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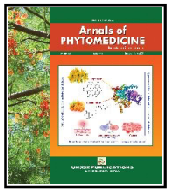

Original Article : Open Access

Binding affinity and stability analysis of apigenin across multiple neuro-degenerative targets: A computational approach

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Abstract

Neurodegenerative disorders such as Alzheimer's and motor neuron diseases pose significant therapeutic challenges due to their multifactorial pathogenesis. In this study, a comprehensive computational evaluation was conducted to assess the binding potential of three natural compounds-apigenin, curcumin, and resveratrol against key protein targets implicated in neurodegenerative diseases, including γ-secretase subunits (4DJU, 3MJL), TDP-43 (6N3C), and inflammation-associated proteins (1A8R, 3LY6). Molecular docking and MM-GBSA binding free energy analyses were performed to determine binding affinities, interaction profiles, and thermodynamic stability.

Apigenin exhibited strong binding affinity to γ-secretase subunits with Glide GScores of – 6.559 and -5.771 kcal/mol for 4DJU and 3MJL, respectively, primarily driven by hydrophobic complementarity and hydrogen bonding. Although, curcumin showed the strongest MM-GBSA binding energy overall (– 55.24 kcal/mol), it exhibited higher conformational strain, indicating potential instability. Resveratrol displayed moderate binding energy (– 34.49 kcal/mol) with the lowest strain energy, suggesting favourable structural compatibility. Against TDP-43, curcumin demonstrated the best docking score (– 8.08 kcal/mol), while apigenin showed high specificity and stability. Apigenin also displayed favourable interaction with the 1A8R protein, although curcumin had the strongest MM-GBSA affinity (– 35.82 kcal/mol). For 3LY6, compound 969516 out performed the other candidates with the strongest binding energy (– 7.64 kcal/mol), despite higher internal strain.

These findings underscore apigenin's potential as a γ-secretase modulator and highlight curcumin broader neuroprotective capacity. Structural optimization of apigenin to reduce solvation penalties and of curcumin to lower strain energy may enhance their therapeutic efficacy. The study offers key insights for the structure-based development of natural neuroprotective agents

1. Introduction

Neurodegenerative diseases (NDDs) such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), ataxia, and motor neuron disease (MND) are characterized by progressive loss of neuronal structure and function, resulting in cognitive, behavioral, and motor impairments (Dugger and Dickson, 2017; Kovacs, 2018). These disorders share common pathogenic mechanisms, including protein misfolding and aggregation, oxidative stress, mitochondrial dysfunction, and chronic neuroinflammation, which provide a basis for multi-target therapeutic approaches (Dugger and Dickson, 2017; Kovacs, 2018).

Protein aggregation plays a key role in the pathology of many NDDs. In SCA1, polyglutamine-expanded ataxin-1 forms toxic aggregates (PDB: 3MJL) (Chen *et al*., 2005; Klockgether *et al*., 2019), while in AD, extracellular amyloid-beta (Aβ) plaques and intracellular tau tangles (PDB: 4DJU) lead to synaptic loss and neurodegeneration (Long and Holtzman, 2019; Julia and Goate, 2017; DeTure and Dickson, 2019; Sehar *et al*., 2022). HD is caused by mutant huntingtin protein with expanded polyQ repeats (PDB: 3LY6), forming aggregates that impair neuronal function (Finkbeiner, 2011; Ross and Tabrizi, 2011). In MND, especially ALS, pathological TDP-43 inclusions (PDB: 6N3C) are commonly observed (Guha, 2023; Taylor *et al*., 2016). PD features dopaminergic neuronal loss and á-synuclein aggregation into Lewy bodies (PDB: 1A8R) (Monzio Compagnoni *et al*., 2020; Schneider and Obeso, 2014; Corvol and Poewe, 2017).

Given the limitations of current treatments, natural compounds with multi-target neuroprotective potential have attracted considerable interest (Salehi *et al*., 2019; Nahar *et al*., 2025). Apigenin (4',5,7-trihydroxyflavone), a dietary flavonoid, exhibits antioxidant, anti-inflammatory, and antiaggregation activities relevant to neurodegeneration (Chagas *et al*., 2022; Shankar *et al*., 2017; Andrade *et al*., 2023). Its ability to cross the blood-brain barrier further enhances its therapeutic promise (Mohammad Khanizadeh *et al*., 2025; Olasehinde and Olaokun, 2024).

Comparative studies with other phytochemicals such as curcumin which modulates amyloid aggregation and neuro-inflammation and resveratrol which activates sirtuins and reduces oxidative stress-are essential (Mishra and Palanivelu, 2008; Baur and Sinclair, 2006;

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Maiti and Dunbar, 2018; Pan *et al*., 2017). However, both suffer from low bioavailability and rapid metabolism (Mishra and Palanivelu, 2008; Baur and Sinclair, 2006), highlighting the need for alternatives with better pharmacokinetic profiles (Choudhury *et al.*, 2018).

Computational methods such as molecular docking and ADME profiling provide cost-effective ways to evaluate such compounds early in drug discovery (Sliwoski *et al*., 2014). By analyzing apigenin's interactions with NDD targets (PDBs: 3MJL, 4DJU, 3LY6, 6N3C, and 1A8R), and comparing its performance with curcumin and resveratrol, this study aims to identify its multi target potential.

This *in silico* investigation offers foundational insights into apigenin's therapeutic promise, guiding future experimental validation and drug development strategies for currently incurable NDDs (Gupta *et al*., 2024; Agu *et al*., 2023; Niazi and Mariam, 2023; Ramsay *et al.*, 2018).

2. Materials and Methods

2.1 ADMET prediction

Prior to molecular docking, the pharmacokinetic and toxicity profiles of the selected ligandsapigenin, curcumin, and resveratrolwere assessed using *in silico* ADMET prediction tools such as Swiss ADME and pkCSM. These tools were employed to evaluate key pharmacokinetic parameters, including absorption, distribution, metabolism, excretion, and toxicity, along with drug-likeness, bioavailability, and blood-brain barrier permeability. This preliminary screening aided in identifying compounds with favorable pharmacokinetic characteristics and minimal predicted toxicity. Among the tested compounds, apigenin demonstrated the most promising CNS-related properties. In this study, curcumin and resveratrol were employed as standard reference compounds to benchmark the potential antipsychotic activity of apigenin.

2.2 Protein preparation

The three-dimensional crystal structures of the target proteins-PDB IDs: 3MJL, 4DJU, 3LY6, 6N3C, and 1A8R were retrieved from the RCSB Protein Data Bank. Protein preparation was performed using Schrödinger's Protein Preparation Wizard (Release 2023-1), which involved adding missing hydrogen atoms, assigning proper bond orders, removing water molecules and co-crystallized ligands, and optimizing protonation states at physiological pH (7.0 ± 2.0) using PROPKA. Energy minimization was conducted using the OPLS4 force field, with a convergence threshold of 0.3 Å RMSD for heavy atoms, to alleviate steric clashes while preserving crystallographic coordinates.

2.3 Ligand preparation

The 3D structures of the ligands apigenin (PubChem CID: 5280443), curcumin (PubChem CID: 9695160), and resveratrol (PubChem CID: 445154) were downloaded from the PubChem database. Ligand preparation was performed using Schrödinger's LigPrep module, which involved generating low-energy conformers, enumerating all likely ionization states at pH 7.0 ± 2.0, desalting, and energy minimization using the OPLS4 force field. The ligands were aligned to a common reference frame to ensure consistency during grid generation and docking procedures.

2.4 Grid generation

Receptor grid generation was executed using Schrödinger's Receptor Grid Generation tool. For each protein, the co-crystallized ligand was defined as the center (centroid) of the docking grid. The grid box was set to dimensions of 20 Å × 20 Å × 20 Å, which was sufficient to accommodate the ligand flexibility and binding pocket coverage. This ensured accurate targeting of the biologically relevant active site in all molecular docking simulations.

2.5 Molecular docking

Molecular docking was performed using Schrödinger's Glide module (version 7.1) in extra precision (XP) mode to evaluate ligand binding affinity. Flexible ligand sampling was enabled to account for conformational freedom during docking. Each docking simulation was centered on the binding site defined by the co-crystallized ligand. Both Glide Score (binding affinity) and Glide energy (interaction stability) values were recorded for all docked poses. The Prime module was not used for docking; all molecular docking was strictly conducted with Glide. Additionally, for validation purposes, standard ligands (known inhibitors or the original co-crystallized compounds) were docked for each protein to compare with the test compounds, thereby establishing a reliable docking baseline.

