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Molecular Docking-Based in Silico Evaluation of Fungal Bioactive Compounds as Inhibitors of Human Acetylcholinesterase for Alzheimer's Treatment

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Abstract: Alzheimer's disease (AD) is a gradually worsening neurodegenerative condition characterized by cognitive decline and memory damage, primarily associated with reduced cholinergic neurotransmission. Acetylcholinesterase (AChE) is essential for the breakdown of acetylcholine, making it an important target for therapeutic intervention. This study investigates the inhibitory potential of selected fungal bioactive compounds against human acetylcholinesterase (AChE; PDB ID: 4EY7) using molecular docking techniques. A library of fungal metabolites was screened and evaluated in comparison with the standard drug donepezil. Docking analysis was carried out using AutoDock Vina, with binding affinities, molecular interactions, and ADMET properties assessed. Several compounds exhibited strong binding affinities and favorable pharmacokinetic characteristics, indicating their promise as potential lead candidates for anti-Alzheimer's drug development.

Keywords: *Alzheimer's Disease, Bioactive Compounds, Molecular Docking, Acetylcholinesterase.*

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I. INTRODUCTION

Alzheimer's disease constitutes more than 60% of dementia cases globally., with increasing prevalence projected in the coming decades. A hallmark feature of AD is the depletion of acetylcholine (ACh) decreased count in the brain, leading to impaired neuronal communication. Acetylcholinesterase (AChE) is accountable for hydrolyzing acetylcholine and convert it into acetate and choline. Inhibition of AChE increases synaptic ACh levels and improves cognitive function. Therefore, AChE inhibitors like donepezil are widely used in AD treatment. Recent studies highlight the importance of molecular docking and computational approaches in identifying novel AChE inhibitors, reducing time and cost in drug discovery. Fungal bioactive compounds represent a rich source of structurally diverse molecules with pharmacological activities, including neuroprotective and enzyme inhibitory effects.

II. PROBLEMS AND OBJECTIVES

➢ *Problems*

- Alzheimer's disease lacks curative treatment; Current medications offer only indicative relief.
- Approved AChE inhibitors (e.g., donepezil) show side effects and limited long-term efficacy [2].
- Drug discovery is expensive and time-consuming, necessitating computational approaches [5].

➢ *Objectives*

- To screen fungal bioactive compounds for potential acetylcholinesterase (AChE) inhibitory activity.
- To perform molecular docking against human AChE (4EY7).
- To compare binding affinities with standard drug (donepezil).

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- To evaluate drug-likeness and ADMET properties.
- To analyze protein–ligand interactions for stability and efficacy.

III. SCOPE AND LIMITATIONS

➢ *Scope*

- Exploration of fungal secondary metabolites as novel anti-Alzheimer agents.
- Use of computational tools (PyRx, AutoDock Vina, Discovery Studio).
- Early-stage drug discovery over virtual screening and docking.
- Identification of lead compounds for further studies.

➢ *Limitations*

- Docking results are predictive and not experimentally validated.
- Protein flexibility is limited in docking simulations.
- ADMET predictions may not accurately represent complex biological systems.
- The absence of molecular dynamics (MD) simulations may restrict insights into stability.

IV. METHODOLOGY USED

➢ *Protein Preparation*

The three-dimensional structure of human acetylcholinesterase (PDB ID: 4EY7) was obtained from the Protein Data Bank. The co-crystallized ligand (donepezil) and water molecules were removed, followed by energy minimization using appropriate force field tools. [1].

➢ *Ligand Preparation*

Fungal bioactive compounds retrieved from PubChem database. Structures converted to appropriate formats (.pdb/. pdbqt). The Energy minimization is done by using Universal Force Field (UFF) tool[1].

➢ *Molecular Docking*

Docking performed using PyRx (AutoDock Vina engine) Active site grid defined based on co-crystallized ligand position. Binding affinity (kcal/mol) used as scoring parameter. Donepezil used as standard reference drug [2].

