitative test
Alkaloids	+
Saponins	+
Flavonoids	+
Tannins	-
Phenols	+
Reducing sugar	+
Glycosides	-

+ Present; - Absent

Table 2: Chemical Composition of Methanolic Fraction of *Enantia chlorantha* bark extracts

Peak	Retention time	% Composition	Chemical composition
1	5.53	0.56	2-Cyclopenten-1-one
2	6.20	0.66	2,4-Dihydroxy-2,5-dimethyl-3(2H)-furan-3-one
3	6.74	0.55	N-[2-(2-Hydroxy-1-naphthylmethyleneamino)-4-methoxyphenyl] acetamide
4	7.57	0.55	Butanoic acid
5	7.96	1.85	4H-Pyran-4-one
6	8.20	2.23	Benzoic acid
7	8.51	0.67	Catechol
8	8.57	0.87	Dianhydromannitol
9	8.70	0.41	Benzofuran
10	9.76	1.04	2-Methoxy-4-vinylphenol
11	10.44	1.3	1,2,3-Benzenetriol
12	10.51	0.66	Vanillin
13	11.90	4.1	Benzene
14	12.45	0.68	Cyclohexene
15	12.66	0.53	Dodecanoic acid
16	12.75	1.52	2H-Pyran-2-one
17	12.94	0.91	p-Menthane
18	13.64	0.99	Tricyclo[5.1.0.0(2,4)]octane-5-carboxylic acid
19	13.86	16.52	Ar-tumerone
20	13.97	7.58	Tumerone
21	14.27	1.39	Benzenebutanal
22	14.33	9.06	Curlone
23	14.40	3.2	Bicyclo[3.1.1]heptan-3-ol

24	14.45	2.42	4-((1E)-3-Hydroxy-1-propenyl)-2-methoxyphenol				en-1-ol
25	14.78	0.72	7-Oxabicyclo [4.1.0] heptane	40	21.64	0.49	10,11-Dihydro-10-hydroxy-2,3-dimethoxydibenz(b,f)oxepin
26	15.08	0.85	1H-Indene				
27	15.21	0.88	2(1H)-Naphthalenone	41	22.03	0.54	Oleoyl chloride
28	15.25	0.54	Prop-2-ynyl	42	22.60	1.48	12-Methyl-E,E-2,13-octadecadien-1-ol
29	15.64	1.28	Z,Z-8,10-Hexadecadien-1-ol				
30	16.04	0.55	Cyclohexanecarboxylic acid	43	23.16	7.57	Conessine
31	16.16	0.53	6Z-2,5,5,10-Tetramethyl-undeca-2,6,9-trien-8-one	44	23.54	0.52	Squalene
				45	23.70	1.52	2-Phenylethylamine
32	16.54	4.38	Palmitic acid	46	24.81	0.73	Octadecanal
33	16.92	1.56	3-Decen-5-one				
34	17.91	2.69	Linoleic acid				
35	18.18	1.44	Stearic acid				
36	18.24	5.1	Oleic Acid				
37	18.67	2.22	Lup-20(29)-en-3-ol				
38	19.76	1.03	gamma.-Sitosterol				
39	20.98	2.98	Z-(13,14-Epoxy) tetradec-11-				

The SMILES chemical formulas of the phytochemicals discovered in the methanolic fraction of *E. Chlorantha* are presented in Table 3. The SMILES formula was utilized for the *in silico* ADME and Toxicological profile presented in Table 4 to 11. The SMILES notations were derived from the chemical structure of each substance. Chemdraw 12.0 is a software program used for creating chemical structures and diagrams.

Table 3: Chemical Composition and SMILES formula of Druggable Compounds from the Methanol Extract of *Enantia chlorantha* bark

Chemical composition	**SMILES Formular**
N-[2-(2-Hydroxy-1-naphthylmethyleneamino)-4-methoxyphenyl] acetamide	CC(NC1=CC=C(OC)C=C1/N=C/C2=C3C=CC=CC3=CC=C2O)=O
ar-Tumerone	C/C(C)=C\C(C[C@@H](C1=CC=C(C)C=C1)C)=O
Tumerone	C/C(C)=C\C(CC(C1=CC=C(C)CC1)C)=O
Curlone	C/C(C)=C\C(CC(C1C=CC(CC1)=C)C)=O
10,11-dihydro-10-hydroxy-2,3dimethoxydibenz (b,f) oxepin	COC1=C(OC)C=C2C(OC3=CC=CC=C3C(O)C2)=C1
Lup-20(29)-en-3-ol	CC1(C)C(O)CC[C@]2(C)[C@@]3([H])CC[C@]4([H])[C@@]5([H])[C@H](C(C)=C)CC[C@@](C)5CC[C@](C)4[C@@](C)3CC[C@@]12[H]
Conessine	C[C@@]12[C@@]3([H])CC[C@]45CN(C)[C@@H](C)[C@@]4([H])CC[C@@]5([H])[C@]3([H])CC=C1C[C@@H](N(C)C)CC2
Squalene	C/C(C)=C\CC/C(C)=C/CC/C(C)=C/CC/C=C(CC/C=C(C)/CC/C=C(C)\C)\C

