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Samelisant, an H3 Receptor Inverse Agonist as an Anti-Alzheimer Potential – A Pilot Study on Molecular Docking

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Abstract

Neurodegenerative diseases have become more prevalent and about 55 million of the population are affected by dementia globally. One of the most important neurodegenerative diseases is Alzheimer's disease which is known for its effect on memory and cognitive impairment. Alzheimer's disease (AD) is an area of intense scientific investigation due to its high prevalence and the lack of a definitive cure. Amyloid precursor protein plays a central role in Alzheimer's disease by serving as the precursor for amyloid-β, the peptide responsible for the formation of toxic amyloid plaques. The dysregulation of APP processing in the amyloidogenic pathway leads to the accumulation of Aβ peptides and hyper-phosphorylation of tau disrupt neuronal function, induce oxidative stress, and activate neuroinflammatory responses. The synthetic drug samelisant that is in clinical trials with narcolepsy where they work as a H3 receptor Inverse Agonist serves as a potential candidate were studied. Recent studies have also shown their potential for treating excessive daytime sleep in Parkinson's disease. The outcomes of the docking studies unveil their potential for treating Alzheimer's disease. The samelisant was concluded to have good binding affinity with acetylcholine esterase, β secretase and tumor necrosis factor α cleaving enzyme, butyrylcholine esterase and binding affinity were found to be above –8 kcal/mol. This provides insights into their potential as an inhibitor or a modulator for AD.

Keywords: Alzheimer's disease, molecular docking, molecular dynamics simulation, pi–pi stacking, samelisant

INTRODUCTION

Population affected by neurodegenerative diseases such as dementia and Alzheimer's is currently burgeoning. AD is predestined and progresses in cognitive decline. Obsession toward finding new molecules and targets for their treatment has increased. By evaluating globally, around 416 million people are affected by Alzheimer's and approximately 50 million with dementia [1]. Pivotal roots for AD are still to be understood more deeply. There are bountiful hypotheses and mechanisms explaining AD, but the main theories continue to be familial AD and sporadic AD forms. The familial AD is pictured as mutations in APP or Presenilin1/2, and sporadic AD as late-onset in association with influence of other external factors [2].

Prominent hallmarks of both familial AD and sporadic AD are Aβ plaques and neurofibrillary tangles. Aβ plaques are formed when the APP is cleaved by β-secretase and γ-secretase. This generates Aβ fragments of length 40–42 causing senile plaques. Familial AD Aβ 42/40 accumulation occurs on behalf of impairment in autophagy ultimately leading to neurodegeneration. In congruence with sporadic AD, the imbalance in production and clearance mechanism causes the Aβ

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plaque accumulation. Tau protein is present in the microtubule which consists of abundant phosphorylating sites. Activation of Tau tubulin kinases promote hyperphosphorylation of tau and their detachment [3]. Several other hypotheses also contribute to the pathology compiling oxidative stress, microvascular dysfunction, blood–brain barrier (BBB) disruption and can induce the activation of inflammatory response within the brain.

On the whole turn up to be resulting in neuronal damage and degeneration. AD is associated with cholinergic systems from initial stages resulting in cognitive decline. When it comes to memory and learning, Acetylcholine plays a pivotal role. Acetylcholine is produced by means of choline acetyltransferase enzyme using Acetyl Co-A and Choline. The cholinergic hypotheses state how the damage of the cholinergic neurons accompanied with reduction in the levels of acetylcholine neurotransmitter [4]. In 1970s, there were severe side effects observed on humans with anticholinergic and choline receptor blockers compared with 1980s target in usage of cholinesterase inhibitors paved way for treating AD. Modern approaches in treating AD is to increase the levels of acetylcholine which is memory and learning abilities [5].

Samelisant is of Indian origin and is also known as SUVN-G3031; it is a histamine H3 receptor Inverse Agonist used for treating excessive daytime sleepiness in adults [6]. Samelisant are specially engineered molecules for the reduction of the baseline activity of H3 receptor. Their action on the receptor enhances the release of neurotransmitters, improving wakefulness and cognitive function. Their role in Alzheimer is an area unexplored and needs attention for more research which in provided in this in silico study.

MATERIALS AND METHODS

Retrieval of Ligand and ADMET Study

SAMELISANT structure was attained from PubChem database. The ADMET study is accomplished by using the tool ADMETlab 3.0. Their structure was downloaded from PubChem database in 3d conformer SDF format and converted to PDB format using openbabel-3.1.1 software.

Retrieval of Target Proteins

The major significant proteins were listed (Table 1) and their structure were collected from Protein Data Bank database (https://www.rcsb.org/) and UniProt (https://www.uniprot.org/). All the proteins obtained from the Database were of Homo sapiens organism. All the proteins were prepared using Autodock Vina tool.

String Analysis of Targeted Proteins

String analysis was carried out using online STRING tool of version 12.0 (https://stringdb.org/). All the target proteins were listed in the MULTIPLE PROTEIN particularly and worked out. The proteins were listed either by names or identifiers one by one.

Visualization of Binding/Active Sites

BIOVIA Discovery Studio is used to view the binding sites. Those sites were visualized and the grid box is assembled on that region while docking. Visualization of the binding site is carried out.

Docking – Autodock 1.5.7 and Viewing – BIOVIA Discovery Studio

The proteins were prepared and molecular docking was carried out. For the analysis the tool Autodock Vina was made used which is a computational technique for finding the interactions between proteins and ligands. After the run, the results were explored using BIOVIA Discovery Studio.

