International Journal for Interdisciplinary Scientific Advancements (*IJISA*)
ISSN: 3085-5012

IJISA, 2026, Volume 7, Issue 1, Page 1-15

Natural Flavones and Phenolic Compounds as Potential Acetylcholinesterase Inhibitors for Alzheimer's Disease: An in Silico Study

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Received: 01/01/2026
Revised: 03/03/2026
Accepted: 14/03/2026
Published: 18/03/2026

Abstract:

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that requires the development of effective and safe therapeutic agents. In this study, several natural flavones and phenolic compounds, including apigenin, quercetin, curcumin, rosmarinic acid, melatonin, and o-vanillin, were evaluated as potential acetylcholinesterase (AChE) inhibitors using an integrated in silico approach. ADMET profiling and BOILED-Egg analysis were performed to assess pharmacokinetic properties, drug-likeness, and blood–brain barrier permeability. Molecular docking studies revealed that curcumin, rosmarinic acid, apigenin, and quercetin exhibited stronger binding affinities toward AChE compared to the reference compound Memogain, interacting with key catalytic residues through hydrogen bonds and hydrophobic interactions. Overall, the results suggest that these natural compounds represent promising lead candidates for further development as anti-Alzheimer agents, deserving experimental validation.

Keywords: Flavones; Alzheimer's disease; Acetylcholinesterase; ADMET; BOILED-Egg model; Molecular docking; Neurodegenerative diseases.

I. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia worldwide. It is clinically characterized by cognitive decline, memory impairment, and behavioral disturbances. Among the multiple pathological mechanisms involved in AD, cholinergic dysfunction represents one of the earliest and most consistent biochemical hallmarks of the disease (Chen et al., 2022). This dysfunction is mainly associated with the excessive hydrolysis of acetylcholine by acetylcholinesterase (AChE), resulting in impaired synaptic transmission (Moreta et al., 2021). Consequently, AChE inhibition remains a validated therapeutic strategy aimed at enhancing cholinergic neurotransmission and improving cognitive function in AD patients (Colovic et al., 2013). However, currently approved AChE inhibitors exhibit limited efficacy and are often associated with adverse effects, highlighting the need for safer and more effective alternatives (Md. H. Rahman et al., 2021). Natural products have been extensively investigated as a valuable source of bioactive molecules for neurodegenerative disorders due to their broad chemical diversity and favorable safety profiles (Stachelska et al., 2025). In particular, flavones and phenolic compounds have attracted significant attention owing to their multifunctional biological activities, including antioxidant, anti-inflammatory, neuroprotective, and anticholinesterase effects(Habtemariam, 2018). Compounds such as apigenin, quercetin, curcumin, melatonin, rosmarinic acid, and o-vanillin have been widely explored for their potential to modulate key pathological pathways in AD (Topkaraoğlu & Tanoğlu, 2023) . In addition to their reported ability to inhibit amyloid-β aggregation, several of these molecules have demonstrated notable AChE inhibitory activity through interactions with both the catalytic active site and the peripheral anionic site of the enzyme (Wu et al., 2023). Despite their promising biological activities, the therapeutic application of many natural coounds is often hindered by unfavorable pharmacokinetic properties, including poor oral bioavailability and limited penetration of the blood–brain barrier (BBB) (M. O. Rahman et al., 2025). Therefore, early assessment of absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties is essential for evaluating their drug-likeness and central nervous system accessibility. Computational prediction tools, such as ADMET modeling, the BOILED-Egg approach, and molecular docking simulations, have emerged as efficient strategies to screen potential AChE inhibitors and to elucidate their molecular interaction patterns at the enzyme level (Lu et al., 2011). In the present study, an integrated in silico approach was employed to evaluate selected flavones and phenolic compounds as potential AChE inhibitors. ADMET profiling and BBB permeability prediction were combined with molecular docking analyses to assess their

pharmacokinetic suitability and binding affinity toward AChE (Mahnashi et al., 2022). Memogain was used as a reference compound for comparative analysis (Lu et al., 2011). This study aims to identify promising lead compounds with favorable drug-like properties that may serve as candidates for further experimental validation and development of novel therapeutic agents targeting acetylcholinesterase in Alzheimer's disease.

