ORIGINAL PAPER

MOLECULAR DOCKING STUDIES OF ALOE VERA-DERIVED FLAVONOIDS AGAINST GLYCOGEN SYNTHASE KINASE-3β PROTEIN INHIBITION

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Abstract. *Flavonoids are a diverse group of polyphenolic compounds widely distributed in the plant kingdom, known for their antioxidant, anti-inflammatory, and anticancer properties. This study focuses on flavonoids identified in Aloe vera, a medicinal plant with numerous bioactive compounds, and investigates their potential as inhibitors of Glycogen Synthase Kinase-3β (GSK-3β)—a key enzyme implicated in various inflammatory and neurodegenerative diseases. A total of ten flavonoid compounds (six hydroxyflavones and four glycosylated flavones) were analyzed using computational methods. Geometry optimization and physicochemical property calculations were performed using HyperChem software, while molecular docking studies were conducted with Hex 8.0 to evaluate interactions with GSK-3β (PDB ID: 1q4l). The results revealed two main docking sites on the enzyme, specific to the structural group of each compound. Key descriptors such as HOMO-LUMO energy levels, dipole moments, polarizability, and molecular hardness were also assessed to understand reactivity and stability. These findings highlight the structural and electronic characteristics that govern flavonoid binding and support the potential of Aloe vera-derived flavonoids as therapeutic agents targeting GSK-3β.*

Keywords: *flavonoids; Aloe vera*; *molecular docking; GSK-3β.*

1. INTRODUCTION

Flavonoids are a large class of naturally occurring polyphenolic compounds synthesized by plants, playing a crucial role in plant pigmentation, UV filtration, symbiotic nitrogen fixation, and defense against pathogens [1]. They are well known for their broad spectrum of pharmacological activities, including antioxidant, anti-inflammatory, antimicrobial, and anticancer effects [2-6]. Structurally, flavonoids share a common backbone consisting of two aromatic rings (A and B) linked by a three-carbon bridge that forms a closed pyran ring (C), giving rise to various subclasses such as flavones, flavonols, flavanones, isoflavones, and anthocyanidins [7,8].

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Aloe vera, a succulent plant widely used in traditional and modern medicine, contains a rich array of phytochemicals including vitamins, enzymes, polysaccharides, fatty acids, and a notable number of flavonoid compounds [1]. The therapeutic potential of *Aloe vera* is attributed to these bioactive constituents, which have demonstrated anti-inflammatory, wound healing, immunomodulatory, and antioxidant properties [9]. Among these, flavonoids contribute significantly to the plant's biological effects due to their chemical versatility and reactivity.

Glycogen synthase kinase-3 (GSK-3) is a serine/threonine protein kinase that exists in two isoforms, GSK-3α and GSK-3β, both widely expressed in mammalian tissues [10]. GSK-3β, in particular, is involved in numerous cellular processes including metabolism, cell proliferation, and apoptosis. Its dysregulation has been implicated in a range of pathological conditions such as Alzheimer's disease, type 2 diabetes, cancer, and inflammatory disorders [11]. Consequently, GSK-3β has emerged as a critical molecular target for therapeutic intervention.

Molecular docking is a powerful computational technique used in drug discovery to predict the preferred orientation of a ligand when bound to a protein receptor, thereby elucidating the strength and nature of interactions at the molecular level [12]. Docking studies allow researchers to visualize and quantify binding affinities, interaction sites, and possible conformational changes within ligand-receptor complexes. In recent years, this method has been extensively applied to identify natural inhibitors of disease-related enzymes, including GSK-3β.

This study aims to investigate the structural and physicochemical properties of flavonoid compounds found in *Aloe vera* and to evaluate their potential as inhibitors of GSK-3β through molecular docking approaches. By understanding the binding behavior and electronic features of these compounds, we aim to contribute to the identification of plant-derived therapeutic candidates for inflammation-related disorders.

