



MOLECULAR DOCKING ASSESSMENT OF *CISSUS QUADRANGULAR* FOR ANTI MALARIAL ACTIVITY

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ABSTRACT

Introduction: *Cissus quadrangularis* is a herb of phytosanitary origin. It has been used to treat inflammatory diseases. The local name *Cissus quadrangularis* is harbhanga. Photochemical probably bioactive, with useful medicinal properties. Even if modern studies, their benefits in anti-malarial have been emphatic. The bioactive phytoconstituents of *Cissus quadrangularis* Linn are studied *in silico* docking for different anti-malarial drug targets against the target Human Dihydrofolate Reductase (HDR) i.e. Saponin, Pallidol, and Quercetin. **Methods:** All the bioactive photochemical that showed expected activity and followed rules were docked into 1MVT and 1u5n protein receptor downloaded form (WWW.RCSB.COM). The structures were drawn using Vlife2D Draw software by modifying the ligands based on the 1MVT and 1u5n protein receptors. Using the same Vlife 3D Modules program, they were subjected to energy minimization using the Compute menu and then saved as Mol extension files which can be accessed via the docking interface. Software version of Vlife MDS 4.6.1 was used for study of molecular docking. **Result:** The docking findings were analyzed on the basis of interaction and hydrophobic relation between hydrogen bonds (H-bond) and Vander Waals (VDW), Aromatic interaction between ligand and receptor. **Conclusion:** Result of the study shows that saponin displayed the highest activity against 1MVT (HDR) with binding affinities of -68.82 and for 1u5n protein it predicts -61.71 respectively, helping to identify the best possible molecular target for malaria virus.

Keywords: - *In-silico* Molecular Docking, *Cissus quadrangularis* Linn, Anti-malarial Target Receptor.

INTRODUCTION

Malaria is still viewed worldwide as a threat, especially in Asia and Africa. Around 97 countries around the world are resistant to malaria. About 3.3 billion people (nearly 50% of the world's population) are at risk of malaria with two Plasmodium species responsible for the majority of infections: *P. falciparum* and *P. vivax*.¹ Infection with malaria spreads from 60 ° north to 40 ° south of the globe where anopheline mosquitoes may live and grow. The disease affects more than 35% of the world's population, where 10 million people are infected with each year and two million die. *P. falciparum* is widespread in Africa, Middle East and South America while *P. vivax* is prevalent in India and the Far East. *P. ovale* and *P. malariae* in Tropical African regions². The first antimalarial drug, quinine, is an alkaloid that is derived from Cinchona tree bark. In 1970, artemisinin was isolated from *Artemisia annua* by Chinese scientists, and its semisynthetic analogs were also used against quinine-resistant *P. falciparum* (Bray *et al.*, 2005)⁴. Because *Plasmodium falciparum* malaria can be more complex than *P. vivax* infection, this requires extra care while the patient is being examined and should be treated as per drug policy. Artesunate should be given to patients with serious malaria through an intravenous or intramuscular route for at least 24 hours or until patients are able to take oral medication. As the world faces the issue of anti-malarial drug resistance, today it is a major challenge to stop malaria spreading to new areas and malaria re-emergence. Thus new drug targets are needed to develop potential disease inhibitors. So for screening potent anti-malarial drugs, a novel drug target *Plasmodium falciparum* phosphoethanolamine methyltransferase gene which is devoid in humans was picked. Phosphatidylcholine is the phospholipid most frequently required to survive the parasites⁵. The above-mentioned challenge has inspired medicinal chemists and scientists to try out novel anti-malarial lead molecules/drug candidates as alternative therapeutic options to cure awful resistant malaria. In this study, *in-silico* molecular docking method screened the bioactive phytoconstituents of *Cissus quadrangularis* Linn for anti-malarial efficacy and drug-like assessment using various *in silico* tools of drug design. The molecular docking of engineered *Cissus quadrangularis* Linn phytoconstituents was basically carried out against targeting of *Plasmodium falciparum*⁶.

