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Research Article

In silico 3-D structure prediction and molecular docking studies of inosine monophosphate dehydrogenase from *Plasmodium falciparum*

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ABSTRACT

Growing resistance in malarial parasites, particularly in *Plasmodium falciparum* needs a serious search for the discovery of novel drug targets. Inosine monophosphate dehydrogenase (IMPDH) is an important target for antimalarial drug discovery process in *P. falciparum* for the treatment of malaria. In the absence of x-ray crystal structure of this enzyme, homology modeling proved to be a reasonable alternate to study substrate binding mechanisms of this enzyme. In this study, a 3-D homology model for *P. falciparum* IMPDH was constructed taking human IMPDH (PDB code 1NF7) as template. Furthermore, an *in-silico* combinatorial library of ribavirin (RVP) derivatives (1347 molecules) was designed and virtually screened for ligands having selectively greater binding affinity with *Plasmodium falciparum* IMPDH relative to human IMPDH II. A total of five Ribavirin derivatives were identified as having greater binding affinity (−126 to −108 Kcal/mol and −9.4 to −8.6 Kcal/mol) with *Plasmodium falciparum* IMPDH. These five inhibitors should be used as selective and potent for *Plasmodium falciparum* IMPDH. Such type of study will provide information to synthetic medicinal chemist to enhance the potential of compounds (RVP derivatives) as chemotherapeutic agents to fight against the increasing burden of malarial infections.

1. Introduction

Malaria is an endemic life threating parasitic infection responsible for mortality, morbidity in underdeveloped countries of the world (Na-Bangchang and Congpuong, 2007). It still remains a hazard to over 3.4 billion peoples around the globe. In 2013, there were 97 countries with regularly spreading malaria transmission, and 7 countries in the prevention of reintroduction phase, making a total of 104 countries and territories in which malaria is currently endemic (World Health Organization, 2013). The global mortality rate for malaria was approximately 1238,000 cases reported by world health organization (WHO) report 2012 (Newman, 2012). After every 40 s one child dies due to malaria, So globally malaria is responsible for per day loss of greater than 2000 premature individuals (Sachs and Malaney, 2002).

According to the WHO's 2016 report, the malaria parasite is responsible for killing around 429,000 people and infect 212 million (World Health Organization, 2016), in the Eastern Mediterranean Region were at risk of malaria. Malaria endemicity is common throughout the world but still there are certain countries which have areas of high malaria spreading including Pakistan, Afghanistan, Djibouti, Somalia, South Sudan, and Yemen (World Health Organization, 2013). In the total world's population 41% exists in the region where malaria is spreading (e.g. some areas of Africa, Asia, the Central East, Middle and south America, Hispaniola, and Oceania) (Eliades et al., 2003). Africa is the highest malarial affected area of the world having approximately 200–450

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million cases annually (Guerin et al., 2002). For the control of malaria African nation annually consume more than US$12 billion (Bi et al., 2003). At present the global fund for malaria eradication is US$ 2.3 billion which is not sufficient for complete elimination of malaria up to 2020 so there is urgent need of new resources require for complete eradication of malaria (Newman, 2012).

Malaria is a vector born disease transmitted by female *anopheles* mosquito and mostly caused by five species, including *Plasmodium falciparum, P. vivax, P.ovale, P. knowlesi* and *P. malariae* (Malmberg, 2012).

There are three families of drugs currently used for malaria, the *antifolates* (*pyrimethamine, sulfadoxine)* the *quinolones* (*chloroquine, primaquine, quinine, mefloquine*) and *artemisinin* derivatives. The *pyrimethamine (sulfadoxine)* and *chloroquine* treatments are limited because of emerging resistance in the malaria protozoa against these drugs while other drugs like *halofantrine, mefloquine, proguanil, atovaquone*, *lumefantrine* and *artemether* are limited in their usage because of high cost (Wiesner et al., 2003).

All parasitic protozoans including *P. falciparum* are auxotropic for purine and complete absence of *de novo* purine biosynthesis shows that only through salvage pathway they can synthesize their purine nucleotides (Reyes et al., 1982; Gardner et al., 2002) while in the human host purines nucleotide can also be synthesized by *de novo* pathway, so in malaria parasite the salvage pathway enzymes can be specific targets for drug discovery (Downie et al., 2008). Inosine monophosphate dehydrogenase (IMPDH, E.C.1.1.1.205) is a key enzyme of salvage pathway for biosynthesis of purine nucleotide and is a potential target for antimalarial drugs (Sintchak and Nimmesgern, 2000; Hedstrom, 2009). Currently a lot of research is being done on targeting nucleotide biosynthesis pathway in *P. falciparum* but so far no computational work has been done on Inosine monophosphate dehydrogenase from *P. falciparum*.

