Integrated Molecular Docking, DFT, ADME Profiling, and Cardiotoxicity Prediction of Artocarpin, Cycloartocarpin, Artocarpanone and Cyanomaclurin as Potential Antimalarial Agents

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Abstract

The escalating resistance of *Plasmodium falciparum* to existing antimalarial treatments necessitates the identification of novel medicines with enhanced efficacy and safety. This study utilized a comprehensive in silico approach to assess the potential of four flavonoids from *Artocarpus heterophyllus* î.e. artocarpin, cycloartocarpin, artocarpanone, and cyanomaclurin as inhibitors of *P. falciparum* dihydrofolate reductase–thymidylate synthase (PfDHFR-TS). Molecular docking demonstrated that artocarpin and cycloartocarpin displayed enhanced binding affinities and advantageous interaction patterns compared to chloroquine. Density functional theory and molecular electrostatic potential investigations corroborated their increased electronic reactivity and binding compatibility. ADME profiling demonstrated satisfactory drug-likeness properties; however, cardiotoxicity prediction revealed artocarpin and cycloartocarpin as non-hERG blockers, unlike chloroquine. Despite the anticipated mild toxicity hazards, the comprehensive computational data underscore artocarpin and cycloartocarpin as prospective lead scaffolds for subsequent optimization. These findings provide a compelling justification for the experimental validation and rational design of safer antimalarial medicines derived from *A. heterophyllus.*

Introduction

Malaria continues to pose a major global health challenge, with *Plasmodium falciparum* responsible for the most severe and deadly infections. Although artemisinin-based combination therapies (ACTs) remain the cornerstone of treatment, the rapid rise in multidrug-resistant Plasmodium strains has significantly undermined their effectiveness [1, 2]. This growing problem of resistance highlights the urgent need to discover new antimalarial agents, particularly those with novel mechanisms capable of bypassing existing resistance pathways.

The tropical plant *Artocarpus heterophyllus* (jackfruit) has attracted considerable scientific attention because of its rich phytochemical profile and wide range of biological activities. Several flavonoid derivatives found in its heartwood, namely artocarpin, cycloartocarpin, artocarpanone, and cyanomaclurin, have been reported to exhibit antibacterial, antioxidant, antiviral, and anti-inflammatory effects. Notably, artocarpin also exhibits in vivo antimalarial activity. The structural resemblance of these flavonoids to other compounds known to disrupt *Plasmodium* metabolism further supports the possibility that they may serve as promising antimalarial agents [3–5].

One molecular target of particular interest is the *Plasmodium falciparum* dihydrofolate reductase–thymidylate synthase (PfDHFR-TS), which plays a central role in folate metabolism and nucleotide synthesis, which are vital for parasite survival. Although PfDHFR-TS has long been targeted by antifolate drugs such as pyrimethamine, widespread resistance has greatly reduced their therapeutic value [6]. Exploring natural compounds that can effectively bind to this enzyme offers a compelling strategy for overcoming resistant strains.

Recent advances in computational chemistry have allowed researchers to investigate potential drug candidates more efficiently using in silico techniques. Molecular docking can predict the strength of binding of a compound to a target protein, whereas Density Functional Theory (DFT) provides insight into the electronic properties and reactivity of the molecule. Molecular Electrostatic Potential (MEP) mapping adds an additional layer of understanding by identifying the regions most likely to interact with the protein's active site [7–9]. These methods, combined with drug-likeness and ADMET assessments, help evaluate whether a compound has the pharmacokinetic and safety characteristics required for further drug development.

Given the therapeutic relevance of PfDHFR-TS and the diverse biological activities of *Artocarpus*-derived flavonoids, a comprehensive computational study is warranted. This study investigated the antimalarial potential of artocarpin, cycloartocarpin, artocarpanone, and cyanomaclurin using an integrated in silico approach, including molecular docking, DFT calculations, MEP visualization, and ADMET profiling. Through these analyses, we aimed to characterize the binding behavior, electronic features, and pharmacokinetic suitability of these compounds, ultimately identifying promising lead compounds for future antimalarial drug development.

Research Methodology

Molecular Docking

In this study, four major phytochemical constituents of *Artocarpus heterophyllus* artocarpin, cycloartocarpin, artocarpanone, and cyanomaclurin [10] were selected as test ligands, with chloroquine serving as the reference drug. Ligand structures (Table 1) were drawn using ChemDraw Professional 15.0 and energy-minimized in MOE 2024.0901 to obtain optimized three-dimensional conformations. The crystal structure of *Plasmodium falciparum* dihydrofolate reductase–thymidylate synthase (PfDHFR-TS; PDB ID: 1J3I) was retrieved from the RCSB protein data bank and prepared using discovery studio visualizer by removing water molecules and heteroatoms, adding hydrogen atoms, repairing missing residues, and assigning partial charges. The structure was further protonated and energy-minimized in MOE before

identifying the active site using Site Finder. Molecular docking was performed in MOE using the triangle matcher placement method and London dG scoring, followed by refinement with GBVI/WSA dG to generate and evaluate 100 binding poses for each ligand [11].

Density functional theory

All structures were first drawn and converted into three-dimensional conformations using ChemDraw and MOE, followed by preliminary energy minimization. The optimized geometries were imported into the Gaussian software for quantum chemical analysis. DFT calculations were performed using the B3LYP hybrid functional with the 6-31G(d,p) basis set, which is a widely validated level of theory for evaluating molecular orbitals and electronic descriptors. For each ligand, the highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO), energy gap (ΔE), dipole moment, and total electronic energy were obtained to assess their chemical reactivity and stability [12]. Molecular Electrostatic Potential (MEP) maps were subsequently generated from the DFT-optimized geometries using GaussView, allowing the identification of electrophilic and nucleophilic regions relevant to protein binding. These combined parameters, that is, HOMO–LUMO distribution, energy gap, charge density, and MEP patterns, were used to infer the electronic behavior of each compound and support the interpretation of the molecular docking results.

