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In silico modeling and molecular docking insights of hesperetin against cancer- target VGFR2

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Abstract

Liv The zebrafish flk1 (VGFR2_ DANRE) gene is expressed specifically in blood vessels, particularly arteries. Treatment of zebrafish with VGFR-2 kinase inhibitors indicated the relevance of VGFR2 for vascular development. Overexpression of VGFR2 can contribute to illness. Solid malignancies can only grow to a certain size without a sufficient blood supply; cancers that express VGFR2 can grow and spread. The endeavor to find a new cancer medicine or vaccine will have enormous promise and popularity. The goal of this research is to identify an effective molecule that can inhibit the anticancer's function. Phyre2 software was used to model the key protein VGFR2 in the cancer process. The optimum interaction between VGFR2 and hesperetin is investigated using autodock. Our findings suggest that hesperetin can be tested *in vitro* and *in vivo* for cancer

Keywords: cancer, malignanciesVGFR-2 kinase and interaction

Introduction

VEGF is a cystine-knot growth factor that belongs to the platelet-derived growth factor family of growth factors. They are key signalling proteins involved in both vasculogenesis (the formation of the embryonic circulatory system from scratch) and angiogenesis (the formation of blood vessels from scratch) (the growth of blood vessels from pre-existing vasculature) [Holmes, D. I et al., 2005].

VEGFR-1 (Flt-1), VEGFR-2 (Flk-1/KDR), and VEGFR-3 are the three VEGF receptor tyrosine kinases that are targets for VEGFfamily-induced signalling (Flt-4). VEGFRs have a 70-amino-acid insert and an extracellular region with seven immunoglobulin-like domains, one transmembrane domain, and a kinase domain. [Shibuya M. 2011] VEGFR-1 and VEGFR-2 are found in vascular EC, while VEGFR-3 is mostly found in lymphatic EC. [Dixelius J et al., 2003] Other cell types, such as brain cells or tumour

cells, can now be found to express VEGFR-1 and -2. VEGF-A, VEGF-B, and P1GF are bound by VEGFR-1; VEGF-A, VEGF-C, and VEGF-D are bound by VEGFR-2; and VEGF-C and VEGF-D are bound by VEGFR-3. [Koch et al., 2012]

VEGFR-2 was shown to be modestly expressed in normal tissues and cells, but it has been proven to be overexpressed in malignancies such as lung, colon, uterine, ovarian, and breast cancers [Giatromanolaki et al. 2007]. VEGFR-2 overexpression is not only associated with cancer, but it is also linked to disease stage, recurrence, and a worse result [Guo, S., et al., 2010].

The zebrafish flk1 (vegfr-2) gene is expressed specifically in blood vessels, particularly arteries. Treatment of zebrafish with VEGFR-2 kinase inhibitors highlighted the relevance of VEGFR-2 for vascular development.[Villefranc et al., 2013] VEGFR-2 kinase inhibitor therapy at the one-cell stage totally suppresses axial and ISV formation, but administration at the 24-hour stage inhibits just the ISV. This temporal sequence is consistent with vasculogenesis forming the axial arteries first and angiogenesis forming the ISV later. Significantly, activated Akt may partially repair the VEGFR-2 vascular phenotype, suggesting that kinase inhibitor-treated embryos are effective models for studying blood vessel development signal transduction pathways.[Thuy L. Phung et al., 2006]

Hesperetin is an important compound that comes from the hydrolysis of hesperdin (hesperetin 7-rhammnoglucoside) and belongs to the flavanones class of flavonoids. It demonstrates a diverse range of biological activities that contribute to human health protection. [Bai X *et al.,* 2017].It contains anti-oxidant and free-radical scavenging [Kim JY et al., 2004] , blood-lipid-lowering [Kim HK et al., 2003], and anti-carcinogenic properties [Kopustinskiene et al., 2020]. In laboratory animals, hesperetin has been demonstrated to suppress chemically induced breast ,urinary bladder and colon carcinogenesis. It's also used to treat haemorrhoids and prevent post-operative thromboembolism [Maiti, K et al., 2009].

