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Original Article

Molecular Modelling and Molecular Docking Studies of Natural Compounds against Parkinson disease

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ABSTRACT

The present study explains computational methods to design thermostable "Parkinson disease 7 domain-containing protein 1" of Homo sapiens enzyme using the sequence available from uniprot (UniProtKB – Q8NB37). Homology modelling study was performed to generate a 3D model of Cytochrome b protein. The model was developed by using Modeler9.17 software tool. The developed model was further docked with natural compounds such as Aaptosamine, Aaptosine, Aaptamine, Sesbanimide C using the AUTODOCK4.2 software tool. After designing the model molecular docking studies were performed by using Autodock4.2 with natural compounds to identify the functional effect of protein. The developed model shows above 90% of the amino acids in most favored region. The docking investigation of modelled "Parkinson disease 7 domain-containing protein 1" with natural alkaloids Aaptosamine, Aaptosine, Aaptamine, Sesbanimide C using Autodock4.2 software. Four natural alkaloids were docked against "Parkinson disease 7 domain-containing protein 1" protein. All the ligands show good binding energy and interactions. These studies provide understanding and interpreting the data produced by these methods. It explains to understand molecular interactions at the active site region.

Key words: Homology modeling, "Parkinson disease 7 domain-containing protein 1", Natural Alkaloids, Molecular Docking.

1. INTRODUCTION

Parkinson's disease (PD) was first coined by Dr. James Parkinson in 1817 as a "shaking palsy."[1] Parkinson's is a disease is a progressive neurological disorder of the nervous system that most people are over 50 years, although it can occur in younger patients. PD develops later stages in life and is characterized by loss of dopaminergic neurons in the SNpc (substantia nigra pars compacta).[2] It is the second most common neurodegenerative disease worldwide[3]. Manifests

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as a tremor, slowed movement (bradykinesia), muscular stiffness, muscle rigidity and difficulty with balance and walking[4]. The disease is common form of parkinsonism[5]. There is no particular test for the diagnosis of Parkinson's disease. It must be diagnosed based on clinical criteria[6]. The main problem to developing neuroprotective remedies is a limited understanding of the main molecular events that provoke neurodegeneration[7]. Several factors contributing to parkinson's disease, they are lysosomal dysfunction, autophagy and mitrochondrial dysfunction which comes under cell autonomous processes. Neuro inflammation, trans synaptic transmission of abnormal proteins and loss of trophic support comes under non cell autonomous processes.[8]

In the present study, an effort was made to generate the 3D structure of the parkinsons protein sequence (Uniprot accession number: Q8NB37) from Homo sapiens. Modeller9.17 was used for the homology modelling. The model was validated by using PROCHECK. Present study could provide useful information to get the functional characterization of these enzymes.

2. METHODOLOGY

Homology modelling

The amino acid sequence of Parkinson disease 7 domain-containing protein 1 was retrieved from Uniprot[9]. A three dimensional model was generated for "Parkinson disease 7 domain-containing protein 1". A sequence similarity search was performed to identify the structural similarity of the query sequence by using Protein BLAST[10] tool by selecting database against Protein Data Bank (PDB) for identifying template for homology model building[11]. The template was identified on the basis of smaller the e-value, >30% identity, maximum score. 1U9C protein was selected as a template for modeled protein. Comparative sequence alignment studies were performed with query and template structure using ClustalX tool and online ClustalW tools[12].

MODELLER9.17 software was used to develop the model. It is an automated approach to comparative modeling by satisfaction of spatial restrains[13]. To align the query and template sequences manually the input file of alignment.ali was used in MODELLER 9.17. After completion of alignment twenty models were generated and all the generated models were thermodynamically minimized using molecular dynamics and simulation approach. By implementing MODELLER9.17 automodel class, calculated 3D models of the target automatically. The best model which is having smallest value was selected on the basis of Lowest Objective Function. It is also known as normalized Discrete Optimized Molecule Energy (DOPE) score. Generate model was then checked in detail for protein structure stereochemistry including Ramachandran plot and Psi/Phi angles using PROCHECK.[14]

Molecular docking studies

All the natural alkaloid molecules were collected from scientific literature and sketched in SYBYL6.7[15] and energetically minimized by adding. The molecules were then saved in .mol2 format for molecular docking purpose.

