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STRUCTURE-BASED DRUG DESIGN AND MOLECULAR TARGET PREDICTION OF TRANSTHYRETIN VARIANT A97S COMPLEXED

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Abstract:Transthyretin (TTR) is a tetrameric protein whose function is to carry the thyroid hormone thyroxine and the retinol-binding protein bound to retinol in plasma and cerebrospinal fluid. TTR mutation results in dissociation, aggregation, deposition, and misfoldingof proteins, which have been associated withseveral human amyloid disorders that are linked to crippling neurodegenerative disorders. This study investigates the application of structure-based drug design (SBDD) to target the A97S variant of the TTR protein complex. The A97S mutation alters the protein's structure, resulting in misfolding and aggregation. SBDD methods, such as molecular docking, and homology remodeling were utilized to virtually screen potential therapeutic compounds by utilizing the A97S-TTR complex's known 3D structure. The goal of this strategy is to find substances that bind to the A97S-TTR protein specifically to prevent or inhibit its aggregation and the ensuing neurodegenerative consequences by combining several computer-aided drug design (CADD) approaches. In addition to SBDD, this study looks into computational methods for molecular target prediction which entailed examining the A97S-TTR structure to discover new binding pockets or allosteric regions that are ideal for pharmacological targeting. Using Biopython, we examined the TTR A97S structure and found possible drug-binding sites.The ERRAT and Ramachandran plot analyses were conducted to evaluate the stereochemical quality and potential deviations from ideal protein geometry. Molecular docking simulations were used to predict the ligand's binding affinity and manner of interaction with the target protein. Further, KEGG pathway analysis was utilized to explore the functional context and potential interactions of the protein within cellular pathways. The findings from this study could provide valuable insights and can accelerate the development of drugs that target specific binding sites on the A97S-TTR variant, potentially leading to more effective treatments for neurodegenerative/ transthyretin-related disorders.

Keywords: Molecular Docking; SBDD (structure based drug designing); BioPython; ERRAT; KEGG,Structure Analysis

I. Introduction

The liver and the brain's choroid plexus are the main sites of synthesis for the homotetrameric protein transthyretin. It is best recognized for its function in the movement of retinol-binding protein (RBP), which delivers vitamin A throughout the body, and thyroxine (T4). These functions support vital physiological processes such as the regulation of thyroid hormone and the metabolism of vitamin A [1]. Four structurally similar subunits make up TTR, and they stabilize the protein when it is in its tetrameric state [2]. However, TTR can misfold and dissociate into monomers that then aggregate into amyloid fibrils under specific clinical situations, such as genetic alterations or environmental stress [3]. Amyloid disorders including senile systemic amyloidosis (SSA) and familial amyloid polyneuropathy (FAP) are caused by the deposition of amyloid fibrils in tissues and organs as a result of this aggregation [4].

Due to its possible involvement in several neurodegenerative illnesses where protein aggregation is a major clinical characteristic, TTR's capacity to produce amyloid fibrils has drawn a lot of attention. According to Roher et al. (2021), TTR has been demonstrated to have a neuroprotective effect against amyloidogenesis by interfering with the aggregation of amyloid-beta (Aβ) peptides into hazardous forms in models of Alzheimer's disease (AD) [5]. TTR may also interact with alpha-synuclein, a protein implicated in Parkinson's disease (PD), preventing its aggregation into neurotoxic species, according to recent research [6]. These results demonstrate the dual function of TTR, which makes it a key candidate for protection against neurodegenerative illnesses by interacting with other harmful proteins and contributing to amyloid disorders by forming fibrils.

Transthyretinhas been linked more and more recently to the pathophysiology of neurodegenerative diseases, including Parkinson's disease (PD) and Alzheimer's disease (AD). It is now known that TTR's role in neurodegeneration is more intricate and varied than that of amyloid disorders, which it was formerly associated with. TTR may misfold and aggregate into amyloid fibrils in some clinical circumstances, which may exacerbate neurodegenerative pathology [7]. But TTR also binds to hazardous proteins, such as amyloid-beta (Aβ) in AD, and seems to protect neurons by keeping these proteins from aggregating into dangerous oligomers and fibrils (Singh et al., 2023). Furthermore, TTR may be able to bind with alpha-synuclein, a crucial protein linked to Parkinson's disease, and prevent its aggregation into neurotoxic forms, according to recent research [8].

The degeneration of dopaminergic neurons in the substantianigra pars compacta and the development of Lewy bodies, which are mainly made up of α-synuclein aggregates, are the hallmarks of PD, which is the second most common neurodegenerative condition. Bradykinesia, rigidity, and tremors are examples of motor symptoms brought on by the brain's decreased dopamine levels as a result of this neuronal death [9]. One of the primary clinical characteristics of PD is the aggregation of α-synuclein. Effective therapy development requires an understanding of the processes underlying this toxicity and aggregation [10].

