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Research Paper

In-Silico Molecular Docking Study of Rivastigmine–Phenolic Acid Complexes Against Acetylcholinesterase (1GQR) For Alzheimer's Disease

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ABSTRACT

This study evaluated the molecular interaction potential of Rivastigmine and Chlorogenic acid against the Alzheimer's disease-associated target protein 1GQR using molecular docking analysis. Rivastigmine was used as the standard drug, while Chlorogenic acid was investigated as a natural therapeutic compound. The docking study assessed binding affinity and ligand–protein interactions, including hydrogen bond formation and binding stability. The results showed favorable interactions with protein 1GQR, indicating the potential inhibitory activity of Chlorogenic acid with combination of the standard drug. These findings suggest that Rivastigmine with Chlorogenic acid may serve as a promising candidate for Alzheimer's disease treatment. However, further studies including ADMET profiling, molecular dynamics simulations, and experimental validation are required to confirm its therapeutic efficacy and safety.

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by memory loss, cognitive decline, and impaired cognitive functions, making it the most common cause of dementia worldwide [1]. The pathological hallmarks of Alzheimer's disease include **amyloid-beta (Aβ) plaque accumulation, tau protein hyper phosphorylation, oxidative stress, and cholinergic dysfunction**, leading to neuronal degeneration and cognitive impairment [2]. The cholinergic hypothesis suggests that reduced acetylcholine levels significantly contribute to memory dysfunction in Alzheimer's patients' [3] Current therapeutic approaches primarily involve **cholinesterase inhibitors**, such as **Rivastigmine**, which inhibit acetylcholinesterase (AChE) and

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butyrylcholinesterase (BuChE), improving cholinergic neurotransmission and temporarily enhancing cognitive function [4]. However, existing therapies mainly provide symptomatic relief and fail to completely prevent disease progression [5]. Natural compounds have gained considerable attention due to their **antioxidant, anti-inflammatory, and neuroprotective properties**, which may contribute to reducing oxidative stress and neurodegeneration associated with Alzheimer's disease [6]. Among these, **Chlorogenic acid**, a naturally occurring phenolic compound, has demonstrated antioxidant activity, neuroprotective effects, and potential inhibitory activity against Alzheimer's disease-related pathways [7]. Molecular docking has emerged as an important computational tool in drug discovery, enabling prediction of **ligand–protein interactions, binding affinity, and molecular stability** before experimental studies [8]. Computational approaches help identify promising therapeutic candidates rapidly and cost-effectively. Therefore, the present study focuses on the **molecular docking analysis of Rivastigmine and Chlorogenic acid against protein 1GQR (Human Acetylcholinesterase)** to evaluate binding affinity, hydrogen bonding interactions, and inhibitory potential against Alzheimer's disease-associated targets. The findings of this study may contribute to the identification of novel lead compounds with improved therapeutic potential for Alzheimer's disease management and support future experimental validation studies.

MOA: Acetylcholinesterase (AChE) is a key enzyme responsible for the hydrolysis of acetylcholine in the central nervous system. In Alzheimer's disease, degeneration of cholinergic neurons leads to reduced acetylcholine levels, causing memory loss, cognitive dysfunction, and impaired neuronal signaling. Increased AChE activity further accelerates acetylcholine degradation and contributes to amyloid-beta plaque formation and neurodegeneration. Protein 1GQR represents the crystal structure of human acetylcholinesterase and is widely used in molecular docking studies for evaluation of anti-Alzheimer's compounds. Rivastigmine is an FDA-approved cholinesterase inhibitor that binds to the active site of AChE and inhibits acetylcholine breakdown, thereby improving cholinergic neurotransmission and cognitive function. Chlorogenic acid is a naturally occurring phenolic compound with antioxidant, anti-inflammatory, and neuroprotective properties that help reduce oxidative stress and neuronal damage. The rivastigmine–chlorogenic acid complex demonstrated strong interaction with protein 1GQR, suggesting potential inhibitory activity against acetylcholinesterase and possible therapeutic benefit in Alzheimer's disease management.

