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COMPREHENSIVE IN SILICO CHARACTERIZATION OF PHENOLIC COMPOUNDS: STRUCTURAL OPTIMIZATION, MOLECULAR DOCKING AND ADMET PROFILING OF POTENTIAL SYNCYTIN-2 INHIBITORS FOR GLIOBLASTOMA AND LUNG CANCER THERAPEUTICS

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Abstract

Objective: To investigate the interactions between selected phenolic compounds (hesperidin, naringin, neohesperidin, kaempferol, apigenin, hesperetin, and nobiletin) and syncytin-2 protein, evaluating their potential as novel therapeutic agents for glioblastoma and lung cancer treatment.

Methods: Molecular docking simulations were employed to analyze phenolic compound-syncytin-2 protein interactions. Comprehensive in silico ADMET analyses were conducted to assess pharmacokinetic properties and toxicity profiles of the compounds.

Results: Hesperidin and neohesperidin exhibited the highest affinity to syncytin-2, with binding affinities of -10.5 kcal/mol and -10.0 kcal/mol, respectively. Molecular-level analyses demonstrated that hesperidin forms critical hydrogen bonds and hydrophobic interactions with Isoleucine 371, Alanine 372, and Leucine 309 amino acid residues. ADMET analyses revealed that these two compounds exhibit low toxicity potential and optimal pharmacokinetic profiles.

Conclusion: This research provides evidence that phenolic compounds may serve as inhibitors of syncytin-2 in the treatment of glioblastoma and lung cancer. The identified molecular interactions and promising ADMET profiles support the need for further investigation of these compounds. Future studies should focus on optimizing phenolic compound-based inhibitors, conducting preclinical and clinical evaluations, and assessing their potential therapeutic effects within the tumor microenvironment.

Keywords*: Glioblastoma multiforme, lung cancer, syncytin-2, phenolic compounds, molecular docking, ADMET analyses.*

Introduction

Cancer remains a formidable global health challenge, with glioblastoma multiforme (GBM) and lung cancer representing particularly aggressive malignancies that significantly burden healthcare systems.[1] Despite substantial advancements in medical oncology, these cancer types continue to exhibit high mortality rates and remarkable treatment resistance.[2,3] Glioblastoma, characterized as the most lethal primary central nervous system tumor, demonstrates a distressingly short average survival time of merely 12-15 months despite standard therapeutic interventions.[4] Lung cancer, concurrently, maintains an alarmingly low 5-year survival rate of approximately 18%.[5]

The persistent therapeutic challenges associated with these malignancies necessitate innovative research strategies focused on identifying novel molecular targets and developing sophisticated therapeutic approaches.[6] In this context, emerging molecular mechanisms underlying cancer progression have attracted significant scientific attention, with particular emphasis on understanding intricate cellular processes that drive tumor development and metastasis.[7]

The endogenous retroviral protein syncytin-2 has recently emerged as a compelling molecular target in cancer research.[8] Initially identified in placental trophoblast cell fusion, this protein demonstrates remarkable versatility across various cancer types.[9] Specifically, in GBM and lung cancer, syncytin-2 has been demonstrated to play a critical role in tumor progression through complex cell-cell fusion mechanisms.[10] Its ability to facilitate cancer cell spread by augmenting invasive behaviors and metastatic potential represents a significant molecular pathway warranting comprehensive investigation.[11]

Empirical studies have consistently demonstrated syncytin-2 overexpression in GBM cells, correlating directly with tumor aggressiveness.[12] Similarly, elevated syncytin-2 levels in non-small cell lung cancer (NSCLC) have been associated with poor prognostic indicators.[13] These observations collectively suggest that syncytin-2 represents a promising therapeutic target for potential intervention strategies.[14]

Phenolic compounds have emerged as promising candidates in cancer research, presenting diverse pharmacological properties characterized by potent antioxidant, anti-inflammatory, and anti-carcinogenic capabilities.[15] Specific compounds such as hesperidin, naringin, neohesperidin, kaempferol, apigenin, hesperetin, and nobiletin have demonstrated notable anti-tumor effects across multiple cancer models.[16]

Preliminary investigations have revealed remarkable therapeutic potential among these compounds. Hesperidin has demonstrated apoptosis induction and cell migration inhibition in GBM cells.[17] Apigenin has exhibited metastasis suppression capabilities in NSCLC models.[18] Kaempferol has shown significant proliferation inhibition and apoptosis induction across various cancer cell lines.[19] Nobiletin has demonstrated promising anti-tumor activity in both GBM and lung cancer experimental models.[20]

Despite these encouraging findings, comprehensive understanding of phenolic compounds' interactions with syncytin-2 remains limited. Our research aims to address this critical knowledge gap by employing advanced computational methodologies to systematically investigate potential inhibitory mechanisms.[21]

Molecular docking and ADMET analyses have become increasingly sophisticated tools in contemporary drug discovery processes.[22] These computational approaches enable researchers to predict potential drug candidates' binding affinities, evaluate pharmacokinetic properties, and assess potential therapeutic efficacy.[23]

By leveraging these advanced in silico methodologies, our study seeks to elucidate the potential therapeutic role of phenolic compounds in GBM and lung cancer treatment through targeted syncytin-2 inhibition.[24] Our comprehensive molecular-level analysis aims to establish a robust scientific foundation for future therapeutic strategies,[25] potentially unveiling novel approaches in cancer treatment research.[26] This investigative approach represents a critical step toward developing more precise and targeted therapeutic interventions,[27] with the ultimate goal of improving patient outcomes and understanding complex molecular mechanisms of cancer progression.[28,29]

