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Docking Of Alkaloid as A Source of Potential Anticholinesterase Inhibitors for The Treatment of Alzheimer's Disease

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Abstract

Alzheimer's dementia affects 6.2 million Americans aged 65 and older, according to estimates. If no medical advances are made to prevent, slow down, or cure AD, this figure might increase to 13.8 million by 2060. The "APP", "APOE4", and "PSEN1" genes, which are responsible for AD, are playing a molecular function in our bodies on chromosomes 21, 19, and 14, depending on whether they are displaying low risk or high risk. This study describes the alternative therapeutic targets, incidence, prevalence, mortality, and morbidity of Alzheimer's disease (AD) and how it affects public health. By using computational methods, it was discovered that the biology underlying those genes. How the Clustal Omega alignment of the sequences of many species gave us 100% identity. The study on the comparative genome viewer based on assembly-assembly alignment published by NCBI came after the Ramachandran plot based on φ and ψ values, where the best model quality was observed by assessing the Q mean or Z score. Once the targets were set, the efficient ligands "ALKALOIDC", "PIPERIDINE", and "SANGUINARINE" in order to continue working on protein structures were studied. One should be familiar with 2D and 3D models of proteins to do this. The demand for new medicines that provide improved symptomatic benefit and disease-slowing capabilities, as well as the identification of several new therapeutic targets, has led to a greater focus on protein-ligand interaction by employing molecular docking. The anticholinesterase activity of alkaloids, together with their structural diversity and physicochemical properties, makes them good candidate agents for the treatment of Alzheimer's disease. Future research should include more rigorous clinical studies of the most promising alkaloids, the further development of recently discovered candidate alkaloids, and the continual search for new alkaloids for relevant drug targets. It remains promising that an alkaloid drug candidate could significantly affect the progression of AD in addition to providing symptomatic relief.

Keywords: Alzheimer's Disease, AlkaloidC, Piperidine, Sanguinarine, Anticholinesterase, Molecular Docking, Ramachandran plot, APOE, APP, PSEN1, PSEN2, BLAST, Z-Score.

Introduction:

The World Health Organization (WHO) has identified Alzheimer's disease (AD) as a global public health concern. There are still no disease-modifying medicines, despite significant advancements in our comprehension of AD pathogenesis and how the disease is conceptualized since Alois Alzheimer described the first case in 1907. A neurodegenerative condition that gradually impairs cognitive function before leading to death. It is important to distinguish AD from other types of dementia, including vascular dementia, dementia with Lewy bodies, dementia caused by Parkinson's disease, frontotemporal dementia, and reversible dementias. The pathological cascade for the disease process is most likely to be: β-amyloid deposition → tau phosphorylation and tangle formation → neuronal death **[1]**.

Pathological Proteins

i) Amyloid-β Protein Precursor

Senile plaque cores and vascular amyloid are mostly composed of a tiny polypeptide called Aβ, which molecular genetic investigations have revealed is a component of the much bigger amyloid-protein precursor (APP), which is encoded on chromosome 21 **[2]**.

ii) Tau Protein

The discovery that phosphorylated tau was the main protein in NFT sparked a plethora of scientific studies on tau metabolism, phosphorylation and dephosphorylation mechanisms, the function of tau processing in disease, and the idea that phosphorylated tau was inherently toxic. As a result, removing phosphorylated tau from the aged brain may be a successful treatment for AD. However, clinicopathological results showing that phosphorylated tau normally resides in live cells and accumulates with aging, frequently in considerable numbers, were lost in the process **[3]**.

Genetics

If your parent or sibling has Alzheimer's disease, your chances of getting it are slightly higher. The genetic factors are most likely complicated, and the bulk of the genetic causes of Alzheimer's disease in families remain unknown. A genetic susceptibility to Alzheimer's disease, as well as a family history of the disease, are important risk factors. If a parent or sibling has Alzheimer's, the person is more likely to develop the disease. Another aspect of heredity is the role of genes such as Apo lipoprotein E4 (Apo E), amyloid precursor protein (APP), presenilin-1 (PS-1) and presenilin-2 (PS-2) whose mutations can increase your risk of developing Alzheimer's disease. Furthermore, by producing anatomical and physiological difficulties in the brain, the proteins can disrupt the connections between normally cooperative brain regions **[4].**