2.6 Prime MM-GBSA binding free energy calculations

Binding free energies were calculated for protein-ligand complexes using the Prime MM-GBSA (Molecular Mechanics-Generalized Born Surface Area) method as implemented in Schrodinger Suite. The binding free energy (ÄGbind) was calculated using the equation:

ÄGbind = Gcomplex–(Gprotein + Gligand)

where, Gcomplex represents the energy of the protein-ligand complex, Gprotein the energy of the unbound protein, and Gligand the energy of the unbound ligand. The VSGB solvation model and OPLS4 force field were employed for all calculations. The Prime MM-GBSA protocol included minimization of all structures and energy evaluation with implicit solvent.

2.7 Interaction analysis

Protein-ligand interactions were analyzed using Schrodinger's Interaction Fingerprint tool. Key interactions including hydrogen bonds, hydrophobic contacts, and δ-stacking were identified and visualized using Maestro's pose viewer. Interaction fingerprints were generated to compare binding modes across different protein targets and ligands.

3. Results

3.1 ADME/T properties of apigenin

Computational ADME/T prediction using Schrödinger's QikProp revealed favorable pharmacokinetic properties for apigenin (Table 1). The compound (MW = 270.241 g/mol) complied with Lipinski's Rule of Five (0 violations), showing moderate aqueous solubility (QPlogS = -3.304), optimal lipophilicity (QPlogPo/w = 1.602), and acceptable human oral absorption (73.5%). The polar surface area (98.868 Å²) and blood-brain barrier penetration value (QPlogBB = -1.425) indicated limited CNS bioavailability. The compound also exhibited low HERG inhibition risk (QPlogHERG = –5.099) and moderate metabolic stability (3 predicted reactions).

Table 1: Comparative molecular docking parameters of apigenin, curcumin, and resveratrol across neurodegenerative disease targets

Disease	Target (PDB ID)	Compound GScore	Glide (kcal/mol)	Emodel (kcal/mol)	Internal Strain (kcal/mol)	vdW Energy (kcal/mol)	Electrostatic Energy (kcal/mol)	H-Bonding Energy (kcal/mol)
Alzheimer's	4DJU	Apigenin	-6.559	–	<4	–	–	-1.544
		Curcumin	-5.90	-60.12	–	-32.17	–	-2.07
		Resveratrol	-6.218	-39.04	–	-26.28	–	-0.67
Ataxia	3MHL	Apigenin	-5.77072	-45.2864	Low	Strong	Strong	–
		Curcumin	-5.10507	–	7.82007	Strong	Strong	–
		Resveratrol	-4.92206	–	Moderate	Moderate	Weak	–
Huntington	3LY6	Apigenin	-4.87	–	Low	Moderate	Moderate	–
		Curcumin	-7.64	–	–	Strong	Strong	–
		Resveratrol	-4.07	–	–	Moderate	Moderate	–
Motor neuron disease	6N3C	Apigenin	Slightly lower	–	0.11	Moderate	Moderate	Strong
		Curcumin	-8.08	–	–	Strong	–	–
		Resveratrol	-7.18	–	–	Moderate	Favourable	–
Parkinson's	1A8R	Apigenin	-1.9996	–	Moderate	Moderate	Moderate	–
		Curcumin	-2.51408	–	Moderate	Moderate	Moderate	–
		Resveratrol	-3.3859	–	Moderate	Strong	Moderate	–

3.2 Molecular docking analysis

Molecular docking studies were performed using co-crystallized ligands as standards for each target protein. Apigenin (test compound) was compared against reference standards curcumin and resveratrol across multiple neurodegenerative disease targets.For γ-secretase (Alzheimer's, PDB ID: 4DJU), docking validation was performed using the co-crystallized inhibitor LY-411575 as reference standard. Apigenin showed the highest binding affinity (Glide GScore = – 6.559 kcal/mol), followed by resveratrol (-6.218 kcal/mol) and curcumin (– 5.90 kcal/mol). Apigenin displayed a favorable combination of lipophilic interactions (– 4.944 kcal/mol), hydrogen bonding (– 1.544 kcal/mol), and low internal strain (<4 kcal/mol).For Ataxia (3MHL), using N-(4-fluorobenzyl)-9H-purin-6-amine as reference standard, apigenin showed the best docking score (– 5.77072 kcal/mol), while curcumin had a higher internal strain (7.82007 kcal/mol) despite stronger van der Waals and electrostatic interactions. In Huntington's disease (3LY6), with co-crystallized ligand 5ZQ as standard, curcumin had the strongest binding (-7.64 kcal/mol), followed by apigenin (– 4.87 kcal/mol), and resveratrol (-4.07 kcal/mol). In Motor neuron disease (6N3C), using staurosporine as reference, curcumin again showed the best score (-8.08 kcal/mol), followed by resveratrol (– 7.18 kcal/mol), while apigenin showed strong hydrogen bonding but lower overall affinity. In Parkinson's (1A8R), with co-crystallized inhibitor SB-203580 as standard, resveratrol performed best (– 3.3859 kcal/mol), with apigenin showing the weakest binding (– 1.9996 kcal/mol).

Table 2: Comparative binding affinities (äg_bind in kcal/mol) of apigenin, curcumin, and resveratrol across neurodegenerative disease targets

Neurodegenerative disease	PDB ID	Apigenin (ΔG_bind)	Curcumin (ΔG_bind)	Resveratrol (ΔG_bind)
Alzheimer's disease	4DJU	-9.45	Moderate (Not specified)	-7.12
Ataxia	3MHL	-23.33	-36.10	-35.38
Huntington's disease	3LY6	-31.91	-34.49	-55.24
Motor neuron disease	6N3C	-48.96	-67.60	-63.62
Parkinson's disease	1A8R	-16.03	-35.82	-29.40

3.3 MM-GBSA binding energy calculations

MM-GBSA binding free energy calculations for γ-secretase (4DJU) confirmed apigenin's strongest binding affinity (ÄG_bind = -9.45 kcal/mol), compared to resveratrol (-7.12 kcal/mol) and curcumin. In Ataxia (3MHL), curcumin had the strongest binding (ÄG_bind = -36.10 kcal/mol), followed by resveratrol and then apigenin. For Huntington's disease (3LY6), resveratrol exhibited the most favorable energy (-55.24 kcal/mol), while apigenin showed weaker interactions (-31.91 kcal/mol). In Motor neuron disease (6N3C), curcumin again led (-67.60 kcal/mol), and apigenin showed the weakest affinity (-48.96 kcal/mol). For parkinson's (1A8R), curcumin showed the best score (-35.82 kcal/mol), while apigenin was weakest (-16.03 kcal/mol).

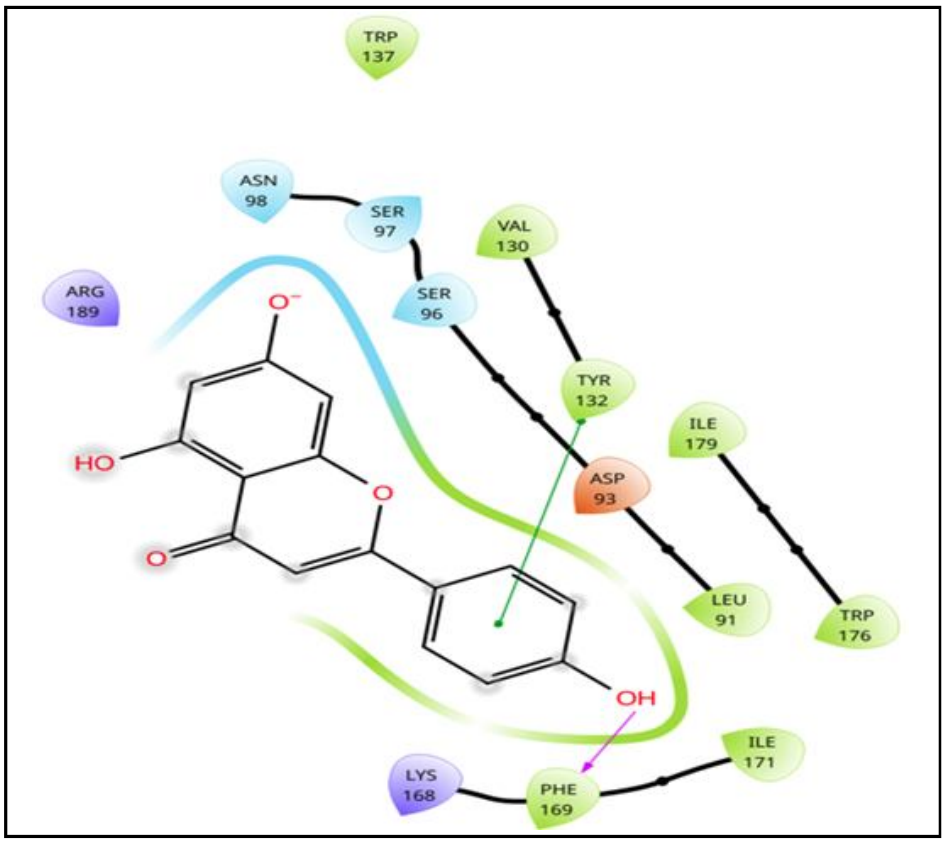

Figure 1a: 2-D interaction diagram of apigenin against Alzheimer's disease (PDB ID-4DJU).