A method of structure prediction based on amino acid sequence similarity to closely related known structures is known as homology or comparative modelling of a protein [Dmitrii M et al., 2018]. Due to time constraints and other technological limitations, millions of sequences were discovered during genome-wide sequencing studies that could not be studied using X-ray crystallography and NMR spectroscopy techniques [Powers R 2009]. Researchers employ bioinformatics to model unknown protein structures because of these challenges .These methods aid in the identification of active sites, the development of ligands and mutants, the prediction of antigenic epitopes, and the determination of protein activities .The purpose of this research is to apply homology modelling to predict the three-dimensional (3D) structure of VGFR2.This protein could be a potential target for anticancer drug development.

Materials and Methods

Protein structure Modelling:

The protein sequence of VGFR2_DANRE was obtained from the uniport database with the accession number Q5GIT4 which is the major protein involved in the mechanism of a biological pathway of major cancers.The template structures was retrieved from the protein Databank was used for the study to model the protein. The sequence of VGFR2_DANRE was modelled using Phyre2 webserver[Achintya Mohan Goswami, 2015].The modelled protein was verified using SAVS server. [Satyanarayana, S et al., 2018].

Ligand Preparation:

The Compound hesperetin was obtained from Pubchem database (https://pubchem.ncbi.nlm.nih.gov/) and was downloaded in the 3D-SDF format. [Saikia A et al., 2021]

Molecular docking:

The protein-ligand binding mechanism of the VGFR2 and hesperetin complexes was performed using Autodock 4.0(Forli et al., 2016).

A semi-flexible docking method was used for the docking analyses. Proteins were kept rigid and ligands were kept flexible in this work. The number of degrees of freedom permitted for ligand molecules is ten. AutoDock specifies the steps for converting molecules to pdbqt format, box type, grid box creation, and so on.The grid box was designed with the active site in the centre of the protein molecule. To obtain the best results, an exhaustivity of 100 was employed, which necessitated more processing power and time for the analysis. However, greater exhaustiveness produces better results. The least energy docking poses were examined utilising the pymol.

Results and Discussion

Sequence Retrieval and modelling:

The sequence length of 1357 amino acids of VGFR2_DANRE was retrieved from Uniprot(Table 1) and The 3Dimensional structure of the protein VGFR2 was modelled by Phyre2 which generated a full-length model of the protein shownin the cartoon representation of the VGFR2 protein Figure 1. With the help of the Ramachandran plot, the Savs is used to examine the stereochemical stability of the modelled protein, which demonstrates that 90% of the amino acids are in the preferred region.

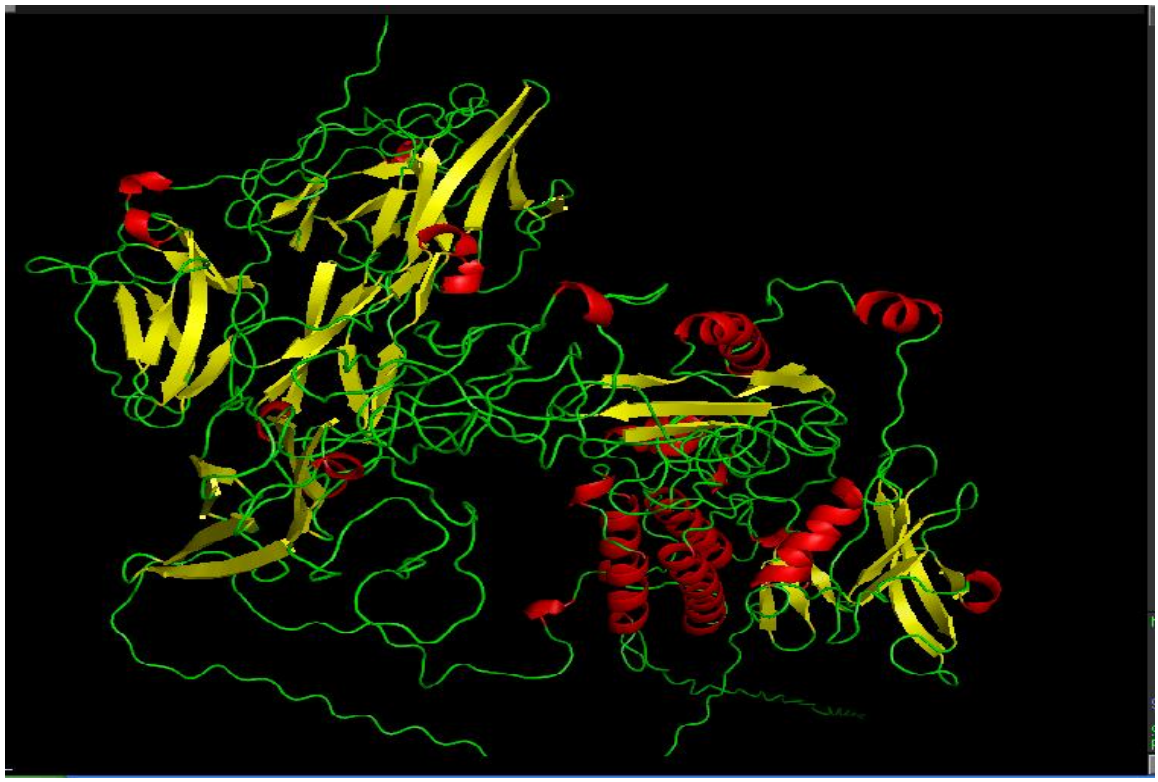
Table1:Amino acid sequence of VGFR2_DANRE from Uniprot

