Anti-angiogenic potential of bioactive phytochemicals from Rosa Damascena targeting VEGFR2 and related protein to fight cancer through molecular docking

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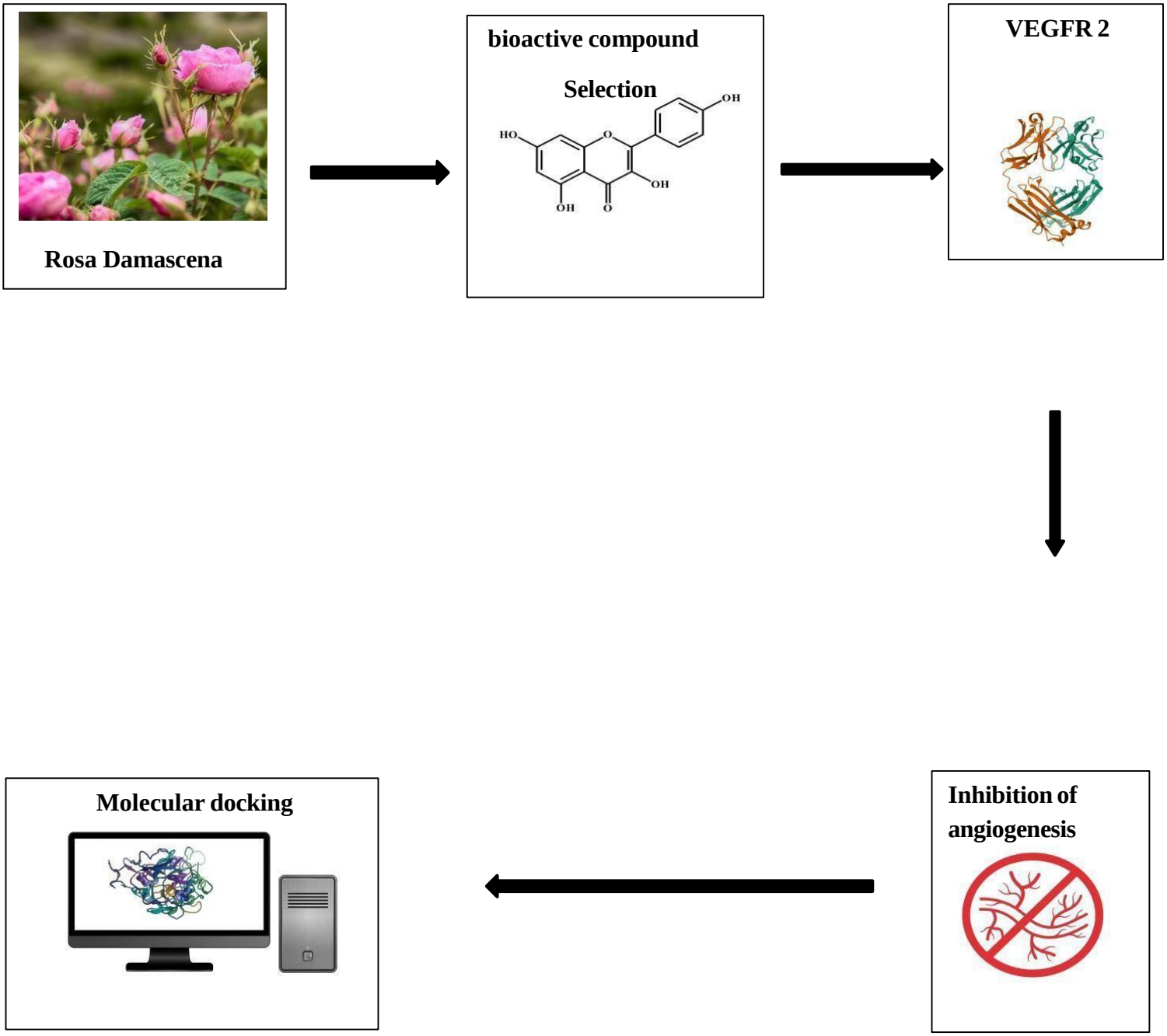
Abstract

Angiogenesis, the process of forming new blood vessels, plays an important role in various physiological and pathological conditions. Cancer is regarded as a major cause of death due to its high morbidity and mortality rate. As a result, development for cancer treatment is required. One important component of anti-angiogenic therapy, a novel and potential cancer treatment, is the vascular endothelial growth factor receptor-2 (VEGFR-2). The present study uses molecular docking experiments on VEGFR2, FGFR1, EGFR, PI3K and other angiogenic receptors to investigate the anti-angiogenic action of bioactive phytochemicals of Rosa Damascena. Quercetin, ellagic acid, and kaempferol were shown to have the highest binding affinity among the bioactive substances examined for anti-angiogenic action. The compounds were downloaded in SDF format from PubChem Database (https://pubchem.ncbi.nlm.nih.gov/).The tools used to carry out this investigation are PyRx Tool and Biovia Discovery Studio (Biovia, D.S. (2019). Discovery Studio Visualizer, San Diego: Dassault Systèmes). These findings indicate that specific phytochemicals from Rosa damascena might be good candidates for anti-angiogenic cancer therapy for further experimental evaluation.

Keywords: - Angiogenesis, Rosa damascena, Docking study, Binding affinities, receptors, Ligands.



Introduction

The process of creating new blood vessels from pre-existing vasculature is known as angiogenesis, and it plays a crucial role in a number of physiological processes, including wound healing, growth, and the function of female reproductive organs. Furthermore, impaired angiogenesis contributes to diseases like neurodegeneration, hypertension, osteoporosis, respiratory disfunction, and ovarian hyperstimulation syndrome, while disruption of the mechanisms of physiological angiogenesis plays a part in the pathogenesis of some diseases like cancer, psoriasis, asthma, and atherosclerosis. With approximately 9.6 million deaths reported in 2018, cancer is the second leading cause of death globally.[1]

Judah Folkman proposed that it is a complicated illness marked by the aberrant growth and dissemination of cancerous cells into neighboring tissues.[2] Since many angiogenesis-related proteins are essential for the development, spread, and advancement of malignancies, overexpression of these proteins is common in many types of cancer. Numerous targets for therapeutic intervention are provided by the angiogenic system's complexity. New molecular targets that are overexpressed in cancer have been found thanks to recent developments in molecular angiogenesis. As a key regulator of angiogenesis, vascular endothelial growth factor receptor-2 (VEGFR-2) is often targeted in the development of anti-angiogenic drugs to combat cancer.[3] Tumor angiogenesis is known to be triggered by the phosphorylation of VEGFR2.[4] Fibroblast growth factor receptors (FGFR1) control angiogenesis, cell proliferation, and differentiation.[5] Tie2 is essential for the development of vascular networks, and its receptors control angiogenesis, vessel maturation, and platelet formation. Many diseases are treated with medicinal herbs. They are thought to be rich sources of traditional remedies, and many contemporary medications are made from these plants. Rosa damascena is commonly known as Damask rose. It is an ornamental and a precious herb with modern pharmacological importance, which are widely used in medicines.

It is famous not only because of its medicinal or pharmacological effects but also for its cultural and religious significance.

Rosa damascena was originated from Iran. So that it is labelled as “Gol-E-Muhammadi” (the flower of Prophet ‘Mohammad’) by the people of Iran because its fragrance reminds them of the Prophet Muhammad.

Rosa damascena is just about 1–2 m in height and life span up to 50 years. This plant is used in treating erectile dysfunction, cardiovascular disorders and respiratory tract infections.

It has anti-inflammatory, antibacterial, anti-cancer and anti-HIV activity.[67] The drug is used against all types of hepatitis and jaundice. It is used as a cosmetic agent, deodorant and disinfectant, and is useful in renal disorders and osteoarthritis. This plant has several pharmacological properties including antioxidant, astringent, antimicrobial and analgesic.[8] This plant is used for the treatment of menstrual bleeding, abdominal pain, chest infection and as laxative agent in constipation.

Excellent results have been obtained while investigating the effects of synthetic and natural

anticancer drugs employing existing tumour cell lines. Numerous natural compounds derived from plants are being considered as alternatives to existing treatments for a variety of cancers due to their lower toxicity.[9]

Various bioactive phytochemicals of Rosa damascena were screened virtually to evaluate their anti-angiogenic potentials targeting VEGFR2, FGFR1, EGFR and PI3K. The study unveiled six potential candidates such as, quercetin, kaempferol, ellagic acid, luteolin, rutin and chlorogenic acid.

These chemical constituents present in rosa damascene namely quercetin, kaempferol, ellagic acid, luteolin, rutin and chlorogenic acid have a strong anticancer activity.

Molecular docking is a computational simulation that predicts interactions between two structures, such as between two proteins or between a protein and a ligand (drug or molecule).[10] In silico models such as molecular docking are gaining popularity in both academic and industrial settings.[11] In order to comprehend their inhibition on cancer-causing proteins, the current work focuses on docking investigations. In conclusion, the aim of these studies was to assess the antiangiogenic properties of selected phytochemicals from Rosa Damascena through the process of molecular docking, compared to the target protein angio-genesis

Materials and Methods

For the purpose of carrying out the present research work, various biological databases like PubChem and Protein Data Bank (PDB) have been used.

The Protein Data Bank is a worldwide data bank that stores three-dimensional structural information on biological macromolecules.[12,13]

This data bank was initially developed at Brookhaven National Laboratory (BNL) in 1971. This data bank stores structural information that has been experimentally determined through X-ray crystallography and NMR spectroscopy. This information is crucial in carrying out computational work. Apart from data bases, other tools that have been used in the present work include molecular modelling tools and docking tools like PyRx and Discovery Studio. These tools have user-friendly interfaces that help in carrying out various tasks. These tools also help in predicting ligand interactions with proteins.

