RESEARCH ARTICLE

Virtual Screening, Molecular Docking, and ADMET Analysis of Flavonoids as a Potential Pi3k Inhibitor for Cancer Treatment

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ABSTRACT

Cancer continues to be a global health burden, necessitating the exploration of innovative anti-cancer therapeutics. This study leverages computational biology tools such as molecular docking, ligand-based virtual screening, and ADMET to evaluate quercetin flavonoids as potential PI3K inhibitors for cancer treatment. Using Swiss Similarity and CB-Dock tools, 51 compounds were identified that showed promising interactions with PI3K. DB01645 exhibited the highest binding affinity among these, with a Vina score of -8.6. ADMET analysis revealed that this compound has favorable physicochemical properties, moderate lipophilicity, and good water solubility. The study adds to the growing evidence that Quercetin flavonoids have significant potential as next-generation anti-cancer agents targeting the PI3K pathway.

Keywords: Cancer, PI3K inhibitors, Quercetin flavonoids, Molecular docking, ADMET analysis, Ligand-based virtual screening, Drug discovery, Computational biology.

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INTRODUCTION

New therapeutic approaches are desperately needed because cancer continues to be a major global killer. The phosphoinositide 3-Kinase (PI3K) signaling pathway is particularly noteworthy among the cellular pathways implicated in cancer. This pathway is crucial for regulating various cellular functions such as growth, survival, and metabolism. Multiple malignancies' initiation and advancement have been linked to their dysfunction.

Recent advancements in computational biology have opened new avenues for drug discovery, particularly in the realm of targeted cancer therapies. Potential anti-cancer drugs are identified and evaluated using state-of-the-art methods like molecular docking, ligand-based virtual screening, and ADMET analysis. In this context, the flavonoid quercetin has emerged as a promising natural compound that can inhibit the PI3K pathway. Quercetin is a polyphenolic compound found in various fruits, vegetables, and medicinal herbs. It has been shown to exhibit anti-cancer properties by targeting the PI3K pathway, thereby inhibiting cell proliferation and inducing apoptosis in cancer cells.[1,2]

For the scope of this paper, we will employ a multi-faceted approach to explore the anti-cancer potential of quercetin and other bioactive compounds. Ligand-based virtual screening

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will be conducted using the SwissSimilarity web tool, focusing on an extensive database that includes approved drugs, bioactive substances, and a plethora of virtual compounds. Molecular docking simulations will be carried out to explore the binding interactions between selected compounds and the target protein. Furthermore, ADMET Analysis will be performed to assess the drug-likeness, bioavailability, and safety profiles of the selected compounds.[3,4]

Through these rigorous methodologies, this paper's goal is to review the literature on PI3K's function in cancer and its suppression as a treatment for cancer. with a special focus on the potential of quercetin flavonoids. We aim to shed light on the potential of PI3K and quercetin inhibitors as cornerstones in the next generation of anti-cancer therapies.[5]

MATERIALS AND METHODS

Selection of Quercetin Flavonoids

An extensive literature review and database searches were conducted to identify potential Quercetin flavonoids for our study. Compounds with known anti-cancer activities and those that are readily available for experimental validation were prioritized. The selection process also considered the diversity of quercetin flavonoids to ensure a comprehensive evaluation.

Protein Structure Preparation and Quality Assessment

The 3-dimensional structure of the target protein implicated in PI3K signaling was obtained from a reliable database, such as the Protein Data Bank (PDB). The protein structure was meticulously prepared, with energy minimized, water molecules removed, and hydrogen atoms added. SAVES was used to evaluate the protein structure preparation (https://saves.mbi.ucla.edu/) and ProSAweb (https://prosa.services.came.sbg.ac.at/prosa.php) servers.[6-8]

Ligand Preparation

The selected quercetin flavonoids were obtained from chemical databases and prepared for molecular docking studies. Ligand structures were cleaned to remove structural anomalies, followed by energy minimization. Partial charges were assigned to the ligands using appropriate force fields, consistent with the protein preparation, and topology files were generated.

Ligand-based Virtual Screening

Swiss Similarity, a web-based application available at (http://www.swisssimilarity.ch), was used to do ligand-based virtual screening. A selected quercetin flavonoid molecule in SMILES format was used as the query. The database for screening was extensive, featuring approved drugs, bioactive substances, and an additional 205 million virtual compounds. The focus was on the bioactive class of compounds, and the full ChEMBL database (version 29) was employed for the screening process.[9,10]

Molecular Docking

Molecular docking simulations were carried out using CB-Dock, a cavity-detection guided blind docking tool. The workflow involved the following key steps:

Cavity detection

Identifying potential binding sites within the protein structure.

Docking Center and Box Size Determination

Defining the search space for docking simulations.