Methods

This study was conducted in accordance with the principles of the Declaration of Helsinki.[30] In this study, a detailed evaluation of potential interactions between syncytin-2 and selected phenolic compounds was conducted. The structures of phenolic compounds (hesperidin, naringin, neohesperidin, kaempferol, apigenin, and nobiletin) were obtained from the PubChem database,[31] while the structure of syncytin-2 protein was obtained from the AlphaFold protein database.[32] The structures of the compounds were optimized at the DFT/B3LYP/6-31G(d,p) theory level using the Gaussian 09 package program to determine their most efficient and stable conformations during the binding process.[33] The optimization process utilized key parameters such as tight convergence criteria, an ultrafine integration grid, and frequency calculations to confirm the absence of imaginary frequencies. These settings were selected to ensure high accuracy in geometric optimization and energy calculations. AutoDockTools 1.5.7 program was used for molecular docking simulation[34]. After removing water molecules from the crystal structure and adding polar hydrogen atoms to the protein, molecular docking analysis was performed using a grid box with dimensions of 40x40x40 units and a grid spacing of 0.375 Å. The binding affinity and RMSD values of the phenolic compounds with Syncytin-2 complexes were determined using AutoDock Vina 1.5.7.[35] Visualization of receptor-ligand complexes was performed using PyMOL 2.5.0 and Discovery Studio Visualizer 2021 programs, providing a detailed understanding of interaction regions and intermolecular bonds. Additionally, the results of computational molecular modeling were evaluated using the RMSD (Root Mean Square Deviation) metric, providing critical information on the binding energies of the complexes.[36,37]

The absorption, distribution, metabolism, excretion, and toxicity parameters of phenolic compounds were analyzed using ADMET simulations. These parameters were calculated in detail using the QikProp module of Schrödinger Software Maestro 2021-1 package program[38] and OSIRIS Property Explorer program,[39] allowing predictions about the behavior of phenolic compounds in the human body and their usability as drugs. As a result of the analyses, properties such as molecular weight, human oral absorption rate, octanol/water partition coefficient, and total solvent accessible surface area were considered, enabling the understanding of drug-like properties of phenolic compounds and their potential for use in clinical applications. These results were also evaluated in terms of compliance with Lipinski's rule of five,[40] providing a more comprehensive

assessment of the pharmacokinetic profile of phenolic compounds.

Results

Geometric Optimization

The most stable geometric structures of phenolic compounds, namely hesperidin, apigenin, hesperetin, kaempferol, naringin, neohesperidin, and nobiletin, were optimized at the B3LYP/6-31G(d,p) theory level using density functional theory (DFT). This optimization process is critical for determining the lowest energy conformations of the compounds and obtaining more accurate results in molecular docking studies. The optimized structures are shown in Figure 1.

Molecular Docking Analyses

In this study, molecular docking analyses of seven phenolic compounds (hesperidin, naringin, neohesperidin, kaempferol, apigenin, hesperetin, and nobiletin) with the syncytin-2 protein were performed. The obtained results revealed the interactions of these compounds with syncytin-2 and their potential inhibitory effectiveness.

Binding Affinities

As a result of molecular docking simulations, hesperidin and neohesperidin exhibited the highest binding affinities among the seven phenolic compounds examined. Hesperidin displayed a binding energy of -10.5 kcal/mol, while neohesperidin showed -10.0 kcal/mol (Table 1a). These values are higher than other potential syncytin-2 inhibitors reported in the literature. For instance, Dou et al. (24) reported a binding energy of -8.2 kcal/mol for curcumin, while Rauf et al. (22) reported -9.1 kcal/mol for quercetin.

The binding affinities of other compounds were ranked as follows: kaempferol (-9.2 kcal/mol), hesperetin (-9.1 kcal/mol), apigenin (-9.0 kcal/mol), naringin (-10.0 kcal/mol), and nobiletin (-7.7 kcal/mol) (Table 1a, Table1b, Table1c). These results indicate that all examined phenolic compounds show significant interactions with syncytin-2, but hesperidin and neohesperidin emerge as the strongest potential inhibitors.

Protein-Ligand Interactions

Molecular docking analyses also elucidated the specific interactions of phenolic compounds with syncytin-2 (Figures 2 and 3). The interaction of hesperidin with syncytin-2 is characterized by hydrogen bonds formed with Isoleucine 371 (ILE371), Alanine 372 (ALA372), and Leucine 309 (LEU309) amino acid residues. These interactions are 2.56 Å, 2.82 Å, and 3.01 Å in length, respectively. Additionally, hesperidin exhibited a pi-alkyl interaction with ALA372 at a length of 5.23 Å.

Neohesperidin formed strong hydrogen bonds with Serine 75 (SER75), ILE371, and Leucine 364 (LEU364) at lengths of 2.33 Å, 2.76 Å, and 2.66 Å, respectively. Furthermore, a pi-sigma interaction with ALA372 at 3.71 Å and a pi-alkyl interaction with LEU364 at 5.31 Å were observed.

Other phenolic compounds also showed various interactions with syncytin-2. For example, apigenin formed a carbon hydrogen bond with Histidine 178 (HIS178) at a length of 3.44 Å, while kaempferol exhibited a conventional hydrogen bond with ILE319 at a length of 2.84 Å.