Molecular Dynamics Simulation – GROMACS Software

MD simulations studied for the protein complex with GROMACS 2024. The proteins were set to use the AMBER99SB-ILDN force field. The ligands were parameterized using the Generalized Amber Force Field combined with AM1-BCC using acype server charges to interact with the protein force

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field. An effective solvation was ensured through the application of the TIP3 water model. Ions were added while maintaining physiological values for the rest, ensuring the balance was kept at 0.15 M NaCl. The steepest descent algorithm was performed with a convergence criterion of 1000 kJ/mol/nm in maximum force, aiming to delete the high-energy contacts and steric clashes. The systems were equilibrated using a two-stage equilibration (NVT and NPT). The MD simulations were performed for 20 ns [7, 8].

RESULTS AND DISCUSSION

Outcomes of ADMET Study

The ADMET study was executed using ADMETLAB 3.0 (web-based tool). The important parameters and radar graph of the ADMET study was listed in Table 1. The pharmacokinetic rule that is used to determine whether compound can be taken by meand of oral is called as Lipinski rule. The chosen drug sticks to follow Lipinski rule. The oral bioavailability of the synthetic drug samelisant seems to be 0.59% and indicate their absorption profile. The results obtained indicate that the drug has moderate distribution. The BBB is 0.998 which confirmed that the drug can cross BBB and available for the treatment targeting CNS. The Log P value of the drug showed them as an ideal drug candidate where the compound is at right balance indicating their solubility. When the Log P values are 2.166 and shows they can be metabolized easily. In context of excretion the compound seems to have a short half-life period and moderate clearance rate [9].

Table 1. Protein–ligand interaction tabulation.

S. N.	Protein name	PDB ID/ uniprot ID	Binding scores	Type of interaction
1.	Acetylcholine Esterase	4pqe	–8.86	Pi–Pi Stacking
2.	Butyrylcholine Esterase	4bds/Po6276	–6.97	Hydrogen Bonding
3.	Beta Secretase	6eqm/P56817	–9.38	Hydrogen Bonding
4.	Tumor Necrosis Factor Alpha Cleaving Enzyme	2i47/P78536	–10.65	Hydrogen Bonding
5.	Glycogen Synthase Kinase 3 Beta	1h8f/P49841	–6.03	Hydrogen Bonding
6.	Cd33	5IHB/P20138	–5.07	Pi–Pi Stacking
7.	App	P05067	–8.06	Pi–Pi Stacking
8.	Cdk5	Q00535/7VDS	–6.28	Hydrogen Bonding
9.	Il1-Beta	P01584/9ilb	–8.01	Hydrogen Bonding
10.	Il6	P05231/1ALU	–6.68	Hydrogen Bonding
11.	Caspase 3	3DEI	–5.98	Hydrogen Bonding
12.	Vascular Endothelial Growth Factor 2	P35968	–6.27	Hydrogen Bonding
13.	Apoe	PO2649	–5.55	Hydrogen Bonding
14.	Caspase 8	P0A749/3KQJ	–5.91	Hydrogen Bonding

Outcomes of String Analysis

String analysis is undertaken for the targeted proteins for this study. The analysis shows how APP is the key network and their connection to proteins such as BACE-1, APOE, GSK3B, CDK5, IL1B, IL6, CD33, and caspases. The analysis gives an outline on how all these proteins are involved in Alzheimer's disease in various aspects in terms of plaque formation, phosphorylation in AD, neuronal functions and neurodegeneration, inflammatory pathways in neurodegeneration and their relation to synaptic function and plasticity. The density of the network connection indicates their complexity of interactions.

String analysis was carried out using the web-based tool (string.org). This analysis was done for the selected target for the study to validate their connection (Figures 1 and 2).

The radar graph was generated using ADMETlab 3.0 denotes the ADMET properties of samelisant.

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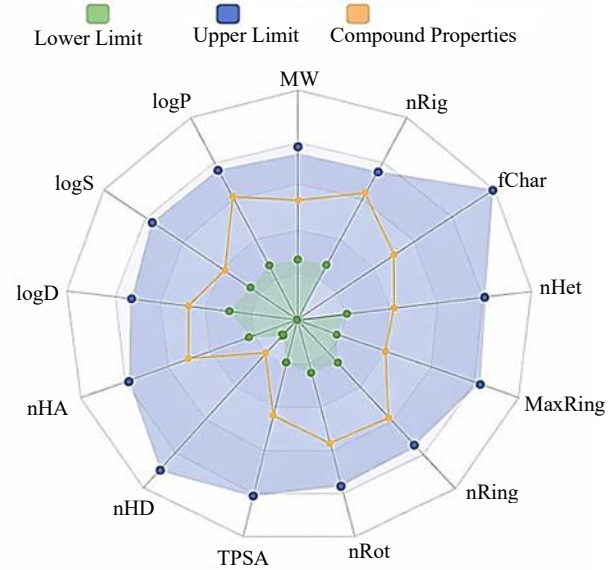

Figure 1. ADMETlab 3.0 radar graph.