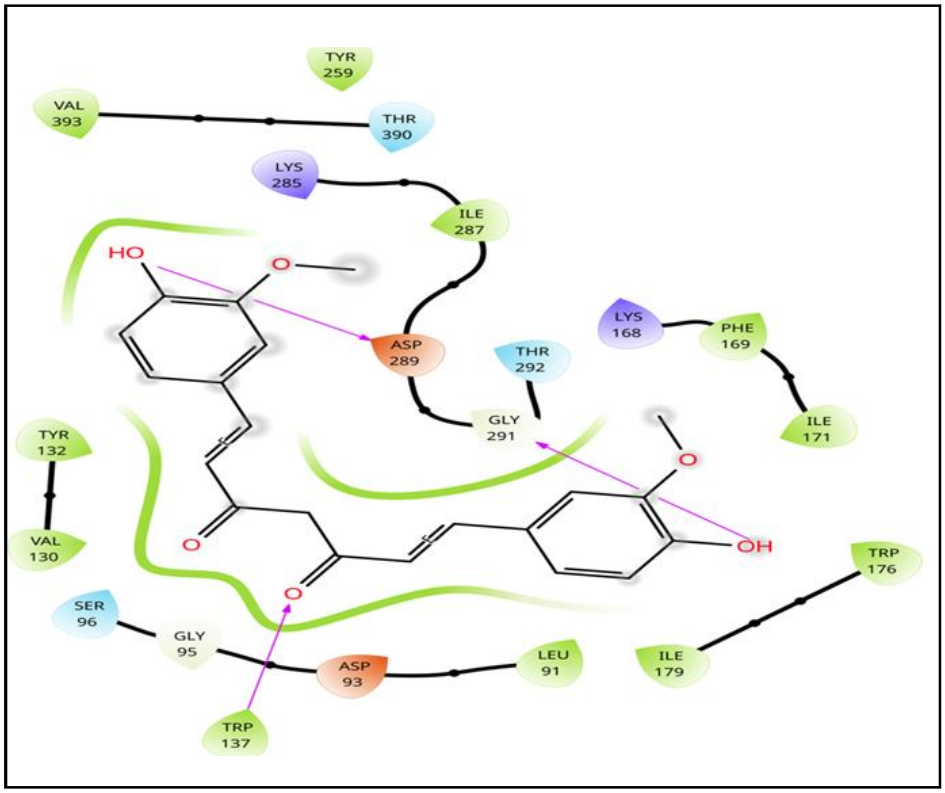

Figure 1b: 2-D interaction diagram of curcumin against Alzheimer's disease (PDB ID-4DJU).

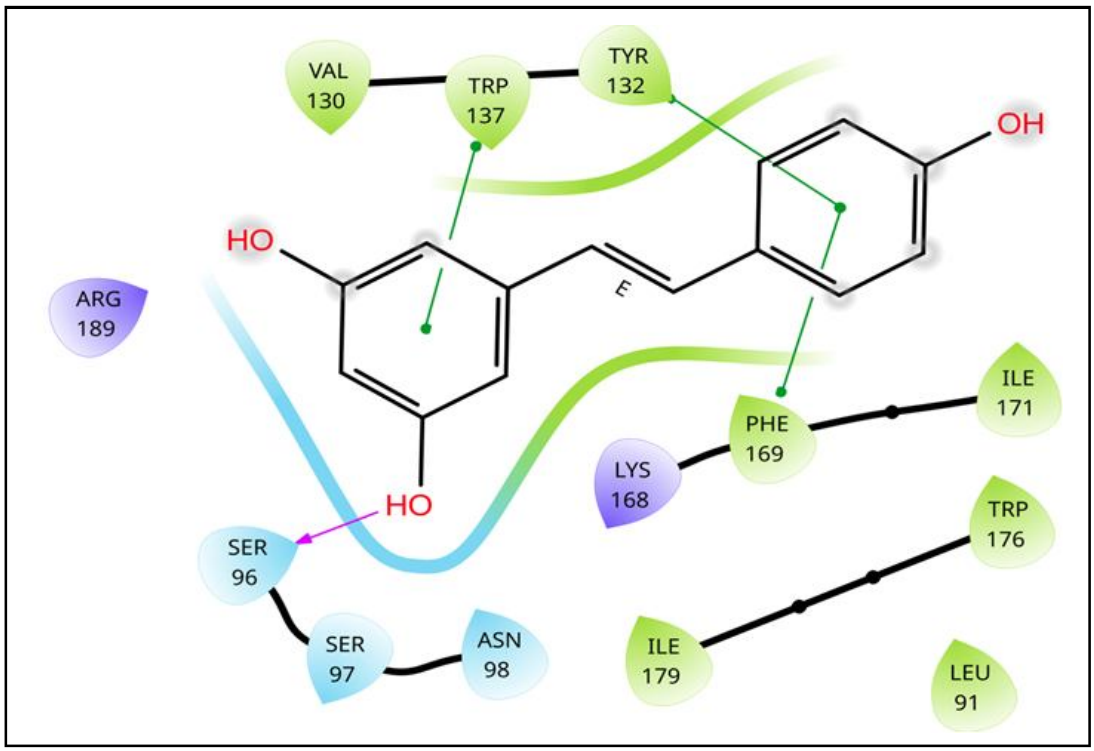

Figure 1c: 2-D interaction diagram of resveratrol against Alzheimer's disease (PDB ID-4DJU).

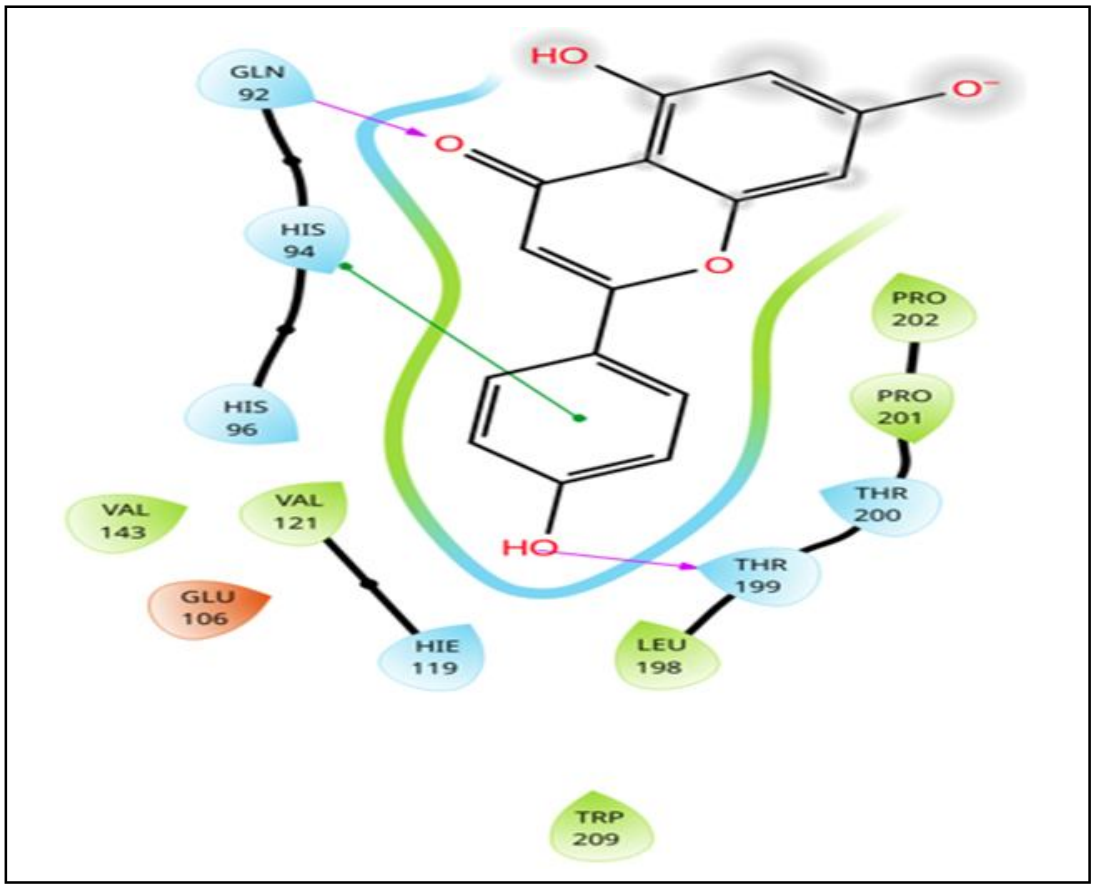

Figure 2a: 2-D interaction diagram of apigenin against ataxia (PDB ID-3MHL).

