Computational Simulations Predict Inhibitors Targeting Parkinson's Disease

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Parkinson's disease is a degenerative neurological condition that impairs a person's capacity to regulate their body's movements. Neurons in the substantia nigra area of the brain gradually degenerate in this illness. Alpha-synuclein protein aggregates in these neurons to create Lewy bodies, which are toxic, fibril-like structures. Thus, blocking these fibrils may be a useful treatment approach for Parkinson's disease. We hypothesize that chemical substances that can bind at the interface can inhibit this binding and stop fibrils from forming. As a result, we have screened 5239 chemical compounds against the alpha-synuclein protein using molecular docking simulations, which stops them from clumping and inhibits the production of fibrils. We chose the top three substances that strongly bind to the protein. Since all of these ligands attach to the protein's hydrophobic region, it is likely that hydrophobic medications—which can pass through the blood-brain barrier—will work better to treat this illness. By docking inhibitor-bound and free fibrils together, we confirmed our hypothesis and discovered that the inhibitor prevents the interaction between the fibril interface. Furthermore, to validate the molecular docking data, we have also computed the drug- gable on the surface of the fibril using the P2Rank web server, a machine learning-based method. The work promises better therapeutic alternatives in the future and opens up new pathways for innovative Parkinson's disease treatment.

1. INTRODUCTION

Parkinson's disease is a progressive neurological disorder mainly affecting movement.(1) This happens because neurons break down in a part of the brain called the substantia nigra. People with Parkinson's disease will likely experience tremors, slowness of movement, and balance issues.(1) As the disease progresses, it can lead to cognitive problems, mood changes, and issues with bodily functions. The exact cause of Parkinson's disease isn't fully understood, but it's believed that environmental factors and genetics are part of the cause. Treatment involves medication to increase dopamine or surgery

like deep brain stimulation.(2)

Molecular docking is a computational technique where scientists try to figure out how two molecules fit together to form a stable complex.(3) This method plays a crucial part in discovering new medicines, as it helps us understand how drugs work on a molecular level. Researchers simulate the binding process, which can help identify the compounds that would work best for further testing. The process involves two main steps.(3) First, the researchers generate possible ways the molecules bind and the scoring of these confirmations.(4)

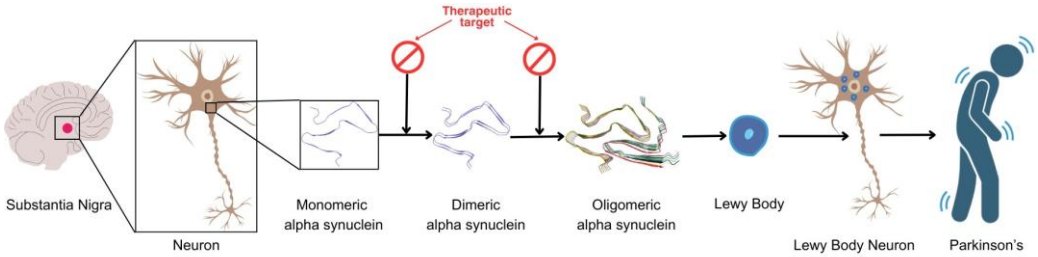

Fig. 1. The progression of Lewy body formation in Parkinson's disease. Neurons in substantia nigra form sticky monomeric alpha-synuclein, which later forms dimeric and oligomeric alpha-synuclein. The oligomers further aggregate to form toxic Lewy bodies. The presence of Lewy bodies disrupts normal cellular functions and spreads to other neurons, leading to neurodegeneration and characteristic symptoms of Parkinson's disease.

