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In silico docking of fucoidan compound against the selective proteins of HEPG2 cell line

Ashok K and Sivakumari K*.

PG and Research Department of Zoology, Presidency College, Chennai, Tamil Nadu, India.

***Corresponding Author:** E-Mail: dr.sivakumari@rediffmail.com

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ABSTRACT

The present molecular docking study stands useful for the design and development of novel compound having better inhibitory activity against the selective proteins of human hepatocellular carcinoma (HepG2) cell line. The docking scores were highest for Caspase-3 with –12.3001 kcal/mol with stronger interaction followed by NF-kappa-B (-11.57 kcal/mol.) and the least score was found in the Cytochrome C (-9.88357kcal/mol), the LogP, lower hydrogen bond counts, confirming the capability of the Fucoidan for binding at the active site of the receptor. This potential drug candidate can further be validated by wet lab studies for its proper function.

Keywords: *In silico* docking, Fucoidan, ARGUS Lab.

1. INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common form of cancer worldwide and the third most common cause of cancer-related deaths. HCC often occurs in the background of a cirrhotic liver [1]. Orthotopic liver transplantation (OLT) is an effective treatment for both HCC and underlying cirrhosis, and is considered the best therapeutic option. Unfortunately, most cases of HCC present in an advanced stage and are not suitable candidates for OLT [2]. In recent years, surveillance strategies in patients at a higher risk of HCC have led to the diagnosis of the disease at much earlier stages. Patients in early stages have a much higher chance of curative response with different treatment options [3, 4].

The oceans of the world have always served as a nutrient source, whether from mollusks, fish or vegetation. The world's animal and human populations have always relied upon the sea for nutrition and sustenance. The value of the sea is becoming ever present as soil quality diminishes due to over farming, pesticide use and urban sprawl [5]. In addition, drought is becoming a predominant player in the lower yields offered by land farming [6,7]. Brown seaweed or kelp has been harvested around the world for centuries. It is perhaps best known for its use in Japan and other Asian countries as sea vegetables. In the United States, kelp experienced a general interest in the mid-60's with its inclusion in many household products (*e.g.* toothpaste, fertilizer, pharmaceutical excipients, thickening agents, *etc.*). Like any other nutrient source, manufacturing processes have continued to improve both the yield and the quality of the raw compound. One such development for brown seaweed is the identification and isolation of fucoidans [8].

Fucoidans are sulphated polysaccharides with a fucose backbone found mainly in brown seaweed and account for more than 40% of the dry weight of the algal cell walls. Fucoidans from seaweeds are heterogenic mixtures of structurally related polysaccharides, with differences in their backbone chains, as well as carbohydrate and non-carbohydrate attachments. Their composition varies with the species, the season, the climate and the extraction method used to isolate them [9].

The objective of the study is to identify the proteins present in the HepG2 cell line, to analyze the domain and active sites, to assess the chemical and physical properties of the protein, to analyze the potentiality of the therapeutic agents in terms of their properties, to perform Docking of the proteins with a Fucoidan compound and to evaluate the compound docking and active site binding.

2. MATERIALS AND METHODS

2.1. Preparation of protein structure

Protein structures of HepG2 cell line protein were obtained from RCSB Protein Data Bank. All water molecules were removed and on

the final stage hydrogen atoms were added to the target protein molecule.

2.2. Preparation of ligand structure

Fucoidan compound used for docking study were selected from the literature [6].ChemSketch, chemically intelligent drawing interface freeware developed by Advanced Chemistry Development, Inc., was used to construct the structure of the ligands. Using draw mode of Chemsketch, the ligands were generated and three dimensional optimizations were done and then saved in .mol file and TORSDOF is used in calculating the change in free energy caused by the loss of torsional degrees of freedom upon binding. After the above conditions are set the ligand is saved in "pdbq" format.

2.3. Preparation of macromolecule

The receptor file used by Open Babel must be in "pdbqs" format which is pdb plus 'q' charge and's' solvation parameters: AtVol, the atomic fragmental volume, and AtSolPar, the atomic solvation parameter which are used to calculate the energy contributions of desolvation of the macromolecule by ligand binding.

2.4. Preparation of docking parameter file

ArgusLab is a program used to build graphic representations of molecular models and design matters by combining different elements such as residues, groups and calculations.

3. RESULTS

In the present study, to understand the interactions between the ligands and HepG2 cell line proteins (Caspase-3, Nuclear factor NF-kappa-B and Cytochrome C) and to explore their binding mode, docking study was performed using Argus Lab.

