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In Silico Identification of Garlic Phytochemicals as a Novel Anti-VEGFR2 Agent to Inhibit Cancer-Associated VEGFR2 Pathways Leading to Cancer

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Abstract **Introduction:** Vascular endothelial growth factor receptor 2 (VEGFR2) plays an important role in cancer progression, especially in tumor growth and metastasis. Although several FDA-approved drugs target VEGFR2, they are often associated with side effects. Therefore, there is a need to identify safer and effective alternative molecules. **Methods:** In this study, the VEGFR2 protein (PDB ID: 2OH4) was obtained from the Protein Data Bank and prepared for molecular docking. A total of 18 garlic-derived phytochemicals and a standard drug, famitinib, were retrieved from the PubChem database. Molecular docking was performed using AutoDock Vina in PyRx to evaluate binding affinity. Basic pharmacokinetic properties of selected compounds were also assessed. **Results:** Among the tested compounds, three molecules (CID: 5280343, 5280863 and 5280805) showed better binding affinity (-9.6, -9.4 and -9.1 kcal/mol, respectively) compared to famitinib (-8.3 kcal/mol). These compounds also formed stable interactions within the VEGFR2 active site and showed acceptable pharmacokinetic properties. **Conclusion:** The results suggest that garlic phytochemicals may act as potential inhibitors of VEGFR2. However, these findings are based on computational analysis and require further validation through experimental studies.

Key Words VEGFR2, Cancer progression, AutoDock Vina, PyRx, Famitinib, Protein Data Bank (PDB ID: 2OH4)

INTRODUCTION

Vascular endothelial growth factor receptor 2 (VEGFR2) (also called kinase insert domain receptor, KDR) or is an important mediator of tumor progression and spread of malignant cells in humans. It has become an important focus in cancer research because it plays a key role in angiogenesis and metastatic progression. VEGFR2 is a transmembrane receptor tyrosine kinase (RTK) that is located predominately on endothelial cells and is structurally related to other RTK family biological agents, including VEGFR1 (Flt-1) and VEGFR3 (Flt-4) [1,2]. A clear understanding of the molecular structure of VEGFR2, its role in cancer-related signaling pathways and its therapeutic potential is important for developing effective targeted treatments for cancer [3,4]. VEGFR2 is a protein complex made of three structural parts, namely an extracellular ligand-binding region, a single transmembrane helix and a tyrosine kinase intracellular domain. The extracellular part has seven immunoglobulin-like (Ig-like) subdomains which are responsible for the ligand recognition and binding, especially to VEGF-A. This signal stimulates the dimerization of receptors and consequent autophosphorylation at critical tyrosine residues in the intracellular segment which triggers downstream signal transduction [3,5].

Phosphorylation of specific tyrosine residues on VEGFR2 activates key signalling pathways such as PI3K/Akt and MAPK. These pathways regulate important endothelial cell functions, including cell growth, migration and increased vascular permeability [5,6]. Structural analysis of VEGFR2 kinase domain revealed that the protein has a typical bilobed conformation shared by tyrosine kinases with an activation loop that is phosphorylated to allow optimal orientation of both the ATP and substrate binding.

Structural studies of the VEGFR2 kinase domain show that it has the typical two-lobed shape seen in many tyrosine kinases. Phosphorylation of the activation loop helps the domain adopt the right conformation for ATP and substrate binding, allowing the enzyme to function efficiently [7]. Engagement of ligands with VEGFR2 triggers receptor

dimerization followed by autophosphorylation that stimulates numerous downstream signaling pathways critical for angiogenesis. One of the pathways is the PI3K/Akt pathway which supports cell survival and proliferation of endothelial cells and Akt activation results in cell cycle progression and inhibition of apoptotic signals [8].

VEGFR2 activates the MAPK/ERK pathway which is essential for endothelial cell growth and migration allowing strong cellular response to growth factors and contributes significantly to tumor-related vascularization [9]. Moreover, the PLCγ/PKC signaling pathway leads to the production of diacylglycerol (DAG) as well as inositol trisphosphate (IP3), which activates protein kinase C (PKC) and triggers release of intracellular calcium, which in turn affect vascular permeability and reorganization of endothelial cytoskeleton [10].

