ORIGINAL ARTICLE

In Silico Screening of Natural Bioactive Compounds against Vascular Endothelial Growth Factor Receptor 2 for Potential Colon Cancer Inhibition

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Abstract

Introduction: Cancer has become a major contributor to cancer-related deaths around the globe. Angiogenesis, largely regulated by vascular endothelial growth factor receptor 2 (VEGFR2), plays a crucial role in supporting tumor development and cancer cell metastasis. Natural bioactive compounds are increasingly recognized as valuable anticancer agents, owing to their wide-ranging biological activities and relatively low toxicity and diverse pharmacological activities. **Materials and Methods:** In the current study, we conducted computational molecular docking to assess chosen natural compounds targeting the VEGFR2 (PDB ID: 4ASD), utilizing AutoDock Vina implemented in the PyRx platform. **Result and Discussion:** We evaluated their binding affinities and interaction profiles. Our results showed that Aiphanol (−9.7 kcal/mol), Silibinin (−9.5 kcal/mol), and Curcumin (−9.4 kcal/mol) demonstrated strong binding with the active site of VEGFR2, forming stable hydrogen bonds and hydrophobic (non-polar) interactions with crucial amino acid residues. The results indicate that certain bioactive compounds may act as effective VEGFR2 inhibitors and hold therapeutic potential in colon cancer treatment.

Key words: Colon cancer, *in silico* screening, molecular docking, natural compounds, phytochemicals, vascular endothelial growth factor receptor 2

INTRODUCTION

Colorectal cancer[1] is a type of malignancy that develops in the colon, which forms the first and largest portion of the large intestine. According to the International Agency for Research on Cancer (2020), it is the world's third most commonly diagnosed cancer. World Health Organization statistics say that worldwide colorectal cancer accounts for roughly 1.9 million new diagnoses and over 900,000 deaths every year. It predominantly affects older individuals, with the majority of cases occurring in people aged 50 and above.[2,3] Colon cancer growth and metastasis rely heavily on angiogenesis (new blood vessel formation). The angiogenic process, essential for tumor progression and dissemination, is primarily regulated by vascular endothelial growth factor (VEGF) and its receptor, VEGFR2.[4]

In healthy tissues, VEGFR2 is usually present at low to moderate levels, but it is markedly overexpressed in various malignancies, including colorectal, lung, uterine, ovarian, and breast cancers. This overexpression contributes to enhanced angiogenesis, cancer development, and spread.[5] Inhibiting VEGFR2 is now considered a viable therapeutic strategy to suppress tumor vascularization in colon cancer.[6] While synthetic inhibitors such as sorafenib and sunitinib exist, they often pose toxicity and resistance issues.[7] Hence, natural compounds offer a safer and biologically active alternative. Curcumin, resveratrol, and quercetin are well-known phytochemicals with anticancer potential, attributed to their ability to promote apoptosis, block cell cycle progression, and reduce angiogenesis.[8-10] The present study focuses on the molecular docking of selected natural compounds against VEGFR2 to identify potential inhibitors that can be further explored as therapeutic approaches for colon cancer.

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MATERIALS AND METHODS

Biological databases

We used online databases such as the PubChem database,[11] PDBsum, a Pictorial database of 3D structures in the Protein Data Bank,[12] Protein Data Bank 3D structural database,[13] and online tools such as Swiss absorption, distribution, metabolism, and excretion (ADME), and toxicity.[14]

Retrieval of target protein and preparation

The VEGFR2 protein structure was obtained from the Protein Data Bank (PDB ID: 4ASD).[15] The Discovery Studio 2025 client was used for removing water molecules and the co-crystallized ligand from the 4ASD protein.[16] After adding polar hydrogens, the structure was transformed into PDBQT format through PyRx software.[17]

Retrieval of ligand and ligand preparation

The structures of fifteen natural bioactive compounds with reported anticancer properties were selected from the PubChem database[18] and literature review. The resulting structures served as inputs for the docking studies. The selected ligand 3D conformers were downloaded from the PubChem compound database in SDF format and converted to PDBQT after energy minimization using PyRx and Open Babel. Compound, molecular formula, source, activity on VEGFR2, and PubChem CID of natural bioactive compounds present in the study are shown in Table 1.

