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Proceeding Paper

A Systematic In Silico Investigation of Phytochemicals from *Artocarpus* Species against *Plasmodium falciparum* Inhibitors †

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Abstract: Artemisinin-resistant *plasmodium* strains are becoming increasingly common in malaria patients, posing a serious threat to successful malaria management. Brosimone, a significant polyphenolic ingredient of *Artocarpus lakoocha*, has previously been shown to have antimalarial activity in vitro. However, research into the precise mechanism of interactions is still in progress. The present study explored molecular modeling research in order to elucidate the likely mechanism of its anti-malarial effect as Falcipain-2 (FP-2) inhibition. Brosimone has the maximum binding affinity (docking score: −8.1 Kcal/mol) against FP-2 from *Plasmodium falciparum*, according to our molecular docking analysis of 50 lakoocha bioactive chemicals. For numerous *Artocarpus lakoocha* polyphenols (ALP), used in-silico pharmacokinetics and toxicities and concluded that critical insights into the mechanism of action of Brosimone and other ALP as a potential therapeutic agent (2GHU) against malaria.

Keywords: malaria; *Plasmodium falciparum*; Brosimone; Falcipain-2; *Artocarpus*

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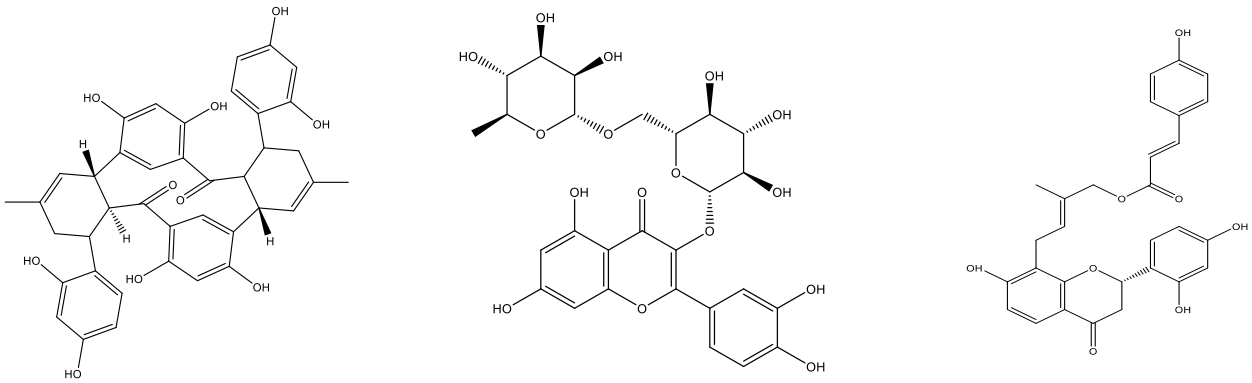
1. Introduction

Parasitic diseases are one of the most deadly and widespread infections on the planet, resulting in millions of morbidities and deaths each year [1]. *Plasmodium falciparum* is the most common vector-borne infectious disease that kills 0.5 million people each year. The single-cell eukaryote has a complicated life cycle and is an obligatory intracellular parasite of hepatocytes and erythrocytes infection can lead to a variety of complications, including severe anemia and cerebral malaria. This can result in death *Plasmodium falciparum* replicates many times inside erythrocytes during the course of 48 h, resulting in rapid disease progression and exponential expansion. No other pathogen has put greater selection pressure on the human genome than the most common infectious illness affecting children. There is no effective vaccination, however, there are various curative therapies. *Plasmodium falciparum* is the most dangerous form of malaria, infecting humans and causing the majority of malaria-related deaths. Despite the fact that the worldwide malaria epidemic has subsided, the World Health Organization predicts that 212 million cases of malaria and 429,000 deaths occurred in 2020 [2,3]. Malaria medications are desperately needed, and traditional malaria treatment procedures could be a viable source of novel antimalarial chemicals [4]. FP-2 and falcipain-3 (FP3) are important papain-family (C1) clan CA trophozoite cysteine proteases that cleave host hemoglobin (native and denatured) and cause erythrocyte rupture in the digestive food vacuole [5–7]. FP-2 is the primary haemoglobinase of *Plasmodium falciparum*, the human malaria parasite. It is currently acquiring clinical significance as a therapeutic target of choice in the fight against malaria [8]. *Plasmodium* cysteine protease is involved in a number of biological processes, including

membrane rupture. Hemoglobin (Hb) is a protein found in red blood cells that distributes oxygen to your body's organs and tissues while also transporting carbon dioxide back to your lungs. Hb breakdown, protein trafficking, and host cell invasion [9,10]. As a result, the interference of crucial indicator protein FP2 is used to monitor the proliferation of malarial parasites it is an appealing target for antimalarial drug development [11]. In this research, the well-known

"PyRx" docking simulation was employed to conduct an experiment on the disease of malaria. At present study, docked 50 different anti-malaria polyphenols with FP-2 (2GHU.pdb) from the protein data bank in order to find the most effective and efficient. With a value of −8.1 Kcal/mol, brosimone was discovered to have the lowest binding energy. As a result, it is a viable candidate for antimalarial medication. Based on our research, polyphenols from *Artocarpus* (Figure 1) [12] have strong pharmacological potential against a variety of biological targets.



