

Research Article

Fungal Metabolites as Multi-Target Modulators of Alzheimer's Disease: An Integrated *In Silico* Docking and Molecular Dynamics Approach

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder with limited therapeutic options offering only symptomatic relief. Natural fungal metabolites have recently gained attention for their neuroprotective potential. In this study, an extensive library of 18,349 fungal compounds was retrieved from the NPAtlas database and systematically screened for drug-likeness, ADMET properties, and toxicity profiles. Successive filtering reduced the dataset to 99 drug-like molecules, of which five candidates—Sonomolide A, Steperoxide A, RP-1551-M2, Illudin J, and Pericoannosin F—were selected for detailed analysis. These compounds demonstrated favourable physicochemical properties, compliance with Lipinski's Rule of Five, high gastrointestinal absorption, blood–brain barrier permeability, and acceptable toxicity margins (Class 6). Molecular docking against five AD-related targets (AChE, CBNR2, CHRM1, CHRM4, & D1B dopamine receptor) revealed strong binding affinities, with Steperoxide A showing the highest affinity for AChE (–8.0 kcal/mol) and CBNR2 (–9.0 kcal/mol), while RP-1551-M2 displayed consistent interactions with muscarinic and dopamine receptors. MD simulations confirmed stable protein–ligand interactions, with RMSD values ranging from 0.10–1.75 nm and hydrogen-bond counts between 47–252 throughout the trajectory. Stable radius of gyration values (2.74–3.95 nm) further indicated the maintenance of structural compactness and binding integrity, and the results also showed good stability and favourable interaction profiles. Collectively, these findings highlight fungal metabolites—particularly Steperoxide A and RP-1551-M2—as promising multi-target neuroprotective scaffolds with potential therapeutic relevance in AD.

Key words: Alzheimer's disease, fungal metabolites, *in silico*, molecular docking, molecular dynamics simulation, neuroprotection

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INTRODUCTION

The progressive degenerative malfunction of the brain is known as Alzheimer's disease (AD). The etiology of AD is complicated, and there is currently no proven treatment (An *et al.* 2006). The World Health Organization (WHO) defines dementia as a chronic or progressive illness characterized by impairment in cognitive function that exceeds normal aging (Shen 2015). Globally, 9% of the population who are over the age of 65 are prone to neurodegenerative disease (ND), with an expected increase to 17% by 2050 (Kovács *et al.*, 2021). The number of ND patients was around 50 million in 2019 and is expected to reach 152 million by 2060 (Armstrong, 2020).

Alzheimer's disease (AD) is diagnosed based on two pathologies: β -amyloid peptide (A β) plaque deposits and neurofibrillary tangles of the microtubule-binding protein tau (Murphy & LeVine III, 2010). PSEN1, PSEN2, and APP genes showed inherited mutations. Carriers of the allelic gene of apolipoprotein E (APOE e4) have a higher

risk of Alzheimer's disease due to a slowed clearance rate. Chronic diseases such as diabetes, obesity, hypercholesterolemia and hypertension increase the risk of dementia and cognitive dysfunction (Castellani *et al.*, 2010; Apostolova, 2016).

Current pharmaceutical therapy for Alzheimer's disease mostly targets and inhibits the enzymes that cause the disease. Traditional medications focus on a single target, reducing symptoms but producing several negative effects. Researchers are increasingly interested in discovering novel inhibitors (Liu *et al.*, 2019; Breijyeh & Karaman, 2020; McGirr, 2020). The most effective treatment for Alzheimer's disease is to improve cholinergic neurotransmission and diminish acetylcholine hydrolysis. In clinical trials, acetylcholinesterase inhibitors (AChEIs) have proven to be the most effective treatment for Alzheimer's disease (Roy, 2023).

Fungi have long been valued for their gastronomic and nutritional worth, but are now recognized for their therapeutic characteristics,

making them the “superfood of the future.” Several species of the phylum Basidiomycota, including *Hericium erinaceus* (Lion’s Mane), *Ganoderma lucidum* (Reishi), *Cordyceps sinensis* (Zombie Fungus) and *Inonotus obliquus* (Chaga), are known as medicinal mushrooms and are widely used in traditional Chinese medicine. Fungal metabolites have antimicrobial, antidiabetic, antioxidant, antiviral, anticancer, antihypercholesterolemic and neuroprotective properties (Dasgupta & Acharya, 2019; Bains *et al.*, 2021; Łysakowska *et al.*, 2023). They are promising candidates for therapeutic interventions against neurodegenerative diseases because they contain bioactive metabolites that have been shown to reduce neurodegeneration and enhance cognitive health, including polysaccharides, ergothioneine, triterpenoids, flavonoids, and phenolic compounds (Liu *et al.*, 2019). A recent study on the marine-derived fungus *Talaromyces* sp. found that compounds with an oxaphenalenone structure can inhibit AChE. To enhance the production of fungal bioactive compounds, researchers are increasingly using methods like epigenetic induction, omics data integration and high-throughput screening, which have become key tools in drug discovery from fungi (Wu *et al.*, 2015). Hence, this study focuses on screening fungal metabolites for drug-likeness and ADMET properties, followed by molecular docking against key Alzheimer’s disease targets and validating the stability of protein-ligand complexes through molecular dynamics simulations.

MATERIALS AND METHODS

Screening of fungal metabolites and ligand preparation

The fungal metabolites (22,995 compounds) were retrieved from the Natural Product Atlas (NpAtlas) (<https://www.npatlas.org/>) database and processed to filter out the metabolites based on molecular weight, polar surface area (TPSA), H-bond donor, H-bond acceptor, rotatable bonds, LogP, LogS, drug-likeness and mutagenic, and irritancy. The lead molecules were further screened using ProtoxII to eliminate highly toxic compounds. Finally, the best five compounds which showed high blood-brain barrier (BBB) penetration were selected as potential compounds against Alzheimer targets.

Preparation of target protein and validation

Protein targets implicated in Alzheimer’s disease were selected based on extensive literature mining and biological relevance to cholinergic, dopaminergic, and neuroprotective signalling pathways. The selected targets included muscarinic acetylcholine receptors M1 (P11229) and M4 (P08173), cannabinoid receptor 2 (P34972), acetylcholinesterase (P22303), and the dopamine D1B receptor (P21918). For the GPCR targets (CHRM1, CHRM4, CB2 & D1B), docking was performed using the prepared receptor structures without explicit incorporation of a lipid bilayer environment. The sequences of the selected target proteins were retrieved from the NCBI GenBank database and subjected to BLAST analysis for template identification. Protein isoforms were identified using the UniProt database and considered for homology modelling. Three-dimensional structures were generated using the SWISS-MODEL server and evaluated using Ramachandran plot, PROCHECK, ERRAT and Verify 3D. Models exhibiting higher Ramachandran plot scores and lower clash scores were selected for subsequent molecular docking studies (Hosen *et al.* 2024).