HepG2 cell line protein structures were derived from PDB and used as a target for docking simulation. The compound selected from the literature was listed in the table 1. Ligands were created and prepared for the docking procedure using ChemSketch. The structures of the ligands obtained from the ChemSketch are shown in Figure 1,2,3,4,5 and 6.

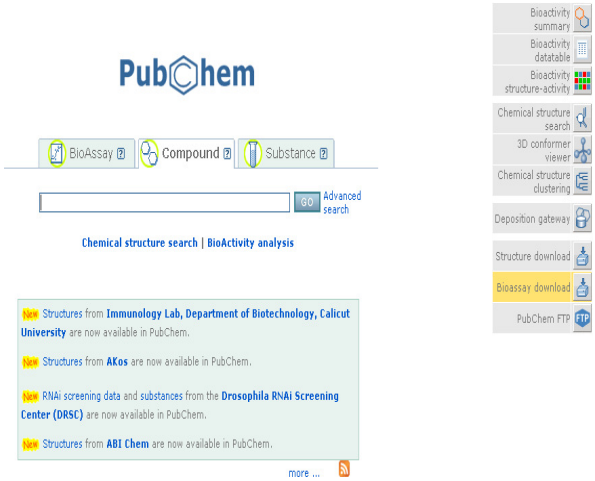

Figure - 1: Pub Chem image of Fucoidan.

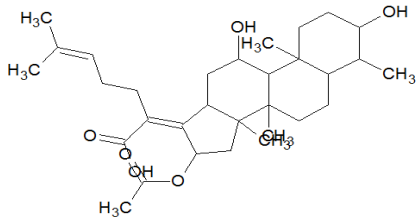

Figure – 2: 2D Structure of Fucoidan.

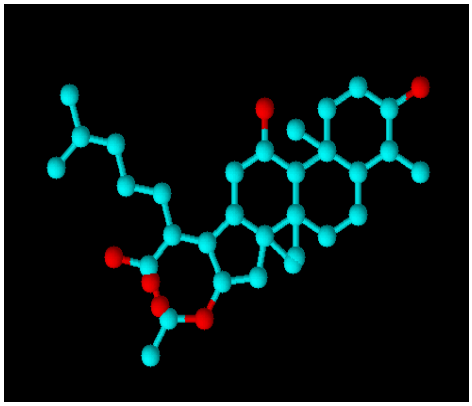

Figure – 3: 3D Structure of Fucoidan

Table - 1: Fucoidan compound details

Name of the compound	Alternative name	Molecular weight	Molecular formula	Description
Fucoidan	Fucose	164.16 g/mol	$C_6H_{12}O_5$	Fucoidan is a sulfated polysaccharide found mainly in various species of brown algae and brown seaweed suchas mozuku, kombu, bladderwrack, wakame, and hijiki (variant forms of fucoidan have also been found in animal species, including the sea cucumber). Fucoidan is used as an ingredient in some dietary supplement products.

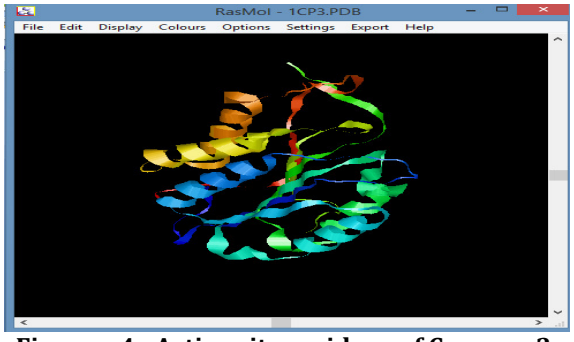

Figure – 4: Active site residues of Caspase-3.

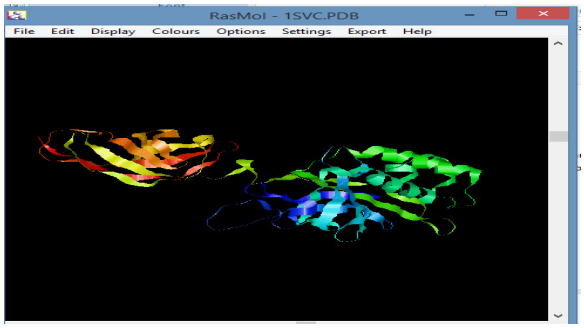

Figure - 5: Active site residues of NF-kappa-B.