Absortption, Distribution, Metabolism, Excretion (ADME)

The pharmacokinetic and toxicity profiles of artocarpin, cycloartocarpin, artocarpanone, and cyanomaclurin were predicted using SwissADME, ADMETlab 3.0, and ProTox 3.0. The SMILES structure of each compound was submitted to SwissADME to evaluate the physicochemical properties, Lipinski compliance, lipophilicity, solubility, gastrointestinal absorption, and blood–brain barrier permeability. ADMETlab 3.0 was used to estimate pharmacokinetic parameters, including volume of distribution, clearance, CYP450 inhibition potential, and organ-specific toxicity. Acute toxicity (LD_{50}) and toxicity class were assessed using ProTox 3.0. All ADME outputs were integrated to determine the drug-likeness and preliminary safety profiles of the compounds as antimalarial candidates

Cardiotoxicity Prediction

Pred-hERG was used to evaluate cardiac toxicity using a probability map, prediction, and assurance of all compounds. The Pred-hERG provider aids users, using a fast, practical interface, for acknowledgment of hERG blockers and non-blockers [13].

Results and Discussion

Molecular Docking

Molecular docking was performed to predict the binding free energy and interaction between four major *Artocarpus heterophyllus* compounds i.e. artocarpin, cycloartocarpin, artocarpanone, and cyanomaclurin against the *Plasmodium falciparum* DHFR-TS enzyme (PDB ID: 1J3I). Chloroquine was used as positive control. Molecular docking results are presented in table 1. Docking simulations showed that artocarpin and cycloartocarpin has binding free energy of −9.506 and−9.407 kcal/mol, respectively. It were exhibited the strongest binding free energy toward PfDHFR-TS. Their values were notably better than those of artocarpanone and cyanomaclurin and were comparable or slightly superior to those of chloroquine. These findings indicate that the two prenylated flavonoids may have significant inhibitory potential against the DHFR domain, making them promising candidates for further antimalarial exploration.

Table 1. Docking results

Ligand	Binding free energy	RMSD	Hydrogen bond	Hydrophobic interaction	Van der Waals interaction	Other interaction	*Binding Factor*
Chloroquine	-8.465	1.154	Phe58. Leu40	Lys49	Asp54	Ala16, Cys15, Gly44, Gly165, Gly166, Ile14, Ile112, Ile164, Leu46, Met55, Pro113, Ser108, Ser111, Tyr170, Val45	19
Cpd1 (*Artocarpin*)	-9.506	1.596	**Phe58,Asp54**	**Lys49**	**Asp54**	**Ala16, Cys15,** Gly41**, Gly44, Gly165, Gly166, Ile14, Ile112, Ile164, Leu40, Leu46, Met55, Pro113, Ser108, Ser111, Val45,** Val195	18
Cpd2 (*Cycloartocarpin*)	-9.407	1.635	**Leu46, Ser111**	**Lys49**	**Asp54**	**Ala16, Cys15, Gly44, Gly165, Gly166, Ile14, Ile112, Ile164, Leu40, Met55, Phe58, Ser108,** Thr107**,** Thr185**,** Trp48**,** Tyr57**, Tyr170, Val45**	18
Cpd3 (*Artocarpanone*)	-7.525	0.880	**Asp54, Gly165**	**Lys49**	**Asp54**	**Ala16, Cys15, Gly166, Ile14, Ile164, Leu40, Leu46, Met55, Phe58, Ser108,** Thr185**,** Trp48**,** Tyr57**, Tyr170**	14
Cpd4 (*Cyanomaclurin*)	-6.777	0.843	**Phe58**	-	**Asp54**	**Ala16, Cys15, Gly44, Gly165, Gly166, Ile14, Ile112, Ile164, Leu40, Leu46, Met55, Ser108, Ser111,** Ser167**, Tyr170,** Val195	16

Note:

Bold : The amino acid residues interacting with Cpd1–Cpd4 are identical to those interacting with the positive control

Underline : catalytic triad

The strong binding free energy observed for artocarpin and cycloartocarpin can be attributed to their ability to form several stabilizing interactions within the active site of the enzyme. Both compounds establish hydrogen bonds with key catalytic residues and are stabilized by extensive hydrophobic contacts deep inside the binding pocket. As shown in Figure 2, interactions with residues such as Ile14, Phe58, Cys59, and Gly44, which are frequently involved in DHFR inhibitor binding, play an important role in maintaining this stability. The presence of hydroxyl groups facilitates hydrogen bond formation, whereas the prenyl side chains contribute additional hydrophobic anchoring. These structural characteristics align well with established structure–activity relationship findings, indicating that prenylated flavonoids often exhibit enhanced binding performance due to increased lipophilicity and improved interactions with the target site [14].

Superimposition analysis (Figure 3) showed that artocarpin and cycloartocarpin adopted binding orientations that closely resembled those of chloroquine. Both compounds occupy similar regions within the active site and display comparable π–π stacking and hydrophobic interactions with the residues. This strong spatial overlap suggests that they may inhibit the enzyme through a similar mechanism, supporting the possibility that these compounds disrupt dihydrofolate reduction that a key process required for synthesis of nucleic acid in *Plasmodium*.

