IN SILICO APPROACH FOR PARKINSON'S DISEASE BY TARGETING MAOB WITH ANTIOXIDANTS

A DISSERTATION

Submitted in partial fulfillment of the requirements for the award of the degree of

MASTER OF SCIENCE

IN

BIOTECHNOLOGY

Submitted By:

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Supriya Singh

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CANDIDATE'S DECLARATION

I, **Supriya Singh**, (Roll No.: 2K22/MSCBIO/51) of **M.Sc. Biotechnology**, declare that this work which is presented in this Major Project titled "**In silico approach for Parkinson's Disease by targeting MAOB with antioxidants**" submitted to the Department of. Biotechnology, Delhi Technological University, Delhi in partial fulfillment of the requirements for the award of the degree of Master of Science, is novel and my own, carried out during a period from 2th January, 2023 to 20th May, 2023, under the supervision of **Prof. Yasha Hasija**.

I also state that this work has not previously formed the basis for the award of any Degree or other similar title or recognition.

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SUPERVISOR CERTIFICATE

Certified that **Supriya Singh (2k22/mscbio/51)** has carried out their search work to the best of my awareness, the project named "**In silico approach for Parkinson's Disease by targeting MAOB with antioxidants"** has never been submitted anywhere else, in whole or in part, for any degree of diploma at the university or anywhere. I further certify that the student's publication and indexing information is accurate.

Place: Delhi

Date:

Prof. Yasha Hasija

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IN SILICO APPROACH FOR PARKINSON'S DISEASE BY TARGETING MAOB WITH ANTIOXIDANTS

ABSTRACT

Parkinson disease (PD) is a central nervous system-affecting neurodegenerative neurological condition (mid brain). PD is marked by aberrant aggregation of protein called α-Synuclein, which is the major pathophysiological hall of disease. Other hallmark of Parkinson disease includes loss of dopaminergic neuron in the substantia nigra compacta (portion of mid brain), chronic activation of microglial cell and astrocytes, mitochondrial dysfunction, cellular toxicity, oxidative stress and brain inflammation. Among the motor and non-motor symptoms of Parkinson's disease are bradykinesia, tremor, and resting tremor. Yet there is no permanent cure of Parkinson disease however certain medication are help in the symptoms and reduce the cellular toxicity like Monoamine oxidase B inhibitors. An enzyme called monoamine oxidase, which is found at the outer membrane of mitochondria, is necessary for the peripheral breakdown of neuroactive and vasoactive amines and the central nervous system, predominantly by oxidative deamination. Drugs are therefore desperately needed to address the underlying illness rather than just its symptoms. Pterostilbene is a natural active compound, which is analog of resveratrol, have properties to lower the oxidative stress generated by H_2O_2 and other ROS. Pterostilbene is a antioxidant which regulate the level of ROS generated due to the increased level od monoamine oxidase B. Thus, pterostilbene can inhibit MAOB and reduce the symptoms of PD. Using molecular

docking, we are investigating the interaction between the ligand and the protein. By evaluating the molecular docking data, we conclude that pterostilbene has lower binding free energy and thus can target PD symtoms.

Keywords– Parkinson's disease, Oxidative stress, molecular docking, antioxidants, Monoamine oxidase B.

PROOF OF PRESENTATION

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Name of the Authors: Supriya Singh and Yasha Hasija*

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Greetings from ICOTET 2024!

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We are pleased to inform you that **Paper ID 2651** entitled **" In silico approach for Parkinson's Disease by targeting MAOB with Pterostilbene "** submitted by you has been accepted by the 2nd International Conference on Optimization Techniques in Engineering and Technology Engineering (ICOTET 2024).

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Thanks & Regards

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LIST OF ABBREVIATION

S.No.	Abbreviation	Full Form
1	PD	Parkinson disease
2	SNc	Substantia nigra compacta
3	ROS	Reactive oxygen species
4	DA	dopaminergic neurons
5	LBs	Lewy Bodies
6	MAO-B	Monoamine oxidase B
7	MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
8	α-Synuclein	Alpha-synuclein
9	NM	Neuromelanin
10	BBB	Blood Brain Barrier
11	PDB	Protein Databank

CHAPTER– 1

INTRODUCTION

1.1 Background

Parkinsonism is a progressive neurodegeneration disease which effected more than 1% population globally. A progressive loss of dopaminergic neurons in the substantia nigra compacta (SNc), a region of the midbrain, is a hallmark of Parkinson's disease (PD). Loss of dopaminergic neurons is linked to the Lewy Body formation, which is pathologically hallmark of PD. Parkinson disease is typically clinically identified based on motor symptoms such as bradykinesia (Slowness of movement and speed), rigidity and resting tremor and non-motor symptoms like anosmia (loss of smell), constipation, depression and other sleep disorder may develop years before the motor abnormalities. Other nonmotor abnormalities such as discomfort, cognitive deterioration, and autonomic dysfunction may appear in the later stages of parkinsonism. PD (Parkinson disorder) hallmark include the dopaminergic neurons disappearing from the midbrain and intraneuronal protein aggregation (α-Synuclein) called Lewy body. It has been believed that motor symptoms triggered the death of 50-7-% of SN dopaminergic neurons, but several other studies suggests that dopaminergic terminal loss in the striatum is relevant [1]. Although Parkinson is not completely curable but several therapeutic strategies may effective, which can show the effective

result on the symptoms and one possible advantage could be the ability to delay the progression of parkinsonism [2].

1.1.1 Microglial cell activation, oxidative stress into parkinsonism

As the age of parkinsonism is rise, the brain homeostasis is being disrupt due to decreased in survival mechanism activation and it will lead to the neuroinflammation. Neuroinflammation may triggers several factors like infection ageing, trauma, pathogenic protein aggregation, which causes a number of health issue. Microglia, neurons, astrocytes and other immune components like cytokines and complement protein to activate an inflammatory response to such stimuli. Microglial cell and astrocytes are main component against the oxidative stress and microglial cell go through a physiological change to being activated, referred as “Reactive state” and release inflammatory signals. Microglial cell are the main component and resident of central nervous system, which play very diverse role in the neuroinflammation as well as neuroprotection, The final challenge is to determine if acute or long-term inflammatory stimuli are present because the chronic neuroinflammatory responses are typically linked to neurodegenerative disease [3]. Glial cell, comprising over 50% of all brain cells, are divided into subtypes, with astrocytes being the most common. The pathogenesis of Parkinson disease is mainly impacted by reactive astrocytes in the central brain which is another key marker. The PARK7 gene, encoded by DJ-1 protein, has been revealed to have a role in astrocytes biology, with astrocytes expressing higher than neurons in human brain samples obtained after death and being elevated

in Parkinson's disease patients. Parkinsonism is developing due to the accumulation of αSynuclein positive cytoplasmic inclusion in neurons, marked by the mutation and duplication of SNCA gene and it prevalent in neurons. Some research suggests that the modest levels in astrocytes may still be functionally relevant [4]. Scientific studies suggest that the MOA activation is regulated by the DJ-1 protein, but there were no significant variations in the protein expression levels between DJ-1 deficient cells and control microglial cells. Monoamine oxidases (MAO) are enzymes that convert amines like dopamine into hydrogen peroxide, leading to increased intracellular hydrogen peroxide production and elevated reactive oxygen species (ROS). This process is linked due to the substantia nigra's dopaminergic neurons dying off, causing oxidative damage [5]. The study explores the function of mitochondria in DAnergic neuron loss in Parkinson's disease (PD) triggered by MPTP's selective toxicity in both non-human primates and humans. In glial cells, mitochondrial monoamine oxidase B (MAO-B) metabolized MPTP, leading to the production of MPP+, which is then accumulated by dopaminergic neurons via the dopamine transporters. MAO-B inhibitors, but not MAO-A inhibitors, protect dopaminergic neurons against MPTP toxicity in vitro and in vivo. Activated microglia contribute to oxidative and nitrative stress inside the brain, which causes protein degradation failure and apoptosis in Parkinson's disease [6].