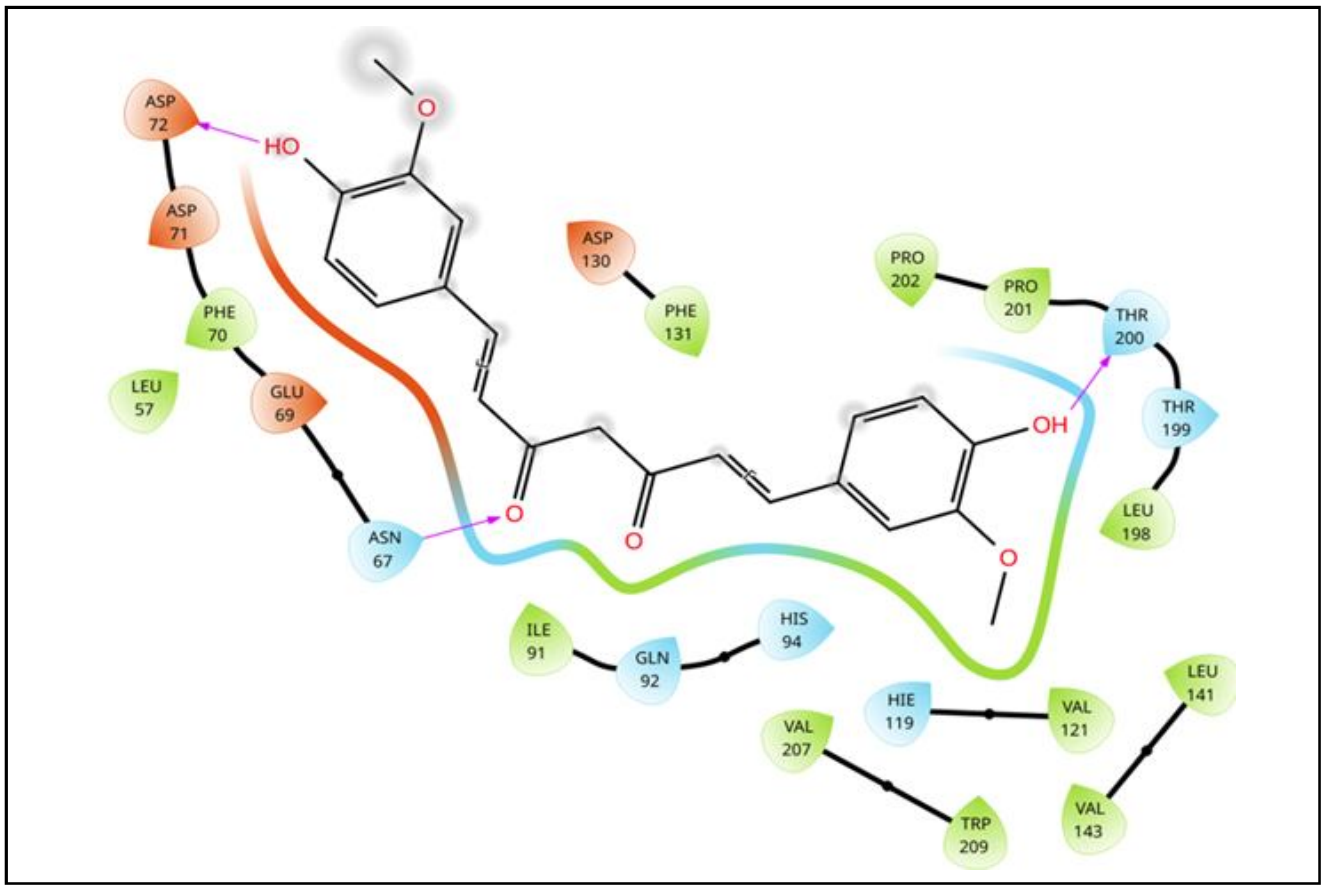

Figure 2b: 2-D interaction diagram of curcumin against Ataxia (PDB ID-3MHL).

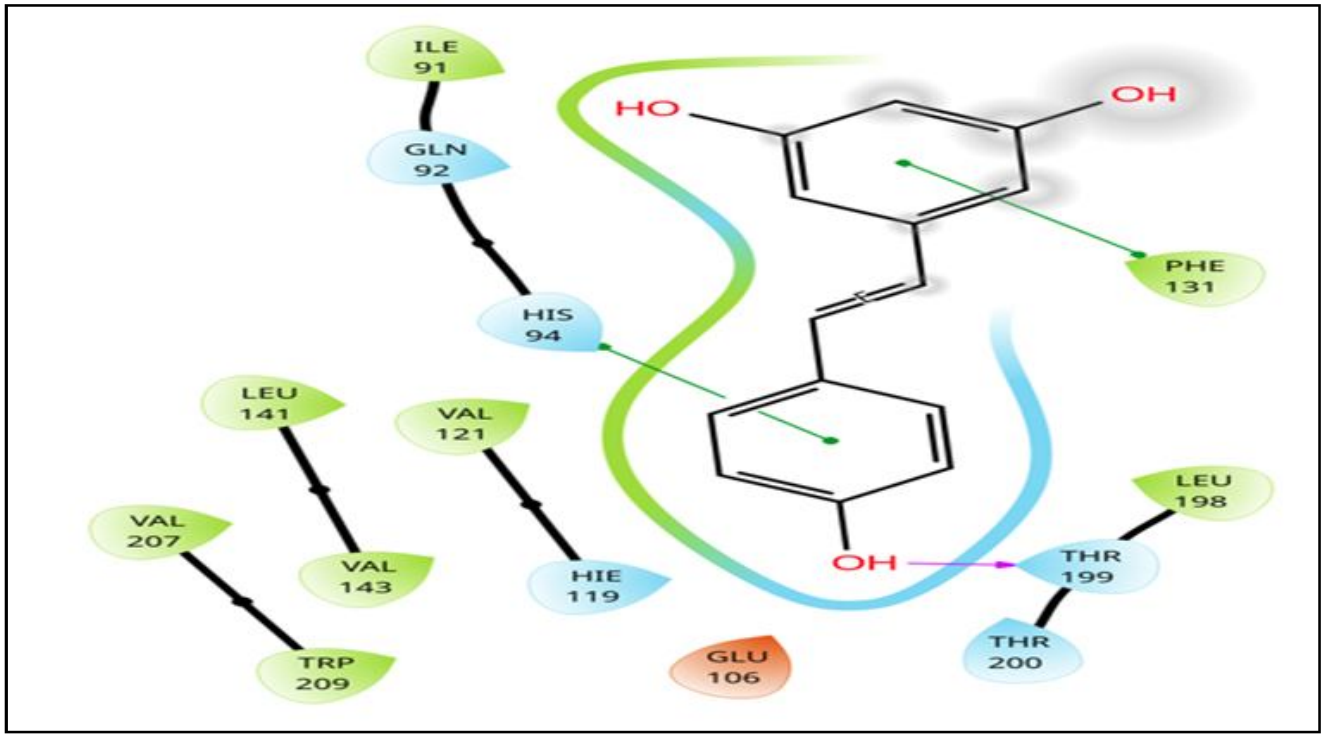

Figure 2c: 2-D interaction diagram of resveratrol against ataxia (PDB ID-3MHL).