Table 4: Physicochemical Properties of the Druggable Phytochemicals in *Enantia chlorantha*

Phytochemicals	MW	Heavy atoms	Aromatic heavy atoms	Fraction Csp3	#Rotatable bonds	#H-bond acceptors	#H-bond donors	MR	TPSA
N-[2-(2-Hydroxy-1-naphthylmethyleneamino)-4-methoxyphenyl] acetamide	334.37	25	16	0.1	5	4	2	100.47	70.92
ar-Tumerone	216.32	16	6	0.4	4	1	0	69.75	17.07
Tumerone	218.33	16	0	0.53	4	1	0	70.88	17.07
Curlone	218.33	16	0	0.53	4	1	0	70.88	17.07
10,11-dihydro-10-hydroxy-2,3dimethoxydibenz(b,f)oxepin	272.3	20	12	0.25	2	4	1	74.92	47.92
Lup-20(29)-en-3-ol	426.72	31	0	0.93	1	1	1	135.14	20.23
Conessine	356.59	26	0	0.92	1	2	0	115.63	6.48
Squalene	410.72	30	0	0.6	15	0	0	143.48	0

Table 5: Lipophilicity Characteristics of the Druggable Phytochemicals in *Enantia chlorantha*

Phytochemicals	iLOGP	XLOGP3	WLOGP	MLOGP	Silicos-IT Log P	Consensus Log P
N-[2-(2-Hydroxy-1-naphthylmethyleneamino)-4-methoxyphenyl] acetamide	3.08	3.26	4.07	2.43	4.1	3.39
ar-Tumerone	3.12	3.98	4.02	3.68	4.38	3.84
Tumerone	3.19	3.33	4.21	3.37	4.04	3.63
Curlone	3.14	4.01	4.07	3.37	3.93	3.7
Lup-20(29)-en-3-ol	4.72	9.87	8.02	6.92	6.82	7.27
10,11-dihydro-10-hydroxy-2,3dimethoxydibenz(b,f)oxepin	2.83	2.58	2.76	1.87	2.92	2.59
Conessine	4.38	4.85	4.43	4.8	3.34	4.36
Squalene	4.38	4.85	10.6	4.8	3.34	4.36

Table 6: Water Solubility Characteristics of Druggable Phytochemicals in *E. chlorantha*

	ESOL				Ali				SILICOS-IT			
	Log S	Solubility		Class	Log S	Solubility		Class	Log S	Solubility		Class
Compounds	(ESOL)	mg/ml	mol/L		(Ali)	mg/ml	mol/L		SILICOS-IT	mg/ml	mol/L	
N-[2-(2-Hydroxy-1-naphthylmethyleneamino)-4-methoxyphenyl] acetamide	-4.11	2.59E-02	7.75E-05	MS	-4.42	1.26E-02	3.77E-05	MS	-6.59	8.52E-05	2.55E-07	PS
ar-Tumerone	-3.7	4.30E-02	1.99E-04	S	-4.04	1.97E-02	9.13E-05	MS	-4.45	7.76E-03	3.59E-05	MS
Tumerone	-3.03	2.05E-01	9.38E-04	S	-3.37	9.42E-02	4.31E-04	S	-3.1	1.75E-01	8.00E-04	S
Curlone	-3.46	7.64E-02	3.50E-04	S	-4.07	1.85E-02	8.49E-05	MS	-2.9	2.77E-01	1.27E-03	S
Lup-20(29)-en-3-ol	-8.64	9.83E-07	2.30E-09	PS	-10.22	2.58E-08	6.05E-11	I	-6.74	7.69E-05	1.80E-07	PS
10,11-dihydro-10-hydroxy-2,3dimethoxydibenz(b,f)oxepin	-3.47	9.32E-02	3.42E-04	S	-3.23	1.59E-01	5.82E-04	S	-4.66	6.01E-03	2.21E-05	MS
Conessine	-5.04	3.25E-03	9.11E-06	MS	-4.72	6.79E-03	1.90E-05	MS	-4.06	3.13E-02	8.79E-05	MS
Squalene	-5.04	3.25E-03	9.11E-06	MS	-4.72	6.79E-03	1.90E-05	MS	-4.06	3.13E-02	8.79E-05	MS

S – Soluble, MS – Moderately Soluble, VS – Very Soluble, PS – Partially Soluble

Table 7: Pharmacokinetics Properties of Druggable Phytochemicals in *Enantia chlorantha*