Dysregulation of VEGFR2 signalling have been found in various cancers such as breast, lung as well as colorectal cancer where overexpression is associated with increased microvessel density, rapid tumor growth and poor clinical outcomes [11]. Different drugs have been developed to inhibit VEGFR2-mediated signaling and impairs tumor vascularization. Ramucirumab is a monoclonal antibody that binds to the extracellular domain of VEGFR2, thereby blocking the receptor engagement of VEGF-A and its associated benefits and clinical data suggests better survival in patients with advanced gastric and colorectal cancer patients [12]. Tyrosine kinase inhibitors (TKIs), such as sorafenib and sunitinib are small molecules which target VEGFR2 and other kinases involved in angiogenesis. They work by competing with ATP for binding to the kinase domain, which prevents receptor autophosphorylation and blocks downstream signaling [13]. Aflibercept is a recombinant fusion protein that binds VEGF with high affinity and prevents it from interacting with VEGFR2 [14].

Nonetheless, in response to anti-VEGFR2 therapies, resistance usually arises by adaptive mechanisms such as activation of other pro-angiogenic signaling pathways and enhanced pericyte colonization to stabilize tumor vasculature [15,16]. These limitations, along with drug-related toxicity, have shifted attention toward combination therapies and alternative treatment approaches. Natural phytochemicals are also emerging as promising anti-angiogenic agents with fewer side effects [17]. For example, curcumin of *Curcuma longa* and resveratrol of grapes suppress VEGFR2 and subsequent Akt/ERK signaling and decreasing the proliferation of endothelial cells [18,19].

Similarly, flavonoids like quercetin and apigenin which are abundant in fruits and vegetables inhibit VEGFR2 phosphorylation, interrupt downstream pathways and reduce microvessel densities in tumor models [20]. Garlic (*Allium sativum*) is a good source of bioactive organosulfur compounds (OSCs) such as allicin, alliin, diallyl sulfide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS), ajoene and S-allyl cysteine that have been extensively studied as anticancer agents. These compounds have a wide range of tumor suppressive mechanisms including phase I and II detoxification enzymes modulations, apoptosis, cell-cycle arrest, metastasis and angiogenesis inhibition [21]. One such mechanism is the inhibition of tumor angiogenesis, a process that plays a crucial role in cancer growth and metastasis.

Recent evidence suggests that some garlic-derived organosulfur compounds (OSCs), a key regulator of tumor-induced angiogenesis, can inhibit the VEGF/VEGFR2 signaling pathway. For example, allicin has been reported to suppress VEGFR2 phosphorylation and inhibit the PI3K/Akt and MAPK/ERK pathways, leading to reduced endothelial cell proliferation, migration and tube formation [22]. Likewise, DATS and DADS have been shown to have anti-angiogenic effects through dampening of VEGFR2-mediated signaling, attenuation of microvessel density and neovascularization in tumor models. These effects also come with inhibition of the matrix metalloproteinase activity which also inhibits the angiogenesis and tumor invasion [23].

Garlic-derived OSCs may support conventional anti-VEGFR2 therapies by targeting this pathway in two ways: directly blocking receptor activation and reducing VEGF production in tumor cells. Their multitargeted actions, lower toxicity profile and natural origin make them promising candidates for incorporation into integrative anticancer strategies, particularly in combination with synthetic VEGFR2 inhibitors to overcome drug resistance and minimize adverse effects.

The objective of this study was to evaluate the binding affinity of selected garlic phytochemicals against VEGFR2 using molecular docking and assess their preliminary pharmacokinetic properties to identify potential lead compounds for further investigation.

METHODS

Retrieval and Preparation of the Target Protein VEGFR2

We retrieved the target protein VEGFR2 with PDB ID: 2OH4 from the Protein Data Bank repository in complex with Hetatom, Benzamide urea inhibitor in PDB format. The retrieved protein has a resolution of 2.05 Å with an attached ligand. The target was prepared by removing the unnecessary components, like the attached ligands, using the Biovia Discovery Studio software. So, the protein was prepared and made ready for molecular docking studies.

Ligand Retrieval and Preparation

All the garlic components were obtained from the Pubchem database in sdf format. The garlic is linked to the family of Amaryllidaceae. We retrieved about 18 compounds and control famitinib from the selected Pubchem database. All the compounds were prepared using academic version of Discovery Studio Software.