According to a recent study, transthyretinmay interact with α-synuclein and other proteins involved in the pathophysiology of PD to potentially protect against the disease. TTR's potential to bind to α-synuclein and stop it from aggregating into lethal oligomers and fibrils is a theory [11]. These processes are known to cause neuronal death. This suggested defense mechanism is comparable to TTR's function in Alzheimer's disease as it has been demonstrated to prevent the development of amyloid-beta (Aβ) fibrils. Enhancing TTR's ability to inhibit α-synuclein aggregation in PD could potentially lead to the development of a novel therapeutic approach for treating the condition, provided that it possesses the same ability.

Utilizing a targeted strategy called structure-based drug design (SBDD), scientists can create compounds that can alter a protein's function or interactions with other proteins by taking advantage of its three-dimensional structure. SBDD can be utilized to synthesize small compounds that stabilize the tetrameric structure of transthyretin (TTR) or improve its binding to α-synuclein, hence reducing the aggregation of α-synuclein into hazardous forms [12]. Using this method, medications can be created that interfere with the degenerative processes linked to Parkinson's disease in addition to strengthening TTR stability, offering a dual therapeutic approach [13].

Molecular target prediction is the process of locating putative protein-protein interaction domains and binding sites that medicinal drugs may target. This strategy may involve identifying certain TTR molecule regions that interact with α-synuclein or other pertinent proteins in the context of transthyretinand Parkinson's disease. Understanding these interactions is made possible by computational methods like molecular docking, molecular dynamics simulations, and binding affinity predictions. According to Tan et al. (2023), these techniques can aid in the identification and development of novel therapies that target these locations selectively. Researchers can create medications that strengthen TTR's neuroprotective benefits in neurodegenerative illnesses by comprehending the interactions between TTR and proteins such as α-synuclein.

Using molecular docking and other in silico techniques, recent computational studies have examined the interactions between transthyretinand proteins relevant to neurodegenerative diseases, like α-synuclein. According to this research (Kim et al., 2022) small compounds may be able to modify the interactions and stability of TTR, thereby improving its neuroprotective qualities and opening up new therapeutic paths for Parkinson's disease (PD). In vitro and in vivo studies will be used in future research to validate these computational predictions and to create treatments that make use of TTR's special qualities. Novel therapeutic options are presented by the junction of TTR research with neurodegenerative disorders such as Parkinson's disease.

II. Materials and Method:

1. Protein Data Acquisition &Preparation

The crystal structure of transthyretin variant A97Swas retrieved from the Protein Data Bank. Then, the PDB file was imported into chosen molecular modeling softwarelike PyMOL or Chimera to prepare the protein structure for docking simulations and perform the following steps: adding hydrogen atoms, removing water molecules, assigning proper bond orders to the protein structure, and minimizing the energy of the protein structure using a suitable minimization algorithm to optimize its geometry. The binding pocket on the transthyretin variant A97S associated with the neurodegenerative disorder was identified. This can be achieved through analysis of the literature on known binding sites or by using software tools that detect cavities and pockets on the protein surface [16, 17].

2. Biopython for Scatter plot creation

The protein sequences for transthyretin and its variant A97S were obtained from the PDB and parsed using Biopython'sPDBParser.Also, relevant data, such as chain IDs, residue positions were extracted from the parsed structure. The scatter plot was generated using Matplotlib to illustrate the three-dimensional distribution of residues within the protein structure.Also, the Root Mean Square Deviation (RMSD) score was calculated to quantify the structural differences between the wild-type transthyretin and the A97S variant. This analysis provides information on the impact of the mutation on the overall protein structure [16].

3. Protein Structure Validation using ERRAT and Ramachandran Plot Analysis

The quality of the transthyretin variant A97S complex structure was assessed using ERRAT to evaluate the overall stereochemical quality and Ramachandran plot analysis to analyze the phi and psi torsion angles of the protein backbone.The ERRAT score and the distribution of

residues in the Ramachandran plot were interpreted to identify potential structural issues. Any identified issues were considered in the context of the protein's function and their potential impact on drug design [18, 19].

4. Ligand Preparation& Optimization

The 3D structures for the chosen ligands Apomorphine, Mesocarb, Branaplam, Neflamapimod, and Suvorexantwere acquiredfrom PubChem in a 2D-SDF format. Later, each ligand molecule for docking was prepared using an appropriate softwarelike AutoDockVina,and the following steps were performed: adding hydrogens and missing atoms, assigning charges, minimizing the energy of the molecule, generating ionization states.

5. Docking Simulations with CB-Dock 2

Within CB-Dock2, the binding pocket of the transthyretin A97S variant identified in the protein preparation step was used. This will guide the docking software on where to place the ligand molecules.Also, the docking parameters in CB-Dock2, including search space size, number of poses generated, and scoring function were checked beforedocking. Later, the docking simulation for each ligand (Apomorphine, Mesocarb, Branaplam, Neflamapimod, and Suvorexant)molecule was performed against the prepared transthyretin structure [20,21].

