



Research Article

In Silico Evaluation of Hesperidin as a Cox-2/ Pge2 Signaling Inhibitor for Renal Cancer Therapy through Docking Analysis and Drug- Likeness Evaluation Analysis

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ABSTRACT

Since renal carcinoma is amongst the most common illnesses in the world, developing novel treatments is crucial. Hesperidin, A naturally derived flavonoid, has remained inspected for prostate cancer and has demonstrated anticancer benefits through the COX-2/PGE2 pathway. Molecular docking simulations involving COX-2 (PDB ID: 5F1A) were undertaken and the outcomes were assessed relative to the co-crystallized ligand (5F1F) and an FDA-approved drug medications including lenvatinib, belzutifan, and cabozantinib. PyRx computational docking used to examine the binding efficacy of hesperidin with respect to other common drugs and the co-crystal ligand. Discovery Studio was utilized to analyse binding interactions. ADMET parameters were examined using pkCSM to look at pharmacokinetic characteristics and drug-likeness. In contrast to the Co - crystal ligand (5F1F-9.4kcal/mol), the binding energy values obtained for hesperidin, lenvatinib, belzutifan, and cabozantinib were -8.4, -7.9, -8.4, and -8.5 kcal/mol, respectively. The findings demonstrated that hesperidin had favourable interactions with significant residues, including ASN222, COH602, and LYS211, VAL291. Comparable to FDA-authorized medications for renal cancer. ADMET study revealed that hesperidin complied with Lipinski's criteria and had favourable drug interactions. Hesperidin showed potent inhibitory potential compared to the COX-2/PGE2 signaling pathway in renal cell carcinoma, affording through in silico molecular docking studies. Given that it demonstrated a binding affinity of comparable with that of traditional drugs, it displays potential as a probable therapeutic alternative for the action of kidney cancer.

KEYWORDS: Hesperidin, molecular docking, renal growth, binding affinity, COX-2/PGE2 pathway, ADMET, binding interactions.

INTRODUCTION

RCC (Renal cell carcinoma) is the more prevalent generous of kidney tumor, making up 80-85% of all renal cancers and contributing significantly to the global well-being problem.^[1,2] Outstanding towards aspects like burning, fatness, hypertension, also hereditary

susceptibility, the incidence of RCC is rising worldwide, especially in developed nations.^[3,4] A deprived diagnosis and great death are caused by the disease's sluggish onset, conflict to conventional chemotherapy and radiation, and numerous late-stage analysis.^[5]

RCC is being treated with surgical resection, immunotherapies, especially immune checkpoint inhibitors, and targeted medicines such targeted kinase inhibitors and mTOR- targeting agents.^[6,7] However, these approaches frequently hindered by high toxicity, the occurrence of resistance, adverse reaction, and high costs, particularly in settings with limited resources.^[8] Natural products, especially flavonoids naturally present in fruits and vegetables have develop likely healing opportunities for cancer management since of their wide range of biological activities, including anti-inflammatory, antioxidant, and anticancer effects.^[4,9] Sensitive oxygen type hunting, inhibition of pro-inflammatory intermediaries like COX-2, modulation of oncogenic signalling passageways like PI3K/Akt/mTOR, NF -Kb, and VEGFS, and induction of apoptosis in malignance cells are just a few of the anticancer mechanisms of flavonoids.^[10,11]

Amongst these, hesperidin a naturally occurring citrus flavonoid. consumes drawn attention due to its capacity to inhibit COX-2/PGE2 pathway, a significant contributor to inflammation and the development of RCC. In kidney cancers, the cyclooxygenase-2 (COX-2) enzyme and this one byproduct the inflammatory mediator prostaglandin E₂ (PGE₂) are often overexpressed, which promotes angiogenesis, tumour growth, and immune evasion.^[12] Therefore, using bioactive substances like hesperidin to target this pathway may offer a novel therapeutic alternative.

