DISCOVERING *GINKGO BILOBA* PHYTOCHEMICALS AS THERAPEUTIC APPROACH FOR PARKINSON'S DISEASE: IN SILICO MOLECULAR DOCKING

A PROJECT REPORT

Submitted in partial fulfilment of the requirement for the degree of

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Submitted by:

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CANDIDATE'S DECLARATION

I **Shivani Srivastava** certify that the work which is being presented in the thesis entitled **"Discovering *Ginkgo Biloba* Phytochemicals as therapeutic approach for Parkinson's Disease: In silico Molecular Docking"** in partial fulfilment of the requirements for the award of the Degree Master of Science in the Department of Biotechnology, Delhi Technological University is an authentic record of my own work carried out during the period to under the supervision of Prof. Jai Gopal Sharma.

The matter presented in this thesis has not been submitted by me for the award of any other degree of this or any other institute.

Shivani .

Place: Delhi

Date: 08/June/2024

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CERTIFICATE BY THE SUPERVISOR

I, hereby certify that the Project Dissertation titled, **"Discovering *Ginkgo Biloba* Phytochemicals as therapeutic approach for Parkinson's Disease: In silico Molecular Docking"** which is submitted by **Shivani Srivastava [2K22/MSCBIO/47]**, Department of Biotechnology, Delhi Technological University, Delhi in partial fulfilment of the requirement for the award of the degree of Master of Science, is a record for the Project work carried out by the student under my supervision. To the best of my knowledge this work has not been submitted in part or full for any Degree or Diploma to this University or elsewhere.

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DISCOVERING *GINKGO BILOBA* PHYTOCHEMICALS AS THERAPEUTIC APPROACH FOR PARKINSON'S DISEASE: IN SILICO MOLECULAR DOCKING

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ABSTRACT

Parkinson's disease poses a substantial global healthcare obstacle, particularly due to the increasing number of elderly individuals, impacting the functioning of nerves in the central nervous system. Multiple mechanisms contribute to its development, such as the degeneration of dopaminergic neurons, the activation of microglia and astrocytes, mitochondrial dysfunction inflammation, and oxidative stress. Typical symptoms consist of reduced mobility and involuntary shaking when at rest. Although there is now no cure, many drugs may successfully control the symptoms of Parkinson's. due to the intricate nature of Parkinson's, it is crucial to develop innovative therapeutic approaches. It is essential to investigate alternative treatments since the existing drugs for Parkinson's disease have limits in term of their efficacy and adverse effects. The historical use of traditional medicinal plants in tradition medicine for treating different diseases has generated curiosity about their potential has novel therapeutic agents for Parkinson's. the study aims to examines the capacity of phytochemicals derived from plant, namely those from *Ginkgo biloba* a Chinese plant, to interact with crucial proteins linked Parkinson's, such as DJ-1 (PARK7), using molecular docking methods. The results of this study indicate that phytochemicals derived from *Ginkgo biloba*, particularly Terpenoids such as Ginkgolides and Bilobalide, have strong affinity for proteins that are important in context of Parkinson's disease. This suggests a favourable outlook for the development of novel therapeutic strategies. Therefore, this work seeks to evaluate the drug-like characteristics of these phytochemicals by conducting in silico studies with relevant Parkinson's disease and aimed to explore the possible therapeutic use of phytochemicals in targeting the aberrant expression of DJ-1 in the development of PD.

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ABBREVIATION

PD	Parkinson's Disease
GB	*Ginkgo biloba*
CNS	Central nervous system
ROS	Reactive oxygen species
SN	Substantia nigra
PARK7	Parkinson's Disease protein 7
DJ-1	Protein Deglycase
AD	Alzheimer Disease
MD	Molecular Docking