Molecular docking is an efficient computational method that is used in identifying potential drug targets.[14] This method is also used in the screening of biologically active compounds.[15] This method is significant in drug development, as it is used in predicting ligand-receptor interactions.[16] It also plays a significant role in drug discovery, as it helps in predicting how a drug will bind to a receptor and how well it will bind.[17] This helps in the virtual screening of compounds and identifying compounds that have high binding potential.

Preparation of Protein Macromolecule

The three-dimensional structural image of the VEGFR2 macromolecule was obtained from the Protein Data Bank (https://www.rcsb.org/). The PDB is a comprehensive and public database that stores experimentally determined three-dimensional protein structures. The structural information for the protein was derived from an X-ray diffraction experiment, and the resolution is provided. Unnecessary elements, including water, and hetero atoms were removed from the PDB file using BIOVIA Discovery Studio Visualizer.

Preparation of ligand

Various biochemical constituents present in the rosa damascena. It involves 3 stages in the docking process. Confirmational analysis of ligand, placement and scoring. Then six compounds which have the best docking scores were selected for further analysis, conformers for biochemical constituents were obtained in the structure data format (SDF) from PubChem (https://pubchem.ncbi.nlm.nih.gov/).

All the SDF files were opened in discovery studio (Biovia, D.S. (2019). Discovery Studio

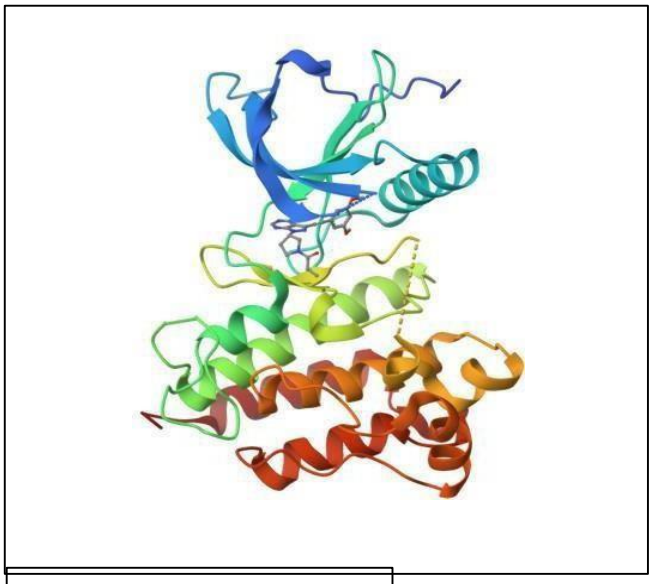
Visualizer, San Diego: Dassault Systèmes.). The docking analysis of Quercetin, Kaempferol, Rutin, ellagic acid, Luteolin and Chlorogenic acid against VEGFR2, EGFR, FGFR1 and PI3K for anti-cancer activity was carried out by PyRx lab docking software. Docking is a method which predicts the preferred orientation of one molecule to a second when a ligand and a target are bound to each other to form a stable complex. Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules. Exhaustiveness value and docking evaluation processes were associated to verify correctness and reliability of results.

Protein ligand interaction

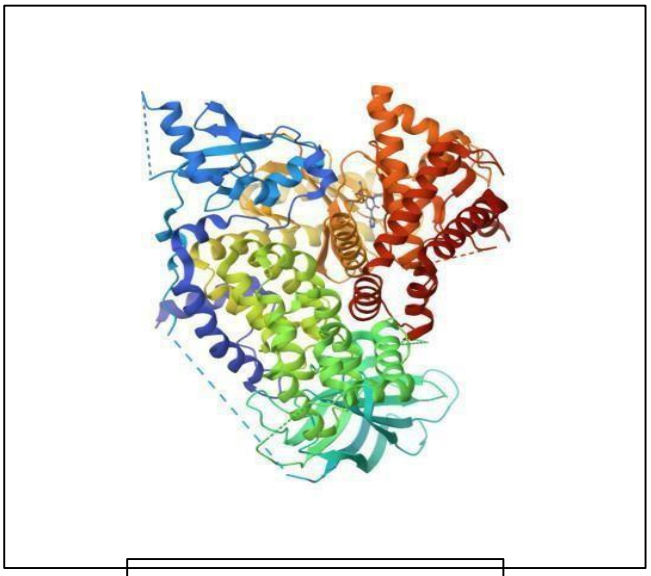
The PyRx is virtual screening software for computational drug discovery which enables users

to dock compounds against drug targets (protein Receptor).[18]

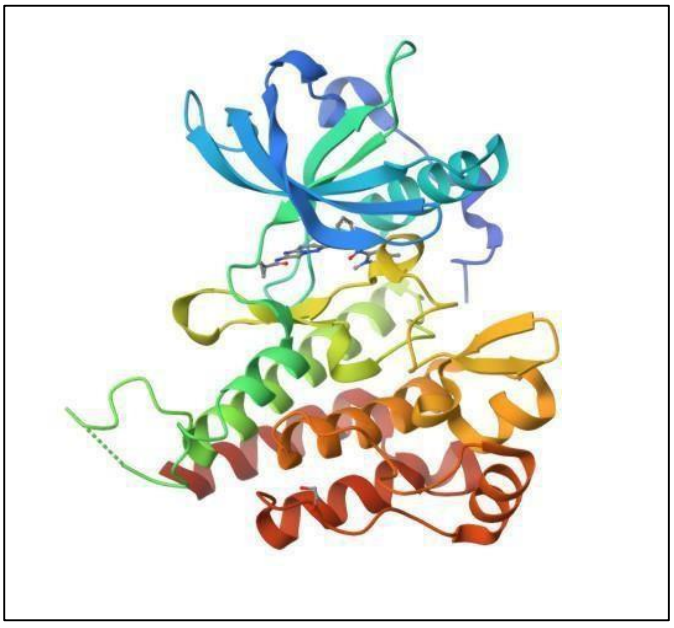
STRUCTURES OF PROTEIN



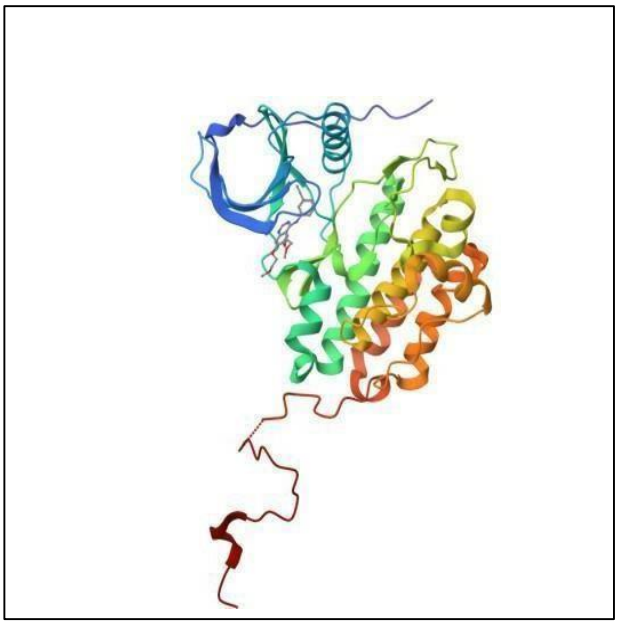
FGFR1



PI3K

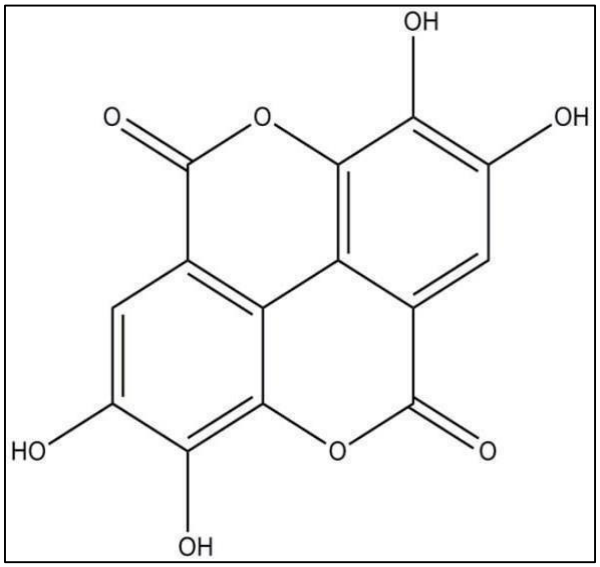


VEGFR2

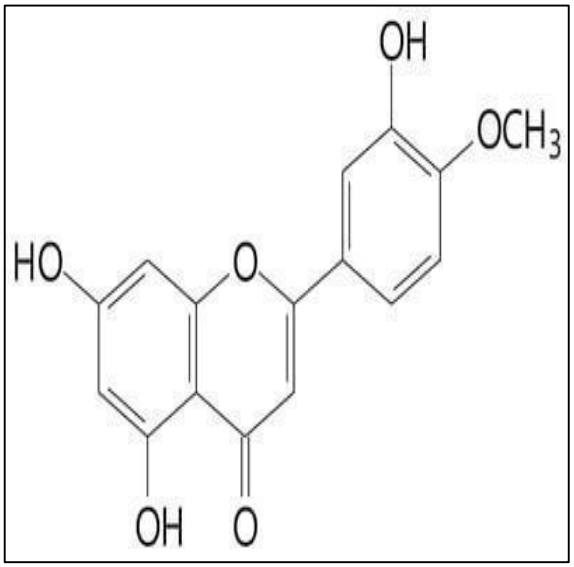


EGFR

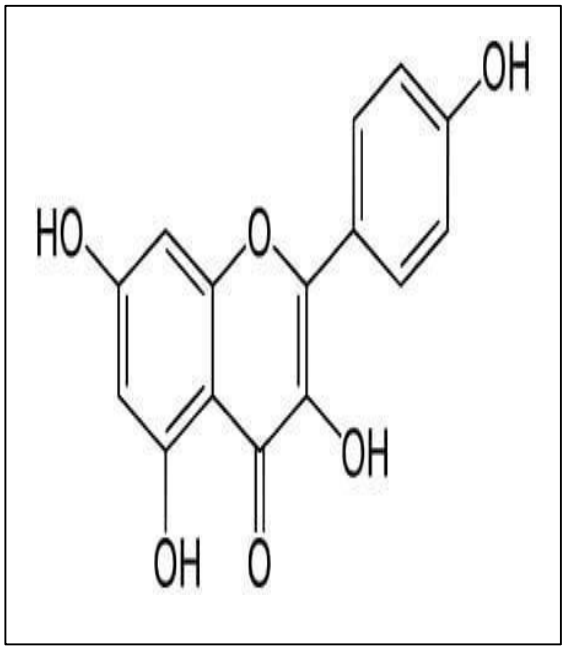
Structures of best selected ligands molecules: -



