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Full Length Research Paper

Potential of mangrove derived compounds against dihydrofolate reductase: An *in-silico* docking study

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Approximately 3 billion people, one half of the world's population, live in at-risk regions for malaria infection leading to about 250 million malaria cases every year and nearly one million deaths. Once the malarial parasite *Plasmodium vivax* and *Plasmodium falciparum* enters the red blood cells its growth is inhibited by Proguanil, a prophylactic antimalarial drug which inhibits the enzyme, dihydrofolate reductase leading to the inhibition of the growth of malarial parasites. Considering the side effects of the antimalarial drugs, the present study was undertaken to substantiate the inhibition potential of mangrove-derived compounds against the receptor protein dihydrofolate reductase. Docking studies by using Argus lab software revealed that among nine mangrove-derived compounds five compounds namely stigmasterol, triterpenoid, tretinoin, pyrethrin and rubrolide-N showed good docking energy score of -14.2239, 12.4725, -11.689, -11.1828 and -10.884 Kcal/mol, respectively against dihydrofolate reductase.

Key words: Malaria, dihydrofolate reductase, mangrove-derived compounds, Pdb, Argus lab.

INTRODUCTION

Malaria continues to be a major public health threat, with over two billion people at risk of contracting this deadly disease. It continues to represent a major threat to world health infecting between 300 and 500 million people annually and causing 1.5 to 2.7 million deaths-equal to 150 to 300 deaths each hour (Snow et al., 2005; WHO, 2008; Breman, 2009). The disease results from infection by parasites belonging to the Plasmodium species and is transmitted by the female mosquitoes of the Anopheles genus. Of the four species of parasite (*Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, and *Plasmodium ovale*) that infect humans, P. *falciparum* is responsible for the majority (95%) of fatalities (Murray and Perkins, 1996). In areas where malaria is prevalent, one of the most crucial obstacles for eradicating malaria is a widespread resistance of malarial parasite to almost all classical antimalarial agents such as chloroquine, mefloquine, and antifolates (Hyde, 2007) has prompted researchers worldwide to consider and to search for other antimalarial drugs of ideally different molecular mechanism(s) of action from those against which malaria parasites have developed resistance (Borstnik et al., 2002a). Therefore, it is very necessary to seek for new drugs that are effective against drug resistant strains in order to combat and relieve this tremendous prevalence.

Dihydrofolate reductase plays an essential role in the building of DNA and other processes. It manages the state of folate, a snaky organic molecule that shuttles carbon atoms to enzymes that need them in their reactions of particular importance, the enzyme thymidylate synthase use these carbon atoms to build thymine bases, an essential component of DNA. After folate has released its carbon atoms, it has to be recycled. Proguanil is a prophylactic antimalarial drug, a biguanide derivative which stops the reproduction of the malaria parasite, *P. falciparum* and *P. vivax*, once it is entered in the red blood cells by inhibiting the enzyme, dihydrofolate reductase, which is involved in the reproduction of the parasite that is, it blocks the

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Table 1. Dihydrofolate reductase binding site.

S/N	Amino acids in the binding pocket	Binding site of amino acids in the structural unit
1	ALA9,ARG137,ASN185	Beta strand
2	ALA86, ASP29	Coil
3	ALA96, ARG36, ASP94	Alpha helix

biosynthesis of purines and pyrimidines, which are essential for DNA synthesis and cell multiplication. This leads to failure of nuclear division at the time of schizont formation in erythrocytes and liver. Common side effects include stomach ache, sore throat, loss of hair, abnormal bruising or bleeding, fever and pale yellow urine. Sometimes, overdose of Proguanil also creates problems. Dihydrofolate reductase has been a primary target for the Proguanil drug (http://www.emedicinehealth.com/drug-atovaquone_ and_proguanil/article_em.htm). Molecular docking is an application, wherein molecular modeling techniques are used to predict how a protein (enzyme) interacts with small molecules (ligands). The ability of a protein (enzyme) to interact with small molecules plays a major role in the dynamics of the protein which may enhance/inhibit its biological function. The necessity of new improved drugs is being felt due to the side effects of antimalarial drugs. Hence, in the present *in silico* study we try to find the suitable analogues with high binding affinity, which could be a possible lead molecule. Moreover, the obtained docking results will enhance an understanding of drug–receptor interactions, which enables a modification of the drug's structure to achieve suitable interactions. Hence, this can bring about a development of new and more effective drugs.

MATERIALS AND METHODS

Protein structure

The targeted protein dihydrofolate reductase (ID: 1MVT), having the resolution of 1.80 A° was retrieved from the protein data bank (PDB) (www.rcsb.org/pdb). Structural and active site studies of the protein were done by using CASTP (Computed Atlas of Surface Topography of Proteins) and pymol molecular visualization software.