Brosimone **Rutin** **Lakoochanone**

Figure 1. Chemical structure of *Artocarpus lakoocha* polyphenols.

2. Materials and Methods

2.1. Molecular Docking Simulations

For this investigation, a set of 50 ALP is well-known. Overall, there are five key processes in molecular docking: protein preparation, ligand preparation receptor grid construction, ligand docking procedure, and docking results viewing. 'ChemDraw' was used to draw all of the necessary structures. The 3D crystal structures of *Plasmodium falciparum* (PDB ID: 2GHU) were downloaded protein data bank (PDB database, https://www.rcsb.org). The binding pocket of 2GHU target enzymes was docked with (co-crystallized ligand). The RMSD value was used to assess the reliability of the docking process. The grid parameter set up was Center X:47.6593 Y:11.7104 Z:−12.9581 and Dimensions (Angstrom) X:250,000, Y:250,000, Z:250,000. The grid was centered on active binding site residues such as His D:19, Glu:222, ALA:157, TRP:206, CYS:39, and so on. 'PyRx' was used to execute the docking study, then Discovery Studio 2020 Visualizer to visualize the results [12–14].

2.2. In-Silico Drug-Likeness and ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) Analysis

50 ALP were subjected to an in-silico ADME analysis using SWISS tools http://www.swissadme.ch, For the toxicity assessments, we used 'SMILES' formats of chemical structures.

3. Result and Discussion

3.1. Molecular Docking Simulations

FP-2 is a promising target for malaria treatment. Despite the fact that various FP-2 inhibitors have been clinically proven for the treatment of malaria in recent years, the quest for new active molecules against FP-2 remains difficult. Our research aims to filter several compounds using molecular docking and virtual screening to find novel anti-FP-2 inhibitors. Molecular docking analysis of 50 ALP on an anti-malarial target suggested that Bromisine had a high affinity towards 2GHU. The docking interactions depicted that this compound had interactions with GLY A:40, HIS A:174, CYS A: 42, ALA A:157, LYS D:37 A:85, GLN D:36, TRP A: 206 amino acids with 3 conventional hydrogen bonds at the receptor site of the target 2GHU (Figure 2) [15]. HIS B:174 formed a carbon-hydrogen bond. Van der Waals interactions were observed for GLY D:40. Pi-donor hydrogen bond was observed for GLN D:36. Pi-alkyl interactions were also observed for TRP D:210 and ALA D:157. Pi-pi amide-pi- pi stacked was observed for CYS D:39. Tables 1 and 2 would give better insights into interaction profiles of studies ALP. From docking analysis of 50 bioactive on 2GHU. And the top 3 best docked hits as Rutin(docking score: −7.4kcal/mol), Lakoochanone(docking score −8kcal/mol) and Brosimone (docking score −8.1kcal/mol). To determine the most effective and efficient compound, 50 distinct polyphenols were docked with FP-2 (2GHU) from the protein data bank. With binding energy of −8.1 Kcal/mol, brosimone was determined to have the lowest binding energy. As a result, it is a viable candidate for anti-malaria treatment.

Table 1. Docking interaction energies* of selected 50 bio-active molecules for target protein **2GHU**.

Molecule	PyRx Interaction Energy
1. Brosimone	**−8.1** *
2. Lakoochanone	**−8**
3. Rutin	**−7.4**

***** Docking scores have been provided only for the higher affinity scored target protein.

Table 2. The energy contribution of the key residues is computed by docking methodology.

Sr. No.	Molecules	Residues with Contribution Energy
1.	Rutin	HIS D:19, GLU D:222, ALA A:157, TRP A:210, GLN A:209, LYS A:37, ASP A:35, CYS A:39
2.	Lakoochanone	GLY A:166, ASP A:155, LYS D:135, PHE A:164
3.	**Brosimone**	**TRP D:210, LYS D:37, TRP D:206, CYS D:39, CYS D:42, GLY D:40, GLN D:40, HIS D:174, ALA D:157**

3.2. In-Silico ADMET Studies

Cytochrome P450 (CYPs) enzymes are essential enzymes involved in a variety of metabolic processes. Table 3 shows in-silico computed ADMET (absorption, distribution, metabolism, excretion, and toxicity) in the body attributes for the top three best-docked hits. Rutin, Lakoochanone, and Brosimone, three ALP, had positive human intestinal absorption profiles, negative Blood-Brain Barrier passage, were non-carcinogenic, non-AMES hazardous, and had class IV acute oral toxicity profiles.