1.1.2 Monoamine oxidase B

The outer membrane contains the monoamine oxidase isozymes A and B of mitochondria which breaks down monoamine neurotransmitter in the central brain and

peripheral tissue and yielding hydrogen peroxide (H_2O_2) as a byproduct in the process. Pharmaceutical variants, 1968 saw the discovery of MAO-A and MAO-B [7]. Several inhibitors of monoamine oxidase-B are utilized nowadays to treat the neuroinflammation and recover the level of dopaminergic neurons so that the symptoms may reduce in Parkinson disorder. The key role of dopamine inhibitors to inhibit the activity of monoamine oxidase so that more amount of dopamine is reserved in central brain to treat the symptoms. The main source of MAO B are the glial cells and platelets, with around 20% of the brain total's MAO activity coming from MAO - A and 80% form MAO-B. Both pharmaceutical variants A and B play key role role in the control of amine neurotransmitters, even dopamine as well. Scientific studies reveal that the population of glial cell is rises in the ageing of neurodegenerative disorder like PD and MAO-B is also rises alongside. MAO-B inhibitors are the types of drugs that slow down the brain's MAO-B activity, stop dopamine from being catabolized, improve dopamine signalling and selectively increases dopamine level at synaptic cleft [8].

1.2 Hallmarks of Parkinson's Disease

Mitochondrial dysfunction is one of the crucial hallmarks in PD. PD relies on several environmental and genetic factor, Large-scale linkage analysis studies found mutations in multiple genes related with familial Parkinson's disease, comprising parkin, α-synuclein, PINK1, DJ-1, LRRK2, and ATP13A2, and rarer genes such as PARK3. Despite in advancement of recent year of treatment, PD still remain permanent

incurable because of complex dysregulation or mass dysregulation of several metabolic pathway simultaneously. Oxidative stress in parkinsonism and mitochondrial abnormalities are the major progressive pathophysiological hallmark [9]. Several antioxidant therapeutic approach may help on non-motor symptoms but not completely effective in motor symptoms and completely neutralisation of ROS species.

1.3 Identification of problem

Despite multiple attempts of treatment still treating of parkinsonism remains a serious difficulty because of several pathophysiological hallmark.

Parkinson's disease motor symptoms are handled predominantly with dopamine-based medications. Initial treatments for tremor in young people consist of dopamine agonists, MAO-B inhibitors, and levodopa formulations. Drugs that are anticholinergic, like trihexyphenidyl, are beneficial, although caution should be exercised owing to potential side effects. Regression of dopamine level is being the most common difficulty in PD and remain completely incurable [10].

CHAPTER– 2

LITERATURE REVIEW

2.1 Parkinson's Disease

Among elderly Americans, the second most common progressive neurodegenerative illness is Parkinson's disease, whose an increase in incidence is anticipated as the nation's population ages. An idiopathic neurological condition called Parkinson's disease is characterized by symptoms affecting both the motor and non-motor systems. This is a neurodegenerative condition that progresses over time and primarily impacts the elderly, while it can also occasionally impact younger persons. PD is the result Neuronal Lewy Bodies are the consequence of pathophysiologic loss or degeneration of dopaminergic neurons in the midbrain's substantia nigra. A primary pathogenic feature of Parkinson's disease is lewy bodies. Numerous risk variables, such as age, genetics, pesticide exposure, and exposure to environmental pollutants like synthetic heroin use, have been linked to Parkinson's disease. Its ultimate reason or causes are not known [11]. "Shaking palsy," as James Parkinson initially referred to the condition in 1817, was subsequently clarified by Charcot in the late 1800s based on the disease's essential clinical characteristics[12]. Parkinson's disease (PD) brain cells deficient in dopamine produce motor difficulties that worsen gradually over years, including stiffness akinesia, postural instability, and resting tremor [13]. Autonomic dysfunction was first described by Charcot in 1879, and in 1893 substantia nigra and Parkinson's disease were found to be related. Nevertheless, the neuropathological and neurochemical features of the illness were not recognized until the second half of the

20th century. Parkinson's disease, which affects 3% of people over 66 and has an unclear origin, is a major source of perioperative morbidity. As the geriatric population ages, it will also become more common among surgical patients [14].

Every ethnic group in the world is affected by Parkinson's disease, albeit there is a little male majority. Between 65 and 90 years of age, the prevalence grows exponentially, with 0.3% of the general population and 3% of those over 65 having it. In 14 636 individuals, the EUROPARKINSON research revealed a prevalence of 1.6% for Parkinson's disease and 2.3% for parkinsonism (Z. X. Zhang & Roman, 1993,Moghal et al., 1994). According to a research, 24% of Parkinson's disease sufferers have only received their diagnosis, underscoring the challenge of making a diagnosis and the possibility of unidentified instances among senior hospital patients. A recent research conducted in London general practices with over 120,000 patients revealed a reduced prevalence [17]. youthful onset Before the age of 40, 5–10% of people have Parkinson's disease; Asians and African Blacks possess the highest frequency, whereas Whites have the lowest. When the illness was initially reported during the Industrial Revolution, it was possible that external pollutants were to blame. Literature has been describing similar circumstances for thousands of years. According to a research on the ten most populated countries in the globe and the number of people with Parkinson's disease (PD) in the five most populous Western European nations is expected to rise significantly between 2005 and 2030, from 4.1 to 4.6 million to 8.7 to 9.3 million. It is projected that the number of PD patients in Asia—which includes from 2.57 million in 2005 to 6.17 million in 2030, the number of people living in China, India, Indonesia, Pakistan, Bangladesh, and Japan will rise. [18]. Non-motor symptoms include anosmia, constipation, depression, and sleep disorders, whereas

motor symptoms include cogwheel stiffness, bradykinesia, and resting tremor. Years before motor symptoms manifest, non-motor symptoms can also get worse as the condition progresses, causing discomfort and cognitive impairment [19].

Table 1. Motor and non-motor symptoms occur in Parkinsonism

S. no	Motor symptom's	Non-motor symptom's
1	Rhythmic tremor	Pain in different part of the body
2	Resting tremors	Depression
3	Bradykinesia (lack & slowness in movement)	Sleeping disorder
4	Rigidity	Anosmia (Loss of smell)
5	Hypomimia (lack of facial movement)	Ageusia (loss of taste)
6	Dysarthria (speech difficulty)	Paresthesia (especially skin)
7	Dysphagia (Difficulty in swallowing)	Apathy (motivational loss)
8	Sialorrhoea (Excessive saliva flow)	
9	Feeding issues	
10	Hygiene issue	
11	Slow activity in day-to-day life	
12	Dystonia (Involuntarily contraction)	
13	Abnormal reflex	

2.1.1 α-synuclein

Following the identification of a genetic connection between SNCA and Parkinson's disease (PD) in 1997, antibodies were developed against a-synuclein, which was shown to be abundantly expressed in Lewy bodies (LBs). Unusual a-synuclein deposition is evidently present early in Parkinson's disease. The protein of 140 amino acids that the SNCA gene generates is referred to as a "natively unfolded protein." When it binds to phospholipids, which are negatively charged lipids in biological membranes, it creates a-helical structures; after extended incubation, it develops b-sheet-rich structures. α-synuclein, β-synuclein and γ-synuclein belongs to the synclein family of proteins. α-synuclein's primary role seems to be controlling neurotransmitter release by interacting with the SNARE complex. Three primarily neuronal proteins that preferentially localize to presynaptic terminals under healthy circumstances make up the family. Extranigral b- and g-synuclein neuritic disease has been documented in synucleinopathies; nevertheless, this condition does not seem to be common [20]. The N-terminal domain, every mutation known to be connected to Parkinson's disease (PD), including Al53Thr, Ala30Pro, His50Gln, Gly51Asp, Glu46Lys, and Ala53Glu, and Ala53Glu. α-synuclein's self-propagation depends on the NAC domain. By using microelectron diffraction to determine their crystal structures, NACore and PreNAC revealed strands that transferred into β-sheets that are characteristic of amyloid assemblies. The solubility of α-synuclein depends on The C-terminal domain is present, although five proline residues indicates a lack of secondary structure. According to the study, α-synuclein's C-terminally shortened versions aggregate more

quickly than the full-length proteins and are essential for interacting with small molecules and other proteins in the nervous system. Each of the three domains contributes to aggregation and may have an effect on the other to either encourage or prevent oligomerization and fibrillation [21]. Alpha-synuclein has the ability to alter its structure, whereas prefibrillar α-syn can cause neurodegeneration by upsetting cellular ion balance, introducing soluble α-syn into aggregates with larger molecular weights, and disturbing cellular proteostasis. Additionally, it prevents neurotrophic factor generated from the brain/kinases linked to tropomyosin B from signaling, which causes dopaminergic neurons to die [22].