Molecular docking studies were performed to explain the binding mode of proteins and alkaloid complexes. All the plant derived complex molecules were docked by using Autodock 4.2 software[16]. All the molecules were docked individually in Autodock4.2. The modelled three dimensional structure of Parkinson disease 7 domain-containing protein 1 protein was imported to Autodock 4.2 and structurally optimized by adding hydrogens to protein allocated with kollaman charges[17]. After adding the hydrogens the model was saved in PDBQT format, later ligands were prepared by optimizing the torsion angles and saved them in PDBQT format. Potential binding site for the Parkinson disease 7 domain-containing protein 1 modelled protein was identified using 3Dligand site[18]. A grid was generated around to identify xyz coordinates (X=21.868, Y=5.384 and Z= 39.33), around binding site of Parkinson disease 7 domain-containing protein 1 protein. Lamarckian genetic algorithm (LGA) was selected for freezing, docking and default parameters used in autodock4.2.

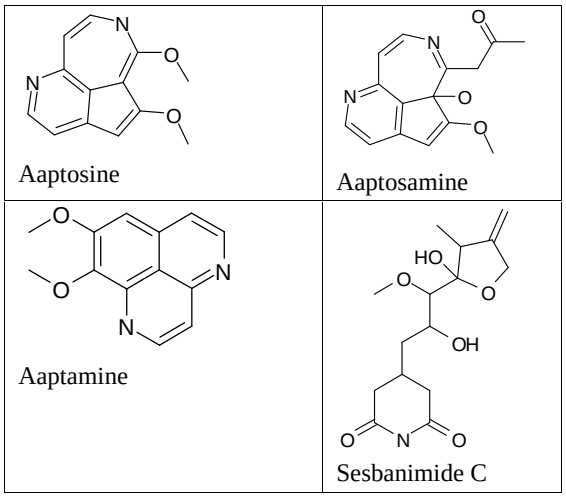


Fig 1: Structures of alkaloids used in the present study

Aaptosine (1,9-Dimethoxy-8H-5,8-diaza-benzo[cd]azulene), Aaptosamine (1-(9a-Hydroxy-1-methoxy-9aH-5,8-diaza-benzo[cd]azulen-9-yl)-propan-2-one), Aaptamine (8,9-Dimethoxy-1H-benzo[de][1,6]naphthyridine), Sesbanimide C (4-[2-Hydroxy-3-(2-hydroxy-3-methyl-4-methylene-tetrahydro-furan-2-yl)-3-methoxy-propyl]-piperidine-2,6-dione)

Electrostatic distribution of the modeled surface:

The electrostatic potential distribution of the modeled 3D structure of Parkinson disease 7 domain-containing protein 1 was analyzed by UCSF Chimera, a highly extensible programme for analysis of molecular structure [19]. It uses C++ code for color calculations. Electrostatic surface mapping of Parkinson disease 7 domain-containing protein 1

was performed for a distribution and charge related properties of molecules and the surface of Parkinson disease 7 domain-containing protein 1 was color coded as per the Coulomb's law.

ASA versus residue Number plot:

Accessible surface area of amino acid residues in a protein helps for localization of active sites. A characteristic 2D spiral plot of solvent accessibility provides a convenient graphical view of residues in terms of their exposed surface areas. In addition sequential plots of bar charts are also provided by the tool for each amino acid residues with the color coding corresponding to their location i.e. either in the surface or in the core. ASA plot of Parkinson disease 7 domain-containing protein 1 was done by ASA-View a database and tools for the solvent accessibility representation in proteins[20].

