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INSILICO DOCKING ANALYSIS OF MARINE DERIVED COMPOUNDS AGAINST ONCOPROTEIN OF CERVICAL CANCER

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ABSTRACT

Cervical cancer remains a major worldwide public health problem in women and it requires a potent lead compound for its control. Therefore, in the present study six compounds derived from marine organisms (algae, sponges and fungi) were tested against viral oncoprotein HPV16 E6 of cervical cancer. The 3D crystal structure of HPV16 E6 was tested for potent inhibitor compounds by insilico docking process. The results revealed that all the six compounds (scalaradial, rubrolide, caulerpin, zeatin, fascaplysine and liphagal) were identified to be efficient in destroying viral oncoprotein responsible for cervical carcinogenesis, based on activation energy.

Key words: cervical cancer, oncoprotein, pdb, HPV16 E6

1. INTRODUCTION

Cervical cancer remains the second most frequent cause of death in women across the world in the last two decades, since the discovery of human papilloma virus (HPV) in 2008. The HPV has been well characterized as a causative agent for cervical cancer. The viral DNA from specific group of HPV can be detected in at atleast 90% of all cervical cancer (Caroline Horvath *et al.*, 2010). HPV is divided into low risk and high risk categories according to its ability to transform epithelilal cells and induce cancer. HPV 16 is by far the most prevalent HPV that causes cervical cancer, being associated with about 50% of the cases Paraskevaidi and Kalantaridou (1999). HPVs are small, non-enveloped double-stranded DNA viruses that belong to the Papovaviridae family. Like other viruses, HPV is an obligatory intracellular parasite and must deliver its genome and accessory proteins into host cells and subsequently make use of the biosynthetic cellular machinery for viral replication. High-risk HPV encode two major oncoproteins termed as E6 and E7, and the respective genes are the only viral genes that are generally retained and expressed in cervical cancer tissues. Since cervical cancer represents the second most common cancer in women, it still is, of considerable interest to elucidate and characterize the oncogenic functions of E6 and E7, Konstantin Matentzoglu and Martin Scheffner (2008). The E6 and E7 proteins target two different tumor suppressors, p53 and the retinoblastoma gene product (pRb), respectively.

HPV16 E6 is a small basic protein of 151 amino acids. The major structural characteristic of E6 is the presence of two atypical zinc fingers. At the base of these zinc fingers are two motifs containing two cysteines (Cys-X-X-Cys), which are conserved in all E6 HPV types (Yves Nomine *et al.*, 2006). Oncoprotein E6 is essential for oncogenesis induced by (HPV). The structure of HPV16-E6 C-terminal domain reveals a zinc binding fold. A model of full-length E6 is proposed and analyzed in the context of HPV evolution. E6 appears as a chameleon protein combining a conserved structural scaffold with highly variable surfaces participating in generic or specialized HPV functions (Dell and Gaston 2001).

The E6 proteins from high-risk HPV types bind to p53 in conjunction with a ubiquitin-ligase known as E6-AP or ubiquitin protein ligase. The ubiquitination of p53 that occurs as a result of complex formation targets this protein for proteasome- mediated degradation, and significantly reduces the half-life of p53. The decrease in p53 levels brought about by E6 is thought to be important for viral replication; An analysis of a small number of cervical tumours and normal controls has suggested that the presence of the p53-R72 allele can be a risk factor in HPV-induced cancer (Clinton Jones 1995).

Human papilloma viruses (HPV) are the etiological agents in nearly 99.7% of cervical cancer. The HPV E6 protein is one of the viral oncoprotein that is expressed virtually in all HPV positive cancers. Therefore, E6 is now an attractive anticancer treatment target. The oncoprotein HPV 16 E6 has not been properly studied for docking with chemical compounds especially those of marine origin. Therefore, the present study was made to screen the six compounds derived from marine organisms for destruction the cervical oncoprotein.

2, MATERIALS AND METHODS

2.1. PDB Protein Structure

The 3-D cry was our target. stal structure of the cervical cancer protein HPV16 E6 It was retrieved from the

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protein data bank (PDB) (WWW.rcsb.org/pdb). PDB (ID: 2FK4). 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.

Lipinski's Rule of Five

- Not more than 5 hydrogen bond donors (OH an NH groups)
- Not more than 10 hydrogen bond acceptors (notably N and O)
- A molecular weight under 500 g/mol
- A partition coefficient log P less than 5
- Rotatable bonds less than 10

The compound which satisfies the Lipinski's rule of five is taken as drug molecules and docking procedure is carried out

2.2. Chemicals screened

Six chemicals namely scalaradial, caulerpin, rubrolide, liphagal, fascaplysine, zeatin identified from marine algae were screened against cervical oncoviral protein.