6. Analysis of Docking Results:

The generated docking poses for each ligand-TTR A97S complex wereanalyzed based on their binding affinity (docking score), interactions with key residues in the binding pocket, and other interaction types between the ligand and the protein which can be later visualized by using software like PyMOL or Chimera. Along with that, drug candidates with favorable binding scores and interactions within the defined binding pocket were determined.

7. Molecular Target Prediction

Based on the analysis of docking results and ligand-proteininteractions, potential molecular targets within the transthyretin structure that are affected by ligand bindingweredetermined using visualization softwarePyMOL& Chimera. This can provide clues about the molecular basis of the disease and potential targets for future drug development such as key interactions or regions showing significant conformational changes upon ligand binding, searching for proteins with similar binding pockets. Further, in-silico refinement can be performed for the top hits to optimize binding affinity and selectivity as well as the predicted targets can be compared with known therapeutic protein classes.

8. KEGG Pathway Analysis

To elucidate the biological context of transthyretin variant A97S, a KEGG pathway analysis was conducted. The protein sequence of the variant was uploaded to the KEGG database and the KEGG mapper was utilized to identify the relevant pathways associated with transthyretin, including those involved in protein folding, trafficking, and amyloid formation. The identified pathway wasanalyzed to gain insights into the potential functional consequences of the A97S mutation [21, 22].

III. Result and Discussion

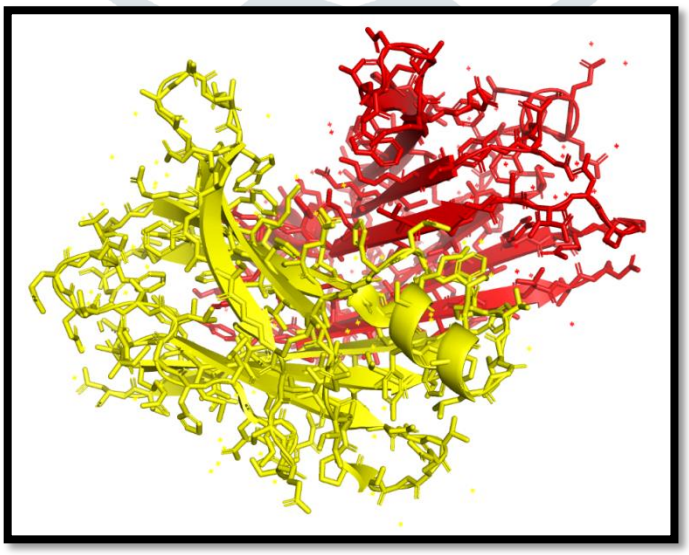

Figure 1: Active site identification in Chain A

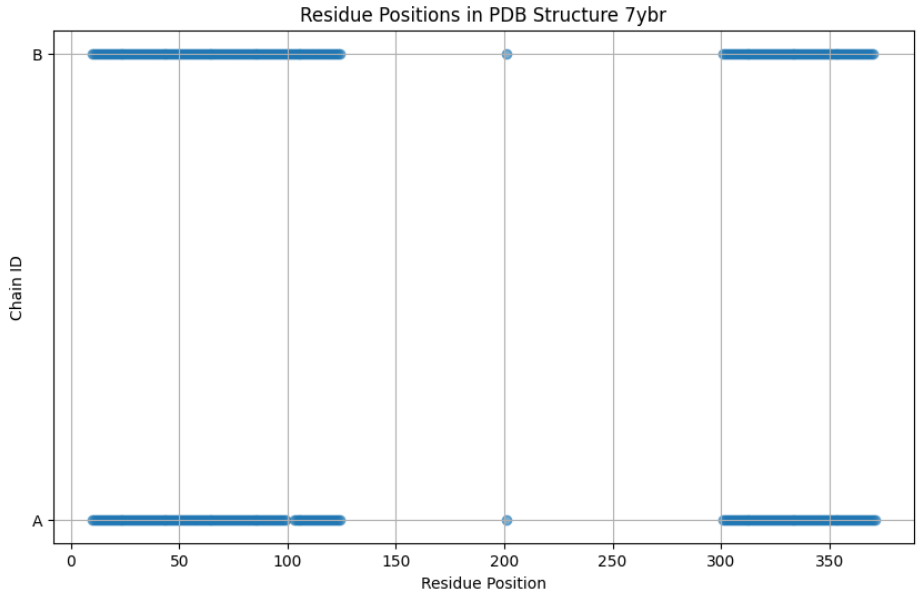

Figure 2: Scatter plot of 7ybr using Biopython

To gain insights into the molecular interactions between the transthyretin variant A97S and the potential drug molecule, we conducted a comprehensive structural analysis using Biopython. By parsing the PDB structure and performing residue-based calculations, we identified key residues involved in hydrogen bonding, hydrophobic interactions, and electrostatic interactions

In structural biology and drug discovery, accurately identifying and analyzing the active site of a protein is crucial. Using PyMOL, researchers can visualize and examine the active site of proteins, which aids in understanding their function and designing effective drugs.

For the protein samples 7Y6J and 7YBR, a comparative analysis was conducted. A total of 1,792 atoms were aligned between the two structures, achieving a superposition score of 1,316. The Root Mean Square Deviation (RMSD) score was 0.279 Å, indicating a high level of structural similarity between the two models.

