MASTER OF SCIENCE (BIOTECHNOLOGY)

KUMUD KAUL

2023

TARGETING NNMT BY JERATININE E USING BIOANALYTICS TO TARGET PARKINSON'S DISEASE

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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MAY, 2023

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I, Kumud Kaul, Roll Number: 2K21/MSCBIO/20, student of M.Sc. Biotechnology, hereby declares that the work which is presented in the Major Project entitled "**Targeting NNMT with Jeratinine E using bioanalytics to target Parkinson's disease** " in the fulfillment of the requirement for the award of the degree of Master of Science in Biotechnology and submitted to the Department of Biotechnology, DTU, is an authentic record of my own carried out during the period from Jan to May 2023, under the supervision of **Prof Pravir Kumar**.

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Title of the Paper: "Fate of Jeratinine E as a potential compound to Target NNMT Protein in Countering Parkinson's Disease"

Author Names: Kumud Kaul, Pravir Kumar

Name of Conference: 2nd International Conference on Smart Technologies and Systems for Next Generation Computing. – IEEE Conference

Date and Venue: 21st -22nd April 2023, Virtual at IFET College of Engineering, Tamil Nadu

Registration: Done

Status of the Paper: Accepted

Date of Paper Communication: 8th March 2023

Date of Paper Acceptance: 14th March 2023

Date of Paper Publication: NA

Kumud Kaul (2K20/MSCBIO/20)

Date

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Pravir Kumar
30/05/2023

Place: Delhi

Prof. Pravir Kumar

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in

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ACKNOWLEDGEMENT

I would like to express my gratitude and respect toward my guide, **Prof Pravir Kumar**. He gave me the opportunity to do this thesis work and provided precious support to this project work. His energy, dedication, and determination have had a huge impact on me and made this thesis a work of ease. This thesis is made only with his guidance.

I would also like to thank **Mr. Sudhanshu, Miss Mehar and Mr. Rohan** for his support and guidance throughout my work. Also, I want to thank Delhi Technological University for providing me with possibilities during my academic career.

Finally, my thanks go to all the people who have supported me during my entire study.

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ABSTRACT

Parkinson's disease (PD), the second most common neurological ailment, is expected to become more common over the following three decades. Despite growing study, it is still difficult to get a precise diagnosis and the early phases of PD are still poorly understood. According to certain ideas, autointoxication may be the cause of Parkinson's disease (PD), as the blood-brain barrier prohibits charged substances from entering the brain and necessitates the existence of the nicotinamide N methyltransferase (NNMT) enzyme for neurotoxicity. It's interesting to note that NNMT activity is more apparent in Parkinson's patients' brains. The creation of certain inhibitors that block the NNMT enzyme may result in considerable improvements in primary and secondary PD preventive methods. The GEO collection gives researchers access to clinical and gene expression data from PD patients, allowing them to further examine this by analyzing patient outcomes and finding potential biomarkers for the illness. Our work connected genes with clinical data using protein-protein interactions (PPI) and functional enrichment approaches, using the GDC data portal to pinpoint the most important genes linked to PD. We identified genes with variable levels of expression between those with the PD mutation and those without by analyzing differential gene expression (DEGs). The importance of these genes in relation to PD was also quantified with the help of the GDC Data website. In our investigation, the naturally occurring substance Jeratinine E showed promise as a therapeutic option. We learned more about the natural compounds' relation with NNMT with the help of molecular docking. This investigation states that Jeratinine E has a stronger affinity for NNMT. Jeratinine E's potential for further research was also assessed while accounting for its pharmacokinetic characteristics using ADMET analysis.

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CHAPTER 1: INTRODUCTION

Parkinson's disease (PD), a neurodegenerative condition that is subsequently most prevalent and a mobility handicap, affects one percent of those over 60.[1] . PD is referred to in medical community as a neurodegenerative illness that affects both motor and nonmotor brain circuits. Progressive movement issues are brought on by it [2]. The PD patients will significantly rise over the following 25 years. [3] . The clinical presentation of PD is inherently complex, the disease progresses quickly, and the risk of complications is substantial [4]. The two main pathologic features of Parkinson disease are the misfolded -synuclein component of Lewy bodies that manifests in several patient systems and the premature selective death of dopamine neurons. Pathologic research has shown that neurons age over a lengthy period in phases, with each damaged location matching to a particular symptomatology of Parkinson disease. A pathologic analysis of the substantia nigra reveals a 30–70% cell loss when motor symptoms first appear [2]. In a nutshell, the disorder is brought on by the pigmented neurons present in the substantia nigra dying off gradually, which reduces dopamine levels in the striatum [5]. This region of the brain loses 50–70% of its neurons by the point of death compared to the same region in unaffected people. [1]. Asymmetric bradykinesia development, rigidity, and resting tremor are characteristics of PD[6] . Similar correlations between more severe PD and gait issues, postural instability, and motor dysfunction have been observed in both dopaminergic and non-dopaminergic brain regions [7] . Approximately forty percent of the variability in PD risk is caused by unknown PD susceptibility genes [8]. Parkinson's disease has been

associated with oxidative stress, but the precise cause is still unclear. Because of their functions in reductive processes and energetics, pyridine nucleotides are crucial in oxidative stress [9]. PD risk is predicted by the CpG site cg10917602, pointing to a predictive causative role for the process of methylation at this locus [10].

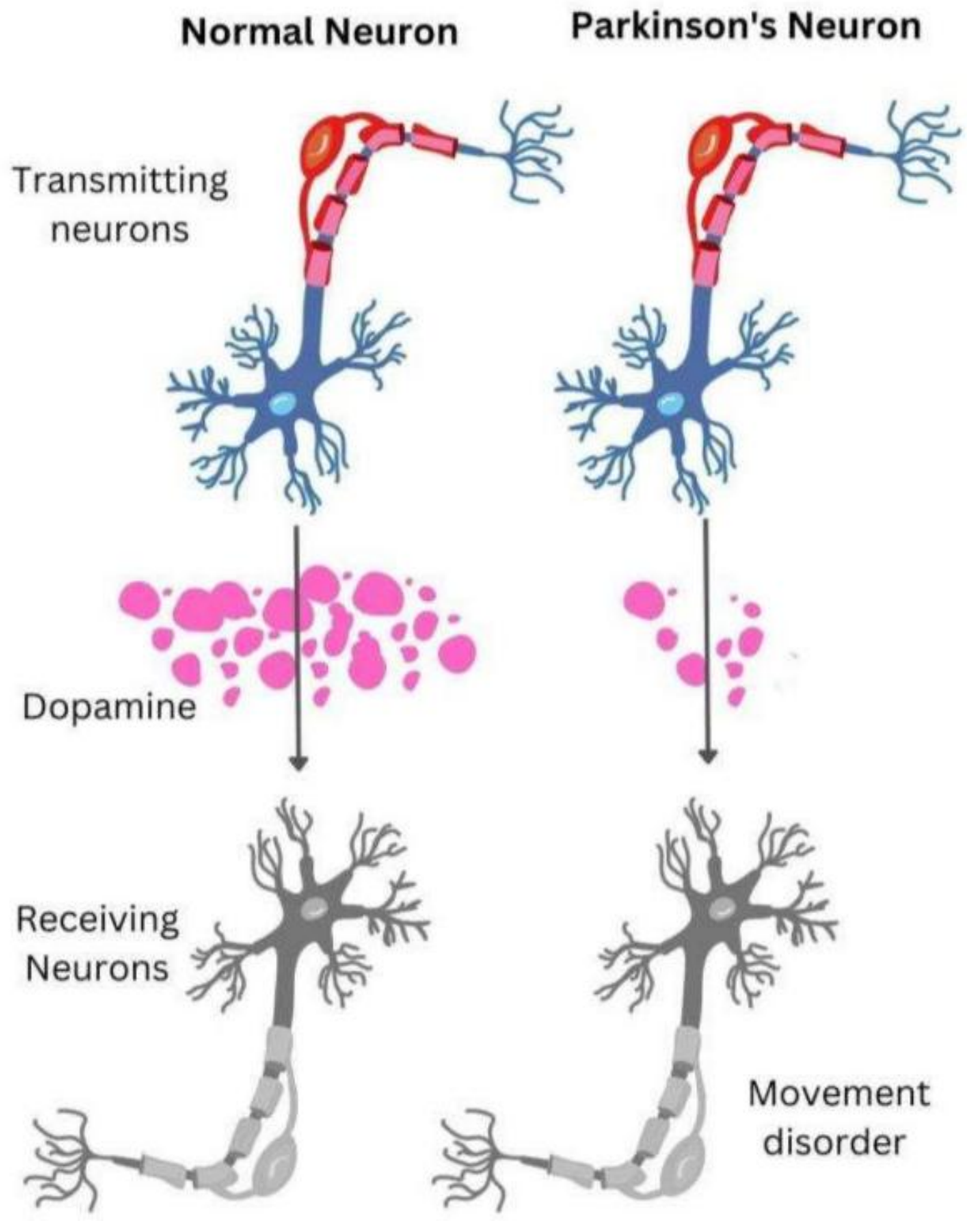

Fig 1 The difference between the normal and Parkinson's diseased neuron

Nicotinamide is methylated by Nicotinamide N-methyltransferase (NNMT) to create 1-methylnicotinamide by using S-adenosylmethionine as a cofactor[11]. NNMT's neuronal mechanisms of action are still unknown, despite epidemiological research suggesting it to be a risk criteria for neurodegenerative conditions like PD and schizophrenia[12] . The metabolism of nicotinamide can be compared to that of natural neurotoxins because it has

a pyridine ring within its structure. Parkinson's disease may be brought on by azahetero cyclic amines' high N-methylation capacity before symptoms appear[13]. Given that methylphenyl pyridinium ion, a well-known dopaminergic neurotoxin, is related to the byproducts of NNMT's N-methylation of pyridines, it is conceivable that NNMT activity in the brain plays a role in the development of Parkinson disease [14]. All human tissues, including the nervous system, contain the NAD+/NADH metabolism-dependent enzyme nicotinamide-N-methyltransferase (NNMT), and it has been hypothesized that NNMT may have an impact on Parkinson's disease. NAD+, a necessary coenzyme for fuel oxidation and the interconversion of several metabolites, frequently changes to NADH during these activities [12]. NNMT is a crucial link among metabolism in cells and epigenetic gene control and there is mounting evidence that it is linked to a few illnesses. Different levels of NNMT, a protein that is exclusively neuronal, are expressed in different parts of the human brain. It has recently been shown that NNMT is crucial for neurotoxicity in the human brain because the blood-brain barrier prevents charged substances from passing. Additionally, it is more pronounced in the parkinsonian brain. N methyl nicotinamide, an MPP+ analogue, would rise with increased enzymatic activity whereas different levels of the neuroprotectant intraneuronal nicotinamide would fall. Therefore, we will concentrate on the NNMT gene and its role in PD in order to examine and correct the same.

