DLSU Research Congress 2025
De La Salle University, Manila, Philippines
June 26 to 28, 2025

Virtual Screening Of Esculetin From Aloe vera (*Aloe barbadensis*) as a Potential VEGF Inhibitor Against Angiogenesis And Excessive DNA Replication

Jeffrey Carlo Belmonte[1], Mac Rigel Gellego[1], Franco Alexis Balmoris[1], Bienvenido Amiel Delos Reyes[1], Jose Miguel Palitog[1], Jianah Chriselle Pondanera[1]. Mary Daphne Gail Ruiz[1], Juriz Grace San Pedro[1], Jane Abigail Santiago[1*]

[1] *College of Science, De La Salle University, City of Manila, 1004 The Philippines*
**Corresponding Author: jane.santiago@dlsu.edu.ph*

Abstract: Cancer is a leading disease worldwide causing about 10 million deaths annually and its destructive metastasis is largely dependent on angiogenesis and lymphangiogenesis. The vascular endothelial growth factors (VEGFs) primarily drive these processes. VEGF-C and VEGF-D play major roles in lymphatic vessel development. They also affect tumor growth and spread through the lymphatic system. This study conducted a structure-based virtual screening of esculetin, a compound from Aloe vera, to test its binding strength and ability to inhibit VEGF-A, VEGF-B, VEGF-C, and VEGF-D using AutoDock Vina. Esculetin showed the highest binding affinity to VEGF-C at -6.5 kcal/mol. It had important interactions in the L1 and L2 loops, which activate VEGFR-2 and VEGFR-3.VEGF-D binding affinity of -5.8 kcal/mol shows the formation of essential hydrogen bonds and hydrophobic contacts at its receptor-binding site; thus, disruption in downstream signaling associated with lymphangiogenesis may occur. Analyses from LigPlot+ and PyMol confirmed that esculetin is stabilized within the binding sites of VEGF-C and VEGF-D. This stabilization arises from hydrogen bonds with residues like PHE152, LYS153, and CYS146, along with hydrophobic interactions. These molecular interaction connections suggest that esculetin can effectively block receptor engagement and signal transmission. Moreover, these docking results were substantiated by the RMSD validation. Therefore, this proves that esculetin might serve as a dual inhibitor of angiogenesis and lymphangiogenesis. This suggests that *in vitro* examination and *in vivo* validation are needed to further warrant esculetin as a candidate for anti-metastatic cancer treatment.

Key Words: angiogenesis; VEGF; aloe vera; esculetin; molecular docking; in silico

1. INTRODUCTION

1.1 Background of the Study

Each year, approximately 10 million people all over the world die from cancer, accounting for about 1 in 6 deaths globally (Bray et al., 2024). Over the years of advancement in the medical field, various treatments have been developed to combat cancer; including surgery that removes tumors even when benign and the process of destroying rapidly proliferating cells through either chemotherapy or radiation therapy. While these treatments have been proven to be effective in fending off cancer, their success heavily relies on the stage of cancer at diagnosis. They also still come with substantial drawbacks such as an increased risk of adverse health complications and a high financial barrier. These challenges have propelled ongoing research into the biological mechanisms that induce cancer

VEGF / VEGFR treatments are increasingly becoming a focal point for anti-cancer therapies. One key strategy in cancer therapy that involves VEGF are

its inhibitors. These agents impede the activity of the said protein by modulating the process of angiogenesis. Current anti-VEGF therapies including monoclonal antibodies like bevacizumab and small molecule tyrosine kinase inhibitors (TKRs) such as sunitinib often come with significant drawbacks, including resistance development, high costs, and adverse side effects like hypertension and thrombosis (Jayson et al. 2016). These limitations have prompted the search for alternative and complementary therapies, particularly those based on natural products that may offer fewer side effects and lower toxicity.

Traditionally, Aloe vera has been known for its medicinal properties and has been used in a wide variety of medical applications from alleviating burns and wound healing, to being considered beneficial to hair growth. Esculetin, a coumarin derivative found in several plant species including Aloe vera, has also garnered attention for its potent anti-angiogenic and anti-cancer properties. Studies have demonstrated that esculetin exerts its anti-angiogenic effects by inhibiting VEGF-induced angiogenesis (Arora et al. 2016). Harnessing Aloe vera, particularly the bioactive compounds found within it, could be a step closer in finding more affordable cancer treatments.