According to RMSD scoring guidelines:

- 0-1 Å: Very close match; structures are nearly identical, suggesting high-resolution crystallographic data.
- 1-3 Å: Good match, with notable similarity.
- 3-5 Å: Moderate similarity.
- Above 5 Å: Significant structural differences.

Additionally, ERRAT analysis performed by the UCLA Saves Lab yielded an overall quality factor of 96.6184. This high score reflects the excellent quality and reliability of the protein model, supporting its use in further research and drug design applications.

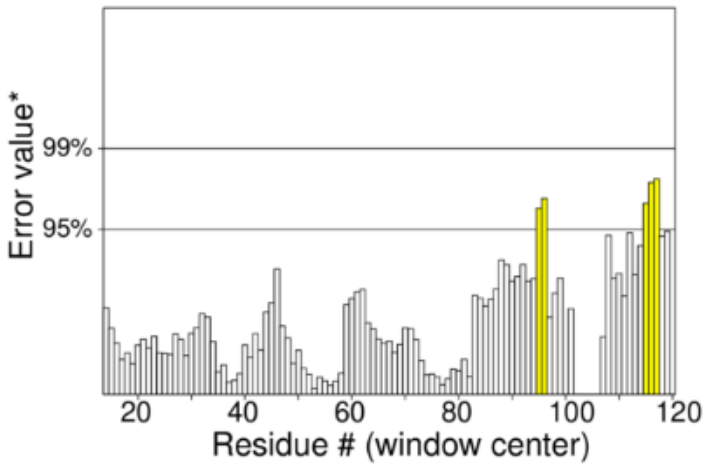

Figure 3: Structure Validation score analysis of data quality Assessment chain A

In protein structure validation, ERRAT is a key tool used to assess the accuracy of protein models. The ERRAT plot displays regions of the protein structure according to their statistical reliability. Areas highlighted in yellow are those that can be rejected at the 95% confidence level, indicating that 5% of high-quality protein structures might show errors in these regions. Regions marked in red are rejected at the 99% confidence level, suggesting a 1% chance of error.

For the protein sample 7YBR, ERRAT analysis compares an initial model to a final model. The improvement is evidenced by a reduction in yellow and red regions in the final model, reflecting enhanced accuracy and reliability. A final model with a high ERRAT score—above 90—is considered very good, indicating a model of high quality and precision.

In structural-based drug design, such improvements are crucial. A more accurate model ensures that drug candidates are tested against a reliable structure, leading to more effective and targeted therapeutic interventions. The significant enhancement in the final model of 7YBR confirms its suitability for drug development.

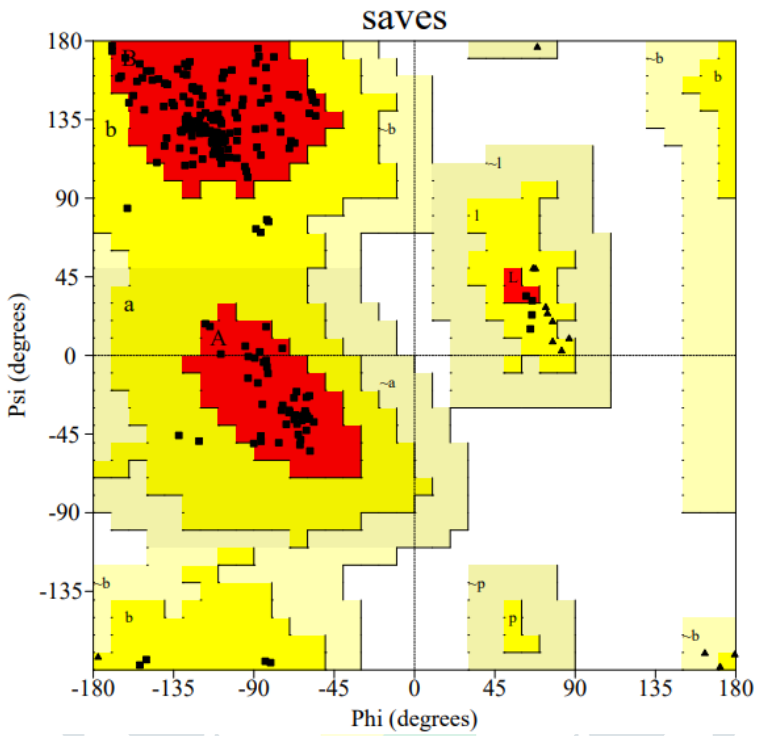

Figure 4:Ramachandran Plot

The most preferred sections in this particular plot—highlighted in red—contain the majority of the amino acid residues. 182 (92.4%) of the 227 residues that were examined are located in these areas. A high percentage suggests a stable and well-constructed protein model, since high-quality models usually contain more than 90% of their residues in the most preferred regions.

