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MOLECULAR DOCKING AND VIRTUAL SCREENING IN DRUG DESIGN FOR PARKINSON'S DISEASE

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Abstract: Discovering new targets for drug development is a crucial phase in drug identification. Drug discovery is a time-consuming and expensive endeavor, especially when addressing complex conditions such as Parkinson's disease. Mutations in the SNCA gene are responsible for Parkinson's disease. The SNCA gene is part of the PARK gene family associated with Parkinson's disease. The paper's primary focus centers around the discussion of virtual screening and docking methods and software tools utilized for molecular docking in the context of Parkinson's disease.

Index Terms: Virtual Screening, In-silico design, Docking, Computer-aided drug design, and Drug discovery.

I. INTRODUCTION

Computer-aided drug design (CADD) has emerged as an essential tool in the drug discovery and development process. Employing computational approaches, CADD facilitates the discovery, development, and analysis of drugs, aiming to identify potential compounds with anticipated biological activities. Positioned at the forefront of high-tech investigations, drug discovery is rapidly advancing, drawing upon recent breakthroughs in molecular biology, quantum physics and chemistry, bioinformatics, and information technologies.

The conventional depiction of drug discovery as a linear and sequential process, commencing with target and lead discovery and progressing through lead optimization to pre-clinical in vitro and in vivo studies, has undergone a profound transformation. The advent of genomics, proteomics, bioinformatics, and advanced technologies such as high throughput screening, virtual screening, and in silico screening has revolutionized the drug discovery process. These innovations have introduced a more dynamic and integrated approach, enhancing the efficiency and effectiveness of identifying potential drug candidates.

Virtual screening has emerged as a dependable, cost-effective, and time-saving technique in the pursuit of lead compound discovery. The approach involves docking small molecules into a known protein structure, making it a potent tool for drug design. This method not only proves to be efficient in identifying potential drug candidates but also contributes significantly to reducing costs and accelerating the drug discovery process.

Molecular docking is a predictive method used to anticipate the optimal spatial arrangement of one molecule concerning another when forming a stable complex. The primary objective of molecular docking is to attain an optimized conformation for both the protein and the ligand. The methods employed in molecular docking exhibit variability in the representation of receptors, treatment of ligands, scoring functions, and search algorithms. This diversity allows for a tailored and nuanced approach to predicting the interactions between molecules, enhancing the precision and applicability of the docking process in drug discovery and design.

Parkinson's disease (PD) is classified among motor system disorders, characterized by the degeneration of dopamine-producing brain cells. The core symptoms include tremors, rigidity, bradykinesia (slowness of movement), and postural instability. These manifestations worsen over time, affecting activities like walking and talking. The SNCA gene, part of the PARK gene family, plays a pivotal role in PD. It encodes alpha-synuclein, a small protein abundant in the brain and present in smaller amounts in other tissues. Alpha-synuclein is

concentrated in nerve cell terminals, where it interacts with lipids and proteins. Mutations in SNCA contribute to Parkinson's disease, with at least 18 mutations identified, particularly associated with early-onset cases before the age of 50.

Parkinson's disease pathogenesis involves destabilization of the alpha-synuclein tetramer, leading to its misfolding and aggregation into Lewy bodies, marking disease progression. Contrary to previous assumptions of alpha-synuclein existing as a monomer, it is now recognized that destabilized tetramers play a crucial role in disease development.

Virtual screening plays a crucial role in Parkinson's disease research and drug discovery by leveraging computational techniques to identify potential drug candidates. virtual screening plays a pivotal role in the early stages of drug discovery for Parkinson's disease, offering a cost-effective and time-efficient approach to identify potential therapeutic compounds. This computational strategy complements traditional experimental methods, contributing to the ongoing efforts to understand and treat Parkinson's disease more effectively.

2. MATERIALS & METHODS

Leveraging bioinformatics tools and databases such as NCBI and GENBANK, an investigation into the gene associated with Parkinson's disease was conducted. The gene sequences, NM_000345.3 for Genomics and NP_000336.1 for Proteomics, were retrieved in FASTA format from NCBI. Employing BioEdit software and various NCBI tools including ORF (Open Reading Frame Finder), Map Viewer, E-PCR, Vec Screen, BLAST (Basic Local Alignment Search Tool), and MSA (Multiple Sequence Alignment), these sequences were utilized to construct phylogenetic trees through the CLUSTALW tool, resulting in a DND file compatible with visualization using Phylodraw.