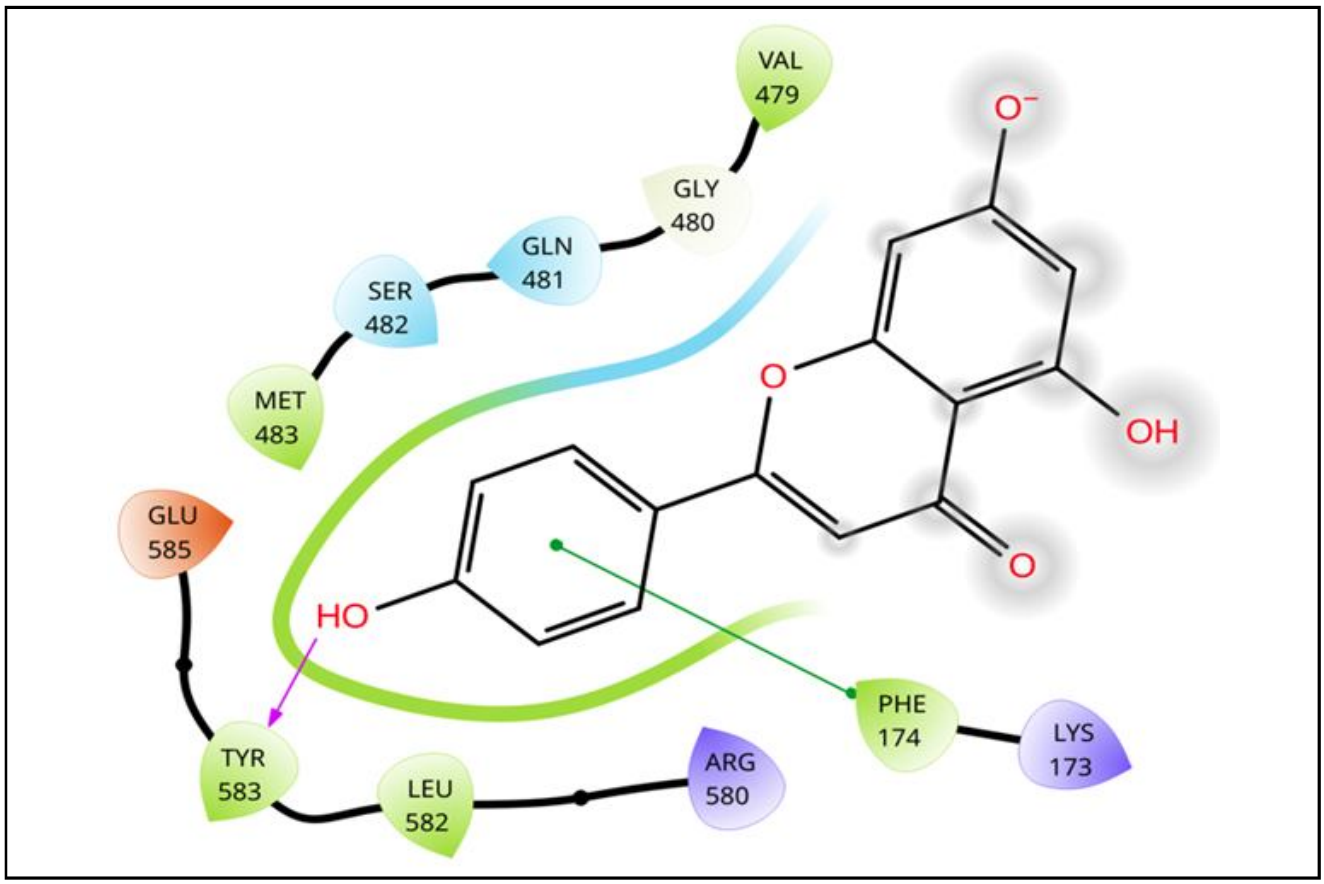

Figure 3a: 2-D interaction diagram of apigenin against Huntington disease (PDB ID-3LY6).

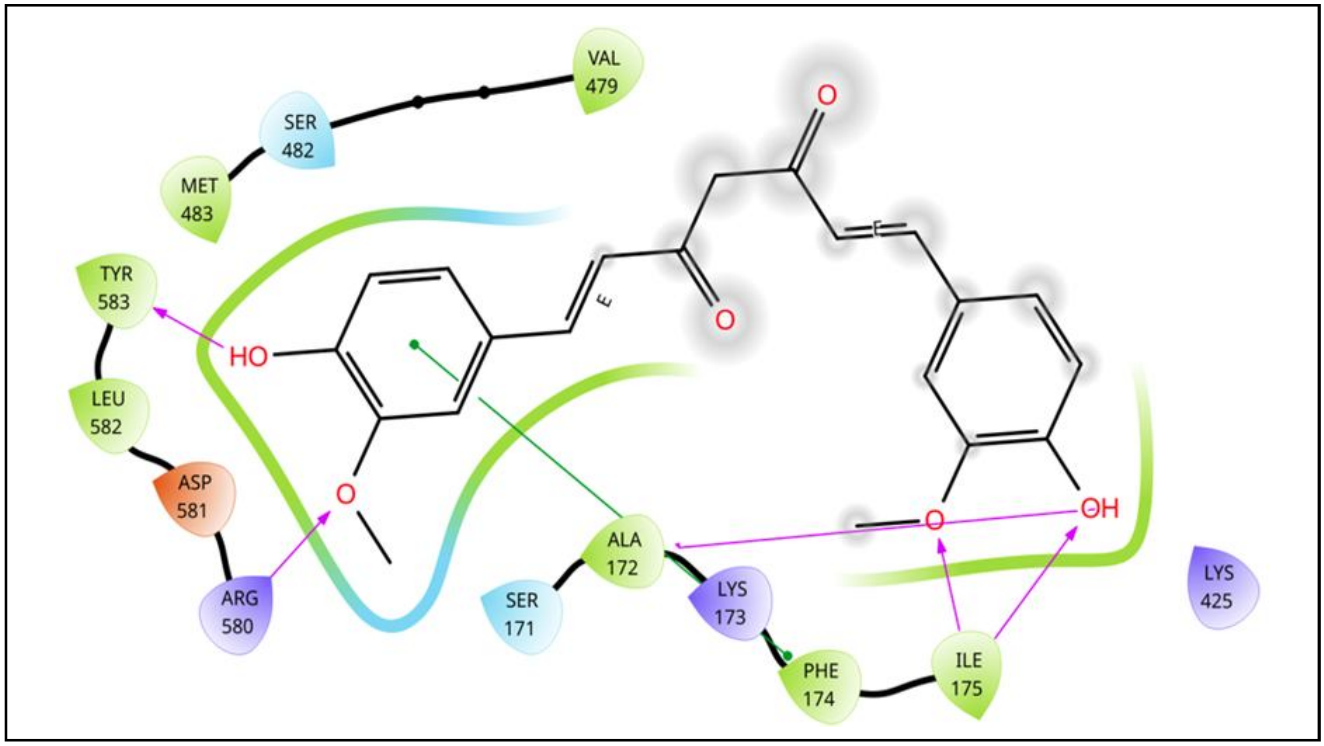

Figure 3b: 2-D interaction diagram of curcumin against Huntington disease (PDB ID-3LY6).