CHAPTER 1

1.1 INTRODUCTION

Neurodegenerative disease, like Parkinson's, are very dangerous for older people, and their number is rising as the world's older population does. The genes and surroundings both play a role in causing this disease, and they often lead to confusion and trouble moving around[1].These disorders are characterized by oxidative stress, the accumulation of protein aggregates, and neuroinflammation. These substances initiate cellular stress, stimulate the generation of brain- derived neurotrophic factor and activate protein kinases via the tropomyosin- related kinase (TrkB) receptor family and neurotrophins [2]Parkinson's disease (PD) is a diverse neurological condition that worsen with time. It is marked by symptoms such as slow movement, shaking, and a range of both physical and non-physical symptoms. Research has shown that persons with PD have more pronounced and influential non-motor symptoms, such as sadness and anxiety[3]Studies suggest that Parkinson's affects peripheral organ as well as central nervous system and this engagement in both peripheral and central nervous systems crucial in initiating brain inflammation [4]. Brain inflammation caused by activation of microglial cell which is a crucial factor for causing inflammation, the activation of microglial cell is controlled by Fractalkine (CX3CL1), which belongs to the chemokine family. It's synthesized by neurons in the CNS, but its receptor, CX3CR1, is abundantly expressed by microglial cells. The disruption of the CX3CL1-CX3CR1Singaling pathway is unequivocally associated with inflammatory responses in the human brain [5]. Variables which responsible for the causing PD including genetic variances, the process of aging, and chances in eating patterns. Reactive oxygen species, selective neuron loss, mitochondrial dysfunction, and ATP depletion are all things that can lead to the formation of PD, also its characterized by a dysfunction in the ubiquitin proteasome system (UPS), which is responsible for the breakdown of damaged proteins [6].

Several gens, such as UCHL1, GYGYF2, OMI/HTRA2, PLA2G6, and FBXO7, have been associated with PD outside the six known genetic varieties. Multiple mutations in PARK- designated genes, as well as small number of other genes, have been associated with a heightened susceptibility to developing PD. Genes such as Parkin, DJ-1, UCH-L1, nuclear receptor- related factor 1 and alpha synuclein are linked to PD or similar disorder [7].

DJ-1(PARK7), It is a protein composed of two identical subunits, consisting of 189 building blocks called amino acids, is present in almost all cells and issues, including the brain. Amino acid sequence of this protein conserved throughout many species resulting in the formation of the DJ-1 superfamily. Reactive astrocytes exhibit an excessive amount of DJ-1, which contributes to the development of illnesses such as

Parkinson's disease [8]. DJ-1 also named as Parkinson's disease protein 7, is a notable biomarker for Parkinson's disease. In addition to its diagnostic usefulness, DJ-1 plays a crucial role in neuronal function that protects cells against oxidative stress, especially in cells that need a lot of energy and have elevated quantities by counteracting reactive oxygen species, which are necessary for preserving neuronal well-being [9] [10]The main purpose of this is to decrease the harmful effects of oxidative damage, also preserving the well-being of mitochondria, controlling inflammatory mechanisms, promoting cell viability, and averting protein misfolding. [10]. Dj-1 also regulates inflammatory responses, inhibits cellular apoptosis pathways, and improves survival under conditions of stress. By preventing protein aggregation, which is associated with illnesses, it maintains cellular integrity and shields cell from different stresses.

Mutations in DJ-1(PARK7) leads to detrimental impacts on brain well-being, dysfunction in DJ-1 may leads to the growth of early-onset Parkinson's disease by intensifying neuronal damage and cellular demise [8].

Hence, it's important to look into new and better ways to treat diseases like PD. Plant metabolites, also called phytochemicals, are being studied more and more these days to see how they might affect PD. The medicine herbs used in this study were carefully chosen because they have been used for a long time in different medical practices and could help find new drugs. Phytochemicals that are often found in many medicinal plants that enhance the functioning of the immune system, control the metabolism of hormones, and also stimulates stress response pathways or function as ligands, attaching to particular receptors and initiating antioxidant actions [11]. *Ginkgo biloba*, a Chinese tree renowned for its therapeutic effects on the heart and lungs, includes flavonoids, Ginkgolic acid, and terpenoids. EGb761, an extract derived from *Ginkgo biloba*, was shown to prevent the loss of dopaminergic nerve terminals induced by MPTP in a long-term study. EGb761 demonstrated a reduction in the neurotoxicity of levodopa in the 6-hydroxydopamine (6- OHDA) PD model, indicating its potential to alleviate the harmful effects of levodopa [12]. EGb761 extract which is the standard leave extract of G biloba plant include a wide range of phytochemicals such as, flavonoids and terpenoids which play important role in the neurodegenerative illnesses like PD, flavonoids (quercetin, kaempferol, and isohamnetin) and Terpenoids (Ginkgolide A, B, C, J and Bilobalide) are the different phytochemicals which shows anti-oxidant, anti-inflammatory effects in Parkinson's diseases.

