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Genomics and Drug Research Approach in Identifying Potential Drug Target Highlighting Alzheimer Disease

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ABSTRACT

Over the past few years research on Alzheimer's disease (AD) has been grown experimentally which is a neurodegenerative disease and the most common form of dementia that cause memory loss and affect the ability to think which can interfere with daily life. The main cause of AD is on the growth of plagues and tangles. AD is most commonly found in the age of 60s, starts with mild memory loss and other disabilities which lead the person to forget things on their daily life. In our research we are trying to identify potential natural based bioactive drug source compound using advanced computational biology to help in exploring clues for the treatment of AD patients using molecular docking method. BACE1 was screened as a potential target receptor in our study for the disease research. We also observed chromen-4-one as potent bioactive compound presenting high docking score of -5.60 Kcal/mol against BACE1 followed by other compounds. This identification will open new scope to future researchers to explore more bioactive compounds which may aid new treatment options against AD followed with wet lab experimentation.

Keywords: APP (Amyloid Precursor Protein), BACE1, Alzheimer disease, Neurodegenerative, Molecular docking, Hydrophobicity

INTRODUCTION

Alzheimer disease (AD) is a most common disease, predominately found in elder age group, which is a form of dementia caused by plaques and tangles. AD is considered as neurodegenerative disease that cause degeneration or loss of neurons in the brain and get shrunk. It is a serious problem which affects the ability to remember, imagine or learn. Nowadays every third person is facing this AD problems, which resulted our research objective to explore more on this disease, its type, causes, treatment and precautions. It depends on two factors, plaques (abnormal clusters of protein fragments) and tangles (made up of twisted strands of another protein). In a bi-

lipid cell membrane APP (Amyloid Precursor Protein) is present which helps in the growth and repair of neuron. APP is a single-pass transmembrane protein expressed at high levels in the brain and metabolized in a rapid and highly complex manner by a series of sequential proteases, including the intramembranous γ-secretase complex, which process other key regulatory molecules.

Half part of APP protein is inside the cell and half of it is present outside of the cell. Alpha secretase is a type of enzyme which cuts the APP protein at some particular points.[1] There is another enzyme known as gamma secretase which is also used to divide the APP protein into two parts. These sections were cut by the alpha and gamma secretase enzyme which are soluble in water that causes APP protein to be dissolved and new APP protein can be developed but when stimulation of beta secretase takes place it cannot be dissolved in water due to side cut which forms plaque. This plaque can obstruct the signals between neurons which produce inflammation leads to degeneration of neurons.

Tau protein can be found in neurons and one of its key roles is to support the microtubule highway system. In AD, tau proteins changes and become abnormally hyperphosphorylated which stop supporting microtubules. Instead, the tau protein binds with other tau proteins, forming long protein threads within the neuron. These threads become protein tangles and interfere with the neuron's ability to function. The proteolysis of APP protein by β- and γ-secretase activities[2] also incur with past research with identification of APP-cleaving enzyme 1 (BACE1) which is the major β-secretase responsible for plaque formation in the brain.[3-6] BACE1 is present in most of body tissues including brain highlighted it as important enzyme protein used as a biomarker for AD.[7-9]

With current advancement in bioinformatics and drug discovery research has opened new areas for exploring the treatment of AD with the help of system biology. In this research, we discovered target receptor BACE1 as potential drug target for AD, it inhibits Aβ production.[10] Bioactive compounds were extracted from plants which act as potent herbal medicine and helps to form a complex which can be used as drug for the treatment of AD. Further, docking studies were carried out in which BACE1 is best docked with chromen-4-one followed by some other bioactive compounds with positive potential result. To cross validate our docking research hypothesis we conducted computational based molecular dynamic (MD) simulation analysis to find potential drug compounds for futurist research.

MATERIALS & METHOD

Collection of data

The protein samples were selected on the basis of extensive bibliographic research literature resulting in identification of certain proteins that can play a vital role in target prediction which will help in the identification of treatment process in Alzheimer's disease. Target protein or receptor sequence was further extracted from universal public domain Uniprot database.

