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Molecular Docking Studies of *Lonchocarpus cyanescens* Triterpenoids as Inhibitors for Malaria

Adejoro IA, Waheed SO and Adeboye OO*

University of Ibadan, Ibadan, Nigeria

Abstract

Malaria is an important parasitic disease in human. It is transmitted through the bite of an infected female Anopheles mosquito and occasionally through blood transfusion. In this study, the molecular docking studies of the triterpenoids using three (3) different malaria targets with PDB codes 3QS1, 1LS5 and 1SME was investigated using AutoDock vina. The docking studies showed that the ligands docked well with the targets and the binding affinity (-7.8, -8.0, -8.8 kcal/mol for OH and -7.7, -7.6, -8.0 kcal/mol for OCH_3) of the three (3) targets with the triterpenoids are in agreement with the values obtained for standard antimalaria drugs with re-docking binding affinity value of (-8.8, -9.5 and -9.0) kcal/mol for the three targets respectively. However, the result showed that the OH derivative of the triterpenoids gave better binding interaction than OCH_3 derivative.

Keywords: Malaria; Molecular docking; AutoDock vina; Binding affinity

Introduction

Malaria is a common and life threatening disease in many tropical and subtropical areas. It is a mosquito borne infectious disease of humans and other animals caused by parasitic protozoan belonging to the genus Plasmodium [1]. The disease causes about one to two million deaths each year, which accounts for about one hundred and fifty (150) to three hundred (300) deaths each hour [2]. Malaria causes symptoms that typically include fever, fatigue, vomiting and headaches. In severe cases, it can cause yellow skin, seizures, coma or death [3].

The disease is transmitted most commonly by an infected female Anopheles mosquito. The mosquito bite introduces the parasites from the mosquito's saliva into a person's blood [1]. The parasites travel to the liver where they mature and reproduce. Five species of Plasmodium can infect and be spread by humans [3]. Most deaths are caused by *Plasmodium falciparum* because *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae* generally cause a milder form of malaria [1,3]. The species *Plasmodium knowlesi* rarely causes disease in humans [1].

Triterpenoids are naturally occuring and are used against several types of human diseases. Triterpenoids have chemopreventive and anticancer potentials. This is achieved by regulating various transcription and growth factor. [4]. *Lonchocarpus cyanescens* is a species of shrub from fabaceae family. It is commonly known as elo and anunu by Igbo people, in Yoruba, as talaki, in Hausa, sauru in Tiv and as ebelu in Edo people. Various studies has been carried out on the bioactivity, phythotherapeutic, anti-psychotic properties [4,5-16] of *Lonchocarpus cyanescens*. Experimental studies on *Lonchocarpus cyanescens* triterpenoids showed that they posses antimalaria effect Moronkola and Oladosu [17]. Bioassay investigation carried out on the leaf extract for anti oxidant activities revealed that the anti oxidant properties correlated with its phenolic and flavonoid contents [18]. Shuaibu et al. [19] used microfluorometric method by fluorometric assay using picogreen for activity-guided isolation of anti-plasmodium compound from different plant extracts, the *in vitro* anti-plasmodial activity of methalonic extracts of these plants showed that the IC_{50} of *Lonchocarpu cyanescens* as determined by the parasite DNA concentration ranged from 20-200 µg/ml for *Plasmodiun falciparium*. It was reported that the extract and the isolated compound did not affect the integrity of human erythrocyte membrane at the observed IC_{50}. It was also stated that the adverse effects manifest in a concentration dependent fashion from $IC_{50} \geq 500$ µg/ml. Direct study of the compounds on the parasites such as inhibition of the hemozoin polymerization on the parasite [20,21] were carried out by the introduction of a new layer into a pre-existing sequence of the DNA (intercalation with DNA) of the parasite [22] and inhibition of the lactase dehydrogenase of the *Plasmodium falciparium* (an essential enzyme used to generate energy within the parasite) was carried out using a disquiterpene extracted from seeds of *Gossypium* species [23,24]. Inhibition of the formation of microgamates by introducing an interference into the formation of the mitotic spindles and the assembly of microtubules into typical axonemes in the gamates were also carried out [25,26]. Studies on the molecular mechanism of anti malaria action of *Lonchocarpus cyanescens* triterpenoids has not been described. Therefore the goal of this work is to present the docking analysis of these triterpenoids using three different malaria proteins with PDB codes 3QS1, 1LS5 and 1SME.

