PREDICTION OF INTERACTION BETWEEN ANTITUMOR COMPOUNDS AND TARGET PROTIENS OF DIFFERENT CANCERS BY *IN SILICO* MOLECULAR DOCKING STUDIES

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Summary

The aim of the present study was to predict the interaction between selected anticancer compounds and cancer target protein of different types of cancer. The following target proteins with their Protein Data Bank (PDB) ID were selected from each type of cancer, breast cancer-1JNX, gastric cancer-1BJ7, brain cancer 1QH4, Lung cancer-2ITO and skin cancer 2VCJ to study its susceptibility to selected anticancer compounds. The 3D and 2D structures of cancer target proteins downloaded from PDB database. The extent of interaction of the selected anticancer compound with a target protein was predicted using i*n silico* molecular docking studies. The anti-cancer drug cabazitaxel showed the binding energy of -709.75 kcal/mol against skin cancer protein (2VCJ) followed by -611.48 kcal/mol with brain cancer protein (1QH4). Among the drugs selected cabazitaxel was found to be effective and interacted strongly with all selected cancer target proteins. The results of our study support the fact that i*n silico* molecular docking studies are very useful in predicting the extent of interaction and binding between selected compounds (ligands) and cancer targets.

Keywords: Auto-dock, Protein Data Bank, Chemsketch, PatchDock, *In silico* docking, Cancer proteins, Anticancer drugs.

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Introduction

Cancer, known medically as a malignant neoplasm, is a term for a large group of different diseases, all involving unregulated cell growth. In cancer, cells divide and grow uncontrollably, forming malignant tumors, and invade nearby parts of the body. Cancer may also spread to more distant parts of the body through the lymphatic system or bloodstream. It is also possible for cancerous cells to break free from the tumor and enter the bloodstream, in turn spreading the disease to other organs and thereby initiates metastasis. When cancer has metastasized and has affected other areas of the body, the disease is still referred to the organ of origination. Cancer is one the leading cause of death worldwide and projected to continue rising with an estimate of 12 million deaths in 2030 (1). Blood cancer includes leukemia or lymphoma are more prevalent worldwide (2).

Brain tumors can be malignant (cancerous) or benign (non-cancerous) can affect both children and adults. Brain cancer types include adult brain tumor, brain stem glioma, cerebellar astrocytoma. Gliomas are a group of central nervous system (CNS) neoplasms with various histological characteristics contributes to 60% (3). They are classified into two major groups as astrocytomas and oligodendrogliomas based on their morphological and histological resemblances between malignant and normal cells (4). The most common form of gliomas in human is the astrocytoma, and the most aggressive type is Glioblastoma multiforme (GBM) (5). Breast cancer is a common type of cancer that affects women and much less commonly, men. More than 200,000 women are diagnosed with breast cancer in the United States each year. Types of breast cancer include ductal carcinoma *in situ* and lobular carcinoma *in situ*. Digestive/gastrointestinal cancers include cancer that affects everything from the esophagus to the anus. They are anal cancer, stomach (gastric cancer) each type is specific and has its own symptoms, causes, and treatments. Nonsmall cell lung cancer (NSCLC) remains a leading cause of death worldwide among patients diagnosed with malignancy. Skin cancer includes cutaneous T-cell lymphoma and Kaposi sarcoma. Non-melanoma skin cancer is the most common type of cancer among men and women. Exposure to the UV rays of the sun is the primary cause for non-melanoma skin cancer and also melanoma skin cancer.

Molecular docking is a key tool in structural molecular biology and computer-assisted drug design. The goal of ligand-protein docking is to predict the predominant binding model(s) of a ligand with a protein of known three-dimensional structure. Nowadays, molecular docking approaches are routinely used in modern drug design to help understand drug–receptor interaction. It has been shown in the literature that these computational techniques can strongly support and help the design of novel, more potent inhibitors by revealing the mechanism of drug–-receptor interaction (6). Hence a study was planned to evaluate the interaction of the selected ligand with a target protein of different types of cancer.

Materials and Methods

Selection of ligands

The following anticancer compounds cocaine, lapatinib, cabazitaxel, apraclonidine and dyclonine were selected from Pubchem database based on their reported anticancer activity. The selected ligands were converted to 3D structures using chemsketch software. Energy minimization was done on each ligand using Chem 3D Ultra (Version 8.0) software.