Homology modeling and physiological characteristics

The target protein sequence was exported to Swiss model server for homology modeling,[11] to determine the 3-dimensional structure. Further, the analysis of the physiochemical properties of target receptor were evaluated using Protparam tool for finding no. of amino acid, molecular weight and theoretical PI and GRAVY value.[12] With the help of SOPMA server secondary structure of target receptor was predicted.[13] Transmembrane properties study were carried out by SOSUI server[14] and Ramachandran plot was created by Procheck server.[15]

Receptor preparation

The protein files extracted from Swiss model were forwarded for receptor

preparation using UCSF Chimera.[16] Receptor preparation with Chimera was preceded further with the removal of residues such as ions, ligands and solvents from protein, for the next step SPDBV is used to carry the energy minimization of the protein. Finally, in receptor preparation pipeline chimera is again used to add hydrogen and charge to the protein then surface binding analysis is done and save the file as final receptor in default .pdb format.

Ligand Preparation

Extensive research literature study suggested us to explore various bioactive compounds that are present in environment as plants and herbs which are useful in the treatment of Alzheimer disease. We screened and downloaded various compounds from PUBCHEM[17] which leads into the library preparation. With the help of OSIRIS and DruLito software, we screened ADMET properties of bio active compounds. OSIRIS Property Explorer helps to design the chemical structures and calculates on-the-fly numerous drug-relevant characteristics to be reasonable for a candidate drug. Prediction results are valued and color coded. Properties with high prospects of unwanted results like mutagenicity or a poor intestinal immersion are shown in red whereas green color indicates drug- behavior.[18] DruoLito (Drug-likeness tools) rules are set of guidelines for the structural properties of compounds, used for fast calculation of drug-like properties of a molecule. These guidelines are not absolute, nor are they intended to form strict cutoff values for which property values are drug-like and which are not drug-like. Nevertheless, they can be quite effective and efficient.

Molecular docking

Molecular docking is a key tool in structural molecular biology and computer-assisted drug design. The goal of ligand-protein docking is to forecast the foremost binding mode(s) of a ligand with a protein of known three-dimensional structure. Docking can be used to perform virtual screening on large libraries of compounds.[19] The receptor BACE1 with target ligands were further subjected for docking studies in CHIMERA-Auto dock Vina. The docking studies states that the docked complex convey a high negative binding energy score ΔG which specify the concept of minimum energy and high security leading to best inter connection between proteins and the ligands. The obtained ligand-receptor docked complex was further predicted in Biovia Discovery studio to explain docking analysis between the bonds of ligands and receptors.

MD simulations

We use molecular dynamics (MD) simulation to computationally validate our analysis using iMOD server[20]. It is a computer program that stimulates the atomic behaviour of molecules.

RESULTS

Physiochemical property analysis of receptor

The analysis of the target receptor was selected on the basis of their GRAVY value in the ProtParam tool, BACE1 receptor was finally selected for target protein receptor study having GRAVY -0.064 shown in Table 1. With the help of SOSUI online tool amino acid sequences of the selected receptor BACE1 can help in the prognosis of the portion of secondary structure of protein shown in Figure 1. SOPMA is a tool to predict the secondary structure of protein which is based on the homologue methods for sequencing. The graph shows expected score curve and different patterns of coils, helix, sheet and turn shown in Figure 2 and Table 2. It also displays parameter like window width and the number states. The BACE1 sequence was also prepared for homology modeling study resulted in the generation of pdb structure for receptor design and docking studies as shown in Figure 3.

Table 1: Parameters computerized by using Expasy ProtParam tool

Protein	No of amino acids	Molecular weight	Theoretical pI	Instability index	Aliphatic index	Grand average of hydropathicity
BACE1	501	55763.79	5.31	44.23	88.14	-0.064