>sp|Q5GIT4|VGFR2_DANRE Vascular endothelial growth factor receptor 2 OS=Daniorerio OX=7955 GN=kdr PE=1 SV=2

MAKTSYALLLLDILLTFNVAKAIELRFVPDPPTLNITEKTIKINASDTLQITCRGRQILE

WSTPHNRTSSETRLTISDCSGDGLFCSTLTLSKAVANETGEYRCFYKSLPKEDGKTSVAVYVFIQDY
RTPFVRIAQDYDVVFIREGEQVVIPCLVSVEDLNVTLYTKYPVKELSTDGKEVIWDSRRGFILPSRV
VSYAGVVYCQTTIRNETFQSSPYIVAVVGYKIYDLTLSPQHERLTVGERLILNCTAHTELNVGIDFQ
WTFPHEKRSVNGSMSTSRYKTSSNKKKLWNSLELSNTLTVENVTLNDTGEYICTASSGQMQKIAQ
ASLIVYEKPFIALSDQLWQTVEAKAGDAEAKILVKYYAYPEPAVRWYKNDQLIVLRDEYRMKFYR
GVHLTIYGVTEKDAGNYTVVMTNKITKEEQRRTFQLVVNDLPRIFEKDVSLDRDVHMYGSSPTLT
CTASGGSSPVTIKWQWMPREDCPVRFLPKSDTRMAKCDKWREMSNNTGKNPLISQTSVDERTLKT
ISTLKIQKAVDHALYRCIATNKMGQDQRVIVFQVTRFLNLSVLPSSSPIEGQDVIMRCVADRLLYYN
LRWYRVANVANHDPPPAAVPCDTLTLSHLHQPNVTVSGLQGTNVTLDMPIPNATMMDQGLYACQ
VEIVGTNEKTCLLHNLRLRALEMSRIVTNLTDQRVNVSDSTTLVCEVSGTPTPTIVWTKDNQTVME
GSGVILKRSNRVLTIQRVKKEDSGLYICTACNQQGCESSEARISVDGAEEKMNVELIMPIGAVVIAM
FLWLLIVFVIRNRKRPNDGDLKTGYLSIILDSDDMPMDEHCERLTYDASKWEFPRDRLKLGEPLGR
GAFGQVVEATAYGIEKATTCTTVAVKMLKEGATSSEYRALMSELKILIHIGHHLNVVNLLGACTK
QGGPLMVIVEYCKHGNLSSYLKSKRGEYSPYKKRTPRMPNRREVQQDEDPREGDLGLGTSTRLDI
CTGTAVCTRTGEQTYKTLQDEQESSDWDHLTMEDLISYSFQVAKGMEFLASRKCIHRDLAARNILL
SENSVVKICDFGLARDVYKDPDYVRKGDARLPLKWMAPETIFDRVYTTQSDVWSFGVLLWEIFSL
GASPYPGVCIDESFCRRLKEGTRMRAPDYATPEIYQTMLDCWLDRPLDRPTFTQLVEHLGNLLQAS
AQQDGKDYIPLTNGEMEEELVAPHLNVTSKRSFYAGNTEAQLHYDNAPPLGFPQQMNSSGVPVN
MTGFVDIPLEHTTVMDGHVDCGVGLSREQMKALDRQAQRPLNFSPLLRCKSKESLASESSNQTSG
YQSGYHSDDAEAPIYANEEMILKRDIRKKPPLPKRNDKFSAEVRYSAPPV