Lewy bodies are clumps of proteins that build up inside nerve cells and are linked to Parkinson's disease.(5) These clumps are made up of a protein called alpha-synuclein. Alpha-synuclein helps with brain cell communication.(5) However, in Parkinson's disease, it sticks together, forming the Lewy bodies. These clumps disrupt how brain cells work, causing them to die. When Lewy bodies gather in the substantia nigra, they cause the movement issues we see in Parkinson's disease, like shaking and stiffness. Figuring out how Lewy bodies form is crucial for finding treatments to stop Parkinson's disease. In the current study, we use computational simulations like molecular docking and protein-ligand interaction profiling to find possible inhibitors that target the aggregation of alpha-synuclein fibrils.(6) By using these resources, we want to comprehend the binding and structural characteristics of substances that can successfully prevent the development of fibrils.(7) Our research offers a methodical assessment of the binding affinities and interactions of particular ligands in addition to highlighting the hydrophobic regions of alpha-synuclein as important druggable locations. This strategy is supplemented by the prediction of druggable sites on the fibril surface using machine learning-based techniques like P2Rank. Finding prospective candidates for additional experimental validation is the ultimate goal of this research, since it may open the door to new treatment methods.

2. METHOD

We obtained the three-dimensional structure of the Tau protein from the Protein Data Bank (PDB ID: 7LC9) (8). Ligands were obtained from the Zinc20 Database, and 5,249 compounds were selected for screening (9). They were selected based on specific criteria, such as 3D model ability, reactivity, and purchasability. Next, Ligands were selected based on LogP values. Finally, the compounds were downloaded in pdbqt file format. Using AutoDock Vina 1.5.6 software, we explored the binding poses of these selected compounds to the Tau protein (10). For each compound, ten poses were generated for all four protein-substrate complexes. Autodock was used to identify the top five candidates that exhibited strong binding affinity. The ligand scoring criteria in the molecular docking simulations was that the ligand should be able to fit in the binding site and formed a strong binding with the fibril. To understand the fibril-ligand binding interaction, we have used the Protein-Ligand Interaction Profiler (PLIP) webserver (11). The image used in this research paper was made using the ChimeraX(12).

3. RESULTS

To find inhibitors that target alpha-synuclein aggregation in Parkinson's disease, this study screens 5,239 compounds using computational simulations. The top candidates are chosen based on how well they bind. Figure 2a tells us about the binding sites of the fibril, and Figure 2b tells us about the electrostatic surface potential of the fibril, with red meaning negative, white meaning neutral, and blue meaning positive. The binding sites are all in the top right of the fibril. To calculate the binding site, we used the software ChimeraX.(12) In Figure 2a, the different colors in the binding site are different regions ranked by how well the drug would bind to the fibril. ESP is electrostatic surface potential. We calculated this using ChimeraX as well.

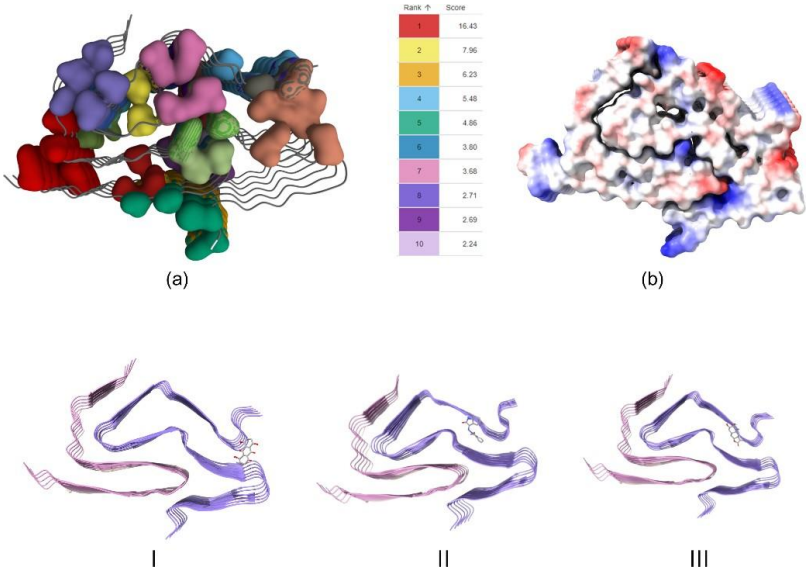

Fig. 2. (a) Binding site of the fibril and (b) electrostatic surface potential (ESP) of the fibril (red is negative, blue is positive, and white is neutral).