RESULTS

Molecular Docking Analysis

We selected 18 phytochemicals from the Pubchem database in .sdf format and the control drug, Famitinib, from the PubChem database. The target protein, VEGFR2, was retrieved from the Protein Data Bank (PDB) along with the attached heteroatoms. The resolution of the kinase retrieved

protein is 2.05 Å with a single chain made of 316 amino acids. The attached peptide chain as a ligand atom was used to determine the active site of the target using the academic version of the Biovia Discovery Visualizer tool. The binding pocket residues of the target under study include Leu838, Val846, Ala864, Lys866, Glu883, Ile886, Leu887, Ile890, Val896, Val897, val914, Glu915, Phe916, Cys920, Leu1033, Ile1042, Cya1043, Asp1044 and Phe1045.

We carried out the molecular docking process using the AutoDock vina module of the PyRx software. The process of active site molecular docking begins with the preparation of the target protein using the protein preparation wizard module of PyRx; the missing residues and terminal residues acting as a cap terminus were added to the protein before docking. The Universal Force Fields (Uff) were applied to garlic compounds and the control drug, Famitinib. After the docking execution, the binding score of each compound was obtained and the compounds were ranked based on binding affinity scores.

After analyzing the docking scores and comparing the binding affinity score of each compound with that of the control drug, we found three potential compounds having a binding affinity score greater than control, famitinib (B.E = -8.3 kcal/mol), as shown in Table 1. The three compounds having higher binding affinity scores than standard include 5280343 (B.E. 9.6 kcal/mol), 5280863 (B.E. 9.4 kcal/mol) and 5280805 (B.E. 9.1 kcal/mol) respectively. Detailed information about the binding score and interaction details is shown in Table 1.

Molecular Interaction Analysis of Famitinib and Lead Compounds with VEGFR2

In our research study we observed that docked complexes of our compounds with the target, VEGFR and our analysis revealed that the docked complexes establish various types of interactions like h-bond interaction, Pi-cation, Pi-alkyl, Sulphur bond and van der Waals interactions. In the Famitinib-Target complex, three hydrogen bonds are formed between the ligand atoms and target residues ASN 921. In the 5280343-target complex, two hydrogen bonds are present between CYS 917 and one bond is present with ASP1044 with bond distances of 2.08396 Å, 2.49856Å and 2.27002 Å, respectively. In the 5280863-VEGFR2 complex, we observed three hydrogen bonds with CYS917 and one hydrogen bond with LEU838, with bond distances of 1.8941 Å, 2.12571Å, 2.45747 Å and 2.43635Å, respectively. Similarly, in 5280805 -target complex, various hydrogen bonds are formed between the residues like ASP1044, ASP1026, ASN1031, LEU1047 and ALA1048 with the bond distances 2.41415Å, 2.070 Å, 1.934 Å, 2.009 Å and 2.066 Å, respectively.

Besides these interactions, the top compound complexes show other types of interactions that support the stability of the protein ligand complexes, as shown in Figure 1 and 2. The various interaction types generated between selected compounds and the target include van der Waals, Pi-Sigma, Pi-Pi stacked, Pi-sulphur and Pi-Alkyl. Based on the binding affinity scores and the interactions generated between chosen molecules and the target, we conclude that the top

Table 1: Docking Score of the Top Three Compounds Along with the Standard, Famitinib and the Interacting Residues of the Active site of the Target Protein