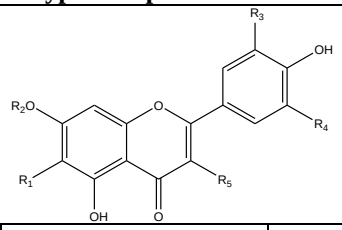
2. MATERIALS AND METHODS

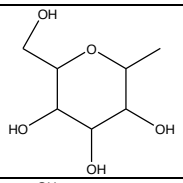
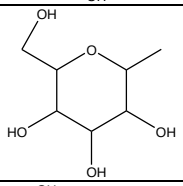
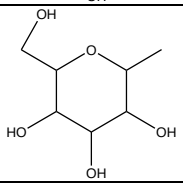
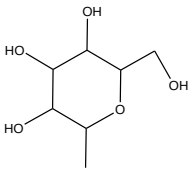
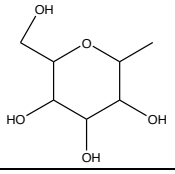
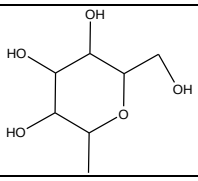
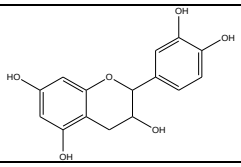
The substances studied in this work are 6-hydroxyflavones and 4-glycosylated flavones, for which the scientific literature reports antioxidant and antimycoplasmic activities (Table 1) [13-15].

The geometry modeling of the studied compounds was performed using the HyperChem Release 8.0 Professional software (Hypercube Inc.) [16], applying the RHF (Restricted Hartree-Fock) method within the semi-empirical PM3 (Parametrization Model 3) approximation. The software also allowed the determination of several physicochemical properties, which represent the 'fingerprint' of the studied compounds.

Ligand (flavonoids)–biological receptor (GSK-3β; PDB ID: 1q4l) [17] interactions were carried out through molecular docking using Hex 8.0 [8], and their visualization was made possible using the Bionova program [18].

Table 1. Flavonoid-type Compounds Present in Aloe Vera [15].



Nr. Crt.	Denumire	M [g/mol]	R_1	R_2	R_3	R_4	R_5
1	apigenin	270	H	H	H	H	H
2	luteolin	286	H	H	OH	H	H
3	isovitexin	432		H	H	H	H
4	isoorientin	448		H	OH	H	H
5	saponarin	594			H	H	H
6	lutonarin	610			OH	H	H
7	kaempferol	286	H	H	H	H	OH
8	quercetin	302	H	H	OH	H	OH
9	myricetin	318	H	H	OH	OH	OH
10	catechin	290					

3. RESULTS AND DISCUSSION

The optimized molecular geometries enabled the use of molecular orbital empirical calculations [19], leading to data on the electronic structure of the investigated substances: molecular electronic levels HOMO and LUMO, electric dipole moment (μ), surface area (SA) and molecular volume (V), hydration energy (E_{hydr}), partition coefficient (log P), molar refractivity (R_M), and molecular polarizability (α). The values for these structural parameters are presented in Table 2.

The analysis of molecular shape descriptor properties—specifically surface area (SA), molecular volume (V), molar refractivity (R_M), and polarizability (α)—reveals a clear correlation between these parameters and the molecular weight of the flavonoid compounds under investigation.

Table 2. Physicochemical properties calculated using HyperChem software.

Nr. crt.	SA [Å^2]	V [Å^3]	μ [D]	E_{hydr} [kcal/mol]	log P	R_M [Å^3]	α [Å^3]	E_{HOMO} [eV]	E_{LUMO} [eV]
1	359.51	721.50	3.83	-25.85	-2.09	79.88	27.27	-9.12	-0.93
2	365.36	738.92	3.65	-29.91	-3.11	81.49	27.90	-9.15	-1.03
3	430.89	1052.60	2.88	-30.67	-4.26	112.24	40.69	-8.97	-0.83
4	435.83	1071.85	3.69	-36.15	-5.28	113.85	41.33	-8.97	-0.89
5	548.22	1369.23	6.88	-42.58	-5.72	144.67	54.11	-9.26	-1.09
6	554.49	1390.23	5.76	-47.51	-6.74	146.28	54.75	-8.71	-0.98
7	359.31	737.35	2.52	-27.04	-2.99	81.56	27.90	-8.77	-1.05
8	366.00	754.98	1.94	-33.07	-4.01	83.17	28.54	-8.80	-1.14
9	372.76	774.48	1.28	-37.55	-5.04	84.77	29.18	-8.84	0.18
10	361.38	776.78	3.21	-30.00	-3.12	80.69	28.65	-8.96	0.08