Therefore, it was in mind that this paper aimed to conduct an in-silico structure-based virtual screening of esculetin as a potential VEGF inhibitor through the use of AutoDock Vina and key binding segment analysis. In order to achieve this key objective, the researchers sought to conduct an analysis of the binding affinities and interaction profiles of esculetin with VEGF receptors, utilizing molecular docking data obtained from AutoDock Vina to characterize the specific ligand-receptor interactions. Using the information gathered, the key binding sites responsible for the prospective inhibition of VEGF receptors by esculetin would then be identified and characterized. By this means, the specific amino acid residues involved in the binding interactions would also be examined. Based on the specific objectives of this study, several considerations and limitations were made for this research. The proteins in this study were limited to only VEGF-A, VEGF-B, VEGF-C, and VEGF-D, as they are known to be the common subfamilies of VEGFs found in humans. Thus, this study does not take into consideration alternatively modified isomeric forms of these proteins.

This research utilized AutoDock Vina as the sole simulation tool for molecular docking. This is based on several factors including effectiveness in previous studies and accessibility to the researchers. As this paper is focused on the virtual screening of esculetin and VEGF docking, this paper will not include experimental procedures such as compound extraction or laboratory-based validation. The genetic information necessary for this study will be gathered from online, publicly available databases such as PubChem and Protein Data Bank. Moreover, PyMol and Ligplot+ were used as the software for visualization for binding patterns.

2. METHODOLOGY

2.1 Materials

The materials utilized in this study include the docking software AutoDock Vina, structural databases—PubChem and SWISS Model, and visualization programs—LigPlot and PyMol.

2.2 Data Collection

The files necessary for this study, the atomic structure of esculetin and the amino acid sequence of VEGFs human variants, were obtained from PubChem and UniProt respectively. These sequences were selected as they were specifically reviewed and verified by their respective database.

2.3 Data Analysis

The amino acid sequence of the VEGF factors was then modelled into 3D structures using SWISS Model and downloaded in the PDB file format. Water molecules were then removed, whilst hydrogen molecules and Kollman's Charges were added through the use of AutoDock (V1.5.7). This was then saved through the PDBQT file format. The docking simulations were executed in AutoDock Vina, with the binding site defined using a grid box around the protein's active site. The resulting docking files were then analyzed. The docking results were examined based on docking scores and binding affinities (kcal/mol), identifying the interactions between Esculetin and VEGF proteins. The binding patterns were visualized using LigPlot+ and PyMol, focusing on key hydrogen bonds and hydrophobic interactions.

The results were further cross-referenced with previous studies to confirm the inhibition potential of Esculetin on angiogenesis.

2.4 Data Validation

The positive control consisted of data validation in redocking well known ligand-protein complexes that are small moleculares or peptides. Each ligand-protein complex is separated, docked with parameters as stated above, and RMSD is calculated in PyMol. An RMSD ≤ 2.0 Å is indicative of a successful pose reproduction.

Table 1. VEGF Sequences Utilized & Identifiers

VEGF	Amino Acid Sequence	RCSB Identifier	Reference
VEGF-A	GQNHHEVVKFMDVYQRSYCHPIETLVDIFQEYPDEIEYIFKPSCV PLMRCGGCCNDEGLECVPTEESNITMQIMRIKPHQGQHIGEMS FLQHNKCECRPKKD	1VPF	(Shahik et al. 2021)
VEGF-B	HQRKVVSWIDVYTRATCQPREVVVPLTVELMGTVAKQLVPSCVT VQRCGGCCPDDGLECVPTGQHQVRMQILMIRYPSSQLGEMSLE EHSQCECRPKKK	2C7W	(Ye et al. 2021) (Shahik et al. 2021)
VEGF-C	DPTEETIKFAAAHYNTEILKSIDNEWRKTQCMPREVAIDVGKEF GVATNTFFKPPCVSVYRCGGCCNSEGLQCMNTSTSYLSKTLFEI TVPLSQGPKPVTISFANHTSCRCMSKLHHHHHH	4BSK	(Ye et al. 2021)
VEGF–D	DPTFYDIETLKVIDEEWQRTQCSPRETAVEVASELGKSTNTFFKP PCVNVFRCGGCCNEESLICMNTSTSYISKQLFEISVPLTSVPELVP VKVANHTGCKCLPTAHHHHHH	2XV7	(Ye et al. 2021)