Docking score of top garlic constituents				
Compound ID's	Docking score	No. of H- bonds	H-bond Distance (Å)	Interacting residues
Famitinib	-8.3	A:GLY920:HN-A:CYS917:O A:ASN921:HN-N:UNK1:O A:ASN921:HD21- A:THR924:OG1 A:SER928:HN-A:THR924:O	2.08274 2.24405 2.18948 2.10164	Leu838, Val846 Ala864, Val914 Glu915, Phe916 Cys917, Phe919 Gly920, Asn921 Thr924, Tyr925 Ser928, Leu1033 Phe1045, Arg1049
5280863	-9.4	N:UNK1:H-A:CYS917:O N:UNK1:H-A:LEU838:O A:LYS866:HZ2-A:GLU883:OE1 A:LYS866:HZ3-A:PHE1045:O A:CYS917:HN-N:UNK1:O A:CYS917:HN-N:UNK1:O A:GLY920:HN-A:CYS917:O	1.8941 2.43635 1.71974 1.92865 2.12571 2.45747 2.08274	Leu838, Val846 Ala864, Lys866 Glu883, Val914 Glu915, Phe916 Cys917, Lys918 Gly920, Leu1033 Phe1045
5280343	-9.6	A:LYS866:HZ2-A:GLU883:OE1 A:LYS866:HZ3-A:PHE1045:O A:CYS917:HN-N:5280343:O A:CYS917:HN-N:5280343:O A:GLY920:HN-A:CYS917:O N:5280343:H-A:ASP1044:O	1.71974 1.92865 2.08396 2.49856 2.08274 2.27002	Leu838, Val846 Ala864, Lys866 Glu883, Val914 Glu915, Phe916 Cys917, Leu1033 Cys1043, Asp1044 Phe1045, Arg1049
5280805	-9.1	N:UNK1:H-A:ASP1044:OD2 N:UNK1:H-A:ASP1026:OD2 N:UNK1:H-A:ASN1031:OD1 A:LYS866:HZ2-A:GLU883:OE1 A:LEU880:HN-A:GLU876:O A:GLU883:HN-A:ALA879:O A:ARG1030:HH11-A:ASP1050:OD2 A:ASN1031:HD21-N:UNK1:O A:ASN1031:HD22-A:ASP1026:O A:LEU1047:HN-N:UNK1:O A:ALA1048:HN-N:UNK1:O A:ARG1064:HH11-A:ASP1026:OD2	2.41415 2.07086 1.93494 1.71974 2.09155 2.10809 2.3587 1.86083 1.95774 2.0091 2.06625 2.07117	Phe843, Lys866, Glu876, Ala879, Leu880, Glu883, Ile886, His1024, Arg1025, Asp1026, Arg1030, Asn1031, Asp1044, Phe1045, Gly1046, Leu1047, Ala1048, Arg1049, Arg1064

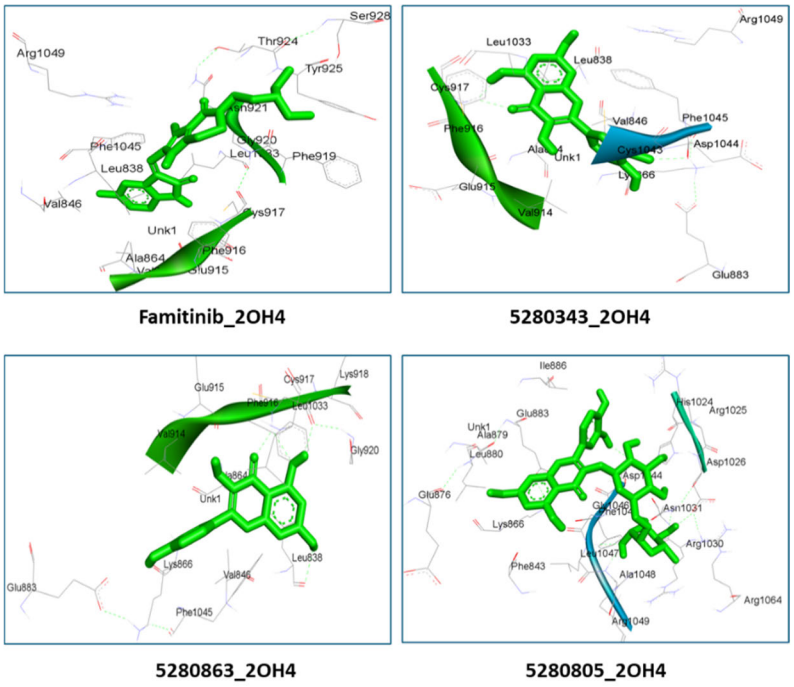

Figure 1: 3D and 2D Representation of the Potential Selected Compounds Indicating the Interaction Pose of the Ligands and the Number and Types of Residues Involved in Generating Interaction Types with the Ligand Molecules