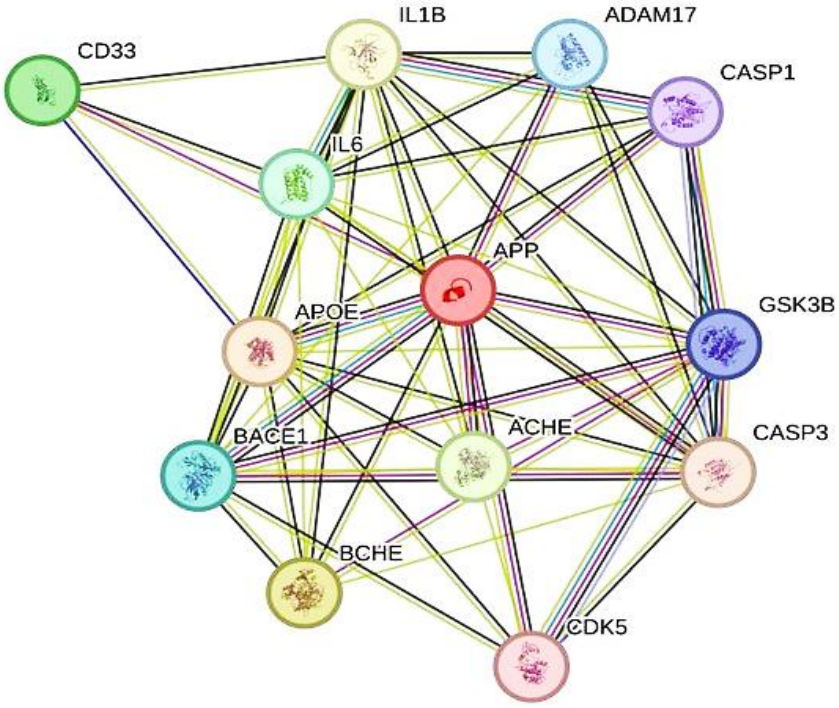

Figure 2. String analysis of the target proteins.

Ramachandran Plot Analysis

The Ramachandran plot for the predicted "2D structure of the protein" was generated to assess the stereo chemical quality of the model for viewing the specific amino acid interaction of protein with the ligand. The analysis revealed that 85% of the residues were found in the favored regions of the plot, indicating a high degree of stereo chemical accuracy. Specifically, 10% of the residues were in the allowed regions, and 3% were in the generously allowed regions, while only 2% of the residues were in the disallowed regions, suggesting minimal steric clashes and a reliable structural model. The proportion of residues in the favored regions is consistent with high-quality protein models, indicating well-defined backbone conformations. These results suggest that the ligand bound with the amino acids in the allowed region as shown in Figure 3(a–d).

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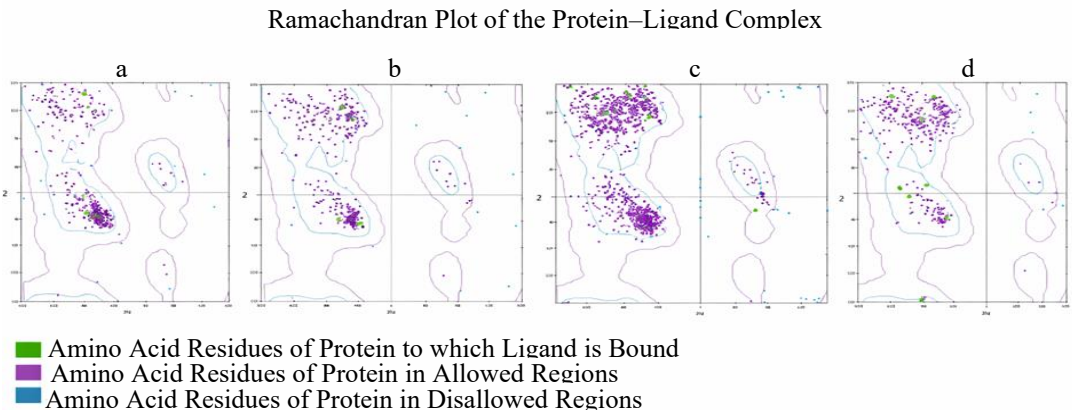
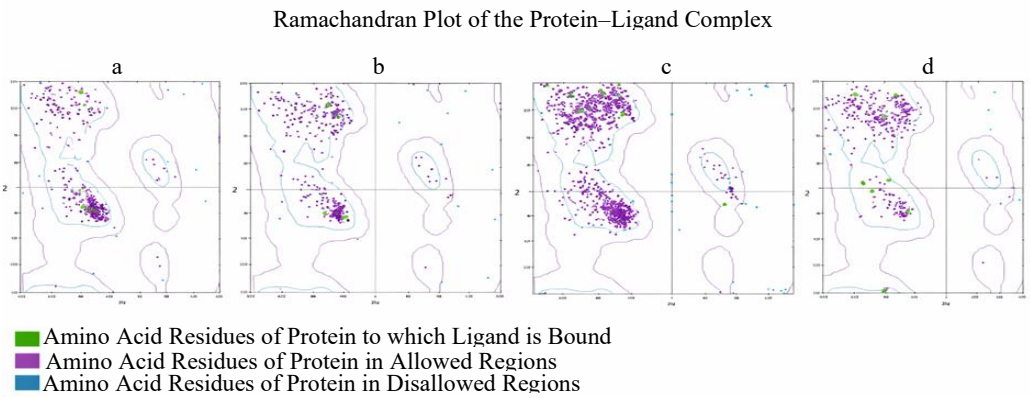
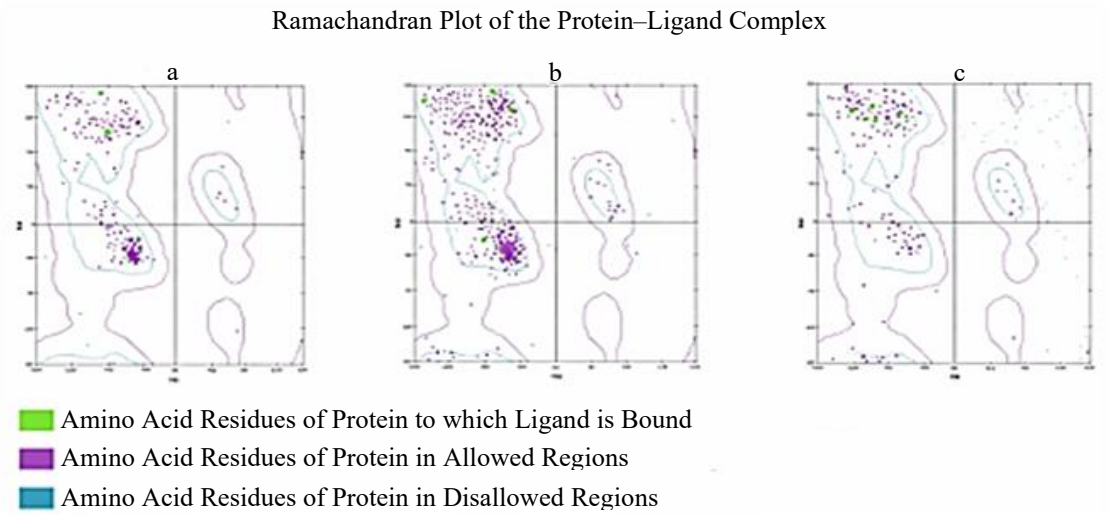
3a – The Ramachandran plot denotes the protein structure and highlights the amino acids ligand bound to A) Acetylcholine esterase, B) Apolipoprotein E, C) Amyloid precursor protein, and D) Beta secretase 1.