Chemicals screened

Nine chemicals namely triterpenoid, stigmasterol, tretinoin, rubrolide-N, pyrethrin, tricin, Heritonin, Haloprogin and N-methylflindersine identified from the coastal mangrove ecosystems (Kathiresan and Qasim, 2005) were screened against the dihydrofolate reductase.

Amino acid binding site

The phytochemical molecules were retrieved the pubchem database. The selected chemical structures were generated from SMILES notation (Simplified Molecular Input Line Entry Specification) by using the Chemsketch Software (www.acdlabs.com). The predicted binding sites, based on the binding energy, and amino acids make up the binding cavity. The predicted ligand binding site residues are listed in Table 1.

Docking methods

Argus Lab 4.01 was used for docking analysis, which is widely distributed public domain molecular docking software. The inhibitor and target protein were geometrically optimized and docked using docking engine Argus dock.

RESULTS

Nine chemicals derived from mangrove ecosystem were docked with dihydrofolate reductase. The docked ligand molecules were selected based on docking energy and good interaction with the active site residues and the results are shown in Table 2. Of the nine ligand molecules, 5 showed the activation energy of greater than -10 Kcal/mol and the remaining four compounds exhibited the values <10 kcal/mol. The highest activation energy (-14.2239 Kcal/mol) was found in stigmasterol (Figures 1a and 1b) followed by triterpenoid, tretinoin, pyrethrin and rubrolide-N (12.4725, -11.689, -11.1828 and -10.884 Kcal/mol respectively). While, the lowest activation energy of -6.74187 Kcal/mol was found in tricin. Thus, the *in silico* docking results, revealed that mangrove derived compounds have the great potential against inhibition of dihydrofolate reductase.

DISCUSSION

Anti-malarial drugs such as proguanil inhibit the dihydrofolate reductase of plasmodia thereby blocking the biosynthesis of purines and pyrimidines, which are essential for DNA synthesis and cell multiplication. This leads to failure of nuclear division at the time of schizont formation in erythrocytes and liver. But, there are several side-effects of Proguanil too. Hence, realizing the necessity of new potential dihydrofolate reductase inhibitory drug, in this present study we screened nine mangrove derived compounds against dihydrofolate reductase protein Molecular docking is a key tool in structural molecular biology and computer-assisted drug

Table 2. Docking results of mangrove derived compounds against dihydrofolate reductase.

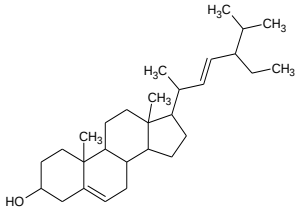
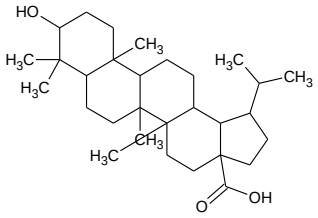
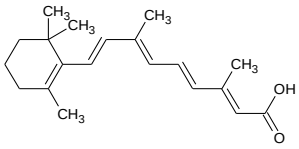
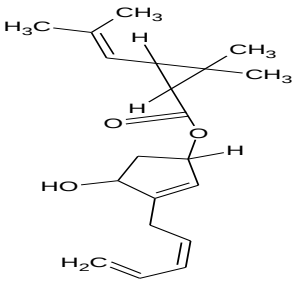
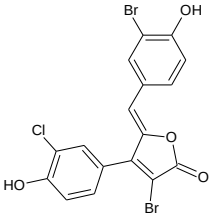
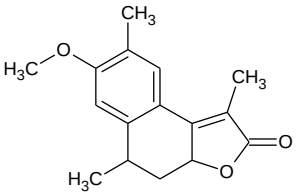
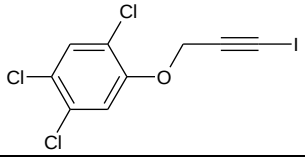
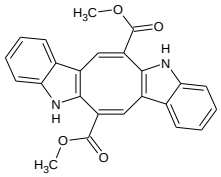
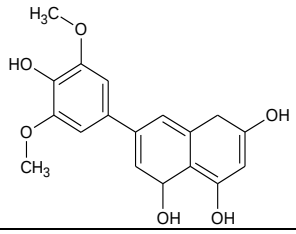
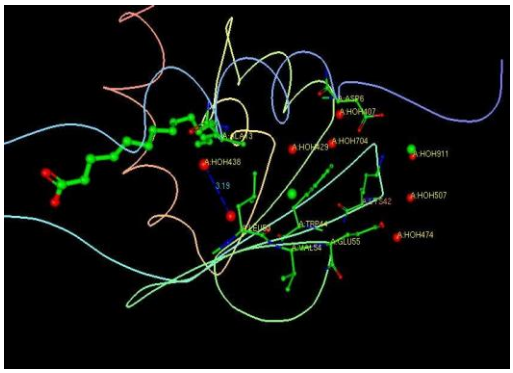
Compound name	Pubchem ID	Compound structure	Molecular weight (g/mol)	Hydrogen donor/acceptor	Docking energy level (Kcal/mol)
Stigmasterol	**CID: 5280794**		**269.082**	**(1,1)**	**-14.2239**
Triterpenoid	**CID: 9804218**		**458.6041**	**(2,3)**	**-12.4725**
Tretinoin	**CID:444795**		**300.43512**	**(1,2)**	**-11.689**
Pyrethrin	**CID:6433155**		**372.454**	**(0,5)**	**-11.1828**
Rubrolide-N	**CID: 5472704**		**472.51196**	**(2,4)**	**-10.884**
Heritonin	**CID:130118**		**258.31232**	**0,3**	**-9.89708**
Haloprogin	**CID:3561**		**361.39093**	**0,1**	**-9.82504**