3. RESULTS AND DISCUSSION

After sequence alignment and homology modeling Parkinson disease 7 domain-containing protein 1 shows highly conserved regions in amino acid sequences. The most homologous template for building a homology model for Parkinson disease 7 domain-containing protein 1 was identified through protein blast algorithm. Based upon the homology search, Crystallographic structure of APC35852, *from* Geobacillus stearo thermophilus (PDB entry: 1U9C) was selected as a template. Twenty models were generated using Modeler 9.17 program. The alignment file was tweaked manually to excellent fit in the sequences. After the generated models for all the primary sequences, the model with least object function was selected for further protein stereochemistry evaluation (phi and psi angles) with Procheck software. Figure 2, 3 and 3a shows Super pose of model and template structures with backbone trace and the cartoon of homology derived protein of Parkinson disease 7 domain-containing protein 1 and Ramachandran plot statistics.

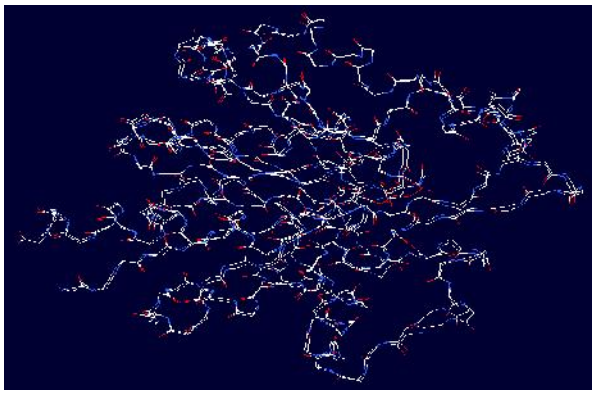


Fig 2: Super pose of model and template structures with backbone trace. The models were superimposed by using swiss pdb viewer (spdbv).