Physiochemical and ADMET analysis

The compound’s SMILES notation was submitted to SwissADME (<https://www.swissadme.ch/>) to predict key pharmacokinetic properties, including gastrointestinal absorption, BBB permeability, P-glycoprotein interaction, and metabolism via major CYP450 enzymes. Toxicity profiles were obtained using ProTox 3.0. Drug-likeness was evaluated based on Lipinski’s Rule of Five, and bioavailability was estimated using molecular descriptors such as cLogP, molecular weight, and hydrogen bonding features.

Molecular docking

Avogadro version 1.2 was used to optimize ligands using the Force Field type MMFF94 and saved in mol2 format. Autodock version 4.2 optimizes protein structures by removing water and other atoms and adding a polar hydrogen group. Autodock supports Autodock 4.2 Tools, MGL Tools, and Rasmol. Autogrid calculated the native ligand position on the binding site by arranging grid coordinates (X, Y, and Z). Docking analyses were performed using Autodock 4.2, PyMOL version 1.7.4.5, and Biovia (Khaerunnisa *et al.* 2020).

Molecular dynamics (MD) simulation

Molecular dynamics simulations were conducted via GROMACS for assessing the stability of the protein-ligand complex. The topology of the protein was created using the AMBER99SB force field together with the TIP3P water model, while the topology of the ligand was built up via ACPYPE, utilizing the GAFF force field. The complex was put into a triclinic box with 1.0 nm of solvated space and neutralized by means of counterions. Following minimization of energy, the complex was equilibrated in NVT and NPT ensembles before the conduct of MD simulation. Trajectories that have been derived from the simulation were analyzed via RMSD, RMSF, radius of gyration, and hydrogen bond interactions using MDAnalysis and MDTraj packages (Grabski & Tiratsuyan, 2018; Rajamanikandan *et al.*, 2017; Mohapatra *et al.* 2023).

RESULT AND DISCUSSION

Screening of fungal metabolites

An initial library of 22,995 fungal metabolites was subjected to a filtering and grouping workflow based on cheminformatics. Following confirmation using SMILES, 18,349 compounds were recovered. The total number of molecules was reduced to 6,086 compounds through a series of filtering procedures based on molecular weight, lipophilicity, polar surface area and (≤ 7), confirming adherence to oral bioavailability and drug-likeness parameters. Morgan fingerprint creation and Tanimoto similarity analysis were used to capture structural diversity. Butina clustering at a cutoff of 0.2 produced 5,050 clusters. The dataset was reduced by more than 99% while maintaining chemical variety thanks to representative selection, which produced 99 different, drug-like molecules (Figure 1). Toxicity screening using Protox II yielded six non-neurotoxic compounds, five of which had good blood-brain barrier (BBB) permeability and were proceeded to ADMET analysis.

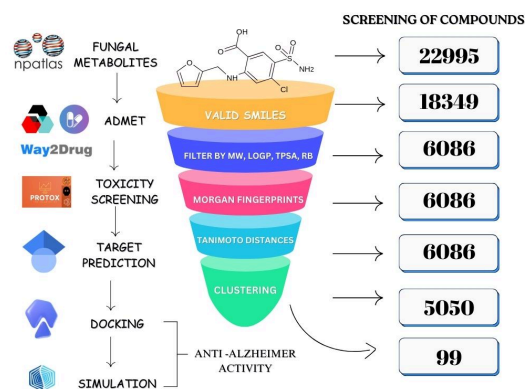


Fig. 1. Virtual screening and computational analysis of fungal metabolites against Alzheimer’s disease.

Physiochemical properties

The five compounds exhibit favourable drug-likeness and potential oral bioavailability, as indicated by their compliance with Lipinski’s Rule of Five (Table 1). Figure 2 represents the 2D structure of selected ligands. In drug discovery, Lipinski’s Rule of Five is a useful approach for determining a compound’s drug-likeness and directing the selection of potentially viable candidates for research (Zhang & Wilkinson, 2007). The Rule of Five (Ro5), which Lipinski

first suggested in 1999 to forecast medication candidates that had satisfactory oral absorption, was later improved for CNS treatments as RoCNS. RoCNS has more stringent limitations than Ro5: MW < 400 Da (as opposed to 500), HBA ≤ 7 (as opposed to 10), and HBD ≤ 3 (as opposed to 5), while CLogP stays ≤ 5 (Fernandes *et al.* 2016). TPSA values (55–67 Å²) are substantially below the 90 Å² threshold, indicating good permeability and absorption; their molecular weights are below 500 g/mol; rotatable bonds ≤ 4; and hydrogen bond donors (1–2) and acceptors (3–4) are within limits.

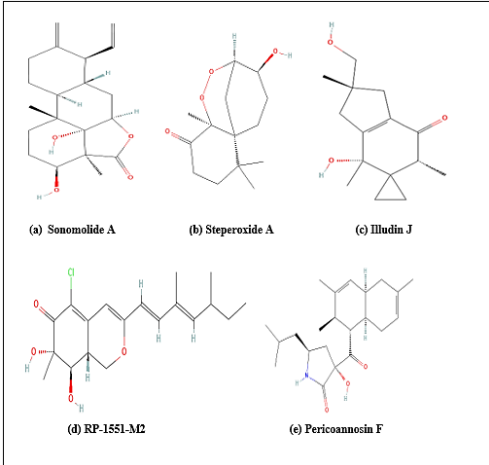


Fig. 2. 2D structure of the compound (a) Sonomolide A, (b) Steperoxide A, (c) Illudin J, (d) RP-1551-M2, and (e) Pericoannosin F.

The solubility and lipophilicity profiles showed promising drug-like properties that were in line with oral bioavailability (Table 2). Steperoxide A likewise has good solubility together with low logP, indicating efficient bioavailability, while Illudin J is likely to have quick absorption due to its very high solubility. With slightly higher logP values and intermediate solubility, sonomolide A and pericoannosin F have a balanced hydrophilic–lipophilic property that could promote membrane permeability. RP-1551-M2 retains an acceptable level of lipophilicity despite its decreased solubility. All

of the compounds show encouraging ADME characteristics that make them appropriate for therapeutic development.

ADMET Prediction

The ADMET properties of the selected fungal metabolites are summarized in Tables 3 and 4. All five compounds exhibited high human intestinal absorption (>90%), moderate Caco-2 permeability, and predicted blood–brain barrier (BBB) penetration, indicating their potential suitability as CNS-active agents. Blood-brain barrier penetration is necessary because drug candidates that operate on the central nervous system (CNS) must bridge the blood-brain barrier, and inactive molecules in the CNS should not overlap to avoid harmful effects on the CNS (Hasan *et al.*, 2024). Steperoxide A and RP-1551-M2 were predicted to be P-glycoprotein inhibitors, whereas the remaining compounds were predicted to be non-inhibitors. Plasma protein binding varied among the compounds, with Steperoxide A showing the lowest binding (53.81%) and Illudin J the highest (96.48%) (McCormick *et al.* 2021; Pathan & Shende, 2021; Hasan *et al.* 2024). All compounds were predicted to be CYP3A4 substrates, although differences were observed in their CYP inhibition profiles. Pericoannosin F exhibited the most favourable metabolic profile with no major CYP inhibition, whereas the remaining compounds inhibited one or more CYP isoforms. The increased metabolism and excretion of substrates for biotransformation are facilitated by CYP2C9, CYP3A4, and CYP2D6 (Khodja *et al.*, 2025). Predicted half-lives ranged from 0.148 to 0.775 h, with clearance rates between 4.7 and 9.8 mL/min/kg. Overall, the selected compounds demonstrated acceptable pharmacokinetic properties, supporting their potential for further investigation as anti-Alzheimer’s candidates. Among them, Steperoxide A showed the most balanced absorption and distribution characteristics, while Pericoannosin F displayed the most favourable metabolic profile (Del Amo *et al.*, 2021).