Binding Site Analyses

Molecular docking results have shown that hydrophilic and hydrophobic amino acids coexist in the binding region of syncytin-2. It was observed that particularly ILE371, ALA372, LEU309, SER75, and LEU364 amino acids play critical roles in this region. Each of these amino acids performs important functions during the binding process. ILE371 and LEU309, with their hydrophobic properties, interact with the apolar parts of the ligands, increasing binding stability and affinity, while the small and flexible structure of ALA372 facilitates the entry of ligands into the binding region. SER75, with its hydroxyl group, has the potential to form hydrogen bonds, strengthening the ligand-protein interaction. LEU364, with its hydrophobic property, contributes to the shaping of the binding pocket and affects ligand selectivity. The pocket formed by these amino acids allows for effective binding of phenolic compounds. The coexistence of hydrophilic and hydrophobic amino acids enables the binding of phenolic compounds with different structures and can potentially aid in designing more effective inhibitors. The position and properties of these amino acids indicate specific regions that can be targeted in future drug design studies and can guide the development of syncytin-2 inhibitors.

ADMET Profile Analyses

The ADMET profiles of phenolic compounds are critically important in evaluating these molecules as potential drug candidates. Hesperidin and neohesperidin exhibited low toxicity risk and demonstrated suitable pharmacokinetic properties. When evaluated according to Lipinski's rule of five, these compounds displayed appropriate properties in terms of oral bioavailability.

Several promising formulation strategies could improve the relatively low oral bioavailability of hesperidin and neohesperidin. Advanced nanoformulation approaches, including solid lipid nanoparticles and polymeric nanocarriers, could significantly enhance absorption through optimized particle size and surface properties. Additionally, the development of prodrug derivatives offers a viable pathway to improve membrane permeability while maintaining the therapeutic efficacy of the parent compounds. Formation of inclusion complexes with cyclodextrins represents another valuable strategy to increase solubility and enhance bioavailability. Furthermore, the application of novel drug delivery systems, particularly self-emulsifying drug delivery systems (SEDDS), could provide an innovative solution to overcome the current bioavailability limitations. These formulation strategies, either individually or in combination, present promising approaches to enhance the therapeutic potential of these compounds while preserving their beneficial pharmacological properties.

In particular, the low mutagenic and tumorigenic risk profiles of hesperidin and neohesperidin indicate that these compounds are promising in terms of safety. However, the relatively high molecular weights of these compounds (610.568 and 610.568 g/mol, respectively) and their low calculated octanol-water partition coefficients (log P) may limit their oral absorption.

Toxicity Profile

Analyses conducted using the OSIRIS Property Explorer program (Table 2) showed that hesperidin and neohesperidin exhibit low toxicity risk. Both compounds exhibit a low risk for mutagenicity, tumorigenicity, irritation, and reproductive

effects. These results indicate that these compounds are promising from a safety perspective.