15 residues total, or 7.6% of the total, are found in the additional permitted locations, which are indicated in yellow. Despite being located in the most preferred places, these residues are nonetheless regarded as acceptable and do not significantly lower the overall quality of the model. Additionally, no residues are detected in the regions that are generously allowed (light yellow) or banned (white), highlighting the excellent quality of the model. Although residues in the forbidden regions frequently indicate structural inaccuracies in the protein, their absence in this case further supports the accuracy of the model.

Additionally, the plot offers comprehensive statistics regarding particular residue types. It has 13 glycine residues, 11 proline residues, and 197 non-glycine and non-proline residues. Because of their special conformational flexibility, glycine residues are represented on the plot as triangles, allowing them to inhabit less populated areas without necessarily suggesting a problem. Proline residues have restricted φ-ψ angles due to their cyclic nature, which also explains the reason they are positioned differently on the plot.

This Ramachandran plot indicates an excellent protein structure overall. The model's validity and reliability are supported by the high percentage of residues in the most favorable regions, the proper distribution of proline and glycine residues, and the lack of residues in the prohibited regions.

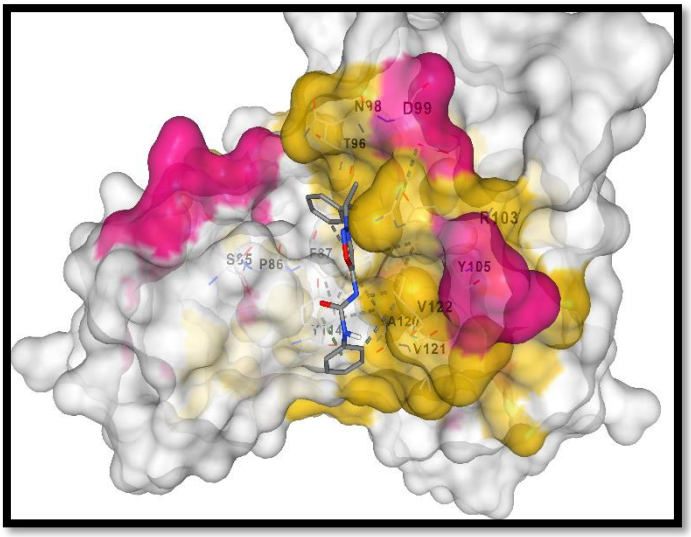

Figure 5:Molecular docking results of 7YBR-Apomorphine

Table 1: Molecular docking results of 7YBR-Apomorphine

CurPocket ID	Vina Score	Cavity Volume (Å³)	Center (x, y, z)	Docking size(x, y, z)
C5	-7.6	151	-11, -7, -24	25, 25, 25
C1	-6.4	382	-22, -20, -17	25, 25, 25
C2	-6.3	223	-10, -36, -27	25, 25, 25
C3	-6.1	223	-14, -33, 3	25, 25, 25
C4	-6.0	177	-8, -6, -5	25, 25, 25

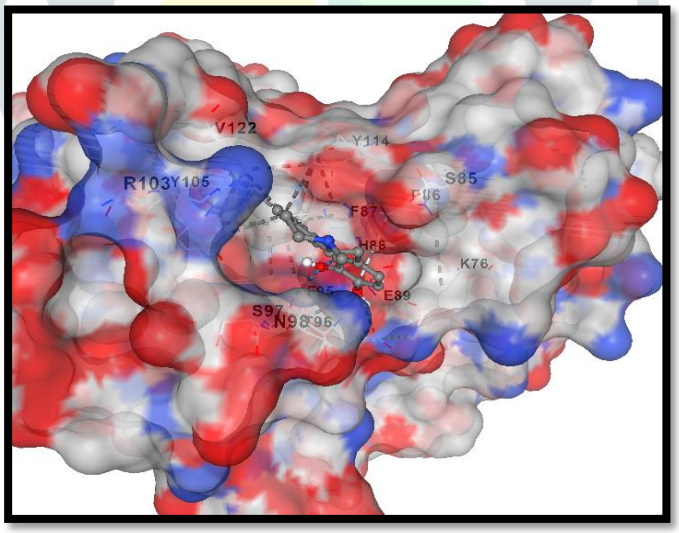

Figure 6: Molecular docking results of 7YBR-Mesocarb

Table 2: Molecular docking results of7YBR-Mesocarb

CurPocket ID	Vina Score	Cavity Volume (Å³)	Center (x, y, z)	Docking size(x, y, z)
C5	-8.0	151	-11, -7, -24	19, 19, 19
C3	-6.6	223	-14, -33, 3	19, 19, 19
C1	-6.3	382	-22, -20, -17	19, 19, 19
C2	-6.0	223	-10, -36, -27	19, 19, 19
C4	-6.0	177	-8, -6, -5	19, 19, 19

