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IN SILICO DESIGNING AND ANALYSIS OF INHIBITORS AGAINST TARGET PROTEIN OF MALARIA

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ABSTRACT

Malaria, initiated by apicomplexan parasite, is an old disease and continues to be a major public health threat in many countries. This article aims to present different aspects of malaria including causes, pathogenesis, prevention, and treatment in an articulate and comprehensive manner and it causes high levels of morbidity and mortality in human beings worldwide. The development of new molecular tools as well as the use of next-generation sequencing (NGS) technologies and novel bioinformatics approaches has improved our knowledge of malarial epidemiology, diagnosis, treatment, vaccine development, and surveillance strategies.The Plasmodium falciparum is the most dangerous species that can infect human. The enzyme hypoxanthine-guanine phosphorybosyltransferase (HGPRT) in the malarial parasite Plasmodium falciparum (Pf) is central to the salvage pathway for purine nucleotide biosynthesis and is a potential antimalarial chemotherapeutic target. As with all metabolic pathways, serious problems occur if steps in the pathway are blocked. Some people inherit a rare defective version of HGPRT, which leads to a serious illness termed Lesch-Nyhan syndrome. Vector and parasite drug resistance are two major challenges for malaria control that require special attention. Artemisinins are sesquiterpene lactones, and has been recently approved for the treatment of malaria due to its endoperoxidase properties. This approach also estimates the ligand-receptor binding free energy by evaluating critical phenomena involved in the intermolecular recognition process. Prodrugs of these compounds have IC50 values in the 4-6 mM range in antimalarial cellbased assays, making them attractive compounds for further development as antimalarial drug leads. The purpose of this review is to examine current molecular docking strategies used in drug discovery and medicinal chemistry, exploring the advances in the field and the role played by the integration of structure- and ligand-based methods.

Keywords: Malaria,plasmodium falciparum, HGPRT, molecular docking,purine, pyrimidine nucleosides

1. Introduction

In india malaria is transmitted disease caused by anopheles mosquiotes. There are 5 species of malaria in which P falciparum ismost dangerous species of malaria that can infect the humans, and about 95% of infections caused by this species and 80% of the infections caused by P vivax.The widest distribution of P. vivax in tropical, subtropical, and temperate zones**[1]**.Approx half of million community expired of this disease each year according to the concern of theWorld Health Organization (WHO [**2]**. Generally children and non-immune individuals suffer by this disease**[3]**.Generally malariais categoriesinto three types: a)asymptomatic, b)uncomplicated, and c)severe**[4]**.When parasites enters the host blood then asymptomatic conditions arises because there are no any clinical symptoms like fever and chills clarified by WHO, during this condition no any antimalarial precaution taken into consider**[5, 6]**.The

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symptoms includes like fever and shivering, chills have shown in uncomplicated malaria but there are no any clinical evidence for severe organ failure during calm condition. According to WHO , the frequent hazardous ou comes seen by the severe condition of malaria,during this various organ failure condition arise such as brain ,lungs and kidneys, person also suffer with anemic condition**[7,8]**. For the adolescent children malaria is threatened, because higher transmission rate is present in India causes high risk of anemia **[9]**.Highest mortality rate was shown in children with age of fiveyears**[10]**. According to WHO (World Health Organization), in every year about half a million people diesto the malaria **[2]**. A person having low immunity and kids are faces frequent fever upto 40o C**[3]**.According to the world health organization, Artesunate is the drug of choice for all the patients having symptoms of malaria with any stage of severity **[11]**. Malaria infection causes haemolysis of infected and uninfected erythrocytes and bone marrow dyserythropoiesis which compromises rapid recovery from anaemia **[12]**.

2. HGPRT

Hypoxanthine guanine phosphoribosyltransferase (HPRT) is a enzyme, which is used for the production of IMP and GMP,inosine and guanine are the ultimate source for the production of IMP and GMP in the cell**[13]**.