Computational methods, such as molecular docking, are being used more often to explore the structure and function of biomolecules, as well as to create medications based on structure. Currently, there is significant emphasis on finding new phytochemicals that have been found to have medicinal potential. Docking studies play a vital role in the first stage of drug development by evaluating the efficacy of drugs that target proteins associated with PD, compressive molecular docking analysis on *Ginkgo biloba* plant, focusing on protein targets linked to PD. Additionally the safety

and effectiveness of G biloba in treating disease were evaluated by assessing its physicochemical, drug-likeness, and ADMET profiles [13].

1.2 OBJECTIVE

This project aims to explore novel therapy approaches for PD using phytochemicals derived from *Ginkgo biloba* using molecular docking to assess the interactions between phytochemicals and crucial protein target linked to PD, the study is to uncover highly promising candidates that have a strong ability to bind to protein associated with PD, uses algorithms hypothesis to predict the strength of binding between phytochemicals and proteins, a fascinating area of research.

CHAPTER 2

REVIEW OF LITERATURE

2.1- NEURODEGENERATIVE DISEASE-

Millions of people worldwide are impacted by a class of neurological illnesses known as neurodegenerative diseases (NDDs), which cause the gradual death of neurons in the central or peripheral nervous systems. Due to neuron's instability to properly renew themselves, this causes the basic communication circuity to break down, impairing memory, cognition, behaviour, sensory perception, and motor function [14]Often inherited from tumours, strokes or toxins. This can worsen over time due to excessive alcohol consumption. Globally, millions are impacted by neurodegenerative illnesses such as Alzheimer's and Parkinson's in the United States, the numbers are close to millions. Over a time, these illnesses lead to death via degeneration of the brain or peripheral nervous system. The risk rises with age, and prevalence may rise as life expectancies rise. It is essential to develop novel therapies and preventative measures.

After death, brain tissue testing is used to detect neurodegenerative illnesses, which are characterized by problems with mobility, cognition, and behaviour. Inflammation, oxidative stress, and protein buildup are common processes. Before symptoms manifest, abnormal proteins can be found, but diagnostic biomarkers are few, with the

exception of rare instances involving known genetic abnormalities [15]. Age is the main cause of neurodegenerative illnesses, which impact millions of people worldwide. These illnesses are not only caused by genes, their development is influenced by a mix of environmental factors and genetic predisposition [16]The majority of neurons originate in the brain, and they are essential for both brain activity and communication. But as people become older, their synthesis decreases, which causes neurodegeneration, a gradual loss of neurons and the abilities they carry out. Numerous neurological conditions result from this, such as prion disease, ALS, Huntington's, Alzheimer's, Parkinson's, spinal muscular atrophy, and spinocerebellar ataxia [17]

2.2- PARKINSON'S DISEASE-

A second most common neurological disease is Parkinson's. It is difficult disease with signs that aren't related to movement. The chance of getting it is 2% for men over 40 and 1.3% for women over 40 in US. This simply means that chances that older individual are more likely to get this. In the early stages, people often have trouble with their balance and walking. These problems get worse as when illness getting worse [18]Condition that affects 6.3 million individuals globally is Parkinson's disease (PD). People with this condition have shaken, slow movement, stiff muscles, and trouble keeping their balance. Some of the signs are anxiety, sadness, trouble sleeping, loss of smell, trouble eating, and mild cognitive damage. PD is caused by Lewy bodies, which are abnormal protein clumps, and brain cells dying in the SN that make dopamine [19] Substantia nigra part of mid brain shows signs such as trembling, bradykinesia, and other motor and non-motor signs [20] researchers studying the biology of the disease have linked to condition to the death of more dopaminergic neurons in the lateral as well as posterior parts of the substantia nigra, tremor is the most common sign of PD. While several dopamine precursor and synergy medicines are used as a first line of treatment for tremors symptoms, none of them fully address dopaminergic depletion in the CNS [21] Bradykinesia is a compound term that combines the terms hypokinesia (disability of motor control) and akinesia (failure in voluntary muscle movement). It may serve as the connection between the process of formulating instructions and carrying them out. Bradykinesia can have secondary root causes, such as muscle weakness, rigidity, rest and action tremor, and variability in movement [22]. Initially thought to be a movement illness, PD is now recognized for its prevalent and incapacitating neuropsychiatric symptoms (NPS). This acknowledgement has come about as a result of recent therapeutic improvements, extended patient lifespans, and more awareness. Cognitive impairment, depression, psychosis, anxiety, insomnia, anxiety control issues, apathy and exhaustion are some of these symptoms. Neurobiological variables, PD therapies, demographics, and different disease pathologies are all linked to the frequency of NPS in PD [23]Intracellular inclusion, known as Lewy bodies, contain ubiquitin and alpha-

