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Identification of the lead compounds for the treatment of breast cancer using phytochemicals: A bioinformatics approach

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Abstract
Among all the type of cancer, the incidence of breast cancer has been increasing despite the fact that the efforts to prevent the disease has been improving. The traditional chemotherapy has been shown to be effective though it exhibit some serious adverse effects as the targets of the chemotherapeutic agents are nonspecific in most cases. Hence the chemotherapeutic agents affects the normal cells leading to the adverse effects. However researchers have been working for the past two decades to find the alternative treatment to the cancer with lesser adverse effect. Natural products or the bioactive compounds from natural sources have been proved to be less toxic. Fucoidan is one such natural polysaccharide of sulphated fucose residues from seaweed. Fucoidan have been used in cancer treatment in many countries. In this study we analyse the ability of fucoidan to treat breast cancer using *in silico* approaches.

Keywords: Breast cancer, sea weed, fucoidan, alternative treatment, in-silico approach

Introduction
Cancers are multifactorial diseases which arise largely as a consequence of acquired genetic mutations that alter cell function leading to neoplastic cells to survival or growth advantages [7]. Cancer causes death mostly through metastatis, which id the spread of tumour cells to distal organs. Unbalance programmed cell death, disordered signalling pathways, angiogenesis (generation of new blood vessels) and poor immune response against cancer lead to the disruption of various pathways in tumour development [2].Breast cancer among all the types of cancer, has been a major concern as the incidence of breast cancer increases though the preventive measures had been increasing. Chemotherapy has been a major treatment for cancer for a period of 60 years. Different chemicals ranging from traditional agents such as methotrexate to synthetic chemicals have been used in chemotherapy [9]. In spite of promising tumour growth inhibitory effects in pre-clinical trial, many of them fail in clinical trial which considers the adverse effects. Normally chemotherapeutic agents targets the cells those proliferate in higher rate, assuming those are the cancer cells. So normal cells, with rapidly dividing capacity also affected during chemotherapy. Recently novel therapeutic agents which targets specific molecules have been designed and used only to found out that they are also not completely free of adverse effect [4]. Moreover chemotherapy causes tumour cell resistance and development of secondary cancers from chemotherapeutic chemicals used. Hence the cancer research focuses on the natural products instead of harmful chemicals [6].
Fucoidan is a polymer of sulphated fucose residues whose richest source is marine algae species such as *Laminaria*and *Fucus* [13]. Fucoidan is preferred in therapy due to its low toxicity, oral bioavailability, multiple mechanism of action and the simple extraction process. Fucoidan affects many pathophysiological processes, including inflammation, carcinogenesis, vascular physiology and oxidative stress [5]. Fucoidan containing food supplements have been administered to cancer patients in Japan, Korea, China and other countries. Fucoidan can directly induce cytotoxicity and apoptosis [15] and indirectly acts as a antiangiogenic agent and has immune-stimulating effects on dentric cells (DCs) [10, 17, 8, 12] and natural killer (NK) cells [1, 3].
In recent years, Computer-aided drug design has been a major breakthrough for discovering lead molecules and to find the relationship between the structure and the activity of small molecules. Molecular docking study predicts the characteristics of the binding of the small molecules with the receptor or the target [11]. In this study we performed molecular docking of various targets for breast cancer with the polysaccharide fucoidan.

The name of the target and their role in cancer has been listed out in the following table.

Materials and methods

The 3D structures of the target proteins were retrieved from the Protein Data Bank (PDB) [14]. The heteroatoms such as the water molecules and the ligands were removed in Accelry's Discovery Studio 4.0. CHARMmforcefield was applied to the protein before finding the possible binding sites from receptor cavities. The 3D structure of the ligand, fucoidan was retrieved from the PubChem database [16]. The ligand geometry was cleaned to perform flexible ligand docking. LIGANDFIT which performs docking based on the cavity detection algorithm was the docking method used for our study (Accelyr's Discovery Studio 4.0) and allow us to virtually screen compounds and predict the strongest binders based on various scoring function. For our study the molecular docking analysis of AP-1 with ligands was carried out using Dreiding parameter in which the partial charges of target protein and ligand in which the Gasteiger charging method was employed to calculate. The energy grid extension was set to 5.0A° and '0' was set as the conformation search number of Monte carlo trial. The number of poses for ligands in receptor cavity was limited to 10 and other input parameters for docking were set as default options and docking was performed. Broyden Flecher Gold Farbshanno (BFGS) methods is employed on LIGANDFIT for the final energy refinement of the ligand pose (or) pose optimization.

Result and discussion

The targets were identified from previously published research articles. The name, role in breast cancer and the PDB ID of the targets are tabulated in the following table.

Table 1.