Chromosome 21	AβPP mutation	↑ Aβ42 peptide
Chromosome 14	Presenilin-1 mutation	↑ Aβ42 peptide*
Chromosome 1	Presenilin-2 mutation	↑ Aβ42 peptide
Down	AβPP	↑ Aβ42 peptide

syndrome	overexpression	
Chromosome 19	APOE polymorphism	↑ Aβ40 plaques, CAA
Chromosome 8	CLU polymorphism	Aβ toxicity **[12]**

[Table.1: Genetic Factors Predisposing to AD [4]]

Treatment of Alzheimer's disease

Alzheimer's disease cannot be cured and its symptoms cannot always be reversed, therefore its progression cannot be slowed. Symptoms may be targeted to improve a person's quality of life and minimize the consequences of the illness's most distressing features. Cholinesterase inhibitors are a class of drugs used to address difficulties with memory, cognition, language, judgement, and other mental processes. The following cholinesterase inhibitors are regularly prescribed: Rivastigmine (Exelon) and Donepezil (Aricept) are both approved to treat mild to moderate Alzheimer's disease. Galantamine (Razadyne) can be used to treat mild to severe Alzheimer's disease. Memantine (Namenda), a distinct type of medication, has been approved by the FDA for the treatment of moderate to severe Alzheimer's disease **[5].**

Materials and Methods:

Preparation of Protein Structure:

The 3D structure of different genes, which are related to AD were retrieved from the Protein Data Bank (http://www.rcsb.org/). All the necessary changes like removal of extra chains, hetatm and connect were done with CHIMERA software **[6]**.

Preparation of Ligand Structure:

A number of inhibitors belonging to the secondary metabolites class alkaloids were selected on the basis of available literature. The sdf files were retrieved from PubChem database (http://pubchem.ncbi.nlm.nih.gov/). The files were then changed to PDB format with the help of an online tool Molecular File Converter (http://www.webqc.org/molecularformatsconverter.php) **[7]**.

Molecular Docking Using Autodock:

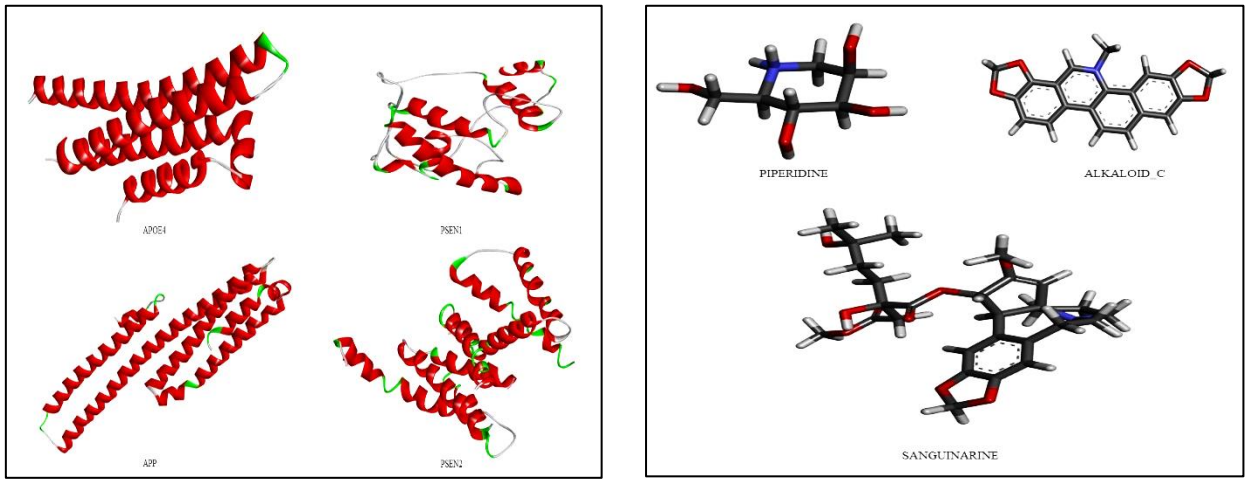
The binding region was at 0.504 Å and grid box dimensions 120 Å × 120 Å × 120 Å for the docking study by AutoDock and which was constructed around the binding site, based on the co-crystallized ligand. Ten genetic algorithm (GA) runs were performed for each compound and 3 ligands were allowed in an attempt to account for mutual ligand/target fit. Each of the GA run was performed on a population of 150 individuals **[8]**. AutoDock 4.0 included Lamarckian Genetic Algorithm search engine and an experimental free energy function for estimating binding energy, inhibitory constant, docking energy, inter-molecular energy, internal energy and torsional energy. The binding free energy was empirically calculated based on these energy terms and a set of co-efficient factors. The value of binding energy was used to rank the docking positions of the molecules. The clusters with lowest binding energy were selected **[9]**.