As the molecular mass increases, so do the values of these descriptors, indicating larger, more spatially extended, and electronically more deformable molecules. Among the ten flavonoids studied, luteolin-7-O-glucuronide (lutonarin), with a molecular weight of 610 g/mol, stands out as the largest and most massive compound.

Lutonarin also displays the lowest hydration energy (E_{hydr}) and the smallest log P (partition coefficient) value, suggesting a strong hydrophilic character. These findings align with its structural features, which include multiple polar functional groups such as hydroxyl and glycosyl moieties, making it the most polar compound in the dataset. Its high polarity not only influences its solubility profile but also its potential biological interactions, particularly with aqueous environments and polar amino acid residues in target proteins.

A key aspect of ligand–receptor interaction involves frontier molecular orbitals, which play a critical role in defining the chemical reactivity and binding characteristics of a molecule. These include the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) [20]. The HOMO represents the ability of the ligand to donate electrons, while the LUMO reflects its capacity to accept electrons. In the context of the enzyme GSK-3β, interaction with the flavonoid ligands can involve bidirectional electron transfer mechanisms: from the HOMO of the ligand to the protein (acting as an electron donor), or from the protein into the LUMO of the ligand (acting as an electron acceptor). These interactions are essential for the formation of a stable ligand–receptor complex and can significantly affect the binding affinity and specificity (Figure 1).

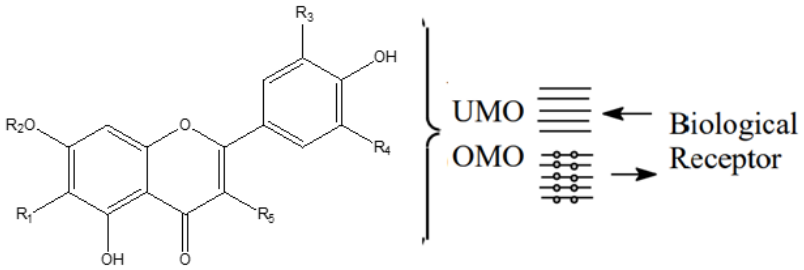


Figure 1. Ligand-Receptor Interaction via Electron Transfer [21].

Understanding these electronic features provides valuable insights into the molecular basis of ligand recognition and interaction, laying the groundwork for rational drug design strategies targeting GSK-3β.

Fig. 2 shows the HOMO–LUMO orbitals for several flavonoids (the smallest and the largest compound, both glycosylated flavones), while Table 3 presents the ΔE difference between the frontier orbital energies, as well as two quantum chemical properties defined based on these orbitals: absolute electronegativity (λ) and absolute hardness (η) [22, 23].