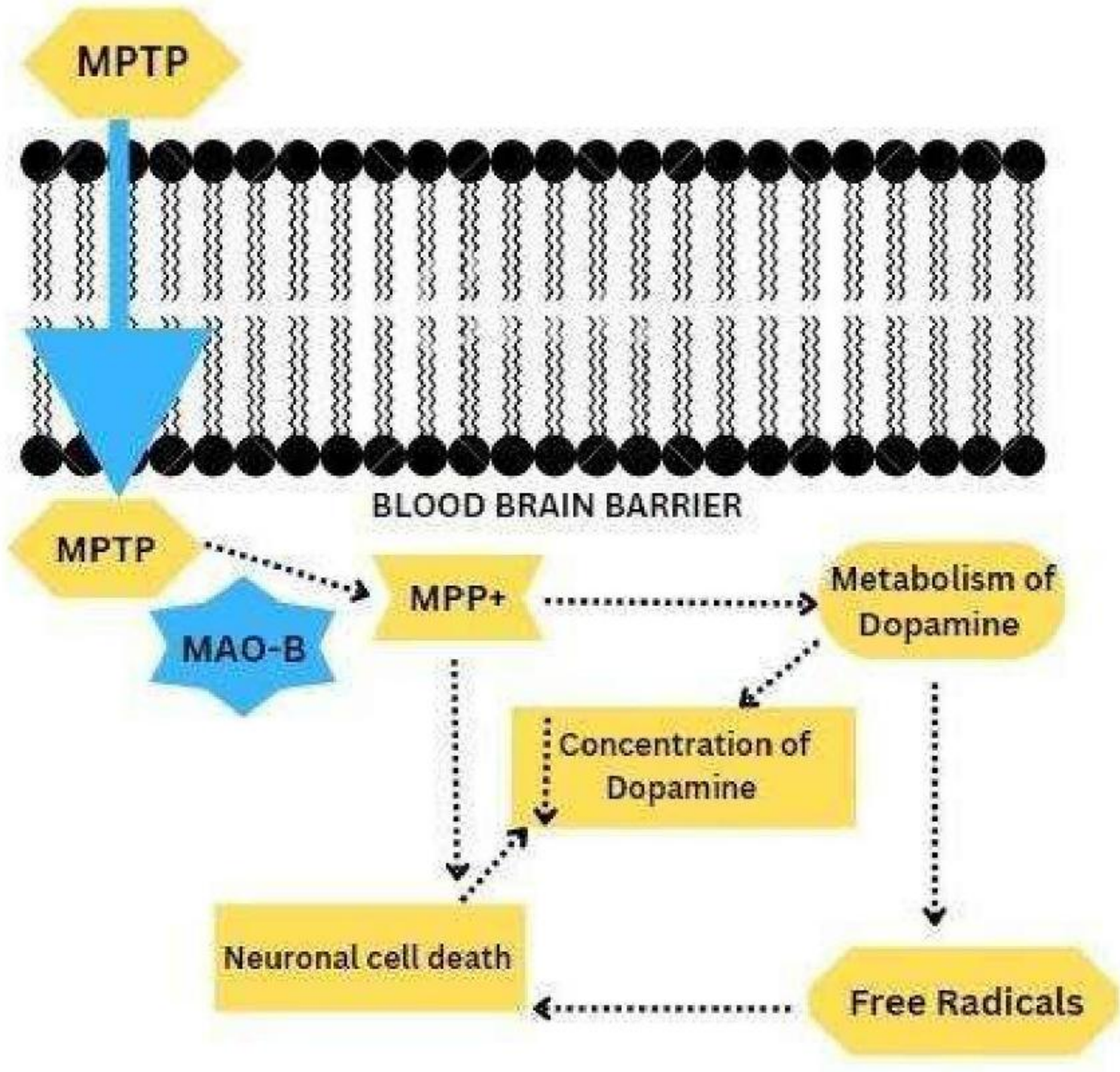

Fig 2 The relation between MPTP, MPP+, and dopamine

CHAPTER 2: Parkinson's disease

The leading cause of disability globally is brain diseases, and Parkinson's disease prevalence is increasing more fast than other neurological conditions. The most prevalent form of parkinsonism is Parkinson's disease, a term used to describe a variety of neurological conditions that have rigidity, slowness, and tremor-like movement issues [15]. Parkinson's is a long-lasting neurological condition causing facial stiffness and tremor, as well as signs of increased muscle tone and poor coordination [4]. The substantia nigra's steady loss of pigmented neurons and the striatum's consequent drop in dopamine levels are what give rise to the disease[5], [15]. Among the motor symptoms are bradykinesia, rigidity of the muscle tone, unsteadiness of posture and tremor while at rest.

Additionally symptoms, including sleep disorders, dementia, altered sensory perception, and autonomic dysfunctions are present in PD patients [2]. PD's etiology is still completely understood, however research indicates that it may be caused by a variety of causes, including genetics, environmental toxins, and aging[16].

Prior to experiencing symptoms associated to movement, Parkinson's disease patients typically experience nonmotor symptoms for years. However, unless expressly questioned, these symptoms are frequently not reported by patients. There are other symptoms that are nonmotor symptoms like depression, lost smell, urinary dysfunction, hypotension, and sleep behaviour disorder. Although these symptoms are not specific to Parkinson's disease, they increase the likelihood that the condition may eventually be identified if they co-occur. Rapid eye movement sleep behavior disorder is significantly linked to an increased

likelihood of receiving a Parkinson disease diagnosis later on [15].

CHAPTER 3: Dopamine

The brain produces the chemical dopamine. Dopamine is created in the substantia nigra, a region of the nervous system. Additionally, it is made in the hypothalamus and ventral tegmental region of the brain. Dopamine's molecular structure is C8H11NO2. Dopamine's aberrant function is thought to contribute to a variety of nervous system illnesses. Due to medication effects and in response to happiness, dopamine levels in the brain rise. Dopamine acts on the brain to regulate bodily movements. Understanding how dopamine controls how the brain controls bodily movement can help us develop crucial treatments for conditions like PD and other psychiatric diseases that are linked to the brain.

3.1 Dopamine metabolism techniques

Tyrosine is used to make dopamine. An activated transport system in the brain then absorbs it. Tyrosine is produced in the liver by the enzyme phenylalanine hydroxylase's activity. Catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO) are two crucial enzymes required for the metabolism of dopamine. These enzymes change dopamine into inactive metabolites. The MAO-A and MAO-B are the two MAO subunits. While catecholaminergic neurons, which are cells of the nervous system, contain MAO-A, astrocytes only contain MAO-B. COMT is released by the glial cells. Neurons either lack this enzyme entirely or just have very modest levels of it. Dopamine is initially converted by MAO to DOPAL (3,4-dihydroxyphenylacetaldehyde). It is then converted to 3,4-

dihydroxyphenylacetic acid (DOPAC) by the activity of aldehyde dehydrogenase [17].