3. RESULTS AND DISCUSSION

3.1 Binding Affinity of VEGF Subtypes with Esculetin using AutoDock Vina

Table 2. AutoDock Vina Results

	VEGF isotype			
Position	VEGF-A	VEGF-B	VEGF-C	VEGF-D
Position 1	-5.4	-5.6	-6.8	-6.8
Position 2	-5.4	-5.5	-6.6	-6.6
Position 3	-5.4	-5.4	-6.1	-6.1
Position 4	-5.4	-5.2	-6.0	-6.1

In table 2, AutoDock Vina consistently reported the most negative binding affinities, with VEGF-C (-6.5 kcal/mol) exhibiting the strongest interaction. This may be attributed to AutoDock Vina's empirical scoring function, which accounts for torsional flexibility and optimizes binding poses based on free energy calculations (Forli et al., 2016). The stronger binding affinity suggests that esculetin could

effectively bind and inhibit VEGF-C, potentially interfering with its receptor interactions. The docking results strongly suggest that esculetin preferentially binds to VEGF-C, a key regulator of lymphangiogenesis. This aligns with studies showing that VEGF-C inhibition can suppress tumor metastasis by reducing lymphatic vessel formation (Tammela & Alitalo, 2010). With these results, it was then validated by calculating the Root Mean Square Deviation (RMSD) values from three independent redocking simulations performed to validate the reproducibility and accuracy of the study's docking protocol across different molecular docking tools.

Table 3. Validation step conducted in AutoDock Vina with associated PDB identifier.

PDB Identifier	AutoDock Vina
3CJG	1.579
3BE2	0.155
3HNG	0.164

RMSD values in Table 3 ranged from 0.155 to 1.579 Å, thereby establishing that the docking simulations corresponded closely to the original crystal structures of the ligands; hence, all values were below the accepted threshold of 2.0 Å, which denotes that docking using AutoDock Vina was accurate and reliable.

3.2 Key Binding Segments of VEGF Subtypes with Esculetin

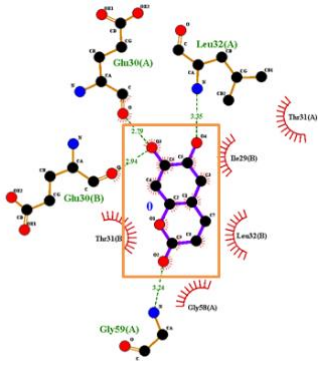

Figure 1. LigPlot Visualization of the binding interactions between Esculetin and VEGF-A based on the top-ranked docking pose from AutoDock

As shown in Figure 1, PyMol-based visualization revealed three polar contacts through hydrogen bonding: LEU32(A), LEU32(B), and GLY59(A). The corresponding LigPlot+ analysis coincides with the three polar contacts and further reveals GLU30(A) and GLU30(B) with hydrophobic interactions (THR31(A), THR31(B), ILE29(B), LEU32(B), and GLY58(A)).

The predicted hydrogen bonds LEU32(A), LEU32(B), GLU30(A), GLU30(B), and GLY59(A) are likely situated within the N-terminal and adjacent loops to VEGF-A regions that are equally likely to be critical in receptor binding. The hydroxyl groups of esculetin can form hydrogen bonds with the side chains of glutamic acid and the backbone of glycine, stabilizing the ligand within the binding pocket. Such interactions could have esculetin anchored in a position that interferes with VEGF-A's ability to engage its two receptors. Moreover, the several identified hydrophobic interactions likely involve van der Waals forces and hydrophobic packing, contributing to the stability of the binding and esculetin's specificity for VEGF-A.