Table 2. Cont'd.

N-Methylflindersine	**CID: 72819**		**241.2851**	**(0,2)**	**-8.09744**
Tricin	**CID: 5281702**		**330.288**	**(3,7)**	**-6.74187**



(A) Stigmasterol

(b) Hydrogen bond, Neighbor residues

Figure 1. Molecular visualization of stigmasterol (a) and its hydrogen bond and neighbor residues (b) by using Pymol software.

design. Our previous docking studies have already proved the efficacy of mangrove derived compounds against oncoprotein of cervical cancer, sterol containing protein (AeSCP-2) and breast cancer protein BRCA1 (Senthilraja et al., 2011; Senthilraja and Kathiresean, 2011ab; Senthilraja et al., 2011). Our docking results showed the highest activation energy (-14.2239 Kcal/mol) in stigmasterol which is much better than the activation energy of the antimalarial drug proguanil (-6.59 Kcal/mol) (Prakash et al., 2010).

Thus, the present *in-silico* docking study also proved that mangrove-derived compounds are capable of blocking dihydrofolate reductase, ultimately which could lead to inhibition of the growth of malaria parasite.

Conclusion

Mangroves are rich source of ecofriendly, safer and cheaper compounds (phenolic) which possess great medicinal value. In this study we have docked the receptor dihydrofolate reductase with the nine different mangrove derived compounds and from the results it can be concluded that these compounds derived from mangrove ecosystem (stigmasterol, triterpenoid, tretinoin, pyrethrin and rubrolide-N) could be a novel inhibitor for dihydrofolate reductase. All the compounds passed the Lipinski rule of five (Lipinski et al., 2001), hence further studies such as ADME/T (Absorption, Distribution, Metabolism, Excretion/Toxicity) properties of the compound could be tested further.

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REFERENCES

Borstnik K, Paik IH, Posner GH (2002a). Malaria: new chemotherapeutic peroxide drugs. Mini-Rev. Med. Chem., 2:573–583.

Lipinski CA, Lombardo F, Dominy BW, Feeney PJ (2001). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv. Drug Del. Rev., 46: 3–26.

Hyde JE (2007). Drug-resistant malaria-an insight. FEBS J., 274:4688-4698.

Kathiresan K, Qasim SZ (2005). Biodiversity of mangrove ecosystems. Hindustan Publishing Corporation Limited, New Delhi 251 pp.

Murray MC, Perkins ME (1996). Chemotherapy of Malaria. Ann. Rep. Med. Chem., 31:141-150.

Prakash N, Patel S, Faldu NJ, Ranjan R, Sudheer DVN (2010). Molecular Docking Studies of Antimalarial Drugs for Malaria. J. Comput. Sci. Syst. Biol., 3:070-073.

Senthilraja P, Kathiresan K, Sunil KS (2011). *Insilico* docking analysis of mangrove-derived compounds against breast cancer protein (BRCA1). IRMJ-Health Sci., 1(1): 09-12.

Senthilraja P, Kathiresan K (2011a). Computational selection of mangrove-derived compounds as mosquito larvicide's by blocking the sterol carrying protein, AeSCP-2. Res Bioscientia., 2(1):1-6.

Senthiraja P, Kathiresan K (2011b). Computational selection of compounds derived from mangrove ecosystem for anti-cervical cancer activity. J. Recent Sci. Res., 2(4):93-98.

Snow RW, Guerra CA, Noor AM, Myint HY, Hay HI (2005). The global distribution of clinical episodes of. *Plasmodium falciparum* malaria. Nature, 434:214-217.

World Health Organisation (2008). WHO- World Malaria Report. Geneva Switzerland.