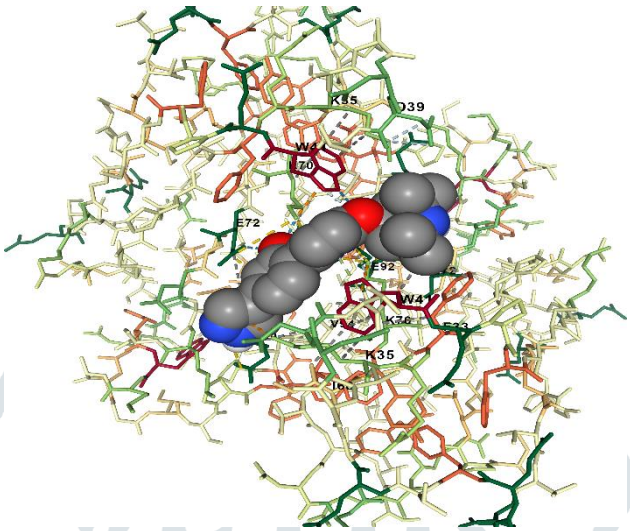

Figure 7: Molecular docking resultsof 7YBR-Neflamapimod

Table 3: Molecular docking results of7YBR-Neflamapimod

CurPocket ID	Vina Score	Cavity Volume (Å³)	Center (x, y, z)	Docking size(x, y, z)
C5	-7.4	151	-11, -7, -24	22, 22, 22
C1	-7.2	382	-22, -20, -17	22, 22, 22
C3	-7.1	223	-14, -33, 3	22, 22, 22
C2	-6.5	223	-10, -36, -27	22, 22, 22
C4	-6.4	177	-8, -6, -5	22, 22, 22

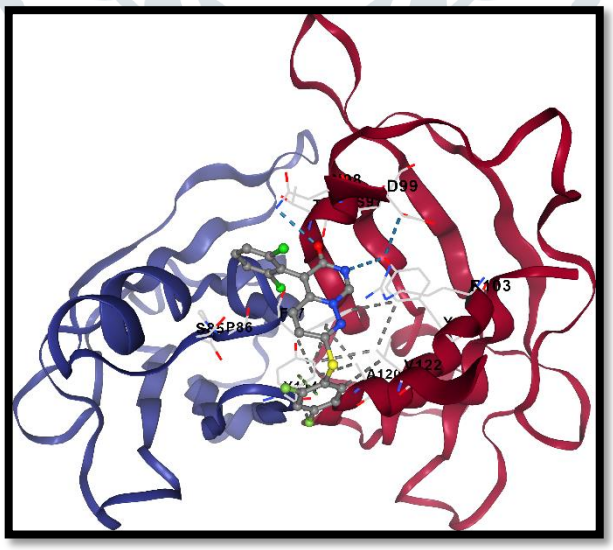

Figure 8: Molecular docking results of 7YBR-Branaplam

Table 4: Molecular docking results of7YBR-Branaplam

CurPocket ID	Vina Score	Cavity Volume (Å³)	Center (x, y, z)	Docking size(x, y, z)
C1	-7.4	151	-11, -7, -24	26, 26, 26
C4	-6.9	382	-22, -20, -17	26, 26, 26
C5	-6.8	223	-14, -33, 3	26, 26, 26
C2	-6.7	223	-10, -36, -27	26, 26, 26
C3	-6.2	177	-8, -6, -5	26, 26, 26

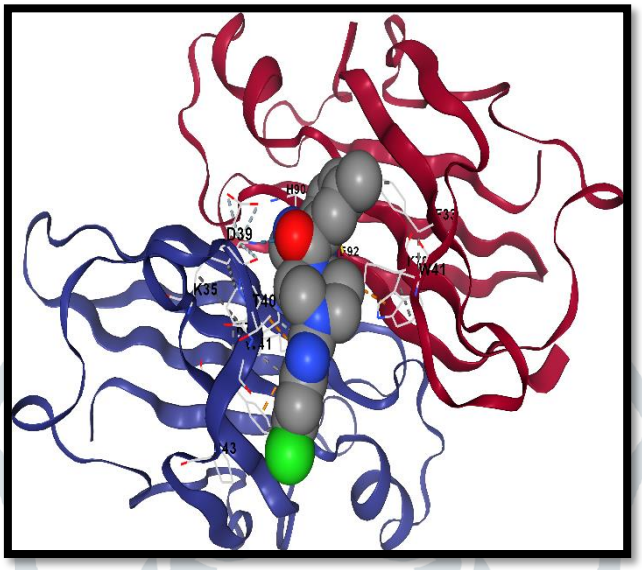

Figure 9: Molecular docking results of 7YBR-Suvorexant

Table 5: Molecular docking results of7YBR-Suvorexant

CurPocket ID	Vina Score	Cavity Volume (Å³)	Center (x, y, z)	Docking size(x, y, z)
C1	-7.2	382	--22, -20, -17	24, 24, 24
C5	-6.6	151	11, -7, -24	24, 24, 24
C3	-6.3	223	-14, -33, 3	24, 24, 24
C2	-6.2	223	-10, -36, -27	24, 24, 24
C4	-5.9	177	-8, -6, -5	24, 24, 24