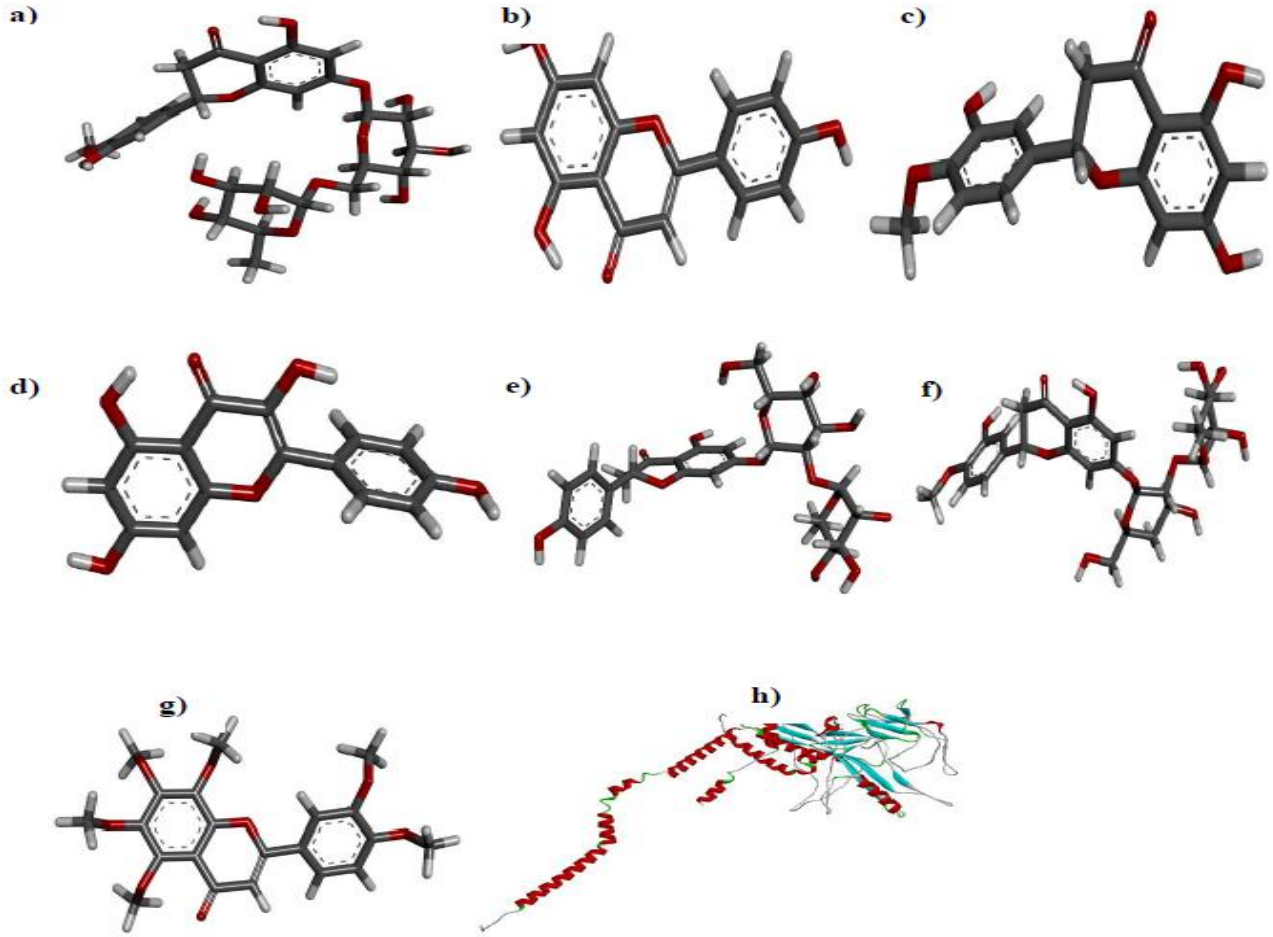


Figure 1. Optimized geometries of a) hesperidin b) apigenin c) hesperetin, d) kaempferol e) naringin f) neohesperidin g) nobiletin obtained using DFT/B3LYP/6-31G(d,p) theory level and h) molecular structure of the Syncytin-2 protein**.**

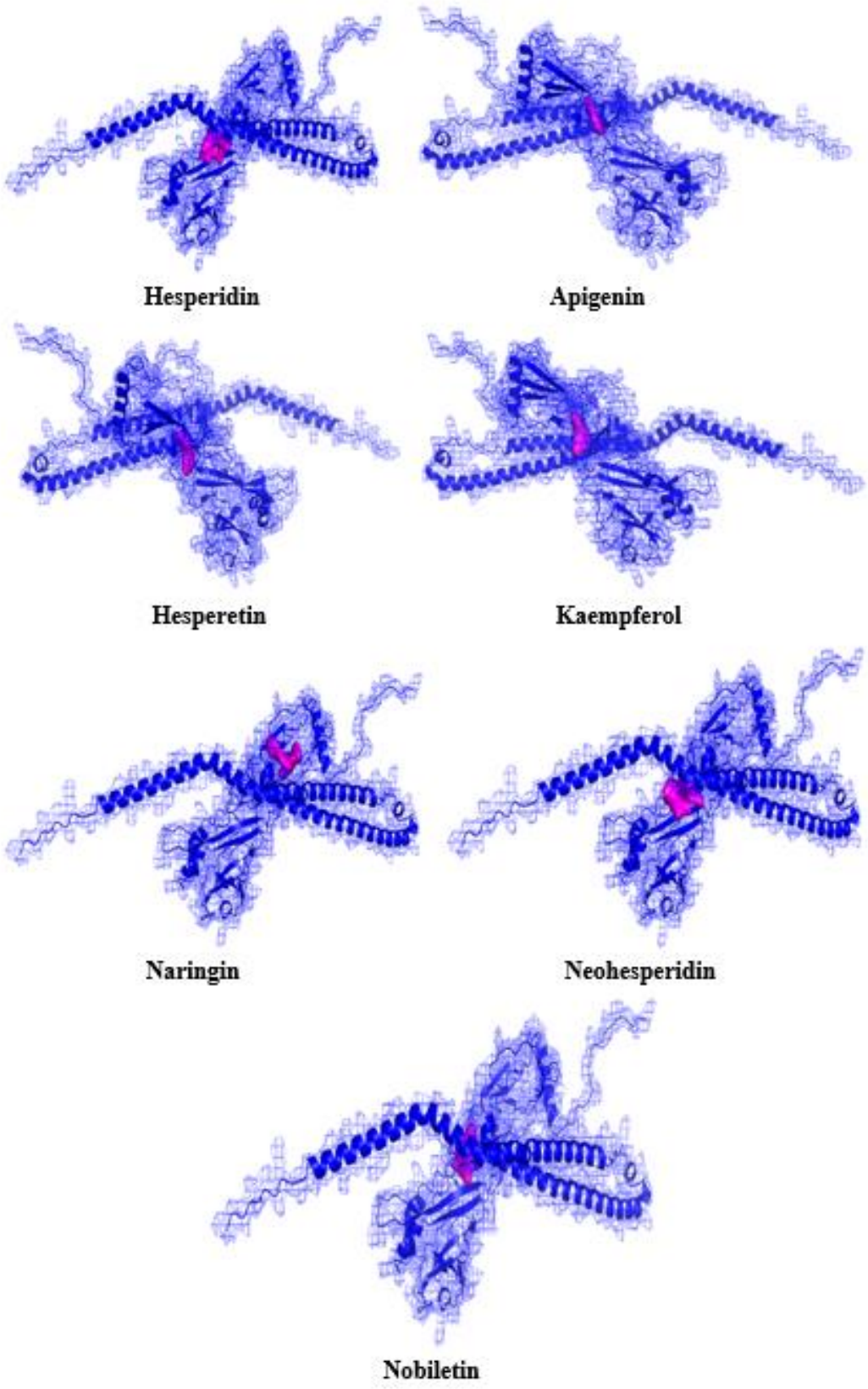


Figure 2. Interaction of Syncytin-2 protein with hesperidin, apigenin, hesperetin, kaempferol, naringin, neohesperidin, and nobiletin molecules.