Figure 1: Modelled protein of VGFR2 using phyre2



Molecular Docking Analysis:

The Autodock software was used to do the molecular docking. Figure 2 show the autogrid generation of the modelled protein. the docking of the lead compound hesperetin had the binding energy (-4.61 kcal mol-1) with VGFR2 Figure 3.

Figure2: Autogrid generation of the modeled Protein

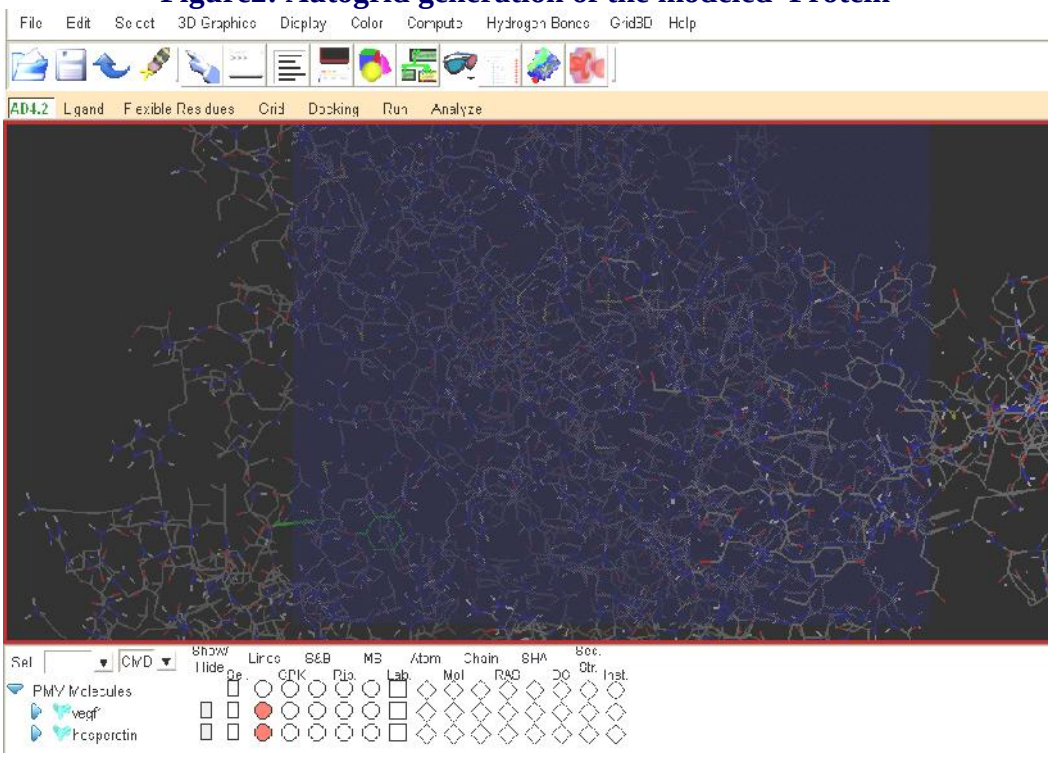
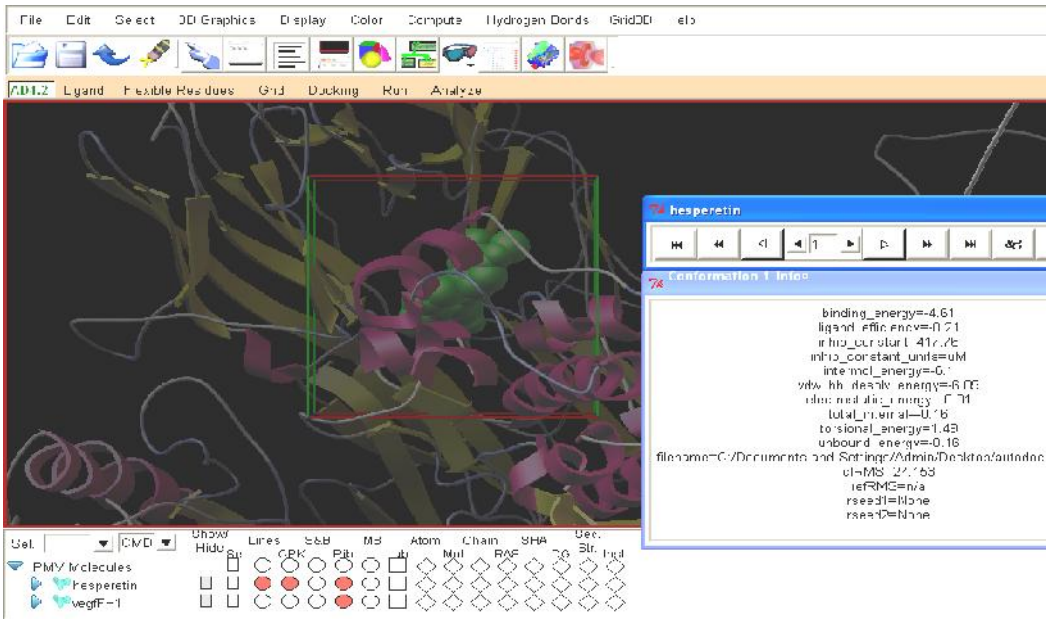