Artocarpanone and cyanomaclurin exhibited lower binding free energy and also fewer stabilizing interactions with the PfDHFR-TS active site. Their binding conformations showed little spatial overlap with the reference ligand and were superficially positioned within the catalytic cavity. Their lower anticipated inhibitory potential is likely caused by their decreased hydrophobic surface area and decreased availability of hydrogen-bonding capabilities.

Density Functional Theory (DFT)

Density Functional Theory (DFT) calculations were conducted to systematically evaluate the electronic structures and reactivity profiles of chloroquine and the four principal compounds derived from *Artocarpus heterophyllus*, namely, artocarpin, cycloartocarpin, artocarpanone, and cyanomaclurin. The energies of the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) were examined, along with the resulting HOMO–LUMO energy gap (ΔE). These quantum chemical parameters are widely recognized as key indicators of molecular stability, electronic reactivity, and propensity of compounds to engage in intermolecular interactions with biological targets. DFT parameter of chloroquine and *A. heterophyllus* compounds are presented in Table 2.

Table 2. DFT results

compound	Total energy (a.u)	Momen Dipol (Debye)	electronic		Energy Gap (ΔE)
			HOMO	LUMO	
Chloroquine (positive control)	-1326.032	4.937	-0.198	-0.315	0.117
Artocarpin	-1458.906	5.686	-0.184	-0.311	0.127
Cycloartocarpin	-1457.712	6.619	-0.194	-0.304	0.110
Artocarpanone	-1069.466	3.332	-0.171	-0.308	0.137
Cyanomaclurin	-1030.129	1.086	-0.154	-0.304	0.150

DFT analysis revealed distinct differences in the electronic characteristics of the examined compounds. Among the *A. heterophyllus* derivatives, cycloartocarpin exhibited the smallest HOMO–LUMO energy gap (0.110), followed closely by artocarpin (0.127). A reduced energy gap is commonly associated with increased electronic reactivity and enhanced molecular polarizability, indicating a greater propensity for these compounds to engage in charge transfer interactions with biological macromolecules. This electronic behavior may contribute to the favorable interaction profiles observed in subsequent molecular docking analyses [15] .

The comparatively low HOMO–LUMO energy gaps (ΔE) observed for artocarpin and cycloartocarpin reflect favorable electronic properties consistent with their strong binding affinities identified in molecular docking analyses. This concordance suggests a meaningful relationship between electronic reactivity and binding efficiency, thereby strengthening the rationale for considering these compounds as potential PfDHFR-TS inhibitors [16]. However, artocarpanone and cyanomaclurin exhibited relatively larger energy gaps, indicating greater molecular stability but diminished electronic reactivity, which may underlie their comparatively weaker docking interactions.

The visualization of the frontier molecular orbitals (Figure 4) revealed that the HOMO distributions of artocarpin and cycloartocarpin were predominantly localized on oxygen-containing functional groups, particularly hydroxyl moieties. Therefore, these regions are likely to act as electron-donating sites during ligand–protein interactions. In contrast, the LUMO distributions were primarily delocalized over the aromatic frameworks and prenylated substituents, indicating their potential role as electron-accepting regions when interacting with electrophilic residues within the enzyme active site.

The observed spatial distributions of the HOMO and LUMO orbitals were consistent with the interaction patterns identified in the molecular docking simulations, in which the hydroxyl functional groups predominantly contributed to hydrogen bond formation, whereas the prenyl substituents enhanced the hydrophobic interactions within the PfDHFR-TS active site. This concordance between the electronic features derived from DFT analysis and docking interaction profiles reinforces the robustness and reliability of in silico predictions.

Molecular Electrostatic Potential (MEP)

Molecular Electrostatic Potential (MEP) analysis was performed to characterize the charge distribution and electrostatic properties of chloroquine and the four compounds derived from *Artocarpus heterophyllus*. MEP mapping offers important insights into molecular regions that are predisposed to electrophilic or nucleophilic interactions, thereby providing a mechanistic understanding of how these compounds recognize and interact with protein targets [17].

As depicted in Figure 5, all evaluated compounds exhibited distinct regions of negative electrostatic potential, predominantly localized around the oxygen atoms, particularly those associated with hydroxyl and carbonyl functional groups. These electron-rich regions are characteristic of sites capable of acting as hydrogen-bond acceptors and are therefore likely to play a key role in stabilizing interactions with amino acid residues within the PfDHFR-TS active-site. Conversely, regions of positive electrostatic potential were primarily distributed over hydrogen-rich alkyl chains and aromatic moieties, indicating electron-deficient areas that may participate in complementary electrostatic interactions during ligand–protein-binding.

All the analyzed compounds exhibited well-defined regions of negative electrostatic potential, predominantly localized around the oxygen atoms, particularly those associated with hydroxyl and carbonyl functional groups [18]. These electron-rich regions represent potential hydrogen-bond acceptor sites and are therefore likely to contribute significantly to stabilizing interactions with amino acid residues within the PfDHFR-TS active site. Conversely, regions of positive electrostatic potential were primarily distributed over hydrogen-rich alkyl chains and aromatic moieties, indicating electron-deficient areas that may participate in complementary electrostatic interactions during ligand–protein-binding.

Artocarpin and cycloartocarpin exhibited well-defined regions of negative electrostatic potential predominantly localized around their hydroxyl functional groups, in agreement with the strong hydrogen-bonding interactions observed in the molecular docking simulations. The presence of prenyl substituents contributed to regions of relatively neutral to mildly positive electrostatic potential, which may favor hydrophobic interactions within the enzyme-binding pocket. This combination of complementary electrostatic and hydrophobic characteristics is likely to enhance both binding complementarity and complex stability. Table 3 are presented the electrostatic features derived from MEP analysis.