Quadrangularis Cissus L. is part of the Vitaceae family. It includes the active biomolecules Polyphenols, Flavonoids and Stilbenes. Thus the Saponin, Pallidol and Quercetin are used for a number of medicinal purposes including metabolic syndrome, weight loss, injuries to the

jaw bone and neuropharmacological effects⁷. With the development of numerical simulation, possible prediction of malaria drug targets and approaches to evaluating Silico have greatly helped in drug design. The protein's inner structure has understood more closely to understanding and its work through the simulation of protein structures. Computational method obtained results accuracy level still has an extensive way of becoming hundred percent, but provides an insight into findings that would take biologists months and in some cases years to achieve results⁸. In this research, *In-Silico* approach and molecular docking studies conducted to predict the binding affinity with preferred orientation of selected bioactive analogs of the *Cissus quadrangularis* Linn with the most desirable target protein Human malaria parasites, while studies may help to detect the possible harmonizing and therapeutically active analogs of proguanil to stop the life cycle of malaria parasites⁹.

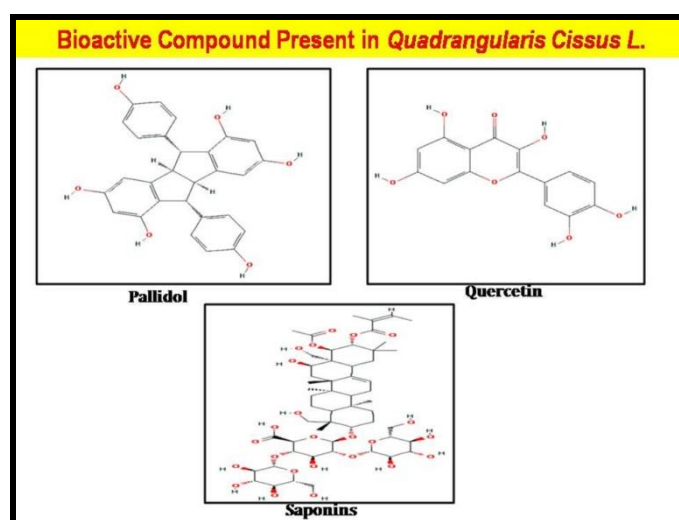


Figure No. 1: Active bioactive compounds present in the *Cissus quadrangularis* Linn

MATERIALS AND METHODS

Spectrometric techniques verified the structure of Pallidol, Quercetin and Saponins. (Meng et al. 2011) Shown and by further evaluation of the anti-malarial ability of *In-silico* molecular docking¹⁰.

a. Generation of proteins by In-silico molecular docking of *Cissus quadrangularis* Linn constituent against Antifolate Binary Complex with Human Dihydrofolate Reductase Proteins files:

Here we present analysis of polymorphic forms of a pyrido[2,3-*d*] pyrimidine N9-C10 reversed-bridge antifolate binary complex with human dihydrofolate reductase is selected as target protein. Data from these two crystal shapes were reset to 1.90 Å for complex R3 (1), with R= 0.186 for 9689 data, and to 1.80 Å for complex R3 (2), with R= 0.194 for 13 305 data. Changes in the configuration of the loop between the two structures in the two R3 lattices result in touch variations in the packaging environments. Molecular docking experiments were carried out using version 4.6.1 of Vlife MDS. Where the protein is used in this study, two different proteins are responsible for Antimalarial and the receptors searched as the structural basis of the Antifolate binary Human Dihydrofolate Reductase (HDR) reversed bridge. Protein Data Bank (PDB ID): 1MVT¹¹. Second is homology model of the PFATP PDB ID: 1U5N were obtained from the PDB (www.rcsb.com). The receptor extracted by X-ray diffraction method with having resolution less than 2.5Å°. Such structures comprise four complexes which were determined using the AMoRe method of molecular replacement. The search functions for rotation and translation were determined with data between 12.0–4.0 Å ° resolution ranges¹².

b. Ligand Preparation:

Saponin, pallidol and Quercetin are the phytoconstituents derived from the *Cissus quadrangularis* Linn farm which were taken from the Chemdraw Ultra 8.0 system and converted to 3D 2D Ligand Structure. Then, these 3D structures were designed using batch optimization for the energy minimization process to capture molecules. For molecular mechanics, MMFF is applied. Or this purpose the parameter is set in force field as pick MMFF from the drop down list. For MMFF Force Field the MMFF atomic charges are picked automatically. Set the interaction values for the electrostatics and vdW 20 and 10 respectively¹³. Systematic search process created compound conformers from the study of systematic analysis of compounds produced conformers. For each of the ligends the docking effects were graded according to the decreasing energies of the different possible conformers. The 3D structure that is drawn describes as follows.

c. Docking Methodology:

i. Molecular Docking

Using Biopredicta software, the binding of the ligands molecule to the protein molecule was analyzed using GRIP Batch docking. The system for finding the correct conformation (with bond rotation, molecule structure is not rigid) and ligand configuration (with whole molecule rotation, molecule structure remains rigid)¹⁴. So that minimum energy structure is obtained. Choose the correct cavity number to dock the docking The parameters used for the docking were selected as the exhaustive and input rotation angle phase size of 30° to rotate the ligand for various poses. Input Number of positions as 30 and Ligand wise results as 5 to get 5 top poses per ligand¹⁵.

ii. The Re-ranked Score function:

The re-ranking score used was computationally more costly than the scoring system used during docking simulation, but generally, it is better than the docking score function to determine the best pose among several poses from the same line. While in Vlife the re-rank score gives an estimate of the strength of interaction¹⁶. The Free Binding Energy (FEB) was defined as the sum of final intermolecular energy (Van Der Waals + Hydrogen bond + Desolvation energy), total internal energy, torsional free energy, and unbound energy of the system¹⁷.

RESULTS AND DISCUSSION

Docking studies:

Thus the amino acid like ASP289A, HIS292A, TYR1088A, ASN1089A, and GLN1090A compliance the tests for binding to the anti-malarial drug and these are an essential part of the antifolate binary complex binding site to the protein HDR. If a ligand could be engineered to block these important sites directly, it could open up the possibility of treating malaria parasites. The complete receptor structure is thus shown in ribbon-shaped format shown in fig.no.2. This all the receptor sections are helpful in the study of the ligand's pharmacokinetics and pharmacodynamics by accessing the drug as assets.

For this purpose, of validation and interactions, the 3 bioactive constituents named as Pallidol, Quercetin and Saponins are found in the *Cissus quadrangularis Linn* plant were compared with those of the native ligand. The behaviors of the molecules under study were predicted based on their ability to dock into the receptor's active site. The molecular activity values dependent on the predictive potential of the molecules Tables No.1 display different receptors as calculated by the docking tests in conjunction with malaria disease.

Table No. 1: Molecular docking results of bioactive constituents present in *Cissus quadrangularis Linn* with protein HDR receptors.

Sr. No.	Molecule	Final energy	Final GRMS value	Dock Score against protein	
				1MVT	1u5n
1.	saponin	-37.9008	0.8572	-68.82	-61.71
2.	pallidol	-29.410	0.9447	-28.26	-60.68
3.	Quercetin	-36.354	0.4060	-53.39	-26.71

GRMS*: conjugate gradient optimization until a root mean squared deviation of the gradient (GRMS) of $0.01 \text{ kcal} \cdot \text{mol}^{-1} \cdot \text{\AA}$

Saponin shows the receptor results 1MVT and 1u5n shown in table no. 1 and the dock score of receptors showed a minimum dock score of -68.82 and -61.71 respectively. This docking score suggested that developed compounds have strong binding affinity for binding to saponin as we compared the result of receptors to the literature. The best pose obtained by docking results is stated (figure no.3.) where it is possible to observe the key interaction between ligand and receptor. At receptor binding for Saponin, all compounds built take on a very similar conformation. A total of five H-bonding interactions with ASP289A, HIS292A, TYR1088A, ASN1089A, and GLN1090A are shown in a fig.no.4 and the second think the 3D visualization of Phytoconstituent's best-docked pose with 1u5n receptor is shown at fig. no.5. Strong binding pocket was found and shown only bonding with hydrogen bond, hydrophobic interaction and VDW Interaction shown in the 2D representation diagram (fig.no.6).

