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POTENTIAL OF MARINE DERIVED COMPOUNDS AGAINST BREAST CANCER (BRCA1): AN *IN-SILICO* DOCKING STUDY

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ABSTRACT
The present study focused on molecular computational analysis to identify the potential compounds, derived from marine organisms (algae, sponges and fungi), which can block the mutated gene (BRCA1) responsible for the breast cancer. Seven compounds were tested against the carcinogenic protein. The 3D crystal structure of the protein (ID: 2IOK) was retrieved from protein data bank (PDB) and the protein binding sites of the test compounds were identified. The results revealed that among seven compounds, tretinoin, stigmasterol, triterpenoid, heritonin, rubrolide , 5-Norbornene-2-carboxylic acid, tricin were found efficient in inhibiting the protein (BRCA1) responsible for breast cancer.
Keywords: Breast cancer, BRCA1 gene, pdb, Carcinogenic, Marine

INTRODUCTION

Breast cancers are thought to be due to a hereditary predisposition to the disease. Two breast-cancer-susceptibility genes, *BRCA*1 and *BRCA*2, have been identified, and mutations in these genes are responsible for most cases in families with a large number of early-onset breast cancers. The role of estrogen in affecting breast cancer risk during pre-menopausal years has remained largely unknown. Several factors related to reproduction appear to predispose women to breast cancer. BRCA1muta-tions confers high lifetime risk of both cancers, but there is evidence that the risk of ovariancancer is heterogeneous. A second breast cancer gene, BRCA2 has recently been localized to chromosome 13q. In contrast to these adverse effects of estrogen on the breast, in certain circumstances, such as during pregnancy that occurs before age 20 years and during the prepubertal period and childhood estrogen actually reduces breast cancer risk. The reduced risk could be achieved through estrogen-induced activation of certain tumor suppressor genes, including BRCA1, p53 that are critical in DNA damage repair and in maintaining genetic stability, thus reducing the likelihood that breast cancer will be initiated, transcriptional regulation as well as other functions .Once breast cancer initiation has taken place, estrogens might promote the growth of transformed cells, leading to the development of detectable breast cancer. Because estrogens increase BRCA1 expression in human breast cancer cells *in vitro* women with defects in either the *BRCA1* or *BRCA2* gene have greater than 80 per cent chance of developing breast cancer. Since, the vulnerability of *BRCA1* is more than *BRCA2* gene in the present study only BRCA1 protein was tested against 7 chemical inhibitors derived from coastal mangrove ecosystem for docking studies[1-18].

MATERIALS AND METHODS

Protein Structure

The 3-D crystal structure of the targeted breast cancer protein BRCA1 (ID: 2IOK) was retrieved from the protein data bank (PDB) (www.rcsb.org/pdb). 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.

Chemicals screened

Seven chemicals namely tretinoin, stigmasterol, triterpenoid, heritonin, rubrolide, 5-Norbornene-2-carboxylic acid, tricin identified from the marine organism [6] were screened. According to Lipinski's rule of five, a compound having not more than 5 hydrogen bond donors (OH an NH groups), not more than 10 hydrogen bond acceptors (notably N and O), molecular weight under 500 g/mol, partition coefficient log P of less than 5 and rotatable bonds of less than 10 is taken as drug molecules and docking procedure was carried out [8] against the breast cancer protein (BRCA1).

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 MarvinSketch Software. The predicted binding sites, based on the binding energy, and amino acids makeup of the binding cavity. The predicted ligand binding site residues are listed in Table 1, fig 1.

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

RESULTS

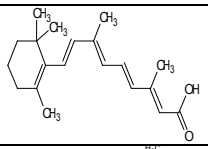
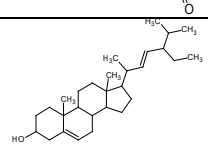
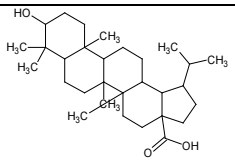
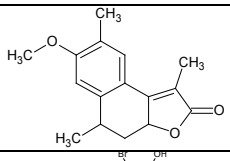
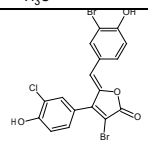
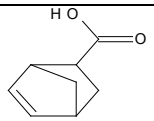
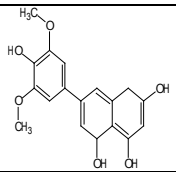
Seven chemicals derived from marine ecosystem were docked with protein responsible for breast cancer (BRCA1). The docked ligand molecules were selected based on docking energy and good interaction with the

active site residues and the results are shown in Table 2. Of the seven ligand molecules, 3 showed the activation energy of greater than -13 kcal/mol and the remaining 4 molecules exhibited the values less than -13 kcal/mol. The highest activation energy (- 16.0254 Kcal/mol) was found with tretinoin (Figure 3) followed by, stigmasterol, triterpenoid, heritonin, rubrolide, 5-Norbornene-2-carboxylic acid. While, the lowest activation energy of -8.06122 Kcal/mol was found with tricin. From the *in silico* docking results, it is quite evident that marine organism (algae, sponges and fungi), derived compounds have the great potential against anti-tumour activity of breast cancer protein BRCA1.