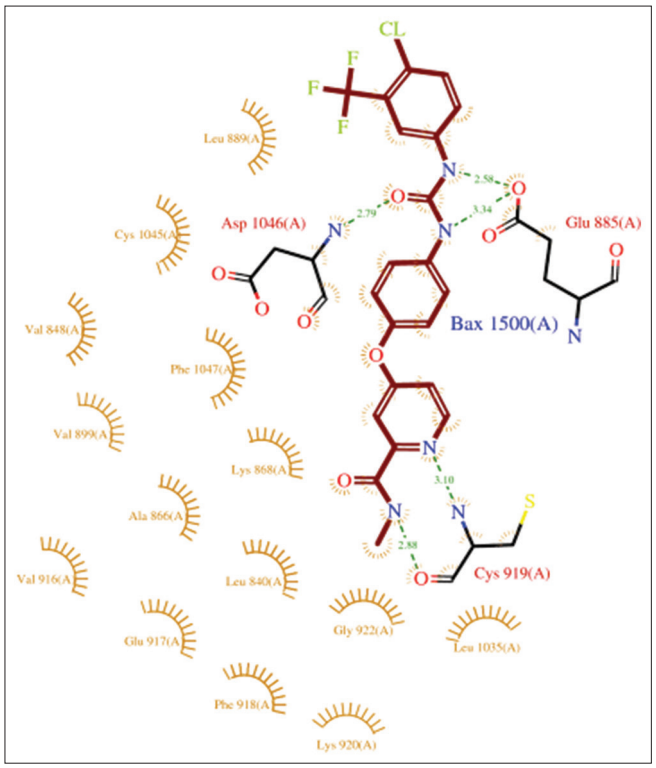

Figure 1: Binding site residues of vascular endothelial growth factor receptor 2 (PDB ID: 4ASD) with co-crystal ligand

Prediction of the prominent active site in protein

Before conducting the docking study, the major active sites of the 4ASD protein were identified using the PDBsum database. PDBsum highlights all amino acids in contact with the BAX1500 ligand. These residues represent the prominent active/binding site of the protein (Figure 1).

ADME properties

ADME refers to the process that explains how a drug or chemical acts within the body. It includes how the substance enters the bloodstream (absorption), moves through different tissues (distribution), is chemically modified into metabolites (metabolism), and is finally removed from the body (excretion). This concept is essential in pharmacology for understanding a drug's overall behavior and effectiveness.[19] The Swiss ADME online tool was employed to assess the ADME properties of the chosen bioactive compounds (Table 2). This freely accessible computational platform facilitates the evaluation of pharmacokinetic behavior, drug-like properties, and the medicinal chemistry suitability of small molecules. The bioactive structures were retrieved from relevant chemical databases, converted into the SMILES format using the import utility available on the Swiss ADME submission interface, and subsequently processed to obtain the predicted ADME profiles.

Molecular docking

Molecular docking is used to study the binding behavior of selected phytochemicals with the binding pockets of the target protein VEGFR2. PyRx virtual screening software was employed to conduct the molecular docking analysis. It is an open-source software featuring a user-friendly interface and compatibility with major operating systems, including Linux, Windows, and macOS.[17] PyRx, a recognized virtual screening software in computational drug discovery, allows users to evaluate large libraries of compounds against prospective drug targets. The functioning of PyRx relies on empirical binding, free energy scoring, and the Lamarckian genetic algorithm. All the ligands and macromolecules are converted from PDB to PDBQT format by choosing the Autodock option in PyRx. The grid box was centered on the active site of VEGFR2 (PDB code: 4ASD). Binding affinities were recorded, and top-ranked poses were visualized using the Discovery Studio 2025 client.