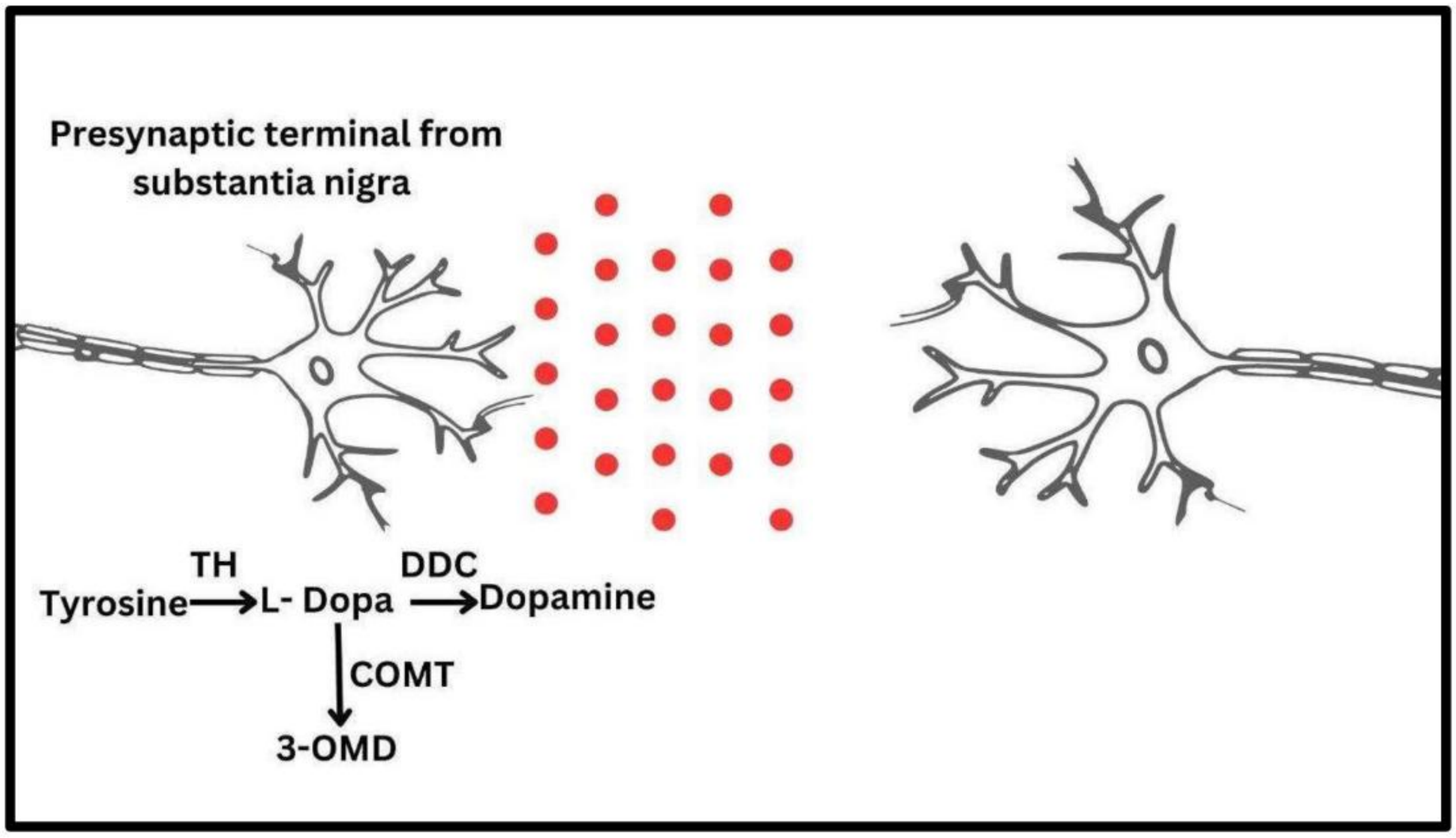

Fig 3 The release of dopamine and the showcase of the presence of enzymes involved

CHAPTER 4: NNMT (N- methyl nicotinamide)

This enzyme produces N-methyl nicotinamide, which is its main metabolite, by N-methylating pyridines, particularly nicotinamide. The remaining is essential to several metabolic processes because it goes on to produce NADH and NADPH. When compared to NADH, NADPH often plays various roles, and it is thought that it mostly contributes to oxidative defense or reductive metabolism. The elimination of peroxide by GSH peroxidase is a key part of the brain's oxidative defense system. It has been shown that the ability to restock GSH for GSSG reductase as a cofactor could rely on the presence of NADPH-reducing equivalents in the end. However, it is believed that NAD(H) plays a valuable role in the energetic production of ATP. Due to impaired energetics, NAD+ depletion is thought to be a crucial element in cell death during oxidative stress.

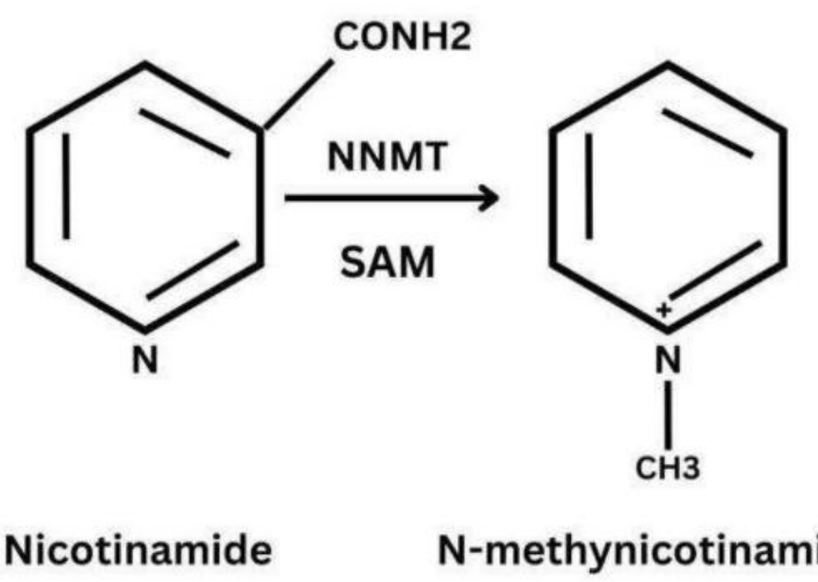

Fig 4 Formation of N-methyl nicotinamide from Nicotinamide

The production of tetrahydrobiopterin, reduced glutathione deficit, which is also known to occur in the starting of PD, and mitochondrial chain complex 1 defects, which are known to occur in MPTP People with Parkinson's disease (PD) are particularly interested in Parkinsonism and the idiopathic illness. Nicotinamide offers cytoprotection using processes like cysteine protease function. Nicotinamide also protects cellular integrity and avoids cellular degeneration through the preservation of DNA integrity and alteration in

phosphatidylserine symmetry in the membrane [18]. When used in cell culture, nicotinamide guards against the toxic effects of MPTP and the adverse consequences of L-DOPA. Dopamine deficit, cell death in the par's compacta, and parkinsonism are all symptoms of experimental nicotinamide shortage, which is brought on by the antimetabolite 6-aminonicotinamide. Dopamine agonists also have a positive effect on these symptoms. The lethal synthesis of NADH and NADPH mimics is the root cause of poisoning.

MPTP, a prototoxin, is converted to MPP+ by MAO-B. The blood-brain barrier prevents the passage of 49 MPP+ and other molecules with comparable charges. If this transition happens inside the brain, MPP+ may be taken up by dopaminergic cells, concentrated via the dopamine active transport system, and then increased in mitochondria until it damages Complex 150.. Oral MPTP consumption is far less toxic because MPP+, which cannot penetrate the blood-brain barrier, is transformed by the liver enzyme MAO-B to MPP. It's interesting to note that MAO-B inhibition has no impact on the course of Parkinson's disease. However, a distinct and quicker method is used to transform pyridines such and 4-phenyl pyridine and nicotinamide into MPP+ and associated molecules. This route's

driving force is NNMT.

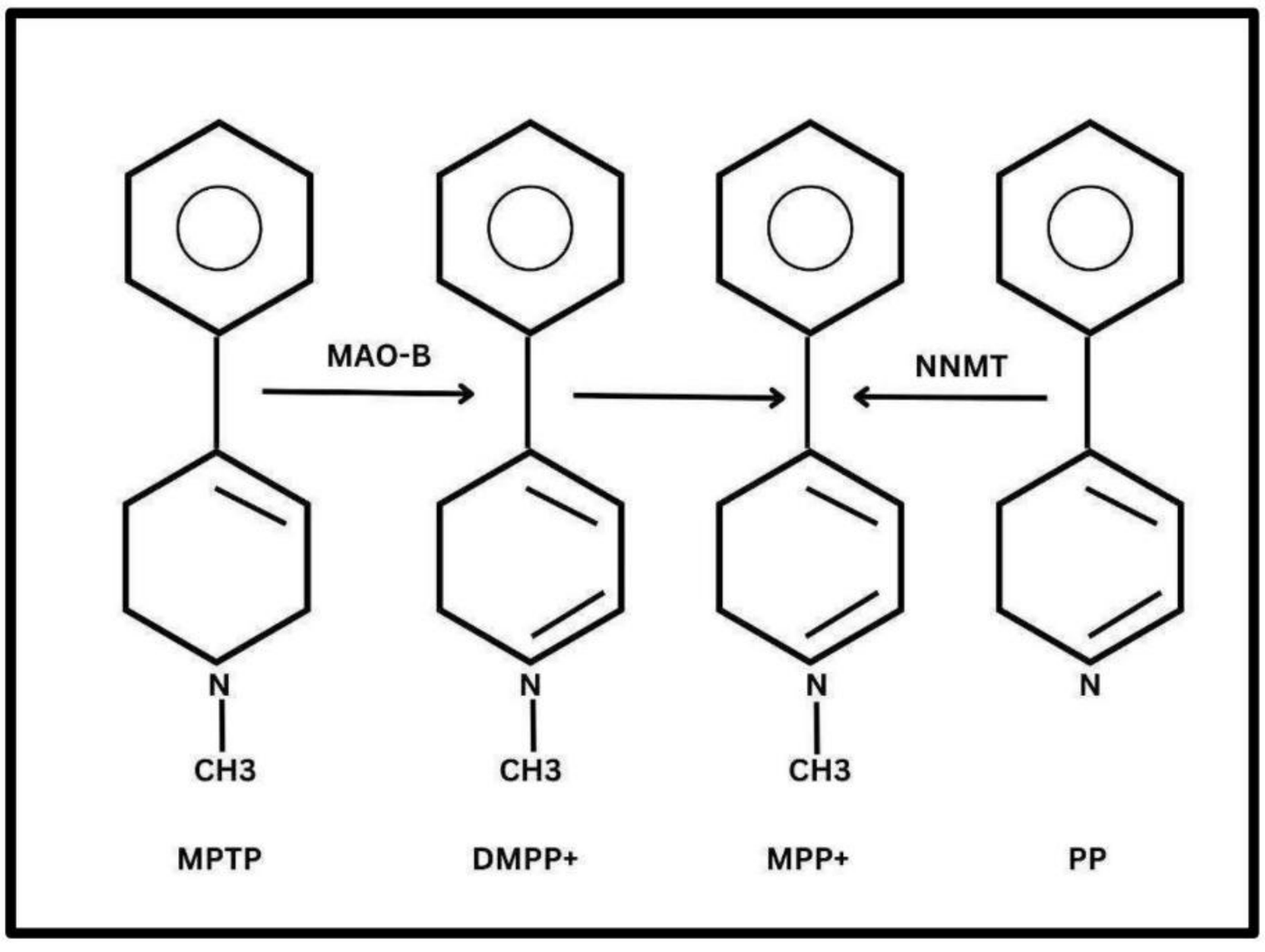

Fig 5 Pathways of formation of MPP+

Both low and high nicotinamide concentrations are hazardous, thus strict control can be required. High dietary nicotinamide intake and poor methylator status caused by genetic vulnerability combined with an inhibitor of NNMT like nicotine may cause PARP depletion when too high or carcinogenesis or developmental issues and degradation when too low. Because it prevents the brain from excreting choline77, another charged N-methylated molecule, N-methyl nicotinamide may have developed a typically advantageous function that increases acetylcholine levels. This might help with cognitive development and even postpone the signs of cholinergic breakdown in those who already have Parkinson's disease (PD), even if it wouldn't be pharmacologically beneficial in those cases. As is the situation