Target	Official full name	Role in breast cancer	PDB ID
BCAR3	breast cancer anti-estrogen resistance	Estrogen-independent proliferation of breast cancer cells	3T6A
BRCA1	breast cancer 1	Maintain genome stability and acts as a tumour suppressor	1JM7
Caspase 3	Caspase 3	Apoptosis	4QTX
BRMS1	breast cancer metastasis suppressor	Reduces the metastatic potential	4AUV
ER α	estrogen receptor alpha	implicated in pathological processes including breast cancer	4JC3
IGF-1R	insulin like growth factor 1 receptor	anti-apoptotic agent	5HZN
MMP9	matrix metallopeptidase 9	tumour invasion	2OVX
MMP3	matrix metallopeptidase 3	tumour initiation	1QIA
PCNA	proliferating cell nuclear antigen	Involved in cell cycle	4ZTD
TGFBR	transforming growth factor beta receptor	Frequently upregulated in tumour cells	3KFD
Cathedepsin D	--	increases the metastasis potential	4OBZ
MMP12	matrix metallopeptidase 12	Involved in metastasis	2N8R
PPARG	peroxisome proliferator activated receptor gamma	Implicated in the pathology of cancer	1WM0
Tenascin	--	Metastasis	2RB8
Twist	--	Tumour denelopment	2MJV
ER β	estrogen receptor β	Tumour development and progression	2YLY
ERBB4	erb-b2 receptor tyrosine kinase 4	Mitogenesis and differentiation	2AHX

Docking was performed between the various targets and the fucoidan residue. Dockscore is a scoring function that depends on many parameters of the interaction. Higher the dockscore, better the interaction or lower the binding energy. The poses which had the maximum dockscore have been selected for further processing. If the ligand has bound with more than one binding site, the final pose which had the highest dockscore among those sites was selected as the ligand binds at the site which requires minimum energy for binding. As a dockscore of 40 is considered good or better interaction, the interactions with a dockscore less than 40 were neglected. The number of binding sites, the site at which the best interaction has occurred and their corresponding dockscore have been listed out in the following table.

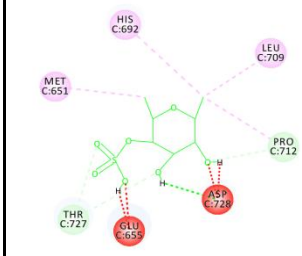
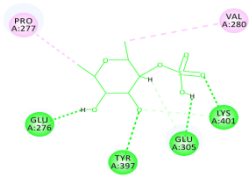
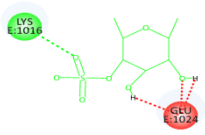
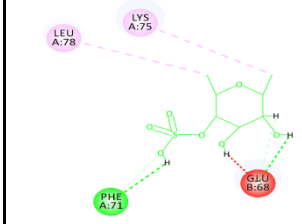
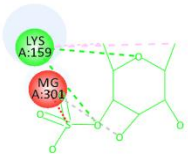
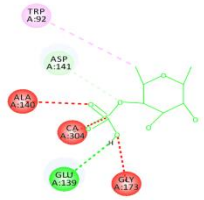
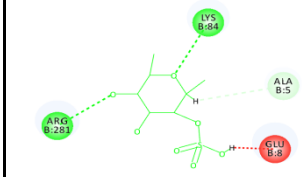
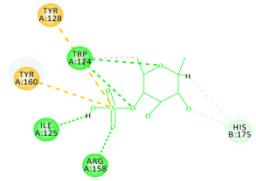
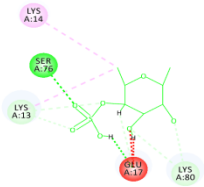
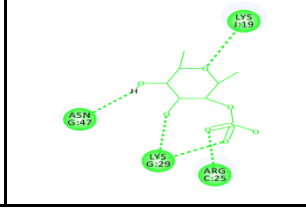
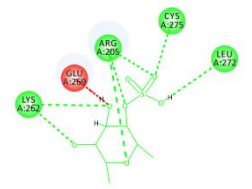
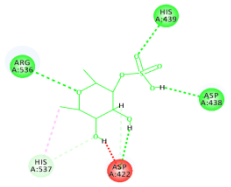
Table 2.

Protein	Dock score	Site	Total binding sites
ER alpha	311.432	2	5
MMP3	228.99	14	18
BCAR 3	61.126	4	22
ER beta	58.817	5	16
IGF 1R	54.465	4	20
Aromatase	53.998	3	13
TGFBR	51.998	2	39
PCNA	51.356	11	29
Estronesulfatse	48.954	12	17
Er Bb-4	48.654	14	16
BRMS	41.071	5	7
MMP9	40.35	6	7

The interacting amino acids of the proteins with the fucoidan were found using view interaction tool in Discovery studio and the 2D diagram of the interactions are shown below. The red, pink, light and dark green colours bonding indicate unfavourable bump, alkyl, carbon hydrogen bond and conventional hydrogen bond respectively. The presence of unfavourable bump does not affect the interaction if it has higher dock score as the dock score is calculated based on all

of these interactions. The number of hydrogen bond also plays a critical role in determining the strength of the interaction. More the number of hydrogen bond of lesser bond length results in better binding. The ligand has been illustrated in green colour. The interacting amino acids are labelled with 3 letter code and their position in the peptide chain with the colour indicating the type of bond it forms with the ligand i.e., fucoidan.

Table 3.

Target	Interaction	Target	Interaction	Target	Interaction
BCAR3		ER β		IGF1R	
BRMS1		ER α		MMP3	
Er Bb4		MMP9		PCNA	
TGFBR		Aromatase		Estronesulfatase	

The above results show that the sulphated polysaccharide has wide range of target for breast cancer including metastasis and proliferation. Thus it can be used as an alternative for chemotherapy, since it has lesser toxicity than that of the chemotherapeutic agents. The availability and the simple extraction procedure also make the preparation easy. Further *in vivo* and *in vitro* experiments has to be performed for analysing the efficacy of fucoidan.

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