3b – The Ramachandran plot denotes the protein structure and highlights the amino acids ligand bound to A) Butyrylcholine esterase, B) caspase 1, C) caspase 3, and D) CD33.



3c – The Ramachandran plot denotes the protein structure and highlights the amino acids ligand bound to A) CDK5, B) Glycogen synthase kinase 3 beta, and C) Interleukin 1 beta.



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3d – The Ramachandran plot denotes the protein structure and highlights the amino acids ligand bound to A) Interleukin 6, B) Tumor necrosis factor alpha cleaving enzyme, and C) Vascular endothelial growth factor 2.

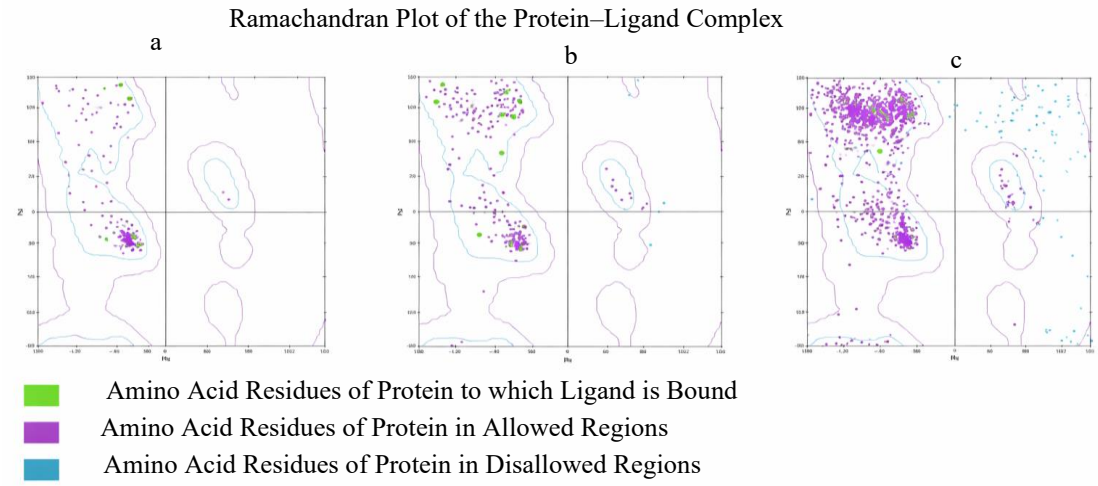

Figure 3. Representation of the Ramachandran plot for the target proteins (A, B, C, D).