All obtained conformations of protein and ligand complexes analyzed the interactions and binding energy of the docked structure using molecular visualization software, i.e., Discovery Studio 4.1 **[10]**.

The best docking complex solutions were analyzed according to the potential intermolecular interactions (ligand/protein) such as hydrogen bonding (H-bonding), cation–π, π–π stacking, hydrophobic, and van der Waals (vdW) using the LPC server, which is used to analyze ligand–protein contacts on PDB files **[11]**.

Results & Discussion:

The level of protein structure at which an entire polypeptide chain has folded into a three dimensional structure. In multi-chain proteins, the term tertiary structure applies to the individual chains. The structure of a protein deposit their data into a database such as Protein Data Bank (PDB). A structure record shows the 3-D coordinates of every atom in the molecule. The ligands were collected from PubChem database are shown below.



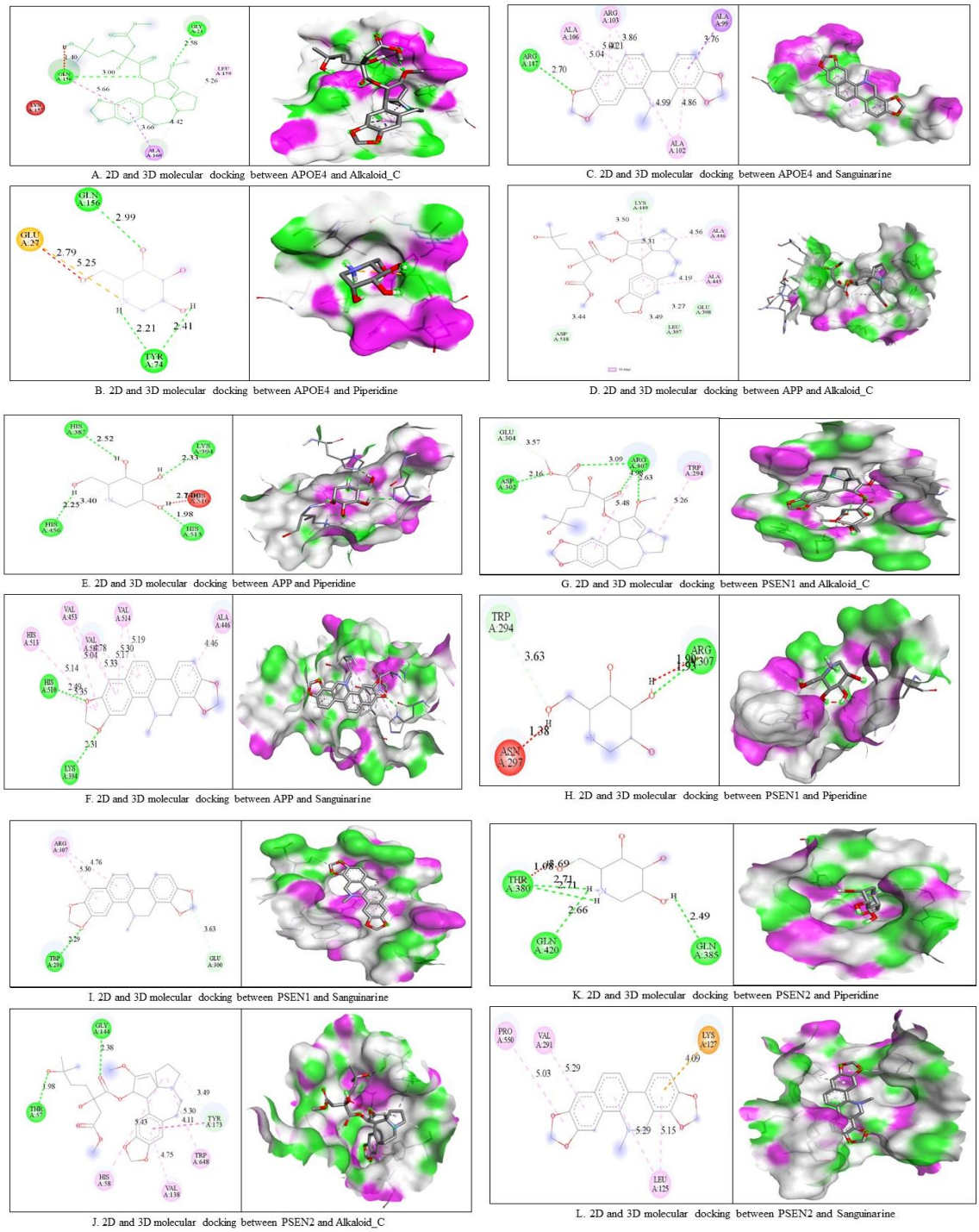
[Fig.1: 3D structure of proteins (APOE4, PSEN1, APP, PSEN2) & ligands (Piperidine, Alkaloid_C, Sanguinarine) respectively]