These findings aligned with prior research into other VEGF inhibitors. Lin et al. (2025) screened over 1000 flavonoids as potential VEGF drug inhibitors via computational docking, and identified -(-)-epicatechin, ononin, and farrerol as the compounds with the highest binding affinity VEGF. These flavonoids formed similar hydrogen bonds as predicted in esculetin binding, such as Ile29, Glu30, Leu32, Thr31, and Cys57. Their docking energies, -

22.4kJ/mol -(-)-epicatechin for instance, suggested strong interaction potentials that correspond with in vitro inhibition of VEGF-mediated wound healing and NF-κB activity.

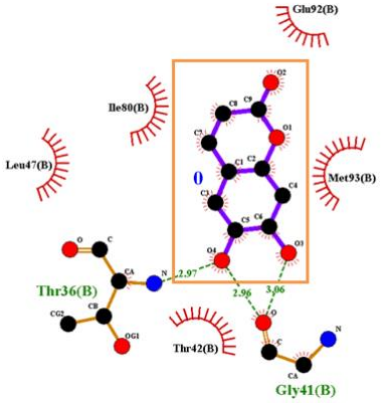

Figure 2. LigPlot Visualization of the binding interactions between Esculetin and VEGF-B based on the top-ranked docking pose from AutoDock.

As presented in Figure 2, the hydrogen bonding contacts in LigPlot reveal THR36(B) and GLY41(B) and hydrophobic interaction groups (GLU92(B), ILE80(B), LEU47(B), and MET93(B)).

The predicted hydrogen bonds – THR36, THR41, and GLY41— are likely located close within the N-terminal or a flexible loop region of the VEGF-B (Iyer et al. 2006), allowing them to support ligand binding through hydrogen bonds. To stabilize esculetin inside the VEGF-B binding pocket, the ligand's hydroxyl groups may form hydrogen bonds with the side chains of Threonine and backbone of Glycine. Such interactions may affix esculetin in a binding position that interferes with VEGF-B's binding affinity with its receptor, VEGFR-1.

Moreover, several hydrophobic interactions are predicted that further stabilize esculetin's binding. Although glutamic acid is primarily hydrophilic, its side chain can engage such interactions when buried in the core of the protein or microenvironments. The nonpolar side chains of isoleucine, leucine, and methionine can further stabilize esculetin by providing a hydrophobic environment and further stabilizing through van der Waals forces. The total binding affinity and specificity of esculetin for VEGF-B are probably influenced by these interactions.

Iyer et al. (2010) revealed structural insights of VEGFR-1 domain D2 binding with VEGF-B by contacting through N-terminal helix (α1 Q11, W17-I18, Y21-T22, T25-Q27) and a ß3-ß4 connecting loop (L2, P62-D63, G65-L66) on monomer one, plus another smaller monomer from the opposite surface (ß2, V48, and loop 3, L81, I83, S88-L90). Notably, the VEGF-B's "hotspots" that are receptor determinant do not include or overlap with esculetin's predicted binding interactions (THR36, THR41, and GLY41), likely outside the key receptor-binding site.

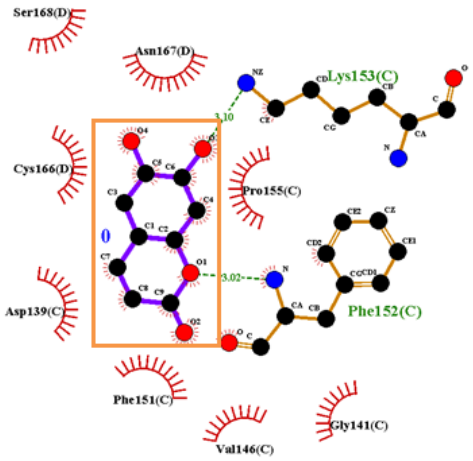

Figure 3. LigPlot Visualization of the binding interactions between Esculetin and VEGF-C based on the top-ranked docking pose from AutoDock.