II. Materials and Methods

II.1. Ligand Preparation

Six flavone compounds (Figure 1), previously reported as potential acetylcholinesterase inhibitors, were prepared using Maestro version 13.8 (Schrödinger, LLC, New York, USA) (Merzouki et al., 2023). Memogain was included as a reference inhibitor and used as a positive control. The molecular structures were processed using the LigPrep module of Schrödinger to assign correct bond orders and generate appropriate ionization states. All ligands were geometry-optimized using the OPLS-2005 force field under default computational settings. The prepared ligands were subsequently exported in SDF format and used for molecular docking studies (Bekkouch et al., 2024).

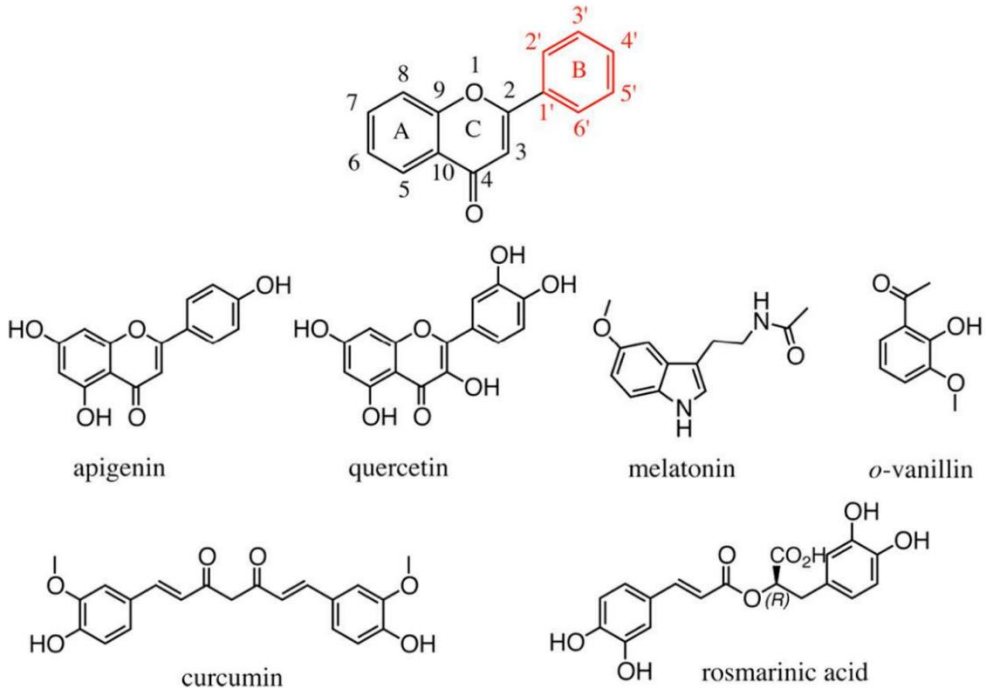


Figure 1. Numbering of the Flavone Skeleton and Chemical Structures of Apigenin, Quercetin, Melatonin, o-Vanillin, Curcumin, and Rosmarinic Acid

II.2. In silico prediction of ADMET properties

The ADMET properties of the selected natural compounds (apigenin, quercetin, curcumin, rosmarinic acid, melatonin, and o-vanillin) were evaluated using in silico approaches and compared with those of the reference compound Memogain, an optimized prodrug form of rosmarinic acid used as a pharmacokinetic and therapeutic benchmark (Merzouki et al., 2024a). Initial assessments of drug-likeness, lipophilicity (LogP), aqueous solubility, topological polar surface area (TPSA), and membrane permeability were performed using the SwissADME platform. Advanced pharmacokinetic parameters, including human intestinal absorption (HIA), tissue distribution, blood–brain barrier (BBB) permeability, cytochrome P450 (CYP450)-mediated metabolism, and excretion pathways, were predicted using the pkCSM server. Acute toxicity endpoints, such as median lethal dose (LD_{50}), mutagenicity (Ames test), hepatotoxicity, and systemic toxicity, were evaluated using ProTox-II (Merzouki et al., 2024b). In addition, the BOILED-Egg model implemented in SwissADME was applied to visualize intestinal absorption and BBB penetration, while P-glycoprotein (P-gp) interactions were analyzed to assess efflux potential and intracellular retention.