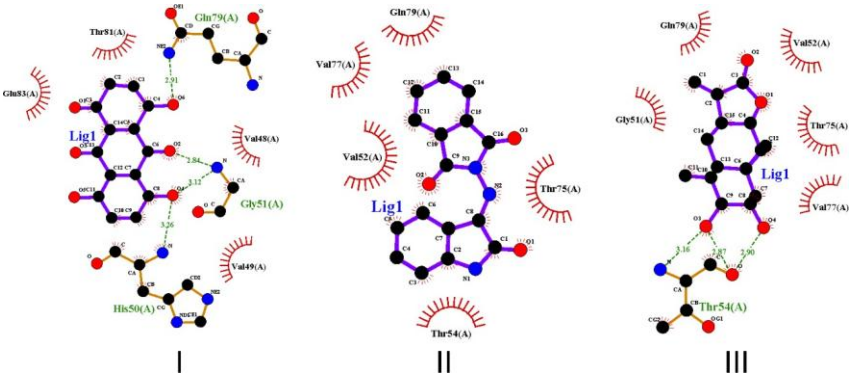

Fig. 3. 2D interaction diagrams of Ligands I–III with the active site residues of the target protein. The molecular interaction maps highlight the specific residues involved in hydrogen bonding (green dashed lines) and hydrophobic interactions (red semicircles) for each ligand.

Molecular docking is finding which drugs can best bind to the protein. We used this to narrow down the large pool of potential drugs and find the best ones. The software we used to do this is Command Prompt. Figure 3 shows us the 2D structure of the ligand and the interactions formed between the amino acids and ligands. Figure 4 shows us the number of hydrophobic actions and the number of hydrogen bonds for each ligand. In the following step, plip analysis was performed on the docked structures. The plip gives us the interactions formed between the ligand and the fibril. For each ligand, it provides examples of the hydrophobic interactions and hydrogen bonds, as shown in Table 1.

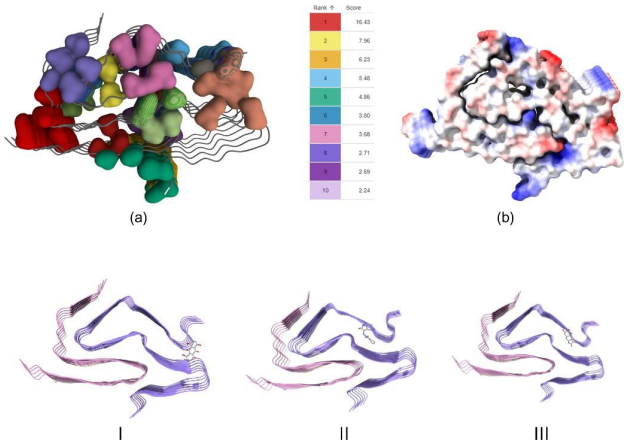

Fig. 4. The 3D structure of the ligand and fibril shows that the ligands bind to the binding site predicted by the P2Rank web server.

4. DISCUSSION

The study's findings demonstrate how computational simulations can be used to find drugs that target alpha-synuclein aggregation in Parkinson's disease. The study shows a promising method for comprehending and preventing the protein-protein interactions that cause fibril formation by concentrating on molecular docking simulations. Targeting these particular regions is crucial, as evidenced by the discovery of three high-performing drugs binding strongly to the alpha-synuclein fibril's hydrophobic portion.(13) This supports the theory that hydrophobic medications can bind firmly to the target protein and traverse the blood-brain barrier, they may be more successful in treating Parkinson's disease.(1)

