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Research Article

Molecular docking analysis of vascular endothelial growth factor receptor with bioactive molecules from *Piper longum* as potential anti-cancer agents

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Abstract:
It is known that vascular endothelial growth factor receptor (VGFR) is linked with cancer. Therefore, it is of interest to document the molecular binding features of bioactive molecules from Piper longum as potential anti-cancer agents with VGFR2 for further consideration. Thus, we document the binding features of four compounds (sesamin, fargesin, longamide and piperlonguminine) with VGFR2 for further consideration in drug discovery.

Key words: VEGFR, *Piper longum,* lung cancer, molecular docking.

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Background:

The most common malignant tumour is lung cancer. An estimated 1.82 million people have been diagnosed with lung cancer and 1.6 million deaths worldwide have been linked to lung cancer in 2012 [1]. For advanced lung cancer, the tumour response rate (tRR) of standard platinum-based chemotherapy is only 25-35 percent, with a median overall survival (mOS) of 8-10 months [2]. Angiogenesis is significant in the development of tumors [3]. The most important pro-angiogenic factor is the Vascular Endothelial Growth Factor (VEGF). A host of stimuli, including oestrogen, nitric oxide and a variety of growth factors, are up-regulated by the VEGF gene, such as platelet growth factor, tumour necrosis factor alpha (TNF-alpha), fibroblast growth factor-4, keratinocyte growth factor, epidermal growth factor (EGF), interleukin (IL-6 and IL-1) [4]. The expression of VEGF is sensitive to the presence of oxygen and is mediated by hypoxia, which is due to the aberrant nature of the vascular supply of most tumours. In various cancers, such as colorectal cancer, breast cancer, non-small cell lung cancer, renal cell cancer, pancreatic cancer, prostate cancer, cancer of the head and neck, gynaecological cancer and haematological malignancies, VEGF plays an important role [5]. For various reasons, the VEGF pathway is a good target for anti-angiogenic therapy, such as: it is generated by growing primary tumours in large quantities; the VEGF pathway induces the production of sprouting blood vessels [6]; the VEGF pathway binds to endothelial cells involved in the formation of blood vessels; the endothelial cells are also genetically stable and spontaneous mutations are rare compared to unstressed mutations. Due to genomic stability, endothelial cells are considered an ideal target for therapies directed against cancer cells [8,9]. VEGF is secreted from the over-expressive tumour and binds to signalling receptors of high affinity on the endothelial cells of existing blood vessels, leading to the development of new blood capillaries that provide the necessary nutrients for the survival and growth of tumour cells [10]. Therefore, it is of interest to document the molecular binding features of bioactive molecules from Piper longum as potential anti-cancer agents with VGFR2 for further consideration.

Materials and Methods

Protein Preparation

The three-dimensional (3D) crystal structures of Vascular endothelial growth factor receptor VEGFR (PDB ID: 1FLT) was downloaded from the Protein Data Bank (PDB) (www.pdb.org/pdb). The protein structure was then refined for docking using the Chimera© (version 1.13) software tool (http://www.cgl.ucsf.edu/chimera).

Ligand Preparation

22 compounds in *Piper longum* were downloaded from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) in SDF format using information gleaned from literature and converted to the PDB format using the Online Smiles Translator.

Molecular docking

The molecular screening was done using the PyRx autodock wizard software [11,12]. The docking was completed using the flexible docking protocol as described by Trott & Olson, (2005) [17] with modifications as described by Sekar *et al.* [18]. The results were further analyzed using PYMOL.

Table 1: List of selected compounds from *Piper longum*

S. No	Compound Name
1	6-Hydroxydopamine_CID_4624
2	asarinine_CID_101612
3	brachystamide_CID_10047263
4	brachystamide-A2D_CID_11761449
5	caryophyllene_CID_5281515
6	dehydropipernonaline piperidine_CID_6439947
7	dihydrocarveol_CID_12072
8	Fargesin_CID_10926754
9	longamide _CID_10902963
10	pcymene2D_CID_46846568
11	pellitorine_CID_5318516
12	pentadecane _CID_12391
13	pipercide_CID_5372162
14	Piperdine_CID_638024
15	piperettine_CID_101878852
16	Piperlongumine_CID_637858
17	piperlonguminine_CID_5320621
18	piperundecalidine_CID_44453654
19	p-methoxy acetophenone_CID_7476
20	Sesamin_CID_72307
21	tetrahydropiperine_CID_581676
22	Thymoquinol _CID_95779

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Table 2: molecular docking results obtained from PyRx