Table 3. Electrostatic features based on MEP analysis

Compounds	Predominant Negative Potential Regions	Predominant Positive Potential Regions	Key functional Groups involved
Chloroquine	Nitrogen atom	Alkyl chain	Amine group
Artocarpin	Oxygen atom	Aromatic region	Hydroxyl group
Cycloartocarpin	Oxygen atom	Aromatic region	Hydroxyl group
Artocarpanone	Oxygen atom	Aromatic region	Carbonyl and hydroxyl group
Cyanomaclurin	Oxygen atom	Aromatic region	Multiple hydroxyl group

Artocarpanone and cyanomaclurin exhibited broader but less distinctly localized regions of negative electrostatic potential, indicating a more evenly distributed electron density across their molecular frameworks. Although these electrostatic features remain compatible with hydrogen bond formation, the less concentrated potential distribution may partially account for their comparatively weaker binding affinities relative to artocarpin and cycloartocarpin.

Absortption, Distribution, Metabolism, Excretion (ADME)

In silico ADME analysis was performed to systematically evaluate the pharmacokinetic characteristics and drug-likeness of artocarpin, cycloartocarpin, artocarpanone, and cyanomaclurin. Assessing these parameters is essential for estimating the translational viability of bioactive compounds beyond their target-binding performance. The predicted ADME profiles are summarized in Table 4.

All four compounds exhibited high predicted oral bioavailability and favorable gastrointestinal absorption, indicating suitable permeability for oral administration. Compliance with Lipinski's rule of five further supports the classification of these compounds as drug-like molecules. Moreover, key physicochemical parameters, including molecular weight and lipophilicity, were within acceptable ranges, suggesting a balanced profile between aqueous solubility and membrane permeability [19].

Table 4. Drug-likeness and ADMET

Parameter	Result				
	Chloroquine	Artocarpin	Cycloartocarpin	Artocarpanone	Cyanomaclurin
Lipinski	Yes	Yes	Yes	Yes	Yes
Molecular weight (g/mol)	319.18	436.50	434.48	302.28	288.25
H-*bond acceptor*	3	6	6	6	6
H-*bond donor*	1	3	2	3	4
Log P	4.733	4.14	4.31	2.01	1.25
TPSA (Å)	28.16	100.13	89.13	96.22	99.38
Ghose	No	Yes	Yes	Yes	Yes
Veber	Yes	Yes	Yes	Yes	Yes
Egan	Yes	Yes	Yes	Yes	Yes
Muegge	Yes	No	No	Yes	Yes
Human Intestinal Absorption (HIA)	0	0.081	0.052	0.006	0
Caco-2 permeability (log cm/s)	-4.981	-5.146	-5.098	-4.989	-6.048
P-glycoprotein inhibitor	0.088	0.978	0.654	0.798	0.013
P-glycoprotein substrate	0.849	0.029	0.035	0.032	0.934
F20%	0.001	0.904	0.93	0.011	0.57
F30%	0	0.99	0.989	0.666	0.98
Plasma Protein Binding (PPB) (%)	49.61	96.994	97.912	91.82	91.499
Blood-Brain Barrier Penetration (BBB)	0.961	0	0	0.005	0.041
Volume distribution (L/kg)	1.076	0.238	0.053	0.058	0.143
Fraction unbound (Fu)(%)	56.319	3.036	2.093	9.118	9.994
CYP1A2 substrate	0.093	0	0.157	0.964	0.05
CYP1A2 inhibitor	0	0.481	0.748	0.998	0
CYP2C19 substrate	0.732	0.988	0.913	0.005	0.537
CYP2C19 inhibitor	0	1.0	0.996	0.996	0.097
CYP2C9 substrate	0	0.009	0.092	0.893	1.0
CYP2C9 inhibitor	0	1.0	0.994	0.907	0.02
CYP2D6 substrate	0.374	0,074	0,009	0,955	0,707
CYP2D6 inhibitor	0.006	0.017	0.008	0.618	0
CYP3A4 substrate	0	0.716	0.97	0.802	0
CYP3A4 inhibitor	0	0.834	0.98	0.955	0
Half time (t1/2)	0.561	1.574	1.236	1.657	2.643
Clearance (mL/min/kg)	5.666	2.28	4.601	2.841	7.719
Human hepatotoxicity (H-HT)	0.727	0.693	0.831	0.611	0.653
hERG blockers	0.958	0.085	0.132	0.119	0.138
Rat oral acute toxicity	0.796	0.537	0.371	0.564	0.436
AMES toxicity	0.512	0.34	0.483	0.679	0,.88
Drug Induced Liver Injury (DILI)	0525	0.717	0.932	0.499	0.503

Carcinogencity	0.204	0.359	0.732	0.672	0.371

All four compounds were predicted to exhibit moderate to high levels of acute oral toxicity in the rat model, along with an associated risk of hepatotoxicity and carcinogenicity. These results indicate that, despite their promising antimalarial potential, as suggested by molecular docking and electronic structure analyses, the safety profiles of these compounds may present substantial challenges for their direct advancement as therapeutic agents. Prediction of toxicity value for all compounds are listed in Table 5.

