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Evaluation and Prediction of Anti-Malarial Activity by Ubiquinol-Cytochrome-C Reductase Inhibition of Active Constituents of Ipomoea Carnea with Marketed Drug Atovaquone

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ABSTRACT

Background: In 2017, 219 million cases of malaria across worldwide were estimated by World Health Organization and there were 435 thousands deaths were expected. African countries have the most number of cases and deaths due to malaria (~90%). Atovaquone is marketed drug used in the treatment of malaria. It shows inhibition of the Ubiquinol-cytochrome-c reductase activity in intra erythrocytes parasitic ETC pathway. Bush Morning Glory also known as *Ipomoea carnea* is a herbal medicinal plant which is used from ancient times to treat various diseases. There are various reported pharmacological activities of *Ipomea carnea* against various disorders. In this study using in silico drug discovery tools, the anti malarial potential is evaluated and compared with Atovaquone.

Method: Anti malarial activity of active chemical constituents of *Ipomoea carnea* was studied with the help of In-silico passonline predication tool and molecular Protein-Ligand docking tool "swissdock".

Result: The data of anti-malarial activity and Molecular Protein-Ligand docking of chemical constituents of *Ipomoea carnea* was compared with Atovaquone data. It was observed that chemical constituents of *Ipomoea carnea* have more Pa value than Atovaquone for anti malarial activity. It was also observed that Stearic acid, Linoleic acid and Hexadecanoic acid binds to Ubiquinol-cytochrome-c reductase with high affinity and low binding affinity energy.

Conclusion: It was also observed that Stearic acid, Linoleic acid and Hexadecanoic acid binds to Ubiquinol-cytochrome-c reductase with high affinity and low binding affinity energy. Therefore, these compounds of *Ipomoea carnea* have potential anti-malarial activity.

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Keywords: Anti-Malarial Activity, Bush Morning Glory, PASS Online Tool, Ubiquinol-Cytochrome-C Reductase, UCSF Chimera Software.

Introduction

In 2017, 219 million cases of malaria across worldwide were estimated by World Health Organization and there were 435 thousands deaths were expected in which most of them were young children. The figures have been decreased by about 37% worldwide since 2000 but the graph of number of cases shows plateauing which emphasize that the current treatment and preventive strategies were need to be improved and find new alternatives and drug discovery. African continent shares the most number of cases and deaths due to malaria (~90%) [1]. There are vigorous research is ongoing to find new, effective and potent drugs for the treatment of this disorder. There are plenty of studies have been reported from past time which supports that ETC pathway inhibition can be a potential target for anti malarial drug design [2-4]. Inhibition of the Ubiquinol-cytochrome-c reductase activity in intra erythrocytes parasitic ETC pathway by Atovaquone is reported where the results had supported the mechanism of action of Atorvaquone in the treatment of malaria [5]. Mitochondrial membrane potential gets disturbed causes damaging, collapsing and death of cells [6-9]. Bush Morning Glory also known as *Ipomoea carnea* shows immunomodulatory effect, antioxidant activity and many other activities. Screening of active chemical compounds of *Ipomoea carnea* for mosquitocidal activity through inhibition of Ubiquinol-cytochrome-c reductase can be potential approach in drug discovery [10, 11].

Material and Methods

Prediction of Anti-Malarial Activity by Following Tools

PASS Online is a online server which provides prediction of various biological activities. https://www.swissdock.ch/ is an online tool used to predict Protein ligand docking and provides Full Fitness and Binding Affinity energy in Kcal/mol unit.

Retrieval of the Macromolecule and Ligand

Ubiquinol-cytochrome-c reductase is the macromolecule which is docked with the ligand (active chemical constituents of *Ipomoea carnea*) with the help of swissdock online portal. The pdb format of Ubiquinol-cytochrome-c reductase was retrieved from https://www.rcsb.org. The structure is stored under the PDB ID: 1BCC. Similarly, ZINC ID structures was retrieved from https://pubchem.nlm.nih.gov and stored.