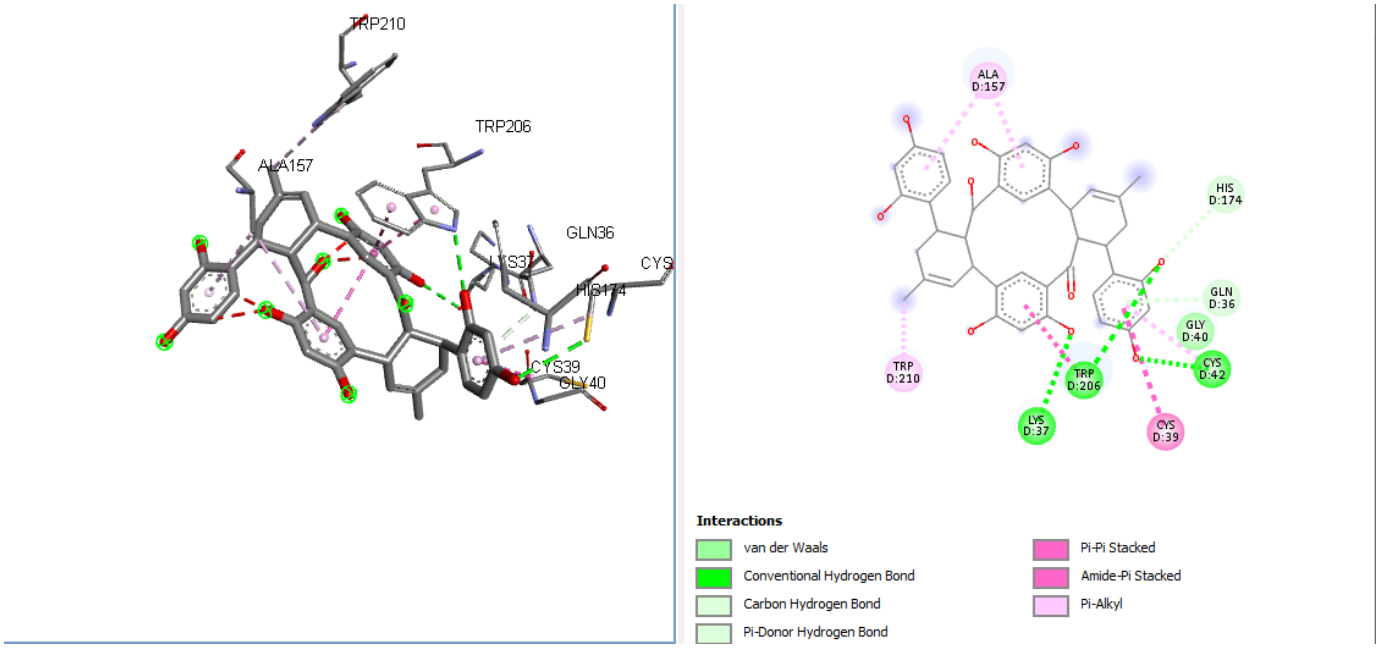


Figure 2. 2D and 3D-interaction profiles for best docked Brosimone with 2GHU.

Table 3. In-silico ADMET profiling for top 3 best-docked hits against target 2GHU.

	GI Absorption	BBB Permeant	P-gp Substrate	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	Lipinski	Bioavailability Score
1. Lakoochanone	Low	No	No	No	No	Yes	No	Yes	0.55
2. Rutin	Low	No	Yes	No	No	No	No	No	0.17
3. Brosimone	Low	No	Yes	No	No	No	No	No	0.17

4. Conclusions

Brosimone has strong interactions with the 2GHU enzyme, according to current research (docking score: −8.1 kcal/mol) (amino acid residues: TRP D:210, LYS D:37, TRP D:206, CYS D:39, CYS D:42, GLY D:40, GLN D:40, HIS D:174, ALA D:157). AMES Toxicity and Carcinogens are not present. Molecular docking analysis was used to explore Brosimone antimalarial properties against the 2GHU enzyme, based on previous literature reports. Given the benefits of ALP, this research could lead to the development of more effective anti-malarial compounds. Furthermore, Brosimone might be evaluated in-vitro for antimalarial properties. For numerous ALP, in-silico pharmacokinetics and toxicities was performed and concluded that critical insights into the mechanism of action of Brosimone and other ALP as a potential therapeutic agent (2GHU) against malaria.

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Conflicts of Interest: The authors declare no conflict of interest.

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