Molecular Docking Simulations

Executing simulations to explore potential binding interactions.

Evaluation of Binding Poses

Assessing the binding poses based on docking scores to identify the most energetically favorable binding conformation.[11]

ADMET Analysis

ADMET properties of selected quercetin flavonoids were assessed using *in-silico* tools such as Swiss ADME. This analysis provided insights into the drug-likeness, bioavailability, and safety profiles of the selected compounds.[12,13]

RESULTS

Selection of Quercetin Flavonoids

We identified quercetin, a flavonoid shown in Figure 1, with known anti-cancer activities and accessibility for experimental validation. This selection encompassed a range of compounds, ensuring a comprehensive evaluation of their potential as PI3K inhibitors.

Assessment of Protein Structure Quality

The quality metrics of the target protein implicated in PI3K signaling were assessed using multiple online analytical tools. The Ramachandran plot (90.01%), ERRAT score (93.1845), verify3d Score (84.75%) and ProSAweb Z-score (-12.09) shown in Figures 2a, b, c and d, respectively. Collective results confirmed the 3D structure's exceptional quality and reliability, making it a strong candidate for further *in-silico* investigations.

Ligand-based Virtual Screening

The screening process yielded a total of 51 hits that showed promising interactions based on our pharmacophore models and 2D fingerprints. Notably, 10 of these hits were from the virtual compounds library, suggesting new avenues for synthesis and further experimental verification. The high-potential candidates are listed in Table 1.

Molecular Docking

Molecular docking simulations revealed strong binding affinities between the selected quercetin flavonoids and the PI3K protein. The binding energies ranged from -8.1 to -8.6, with DB01645 displaying the highest binding affinities. These findings are summarized in Table 2. DB01645 shows hydrogen bond interaction Glu: 880, Leu 657, Tyr 867. Pai

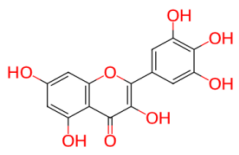


Figure 1: Structure of quercetin flavonoids

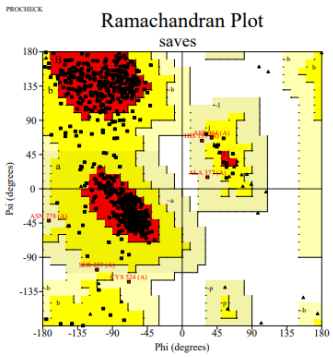


Figure 2a: Ramachandran plot

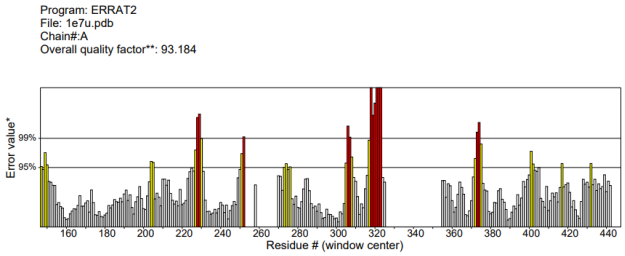


Figure 2b: ERRAT chart

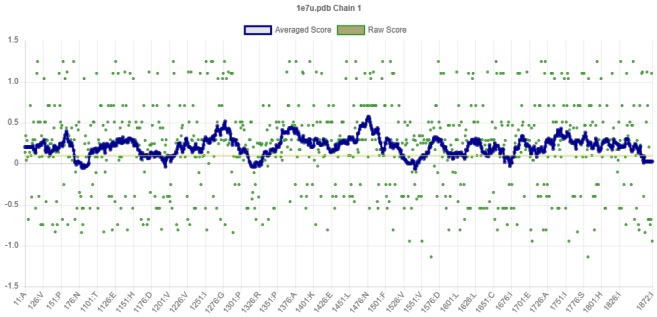


Figure 2c: VERIFY3D chart

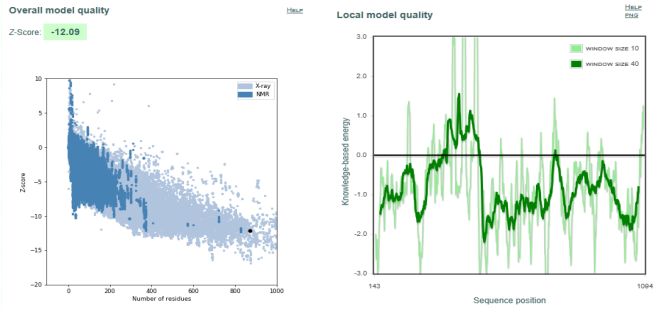


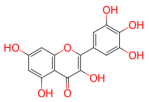
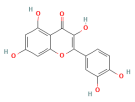
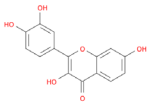
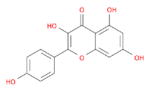
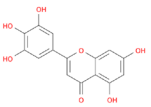
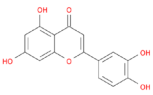
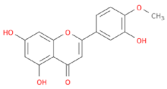
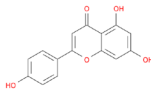
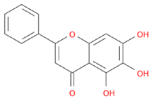
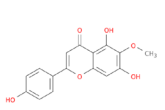
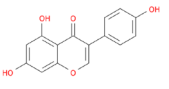
Figure 2d: ProSA chart