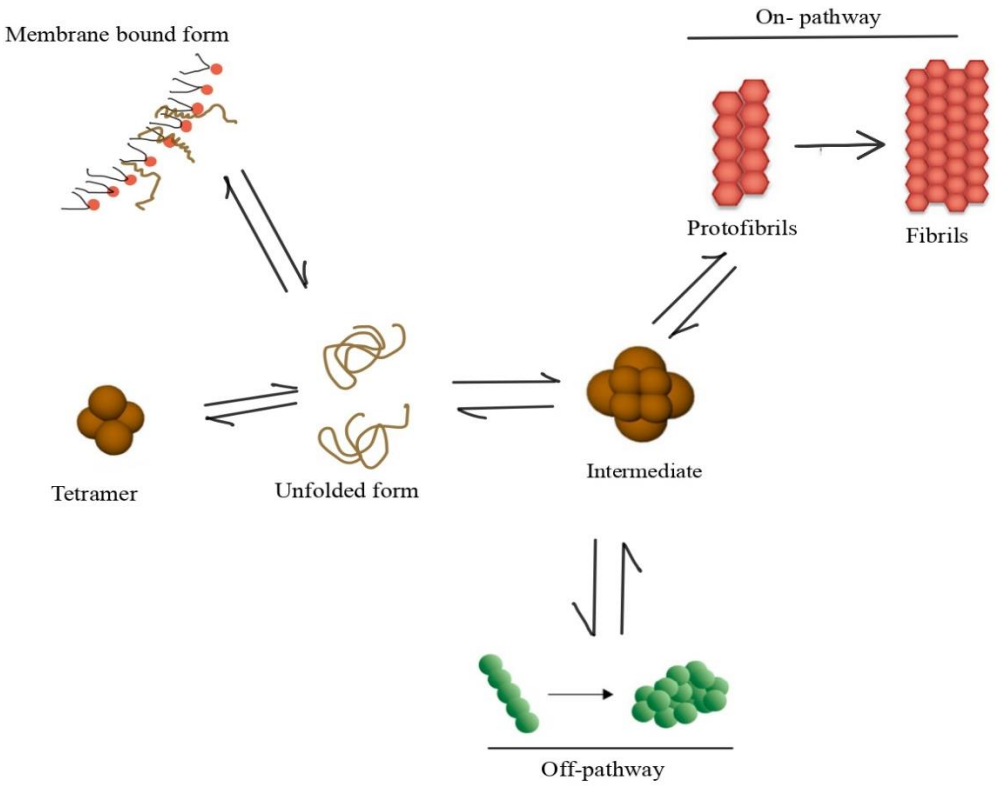

Fig 2.1 The process of accummulation and aggregation of alpha synuclein. Disrupting the balance between alpha-synuclein generation and clearance leads to the aggregation of monomers into oligomers, which can be on or off pathway oligomers.

2.1.2 Lewy Body

The Lewy Bodies, published in 1912, describes Lewy's life and investigation into Parkinson's disease. The diseased anatomy was initially described in detail by Lewy of Parkinson's disease, resulting in his important contribution in 1912, which Eosinophilic inclusion bodies in neurons within the brainstem. Lewy was named head

of Berlin's Neuroscience Research Institute and Clinic after seven years of hard effort in 1932 [23]. There are two forms of Lewy bodies (LBs): cortical and brainstem-type. Brainstem-type LBs are eosinophilic masses having a peripheral halo and dense center, while cortical LBs are erratic and ill-defined structures that lack a core. LBs are also discovered in the intraneuritic projections of neuronal cells LBs or Lewy neurites. Axons make up the majority of LB-containing processes, while filamentous structures make up both brainstem-type and cortical LBs [24]. Lewy bodies, a form of Parkinson's disease, are frequently studied using postmortem samples, which are static measurements of pathology. However, the investigational treatment of Parkinson's disease with fetal cell implantation in the 1980s and 1990s shed light on their biology. Despite variable therapeutic outcomes, several individuals treated with these cells had postmortem neuropathological examinations. Two noteworthy findings were that some of the fetal cells were able to integrate into the basal ganglia and that these newly formed cells looked to have Lewy body disease. This suggests that the elderly, sick cells around the implant may become the new integrated cells where α-synuclein aggregation could occur, resulting in Lewy bodies [25], [26].