Toxicity prediction

ProTox 3.0, a platform for predicting small molecule toxicity, was used to validate the LD₅₀ and toxicity class of novel compounds before *in vivo* testing (Banerjee *et al.*, 2024). Oral toxicity projections revealed that all five substances were classified as toxicity Class 6, indicating a non-toxic to low-toxic safety profile. With an

Table 1. Physiochemical properties.

Compounds	Formula	Molecular weight (g/mol)	No of heavy atoms	No of aromatic heavy atom	No of Rotatable bond	No of H-bond Acceptor	No of H-bond Donor	Total polar surface area Å²
Sonomolide A	C ₂₀ H ₂₈ O ₄	332.43	24	0	1	4	2	66.76
Steperoxide A	C ₁₄ H ₂₂ O ₄	254.32	18	0	0	4	1	55.76
RP-1551-M2	C ₁₉ H ₂₅ ClO ₄	352.85	24	0	4	4	2	66.76
Illudin J	C ₁₅ H ₂₂ O ₃	250.33	18	0	1	3	2	57.53
Pericoannosin F	C ₂₂ H ₃₃ NO ₃	359.50	26	0	4	3	2	66.40

Table 2. Solubility and lipophilicity properties.

Compounds	Solubility (mg/mL)	Class	Log Po/w	Consensus Log Po/w	Lipinski rule of 5	Bioavailability Score
Sonomolide A	1.19e-01	Soluble	2.53	2.71	Yes; 0 violation	0.55
Steperoxide A	9.16e-01	Soluble	1.84	1.86	Yes; 0 violation	0.55
RP-1551-M2	3.43e-02	Moderately soluble	3.06	3.09	Yes; 0 violation	0.55
Illudin J	4.88e+00	Very Soluble	2.31	1.86	Yes; 0 violation	0.55
Pericoannosin F	6.95e-02	Soluble	3.38	3.14	Yes; 0 violation	0.55

LD₅₀ of 33600 mg/kg, Sonomolide A showed the highest tolerance among them. Steperoxide A (10000 mg/kg), Illudin J (9000 mg/kg), Pericoannosin F (8300 mg/kg), and RP-1551-M2 (5105 mg/kg) were next in line. According to the network-based toxicity profile (Figure 3a-e), blood–brain barrier (BBB) penetration was consistently projected to be active across the drugs, while the majority of endpoints, including cardio, immuno, mutagen, nephro, clinical, cyto, and others, were expected to be inactive (Table 5). This characteristic supports the therapeutic relevance of these candidates as well as their favourable safety margin, which is especially beneficial for Alzheimer’s therapy since adequate CNS distribution is necessary for drug activity.

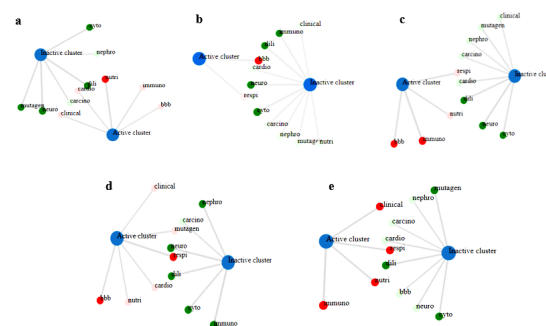


Fig. 3. Network chart of predicted toxicity of ligands (a) Sonomolide A, (b) Steperoxide A, (c) RP-1551-M2, (d) Illudin J, and (e) Pericoannosin F (Inactive (≥ 0.7 , dark green); Inactive (< 0.7 , light green); Active (≥ 0.7 , red); Active (< 0.7 , pink)).

Homology modelling

The conformations showing high Ramachandran plot values and low clash score were selected for further processing (Table 6). The stereochemical quality of the protein structures was assessed utilizing the Ramachandran plot analysis. For all targets, the ma-

Table 3. *In silico* prediction of absorption and distribution properties.

Compound name	Human intestinal Absorption	Caco-2 permeability	Log Kp (skin permeation) (cm/s)	P-glycoprotein inhibitor	BBB penetration	Plasma Protein Binding
Sonomolide A	92.6828	17.8168	-6.51	Non inhibitor	Yes	90.1948
Steperoxide A	93.2323	19.6755	-6.69	Inhibitor	Yes	53.8053
RP-1551-M2	93.8937	22.1809	-5.92	Inhibitor	Yes	83.6621
Illudin J	90.4789	20.8991	-7.39	Non inhibitor	Yes	96.4832
Pericoannosin F	93.0938	23.1111	-6.34	Non inhibitor	Yes	89.9139

Table 4. *In silico* prediction of metabolism and excretion.

Compound name	CYP3A4 substrate	CYP3A4 inhibition	CYP2C19 inhibition	CYP2D6 substrate	CYP2D6 inhibition	CYP2C9 inhibition	T _{1/2} (half-life)	Clearance rate (mL/min/kg)
Sonomolide A	Substrate	Inhibitor	Non inhibitor	No	Non inhibitor	Inhibitor	0.177	9.675
Steperoxide A	Substrate	Inhibitor	Non inhibitor	No	Non inhibitor	Inhibitor	0.775	8.688
RP-1551-M2	Substrate	Non inhibitor	Inhibitor	No	Non inhibitor	Inhibitor	0.317	5.478
Illudin J	Substrate	Inhibitor	Non inhibitor	No	Non inhibitor	Inhibitor	0.148	4.707
Pericoannosin F	Substrate	Non inhibitor	Non inhibitor	No	Non inhibitor	Non inhibitor	0.229	9.824

Table 5. Results of LD₅₀ value of the compound estimated with Protox 3.0.

Compounds	Oral toxicity prediction	Predicted Toxicity Class
Sonomolide A	33600 mg/kg	Class 6
Steperoxide A	10000 mg/kg	Class 6
RP-1551-M2	5105 mg/kg	Class 6
Illudin J	9000 mg/kg	Class 6
Pericoannosin F	8300 mg/kg	Class 6

jority of residues were located in the most favoured regions, with AchE (90.1%), CBNR2 (91.6%), CHRM4 (86.3%), CHRM1 (86.8%), and Dopamine receptor (84.0%) demonstrating good conformational reliability. Residues in additional authorized areas ranged from 3.4% (CBNR2) to 11.2% (Dopamine receptor), whereas generously allowed sections accounted for 0.5–3.6% of all proteins. Only a small number of residues were found in forbidden locations, ranging from 0.2% (AchE) to 2.0% (CHRM1), showing appropriate backbone geometry (Table 7). Overall, our findings demonstrate that all modelled protein structures have acceptable stereochemical quality, making them appropriate for future molecular docking and simulation research.

