

# Insilico docking and interaction analysis of bioactive marine compound (sulfated fucose) against the human mutant p53 protein involved in carcinogenesis

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## ABSTRACT:

The p53 family plays a pivotal role in the regulation of many critical cellular functions and biological process in normal cells. The abnormal expression of p53 contributes to carcinogenesis. In an effort to develop potent anticancer drug from marine flora this study aims to evaluate the inhibition effect of sulfated fucose against cancer associated protein by computational molecular docking studies. Docking studies were performed for sulfated fucose, a monomer of a polysaccharide fucoidans with p53 protein involved in cancer by Glide 8.5 module of Schrodinger suite. Molecular docking studies of sulfated fucose with Human p53 protein exhibited binding interactions. The results showed that the selected ligand showed binding energy ranging from 134.817 kcal/mol to 185.738 kcal/mol. This molecular docking studies could contribute for the further development of p53 mutant inhibitors for the prevention and treatment of cancer. This study concludes that marine natural products with interesting biological properties and structural diversity may serve as valuable lead drug candidates for the treatment of human ailments including cancer of different types in close proximity to future.

Key words: sulfated fucose, docking, p53, Glide

## INTRODUCTION:

The p53 family regulates many vital biological processes, including cell differentiation, proliferation, cell cycle checkpoints and apoptosis<sup>[1,2]</sup>. p53 gene is located on chromosomes 17p13.1. Dysregulation of the p53 family plays a critical role in tumor genesis and significantly affects tumor response to therapy<sup>[3]</sup>. Loss of function in p53 pathway plays a significant role in the development of most human cancers. The TP53 gene product, p53 protein, guards against genomic instability and Oncogene expression by inducing both arrest of the cell cycle and apoptosis<sup>[4]</sup>. The Role of p53 in Tumor Formation is mainly due p53 mutations, the p53 gene and its protein product have become the center of intensive study ever since it became clear that slightly more than 50% of human cancers contain mutations in this gene<sup>[5]</sup>. Hence in this present study we identified Human p53 Core Domain Mutant as target protein.

Computational Biology and bioinformatics have the potential not only of speeding up the drug discovery process but reduces the costs, and also of changes the way drugs are designed. Rational drug design helps to

facilitate and speedup the drug designing process, which involves variety of methods to identify novel compounds. One such method is the docking of the drug molecule with the target receptor<sup>[6]</sup>. The *In silico* methods are widely applied in pharmacology hypothesis development and testing which includes database searching, quantitative structure-activity relationships, similarity searching, pharmacophore identification, computational modeling and docking<sup>[7]</sup>. There is a wide range of software packages available for the conduct of molecular docking simulations like, AutoDock, FlexX<sup>[8]</sup> GOLD and GLIDE XP<sup>[9]</sup>.

Fucoidans are water-soluble<sup>[10,11]</sup> high molecular weight sulfated polysaccharides which are widely dispersed in the cell walls of brown seaweed<sup>[12]</sup>. The acid polysaccharides are mainly composed of alginic acids and sulfated fucans (also known as fucoidan)<sup>[13,14]</sup>. Algal sulfated fucans are polymers mainly formed by sulfated  $\alpha$  L-fucose but also containing small proportions of other sugars such as mannose and galactose<sup>[15,16,17,18]</sup>. The fucoidan from brown seaweeds can beneficially impact immune system health by stimulating immunoreactions of the humoral and cellular types, and by enhancing macrophage phagocytosis<sup>[19,20,21]</sup>.

Brown algae represent a rich and easily regenerated source of polysaccharides with structural interests and biological activity. Fucoidans have antineoplastic, anticoagulant, anticomplementary, antiviral activities, including anti-HIV infection, herpes and hepatitis viruses<sup>[22,23,24,25,26]</sup> and also the crude extracts of brown algae is known to exert broad range of biological activities such antibacterial<sup>[27]</sup>, antiviral<sup>[28]</sup>, antipyretic, analgesic, antiinflammatory, antiedema<sup>[29]</sup> and so on. In the light of above given literature review sulfated fucose a monomer of a polysaccharide derived from the cell wall brown algae was selected as the ligand.

Extensive review of literature concludes that both the terrestrial and marine medicinal plants have known to exert potent biological activity. However, when compared with terrestrial plants very little research has been carried out so far on the anticancer studies with marine plants. Therefore this study aims to evaluate the *In silico* cancer inhibition effect of sulfated fucose, a monomer of polysaccharide fucoidan which has been originally isolated from the cell wall of marine algae.

## **MATERIALS AND METHODS**

### **Computational and Software's requirements**

Pharmacophore properties prediction was done using Discovery studio version 2.1 and Molecular docking studies was performed using Glide version 8.5, a molecular docking software installed in a single

machine running on Intel Core™<sup>2</sup> Duo processor with 2GB RAM and 160 GB hard disk with CentOS Linux Enterprise version as the operating system.