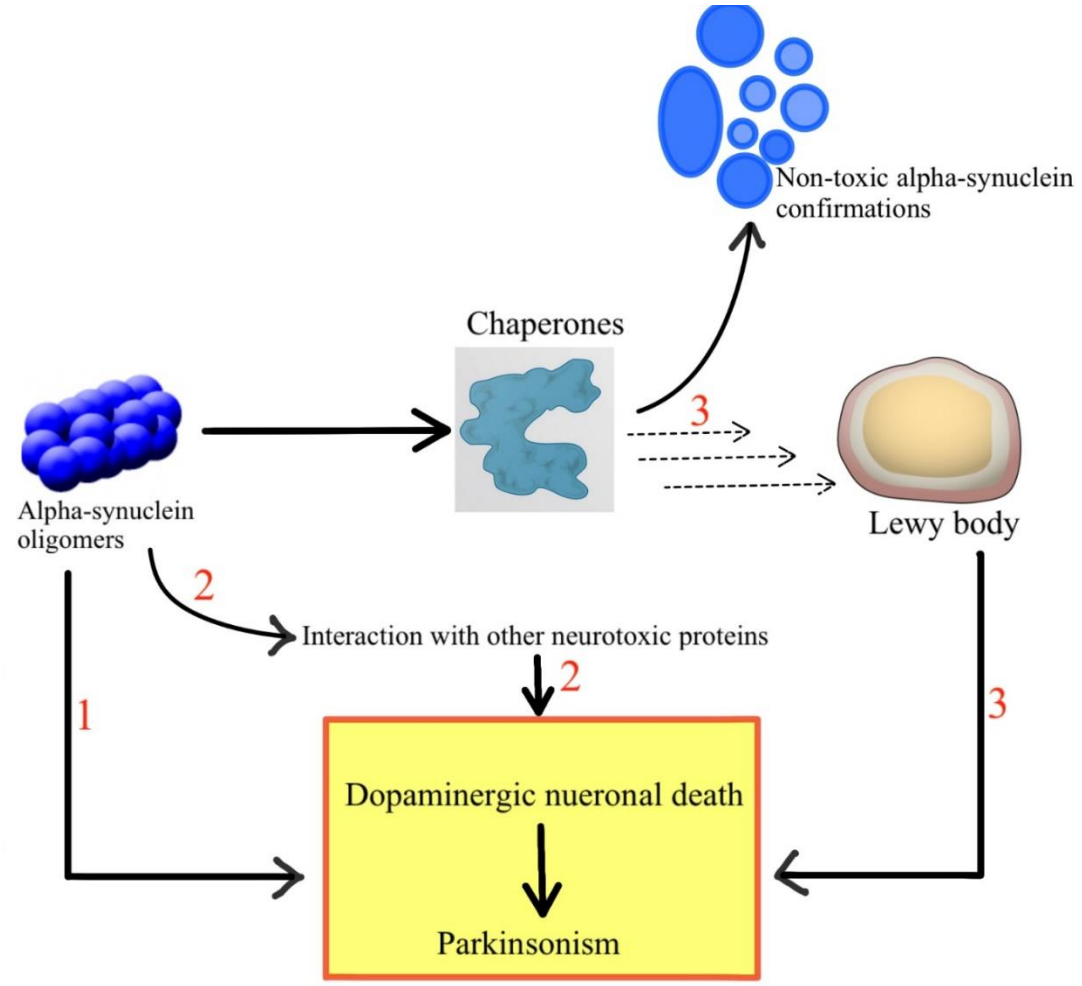

Fig 2.2 Different pathological hallmark of Parkinson disease, 1. Alpha synuclein oligomers aggregation leads to the dopaminergic neuron death, 2. α-Synuclein oligomers in mid brain interacts with other neurotoxic protein which ultimately leads to parkinsonism.

2.2 Oxidative stress

The results of the investigation indicated that oxidative stress levels were elevated in SN in both kin-related and irregular Parkinson's illness. The main cause of this stress is the body's natural process of producing oxygen free radicals during aerobic

respiration, which happens when mitochondria convert billions of molecules of molecular oxygen into water molecules [27]. During microbial infections, phagocytic cells generate large quantities of NO, O2−•, and H2O2 in order to destroy infectious organisms and harm healthy body cells [28]. Peroxisomes, the oxidative metabolism of toxins, and brain enzymes involved in dopamine metabolism, like tyrosine hydroxylase, L-amino acid oxidase, and monoamine oxidase (MAO), all create H_2O_2. The usual consequence of these enzymes is H_2O_2, which implies that dopamine and its metabolites have a function in producing reactive oxygen species (ROS) [29]. There are several methods to manufacture free radicals (ROS), such as by smoking, drinking coffee, and having certain medical conditions. Every human tissue, including SN, uses these universal pathways. On the other hand, reactive iron accumulated at neuromelanin (NM), inflammation, dopamine metabolism, and mitochondrial dysfunction are the particular ways whereby nigrostriatal DAergic neurons create ROS:

1. Reactive oxygen species (ROS) are primarily produced by the metabolism of dopamine, wherein H2O2 is produced by enzymes found in the brain, including tyrosine hydroxylase, L-amino acid oxidase, and MAO. ROS are produced by dopamine and its metabolites, with extra dopamine being retained in synaptic vesicles in neurons that are dopaminergic. Excess cytosolic dopamine is catabolized to ROS by the mitochondrial enzyme MAO [30].

2. Because mitochondrial impairment inhibits mitochondrial complex I, which results in ROS formation and apoptosis, it plays a major role in the creation of reactive oxygen species (ROS) in the DAergic neurons of SN in the brains of Parkinson's disease

patients [31]. Research conducted in the latter part of the 20th century revealed that certain mitochondrial complex I inhibitors, including rotenone and 1,2,3,4-tetrahydropyridine-1,2-methyl-4, can cause specific dopaminergic degeneration in the nigrostriatal region, producing a phenotype that is nearly identical to Parkinson's disease. This led to the creation of animal models for the condition [32].

3. One major source of reactive oxygen species (ROS) in New Mexico is the reactive iron stored there. There are two sides to NM's attraction for transition metals like iron, copper, and zinc. It has both high-affinity and low-affinity iron binding sites. The SN of a PD brain is saturated at high concentrations with high-affinity sites, which are where most irons bind. Fenton's reaction is catalyzed by iron that binds to low-affinity sites and accumulates in a reactive state[33].

4. Oxidative stress and inflammation are related, which is a major issue in this essay. Oxidative stress produces protein aggregates and dead cell debris, which cause the primary immune cells in the brain, microglia, to become inflamed. These microglia elevate the degree of oxidative stress and release certain kinds of reactive oxygen species (ROS) [34].

2.3 Mitochondrial dysfunction

In Parkinson's disease, increased reactive oxygen species (ROS) generation is linked to mitochondrial dysfunction. The main process by which the mitochondria produce energy is oxidative phosphorylation. Superoxide and hydrogen peroxide are produced by this metabolic pathway, which aids in the disease process and the propagation of free radicals [35], [36]. Mutations in proteins such as α-syn, parkin, DJ-1, and PINK promote mitochondrial dysfunction connected to oxidative stress and damage to DA cells. These mutations suggest a shared function in the mitochondrial stress response, which may account for the pathophysiology of Parkinson's disease [37], [38]. These genes' mutations have a major effect on the integrity and function of the mitochondria, which increases oxidative stress. Protease, lysosomal, and mitochondrial systems are impacted by ROS, and these systems in turn control how cells react to oxidative injury [39]. Parkinson's disease (PD) family variants are connected to changes in the proteins found in the mitochondria parkin, DJ-1, and PINK. Parkin-deficient animals exhibit reduced oxidative damage and striatal respiratory chain activity, whereas individuals with parkin gene mutations have lower Complex I activity inside their cellular structure [40], [41]. Mice's mitochondria fragmentation is caused by the mitochondrial-enriched protein DJ-1, which scavenges H_2O_2. KO mice have a mitochondrial phenotype that is fragmented and collect more ROS. Overexpression of mutant α-synuclein results in aberrant mitochondrial shape and function since α-synuclein interacts with the membranes of the mitochondria and prevents Complex I [42], [43].

CHAPTER– 3

MATERIALS AND METHODOLOGY

3.1 Data Set collection

A list of natural substances with the ability to impede the progress of neurodegenerative diseases was created through a review of the literature.The SMILE structures of all the compounds were resourced from the PubChem database. All the selected compounds were then submitted Light BBB, which is a online predictor for Blood Brain Barrier permeability. Four compounds i.e. ethoxyquin, dicarbine, farnesol and pterostilbene were observed as BBB permeable oot of all selected compounds.

3.2 Preparation of protein and ligands

The PDB crystal 1S2Q has chain A and B and sequence with a length of 520aa. The target protein, MAOB (monoamine oxidase B), was generated using BIOVIA Discovery Studio in order to dock the protein with the chosen compounds. After eliminating crystalline water molecules and heteroatoms (hetatoms), polar hydrogen atoms were introduced. After format. All the ligands (compounds) were obtained from PubChem in SDF format, and then they were converted using the web application Open Babel into PDB format. Both ligand and receptor, then converted into PDBQT file using Autodock tool by adding KOLLMANN charges.