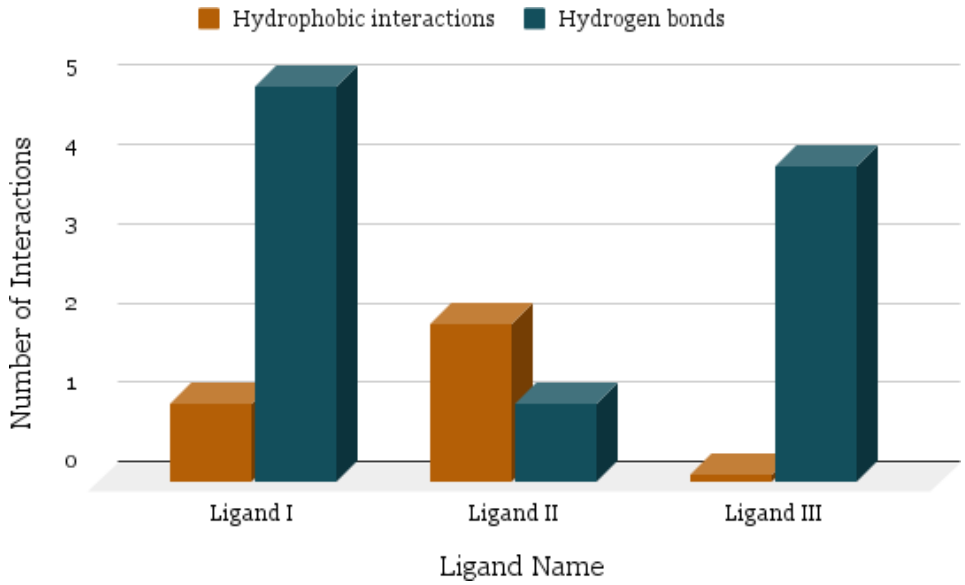

Fig. 5. Comparison of hydrophobic interactions and hydrogen bonds formed by Ligands I–III with the target protein. The bar graph illustrates the number of hydrophobic interactions (in orange) and hydrogen bonds (in teal) observed for each ligand. Ligand I exhibits the highest number of hydrogen bonds (5), indicating strong polar interactions with the protein binding site. Ligand II shows a balanced interaction profile with both hydrophobic (2) and hydrogen bond interactions (2), suggesting moderate binding affinity. Ligand III predominantly forms hydrogen bonds (4), with minimal hydrophobic interaction, emphasizing the importance of polar contacts in its binding mechanism. These interaction profiles provide insights into the binding efficiency and specificity of each ligand.

The current study offers detailed insights into targeting alpha-synuclein aggregation in Parkinson's disease. However, certain limitations exist, primarily due to only molecular docking simulations and not including molecular dynamics (MD) simulations. The MD simulations will provide more detailed dynamics of the fibril-ligand binding interactions. In addition, in the future, we will increase the dataset to reveal more potential fibril inhibitors. Finally, all these results should be further validated in the experimental lab.

In summary, this study looks at the possibility of using drugs to stop harmful fibrils from causing Parkinson's disease by targeting a protein called alpha-synuclein. The study found five chemicals that stick to the hydrophobic area of the protein using molecular docking. This suggests that drugs that can pass the blood-brain barrier might work well. The study confirmed that these inhibitors could prevent fibrils from interacting with each other. Using neural networks and machine learning, druggable sites were pinpointed on the fibril surface, which could help develop new inhibitors. This research opens up possibilities for creating advanced treatments for Parkinson's disease, which could result in more effective therapies.

Ligand I	Residue	Distance
Hydrophobic interactions		Val493.67
	Val49	2.21
	His50	2.45
Hydrogen bonds	Gly51	2.19
	Gln79	2.25
	Gln79	2.95
Ligand II		
Hydrophobic Interactions	Val52	3.52
	Val77	3.51
Hydrogen Bonds	Thr75	3.04
Ligand III		
	Val52	2.81
	Thr54	2.18
Hydrogen bonds	Thr75	3.04
	Thr75	2.96

Table 1: Amyloid-ligand bond interaction table. Hydrophobic and hydrogen bonding interactions between Ligands I–III and the target protein, highlighting key residues involved in molecular recognition.

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