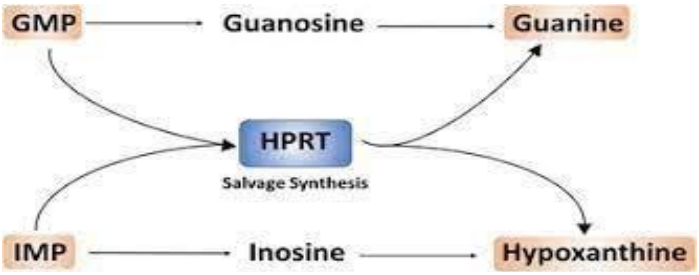

Fig. 1 The mechanism of HGPRT

Humans able to synthesize purine bases by de novo pathwayand InP. falciparumlack of de novo pathway so, parasites completely depends on the human host for the supply of purines externally from human cell **[14]**.The length of the HGPRT gene is 47,827 base pair and resides on the long arm of the X chromosome. The gene is comparatively large in size,more than ever a small portion of the transcribed DNA is taking into considerance for translation at a time. Approx 1.3% of the original genomic message was reported, in which 217-amino acid protein that coded by the 9 axons **[15,16,17]**.The HGPRT enzyme is consist of6 alpha helices and 10 beta strands whichforming the nucleus of the enzyme**[18]**. The HGPRT protein subsist two matching subunits a dimer or a tetramer which is only depends on the pH of adjacent tissue**[18, 19,20]**.The molecular weight of each of the HGPRT protein subunits is 48.9 kDa**[18]**.

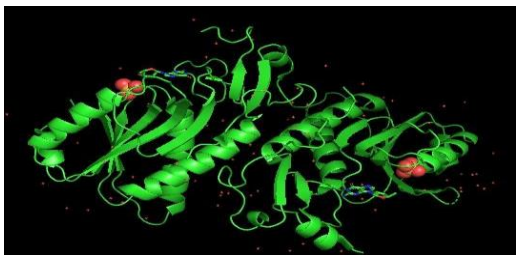

Fig. 2 The structure show HGPRT locus

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2.1 Hypoxanthine salvage in *plasmodium falciparum*

The eukaryotic cells contains two different pathways for the production of purines and pyrimidines such as de novo synthesis and the salvage pathway **[21]**. The HGPRT enzyme having appropriate nucleotide puine bases**[22]**. In vivo conditions theprimary source of parasites for the production of purine-based nucleic acid synthesis is hypoxanthine of RBC cells**[23,24,25]**.Schematicdiagram of hypoxanthine salvage process in a parasite-infected RBC cell**[26,27]**.

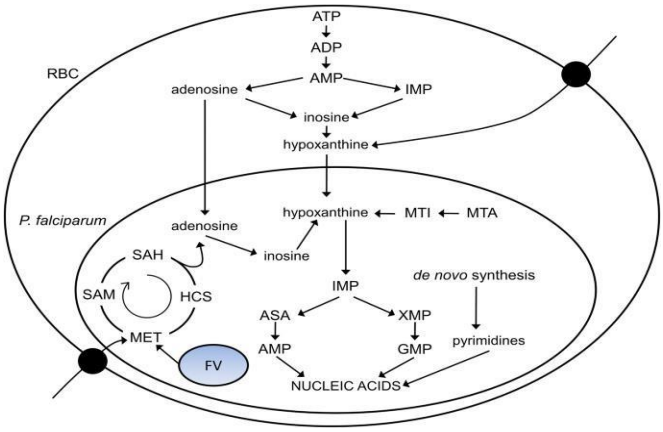

Fig. 3 Schematic showing hypoxanthine salvage in *Plasmodium falciparum.*

2.2 HGPRT as reporter gene

HGRPT protein with degree of difference appear, HGPRT has the prospective tool for the monitoring and conduct the proper treatment after categories the carcinogenic stage of cancer cells**[29]**. A metamorphosis of different cancer cell can be resolve with the help of HGPRT locus among the diversity of repair-gene disorder**[30]**.During the treatment of cancer with radiotherapy and chemotherapy at that time HGPRT locus can be used for the supervision of metamorphosis rate of carcinogenic cell in women breast as reporter gene**[31]**.HGPRT locus has been used as prominent biomarker in the field of cancer therapy and considerable parameter for the monitoring of patient taking cancer treatment **[32]**.

3.Lesch–Nyhan Disease and deficiency of HGPRT

Lesch–Nyhan syndrome build up when efficient loss of HGPRT enzyme occur, and fractional loss of enzyme create symptoms as a gout and distinguishingKelley–Seegmiller syndrome**[33]**. Alteration in the enzyme HGPRT gene-1shows Lesch–Nyhan disorder, which is held due to the disruption in metabolism process, create several other dystrophy like as hyperuricemia, intellectual disability, a dystonic movement disorder, and compulsive self-injury with self-mutilation **[34]**. The translation of IMP and GMP from hypoxanthine and guanine nucleoside bases is totally based on enzyme HGPRT due to lack of this enzyme Lesch–Nyhan disorder arises**[35]**.