Phytochemicals	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	log Kp (cm/s)
N-[2-(2-Hydroxy-1-naphthylmethyleneamino)-4-methoxyphenyl] acetamide	High	Yes	No	Yes	Yes	Yes	Yes	Yes	-6.03
ar-Tumerone	High	Yes	No	No	No	No	No	No	-4.79
Tumerone	High	Yes	No	No	No	Yes	No	No	-5.27
Curlone	High	Yes	No	No	Yes	Yes	No	No	-4.78
Lup-20(29)-en-3-ol	Low	No	No	No	No	No	No	No	-1.9
Conessine	High	Yes	No	No	No	No	No	No	-5.03
10,11-dihydro-10-hydroxy-2,3dimethoxydibenz(b,f)oxepin	High	Yes	Yes	Yes	Yes	No	Yes	Yes	-6.13
Squalene	High	Yes	No	No	No	No	No	No	-5.03

Table 8: Drug-likeness and Bioavailability Score of Druggable Phytochemicals in *E. chlorantha*

Phytochemicals	Lipinski #violations	Ghose #violations	Veber #violations	Egan #violations	Muegge #violations	Bioavailability Score
N-[2-(2-Hydroxy-1-naphthylmethyleneamino)-4-methoxyphenyl] acetamide	0	0	0	0	0	0.55
ar-Tumerone	0	0	0	0	1	0.55
Tumerone	0	0	0	0	1	0.55
Curlone	0	0	0	0	1	0.55
Lup-20(29)-en-3-ol	1	3	0	1	2	0.55
10,11-dihydro-10-hydroxy-2,3dimethoxydibenz(b,f)oxepin	0	0	0	0	0	0.55
Conessine	1	0	0	0	0	0.55
Squalene	1	0	0	0	0	0.55

Table 9: Medicinal Chemistry Properties of Druggable Phytochemicals in *Enantia chlorantha*

Phytochemicals	PAINS #alerts	Brenk #alerts	Leadlikeness #violations	Synthetic Accessibility
N-[2-(2-Hydroxy-1-naphthylmethyleneamino)-4-methoxyphenyl] acetamide	0	1	0	2.97
ar-Tumerone	0	1	2	2.4
Tumerone	0	1	1	4.3
Curlone	0	1	2	4.17
Lup-20(29)-en-3-ol	0	1	2	5.49
10,11-dihydro-10-hydroxy-2,3dimethoxydibenz(b,f)oxepin	0	0	0	3.43
Conessine	0	1	2	5.84
Squalene	0	1	2	5.84

Table 10: *In silico* Toxicological Profile of Druggable Phytochemicals in *E. chlorantha*

Compound Name	LD_{50} value and Tox Class	Prediction Accuracy (%)	Immunotoxicity	Carcinogenicity	Mutagenicity	Cytotoxicity
N-[2-(2-Hydroxy-1-naphthylmethyleneamino)-4-methoxyphenyl] acetamide	1000 mg/Kg **4**	67.38	Active (0.90)	Active (0.57)	Active (0.70)	Active (0.73)
ar-Tumerone	2000 mg/Kg **4**	68.07	Inactive	Inactive	Inactive	Inactive
Tumerone	2500 mg/Kg **3**	68.07	Inactive	Inactive	Inactive	Inactive
Curlone	4600 mg/Kg **5**	69.26	Inactive	Inactive	Inactive	Inactive
10,11-dihydro-10-hydroxy-2,3dimethoxydibenz (b,f) oxepin	500 mg/Kg **4**	67.38	Active (0.50)	Inactive	Active (0.59)	Inactive
Conessine	390 mg/Kg **4**	100	Active (0.99)	Inactive	Inactive	Inactive
Squalene	5000 mg/Kg **5**	100	Inactive	Inactive	Inactive	Inactive
Artemether	567 mg/Kg **4**	100	Active (0.92)	Inactive	Inactive	Inactive
Lumefantrine	5000 mg/Kg **3**	67.38	Active (0.99)	Inactive	Inactive	Inactive

Table 11: Binding Energies Profile of the Phytochemicals towards *Plasmodium falciparum* dihydrofolate reductase-thymidylate synthase proteins

Phytochemicals in *E. chlorantha*	Binding Energy (Affinity) (kcal/mole)	MM-GBSA (ΔG_{Bind}) (kcal/mole)
N-[2-(2-Hydroxy-1-naphthylmethyleneamino)-4-methoxyphenyl] acetamide	-9.4	-64.14
Squalene	-8.6	-63.74
Ar-tumerone	-7.9	-34.73
Tumerone	-7.8	-41.78
10,11-Dihydro-10-hydroxy-2,3-dimethoxydibenz(b,f)oxepin	-7.8	-32.07
Curlone	-7.7	-37.85
Artemeter	-7.6	-23.39
Lumefrantine	-6.6	-43.01