DOCKING RESULTS

The synthetic drug samelisant was docked with multiple targets to evaluate their potential role in treatment of Alzheimer's disease. Acetylcholinesterase breaks down the acetylcholine which is involved in memory and learning. Butyrylcholinesterase also targets in breakdown in acetylcholine but their levels are usually elevated in course of AD patients. β-secretase is an enzyme involved in formation of Amyloid β plaques. The role of the enzyme choline acetyltransferase is essential in memory and learning where they are involved in production of acetylcholine. Tumor necrosis factor α cleaving enzyme-1 is involved in production of the amyloid β plaques by cleaving APP [7]. Glycogen synthase kinase enzyme plays a pivotal role in phosphorylation of the neurofibrillary tangles. Cd33 is a cell surface receptor that is associated with AD in terms of genetic risk and clearance of amyloid β plaque. Amyloid precursor protein is the crucial protein in Alzheimer's disease which is associated in formation of amyloid β plaque, a hallmark of Alzheimer's pathology. Cdk5 is an important enzyme involved in phosphorylation of the tau proteins which is a hallmark of Alzheimer's pathology. IL1β and IL6 are important protein involved in neuroinflammation which exacerbates amyloid β plaque and neurofibrillary tangles accumulation and leading to increased progression in cognitive impairment and memory. Vascular endothelial growth factor 2 plays a vital role in maintaining the BBB integrity and neurovascular function. Apo E plays a crucial role in amyloid β clearance and aggregation, and their Apo E 4 alleles are involved in increasing the course of the disease by means of neuroinflammation and neurotoxicity. Caspases meditate apoptosis and neuroinflammation, they increase the course of the disease by activating the apoptotic pathways in the neurons (Figures 4 and 5) [8].

The best docking results were considered to be above –8 kcal/mol. The interaction of samelisant with acetylcholine esterase (–8.86), β secretase (–9.38), tumor necrosis factor α cleaving enzyme (–10.65), interleukin 1 β (–8.01) and Amyloid precursor protein (–8.06) were considered to have good binding affinity. The acetylcholine esterase shown pi–pi stacking by forming bonds tyr 337, tyr 341, trp 86, and trp 286. B secretase has shown hydrogen bonding with lys 107 and also shown convectional hydrogen bonding with phe 109. In tumor necrosis factor α cleaving enzyme 1, pipi stacking (leu 401, ala 439, val 440, lys 432, leu 348, val 402, leu 350, his 409), carbon hydrogen bonding (glu 406, his 405, tyr 436) and hydrogen bonding (his 415, gly 349) were seen. The docking with the domain of Amyloid precursor protein indicates many pi–pi interaction such as pi-anion (asp 24), pi alkyl (phe 33, tyr 22, ala 9) and carbon hydrogen bonding (ala 9). Interleukin 1 β has shown hydrogen bonding (leu 28, leu 26). All the targets were chosen to investigate all the aspects of the disease. More indepth exploration

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and research is needed to validate the role of the samelisant contributing as an inhibitor or a modulator [10].