4. Relation between HGPRT and malaria

The development of the P.falciparuminside the host is capture after the proper anticipation of de novo drug for the inhibition of HG(X)PRT**[27, 36]**. To be sure that inhibitory action of the inhibitors is designed towards the Pf HG(X)PRT because both human and Pf HGPRT enzyme having same DNA sequencing and severe disorders have been generated in human due to deficiency, such as: Lesch-Nyhan syndrome and moderate condition causes gout**[37]**.

5. Difference between human HGPRT and Pf HG(X)PRT

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For the development of drug which was target the Pf HG(X)PRT rather then HGPRT differ in the Ki values (inhibitor constant) and drug target binding affinities.The justification of making proper taget for PfHG(X)PRT are :(i) the manipulation create in length of the linker between drug target and the purine base of enzyme; (ii) the manipulation in the linker by oxygen atom; and (iii)the purine base of both human HGPRT and PfHG(X)PRT itself identify and inhibit the action**[38]**.

6. Preferred inhibitor for PF HG(X)PRT

According to the de novo dug design PfHG(X)PRT are the predictable target for the production of antimalaria drugs which is extremely recognized target for the today's therapeutics against parasite**[14]**.The resistance rate of Plasmodium falciparum against all current available antimalarial drugis too much high , so it is necessary to develop the new drug against the activity shows by the Plasmodium falciparum and stop the reoccurrence and clarify the infection inside the host blood stream **[39,40]**.

6.1 Acyclic nucleoside phosphonates (ANPS)

Acyclic nucleoside phosphonates (ANPs), are the effective purine nucleotides for arrest the growth of P. falciparum by inhibiting the HG(X)PRT enzyme **[41,42,43]**,and the better activity of ANPs have been shown having the IC50 values up to 1 µM aligned with the enzyme HG(X)PRT of Plasmodium falciparum cultures **[44]**.Acyclic nucleoside phosphonates (ANPs) are comes under the class of 6-oxopurine phosphoribosyltransferases inhibitors **[45]**.The acyclic nucleoside phosphonates (ANPs)are comes under the class of antiviral agents these are structural analogues of the nucleoside monophosphates **[46]**.Acyclic nucleoside phosphonates (ANPs) are comes under the class of 6-oxopurine phosphoribosyltransferases inhibitors**[45]**.A phosphonate group is attached to the 6-oxopurine base in the probable acyclic nucleoside phosphonates (ANPs) , it show the central structure of the drug and acquire broad range of Ki (inhibitor constant) values for the PfHG(X)PRT**[47]**.The binding affinities of acyclic nucleoside phosphonates (ANPs) having Ki values 0.5 1M for human HGPRT enzyme with 5 or 6 atoms linker chain.On the other hand Pf HG(X)PRT have shown less binding affinities towards long chain linker except this oxygen atom attached to the 3-position**[48]**.

6.2 New designed acyclic nucleoside phosphonates (ANPS)

The 2-(phosphonoethoxy) ethylguanine(PEEG) and 2-(phosphonoethoxy)ethylhypoxanthine (PEEHx) are two new designed acyclic nucleoside phosphonates (ANPs) having 5 atom link chain that imitate the 6-oxopurine nucleoside monophosphates with four carbons and one oxygen **[49,50]**. These are show better activity for inhibition of PfHG(X)PRT with Ki values of 0.1 and 0.3 mM, correspondingly.The Ki (inhibitor constasnt) values for human HGPRT are 10- times more effective with respect to the PEEG and PEEHx and 3.6 Mm. Accordingly, the newly synthesized ANPs are more effectively inhibit PfHG(X)PRT then human HGPRT. The modulation have been occurred in PEE linker which change its action by adding some extra substituent on it **[51,52]**,or fully repel the selectivity**[53]**.

6.3 Sulfur-containing ANPS

A sulfide or sulfoxide or a sulfone are attaché to the PEE-linker at the place of oxygen atom.A second variation is to move the sulfur moiety further along the "linker" so that it is one atom distal from the purine base. Earlier, only a small sulfur-containing acyclic nucleoside phosphonates (ANPs) had been reported to possess antiviral activityor purine nucleoside phosphorylase inhibitors.