Molecular docking

Alzheimer's disease (AD) is a progressive neurodegenerative disorder for which there is presently no cure or disease-modifying therapy; existing pharmacological medicines such as donepezil, rivastigmine, galantamine, and memantine offer very minimal symptomatic relief (Herrmann *et al.*, 2011; Habtemariam, 2019). Hence, as an alternative, in recent years medicinal fungi have developed as a prospective source of bioactive secondary metabolites that could be used to treat complex disorders.

Sonomolides A (Ligand 1) and B are diterpenoid γ -lactones derived from a Coprophilous fungus in Sonoma Valley. They were initially identified as broad-spectrum antifungal agents and are the first cleistanthane- and cassane-type diterpenes to have such action. Their distinctive structure and low toxicity make them interesting candidates for future pharmaceutical research (Morris *et al.*, 1995). Steperoxide A (Ligand 2), an uncommon chamigrane-type sesquiterpene, was previously identified from the hydroid fungus *Steccherinum ochraceum* (Phanerochaetaceae). Previous studies emphasized its anticancer and antibacterial properties against *Staphylococcus aureus* (Liu *et al.*, 2010; Rahaman *et al.*, 2020). Ligand 3, i.e., RP-1551-M2, is an azaphilone molecule isolated from *Penicillium* sp. SPC-21609 that inhibits platelet-derived growth factor (PDGF) receptors as well as having antibacterial effects. It inhibits PDGF AA

binding to the PDGF alpha-receptor; however, the precise mechanism of action involves irreversible interactions with the receptor's extracellular domain (Toki *et al.*, 1999). Illudins (Ligand 4) are sesquiterpene metabolites extracted from the fungus *Coprinopsis episcopalis*. They have antibacterial (including MRSA) and strong cytotoxic properties. Derivatives such as HMAF (MGI-114) have moved to anticancer clinical studies (Gonzalez Del Val *et al.*, 2003). Pericoannosin F (Ligand 5), an indole-diterpenoid alkaloid isolated from an endophytic fungus, is noted for its wide range of pharmacological properties. Biological investigations revealed that Pericoannosin F has antimicrobial properties, cytotoxic effects and strong anti-HIV activity at micromolar concentrations (Zhang *et al.*, 2015; Azhari & Supratman, 2021). However, no noteworthy evidence has demonstrated that these ligands have neuroprotective properties to date. Hence, this study focuses on the neuroprotective effect of these fungal metabolites.

The molecular docking results of the selected ligands with AchE, CBNR2, CHRM1, CHRM4, and Dopamine receptor are summarized in Tables 8 to 12, respectively. Alzheimer's disease (AD) causes early loss of basal forebrain cholinergic neurones, which reduces cholinergic signalling. This impairment can be addressed by acetylcholinesterase (AChE) inhibitors or muscarinic and nicotinic receptor modulators. AChE, a serine hydrolase found in neuromuscular junctions and synapses, generally degrades acetylcholine (ACh) into acetate and choline, thereby terminating signal transmission. Its inhibition reduces ACh breakdown, resulting in higher synaptic ACh levels, which may benefit neurotransmission and cognition in AD (Rawat *et al.*, 2024). Steperoxide A had the highest binding affinity (-8.0 kcal/mol) to AChE, with interactions involving Asn B:564 (3.39 Å) and a carbon-hydrogen bond with Gln B:444 (3.16 Å). Previous research has demonstrated that Rutin interacts with AChE via key residues such as Asp264, Asn564, His436, Arg327, Pro399, and Glu344. Notably, Pro399 has been shown to generate covalent hydrogen bond contacts (Vijayakumar *et al.*, 2018). In this study, steperoxide A is found to have a high binding affinity for

Table 6. Ramachandran plot and clash score of selected targets.

Target	Isoforms	Ramachandran favoured (%)	Clash score	Qmean
AchE	1	92.16	0.32	0.93
	2	97.11	0.91	0.91
	3	96.26	0.18	0.91
CBNR2	1	93.30	0.18	0.84
CHRM4	1	87.84	0.40	0.76
CHRM1	1	90.26	4.05	0.61
	2	86.06	0.28	0.75
DOPAMINE	1	84.42	0.00	0.69

Table 7. Ramachandran plot analysis.

Ramachandran plot Calculation	AchE	CBNR2	CHRM4	CHRM1	DOPAMINE
Residues in most favoured regions [A, B, L]	90.1	91.6	86.3	86.8	84.0
Residues in additional allowed regions [a, b, l, p]	9.2	3.4	8.7	10.2	11.2
Residues in generously allowed regions [a, b, l, p]	0.5	4.0	3.5	1.0	3.6
Residues in disallowed regions	0.2	0.9	1.4	2.0	1.2

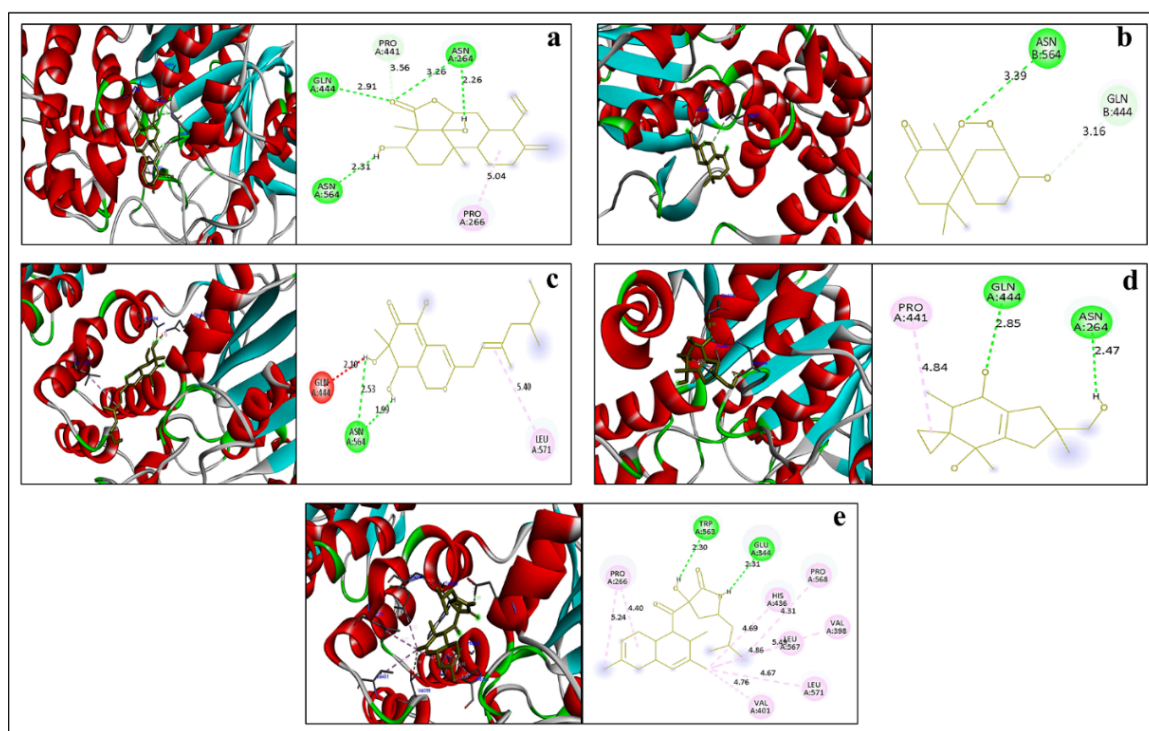


Fig. 4. Molecular docking interactions of ligands (a) Sonomolide A, (b) Steperoxide A, (c) RP-1551-M2, (d) Illudin J, and (e) Pericoannosin F with the target AchE, showing 3D binding poses and 2D interaction maps.