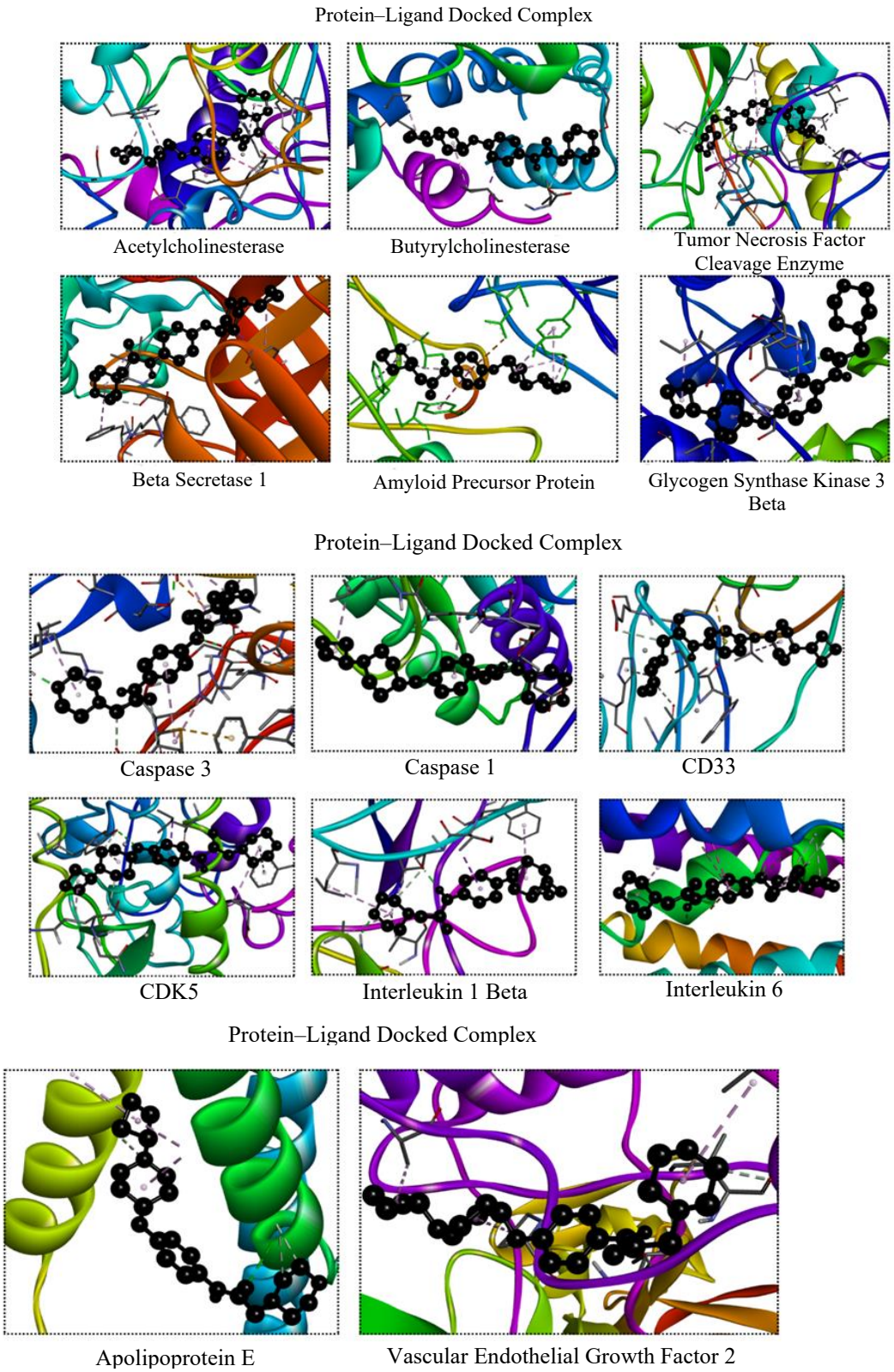

Figure 4. Docking results of Samelisant and the target proteins showing the 3D Image of protein–ligand complex (A, B, C).

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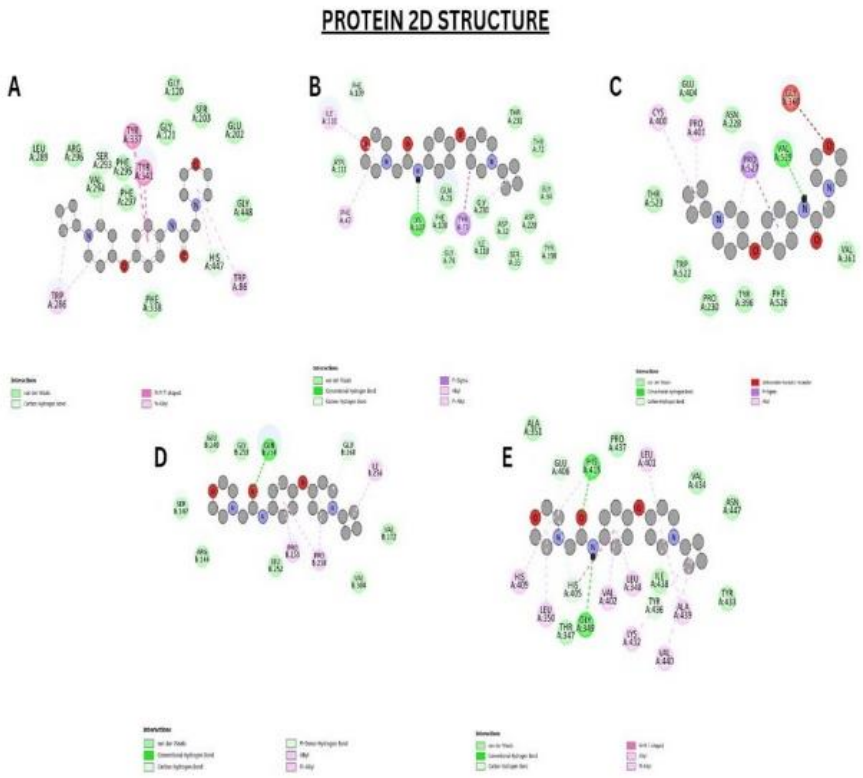
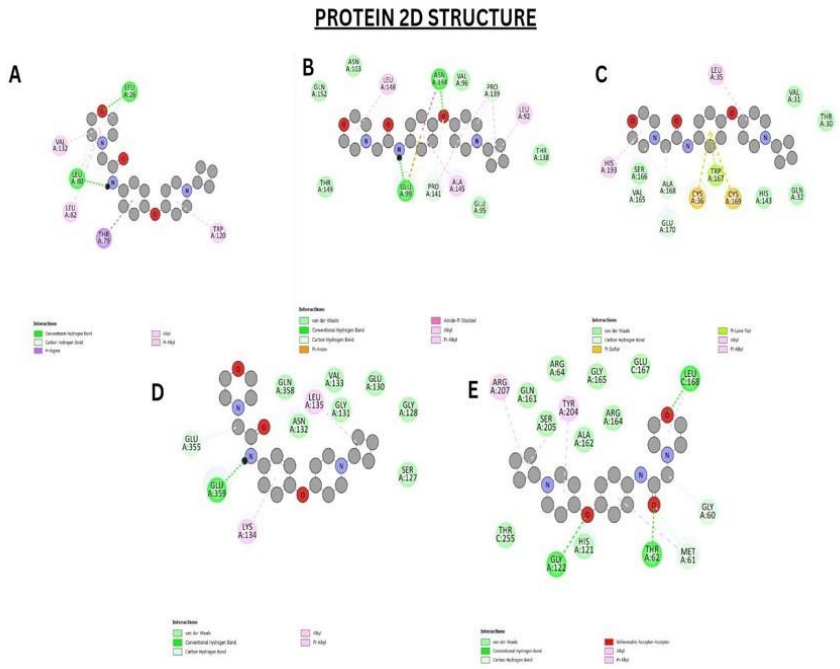
5a – The 2d images of the complexes are represented, respectively. A) Acetylcholine esterase; B) Betasecretase 1; C) Butyrylcholine esterase; D) Glycogen synthase kinase 3 beta; and E) Tumor necrosis factor alpha cleaving enzyme 1.



5b – The 2d images of the complexes are represented, respectively. A) Interleukin 1 beta; B) Interleukin 6; C) CD33; D) Caspase 1; and E) Caspase 3.