synuclein. When examined histologically, they appear as big, round, strongly eosinophilic inclusions. During studied on Parkinsonism in 1912, Lewy made the initial identification of these bodies [24]. Lewy bodies, or the aggregation of alpha synuclein protein, and inclusion bodies are the hallmarks of Parkinson's disease. Larger fibrillar alpha synuclein aggregates may be beneficial because they trap harmful proteins, according to research. However, if the cells continue to produce harmful proteins, according to research. However, if cells continue to produce harmful proteins and Lewy bodies continue to break them down, this might result in an ongoing cycle of cellular destruction [25]

Genetic classifications influence PD etiology, therapies, and prognosis. Subgroups include familial vs sporadic, early vs late onset, and monogenetic vs idiopathic processes. Genes like PRKN, PINK1, and PARK7(DJ 1) influence mitochondrial function. Monogenic PD genes often have common variations in genome-wide association studies, such as the MAPT gene and SNCA variants [26]

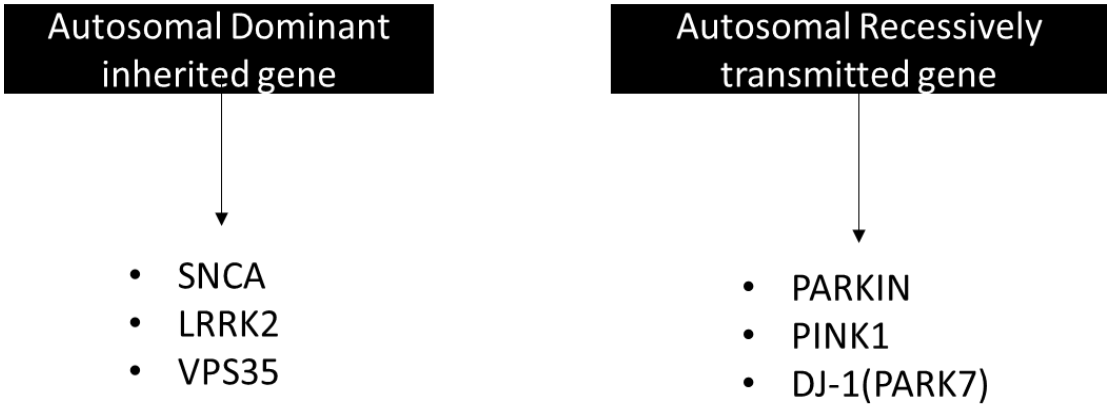


Fig 2.1- Represents the different enzymes involved in Parkinson's diseases which causes autosomal and recessive PD.

Autosomal dominant PD-

The first case of familial Parkinson's disease was identified in 1997 due to a mutation in the alpha-synuclein gene. Since then, four more genes' duplications and point mutations associated with autosomal dominant PD have been identified, with Leucine-rich repeat kinase 2 (LRRK2) gene mutations being the most frequent cause accounting for 1% of sporadic cases and 4% of familial globally. The most prevalent mutation in this gene is p. G2019S [27]

Autosomal Recessive PD-

This form of PD usually manifests sooner than conventional PD. PRKN, PINK1, Dj-1, and PARK genes are associated with metabolic regulation. In combination, PINK1 and parkin are involved in mitophagy; up to 50% of cases with early onset are caused by changes in PRKN. Unusually parkinsonism is also caused by different autosomal recessive genes, including ATP132A, PLA2G6, FBX07 and SYNJ1 [27]

