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IN SILICO MOLECULAR DOCKING OF BIOACTIVE COMPOUND PREGNAN-20-ONE,5,6-EPOXY-3,17,DIHYDROXY-16 METHYL-[3A,5A,6A,16A] WITH BRAIN CANCER PROTEIN(1QH4) : A PROMISING MOLECULAR TARGET

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Abstract. Molecular docking is a key tool in structural molecular biology and computer-assisted drug design. In this study marine bioactive ligand Pregnan-20-one,5,6-epoxy-3,17,dihydroxy-16 methyl-[3a,5a,6a,16a] was docked against the brain cancer protein BCP (1QH4). The docking analysis was carried out by Auto dock tools (ADT) v1.5.4 and Autodock v4.2 programs. The hydrophobic effect of ligand was retrieved by ALOGPS 2.1.Polar hydrogen charges of the Gasteiger-type were assigned and the nonpolar hydrogens were merged with the carbons. The probable binding sites of preferred target receptors were searched using Q-site Finder to predict the ligand binding site. All the visualization of the structure files were done using PyMol molecular graphics system. The results showed that the selected ligand showed binding energy ranging from -7.82.kcal/mol to -6.63 kcal/mol. The binding profile of the Pregnan-20-one,5,6-epoxy-3,17,dihydroxy-16 methyl-[3a,5a,6a,16a] (ligand - $C_{22}H_{34}O_4$) docked with brain cancer protein 1QH4 showed that ligand interacted with one polar amino acid THR108 and non polar amino acid PHE271. The present study concluded that the marine alga derived compound Pregnan-20-one,5,6-epoxy-3,17, dihydroxy-16 methyl-[3a,5a,6a,16a] (ligand - $C_{22}H_{34}O_4$) are capable of blocking this oncoprotein 1QH4 responsible for brain cancer.

Keywords: Brain Cancer, Autodock tools and Natural products.

1. INTRODUCTION

Marine organisms are source material for structurally unique natural products with pharmacological and biological activities (Faulkner, 2001). Cancer is possibly one of the most dangerous diseases and cure for it has not yet been found. Therefore, prevention of cancer through good diet practices is well promoted as a chemoprevention strategy; marine edible seaweeds are promising candidates in this regard. Long chain polyunsaturated essential fatty acids from the omega 3-family (LC-PUFA omega 3) such as Eicosapentaenoic acid and C20:5 omega 3, extracted from macro algae were reported to reduce the risk of heart disease, thrombosis and atherosclerosis (Khotimchenko et al.,2002). Several species of algae have been found to be the source of polysaccharides and glycoprotein with immune stimulant, antioxidant and antitumoural and antiviral activity (Kamat et al., 1992; Mishra, et al., 1993).

Isolation of cytotoxic antitumor substances from marine organisms has been reported in several references during the last 40 years (Burrows, 1991; Fadli et al., 1991). In recent years, hundreds of potential anti tumour agents have been isolated from marine origin especially from marine algae (Adams, 1994 and Fadli et al., 1991).

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, 2011); Senthilraja et al., 2011), MCU1 oncoprotein (Rajamanikandan et al., 2011). Mangrove -derived compounds such as triterpenoid and stigmasterol have been studied for computation selection against sterol carrying protein, AeSCP-2 (Senthilraja and Kathiresan, 2011) and cervical viral oncoprotein, HPV16 E6 (Senthilraja and Kathiresan, 2011). Computational chemistry tools have become very important to ascertain the targets for different ligand (Richon, 1994). It generates new knowledge that is useful in such fields as drug design and develops new software tools to create that knowledge. Experimental determination of drug efficacy and safety is a time and cost consuming procedure. Molecular docking is a key tool in structural molecular biology and computer-assisted drug design. The identification of oncogenes involved in the initiation and progression of tumors has generated targets for the development of new anticancer drugs (Rajamanikandan et al., 2011). The field of molecular docking has emerged during the last three decades and now is becoming an integral aspect in drug discovery and development (Meshram and Jangle, 2009). In this study, using bioinformatics tools we aim to assess the docking of C. aerea secondary metabolite Pregnan-20-one,5,6-epoxy-3,17,dihydroxy-16 methyl-[3a,5a,6a,16a] with active sites of Brain cancer (PDB-1QH4).