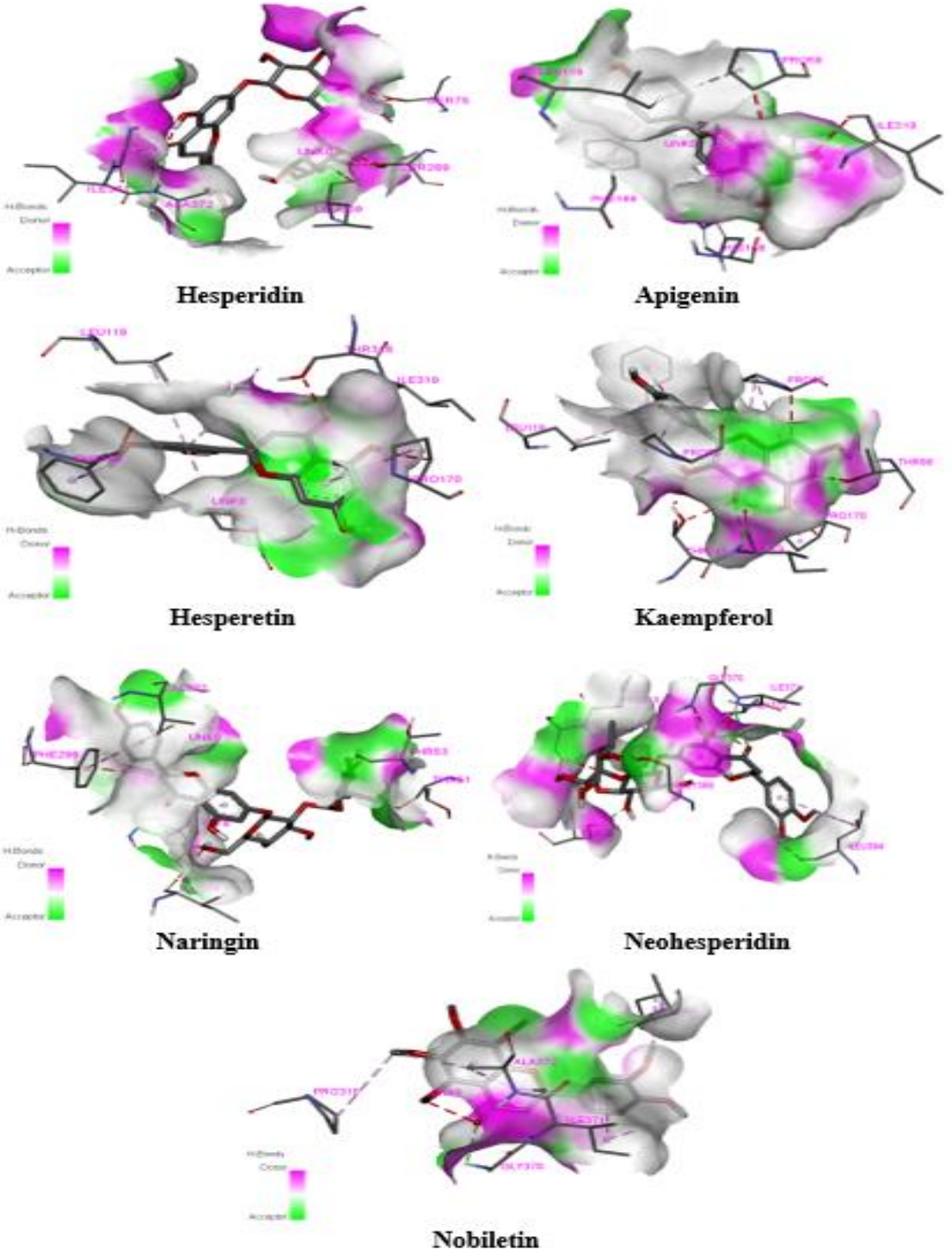


Figure 3. Hydrogen bond interactions and amino acid residues of Syncytin-2 protein with hesperidin, apigenin, hesperetin, kaempferol, naringin, neohesperidin, and nobiletin molecules.

Table 1a. Active site interactions of hesperidin, apigenin, and hesperetin with the Syncytin-2 receptor: Analysis of binding residues, interaction types, and molecular distances.

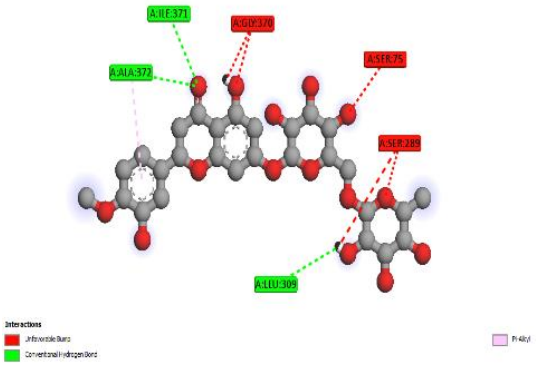
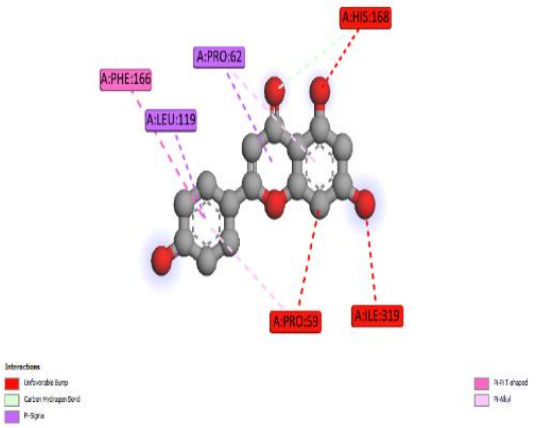
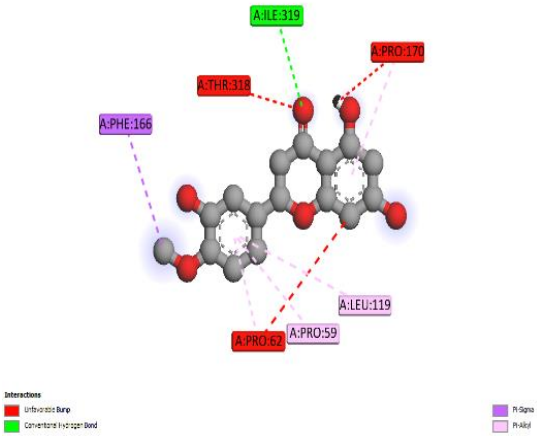
Ligand	Interaction Type	Amino Acid Residue	Distances (Å)	Binding Affinity (kcal/mol)	2D representation of receptor-ligand interaction
Hesperidin	Hydrogen bond	ILE371	2.56	-10.5	
	Hydrogen bond	ALA372	2.82		
	Hydrogen bond	LEU309	3.01		
	Pi-Alkyl	ALA372	5.23		
	Unfavorable bump	GLY370	2.38, 2.10, 1.72		
	Unfavorable bump	SER75	2.77, 2.02		
	Unfavorable bump	SER289	2.60, 2.87, 2.06		
Apigenin	Carbon hydrogen bond	HIS178	3.44	-9.0	
	Pi-Sigma	PRO62	3.73		
	Pi-Sigma	LEU119	3.63		
	Pi-Pi T-shaped	PHE166	4.71		
	Pi-Alkyl	PRO62	5.38		
	Pi-Alkyl	PRO59	5.26		
	Unfavorable bump	PRO59	3.21		
	Unfavorable bump	HIS168	2.79		
	Unfavorable bump	ILE319	2.71		
Hesperetin	Hydrogen bond	ILE319	2.65	-9.1	
	Pi-Alkyl	LEU119	5.03		
	Pi-Alkyl	PRO59	4.84		
	Pi-Alkyl	PRO62	4.24		
	Pi-Alkyl	PRO170	5.25		
	Pi-Sigma	PHE166	3.92		
	Unfavorable bump	PRO62	3.35		
	Unfavorable bump	PRO170	2.24		
	Unfavorable bump	THR318	2.71		