6.4 Nitrogen containing (AZA-ANPS)

The two dissimilar phosphonate groups have been attached in newly synthesized aza-acyclic nucleoside phosphonates (aza-ANPs) which include trisubstituted nitrogen atom **[54]**.According to the recent work two new drug for enzyme target was developed with the high rate of selectivity towards the enzyme [HG(X)PRT] inhibition a) iso-mukaadial acetate (IMA) and b) ursolic acid acetate (UAA) by using computational docking in different wet-lab approaches**[55]**.

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7. Molecular docking

For bring off high-through screening from the database, the molecular docking is essential tool for researchers to understand interaction among the drug and the target molecule**[56]**. The conformation and orientation (mentioncollectively as the "pose") of molecules hooked on the binding site of a macromolecular target is examine with the help of molecular docking **[57]**. 10 to 1000 of probable poses of ligand are synthesized with the help of molecular docking which based on protein structures; a scoring function (SF) is used to calculate the binding poses **[58]**, ligand poses can be estimated by this . Scoring functions are the mainly used in molecular docking, it have 3 most important functions **[59,60,61]**.

- The first function is used to find out the binding mode and site of a ligand binding to a protein **[62]**.
- The second function is used to calculate the absolute binding affinity among the protein and ligand in lead optimization**[63,64]**.
- The third function is involve the virtual screening, for a given protein target the probable drug leads can be recognize with the help thorough large ligand database **[65,66]**.

7.1 Preparation of hybrids by using molecular docking

The complication interrelated to drug resistance, drug-drug interaction, drug delivery, poor solubility etc are resolve after the production of hybrid drugs by using molecular docking which can applaud the dual mode of action **[67]**.The strategy adopted for the preparation of molecular hybridization in which two or more than two active pharmacophores are attached covalently and form one molecule it ensure that the action of drug on multiple targets **[68]**. Due to this enhance the probability of development of a new drug because in which two structurally different compounds may be merged by using hybridization **[69]**. The Lipinski's rule of five were apply after the preparation of functional hybrid compounds, in which is a no. of in silico guidelines applied to expect possibility of high oral absorption**[70]**. A compound which is made for oral intake have required Lipinski's Rule below 2 violations **[71]**.Consequently violating 1 of the Ro5 for few compounds having molecular weight greater than 500Da.

7.2 Computational docking studies

The majority of the functional hybrids dock suitable inside the binding site of HGPRT protein the whole consequence have been appeared with the help of computational docking. In silico the majority of functional hybrids appeared that these compounds acquire better pharmacokinetic behavior according to the ADME predictions**[72]**. Pharmacological activities shows by the functional components after bind to the consequent targets is the key features of the hybrid drugs**[73]**. The summary behind the formation of drug-receptor complex and interacts after the binding of amino acid residue with drug molecules, it is generally based on the intermolecular electrostatic interaction and ionic bond, hydrogen bond, and Van der Waals forces, etc. by this means the receptor shows the activities like as inhibition or activation **[74,75]**.

A number of software were developed throughout the most recent years, some frequently used and most useful software are as follows. AutoDock**[76],** AutoDock Vina**[77],** DockThor**[78,79],** GOLD**[80,81],** FlexX **[82]** and Molegro Virtual Docker **[83]**

By the use of computer we pretend that the tiny functional molecules (ligands) is fit inside the binding area of the macromolecules targets (receptors) , that assume the binding forces of that molecules and models of the ligand–receptor complexes, after enumerate the physical and chemical parameters, as a result we achieve high-throughput, virtual screening of the unidentified compounds and computational docking enhance the rate of new drugs discovery towards the different targets **[84,85]**.

7.3 Structure based drug design (SBDD)

SBDD is a most precise, proficient and fast method for de novo drug development and optimization of the lead. The main requirement for SBDD is complete knowledge about 3- dimensional structures of functional targets. At the moment the huge no. of 3-dimentional structures of the target protein are available, this work is attributed to the

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advances in bioinformatics and Human Genome Project completion. The complete knowledge about the macromolecular targets generally protein or RNA is gather with the help of SBDD method for investigation, to recognize key sites and interactions with the aim of particular biological function for definite target. The conformational changes throughout the procedure of docking are estimated, interface of ligand-protein and calculation of binding energy with the help of SBDD.**[86,87,88,89]**.