acetylcholinesterase (AChE), implying a potential new function in neurodegenerative disorder intervention. Sonomolide A (−7.7 kcal/mol) established several hydrogen bonds with Asn A:264 (2.26, 3.26 Å), Gln A:444 (2.91 Å), and Asn A:564 (2.31 Å), as well as a carbon-hydrogen bond with Pro A:441 (3.56 Å). Pericoannosin F (−7.4 kcal/mol) interacted with Trp A:563 (2.30 Å) and Glu A:344 (2.31 Å), whereas RP-1551-M2 (−6.5 kcal/mol) formed strong hydrogen bonds with Asn A:564 (1.99, 2.53 Å). Illudin J had the lowest binding affinity (−6.3 kcal/mol), with traditional hydrogen bonding to Gln A:444 (2.85 Å) and Asn A (Figure 4).

Cannabinoid type 2 receptors (CB2Rs), which are predominantly found on immune cells and microglia, are increased during inflammatory conditions such as ischaemic stroke (Cristino *et al.*, 2020; Reusch *et al.* 2022). CB2R activation in Alzheimer's disease provides neuroprotection by lowering Aβ toxicity, decreasing microglial activation, restoring cognition, and enhancing memory in amyloidosis models (Scheiner *et al.*, 2019; Zhao *et al.*, 2020). For CBNR2, Steperoxide A had the strongest binding (−9.0 kcal/mol) via His A:95 and Phe A:91, followed by Pericoannosin F (−8.2 kcal/mol, Ser A:75, Gly A:78) and Illudin J (−8.0 kcal/mol, Ser A:90). RP-1551-M2 (−7.4 kcal/mol) interacts with Ser A:285, Cys A:288, and Thr A:114, while Sonomolide A (−7.0 kcal/mol) binds Leu A:71. Besides

targeting cholinesterases (ChEs), the endocannabinoid system can be an alternative target for Alzheimer (Figure 5).

Muscarinic acetylcholine receptors (mAChRs) are G-protein-coupled receptors that control cognitive, memory, and psychotic functions in the central nervous system. Selective manipulation of M1 and M4 subtypes is being investigated in order to maintain therapeutic benefits while minimizing peripheral adverse effects (Rook *et al.* 2014). Molecular docking of ligands with CHRM1 (Figure 6) revealed that RP-1551-M2 (−7.8 kcal/mol) and Pericoannosin F (−7.6 kcal/mol) had the greatest binding, creating several traditional H-bonds with important residues such as Asn60, Thr58, and Asn422. Sonomolide A likewise exhibited favourable binding (−7.5 kcal/mol), although Steperoxide A and Illudin J had poorer interactions. For CHRM4 (Figure 7), RP-1551-M2 (−6.8 kcal/mol) and Sonomolide A (−6.6 kcal/mol) had the strongest binding, interacting with residues such as Arg223, Tyr215, and Thr401. Overall, RP-1551-M2 showed significant and consistent interactions with CHRM1 and CHRM4, indicating potential subtype selectivity.

The D1B dopamine receptor, commonly referred to as the D5, is a subtype of the D1-like dopamine receptor family. It modulates cognition and synaptic plasticity, particularly in the prefrontal cortex and hippocampus. Activation of D1B receptors has been linked to

Table 8. Binding energy and bond length of compounds with target protein AchE.

S.No	Ligands	Binding energy (kcal/mol)	Conventional H bond	Carbon H bond
1	Sonomolide A	−7.7	Asn A:264 (2.26,3.26), Gln A:444 (2.91), Asn A:564 (2.31)	Pro A:441 (3.56)
2	Steperoxide A	−8.0	Asn B:564 (3.39)	Gln B:444 (3.16)
3	RP-1551-M2	−6.5	Asn A:564 (1.99,2.53)	–
4	Illudin J	−6.3	Gln A:444 (2.85), Asn A	–
5	Pericoannosin F	−7.4	Trp A:563 (2.30), Glu A:344 (2.31)	–

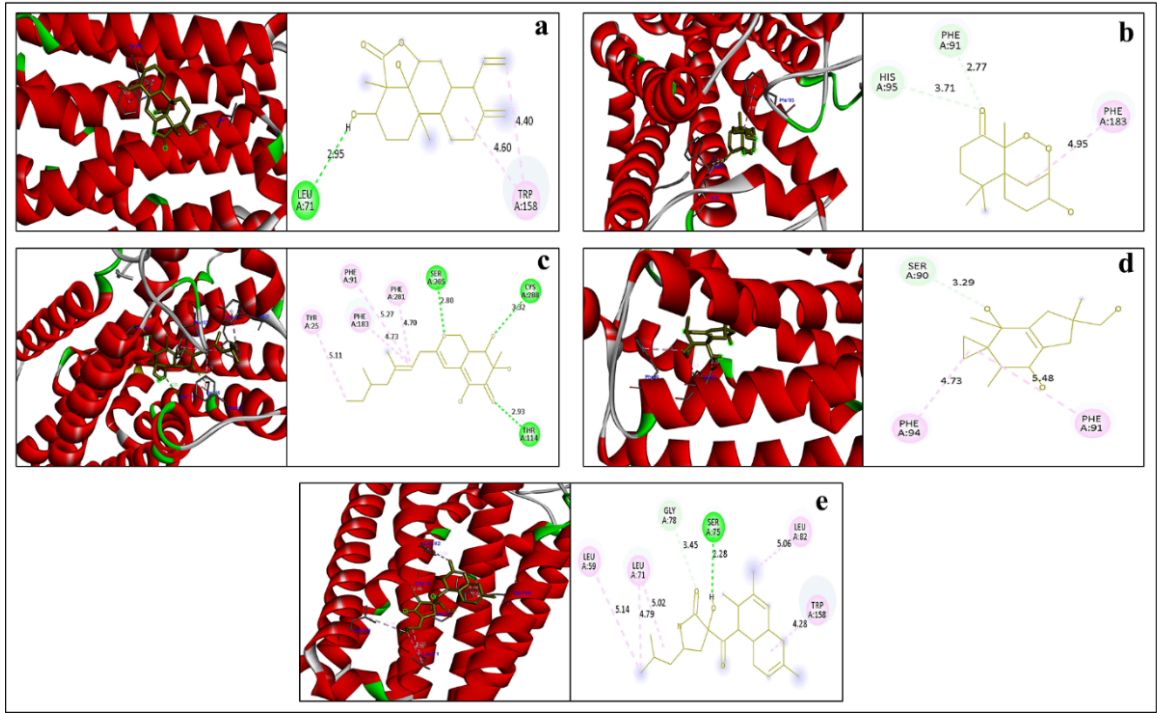


Fig. 5. Molecular docking interactions of ligands (a) Sonomolide A, (b) Steperoxide A, (c) RP-1551-M2, (d) Illudin J, and (e) Pericoannosin F with the target CBNR2, showing 3D binding poses and 2D interaction maps.

