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Original Article

STRUCTURE-BASED DRUG DESIGN METHOD: MOLECULAR DOCKING STUDY AND PHARMACOPHORE MODELLING OF APIGENIN AS AN ANTIMALARIAL

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ABSTRACT

Objective: Uses molecular docking and pharmacophore modeling methods to examine the antimalarial activity of apigenin (API) on distinct kinds and varieties of *P. falciparum* (Pf) receptors.

Methods: Using Autodock 4.0.1 and ligandscout software, molecular docking was conducted on multiple types of Pf receptors, including lactate dehydrogenase (Oxidoreductase), Enoyl-acyl carrier-protein (Oxidoreductase), Triose-phosphate (Isomerase), and plasmepsin II (Hydroxylase).

Results: The lowest free energy binding values found in two of the four investigations (API on an enoyl-acyl carrier and triose-phosphate receptors) suggested a potential effect. These values were-8.06 kcal/mol and-8.76 kcal/mol, respectively. The API had lower values of the inhibitory constant on the lactate dehydrogenase, enoyl-acyl carrier-protein, Triose-phosphate, and plasmepsin II receptors (44.06 µM, 1.24 µM, 376.76 nM, and 57.04 µM, respectively). In terms of the essential elements of amino acid residue interaction, the API and the native ligand were identical (SER218 for 1LF3 receptor; LEU315, GLY110, and TYR111 for 1NWH receptor; VAL212, LYS12, ASN233, and GLY232 for 1O5X receptor; and ILE31, PRO250, and PRO246 for 1U4O receptor). According to the findings of the pharmacophore modeling, the functional groups of hydroxyl were the most important functional groups to interact with the important amino acid residues of the receptors.

Conclusion: The API considerably displays competitive antimalarial potency in various Pf receptors.

Keywords: Antimalarial, *Plasmodium falciparum*, Apigenin

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INTRODUCTION

Worldwide, 247 million malaria cases in 2021 were in children under five. Geographically, roughly 92% (200 million) of malaria cases and 404,550 fatalities were in Africa [1]. Each year, this illness claims a sizable number of lives throughout Africa. The main causes of the common disease are the protozoan parasites *Plasmodium falciparum* (Pf) and *Plasmodium vivax* (Pv). High mortality and morbidity rates exist dependent on the parasite that caused the infection [2].

Malaria is treated and prevented using the combination therapy of artemisinin and antibiotics. We are conscious that varied drug resistance and issue-related adverse effects of these medications continue to be the principal therapeutic barriers [3]. Herbal medication is a potential option and alternative malaria treatment. A natural substance called apigenin (API), which belongs to the flavone subclass of flavonoids, is found in many plants, including celery, parsley, grapes, chamomile, onions, maize, tea, sugar, and sprouts. Numerous pharmacological effects of API include anti-inflammatory, antidiabetes, vasodilators, anticoagulant, antidiabetic, anti-cancer, and antimalarial properties [4–6].

Previous studies investigated API antimalarial properties. The outcome demonstrates that API can inhibit *Plasmodium falciparum* RIO-2 kinase. Apigenin could act as an antioxidant by affecting the cellular signaling system, and it could also reduce inflammation by preventing the release of proinflammatory TNF-α cytokines. These cytokines can be inhibited to stop the inflammation that results from cerebral malaria. Antioxidants can help reduce the negative effects of oxidative stress by using antimalarial drugs [4, 5].

However, the report does not mention specific target receptors or cellular mechanisms where API acts. As a result, the authors undertook a molecular docking experiment to test API antimalarial efficacy on various types and classes of receptors. We also researched the pharmacophores model to learn more about the molecular processes by which the functional group interacts with the receptor's amino acids.

MATERIALS AND METHODS

Determine target receptors and the lead compounds

Based on the receptors widely employed to assess antimalarial effects, primarily from the protein of Pf, the targets for this investigation were found. The lead chemicals and receptor targets underwent initial screening based on various factors, including the method used to extract the receptor, the number of amino acids present, the organism's origin, and the resolution of each receptor.