with MPTP overdose, N-methyl compounds may in any case migrate from different other regions of the brain and be absorbed by dopaminergic cells. Complex I is where the majority of the ATP synthesis process starts, and it is assisted by Nicotinamide Adenine Dinucleotide (NADH), which functions as a hydrogen and electron donor. In mammalian cells, nicotinamide is mostly converted into NADH by metabolic activities. This method uses the genetically tightly controlled enzyme nicotinamide N-methyltransferase (NNMT), which catabolizes nicotinamide irreversibly into its quaternary N-methyl derivative. We reasoned that the dopaminergic neuron may have high levels of this enzyme and can lead to reduced quantities of nicotinamide that are readily available and, consequently, NADH, which would lead to lower levels of ATP generation. This might lessen the neuron's viability over its lifetime.

A source of MPP-like substances could also come from high NNMT expression, which would be harmful. A substance called 4-phenyl pyridine, which can be transformed into MPP, is present in some meals. N-methyl analogues are unique dopaminergic neurotoxins that act by blocking Complex I, and they can be made from natural substances like b-carbolines and tetrahydroisoquinolines. Decreased ATP synthesis and increased exposure to compounds that resemble MPP are hence two risks that may be presented by raised NNMT levels. A threat of this nature, however, can only exist if NNMT molecule is present in the dopaminergic neurons of the central nervous system, MPP, the produced ion, is poisonous. The glial monoamine oxidase-B (MAO-B) enzyme oxidises this as it crosses the blood-brain barrier, creating the compound which is unstable 2,3-dihydro-1-methyl-4-phenylpyridine (DMPP), which is then converted into MPP. The dopaminergic neurons then allow the poison to enter the body. Pathway B involves either consumption or

production of precursor chemicals such 4-phenyl pyridine (PP), which are produced naturally as part of human metabolism. Nicotinamide N-methyltransferase (NNMT) methylates these molecules in neurons, particularly pigmented dopaminergic neurons, to produce MPP and related methylated ions [5].

NADH and methylated pyridine levels may initially be unaffected by increased NNMT expression, but later on, for example in a disease with a lengthy preclinical stage and a late onset, it may have a causally significant impact [5].

4.1 NNMT and dopamine

PD is biologically, the reduction in dopaminergic neurons in many brain areas, particularly in the substantia nigra region [19].Rac1 and RhoA , are Rho GTPase family members, control actin mobility, which is crucial for brain development, to control neurite branchingThe actin myosin system is regulated by extracellular inhibitory signal molecules, which cause Rac1 and RhoA to connect to GTP, activate ROCK, and ultimately halt neurite outgrowth. While once there is hydrolyzation of GTP into GDP, Rac1 and RhoA stop working. The Rho GDP dissociation inhibitor (RhoGDI) enhances neurite formation, differentiation, and neuroplasticity by preventing GDP from leaving Rac1 and RhoA and inactivating them. Rac1 and RhoA undergo post-translational methyl modification at the C-terminal cysteines in order to mature and activate. SAM serves as a donor of methyl coenzyme in this process. The enzyme known as isoamyl cysteine carboxyl methyltransferase 1 (LCMT1) is responsible for catalyzing this reaction. According to studies, blocking LCMT significantly lowers Rac1 and RhoA activation.

This is due to the fact that both proteins have a higher affinity for RhoGDI when their methylation is missing. When combined with GTP and methylated, Rac1 and RhoA restrict the growth of neurites. Rac1 and RhoA are kept inactive and neurite formation is promoted by RhoGDI because it prevents Rac1 and RhoA from dissociating from methylated or unmethylated GDP (Bradke and Dotti, 2000). Cocaine enhances dendritic spines while decreasing Rac1 and RhoA activity in the nucleus accumbens (NAc). Dopamine encourages neurite growth and decreases RhoA activity in cultured neurons [20].

CHAPTER 5: Targeting NNMT with Jearitinine E

PD and many different neurodegenerative diseases have been linked to abnormalities in NAD+ metabolism and depletion. [21]. NAD+ levels in cells are crucially maintained via the NAD+ salvage pathway, which includes enzymes like nicotinamide N-methyltransferase (NNMT). The aetiology of PD has been connected to deregulation of this system, including altered NNMT activity. [22].By focusing on NNMT in the brain, one would be able to alter NAD+ metabolism and raise its levels, which might improve cellular processes and possibly slow the neurodegenerative process . It may be feasible to change the equilibrium of NAD+ metabolism and boost its availability for cellular functions by blocking or altering NNMT's action. In preclinical models of neurodegenerative disorders, elevated NAD+ levels have been linked to neuroprotective effects [23] . The maintenance of neuronal health and function depends on the proper functioning of several cellular processes, including energy metabolism, mitochondrial

function, and cellular stress responses [24]. These activities can all be affected by the restoration of NAD+ levels.

Dysregulation of NAD+ metabolism, particularly the activity of NNMT, is the root cause of Parkinson's disease. It may be possible to modify cellular processes and influence the neurodegenerative process by changing NAD+ levels by concentrating on NNMT in the brain.

Therefore, Jeratinine E can target the activity of NNMT to increase the dopamine production which can increase the motor movements and thereby, can be a cure of Parkinson’s disease.

CHAPTER 6: METHODOLOGY

6.1 Data Set Collection

The comprehensive database by the National Centre for Biotechnology Information (NCBI) may be of considerable use to researchers and scientists in the domains of biotechnology and the biological sciences. In the United States, the (NCBI) was established in 1988. The NCBI database is a huge deposit of biological knowledge that contains a wide range of data types, including genome assemblies, scholarly publications, medical literature, DNA and protein sequences, and more. It is an essential tool for academics working in the domains of bioinformatics, genomics, and related disciplines since it provides free and open access to a significant collection of biological data.

GenBank, a comprehensive collection of publicly accessible DNA sequences, is one of the most notable parts of the NCBI database. Sequences from a variety of species, including bacteria, fungi, plants, mammals, and viruses, are included in GenBank. It is an essential tool for researchers looking at gene function, evolutionary links, and genetic variation. The NCBI database also has a number of specialized tools and datasets that address particular research requirements. For instance, the PubMed database gives users access to millions of full-texts and abstracted biomedical literature articles, allowing researchers to keep up with the most recent scholarly works. Another important element is PubMed Central (PMC), which offers free access to a sizable database of full-text, peer-reviewed papers.

The Protein Database (PDB), which contains protein structures found by experiment, and

the Sequence Read Archive (SRA), which houses raw sequencing data from high-throughput sequencing technology, are two more databases that are hosted by the NCBI database. These tools aid in the discovery of intricate biological systems as well as structural biology and functional genomics research. The NCBI provides a variety of strong analytical and search tools in addition to these main databases to help researchers access and understand the data. With the help of the frequently used Basic Local Alignment Search Tool (BLAST), users can equivalence their arrangements to those in the database to find similar sequences and deduce functional annotations. The NCBI database is constantly changing and growing, adding new data types and enhancing the services that are already available. It encourages the sharing and fusion of biological data by supporting data input from researchers across the globe. To aid in effective data retrieval, analysis, and interpretation, the NCBI also offers substantial documentation, tutorials, and user support.

The countless research publications and reviews that use the NCBI database as a source of information demonstrate its importance in scientific study. The evolutionary relationships of a particular group of plants can be viewed by using GenBank sequences from the NCBI database . They used BLAST to find closely related sequences and phylogenetic analysis to determine how the taxa had evolved over time. A systematic review of clinical trials for a specific medicinal intervention was carried out by Johnson et al. (2022) using the PubMed database. They ensured a thorough examination of the current literature by conducting an extensive search utilizing particular keywords and filters accessible in PubMed. With its essential platform for data storage, retrieval, and analysis, the NCBI database has become a crucial component of contemporary biological research. It is a

vital resource for scientists working in a variety of fields due to its accessibility, variety of data kinds, and user-friendly tools. The NCBI database will remain a crucial tool in deciphering the intricacies of biological systems and expanding scientific understanding as researchers continue to delve into the broad domains of biotechnology and life sciences.

The structure of the NCBI-GEO record, which is reachable at https://www.ncbi.nlm.nih.gov/gds, made it possible to create the gene expression datasets applied in this research. We examined the gene expression in 20 PD patients with diverse degrees of severity and nine healthy controls using 32 different microarrays to come to these conclusions. The levels of gene expression for every gene were then compared between the 32 cases. Our results elicited a robust transcriptional response in thousands of genes associated with PD indicators. Only individuals with early-stage PD and healthy controls were included when hundreds of these genes were linked to PD indicators. The selection criteria were Log(fold change)| > 1.2 and P 0.05 for DEGs.

6.2 DEGs' Functional Enrichment Analysis

Gene expression data and other high-throughput genomic information can be interpreted using the potent computational technique known as functional enrichment analysis. With the help of this method, it is possible to gain knowledge about the biological processes, molecular mechanisms, and cellular elements that are overrepresented in a group of differentially expressed genes (DEGs). Researchers can discover the underlying biological mechanisms and pathways connected to particular conditions or experimental

treatments by finding the enriched functional categories. The functional enrichment analysis of DEGs will be thoroughly examined in this essay, with special emphasis placed on its significance in biological research and the numerous techniques and equipment frequently used in this area.

