Molecular docking studies of flavonoids against driver markers in low-grade glioma: exploring novel therapeutic approaches

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Submission date: 28-Jan-2025 10:50PM (UTC-0800)
Submission ID: 2559699364
File name: IJAR-50062.docx (24.49K)
Word count: 1698
Character count: 10218

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Abstract

Low-grade gliomas (LGGs) are a group of slow-growing brain tumors that often exhibit long-term survival in patients. However, the lack of effective therapeutic strategies and the eventual progression to high-grade gliomas pose significant clinical challenges. Driver markers, such as IDH1, TP53, and ATRX mutations, play pivotal roles in the molecular pathogenesis of LGGs. Flavonoids, a group of polyphenolic compounds found in fruits and vegetables, have been recognized for their potential anticancer properties. In this study, we employed molecular docking to evaluate the binding affinities of flavonoids against IDH1, a key driver marker in LGG. Our results demonstrate that certain flavonoids exhibit strong binding interactions with the active site of IDH1, suggesting their potential as novel therapeutic agents for LGG. This study provides insights into the development of flavonoid-based therapies targeting driver markers in LGG.

Keywords: Low-grade glioma, driver markers, IDH1, molecular docking, flavonoids, cancer therapy.

1. Introduction

Low-grade gliomas (LGGs) are a subset of primary brain tumors classified by their slow growth and relatively better prognosis compared to high-grade gliomas (HGGs). Despite this, the progression of LGGs to more aggressive forms and the challenges associated with their treatment necessitate the development of novel therapeutic approaches. Recent molecular characterization of LGGs has identified key driver mutations that contribute to tumorigenesis, such as mutations in isocitrate dehydrogenase 1 (IDH1), tumor suppressor p53 (TP53), and ATRX. IDH1 mutations, in particular, have emerged as a hallmark of LGG and offer promising targets for therapeutic intervention [1,2].

Flavonoids, a large group of naturally occurring polyphenolic compounds, are well-known for their antioxidant, anti-inflammatory, and anticancer properties. Many flavonoids, such as quercetin, kaempferol, and apigenin, have shown promising effects in preclinical models of various cancers, including gliomas [3]. However, the molecular mechanisms underlying their effects on LGG driver markers remain poorly understood.

Molecular docking studies provide a powerful tool to predict the interaction between small molecules and protein targets [4]. In this study, we aim to utilize molecular docking to investigate the binding affinities of several flavonoids against the IDH1 protein, focusing on their potential as novel therapeutic agents for LGG treatment.

2. Materials and methods

2.1. Selection of flavonoids

The flavonoids selected for docking studies were based on their known anticancer properties and accessibility in the literature. These included quercetin, kaempferol, apigenin, and luteolin. The chemical structures of these compounds were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/) [5].

2.2. Target protein preparation

The crystal structure of IDH1 (PDB ID: 4I3L) was retrieved from the Protein Data Bank (https://www.rcsb.org/). The protein structure was prepared using AutoDockTools to remove water molecules, add hydrogen atoms, and assign the appropriate charges to the protein structure [6].

2.3. Molecular docking

Molecular docking simulations were performed using AutoDock Vina (version 1.1.2) to predict the binding affinities of the selected flavonoids against IDH1 [6]. The docking grid box was centered around the active site of the IDH1 protein. The binding sites were identified based on known co-crystallized ligands and literature reports on the active sites of IDH1. The docking procedure was carried out with default settings [7], and the top-ranked docking poses were analyzed based on the docking score and binding energy.

2.4. Binding affinity and interaction analysis

The binding affinity of each flavonoid to IDH1 was evaluated based on the docking scores (in kcal/mol). The binding poses were analyzed using PyMOL (version 2.5) to visualize the

interactions between the flavonoids and the protein's active site [7]. Hydrogen bonds, hydrophobic interactions, and electrostatic interactions were identified to understand the molecular basis of binding.

2.5. ADMET prediction

To evaluate the drug-likeness and potential toxicity of the flavonoids, we used the ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) prediction tool available through the SwissADME web server (http://www.swissadme.ch/) [8].

3. Results

3.1. Molecular docking of flavonoids with IDH1

Molecular docking results revealed that all selected flavonoids exhibited promising binding interactions with the active site of IDH1. The docking scores for the flavonoids were as follows: quercetin: -7.8 kcal/mol, kaempferol: -7.4 kcal/mol, apigenin: -7.5 kcal/mol, luteolin: -7.4 kcal/mol. Among these, quercetin demonstrated the strongest binding affinity to IDH1, with a docking score of -7.8 kcal/mol, suggesting that it binds more tightly to the protein than the other flavonoids (**Table 1**).

