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MOLECULAR DOCKING OF L-DOPA WITH PERIPHERAL MYELIN PROTEIN TO POTENTIALLY REDUCE STRESS LEVELS IN CHARCOT-MARIE TOOTH DISEASE

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ABSTRACT

Neurogenetic disorders are few diseases that bring depression and Muscular restrictions into the human body. One such Disease is Charcot-Marie-Tooth (CMT) disease which is due to the alterations of the Peripheral Myelin Protein (PMP) gene in the Peripheral Nervous System. Recent researches have revealed that it might also be due to hypomyelination and decreased dopamine levels in the Peripheral Nervous system. Since L-Dopa is already used for Parkinson's disease (PD) to regulate dopamine levels, an in-silico investigation is done to recognize L-Dopa for CMT disease as well. This research work is about molecular docking of L-Dopa with PMP to identify the binding affinity and investigate the binding properties so that it can be used in CMT affected persons to decline stress levels. The initial phase of our research work is to dock L-Dopa with ASN and further to dock L-Dopa with PMP. Our docking study results revealed 2 hydrogen bonds for ASN and 6 hydrogen bonds for PMP. Hence, Increasing dopamine will have an impact on reducing stress and depression caused due to CMT.

Keywords: Charcot-Marie Tooth (CMT) disease, L-Dopa, Neuro-genetic disorder, Peripheral Myelin Protein (PMP)

1.INTRODUCTION:

Diseases are either hereditary or non-hereditary. The neurogenetic disease is mostly hereditary that occurs due to the alterations in the normal level of the required gene or the structural modifications in the chromosome. Neurogenetic disorders result in muscular dystrophy along with stress and depression. While neurogenetic disorders cannot be cured completely, the stress levels in affected persons can be reduced so that they can be trained for a normal life. Charcot Marie Tooth (CMT)/ peroneal muscular atrophy is a Neurogenetic disorder in which the affected person has poor foot muscle orientation, high arch, and claw toes. A Molecular docking study is carried out to detect a drug that can support and assist CMT infected persons. The objective of this research work is to identify whether drug-like L-Dopa prominently used for Parkinson's disease (PD) can be used for Charcot-Marie Tooth (CMT) disease to bring down the stress levels.

2. RELATED LITERATURE:

2.1. Neurogenetic Disorders (ND)

Neurogenetic Disorders (ND) are caused due to changes in the chromosome and genes which may affect the Nerves, Brain, Spinal cord, and muscles. These disorders may occur at any stage during the lifetime. Children are most often prone to Neurogenetic disorders. Ataxia, Charcot-Marie-Tooth disease, Familial dystonia, Huntington's's disease, Niemann-Pick disease, Fabry disease, Wilsons Disease are few Neurogenetic Disorders where researchers put their expertise to evolve drugs for long term relief. There are few diseases like Alzheimer's disease and Parkinson's disease which occur commonly in elderly people due to lack of protein intake periodically. This may also result in stress, depression, rheumatism, etc. Neurotoxicity occurs due to protein misfolding and aggregation in any pathophysiological processes. There are various proteins responsible for neurogenetic disorders. The naturally occurring protein Amyloid beta's misfolding and aggregation leads to Alzheimer's disease. The docking results in **[5]** have identified l-dopa and dopamine derivatives of naphthalene diimide (NDI) as therapeutic agents for the treatment of Alzheimer's disease. It is stated in **[3]** that there is a potential link between dopamine levels and myelin dysfunction in schizophrenia. The link between dopamine and myelin dysfunction is also based on a research study done in **[5]**.

2.2. Charcot Marie Tooth Disease

Charcot-Marie-Tooth (CMT) disease, an inherited ND that causes damage to the peripheral nerve. They

mainly affect the sensory and motor nerves that connect the spinal cord and brain to the entire body. Since these nerves are fragile, it can be damaged easily. To fix nerve damage, it may be cut and replaced by a section of a healthy nerve. But when the whole peripheral nervous system gets affected, it needs a drug to heal or reduce the consequences of the nerves getting affected more. CMT might lead to myelin dysfunction or axonal Dysfunction. Hypomyelination is a reason for a type of CMT disorder **[6]**.

2.3. Peripheral Myelin Protein

Myelin P2 protein in humans is encoded by the PMP2 gene. The peripheral Nervous system has a myelin protein P2. P2 stabilizes the myelin in the peripheral nervous system and plays a vital role in lipid transport. Recent research has identified that the mutations in Peripheral myelin protein are a novel cause for CMT disease. In our Investigation, We have chosen the PMP2 protein to perform the docking study.PMP2 helps to stiffen the myelin sheath of the peripheral nervous system. In **[6]**, it is identified that Peripheral Myelin Protein 2 (PMP2) is a novel cause for causing CMT disease. Researchers **[1]** have performed a study to examine whether dopamine can regulate myelination in stress-induced depression by inspecting myelination changes for chronic stress. It is also proven that myelin production and dopamine synthesis also has a relationship **[2]**.