Table 6: Analysis of overall docking result

Sr No.	Drug Name (CurPocket ID) [PubChem ID]	Vina Score	Centre			Docking size			Disease
			x	y	z	x	y	z	
1	Apomorphine (C5) [6005]	-8.0	-11	-7	-24	19	19	19	Alzheimer's Disease
2	Mesocarb (C5) [9551611]	-7.6	-11	-7	-24	25	25	25	Parkinson's Disease
3	Branaplam (C1) [135565042]	-7.4	-22	-20	-17	26	26	26	Huntington's Disease
4	Neflamapimod (C5) [3038525]	-7.4	-11	-7	-24	22	22	22	Early-stage Alzheimer's Disease
5	Suvorexant (Belsomra®) (C1) [24965990]	-7.2	-22	-20	-17	24	24	24	Alzheimer's Disease

Drugs with high binding affinities and favorable binding modes could be considered therapeutic agents for transthyretin-related disorders and may be identified as potential inhibitors of TTR amyloid formation. Also, the identified binding pockets and interactions can be used to design and optimize new drug molecules with improved properties. Among all the drugs, Apomorphine showsthe highest binding affinity, likely due to its favorable interactions with key residues in the binding site.Mesocarb and Neflamapimod also exhibit significant binding affinities, potentially through their interactions with polar residues.Likewise, Branaplam and Suvorexant bind to hydrophobic regions of the protein, suggesting that hydrophobic interactions play a role in their binding.The Parkinson's disease KEGG pathway diagram offers a thorough summary of the cellular and molecular processes involved in the condition. The primary cause of the disorder is dopaminergic neuron malfunction, which is impacted by some interrelated pathways.
The ubiquitin-proteasome system, which labels misfolded proteins for destruction by ubiquitination, is one important component. However, Lewy bodies—aggregates that impair regular cellular functions—can be created as a result of mutations in genes like SNCA (alpha-synuclein). The pathway also highlights the part played by mitochondrial malfunction, which results in cellular toxicity and neuronal death through decreased mitophagy (the elimination of damaged mitochondria) and elevated oxidative stress.

