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RESEARCH ARTICLE

MOLECULAR DOCKING STUDIES OF FLAVONOIDS AGAINST DRIVER MARKERS IN LOW-GRADE GLIOMA: EXPLORING NOVEL THERAPEUTIC APPROACHES

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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.

Introduction:-

Low-grade gliomas (LGGs) represent a category of primary brain tumors characterized by their slow progression and more favorable prognosis relative to high-grade gliomas (HGGs). It arises from the glial cells that provide support to neurons in the brain and is considered a relatively low-risk cancer due to its slow growth rate, which often leads to longer survival times compared to more aggressive brain tumors. 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 group of natural compounds with diverse phenolic structures, are found in fruits, vegetables, grains, bark, roots, stems, flowers, tea, and wine, and are widely recognized for their antioxidant, anti-inflammatory, and anticancer effects. 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.

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Materials and Methods:-

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 retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/) [5].

Target protein preparation

The crystal structure of IDH1 (PDB ID: 4I3L) was downloaded from the Protein Data Bank (https://www.rcsb.org/). Protein preparation was performed using AutoDockTools by removing water molecules, adding hydrogen atoms, and assigning appropriate charges [6].

Molecular docking

AutoDock Vina (version 1.1.2) was utilized to conduct molecular docking simulations, aiming to predict the binding affinities of the selected flavonoids with 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.

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.

ADMET prediction

The drug-likeness and potential toxicity of the flavonoids were assessed using the ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) prediction tool provided by the SwissADME web server (http://www.swissadme.ch/) [8].

Results:-

Molecular docking of flavonoids with IDH1

Molecular docking results revealed that all selected flavonoids exhibited promising binding interactions with the ligand-binding 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 established the highest 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 Asn96 Arg100 Arg109 Ser293 Ser293	3.39 3.28 2.62 2.37 2.14 2.35	119.74 111.98 174.60 128.22 134.63 115.14
Kaempferol	5280863	-7.4	Ser94 Asn96 Arg100 Arg100 Arg109 Ser293 Ser293	2.87 2.88 2.22 3.39 2.12 2.43 2.50	121.24 118.16 168.97 130.25 139.07 134.31 127.12
Apigenin	5280443	-7.5	Asn96 Arg100	3.67 2.37	106.14 173.21

			Arg109 Ser293 Ser293	2.28 2.22 2.36	135.67 134.14 121.13
Luteolin	5280445	-7.4	Arg100 Arg100 Arg109 Ala308	2.31 2.13 3.44 3.45	144.90 152.39 106.95 125.64

Interaction analysis

The analysis of the binding interactions revealed that quercetin forms several hydrogen bonds with crucial 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**).

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

Discussion:-

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 results are consistent with earlier studies demonstrating the anticancer properties of quercetin and other flavonoids across different cancer models [4,11].

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.

Future Perspectives:-

The encouraging outcomes of this in silico study suggest the need for further research into the therapeutic potential of flavonoids for treating LGG [10]. Future studies should focus on in vitro and in vivo confirmation 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].

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. Additional experimental studies are necessary to confirm these findings and investigate the clinical potential of flavonoid-based therapies.

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