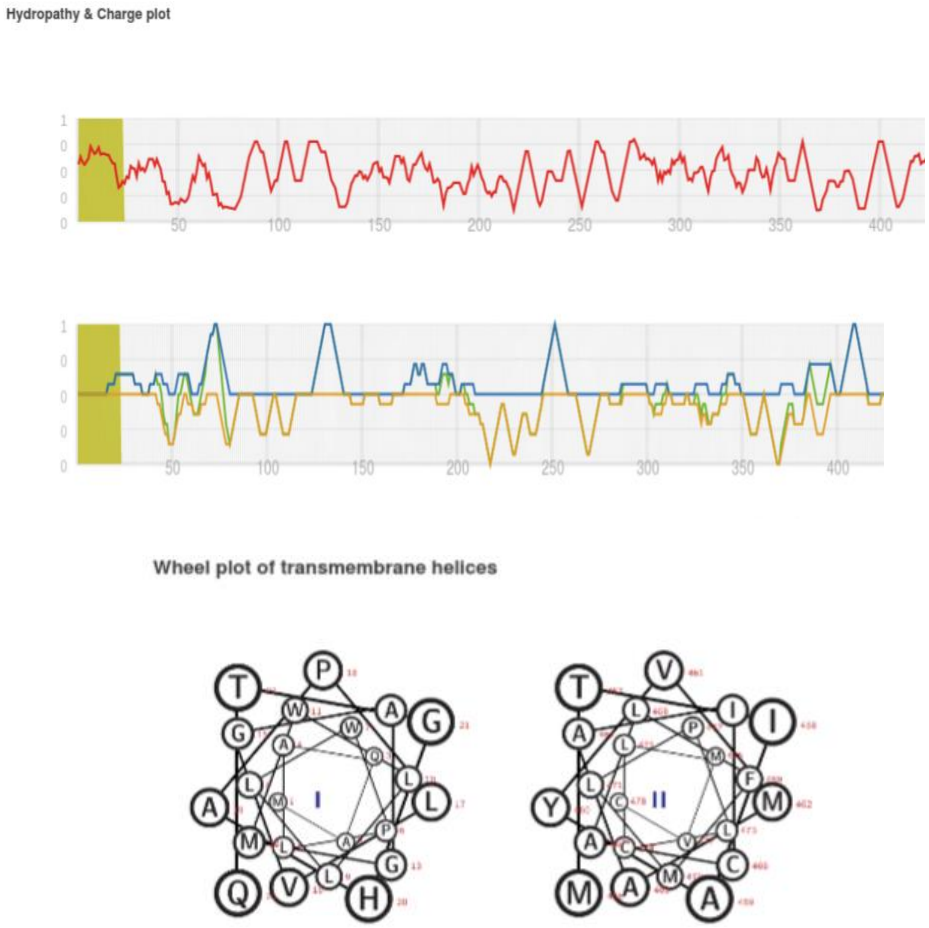


Figure 1: (a) Hydrophobicity of BACE1 receptor (b) Net charge density of BACE1 receptor (c) wheel plot of transmembrane helices.

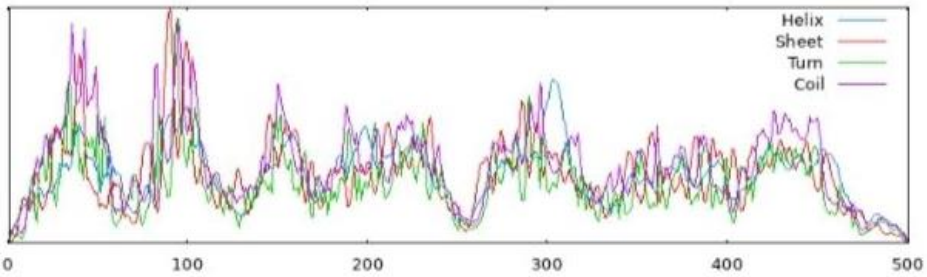


Figure 2: Showing the representational distribution of secondary structure prediction of BACE1 receptor having different pattern of Helix, sheet, turn and coil.

Table 2: Secondary structure elements calculated using SOPMA

Protein	BACE1
Alpha helix (Hh)	20.76%
310 helix (Gg)	0.00%
Pi helix(Ii)	0.00%
Beta bridge (Bb)	0.00%
Extended strand(Ee)	26.55%
Beta turn(Tt)	6.59%
Bend region(Ss)	0.00%
Random coil(Cc)	46.11%
Ambiguous State (?)	0.00%
Other states	0.00%

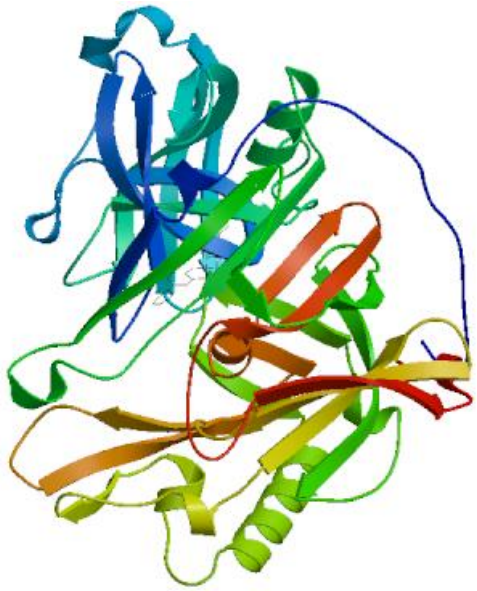


Figure 3: 3-dimensional protein structure of BACE1 receptor.