improved learning and memory abilities. In Alzheimer’s disease (AD), changes in dopamine receptor signalling, notably D1B, have been linked to cognitive loss. Targeting D1B receptors could be a promising therapeutic method for improving cognitive problems in AD (Kawahata *et al.*, 2024; Saggu *et al.*, 2024). Molecular docking with the target D1B receptor revealed that RP-1551-M2 (-7.6 kcal/

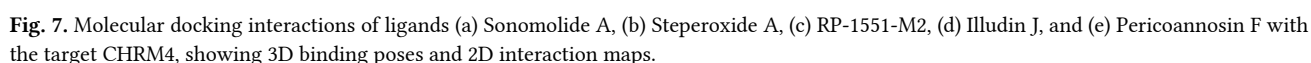
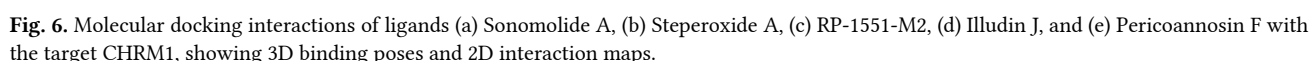
mol) and Pericoannosin F (-7.3 kcal/mol) were the strongest binders, forming traditional H-bonds with critical residues including Lys293 and Thr246. Sonomolide A (-7.0 kcal/mol) also had good binding, although Steperoxide A and Illudin J had poorer interactions. Overall, RP-1551-M2 and Pericoannosin F exhibited stable

Table 9. Binding energy and bond length of compounds with target protein CBNR2.

S.No	Ligands	Binding energy (kcal/mol)	Conventional H bond	Carbon H bond
1	Sonomolide A	-7.0	Leu A:71 (2.95)	-
2	Steperoxide A	-9.0	-	His A:95 (3.71), Phe A:91 (2.77)
3	RP-1551-M2	-7.4	Ser A:285 (2.80), Cys A:288 (3.32), Thr A:114 (2.93)	-
4	Illudin J	-8.0	-	Ser A:90 (3.29)
5	Pericoannosin F	-8.2	Ser A:75 (2.28)	Gly A:78 (3.45)

Table 10. Binding energy and bond length of compounds with target protein CHRM1.

S.No	Ligands	Binding energy (kcal/mol)	Conventional H bond	Carbon H bond
1	Sonomolide A	-7.5	Thr A:58 (2.38) and Asn A:60 (2.83)	-
2	Steperoxide A	-5.9	Glu A:55 (2.35)	-
3	RP-1551-M2	-7.8	Arg A:123 (2.81), Asn A:60 (2.77), Thr A:366 (2.89)	Lys A:359 (4.91), Cys A:421 (3.44)
4	Illudin J	-6.0	Lys A:362 (3.21), Glu A:282 (3.39), Asn A:422 (3.08)	-
5	Pericoannosin F	-7.6	Asn A:61 (2.03, 3.19), Thr A:58 (2.86), Asn A:422 (2.92), Asn A:60 (3.37)	-



Molecular dynamics simulations demonstrated that both RP-1551-M2 and Steperoxide formed stable complexes with their respective target proteins. The analyzed systems maintained structural integrity, favourable compactness, and persistent intermolecular interactions throughout the simulation period.

The CBNR2–Steperoxide complex displayed higher conformational rearrangements than other systems, as reflected by higher RMSD

values. Despite these transitions, Rg remained stable, and hydrogen bonds were consistently maintained. The results suggest that Steperoxide remains securely bound to CBNR2 while allowing adaptive structural changes (Figure 10).

The CHRM1–RP-1551-M2 complex maintained structural stability with moderate conformational drift and a stable radius of gyration (Figure 11). RMSF analysis identified flexibility in selected residues, but controlled conformational changes. Persistent hydrogen-bond

interactions further confirmed strong ligand retention throughout the simulation.

The CHRM4–RP-1551-M2 complex exhibited stable structural behaviour throughout the simulation (Figure 12). RMSD and Rg analyses indicated maintenance of overall protein compactness, while RMSF revealed localized flexibility in specific loop regions. Overall, RP-1551-M2 formed a stable and adaptable interaction with CHRM4.

Table 11. Binding energy and bond length of compounds with target protein CHRM4.

S.No	Ligands	Binding energy (kcal/mol)	Conventional H bond	Carbon H bond
1	Sonomolide A	−6.6	Arg A:223 (3.11, 3.34), Tyr A:215 (2.82)	–
2	Steperoxide A	−6.0	Tyr A:215 (3.15, 2.90)	Ser A:219 (3.40)
3	RP-1551-M2	−6.8	Thr A:401 (2.99), Asn A:68 (2.37), Arg A:394 (3.08)	Val A:398 (3.40)
4	Illudin J	−5.6	Tyr A:69 (3.16), Trp A:157	–
5	Pericoannosin F	−6.3	Ser A:222 (2.99), Tyr A:215 (2.24)	–

Table 12. Binding energy and bond length of compounds with target protein Dopamine.

S.No	Ligands	Binding energy (kcal/mol)	Conventional H bond	Carbon H bond
1	Sonomolide A	−7.0	Ser A:299 (3.05)	–
2	Steperoxide A	−6.3	Thr A:246 (3.02)	–
3	RP-1551-M2	−7.6	Lys A:293 (2.73), Thr A:297 (3.25, 2.07)	–
4	Illudin J	−6.5	Ser A:299 (2.88), Thr A:246 (2.87)	–
5	Pericoannosin F	−7.3	Thr A:246 (2.94)	–