➢ *Interaction Analysis*

Imagining was done by using BioVia Discovery Studio 2025. Analysis of hydrogen bonds and various hydrophobic interactions, π–π stacking are studied.

➢ *ADMET Prediction*

Drug-likeness evaluated using Lipinski's Rule of Five. ADMET properties predicted using SwissADME tool [1].

➢ *Statistics Used*

- Binding Energy Analysis (kcal/mol): Lower values reflect stronger binding affinity.
- Comparative Analysis: Docking scores of fungal compounds vs. donepezil.
- Descriptive Statistics: Mean, standard deviation of docking scores.
- Ranking Method: Compounds ranked based on binding affinity.
- Correlation Analysis: Between Physicochemical properties and Docking scores.

Table 1 Selected Fungal Compounds with its Chemical Formula, PubChem ID and Source.

Sr. No.	Compound	Chemical Formula	PubChem ID	Source
1	Gliotoxin	$C_{13}H_{14}N_2O_4S_2$	6223	*Aspergillus fumigatus*
2	Cordycepin	$C_{10}H_{13}N_5O_3$	6303	*Cordyceps militaris, Cordyceps sinensis*
3	lovastatin	$C_{24}H_{36}O_5$	53232	*Aspergillus terreus*
4	Paxilline	$C_{27}H_{33}NO_4$	105008	*Penicillium paxilli*
5	Fonsecin	$C_{15}H_{14}O_6$	216328	*Aspergillus fonsecaeus.*
6	Fumitremorgin C	$C_{22}H_{25}N_3O_3$	403923	*Aspergillus fumigatus*
7	Griseofulvin	$C_{17}H_{17}ClO_6$	441140	*Penicillium griseofulvum*
8	Mycophenolic acid	$C_{17}H_{20}O_6$	446541	*Penicillium stoloniferum, Penicillium brevicompactum*
9	Asterric acid	$C_{17}H_{16}O_8$	3080568	*Aspergillus terreus*
10	Sterigmatocystin	$C_{18}H_{12}O_6$	5280389	*Aspergillus versicolor, Aspergillus nidulans*
11	Norlichexanthone	$C_{14}H_{10}O_5$	5281657	*Pertusaria laeviganda*
12	Brefeldin A	$C_{16}H_{24}O_4$	5287620	*Penicillium brefeldianum*
13	Hericenone J	$C_{19}H_{24}O_4$	44588895	*Hericium erinaceus*
14	Aspulvinone E	$C_{17}H_{12}O_5$	54675753	*Aspergillus terreus*
15	Donepezil*	$C_{24}H_{29}NO_3$	3152	Synthetic

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Note: - Donepezil is FDA Approved Standard Drug.

Table 2 Physicochemical Properties of Compounds

Sr. No.	Compound	Molecular Weight (≤ 500 Dalton)	Number of rotatable bonds (≤ 10)	Number H-bond acceptors (≤ 10)	Number of H-bond Donors (≤ 5)	TPSA (Å²) (≤ 140)	Consensus Log $P_{o/w}$ (<5)
1	Gliotoxin	326.39	1	4	2	131.68	-0.19
2	Cordycepin	251.24	2	6	3	119.30	-0.85
3	lovastatin	404.54	7	5	4	72.83	3.88
4	Paxilline	435.56	1	4	3	82.55	3.57
5	Fonsecin	290.27	1	6	3	96.22	1.65
6	Fumitremorgin C	379.45	2	3	1	65.64	2.53
7	Griseofulvin	352.77	3	6	0	71.06	2.41
8	Mycophenolic acid	320.34	6	6	2	93.06	2.72
9	Asterric acid	348.30	6	8	3	122.52	2.18
10	Sterigmatocystin	324.28	1	6	1	78.13	2.62
11	Norlichexanthone	258.23	0	5	3	90.90	2.01
12	Brefeldin A	280.36	0	4	2	66.76	1.86
13	Hericenone J	316.39	6	4	1	55.76	4.23
14	Aspulvinone E	296.27	2	5	3	86.99	2.23
15	Donepezil*	379.49	6	4	0	38.77	4.00