Screening of ligands

For our research analysis we extracted total 400 bioactive compounds which are Caffeic, Ferulic acid, Gallotannins, Procyanidins, Rhamentin, Acetylcholine, Bilobetin, Carotenoids, Donepeziel, Hydroxyethul starch, Isorhamnetin, L.Rhamnose, L.Glutamate, Luteolin, Memantine, Rivastigmine, Tacrine, Tamarixetin, Terpenoid etc. through Pubchem database. Moreover, OSIRIS and DruLito resulted in screening of the drug likeness and prepare libraries of these bioactive compounds. Finally, 20 bioactive compounds were extracted as ligands for molecular docking using AutoDock vina. Further, we evaluate the docking of these ligands with the selected receptor BACE1 and produced different docking scores; among these dockings we selected best five bioactive compounds or ligands. The ligands were selected with the parameters of higher the negative score which is directly proportional to high binding efficiency. Moreover, we use Pubchem to cross-check the chemical information of these five selected bioactive compounds such as Pubchem CID:16830 with ΔG -5.3 kcal/mol, Puchem CID:14546 with ΔG -5.3 kcal/mol and Pubchem CID: 16848 with ΔG -5.5 kcal/mol docking scores are the isomers of ferulic acid, Pubchem CID:10286 with ΔG -5.6 kcal/mol docking score is the isomers of rhamentin and Pubchem CID:23879 with ΔG -5.4 kcal/mol docking score is the isomers of caffeic shown in Table3 and Figure 4-8).

Table 3: Pubchem CIDs with IUPAC Name, Molecular Weight and Docking Scores.

Pubchem CID	IUPAC Name	Molecular Weight	Docking Scores
10286	chromen-4-one	146.14g/mol	-5.6
16848	3-(3,4-dimethoxyphenyl) prop-2-enoic acid	208.21g/mol	-5.5
23879	3-(3-chlorophenyl) prop-2-ynoic acid	180.59g/mol	-5.4
14546	3-(2,4-dichlorophenyl) prop-2-enoic acid	217.05g/mol	-5.3
16830	methyl 3-(4-hydroxy-3-methoxyphenyl) prop-2-enoate	208.21g/mol	-5.3

Figure 4: 2D and 3D structure of docking complex between BACE1 receptor and chromen-4-one through Biovia Discovery.

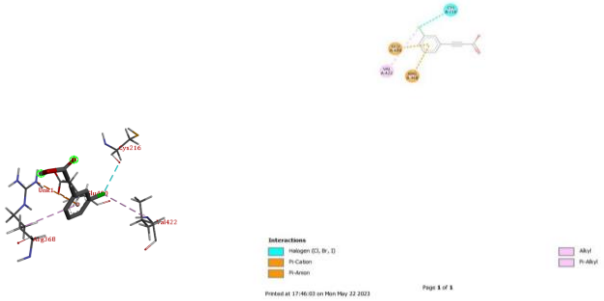


Figure 5: 2D and 3D structure of docking complex between BACE1 receptor and ligand 3-(3,4-dimethoxyphenyl) prop-2-enoic acid through Biovia Discovery.

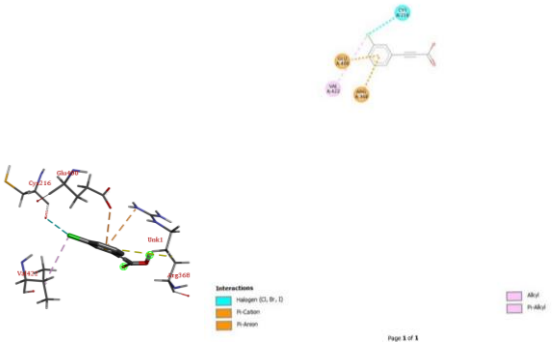


Figure 6: 2D and 3D structure of docking complex between BACE1 receptor and ligand 3-(3-chlorophenyl) prop-2-ynoic acid through Biovia Discovery.