Validation using the molecular docking method

The molecular docking method validation process used several Pf receptor structures from different classes [7, 8]. On several families of Pf receptors, including lactate dehydrogenase (Oxidoreductase), Enoyl-acyl carrier-protein (Oxidoreductase), Triose-Phosphate (Isomerase), and Plasmepsin II (Hydroxylase), the molecular docking validation approach was used. The receptors were originally downloaded from the Protein Data Bank database at (https://www.rcsb.org/) in (.pdb) format [9–11]. Then, using discovery studio visualizer software, each receptor was prepared by removing it from the complex lead compounds. The water molecule at the receptor was eliminated to lessen the variance in the formation results of the hydrogen bonding interaction. Using Autodock 4.0.1, the Compute Gasteiger and Kollman charges were added to the Native ligand or lead compound and each receptor, respectively, before adding non-polar merged hydrogen to the ligand molecules and polar hydrogen the protein molecule to finish the process. Once the entire preparation was finished, the data were saved in the (.pdbqt) format, where pdbq stands for protein data bank partial charge (q), and t refers to atom type (t). Then, using GA Runs 100 and the energy analysis (2500000), the data for the receptor (.pdbqt) and ligand (.pdbqt) were merged, and further docking parameters were set to create the Grid Parameter File (.gpf) and the Docking Parameter File (.dpf). Redocking was done as the final step to examine the information gleaned from the molecular docking validation results using the Command Prompt (CMD) tools.

Virtual screening on test compound

The use of the structure-based drug design (SBDD) method, the antimalarial activities of API as the test compound, was examined in this study. The test targets included many Pf receptor structures, while the lead compounds included the inhibitor EH58, nicotinamide adenine dinucleotide, 2-phosphoglycerate, and 2,6-naphthalene dicarboxylic acid [12]. The molecular test substance was modeled using ChemDraw 2D, and the model energy minimization process was carried out using ChemDraw 3D. The results of the structures were saved in (.pdb) format following the minimization process. Then, using the Autodock 4.0.1 software, the Compute Gasteiger Charge and non-polar merged hydrogen were applied to the test compounds. The test compound was paired with each target receptor in the final steps to create a (.gpf) file and a (.dpf) file [13].

Pharmacophore modeling

Each API-receptor complex previously docked in molecular docking research was modeled using the SBDD method. Ligandscout 4.4 was used to load each complex into the structure-based perspective. The development of the pharmacophore and its 2D depiction were then used to interpret and evaluate the results after the interaction had been studied by selecting the yellow box [6, 14–16].

RESULTS AND DISCUSSION

Table 1 depicts the results of the evaluation methods using the Root Mean Standard Deviation (RMSD) results, where the population cluster is the critical parameter. The maximum requirement number is 2 Armstrong, and RMSD measures the difference between the native ligands' positions before docking and after redocking [17]. The data from the test results showed that three of the four receptors met the requirements since their respective RMSD values for the receptors for enoyl-acyl-carrier protein, triose-phosphate isomerase, and lactate dehydrogenase are all below 2A, i.e., 0.940 A, 1.522 A, and 1.940 A. Besides the Plasmepsin II receptor, the RMSD value exceeded the requirement (2.638 A). Due to how those receptor clusters distributed the data from 100 different docking conformations, they are referred to as the best receptor clusters and molecular docking [18]. The RMS tolerance provided by "rmstol" in the docking parameter file defined how the docked conformations were clustered (dpf). The more clusters, the greater the probability that the preferred conformation will bind to the protein target [19].