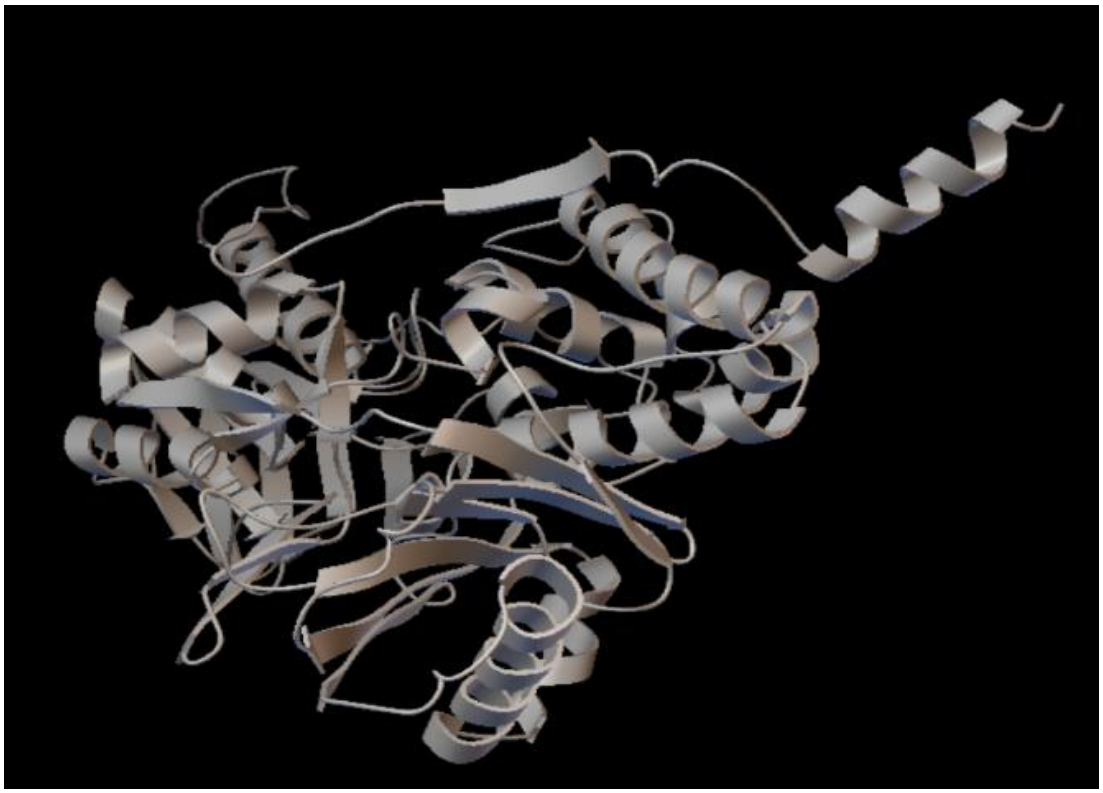

Fig 3.1 Structure of prepared protein.

3.3 Molecular docking using Autodock Vina

The virtual screening tool Autodock Vina is used to examine how protein (receptor) and compound (ligand) interact with each other. Active molecules were docked against the prepared protein structure using Autodock Vina. A config file was developed in order to define grid settings (Grid box centre: X-axis = 53.1832; Y-axis = 148.790; Z-axis = 30.3608, Coordinates: X-axis = 50.69; Y-axis = 72.14; Z axis= 62.43), ligand name, receptor name and exhaustiveness, which plays a critical role in dictating how much conformational sampling is necessary in the molecular docking. Exhaustiveness

is employed 8 in this study for sufficient binding options for the ligand and receptor without requiring computational exhaustiveness. For Vina analysis, Autodock produced output and log files that were examined to identify ligand molecule's binding affinity. In order to identify the interacting residues, the compound's output file was analyzed.

3.4 Interpretation of docked structure using BioVia software

To asertain the structural interaction between ligand and protein, BioVia Discovery Studio was used to evaluate the auto dock data. The investigation also looked at how amino acid ligand and the receptor interacted. The protein-ligand complex can be submitted to visualize the 2D structure of an interaction.

3.5 SWISS ADME investigation

To verify a drug's efficacy and potency, a detailed analysis of elements including lipophilicity, pharma kinetics, water solubility, physiochemical properties and medicinal chemistry is known as absorption, dispersion, metabolic activity, and excretion or ADME. A web-based application called SWISS ADME evaluates the agonist compounds according to specific parameters. Canonical SMILES were uploaded to the server and made available for analysis.

CHAPTER– 4

RESULTS

4.1 Interaction between MAOB and Ligands (Ethoxyquin, Dicarbine, Farnesol, Pterostilbene)

Amino acid residues that are interacting with MAOB in Ethoxyquin, Dicarbine, Farnesol, Pterostilbene are PHE103; PHE343, TYR326, LEU171, TYR398, TYR435; LYS296, PHE343, TYR398, TYR435, LEU171, TYR326; PHE343, LYS296, TYR398, MET436 and LEU171 respectively with the help of pi-pi stacked, pi-alkyl, alkyl and various hydrogen bonds.