Table 5. Toxicity prediction

Compound	LD_{50}	Toxicity class	Hepatotoxicity
Chloroquine	750 nmg/kg	Class 4 low toxicity	Inactive (0,65)
Artocarpin	4000 mg/kg	Class 5 Very low toxicity	Inactive (0,68)
Cycloartocarpin	475 mg/kg	Class 4 low toxicity	Inactive (0,67)
Artocarpanone	2000 mg/kg	Class 4 low toxicity	Inactive (0,71)
Cyanomaclurin	2500 mg/kg	Class 5 Very low toxicity	Inactive (0,80)

The prediction of hepatotoxicity deserves particular attention, given the central role of the liver in drug metabolism and detoxification processes. Compounds with hepatotoxic potential may accumulate in liver tissue or be converted into reactive metabolites, ultimately causing cellular damage in the liver. This concern is supported by the low predicted clearance values observed in the ADME analysis, which suggests prolonged systemic exposure and, consequently, an increased likelihood of toxicity [20].

Although these toxicity concerns are important, they do not necessarily rule out further developments. Many biologically active natural products initially exhibit safety liabilities that can be reduced through structural refinement, targeted modification of functional groups, or appropriate formulation approaches. Artocarpin and cycloartocarpin, which exhibited the most favorable binding affinities and electronic characteristics, represent promising lead scaffolds for developing safer and more selective antimalarial derivatives.

Cardiotoxicity Prediction

Cardiotoxicity, defined as drug-induced damage to cardiac tissue, represents a major challenge in pharmaceutical development and is a leading cause of late-stage drug attrition during both preclinical and clinical evaluation. Because interference with cardiac electrophysiology can result in life-threatening arrhythmias, cardiotoxicity remains one of the most serious and closely monitored adverse effects in new drug candidates [21]. The cardiac safety profile of the studied compounds was therefore evaluated using the PRED-hERG model, and the results are summarized in Table 6.

This computational model provides a reliable assessment of a compound's likelihood to interact with the hERG potassium channel, a key regulator of cardiac repolarization. By predicting hERG liability, this analysis offers important insight into the potential cardiac risks associated with the investigated chemical entities.

This classification provides an estimate of the likelihood that the tested compounds may inhibit the hERG channel, an event that can trigger potentially life-threatening cardiac arrhythmias. The reliability of each prediction is indicated by the "Confidence (%)" value reported by the model. In addition, the "Applicability Domain" parameter is critical for interpreting these results, as it reflects whether a compound falls within the chemical space on which the model was trained. Notably, cycloartocarpin and cyanomaclurin listed in Table 4 lie outside the model's applicability domain, which introduces a degree of uncertainty and suggests that the predictions should be interpreted with caution.

The predicted cardiotoxic profiles of ligands are summarized in Table 4, including their confidence scores, applicability domains, potency classifications, and associated reliability within those domains. As cardiotoxicity reflects a compound's potential to disrupt normal cardiac function or cause myocardial injury, it represents a critical safety concern in drug discovery and development.

Chloroquine, used as a reference compound, was predicted to be a hERG blocker with exceptional reliability (99.5 %), corroborating its well-established cardiotoxic potential. The model designated chloroquine within the applicability domain, reflecting a high degree of confidence in this prediction [22]. The predicted IC_{50} value of 5.579 further corroborates its robust interaction with the hERG channel, aligning with clinical findings of QT prolongation and arrhythmogenic risk associated with chloroquine treatment.

Artocarpin, cycloartocarpin, and artocarpanone were all anticipated to be non-inhibitors of the hERG channel. Cycloartocarpin had the highest confidence, with a binary reliability of 95.76%, followed by artocarpanone (77.74 %) and artocarpin (76.27 %). Significantly, all three substances were categorized within the applicability domain, signifying that their chemical characteristics reside within the validated prediction space of the model and that their anticipated safety profiles are dependable. Their anticipated IC_{50} values (5.192–5.327) were marginally lower than those of chloroquine, indicating diminished or less functionally significant interactions with the hERG channel.

Conclusions

This study demonstrates that flavonoids derived from Artocarpus heterophyllus, specifically artocarpin and cycloartocarpin, exhibit significant in silico inhibitory efficacy against Plasmodium falciparum DHFR-TS. Combined molecular docking and quantum chemistry investigations showed that the enzyme's active site had good binding affinities, electronic reactivity and complementary interaction patterns. Predicting cardiotoxicity showed that neither chemical was a hERG blocker, which means that they are safer for the heart than chloroquine. Although moderate toxicity risks are expected, these constraints can be addressed through logical structure optimization. In summary, these results suggest that artocarpin and cycloartocarpin are promising candidates for further research and the development of antimalarial drugs.

Declarations

Data Availability

No datasets were generated or analysed during the current study.

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Author Contribution

All authors contributed to the research design, collection, analysis, and interpretation of data. The first draft of the manuscript was written by Neni Frimayanti. All authors commented on the previous drafts of the paper. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could appear to have influenced the research reported in this paper.

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Table

Table 6 is available in the Supplementary Files section.