Computational Procedures

The pdb files 3QS1, 1LS5 and 1SME for the three malaria receptors were obtained from the Protein Data Bank. The initial preparation of the pdb files to select the needed chains, delete multiple ligands and non-protein parts using Discover Studio 4.1 visualizer and ligand explorer, OpenBabel GUI version 2.3.2a was used to convert the pdb file format, Spartan 14 version 1.18 was used for geometry optimization and geoemtric analyses of the ligands. AutoDock Tools 1.5.6 and AutoDock Vina version 1.1.2 was used for molecular docking process (downloaded from http://autodock.scripps.edu) for molecular docking process. EduPymol version 1.7.4.4 was used for analysing docking results. The exhaustiveness which determines how comprehensive the software search for the best binding mode was set to the default

***Corresponding author:** Adeboye Omolara, University of Ibadan, Ibadan, Nigeria, Tel: +23408058484417; E-mail: moadeb5848@yahoo.com

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value of 8 Angstrom which accompanied the ligands from the list of protein residues reported in the literature to characterise their binding sites for all the docking runs. Before the docking runs, Autodock tools (ADT) was used to add polar hydrogen to the prepared receptor. The three-dimesional affinity and electrostatic grid boxes were generated to cover the entire active site using autogrid. The number of grid points in the x, y, z axes 40 × 40 × 40 mm each separated by 1.000 Angstrom. The grid center x, y and z were also specified and it varied from one receptor to another (Table 1). The protein was prepared by adding Gasteiger charges. The Authodock vina were the analysed with Edu Plymol version 1.7.4.4. The receptor in the pdbqt file format as well as the different binding modes of the ligand obtained after the calculation was opened with EduPlymol to check the best binding mode that fitted well with the protein binding site. Two derivatives (OH and OCH_3) of the tripterpenoids of L. *cyanescens* were used as ligands in the docking. The ^{1}H-NMR and ^{13}C-NMR analyses, (Moronkola and Oladosu, 2013) showed that they are triterpenoids that have the sturctures as shown in Figure 1. The converted structures were energetically minimized and then optimized geometrically using Molecular Mechanics Force Field (MMFF) in Spartan'14.

Docking Studies

The docking studies were carried using AutoDock Vina programme. The grid dimension used for all the three (3) proteins are 40 × 40 × 40 Å (grid size) with point separated by 1.000 Å (grid-point spacing). The X, Y, and Z coordinates (grid centres) were also specified and it varied from one receptor to another (Table 1). Also, the exhaustiveness was set to the default value of eight (8) for all the docking runs. The binding energy/affinity of the ligand to the protein was computed using the AutoDock Vina software package by search Algorithm. After the successful completion of the docking runs, different conformations of the ligands known as Binding modes were obtained with their respective binding energy/affinity and the stable one which happens to be the one with the lowest binding energy/affinity was picked as the pose and was employed in the post-docking analysis using Edupymol The inhibition constants K_i were calculated using the equation:

$\Delta G = RT\ln K_i$

$K_i = \text{exponential}(\Delta G/RT)$

where ΔG is the binding affinity/energy in Kcal/mol, R is gas constant, 1.987 cal/mol/K and T is absolute temperature, assumed to be room temperature, 298.15 [27].

Post-docking analysis

The AutoDock Vina results were analysed using Edu Pymol version 1.7.4.4. The receptors in the PDBQT file format as well as the different binding modes of the ligands obtained after running AutoDock vina which were also in PDBQT file format were opened with Edu Pymol to check the best binding mode that fitted well with the binding site cavity.

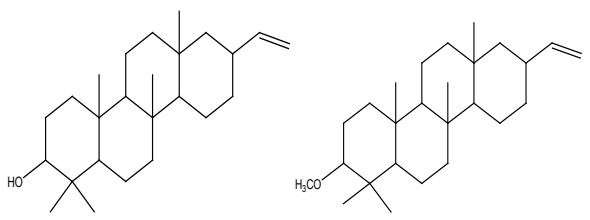

Figure 1: Structures of the Ligands.

Receptors	Centre X (Å)	Centre Y (Å)	Centre Z (Å)
3QS1	22.535	-3.483	2.825
1LS5	-27.373	31.309	45.59
1SME	49.302	56.963	21.164

Table 1: Grid centers (X, Y and Z) used for the docking runs.

Also, the protein-ligand hydrogen interactions were also viewed and the various atomic distances were measured using the same software.