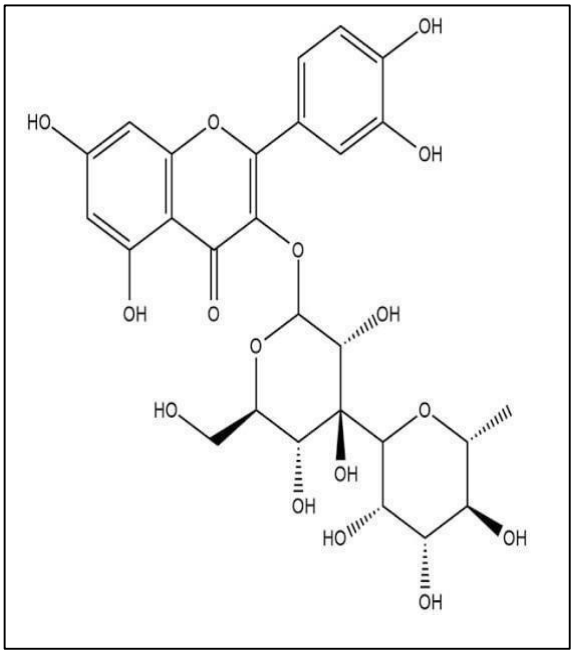
ELLAGIC ACID



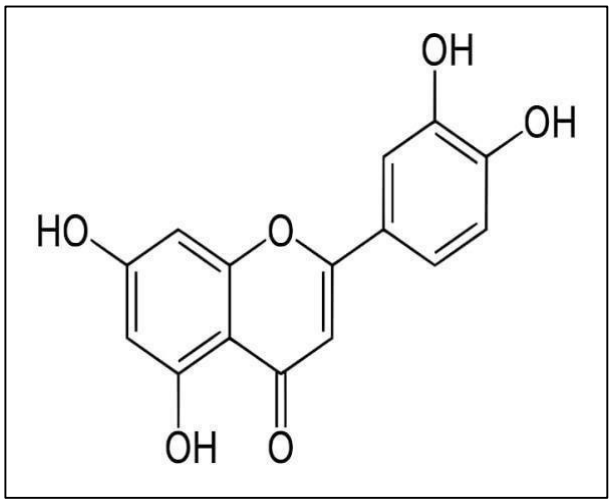
QUERCETIN



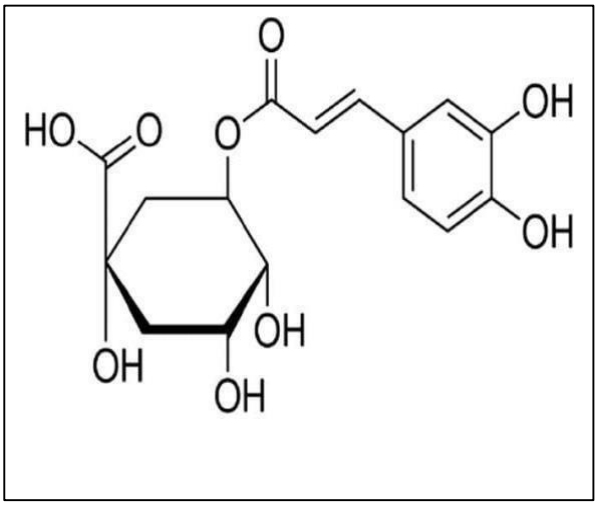
KAEMPFEROL



RUTIN



LUTEOLIN



CHLOROGENIC ACID

Result: -

Analysis and visualization of docking studies

The binding energy of the protein–ligand complexes and the analysis of docking results were evaluated using molecular docking studies and Discovery Studio Visualizer v16.1.0.15350. After completion of the docking process, Quercetin exhibited a strong binding affinity of −10.2 kcal/mol with 3VO3 (VEGFR2) among all the selected receptor proteins. The binding affinities of Quercetin with 6MZQ(FGFR1),1M17 (EGFR) and 4FA6(PI3K) were found to be −9.1, -8.5 and −8.5 kcal/mol, respectively, calculated using Auto Dock Vina on the PyRx platform.

Kaempferol showed the highest binding affinity of −10.2 kcal/mol with 3V03(VEGFR2) protein, followed by slightly lower affinities with 6MZQ(FGFR1),1M17(EGFR) and 4FA6(PI3K), recorded as −8.7, −8.3 and −8.1
kcal/mol, respectively.

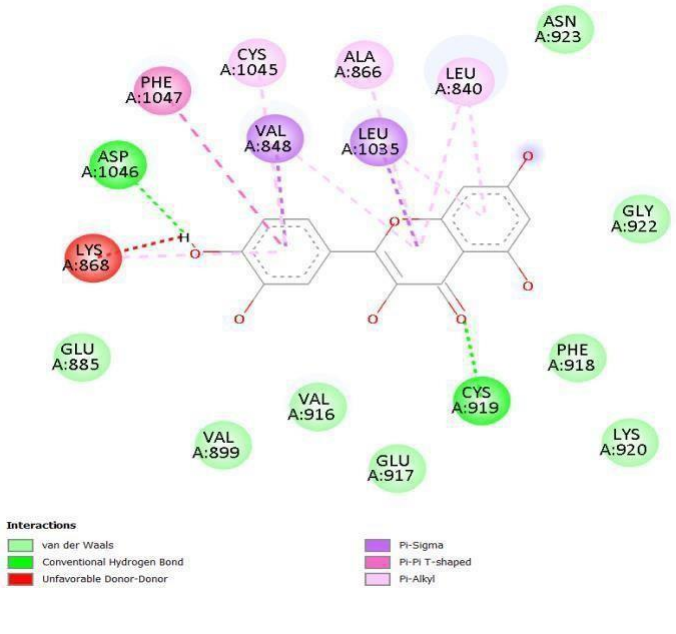
Rutin demonstrated its best binding affinity of −9.6 kcal/mol with 4FA6(PI3K), while its affinities with 3VO3 (VEGFR2),1M17(EGFR) and 6MZQ(FGFR1) were −9.4, −9.1 and −9.4 kcal/mol, respectively.

Ellagic acid showed comparatively lower binding affinities with 6MZQ (FGFR1), 3VO3 (VEGFR2),4FA6(PI3K) and 1M17 (EGFR), recorded as −5.3,
−6.2, − 6.5 and −5.7 kcal/mol respectively. Luteolin exhibited its highest binding affinity of −10.3 kcal/mol with 3VO3 (VEGFR2), while its interactions with 1M17 (EGFR), 6MZQ (FGFR1), and 4FA6(PI3K) were −8.4, −9.3, and −8.5

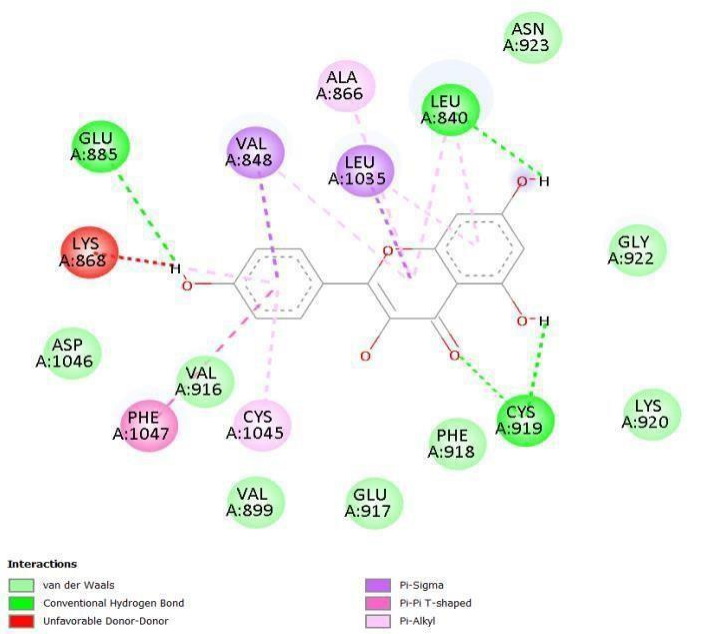
kcal/mol, respectively.

The compound Chlorogenic acid showed binding affinities of −8.2 kcal/mol with 3VO3 (VEGFR), −7.5 kcal/mol with 6MZQ(FGFR1), −6.6 kcal/mol with 1M17 (EGFR), and −7.2 kcal/mol with 4FA6(PI3K). Free energy plays a crucial role in determining the interaction strength between binding partners. Positive free energy values indicate non-spontaneous interactions requiring energy input, whereas negative values suggest spontaneous binding. In this study, all obtained values were negative, indicating that the ligand–protein interactions occur spontaneously.