Figures

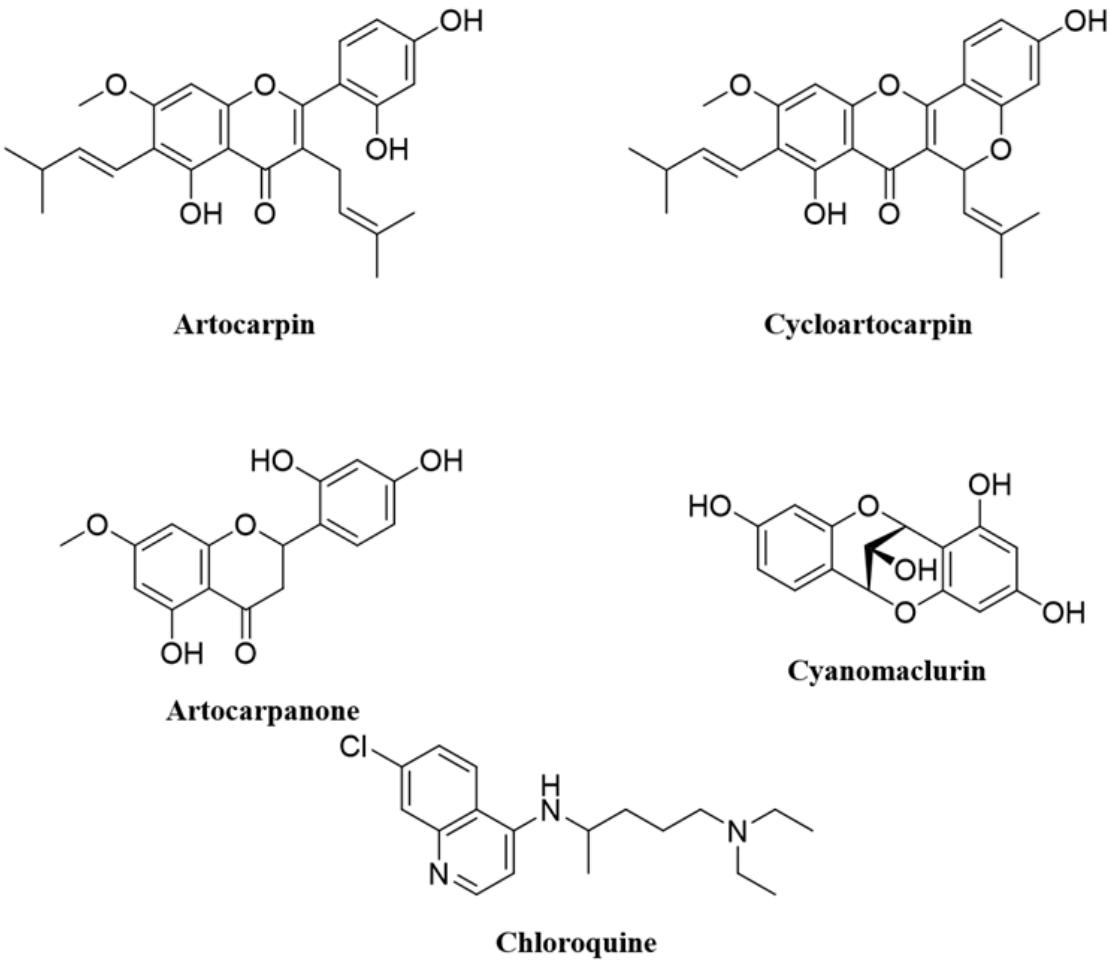

Figure 1

Sturucture ligand

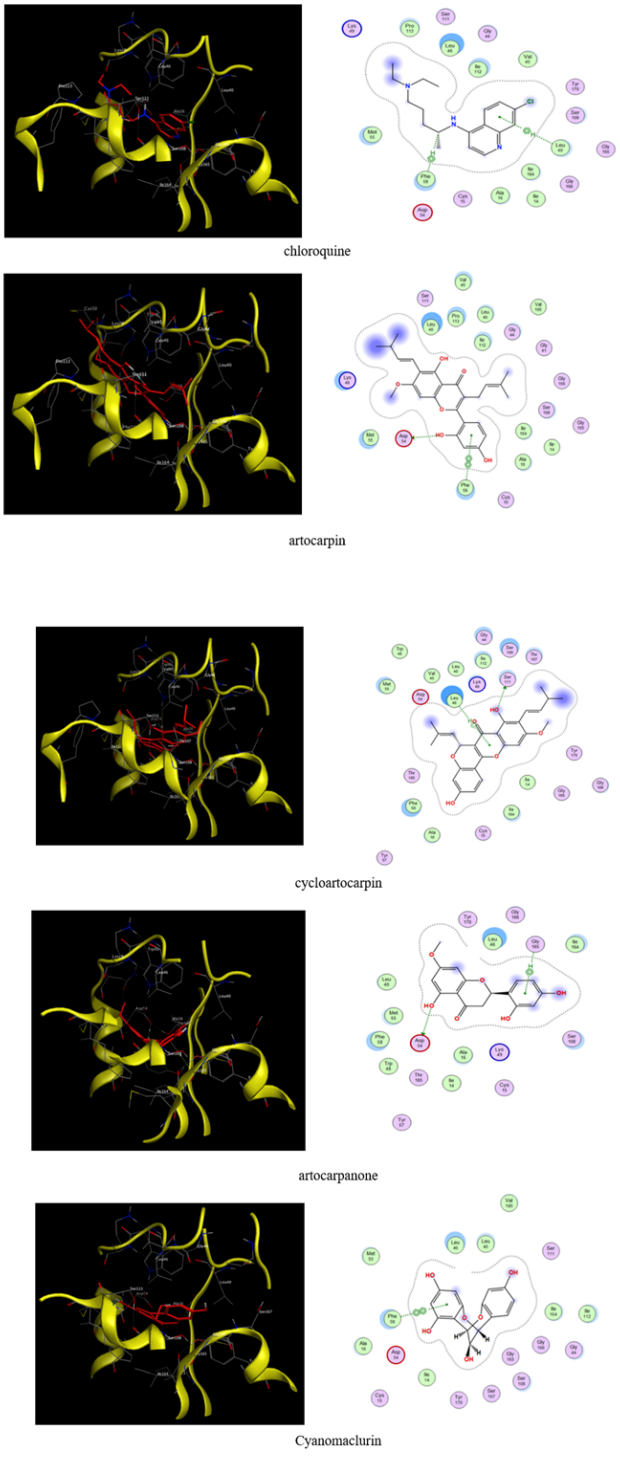

Figure 2

2D and 3D spatial arrangement for all ligand