Table 3 Pharmacokinetics and Drug Likeness Properties of Selected Fungal Compounds

Sr. No.	Compound	GI Absorption	BBB	Drug likeness (Lipinski's Rule of 5)	Water Solubility Log *S* (ESOL)
1	Gliotoxin	High	No	Yes; 0 violation	Very soluble
2	Cordycepin	High	No	Yes; 0 violation	Very soluble
3	lovastatin	High	Yes	Yes; 0 violation	Moderately soluble
4	Paxilline	High	No	Yes; 0 violation	Moderately soluble
5	Fonsecin	High	No	Yes; 0 violation	Soluble
6	Fumitremorgin C	High	Yes	Yes; 0 violation	Moderately soluble
7	Griseofulvin	High	Yes	Yes; 0 violation	Soluble
8	Mycophenolic acid	High	No	Yes; 0 violation	Soluble
9	Asterric acid	High	No	Yes; 0 violation	Soluble
10	Sterigmatocystin	High	Yes	Yes; 0 violation	Moderately soluble
11	Norlichexanthone	High	No	Yes; 0 violation	Soluble
12	Brefeldin A	High	Yes	Yes; 0 violation	Soluble
13	Hericenone J	High	Yes	Yes; 0 violation	Moderately soluble
14	Aspulvinone E	High	No	Yes; 0 violation	Soluble
15	Donepezil*	High	Yes	Yes; 0 violation	Moderately soluble

V. RESULTS

Table 3 Docking Score Result of Selected Compounds Obtained by PyRx Tool.

Sr. No.	Compound	Docking Score (kcal/mol)
1	Gliotoxin	-9.2
2	Cordycepin	-8.2
3	lovastatin	-9.1
4	Paxilline	-6.8
5	Fonsecin	-8.5
6	Fumitremorgin C	-9.0
7	Griseofulvin	-8.6
8	Mycophenolic acid	-9.1