2.4. L-Dopa

Dopamine is responsible for the proper functioning of the brain and the nervous system. Dopamine level in the Nervous System can be increased by L-Dopa drug, prominently used for the treatment of Parkinson's disease (PD). It is recommended by physicians to release dopamine in the Alpha-synuclein, which can stop the patients from getting worse. As stated in **[1]**, Dopamine helps to lower depression and stress levels thereby it regulates and improves the emotional behavior of persons affected by PD. Dopamine has also been testified to modulate CNS myelination as per **[1]**.

3. METHODOLOGY

The structure and functional characteristics of the peripheral myelin protein P2 in the human nervous system comprehended in **[4]** are thoroughly reviewed. Subsequently, this investigation is carried out to dock the Peripheral myelin protein with L-Dopa and recognize the binding affinity. The core idea behind this docking is to find whether L-Dopa binds with PMP2. If so, L-Dopa can be suggested for reducing stress levels and depression in persons affected with CMT disease. The docking study is carried out in Autodock Tool. To perform Molecular docking of the

ligand and the protein, the following steps were performed:

1. Retrieving the protein and Ligand structure
2. Protein structure preparation
3. Ligand structure preparation
4. find the active or residue sites of the protein
5. fixing grid for the protein
6. perform docking of the prepared protein and ligand

Finally, the Results about the binding energy, ligand efficiency, etc. are being analyzed.

4. RESULTS & DISCUSSION

The docking of Levodopa (L-Dopa) with Alpha-Synuclein (ASN) is performed to identify the binding to understand the binding energy levels and possible hydrogen bonds. There are 2 hydrogen bonds formed while docking L-Dopa with ASN (1XQT). Next, the docking of Peripheral myelin protein (PMP2-2WUT) with L-Dopa is accomplished and it is found that 6 hydrogen bonds are formed. The binding energy reflects that the L-Dopa is stable in attaching to the PMP2 protein which can reduce the hypomyelination and increase the dopamine levels in the peripheral Nervous System.

Figure 1.a and 1.b depict the complex molecule formed after the interaction of L-Dopa with ASN and PMP2. The yellow color molecule in the figure is L-Dopa and the Dark blue molecule in the figure is the proteins. The numbered blue bonds are the hydrogen bonds. **Table 1** displays the Docking properties of L-Dopa with ASN and PMP2.

Table 1: Docking Results of L-Dopa with ASN and PMP2 respectively

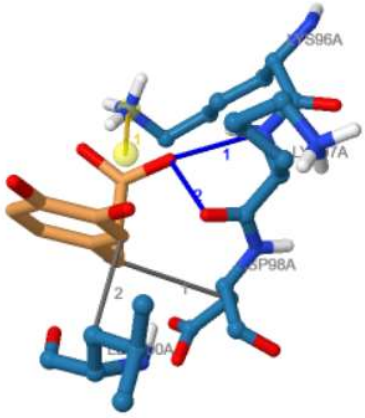

Fig.1. a. L-Dopa with ASN

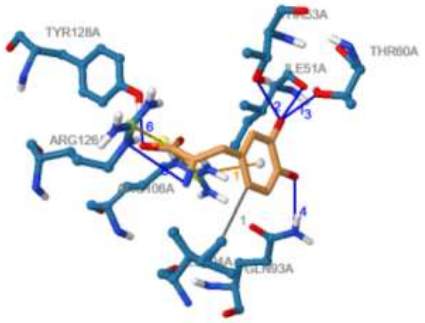

Fig. 1. b. L-Dopa with PMP2

Property	L-Dopa+ASN	L-DOPA+PMP2
Binding energy	-4.67	-5.36
Ligand efficiency	-0.33	-0.38
Inhib_constant	379.05	118.76
Intermol _energy	-5.56	-6.25
Electrostatic energy	-1.69	-0.94
Torsional energy	0.89	0.89
Unbound energy	-0.19	-0.16
Total energy	-0.19	-0.16
clRMS	0.0	0.0
refRMS	227.4	27.18
hydrogen bonds formed	2	6

5. CONCLUSION AND FUTURE WORK

This molecular docking investigation (as in Table 1) reveals that L-Dopa has good binding capabilities with PMP2 (binding energy of -5.36) when compared to its binding affinity with ASN (binding energy=-4.67). Since L-Dopa is proven to be successful in the treatment of Parkinson's disease to increase dopamine levels, our study triggers an idea to use levodopa for CMT to avoid hypomyelination and increase dopamine levels. Though L-Dopa is not proven to cure CMT, the drug can then be revamped and designed to reduce the stress and depression levels in persons who are affected with CMT.

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