Pai- Stacking: Phe 694 and hydrophopbic contacts: Phe-698, Leu-660, Arg-849, Tyr-787, Cation-Pai Interaction Arg-849 shown in Figure 3.

ADMET Analysis

The ADMET analysis assessed the drug-likeness and safety profiles of the selected quercetin flavonoids (Table 3). The compound of interest displayed a variety of properties that provide insight into its suitability for drug development.

Table 1: Result of ligand-based virtual screening

Sr. no.	*Drug Bank ID; Similarity Score; Usual Name; SMILES*	*STRUCTURE*	*Auto Dock Vina Score*
1	DB02375; 1.000; Myricetin; OC1=CC(O)=C2C(OC(=C(O)C2=O)C2=CC(O)=C(O)C(O)=C2)=C1		-8.5
2	DB04216; 0.999; Quercetin; OC1=CC(O)=C2C(OC(=C(O)C2=O)C2=CC=C(O)C(O)=C2)=C1		-8.1
3	DB07795; 0.999; Fisetin; OC1=CC=C2C(OC(=C(O)C2=O)C2=CC=C(O)C(O)=C2)=C1		-8.2
4	DB01852; 0.998; Kaempherol; OC1=CC=C(C=C1)C1=C(O)C(=O)C2=C(O)C=C(O)C=C2O1		-8.4
5	DB08230; 0.998; Tricetin; OC1=CC(O)=C2C(=O)C=C(OC2=C1)C1=CC(O)=C(O)C(O)=C1		-8.3
6	DB15584; 0.997; Luteolin; OC1=CC(O)=C2C(=O)C=C(OC2=C1)C1=CC(O)=C(O)C=C1		-8.2
7	DB11259; 0.992; Diosmetin; COC1=C(O)C=C(C=C1)C1=CC(=O)C2=C(O)C=C(O)C=C2O1		-8.3
8	DB07352; 0.991; Apigenin; OC1=CC=C(C=C1)C1=CC(=O)C2=C(O)C=C(O)C=C2O1		-8.5
9	DB16101; 0.983; Baicalein; OC1=C(O)C(O)=C2C(=O)C=C(OC2=C1)C1=CC=CC=C1		-8.3
10	DB14008; 0.981; Hispidulin; COC1=C(O)C=C2OC(=CC(=O)C2=C1O)C1=CC=C(O)C=C1		-8.3
11	DB01645; 0.806; Genistein; OC1=CC=C(C=C1)C1=COC2=CC(O)=CC(O)=C2C1=O		-8.6

The compound with the formula C15H10O5 has a molecular weight of 270.24 g/mol and exhibits various characteristics that make it a suitable candidate for drug development.

Table 2: Molecular docking

Vina score	*Cavity size*	*Center*			*Size*		
		x	*y*	*z*	*x*	*Y*	*z*
-8.6	5149	20	55	25	35	29	21
-8.6	3827	28	48	37	33	21	31
-8.2	1451	56	28	27	27	21	21
-7.7	834	50	49	38	21	21	28
-5.9	732	51	36	9	21	21	21

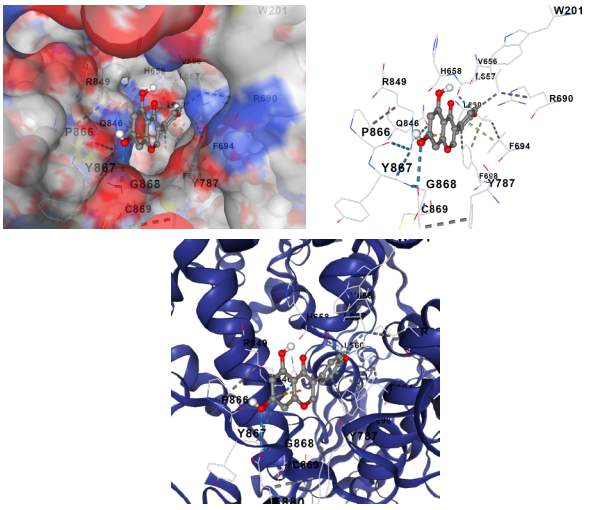


Figure 3: Interactions of compounds with protein

Physicochemical properties

It possesses 20 heavy atoms, with 16 of them being aromatic heavy atoms. The molecule has zero fraction of Csp3 and a single rotatable bond. Its high number of hydrogen bond acceptors (5) and donors (3) contribute to its specific interaction with biological targets.