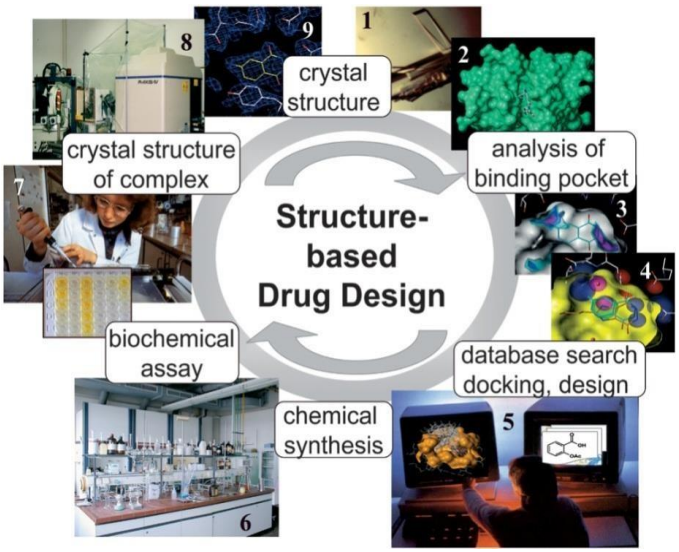

Fig.4 Structure based Drug Design

In the last two decades, computational, X-ray crystallography and NMR etc. are the scientific method with upgrade investigational knowledge, thesemethods make easier progression of SBDD which play essential role in new drug molecule development. Owing to the substantial increase in the availability of huge number of 3-dimentional structure of targets and the rapid progression in computational chemistry. The working plan of SBDD in oppositionwith the targets which are implicated in the disease procedure can be useful criteria for the investigation of numerous drugs **[90]**.

7.4 Structure-Based Virtual Screening (SBVS)

In SBVS, the target is ready to dock with the compound database inside the binding site **[91]**. The status of the docked molecules is come up with the help of SBVS through the prophecy of binding mode. The functional movement of the specified drug compounds are evaluated during the experiment on the molecular target under investigation **[92]**.

7.5 Ligand-Based Virtual Screening (LBVS)

In the recent study, for the development of drug molecules both virtual screening method(SBVS & LBVS) are coalesce, it is the usefulness of structure based method. The literature carry numeral amount of reviews which is based on LBVS. **[93,94]**. The investigation of molecular descriptors collected from functional compound, this knowledge is utilize by LBVS **[93,95]**. A lay of reciprocal features of a compound sequence is recognize, that are practically use as a molecular filter at a subsequent time. Precisely calculate molecular descriptors for database

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filtering with the help of a number of liberally present software packages. Natalmovement, like as solubility, protonation state and molecular volume serve as essential property which have predicted by using these programs **[96].**

7.6 Evaluation of Binding Energetics

The estimation of binding energetic of specified ligand-receptor complexes by the applying scoring functions are the features of molecular docking programs. The binding constant (Kd) and the Gibbs free energy (ΔGL**)** are used to calculate the energy variation which is arises after the development of the ligand-receptor structure **[97]**. The evaluation of desolvation and entropic effect and the main feature that is physical-chemical phenomena concerned in ligand-receptor binding, together with intermolecular interactions, are used for calculation of the binding energy [**98]**.As a result, the considerable precision of the scoring function, is mainly depend on the evaluation of highest number of the physical-chemical parameters. On the other hand, the outlay for the number of computational variables is increases with respect to the incorporation of functions that's mean greater no. of physical and chemical parameter, greater will be the cost, the yield of the docking algorithm is bring down with inadequate no.of variables. Preferably, the balance among precision and velocity ought to recommend by the well-organized scoring functions,as soon as working alongbulky ligand sets is a serious fact. Scoring functions are classified into the three subsequent groups: a) force-field-based, b) empirical, and c) knowledge-based functions **[99,100]**.

8. Protein-Protein Interaction Inhibitors and Molecular Docking

Connection among different classes of protein are mostly used for proceeding cellular and biochemical processes **[101]**. Many diseases, such as malaria, can be imputed to defective protein-protein interactions (PPIs); for that reason, protein protein interaction is mostly used for designing attractive target for drug delivery **[102]**. HGPRT enzyme inhibitors act like a small-molecule compounds which openly bind with specific protein and inhibit its activity **[103]**. In current scenario the advance action of HGPRT inhibitors have challenged for all previous developed targeting HGPRT because it was inappropriate for targeting HGPRT enzyme **[104]**.

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