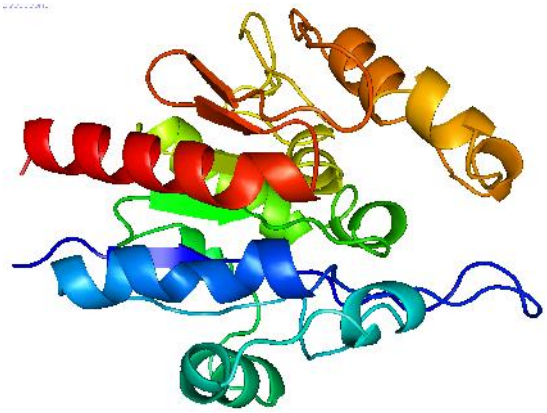


Fig 3: The cartoon of homology derived protein of parkinson's protein

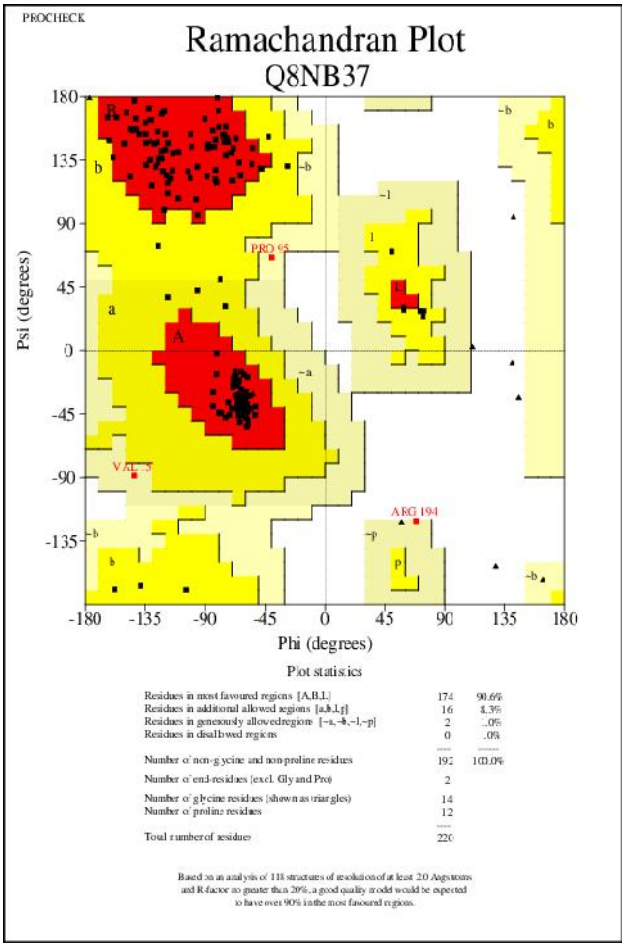


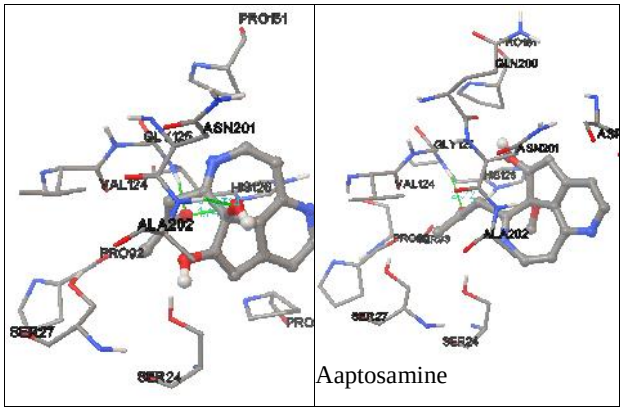
Fig 3(a): Ramachandran Plot of modelled protein

The three (Ø, Ψ and ω) backbone torsion angles are important determinants of a protein fold. PROCHECK software generates a number of scatter plots, these are known as Ramachandran plots. These plots show complete residue by residue data and the assessment of the generally excellence of the producing structure as compared to well refined structures of the same resolution [26]. The Ramachandran plot is the main indicator to check the intrinsic quality of the protein structure. The Ramachandran plot of the 1U9C shows 178 amino acid residues (93.7 %) in

most favorable regions with 11 amino acid residues (5.8 %) falling into additionally allowed regions, and it shows one amino acid in disallowed region (0.5%), whereas for the modeled protein shows, 174 amino acid residues (90.6 %) in the most favorable region, 16 amino acid residues (8.3 %) and amino acid residue present in generously allowed region (1.0%). There is no amino acid residue present in disallowed region. These results clearly indicate that the generated protein model is more conformationally superior to the template structure. The modeled structure was superimposed with the template 1U9C by using SPDBV, it was observed that RMSD value on superposition of the modeled structure of Parkinson disease 7 domain-containing protein 1 with the template structure was also calculated.

Molecular docking of plant secondary metabolites into the binding site of a receptor and estimating the binding affinity of the ligand is a most important part of the structure based drug design process. The molecular docking results indicate that all of the studied alkaloid compounds occupy an almost similar space in the binding site. Aaptosine shows best possible binding mode against modelled parkinson's protein is illustrated in Figure 4. During the molecular docking procedure, the program selects only best fit active site pocket of the protein with respect to the ligands in order to dock them. AutoDock 4.2, provides information on the binding orientation of ligands at the active site region. The docking program place both ligand and protein in different orientations, conformational positions and the lowest energy confirmations which are energetically favorable are evaluated and analyzed for interactions. Free energies of binding (ΔGb) and dissociation constants (Ki) as calculated by AutoDock are summarized.

For all the molecules binding affinity was characterized by binding energy (ΔG) value. Ligand Aaptosine shows highest binding energy of -5.76 kcal/mol with interacting His126 with distance of 2.012 Å. Aaptosamine interacts with two amino acid residues His126 and Ala202 with a docking score of -5.18 kcal/mol. Aaptamine shows binding energy of -5.15 kcal/mol with interacting Ser24 and Sesbanimide C shows -4.58 kcal/mol score. Among 4 metabolites Aaptosine shows best binding energy and interactions. All the docking poses of the molecules were shown in Figure 4.