Table 1: Validation using molecular docking method

PDB ID (Resolution)	Organism	Receptor (Classification)	Complexed ligand	Amino acid interaction	Free energy (ΔG Gibs)	Inhibition constant (CI)	RMSD
1LF3 (2.70 A)	*Plasmodium Falciparum*	Plasmepsin II (Hydrosilase)	Inhibitor EH58	GLY216, SER218, LEU131, LEU292, ILE123, ILE300, MET15, TYR77, VAL78	-9.27 kcal/mol	160.60 nM	2.638 A
1NHW (2.35 A)	*Plasmodium Falciparum*	Enoyl-acyl-carrier-protein (Oxidoreductase)	NAD, TCC	LEU315, SER317, TYR111, ALA217, ASP168, ALA169, LYS285, TYR277, TYR267, ALA312, THR266, GLY110, LEU216, TRP131, SER215.	-12.50 kcal/mol	682.27 pM	0.940 A
1O5X (1.10 A)	*Plasmodium Falciparum*	Triose-phosphate isomerase (Isomerase)	2-phosphoglycerate	VAL212,GLY232, THR172, ALA234, ASN233, GLY173, SER211, LYS12, GLY171	-5.97 kcal/mol	41.97 µM	1.522 A
1U4O (1.70)	*Plasmodium Falciparum*	lactate dehydrogenase (Oxidoreductase)	2,6-naphthalene dicarboxylic acid	PRO246, ILE31, MET30, PRO250	-5.87 kcal/mol	50.19 µM	1.94 A

The validation results from the docking method show that the inhibitor EH85, nicotinamide adenine dinucleotide, 2-phosphoglycerate, and 2,6-naphthalene dicarboxylic acid have free energy binding values of 9.27 kcal/mol, 12.50 kcal/mol, 5.97 kcal/mol, and 5.87 kcal/mol, respectively, and that these values correspond to an inhibitory constant of 160.60 nM, 682.27 pM, 41.97 µM, and 50.19 µM.

Table 2: Virtual screening results

PDB ID	Amino acid residue		Free energy (ΔG Gibs)		Inhibition constant	
	Apigenin	Native ligand	Apigenin	Native ligand	Apigenin	Native ligand
1LF3	ASP34, SER218, ASP214, THR217	GLY216, SER218, LEU131, LEU292, ILE123, ILE300, MET15, TYR77, VAL78	-5.79	-9.27 kcal/mol	57.04 µM	160.60 nM
1NHW	ASP107, GLY106, LEU315, GLY110, TYR111	LEU315, SER317, TYR111, ALA217, ASP168, ALA169, LYS285, TYR277, TYR267, ALA312, THR266, GLY110, LEU216, TRP131, SER215.	-8.06	-12.50 kcal/mol	1.24 µM	682.27 pM
1O5X	VAL212, GLY210, GLU165, LYS12, LEU230, ASN233, GLY232, VAL231	VAL212, GLY173, ASN233, THR172, GLY232, ALA234, SER211, LYS12, GLY171	-8.76	-5.97 kcal/mol	376.76 nM	41.97 µM
1U4O	SER245, ARG171, ILE31, PRO250, ALA236, PRO246	PRO246, ILE31, MET30, PRO250	-5.94	-5.87 kcal/mol	44.06 µM	50.19 µM

According to table 2, using the SBDD approach with GA runs 100 and medium energy 250.000, the virtual screening result of the test chemical on Pf receptors was compared to the native ligands of each receptor. The data consists of the residues of amino acids (a parameter used to compare the activity of the test molecule and the lead compounds depending on the kind of interaction and amino acids), the free energy, and other information (a factor used to measure the degree of the interaction formed; the stronger the bond and the spontaneous link formed, the lower the energy) [20], the constant inhibition values (using the value of the inhibition constant to estimate the drug potential, in which the inhibition constant is used to estimate the strength of the interaction formed) [21].

Fig. 1A-D 3D shows the API binding site on the Pf receptors, and this data can be utilized to determine if the drug has a competitive or non-competitive inhibitory effect. Based on these results, API shared the same active site with the lead compounds in all tests of its ability to bind to Pf receptors. We discovered that the lead compounds and

the API amino acid residues had interacted similarly (SER218 for 1LF3 receptor; LEU315, GLY110, and TYR111 for 1NWH receptor; VAL212, LYS12, ASN233, and GLY232 for 1O5X receptor; and ILE31, PRO250, and PRO246 for 1U4O receptor). This necessary amino acid can be utilized to show how similar each receptor is to the active lead compounds and the API molecule [22–24].