RESULTS AND DISCUSSION

All selected phytochemicals showed favorable binding energies with VEGFR2. Table 3 has shown the aiphanol

Table 1: Compound, molecular formula, source, activity on VEGFR2, and PubChem CID of natural bioactive compounds

Sr. No.	Compound	PubChem CID	Molecular formula	Source	Activity on VEGFR2
1	Curcumin	969516	$C_{21}H_{20}O_6$	Turmeric	Inhibits VEGFR2 phosphorylation
2	Resveratrol	445154	$C_{14}H_{12}O_3$	Grapes/Red Wine	Suppresses the VEGF–VEGFR2 axis
3	Epigallocatechin gallate (EGCG)	65064	$C_{22}H_{18}O_{11}$	Green Tea	Blocks VEGFR2 autophosphorylation
4	Luteolin	5280445	$C_{15}H_{10}O_6$	Parsley, Green Pepper	Inhibits VEGFR2 kinase activity
5	Genistein	5280961	$C_{15}H_{10}O_5$	Soy Products	Inhibits tyrosine kinases, including VEGFR2
6	Apigenin	5280443	$C_{15}H_{10}O_5$	Chamomile, Parsley	Inhibits VEGF-mediated angiogenesis
7	Quercetin	5280343	$C_{15}H_{10}O_7$	Apples, Onions	Inhibits VEGFR2 and PI3K/AKT
8	Hesperetin	72281	$C_{16}H_{14}O_6$	Citrus Fruits	Suppresses VEGFR2 and ERK/MAPK
9	Aiphanol	10366595	$C_{25}H_{24}O_8$	*Smilax glabra*, stilbenolignan	Inhibits VEGFR2/VEGFR3 signaling
10	Ajmaline	441080	$C_{20}H_{26}N_2O_2$	*Rauwolfia serpentina*	Alkaloid; potential kinase interactions (limited VEGFR2 data)
11	Ajmalicine	441975	$C_{21}H_{24}N_2O_3$	*Rauwolfia serpentina*	Indole alkaloid; may modulate VEGF/ kinase pathways
12	Yohimbine	8969	$C_{21}H_{26}N_2O_3$	*Rauwolfia serpentina*	Indole alkaloid; adrenergic receptor modulator, possible VEGF pathway effects
13	Ethyl cinnamate	637758	$C_{11}H_{12}O_2$	*Kaempferia galanga* (rhizome)	Anticancer and antiangiogenic potential
14	Voacangine	73255	$C_{22}H_{28}N_2O_4$	*Voacanga africana* (and related species)	Direct VEGFR2 kinase inhibitor; blocks VEGF-induced phosphorylation
15	Silibinin	31553	$C_{25}H_{22}O_{10}$	Silibinin is a flavonolignan isolated from Milk thistle	Anticancer effects against human colon cancer cells

VEGFR2: Vascular endothelial growth factor receptor 2

Table 2: Physicochemical properties (approximate/rounded)

Sr. No.	Ligand	Mol. Wt ($g \cdot mol^{-1}$)	Rotatable bonds (count)	H-bond donors	H-bond acceptors	clogP (approx)	Solubility logS (ESOL)	TPSA ($Å^2$)
1	Curcumin	368.4	8	2	6	3.03	−3.94	93.06
2	Resveratrol	228.2	2	3	3	2.48	−3.62	60.69
3	Epigallocatechin gallate (EGCG)	458.4	4	8	11	0.95	−3.56	197.37
4	Luteolin	286.2	1	4	6	1.73	−3.71	111.13
5	Genistein	270.2	1	3	5	2.04	−3.7	90.90
6	Apigenin	270.2	1	3	5	2.11	−3.94	90
7	Quercetin	302.2	1	5	7	1.23	−3.16	131.36
8	Hesperetin	302.3	2	3	6	1.91	−3.6	96.22
9	Aiphanol	452.45	6	4	8	2.99	−4.98	117.84
10	Ajmaline	326.43	1	2	3	1.35	−3.12	46.94
11	Ajmalicine (Raubasine)	352.4	2	1	5	2.6	−3.88	54.56
12	Yohimbine	354.44	2	2	4	2.51	−4.1	65.56
13	Ethyl cinnamate	176.2	4	0	2	2.5	−2.89	26.30
14	Voacangine	368.47	4	1	4	2.0–3.5	−3 to−5	54.56
15	Silibinin	482.4	4	5	10	1.51	−4.14	155.14