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5c – The 2d images of the complexes are represented, respectively. A) Apolipoprotein E; B) Amyloid precursor protein; C) Vascular endothelial growth factor 2; and D) CDK5.

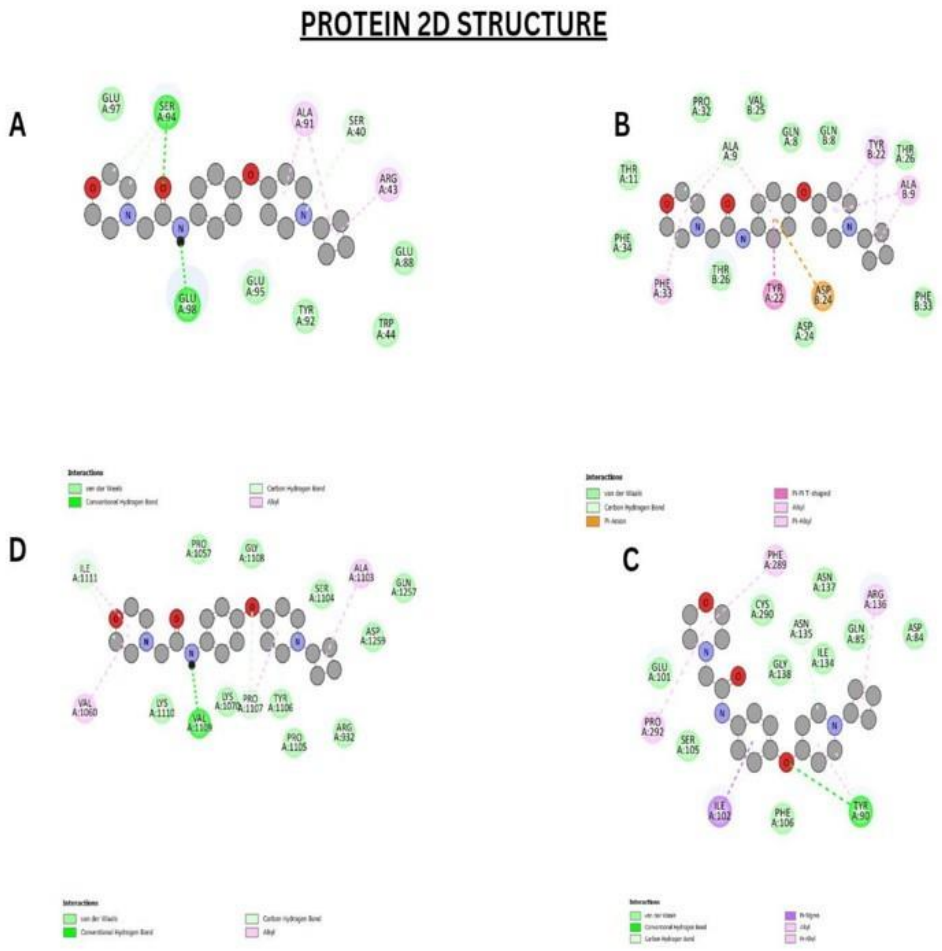

Figure 5. Docking results of samelisant and the target proteins showing the 2D Image of Protein–ligand complexes (A, B, C).

MOLECULAR DYNAMICS SIMULATIONS

In this study, the molecular dynamics simulations were done using GROMACS. This study evolves on how pi–pi stacking plays a pivotal role in inhibition. In pi–pi stacking, the aromatic rings are involved in stabilizing the binding and enhancing the effects as an inhibitor.

The pi–pi stacking is mainly involved in creating non-covalent interactions. Stable pi–pi interaction shows good affinity in protein–ligand interaction. The presence of pi–pi stacking decreases adverse effects of drugs.

The stimulation was carried out for 20 nanoseconds. The significant parameters were analyzed which include Root Mean Square Deviation (RMSD), Root Mean Square Fluctuation (RMSF), Radius of Gyration (Rg), and ligand RMSD. The RMSD plot indicates how stable the protein structure is throughout the simulation time.

The backbone RMSD increases slowly and stabilizes at 0.2–0.25 nm, which indicates the system has achieved equilibrium. Initially, the system fluctuates in the first few nanoseconds to show it is reaching equilibrium in the simulated environment before stabilizing.

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The RMSF plot indicates how flexible the different parts of the protein are, with most of the residues having low fluctuations (<0.15 nm), which indicates that the structure is very rigid.

Higher fluctuations in the end parts and loop regions indicate expected flexibility, typical in proteins. A sharp rise towards the Cterminal region indicates high levels of movement in the region. The ligand RMSD provides information on how stable the binding is.

The ligand is very stable with an RMSD of 0.5–0.7 nm, which indicates that it remains bound without moving significantly apart.

The changes observed indicate slight changes in the binding pocket rather than complete separation. The overall Rg value remains stable around 2.5 nm, indicating that the protein does not expand or fold significantly. The changes in different axes indicate slight changes in shape but no significant structural issues were seen (Figures 6 and 7) [11].