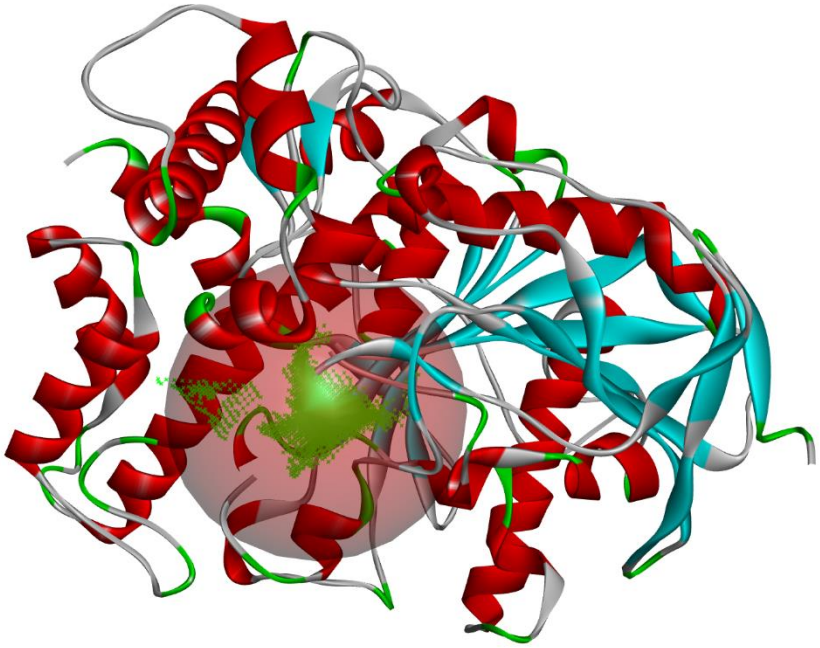


Figure 2. Three-dimensional structure of acetylcholinesterase (ache) from Alzheimer's disease showing the active site used for molecular docking in this study

II.3. Protein Preparation and Molecular Docking

The target protein used for the docking study was acetylcholinesterase (AChE) from Electrophorus electricus (PDB ID: 1C2B, resolution: 4.50 Å) (Wihadi et al., 2024). The crystal structure of the protein

was retrieved from the Protein Data Bank (PDB) (Figure 2). Protein preparation was carried out using the Protein Preparation Wizard implemented in Schrödinger Suite 2021-2. During this process, all water molecules and co-crystallized ligands were removed, and the active site was defined as the docking center. Energy minimization was performed using default parameters, with a root mean square deviation (RMSD) cutoff of 0.3 Å (Sharma et al., 2025). Missing hydrogen atoms were added, and protonation states were generated using Epik at physiological pH (7.0 ± 2.0). A receptor grid was generated to encompass the entire active site, using the coordinates (x = 21.57, y = 83.39, z = 20.57). Subsequently, the protein structure was further minimized using the OPLS_2005 force field. Molecular docking was performed using the Glide Standard Precision (SP) protocol. Docking scores were expressed as binding affinity values (kcal/mol) to evaluate ligand–protein interactions. The docking pose exhibiting the lowest binding energy was selected as the most favorable conformation. The resulting interactions were analyzed and visualized in both two-dimensional and three-dimensional representations using BIOVIA Discovery Studio 2021 (Alshahateet et al., 2024).

III. Results and Discussion

III.1. ADMET Properties Analysis

When comparing the ADMET characteristics of the selected natural compounds to the formulated reference compound Memogain, clear differences emerge across all pharmacokinetic and safety dimensions. Memogain, a prodrug-based optimized form of rosmarinic acid, consistently demonstrates superior pharmacokinetic behavior, largely due to its enhanced formulation, which improves solubility, membrane permeability, and systemic stability.