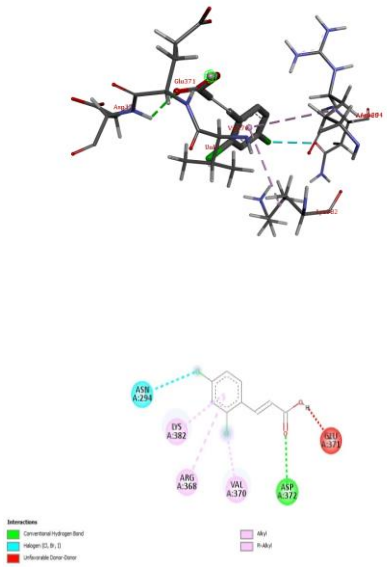


Figure 7: 2D and 3D structure of docking complex between BACE1 receptor and ligand 3-(2,4-dichlorophenyl) prop-2-enoic acid through Biovia Discovery.

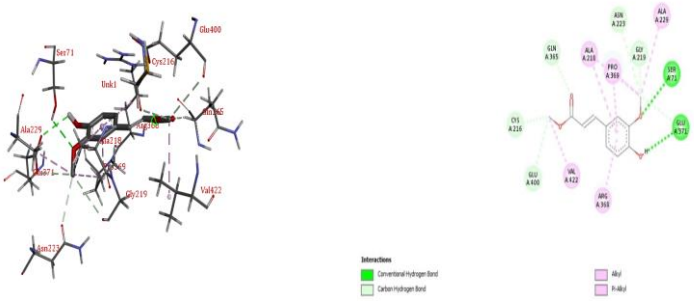


Figure 8: 2D and 3D structure of docking complex between BACE1 receptor and ligand methyl 3-(4-hydroxy-3-methoxyphenyl) prop-2-enoate through Biovia Discovery.

The best docking score having Pubchem CID 10286 with ΔG -5.6 Kcal/mol docking score was selected for further analysis by using iMOD server. The result obtained were graphs based on deformability, bfactor, atom index etc. The eigenvalue of Pubchem CID 10286 is 5.223176e-04 as shown in Figure 9-10.

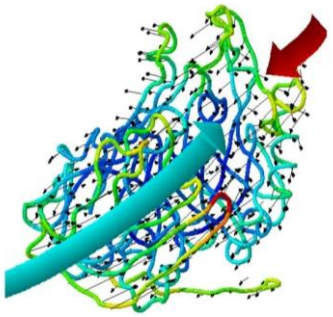
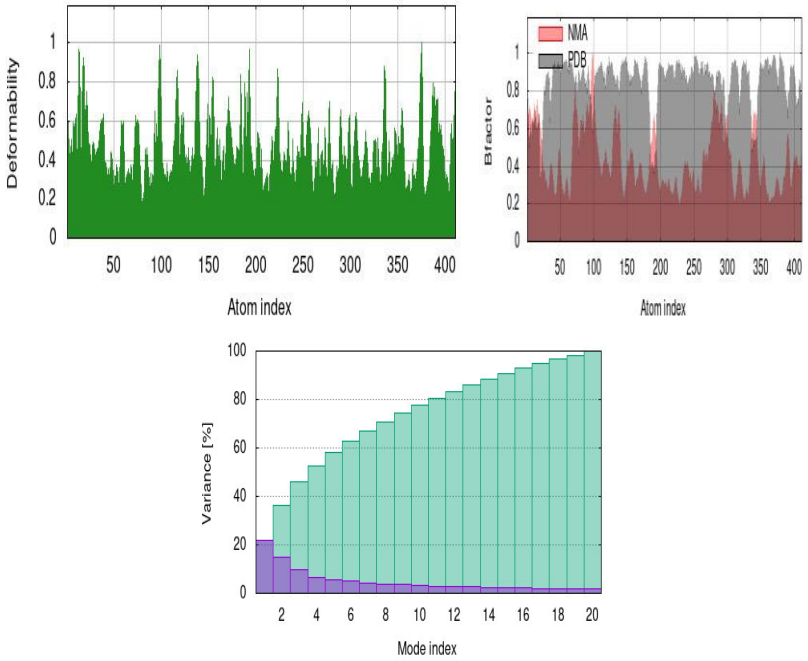


Figure 9: Showing 3D structure obtained from iMod server.