DRUG PROFIL:

(1) Rivastigmine is a widely used **cholinesterase inhibitor** for the symptomatic treatment of mild to moderate Alzheimer's disease and dementia associated with Parkinson's disease [9]. It acts by inhibiting both **acetylcholinesterase (AChE)** and **butyrylcholinesterase (BuChE)** enzymes, thereby increasing acetylcholine levels in the brain and improving cognitive function, memory, and learning ability in Alzheimer's patients [10].
However, Rivastigmine mainly provides **symptomatic relief** and does not completely prevent the progression of neurodegeneration associated with Alzheimer's disease [11]. Long-term use may also be associated with adverse effects such as **nausea, vomiting, dizziness, gastrointestinal disturbances, and reduced patient compliance** [12].
Rivastigmine improves cholinergic neurotransmission by reducing the breakdown of

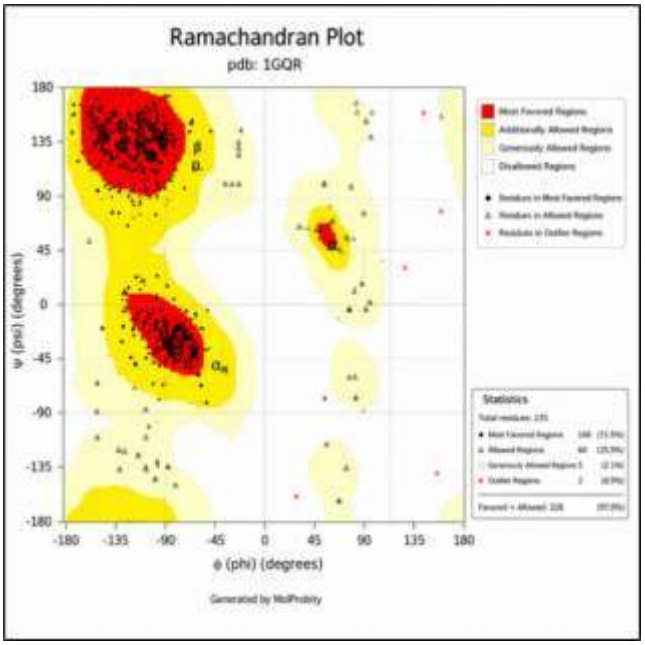
acetylcholine, which helps compensate for cholinergic deficits observed in Alzheimer's disease [13]. Due to its established therapeutic effectiveness, Rivastigmine is commonly used as a **standard reference drug in molecular docking studies** for evaluating the anti-Alzheimer potential of novel compounds and phytochemicals [14].

(2) Phenolic acids are naturally occurring phytochemicals widely distributed in fruits, vegetables, coffee, cereals, and medicinal plants [15]. They possess strong antioxidant, anti-inflammatory, neuroprotective, and anti-amyloid activities, making them promising therapeutic candidates for Alzheimer's disease management [16]. Phenolic acids help reduce oxidative stress, inhibit amyloid-beta aggregation, and protect neuronal cells from degeneration [17]. Several phenolic acids also exhibit moderate acetylcholinesterase inhibitory activity, which supports cholinergic neurotransmission and cognitive function [18]. In the present study, phenolic acids such as gallic acid, ferulic acid, vanillic acid, caffeic acid, and chlorogenic acid were selected due to their reported neuroprotective and multi-target therapeutic potential against Alzheimer's disease [19].

TARGET SELECTION, PREPERATION AND VALIDATION: Protein preparation is an essential step in molecular docking studies because the structural quality of the protein directly affects docking accuracy and binding interaction analysis. In the present study, only protein 1GQR was selected from the Protein Data Bank (PDB) for docking analysis with the rivastigmine–chlorogenic acid complex. Protein 1GQR represents acetylcholinesterase (AChE) complexed with rivastigmine and was determined by X-ray diffraction with a resolution of 2.20 Å, indicating good structural quality for computational studies. Acetylcholinesterase is responsible for the hydrolysis of acetylcholine in the brain, and increased AChE activity contributes to cognitive decline and amyloid-beta aggregation in Alzheimer's disease. Before docking, water molecules and unwanted ligands were removed, followed by energy minimization and conversion of the protein into PDBQT format for molecular docking analysis using AutoDock Vina.

Preparation: Protein 1GQR was retrieved from the Protein Data Bank (PDB) with a resolution of 2.20 Å. During protein preparation, water molecules, unwanted ligands, and heteroatoms were removed using BIOVIA Discovery Studio followed by energy minimization to obtain a stable protein structure. Finally, the prepared protein was converted into PDBQT format for molecular docking analysis using PyRx.