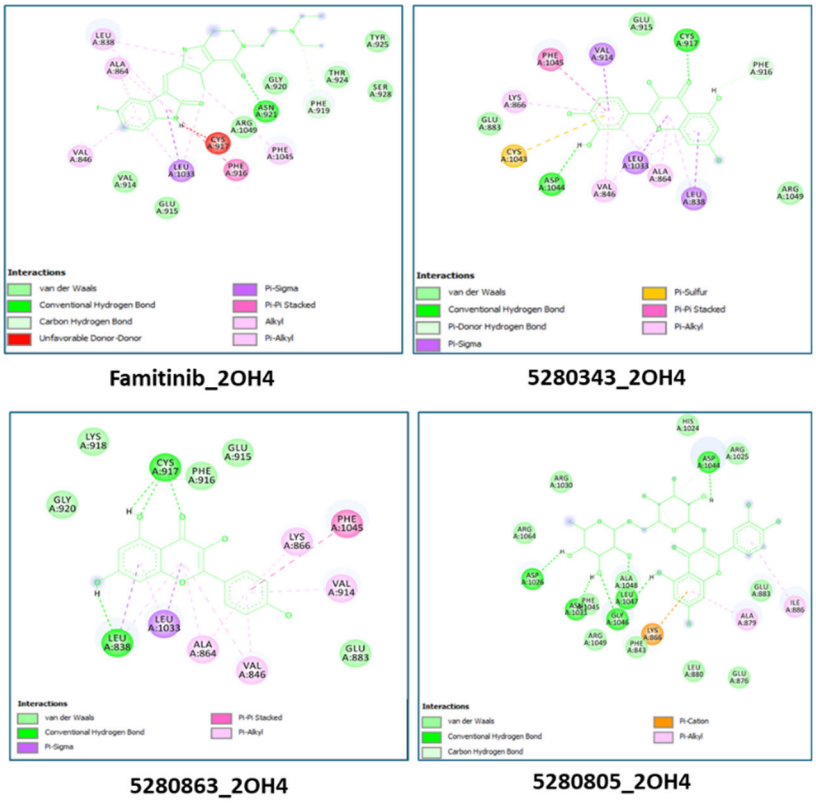

Figure 2: 3D surface representation of the top leads indicating the interaction pose of the ligands and the number and types of residues involved in generating interaction types with the ligand molecules

compounds from garlic may prove very potent molecules against cancer by targeting the active site of the VEGFR2 tyrosine kinase.

DISCUSSION AND CONCLUSION

Vascular endothelial growth factor receptor being a critical target is predominantly involved in cancer metastasis.

Various pathways like PI3K-mTOR, MAPK, JAKSTAT, AKT/PKB etc. are initiated via dimerization that leads to cancer cell growth, proliferation, differentiation and metastasis. Being the critical target to treat cancer, various FDA approved drugs have been used to inhibit the VEGFR2 cancer associated activity of the receptor tyrosine kinase, VEGFR. The anti-VEGFR2 TKI's like Sorafinib, Sunitinib, Axitinib, Pazopanib, famitinib etc. have shown better efficacy and progression free survival but due to emerging mutational resistance, side effects and bypassing signaling, the approved drugs exhibit failure to inhibit VEGFR2 functional activity. So, there is need for the identification of the novel TKIs inhibitors that can target VEGFR2 with good pharmacokinetics profile.

Natural substances seem to be an alternative to obtaining the new anti-VEGFR chemical species. In this research work we have selected garlic constituents to get insights into their possible inhibiting activity for VEGFR2 to treat cancer. The garlic contains huge number of anti-cancer compounds. The flavonoids, saponins and phenolic compounds have shown anti-proliferation and anti-oxidative features in various cancer cell lines. In our study we retrieved 18 garlic constituents from TIP database in .sdf format.

The standard drug, Famitinib was obtained from the PubChem database in 3D .sdf format. The retrieved compounds were docked with the active site of the target protein VEGFR2, obtained from the protein data bank database. The molecular docking was performed by using the PyRx tool that possesses all the modules for grid generation and docking process. The ligands were docked with the active site of the receptor protein, VEGFR2 and the binding affinities of all the compounds along with the standard, Famitinib were obtained and analyzed for best hit identification.

After comparing the binding affinities garlic constituents with the binding affinity score of the standard, famitinib we found top three compounds for consideration. The top three compounds include 5280343, 5280863 and 5280805 With docking score of -9.6, -9.4 and -9.1 kcal/mol, respectively. While the identified compounds demonstrated better docking scores than famitinib, it is important to note that molecular docking provides only a predictive estimation of binding affinity. These results do not confirm biological activity. The observed interactions suggest that garlic phytochemicals may bind effectively within the ATP-binding pocket of VEGFR2; however, further validation through molecular dynamics simulations and experimental studies is required. Based on the findings obtained we can say that the newly identified compounds may have the potential to synergistically inactivate the cancer activity of the VEGFR2 involved in cancer metastasis.

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Ethical Statement

This study was based on computational and database analysis only and did not involve human participants or animals.

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