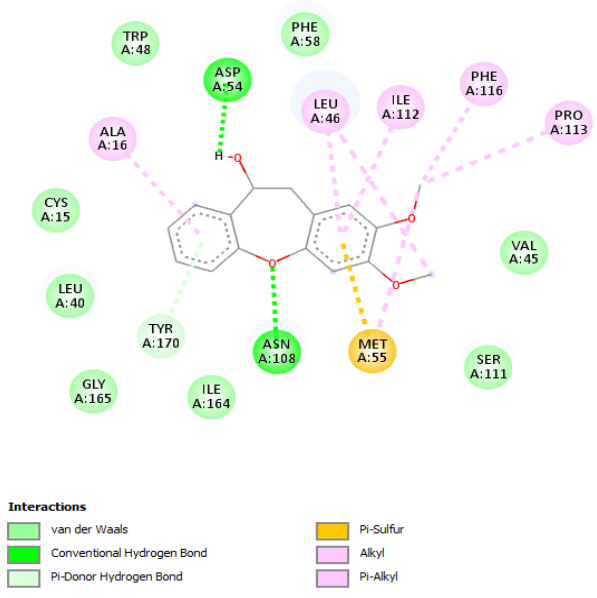

Figure 1: 2D Interaction of *P. falciparum* dihydrofolate reductase-thymidylate synthase proteins binding pockets with 10,11-dihydro-10-hydroxy-2,3-dimethoxydibenz (b,f) oxepin

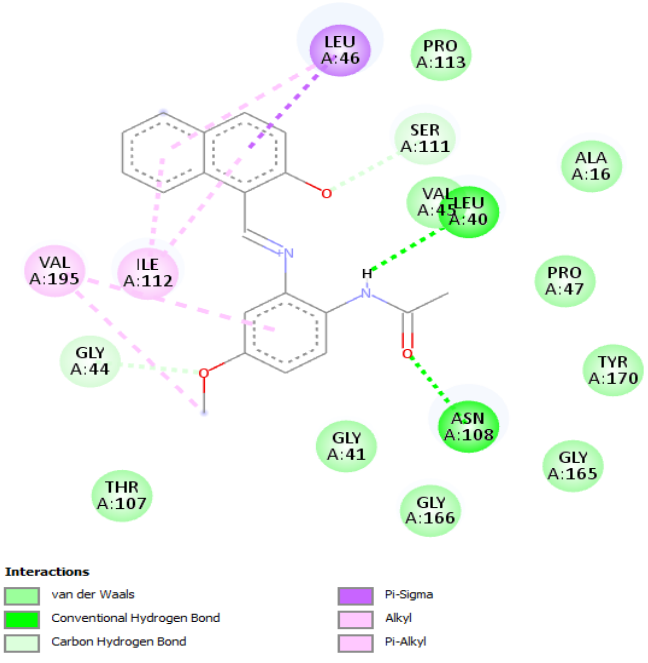

Figure 2: 2D Structure of the *P. falciparum* dihydrofolate reductase-thymidylate synthase proteins binding pockets with N-[2-(2-Hydroxy-1-naphthylmethyleneamino)-4-methoxyphenyl] acetamide

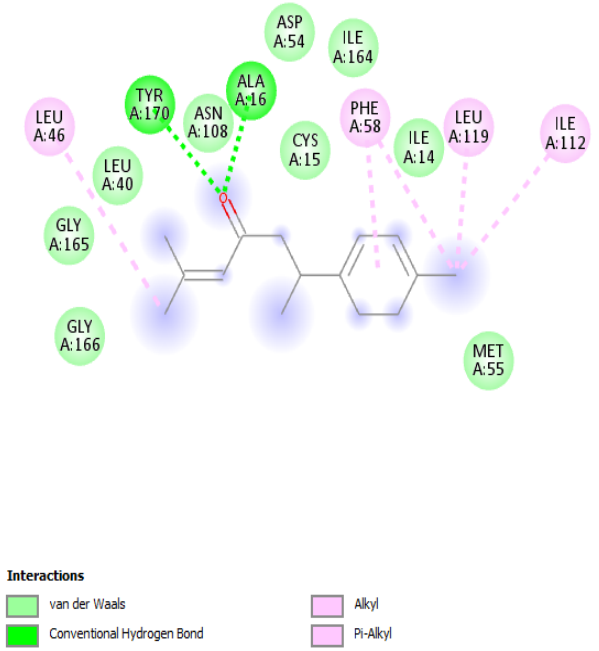

Figure 3: 2D Structure of the *P. falciparum* dihydrofolate reductase-thymidylate synthase proteins binding pockets with Turmerone