Figure3: Molecular docking of the Hesperetin with VGFR2



Conclusion

The molecular docking research of hesperetin with the modelled protein VGFR2 demonstrated that hesperetin has a good contact in a favourable pose with the protein, which is explained by the lowest binding energy with the active site of the hesperetin molecule. Thus, hesperetin can be employed as a lead molecule for its apoptotic effect in cancer cells, and this in-silico study can be immediately paired with expedited scientific investigation to reveal the importance of naturally occurring molecules working against this fatal disease.

Conflict of interest:

The authors declare they have no competing interests.

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References

Achintya Mohan Goswami, 2015. Structural modeling and in silico analysis of non-synonymous single nucleotide polymorphisms of human 3β-hydroxysteroid dehydrogenase type 2.Meta Gene.Volume 5, Pages 162-172.

Alexandra Giatromanolaki, StamatiaKotsiou,Michael I. Koukourakis, and Efthimios Sivridis .2007. Angiogenic Factor Expression in Hepatic Cirrhosis. Mediators of Inflammation.1-4.

Bai, X., Yang, P., Zhou, Q., Cai, B., Buist-Homan, M., Cheng, H., Jiang, J., Shen, D., Li, L., Luo, X., Faber, K. N., Moshage, H., & Shi, G. 2017. The protective effect of the natural compound hesperetin against fulminant hepatitis in vivo and in vitro. *British journal of pharmacology*, *174*(1), 41–56.

Dixelius J, Makinen T, Wirzenius M, Karkkainen MJ, Wernstedt C, Alitalo K, Claesson-Welsh L. 2003.Ligand-induced vascular endothelial growth factor receptor-3 (VEGFR-3) heterodimerization with VEGFR-2 in primary lymphatic

endothelial cells regulates tyrosine phosphorylation sites. J Biol Chem. Oct 17;278(42):40973-9.

Dmitrii M. Nikolaev, Andrey A. Shtyrov, Maxim S. Panov, Adeel Jamal, Oleg B. Chakchir, Vladimir A. Kochemirovsky, Massimo Olivucci, and Mikhail N. Ryazantsev.2018. A Comparative Study of Modern Homology Modeling Algorithms for Rhodopsin Structure Prediction.ACS Omega , 3, 7, 7555–7566

Forli S, Huey R, Pique ME, Sanner MF, Goodsell DS, Olson AJ. Computational protein-ligand docking and virtual drug screening with the AutoDock suite. Nat Protoc. 2016 May;11(5):905-19.

