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INVITED ARTICLE

DOCKING STUDY OF MARKETED ANTIMALARIALS ON *PLASMODIUM FALCIPARUM* DIHYDROFOLATE REDUCTASE (*Pf* DHFR)

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ABSTRACT

Malaria is one of the most pivotal parasitic diseases in humans and the malarial parasite transmission in above 100 countries of a population of five million people. In this study, we selected marketed antimalarial drugs hydroxychloroquine, artemisinin and primaquine and performed docking study using Auto Dock on *Plasmodium falciparum* dihydrofolate reductase (*Pf*DHFR). Docking study suggested about the binding of the drugs at the active site. Docking study also demonstrated about the potency of the drug and their binding affinity with the target. Different binding modes of marketed drugs were observed with different amino acid interactions with different features like hydrophobic, hydrogen bonding, and van der Waals interactions. The least binding energy interaction structures were selected to observe the dock pose of drugs at the active site of *Pf*DHFR.

Keywords: Malaria; Antimalarial Drugs; Docking; *Plasmodium falciparum* dihydrofolate reductase (*Pf*DHFR)

INTRODUCTION

Malaria is a severe infectious disease caused by a genus protozoan plasmodium parasite. Malaria is one of the most pivotal parasitic diseases in humans and the malarial parasite transmission in above 100 countries of a population of five million people. Malaria is primarily occur by genus *Plasmodium* protozoan parasites [1,2]. Most of the transmission occurs by female anopheles mosquito. The other infecting species are a variety of hosts,

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including reptiles, birds, rodents and primates. Malaria is caused by different *Plasmodium* species, including four well-known *Plasmodium* species triggering human malaria, namely *P. falciparum, P. vivax, P. ovale and P. malariae*. The fifth one is *P. knowlesi* has recently been recorded to cause human infection in many other Southeast Asian countries. *P. falciparum* causes the most severe illnesses and malaria deaths. Many antimalarial drugs are available in the market for the treatment of malaria and they act on different stages of malaria life cycle [3]. Novel antimalarial targets are known and they are well recognized for the development of new targeted antimalarial agents. In this study, we performed docking study of well-known commonly used antimalarial drugs hydroxychloroquine, artemisinin and primaquine on *Pf*DHFR. *Plasmodium falciparum* dihydrofolate reductase is a recognized target for antimalarial dug development [4]. DHFR catalysis involves the conversion of 7,8 dihydrofolate to 5,6,7,8 tetra hydrofolate reductase a using the NADPH as a co-enzyme. The pivotal stage is the hydride molecule to substrate and it will utilizing the reaction mechanism with the specifying transition state. DHFR utilizes dihydrofolate produced during DNA synthesis pathway and recycles it into tetrahydrofolate. There are several biological pathways, which produces DHF as a product, but one of the most important is a thymidine synthase pathway. This pathway requires oxidation of methylene tetrahydrofolate into dihydrofolate and methylene tetrahydrofolate derives from regular tetrahydrofolate. If the reaction proceeded into infinity, it eventually developed DHF and THF depletion that blocked the DNA pathway by completely inhibiting DNA synthesis through inducing cell death. The active site is located between DHFR's two subdomains 1) adenosine binding subdomain, which contain three short sequence of amino acids residues called loops (residue10-20) and other subdomain are 2) FG loop (residue 117-131) and GH loop (residue 146-148). GH loop of amino acids is pivotal for stabilizing nicotinamide structure ring and NADPH enzyme [5].

MATERIALS AND METHODS

In this study, we used Auto Dock 4.2.6. Software [6] available at http://autodock.scripps.edu/ for docking study. *Plasmodium falciparum* dihydrofolate reductase (PDB ID: 3QGT) [7] was download from https://www.rcsb.org/ as PDB file of receptor and converted into .pdbqt file of the receptor. Ligands (hydroxychloroquine, artemisinin and primaquine) were selected and prepared in same way as receptor preparation and named as a ligand .pdbqt. A grid box was chosen with the required dimensions (center x = 23.088, y = 4.837, and z = 12.307). Once this all the things were done, a command prompt was opened to give the commands. After running docking study, the results were showed as binding pose and the binding energies. Finally, different binding interactions of

the ligands and receptor were observed and studied.

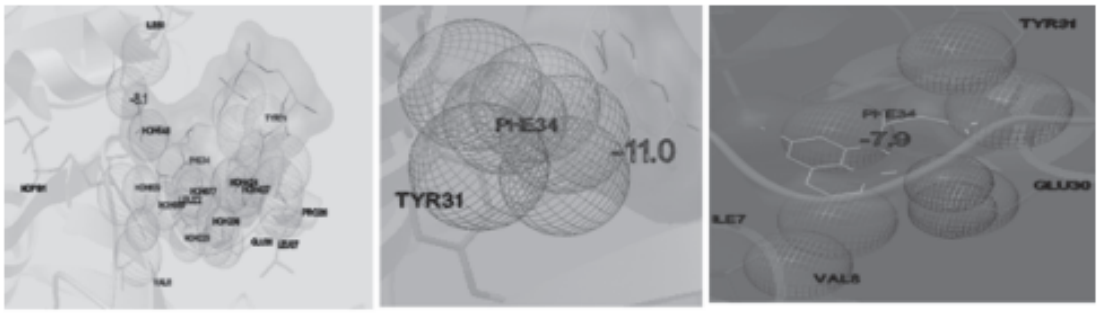
RESULTS AND DISCUSSION

Docking study was performed with known marketed drugs hydroxychloroquine, artemisinin and primaquine on *Pf*DHFR in order to understand the binding of these well-known drugs on an antimalarial drugs target. All these three drugs binds at the active site of the receptor and showed very good binding energy (kcal/mol). The results of docking study are shown in **Table 1**.

*Pf*DHFR enzyme interacted with these marketed drugs with different amino acids at the binding site. These three compounds were mainly interacted with H-bond formation, they also formed pi-pi stacking with the ring. Along with this some lipophilic interactions were also observed at alanine and valine residues. Binding free energy analysis ensured that artemisinin had better binding free energy than other two drugs. The results indicated that dihydrofolate reductase enzyme can be inhibited by these potent antimalarial drugs. Different binding pose of these drugs were generated at the binding site of *Pf*DHFR, and the pose with the good binding free energy value is given in the **Figure 1**.

Table 1: Docking results with binding energy and amino acid residue

Sr. No	Name of antimalarial drug	Binding Energy (Kcal/mol)	Binding site amino acid residue and water molecules
1	Hydroxychloroquine	-8.0	ALA9, VAL8, HOH677, HOH230
2	Artemisinin	-11.0	PHE34, TYR31
3	Primaquine	-7.9	GLU30,TYR31,PHE34, VAL8



(A) (B) (C)

Figure 1. Binding pose of (A) Hydroxychloroquine, (B) Artemisinin and (C) Primaquine at the active site of *plasmodium falciparum* dihydrofolate reductase (*Pf*DHFR).

CONCLUSIONS

In this study, we selected *Pf*DHFR antimalarial drug target and performed docking study in order to study the binding model of well-known antimalarial drugs on the target using Auto Dock software. We performed docking of old as well as new drugs to study their binding with this potential drug target of malaria. We identified different binding modes of drugs with different amino acid interactions with different features like hydrophobic, hydrogen bonding, and van der Waals interactions and from that the least binding energy interaction drug's poses were selected. This study helped us to understand the binding mode of known drugs using docking study.

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