**INTERNATIONAL JOURNAL OF CURRENT ADVANCED RESEARCH**
*ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614*
*Available Online at www.journalijcar.org*
*Volume 11; Issue 10(A); October 2022; Page No. 1609-1612*
*DOI: http://dx.doi.org/10.24327/ijcar.2022.1612.0359*

*Research Paper* *Insilico Anticancer Study*

# MOLECULAR DOCKING ANALYSIS OF VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) RECEPTOR WITH BIOACTIVE MOLECULES FROM CYANOBACTERIA AS POTENTIAL ANTI-CANCER AGENTS

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**A R T I C L E I N F O**

***Article History:***

Received 12th September, 2022
Received in revised form 21st September, 2022
Accepted 12th October, 2022
Published online 28th October, 2022

***Key words:***

VEGF, ADMET, Molecular docking, Flavone, Cyanobacteria.

**A B S T R A C T**

Cyanobacteria are a great source of a wide variety of bioactive substances. The present study reports an anticancer bioactive compound from cyanobacterium *Nostoc sp*., *Lyngbya* sp., and *Phormidium sp*. using GC-MS analysis. The extracted samples were processed with JEOL GCMATE II with high resolution data system. The micro algal compounds (Strigol, Allyl-(2-methylphenyl)-sulfide, Flavone, Octonic acid, Ethyl iso-allocholate, Quinazolin and Quinolin) are characterized by GC-MS. Further, retrieve the required target protein (VEGF: 2VPF) from the RCSB protein data bank as a PDB file and the marine algal compounds were scrutinized through molecular docking and ADMET risk assessment. There were a total of seven compounds found, which were further examined for Log P, oral bioavailability, synthetic accessibility, lead-likeness and alarms for PAINS & Brenk. In addition, the compliance of the pharmacokinetics of the metabolites of particular medications was investigated. Our study provides the greatest illustration of a computationally driven tool for selection and finding new drug with high therapeutic windows and a binding energy of Flavone -5. 44 kcal/mol for VEGF receptor affinity. The SWISS ADME and admet SAR were used to evaluate the ADMET parameters.



## INTRODUCTION

Blue-green algae (also called cyanobacteria) are found in hyper saline lakes, coastal hyper saline lagoons, saltern evaporation ponds, seawater, saline springs and reservoirs (Aharon Oren, 2015).The physiology of the cell must be modified specifically for life in high salt environments. The production of a wide range of secondary metabolites by cyanobacteria is well known. Cyanobacterial medicinal properties were initially recognized as early as 1500 BC, when *Nostoc* species were employed to treat gout, fistulas and various cancers (Rahul *et al*., 2011). An anti-cancer factor has been identified in *Scytonema* sp., *Phormidium tenue* and *Anabaena variabilis*. Borophycin, isolated from a *Nostoc sp*., showed cytotoxicity against human epidermoid carcinoma (LoVo) and human colorectal adenocarcinoma activity and Apratoxin A, isolated from *Lyngbya boulloni*, showed cytotoxicity against to adenocarcinoma (Nguyen *et al*., 2019). Symplostatin 3 isolated from *Symploca* sp., showed cytotoxicity against epidermoid carcinoma cell line (Hendrik *et al*., 2002), *Scytonema ocellatum* depolymerized actin to disturb cell division and seems to be a potent anti-cancer drug.

The third most typical malignancy among Indian women is ovarian cancer. Epithelial cells, germ cells and stromal cells are three different cell types that make up the ovaries. Different forms of tumours can develop from each of these cell types. Nine out of ten ovarian tumours start in epithelial cells. In India, 43,886 new cases of ovarian cancer were reported in 2020, according to statistics (Prashant *et al*., 2020). Most ovarian cancer cases start to appear after menopause. Ovarian cancer risk is increased in women who have had more cycles during their lives. Ovarian cancer is first caused by a DNA mismatch in the BRCA1 and BRCA2 genes (Robert *et al*., 2017). Women who have a family history of ovarian cancer are more likely to get the disease. High-grade, severe, non-mucinous ovarian cancer is linked to BRCA mutations, whereas mismatch repair gene alterations are the cause of Lynch syndrome. Therefore, finding newer inhibitors and medications is absolutely essential for improving ovarian