Results and Discussion

Docking score results

The results in Table 2 showed that the synthesized ligands compared favourably well with the standard ligands. The OH and OCH_3 derivatives triterpenoids gave binding affinities values (-8.2 Kcal/mol for 3QS1, -7.5 Kcal/mol for 1LS5 and -7.8 Kcal/mol for 1SME receptors) and (-8.1 Kcal/mol for 3QS1, -7.0 Kcal/mol for 1LS5 and -7.7 Kcal/mol for 1SME receptors) respectively against the standard ligands value (-9.3 Kcal/mol for 3QS1, -8.1 Kcal/mol for 1LS5 and -8.0 Kcal/mol for 1SME receptors). Also, the results showed that the OH derivative of the triterpenoids gave better binding interaction than OCH_3 derivative (Figures 2a, 3a and 4a for redocking and Figures 2b, 2c, 3b, 3c, 4b and 4c for OH and OCH_3 respectively) which implies that the OH derivative of the synthesized triterpenoids will be more effective than OCH_3 derivative in the treatment of the disease. The binding affinity and inhibition constant for the OCH_3 are very high. This is as a result of the inductive (electron releasing) effect of the methyl group. Furthermore, the residues involved in the binding of the ligands to 3QS1 receptors are Gly-217, Ile-287, Ser-287, Tyr-189, Val-76, Asp-215, Thr-222, Ser-77, Asn-292, Lys-296 while Gly-78, Ser-79, Gly-216, Asp-34, Tyr-192, Asp-214, Leu-290 and Asp-214, Thr-217, Val-219, Ala-351, Gly-216, Asn-92, Val-349 are also involved in the binding of the ligands to 1LS5 and 1SME receptors respectively. The result is in agreement with the result obtained from previous study on a triterpenoid isolated from the stem of *Ganoderma sinense (*ganoderiol-F) which showed higher affinity towards HIV-1 protease (binding energy=-11.40 kcal/mol and K_i=4.68 nM) than to plasmepsin I (binding energy=-9.96 kcal/mol and K_i=50.94 nM). Computational studies of *G. lucidum* triterpenoids with aspartic protease enzymes of HIV 1 and plasmepsin I, performed using Nelfinavir and KNI-10006 as the standards for HIV-1 protease and plasmepsin I, respectively. It was observed that the four triterpenoids are able to interact with both enzymes. Ganoderat acid-B showed the best affinity to HIV-1 protease (binding energy=-7.49 kcal/mol and K_i=0.001 mM) which is better than nelfinavir. Furthermore, the best affinity to Plasmepsin I is showed by ganodermanondiol (binding energy=-7.14 kcal/mol and Ki=0.005 mM which is better than KNI-10006 [28].

The Lipinski properties (Table 3) such as Molecular Weight (358.610 for OH ligand derivative and 372.637 for OCH_3 ligand derivative), Partition coefficient value (Log P) (3.20 for OH ligand derivative and 3.42 for OCH_3 ligand derivative) which indicates the Lipophilicity of the ligand; number of Hydrogen Bond Donor (1 for OH ligand derivative and 0 for OCH_3 ligand derivative) and number of Hydrogen Bond Acceptor (1 for OH ligand derivative and1 for OCH_3 ligand derivative) for the ligands were obtained (Table 2). Based on the Lipinski's rule of five, the drug must have Molecular Weight value of ≤ 500, Hydrogen Bond Donor ≤ 5, Hydrogen Bond Acceptor ≤ 10 and Partition coefficient (Log P) value ≤ 5. From the results in Table 2, the synthesized ligands passed the Lipinski's rule of five.

Receptors	Re-docking		OH derivative		OCH_3 derivative	
	E_i	K_i	E_i	K_i	E_i	K_i
3QS1	-9.3	0.15	-8.2	0.96	-8.1	1.14
1LS5	-8.1	1.14	-7.5	3.13	-7.0	7.29
1SME	-8	1.35	-7.8	1.89	-7.7	2.24

Table 2: Docking score results for malaria receptors.
E_i=Binding affinity (Kcal/mol); K_i=Inhibition constant (μM)

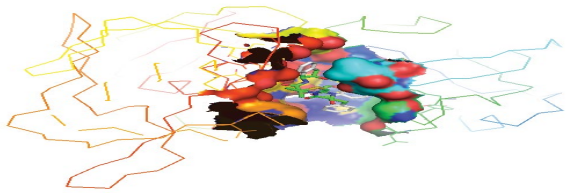

Figure 2a: Re-docking Analysis of 3QS1 Receptor (Surface Representation).

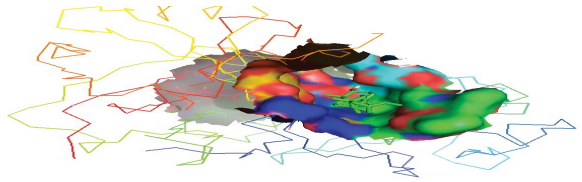

Figure 2b: Docking Analysis of 3QS1 Receptor VS OH derivative ligand (Surface Representation).

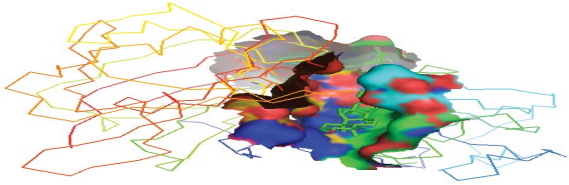

Figure 2c: Docking Analysis of 3QS1 Receptor VS OCH_3 derivative ligand (Surface Representation)..