Additionally, Genscan was employed to identify suboptimal exons with a probability greater than 1.000. In the realm of Proteomics, ExPASy tools such as Protparam and ProtScale were utilized for primary structure analysis, while GOR and SOPMA were employed for secondary structure analysis. Post-translation predictions were conducted using Signal P, NET-C-Glycine, NET-O-Glycine, Net Acetylation, Net Phosphorylation, and Sulfinator. Further, SOSUI was applied for protein structure prediction.

The process of protein modeling commenced using SPDBV, followed by the application of Q-site Finder to identify potential drugs. Five drugs were selected, each accompanied by their respective molecular weights: Levodopa (197.18), Carbidopa (226.24), Memantine (179.30), Dopamine (153.17), and Apomorphine (267.32). Subsequently, drug modeling was conducted, and individual docking procedures were performed using SPDBV.

For each drug, three analogous molecules were considered, including:

1. (9R)-9-(dimethylamino)-8-ethyl-9,10-dihydrophenanthrene-3,4-diol: CID 3038908

2. (1S)-1-[(3,4-dihydroxy phenyl)methyl]-2-methyl-3,4-dihydro-1H-isoquinoline-6,7-diol: CID 688014

3. 5-(dipropylamino)-5,6,7,8-tetrahydronaphthalene-1,2-diol: CID 53932796

4. 2-ammonio-3-(3,4-dihydroxy phenyl)-2-methylpropanoate: CID 25202646

5. 2-amino-2-[(3,4-dihydroxyphenyl)methyl]butanoic acid: CID 23334216

6. Benzyl-[4-[(5-hydroxy-2,4-disulfophenyl)-[4-[(4-sulfophenyl)methylamino]phenyl]methylidene]cyclohexa-2,5-dien-1-ylidene]-methylazanium CID: 122320

7. Dopamine CID: 3713609

8. Dopaminoquinone CID: 162602

9. Coryneine CID: 165581

10. Levodopa methyl ester CID: 23497

11. Etilevodopa CID: 170345

12. 3-methyladamantan-1-amine CID: 3010128

13. 3,5-dimethyladamantan-1-aminium: CID 3833001

14. 3-butyladamantan-1-amine: CID 157778

VEGA ZZ was employed to create a database, and repeated database docking was noted. These docking results were then assessed concerning their interactions with amino acids in the active site of the protein. The entire process contributes to the exploration and identification of potential drug candidates for further investigation.

Following the individual docking process, a final molecule was selected based on criteria such as the lowest energy levels and favorable interactions with a maximum number of amino acids. This selection was carried out using Argus Lab. Subsequently, the chosen molecule underwent further analysis using HyperChem and CAChe. Various analyses were conducted, including Single Point, Geometric Optimization, and an assessment of the final molecule's QSAR properties. Additionally, UV Visible Transition and Proc IR analyses were performed.

RESULTS AND DISCUSSION

Bioedit- Genomics: DNA molecule: gi|225690599|ref|NM_000345.3| Homo sapiens synuclein, alpha (non A4 component of amyloid precursor) (SNCA), transcript variant 1, mRNA

Length = 3215 base pairs
Molecular Weight = 970814.00 Daltons, single stranded
Molecular Weight = 1948068.00 Daltons, double stranded
G+C content = 38.35%
A+T content = 61.65%