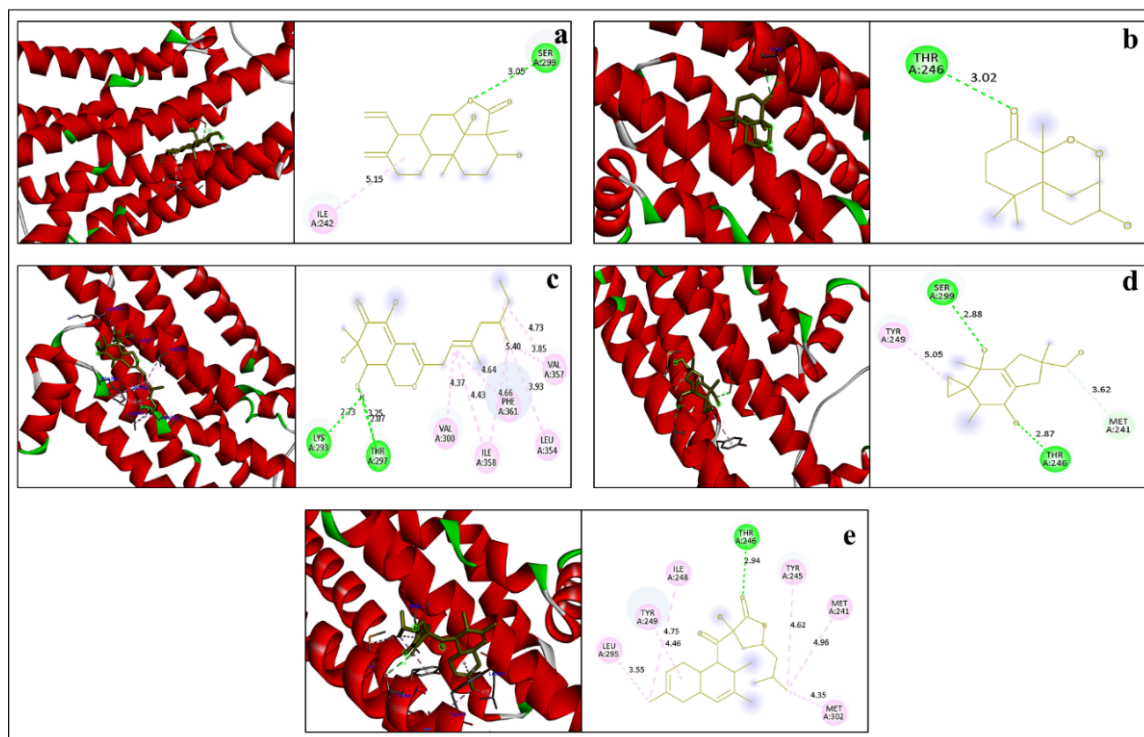


Fig. 8. Molecular docking interactions of ligands (a) Sonomolide A, (b) Steperoxide A, (c) RP-1551-M2, (d) Illudin J, and (e) Pericoannosin F with the target Dopamine, showing 3D binding poses and 2D interaction maps.

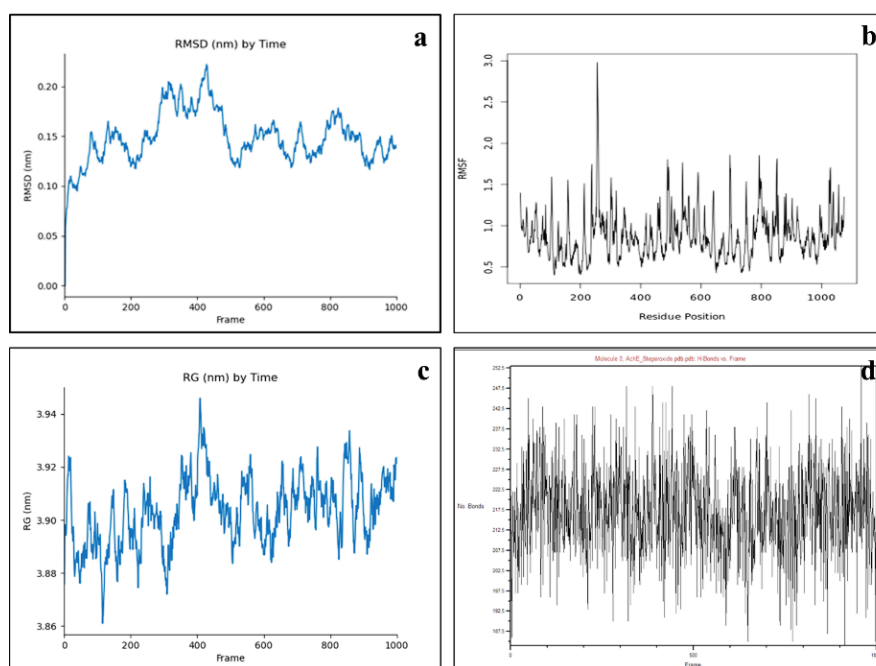


Fig. 9. Molecular simulation of Steperoxide with the target protein AChE. (a) RMSD, (b) RMSF, (c) Radius of Gyration, (d) Hydrogen analysis.

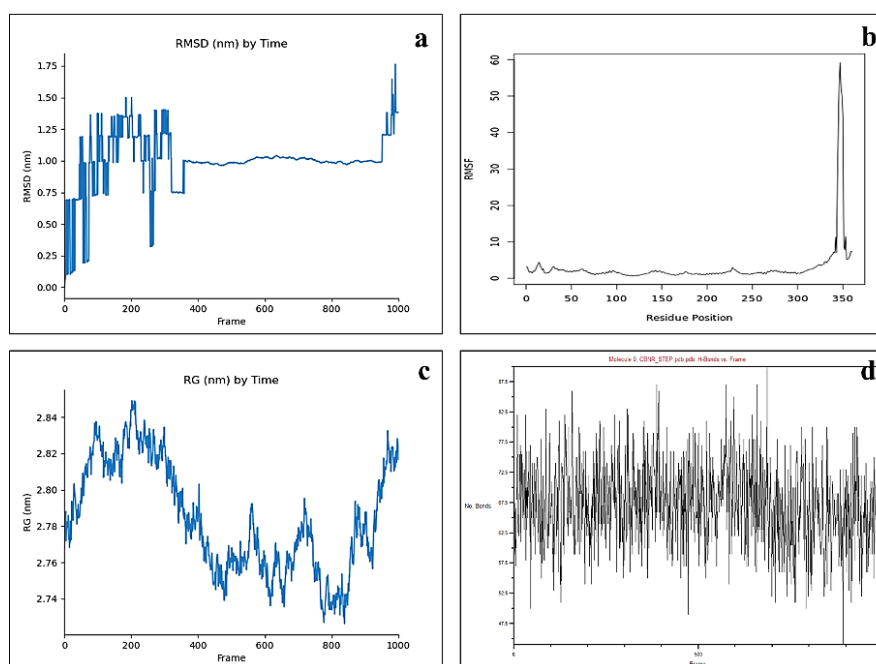


Fig. 10. Molecular simulation of Steperoxide with the target protein CBNR2. (a) RMSD, (b) RMSF, (c) Radius of Gyration, (d) Hydrogen analysis.

The Dopamine-RP-1551-M2 complex showed gradual structural adaptation during the simulation, with RMSD stabilizing at later stages (Figure 13). RMSF analysis indicated flexible regions and conformational transitions, whereas stable hydrogen-bond interactions and consistent compactness suggested sustained ligand binding. These findings support a stable and dynamic interaction between RP-1551-M2 and dopamine.

Among the studied complexes, AChE-Steperoxide showed the greatest stability, whereas CBNR2-Steperoxide exhibited higher conformational adaptability while preserving binding interactions. Collectively, the results indicate that these ligands possess favourable binding stability and dynamic compatibility with their target proteins, supporting their potential biological relevance and therapeutic applicability.