Selection of target enzymes

Crystal structure of BRCT repeat region from the breast cancer associated protein, BRCA1(1JNX) from breast cancer, Bovine lipocalin allergen BOS D2 (1BJ7) from gastric cancer, crystal structure of chicken brain-type creatine kinase (1QH4) at 1.41 Å resolution from brain cancer, 4,5 diaryl isoxazole HSP90 chaperone (2VCJ) from skin cancer, crystal structure of EGFR kinase domain G719S mutation (2ITO) from lung cancer were selected as targets for docking with a particular ligand.

Functional Site Identification

Predictions of functional sites in target proteins were performed based on Conserved Functional Group (CFG) analysis using siteFiNDER|3D server. It is a fully integrated, web-based implementation of the CFG analysis method for functional site prediction (7).

Molecular Docking Simulation

In order to carry out the docking simulation, AutoDock 4.0 suite molecular-docking tool was used and the methodology was followed as described earlier (8). The ligand was manually docked into functional sites respective protein individually and the docking energy was monitored to achieve a minimum value. AutoDock 4.0 is widely distributed as public domain molecular docking software which performs the flexible docking of the ligands into a known protein structure. The default parameters of the automatic settings were used. Each docking experiment consisted of 10 docking runs with 150 individuals and 500,000 energy evaluations. The search was conducted in a grid of 40 points per dimension and a step size of 0.375 centered on the binding site of enzyme. The Auto Dock results indicated the binding position and bound conformation of the peptide, as well as a rough estimate of its interaction. The docked conformation which had the minimum binding energy was selected to analyze the mode of binding. All the docking runs were performed in Intel Pentium® D CPU @ 3.20 GHz of Lenovo think centre origin, with 2 GB DDR RAM. Auto-Dock 4.0 was compiled and run under Linux operating system.

PatchDock Simulation

Patch Dock was used as an algorithm for molecular docking. Surfaces of two molecules were divided into patches according to the surface shape. These patches correspond to patterns that visually distinguish between puzzle pieces. The identified patches were superimposed by using shape matching algorithms and verified by all three major stages which include molecular shape representation, surface patch matching and followed by filtering and scoring. The protein

and the ligand molecules obtained as PDB files were uploaded and submitted. It was run 20 solutions and out of which the solution with the highest minimum energy was downloaded

Results and discussion

Docking of cabazitaxel to brain cancer protein 1QH4 (crystal structure of chicken brain-type creatine kinase at 1.41 Å resolution) produced the binding energy of-611.48 Kcal/mol (Fifure 1 a,b). The interaction of cabazitaxel with 1QH4 was comparatively higher than other selected ligands. CK is involved in regeneration of ATP at the expense of phosphocreatine. CK has been shown to be involved in numerous pathogenesis and reported to be over expressed in wide range of solid tumors.