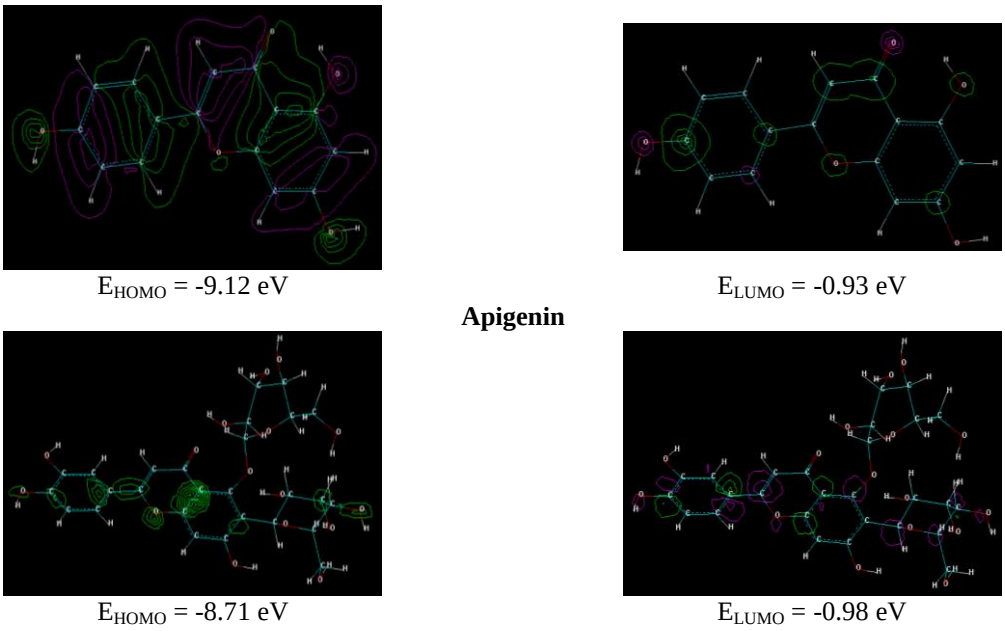


Figure 2. HOMO-LUMO Frontier Orbitals for Apigenin (M = 270 g/mol) and Lutonarin (M = 610 g/mol). Green color indicates positive polarity, while violet color indicates negative polarity.

The energy of the HOMO level (E_{HOMO}) provides an indication of a molecule's donor properties and its tendency to oxidize. Similarly, the energy of the LUMO level (E_{LUMO}) allows for the evaluation of the molecule's acceptor properties or its tendency to decrease. The energy gap $\Delta E = E_{LUMO} - E_{HOMO}$ is a parameter that reflects the stability of the molecule, with lower values indicating a highly reactive molecule. From this perspective, the values presented in Table 3 suggest that catechin is the most stable molecule, while quercetin, kaempferol, and luteolin are the least stable (more reactive).

The electronegativity parameter (λ) describes the tendency of molecules to donate or accept electrons, while hardness describes the resistance of the molecular system to changes in its electronic density [22].

Electronegativity is a fundamental quantum chemical descriptor that reflects a molecule's tendency to attract electrons. Generally, a higher electronegativity value corresponds to increased chemical reactivity, particularly in polar and electron-driven interactions. Based on calculated electronegativity (λ) values, the ten flavonoid compounds derived from Aloe vera exhibit the following descending order of reactivity: compound **5** > **2** > **1** > **8** > **7** > **4** > **3** > **6** > **10** > **9**. This trend indicates that compound **5** (saponarin) is the most chemically reactive, while compound **9** (myricetin) is the least. Notably, this order also aligns with the observed molecular interaction tendencies and docking performance, confirming electronegativity as a reliable predictor of reactivity within this class of natural products.

Table 3. Values of molecular parameters.

Compound code	IUPAC name (Synonim)	ΔE [eV]	Λ [eV]	η [eV]
1	5,7-Dihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one (Apigenin)	8.186	5.024	4.093
2	2-(3,4-Dihydroxyphenyl)-5,7-dihydroxychromen-4-one (Luteolin)	8.121	5.092	4.061
3	5,7-Dihydroxy-2-(4-hydroxyphenyl)-6-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]chromen-4-one (Isovitexin)	8.145	4.899	4.072
4	2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-6-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]chromen-4-one (Isoorientin)	8.076	4.934	4.038
5	5-Hydroxy-2-(4-hydroxyphenyl)-6-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]-7-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxychromen-4-one (Saponarin)	8.170	5.174	4.085

Compound code	IUPAC name (Synonim)	ΔE [eV]	Λ [eV]	η [eV]
6	2-(3,4-Dihydroxyphenyl)-5-hydroxy-6-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]-7-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxychromen-4-one (Lutonarin)	7.725	4.843	3.863
7	3,5,7-Trihydroxy-2-(4-hydroxyphenyl)chromen-4-one (Kaempferol)	7.718	4.913	3.859
8	2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one (Quercetin)	7.665	4.969	3.833
9	3,5,7-Trihydroxy-2-(3,4,5-trihydroxyphenyl)chromen-4-one (Myricetin)	8.662	4.509	4.331
10	(2R,3S)-2-(3,4-Dihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol ((-)-Catechin)	8.872	4.520	4.436

Another key molecular property influencing interaction with biological targets is the electric dipole moment (μ), which quantifies the overall molecular polarity and is closely related to the distribution of charges across the molecule. The highest dipole moment was again observed for compound 5 (saponarin; μ = 6.885 D), closely followed by compound **6** (μ = 5.759 D). These elevated values suggest a strong degree of molecular asymmetry and high potential for interactions via polar contacts, such as hydrogen bonding and dipole–dipole interactions.