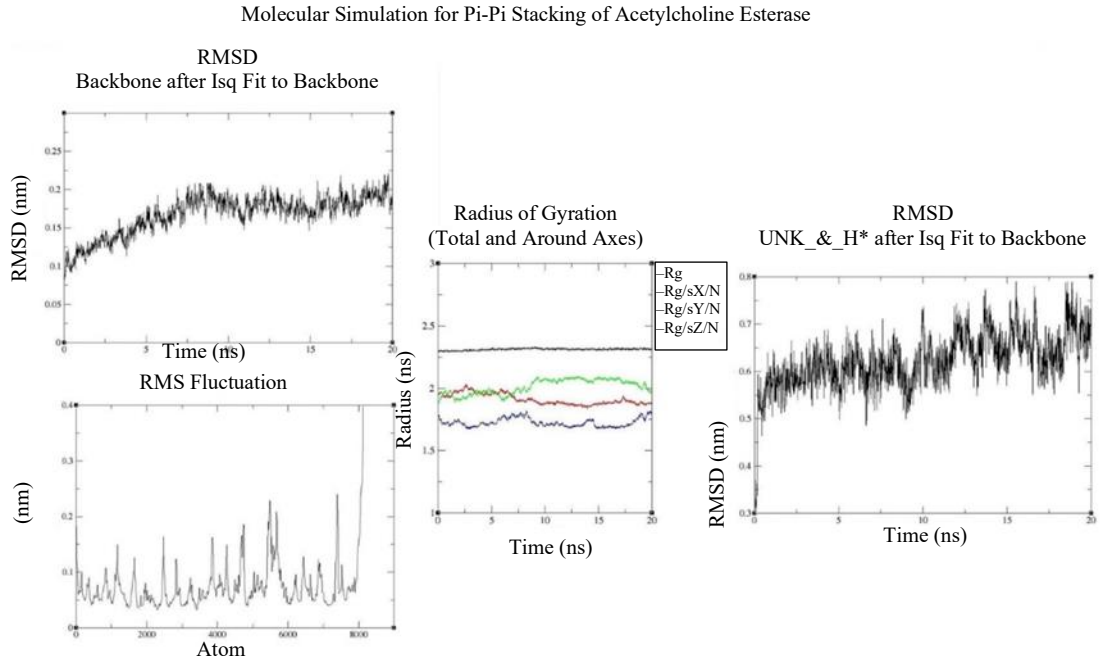

Figure 6. Molecular dynamics simulations results in terms of Pi–Pi stacking for ACHE.

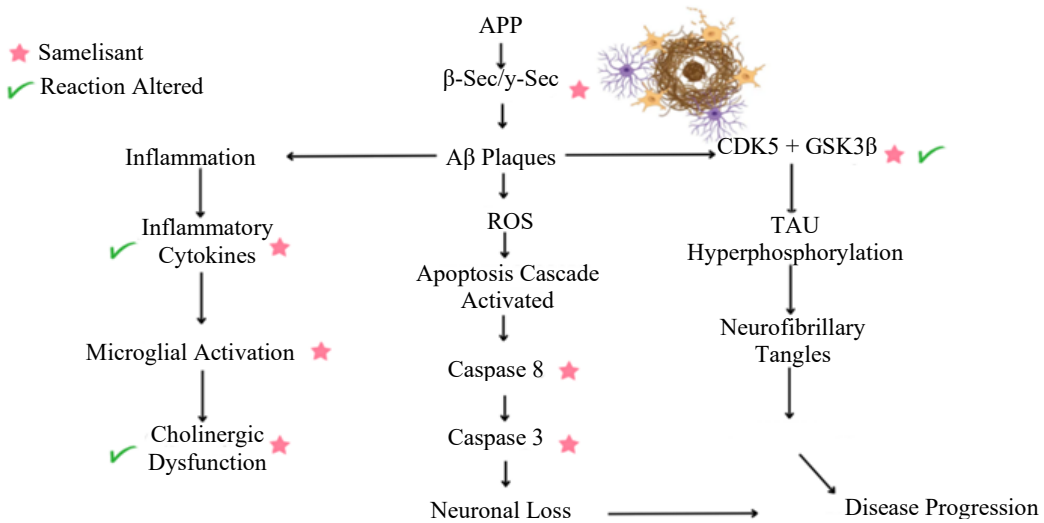

Figure 7. The following image shows the overall role of samelisant in Alzheimer's disease.

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CONCLUSION

Docking results show that samelisant is a viable candidate for future studies on treatments for Alzheimer's disease. As part of the docked proteins, acetylcholinesterase, beta-secretase, and tumor necrosis factor-alpha cleaving enzyme showed good results. All binding scores were above –8 kcal/mol. The interaction of samelisant with target proteins shows its competence to act as an inhibitor or a modulator for treatment of Alzheimer's disease. Molecular dynamics were conducted for acetylcholinesterase, which contained pi–pi stacking and carbon–hydrogen bonds. These simulations revealed high stability for the protein–ligand complex. The next phase of research using samelisant solely as a treatment will provide more valuable insights; more in-depth exploration is needed to validate the role of samelisant as a potential inhibitor or a modulator.

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Conflict of Interest

The authors declare no potential conflict of interest during the preparation of the current manuscript.

Author Contribution

The corresponding author Dr. T. Sumathi, Associate Professor, conceptualized and designed the study, supervised the progress of the research, formally analyzed the manuscript and delivered comments on all previous versions of the manuscript for improvision. Ms. Annie Aishwarya has contributed toward methodology, data collection, and analysis of the data. All authors contributed equally toward the research work and approved final version of the manuscript.

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