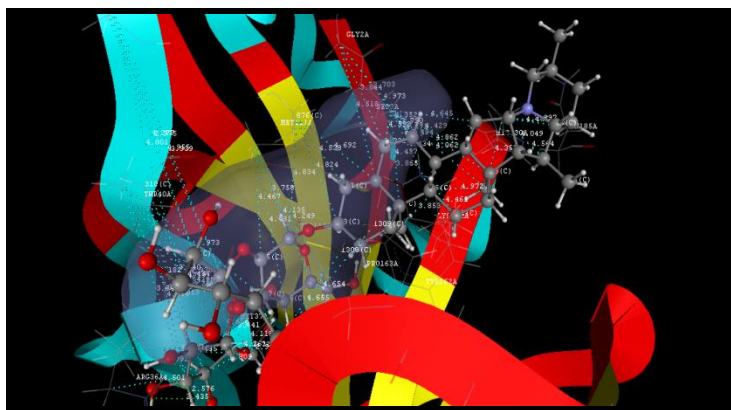


Figure No. 2: 3D Ribbon Dock poses of Saponin against 1MVT receptor

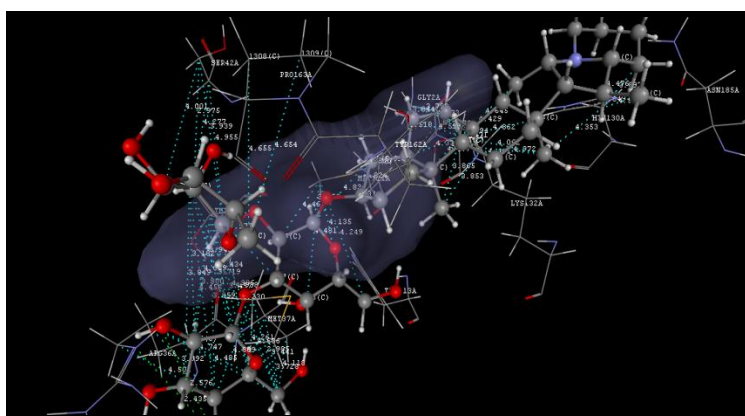


Figure No. 3: 3D poses of Saponin against 1MVT receptor

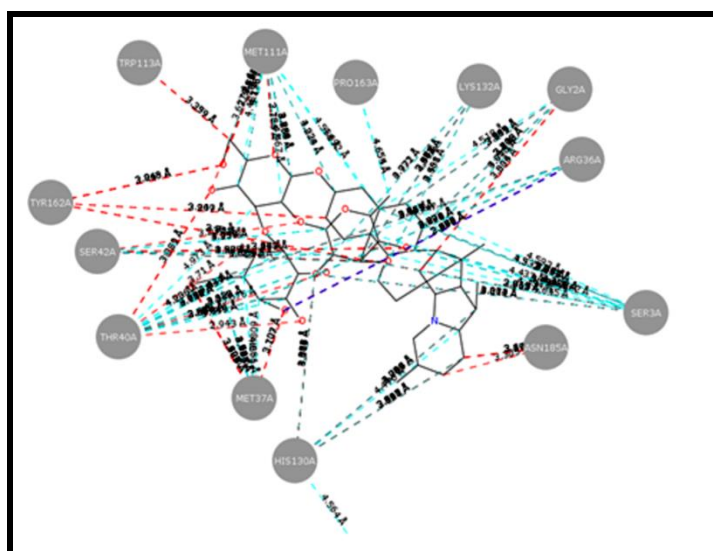


Figure No. 4: 2D representation of Saponin against 1MVT receptor

Table No. 2: Data for interaction of Receptor Saponin with 1MVT receptor Amino Acid

Amino acid	Atom of Ligand	Type of Interaction
ARG36A	50O	Hydrogenbond Interaction
ARG36A	50O	Hydrogenbond Interaction
ARG36A	44C	Hydrophobic Intraction
GLY2A	15C	VDW Interaction
SER3A	15C	VDW Interaction