Lipophilicity

The compound shows a range of Log Po/w values, with a consensus Log Po/w of 2.04, indicating moderate lipophilicity which is favorable for membrane permeability.

Water Solubility: Although its water solubility varies depending on the method used to calculate it, the compound is generally classified as soluble to moderately soluble. This feature could contribute to its bioavailability.

Pharmacokinetics

The compound has high gastrointestinal absorption but is not BBB permeant, making it suitable for peripheral targets but not for central nervous system targets. It is not a P-gp substrate, which is a positive indicator for bioavailability. It also inhibits multiple CYP enzymes (CYP1A2, CYP2D6, CYP3A4), suggesting potential for drug interactions that would need to be carefully managed.

Drug likeness and medicinal chemistry

According to various drug-likeness rules like Ghose, Lipinski, Egan, Veber, and Muegge, the compound meets all the criteria with zero violations, indicating a high likelihood of being drug-like. Additionally, it scores well in synthetic accessibility

Table 3: Results of ADMET analysis

Property category	*Property*	*Value*
Physicochemical	Formula	C15H10O5
	Molecular weight	270.24
	heavy atoms	20
	Aromatic heavy atoms	16
	Rotatable bonds Fraction	1
	Csp3	0.00
	H-bond donors	3
	H-bond acceptors	5
	TPSA	90.90
	Molar Refractivity	73.99
Lipophilicity (Log Po/w)	(WLOGP)	2.58
	(XLOGP3)	2.67
	(iLOGP)	1.91
	(SILICOS-IT)	0.52
	(MLOGP)	2.52
	Consensus Log Po/w	2.04
Water Solubility	Class	Soluble
	Log S (ESOL)	-3.72
	Log S (Ali)	-4.23
	Solubility	5.11e-02
	Solubility	1.59e-02
	Class	Moderately soluble
	Solubility	1.07e-02
	Log S (SILICOS-IT)	-4.40
	Class	Moderately soluble
Pharmacokinetics	P-gp substrate	No
	GI absorption	No
	BBB permeant	High
	Inhibitor of CYP2C9	Yes
	Inhibitor of CYP2C19	No
	Inhibitor of CYP1A2	No
	Inhibitor of CYP3A4	Yes
	Inhibitor of CYP2D6	Yes
	Log Kp (skin permeation)	-6.05
Druglikeness	Ghose	Yes
	Lipinski	Yes; 0 violation
	Veber	Yes
	Muegge	Yes
	Egan	Yes
	Bioavailability Score	0.55
Medicinal Chemistry	Brenk	0 alert
	PAINS	0 alert
	Synthetic accessibility	2.87
	Lead likeness	Yes

and shows no PAINS or Brenk alerts, further supporting its potential as a drug candidate.

The compound presents a balanced profile of physicochemical, pharmacokinetic, and drug-like properties, making it a promising candidate for further evaluation and development. However, its ability to inhibit multiple CYP enzymes could be a double-edged sword, offering both therapeutic opportunities and challenges related to drug-drug interactions.

CONCLUSION

This study aimed to explore the anti-cancer potentials of quercetin flavonoids through the inhibition of phosphoinositide 3-Kinase (PI3K), a key signaling pathway implicated in various forms of cancer. Through rigorous computational methods, quercetin was discovered by a battery of methods, including molecular docking, ligand-based virtual screening, and ADMET analysis, as a possible inhibitor of PI3K.

The quality assessment of the target protein structure confirmed its suitability for *in-silico* investigations, thereby validating the robustness of our computational approach. Our ligand-based virtual screening yielded several high-potential candidates, further narrowing down the scope for experimental validation. Molecular docking simulations revealed strong binding affinities between quercetin flavonoids and the PI3K protein, suggesting their potential as effective PI3K inhibitors.

The ADMET analysis provided valuable insights into the selected quercetin flavonoids' drug-likeness, safety profiles, and bioavailability. While the compound displayed promising attributes, it also presented challenges in terms of solubility and pharmacokinetics, indicating areas for further optimization.

Quercetin flavonoids may have anti-cancer effects, however, this needs to be confirmed in future studies using *in-vitro* and *in-vivo* validations. Further optimizations are required to improve the compound's pharmacokinetic properties and bioavailability. Given the preliminary findings of this study, quercetin flavonoids hold promise as novel anti-cancer agents through PI3K inhibition, warranting more comprehensive investigations.

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