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Research Article

In silico Docking Studies of Secondary Metabolites from Marine Sponge *Discodermia calyx* – Natural Inhibitor for Breast Cancer

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ABSTRACT

Objective: The present study is concerned with the docking of secondary metabolites of marine sponge *Discodermia calyx* and their application as anticancer agent in order to arrive at an effective drug like molecule targeting the Human Estrogen Receptor alpha (ERα) mainly responsible for Breast Cancer. Method: The tools and software used are Protein Data Bank, to retrieve the structure of the protein; Pubchem compound database, to retrieve the chemical structure of the Estrogen Receptor inhibitors, Discovery Studio2.0 for pharmacophore and the docking analysis. Result: The results show that the compounds Cis-3,4- Dihydrohamacanthin B, Deoxytopsentin, Isobromodeoxytopsentin, Bromodeoxytopsentin, Ent kurospongin are more favourable to bind with Glutamic acid353 (GLU 353), the amino acid present in the active site of the protein. Conclusion: Docking analysis reveals that among five compounds Cis-3,4- Dihydrohamacanthin shows good binding affinity with the active site of the Human Estrogen Receptor protein and can be used as a potential Estrogen Receptor inhibitor.

Keywords: *Discodermia calyx*, Human Estrogen Receptor Alpha, Accelrys Discovery Studio2.0, Glutamic acid, Cis-3,4-Dihydrohamacanthin.

INTRODUCTION

Estrogens control multiple physiological processes including the growth, differentiation and function of the reproductive system. In females, the main target organs are the uterus; vagina, ovaries and mammary gland while in males target organ comprise the testes, prostate and epididymis[1]. Most of the actions of estrogens are mediated by Estrogen Receptor (ER). A high level of Estrogen is linked with increased risk of Breast cancer by stimulating breast epithelial cell proliferation. Estrogens Receptor exists in two forms ER alpha and ER beta (ERα & ERβ)[2]. ERα and ERβ may have different roles in the formation and progression of breast cancer. Most of the breast cancer is identified by abnormal expression of Estrogen Receptor α-positive affecting about 70% of the primary breast cancer patients. Estrogen stimulated cell proliferation and increased tumor formation occurs, when only ERα is present[3]. Hence, inhibition of Estrogen Receptor alpha is a major approach to prevent the Breast cancer.

Marine Sponges are rich resources of natural active compounds; to date a various secondary metabolites have been reported from marine sponges, which act against many diseases such as cancer, diabetes etc.[4]. *Discodermia calyx* marine sponge is isolated from the coast of Jeju Island, South Korea by Prof. Chung Ja Sim, Hannam University[5]. The marine Sponge *Discodermia calyx* (order Lithistida, family Theonellidae) is reported to contain antitumor activity[6]. Calyculins is a reported unique polyketides compound isolated from *D.calyx* bearing nitrogen and phosphorous function[7] showing anticancer activity.

MATERIALS AND METHODOLOGY

Preparation of Receptor and Ligand

The Xray Crystallographic structure of the Human Estrogen Receptor with 1.6Å resolution was retrieved from Protein Data Bank (PDB), PDB ID: 2IOG was used as a potential anticancer drug target[8]. Further hydrogen atoms were added and hetero atoms were removed from the protein structure.

From Literature evidence 11 secondary metabolites isolated form *Discodermia calyx* was collected[5]. 3D structure of the 11 compounds was taken from PUBCHEM database. The list of compounds and their corresponding ID is shown in the Table 1.

Structure based drug design is the method of performing Molecular Docking using known protein docked with known ligand. In this study Human Estrogen Receptor (PDB ID 2IOG) is docked with 11 chemical compounds retrieved from Marine Sponge Discodermia calyx. Docking analysis was done by Accelrys Discovery Studio2.0 and the results in terms of hydrogen bonding and the scoring function were noted[9]. Various binding sites and ligand conformations were tested and the best was selected based on internal energy.

RESULT AND DISCUSSION

The goal of ligand protein docking is to predict the predominant binding model of a ligand with a protein of

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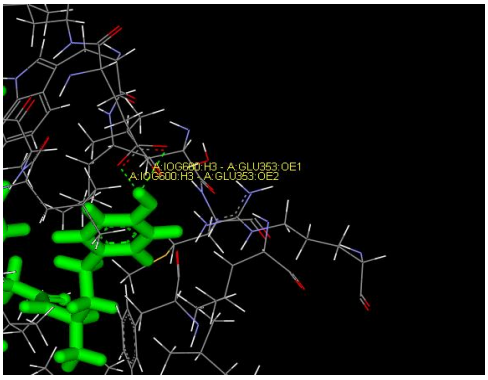

Figure 1: Interaction of Human Estrogen Receptor with Bromodeoxytopsentin with a dock score 16.191

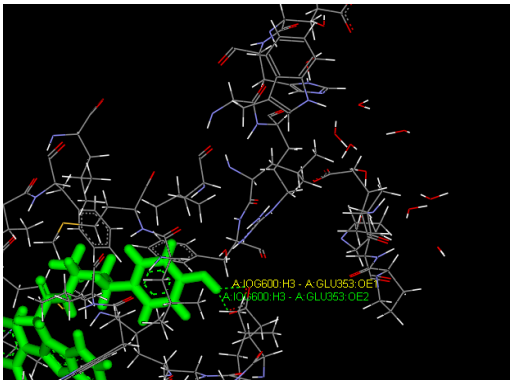

Figure 2: Interaction with Human Estrogen Receptor with Cis-3,4-Dihydrohamacanthin B with dock score 23.698