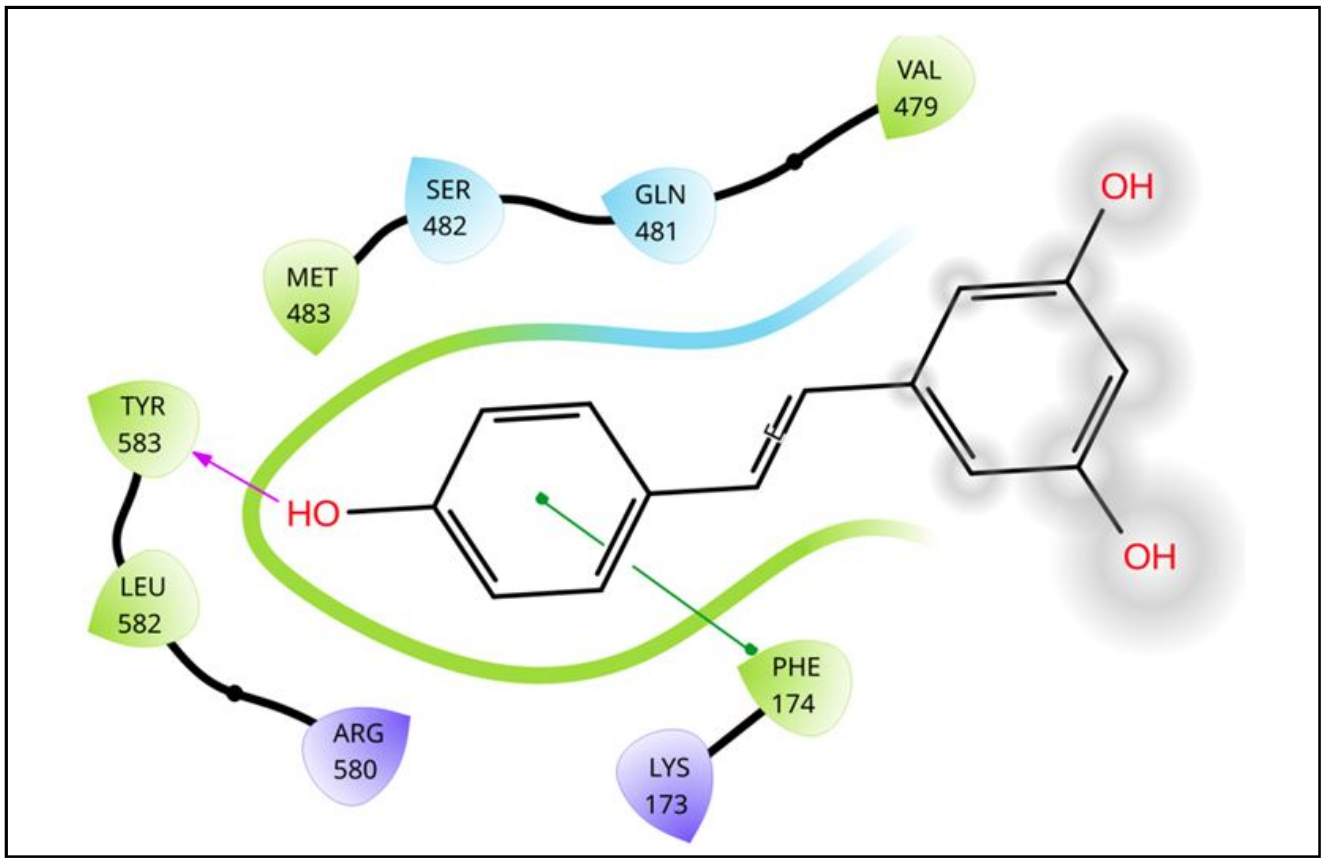

Figure 3c: 2-D interaction diagram of resveratrol against Huntington disease (PDB ID-3LY6).

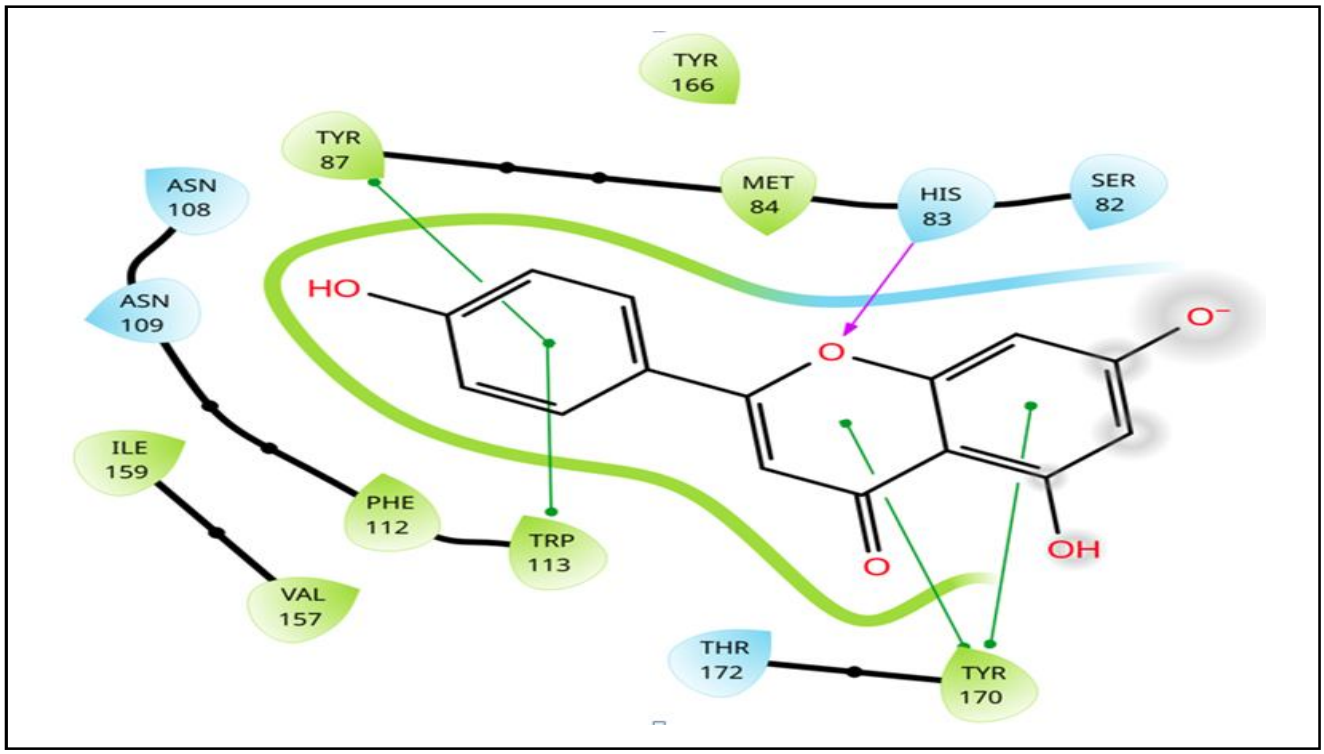

Figure 4a: 2-D interaction diagram of apigenin against Motor neural disease (PDB ID-36N3C).

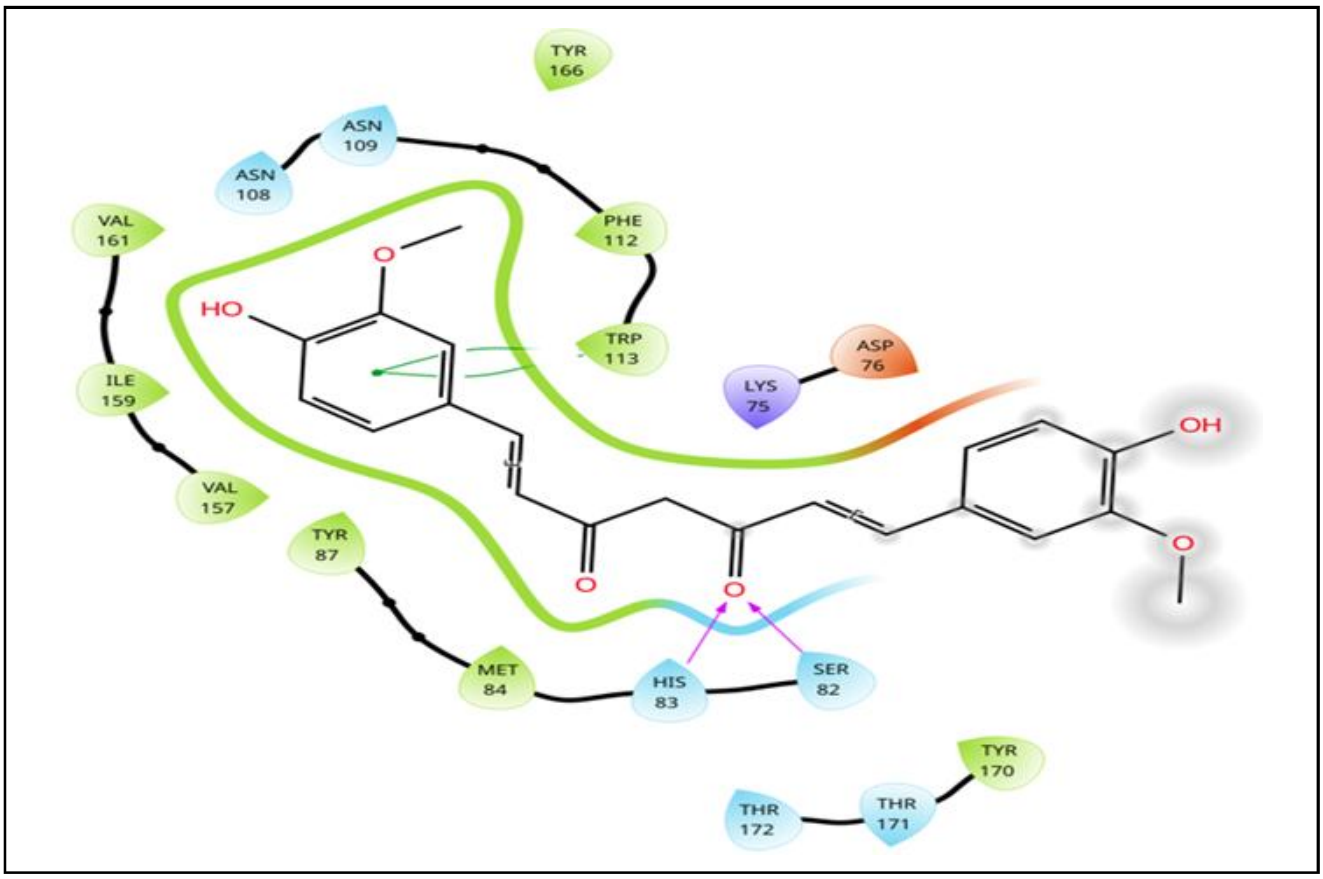

Figure 4b: 2-D interaction diagram of curcumin against Motor neural disease (PDB ID-6N3C).