Insilico Screening of Anti-malarial Activity by PASS Online

All the active chemical constituents of *Ipomoea carnea* & Atovaquone were predicted by uploading the structures of chemical compounds and the results were downloaded in xls. Format.

Anti-malarial Screening of Chemical Constituents of *Ipomoea carnea* by Molecular Protein Ligand Docking Analysis

Those ligand molecules were docked which have Pa value more than 0.8in PASS prediction and which don't have too floopy (entropy) for docking [12,13]. Firstly the target macromolecules of Ubiquinol-cytochrome-c reductase was uploaded in the target selection and then selected A and B chain of macromolecules for docking. Then each compound was uploaded in the ligand selection. Then clicked on start docking and data was downloaded in csv file.

Data Analysis

The results of molecular protein docking were analysed using UCSF chimera software to find out the interaction between each chemical compound of *Ipomoea carnea* & Atovaquone then the best values of molecular protein docking interaction was determined by the best binding affinity value in Kcal/mol.

Table 1: Predicted value of Anti-malarial activity of Atovaquone

S. No.	Active Chemical Constituents	Activity	Pa	Pi
1	Atovaquone	Ubiquinol-cytochrome-c reductase inhibitor	0.802	0.032

Table 2: Predicted value of Ubiquinol-cytochrome-c reductase inhibitor

Activity of Active Chemical Constituents of *Ipomoea carnea*

S. No.	Active Chemical Constituents	Pa	Pi
1	Swainsonine	0.639	0.092
2	Squalene	0.911	0.004
3	2-Ethyl-1,3-dimethylbenzene	0.820	0.026
4	2-(12-Pentadecynyloxy)-tetrahydro2H-pyran	0.590	0.111
5	Hexadecanoic Acid	0.907	0.005
6	Linoleic Acid	0.870	0.011
7	Epiglobulol	0.606	0.105
8	1-Octadecanol	0.937	0.003
9	Stearic Acid	0.907	0.005
10	1, 2-diethyl phthalate	0.852	0.016
11	Octacosane	0.934	0.003
12	Hexatriacontane	0.934	0.003
13	Tetracontane	0.934	0.003
14	3-diethylamino-1-propanol	0.833	0.022
15	Calystegine B1	0.675	0.078
16	Calystegine B2	0.715	0.063
17	Calystegine C1	0.715	0.063

Table 3: Molecular Protein-Ligand Docking of Ubiquinol-cytochrome-c reductase with Potential Active Chemical Constituents of *Ipomoea carnea*

S. No.	Active Chemical Constituents	Molecular Formula	PubChem CID	Ubiquinol-cytochrome-c reductase	
				Full Fitness (Kcal/mol)	Binding Affinity (Kcal/mol)
1	Hexadecanoic Acid	$C_{16}H_{29}O_2^{-3}$	5326436	-4228.32	-9.38
2	1, 2-diethyl phthalate	$C_{12}H_{14}O_4$	6781	-4151.60	-6.85
3	3-diethylamino-1-propanol	$C_5H_{13}NO$	76646	-4193.38	-7.61
4	Stearic Acid	$C_{18}H_{36}O_2$	5281	-4228.20	-9.94
5	Linoleic Acid	$C_{18}H_{32}O_2$	5280450	-4207.34	-9.43

Result

The data of anti-malarial activity and protein- ligand docking of chemical constituents of *Ipomoea carnea* was compared with Atovaquone data. The Pa value of Atovaquone was found to be 0.802 & the Pa value of Swainsonine, Squalene, 2-Ethyl-1,3-dimethylbenzene, 2-(12-Pentadecynyloxy)-tetrahydro2H-pyran, Hexadecanoic Acid, Linoleic Acid, Epiglobulol, 1-Octadecanol, Stearic Acid, 1, 2-diethyl phthalate, Octacosane, Hexatriacontane, Tetracontane, 3-diethylamino-1-propanol, Calystegine B1, Calystegine B2, Calystegine C1 were found to be 0.639, 0.911, 0.820, 0.590, 0.907, 0.870, 0.606, 0.937, 0.907, 0.852, 0.934, 0.934, 0.934, 0.833, 0.675, 0.715, 0.715 respectively stated in Table 1 and 2. In table 3, analysis of protein ligang docking data were placed. Stearic acid, Linoleic acid, Hexadecanoic acid shows binding affinity (Kcal/mol) value of -9.94, -9.43, -9.38 respectively. It was observed that chemical constituents of *Ipomoea carnea* have more Pa value than Atovaquone for antimalarial activity. It was also observed that Stearic acid, Linoleic acid and Hexadecanoic acid binds to Ubiquinol-cytochrome-c reductase with high affinity and low binding affinity energy. Therefore these compounds of *Ipomoea carnea* have potential anti-malarial activity.