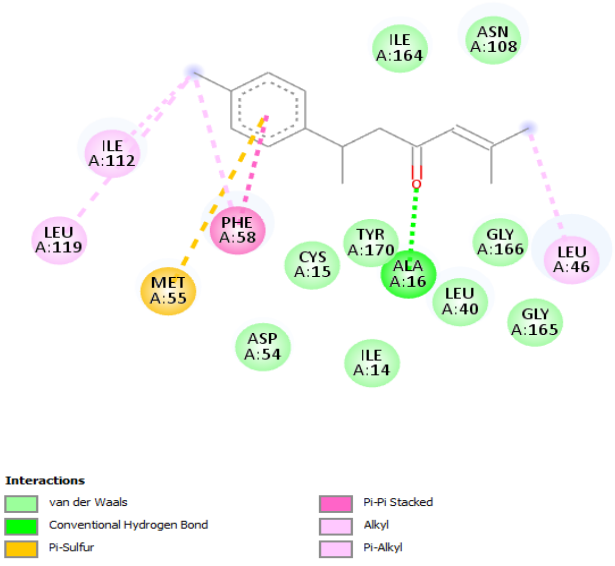

Figure 4: 2D Structure of the *Plasmodium falciparum* dihydrofolate reductase-thymidylate synthase proteins binding pockets with Ar-turmerone

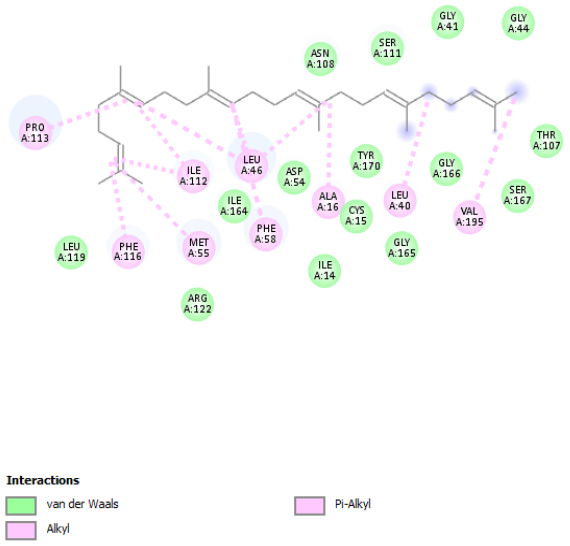

Figure 5: 2D Structure of the *Plasmodium falciparum* dihydrofolate reductase-thymidylate synthase proteins binding pockets with Squalene

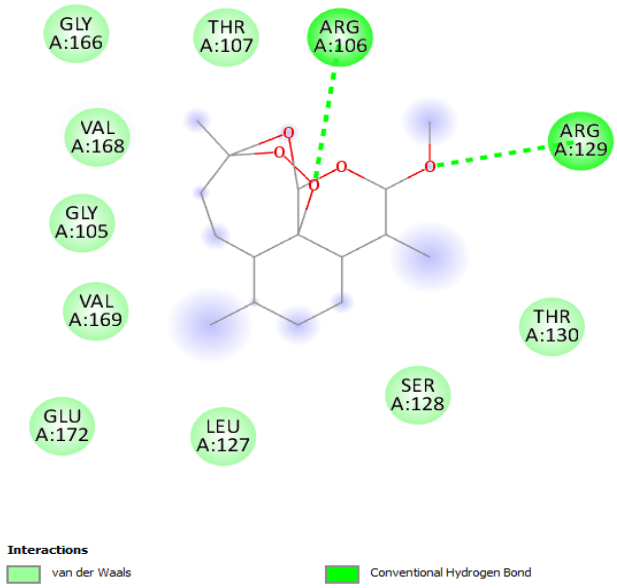

Figure 6: 2D Structure of the *Plasmodium falciparum* dihydrofolate reductase-thymidylate synthase proteins binding pockets with Artemether used as control

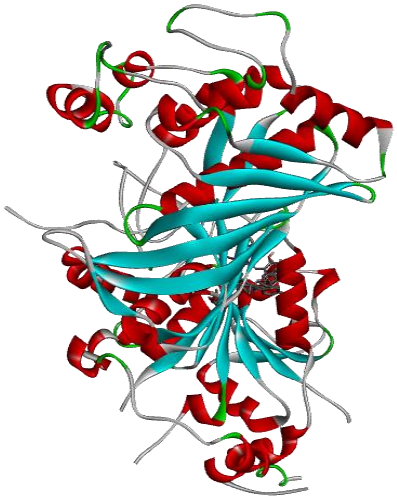

Figure 7: 3D Validation Structure of the Phytochemicals binding with *Plasmodium falciparum* dihydrofolate reductase-thymidylate synthase proteins