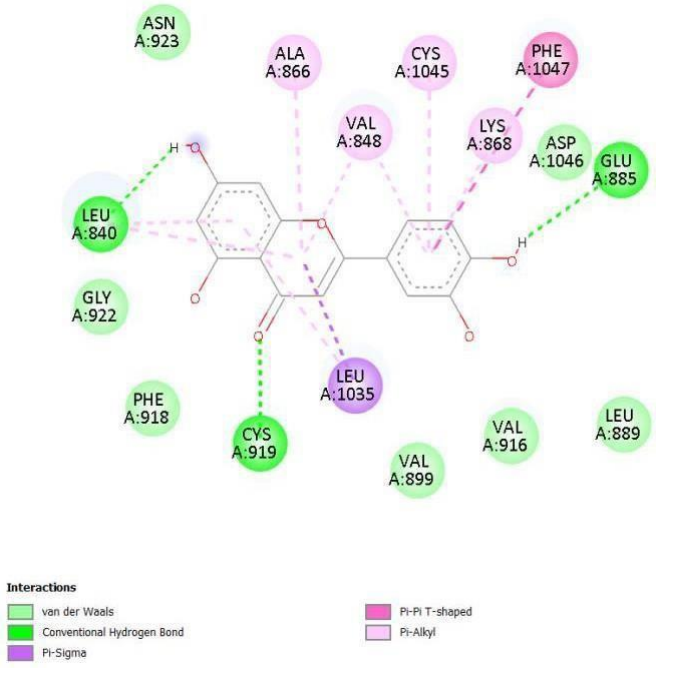
The consistently negative binding energy values obtained in this study suggest energetically favorable ligand–protein interactions, indicating a strong tendency for spontaneous binding.[19] By targeting key receptors such as VEGFR2, FGFR1, PI3K and EGFR, these phytochemicals may disrupt essential processes involved in angiogenesis, including endothelial cell proliferation, migration, and formation of new blood vessels.[20] Consequently, this may lead to inhibition of tumor growth and metastatic spread. These findings align with earlier reports demonstrating that flavonoids like Quercetin and Kaempferol can suppress angiogenesis by modulating VEGF signaling pathways. The Quercetin and luteolin is the most stable interactions with VEGFR 2 receptor to shows strong inhibitory potential.



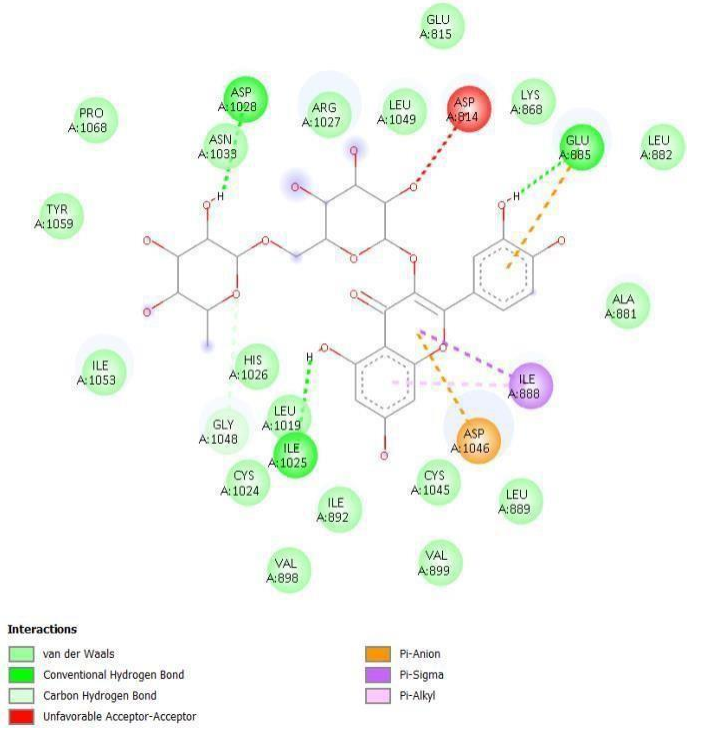
Molecular interaction of Quercetin with 3VO3 (VEGFR2) protein



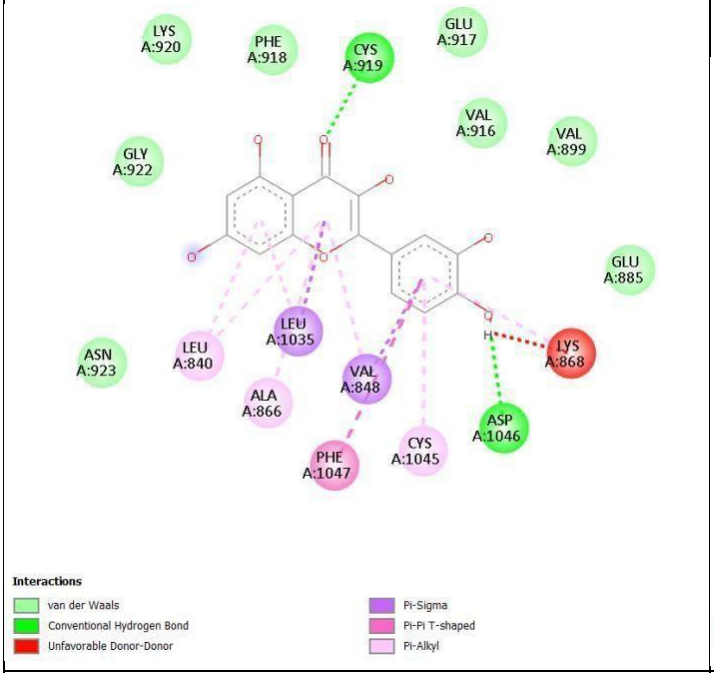
Molecular interaction of kaempferol with 3VO3 (VEGFR2) protein



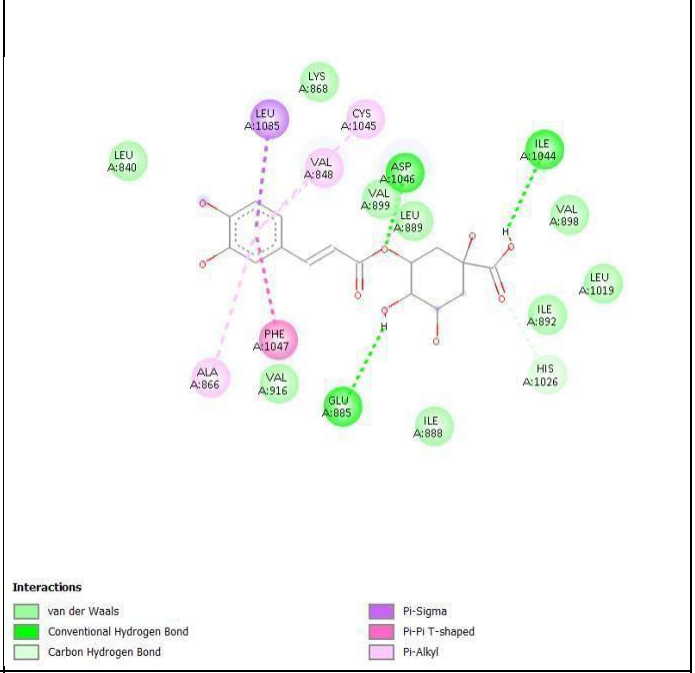
Molecular interaction of Luteolin with 3VO3 (VEGFR2) protein



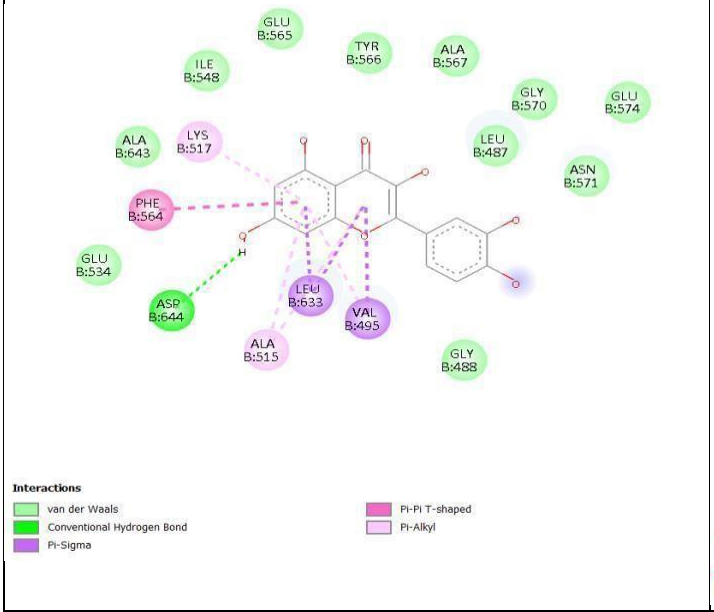
Molecular interaction of rutin with 3VO3 (VEGFR2) protein



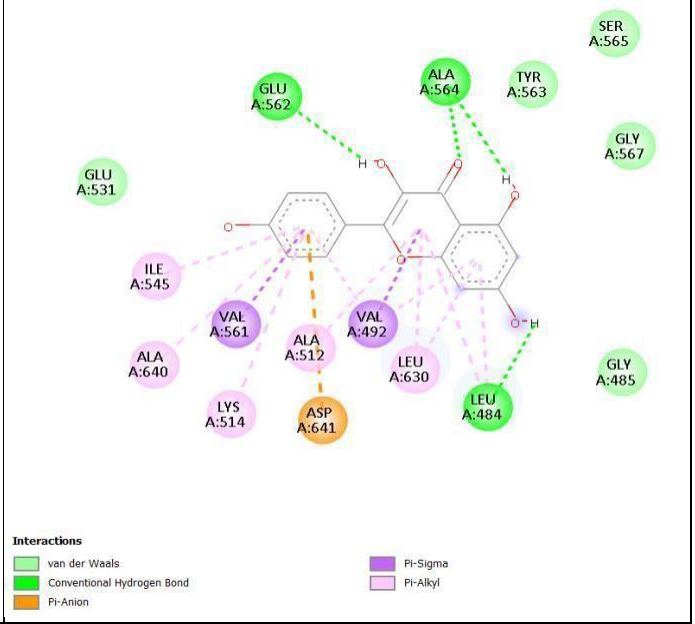
Molecular interaction of ellagic acid with 3VO3 (VEGFR2) protein