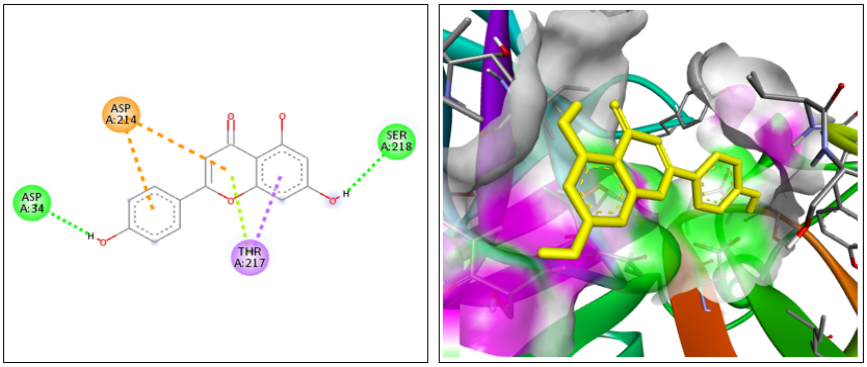

Fig. 1A: 2D and 3D visualization between API and plasmepsin II

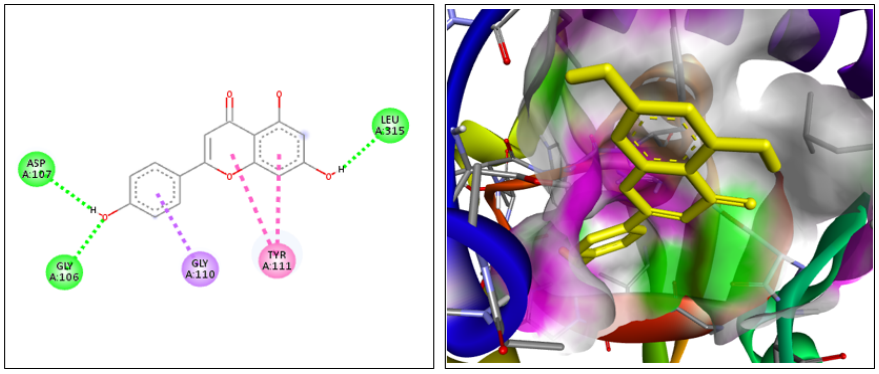

Fig. 1B: 2D and 3D visualization between API and enoyl-acyl carrier protein

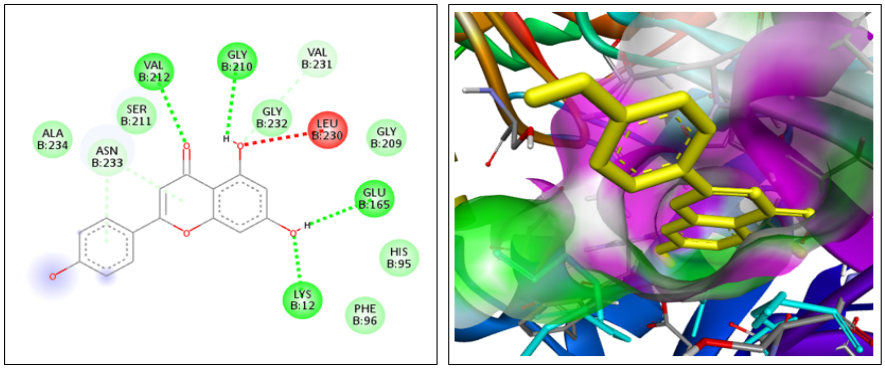

Fig. 1C: 2D and 3D Visualization between API and triose-phosphate isomerase