2. MATERIALS AND METHODOLOGY

2.1 Protein identification and purification

The Protein Data Bank (PDB) provided the protein target employed in this investigation, which exhibits at a with a crystal structure resolution of 1.80 Å and PDB ID 1Q0R. The Swiss-PdbViewer (SPDBV), a molecular visualization tool was used to optimize the structural model of the protein by eliminating hetero atoms, water molecules and unnecessary ligands. After processing, the structure was saved in PDB format for later examination.^[13]

2.2 Selection of ligands

Both some flavonoids and common medications employed in the management of renal cancer have been

chosen as ligands to validate this investigation. By inputting the target proteins these drug contestants stayed selected from therapeutic banks, enabling screening for FDA-approved therapies and assisting in the identification of compounds with chemical structures comparable to approved medications and medications utilized in renal growth therapy.^[11,14]

2.3 Molecular docking studies

Hesperidin remained assessed as per a likely inhibitor of the COX-2/PGE2 pathway in renal tumour by a thorough computational method utilising a range through bioinformatics platforms and datasets. In order to choose high-resolution protein model, the construction of the entity protein was first acquired from the Protein Data Bank (PDB) and filtered for important characteristics.^[15] Hesperidin's three- dimensional (3D) and two-dimensional (2D) structures were obtained from PubChem, a well-known chemical database.^[16] Swiss PdbViewer (Swiss Pdbv), which affords a more accurate docking environment, remained working for protein processing, including the removal of unwanted chains, ions, and co-crystals. In order to enhance ligand compounds additional investigation, chemical clusters were subsequently made in Discovery Studio.^[17]

2.4 Building the protein –ligand complex

In this instance, a specific medication and protein are formed complex and protected in PDB layout using the PYMOL software, which is utilised for visualisation.

2.5 Studying the protein- ligand interactions

The ligands are clustered and the protein-ligand interactions are visualised using the Discovery Studio program. The resulting complex is loaded into Discovery Studio and examined for interactions in the form 2D and 3D structures.

2.6 ADMET Studies

After the molecular docking studies, the ligand properties) were analysed by the PKCSM Website. The toxicity and effectiveness of the ligand were ascertained with the aid of the information achieved after the online grin translator.

3. RESULTS AND ANALYSIS

3.1 Molecular Docking Studies- Selected target protein

Table 1: Molecular Docking Studies- Selected target protein.

Target Protein ID	Pathway	Ligands	Docking score
5F1A	COX2	Hesperidin	-8.4
		Co-crystal (5F1A)	-9.4
		Lenvatinib	-7.9

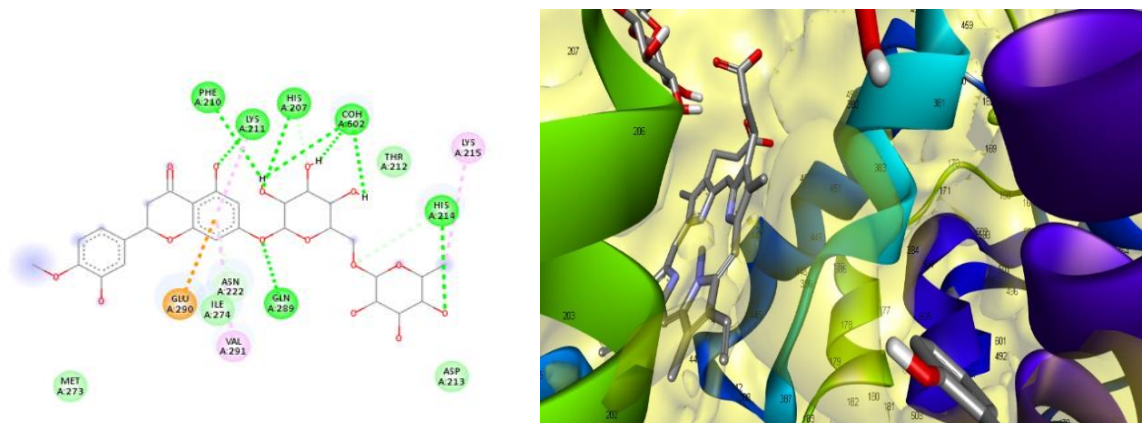


Fig. 1: 2D and 3D Interaction of Hesperidin.

2. Computational interaction studies of flavonoids

Table 2: Binding affinities of selected flavonoids.

Molecule	Docking	Interacting residues	Interaction profiles
Hesperidin	-8.4	HIS207, PHE210, LYS211, HIS214, COH602, GLN289, LYS215, VAL297	Conventional hydrogen bonds Pi-Anion Pi- Alkyl
Co-crystal (5F1A)	-9.4	THR212, LYS215, ILE274, HIS207, LEU294, TYR409	Conventional hydrogen bonds pi-sigma Pi-Pi Stacked Pi-Alkyl
Lenvatinib	-7.9	ASN222, LYS211, PRO276, VAL291, TYR409, COH602	Conventional hydrogen bonds Pi-Alkyl