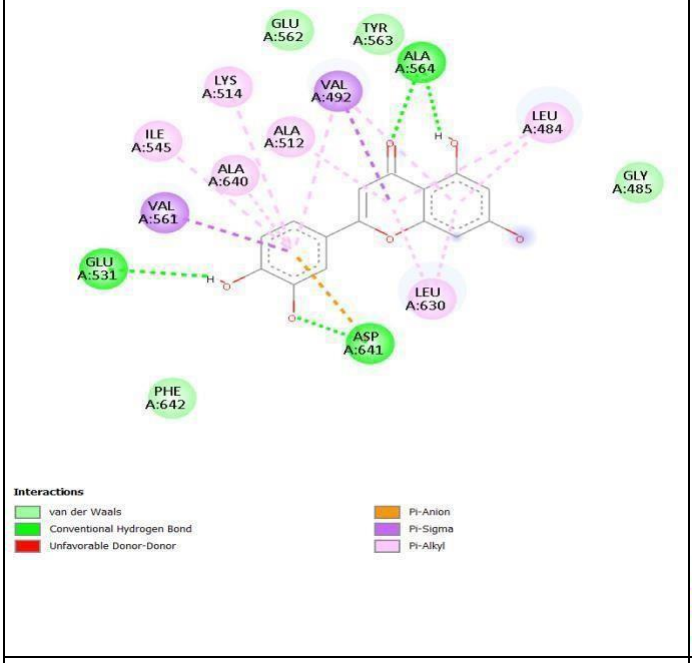
Molecular interaction of chlorogenic acid with 3VO3 (VEGFR2) protein



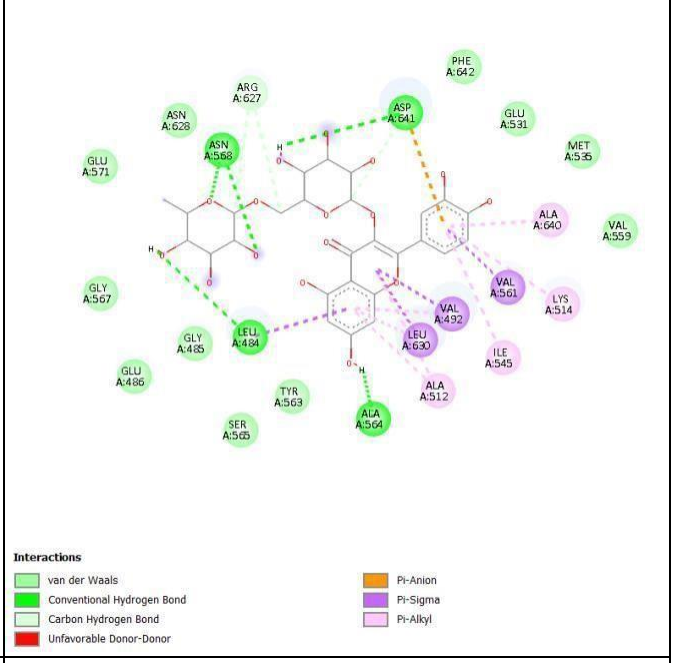
Molecular interaction of quercetin with 6MZQ (FGFR1) protein



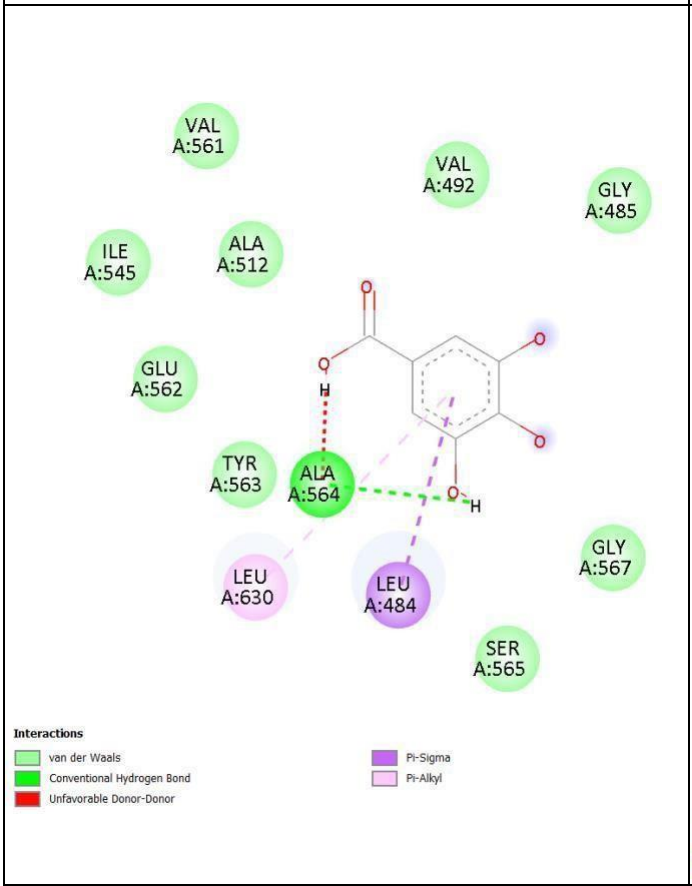
Molecular interaction of Kaempferol with 6MZQ (FGFR1) protein



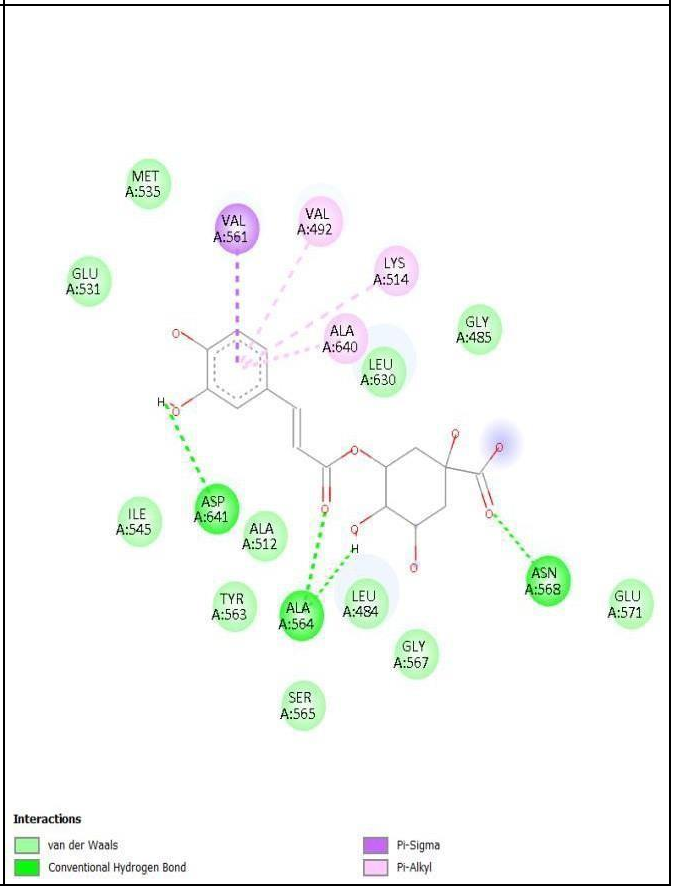
Molecular interaction of Luteolin with 6MZQ (FGFR1) protein



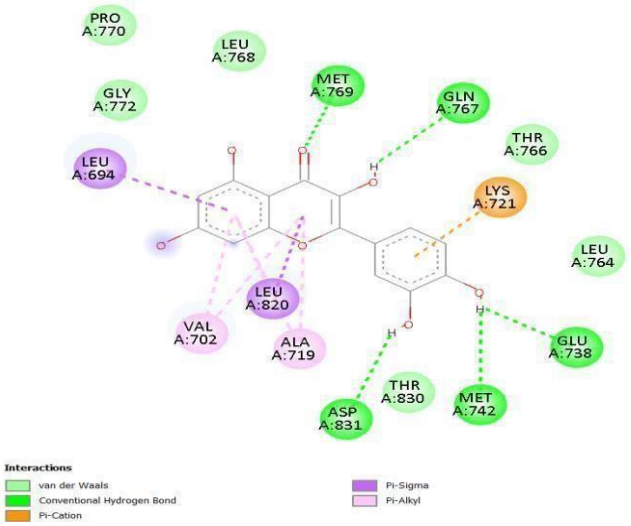
Molecular interaction of Rutin with 6MZQ (FGFR1) protein

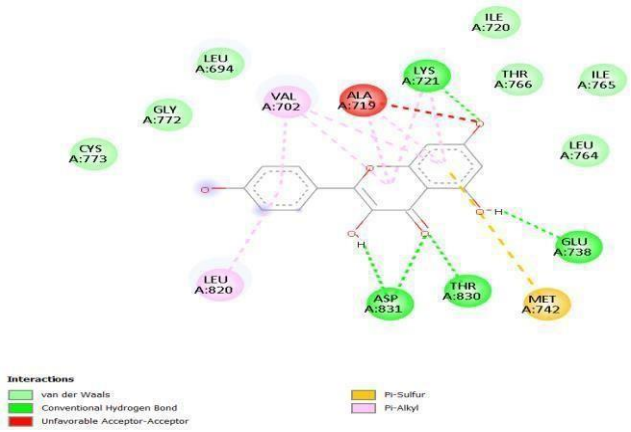


Molecular interaction of Ellagic acid with 6MZQ (FGFR1) Protein (FGFR1) protein



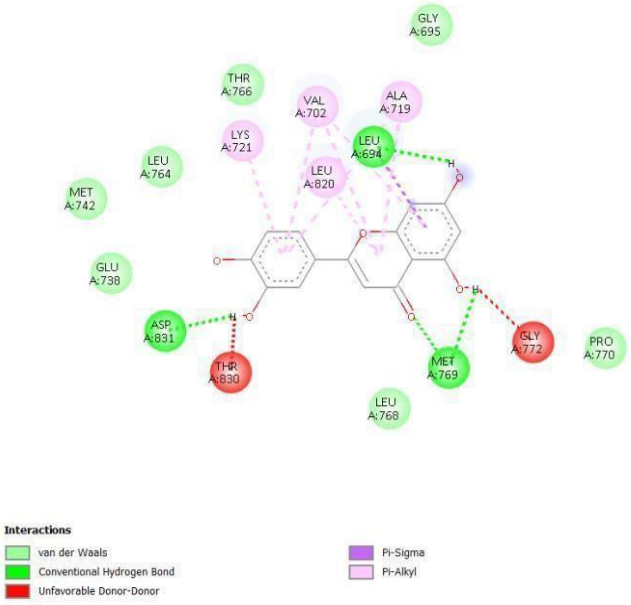
Molecular interaction of Chlorogenic acid with 6MZQ