4.1.1 Ethoxyquin docked with MAOB

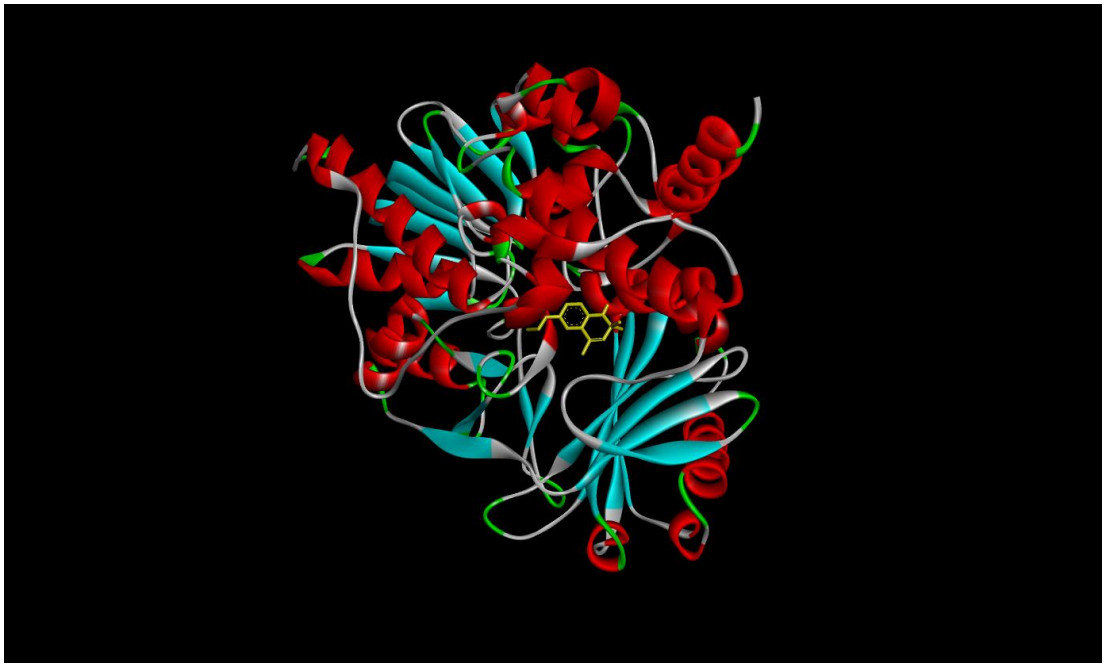

Fig 4.1 Interaction of MAOB and Ethoxyquin

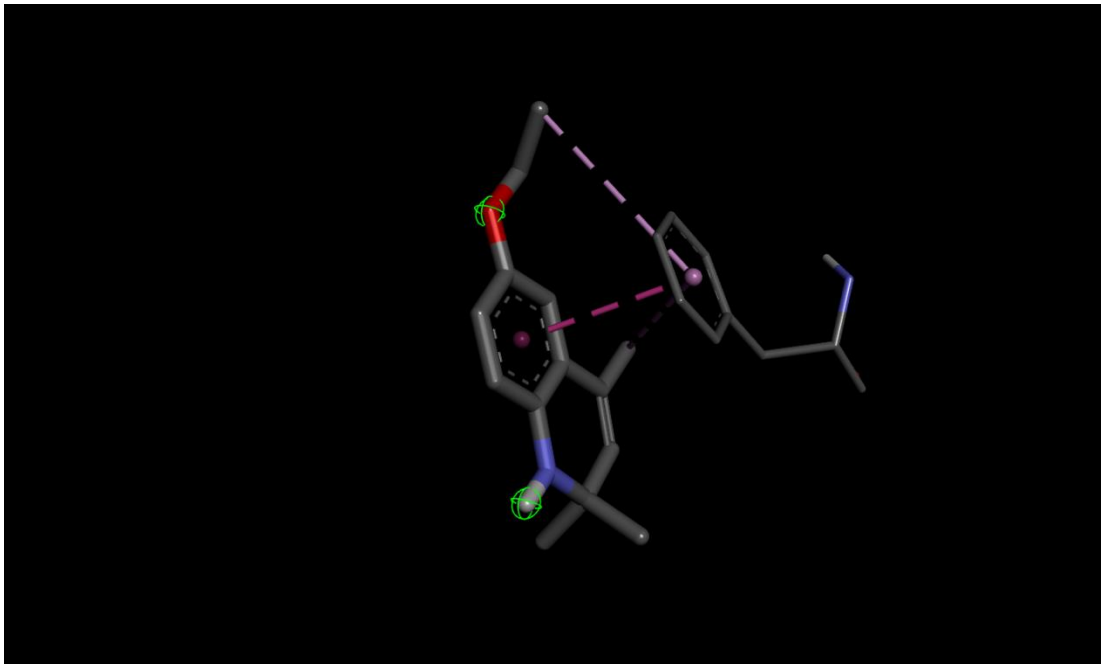

Fig 4.2 3D-Ligand interactions (Ethoxyquin) with MAOB

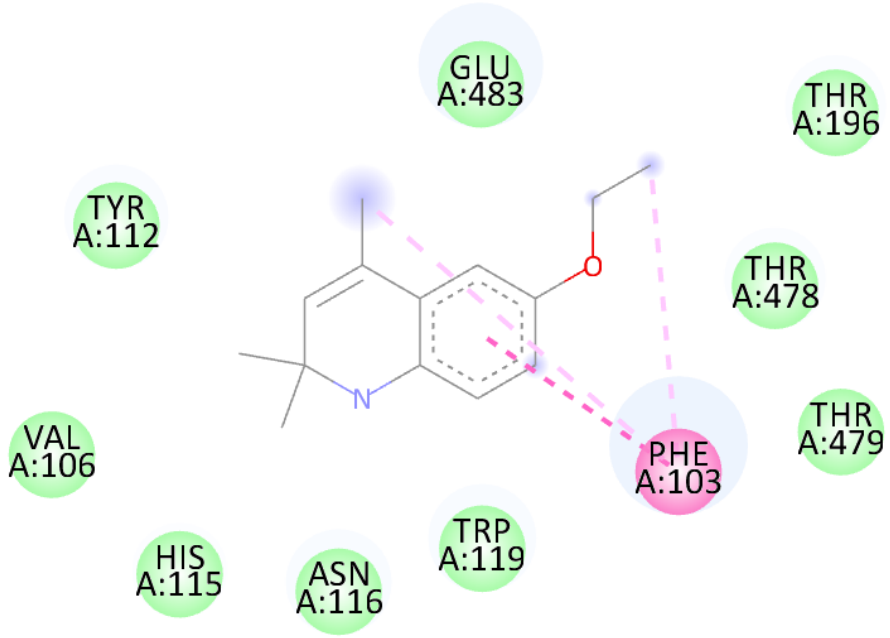

Fig 4.3 2D-Ligand interactions (Ethoxyquin) with targeted protein.

4.1.2 Dicarbine docked with MAOB

Fig 4.4 Interaction of MAOB and Dicarbine

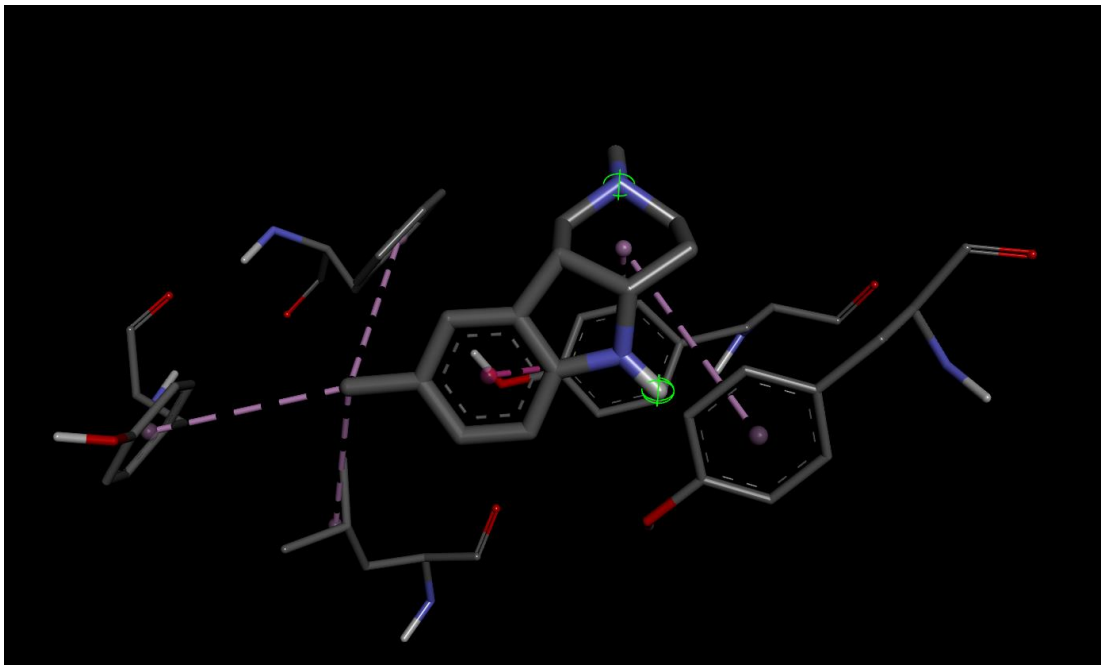

Fig 4.5 3D-Ligand interactions (Dicarbine) with MAOB

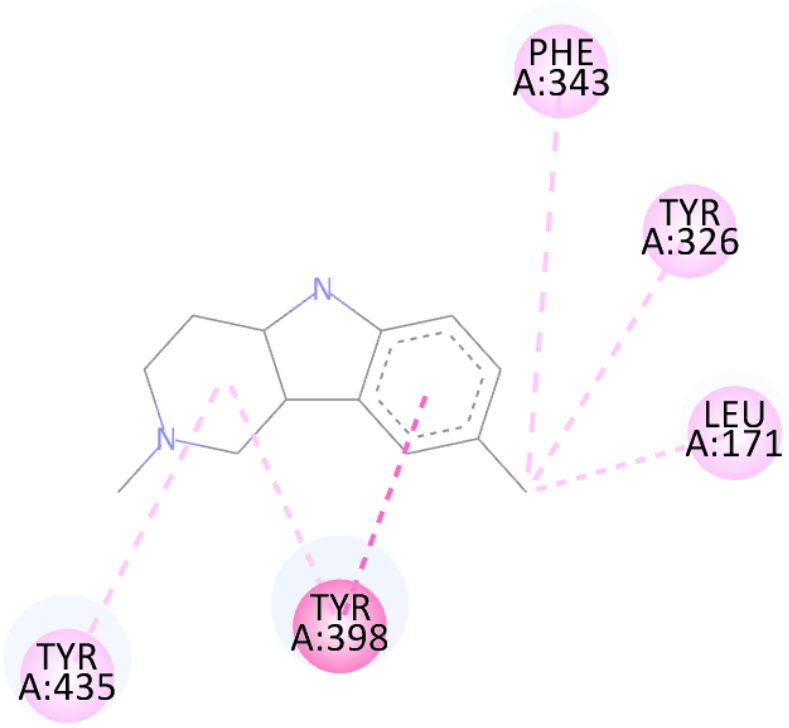

Fig 4.6 2D-Ligand interactions (Dicarbine) with targeted protein.