In view of promising use of alkaloids, namely alkaloidC, piperidine and sanguinarine for treatment of AD, in the present study, Table:1 shows the result based on the docking parameters, namely binding energy and rmsd value.

Protein	Ligand	Affinity (kcal/mol)	dist from rmsd l.b.	best mode rmsd u.b.
APOE4	Alkaloid_C	-6.4	0.000	0.000
	Piperidine	-4.5	0.000	0.000
	Sanguinarine	-6.0	0.000	0.000
APP	Alkaloid_C	-6.6	0.000	0.000
	Piperidine	-4.9	0.000	0.000
	Sanguinarine	-7.9	0.000	0.000
PSEN1	Alkaloid_C	-6.2	0.000	0.000
	Piperidine	-3.6	0.000	0.000
	Sanguinarine	-7.1	0.000	0.000
PSEN2	Alkaloid_C	-8.3	0.000	0.000
	Piperidine	-5.5	0.000	0.000
	Sanguinarine	-8.6	0.000	0.000

[Table.1: Binding affinity (kcal/mol), rmsd value which gives best docking results]

The amino acids residues of genes involved in binding and interaction with the ligands at the active site are presented in Fig. 2 and Table 2 shows the distance between protein and ligand, bonds present between them.



[Fig.2: 2D & 3D molecular docking results between protein (APOE4, APP, PSEN1, PSEN2) & ligands (Alkaloid_C, Piperidine, Sanguinarine) respectively]

APOE4_ALKALOIDC

NAME	DISTANCE	CATEGORY	TYPES
A:GLY23:HT1 - :UNL1:O	2.5802	Hydrogen Bond	Conventional Hydrogen Bond
A:GLN156:HE21:B - :UNL1:O	3.00386	Hydrogen Bond	Conventional Hydrogen Bond
:UNL1:H - :UNL1:O	2.64446	Hydrogen Bond	Conventional Hydrogen Bond
A:ALA160:CB - :UNL1	3.66054	Hydrophobic	Pi-Sigma
A:GLN156:C,O:LYS157:N - :UNL1	5.66335	Hydrophobic	Amide-Pi Stacked
A:LEU159 - :UNL1	5.25898	Hydrophobic	Alkyl
A:ALA160 - :UNL1	4.42372	Hydrophobic	Alkyl

APOE4_PIPERIDINE

NAME	DISTANCE	CATEGORY	TYPES
:UNL1:N - A:GLU27:OE2	5.24576	Electrostatic	Attractive Charge
A:GLN156:HE21 - :UNL1:O	2.98516	Hydrogen Bond	Conventional Hydrogen Bond
:UNL1:H1 - A:TYR74:OH	2.20695	Hydrogen Bond	Conventional Hydrogen Bond
:UNL1:H - A:TYR74:OH	2.40954	Hydrogen Bond	Conventional Hydrogen Bond