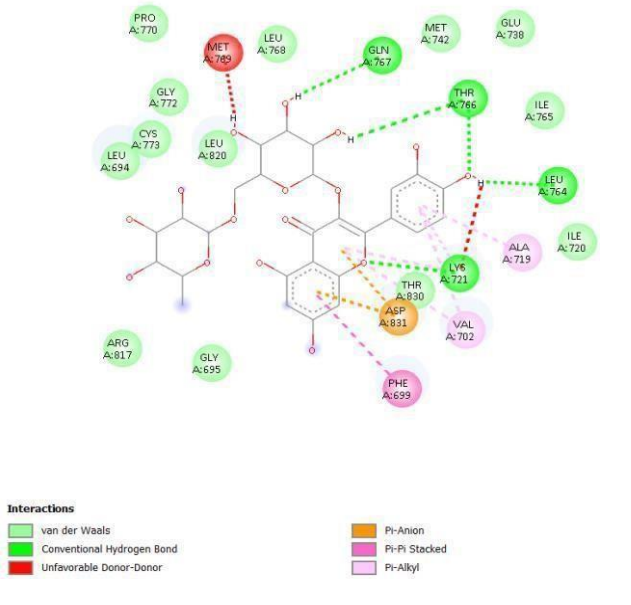




Molecular interaction of quercetin with 1M17(EGFR) Protein

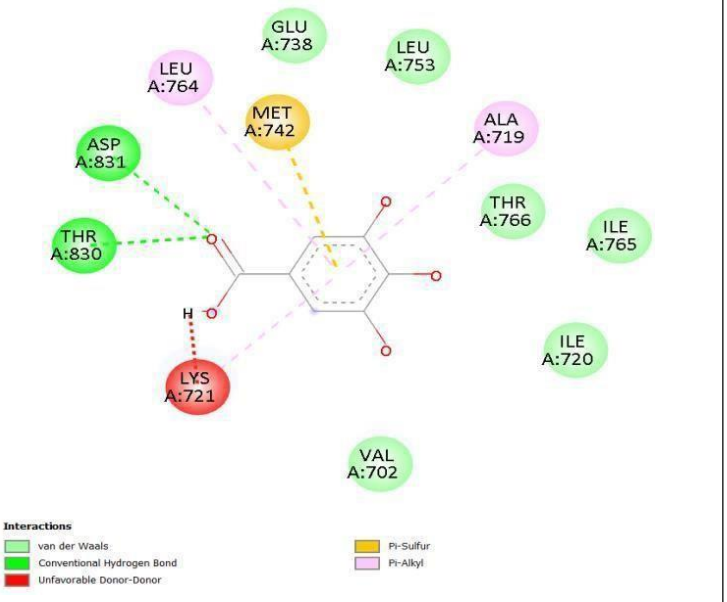
Molecular interaction of Kaempferol with 1M17(EGFR) Protein

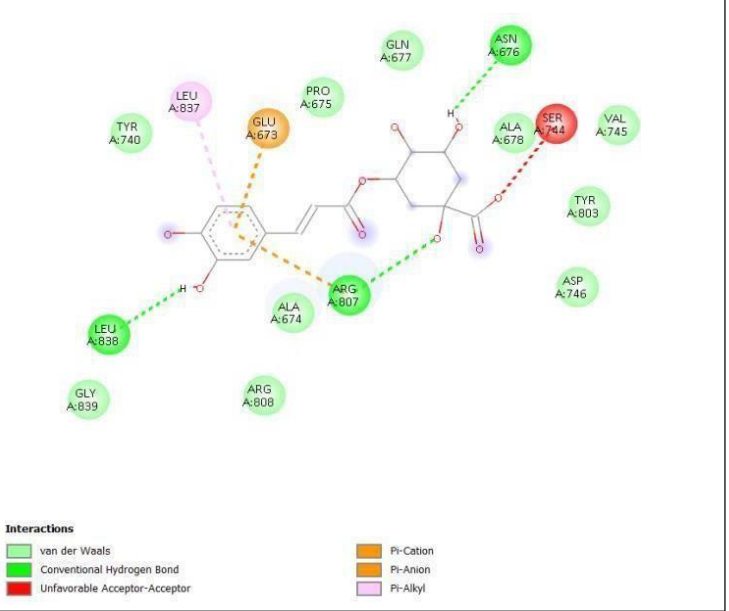




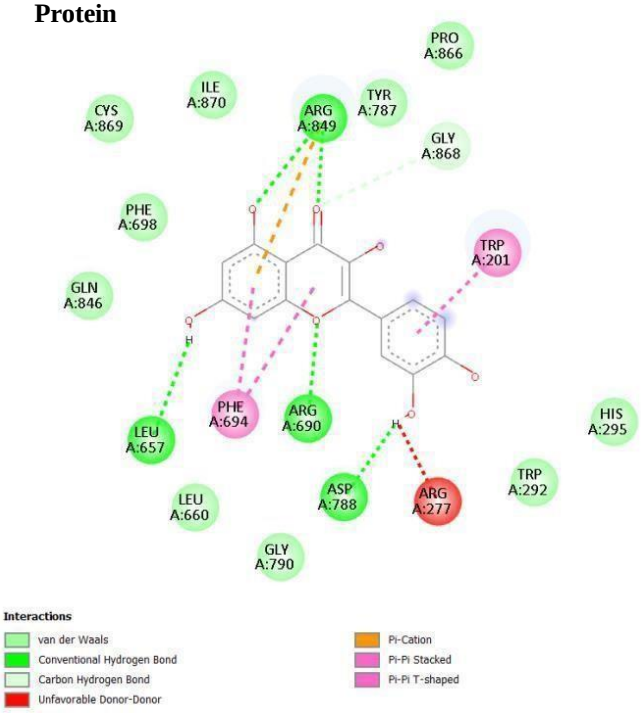
Molecular interaction of luteolin with 1M17(EGFR) Protein