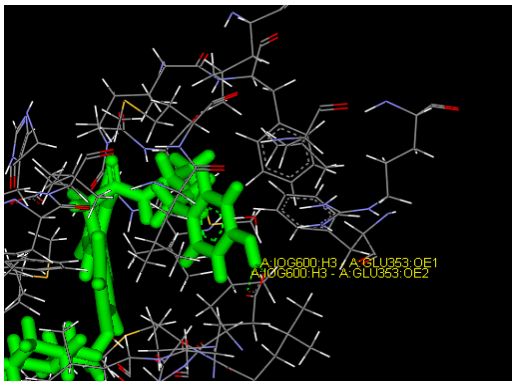

Figure 3: Interaction with Human Estrogen Receptor with Deoxytopsentin with dock score 22.516

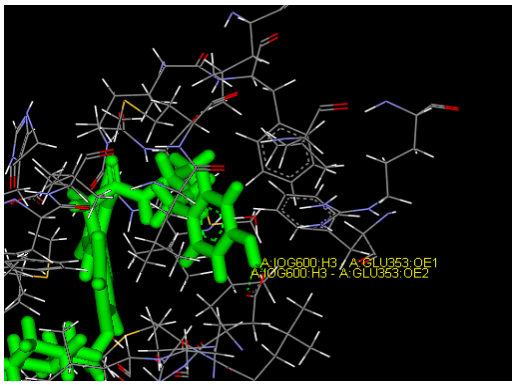

Figure 4: Interaction with Human Estrogen Receptor with Ent kurospongin with dock score 15.261

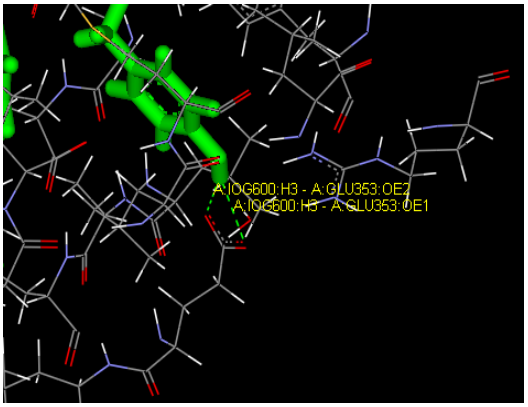

Figure 5: Interaction with Human Estrogen Receptor with Isobromodeoxytopsentin with dock score 22.176

known three dimensional structures[10]. Estrogen metabolism is highly complex and is also important in functioning and development of many tissues and activities[11-13]. In the present study, docking analysis was performed to understand the interactions between the ligand molecules and Human Estrogen Receptor using Accelrys Discovery Studio.

The binding analysis indicates that the Human Estrogen Receptor was successfully docked with the five compounds retrieved from *Discodermia calyx*. The possible binding modes of the five compounds with Human Estrogen Receptor protein is shown in Fig1-5. GLU353 present in the human Estrogen Receptor residue is found to have hydrogen bond interactions with Bromodeoxytopsentin, Cis-3,4- Dihydrohamacanthin B, Deoxytopsentin, Ent kurospongin, Isobromodeoxytopsentin, ligand molecules[14]. Our result is in correlation with the observation which says that the residue GLU353, present in the third helix of the ligand binding domain of the ER alpha[14]. Therefore, it is readily seen that all the compounds are expected to have near similar activity against Human Estrogen Receptor.

CONCLUSION

In this study, the molecular docking was applied to explore the binding mechanism and to correlate its docking score with the activity of Bromodeoxytopsentin, Cis-3,4-Dihydrohamacanthin B, Deoxytopsentin, Ent kurospongin, Isobromodeoxytopsentin, compounds from *Discodermia calyx*. Among all five compounds Cis-3,4-

Table 1: Chemical constituents present in Discodermia calyx.

Chemical Constituents	Pubchem ID
(R)-6'-Debromohamacanthin A	CID 11452527
(R)-6'-Debromohamacanthin B	CID 21778317
Bromodeoxytopsentin	CID 400452
Calyculin	CID 16760341
Cis-3,4-Dihydrohamacanthin B	CID 10624851
Deoxytopsentin	CID 183527
Ent kurospongin	CID 10449789
Hamacanthin A	CID 461371
Hamacanthin B	CID 188235
Isobromodeoxytopsentin	CID 400453
Tetrahydrofurospongin2	CID 21672086

Table 2: Dock score and Internal Energy of Compounds with binding site of the target protein.

Compounds	Dock score in Kcal/mol	Internal energy
Site 1		
Cis-3,4-Dihydrohamacanthin	23.698	-1.636
Deoxytopsentin	22.516	-5.194
Isobromodeoxytopsentin	22.176	-5.227
Bromodeoxytopsentin	16.191	-5.477
Ent kurospongin	15.261	-1.887

Dihydrohamacanthin B shows higher Dock score 23.698Kcal/mol. The results of our present study can be useful for the design and development of drugs having better inhibitory activity against Human Estrogen Receptor protein. These potential drug candidates can further be validated in wet lab studies for its proper function.

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