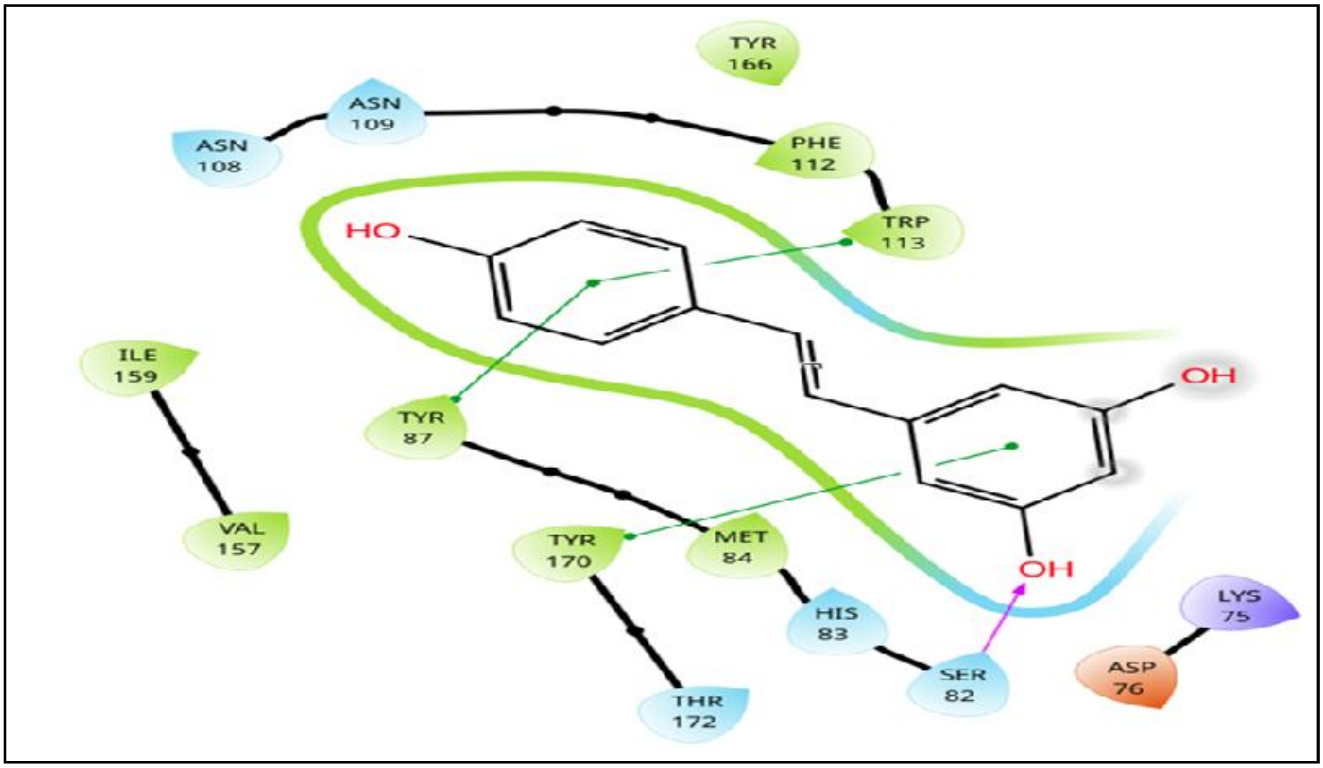

Figure 4c: 2-D interaction diagram of resveratrol against Motor neural disease (PDB ID-6N3C).

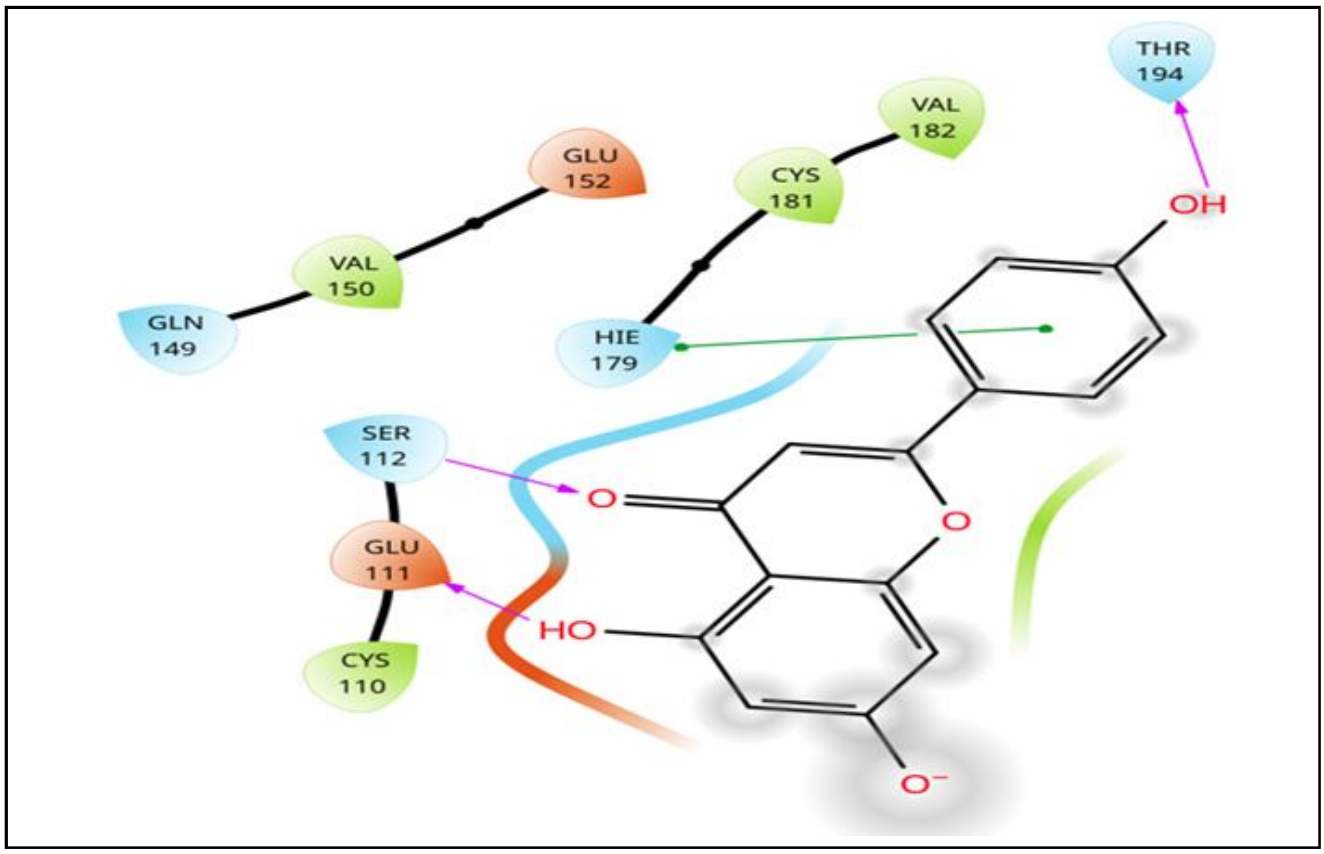

Figure 5a: 2-D interaction diagram of apigenin against Parkinson's disease (PDB ID-1A8R).

