Targeting ASYN in Parkinson's Disease Treatment: Identification of Effective Inhibitors of A-Synuclein Aggregation Through *In silico* Methods

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ABSTRACT

Introduction: Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide, with prevalence skyrocketing over the past 32 years. In 2021, 11.77 million cases were reported, accounting for an increase of over 100% since 2000. Parkinson's disease is primarily characterized by bradykinesia and a loss of dopamine-producing neurons beginning in the substantia nigra pars compacta. A key pathological hallmark of PD is the misfolding and aggregation of α-synuclein (ASYN), oftentimes owing to single nucleotide polymorphisms (SNPs), and leading to the formation of Lewy bodies. Current treatments do not target disease progression. Rather, their role is majorly limited to managing motor symptoms by regulating dopamine levels.

Objectives: This study begins with the secondary analysis of published RNA-sequencing data comparing the transcriptomic profiles of port-mortem Parkinson's disease brain samples versus healthy controls. The primary objective, however, is to identify FDA-approved drugs or phytochemicals that can act as small-molecule inhibitors against the aggregation of pathological α-synuclein monomers by binding to its aggregation-prone pocket, thereby preventing the progression of Parkinson's disease.

Methodology: RNA-seq data obtained from EMBL-EBI was used to identify Differentially Expressed Genes (DEGs) through R programming. This was followed by Gene Set Enrichment Analysis (GSEA), Gene Ontology (GO), and pathway and network analyses, for which KEGG BlastKOALA and STRING were used, respectively. Single Nucleotide Polymorphism (SNP) analysis of the α-synuclein gene was also performed. These helped highlight the clinical significance of α-synuclein in Parkinson's disease pathology. Further computational tools were used to predict the protein's binding pockets, followed by screening a large library of approved drugs to identify small molecules that could potentially bind to the pocket of interest, while literature was searched for promising phytochemical inhibitors. ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) analysis of these molecules was performed using online web servers, and candidates were shortlisted based on their ability to cross the blood-brain barrier and their toxicity levels. These molecules were then docked against the protein of interest using the PyRx software, and binding energies were compared. The receptor-ligand complexes that exhibited the highest binding energies were indicative of the most effective FDA-approved drugs or phytochemicals that could serve as inhibitors for α-synuclein aggregation.

Key Findings: As a result of our RNA-sequencing data analysis, we concluded that α-synuclein was indeed an upregulated gene in Parkinson's disease patients, albeit technical hindrances did not highlight it as a significant contributor to the transcriptomic differences in PD versus healthy conditions. Drospirenone is a progestin-like synthetic hormone found in birth control pills and used in hormone therapy. It displayed the greatest binding energy with α-synuclein at -7.6 kcal/mol among all shortlisted FDA-approved drugs. The most potent phytochemical in the study was Sesamin, a bioactive compound found in sesame seeds and oil. It is known for its antioxidant and anti-inflammatory properties, both of which support its role in targeting

Parkinson's disease progression. It displayed a binding energy of -7.2 kcal/mol.

Conclusion: Our study's main focus was to identify effective inhibitors of α-synuclein aggregation using a classical computational pipeline. The results signify the importance of in silico approaches in drug discovery and repurposing, and provides a foundation for future in vitro and in vivo validation studies, exploring the efficacy of both Drospirenone and Sesamin in preventing the formation of toxic α-synuclein polymers, and their effects on the progression of Parkinson's disease.

Keywords: Alpha-Synuclein Protein, Molecular Docking, Neurodegenerative Disease, Parkinson's Disease, SNCA Gene..

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