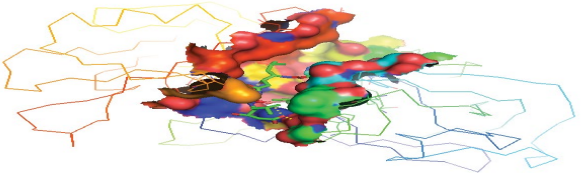

Figure 3a: Re-docking Analysis of 1LS5 Receptor (Surface Representation)..

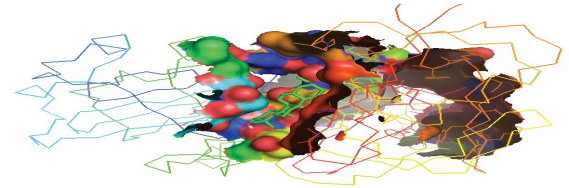

Figure 3b: Docking Analysis of 1LS5 Receptor VS OH derivative ligand (Surface Representation).

Also, the Polar Surface Area (PSA) which is an indicator of the ligand hydrophilicity plays an important role in shaping the protein-

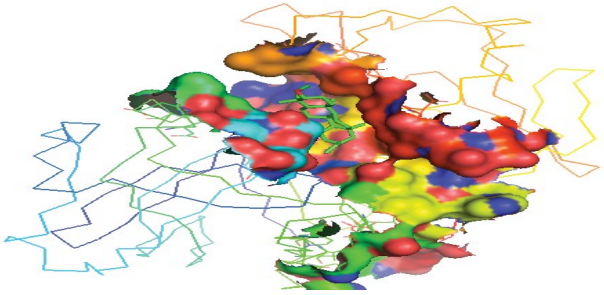

Figure 3c: Docking Analysis of 1LS5 Receptor VS OCH_3 derivative ligand (Surface Representation).

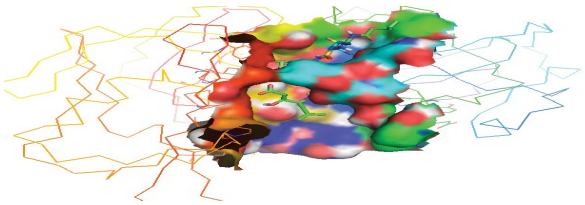

Figure 4a: Re-docking Analysis of 1SME Receptor (Surface Representation).

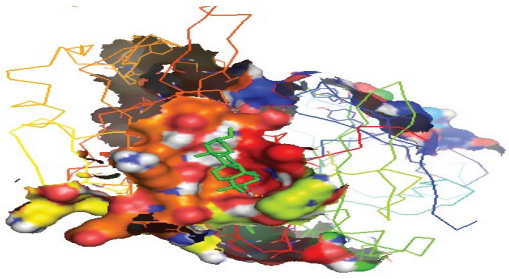

Figure 4b: Docking Analysis of 1SME Receptor VS OH derivative ligand (Surface Representation).

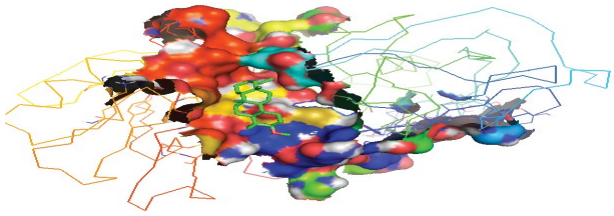

Figure 4c: Docking Analysis of 1SME Receptor VS OCH_3 derivative ligand (Surface Representation).

Properties	OH derivative	OCH_3 derivative
Molecular Formula	$C_{25}H_{42}O$	$C_{26}H_{44}O$
Molecular weight (amu)	358.61	372.637
Area ($Å^2$)	379.24	402.64
Volume ($Å^3$)	410	430.9
Polar Surface Area (PSA) ($Å^2$)	18.841	6.274
Hydrogen Bond Donor (HBD)	1	0
Hydrogen Bond Acceptor (HBA)	1	1
Polarizability	71.99	73.71
Log P	3.2	3.42

Table 3: QSAR properties of the ligands.

ligand interaction by affecting the non-bonded contribution to the binding energy. Molecules with PSA greater than 140 $Å^2$ are usually believed to be poor at penetrating cell membranes. For molecules to penetrate the blood-brain barrier, PSA should be less than 60 $Å^2$ [29] which the ligands also fulfilled (Table 2).

Conclusion

Structure-based methods remain one of the most logical approaches in drug discovery. In the present work, the studies revealed that the ligands docked well with the targets suggesting that the ligands are efficacious in the treatment of malaria.

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