As shown in Figure 3, visualization conducted in LigPlot reveals PHE152(C) and LYS153 as significant amino acid residues for hydrogen bonding alongside the hydrophobic interactions (SER168(D), ASN167(D), PRO155(C), ASP139(C), PHE151(C), VAL146(C), and GLY141(C)).

The predicted hydrogen bonds with residues THR150, PHE152 and LYS153 are situated within Loop L1, and CYS166 is located within Loop L2 of VEGF-C, which is a critical loop region for receptor specificity (Leppänen et al. 2010, 2013). Esculetin's hydroxyl groups can be stabilized within VEGF-C's binding pocket by forming hydrogen bonds with its side chains of lysine and threonine residues. Cysteine residues – specifically Cys166 – may partake either in

hydrogen bonding or use disulfide bonds to support the binding site's structural stability.

In addition, several predicted hydrophobic interactions that likely involve in van der Waals forces and hydrophobic packing, contributing to the overall affinity and specificity of esculetin for VEGF-C. Notably, these residues are located on the Loop L1 and Loop 2 with adjacent residues are known to mediate VEGF-C's interactions with VEGFR-2 and VEGFR-3.

The findings of Leppanen et al. (2010) provide critical context for interpreting interactions observed between esculetin and VEGF-C. Their structural study of VEGFR-2 domains D2 and D3 revealed that VEGF-C engages its receptor via three peptide loops – Loop 1 (residues 139-155), Loop 2 (167-171), Loop 3 (188-196) – as well as the N-terminal α1 helix. Notably, L1 and L3 contribute to a hydrophobic binding interface (site 2) with VEGFR-2 D2 and D3, while L2 (site 1) includes the highly conserved GLU169, which forms a salt bridge and hydrogen bonds that are critical for high affinity binding, especially with VEGFR-3. Esculetin's binding interactions within loops L1 and L2 could therefore disrupt essential contacts with its receptor, providing a mechanistic explanation for its potential inhibitory properties. Furthermore, esculetin's predicted interactions overlapping with VEGF-C regions responsible for receptor recognition compounds esculetin's potential as a competitive or allosteric inhibitor.

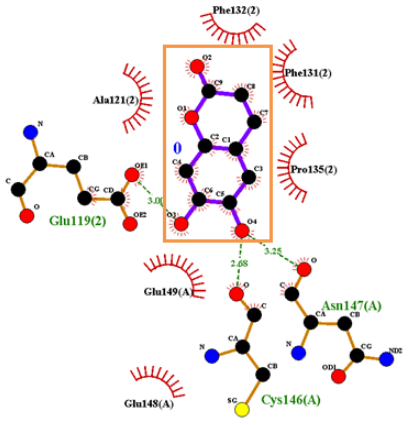

Figure 4. LigPlot Visualization of the binding interactions between Esculetin and VEGF-D based on the top-ranked docking pose from AutoDock.

As presented in Figure 4, LigPlot+ reveals GLU119(2), CYS146(A), and ASN147(A) in hydrogen bonding, and PHE132(2), PRO135(2), GLU148(A), GLU149(A), and ALA121(2) in hydrophobic interactions.

GLU148 and GLU119, two negatively charged glutamic acid residues, are projected to form strong hydrogen bonds and electrostatic interactions with the esculetin hydroxyl groups. Esculetin is likely stabilized within a critical region of the VEGF-D binding pocket by this type of interaction. Interestingly, the polar residue ASN147 may either donate or accept hydrogen bonds, further assisting optimization and contribution to ligand anchoring, depending on the surrounding environment. CYS146 is less frequently discussed in ligand binding, however, may participate in hydrogen bonding or serve as a stabilizing element due to its ability for disulfide linkages and local structure rigidity (Leppänen et al. 2011).

Esculetin's binding is further reinforced by several hydrophobic interactions on top of hydrogen bonding. PHE132 is an aromatic residue that can π-π stack with the aromatic rings of esculetin, a frequent mechanism in protein-ligand stabilization. It can be found in lists of hydrogen bonding and hydrophobic interactions. The non-polar residues PRO132 and ALA121 assist to create a hydrophobic environment that strengthens van der Waals interactions and encourages dense ligand packing in the cavity. GLU148 and GLU149 are essential to the overall ligand stabilization network because of their functions in both hydrogen and hydrophobic interactions, indicating that they are located at the interface between polar and nonpolar areas.