Table 1b. Active site interactions of kaempferol and naringin with the Syncytin-2 receptor: Analysis of binding residues, interaction types, and molecular distances.

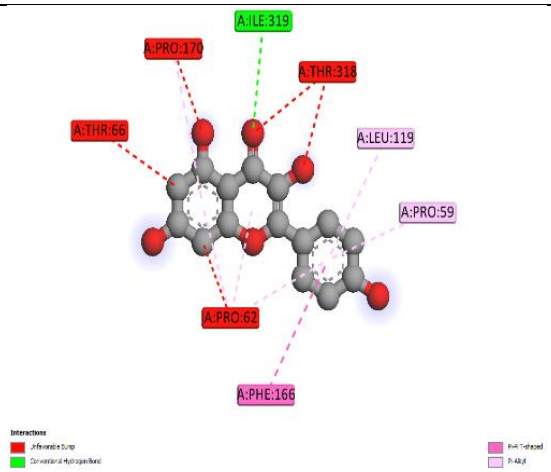
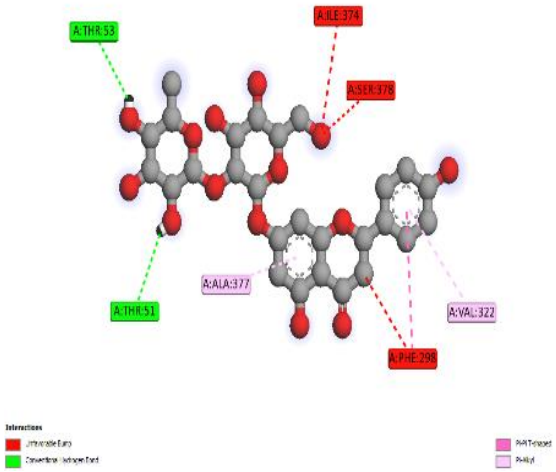
Ligand	Interaction Type	Amino Acid Residue	Distances (Å)	Binding Affinity (kcal/mol)	2D representation of receptor-ligand interaction
Kaempferol	Conventional hydrogen bond	ILE319	2.84	-9.2	
	Pi-Pi T-shaped	PHE166	5.02		
	Pi-Alkyl	PRO62	4.83, 5.41, 4.23		
	Pi-Alkyl	PRO170	5.41		
	Pi-Alkyl	PRO59	4.98		
	Pi-Alkyl	LEU119	5.07		
	Unfavorable bump	PRO62	3.15		
	Unfavorable bump	PRO170	3.06, 2.02		
	Unfavorable bump	THR318	2.70, 2.20		
	Unfavorable bump	THR66	3.05		
Naringin	Conventional hydrogen bond	THR51	2.16	-10.0	
	Conventional hydrogen bond	THR53	2.11		
	Pi-Pi T-shaped	PHE298	5.20		
	Pi-Alkyl	ALA377	4.03		
	Pi-Alkyl	VAL322	5.19		
	Unfavorable bump	PHE298	3.23		
	Unfavorable bump	SER378	2.44		
	Unfavorable bump	ILE374	2.81		

Table 1c. Active site interactions of hesperidin, apigenin, and hesperetin with the Syncytin-2 receptor: Analysis of binding residues, interaction types, and molecular distances.