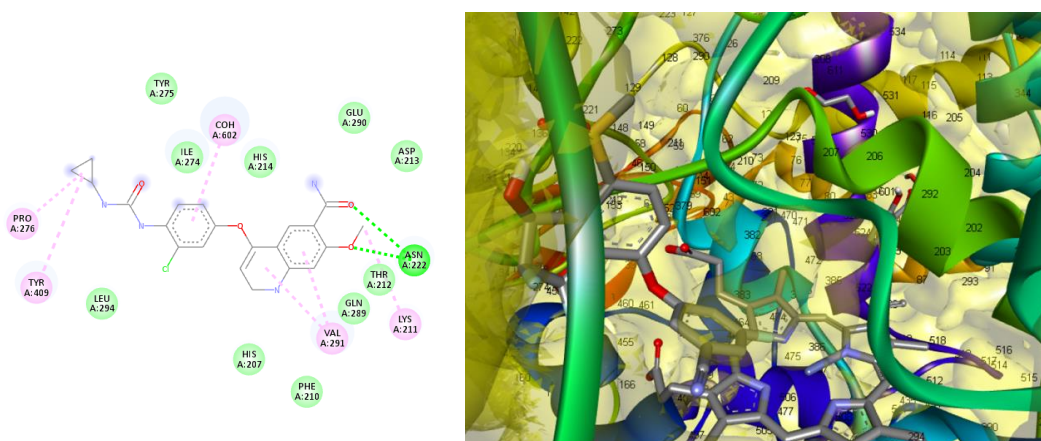


Fig. 2: 2D and 3D Interaction of Lenvatinib.

ADMET studies: A drug's likeness is determined by the Lipinski rule of five, which states that a medicine must have a molecular mass of at less 500, a minimum of five hydrogen donors, ten hydrogen acceptors, and an A Log

P of at least five. Table 3-8 illustrates how these five factors enhance permeability, bioavailability, and absorption.

ADMET studies

Drug-likeness and ADMET analysis

Table 3: Lipinski's drug-likeness prediction of ligands.

Flavonoid	Molecular weight	Log P	Rotatable bonds	Acceptors	Donors	Surface area
Hesperidin	610.56	-1.15	7	15	8	244.50

Table 4: Absorption properties.

Flavonoid	Water solubility (log mol/L)	Caco2 permeability (log papp in 10 ⁻⁸ cm)	Intestinal absorption (human) (%) Absorbed)	Skin permeability (log KP)	P-glycoprotein substrate (Yes/No)	P-glycoprotein inhibitor (Yes/No)	P-glycoprotein II inhibitor (Yes/No)
Hesperidin	-3.01	0.50	31.48	-2.73	Yes	No	No

Table 5: Distribution possessions.

Flavonoid	VDss (human) (log L/KG)	Fraction unbound (human) (Fu)	BBB penetrability (log BB)	CNS Penetrability (log P S)
Hesperidin	0.99	0.10	-1.71	-4.80

Table 6: Metabolism Possessions.

Flavonoid	CYP2D6 substrate (yes/no)	CYP3A4 substrate (yes/no)	CYP1A2 inhibitor (yes/no)	CYP2C19 inhibitor (yes/no)	CYP2C9 inhibitor (yes/no)	CYP2D6 inhibitor (yes/no)	CYP3A4 inhibitor (yes/no)
Hesperidin	no	no	no	no	no	no	no

Table 7: Elimination properties.

Flavonoid	Total clearance (log) ml/min/kg)	Kidney OCT2 substrate (yes/no)
Hesperidin	0.211	no

Table 8: Noxiousness properties.

Flavonoid	AMES toxicity (yes/no)	Max. tolerated dose (human) (log mg/kg/day)	herg I inhibitor (yes/no)	herg II inhibitor (yes/no)	Hepatotoxicity (yes/no)	Skin sensitisation (yes/no)
Hesperidin	no	0.52	no	yes	no	no

4. CONCLUSION

Hesperidin's capacity to connect by means of the COX-2 protein and possibly block the COX-/PGE2 signalling path, which is crucial for the development of tumours and inflammation, makes it a likely natural agent evaluated for renal cell carcinoma. According to in silico molecular docking studies, Hesperidin exhibits favourable interactions with key residues and a substantial binding affinity, which is equivalent to RCC medications that are utilised in clinical settings. Hesperidin's favorable pharmacokinetic properties, low level of toxicity, and adherence to drug- likeness parameters were further verified by ADME-T analysis, indicating that the subject has the probable chosen harmless and vocally bioavailable. These findings bolster hesperidin's potential as a plant-based, multi-targeted treatment for RCC. To additional discover its healing potential and clear the path for clinical development, more experimental research is required, containing *in vitro* and *in vivo* validation.

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6. CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

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