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COMPUTATIONALLY TARGETING MALARIA DRUG TARGET PROTEIN PLASMEPSIN II USING NEEM SECONDARY MEATBOLITES

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ABSTRACT

Vector borne diseases become very common in India especially, the malarial diseases caused by parasites. In this current study, we have retrieved the neem metabolites from pubchem database to target against a drug target protein PDB-1LF2, Plasmepsin II for malarial disease using computational biology techniques. The dock score and interaction amino acid residue of plasmepsin II with isomargololone shows 19.04 Kcal/mol at residues ASP34, myrictinin is 33.29 Kcal/mol at residues THR217, ASP34. Morgolonone shows a dock score of 13.29 Kcal/mol at residues THR217, morgolone is 9.35 Kcal/mol at residues THR21, meldenin is 42.71Kcal/mol at residues THR21. In addition, we compared with standard drug halofantrine, its docked results gives dock score of 31.16 Kcal/mol interacting at residues A: THR217.Meldenin shows the high dock score than the myrictin but the interaction with aspartic acid residue was observed only in myrictin and isomargololone. Hence, further in-vitro and in-vivo studies were need to be carried to confirm the efficiency of these three compounds against malaria

KEYWORDS: **Vectorborne, malarial, PlasmepsinII, secondary metabolites.**

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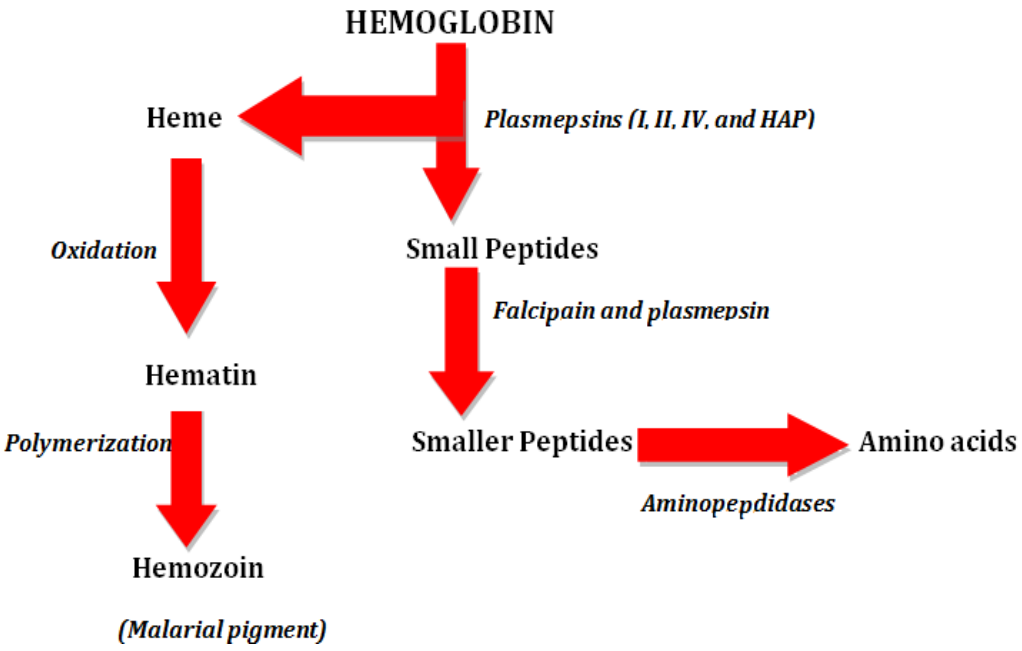
INTRODUCTION