Figure 1 a Figure 1 b

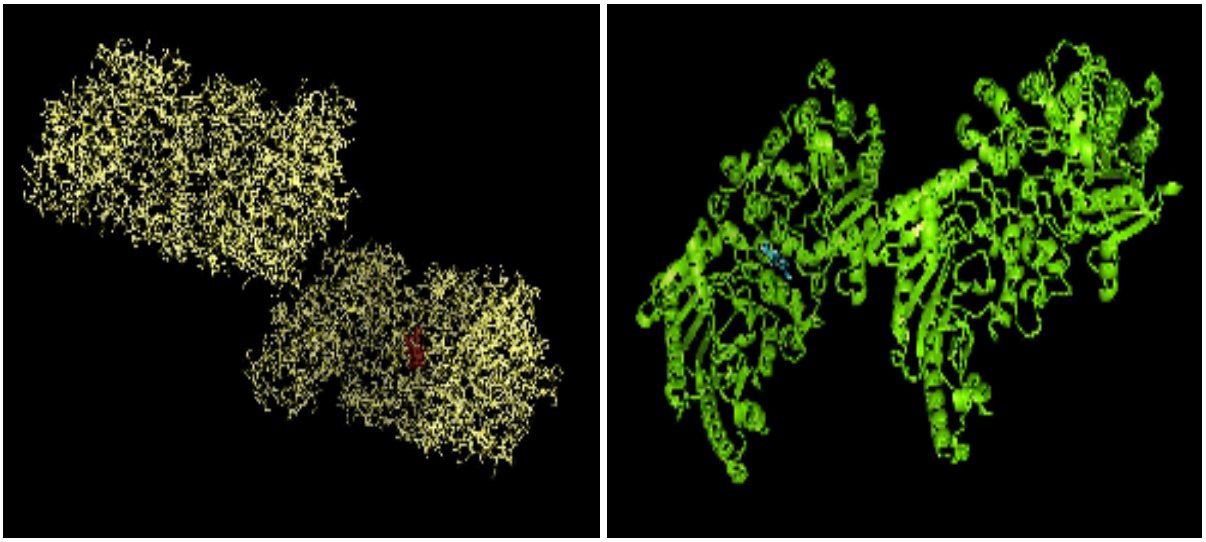

Fig. 1 *In silico* binding of cabazitaxel with brain cancer protein 1QH4 given under different (a & b) schematic representations.

The ligand cabazitaxel showed least binding energy -709.75 kcal/mol with skin cancer protein (2VCJ) followed by -611.48 kcal/mol with brain cancer protein 1QH4, -587.21 kcal/mol with breast cancer protein, -513.08 kcal/mol with lung cancer protein 2ITO and -404.48 kcal/mol gastric cancer protein 1BJ7 (Table 1). The interaction of different ligands with cancer drug target protein of different types of cancer is given in Table 2. The ligand apraclonidine showed the binding energy of -395.12 kcal/mol (Fig.2 a, b) with the lung cancer protein 2ITO. Mutations in the EGFR kinase have been reported to be the major cause of non-small-cell lung cancer. Cabazitaxel has been reported to increase the survival of castration resistant prostate cancer (CRPC) patients (9).

Table 1. Summary of molecular docking results of cabazitaxel with drug target protein of different type of cancers

Type of Cancer	Protein (PDB ID)	Drug	Binding energy (kcal/mol)
Skin cancer	2VCJ	Cabazitaxel	-709.75
Brain cancer	1QH4	Cabazitaxel	-611.48
Breast cancer	1JNX	Cabazitaxel	-587.21
Lung cancer	2ITO	Cabazitaxel	-513.08
Gastric cancer	1BJ7	Cabazitaxel	-404.48

Table 2. Summary of molecular docking results of drug target protein of different cancers with selected ligands

Type of Cancer	Protein (PDB ID)	Drug	Binding energy (Kcal/mol)
Brain cancer	1QH4	Cabazitaxel	-611.48
Lung cancer	2ITO	Apraclonidine	-395.12
Breast cancer	1JNX	Cocaine	-297.27
Skin cancer	2VCJ	Dyclonine	-274.49
Gastric cancer	1BJ7	Lapatinib	-221.69

Figure 2a

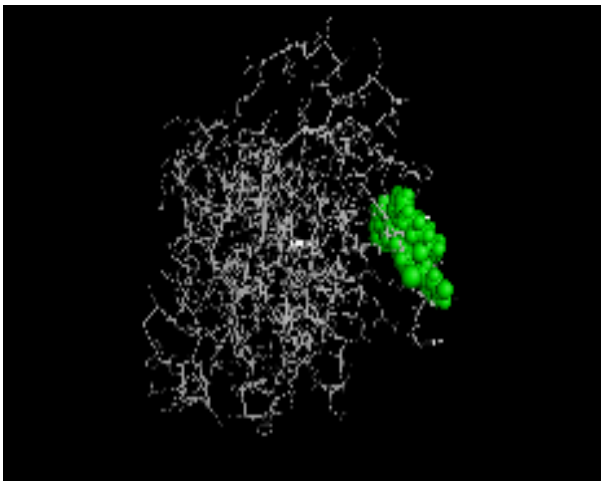

Figure 2 b

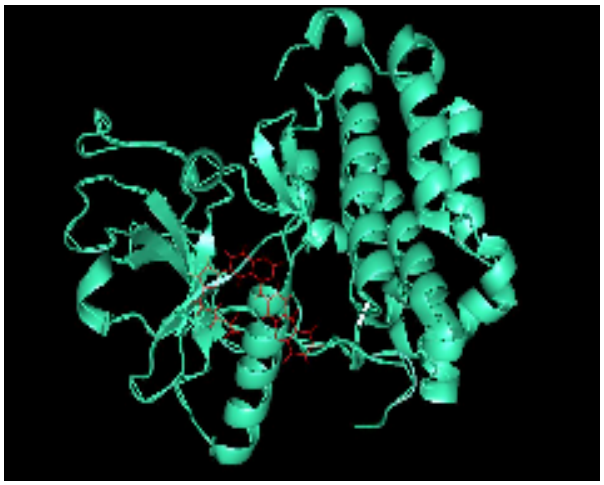

Fig. 2 *In silico* binding of apraclonidine with lung cancer protein 2ITO given under different (a & b) schematic representations