### **Target Protein Identification and Preparation**

The three dimensional structure of cancer associated p53 protein [PDB id: 2QXB] was obtained from the RCSB protein data bank (<http://www.rcsb.org/pdb>)<sup>[30]</sup>. This structure was determined using X-ray Diffraction. The X ray crystal structures of Human p53 Core Domain Mutant was selected after evaluating numbers of entries, the best proteins were selected by analyzing the protein with Ramachandran plot and regions. After selection, Protein preparation wizard of Schrodinger suite has been used to prepare protein. The proteins were preprocessed separately by deleting the substrate cofactor as well as the crystallographically observed water molecules (water without H bonds), correcting the mistakes in PDB file, hydrogen bonds optimization was done.

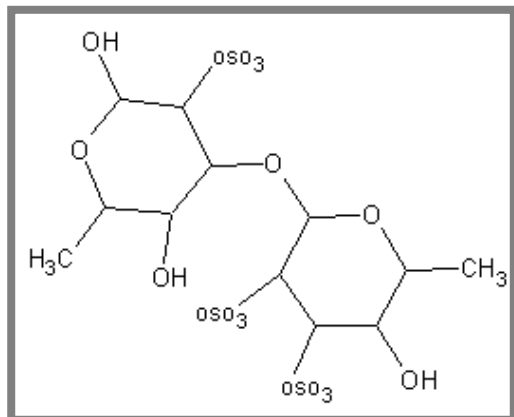
### **Ligand Identification and Preparation**

The 2D structure of sulfated fucose was identified from the documented literature<sup>[31]</sup> and the 2D structure of sulfated fucose, a monomer of polysaccharide fucoidan (**Fig-1**) was drawn by using ChemSketch (ACDLABS 12.0)<sup>[32]</sup> and converted to 3D structure (**Fig-2**) with the help of 3D optimization tool. The Pharmacophore properties of ligand sulfated fucose was studied using Discovery studio version 2.1 (Accelrys, 2008)<sup>[33]</sup>. By using the LigPrep (2.2) module (Ligprep, Version 2.2, 2008)<sup>[34]</sup>, the drawn ligand was geometry optimized by using the Optimized Potentials for Liquid Simulations 62005 (OPLS62005) force field with the Steepest Descent followed by truncated Newton Conjugate gradient protocol. Partial atomic charges were computed using the OPLS62005 force field. The LigPrep is a utility in Schrodinger software suite that combines tools for generating 3D structures from 1D (Smiles) and 2D (SDF) representation, searching for tautomers and steric isomers and geometry minimization of ligands. Finally, 3 poses were selected with different tautomeric and steric features and used further for docking studies.

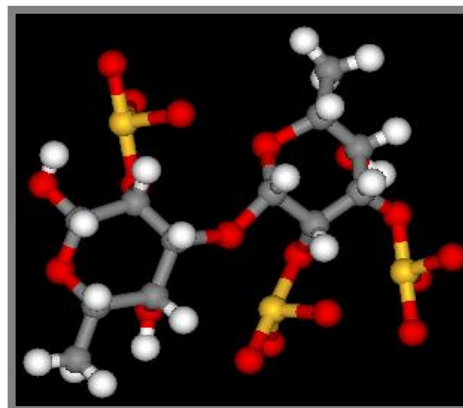
### **Glide extra precision mode (XP mode)**

Protein Preparation Wizard Workflow implemented in Maestro 8.5 was used to prepare the protein using the default settings (Schrödinger 2008)<sup>[35]</sup>. The ligand structure fucose was prepared using LigPrep 2.2 (Schrödinger 2008)<sup>[34]</sup>. Both protein and ligands were parameterized with the OPLS force field. The Receptor Grid Generation panel generated the grid map for the receptor. The center of the grid was located in the catalytic cleft. Docking calculations were performed in Extra Precision (XP) mode using the Ligand Docking panel. The

Receptor Grid Generation and Ligand Docking panels are functions in the Glide (Grid-based Ligand Docking with Energetics) module. The XP mode combines a powerful sampling protocol with the use of an XP scoring function that is designed to specify only good ligand poses (Schrödinger 2008)<sup>[36]</sup>.