There is molecular diagnostics accessible for genes like PRKN, PINK1, DJ-1 and LRRK2 which linked to PD. Since patterns of inheritance vary, treatment and diagnosis can be difficult. PRKN mutations are advised for individuals whose onset occurs before the age of 40 and are reasonably priced. While LRRK2 mutations may be suitable for later-onset idiopathic PD, PINK1 and DJ-1 mutations may be taken into consideration for early-onset PD. Only people diagnosed with Parkinson's disease should consider genetic testing since certain variants have little predictive value [28]

2.3 DJ-1 (PARK7)

The location of the Dj-1 gene onto chromosome 1p36 [29]This gene was discovered by Nagakubo et al. in 1997, as an oncogene, when paired with H-Ras, Dj-1 may convert mouse NIH3T3 cells. Bonifati et al. detected alteration in the PARK7 gene in a Dutch and Italian family with early onset parkinsonism in 2003, which led to the discovery of the link between Dj-1 and Parkinson disorder [30] the function of human Dj-1, a protein present in both bacteria and mammals, in neurodegeneration and autosomal recessive illnesses such as cancer and Parkinson's disease has been extensively researched. Its 189 amino acid structure is linked to parkinsonism and dopaminergic neurodegeneration, and it forms dimers [31]. amino acid protein that is engaged in cell signalling pathways that are connected to cell proliferation. It is found in the cytoplasm, mitochondria, and nucleus, among other biological compartments, and forms dimers. Many researched its structure in great details. Dj-1 is an important component of cellular defence systems since it is not only an antioxidant but also helps shield cells from damage caused by ROS [32]. As a protein sensor, Dj-1 keeps cells safe from the harm that caused by (ROS), by responding to oxidative stress. ROS are biochemical substances which include oxygen, such as peroxides, hydroxyl radicals, and superoxide. These species can be produced chemically in response to exposure to UV light, Tabacco smoke, medicines, xenobiotics, and pesticides. Among them, pesticides and xenobiotics are especially high relevance for the development of the onset of Parkinson's disease [33] DJ-1 associated with male infertility due to its decreased expression in sperm and epididymites. When exposed to high glucose levels, Dj-1 levels rise in pancreatic beta cells, indicating a protective function. The precise chemical processes behind Dj-1 defence against oxidative stress. Its primary target for oxidative alteration is Cys106, a critical cysteine residue that is necessary for its operation. Cys106 can change into sulfinic and sulfonic acid forms when under oxidative stress; the sulfonic form is more prone to aggregation and more unstable [10].

Dj-1 is crucial for controlling transcription, mitochondrial activity, and free radical elimination. It is involved in cell growth and control through mechanism like the phosphoinositide-3 kinase pathway, which is triggered by EGF. When PTEN is deleted, the P13 K/Akt pathway is inhibited, reducing Akt phosphorylation and neuronal death. DJ-1 also regulates mitochondrial function, which is associated with neurodegenerative disease. In PD, PTEN is inactivated, reducing Akt phosphorylation and neuronal death [8].

- **Dysfunction of mitochondria**

  DJ-1 is required to provide energy and modulate calcium signalling, maintaining mitochondrial function, and survival. Mitochondrial impairment or dysfunction is also linked to a decrease in energy production and ROS emission, while the progression of PD involves impaired mitochondrial function. For example, DJ-1 gene mutations lead to a disequilibrium of the mitochondrial function ultimately resulting in energy deficit, increased ROS levels and subsequent neurodegeneration.

- **Oxidative stress**

  A central player in the control of oxidative stress, generated when ROS production exceeds antioxidant defences. Moreover, it scavenges ROS and promotes the expression of antioxidant enzymes to increase cellular resistance against oxidative damages. However, if the DJ-1 gene is faulty in any way, that protective process may not work as well and neurons could be more susceptible to damage caused by oxidative stress.

- **Protein misfolding**

  DJ-1, which plays an important role in sustainment of cellular equilibrium by constructing and decomposing proteins it uses proteases and chaperons to remove misfolded proteins for decoration. Without changes, the DJ-1 gene functions to enable cells within the brain to get rid of proteins that are no longer useful or necessary for cellular function, but if there are mutations in the DJ-1 gene then this process is less effective and can leave behind harmful proteins.