In parallel, the polarizability (α) of these molecules, which measures their electronic deformability in response to an external electric field, was also highest for the same compounds: α(5) = 54.11 Å³ and α(6) = 54.75 Å³. This reinforces their potential for dynamic adaptation during molecular recognition events, particularly within the binding pocket of polar or charged biomolecular targets.

The rigidity of the flavonoid molecules (η), inversely related to their flexibility and deformability, was also assessed. The descending order of molecular rigidity was found to be: **10** > **9** > **1** > **5** > **3** > **2** > **4** > **6** > **7** > **8**, with catechin (compound **10**) and myricetin (compound **9**) being the most structurally rigid. These molecules, although less polar, may benefit from shape complementarity during docking due to their compact and fixed conformations.

As outlined in the introductory section, Aloe vera possesses a broad range of biological activities, including well-documented anti-inflammatory effects. The Glycogen Synthase Kinase 3β (GSK-3β) enzyme is a crucial mediator of intracellular signaling pathways related to inflammation and other pathophysiological processes. Consequently, this study focused on exploring the molecular interactions between Aloe vera-derived flavonoid compounds and the GSK-3β enzyme through molecular docking simulations.

Molecular docking allows for the visualization and prediction of ligand–receptor binding, offering insights into the preferred binding sites, orientations, and conformational stabilities of the resulting complexes. In this case, docking experiments (Fig. 3) revealed that these flavonoid compounds interact with GSK-3β in structurally distinct binding regions, depending on the compound's hydroxylation pattern and glycosylation. The resulting conformations suggest that both capabilities of the ligands electron-donating (HOMO) and electron-accepting (LUMO) are critical for binding affinity, supporting a mechanism involving electronic complementarity and non-covalent forces such as hydrogen bonds and van der Waals interactions.

These findings provide a valuable framework for understanding the potential of Aloe vera flavonoids as natural inhibitors or modulators of GSK-3β, contributing to the growing interest in polyphenolic compounds as therapeutic agents in inflammation-related diseases.

As illustrated in Fig. 3, molecular docking analysis revealed that the ten flavonoid compounds studied interact with the GSK-3β enzyme by binding to two distinct regions within the protein's structure. This selective binding behavior is structurally driven: the six hydroxylated flavonoids (non-glycosylated) preferentially dock into one specific active site of the enzyme, while the four glycosylated flavonoids occupy a separate binding pocket.

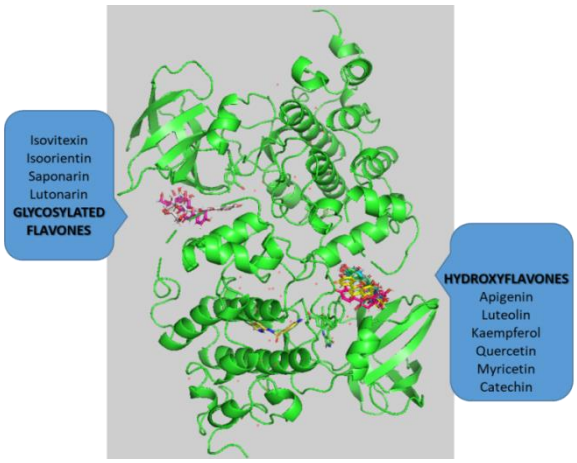


Figure 3. The Interaction of the 10 Flavonoid Compounds with the GSK3β Protein.