Molecular interaction of Rutin with 1M17(EGFR) Protein

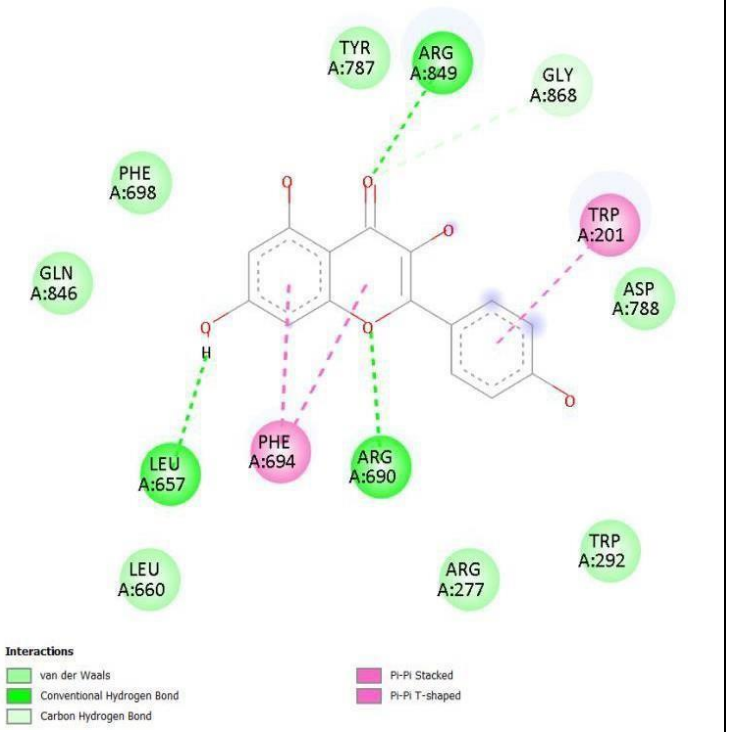




Molecular interaction of Ellagic acid with 1M17(EGFR) Protein

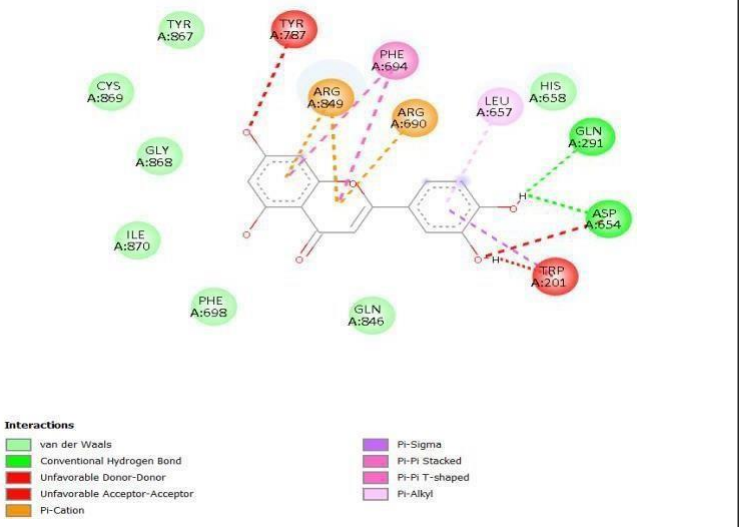


Molecular interaction of chlorogenic acid with 1M17(EGFR) Protein

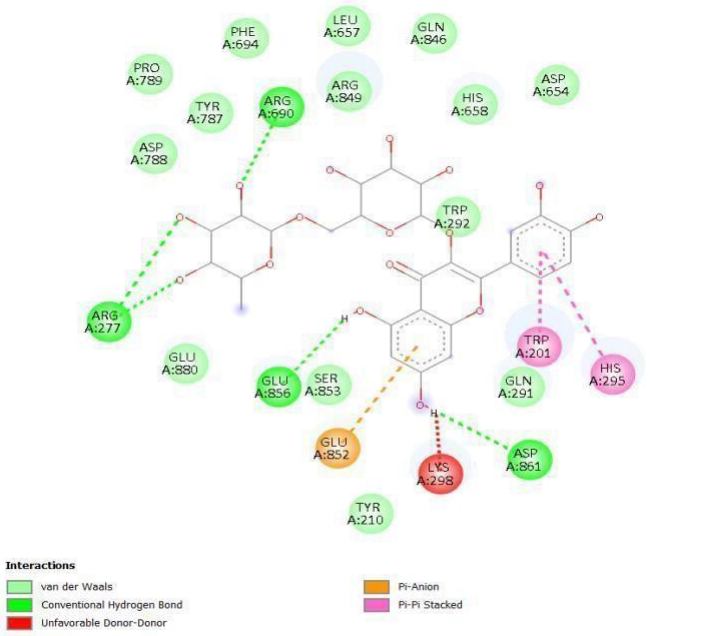


Molecular interaction of quercetin with 4FA6(PI3K) Protein

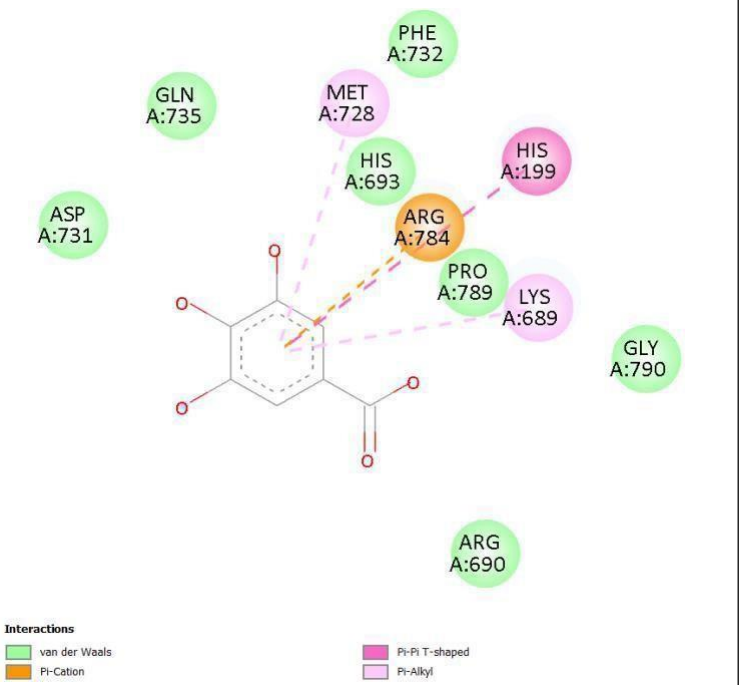
Molecular interaction of kaempferol with 4FA6(PI3K) Protein



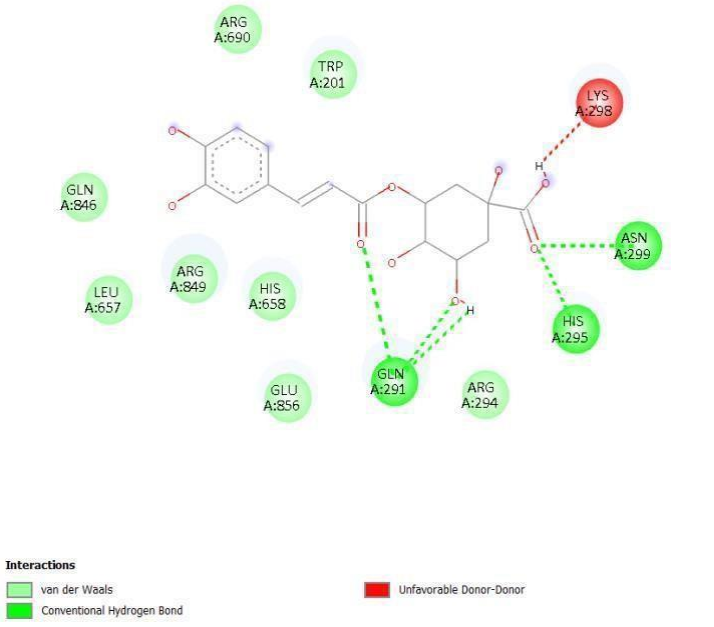
Molecular interaction of luteolin with 4FA6(PI3K) Protein



Molecular interaction of Rutin with 4FA6(PI3K) Protein



Molecular interaction of ellagic acid with 4FA6(PI3K) Protein Protein



Molecular interaction of chlorogenic acid with 4FA6(PI3K)

Interaction between chemical constituent of plant name: Rosa Damascena and 3VO3 PDB DOI:

Drug	Docking Score/ binding Energy (kcal/mol)	Van der Waals	H bond	Pi-sigma	Pi-Alkyl
Kaempferol	-10.2	ASP A:1046 VALA:916 VALA:899 GLU A:917 PHE A:918 LYS A:920 GLY A:922 ASN A:923	GLU A:855 LEU A:804 CYS A:919	VALA:848 LEU A:1035	CYS A:1045 ALA A:866
Quercetin	-10.2	GLU A:885 VALA:899 VALA:916 GLU A:917 PHE A:918 LYS A:920 GLY A:922 ASN A:923	ASP A:1046 CYS A:919	VALA:848 LEU A:1035	CYS A:1045 ALA A:866 LEU A:840
Ellagic acid	-6.2	LYS A:920 GLY A:922 ASN A:923 PHE A:918 GLU A:917 VAL A:916 VAL A:899 GLU A:885	ASP A:1046 CYS A:919	LEU A:1035 VAL A:848	LEU A:840 ALA A:866 CYS A:1045
Rutin	-9.4	HIS A:1026 GLY A:1048 CYS A:1024 VAL A:898 ILE A:892 CYS A:1045 LEU A:889 VAL A:899	ILE A:1025 GLU A:885 ASP A:1028	ILE A:888	
Luteolin	-10.3	GLY A:922 ASN A:923	LEU A:840 CYS A:919	LEU A:1035	ALA A:866 VAL A:848

		PHE A:918	GLU A:885		LYS A:868
		VAL A:899 VAL A:916 ASP A:1046			CYS A:1045
Chlorogenic acid	-8.2	VAL A:916 LYS A:868 VAL A:899 LEU A:889 ILE A:888 VAL A:898 LEU A:1019 ILE A:892	HIS A:1026	LEU A:1035	VAL A 848 CYS A 1045 ALA A:866

Interaction between chemical constituent of plant name: Rosa Damascena and EGFR PDB DOI:

Drug	Docking Score/ binding Energy (kcal/mol)	Van der Waals	H Bond	Pi-Sigma	Pi-Alkyl
Kaempferol	-8.3	CYS A:733 GLY A:772 LEU A:694 LLE A:720 THR A:766 ILE A:765 LEU A:764	LYS A:721 GLU A:738 THR A:830 ASP A:831		LEU A:820 VAL A:702
Quercetin	-8.5	GLY A:772 PRO A: 770 LEU A:768 THR A: 766 THR A:830 LEU A:764	MET A:769 MET A :742 GLN A:767 GLV A:738 ASP A:831	LEU A:694 LEU A:820	VAL A:702 ALA A:719
Ellagic acid	-5.7		THR A:830 ASP A:831		ALA A:719 LEU A:764
Rutin	-9.1	PRO A:770 GLY A:772 CYS A:773 LEU A:694 LEU A:820 ARG A:817 GLY A:695 LEU A:768	GLN A:767 THR A:766 LEU A:764 LY6 A:721		ALA A:719 VAL A:702

		THR A:830 MET A:742 GLU A:738			
		ILE A:765 ILE A:720			
Luteolin	-8.4	LEU A:764 MET A:742 GLU A:738 THR A:766 GLY A:695 LEU A:768 PRO A:770	ASP A:831 LEU A:694 MET A:769		LYS A:721 VAL A:702 LEU A:820 ALA A:719
Chlorogenic acid	-6.6	GLY A: 839 ARG A: 808 ALA A: 674 TYR A: 740 PRO A: 675 GLN A: 677 ALA A: 678 VAL A:745 TYR A:803 ASP A:746	LEU A:838 ARG A:807 ASN A:676		LEU A:837

Interaction between chemical constituent of plant name: Rosa Damascena and FGFR1

PDB DOI:

Drug	**Docking Score/ Binding Energy (kcal/mol)**	**Van Der Waals**	**H Bond**	**Pi-sigma**	**Pi-Alkyl**
Kaempferol	-8.7	GLU A:531 GLY A:485 TYR A:563 GLY A:567	LEU A:484 ALA A:564 GLU A:562	VAL A:561 VAL A:492	ILE A:545 ALA A:640 LYS A:514 ALA A:512 LEU A:630
Quercetin	-9.1	GLY A:485 GLY A:567 SER A:565 TYR A:563 PHE A:642 GLU A:531 MET A:535	ALA A:564 GLU A:562 ASP A:641	VAL A:492 ELU A:630 VAL A:561	LEU A:484 ALA A:512 LYS A:514 ILE A:545 ALA A:6430