S.No	Compound Name	Binding Energy kcal/mol	Details of Hydrogen bond interaction
1	Sesamin_CID_72307	-7.4	CYS-102
2	Fargesin_CID_10926754	-6.9	HIS-27 CYS-102
3	Longamide _CID_10902963	-6.6	GLU-30 THR-31 LEU-32
4	Piperlonguminine_CID_5320621	-6.1	LEU-32 GLY-59

Please provide Figure 1 as a single image file in TIFF format with 300 DPI

Figure 1: Molecular docking interaction of VEGF with (a) Sesamin, (b) Fargesin, (c) Longamide and (d) Piperlonguminine

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Results and Discussion:

Vascular endothelial growth factor receptor has been found in high concentrations in various cancer diseases and is known as targets for anticancer agents, as mentioned earlier. Docking is the process within the active site of a protein receptor with a known structure that identifies the best binding conformation or poses for a ligand [13,14]. Molecular docking was therefore carried out on VEGFR with the phytocompounds in the present study to elucidate their interactions and to obtain additional information from all the compounds in molecular binding mode. The molecular docking results include appropriate interactions of the chemical constituents with the main residues of amino acids at the protein active site. The results of molecular docking between the active compounds assessed with VEGFR are shown in Table 2 and Figure 1.1. The results of the docking indicate that all piperlongum bioactive compounds show better binding positions with VEGFR. For docking studies, 22 piperlongum compounds were selected in total. The strong binding in terms of binding power and hydrogen bonding was shown by compound Sesamin among them. Sesamin's binding energy is -7.4 kcal.mol. We have selected three other compounds based on the binding energy, namely Fargesin (-6.9kcal/mol), Longamide (-6.6kcal/mol), Piperlonguminine (-6.1). All four of these compounds demonstrated strong binding with VEGFR (Table 2). Molecular docking analysis has shown that the selected bioactive compounds have interacted with a different binding mode at a similar site. These bioactive compounds have established hydrogen interactions at the VEGFR binding site with CYS-102, HIS-27, CYS-102, GLU-30, THR-31, LEU-32, LEU-32 and GLY-59. The interaction of this bioactive compound with the amino acids listed above indicates that the compound has penetrated deeply into the VEGFR binding site. (Figure 1) could be the reason why it also had the lowest binding energy to inhibit the role of VEGFR in angiogenesis. It is clear from the results that these phytocompounds had relatively good binding energy and, just like the standard drug, they were able to bind to VEGF.

Conclusion:

We document the binding features of four compounds (sesamin, fargesin, longamide and piperlonguminine) with VGFR2 for further consideration in drug discovery.

Reference:

[1] Ferlay J *et al. Int J Cancer*. 2015 **136**:E359 [PMID: 25220842].
[2] Siegel RL, *et al. CA Cancer J Clin*. 2017;67(1):7-30 [PMID: 28055103].
[3] Carmeliet P, *Nat Med*. 2003; 9(6):653-60 [PMID: 12778163].
[4] Claesson-Welsh L, *Biochem Soc Trans*. 2003;31(Pt 1):20-4 [PMID: 12546646].
[5] Takahashi H, *et al. Clin Sci (Lond)*. 2005;109(3):227-41 [PMID: 16104843].
[6] Ciardiello F, *et al. Ann Oncol*. 2006;7: vii109-14 [PMID: 16760272].
[7] Smith NR, *et al. Clin Cancer Res*. 2010;16(14):3548-61 [PMID: 20606037].
[8] Frumovitz M, *et al. Gynecol Oncol*. 2007;104(3):768-78. [PMID: 17306693].
[9] Mesiano S, *et al. Am J Pathol*. 1998; 53(4):1249-56 [PMID: 9777956].
[10] Kazazi-Hyseni F, *et al., Oncologist*. 2010;15(8):819-25 [PMID: 20688807].
[11] Trott O *et al. J Comput Chem*. 2010;31(2):455-461. [PMID: 19499576].
[12] Morris GM, *et al. J Comput Chem*. 2009;30(16):2785-2791[PMID: 19399780].
[13] Vijayalakshmi P, *et al. J Recept Signal Transduct Res*. 2015;35(1):15-25.[PMID: 25055026]
[14] Vijayalakshmi P, *et al. Interdiscip Sci*. 2014;6(4):331-9. [PMID: 25519150]

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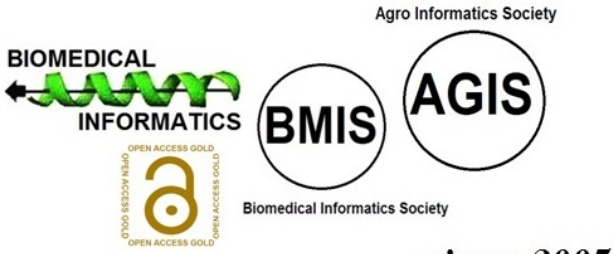

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