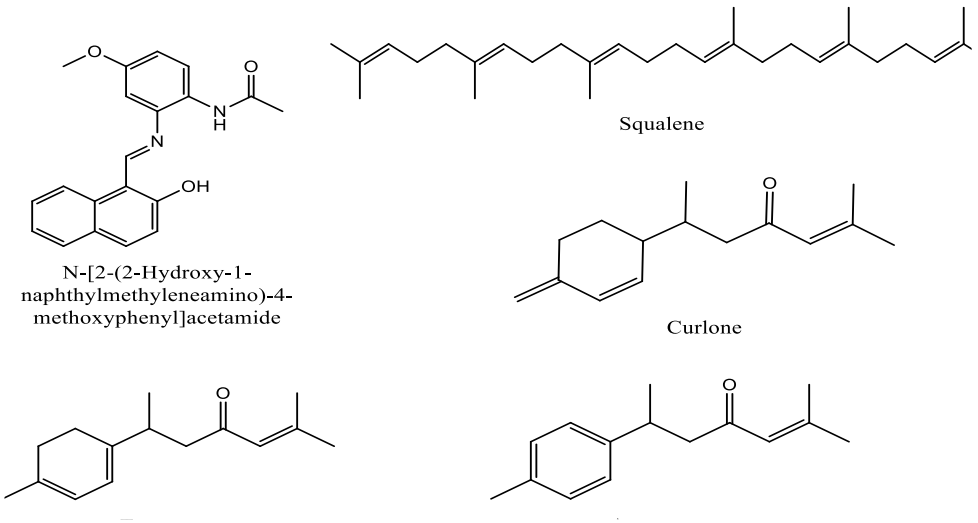

Figure 8: Chemical formula of Five (5) promising Antimalaria compounds from *E. chlorantha methanolic extracts*

4. Conclusion

The pharmacokinetic and virtual assessments of the phytochemicals in Enantia chlorantha suggest their potential as inhibitors of Plasmodium falciparum dihydrofolate reductase-thymidylate synthase, a key protein in malaria pathogenesis. These findings highlight the potential value of these phytochemicals in combating malaria, particularly in tropical regions of Africa.

Further in vivo investigations are recommended to evaluate the efficacy of individual phytochemicals and their synergistic antimalarial effects against other species of malaria-causing parasites. Such studies will provide deeper insights into their mechanism of action, molecular dynamics, and confirm their suitability as effective antimalarial agents.

5. Reference

[1] D. G. Paton, L. M. Childs, M. A. Itoe, I. E. Holmdahl, C. O. Buckee, and F. Catteruccia, "Exposing Anopheles mosquitoes to antimalarials blocks Plasmodium parasite transmission," *Nature*, vol. 567, pp. 239-243, 2019.

[2] S. Zareen, H. U. Rehman, N. Gul, H. Zareen, M. Hisham, I. Ullah, M. U. Rehman, S. Bibi, A. Bakht, and J. Khan, "Malaria is still a life threatening disease review," *J. Entomol. Zool. Stud*, vol. 105, pp. 105-112, 2016.

[3] J. Talapko, I. Škrlec, T. Alebić, M. Jukić, and A. Včev, "Malaria: the past and the present," *Microorganisms*, vol. 7, p. 179, 2019.

[4] F. Jamshidi-Kia, Z. Lorigooini, and H. Amini-Khoei, "Medicinal plants: Past history and future perspective," *Journal of herbmed pharmacology*, vol. 7, pp. 1-7, 2017.

[5] S. R. Dwivedi, L. C. Mishra, and G. Mishra, "An Analytical Approach to Progression in Malaria Therapeutics," in *Natural Product Based Drug Discovery Against Human Parasites: Opportunities and Challenges*, ed: Springer, 2023, pp. 471-490.

[6] R. Charoensup, T. Duangyod, P. Phuneerub, and R. Pimpa, "Validation of Thai traditional medicine: Current scenario," in *Evidence-based validation of herbal medicine*, ed: Elsevier, 2022, pp. 691-701.

[7] H. Biruk, B. Sentayehu, Y. Alebachew, W. Tamiru, A. Ejigu, and S. Assefa, "In vivo antimalarial activity of 80% methanol and aqueous bark extracts of Terminalia brownii fresen.(Combretaceae) against Plasmodium berghei in mice," *Biochemistry Research International*, vol. 2020, 2020.

[8] B. Hanboonkunupakarn and N. J. White, "Advances and roadblocks in the treatment of malaria," *British journal of clinical pharmacology*, vol. 88, pp. 374-382, 2022.

[9] R. M. Fairhurst and A. M. Dondorp, "Artemisinin-resistant Plasmodium falciparum malaria," *Microbiology spectrum*, vol. 4, pp. 10.1128/microbiolspec. ei10-0013-2016, 2016.