Table 1 Breast cancer protein BRCA1 binding site

Amino acid binding packet	Binding atoms
LEU	354
LEU	354
LEU	354
MET	357
MET	357
MET	357
ILE	358
ILE	358
LEU	379
LEU	379
LEU	379
TRP	383
LEU	536
LEU	536
LEU	540
SER	329

Table 2: **Docking results of mangrove derived compounds against BRCA1 protein**

Compound name	Pubchem ID	Compound structure	Molecular formula	Molecular weight(g/mol)	Hydrogen bound donor/acceptor	Docking energy(cal/mol)
Tretinoin	CID:444795		$C_{20}H_{28}O_2$	300.43512	(1,2)	-16.0254
stigmasterol	CID: 5280794		$C_{30}H_{50}O_3$	269.082	(1,1)	-15.6471
Triterpenoid	CID: 9804218		$C_{30}H_{50}O_3$	458.6041	(2,3)	-14.8644
Heritonin	CID:130118		$C_{16}H_{18}O_3$	258.31232	(0,3)	-12.4269
rubrolide	CID 5472704		$C_{17}H_9Br_2ClO_4$	472.51196	(2,4)	-11.597
5-Norbornene-2-carboxylic acid	CID 78949		$C_8H_{10}O_2$	138.1638	(1,2)	-9.8923
tricin	CID: 5281702		$C_{17}H_{14}O_7$	330.288]	(3,7)	-8.06122

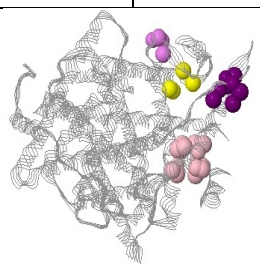


Figure 1: Breast cancer protein BRCA1 binding site

Figure 2: 3D structure of tretinoin

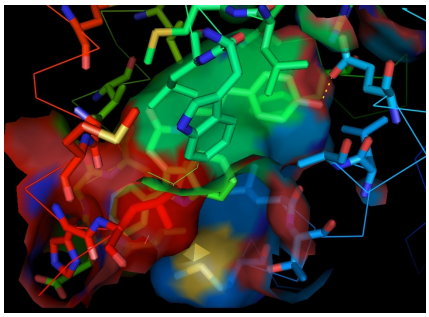


Figure 3: protein(breast cancer) ligand(tretinoin) docking

DISCUSSION

Recent studies have shown that small deletions, insertions, nonsense mutations and splicing aberrations account for 87% of all pathogenic mutations of the *BRCA1* gene, resulted in the generation of truncated BRCA1 protein[2]. Molecular docking is a key tool in structural molecular biology and computer-assisted drug design. Marine derived compounds such as tretinoin followed by triterpenoid , heritonin, tricin stigmasterol, pyrethrin, N-methylflindersin and rubroliden have already been studied for mangrove-derived compounds against breast cancer protein (BRCA1)[14] and cervical viral oncoprotein, HPV16 E6 [13]. The present study also proved that the coastal marine (algae, sponges and fungi) derived compounds are capable of blocking the oncoprotein, responsible for breast cancer.

CONCLUSION

These compounds are eco-friendly, safer and cheaper for application. Identification of BRCA1 will facilitate early diagnosis of breast and ovarian cancer susceptibility in some individuals as well as a better understanding of breast cancer biology. The results obtained from this study would be useful in both understanding the inhibitory mode of marine derived compounds as well as in rapidly and accurately predicting the activities of newly designed inhibitors on the basis of docking scores. Here we concluded that these compounds derived from marine ecosystem (tretinoin, stigmasterol, triterpenoid, heritonin, rubrolide, 5-Norbornene-2-carboxylic acid, tricin) could be novel chemical inhibitors for BRCA1 protein preventing the uncontrolled cell division. Further research is needed for refinement to enrich the activity of the ligands and destroying mechanism of the breast cancer protein, especially in the animal model system, and also to determine the dosage of safety levels, in order to explore this promising avenue for breast cancer control and to ensure the healthy state of women.

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