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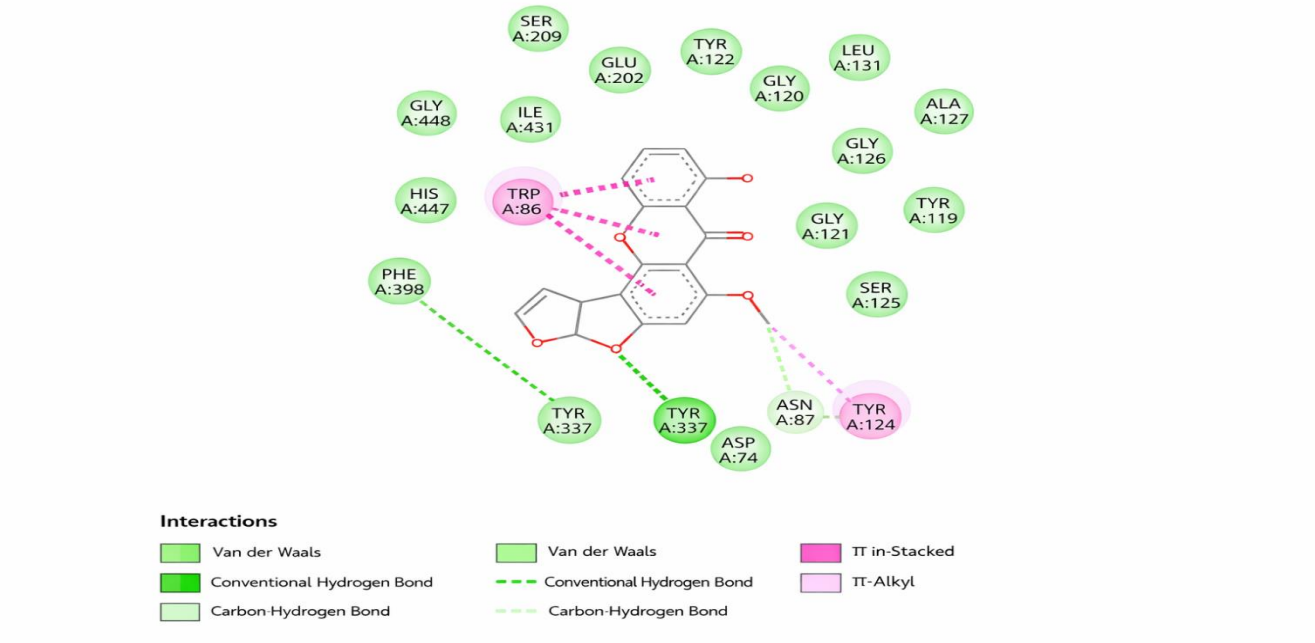
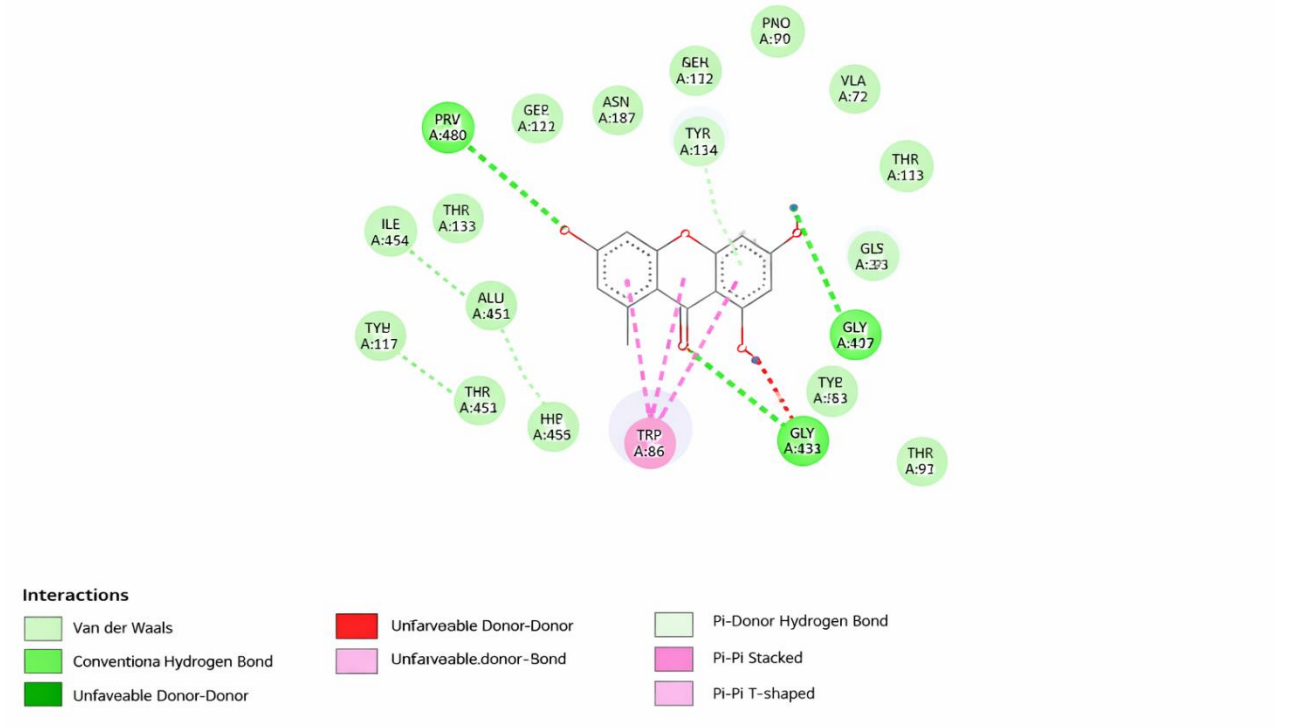
9	Asterric acid	-9.5
10	Sterigmatocystin	-10.2
11	Norlichexanthone	-10.0
12	Brefeldin A	-8.8
13	Hericenone J	-9.5
14	Aspulvinone E	-9.1
15	Donepezil*	-9.4