3.3 Potential Inhibitory Effects on VEGF-Mediated Angiogenesis

As such, esculetin shows great promise as a potential VEGF-mediated angiogenesis inhibitor, confirming its anti-angiogenic properties.

Notably, esculetin exhibits high predicted affinities for VEGF-A and VEGF-C, key mediators of angiogenesis and lymphangiogenesis, respectively. As esculetin binds to significant residues in the receptor-binding loops and dimerization interface of VEGF-A (such as LEU32, GLU30, and GLY59), esculetin may

prevent the ligand from activating VEGFR-2, which would inhibit endothelial proliferation and neovascularization. Similarly, esculetin may prevent receptor binding and subsequent receptor dimerization by interacting with VEGF-C, particularly within the L1 and L2 loops that engage VEGFR-2 and VEGFR-3. This would limit signal transduction pathways that are crucial for vascular remodeling.

These computational findings are supported by experimental studies. For instance, a study demonstrated that esculetin inhibits VEGF-induced proliferation and DNA synthesis in human umbilical vein endothelial cells (HUVECs) without cytotoxic effects (Parveen et al. 2019). The compound induced G1-phase cell-cycle arrest and downregulated the expression of cyclins and cyclin-dependent kinases via the upregulation of p27^KIP1^. Furthermore, esculetin reduced the phosphorylation of VEGFR-2 and downstream signaling pathways, including ERK1/2 and eNOS/Akt, leading to suppressed tube formation and migration of HUVECs. In vivo, esculetin inhibited microvessel outgrowth in an aortic ring assay and reduced neovascularization in a Matrigel plug model, confirming its anti-angiogenic properties.

In summary, these multifaceted actions establish esculetin is a promising candidate in inhibiting VEGFR-mediated angiogenesis and lymphangiogenesis by binding to receptor-specific residues on VEGF-A/C/D. On top of its traditional qualities, its capacity to target several elements of the angiogenic cascade provides a thorough strategy to prevent tumor growth and metastasis. Further clinical investigations are required to verify its therapeutic potential and application in oncology.

4. CONCLUSIONS

The potential of the coumarin derivative, esculetin, from Aloe vera as a promising inhibitor against four VEGF subtypes: VEGF-A, VEGF-B, VEGF-C, and VEGF-D. It was demonstrated using AutoDock Vina, an in-silico molecular docking software. The aim was to evaluate its potential as an agent to block blood vessel and lymph vessel formation. Of the four screened subtypes of VEGF, results show that esculetin has the strongest binding affinity for VEGF-C (-6.5 kcal/mol) and VEGF-D (-5.8 kcal/mol), based on AutoDock Vina's scoring system. These values suggest that esculetin could significantly block lymphatic pathways related to VEGFR-2 and VEGFR-3 and done through targeting essential regions like the L1 and L2 loops in VEGF-C and the receptor-binding site of VEGF-D.

LigPlot+ and PyMol visualization studies suggested consistent hydrogen bonding and hydrophobic interactions between the VEGF subtypes and esculetin. This implies the presence of esculetin amply fitting in the VEGF ligand pockets. This in turn may disturb their linking to receptors on endothelial cells which trigger essential signaling pathways that will lead to angiogenesis. RMSD calculations that ranged between 0.155 and 1.579 Å were additionally applied to validate these docking results. This has further strengthened the binding affinity predictions made by AutoDock Vina. In addition, for the other VEGF subtypes, esculetin showed moderate binding affinities for VEGF-A and VEGF-B. Thus, it suggests that it may inhibit several targets within the VEGF family. The specific binding patterns and residue interactions support esculetin's role in blocking both blood vessel and lymph vessel formation, which are key processes in cancerous tumor growth and spread.

Additional studies integrating *in vitro* and *in vivo* approaches will hence be required to further validate these computational results as well as to assess the other pharmacological properties of esculetin as these results and investigate the potential therapeutic application in cancer treatment methods. Additionally, consideration of synergistic interactions with existing anti-angiogenic therapies may provide a more coherent and comprehensive basis for the intrinsic limitations in current modalities for treating cancer.