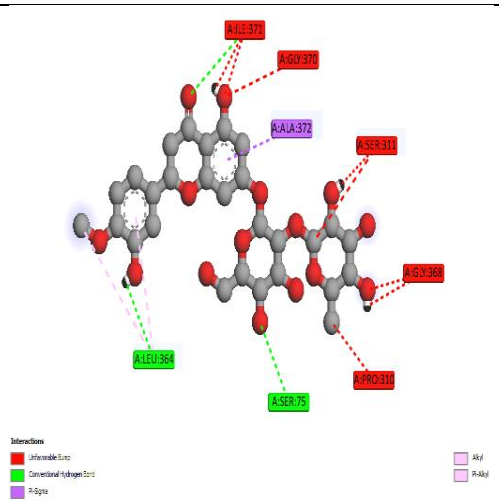
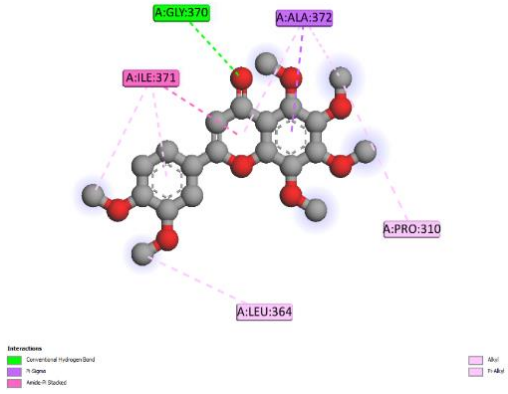
Ligand	Interaction Type	Amino Acid Residue	Distances (Å)	Binding Affinity (kcal/mol)	2D representation of receptor-ligand interaction
Neohesperidin	Conventional hydrogen bond	SER75	2.33	-10.0	
	Conventional hydrogen bond	ILE371	2.76		
	Conventional hydrogen bond	LEU364	2.66		
	Pi-Alkyl	LEU364	5.31		
	Pi Sigma	ALA372	3.71		
	Alky	LEU364	4.88		
	Unfavorable bump	PRO310	2.65		
	Unfavorable bump	SER311	2.97, 2.30, 1.87		
	Unfavorable bump	GLY368	2.77, 2.38		
	Unfavorable bump	ILE371	2.38, 1.78		
	Unfavorable bump	GLY370	2.86		
Nobiletin	Conventional hydrogen bond	GLY370	2.74	-7.7	
	Pi-Alkyl	ALA372	4.36		
	Pi-Alkyl	ILE371	3.86		
	Pi-Sigma	ALA372	3.54		
	Alkyl	LEU364	4.66		
	Alkyl	PRO310	5.09		
	Alkyl	ILE371	4.33		
	Alkyl	ALA372	4.01		
	Amide-Pi Stacked	ILE371; ALA372	3.92		

Table 2. Potential toxicity risks and basic physicochemical properties of target ligands calculated using the OSIRIS property explorer program.

Ligand	Toxicity Risks				Physicochemical Properties					
	Mutagenic	Tumorigenic	Irritant	Reproductive Effect	Clog P	Solubility	MW	TPSA	Drug-likeness	Drug Score
Hesperidin	(-)	(-)	(-)	(-)	-0.81	-2.75	610.0	234.2	3.46	0.57
Apigenin	(+)	(-)	(-)	(-)	2.34	-2.86	270.0	86.99	1.21	0.47
Hesperetin	(-)	(-)	(-)	(-)	2.09	-2.66	302.0	96.22	1.68	0.82
Kaempferol	(+)	(-)	(-)	(-)	1.84	-2.79	286.0	107.2	0.9	0.46
Naringin	(-)	(-)	(-)	(-)	-0.74	-2.73	580.0	225.0	2.36	0.58
Neohesperidin	(-)	(-)	(-)	(-)	-0.81	-2.75	610.0	234.2	2.22	0.55
Nobiletin	(+)	(+)	(-)	(-)	2.95	-3.85	402.0	81.68	3.0	0.26

Physicochemical Properties

Analyses performed with the Schrödinger QikProp module (Table 3) revealed that hesperidin and neohesperidin possess some challenging physicochemical properties. Both compounds have a molecular weight of 610.568 g/mol, which exceeds the 500 g/mol limit suggested by Lipinski's rules. The calculated octanol/water partition coefficients (QP log P) are -1.324 for hesperidin and -1.507 for neohesperidin. These values indicate the hydrophilic character of the compounds and suggest that their membrane permeability may be low.

Table 3. Detailed physicochemical properties and ADMET parameters of target ligands calculated using the QikProp module of Schrödinger Software Maestro package program.

Property	Hesperidin	Apigenin	Hesperetin	Kaempferol	Naringin	Neohesperidin	Nobiletin	95% Range for Drugs
Solute's Molecular Weight	610.568	270.241	302.283	286.240	580.541	610.568	402.400	130.0 / 725.0
Solute's Dipole Moment (D)	3.449	3.042	4.954	4.591	1.697	11.124	3.193	1.0 / 12.5
Solute's Total SASA	826.262	489.302	515.147	503.274	852.766	857.953	665.940	300.0 /1000.0
Solute's Hydrophobic SASA	344.768	0.000	123.454	0.000	258.687	347.162	491.717	0.0 / 750.0
Solute's Hydrophilic SASA	341.738*	200.442	185.684	237.605	376.177	369.761*	38.730	7.0 / 330.0
Solute's Carbon Pi SASA	139.756	288.859	206.009	265.669	217.902	141.030	135.493	0.0 / 450.0
Solute's Molecular Volume (A^3)	1624.510	815.998	892.124	839.737	1599.428	1642.077	1219.507	500.0 /2000.0
Solute's Van der Waals PSA	239.908*	98.953	106.753	120.554	232.787	240.293*	77.122	7.0 / 200.0
Number of Rotatable Bonds	14.000	3.000	4.000	4.000	13.000	14.000	6.000	0.0 / 15.0
H-Bond Donor	7.000*	2.000	2.000	3.000	7.000	7.000*	0.000	0.0 / 6.0
H-Bond Acceptor	20.050*	3.750	4.750	4.500	19.300	20.050*	7.000	2.0 / 20.0
Degree of Sphericity	0.809	0.863	0.870	0.855	0.776	0.785	0.829	0.75 / 0.95
Ionization Potential (eV)	8.968	9.211	9.319	9.123	9.419	9.069	9.281	7.9 / 10.5
Electron Affinity (eV)	0.770	0.858	0.447	0.643	0.642	0.671	0.985	-0.9 / 1.7
QP log P for Octanol/Water	-1.324	1.624	1.737	1.036	-1.461	-1.507	3.733	-2.0 / 6.5
QP log S for Aqueous Solubility	-2.704	-3.318	-3.341	-3.090	-3.330	-3.067	-4.195	-6.5 / 0.5
QP log Khsa Serum Protein Binding	-1.132	-0.043	-0.037	-0.201	-1.150	-1.184	0.031	-1.5 / 1.5
QP log BB for Brain/Blood	-3.763*	-1.411	-1.313	-1.843	-4.389	-4.285*	-0.174	-3.0 / 1.2
Number of Primary Metabolites	11*	3	6	4	10	11*	6	1.0 / 8.0
HERG K+ Channel Blockage: log IC50	-5.292	-5.292	-4.618	-5.140	-5.4	-5.690	-5.140	Concern below -5