4.1.3 Farnesol docked with MAOB

Fig 4.7 Interaction of MAOB and Farnesol

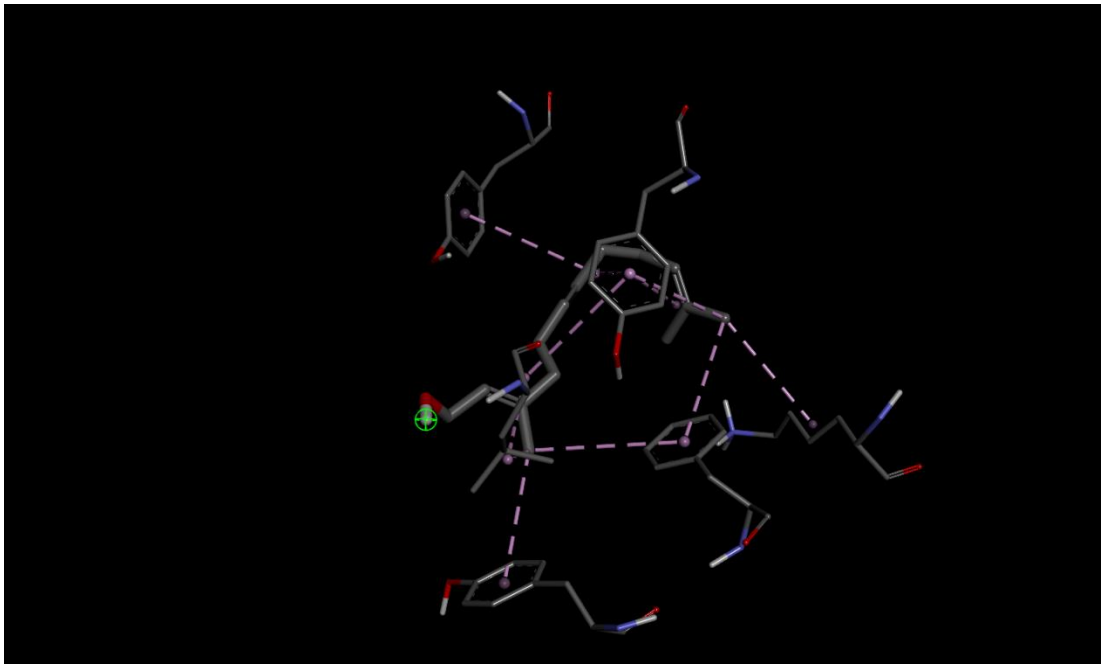

Fig 4.8 3D-Ligand interactions (Farnesol) with MAOB

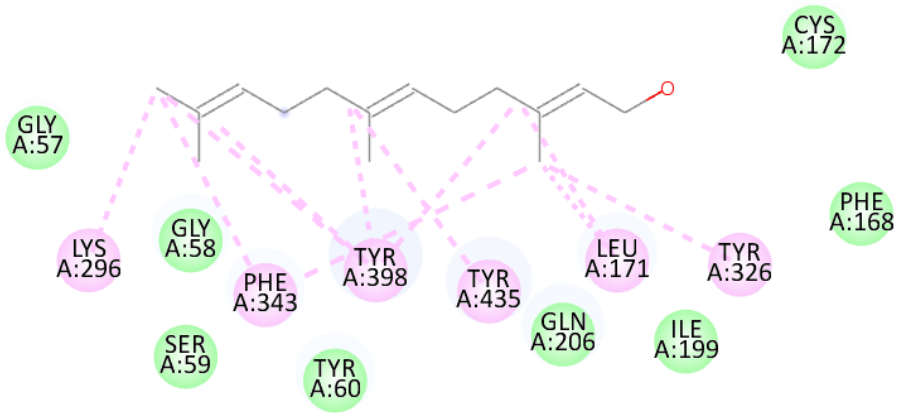

Fig 4.9 2D-Ligand interactions (Farnesol) with targeted protein.

4.1.4 Pterostilbene docked with MAOB

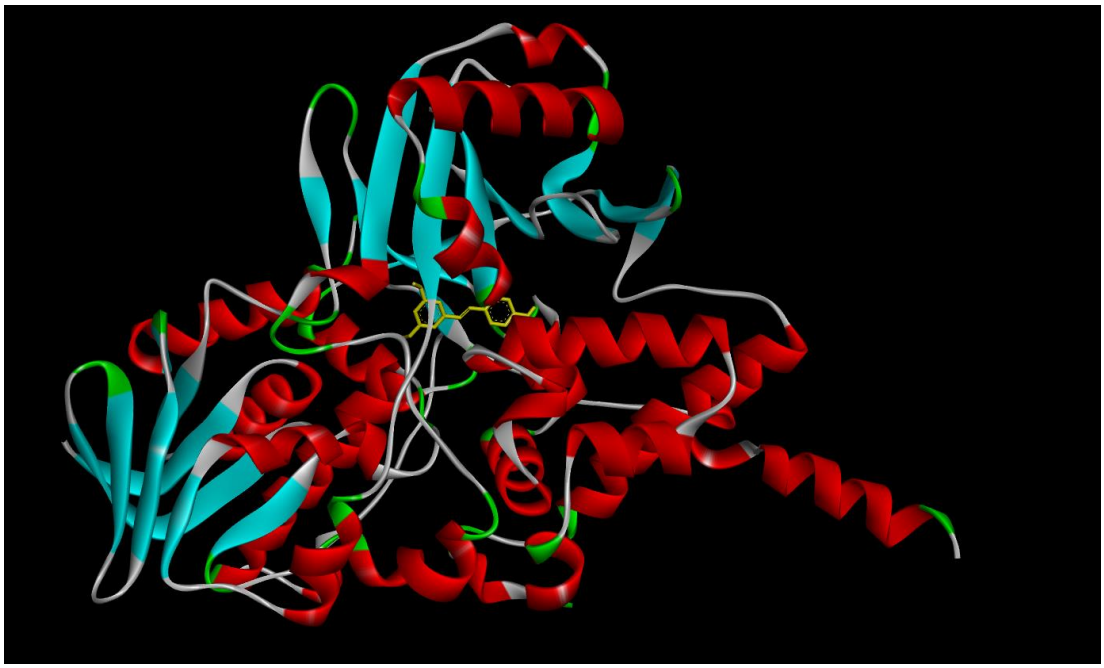

Fig 4.10 Interaction of MAOB and Pterostilbene

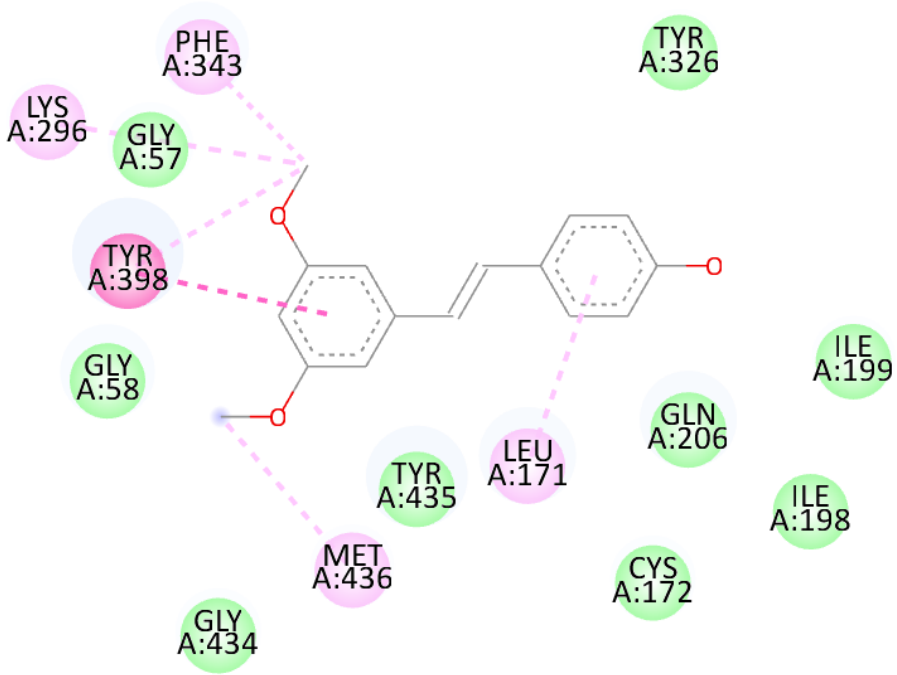

Fig 4.11 2D-Ligand interactions (Pterostilbene) with targeted protein.