2.3.Amino acid binding site

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

Table 1. Cervical cancer proteinHPV16 E6 binding site

Amino acids in the binding pocket	Binding site amino acids in the structural unit
ALA1,ARG40ASP21,ASP21,GLN39	Alpha Helix
ARG52,GLN14	Coil
ARG25,LEU23,ARG47,ARG64,ASN50	Beta strand

2.3. Docking methods

The molecular docking was performed using Argus Lab, a widely distributed public domain molecular docking software. The inhibitor and target protein were geometrically optimized and docked using docking engine Argus dock.

2.4 Argus Lab

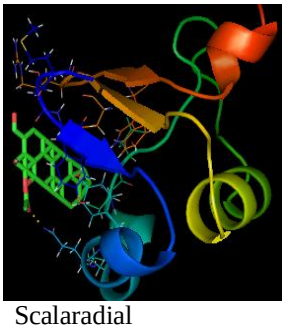
Argus lab is molecular modeling software that runs on windows as a free software and can be easily accessed by the public. It consists of a user interface that displays the graphical structure of the molecules and runs quantum mechanics calculation using Argus computing server. By using lab we can able to build an atom, build molecules using templates, to change the structure of an atom and bond types, and to build new structures from the pre-existing structures. The minimum potential energy was calculated for drug receptor interaction through the geometry convergence map in Argus lab software

2.5. PROTEIN-LIGAND DOCKING

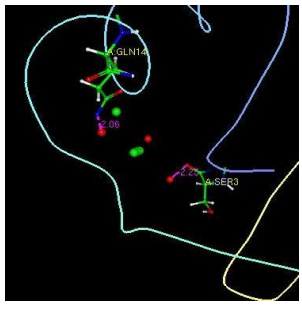
Protein-ligand docking is a molecular modeling technique. The goal of protein-ligand docking is to predict the position and orientation of a ligand (a small molecule) when it is bound to a protein receptor or enzyme. In the field of molecular modeling, docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex between two molecule. Docking is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets in order to in turn predict the affinity and activity of the small molecule. Hence docking plays an important role in the rational design of drugs

3. RESULTS

Six chemicals derived from marine ecosystem were docked with protein responsible for cervical cancer. 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 6 ligand molecules, 2 showed the activation energy of greater than 10 kcal/mol and the remaining 4 molecules exhibited the values <10 kcal/mol. The highest activation energy (-12.0691 Kcal/mol) was found associated with scalaradial followed by rubrolide, caulerpin and liphagal. The lowest activation energy was found in zeatin (7.31076 Kcal/mol).



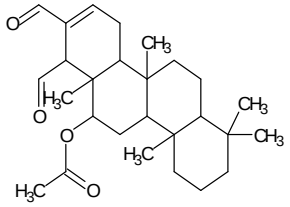
Scalaradial



hydrogen bond, Neighbor residues

4. DISCUSSION

Docking is a computation technique that samples confirmatory of small molecules in protein binding sites. Scoring functions are used to assess which of these confirmatory best complements the protein binding site. The targeting study is on cervical cancer protein, HPV16 The present study proved that the coastal marine-derived compounds were found capable of blocking the protein,

Compound Name	Pubchem ID	Compound structure	Molecular Weight/molecular formula	Hydrogen donor/ acceptor	Docking Energy Level
Scalaradial	CID 119491		428.6041 [g/mol] $C_{27}H_{40}O_4$	(0,4)	***-12.0691 k cal/mol***
rubrolide	CID 5472704	472.51196 [g/mol] $C_{17}H_9Br_2ClO_4$		(2,4)	**-11.2995 kcal/mol**
liphagal	CID 11638999		356.45532 [g/mol] $C_{22}H_{28}O_4$	(2,4)	**-9.58178 k cal/mol**
caulerpin	CID 5326018		398.41072 [g/mol] $C_{24}H_{18}N_2O_4$	(2,4)	**-9.86183 k cal/mol**
fascaplysine	CID 73293		271.29274 [g/mol] $C_{18}H_{11}N_2O^+$	(1,1)	**-8.58583 k cal/mol**
Zeatin	CID 449093		219.24312 [g/mol] $C_{10}H_{13}N_5O$	(3,5)	**-7.31076 k cal/mol**

responsible for cervical carcinogenesis. In the present study five chemicals, known to be present in marine ecosystem, were found to be good analogs, and were allowed to dock with the cervical cancer protein

5. CONCLUSION:

The present project aims at INSILICO DOCKING ANALYSIS OF MARINE DERIVED COMPOUNDS AGAINST ONCOPROTEIN OF CERVICAL CANCER. Six compounds derived from marine organisms were screened against the protein responsible for cervical carcinogenesis. The chemical interaction between selected ligand(scalaradial,rubrolide,caulerpin zeatin, fascaplysine and liphagal) and the target protein E6 was found to be efficient based on the binding energy and interaction scores.so on analysis its clear that,scalaradial is the good inhibitor and can be used as inhibitor for viral oncoprotien E6.

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