Ellagic acid	-5.3	TYR A:563 GLU A:562 ILE A:545 ALA A:512 VAL A:561 VAL A:492 GLY A:485	ALA A:564	LEU A:484	LEU A:630

Rutin	-9.4	GLU A:486 SER A:565 TYR A:563 GLY A:485 GLU A:571 ARG A:627 VAL A:559 GLU A:531	ALA A:564 LEU A:484 ASN A:568 ASP A:641	LEU A:630 VAL A:492 VAL A:561	ALA A:640 LYS A:514 ILE A:545 ALA A:512
Luteolin	-9.3	PHE A:642 GLU A:562 TYR A:563 GLY A:485	GLU A:531 ASP A:641 ALA A:564	VAL A:561 VAL A:492	ILE A:545 ALA A:512 ALA A:640 LYS A:514 LEU A:630 LEU A:484
Chlorogenic Acid	-7.5	GLU A:571 GLY A:567 LEU A:484 SER A:565 ALA A:512 TYR A:563 ILE A:545 GLU A:531 MET A:535	ASN A:568 ALA A:564 ASP A:641	VAL A:561	VAL A:492 LYS A:514 ALA A:640

Interaction between chemical constituent of plant name: Rosa Damascena and PI3K PDB DOI:

Drug	**Docking score/ Binding Energy (kcal/mol)**	**Van der Waals**	**H Bonds**	**Pi-Sigma**	**Pi-Alkyl**
Kaempferol	-8.5	LEU A:660 GLN A:846 PHE A:698 TYR A:787 GLYT A:868 ASP A:788 TRP A:292	LEU A:557 ARG A:690 ARG A:849	PHE A:694 TRP A:201	
Quercetin	-8.5	GLY A:790 LEU A:660 GLN A:846 PHE A:698 CYS A:869 ILE A:870	ARG A:690 ASP A:788 LEU A:657 ARG A:849		TRP A:201 PHE A:694
		TYR A:787 PRO A:866 HIS A:295			

Ellagic acid	-6.5	ASP A:731 GLN A:735 PHE A:732 HIS A:693 PRO A:789 GLY A:790 ARG A:690			MET A:728 LYS A:689
Rutin	-9.6	PRO A:789 ASP A:788 GLU A:880 SER A:853 GLN A:291 TYR A:210 ARG A:249 HIS A:658 ASP A:654 GLP A:846	ASP A:861 GLU A:856 ARG A:277 ARG A:690		TRP A:201 HIS A:295
Luteolin	-8.5	TYR A:867 GLY A:8689 ILE A:870 PHE A:698 GLN A:846 HIS A:658	GLN A:291 ASP A:654		LEU A:657
Chlorogenic acid	-7.2	ARG A:690 GLN A:846 LEU Aa:657 ARG A:849 HIS A:856 GLU A:856 ARG A:294 TRP A:201	GLN A:291 HIS A:295 ASN A: 299		

Discussion: -

The molecular docking study indicated that phytochemicals exhibited varying degrees of binding affinities to the target protein involved in angiogenesis and cancer progression. Out of all the phytochemicals, quercetin was found to possess a higher degree of binding affinity to VEGFR2 than other phytochemicals, followed by kaempferol, as shown in the above figures. This is consistent with previous studies that found flavonoids to have potent anti-cancer and anti-angiogenic activities. Nevertheless, Ellagic acid and Chlorogenic acid showed a lower binding affinity to VEGFR2, indicating a lower level of interaction with the active site of the receptor protein. Likewise, other phytochemicals, such as rutin and luteolin exhibited moderate degrees of binding energy to different receptor proteins, such as FGFR1, EGFR, and PI3K. The varying degrees of binding affinity of phytochemicals to receptor proteins could be attributed to differences in structure and interaction potential of phytochemicals with amino acid residues at the active site of the receptor protein. The negative value of the

binding energy of phytochemicals to receptor protein indicates that the interaction of phytochemicals and protein is spontaneous and energetically favorable.

Conclusion: -

In this study, the molecular docking simulation found that Quercetin, Kaempferol, Rutin, Luteolin, Chlorogenic acid and Ellagic acid are potential anti-angiogenic compounds against VEGFR2 and other angiogenic receptors. These are potential anti-angiogenic compounds with high binding affinities and good molecular interactions, suggesting that they have potential uses in the treatment of cancer by inhibiting pathological angiogenesis. These findings are significant in supporting the discovery of anti-angiogenic compounds for the treatment of cancer using natural resources. These findings also support the advantages of using phytochemicals in drug discovery. Although the use of molecular docking is valuable tool in selecting potential drug candidates, it is also important to note that experimental studies are also significant. These anti-angiogenic compounds need to be tested in vitro to evaluate their potential to inhibit endothelial cell proliferation, migration, and tube formation. These anti-angiogenic compounds also need to be tested in vivo to evaluate their pharmacokinetic, bioavailability, and toxicity profile. If successful in preclinical studies, these types of agents have the potential to be a foundation for new, and less toxic, anti-angiogenic treatments for cancer patients. Overall, the present research demonstrates the enormous potential of natural agents in contemporary medicine and underlines the value of a hybrid approach, combining both computational and experimental methods, in drug discovery research. With the pharmacological potential of plant compounds, researchers are likely to lay the foundation for more targeted and less toxic cancer treatments.

Reference

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424. doi:10.3322/caac.21492

2. Sherwood LM, Parris EE, Folkman J. Tumor Angiogenesis: Therapeutic Implications. *New England Journal of Medicine*. 1971;285(21):1182-1186. doi:10.1056/NEJM197111182852108

3. Chaudhari PJ, Nemade AR, Shirkhedkar AA. Recent updates on potential of VEGFR-2 small-molecule inhibitors as anticancer agents. *RSC Adv*. 2024;14(45):33384-33417. doi:10.1039/D4RA05244G

4. Shah FH, Nam YS, Bang JY, et al. Targeting vascular endothelial growth receptor-2 (VEGFR-2): structural biology, functional insights, and therapeutic

resistance. *Arch Pharm Res*. 2025;48(5):404-425. doi:10.1007/s12272-025-01545-1

5. KATOH M. FGFR inhibitors: Effects on cancer cells, tumor microenvironment and whole-body homeostasis (Review). *Int J Mol Med*. 2016;38(1):3-15. doi:10.3892/ijmm.2016.2620

6. Mahboubi M. Rosa damascena as holy ancient herb with novel applications. *J Tradit Complement Med*. 2016;6(1):10-16. doi: 10.1016/j.jtcme.2015.09.005

7. Khezerlou A, Mohammadi K, Abedini A, Sani MA, Sani MA, McClements DJ. Phytochemicals and bioactive functional ingredients from rosa damascena: from extraction to application in the food and healthcare sectors. *Food Chem X*. 2025; 31:103202. doi: 10.1016/j.fochx.2025.103202

8. Nayebi N, Khalili N, Kamalinejad M, Emtiazy M. A systematic review of the efficacy and safety of Rosa damascena Mill. with an overview on its phytopharmacological properties. *Complement Ther Med*. 2017; 34:129-140. doi: 10.1016/j.ctim.2017.08.014

9. Subbaraj GK, Kumar YS, Kulanthaivel L. Antiangiogenic role of natural flavonoids and their molecular mechanism: an update. *Egypt J Intern Med*. 2021;33(1):29. doi:10.1186/s43162-021-00056-x

10. Meng XY, Zhang HX, Mezei M, Cui M. Molecular Docking: A Powerful Approach for Structure-Based Drug Discovery. *Current Computer Aided-Drug Design*. 2011;7(2):146-157. doi:10.2174/157340911795677602

11. Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer*. 2019;144(8):1941-1953. doi:10.1002/ijc.31937

12. Berman HM. The Protein Data Bank: a historical perspective. *Acta Crystallogr A*. 2008;64(1):88-95. doi:10.1107/S0108767307035623

13. Burley SK, Wu-Wu A, Dutta S, Ganesan S, Zheng SXF. Impact of structural biology and the protein data bank on us FDA new drug approvals of low molecular weight antineoplastic agents 2019–2023. *Oncogene*. 2024;43(29):2229-2243. doi:10.1038/s41388-024-03077-2

14. Karar J, Maity A. PI3K/AKT/mTOR Pathway in Angiogenesis. *Front Mol*

Neurosci. 2011;4. doi:10.3389/fnmol.2011.00051

15. Pratheeshkumar P, Budhraja A, Son YO, et al. Quercetin Inhibits Angiogenesis Mediated Human Prostate Tumor Growth by Targeting VEGFR- 2 Regulated AKT/mTOR/P70S6K Signaling Pathways. *PLoS One*. 2012;7(10): e47516. doi: 10.1371/journal.pone.0047516

16. Lupo G, Cambria MT, Olivieri M, et al. Anti-angiogenic effect of quercetin and its 8-methyl pentamethyl ether derivative in human microvascular endothelial cells. *J Cell Mol Med*. 2019;23(10):6565-6577. doi:10.1111/jcmm.14455

17. Soler A, Angulo-Urarte A, Graupera M. PI3K at the crossroads of tumor angiogenesis signaling pathways. *Mol Cell Oncol*. 2015;2(2): e975624. doi:10.4161/23723556.2014.975624

18. Dr. Pradnya Jagtap MNJMrSKMSJadhav. Anti-angiogenic potential of bioactive phytochemicals from caraway (Caramel carvi) targeting protein to fight cancer through Molecular Docking. *INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT*. 2025;10(2025):1-13.

19. Gao S, Hu J, Wu X, Liang Z. PMA treated THP-1-derived-IL-6 promotes EMT of SW48 through STAT3/ERK-dependent activation of Wnt/β-catenin signaling pathway. *Biomedicine & Pharmacotherapy*. 2018; 108:618-624. doi: 10.1016/j.biopha.2018.09.067

20. Li R, Song X, Guo Y, Song P, Duan D, Chen ZS. Natural Products: A Promising Therapeutics for Targeting Tumor Angiogenesis. *Front Oncol*. 2021;11. doi:10.3389/fonc.2021.772915