**Fig-1:2D**  
**Sulfated**  
**Fig-2:3D**

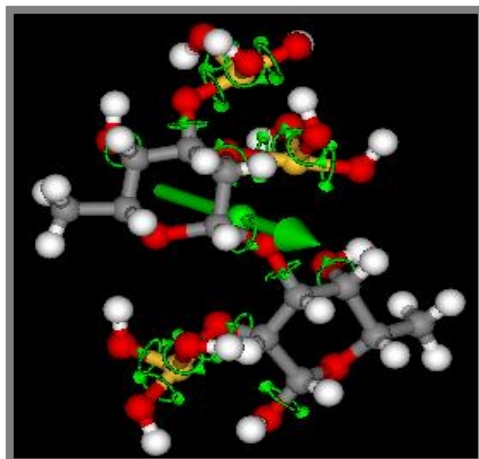


**Structure of**  
**fucose**  
**Structure of**

**Sulfated fucose**

## RESULT AND DISCUSSION

The molecular formula of sulfated fucose is found to be  $C_{12}H_{28}O_{18}S_3$  with the molecular weight of 556.044 (g/mol). The Pharmacophore feature view (**Fig-3**) and pharmacophore properties of sulfated fucose were predicted (**Table-1**). The docking simulation technique was performed using Glide module (Schrodinger suite) with fucose a monomer of polysaccharide fucodan derived from the cell wall of brown algae was docked into target protein Human p53 Core Domain Mutant and docking results (**Table-2**) and binding interactions (**Fig-4**) were analyzed. In pose I docking, The fucose forms hydrogen bonding interaction with the amino acid Asp 208, Ser 99, Pro 98 of p53 protein with the binding energy of 134.817 and G Score value -3.875254. In pose II docking, the fucose molecule forms hydrogen bonding interaction with the amino acid Thr 211, Ser 99, Thr 256 of p53 protein with the binding energy of 160.633 and G Score value -3.477388. In pose III docking, the fucose forms hydrogen bonding interaction with the amino acid Asp 208, Leu 264 and Arg 267 of p53 protein with the binding energy of 185.738 and G Score value -3.351469



**Fig- 3 Pharmacophore feature view of ligand –Sulfated fucose**

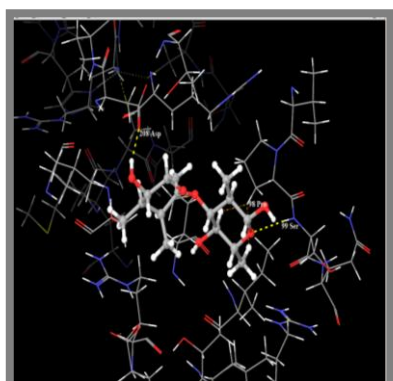
Pharmacophore properties	Sulfated fucose
No of atoms	52
Molecular Formula	C <sub>12</sub> H <sub>28</sub> O <sub>18</sub> S <sub>3</sub>
Molecular Composition	C:0.259,H:0.051, O:0.0517,S:0.173
Molecular Weight	556.044 g/mol
Molecular density	1.6 g/cm <sup>3</sup>
No of chiral centre	10
H - bond acceptors	21
H- bond donors	12
Polarizability	17.702
Energy Value	-167.806 kcal/mol
Log P value	-3.885
Dipole Magnitude	7.818
Lipinski Violations	3
Surface Area	377.059

**Table-1 predicted Pharmacophore properties of sulfated fucose**

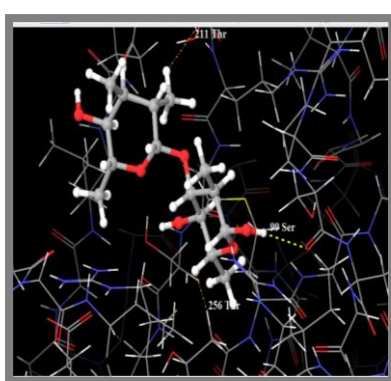
p53 protein	Potential energy score	Glide score	Glide energy
Pose I	134.817	-3.875254	-25.86222
Pose II	160.633	-3.477388	-25.601975
Pose III	185.738	-3.351469	-27.436137

**Table-2 Docking result of the ligand, sulfated fucose with 3 Poses**

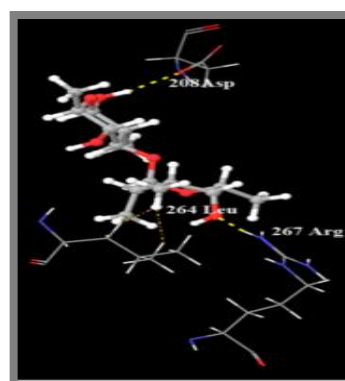
**Pose –I**



**Pose –II**



**Pose -III**



#### **Fig- 4 Docked pose of Human mutant p53 protein with Sulfated fucose.**

Marine floral resources need to be extensively investigated for their identification of potent bioactive compounds which are hidden due to the lack of in depth research on marine in this area<sup>[27]</sup>. This study concludes that marine natural products with interesting biological properties and structural diversity may serve as valuable lead drug candidates for the treatment of human ailments including cancer. This study may provide an insight for exploitation of drugs from marine compounds against different types of cancer of different types in close proximity to future.

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