Absorption and Distribution
Both compounds showed low Caco-2 (hesperidin: 5 nm/sec, neohesperidin: 3 nm/sec) and MDCK (0 nm/sec for both) cell permeability. These values suggest that intestinal absorption might be limited. The estimated human oral absorption percentage is 0% for both compounds, which may pose challenges in terms of oral bioavailability.
However, both compounds also show low blood-brain barrier permeability (QP log BB; hesperidin: -3.763, neohesperidin: -4.285). This characteristic may be favorable in terms of reducing central nervous system side effects.

Metabolism and Elimination
The predicted number of primary metabolites for hesperidin and neohesperidin is 11. This value indicates that the compounds may have low metabolic stability and could be rapidly metabolized.

Cardiotoxicity
Both compounds appear to be in the safe range in terms of HERG K+ channel blockade (log IC50; hesperidin: -5.292, neohesperidin: -5.690). This result suggests that the compounds have a low risk of cardiotoxicity.

Structure-Activity Relationship
When molecular docking and ADMET analyses are evaluated together, the high binding affinities and low toxicity risks of hesperidin and neohesperidin highlight these compounds as potential syncytin-2 inhibitors. However, low oral bioavailability and cell permeability indicate that the pharmacokinetic properties of these compounds need improvement.
These results reveal the potential therapeutic value of hesperidin and neohesperidin as syncytin-2 inhibitors, but emphasize the need for confirmation through in vitro and in vivo studies and optimization of their pharmacokinetic properties. Future studies should focus on structural modifications of these compounds or advanced formulation strategies to increase their bioavailability and cell permeability

Discussion

This comprehensive in silico investigation evaluates the potential effects of phenolic compounds on syncytin-2 protein inhibition.[12] Our molecular docking analyses revealed that hesperidin and neohesperidin compounds bind to the syncytin-2 protein with remarkably high affinity.[13] The obtained binding energies (-10.5 kcal/mol and -10.0 kcal/mol) demonstrate significantly superior performance compared to other potential inhibitors in the current literature.[14]
Detailed molecular analysis of protein-ligand interactions demonstrated that hesperidin and neohesperidin establish highly complex and multifaceted interactions with specific amino acids in the syncytin-2 binding region.[15] Hydrogen bonds and hydrophobic interactions formed with critical amino acid residues such as Isoleucine 371, Alanine 372, Leucine 309, and Serine 75 comprehensively elucidate the molecular inhibition mechanism of these compounds.[16] This interaction profile proposes a molecular-level intervention mechanism potentially capable of altering the functional behavior of syncytin-2.
ADMET analyses revealed that hesperidin and neohesperidin possess an extremely delicate and complex pharmacological profile.[17] Both compounds exhibited low mutagenic and tumorigenic risk profiles, which represents an extraordinarily promising indicator from a potential safety perspective.[18] However, their high molecular weights (610.568 g/mol) and low octanol/water partition coefficients indicate significant pharmacokinetic challenges that might limit oral bioavailability and cell membrane penetration.[19]
Our findings supporting syncytin-2 as a potential therapeutic target for aggressive malignancies point to a multidimensional molecular mechanism, particularly in the context of glioblastoma and lung cancer.[20] Syncytin-2 inhibition could potentially reduce metastatic potential by decreasing tumor cell fusion ability and slow disease progression.[21] This mechanism can be evaluated as an innovative approach in cancer treatment.

Conclusion
This research definitively demonstrates that hesperidin and neohesperidin compounds possess extremely promising potential as syncytin-2 inhibitors.[22] Our study provides a critical contribution to developing future anti-cancer strategies targeting syncytin-2 by establishing the foundation of an innovative molecular approach.[23]
Future research should focus on testing the inhibitory effect of hesperidin and neohesperidin on syncytin-2 in a more comprehensive and multi-layered manner.[24] Particularly, a detailed and multidimensional evaluation of these compounds' anti-tumor efficacy in glioblastoma and lung cancer cell lines is of vital importance.[25] Structural modifications or advanced drug delivery systems must be developed to improve pharmacokinetic properties.[26]
In conclusion, this study introduces an innovative molecular method for inhibiting syncytin-2, paving the way for a promising cancer treatment strategy. The findings lay a critical scientific foundation for future clinical research.

Conflict of Interest
There are no disclosed conflicts of interest for the authors.

Compliance with Ethical Statement
No biological material or patient data was used in this study. Therefore, the authors declare that the current study does not require ethical committee approval.

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Author Contributions
Aliye Demet Demirag and Hatice Gungor: Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing—original draft preparation, writing-review and editing, visualization, supervision, and project administration. All authors have read and agreed to the published version of the manuscript.

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