Various amino acid residues are interacting with protein MAOB (monoamine oxidase B), which are shown below (Fig 4.1, fig 4.2, fig 4.3, fig 4.5, fig 4.6, fig 4.7, fig 4.8, fig 4.9, fig 4.10, fig 4.11). The autodocking technique produced favorable results that showed a high level of interaction between MAOB and ligand (Ethoxyquin, Dicarbine, Farnesol, pterostilbene). Docking score indicate that the ligand (Ethoxyquin, Dicarbine, Farnesol, pterostilbene) binds to the MAOB protein effectively. The binding energy is computed as follows: -7.3 kcal/mol, -8.0 kcal/mol, -7.0 kcal/mol, -8.8 kcal/mol respectively and the Cluster RMSD value 0. The topology of the compound's interaction with the target protein was evaluated docking data; this interaction is shown as a helical structure made up of an A chain whereas the potential target is illustrated by the spheroid and linear structure between the helical structure.

Table 2. Binding affinity of antioxidants in different confirmations

S.No.	Ligand	Binding Affinity	rmsd/ub	rmsd/lb
1	1s2q_3293_uff_E=136.77	-7.3	0	0
2	1s2q_3293_uff_E=136.77	-6.8	3.559	2.156
3	1s2q_3293_uff_E=136.77	-6.3	6.017	2.293
4	1s2q_3293_uff_E=136.77	-6.2	5.008	2.397
5	1s2q_3293_uff_E=136.77	-6.1	5.502	2.906
6	1s2q_3293_uff_E=136.77	-6.1	5.461	2.421
7	1s2q_3293_uff_E=136.77	-5.9	13.895	11.999
8	1s2q_3293_uff_E=136.77	-5.8	14.578	12.5
9	1s2q_3293_uff_E=136.77	-5.8	14.023	12.102
10	1s2q_65684_uff_E=344.96	-8	0	0
11	1s2q_65684_uff_E=344.96	-6.8	20.492	19.574
12	1s2q_65684_uff_E=344.96	-6.7	7.47	5.055
13	1s2q_65684_uff_E=344.96	-6.4	22.596	20.899
14	1s2q_65684_uff_E=344.96	-6.2	25.468	23.493
15	1s2q_65684_uff_E=344.96	-6.1	22.18	20.878
16	1s2q_65684_uff_E=344.96	-5.8	18.366	15.854
17	1s2q_65684_uff_E=344.96	-5.7	28.78	26.765
18	1s2q_65684_uff_E=344.96	-5.6	23.432	21.496
19	1s2q_445070_uff_E=148.85	-7	0	0
20	1s2q_445070_uff_E=148.85	-7	10.091	6.314
21	1s2q_445070_uff_E=148.85	-6.7	2.983	2.233
22	1s2q_445070_uff_E=148.85	-6.6	11.32	7.449
23	1s2q_445070_uff_E=148.85	-6.5	21.991	20.47
24	1s2q_445070_uff_E=148.85	-6	17.991	14.127
25	1s2q_445070_uff_E=148.85	-5.7	21.55	20.331
26	1s2q_445070_uff_E=148.85	-5.6	22.176	20.183
27	1s2q_445070_uff_E=148.85	-5.6	25.023	21.475
28	1s2q_5281727_uff_E=188.20	-8.8	0	0
29	1s2q_5281727_uff_E=188.20	-8.8	2.805	0.122
30	1s2q_5281727_uff_E=188.20	-8.4	2.659	1.699
31	1s2q_5281727_uff_E=188.20	-7.9	9.354	3.019
32	1s2q_5281727_uff_E=188.20	-7.9	21.437	19.836
33	1s2q_5281727_uff_E=188.20	-7.9	21.942	20.728
34	1s2q_5281727_uff_E=188.20	-7.8	21.251	19.453
35	1s2q_5281727_uff_E=188.20	-7.8	21.749	19.539
36	1s2q_5281727_uff_E=188.20	-7.7	22.571	21.305

4.2 ADME study of ligands

Defining the ADME analysis of ligands used in this study. Considering Lipinski's value as necessary and its shown solubility in water under logs (ESOL); logs (Ali), and logs (SILICOS-IT) segment with a value of -3.29, -3.22, -4.72; 2.86, -2.29, -3.48; -4.17, -5.60, -3.15; -4.01, -4.29, -4.69 of ethoxyquin, dicarbine, farnesol, pterostilbene respectively. The skin permeation value (log Kp) is less, with values of 5.42cm/s, -5.88cm/s, -3.81cm/s, -5.18cm/s respectively. The drug's lipophilicity was evaluated using cast log PO/W (XLOGP3).

CHAPTER– 5

DISCUSSION AND CONCLUSION

This chapter, provides a thorough examination of a study's findings, evaluating their relevance, shortcomings, and suggestions for more study in the treatment of Parkinson disease (PD), while also addressing the study's limitations.

5.1 Interpretation and analysis of results

The second most common neurodegerative disease is parkinson’s disease (PD), which is challenging to diagnose since there isn’t enough data to describe the condition early on. It has been projected that the prevalene of parkinson’s disease (PD) would double over the next 30 years [9]. PD is a condition defined by stiffness, tremor, and bradykinesia, with Parkinson's disease as the primary cause. It is asymmetric and responds to dopaminergic therapy, with no history or examination evidence. Pathological results show reduced nigral dopamine neurons and Lewy bodies in the surviving neurons [44]. Different environmental and genetic variables which reveal the pathological hallmark of PD. Five more mutant genes associated to familial Parkinson's disease (PD), which includes parkin, PTEN-induced putative kinase 1, DJ-1, HTRA2, and LRRK2, have been found. These genes may be involved in oxidative stress and mitochondrial dysfunction in Parkinson's disease. Several scientific studies support that uncontrolled formation of ROS (reactive oxygen species) is a common

feature in oxidative stress and mitochondrial dysfunction cascade [45]. So, the application of in silico techniques such as molecular docking has greatly improvedthe process of developing new drugs in recent years. Recent research has explored the potential of substances such as rasagiline, selegiline, safinamide and others to bind and inhibit MAOB by docking with positive outcomes. Various antioxidants were studied that inhibit the MAOB, but there is very limited study on the antioxidants taken in this study, which may inhibit the MAOB by decreasing the level of oxidative stress. Thus, applying molecular docking to target MAOB using ethoxyquin, dicarbine, farnesol, pterostilbene. The results of this investigation demonstrated a effective connection between ligand and protein, with predicted binding energy value of -7.3kcal/mol, -8.0 kcal/mol, -7.0 kcal/mol, -8.8 kcal/mol. Due to this less binding energy, PD symptoms are ameliorated.

5.2 Future scope

The results of this study confirms that these compounds are optimal option for the intended use due to its high binding values and they are permeable to Blood Brain Barrier. Based on docking study, pterostilbene is the most effective ligand among the four. Even though there is not yet a cure fo this illness, these findings might be helpful in future research and further study can lead to more effective treatment option for PD. To investigate the stability of ligand binding, the study suggests using molecular

dynamic modeling. In order to assess the biological activity of the suggested ligands, both in-vitro and in-vivo experiments should be performed.

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