A list of DEGs determined through statistical analysis, often produced by contrasting gene expression profiles between various experimental conditions or groups, serves as the foundation for functional enrichment analysis. These DEGs are then put through functional annotation, which entails giving each gene biological annotations based on already-existing biological databases and resources, such as GO- Gene Ontology terminology or KEGG- Kyoto Encyclopaedia of Genes and Genomes pathways. The enhancer analysis is used to find the functional categories that are considerably overrepresented in the set of DEGs compared to what would be predicted by chance after the genes have been annotated.For functional enrichment analysis, a number of statistical techniques have been created, such as network-based enrichment, overrepresentation analysis, gene group enrich analysis. The most popular method, ORA, uses statistical tests to evaluate whether a specific functional category is overrepresented in the DEG set. GSEA, on the other hand, considers the list of genes that have been sorted according to their differential expression values and determines if a set is predetermined either at the top of the list or at the bottom. PPI networks or gene regulatory networks are used in network-based enrichment analysis to find functional modules or pathways that have been significantly altered in the DEG collection.

Multiple testing corrections are made to account for the various hypotheses being tested

concurrently to guarantee the reliability of the results. These adjustments aid in reducing the problem of false positives and raise the precision of the enrichment analysis. In numerous biological research, functional enrichment analysis has been widely used. For example, it has been crucial in uncovering the molecular pathways and processes linked to tumour growth, progression, and medication response in cancer research. Researchers can learn more about the dysregulated biological processes and potential treatment targets by comparing the DEGs in cancerous and healthy tissue samples. The functional enrichment analysis of DEGs in colorectal cancer found enrichment in processes related to cell adhesion, extracellular matrix organisation, and immune response, underlining their significance in tumour invasion and metastasis [25] .

Functional enrichment analysis has been used in numerous disciplines, including neuroscience, developmental biology, and immunology, in addition to cancer research. Enrichment analysis of DEGs in the central nervous system identified specific functional categories related to myelination and neuronal development, offering insightful information into the molecular mechanisms underlying neural differentiation and myelination processes[26] . In a similar manner, enriched pathways are discovered to be involved in limb patterning and skeletal morphogenesis using functional enrichment analysis of DEGs in a mouse model of embryonic limb development [27].

Several bioinformatics tools and databases have been created to aid functional enrichment analysis. Additionally, user-friendly interfaces for doing enrichment analysis and displaying the findings are offered by software programmes like Enrichr, clusterProfiler, and g:Profiler. In summary, a critical step in the investigation of DEGs' functional

enrichment is the interpretation of high-throughput genomic data. It enables scientists to understand the biological mechanisms and pathways connected to various experimental settings or disease states. Enrichment analysis assists in determining the functional categories that are noticeably overrepresented in the DEG set by using a variety of statistical methodologies and corrective strategies. Functional enrichment analysis has advanced our knowledge of biological mechanisms and given us invaluable new information for future research through its use in the study of cancer, brain, and other areas.

6.2.1 EnrichR

In order to analyze and understand gene lists in the context of biological pathways, gene ontology words, transcription factor targets, and other functional annotations, researchers can use EnrichR, a complete online bioinformatics application. It provides an intuitive user interface and a wide range of databases to do enrichment analysis, enabling researchers to learn important new things about the underlying biological functions and processes connected to their gene lists [28].

Data from numerous publicly accessible databases and tools, such as the GO, KEGG, Transcription Factor Targets, and many others are combined in EnrichR. By making use of these tools, EnrichR offers researchers a strong platform to investigate the functional importance of their gene lists and discover probable biological processes underlying their

experimental findings. EnrichR's primary function is enrichment analysis, which assesses whether specific biological annotations are more or less prevalent in a given gene data than would be predicted by coincidental. Gene ontology enrichment, pathway enrichment, transcription factor targets analysis, and other enrichment techniques are available through EnrichR.

Using EnrichR's Gene Ontology enrichment analysis, researchers can determine the biological functions, cellular elements, and molecular processes that are overrepresented in their gene list. EnrichR can determine the functional categories that are statistically enriched by annotating genes with GO keywords, and it can also offer insights into the underlying biological themes.Researchers can find pathways or groups of genes that are noticeably overrepresented in their gene list by using EnrichR's pathway enrichment analysis. It incorporates information from numerous pathway databases, including KEGG, Reactome, and WikiPathways, and evaluates the enrichment of genes along biological pathways. The biological context and signaling pathways that might be implicated in the researchers' gene list are better understood thanks to this investigation [29] .

EnrichR provides transcription factor target analysis in addition to gene ontology and pathway enrichment. It makes use of computer methods and curated databases to forecast transcription factor (TF) targets within a given gene list. The regulatory mechanisms and potential transcriptional networks connected to the input genes can be better understood by this approach.The output files from EnrichR are available for download, and its results are presented in an interactive and user-friendly format with graphical visualizations and statistical indicators. The programme offers thorough annotations and information about

enriched phrases or pathways, including gene lists linked to each term and p-values, adjusted p-values, fold enrichment, and p-values. These properties make it easier to comprehend and explore the findings, enabling scientists to get valuable biological insights from their gene lists.

The biological research disciplines of genomics, transcriptomics, proteomics, and systems biology have all used EnrichR to a large extent. It has been used to evaluate and analyze high-throughput data from numerous experimental methods, including mass spectrometry, microarrays, RNA sequencing, and ChIP-seq. Researchers have been able to decipher the functional importance of their data and produce ideas for additional experimental validation by including EnrichR into their analysis.EnrichR uses well-curated, frequently updated databases that cover a numerous species and biological diversity annotations in order to guarantee its accuracy and dependability. These databases come from reliable sources and go through stringent quality control checks to keep the data integrity. In addition, EnrichR offers references and connections to the annotations' original sources, allowing researchers to obtain additional data and confirm their conclusions.The functional interpretation of gene lists is facilitated by EnrichR, a potent bioinformatics tool, by performing enrichment analysis. EnrichR helps researchers discover the biological processes, pathways, and regulatory networks connected to their gene lists by utilizing a variety of databases and annotation tools. It is a useful tool for academics looking to understand the functional importance of their genomic data because of its user-friendly interface, thorough annotations, and interactive visualizations.

EnrichR, uses an online tool for gene set enrichment analysis (GSEA),by which the

pathway and GO analyses were carried out based on the discovered DEGs shared by the PD datasets. P 0.05 was used as the threshold for this study's biological process GO annotation source. The results of KEGG pathway enrichment were analyzed in a statistically important output at a maximum p-value of 0.05.

6.3 Network analysis of Protein-Protein Interactions (PPI)

Many biological processes, such as signal transduction, enzyme control, and cellular communication, depend on PPIs, which are a key component of many of these activities. Understanding the intricate interactions among biological systems and determining potential treatment targets for different diseases depend on the research of PPIs and their networks. The investigation and interpretation of these complex interaction patterns can be done effectively via network analysis of PPIs. PPI network analysis entails the creation and study of graphs in which proteins are modeled as nodes, and their interactions are modeled as edges.. With this method, researchers can investigate the overall structure and dynamics of cellular networks, discover significant players (hubs), visualize and quantify the interactions between proteins, find functional modules, and identify essential actors in a network of proteins.

The creation of the interaction network is the initial stage in PPI network analysis. This offers important insights into the physical interactions that directly occur between proteins. Several network analysis approaches can be used after the PPI network has been built to obtain useful data. Node degree, which indicates how many connections a protein has, is one of the key metrics in PPI network analysis. High degree (hub) proteins

frequently play crucial roles in cellular functions and may be used as therapeutic targets [30]

A further crucial component of PPI network analysis is network topology analysis. Measures that shed light on the network's local and global connection include clustering coefficient, betweenness centrality, and closeness centrality. Proteins that are critical for preserving the overall network structure are identified by centrality measures, which use the clustering coefficient to show how densely interconnected proteins are within a neighborhood [31] A key objective of PPI network analysis is functional module discovery. A set of proteins known as a functional module typically interacts with other members of the module but less frequently with proteins outside the module. To find these modules, several techniques, including MCODE [32], [33] and Cluster ONE [33], have been developed. Functional modules can shed light on the way cellular systems are organized and frequently correspond to particular biological activities or pathways.

The incorporation of additional biological data, such as gene expression profiles or protein annotations, is a crucial component of PPI network analysis. Researchers can uncover probable disease-associated modules or protein complexes and acquire a clearer knowledge of the functional ramifications of the interactions thanks to this integration [34] . PPI network analysis can also be used to anticipate novel interactions and guess the activities of proteins. It is possible to predict interactions that have not been experimentally characterized by using computational techniques including sequence homology-based methods, protein domain interactions, and machine learning algorithms. These hypotheses can direct experimental verification and advance our understanding of

PPI networks [35].

FPPI network analysis is important for understanding both normal cellular processes and disease mechanisms. By including genetic information related to the disease, such as gene expression patterns from diseased tissues or genome-wide association studies (GWAS), disease-specific PPI networks can be created. These networks can aid in the identification of important proteins or processes that are linked to specific diseases in addition to the determination of potential treatment targets [36]. In conclusion, PPI network analysis offers a strong foundation for researching the complex interactions between proteins. It provides insightful information on the structure, behavior, and practical implications of cellular networks. Researchers can better comprehend cellular processes and disease mechanisms and decipher the intricacy of PPI networks by combining experimental data, network analytic methods, and computational predictions.

6.3.1. STRING tool

For scientists researching protein-protein interactions (PPIs) and functional relationships, STRING - Search Tool for the Retrieval of Interacting Genes/Proteins tool is useful . STRING combines information from a variety of sources, including curated databases, algorithmic predictions, and experimental research. To evaluate the likelihood and functional relevance of protein interactions, it makes use of a wide variety of algorithms and techniques. Researchers from a variety of fields, including molecular biology, systems biology, and drug development, frequently use the technology to investigate protein networks and decipher intricate biological pathways.