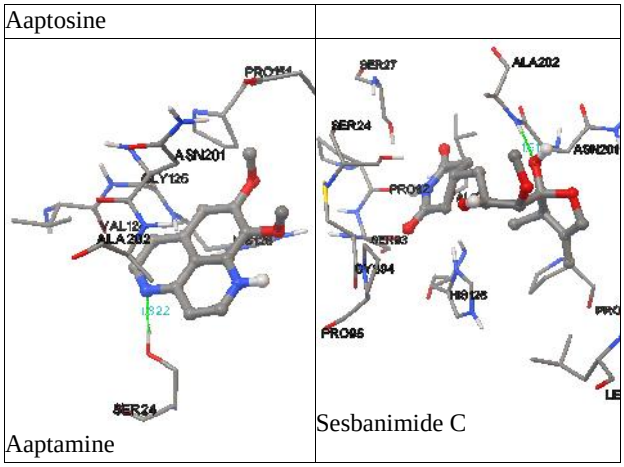


Fig 4: Docking interactions of parkinson's with Aaptosine, Aaptosamine, Leucocyanidin, Aaptamine and Sesbanimide C

ASA describes structure stability receptor binding mode of the protein. ASA vs residue number plot by ASA-View the colors are coded as Red for Negative charged residue (D,E), Blue for Positive charged residues (R, K, H), Yellow for Cystein and Gray for Hydrophobic residues (All others), Green for Polar uncharged residues (G, N, Y, Q, S, T,W) for both model and template. Relative solvent accessibility plots in the original order of the residues of both model and template. Figure 5. Hydrophobic residues and polar uncharged residues are more in the modelled protein.

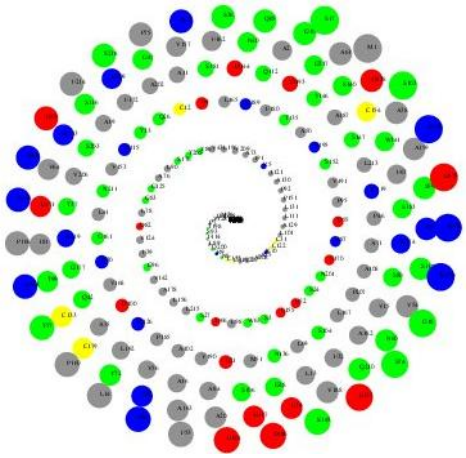


Fig 5: ASA vs residue number plot by ASA-View the colors are coded as Blue for Positive charged residues (R, K, H), Red for Negative charged residue (D,E), Green for Polar uncharged residues (G, N, Y, Q, S, T,W), Yellow for Cystein and Gray for Hydrophobic residues (All others) for template.

Electrostatic surface distribution of the modeled surface (by UCSF Chimera) the surface were color coded as per the standard protocol of UCSF Chimera, each amino acids were marked with standard code (red for negative potential, to white near neutral, to blue for positive potential). UCSF Chimera showed that parkinson's protein has more positive charge residues displayed in blue color (figure 6) on the outer surface suggesting the fact that the

residues are the part of the conserved domain which have specific functionalities i.e. receptor binding.