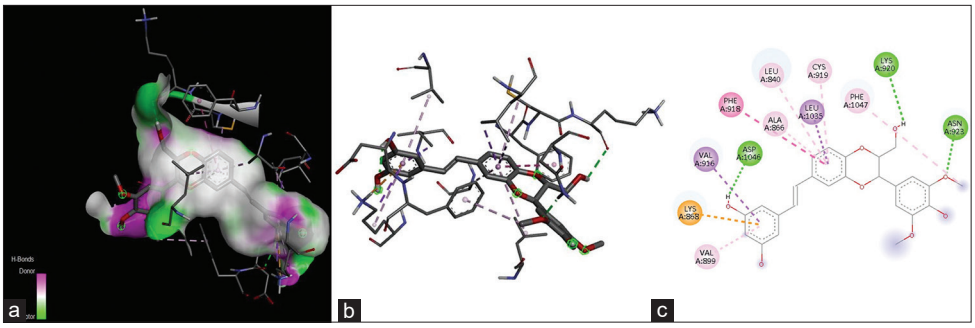

Figure 2: Docking result against the anticancer vascular endothelial growth factor receptor 2 protein (PDB ID: 4ASD) for CID −10366595 with binding energy −9.7 kcal/mol. (a) The ligand molecule is docked inside the binding pocket of the target protein. The hydrogen bond donor and acceptor region are shown. (b) The amino acid residues of the target protein are shown. (c) The most important interactions between the ligand and the target protein are shown

Table 3: Binding Affinity Table: Best Docking results obtained against PDB ID: 4ASD

Compound	Binding affinity (kcal/mol)	Key interacting residues
Aiphanol (CID: 10366595)	−9.7	ASP1046, LYS920, ASN923, VAL916, LEU1035, PHE918, ALA866, and LYS868
Silibinin (CID: 31553)	−9.5	ASP1046, VAL916, LEU889, ASP814, CYS1045, and ARG1027
Curcumin (CID: 969516)	−9.4	CYS919, LEU889, LEU1035, ALA866, VAL898, LEU1019, and ILE1044

exhibited the strongest binding energy (−9.7 kcal/mol), interacting with residues ASP1046, LYS920, ASN923, VAL916, LEU1035, and LYS868. Silibinin also showed strong binding (−9.5 kcal/mol), interacting with ASP1046, VAL916, and ARG1027. Other compounds such as curcumin, apigenin, and ajmaline had moderate affinities, suggesting potential for structural optimization.

The interactions involved key residues in the ATP-binding pocket, indicating that these natural compounds may act as competitive inhibitors. The structural stability and pharmacophoric alignment of these molecules with the VEGFR2 active site support their role as antiangiogenic agents in colon cancer therapy.

Interaction diagrams

Representative interaction diagrams (Figure 2) for aiphanol bound to VEGFR2 were generated using Discovery Studio. The hydrogen bonds, pi-stacking, and hydrophobic contacts were identified and visualized.

CONCLUSION

This computational study highlights aiphanol, silibinin, and curcumin as promising natural inhibitors of VEGFR2 protein, relevant for colon cancer inhibition. These findings lay the groundwork for further *in vitro* and *in vivo* validation and suggest that plant-based compounds could offer low-toxicity alternatives to synthetic VEGFR2 inhibitors.

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