Nucleotide	Number	Mol%
A	975	30.33
C	546	16.98
G	687	21.37
T	1007	31.32

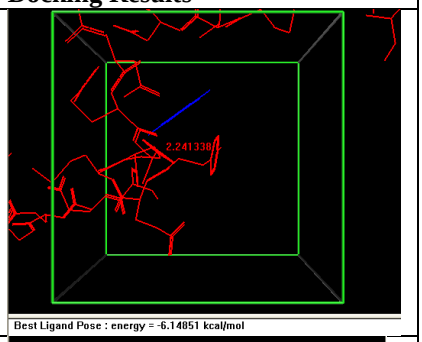
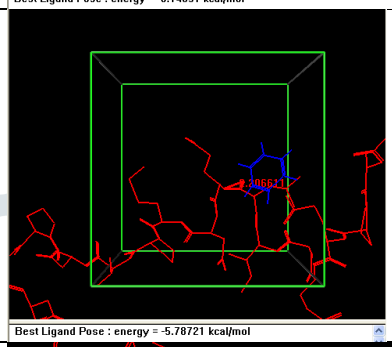
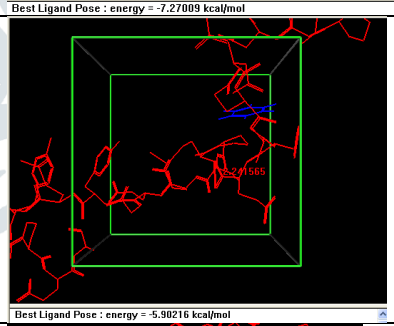
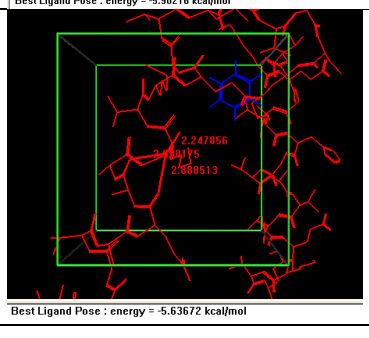
Table 1: Nucleotide information for the given molecule

Bioedit-Proteomics: Protein: gi|4507109|ref|NP_000336.1| alpha-synuclein isoform NACP140 [Homo sapiens]
Length = 140 amino acids
Molecular Weight = 14459.46 Daltons

Amino Acid	Number	Mol%
Ala A	19	13.97
Cys C	0	0.00
Asp D	6	4.29
Glu E	18	12.86
Phe F	2	1.43
Gly G	18	12.86
His H	1	0.71
Ile I	2	1.43
Lys K	15	10.71
Leu L	4	2.86
Met M	4	2.86
Asn N	3	2.14
Pro P	5	3.57
Gln Q	6	4.29
Arg R	0	0.00
Ser S	4	2.86
Thr T	10	7.14
Val V	19	13.57
Trp W	0	0.00
Tyr Y	4	2.86

Table 2: Amino acid information for the given molecule

Individual docking results

S.no	Compounds	Docking Results
1	Levodopa	
2	Carbidopa	
3	Memantine	
4	Dopamine	
5	Apomorphine	

In the drug design process targeting Parkinson's Disease, compounds with known therapeutic effects such as Apomorphine, Carbidopa, Levodopa, Dopamine, and Memantine were selected. Similar molecules for each of these drugs were sourced from ChemOffice. The subsequent step involved Individual Docking, where each drug was individually docked with the active site amino acids of the side chain protein using Argus Lab software.

The results of database docking unveiled that three similar molecules, namely 2-(3,4-dihydroxyphenyl)ethanaminium, Dopamine quinine, and Coryneine, exhibited a notable affinity to bind with the respective drugs. The associated energy values for these interactions were

recorded as -6.82157, -6.43931, and -6.24857, respectively. These findings provide crucial information on the potential binding affinity and interactions between the selected drugs and their analogous compounds, contributing to the understanding of their therapeutic mechanisms in the context of Parkinson's Disease drug development.

CONCLUSION

In this research project, the primary objective was to identify a specific drug capable of targeting Parkinson's disease. Based on the docking results and considering the energy values, the drug 2-(3,4-dihydroxyphenyl)ethanaminium emerged as the final candidate, exhibiting a docking score of -6.82157. Subsequently, using HyperChem software, geometric optimization was performed, and various QSAR (Quantitative Structure-Activity Relationship) properties of the final drug were extracted. These properties include:

- Partial Charges: 0.00e

- Surface Area (approx): 400.72 $Å^2$

- Surface Area (grid): 306.90 $Å^2$

- Volume: 450.59 $Å^3$

- Hydration Energy: -9.44 kcal/mol

- Log P: 1.85

- Refractivity: 40.59 $Å^3$

- Polarizability: 12.57 $Å^3$

- Mass: 142.09 amu

Finally, the IR (Infrared) transition graph was generated using computer-aided chemistry software, specifically CAChe. These comprehensive analyses contribute valuable insights into the potential therapeutic properties and characteristics of the identified drug candidate for Parkinson's disease.

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