Vector borne diseases become very common in India, especially the malarial diseases caused by parasites, recent statistics report states that nearly 1.2 billion population in India lives in malaria risk areas it is about 80.5%.Of this 4.2% lives in high risk areas of malaria and about 32.5% and 43.8% lives in moderate and low risk areas respectively[1-2]. For the people living in most backward and remote sending areas the malaria as become biggest burden in India, our government was taking several steps to free India from malaria[3]. The two important species such as *P. falciparum* and *P.vivax* are very common in India to spreads the malarial disease, more than 40% of *P. falciparum* malaria cases and nearly 20–30% of deaths caused by malaria in India[4].A female mosquito Anopheles belongs to plasmodium genus transmits the infection form sporozoite to host of humans transmits in the form of vector, this mosquito takes to host in living period. The sporozoite travel through blood vessels to reach hepatocytes, and produces thousand of merozoites asexually, again the infected blood cells undergo the cell division so that a series of asexual multiplication cycles commonly known as blood schizogony. Further, multiplication of cells produces the largest number of infective merozoites, Other merozoites develop into immature gametocytes. Gametocytes are taken up with the blood and mature in the mosquito gut and the fusion of male and female form ookinete, further ookinetes develop into new sporozoites that migrate to the insect's salivary glands which affect the second host seriously [5,6]. Many scientist and researches in worldwide were to find the potential drug targets for malaria one among such a drug target is Plasmepsin II [7]. *P. falciparum* has capable to produce the ten different enzymes of plasmepsins, expression of these enzymes occur only during erythrocytic and exo-erythrocytic cycle, these Plasmepsins contains two aspartic acid residues in their active site so it belongs to aspartic acid proteases[8,9]. In this current study, Plasmepsin II was chosen as a drug target and the degradation pathway of hemoglobin is shown in the figure1.

Figure 1
Hemoglobin degradation in Plasmodium falcipuram



Drug resistance to the target protein is more popular nowadays, thus natural metabolites from herbal plants are necessary to prevent this issue [10]. Arteether and Artemether were used in primary treatment of malaria in tablet or injection form, Insilco studies on tuberculosis reported that Arteether and its analog have bioefficay to act upon tuberculosis [11,12]. In this current study, we have worked on neem metabolites to target the Plasmepsin II for malarial disease, already mains reviews and papers were reported that extract from as capable of curing malarial , but here were reports the which metabolite shows high efficiency of interaction with Plasmepsin II for malarial treatment.

MATERIALS AND METHODS

Retrieval of natural compounds

The aromatic compounds with bulkier groups of secondary metabolites from neem such as Meldenin (CID 4114), Myrictinin (CID 497359), Isomorgololone (CID 189727) , Morgolonone (CID 189726) , Morgolone (CID 189728) and epicatechin (CID 72276) were retrieved from pubchem database (https://www.ncbi.nlm.nih.gov/pccompound)

Retrieval of drug target form PDB database

The drug target protein Crystal Structure Of Plasmepsin II From *P. Falciparum* in Complex with inhibitor RS370 of ID 1LF2 and its X-ray crystallographic structure with 1.80 Á resolution with UniProtKB unique identification number is P46925 with amino acid sequence of 331 was retrieved from PDB database. (http://www.rcsb.org/pdb/home/home.do).

Preparation of protein and active site prediction

The water and ligand that bound to the protein Plasmepsin II was removed, initially force field CHARMm was applied to remove the bad clashes and non-bonded interactions followed by the respective drug target protein was saved in the current mode of protein data bank. Now active site of the protein was automatically predicted using flood filling algorithm available through acclerys discovery studio 2.1v