When a user enters a protein of interest, the programme searches the database for known and anticipated interactions. In order to visualize the relationships between proteins in a biological context, these interactions are presented as nodes (proteins) and edges (connections amongst proteins). The functional relationships between proteins and the overall structure of cellular processes are better understood by researchers thanks to this network view. Additionally, STRING offers a number of metrics for evaluating the accuracy and dependability of the projected interactions. Based on the evidence supporting each interaction, including experimental data, co-expression patterns, and functional annotations, it assigns a confidence score to that interaction. Additionally, STRING enables users to investigate the evolutionary preservation of protein connections between various species. The examination of conserved protein interactions and their functional ramifications is made easier by the orthology predictions it gives that pinpoint homologous proteins in other animals. Numerous research studies have made extensive use of the STRING web tool. It has been used to analyze protein networks and identify essential actors in diseases like cancer, neurological disorders, and infectious diseases[37], [38] . In order to find possible therapeutic targets and foresee off-target effects, it has also been used in drug development efforts [39]. Finally, the STRING web-based tool is an effective tool for learning about protein-protein interactions and understanding intricate physiological processes. STRING helps researchers find functional relationships, recognize protein complexes, and clarify biological processes by offering a comprehensive database of known and expected interactions, coupled with confidence scores and extra analysis tools. It is widely used in many research domains and advances our knowledge of protein networks and how they affect both health and illness.The common DEGs were organized into a network of PPI using the online

visualization tool STRING . A database known as the PPI network is used to link the structural and functional characteristics of proteins.

6.4 Data Collection for Molecular Docking

To predict how a tiny molecule ligand will attach to a target protein, scientists utilise a computer technique known as molecular docking. It is essential to the identification and development of new drugs since it sheds light on the affinity and orientation of conceivable drug candidates with respect to the target binding site. A crucial step prior to completing molecular docking is, however, the gathering of pertinent information that enables precise and dependable predictions. A number of crucial steps are involved in the data gathering procedure for molecular docking, incorporating protein structure selection, the synthesis of ligands, and the gathering of extra data to improve docking accuracy. For significant outcomes to be produced, each step must be well thought out and validated. The selection of protein structures is the primary process in the data collection. The Protein Data Bank (PDB) [40] or homology modelling methods can be utilised to obtain the protein structure that is employed in docking research. The target of interest should be represented by a protein structure that has a resolved and trustworthy three-dimensional (3D) structure. The production of the ligand comes after the protein structure has been determined. Ligands can be found in databases, created in the lab, or discovered through virtual screening methods. Energy minimization, determining the ionisation state, and counting the number of tautomeric and stereoisomer forms are just a few of the tasks involved in ligand production. It is usual practise to prepare ligands using tools and software like Open Babel [41] and RDKit ,which guarantees that ligands are in an

appropriate conformation and format for docking simulations.

To increase the precision of molecular docking predictions, extra data can be gathered in addition to protein and ligand data. This provides details on the binding location, ligands that are known to be active, and experimental binding affinities. It is possible to estimate the binding site using algorithms like SiteMap [42]or PocketFinder or to collect the information from experimental constructions. The docking simulations can be directed and the docking results can be validated by knowing the active ligands and their binding affinities.

It's also possible that other elements that affect docking accuracy will be taken into account during the data collection procedure. The selection of scoring functions, proper handling of water molecules, and taking protein flexibility into account are some of these considerations. The ligand and protein's capacity to bind to each other is assessed using scoring tools like AutoDock [43] or Vina [44], which also aid in sorting candidate ligands according to their anticipated binding energies. Given that water molecules are so important in ligand-protein interactions, how those molecules are handled at the binding site can affect how the docking process turns out. Water effects can be taken into account using techniques like explicit or implicit water models. For the purpose of precisely capturing conformational changes brought on by ligand interaction, protein flexibility must also be taken into account, either by rigid or flexible docking. Data gathering is an important phase in the molecular docking process. In order to improve the precision of docking predictions, it entails choosing the right protein structures, getting ready the ligands, and obtaining more data. For outcomes that are trustworthy and meaningful, each

step must be well thought out, and the right tools and software must be used. The development of drugs must be sped up in order to find new drug candidates. The data gathered is used as the basis for further docking simulations.

6.4.1 COCONUT- COlleCtion of Open Natural Products database

In-depth and openly available, the COCONUT database intends to gather and curate data on natural products generated from a variety of sources, including plants, fungus, bacteria, and marine organisms . It is a useful tool for scientists and researchers working on the discovery and development of drugs from natural products. To produce a centralised collection of data on natural products, the database combines data from several open-access sources, such as scientific publications, patent databases, and chemical databases. The COCONUT database offers a practical platform for researchers to investigate and evaluate the chemical and biological aspects of natural products by combining data from various sources.

The COCONUT database offers annotations and links to external resources, such as protein targets, metabolic pathways, and gene clusters involved in biosynthesis. By linking to other databases and resources, the COCONUT database is made more valuable and adaptable and enables researchers to look at the potential mechanisms of action of natural substances in a broader perspective. The COCONUT database has been utilised in several studies and applications pertaining to the study of natural products. Researchers have used it to look into the chemical space of natural compounds, develop novel scaffolds, forecast properties, and predict bioactivities in order to find new drug

candidates [45]. The COCONUT database is an extensive, open-access tool that compiles data on natural products from a variety of sources. It offers scientists a centralized platform to investigate the biological activities, diverse structural makeup, and potential therapeutic uses of natural compounds. The database has shown to be a useful resource for finding novel lead compounds and advancing research in this crucial area in the area of finding new drugs from natural products.

40 naturally occurring substances with alkaloidal qualities and the reference F0P were used when looking for possible organic therapies for PD. These medications' SDF structures were taken from PubChem. Jerantinine E was docked using a tool called Discovery Studio. 32 compounds were converted by Discovery Studio into mol2 format. The procedure of molecular docking was carried out utilising the web-based computational biology and drug discovery programme Webina after the ligands and proteins were synthesised, and the results were then analysed.

6.5 ADMET Evaluation

ADMET - Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) studies, which assess the pharmacokinetic and pharmacodynamic properties of potential drug candidates, are extremely helpful in the discovery and development of new medications. This thorough evaluation aids researchers in assessing a compound's uptake by the body, distribution to target tissues, enzymatic metabolism, excretion methods of elimination, and potential toxicity problems. Researchers can increase medication safety profiles, optimise lead compounds, and boost therapeutic efficacy by incorporating

ADMET analysis in the initial points of medication detection.

A crucial factor in determining a medication candidate's bioavailability and therapeutic potential is absorption. Researchers can predict a compound's oral absorption to find out if it can pass through bodily barriers like the gastrointestinal tract.Physiologically based pharmacokinetic (PBPK) models and quantitative structure-activity relationship (QSAR) models are two examples of computer models used to evaluate absorption quality [46] . These models take into account physicochemical traits, such as lipophilicity, molecular mass, and hydrogen bonding which affect a compound's permeability and likelihood of oral absorption.The term "distribution" describes how a medicine travels through the body and builds up in its target regions. Researchers can evaluate a drug's potential efficacy and choose the best dosing regimens by predicting the distribution of the compound. The distribution of a medicine in tissue is influenced by its physicochemical characteristics, including ionisation and lipophilicity. Additionally, a drug's distribution and availability at the target site may be impacted by its affinity for plasma proteins. Based on variables like blood flow, tissue makeup, and binding affinity to plasma proteins, computational models, such as PBPK models, can shed light on a compound's distribution [47].

Drug metabolism in the body depends heavily on metabolism. Drug metabolism takes place mostly in the liver, where a variety of processes are catalysed by enzymes, mainly those from the cytochrome P450 (CYP) family. Predicting a compound's metabolism can assist researchers in understanding its stability, potential for drug-drug interactions, and creation of metabolites that may contribute to efficacy or toxicity. Drug metabolism can be predicted and described using in silico technologies, such as software that uses

machine learning algorithms and databases of known metabolic reactions[48]. To forecast prospective metabolic pathways, these techniques take into account the compound's structural characteristics and its similarity to well-known substrates.

Excretion is the process through which medicines and their metabolites are removed from the body. Through renal filtration, active secretion, and reabsorption mechanisms, the kidneys are important in the excretion of drugs. The removal of substances and their metabolites is also aided by hepatic excretion and biliary elimination. Understanding a drug's clearance and potential for buildup or toxicity requires an understanding of its excretion mechanisms. In vitro cell culture systems and physiologically based pharmacokinetic models are two examples of renal clearance models that shed light on a substance's renal elimination[49] . Hepatic excretion can be estimated using hepatic clearance models that incorporate metabolic enzymes and transporters[47] . A key component of ADMET analysis is toxicity evaluation, which ensures the security of possible medication candidates. The ability to predict a compound's toxicological profile aids researchers in spotting potential hazards and selecting the best course of action for further investigation. Structure and physicochemical features are used in silico models, such as Quantitative structure-toxicity relationship (QSTR) models and expert systems, to forecast toxicity endpoints. Based on structural similarity to known dangerous substances, these models can evaluate acute toxicity, mutagenicity, carcinogenicity, and other toxicological aspects.

By incorporating ADMET analysis into the drug discovery process, it is possible to gain important knowledge on the pharmacokinetic and pharmacodynamic characteristics of a

molecule. It facilitates the choice and optimisation of lead candidates and enables the discovery of compounds with desirable ADMET profiles. It's crucial to remember that ADMET analysis is a complementary tool and that experimental validation should come next in order to validate and improve the predictions.