Validation: The Ramachandran plot was used to validate the structural quality of protein 1GQR. The analysis showed that 168 residues (71.5%) were present in the most favored regions, 60 residues (25.5%) in additionally allowed regions, 5 residues (2.1%) in generously allowed regions, and only 2 residues (0.9%) in outlier regions. Overall, 97.0% of residues were present in favored and allowed regions, indicating that the protein structure is stable and suitable for molecular docking studies.

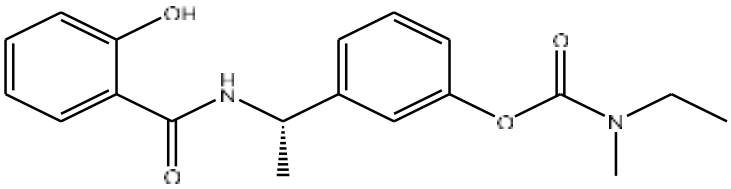
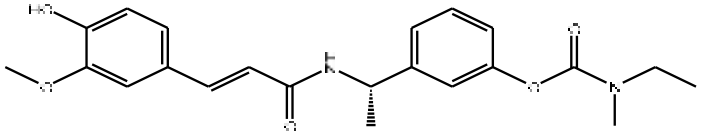
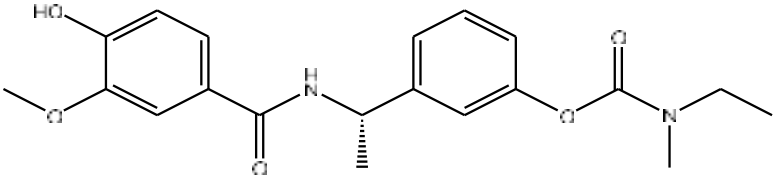
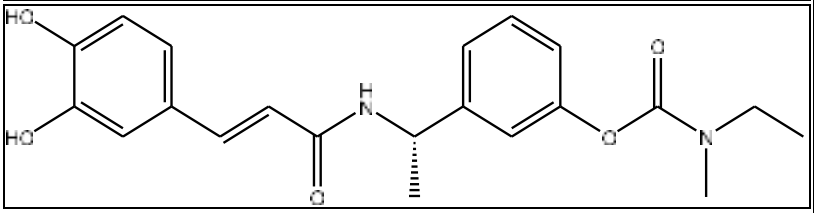
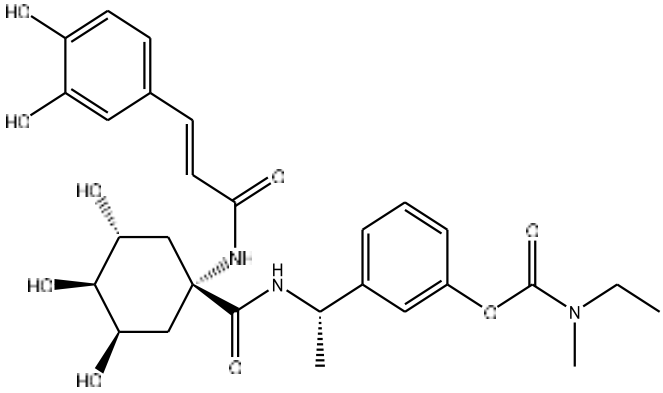


LIGAND SELECTION, PREPERATION AND VALIDATION: In the present study, rivastigmine and chlorogenic acid were prepared using ChemDraw and ChemDraw 3D. Ligands such as rivastigmine complexes with gallic acid, ferulic acid, vanillic acid, caffeic acid, and chlorogenic acid were prepared using chemical structure designing and reaction modelling in ChemDraw and ChemDraw 3D software. The ligand structures were generated by forming molecular complexes between rivastigmine and the selected phenolic acids, followed by geometry optimization and energy minimization to obtain stable conformations for molecular docking studies.

Validation: The prepared ligand complexes were validated by visual inspection, geometry optimization, and energy minimization using ChemDraw 3D. Bond lengths, bond angles, and molecular conformations were checked to ensure structural stability and correctness. The optimized ligands were then converted into PDBQT format for accurate molecular docking analysis against protein 1GQR.