Structure based drug designing

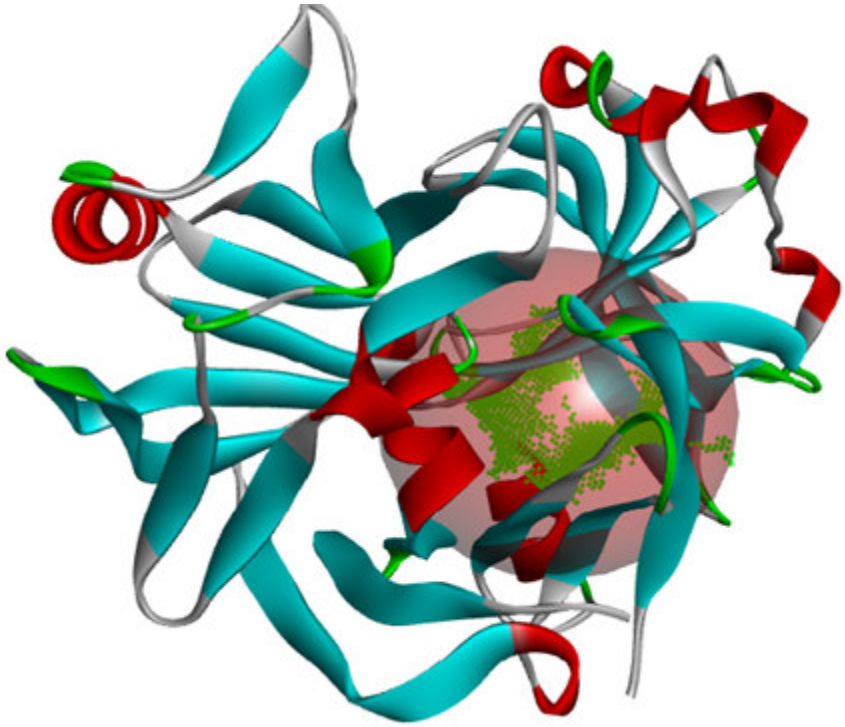
The concept of structure based drug designing was applied since the ligand and drug target protein was known, a series of natural metabolites from neem was docked with Plasmepsin II to check the binding interaction and dock score of the each compound for Plasmepsin II

RESULTS AND DISCUSSION

Protein and its active site

Plasmepsin-2 drug target protein belongs to the enzyme family of acid proteases. There are twelve different X-ray structures of Plm II are presently available in the Brookaven protein database (www.pdb.org). In the current study, we proceeded with PDB 1LF2 structures, which is a crystallographic artifact and the biologically active form is monomer, the proteins are crystallized with inhibitors. The secondary structure of the protein and its active site is shown in the figure 2.

Figure 2
Structure of the protein and its active site



Receptor ligand interaction

Molecular interaction in between the ligand with the active site amino acid of protein generally determines the efficacy of the ligand. High affinity low-affinity results good or less intermolecular force of attraction between the ligand and receptor. The protein Plasmepsin II was given as input and docked with neem ligands, the interactions of Plasmepsin II with neem compounds were shown in the table 1 and figure 3 and dock score of the each compounds with standard drug was listed in table 2.

Table 1
Interactions of Plasmepsin II with neem compounds

S.no	Compound	Interaction between compounds and active site amino acid	H-Bond Length in Å
1	Meldenin	A:THR217:hg1- Meldenin:o9	2.359
2	Myrictinin	A:THR217:hg1- Myrictinin:o21	1.634
		A:ASP34:od1- Myrictinin:h30	1.528
		A:ASP34:od1- Myrictinin:h32	2.062
		A:THR217:og1- Myrictinin:h32	2.228
3	Isomorgololone	A:ASP34:od1- Isomorgololone:h25	1.425
4	Morgolonone	A:THR217:hg1- Morgolonone:o1	2.452
5	Morgolone	A:THR217:hg1- Morgolone:o21	2.386
6	Standard- Halofantrine	A:THR217:Hg1- Halofantrine:022	1.360