III.1.1. Absorption Patterns and Bioavailability Analysis

Among all compounds, Memogain exhibits one of the most favorable absorption profiles (Table 1). While melatonin also shows excellent bioavailability due to its simple structure and high permeability, most polyphenols such as apigenin, quercetin, and curcumin suffer from limited absorption driven by low aqueous solubility and rapid intestinal metabolism. Rosmarinic acid, the parent compound of Memogain, displays poor permeability and reduced intestinal absorption, illustrating the substantial improvement provided by the Memogain formulation. Thus, compared with Memogain, the natural polyphenols generally exhibit inferior bioavailability.

Table 1. Absorption and Bioavailability Parameters of the Studied Compounds

Compound	Oral Bioavailability	Solubility	Permeability	Key Comments
Apigenin	Moderate (~50%)	Low	High	Limited by poor aqueous solubility
Quercetin	Very Low (1-10%)	Low	Moderate/High	Extensive first-pass metabolism
Melatonin	Excellent (>90%)	Moderate	High	Rapid and complete absorption
o-Vanillin	Good	Moderate	High	Good absorption due to small molecular size
Curcumin	Very Low (<1%)	Very Low	High	Major issues with solubility, stability, metabolism
Rosmarinic Acid	Low–Moderate	Low	Low	Polar and hydrolyzed in intestine
Memogain	Moderate–Good	Enhanced	Enhanced	Formulation optimizes bioavailability

III.1.2. Pharmacokinetic Distribution Parameters

Memogain shows enhanced tissue distribution, particularly to the central nervous system, outperforming its natural counterparts. While melatonin, apigenin, and quercetin can cross the blood–brain barrier to varying degrees, this capacity is strongly limited by extensive protein binding (quercetin) or poor systemic availability (apigenin) (Table 2). Hydrophilic molecules such as rosmarinic acid and o-vanillin display limited distribution and negligible BBB permeability. In contrast, Memogain, owing to its optimized lipophilicity and formulation, achieves superior brain targeting, positioning it as a more effective neuroactive compound.

Table 2. Distribution and Barrier Permeability of Selected Compounds

Compound	Log P	Protein Binding	Barrier Permeability	Key Comments
Apigenin	2.68	Moderate	Crosses BBB	Good tissue distribution
Quercetin	1.82	Very High	Crosses BBB	High protein binding
Melatonin	1.64	Low	Excellent BBB penetration	Designed for CNS access

o-Vanillin	1.48	Low	Good	General distribution
Curcumin	3.29	High	Crosses BBB	Wide distribution but poor absorption
Rosmarinic Acid	1.55	Low	Limited	Hydrophilic
Memogain	Enhanced	Variable	CNS targeted	Formulation enhances brain delivery

III.1.3. Metabolism Analysis

Compared with Memogain, most of the natural molecules undergo more extensive or more rapid metabolism (Table 3). Polyphenols like quercetin and curcumin experience intense first-pass metabolism, significantly reducing their circulating levels. Although melatonin undergoes a relatively simple metabolic pathway, it is metabolized extremely rapidly, yielding a short systemic half-life. o-Vanillin is rapidly oxidized into vanillic acid and cleared swiftly. Memogain demonstrates a more controlled metabolic profile, with moderate biotransformation and improved stability relative to rosmarinic acid. This moderated metabolism contributes to prolonged systemic exposure and enhanced pharmacological duration compared with the unformulated natural compounds.

Table 3. Metabolism Profiles of Selected Compounds

Compound	Major Site	Key Pathways	Extent	Key Comments
Apigenin	Liver	CYP1A2, CYP2C9, glucuronidation	Extensive	Active metabolites
Quercetin	Intestine & Liver	Glucuronidation, CYP450	Very Extensive	Strong pre-systemic metabolism
Melatonin	Liver	CYP1A2	Rapid	Simple pathway
o-Vanillin	Liver	Oxidation, conjugation	Rapid	Converted to vanillic acid
Curcumin	Intestine & Liver	Reduction, conjugation	Very Extensive	Rapid degradation
Rosmarinic Acid	Intestine & Liver	Hydrolysis, conjugation	Moderate	Breaks into caffeic acid derivatives
Memogain	Intestine & Liver	Hydrolysis, conjugation	Moderate	Formulation alters metabolism

III.1.4. Excretion Analysis

Excretion patterns further highlight the advantages of Memogain. Many polyphenols (quercetin, rosmarinic acid, apigenin) are rapidly conjugated and eliminated, resulting in limited bioactive residence time (Table 4). Curcumin is largely excreted unchanged through feces due to poor absorption. Melatonin is cleared quickly via urinary excretion, consistent with its short half-life. Memogain, however, shows indications of prolonged excretion, likely due to controlled release and reduced metabolic turnover, allowing for more sustained systemic presence than any of the unformulated natural molecules.