Software and Tools Used: The Protein Data Bank (PDB)[1] was used to retrieve the 3D structure of protein 1GQR for docking studies. PyRx[2] with AutoDock Vina was used for ligand preparation, energy minimization, and molecular docking analysis. SwissADME[3] was used for prediction of drug-likeness and pharmacokinetic properties. ChemDraw[4] and Chem3D were used for designing and optimization of rivastigmine–phenolic acid ligand complexes. BIOVIA Discovery Studio[5] was used for protein visualization and analysis of ligand–protein interactions.

Chemical reaction between rivastigmine and phenolic compounds:

Sr. No.	Drug Used	Phenolic Compound	Final Product
1	**Rivastigmine**	Salicylic acid	
2	**Rivastigmine**	Ferulic Acid	
3	**Rivastigmine**	Vanillic Acid	
4	**Rivastigmine**	Caffeic Acid	
5	**Rivastigmine**	Chlorogenic Acid	

Molecular Docking: Molecular docking is a computational technique used to predict the binding affinity, orientation, and interaction of a ligand molecule within the active site of a target protein. In the present study, molecular docking was performed to evaluate the interaction of rivastigmine–phenolic acid complexes with Alzheimer's disease target protein 1GQR using PyRx.. Protein 1GQR represents human acetylcholinesterase (AChE), an important enzyme involved in acetylcholine hydrolysis and cognitive function**.**

NEED OF MOLECULAR DOCKING:

1. To predict ligand–protein interaction at the molecular level.
2. To evaluate binding affinity of rivastigmine–phenolic acid complexes with protein **1GQR**.
3. To identify potential inhibitors against acetylcholinesterase (**AChE).**
4. To reduce time, cost, and experimental workload in drug discovery.
5. To analyse stability and interaction of ligands within the active site of the protein.

ADVANTAGE OF MOLECULAR DOCKING:

1. Rapid and cost-effective computational technique.
2. Helps identify potential lead compounds.
3. Predicts hydrogen bonding and hydrophobic interactions.
4. Supports structure-based drug design.
5. Improves selection of compounds for further in vitro and in vivo studies.
6. Can be integrated with **ADMET** analysis for drug-likeness prediction.

Steps Involved in Molecular Docking:

1. **Preparation of Protein and Ligand**
   Prepared protein 1GQR and ligand structures were converted into PDBQT format after removal of water molecules, addition of hydrogen atoms, and energy minimization.
2. **Grid Box Generation**
   A docking grid was positioned around the active binding pocket of protein 1GQR to identify the ligand interaction region during docking analysis.
3. **Docking Simulation**
   Docking was performed using AutoDock Vina in PyRx to predict ligand binding orientation, binding affinity, and molecular interactions with the target protein.
4. **Binding Affinity Evaluation**
   Binding affinity values were obtained in kcal/mol, where lower energy values indicated stronger and more stable ligand–protein interactions.
5. **Interaction Analysis**
   Docked complexes were analysed using BIOVIA Discovery Studio to study hydrogen bonding and hydrophobic interactions.

ADMET: ADMET analysis is a computational method used to evaluate the pharmacokinetic and toxicity properties of compounds, including Absorption, Distribution, Metabolism, Excretion, and Toxicity. In the present study, ADMET properties of rivastigmine–phenolic acid complexes were predicted using SwissADME.

Importance of ADMET Prediction:

1. Evaluates drug-likeness and pharmacokinetic behaviour.
2. Identifies toxic or poorly bioavailable compounds at an early stage.
3. Helps select safe and effective therapeutic candidates.
4. Supports optimization of lead compounds for drug development.

Parameters Evaluated:

1. **Absorption** – GI absorption, water solubility, and LogP.
2. **Distribution** – Blood–brain barrier (BBB) permeability.
3. **Metabolism** – CYP450 enzyme interaction and metabolic stability.
4. **Excretion** – Clearance and elimination prediction.
5. **Toxicity** – Hepatotoxicity, mutagenicity, and carcinogenicity analysis.