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cancer patient survival. Vascular endothelial growth factor (VEGF) is a key regulator of the angiogenic process in physiological and pathological processes in both the embryo and the adult (Masabumi, 2011). Although several numbers of the VEGF inhibitor compounds are currently available such as Votrient, Sutent, Avastin, Nexavar and Stivarga. Bevacizumab, a recombinant monoclonal antibody that suppresses the VEGF signaling pathway by binding to circulating VEGF A, is a drug that has gained significant recognition for treating ovarian cancer. VEGF has a significant role in a variety of cancers, including colorectal cancer, breast cancer, non-small cell lung cancer, renal cell carcinoma, pancreatic cancer, prostate cancer, head and neck cancer, gynaecological cancer and haematological malignancies (Gang and Xiaoyuan, 2010). The VEGF pathway binds to endothelial cells, which are also genetically stable and have a low rate of spontaneous mutations as compared to unstressed mutations. Endothelial cells are viewed as an excellent target for treatments aimed at cancer cells because of their genetic stability (Kyoko *et al*., 2018).A number of optical aptasenor-based VEGF detection techniques were presented by Freeman *et al* (2012). A surface-enhanced fluorescent apt sensor that targets VEGF165, a crucial marker of tumour angiogenesis, was recently developed by Cho *et al*, (2012).

## MATERIAL AND METHODS

### *Molecular docking studies of Anticancer compound VEGF protein*

Docking requires the followings Window 7,8,10 and AutoDock vina or PyMOL. Retrieve the required target protein (complex coordinates) from the RCSB protein data bank as a PDB file. Next step, delete all the water and the solvent molecules and all non-interacting ions, clean the minimized complex.

The PDB file visualized by using PyMOL/AutoDock vina software. VEGF protein is considered as the potential target in this study. VEGF protein (2VPF) is ready for preparation and the several force fields that are widely used to calculate the interatomic interaction between amino acid residues to describe the conformational energy of poly peptide or protein. After this, protein is ready for docking. PyMOL/AutoDock vina makes the broad use of a python script coding collection for the support of docking runs. PyMOL allows carrying out the molecular docking, molecular visualization and binding site analysis. The CASTp detects pockets and voids in protein structures to determine and characterize binding sites, the program uses Delaunay triangulation and alpha shapes Algorithm to determine the cavities and pockets. CASTp triangulates the surface atoms and clusters triangles by merging small triangles with neighboring large triangles. The pluginis an online support tool, with easy access to electrostatic calculation and visualization of potential energy surface and charges densities of the protein surface. The ligand preparation (Micro Algal compounds) is similar to a protein preparation. The ligand lacks hydrogen atoms, first step, extract the ligand atoms from the PDB and load the ligand structure, separating the minimized protein complex to act as a lock and the ligand to act as a key. The prepared docking ".pdbqt" file format is suitable for the lock and key model. Next step, prepare all needing files such as grid parameter files, map files, and docking parameter files. Finally, run the program and analyses the docking results.

## RESULT AND DISCUSSION

Virtual screening was done for all the obtained compounds from GC-MS studies. Seven compounds obey lipinski's rule from the total list with good molecular properties. All the seven compounds (Allyl-(2-methylphenyl)-sulfide,2H-Inde-[1,2-b]-furan-2-one,3,3a,4,5,6,7,8,8b-octahydro-8,8-dimethyl (Strigol), Octanoicacid, Ethyl iso-allocholate, Flavone, Quinazolin and Quinolin) were docked with VEGF protein separately with the predicted active site residues. Active site residues of VEGF (2VPF) protein were GLU67, VAL69, ARG105, PRO106, LYS108; binding energy table of all the seven docked complexes is given in Table 1.

**Table 1** Auto dock scoring and interaction of amino acid residue of VEGF (2VPF) binding with Micro Algal compounds and $H_2$ bond, Pi, alkyl and Vander walls interaction