APOE4_SANGUINARINE

NAME	DISTANCE	CATEGORY	TYPES
A:ARG147:HH11 - :UNL1:O	2.70215	Hydrogen Bond	Conventional Hydrogen Bond
A:ALA99:CB - :UNL1	3.75759	Hydrophobic	Pi-Sigma
:UNL1 - A:ALA102	4.99047	Hydrophobic	Pi-Alkyl
:UNL1 - A:ARG103	3.86365	Hydrophobic	Pi-Alkyl
:UNL1 - A:ALA106	5.00143	Hydrophobic	Pi-Alkyl
:UNL1 - A:ALA102	4.85564	Hydrophobic	Pi-Alkyl
:UNL1 - A:ARG103	4.21102	Hydrophobic	Pi-Alkyl
:UNL1 - A:ALA106	5.04471	Hydrophobic	Pi-Alkyl

PSEN1_ALKALOIDC

NAME	DISTANCE	CATEGORY	TYPES
A:ASP302:HN - :UNL1:O	2.15587	Hydrogen Bond	Conventional Hydrogen Bond
A:ARG307:HE - :UNL1:O	2.13027	Hydrogen Bond	Conventional Hydrogen Bond
A:ARG307:HE - :UNL1:O	3.08677	Hydrogen Bond	Conventional Hydrogen Bond
A:ARG307:HH21 - :UNL1:O	2.63489	Hydrogen Bond	Conventional Hydrogen Bond
A:ARG307:HH21 - :UNL1:O	2.093	Hydrogen Bond	Conventional Hydrogen Bond
:UNL1:C - A:GLU304:OE2	3.57234	Hydrogen Bond	Carbon Hydrogen Bond
A:TRP294 - :UNL1	5.25995	Hydrophobic	Pi-Alkyl
:UNL1 - A:ARG307	5.47549	Hydrophobic	Pi-Alkyl

PSEN1_PIPERIDINE

NAME	DISTANCE	CATEGORY	TYPES
A:ARG307:HE - :UNL1:O	1.93068	Hydrogen Bond	Conventional Hydrogen Bond
A:TRP294:CA - :UNL1:O	3.6302	Hydrogen Bond	Carbon Hydrogen Bond

PSEN1_SANGUINARINE

NAME	DISTANCE	CATEGORY	TYPES
A:TRP294:HE1 - :UNL1:O	2.28595	Hydrogen Bond	Conventional Hydrogen Bond
:UNL1:C - A:GLU300:O	3.62582	Hydrogen Bond	Carbon Hydrogen Bond
:UNL1 - A:ARG307	4.75538	Hydrophobic	Pi-Alkyl
:UNL1 - A:ARG307	5.29565	Hydrophobic	Pi-Alkyl

APP_ALKALOIDC

NAME	DISTANCE	CATEGORY	TYPES
A:GLU398:CA - :UNL1:O	3.27035	Hydrogen Bond	Carbon Hydrogen Bond
A:LYS449:CE - :UNL1:O	3.49857	Hydrogen Bond	Carbon Hydrogen Bond
:UNL1:C - A:LEU397:O	3.48544	Hydrogen Bond	Carbon Hydrogen Bond
:UNL1:C - A:ASP518:OD2	3.43795	Hydrogen Bond	Carbon Hydrogen Bond
A:ALA446 - :UNL1	4.56489	Hydrophobic	Alkyl
:UNL1 - A:ALA445	4.18921	Hydrophobic	Pi-Alkyl
:UNL1 - A:LYS449	5.30793	Hydrophobic	Pi-Alkyl

APP_PIPERIDINE

NAME	DISTANCE	CATEGORY	TYPES
A:LYS394:HZ3 - :UNL1:O	2.33008	Hydrogen Bond	Conventional Hydrogen Bond
A:HIS513:HD1 - :UNL1:O	1.97846	Hydrogen Bond	Conventional Hydrogen Bond
:UNL1:H - A:HIS387:NE2	2.52011	Hydrogen Bond	Conventional Hydrogen Bond
:UNL1:H - A:HIS456:NE2	2.24629	Hydrogen Bond	Conventional Hydrogen Bond
:UNL1:CA - A:HIS456:NE2	3.39823	Hydrogen Bond	Carbon Hydrogen Bond
:UNL1:H - A:HIS513	2.74072	Hydrogen Bond	Pi-Donor Hydrogen Bond