Table 4. Excretion and Half-Life of Selected Compounds

Compound	Primary Route	Half-Life	Key Comments
Apigenin	Fecal	Moderate	Enterohepatic recirculation possible
Quercetin	Urine & Feces	11–28 h	Long metabolite half-life
Melatonin	Urinary (>90%)	20–60 min	Rapid rhythmic excretion
o-Vanillin	Urinary	Short	Rapid clearance
Curcumin	Fecal	<2 h	Mostly excreted unchanged
Rosmarinic Acid	Urinary	Short	Rapid clearance
Memogain	Urinary	Prolonged	Formulation modifies kinetics

III.1.5. Toxicity and Safety Evaluation

In terms of safety, Memogain compares favorably with all investigated compounds. Most natural molecules exhibit high LD_{50} values and excellent tolerability, with minimal risk of mutagenicity or organ toxicity (Table 5). Quercetin shows a mild positive Ames signal under metabolic activation, but this effect is dose-dependent and not clinically relevant. Memogain displays a similarly safe toxicity profile but with the added advantage of controlled pharmacokinetics, reducing the risk of high peak concentrations and enhancing therapeutic predictability. Thus, when comparing overall safety and therapeutic margin, Memogain performs at least as safely as the natural compounds, while offering a more optimized pharmacokinetic profile.

Table 5. Toxicity and Safety Profiles of Selected Compounds

Compound	LD50	Major Concerns	Mutagenicity	Safety Profile
Apigenin	>5000 mg/kg	Low	Negative	Very well tolerated
Quercetin	>2000 mg/kg	Pro-oxidant at high doses	Positive with S9	Safe at dietary doses
Melatonin	Very High	Drowsiness	Negative	Very safe
o-Vanillin	~2000 mg/kg	Irritant	Debated	Safe as additive
Curcumin	>2000 mg/kg	GI irritation	Negative	Very safe
Rosmarinic Acid	Very High	None	Negative	Safe antioxidant
Memogain	Very High	None	Negative	Excellent safety

III.2. BOILED-Egg Model Analysis

The obtained BOILED-Egg model (Figure 3) clearly highlights differences in permeability and absorption among the studied compounds. Melatonin and o-Vanillin are entirely located within the yellow region, indicating a high potential to cross the blood–brain barrier (BBB), which is consistent with their low molecular weight and moderate logP values. In contrast, Apigenin, Curcumin, Quercetin, and Rosmarinic Acid are positioned within the white region, suggesting high intestinal absorption (HIA) but very limited BBB penetration, primarily due to their elevated TPSA values and more polar characteristics. None of the compounds appear in the PGP+ zones, indicating that all are predicted as non-substrates of P-glycoprotein, favoring intracellular retention. Overall, the results show that only Melatonin and o-Vanillin exhibit profiles compatible with potential central nervous system activity, whereas the other compounds, despite being well absorbed, are more likely to act on peripheral targets, in agreement with their previously determined ADMET properties.