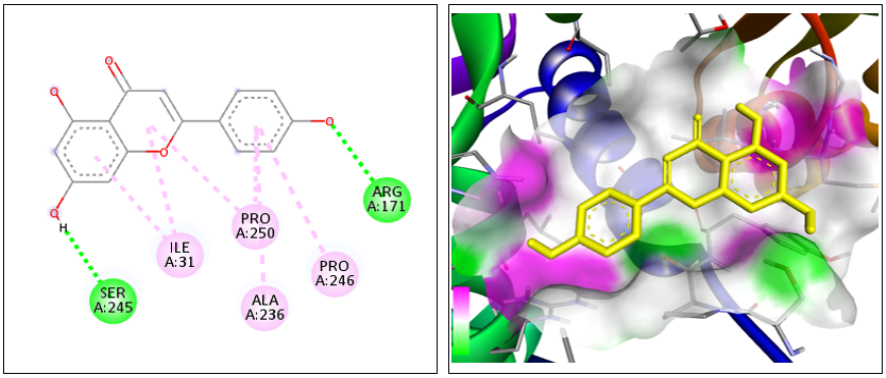

Fig. 1D: 2D and 3D visualization between API and lactate dehydrogenase

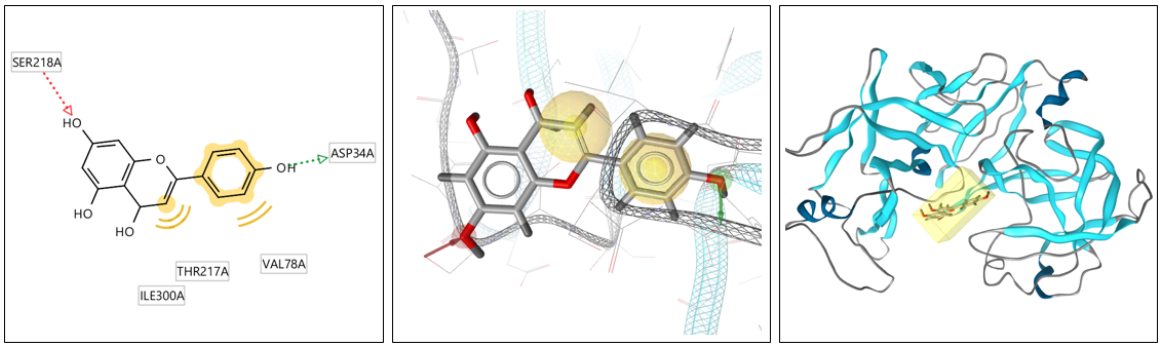

Fig. 2: A visualization of pharmacophore modeling between API with plasmepsin II

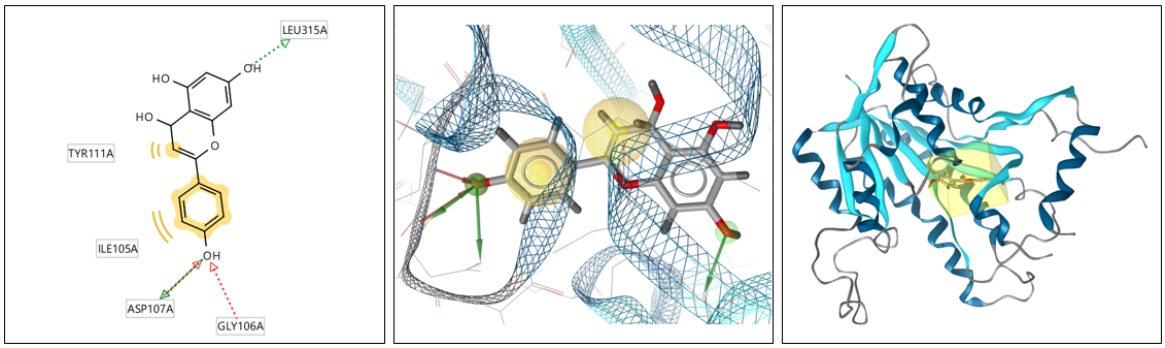

Fig. 2: B 2D-3D visualization of pharmacophore modeling between API with enoyl-acyl carrier protein