Table 4 2D Structures of Highly Active Fungal Compounds



2D Structure of Sterigmatocystin



2D Structure of Norlichexanthone

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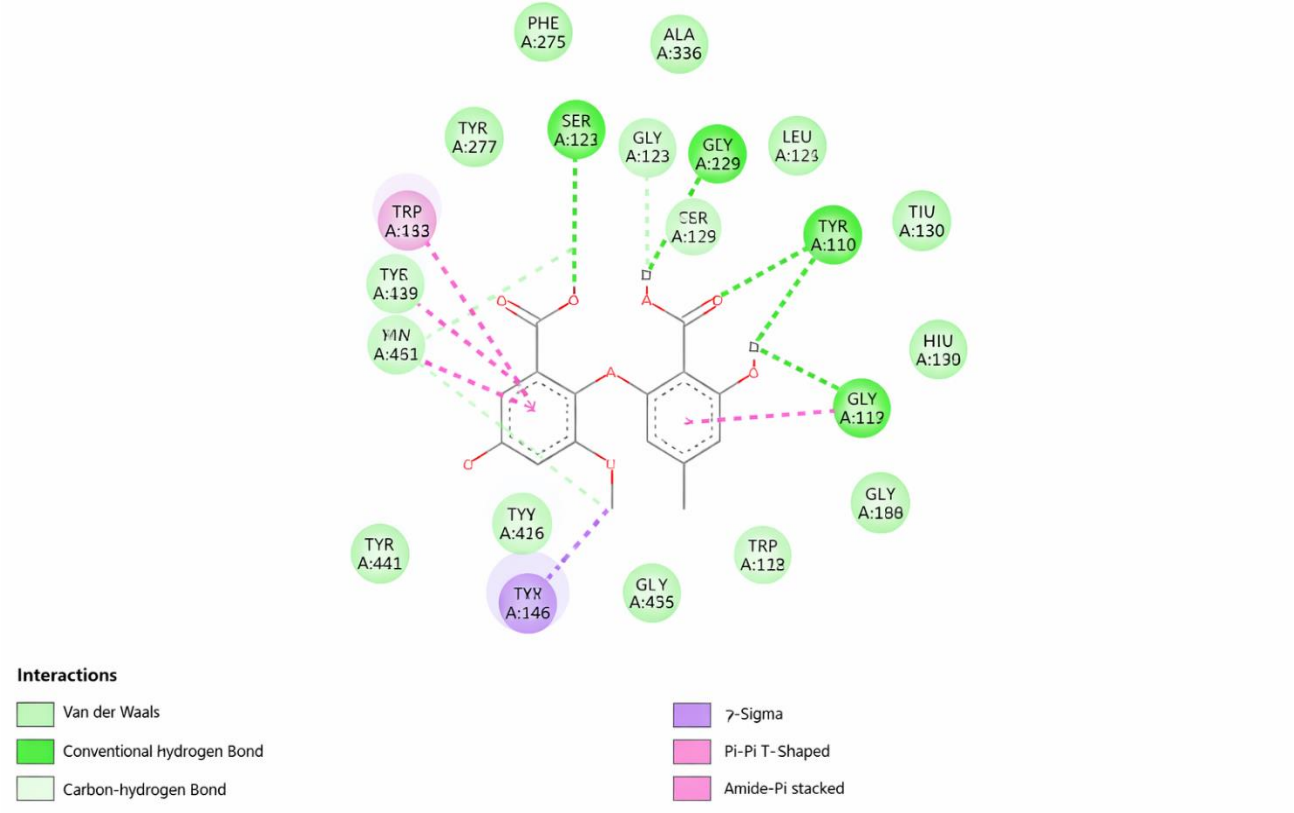
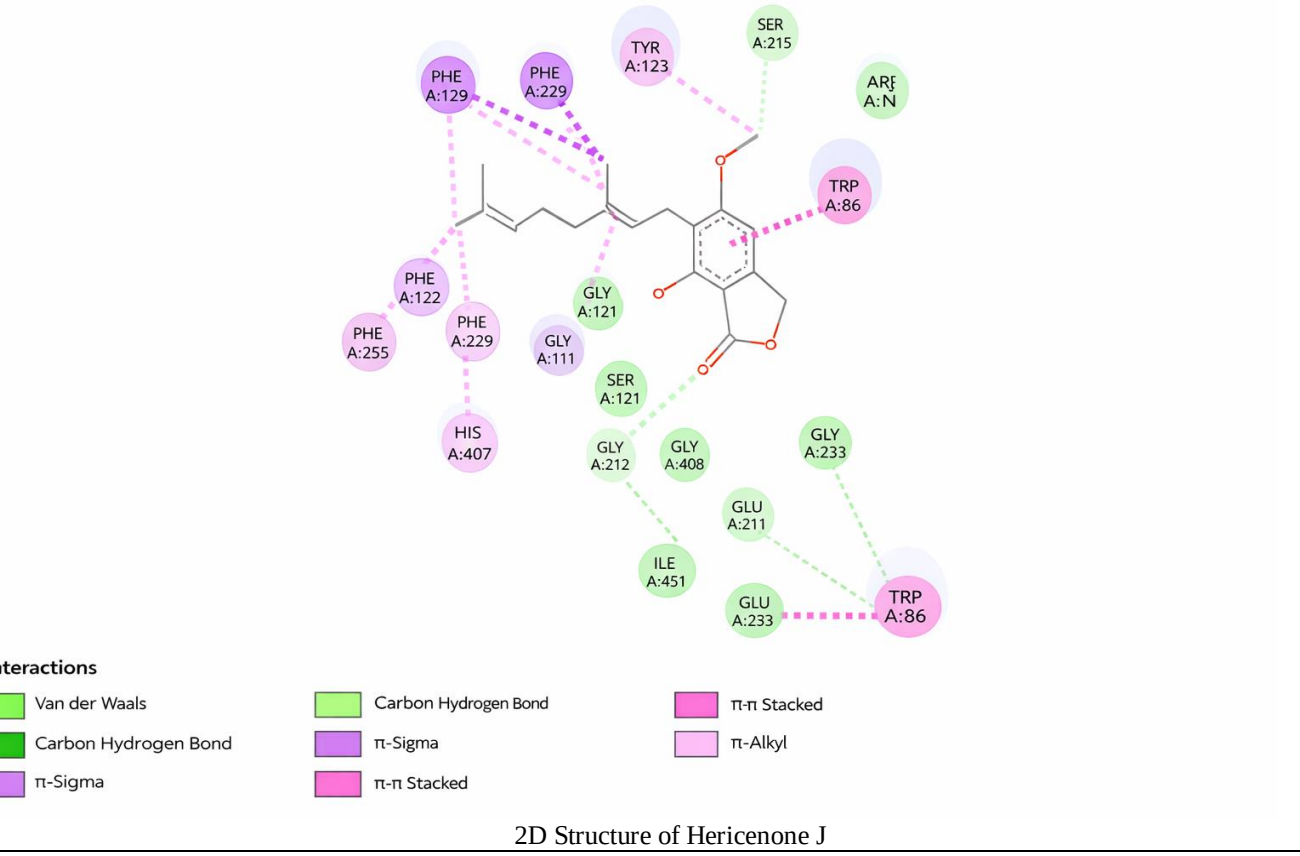