Table 1: Binding mode of flavonoids against the active site of IDH1.

Name	PubChem ID	Binding energy (kcal/mol)	Hydrogen bond interactions		
			AA Residue	Distance (Å)	Angele (°)
Quercetin	5280343	-7.8	Ser94	3.39	119.74

			Asn96	3.28	111.98
			Arg100	2.62	174.60
			Arg109	2.37	128.22
			Ser293	2.14	134.63
			Ser293	2.35	115.14
Kaempferol	5280863	-7.4	Ser94	2.87	121.24
			Asn96	2.88	118.16
			Arg100	2.22	168.97
			Arg100	3.39	130.25
			Arg109	2.12	139.07
			Ser293	2.43	134.31
			Ser293	2.50	127.12
Apigenin	5280443	-7.5	Asn96	3.67	106.14
			Arg100	2.37	173.21
			Arg109	2.28	135.67
			Ser293	2.22	134.14
			Ser293	2.36	121.13
Luteolin	5280445	-7.4	Arg100	2.31	144.90
			Arg100	2.13	152.39
			Arg109	3.44	106.95
			Ala308	3.45	125.64

3.2. Interaction analysis

The analysis of the binding interactions revealed that quercetin forms several hydrogen bonds with key residues in the active site of IDH1, including Ser94, Asn96, Arg100, Arg109, Ser293 and Ala308. Additionally, hydrophobic interactions with residues like Asn96 stabilize the flavonoid-protein complex. Similar interactions were observed with kaempferol and luteolin, though with slightly weaker binding energies (**Table 1**).

3.3. ADMET predictions

The ADMET predictions for the flavonoids indicated that quercetin and kaempferol have favorable drug-likeness profiles, with good oral absorption, no major toxicity concerns, and adequate GI absorption and CYP450 inhibitor permeability. Apigenin and luteolin also displayed favorable ADMET properties, though their GI absorption penetration was predicted to be lower than that of quercetin and kaempferol (**Table 2**).

Table 2. Physicochemical and ADME properties of selected flavonoids.

Property	Quercetin	Kaempferol	Apigenin	Luteolin
Physicochemical Properies				
MW	302.24	286.24	270.24	286.24
HBAs	7	6	5	6
HBDs	5	4	3	4
TPSA	131.36	111.13	90.9	111.13
XLOGP3	1.54	1.9	3.02	2.53
Absorption				
GI absorption	High	High	High	High

Distribution				
BBB permeant	No	No	No	No
Pgp substrate	No	No	No	No
Metabolism				
CYP1A2 inhibitor	Yes	Yes	Yes	Yes
CYP2C19 inhibitor	No	No	No	No
CYP2C9 inhibitor	No	No	No	No
CYP2D6 inhibitor	Yes	Yes	Yes	Yes
CYP3A4 inhibitor	Yes	Yes	Yes	Yes
Excretion				
log Kp (cm/s)	-7.05	-6.7	-5.8	-6.25

4. Discussion

4.1. Flavonoids as potential therapeutic agents for LGG

Our study demonstrates that flavonoids, particularly quercetin, have strong binding affinities for the IDH1 protein, a key driver marker in LGG. The interaction of quercetin with the active site of IDH1 suggests that it may modulate the activity of this enzyme, potentially influencing the metabolic pathways involved in glioma progression. These findings align with previous studies that have shown the anticancer effects of quercetin and other flavonoids in various cancer models [4,11].

4.2. Mechanisms of action

The interactions identified between flavonoids and IDH1, including hydrogen bonding and hydrophobic interactions, suggest that flavonoids may directly inhibit IDH1 activity or disrupt its enzymatic function [9,12]. Further experimental validation is needed to confirm whether quercetin and other flavonoids can effectively inhibit IDH1 and modulate glioma cell metabolism.

4.3. Future perspectives

The promising results of this in silico study warrant further investigation into the therapeutic potential of flavonoids in the treatment of LGG [10]. Future studies should focus on in vitro and in vivo validation of the molecular docking results, as well as the development of flavonoid-based delivery systems to enhance GI absorption and bioavailability. Combination therapies involving flavonoids and other targeted treatments could also provide synergistic effects in managing LGG [13].

5. Conclusion

In conclusion, molecular docking studies revealed that flavonoids, particularly quercetin, may serve as promising therapeutic agents targeting IDH1, a key driver marker in low-grade gliomas. The identified strong binding interactions and favorable ADMET profiles suggest that flavonoids could be developed as part of a novel therapeutic strategy for LGG treatment. Further experimental studies are required to validate these findings and explore the clinical applicability of flavonoid-based therapies.

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