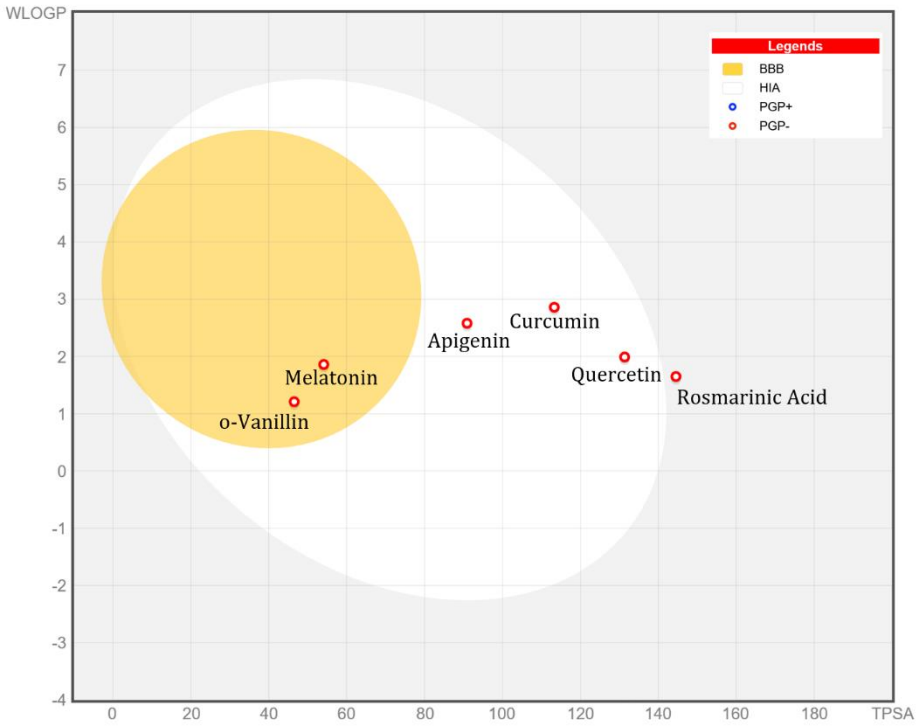


Figure 3. BOILED-Egg model of ADMET properties of selected compounds

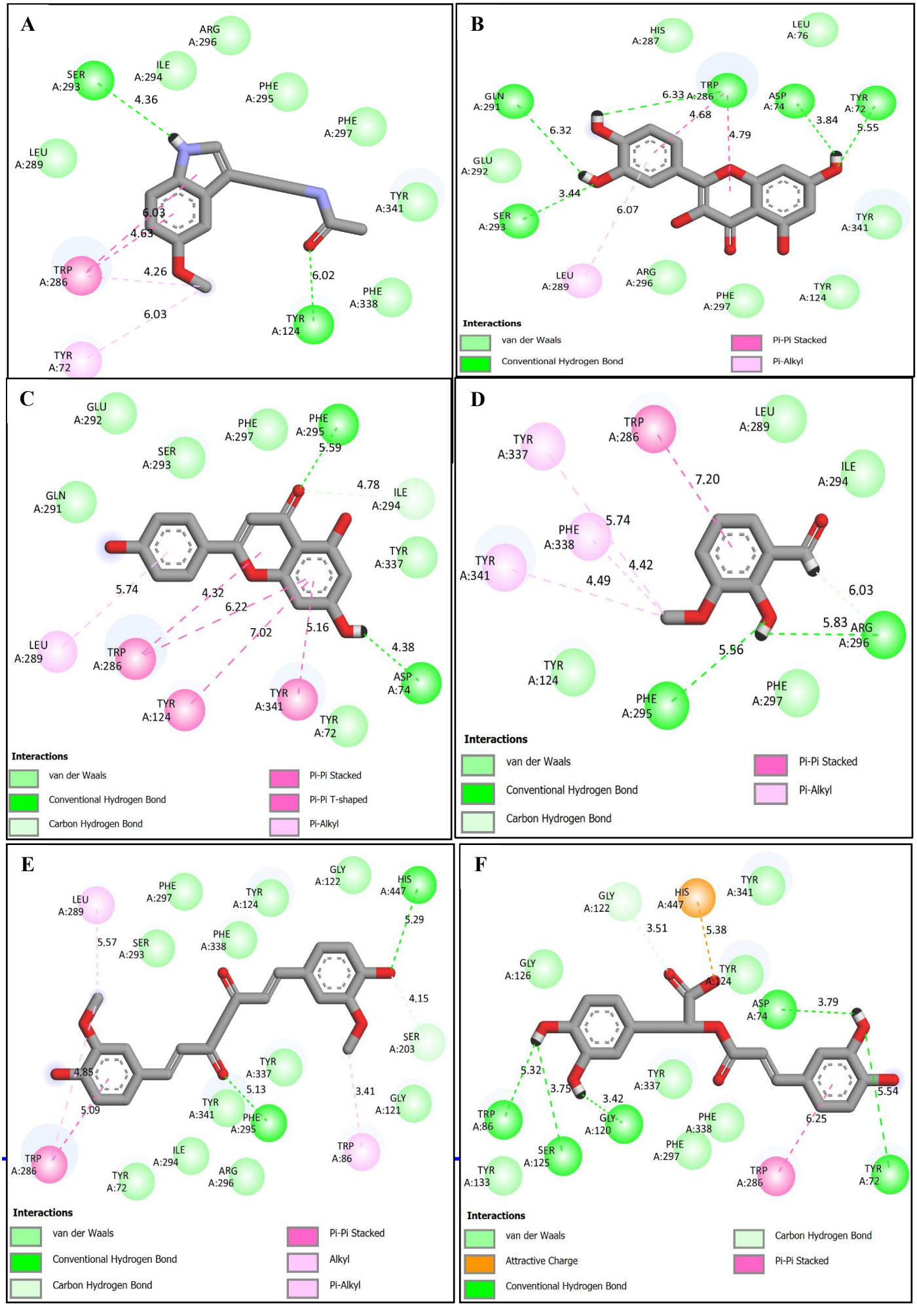
III.3. Molecular Docking Analysis

The molecular docking analysis revealed notable differences in the binding affinities and interaction patterns of the selected compounds toward acetylcholinesterase (AChE), a key therapeutic target in Alzheimer's disease (Table 6). Among the tested molecules, curcumin exhibited the most favorable docking score (−8.105 kcal/mol), indicating the strongest predicted binding affinity compared to the reference compound Memogain (−6.860 kcal/mol). Curcumin formed stable interactions within the catalytic gorge, involving key residues such as HIS447, PHE295, SER203, TRP286, and LEU289, which are known to play crucial roles in AChE inhibition. The presence of hydrogen bonds with HIS447 and PHE295 further supports the stability of the ligand–enzyme complex (Figure 4). Rosmarinic acid also demonstrated a strong binding affinity (−7.797 kcal/mol), surpassing that of Memogain. Its interaction network included several critical residues of both the catalytic active site and peripheral anionic site (PAS), notably TYR72, ASP74, SER125, TRP286, and HIS447, suggesting a potential dual-binding mode that may enhance inhibitory efficacy. Multiple hydrogen bonds, particularly with ASP74, SER125, and GLY120, contributed to the stabilization of the complex. The flavonoids apigenin and quercetin showed comparable docking scores (−7.147 and −7.097 kcal/mol, respectively), both outperforming Memogain. Their binding modes were characterized by interactions with essential aromatic residues such as TRP286, PHE295, TYR72, and TYR341, which are associated

with π–π stacking and hydrophobic interactions within the active gorge. Hydrogen bonding with ASP74, SER293, and TYR72 further reinforced ligand binding, highlighting the importance of hydroxyl groups in flavonoid–AChE recognition. In contrast, melatonin and o-vanillin displayed moderate docking scores (−5.846 and −6.108 kcal/mol, respectively), lower than that of Memogain. Although both compounds interacted with key residues including TRP286 and TYR124, their reduced binding affinity may be attributed to their smaller molecular size and limited capacity to establish multiple stabilizing interactions within the active site. Overall, the docking results indicate that curcumin, rosmarinic acid, apigenin, and quercetin exhibit stronger predicted inhibitory potential against AChE than the standard Memogain, as evidenced by their lower docking scores and extensive interaction networks involving catalytic and peripheral site residues. These findings suggest that polyphenolic compounds, particularly those capable of forming multiple hydrogen bonds and aromatic interactions, may serve as promising candidates for further development as AChE inhibitors in Alzheimer's disease therapy.

Table 6. Docking scores and key binding residues of Alzheimer's disease (AChE) target protein interacting with the selected compounds, generated using SP docking