The ligand cocaine showed the binding energy of -297.27-kcal/mol (Fig.3 a, b) with the breast cancer protein 1JNX. It has been shown that C-terminal BRCT region of BRCA1 is essential for DNA repair, transcriptional regulation and tumor suppressor functions. Here we determine the crystal structure of the BRCT domain of human BRCA1 at 2.5 angstrom resolution. The domain contains two BRCT repeats that adopt similar structures and are packed together in a head-to-tail arrangement. Cancer-causing missense mutations are reported to occur at the interface between the two repeats and thereby destabilize the structure.

Figure 3a Figure 3 b

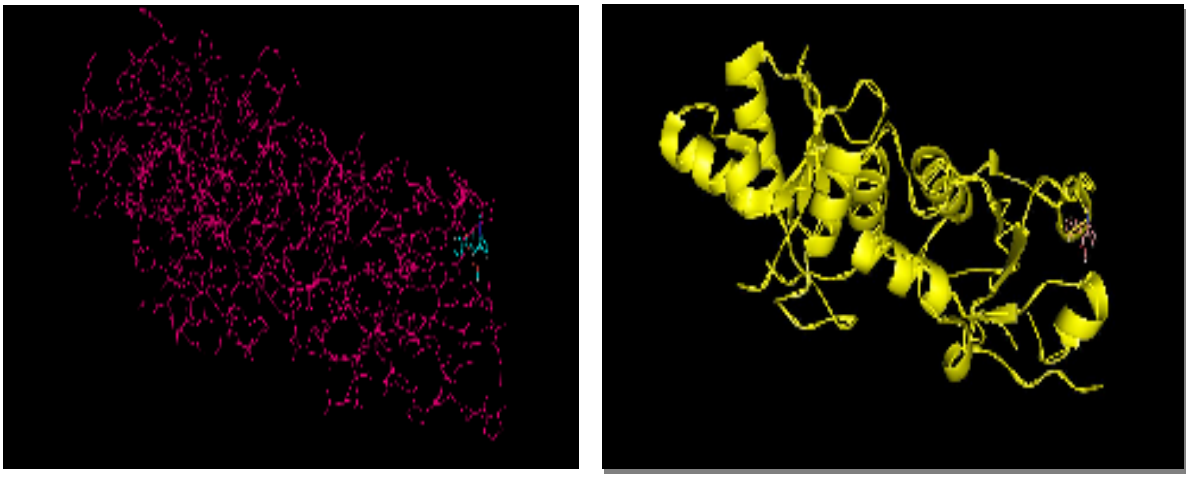

Fig. 3 *In silico* binding of cocaine with the breast cancer protein 1JNX given under different (a & b) schematic representations

The ligand dyclonine showed the binding energy of -274.49-kcal/mol (Fig.4 a, b) with the skin cancer protein 2VCJ. The protein 4,5 diaryl isoxazole HSP90 chaperone (2VCJ) has been reported as potential therapeutic agent for the treatment of cancer. Inhibitors of the Hsp90 molecular chaperone are showing considerable promise as potential chemotherapeutic agents for cancer.