Figure 3
Interaction of Plasmepsin II active site amino acid with neem compounds

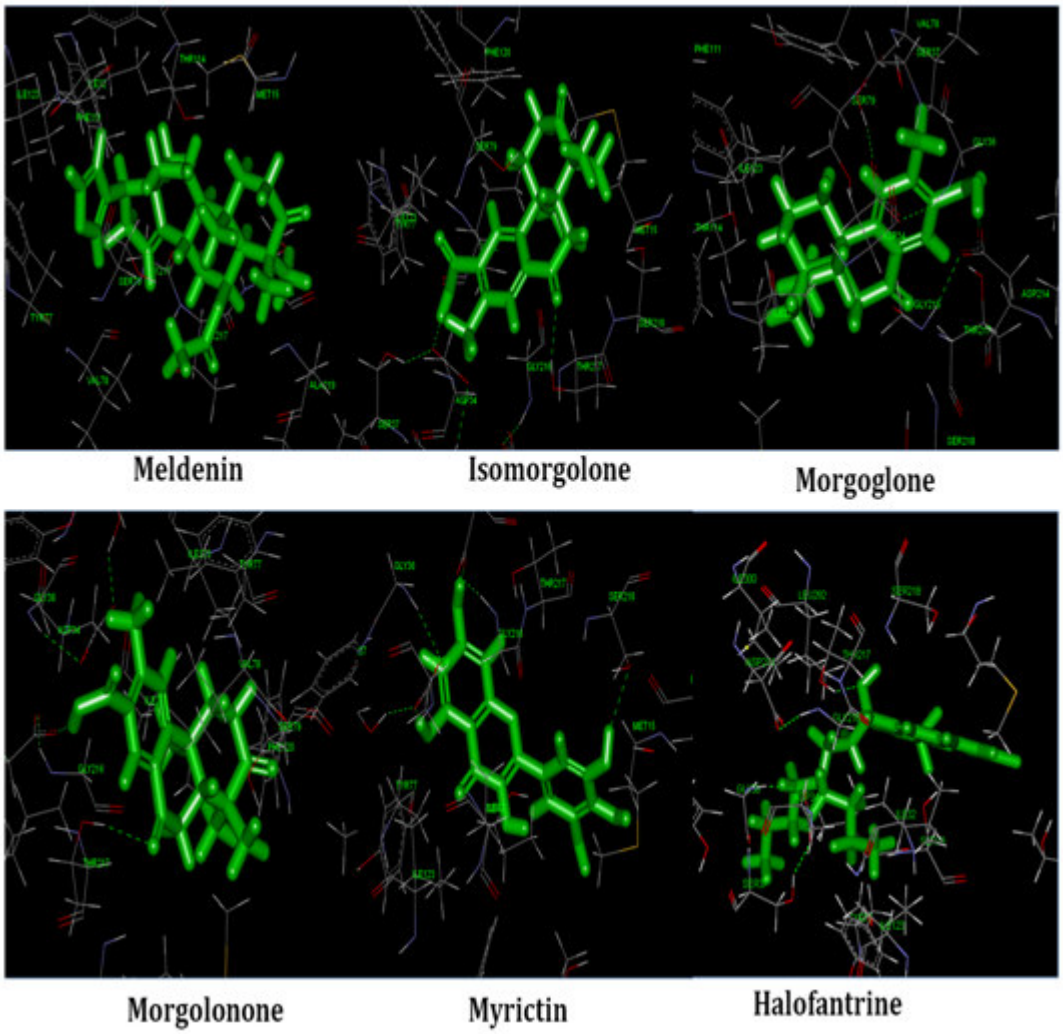


Table 2
Dock score of the each compounds with standard drug

S.no	Compound	Dock score in kcal/mol
1	Meldenin	42.71
2	Myrictinin	33.29
3	Isomorgololone	19.04
4	Morgolonone	13.29
5	Morgolone	9.35
6	Standard- Halofantrine	31.16

The malarial protein plasmepsin II is loaded into discovery studio , the active sites of protein plasmepsin II is found and docked with list of neem compounds the various neem compounds are meldenin, Isomargololone, margololone, margolone and myrictin,. The dock score and interaction amino acid residue of plasmepsin II with isomargololone shows 19.04 Kcal/mol at residues ASP34, myrictinin is 33.29 Kcal/mol at residues THR217,ASP34. Morgolonone shows dock score of 13.29 Kcal/mol at residues THR217, morgolone is 9.35 Kcal/mol at residues THR21, meldenin is 42.71Kcal/mol at residues THR21. Also, we

compared with standard drug Halofantrine, its docked results gives dock score of 31.16 Kcal/mol interacting at residues A: THR217.Even though ,meldenin shows high dock score than the myrictin but the interaction with aspartic acid residue was observed only in myrictin and isomargololone.

CONCLUSION

The homologous plasmepsin I and plasmepsin II are responsible for the initial attack on the hemoglobin alpha chain between the residues phe33 and leu34 in the hinge region. This plasmepsin II is the proteins responsible for cleavage of haemoglobin and plays a major role in malarial diseases. The protein plasmepsin II is retrieved from the uniprot and its structure is retrieved from pdb and then docked with neem ligands in discovery studio. The docking results show that meldenin and myrictin has high anti-malarial activity of the other neem compounds. Hence, further invitro and invivo studies were needed to be carried to confirm the efficiency of these three compounds against malaria.

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