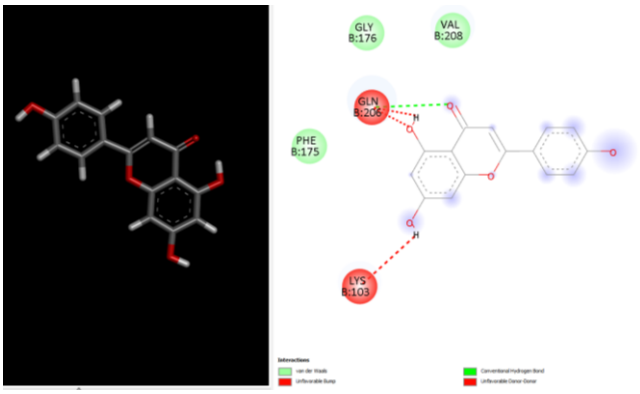
This bifurcated binding mode reflects the influence of structural variations—specifically the presence or absence of sugar moieties—on the spatial orientation and binding compatibility of the molecules. Despite these differences, the common flavone backbone present in all compounds ensures a degree of molecular recognition and compatibility with the enzyme's surface topology.

The binding interactions between the flavonoid ligands and the GSK-3β enzyme are primarily stabilized by non-covalent intermolecular forces, predominantly hydrogen bonding and van der Waals interactions. These interactions involve functional groups such as hydroxyl (–OH) and carbonyl (C=O) oxygen atoms, which serve as key electron-rich sites. Depending on their electronic configuration, these atoms can function either as electron donors (through their participation in the highest occupied molecular orbital, HOMO) or as electron acceptors (through the lowest unoccupied molecular orbital, LUMO) during the formation of the ligand–receptor complex.

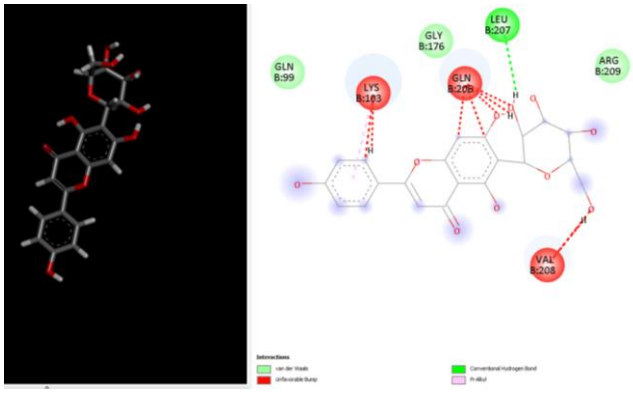
This dual mechanism of electron exchange underlies the molecular affinity of flavones for GSK-3β, with different binding energies and docking scores reflecting variations in orbital energy alignment and steric compatibility [20]. Fig. 4 shows the two-dimensional (2D) conformational representations of selected ligand–receptor interactions, clearly illustrating the spatial arrangement of the flavonoid derivatives within the enzyme's active and auxiliary binding sites. The visualization further highlights the critical hydrogen bonds and proximity to catalytically relevant amino acid residues, offering insights into potential inhibitory activity and specificity.

These observations underscore the importance of flavonoid structure, including glycosylation patterns and hydroxylation levels, in determining their binding behavior, which has significant implications for their potential biological activity and therapeutic targeting of inflammation-related pathways mediated by GSK-3β.

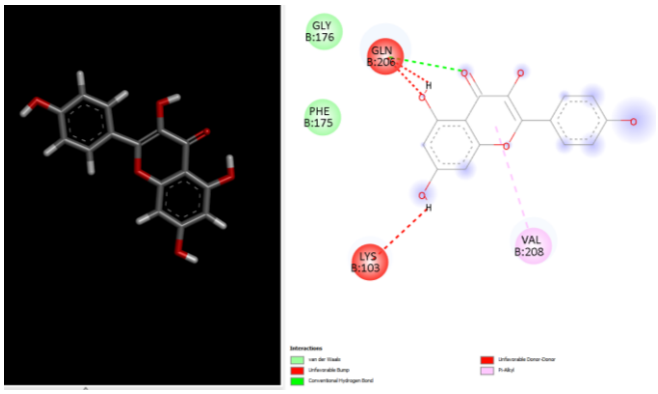
As demonstrated in Fig. 4, molecular docking simulations revealed that the flavonoid compounds under investigation exhibit selective binding affinities toward two distinct binding regions within the GSK-3β enzyme, determined largely by their structural characteristics. Specifically, the six hydroxylated flavonoids preferentially interact with a defined active site, whereas the four glycosylated flavonoids are accommodated within an alternate binding pocket. This differential binding pattern is attributable to variations in molecular architecture, particularly the presence of glycosidic residues, which significantly influence steric complementarity and electronic distribution. Nevertheless, the conserved flavone scaffold shared among all compounds contributes to their general compatibility with the enzyme's binding surface.