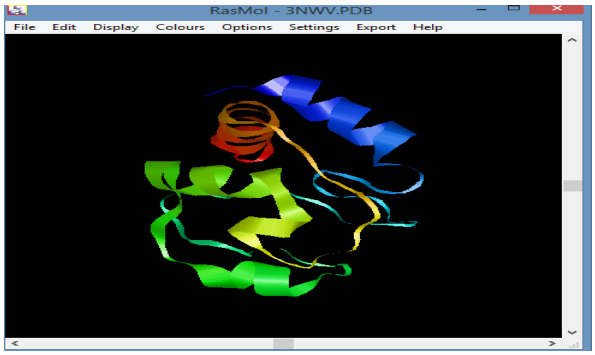

Figure - 6: Active site residues of Cytochrome C.

3.1. Interaction studies

The goal of ligand-protein docking is to predict the predominant binding model(s) of a ligand with a protein of known three dimensional structures.

To study the binding mode of Fucoidan compound in the binding site of HepG2 cell line protein, intermolecular flexible docking simulations were performed and energy values were calculated from the docked conformations of the HepG2 cell protein-inhibitor complexes. Docking studies yielded 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 binding affinity of the HepG2 cell line proteins with the Fucoidan compound were measured by kcal/mol.

The docking scores were highest for Caspase-3 with – 12 .3001 kcal/mol with the stronger interaction followed by NF-kappa-B (- 11.57 kcal/mol.) and the least score was found in the Cytochrome C (- 9.88357kcal/mol) as shown in the table 2 and Figure 7, 8 and 9.

Table - 2: Docking Score and Number of Hydrogen Bonds formed between the proteins and a Fucoidan compound.

PROTEINS	FUCOIDAN	
	Docking score (KCal/mol)	H-BOND
Caspase-3	-12.3001	1
NF-kappa-B	-11.57	3
Cytochrome C	-9.88357	1

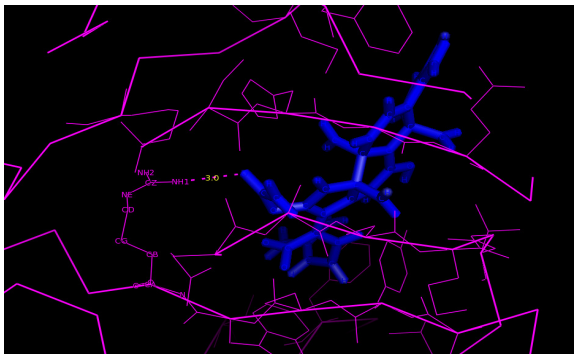

Figure – 7: Crucial Interaction between Fucoidan (Blue) and Caspase-3 (Rose).

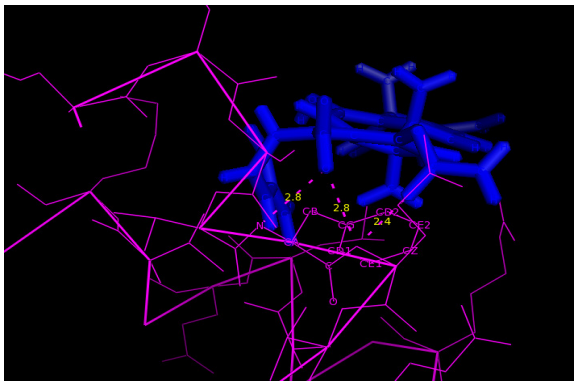

Figure – 8: Crucial Interaction between Fucoidan (Blue) and Nuclear factor NF-kappa-B (Rose).

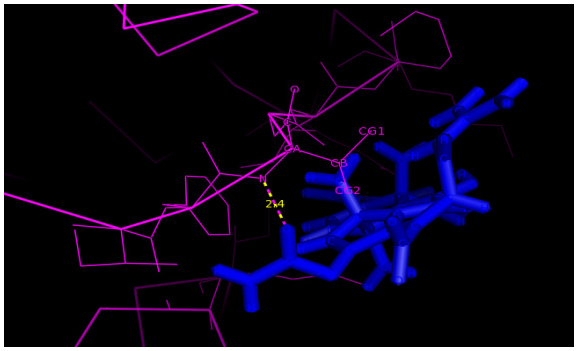

Figure – 9: Crucial Interaction between Fucoidan (Blue) and Cytochrome C (Rose).

4. DISCUSSION

Analysis of ligand binding interaction with the HepG2 cell line protein can be useful for new preventive and therapeutic drug for cancer. 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.

5. CONCLUSION

In this study, the molecular docking was done to explore the binding mechanism and to correlate its docking score with the activity of Fucoidan compound. The results of our present study can be useful for the design and development of novel compound having better inhibitory activity against several type of cancer. This potential drug candidate can further be validated by wet lab studies for its proper function.

Acknowledgement

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