Parkinson's Disease that starts earlier and likely to run in families has been caused when mutation in DJ-1 gene occurs, DJ-1 a member of the DJ-1/Thil/Pfpl class of proteins. It appears to have more than one job, possibly as an antioxidant, a chaperone (which helps proteins fold properly), or even a protease (which breaks fold properly), or even a protease (which breaks down proteins). Study found that people with PD had both copies of their DJ-1 gene removed (homozygous deletion). This highly suggested that the loss of DJ-1 activity plays a role in the damage to nerve cells that happens in the disease[34]. PD is linked to over 20 Dj-1 mutations, which alter the enzyme's

structure and function, leading to unstable monomers that are more prone to breakdown. Other mutations such as L10P and P158, obstruct homodimerization. The E64D mutation reduces intracellular protein levels due to incorrect pre-mRNA splicing. DJ-1 mutation carriers typically experience early onset, progressive parkinsonism, similar to other neurodegenerative conditions. The main Dj-1 loss include mitochondrial malfunction and reduced dopaminergic differentiation potential when cells from PD patients lacking Dj-1 are used for cell production [35]. Certain pesticides suppress Dj-1, which may contribute to PD development. Chronic exposure to heavy metals and environmental pollutants raises the likelihood of developing Parkinson's disease. Pesticides inhibiting Dj-1 can leads to disease and ROS species buildup. Mutated Dj-1s lose their ability to bind metals, causing neuronal loss through processes like neuroinflammation, oxidative stress, DNA damage, mitochondrial malfunction, and apoptosis. Chronic exposure to heavy metals increases the lifelong risk of developing PD [36]. Mutations can cause disruption to Dj-1, a protein which involved in cellular functions such as the control of protein folding and

the oxidative stress response. This can result in neuronal injury and cellular malfunctions. Mutations in PARK7 cause absence of functional DJ-1 and due this dysfunction of mitochondrial, inflammation of the nervous system, lack of dopamine and death of cell takes place which causes early onset of Parkinson's (Autosomal recessive PD).

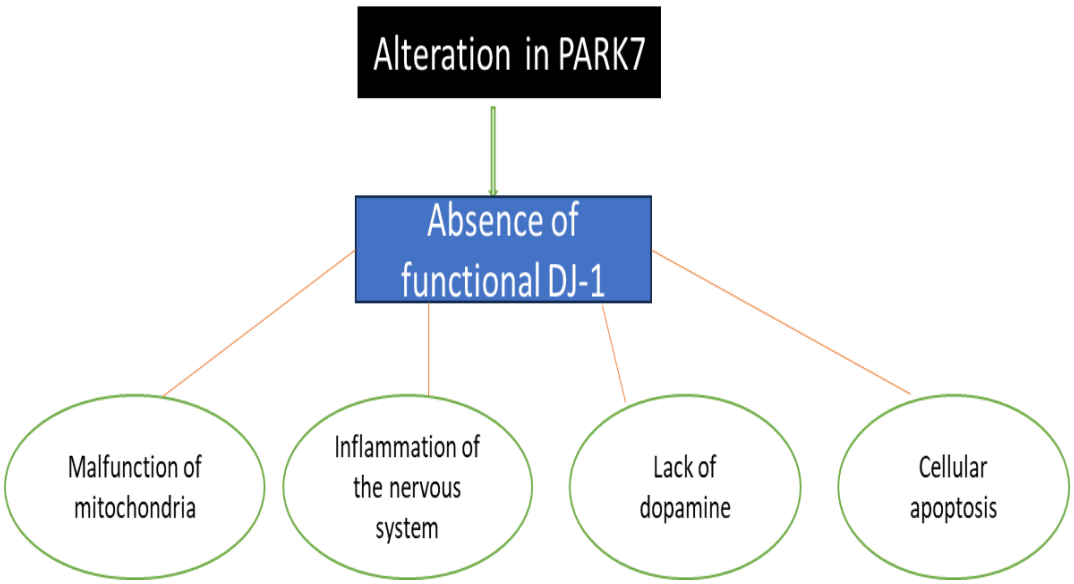


Fig 2.2- Represents the mutations in DJ-1 leads to early–onset of PD.