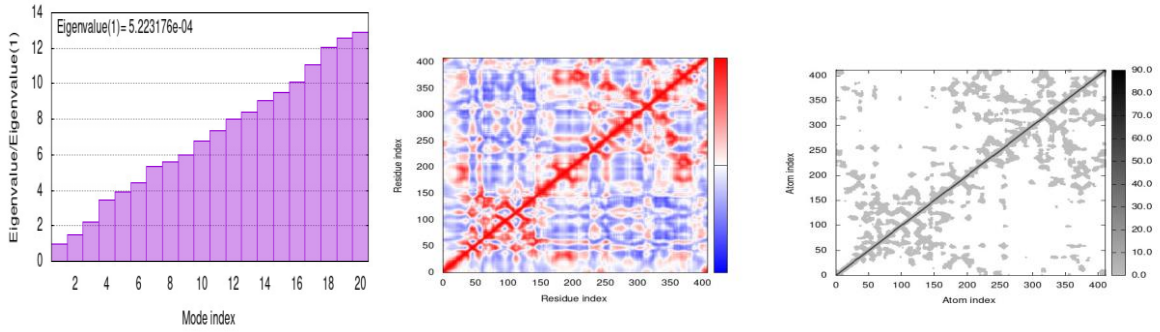


Figure 10: (a) Molecular dynamics simulations done through iMODS server of rhamentin against BACE1 receptor depicting (a) Deformability (b) bfactor (c)Varience (d) Eigenvalue 5.223176e-04 (e) Covarience matrix (f) Atom index.

DISCUSSION

AD is a progressive disease that destroys memories and other important cognitive functions. In our research we collected information of different properties of several bioactive natural compounds by using different web servers like SOPMA, SOSUI, DruLito, Prochecker[21], OSIRIS[22] and concluded that BACE1 act as a potential receptor that plays an important role in curing AD[23]. BACE1 inhibition together with other strategies, including immunotherapy which is designed to clear brain amyloid plaques or neurofibrillary tangles, is likely to be more effective in improving cognition in AD.

BACE1 receptor is essential for the generation of all monomeric forms of amyloid-β. BACE1 initiates production of β-amyloid peptides (Aβ), which is connected with reasonable disorder in Alzheimer's disease (AD) due to unusual oligomerization and accumulation.[23] In our study BACE1 receptor was finally selected for target protein receptor study having hydrophobic property with GRAVY -0.064 followed by secondary structure analysis. Similarly, various research studies on BACE 1 as a prime drug target for the remedial inhibition of Aβ production in AD. BACE1 inhibitors should offer benefit for AD patients and structural analysis of BACE1 inhibitor complexes has proved useful for drug development. [24]

Various dataset contain various compounds with different physical and chemical properties covering an extensive chemical space in drug like range. Screening of bioactive compounds such as Pubchem CID:16830 with ΔG -5.3 kcal/mol, Puchem CID:14546 with ΔG -5.3 kcal/mol and Pubchem CID: 16848 with ΔG -5.5 kcal/mol docking scores, Pubchem CID:10286 with ΔG -5.6 kcal/mol docking score and Pubchem CID:23879 with ΔG -5.4 kcal/mol docking score show active potential candidate drug compound in AD treatment. Similar research studies show antioxidant and anti-inflammatory properties with natural bioactive drug compound complex, Rasmarinic acid against CASP8 with a docking score of -8.0 kcal/mol and PTPN11 against Carnosol with a docking score of -9.1 kcal/mol helps in the treatment of AD. [25] Another, similar literatures shows variety of natural bioactive compounds having pure pharmacological moieties showing multitargeting activities and others exhibiting specific beta-site amyloid precursor protein-cleaving enzyme 1 inhibition have superior biosafety. [26] Many of these compounds, which are isolated from medicinal herbs and marine flora, have been long used for the treatment. Thus, with the use of this potential bioactive compounds like chromen-4-one with positive MD simulation provide us new research perception to explore more bioactive compounds against AD treatment followed by wet lab validations.

CONCLUSION

Several studies proposed that BACE1 inhibitor highlighted therapeutic potential for deceleration of long term progression of AD. In our study BACE1 protein was

selected as target receptor followed by docking studies against screened potential natural bioactive compounds like chromen-4-one as best docked complex. This computational bioinformatics based finding will explore more potential scope in exploring bioactive compounds against AD treatment and its cure followed by wet-lab experimental validation by futuristic researchers leading to effective new candidate drugs against AD.

Declaration by Authors

Ethical Approval: Not Applicable.

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Conflict of Interest: The authors declare no conflict of interest.

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