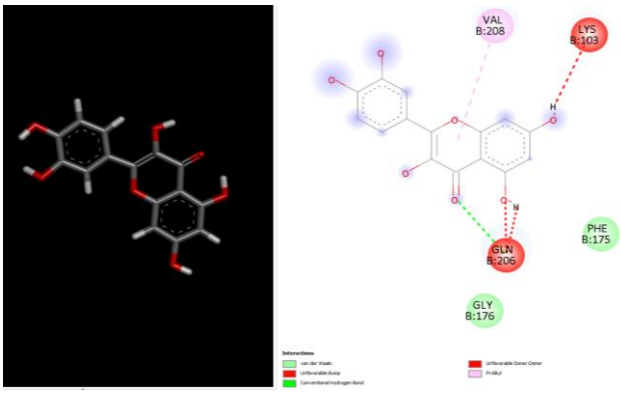
5,7-Dihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one (Apigenin)



5,7-Dihydroxy-2-(4-hydroxyphenyl)-6-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]chromen-4-one (Isovitexin)



3,5,7-Trihydroxy-2-(4-hydroxyphenyl)chromen-4-one (Kaempferol)



2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one (Quercetin)

Figure 4. 2D Representations of Ligand-Receptor Interactions.

The ligand–receptor interactions are predominantly governed by non-covalent forces, with a major contribution from hydrogen bonds and van der Waals interactions. These interactions typically involve oxygen atoms from hydroxyl or carbonyl functional groups within the flavonoid structures [24,25]. Depending on the electronic configuration, these atoms function either as electron donors, through the highest occupied molecular orbital (HOMO), or as electron acceptors, via the lowest unoccupied molecular orbital (LUMO), thereby facilitating the stabilization of the enzyme–ligand complex.

The binding conformations and molecular interactions are further visualized in Fig. 4, which illustrates the two-dimensional representations of selected flavonoid–GSK–3β complexes. These visualizations highlight the spatial orientation of the ligands within the active sites, as well as the specific amino acid residues involved in the interactions. Such insights are critical for understanding the molecular basis of flavonoid bioactivity and their potential to modulate GSK-3β function, a key regulator in inflammatory and metabolic signaling pathways.

Collectively, these findings underscore the importance of structural features, such as hydroxylation and glycosylation patterns, in modulating the binding behavior and biological efficacy of flavonoid compounds [26]. The docking results support the hypothesis that flavones derived from Aloe vera may exert bioactive effects through direct interaction with GSK-3β, offering promising avenues for therapeutic exploration.

4. CONCLUSIONS

This study provides comprehensive computational insights into the structural, electronic, and binding characteristics of ten flavonoid compounds identified in Aloe vera. The analysis revealed distinct molecular descriptors—such as HOMO-LUMO energy gaps, dipole moments, polarizability, and molecular hardness—that influence the stability and reactivity of each compound. Molecular docking studies demonstrated that the flavonoids interact with GSK-3β through specific binding sites, with hydroxyflavones and glycosylated flavones favoring different regions of the protein. These interactions are primarily mediated by hydrogen bonding and van der Waals forces, involving key amino acid residues such as GLN 206, LYS 103, and PHE 175.

The results support the hypothesis that Aloe vera-derived flavonoids have promising potential as natural inhibitors of GSK-3β, a target associated with several inflammatory, neurodegenerative, and metabolic disorders. These findings not only enhance our understanding of flavonoid–protein interactions but also lay the groundwork for further experimental validation and drug development efforts based on plant-derived bioactive molecules.

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