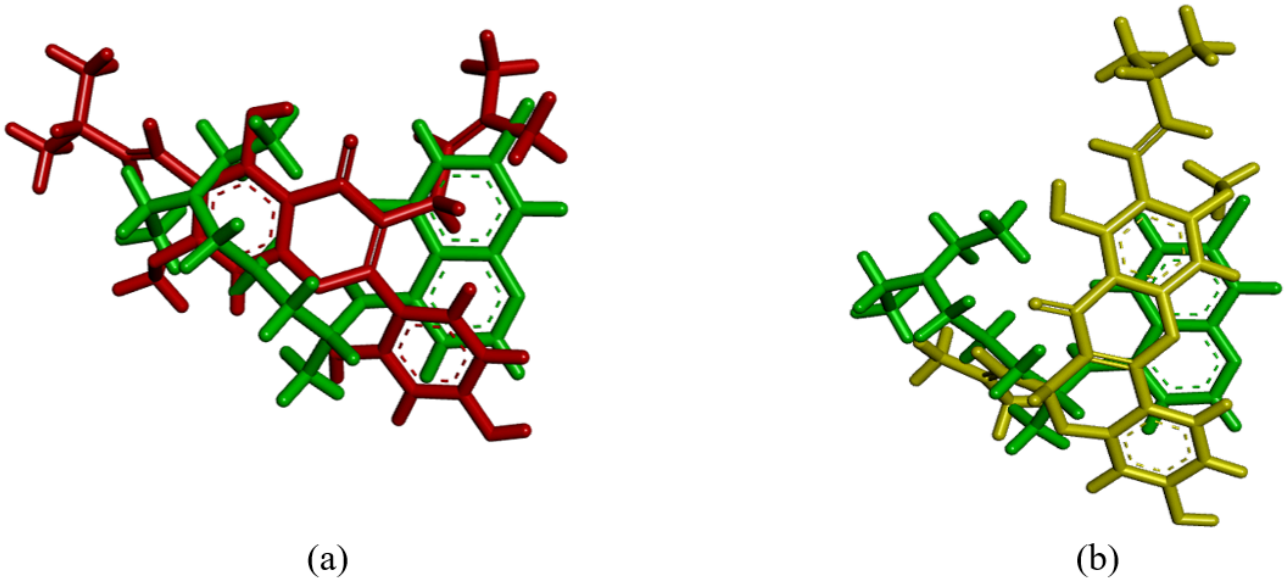

Figure 3

Superimposition for chloroquine (green) with (a) artocarpin (red) and (b) cycloartocarpin (yellow)