CONCLUSION

This study highlights the therapeutic promise of fungal metabolites as multi-target agents against Alzheimer's disease through an integrated *in silico* approach. From an initial library of over 18,000 compounds, five drug-like candidates—Sonamolide A, Steperoxide A, RP-1551-M2, Illudin J, and Pericoannosin F—were identified based on favourable physicochemical, pharmacokinetic and toxicity profiles. Docking studies revealed strong binding affinities with key AD-related targets, particularly Steperoxide A with acetylcholinesterase and cannabinoid receptor 2, and RP-1551-M2 with muscarinic and dopamine receptors. ADMET predictions confirmed their oral bioavailability, blood-brain barrier permeability and acceptable safety profiles. Molecular dynamics simulations further validated the stability and favourable interaction patterns of the protein-ligand complexes. Collectively, these findings suggest that

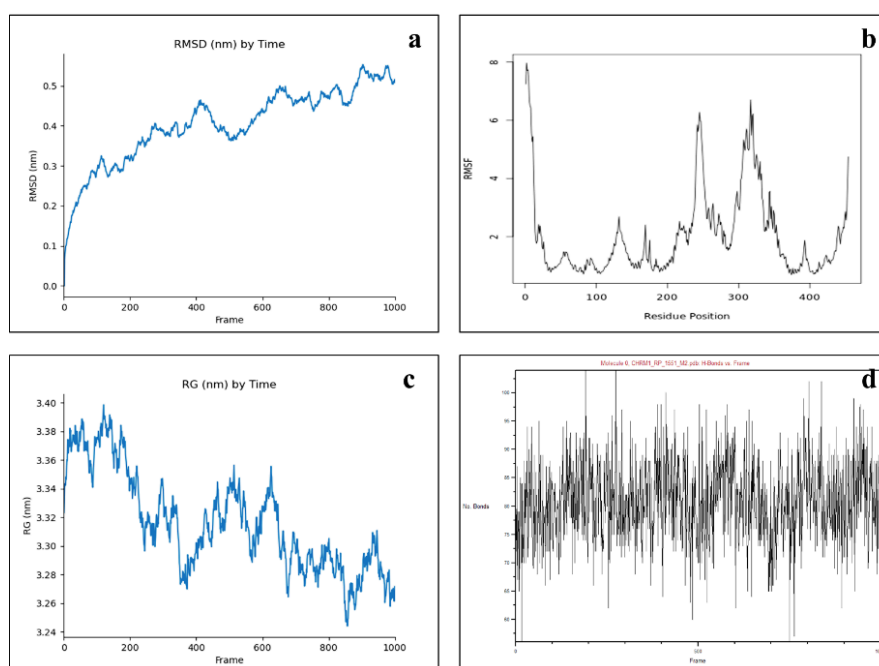


Fig. 11. Molecular simulation of RP-1551-M2 with the target protein CHRM1. (a) RMSD, (b) RMSF, (c) Radius of Gyration, (d) Hydrogen analysis.

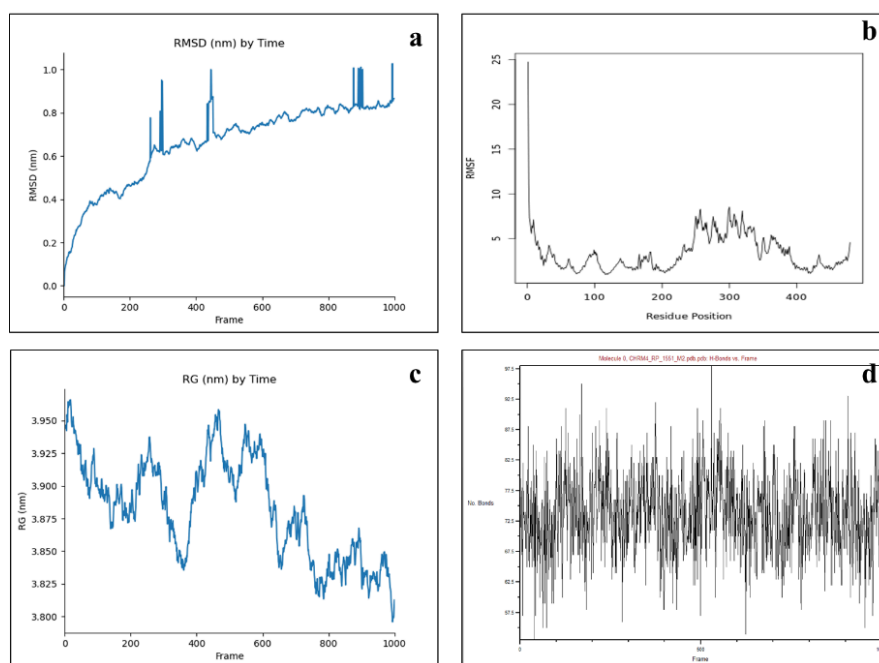


Fig. 12. Molecular simulation of RP-1551-M2 with the target protein CHRM4. (a) RMSD, (b) RMSF, (c) Radius of Gyration, (d) Hydrogen analysis.

fungal metabolites, especially Steperoxide A and RP-1551-M2, hold significant multi-target neuroprotective potential and merit further experimental validation as novel leads for Alzheimer's disease therapeutics.

ETHICAL STATEMENT

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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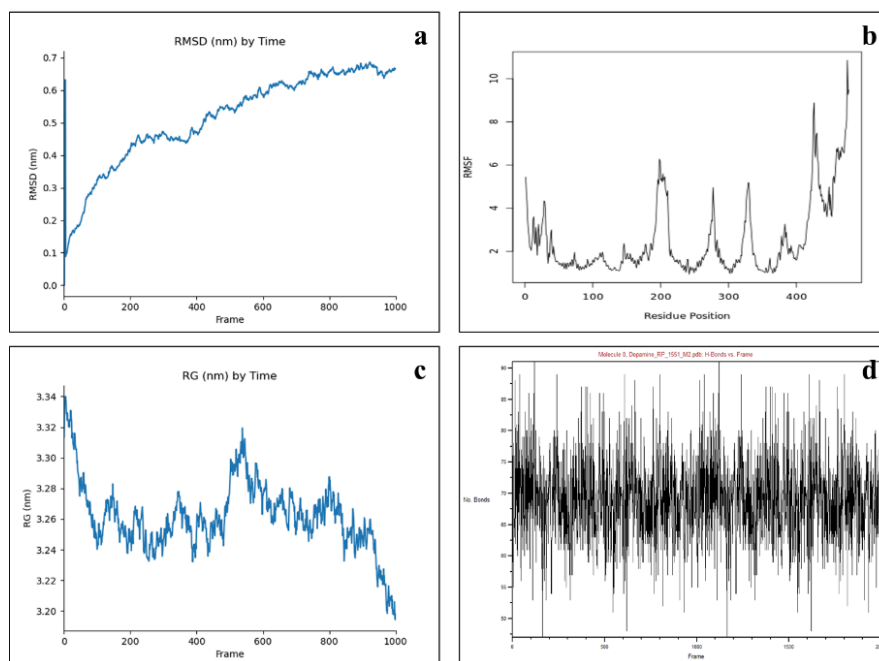


Fig. 13. Molecular simulation of RP-1551-M2 with the target protein Dopamine. (a) RMSD, (b) RMSF, (c) Radius of Gyration, (d) Hydrogen analysis.

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