| Compound | Dock score (Kcal/mol) | $H_2$ bond | Pi interaction | Alkyl | Vander walls |
|---|---|---|---|---|---|
| Allyl(2-methylphenyl) sulphide | -3.38 | | LYS108, PRO106, ARG105 | VAL69 | LYS107, GLU67 |
| 2H-Indeno(1,2-b) furan-2-one,3,3a,4,5,6,7,8,8b-octahydro-8,8-dimethyl | -4.72 | LYS107 | | CYS68, CYS61 | VAL69, GLU67, GLY58, GLY59, CYS60, LEU66 |
| Octanoic acid, 4-nitrophenyl ester | -4.42 | LYS107, CYS68, GLU64 | GLU67, CYS61 | ARG56, HIS99 | GLY59, CYS60, CYS57, GLY58, LEU66, ASP63 |
| Ethyl iso-allocholate | -5.03 | PRO70, GLU73 | VAL69, HIS99 | CYS57 | CYS68, GLY58, GLU67, LEU97 |
| Flavone | -5.44 | LYS107, CYS68 | LEU66 | CYS61 | VAL69, CYS60, GLU67, ASP63, GLU64 |
| Quinazolin-4(3H)-one,3(3-methoxyphenyl)-2-(2-phenylethenyl)- | -5.10 | ARG105, PRO106 | VAL69 | LYS108 | GLU67, LYS107 |
| Quinolin, 5-nitro-, 1-oxide | -5.17 | ARG105 | | VAL69, LYS108 | PRO70, THR71, PRO106, LYS107, GLU67 |

docked complexes is displayed in Figure.1, 2, 3, and 4. Among the seven docked complexes, VEGF with Flavone has the best binding energy of -5.44 kcal/mol and also has strong hydrogen bond interaction with CYS68and LYS107,

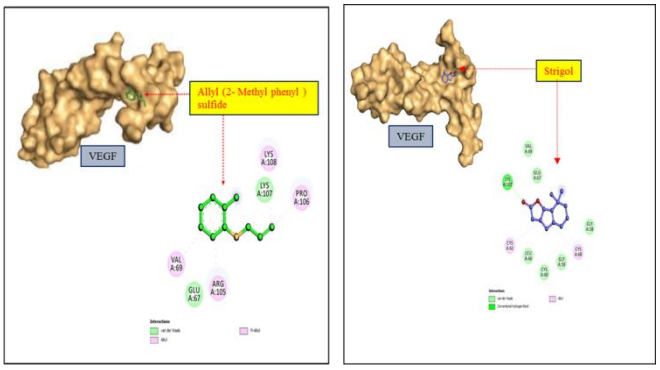


**Figure 1** Interaction pattern: VEGF protein structure is represented as surface model. Allyl (2-methylphenyl) sulfide complex and Strigol represented as stick model using PyMOL.

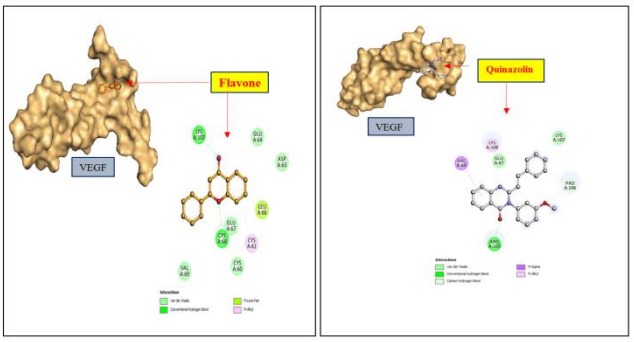


**Figure 3** Interaction pattern: VEGF protein structure is represented as surface model. Flavone and Quinazolin-4(3H)-one, 3(3 methoxyphenyl)-2-(2-phenylethenyl) - represented as stick model using PyMOL.

Table 2 ADMET characteristics of marine compound Flavone

| Flavone | Value | Probability |
|---|---|---|
| LogP | 2.55 | |
| AlogP | 3.46 | |
| Human Intestinal Absorption | + | 1.0000 |
| Caco-2 | + | 0.7413 |
| Blood Brain Barrier | - | 0.5250 |
| Human oral bioavailability | + | 0.7714 |
| Subcellular localzation | Mitochondria | 0.5940 |
| CYP1A2 inhibition | + | 0.9644 |
| Carcinogenicity (binary) | - | 0.9213 |
| Hepatotoxicity | + | 0.6625 |
| Acute Oral Toxicity (c) | III | 0.5110 |
| Water solubility logS | -3.425 | |
| Plasma protein binding | 0.927 | 100% |
| Acute Oral Toxicity log (1/(mol/kg)) | 2.077 | |
| Lipinski | Yes | 0 violation |
| Ghose | Yes | 1 violation: #atoms>70 |
| Veber | Yes | |
| Egan | Yes | |
| Muegge | Yes | |
| Bioavailability Score | Yes | 0.55 |
| Pains | 0 alert | |
| Brenk | 0 alert | |
| Lead-likeness | No | 2 violations: MW<250, XLOGP3>3.5 |
| Synthetic accessibility | Yes | 2.88 |