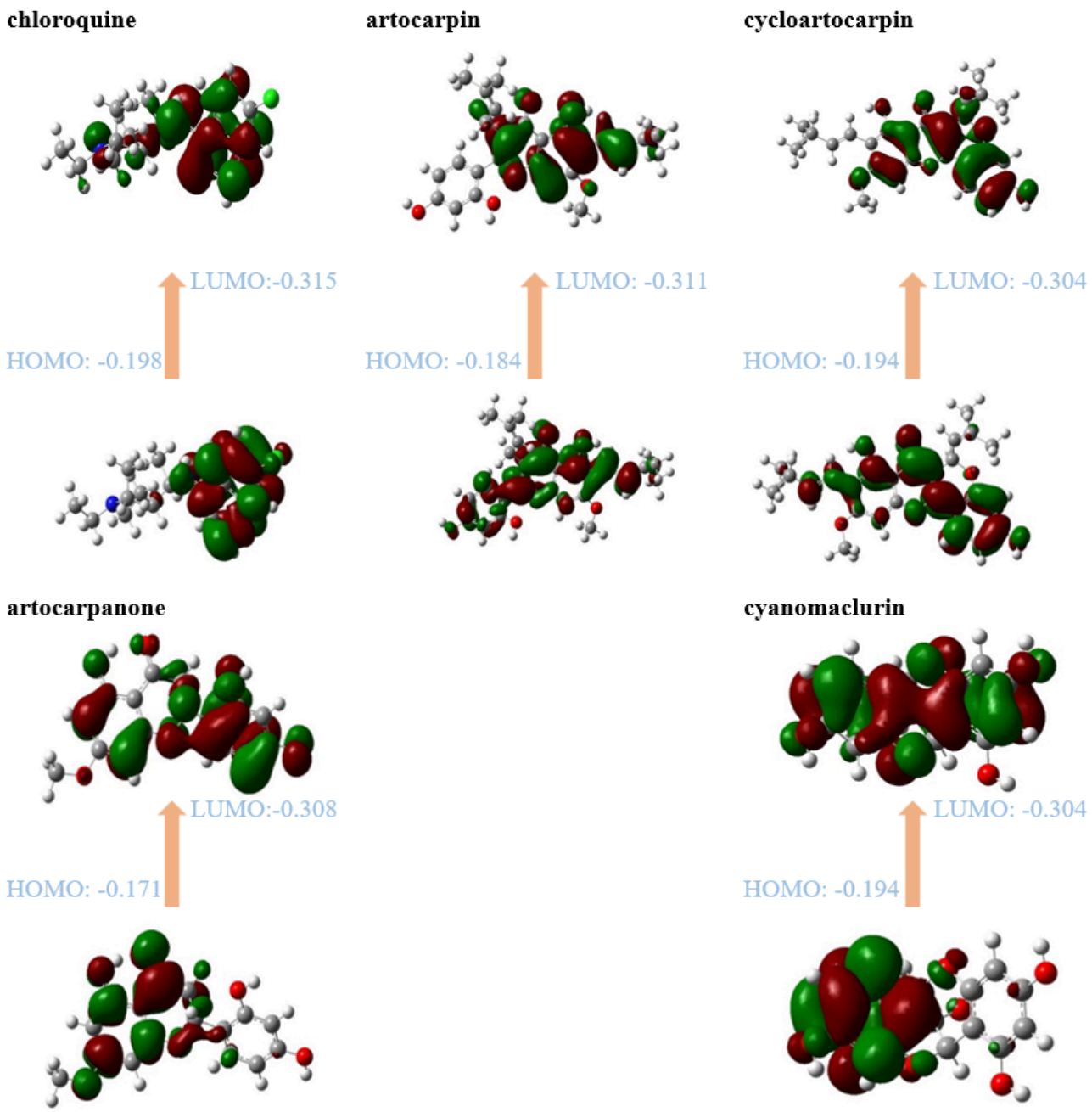

Figure 4

DFT study of isolated compound from *A. heterophyllus* and LUMO HOMO structure

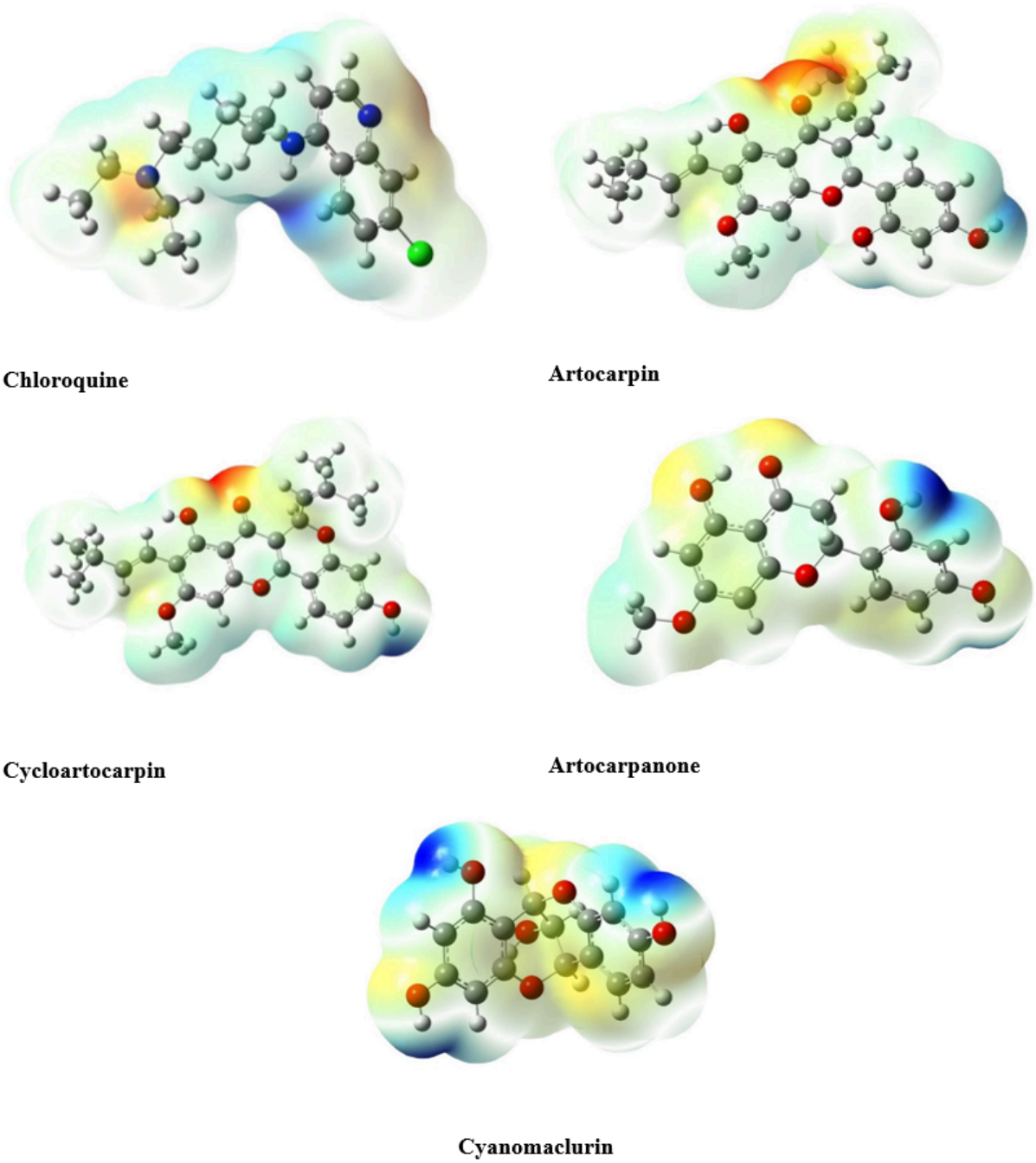

Figure 5

Molecular electrostatic potential (MEP) maps of the studied compounds

Supplementary Files

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- Table6.docx