2D

Structure of Asterric acid



2D Structure of Hericenone J

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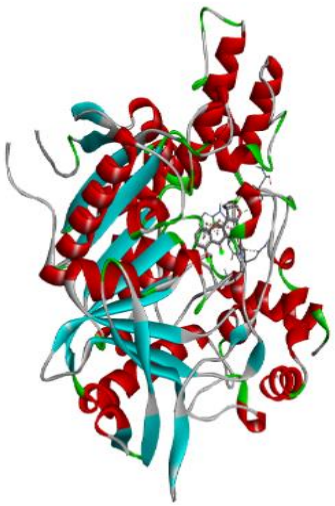
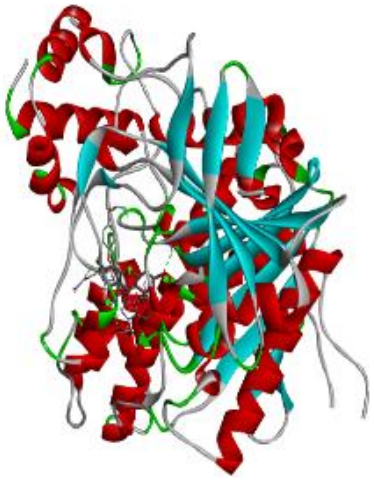
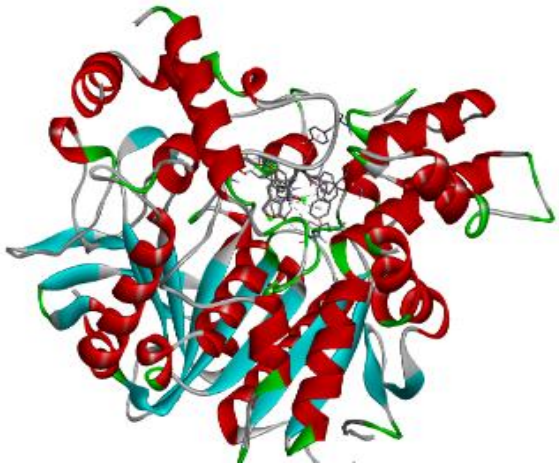
Table 5 3D Structures of Highly Active Fungal Compounds

 Sterigmatocystin	 Norlichexanthone
 Asterric acid	 Hericenone J

➢ *Protein – Ligand Interactions*

- The 2D protein–ligand interaction analysis of Sterigmatocystin (PubChem ID - 5280389) With Human Acetylcholinesterase Enzyme (PDB ID: 4EY7) reveals that the ligand forms several key stabilizing interactions within the active site. Three predictable hydrogen bonds are detected with residues THR A:83, ASP A:74, and ASN A:87, which contribute significantly to binding affinity and specificity. Furthermore, a carbon hydrogen bond is formed with TRP A:86. Notably, TRP A:86 also participates in a π–π stacked interaction concluded the aromatic ring of the ligand, highlighting its crucial role in stabilizing the complex. Another aromatic interaction, a π–alkyl interaction, is observed with TRP A:124. The ligand is further surrounded by multiple residues engaging in van der Waals interactions, including SER A:203, GLU A:202, TYR A:133, GLY A:120, LEU A:130, ALA A:127, GLY A:126, TRP A:119, GLY A:121, SER A:128, GLY A:448, ILE A:451, HIS A:447, PHE A:338, and TYR A:337, which collectively contribute to the overall stability and proper orientation of the ligand within the binding pocket. Overall, the combination of hydrogen bonding, π-interactions, and van der Waals forces specifies a strong and stable ligand–protein interaction, with TRP A:86 playing a particularly significant role.

- The 2D interaction analysis of Norlichexanthone (PubChem ID: 5281657) with Human Acetylcholinesterase (PDB ID: 4EY7) reveals a mixture of hydrogen bonding, π-interactions, and van der Waals forces contributing to stable ligand binding within the active site. The ligand forms a predictable hydrogen

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bond with TYR A:337, which serves a key function in anchoring the ligand. Additionally, unfavorable donor–donor interactions are observed near the ligand's oxygen atoms, indicating minor steric or electrostatic strain in the binding environment.

Significant π–π stacked interactions are formed between the aromatic rings of Norlichexanthone and TRP A:86, a key residue in the catalytic gorge of acetylcholinesterase, highlighting its crucial role in ligand stabilization. Furthermore, π–π T-shaped interactions also involve TRP A:86, enhancing aromatic stacking and strengthening the binding affinity. A π–donor hydrogen bond interaction is also present, contributing additional stabilization through electron-rich aromatic systems.