Saponin shows the results of 1u5n of the receptor shown in table. No. 2 and 1u5n receptor dock score-61.71 showed second minimum dock score as opposed to the anther receptor. This docking score indicated that established compounds have a high binding affinity to *Cissus quadrangularis* Linn when we compared receptor findings with literature. The best pose obtained through the docking results is described (fig. no.5.) and ribbon shaped described in (fig. no.6.). All built compounds follow a very similar conformation at the binding pocket AASP289A, HIS292A and TYR1088A showing only Hydrogen bond interaction with amino acid discussed in the table. No.3. No. Represented also in 2D representation (fig. 7).



Figure No. 5: 3D Dock poses of Saponin against 1u5n receptor

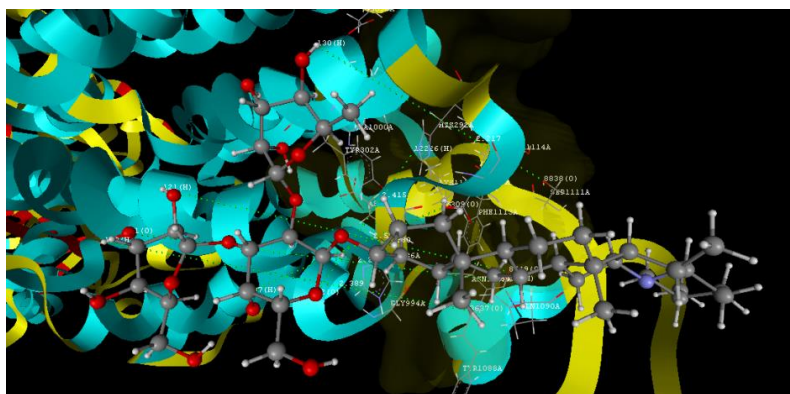


Figure No. 6: 3D Ribbon Dock poses of Saponin against 1u5n receptor

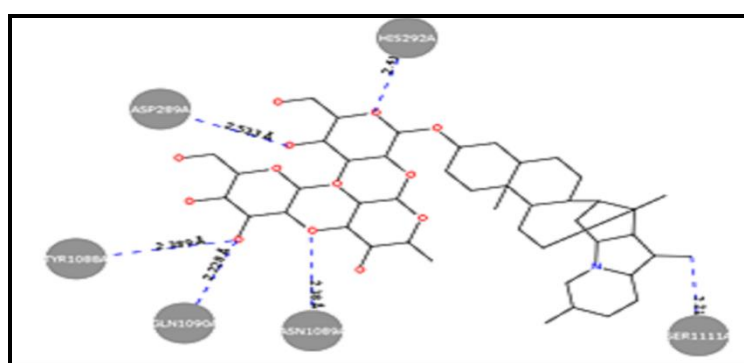


Figure No. 7: 2D representation of Saponin against 1u5n receptor

Table No. 3: Data for interaction of Receptor Saponin with 1u5n receptor Amino Acid

Amino acid	Atom of Ligand	Type of Interaction
ASP289A	38 O	Hydrogen bond interaction
HIS292A	32 O	Hydrogen bond interaction
TYR1088A	51 O	Hydrogen bond interaction
ASN1089A	52 O	Hydrogen bond interaction
GLN1090A	51 O	Hydrogen bond interaction

CONCLUSION

From this study, it is concluded that the Saponin and pallidol isolated from *Cissus quadrangularis* Linn in that the Saponin has the best dock score for receptor 1MVT and 1u5n thus predicts that plant bioactive components show prominent activity against malarial which ultimately confirms that they have high binding capability against 1MVT and 1u5n dock

score of -68.82 and -61.71 respectively. It also notes that the bond between amino acid and functional element has strong ability to bind with interaction of only hydrogen bonds. We concluded from this that *Cissus quadrangularis* Linn with a phytoconstituent called saponin and pallidol with prominent malaria activity will be used as an effective antimalarial agent.

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