2. MATERIALS AND METHODS

2.1. **Molecular-docking.** The chemical structures of the compound Pregnan-20-one,5,6-epoxy-3,17,dihydroxy-16 methyl-[3a,5a,6a,16a] formula $C_{22}H_{34}O_4$ are drawn using the Chem sketch package 11.0 belonging to the ACD Chem laboratory (Baskaran and Ramachandran 2012 and Balamurugan et al., 2012). Three dimensional structures of Brain cancer (PDB-1QH4) was retrieved from the Protein Data Bank (PDB) http://www.pdb.org. The probable binding sites of preferred target receptors were searched using Q-site Finder to predict the ligand binding site. The docking analysis was carried out by Auto dock tools (Wallace et al., 1995) (ADT) v1.5.4 and Autodock v4.2 programs; (Autodock, Autogrid, Autotors, Copyright-1991-2000) from the Scripps Research Institute, http://www.scripps.edu/mb/olson/doc/ autodock. The searching grid extended above the preferred target proteins; polar hydrogens were added to the ligand moieties. Kollman charges were assigned and atomic solvation parameters were added. Polar hydrogen charges of the Gasteiger-type were assigned and the nonpolar hydrogens were merged with the carbons and the internal degrees of freedom and torsions were set. The search was carried out with the Lamarckian Genetic Algorithm; populations of 150 individuals with a mutation rate of 0.02 were evolved for 10 generations. Evaluation of the results was done by sorting the different complexes with respect to the predicted binding energy. A cluster analysis based on root mean square deviation values, with reference to the starting geometry, was subsequently performed and the lowest energy conformation of the more populated cluster was considered as the most trustable solution. The hydrophobic effect of the ligand was retrieved by ALOGPS 2.1. All the visualization of the structure files were done using PyMol molecular graphics system (www.pymol.org).

3. RESULTS AND DISCUSSION

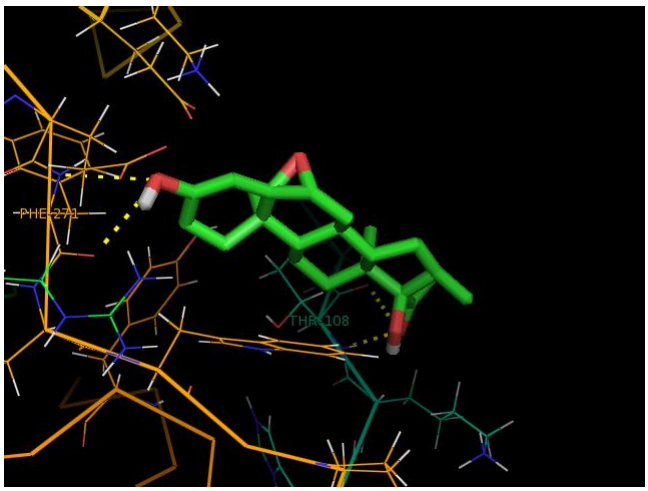
The goal of ligandprotein docking is to predict the predominant binding model(s) of a ligand with a protein of known three dimensional structures. Docking studies yield crucial information concerning the orientation of the inhibitors in the binding pocket of the target protein. Several potential inhibitors have been identified through the docking simulation. The majority of the ligands had a greater binding affinity with the target cancer proteins. Inhibition was measured by the binding energy of the best ligand pose measured in kcal/mol.

The binding profile of the Pregnan-20-one,5,6-epoxy-3,17,dihydroxy-16 methyl-[3a,5a,6a,16a] (ligand) docked with brain cancer protein 1QH4 shows that the ligand has interacted with one polar amino acid THR108 and non polar amino acid PHE271, one acidic polar amino acid GLU1879 and one non polar amino acid LEU1795.(Plate1).

The docking scores were the highest for Pregnan-20-one,5,6-epoxy-3,17,dihydroxy-16methyl-[3a,5a,6a,16a] (7.82 kcal/mol). Gaikwad, et al. (2011) docked the antitumor compounds against the cancer proteins. The ligand cabazitaxel showed the least binding energy of -709.75 kcal/mol with skin cancer protein (2VCJ). In this study, most of the amino acid residues in the active

site are hydrophobic due to which they are the main contributors to the receptorligand interaction.Analysis of ligand binding interaction with the cancer proteins can be useful for new preventive and therapeutic drug for cancer (Sindhu et al., 2011).

Plate 1. Binding of **Pregnan-20-one,5, 6-epoxy-3,17,dihydroxy-16 methyl-[3a,5a,6a,16a]** with cancer target protein (1QH4).



Molecular docking is a key tool in structural molecular biology and computer-assisted drug design. The identification of Oncogenes involved in the initiation and progression of tumors has generated targets for the development of new anticancer drugs (Rajamanikandan et al.,2011). The field of molecular docking has emerged during the last three decades and now is becoming an integral aspect in drug discovery and development area (Meshram and Jangle, 2009).

4. Conclusion

The results obtained from this study would be useful in both understanding the inhibitory mode as well as in rapidly and accurately predicting the activities of new inhibitors on the basis of docking scores (Baskaran and Ramachandran, 2012). The present study concluded that the marine alga derived compound Pregnan-20-one,5,6-epoxy-3,17,dihydroxy-16 methyl-[3a,5a,6a,16a] (ligand - $C_{22}H_{34}O_4$) are capable of blocking this oncoprotein 1QH4 responsible for brain cancer.

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