Compound Name	Docking Score (Kcal/mol)	Contributing Binding Residues	Hydrogen bonds	Bond Distance (Å)
Apigenin	-7.147	PHE295, ASP74, TYR341, TYR124, TRP286, LEU289	PHE295 ASP74	5.59 4.38
Quercetin	-7.097	TYR72, ASP74, TRP286, GLN291, SER293, LEU289	TYR72 ASP74 TRP28 GLN291 SER293	5.55 3.84 6.33 6.32 3.44
Melatonin	-5.846	SER293, TYR124, TRP286, TYR72	SER293 TYR124	4.36 6.02
o-Vanillin	-6.108	ARG296, PHE295, TYR341, PHE338, TYR337, TRP286	ARG296 PHE295	5.83 5.56
Curcumin	-8.105	HIS447, PHE295, SER203, TRP86, TRP286, LEU289	HIS447 PHE295	5.29 5.13
Rosmarinic Acid	-7.797	TYR72, ASP74, SER125, TRP86, GLY120, TRP286, HIS447	TYR72 ASP74 SER125 TRP86 GLY120	5.54 3.79 3.75 5.32 3.42
Memogain	-6.860	TYR72, PHE295TYR341, TRP286, TYR124, SER293, ILE294, TYR341	TYR72 PHE295	4.64 5.52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SER A:293
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LEU A:289
TYR A:341
TRP A:286
PHE A:338
TYR A:124
TYR A:72
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6.03
4.63
4.26
6.02
6.03
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TRP A:286
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Interactions
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Pi-Alkyl
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GLN A:291
ILE A:294
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5.74
4.32
6.22
7.02
5.16
4.38
Interactions
van der Waals
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Carbon Hydrogen Bond
Pi-Pi Stacked
Pi-Pi T-shaped
Pi-Alkyl
D
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TRP A:286
LEU A:289
ILE A:294
PHE A:338
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ARG A:296
TYR A:124
PHE A:295
PHE A:297
7.20
5.74
4.42
4.49
6.03
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5.56
Interactions
van der Waals
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Carbon Hydrogen Bond
Pi-Pi Stacked
Pi-Alkyl
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GLY A:122
HIS A:447
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Interactions
van der Waals
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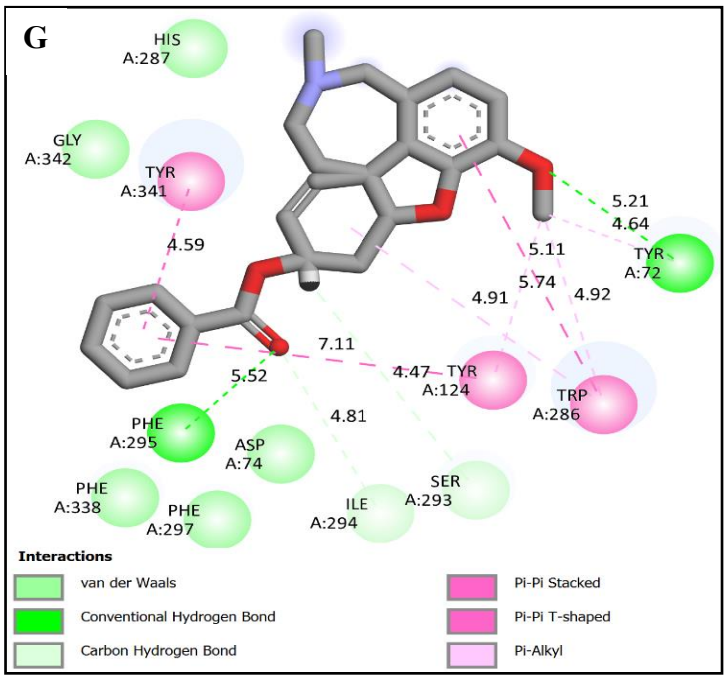

Figure 4. 2D intermolecular interactions between (A) Apigenin, (B) Quercetin, (C) Melatonin, (D) o-Vanillin, (E) Curcumin, (F) Rosmarinic Acid, (G) Memogain (standard) with the active site of AChE (PDB: 1C2B) protein

Conclusion

This study combined ADMET profiling, BOILED-Egg analysis, and molecular docking to evaluate selected flavones and phenolic compounds as potential acetylcholinesterase (AChE) inhibitors for Alzheimer's disease. The results highlighted curcumin, rosmarinic acid, apigenin, and quercetin as promising candidates due to their strong binding affinities and favorable interactions with key AChE residues compared to Memogain. Despite limitations in blood–brain barrier permeability for some flavones, the overall findings support their potential as lead compounds, warranting further experimental validation and pharmacokinetic optimization.

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