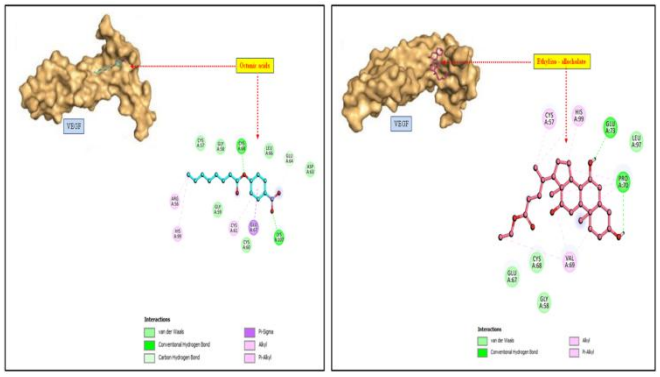

**Figure 2** Interaction pattern: VEGF protein structure is represented as surface model. Octonic acid and Ethyl iso-allocholate represented as stick model using PyMOL.

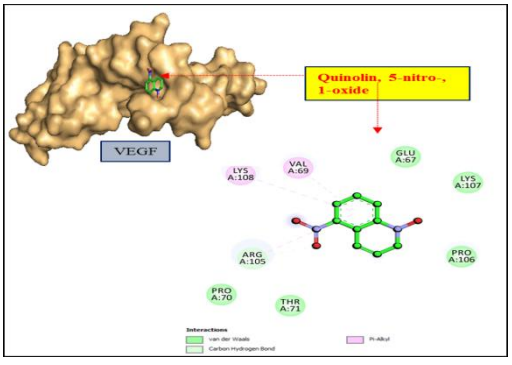


**Figure 4** Interaction pattern: VEGF protein structure is represented as surface model. Quinolin, 5-nitro-, 1-oxide represented as stick model using PyMOL.

vanderwaal's interaction with the residues GLU64, ASP63, GLU67, CYS60 and VAL69, a strong Pi-lone pair interaction with the residue LEU66 and strong Pi-Alkyl interaction with

the residue CYS61. This *In-silico* study proves that Flavone may possibly act as a potent anticancer drug against the VEGF protein which plays a vital role in angiogenesis and cancer. By applying molecular docking methods, we can identify different protein-ligand binding processes. The ligands are examined to ensure that they adhere to Lipinski's regulations orhave no more than one violation of Ro5. Overall, the compounds exhibit good compatibility in Table 2, which includes the microalgal compound Flavone. However, they also exhibit good gastric absorption. This indicates that the substances exhibit good permeability, which allows them to pass through the cell membrane and allow them to bind to the receptor.

## CONCLUSION

The natural micro algal compounds interacted well in the VEGF receptor, with their docking scores above-5 kcal/mol (Ethyl iso-allocholate, Flavone, Quinazolin-4(3H)-one, and Quinolin) equivalent with their standards. The molecular interactions are based on various parameters such as binding free energy, polar interactions, hydrophobic interactions, and hydrogen bond interactions. Further. ADMET properties reported that all the compounds were found, to have properties within the standard limit. The activities of the Flavones are more effective against specific receptors VEGF. Thus, this study suggests that micro algal compounds can be further investigated to validate their anticancer inhibitory potentials by *in-vivo* studies.

***Compliance with ethical standards Acknowledgments***

The authors gratefully acknowledge Dr. Mohana Priya Arumugam, Department of School of Bio Sciences and Technology, Vellore Institute of Technology.

**CONFLICT OF INTEREST**

Conflict of interest declared none.

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**How to cite this article:**

Yuvaraj Sampathkumar *et al.,* (2022*).* Molecular Docking Analysis of Vascular Endothelial Growth Factor (VEGF) Receptor with Bioactive Molecules from Cyanobacteriaas Potential Anti-Cancer Agents', *International Journal of Current Advanced Research*, 11(10), pp. 1609-1612. DOI: http://dx.doi.org/10.24327/ijcar.2022.1612.0359

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