5. ACKNOWLEDGMENTS

The researchers would like to acknowledge the De La Salle University Department of Biology for their support and assistance throughout the course of this research. We would also like to thank our friends, family, and loved ones for their continuous and unwavering support.

6. REFERENCES

Arora, R., Sawney, S., Saini, V., Steffi, C., Tiwari, M., & Saluja, D. (2016). Esculetin induces antiproliferative and apoptotic response in pancreatic cancer cells by directly binding to KEAP1. *Molecular Cancer*, *15*(1). https://doi.org/10.1186/s12943-016-0550-2

Bray, F., Laversanne, M., Sung, H., Ferlay, J., Siegel, R. L., Soerjomataram, I., & Jemal, A. (2024). Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA a Cancer Journal for Clinicians*, *74*(3), 229–263. https://doi.org/10.3322/caac.21834

Forli, S., Huey, R., Pique, M. E., Sanner, M. F., Goodsell, D. S., & Olson, A. J. (2016). Computational protein–ligand docking and virtual drug screening with the AutoDock suite. *Nature Protocols*, *11*(5), 905–919. https://doi.org/10.1038/nprot.2016.051

Iyer S, Scotney PD, Nash AD, Ravi Acharya K. 2006. Crystal Structure of Human Vascular Endothelial Growth Factor-B: Identification of Amino Acids Important for Receptor Binding. Journal of Molecular Biology. 359(1):76–85. doi:https://doi.org/10.1016/j.jmb.2006.03.002. [accessed 2023 Nov 26]. https://www.sciencedirect.com/science/article/pii/S0022283606003093.

Jayson, G. C., Kerbel, R., Ellis, L. M., & Harris, A. L. (2016). Antiangiogenic therapy in oncology: current status and future directions. *The Lancet*, *388*(10043), 518–529. https://doi.org/10.1016/s0140-6736(15)01088-0

Leppanen V-M ., Prota AE, Jeltsch M, Anisimov A, Kalkkinen N, Strandin T, Lankinen H, Goldman A, Ballmer-Hofer K, Alitalo K. 2010. Structural determinants of growth factor binding and specificity by VEGF receptor 2. Proceedings of the National Academy of Sciences. 107(6):2425–2430. doi:https://doi.org/10.1073/pnas.0914318107.

Leppänen V-M, Jeltsch M, Anisimov A, Tvorogov D, Aho K, Kalkkinen N, Toivanen P, Ylä-Herttuala S, Ballmer-Hofer K, Alitalo K. 2011. Structural determinants of vascular endothelial growth factor-D receptor binding and specificity. Blood. 117(5):1507–1515. doi:https://doi.org/10.1182/blood-2010-08-301549.

Leppänen V-M, Tvorogov D, Kisko K, Prota AE, Jeltsch M, Anisimov A, Markovic-Mueller S, Stuttfeld E, Goldie KN, Ballmer-Hofer K, et al. 2013. Structural and mechanistic insights into VEGF receptor 3 ligand binding and activation. Proceedings of the National Academy of Sciences. 110(32):12960–12965. doi:https://doi.org/10.1073/pnas.1301415110.

Lin S, Tang RW-L, Ye Y, Xia C, Wu J, Duan R, Leung K-W, Dong TT-X, Tsim KW-K. 2025. Drug Screening of Flavonoids as Potential VEGF Inhibitors Through Computational Docking and Cell Models. Molecules. 30(2):257–257. doi:https://doi.org/10.3390/molecules30020257.

Parveen A, Subedi L, Kim H, Khan Z, Zahra Z, Farooqi M, Kim S. 2019. Phytochemicals Targeting VEGF and VEGF-Related Multifactors as Anticancer Therapy. Journal of Clinical Medicine. 8(3):350. doi:https://doi.org/10.3390/jcm8030350.

Tammela, T., & Alitalo, K. (2010). Lymphangiogenesis: molecular mechanisms and future promise. *Cell*, *140*(4), 460–476. https://doi.org/10.1016/j.cell.2010.01.045