Guo, S., Colbert, L. S., Fuller, M., Zhang, Y., & Gonzalez-Perez, R. R. 2010. Vascular endothelial growth factor receptor-2 in breast cancer. *Biochimicaetbiophysicaacta*, *1806* (1), 108–121.

Holmes, D. I., & Zachary, I. 2005. The vascular endothelial growth factor (VEGF) family: angiogenic factors in health and disease. *Genome biology*, *6*(2), 209.

Kim HK, Jeong TS, Lee MK, Park YB, Choi MS. Lipid-lowering efficacy of hesperetin metabolites in high-cholesterol fed rats. ClinChimActa. 2003 Jan; 327(1-2):129-37..

Kim JY, Jung KJ, Choi JS, Chung HY. 2004. Hesperetin: a potent antioxidant against peroxynitrite. Free Radic Res. Jul; 38(7):761-9..

Koch, S., &Claesson-Welsh, L. 2012. Signal transduction by vascular endothelial growth factor receptors. *Cold Spring Harbor perspectives in medicine*, *2*(7), a006502.

Kopustinskiene, D. M., Jakstas, V., Savickas, A., &Bernatoniene, J. (2020). Flavonoids as Anticancer Agents. *Nutrients*, *12*(2), 457.

Maiti, K., Mukherjee, K., Murugan, V., Saha, B. P., & Mukherjee, P. K. (2009). Exploring the effect of Hesperetin-HSPC complex--a novel drug delivery system on the in vitro release, therapeutic efficacy and pharmacokinetics. *AAPS PharmSciTech*, *10*(3), 943–950.

Powers R. (2009). Advances in Nuclear Magnetic Resonance for Drug Discovery. *Expert opinion on drug discovery*, *4*(10), 1077–1098.

Saikia A, Palherkar DA, Hiremath L. 2021.In silico analysis and structural prediction of a hypothetical protein from Leishmania major. Biomed Biotechnol Res J;5:320-6

Satyanarayana, S., Krishna, M., Pavan Kumar, P., &Jeereddy, S. (2018). *In silico* structural homology modeling of nifA protein of rhizobial strains in selective legume plants. *Journal, genetic engineering & biotechnology*, *16*(2), 731–737.

Shibuya M. 2011. Vascular Endothelial Growth Factor (VEGF) and Its Receptor (VEGFR) Signaling in Angiogenesis: A Crucial Target for Anti- and Pro-Angiogenic Therapies. *Genes & cancer*, *2*(12), 1097–1105.

Thuy L. Phung, KerenZiv, DonnetteDabydeen, GodfredEyiah-Mensah, Marcela Riveros, Carole Perruzzi, Jingfang Sun, Rita A. Monahan-Earley, Ichiro Shiojima, Janice A. Nagy, Michelle I. Lin, Kenneth Walsh, Ann M. Dvorak, David M. Briscoe, Michal Neeman, William C. Sessa, Harold F. Dvorak, Laura E. Benjamin. 2006.Pathological angiogenesis is induced by sustained Akt signaling and inhibited by rapamycin,Cancer Cell.Volume 10, Issue 2, 159-170,

Villefranc, J. A., Nicoli, S., Bentley, K., Jeltsch, M., Zarkada, G., Moore, J. C., Gerhardt, H., Alitalo, K., & Lawson, N. D. 2013. A truncation allele in vascular endothelial growth factor c reveals distinct modes of signaling during lymphatic and vascular development. Development (Cambridge, England), 140(7), 1497–1506.

Wilcox, Lisa &Borradaile, Nica& Huff, Murray. (2006). Antiatherogenic Properties of Naringenin, a Citrus Flavonoid. Cardiovascular Drug Reviews.

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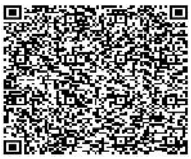	Website: www.ijarbs.com
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