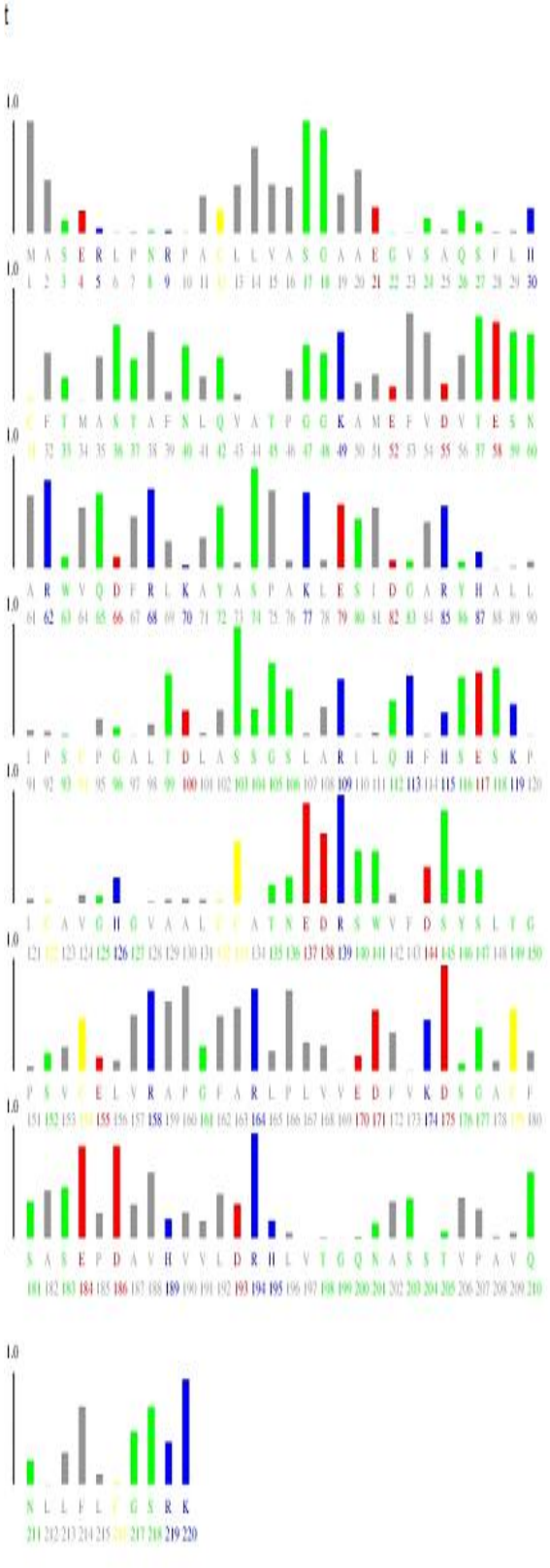


Fig 6: Relative solvent accessibility plots in the original order of the residues of the modelled protein

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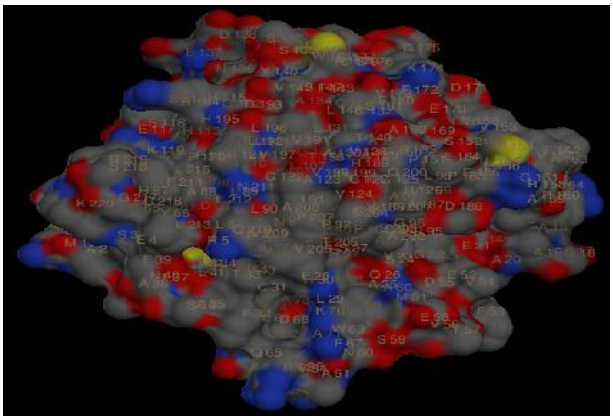

Fig 7: Electrostatic surface distribution of the modeled surface (by UCSF Chimera) the surface were color coded as per the standard protocol of UCSF Chimera, each amino acids were marked with standard code (blue for positive potential, white for neutral potential and red for negative potential).

4. CONCLUSION

In this work, homology modeling and molecular docking studies were performed to explore structural features and binding mechanism of alkaloid derivatives as Parkinson disease 7 domain-containing protein 1 inhibitors, and to construct a model for designing new Parkinson disease 7 domain-containing protein 1 protein. Homology derived model statistics are similar to template i.e., crystal structure. Docking the modelled Parkinson disease 7 domain-containing protein 1 protein with natural compounds provided insight into the binding and interaction of compounds with the enzyme. Further, the structure based drug discovery process along with protein information of drug targets may improve our understanding towards in-sight of mechanism of protein-ligand interactions and their binding patterns.

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