6.5.1 Swiss ADME tool

For predicting and analyzing the ADME properties of small compounds in drug discovery and development, the SwissADME web-based application is an invaluable tool. The SwissADME tool's capacity to evaluate drug-likeness, which is crucial for discovering new therapeutic candidates, is one of its important advantages. It evaluates structures such as hydrogen bond contributors, acceptors, lipophilicity, and molecular weight using the rules of Lipinski's Rule of Five, a principle that is frequently used in medicinal chemistry. Compounds that meet these requirements are more likely to be orally bioavailable and can be used as the basis for drug development programmes, in accordance with Lipinski's Rule [50].

The SwissADME tool offers forecasts for several physicochemical parameters in addition to drug-likeness evaluation. These characteristics, such as lipophilicity, polarizability, and surface area, have an impact on a molecule's solubility, permeability, and capacity to overcome biological barriers. A compound's absorption into the bloodstream and subsequent distribution throughout the body must be predicted accurately in order to avoid errors[51] . SwissADME provides researchers with further support by forecasting aqueous solubility, a crucial element in drug development. A compound's medicinal

efficacy may be restricted by poor solubility, which can interfere with bioavailability. Researchers can find compounds with suitable solubility profiles and improve formulation strategies to improve drug delivery by analyzing solubility . Another important feature of SwissADME is the prediction of metabolism. Based on structural similarity with recognised cytochrome P450 (CYP) substrates, the programme calculates the sites of metabolism and probable metabolites.

The results are presented using a user-friendly style by the SwissADME web application, making it simple to understand and analyze the data. Each projected property is given numerical numbers, graphic representations, and thorough explanations by the tool. Researchers can compare several compounds, visualize the characteristics of their target molecules, and spot potential problems or opportunities for development. Despite the fact that SwissADME is a useful tool, it is crucial to remember that the predictions it makes are based on computer models and algorithms. To validate and improve these hypotheses, further in-depth investigation and experimental validation are required. Nevertheless, the technology aids researchers in the selection and prioritization of compounds for further experimental characterisation and optimization as an efficient and economical initial screening technique.

In conclusion, researchers working on drug discovery and development can benefit greatly from the SwissADME web-based platform. It assists in the early identification and ranking of promising drug candidates by offering predictions and analysis of ADME features. For compound optimization and decision-making, the tool's assessments of drug-likeness, physicochemical characteristics, metabolism, protein binding, and toxicity offer

insightful information. To choose the right molecule and proceed with further research, it is crucial to combine computer predictions with experimental data and expert knowledge. With the help of SwissADME, a web-based application (http://www.swissadme.ch), we were able to calculate ADME parameters for the discovery of drugs. All 32 ligands' virtual properties, such as their BBB permeability, pharmacokinetics, and drug-likeness metrics, are examined using the SwissADME tools. From PubChem, the Canonical SMILES were gathered.

CHAPTER 7: RESULTS

7.1 Differentially Expressed Genes' (DEGs) Identification

Finding DEGs in microarray data sets comparing healthy people to PD cases offers important knowledge on the molecular alterations connected to PD. These DEGs may be used as therapeutic targets, disease-progression markers, or prospective biomarkers. To completely understand their involvement in PD pathogenesis and find new approaches for diagnosis and treatment, more validation, functional characterization, and integration with other omics data are needed. The selected microarray dataset was compared to healthy samples and PD cases. 32 genes in all have been found.

7.2 Functional Enrichment Analysis

Functional enrichment analysis is a popular strategy for comprehending the molecular functions and processes connected to PD. This technique aids in the discovery of biological pathways and gene ontology (GO) keywords that are noticeably enriched among genes that are differently expressed in Parkinson's disease (PD). The biological procedure GO and KEGG pathways basic analysis used 32 differentially expressed genes to display the molecular processes and functions related to PD. TABLE I and TABLE II, respectively, exhibit the KEGG and GO pathways that are linked to Parkinson's disease and CNS- central nervous system.

TABLE I. KEGG PATHWAY

Term	Overlap	P-value	Adjusted P-value	Odds Ratio	Combined Score	Genes
Calcium signaling pathway	3/240	0.006547666903	0.2911169792	8.612396333	43.3086966	CAMK1D; ORAI2;GRIN1
Tight junction	2/169	0.02982692652	0.2911169792	7.904590818	27.76363991	MPP4; TUBA8
Nicotinate and nicotinamide metabolism	1/35	0.05454814878	0.2911169792	18.91271347	55.01087073	NNMT
Nicotine addiction	1/40	0.06210151106	0.2911169792	16.48387097	45.80842946	GRIN1
Prion disease	2/273	0.07044757029	0.2911169792	4.845510455	12.85458942	GRIN1; TUBA8
Cocaine addiction	1/49	0.07555050634	0.2911169792	13.38709677	34.57825366	GRIN1
Vibrio cholerae infection	1/50	0.07703325543	0.2911169792	13.11323239	33.61600808	KDELR3
Huntington disease	2/306	0.08574379907	0.2911169792	4.312280702	10.5926497	GRIN1;TUBA8
Glutathione metabolism	1/57	0.08734818103	0.2911169792	11.47004608	27.96228702	CHAC1
Lysine degradation	1/63	0.09610058865	0.2911169792	10.35691988	24.25963339	HYKK
Cortisol synthesis and secretion	1/65	0.09899994384	0.2911169792	10.03225806	23.20096112	KCNA4

TABLE II. BIOLOGICAL FUNCTION

Term	Overlap	P-value	Adjusted P-value	Odds Ratio	Combine Score	Genes
Voltage Gated Potassium Channels R-HSA-1296072	2/43	0.00214964971 4	0.2107872633	32.40162602	199.0253798	KCNV1;KCNA4
RUNX1 Regulates Transcription Of Genes Involved In WNT Signaling R-HSA-8939256	1/6	0.00956277225 1	0.2107872633	128.7935484	598.8742369	RSPO3
Potassium Channels R-HSA-1296071	2/102	0.01156369378	0.2107872633	13.24533333	59.0726626	KCNV1;KCNA4
Phase II - Conjugation Of Compounds R-HSA-156580	2/107	0.01266811495	0.2107872633	12.61142857	55.09513279	NNMT;CHAC1
Metabolism Of Ingested SeMet, Sec, MeSec Into H2Se R-HSA-2408508	1/8	0.01273064621	0.2107872633	91.98617512	401.4040374	NNMT
Lysine Catabolism R-HSA-71064	1/12	0.01903697989	0.2107872633	58.52492669	231.8389989	HYKK
Glutathione Synthesis And Recycling R-HSA-174403	1/12	0.01903697989	0.2107872633	58.52492669	231.8389989	CHAC1
Synthesis Of IP2, IP, And Ins In Cytosol R-HSA-1855183	1/14	0.02217549735	0.2107872633	49.51612903	188.5954142	INPP4A
Methylation R-HSA-156581	1/14	0.02217549735	0.2107872633	49.51612903	188.5954142	NNMT
Response Of EIF2AK1 (HRI) To Heme Deficiency R-HSA-9648895	1/15	0.02374110642	0.2107872633	45.97695853	171.9789874	CHAC1
Elevation Of Cytosolic Ca2+ Levels R-HSA-139853	1/15	0.02374110642	0.2107872633	45.97695853	171.9789874	ORAI2