The ligand is further surrounded by several residues engaging in van der Waals interactions, including GLY A:120, SER A:203, GLY A:121, GLY A:122, ALA A:204, PRO A:80, ASN A:87, TRP A:117, PHE A:338, GLU A:202, GLY A:448, HIS A:447, ILE A:451, and TYR A:337, which collectively help maintain the ligand within the binding pocket. Overall, the interaction profile suggests that Norlichexanthone exhibits stable binding with acetylcholinesterase, primarily driven by strong aromatic interactions with TRP A:86 and supported by hydrogen bonding and van der Waals contacts.

- The 2D interaction analysis of Asterric acid (PubChem ID: 3080568) with human acetylcholinesterase (PDB ID: 4EY7) demonstrates a diverse set of stabilizing interactions within the enzyme's active site. he ligand establishes conventional hydrogen bonds with GLY A:122, SER A:203, and GLU A:202, which are critical for anchoring the ligand and enhancing binding specificity. In addition, a carbon hydrogen bond is observed with PHE A:295, contributing further to ligand stabilization.

Aromatic interactions play a vital role in the binding mechanism. TRP A:86 is involved in π–sigma interaction, while TRP A:86 and TYR A:337 also participate in π–π T-shaped interactions with the aromatic rings of Asterric acid. Additionally, HIS A:447 exhibits an amide–π stacked interaction, further strengthening the ligand–protein complex through aromatic stacking.

The ligand is also surrounded by numerous residues forming van der Waals interactions, including PHE A:295, ALA A:204, GLY A:122, SER A:203, GLU A:202, ILE A:451, TYR A:133, TRP A:119, LEU A:130, GLY A:120, SER A:125, GLY A:126, GLY A:448, TYR A:124, TYR A:341, and ASN A:87, which collectively help maintain proper ligand orientation and stability within the binding pocket. Overall, the interaction profile indicates that Asterric acid binds effectively to acetylcholinesterase through a combination of hydrogen bonding, π-interactions, and extensive van der Waals contacts, with TRP A:86 and TYR A:337 playing key roles in stabilizing the complex.

- The 2D interaction analysis of Hericenone J (PubChem ID: 44588895) with human acetylcholinesterase (PDB ID: 4EY7) reveals multiple stabilizing interactions within the active site. The ligand forms a carbon hydrogen bond with GLY A:121, contributing to its proper positioning in the binding pocket.

Aromatic interactions are prominent in this complex, with TRP A:86 showing strong involvement through both π–π stacked and π–alkyl interactions, indicating its key role in ligand stabilization. Additionally, HIS A:338 and TYR A:337 participate in π–π stacked interactions with the aromatic rings of Hericenone J, further enhancing binding affinity. A π–sigma interaction is also observed with PHE A:297, contributing additional stabilization through hydrophobic and electronic interactions.

The ligand is further surrounded by several residues contributing van der Waals interactions, including SER A:125, ASP A:74, GLY A:121, GLY A:122, GLU A:202, GLY A:448, ILE A:451, THR A:83, PHE A:295, HIS A:447, ALA A:204, and GLU A:202, which collectively help maintain the ligand within the catalytic gorge of the enzyme. Overall, the binding of Hericenone J to acetylcholinesterase is stabilized by a combination of aromatic π-interactions, hydrogen bonding, and extensive van der Waals contacts, with TRP A:86, TYR A:337, and HIS A:338 playing key roles in the interaction network.

VI. CONCLUSION

Fungal bioactive compounds Sterigmatocystin and Hericenone J demonstrated significant binding affinity toward AChE. These compounds showed greater docking scores superior to Donepezil. The FDA Approved Standard drug Donepezil is widly used in treatment of Alzheimer's disease. Key interactions involved catalytic residues (Ser203, His447, etc.), indicating effective inhibition potential. Computational screening proved efficient for identifying potential anti-Alzheimer candidates. The study supports fungal metabolites as promising sources for novel AChE inhibitors.

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