[10] M. S. Hossain, R. J. Commons, N. M. Douglas, K. Thriemer, B. H. Alemayehu, C. Amaratunga, A. R. Anvikar, E. A. Ashley, P. B. Asih, and V. I. Carrara, "The risk of Plasmodium vivax parasitaemia after P. falciparum malaria: an individual patient data meta-analysis from the WorldWide Antimalarial Resistance Network," *PLoS Medicine*, vol. 17, p. e1003393, 2020.

[11] P. J. Guerin, P. Olliaro, F. Nosten, P. Druilhe, R. Laxminarayan, F. Binka, W. L. Kilama, N. Ford, and N. J. White, "Malaria: current status of control, diagnosis, treatment, and a proposed agenda for research and development," *The Lancet infectious diseases*, vol. 2, pp. 564-573, 2002.

[12] T. T. Olivier, N. T. Francis, S. Armel, K. J. Jackson, and N. Justin, "Ethnobotanic survey of medicinal plants used for malaria therapy in western Cameroon," *J Med Plants*, vol. 4, pp. 248-58, 2016.

[13] I. Ishola, I. Oreagba, A. Adeneye, C. Adirije, K. Oshikoya, and O. Ogunleye, "Ethnopharmacological survey of herbal treatment of malaria in Lagos, Southwest Nigeria," *Journal of herbal medicine*, vol. 4, pp. 224-234, 2014.

[14] A. Adesokan and M. Akanji, "Antimalarial bioactivity of Enantia chlorantha stem bark," *Medicinal plants: phytochemistry, pharmacology and therapeutics, Volume 1*, pp. 441-447, 2010.

[15] M. Zubair, O. Atolani, S. Ibrahim, O. Adebisi, A. Hamid, and R. Sowunmi, "Chemical constituents and antimicrobial properties of Phyllanthus amarus (Schum & Thonn)," *Bayero Journal of Pure and Applied Sciences*, vol. 10, pp. 238-246, 2017.

[16] K. M. Al Azzam, E.-S. Negim, and H. Y. Aboul-Enein, "ADME studies of TUG-770 (a GPR-40 inhibitor agonist) for the treatment of type 2 diabetes using SwissADME predictor: In silico study," *Journal of Applied Pharmaceutical Science*, vol. 12, pp. 159-169, 2022.

[17] S. O. Ibrahim, H. Y. Lukman, M. F. Zubair, O. T. Amusan, F. R. Abdulkadri, B. Lawal, L. B. Abdulfatah, and O. Atolani, "An Insight into the Physicochemical, Drug-likeness, Pharmacokinetics and Toxicity Profile of Kigelia africana (Lam) Bioactive Compounds," *Al-Bahir Journal for Engineering and Pure Sciences*, vol. 4, p. 4, 2024.

[18] R. Shukla and T. Tripathi, "Molecular dynamics simulation of

protein and protein–ligand complexes," *Computer-aided drug design*, pp. 133-161, 2020.

[19] M. C. Childers and V. Daggett, "Insights from molecular dynamics simulations for computational protein design," *Molecular systems design & engineering*, vol. 2, pp. 9-33, 2017.

[20] 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, pp. 455-461, 2010.

[21] J. O. Aribisala and S. Sabiu, "Cheminformatics identification of phenolics as modulators of penicillin-binding protein 2a of Staphylococcus aureus: A structure–activity-relationship-based study," *Pharmaceutics*, vol. 14, p. 1818, 2022.

[22] N. Muddagoni, R. Bathula, M. Dasari, and S. R. Potlapally, "Homology modeling, virtual screening, prime-MMGBSA, AutoDock-identification of inhibitors of FGR protein," *Biointerface Res. Appl. Chem*, vol. 11, pp. 11088-11103, 2021.

[23] F. F. Boyom, E. M. Kemgne, R. Tepongning, V. Ngouana, W. F. Mbacham, E. Tsamo, P. H. A. Zollo, J. Gut, and P. J. Rosenthal, "Antiplasmodial activity of extracts from seven medicinal plants used in malaria treatment in Cameroon," *Journal of Ethnopharmacology*, vol. 123, pp. 483-488, 2009.

[24] I. O. Evbuomwan, O. S. Adeyemi, and O. M. Oluba, "Aqueous extract of Enantia chlorantha Oliv. demonstrates antimalarial activity and improves redox imbalance and biochemical alterations in mice," 2024.

[25] A. Abubakar, N. S. Ahmad, H. O. Akanya, A. Abdulkadir, and A. N. Abubakar, "Antiplasmodial activity of total alkaloids and flavonoids of stem bark extracts of Enantia chlorantha in mice," *Comparative Clinical Pathology*, vol. 29, pp. 873-881, 2020.