7.3 Analysis of the Protein-Protein Interactions Network

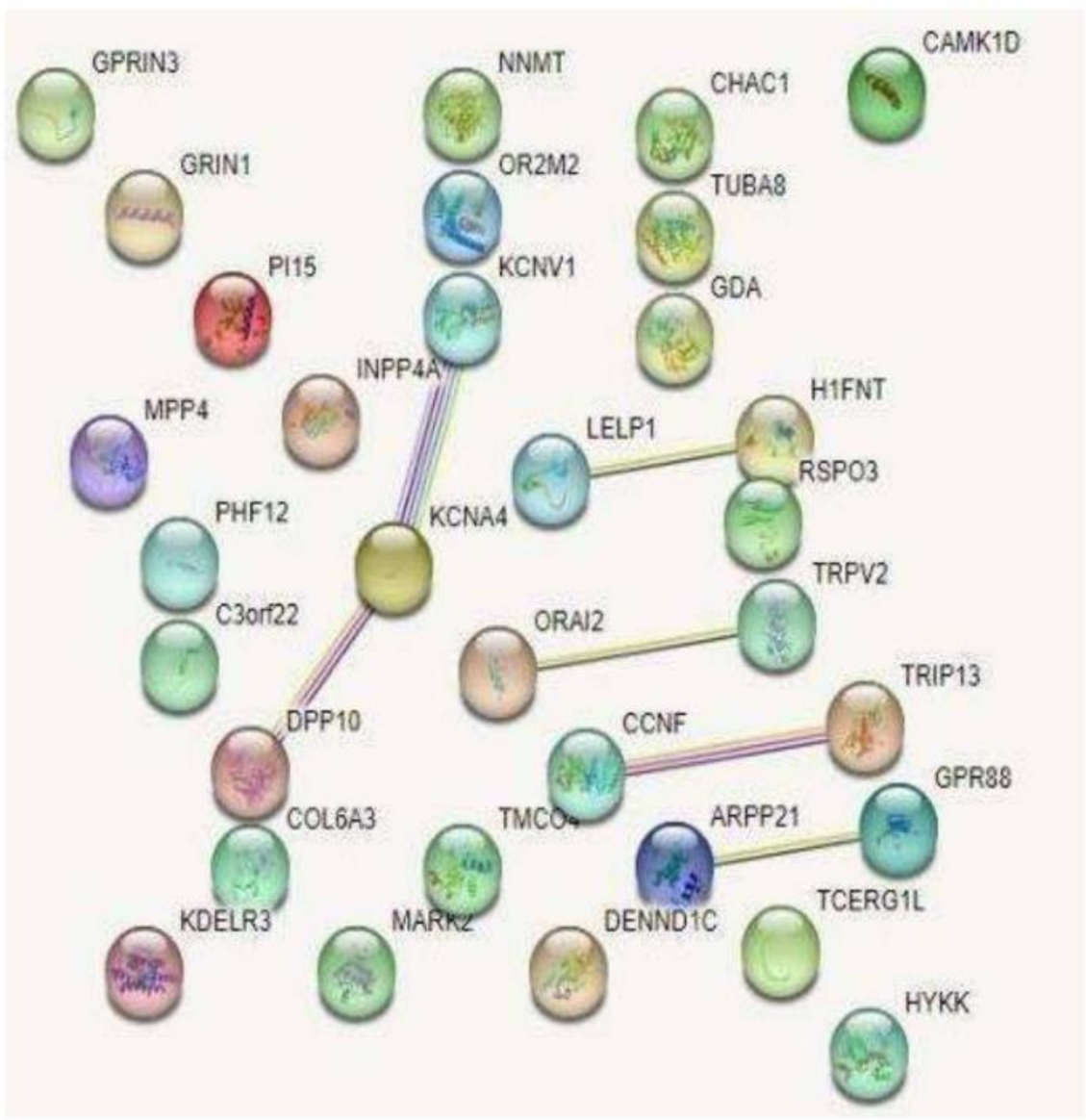

Fig 6 The PPI network

A comparison between samples from healthy people and those who had Parkinson's disease (PD) was done in order to analyze the selected microarray dataset. Finding diseased linked genes that were differentially expressed was the goal of the dataset analysis. The dataset's gene expression patterns can be compared to reveal the molecular processes underlying the pathophysiology of PD. The identification of certain genes may provide crucial information regarding disease-related mechanisms, potential biomarkers, and therapeutic targets. They were able to see these genes.

7.4. Molecular Docking Result

By predicting the two molecules' binding affinities and providing details on their chemical interactions, a molecular docking tool called Webina makes it easier to investigate protein-ligand interactions. Webina enables virtual screening of possible ligands against target proteins using scoring functions and algorithms, making it easier to find candidates for drug discovery. Its user-friendly interface and detailed visualization of the docking data help users better grasp how ligands and proteins interact.

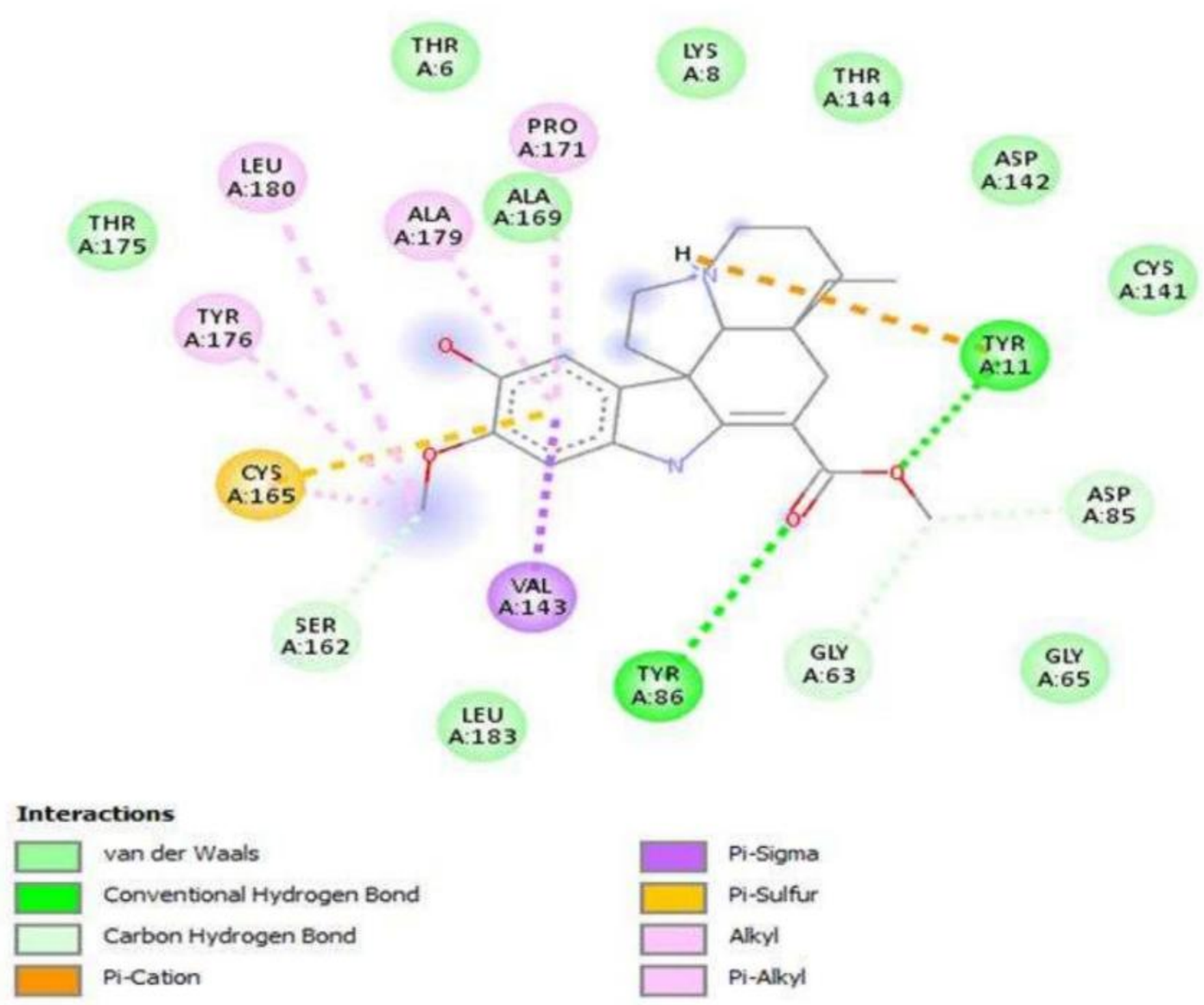

Fig 7 Molecular Docking result of Jeratinine E with NNMT

NNMT protein interaction with chemical substances was investigated using Webina. Among the 40 natural compounds examined, Jeratinine E had the greatest as depicted in Fig. 2, the protein has a low affinity for binding.

7.5. ADMET Analysis

SwissADME is a useful online tool for ADMET analysis, including forecasts and analysis of many features important for drug development and discovery. Compound optimization, prioritization, and risk assessment are aided by its capacity to evaluate drug-likeness, physicochemical characteristics, metabolism, protein binding, and toxicity. While SwissADME's forecasts provide direction, additional experimental validation is necessary to verify and improve the findings.

According to SwissADME's ADMET analysis, jeratinine E is BBB permeant and has a high capacity for GI absorption. One of the most popular methods for judging how drug-like a tiny molecule is is the Lipinski rule. Jeratinine E meets the drug-likeness requirements of the Lipinski rule for bioavailable drugs with a bioavailability score of 0.55 and 0 infractions. A more thorough study is presented in TABLE III.

TABLE III. MOLECULAR DOCKING /ADMET ANALYSIS RESULT

Compound	**GI absorption**	**Lipinski**	**BBB permeant**	**Log Kp (skin permeation)**	**Num. H-bond acceptors**	**Num. H-bond donors**	**Molar Refractivity**	**Molecular weight**	**Affinity(kcal/mol)**
3-O-Acetylnarcissidine	High	Yes; 0 violation	No	-8.49 cm/s	7	1	100.95	375.42 g/mol	-7.6
5Hydroxyacridine2methanol	High	Yes; 0 violation	Yes	-6.28 cm/s	3	2	67.4	225.24 g/mol	-8.6
6hydroxymetatacarbolineF	Low	Yes; 1 violation: NorO>10	No	-7.64 cm/s	8	5	134.9	496.51 g/mol	-8.7
7Methylxanthosine5monophosphate	Low	No; 2 violations: NorO>10, NHorOH>5	No	-11.18 cm/s	9	6	87.64	380.25 g/mol	-8.8
Asperindole D	High	Yes; 1 violation: MW>500	No	-7.56 cm/s	8	2	153.62	577.66 g/mol	-8
Jerantinine E	High	Yes; 0 violation	Yes	-6.44 cm/s	5	2	113.44	384.47 g/mol	-10
Atranone	High	Yes; 0 violation	No	-7.62 cm/s	7	2	114.07	432.51 g/mol	-7.9
Bohemamine G	High	Yes; 0 violation	Yes	-6.25 cm/s	2	1	79.09	262.35 g/mol	-8.1
Brevianamide Q	High	Yes; 0 violation	No	-6.50 cm/s	3	3	111.73	365.43 g/mol	-8.5

CHAPTER 8: DISCUSSION

To ascertain the molecular function of the typical DEGs, we carried out GO biological process and KEGG pathway research. A schematic analysis of the PPI network was conducted to assess potential protein interactions using the observed overlapped DEGs. In silico methods like molecular docking, there is growth in the usage of natural compounds recently as pharmaceuticals to speed up the medication development process. This method allowed us to foresee that Jeratinine E would function in Parkinson's as a strong NNMT gene inhibitor. It has potential benefits as a better inhibitor and has a lower binding energy than other compounds (-10). Additionally, study shows that it is BBB permeable and exhibits favorable drug-like qualities.

CHAPTER 9: CONCLUSION & FUTURE SCOPE

In this work, the gene expression of 20 patients with varying degrees of severity and 20 healthy individuals was examined using 32 different microarrays. The NNMT gene was found to be one of 32 genes linked with the aetiology of PD. For controlled autophagy, the prognostic marker NNMT might be trustworthy. Jeratinine E may be a useful treatment for Parkinson's, rendering to the significances of a molecular docking study combining NNMT genes and 40 naturally occurring compounds. Jeratinine E adheres to the Lipinski rule, is more drug-like, and permeates the BBB, as per the results of the ADMET analysis. The in real wet lab work will be beneficial in determining whether to target the Jeratinine E molecule.

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