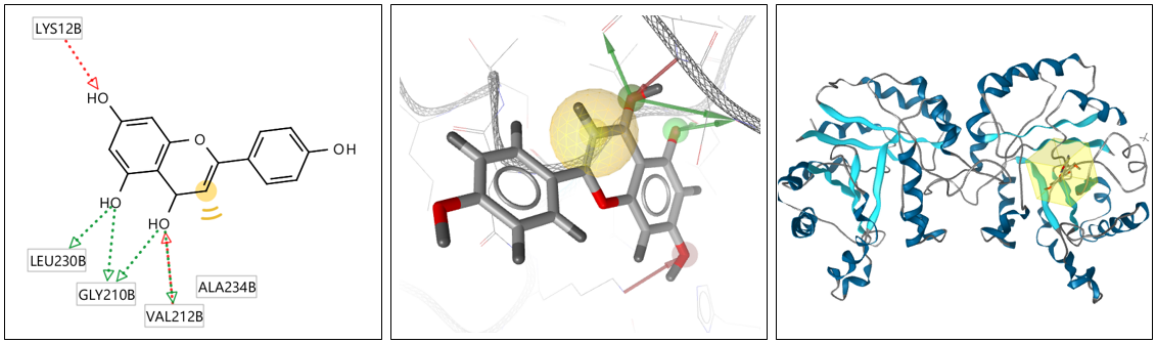

Fig. 2: C 2D-3D visualization of pharmacophore modeling between API with triose-phosphate isomerase

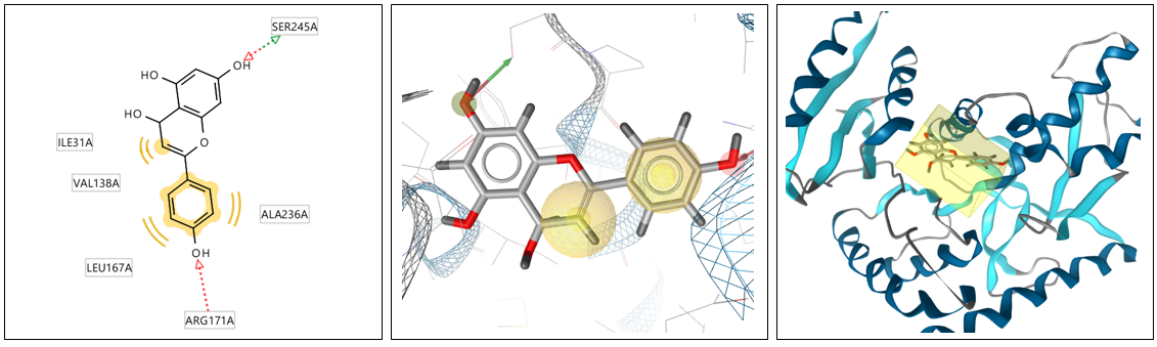

Fig. 2: D 2D-3D Visualization of pharmacophore modeling between API with lactate dehydrogenase

Fig. 2 Depicted is the API pharmacophore model on Pf receptors. To study the functional groups interacting with the targets and possible structural changes that may be made to increase effectiveness and address the API physicochemical restrictions, pharmacophore modelling was used [14, 25]. The findings indicated that benzopyran emerged as a potential element that could be modified in subsequent drug development due to its unintended interaction with the amino acid residues. At the same time, hydroxyl was the primary functional group responsible for bonding with the significant amino acid residues on each receptor. We came to the same conclusions after

doing a literature study on the effects of API compounds on diverse targets from various disorders. Hydroxyl functional groups are necessary for the interaction of amino acids with receptors [26].

DISCUSSION

Based on analytical data from the protein data bank database, the structural properties of the receptors were identified using NMR spectroscopy, electron microscopy and X-ray crystallography. Each strategy comes with its own set of benefits and drawbacks. The X-ray diffraction pattern in X-ray crystallography revealed the molecules' structures, which provides details on the conformation and separation of close-knit atoms for NMR spectroscopy. The final atomic model was created using a variety of data points for each method. The Pf receptors used in this work were obtained using X-ray.