In purine salvage pathway, the IMPDH can catalyze the conversion of inosine monophosphate (IMP) to Xanthosine monophosphate (XMP). The continues supply of purine nucleotide is important for protozoan nucleic acid biosynthesis (DNA and RNA) and therefore inhibition of IMPDH will interrupt nucleic acid biosynthesis resulting in the death of *P. falciparum* (Sintchak et al., 1996).

IMPDH is about 55 KDa proteins and exist as a homotetramer. Each subunit of IMPDH has two domains, a C-terminal domain of 400–450 amino acid residues and N –terminal domain of 200 residues, N-terminal domain is not required for catalytic activities while active site is located at C-terminal domain (Ji et al., 2006). There are two binding regions where catalysis take place in each IMPDH structure, a substrate binding region where IMP binds and a cofactor binding region where NAD binds (Clark, 2012).

There are two classes of inhibitors, substrate site inhibitor (competitive) and the cofactor site inhibitor (uncompetitive) (Clark, 2012). *Mycophenolic acid* (MPA) and *phenyl-oxazole urea* compounds are the examples of cofactor site inhibitors while substrate site inhibitors include *ribavirin* and *mizoribine* (Petrelli et al., 2013).

The proposed work aims at predicting the 3-D structure of *P. falciparum* IMPDH through comparative modeling. Moreover, *in-silico* study was carried out for *Falciparum* IMPDH and compared with human IMPDH to analyze the structural differences in the ligand binding pocket. These structural differences at the ligand binding pocket was exploited for designing selective IMPDH inhibitors. *In-silico* combinatorial library of Ribavirin molecules was constructed and screened for identifying the compounds having greater binding affinity for *P. falciparum* IMPDH. These compounds were computationally evaluated as selective inhibitors for *Falciparum* IMPDH.

2. Methodology

2.1. Overall scheme

The 3-D structure 1NF7 (human IMPDH II) was selected as a template, while *P. falciparum* IMPDH and human IMPDH II sequences were taken as target proteins. When the models (PLF1 and UNF7) were constructed these models were superimposed on each other in order to identify the comparative binding pocket of both proteins then combinatorial library was designed for the docking studies and finally the potent ligands were identified for the *P. falciparum* IMPDH having high affinity (Fig. 1).

2.2. Homology modeling

2.2.1. Sequences retrieval and template selection

The target sequences of *P. falciparium* IMPDH (Uniprot I. D = Q8I2U5) and human IMPDH II (Uniprot I.D = P12268) were reterived from Uniprot knowledge database (DeLano, 2002a). The human crystal structure (accession code of 1NF7) was selected as a template for IMPDH homology model building using BLAST tool with a sequence coverage of 97% (Altschul et al., 1990; Berman et al., 2000). The template 1NF7 has 48% sequence identity with the target protein and has minimum gaps in the structure relative to other available structures in the PDB.

2.2.2. Model building

Human IMPDH II 3-D structure contains gaps therefor a gapless structure of human IMPDH was required for comparative docking and ligand interaction studies. The human IMPDH 1NF7 was used as template to construct the homology models of *Plasmodium falciparum* and human IMPDH II with no gaps. The template and

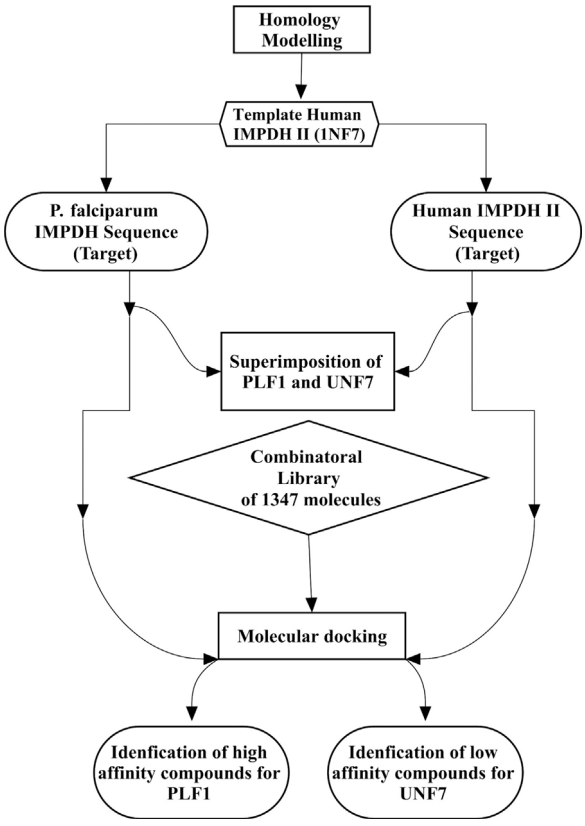

Fig. 1. A schematic representation of experimental work.