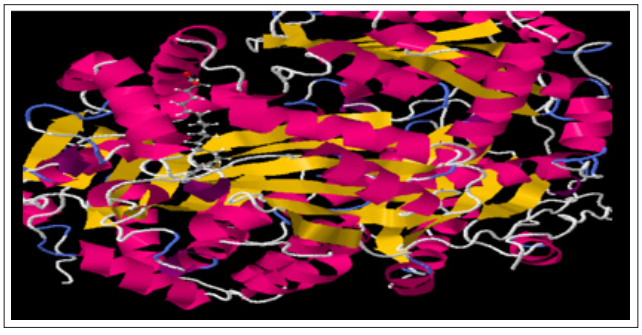

Figure 1: Molecular Protein-Ligand Docking of Ubiquinol-cytochrome-c reductase with Stearic Acid

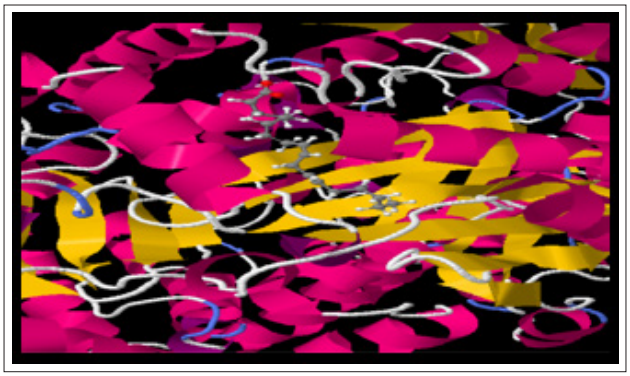

Figure 2: Molecular Protein-Ligand Docking of Ubiquinol-cytochrome-c reductase with Linoleic Acid

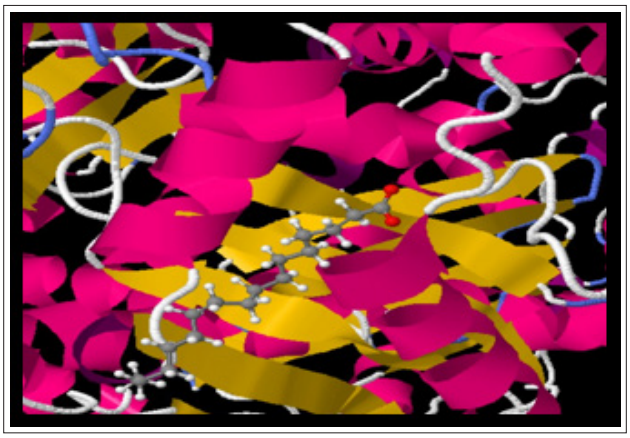

Figure 3: Molecular Protein-Ligand Docking of Ubiquinol-cytochrome-c reductase with Hexadecanoic Acid

Conclusion

Drug discovery and development using advance computational and artificial intelligence are new branch of science, which helps to reduce the error and time consumption of new drug development process. Medicinal herbal plant such as Ipomea carnea have chemical constituents which may have potential for treatment of malaria. It was found that chemical constituents of *Ipomoea carnea* have more Pa value than Atovaquone for antimalarial activity. It was also observed that Stearic acid, Linoleic acid and Hexadecanoic acid binds to Ubiquinol-cytochrome-c reductase with high affinity and low binding affinity [14-18].

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