Figure 4a Figure 4 b

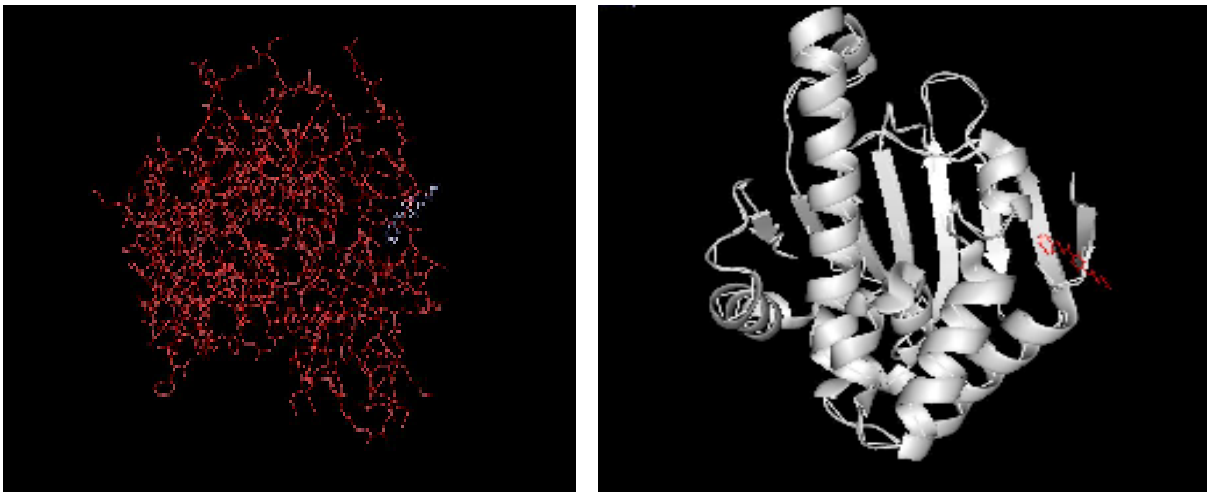

Fig. 4 *In silico* binding of dyclonine with the skin cancer protein 2VCJ. given under different (a & b) schematic representations

The ligand lapatinib showed the binding energy of -221.69 kcal/mol (Fig.5 a, b) with the gastric cancer protein 1BJ7. It was reported that bovine lipocalin allergen BOS D 2 is a member of the lipocalin family comprising proteins with transport functions. There was a flat small cavity inside the BOS D 2 protein core suitable for ligand binding, and Glu115 and Asn37 inside the core were responsible for forming hydrogen bonds with the ligand. Lapatinib has been reported as an anticancer agent (10) acts as inhibitor of oncogenic tyrosine kinases. Tyrosine kinases are known for their important role in the modulation of growth factor signaling.

Figure 5a Figure 5 b

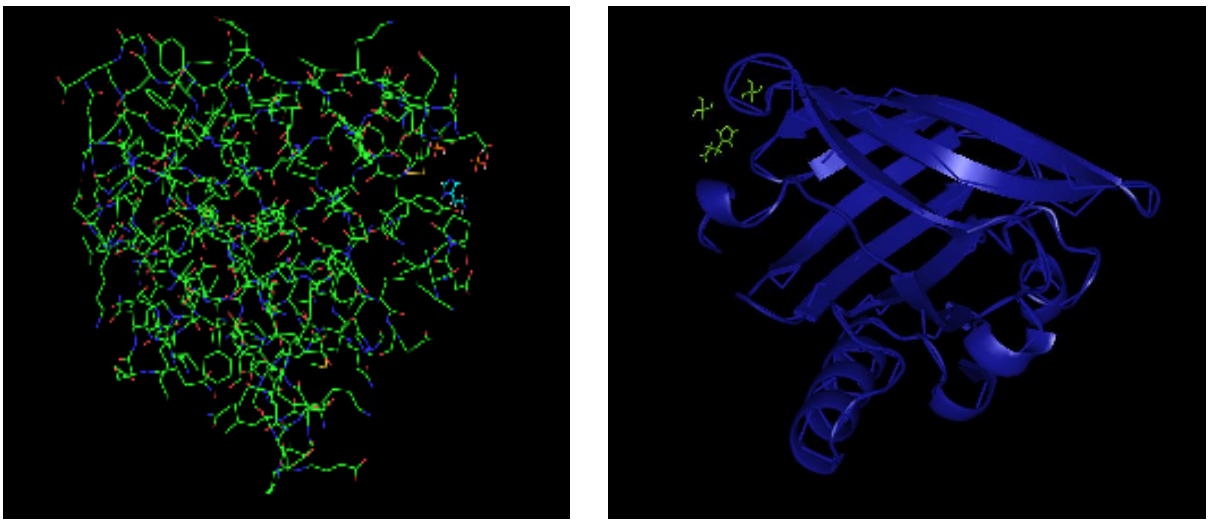

Fig. 5 *In silico* binding of lapatinib gastric cancer protein1BJ7 given under different (a & b) schematic representations

Conclusions

The results of our study clearly showed that cabazitaxel is capable making strong interaction and binding with target proteins evidenced by having least binding energy when compared to other tested ligands. Based on results of our study it can be concluded that the drug cabazitaxel is one of the very effective anticancer drug capable of interacting with tested targets of different types of cancer. However, further *in vitro* / *in vivo* studies are needed to establish its anticancer potential against variety of cancer types based on the predictions of our *in silico* studies.

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