Additionally, the Pf protein-derived receptors were a great model for malaria receptors. Since the receptor with resolution value 3A was closest to 2 Armstrong, it was considered the most acceptable receptor for the standard [27]. The resolution value describes how closely the generated structure mimics the original receptor structure. The validation results of the molecular docking approach on the Pf receptors showed the importance of the RMSD values. The RMSD number, which had to be less than 2 Armstrong, was used to reflect the variation in native ligand locations during docking and redocking [28]. The results showed that all four receptors, triose-phosphate, lactate dehydrogenase enoyl-acyl carrier and plasmepsin II had RMSD values of 1.522 A, 1.94 A, 0.940 A and 2.638 A respectively; the values for free energy binding were 5.97 kcal/mol, 5.87 kcal/mol, 12.50 kcal/mol, and 9.27 kcal/mol (table 1). The receptors interacted with hydrogen and non-hydrogen bonds on various amino acid residues. The findings of the molecular docking screening show that these values met the criteria for evaluating API as an antimalarial [29]. The results showed that two of the four experiments (Apigenin on Enoyl-Acyl Carrier and Triose-Phosphate receptors) suggested a potential effect, as evidenced by the lowest free energy binding values observed at-8.06 kcal/mol and-8.76 kcal/mol, respectively. Lower energy activation is correlated with lower free energy binding. As a result, there's a probability that the Apigenin substance and the receptors will interact with one another and trigger a spontaneous reaction [30]. In Addition, concerning Triose-Phosphate, Lactate Dehydrogenase, Enoyl-Acyl Carrier Protein, and Plasmepsin II, the API molecule has a lower value of the inhibition constant as indicated by the constant inhibition results (376.76 nM, 44.06 M, 1.24 M, and 57.04 M, respectively). A relatively low number is considered to have substantial power since the molecule has a significant inhibitory capacity at low doses, which signifies the ability of the substance to block receptors or enzymes [31]. When the energy and inhibition constants are considered, one of the variables influencing the compound's activities is how its structure interacts with the amino acids at its receptors. Through similar amino acid residues (SER218 for the 1LF3 receptor, LEU315, GLY110, and TYR111 for the 1NWH receptor, VAL212, LYS12, ASN233, and GLY232 for the 1O5X receptor, and ILE31, PRO250, and PRO246 for the 1U4O receptor), the API molecule interacts similarly with the native ligands (fig. 1.) Since we are aware that this contact is reversible and substantially stronger than other forms of interaction, we additionally highlighted the hydrogen bonding interaction of the API (table 2) based on the data [32,33]. The comparative experiment demonstrates the same activity in binding the receptor between the lead and API compounds. API competitive binding to receptors' active pockets can prevent this Pf from activating. This mechanism of action slows down the growth of Pf. The API compound hydroxyl functional groups behave as hydrogen-bonding donors. Acceptors in pharmacophore modeling studies, interacting with receptor amino acids including ASP34, SER218, ASP107, GLY106, LEU315, VAL212, GLY210, GLU165, LYS12, SER245, and ARG171 (fig. 2). The key elements that form bonds with significant amino acid residues of receptors are hydroxyl. At the same time, the benzopyran group may play a part in altering the structure of this molecule during drug development in the future due to their possible interaction with significant amino acid residues, as observed from the results of pharmacophore modeling. As a result, API may eventually be developed into a medication with high efficacy, favorable physicochemical characteristics, and minimal side effects.

CONCLUSION

The *Plasmodium falciparum* receptors are competitively inhibited by API, which has antimalarial properties. When compared to the native ligands of the receptors, it exhibits a considerable number of hydrogen bonding interactions, a low value of inhibitory constants, and a similar kind of amino acid interaction. The hydroxyl functional group is the leading active group in charge of interacting with the essential amino acid residues of the receptors, and benzopyran appears as a potential subject that may be studied and changed in subsequent drug development, according to the pharmacophore modeling.

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Nil

AUTHORS CONTRIBUTIONS

Each author has made equal contributions.

CONFLICTS OF INTERESTS

Declared none

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