RESULTS AND DISCUSSION:

Molecular docking analysis was performed using AutoDock Vina to evaluate the interaction between the rivastigmine–chlorogenic acid complex and Alzheimer's disease target protein 1GQR. The docking result was analyzed based on binding affinity, hydrogen bonding, and stability of the ligand–protein complex. The rivastigmine–chlorogenic acid complex showed a strong binding affinity of -8.3 kcal/mol against protein 1GQR, indicating stable interaction and promising inhibitory potential against acetylcholinesterase associated with Alzheimer's disease. The molecular docking study revealed that the rivastigmine–chlorogenic acid complex showed strong interaction with protein 1GQR with a binding affinity of **-8.3 kcal/mol**. The complex demonstrated stable ligand–protein interaction through hydrogen bonding and hydrophobic interactions within the active site of acetylcholinesterase. The highly negative docking score indicates good binding stability and promising inhibitory potential against the Alzheimer's disease target protein **1GQR.**

Sr. No.	Ligand Complex	Target Protein	Binding Affinity (kcal/mol)	Interaction Strength
1	Rivastigmine–Gallic Acid Complex	**1GQR**	**-7.6**	**Moderate**
2	Rivastigmine–Ferulic Acid Complex	**1GQR**	**-7.0**	**Moderate**
3	Rivastigmine–Vanillic Acid Complex	**1GQR**	**-8.1**	**Strong**
4	Rivastigmine–Caffeic Acid Complex	**1GQR**	**-7.6**	**Moderate**
5	*Rivastigmine–Chlorogenic Acid Complex*	***1GQR***	***-8.3***	***Very Strong***

ADMET ANALYSIS:

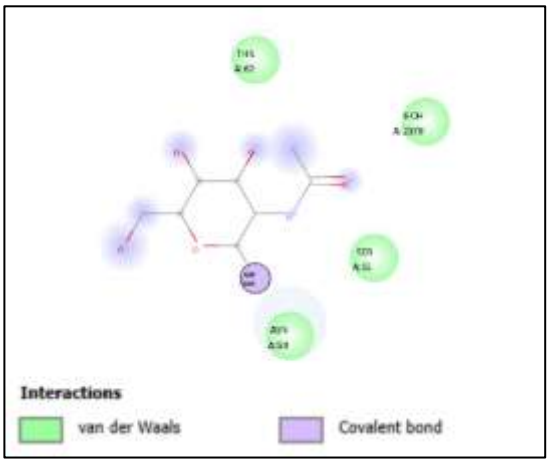
the ADMET analysis of the rivastigmine–chlorogenic acid complex was performed using SwissADME to evaluate its pharmacokinetic and drug-likeness properties. The complex showed moderate gastrointestinal (GI) absorption, moderate blood–brain barrier (BBB) permeability, and successfully passed Lipinski's Rule of Five, indicating favorable drug-likeness characteristics. The bioavailability score was found to be 0.55 with low predicted toxicity, suggesting that the compound possesses acceptable pharmacokinetic behavior and potential suitability as an anti-Alzheimer's compound.

Parameter	Result
Target Protein	1GQR
GI Absorption	Moderate
BBB Permeability	Moderate
Lipinski Rule	Passed
Bioavailability Score	0.55
Toxicity Prediction	Low

ADMET ANALYSIS

Parameter	Result
Molecule	Molecule 1
Formula	C28H22N3O9
Molecular Weight (MW)	544.49
Heavy Atoms	40
Rotatable Bonds	12
H-bond Acceptors	9
H-bond Donors	7
GI Absorption	Moderate
BBB Permeant	Good
Pgp Substrate	Yes
Bioavailability Score	0.55
Synthetic Accessibility	4.8

2D Interaction of Rivastigmine–Chlorogenic Acid Complex with Protein 1GQR



The 2D interaction analysis revealed that the rivastigmine–chlorogenic acid complex interacted with active site residues ASN A:59, SER A:61, and THR A:62 of protein 1GQR. The complex showed van der Waals and covalent interactions, indicating stable ligand–protein binding within the active site region of acetylcholinesterase.

CONCLUSION

The molecular docking study showed that **Chlorogenic acid** exhibited the strongest binding affinity against protein 1GQR with a docking score of **−8.3 kcal/mol**, indicating stable ligand–protein interaction and potential anti-Alzheimer activity, compared to **Rivastigmine**, which showed moderate inhibitory interaction. ADMET analysis revealed moderate GI absorption, moderate BBB permeability, Lipinski rule compliance, bioavailability score of **0.55,** and low toxicity prediction**,** suggesting favorable drug-likeness. These findings indicate that Chlorogenic acid may be a promising candidate for Alzheimer's disease treatment, requiring further experimental validation

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