APP_SANGUINARINE

NAME	DISTANCE	CATEGORY	TYPES
A:LYS394:HZ1 - :UNL1:O	2.30793	Hydrogen Bond	Conventional Hydrogen Bond
A:HIS510:HD1 - :UNL1:O	2.49229	Hydrogen Bond	Conventional Hydrogen Bond
A:VAL453 - :UNL1	5.04216	Hydrophobic	Alkyl
A:HIS510 - :UNL1	5.35205	Hydrophobic	Pi-Alkyl
A:HIS513 - :UNL1	5.13894	Hydrophobic	Pi-Alkyl
:UNL1 - A:VAL514	5.19252	Hydrophobic	Pi-Alkyl
:UNL1 - A:VAL517	5.17492	Hydrophobic	Pi-Alkyl
:UNL1 - A:ALA446	4.46356	Hydrophobic	Pi-Alkyl
:UNL1 - A:VAL453	4.78147	Hydrophobic	Pi-Alkyl
:UNL1 - A:VAL514	5.29524	Hydrophobic	Pi-Alkyl
:UNL1 - A:VAL517	5.32818	Hydrophobic	Pi-Alkyl

PSEN2_ALKALOIDC

NAME	DISTANCE	CATEGORY	TYPES
A:THR57:HG1 - :UNL1:O	1.97734	Hydrogen Bond	Conventional Hydrogen Bond
A:GLY144:HN - :UNL1:O	2.38255	Hydrogen Bond	Conventional Hydrogen Bond
:UNL1:C - A:TYR173:O	3.49008	Hydrogen Bond	Carbon Hydrogen Bond
A:TYR173 - :UNL1	4.11093	Hydrophobic	Pi-Pi Stacked
A:HIS58 - :UNL1	5.42878	Hydrophobic	Pi-Alkyl
A:TRP648 - :UNL1	5.29868	Hydrophobic	Pi-Alkyl
:UNL1 - A:VAL138	4.74526	Hydrophobic	Pi-Alkyl

PSEN2_PIPERIDINE

NAME	DISTANCE	CATEGORY	TYPES
:UNL1:H1 - A:THR380:O	2.71434	Hydrogen Bond	Conventional Hydrogen Bond
:UNL1:H2 - A:THR380:O	2.70964	Hydrogen Bond	Conventional Hydrogen Bond
:UNL1:H2 - A:GLN420:O	2.6561	Hydrogen Bond	Conventional Hydrogen Bond
:UNL1:H - A:GLN385:OE1	2.48744	Hydrogen Bond	Conventional Hydrogen Bond
:UNL1:C - A:THR380:O	3.68557	Hydrogen Bond	Carbon Hydrogen Bond

PSEN2_SANGUINARINE

NAME	DISTANCE	CATEGORY	TYPES
A:LYS127:NZ - :UNL1	4.09225	Electrostatic	Pi-Cation
A:PRO550 - :UNL1	5.02522	Hydrophobic	Alkyl
:UNL1 - A:LEU125	5.29032	Hydrophobic	Pi-Alkyl
:UNL1 - A:LEU125	5.15297	Hydrophobic	Pi-Alkyl
:UNL1 - A:VAL291	5.28998	Hydrophobic	Pi-Alkyl

[Table.2: Distance between protein & ligand, category & types of bonds present]

Conclusion:

From this study we conclude that a patient with AD doesn't really care about the disease being changed; instead, they want their symptoms to be better or for the disease to be stopped in its tracks. Consequently, we must consider how to significantly enhance cognitive and functional status during the symptomatic phase, or, if we are aiming for disease modification, how to significantly reduce functional decline. New targets that may enhance cognitive function independent of pathology have been found, and many targets that were originally thought to be untargetable have been effectively targeted. Many natural alkaloids continue to have significant effects when treating a variety of Neurodevelopmental Disorders (NDDs).

As a result, natural alkaloids have a variety of mechanistic methods for treating NDDs. We have studied on three drugs that is Alkaloid_C, Pepridine, Sanguinarine, the most effective drug is alkaloid C. Alkaloids are organic substances that are naturally occurring and largely found in plants, particularly in some flowering plants contain carbon, hydrogen, nitrogen, and oxygen only contains a small variety of alkaloids. It reduces the activity of the acetylcholinesterase (AChE) enzyme, increase levels of gamma-aminobutyric acid (GABA), and function as NMDA. It has been suggested that the selection of natural alkaloids in the treatment of NDDs is safe as compared to synthetic drug, natural alkaloids are inspiring hope for slowing the onset and progression of NDDs, it is imperative to design clinical trials for such substances that have not even been included in clinical trials to date.

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Conflict of Interest:
Nil

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