[26] A. S. Bagad, J. A. Joseph, N. Bhaskaran, and A. Agarwal, "Comparative evaluation of anti-inflammatory activity of curcuminoids, turmerones, and aqueous extract of Curcuma longa," *Advances in Pharmacological and Pharmaceutical Sciences*, vol. 2013, 2013.

[27] H.-S. Lee, "Antimicrobial properties of turmeric (Curcuma longa L.) rhizome-derived ar-turmerone and curcumin," *Food Science and Biotechnology*, vol. 15, pp. 559-563, 2006.

[28] A. O. Oriola, G. M. Miya, and A. O. Oyedeji, "Physicochemical Characterization, Antioxidant, and Anti-Inflammatory Activities of Turmeric-Black Cumin Homegrown COVID-19 Herbal Mixture," in *Sustainable Uses and Prospects of Medicinal Plants*, ed: CRC Press, 2023, pp. 413-429.

[29] A. H. Ahmed and Y. I. Alkali, "In silico pharmacokinetics and molecular docking studies of lead compounds derived from Diospyros mespiliformis," *PharmaTutor*, vol. 7, pp. 31-37, 2019.

[30] A. Saleem, M. Afzal, M. Naveed, S. I. Makhdoom, M. Mazhar, T. Aziz, A. A. Khan, Z. Kamal, M. Shahzad, and M. Alharbi, "HPLC, FTIR and GC-MS Analyses of Thymus vulgaris Phytochemicals Executing in vitro and in vivo Biological Activities and Effects on COX-1, COX-2 and Gastric Cancer Genes Computationally," *Molecules*, vol. 27, p. 8512, 2022.

[31] R. S. Tagne, B. P. Telefo, J. N. Nyemb, D. M. Yemele, S. N. Njina, S. M. C. Goka, L. L. Lienou, A. H. N. Kamdje, P. F. Moundipa, and A. D. Farooq, "Anticancer and antioxidant activities of methanol extracts and fractions of some Cameroonian medicinal plants," *Asian Pacific journal of tropical medicine*, vol. 7, pp. S442-S447, 2014.

[32] H. M. A. AlSheikh, I. Sultan, V. Kumar, I. A. Rather, H. Al-Sheikh, A. Tasleem Jan, and Q. M. R. Haq, "Plant-based phytochemicals as possible alternative to antibiotics in combating bacterial drug resistance," *Antibiotics*, vol. 9, p. 480, 2020.

[33] M. Mahanthesh, D. Ranjith, R. Yaligar, R. Jyothi, G. Narappa, and M. Ravi, "Swiss ADME prediction of phytochemicals present in Butea monosperma (Lam.) Taub," *Journal of Pharmacognosy and Phytochemistry*, vol. 9, pp. 1799-1809, 2020.

[34] B. Xiong, Y. Wang, Y. Chen, S. Xing, Q. Liao, Y. Chen, Q. Li, W. Li, and H. Sun, "Strategies for structural modification of small molecules to improve blood–brain barrier penetration: a recent perspective," *Journal of Medicinal Chemistry*, vol. 64, pp. 13152-13173, 2021.

[35] J. A. Arnott and S. L. Planey, "The influence of lipophilicity in drug discovery and design," *Expert opinion on drug discovery*, vol. 7, pp. 863-875, 2012.

[36] C. A. Lipinski, "Lead-and drug-like compounds: the rule-of-five revolution," *Drug discovery today: Technologies*, vol. 1, pp. 337-341, 2004.

[37] W. M. Pardridge, "Drug transport across the blood–brain barrier," *Journal of cerebral blood flow & metabolism*, vol. 32, pp. 1959-1972, 2012.

[38] P. Banerjee, A. O. Eckert, A. K. Schrey, and R. Preissner, "ProTox-II: a webserver for the prediction of toxicity of chemicals," *Nucleic acids research*, vol. 46, pp. W257-W263, 2018.

[39] R. Patil, S. Das, A. Stanley, L. Yadav, A. Sudhakar, and A. K. Varma, "Optimized hydrophobic interactions and hydrogen bonding at the target-ligand interface leads the pathways of drug-designing," *PloS one*, vol. 5, p. e12029, 2010.

Abbreviations

ACTs)	-	Artemisinin combination treatments
ADME	-	Absorption, Digestion, Metabolism and Excretion
BBB	-	Blood-brain barrier
E. chlorantha	-	*Enantia chlorantha*
GC-MS	-	Gas Chromatography - Mass Spectroscopy
GI	-	Gastrointestinal
FDA	-	Food and Drugs Administration
MW	-	Molecular Weight (
MR	-	Molecular Refractivity
MS	–	Moderately Soluble
PAINS	-	Pan Assay Interference compounds
P. falciparum	-	*Plasmodium falciparum*
PS	–	Partially Soluble
PSA	-	Polar Surface Area
P. vivax	-	*Plasmodium vivax*
S	–	Soluble
VS	–	Very Soluble