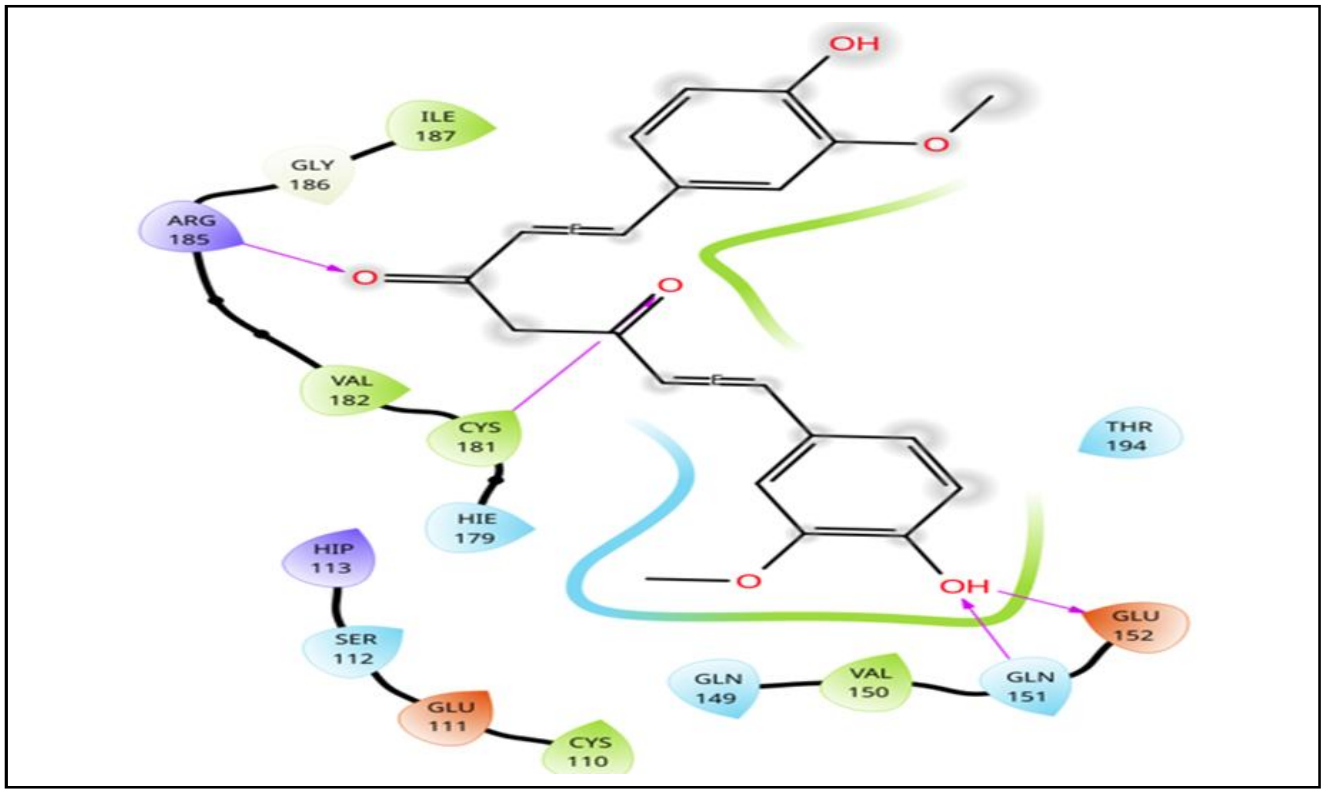

Figure 5b: 2-D interaction diagram of curcumin against Parkinson's disease (PDB ID-1A8R).

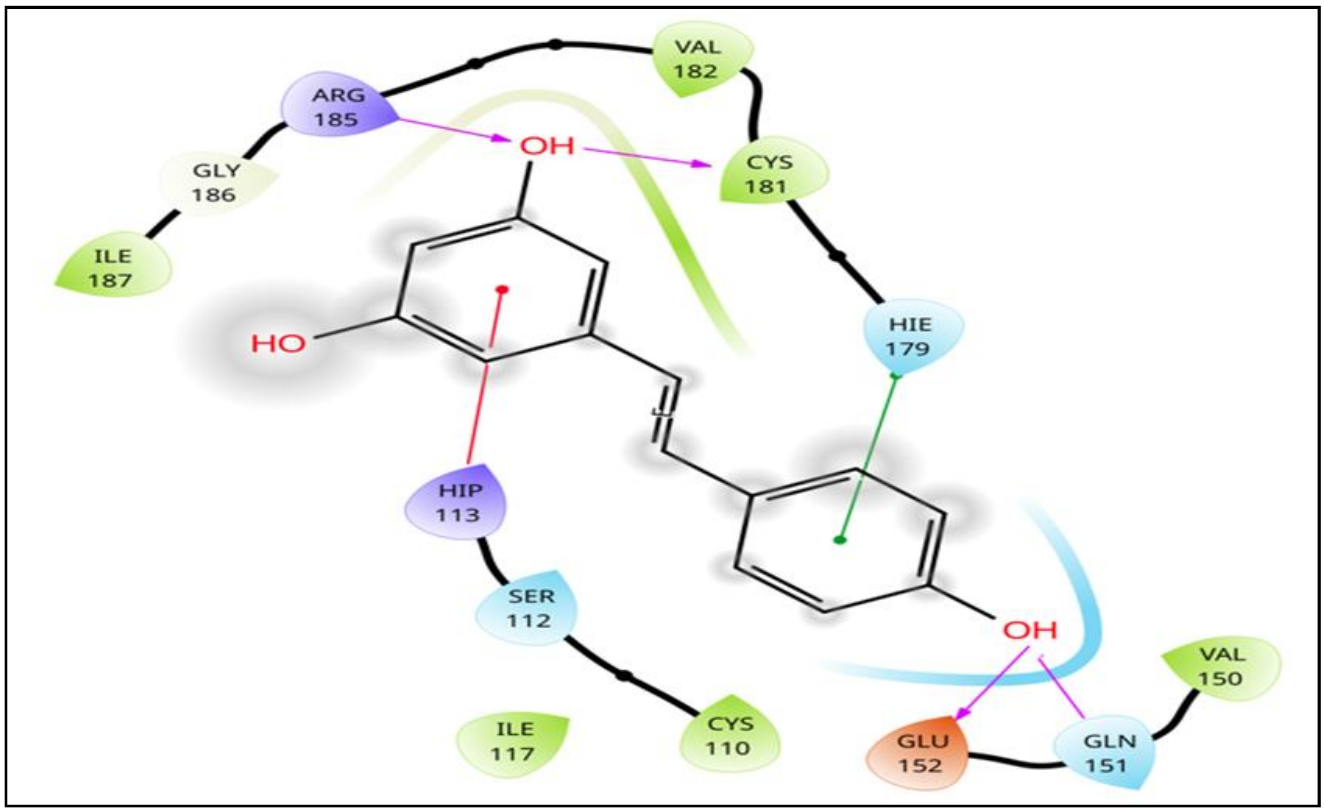

Figure 5c: 2-D interaction diagram of resveratrol against Parkinson's disease (PDB ID-1A8R).

2. Discussion

The computational ADME/T properties suggest that apigenin possesses a balanced pharmacokinetic profile suitable for oral administration, with no violations of Lipinski's Rule of Five, making it a viable drug-like candidate. However, its limited predicted BBB permeability (QPlogBB = –1.425) may reduce its potential for CNS disorders unless modified structurally to enhance CNS delivery.

In the molecular docking studies validated using co-crystallized ligands as standards (LY-411575 for 4DJU, N-(4-fluorobenzyl)-9H-purin-6-amine for 3MHL, 5ZQ for 3LY6, neur for 6N3C, and SB-203580 for 1A8R), apigenin (test compound) exhibited superior binding affinity to γ-secretase (-6.559 kcal/mol), which is crucial for Alzheimer's therapy, indicating that it may directly influence APP processing. Reference standards curcumin and resveratrol also showed therapeutic potential but with different strengths: resveratrol had better overall affinity (-6.218 kcal/mol), while curcumin demonstrated a wider interaction network, especially in hydrogen bonding (-2.07 kcal/mol) and van der Waals forces (-32.17 kcal/mol).

The results for other neurodegenerative disease targets reveal a more nuanced picture. Apigenin performed well in Ataxia (3MHL; -5.77072 kcal/mol) but was out performed by curcumin (3LY6: -7.64 kcal/mol; 6N3C: – 8.08 kcal/mol) and resveratrol (1A8R: -3.3859 kcal/mol) in Huntington's, Motor neuron disease, and Parkinson's. Notably, curcumin consistently demonstrated strong docking scores and favorable MM-GBSA binding energies (e.g., -67.60 kcal/mol for 6N3C), indicating robust and stable binding conformations, particularly due to extensive van der Waals and electrostatic interactions.

Apigenin's low internal strain (<4 kcal/mol) and strong hydrogen bonding network (-1.544 kcal/mol) suggest high specificity in binding, which may be valuable in precision-targeted therapies. However, its comparatively weaker affinity in some targets (*e.g.*, -16.03 kcal/mol for 1A8R) indicates that structural optimization (*e.g.*, BBB-penetrating modifications) could enhance its utility across broader neurodegenerative applications.

Collectively, these findings suggest that while curcumin emerges as the most promising broad-spectrum candidate, apigenin holds significant promise, particularly in Alzheimer's disease. Resveratrol occupies a middle ground, offering balanced binding and efficient interactions. Further *in vitro* and *in vivo* validation studies are recommended to substantiate these computational predictions and guide drug development strategies.

5. Conclusion

Apigenin demonstrates superior binding affinity and stability in alzheimer's disease and ataxia compared to the standards curcumin and resveratrol, highlighting its potential as a selective neurotherapeutic agent. However, in Huntington's, Motor neuron disease, and Parkinson's, curcumin and resveratrol show consistently stronger binding and interaction profiles. While curcumin emerges as the most effective broad-spectrum candidate, and resveratrol follows closely, apigenin favourable hydrogen bonding, low strain, and ligand efficiency suggest it remains a valuable candidate for targeted optimization, particularly in alzheimer's therapy.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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