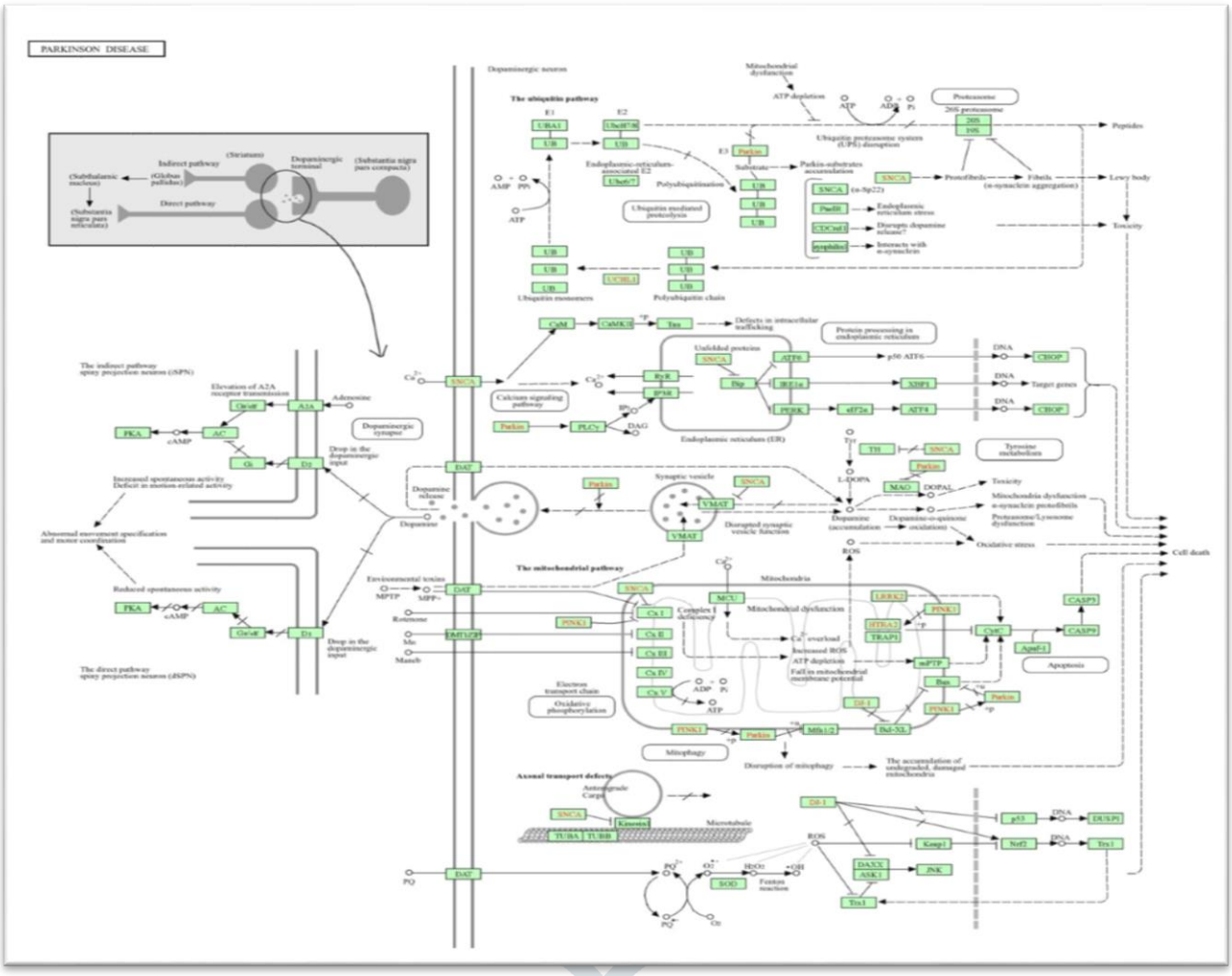

Figure 10: KEGG Pathway

Direct and indirect disruption of dopaminergic transmission occurs. The graphic illustrates how mechanisms that impact synaptic transmission and neuronal survival, such as cAMP-PKA signaling, are involved. Toxins from the environment and genetics aggravate these dysfunctions, hastening the neurodegenerative process.The pathway also emphasizes the role of endoplasmic reticulum stress and the unfolded protein response, which further encourages the build-up of hazardous protein aggregates. Contributing causes include synaptic vesicle transport abnormalities and dysregulation of calcium.

The transthyretin (TTR) A97S variant study makes a strong argument for using structure-based drug design (SBDD) to treat neurodegenerative diseases associated with protein misfolding and aggregation. Mutations in TTR, a tetrameric protein that transports retinol-binding protein and thyroxine in plasma and cerebral fluid, result in structural and functional changes. Particularly, the TTR gene's A97S mutation has been linked to pathological alterations that result in protein aggregation, which is a defining feature of several amyloid-related neurodegenerative diseases.

This work sought to find possible therapeutic compounds that could preferentially bind to the A97S-TTR variant and prevent or inhibit its aggregation by using SBDD techniques. The three-dimensional structure of the A97S-TTR complex was thoroughly analyzed thanks to the thorough methodology used in this work, which included molecular docking, homology modeling, and virtual screening. The discovery of new binding pockets and allosteric sites was made easier by these methods, which are essential for the development of medications that have the ability to alter the behavior of proteins.

The ability to anticipate the binding affinities and interaction patterns of different ligands with the A97S-TTR protein was made possible through the use of molecular docking simulations. The work shed light on how these substances might stabilize the protein structure, stop misfolding, and eventually limit aggregation by modeling the molecular interactions between the protein and possible therapeutic chemicals. The promise of SBDD in expediting the drug discovery process for neurodegenerative illnesses linked to TTR mutations is highlighted by the identification of particular binding sites and the analysis of ligand-protein interactions.

Based on the docking results, Apomorphine appears to be the most promising candidate for further investigation as a potential inhibitor of the A97S variant of transthyretin. However, additional experimental studies are needed to confirm its binding affinity, selectivity, and efficacy in inhibiting amyloid formationsuch as such as X-ray crystallography or biophysical assays.

The study's conclusions emphasize the significance of focusing on certain binding sites in order to achieve therapeutic efficacy and further our understanding of the structural dynamics of the A97S-TTR variation. Finding substances that can interact with these crucial areas helps to pave the way for the development of medications that may slow or even reverse the course of amyloid illnesses linked to TTR. Additionally, by investigating computational techniques for molecular target prediction, the study enhances the precision of the drug design process and facilitates the identification of allosteric modulators that may open up new therapeutic options.

Finally, our work highlights the effectiveness of structure-based medication design in tackling the problems caused by misfolded and aggregated proteins in neurodegenerative diseases. Prospects for the development of tailored therapeutics are bright because molecular docking and other computational approaches have been successfully applied to the A97S-TTR variation. Through the identification of certain binding locations and the utilization of the A97S-TTR complex's structural understanding, this discovery opens the door to more potent treatments that can lessen the crippling effects of amyloid-related neurodegeneration. The knowledge acquired by this work advances not only the field of illness research connected to TTRs but also advances our understanding of how SBDD can be used to address difficult biological problems. The methodologies described in this study may provide a model for future drug development initiatives targeting neurodegenerative illnesses as the search for potent therapeutics for these debilitating conditions rages on.

IV. Conclusion:

The structure-based drug design and molecular target prediction hold immense promise for developing therapeutic interventions for transthyretin variant A97S-related diseases. By elucidating the structural intricacies of this complex, researchers can identify potential drug-binding sites and design molecules with high affinity and specificity. This approach can accelerate the drug discovery process and increase the likelihood of identifying effective compounds. Furthermore, advancements in computational modeling and AI will enable more accurate predictions of molecular targets, leading to a deeper understanding of disease mechanisms and the identification of novel therapeutic targets as well as the rapid screening and identification of promising compounds. Ultimately, these advancements could lead to the development of effective treatments for patients with transthyretin-related disorders.

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