2.4 Medicinal plant

Medicinal plants are those that have therapeutic properties that are beneficial to the human or animal body. Use of herbal natural products are gaining traction because of their accessibility, affordability, and lack of negative side effects. Among other substances, plants contain phytochemicals (terpenoids, flavonoids, and alkaloids) that have a range of therapeutic benefits. The development of conventional remedies in the treatment of various diseases like neurodegenerative diseases, cancer, skin wounds etc [37]. Plants have a long history, a big influence on social, cultural, and economic life, and are essential for the health and well-being of local populations. The world health organization (WHO) states that 75-90% of rural communities worldwide are impacted by traditional medicine, which is defined as knowledge and practices that have been passes down through generations. Not only is it reasonable price, but it also takes psychology into account and is culturally appropriate [38]. Like nature's pharmacies, plants have been utilized for ages to treat a wide range of medical conditions. These days, a lot of the medications take originate from jewels found in plants that may ward against pathogens. Molecules originating from plants, animals, fungi, algae, prokaryotes, and other organism can be found naturally, either in their unadulterated state or mixed with other molecules. Scientists are examining the abundance of knowledge found in traditional medicine to find potential new drugs [39].

The use of medicinal plants has been a major benefit to traditional medical practices in many different cultures across the world. These plants are rich in Terpenoids, flavonoids, alkaloids and other bioactive compounds. These chemicals have many medical uses, like reducing inflammation, killing germs, protecting cells from damage, and fighting cancer.

2.4.1 Ginkgo Biloba

Fig 2.3- Ginkgo biloba (Maidenhair tree) [40]

Classification and taxonomy:

KINGDOM: Plantae
PHYLUM: Pinophyta
CLASS: Ginkgopsida
ORDER: Ginkgoales
FAMILY: Ginkgoaceae
GENUS: Ginkgo [41]

Palaeobotanists investigate ancient Ginkgoaceae plants, which serve as amazing time capsule dating back to 300 million years ago in the Permian era and 200 million years ago in the Jurassic period. Despite enduring substantial extinctions and temperature fluctuations throughout history, Ginkgo biloba L, the only remaining species, flourishes in its native environments across China. These plants are said to be resilient [41]. It has been used medicinally in China for around 5000 years, including for treating diseases [42]. Renowned for their tenacity and beauty, ginkgo tress may be found all over the world, even on college campuses and in urban areas. They are very important in East Asia, where they stand for peace and optimism. Ginkgo leaves have been utilized for generations to cure heart and brain health concerns, and its smell has been enjoyed for millennia as well. People have been aware for their usefulness in preserving smooth blood arteries since the 1960s, which makes them an important tool for preserving general health [40]. Because of its medicinal qualities, ginkgo biloba leaf extract is a widely used herbal treatment and supplement worldwide. Free radicals are scavenged, oxidative stress is decreased, the neurological system is shielded, and platelet aggregation is prevented. Its efficacy in treating cognitive deficiencies and illnesses of CNS [43]. Flavone glycoside and terpenoids are present in ginkgo biloba extract (EGb), which is made from the leaves of the maidenhair tree. These molecules are abundant in the standardized form EGb761, which has fewer than 5 ppm of ginkgolic acids. Rereach on age- related illness such as brain dysfunction, cardiovascular diseases, metabolism of carcinogens, and disorders of the sensory tissues uses EGb [44]. The therapeutic properties of the ginkgo biloba tree are being investigated for possible uses in supplements. In leaves and seeds active ingredients found which enhance blood flow, fortify capillary walls, and shield nerve cells. Extracts are used to treat AD, PD and dementia- related conditions. Antidepressant and neuroprotective properties, may enhance cerebral blood flow, which lowers weariness. It also possesses a little antidepressant and anti- anxiety effect [42].

Neurodegenrative illness is rising, prompting research into their causes and potential research into their causes and potential treatments. G biloba reduces pathological hyperactivity, a key factor in brain cell death, by enhancing cerebral blood flow. GB seeds contain trepenoids and flavonoids that improve blood flow to the brain. Extract has shown potential in treating brain ischemia and AD, PD diseases. Proper GB intake

strengthens toxicity resistance, but excessive amounts weaken the immune systems, requiring dose adjustment [45]

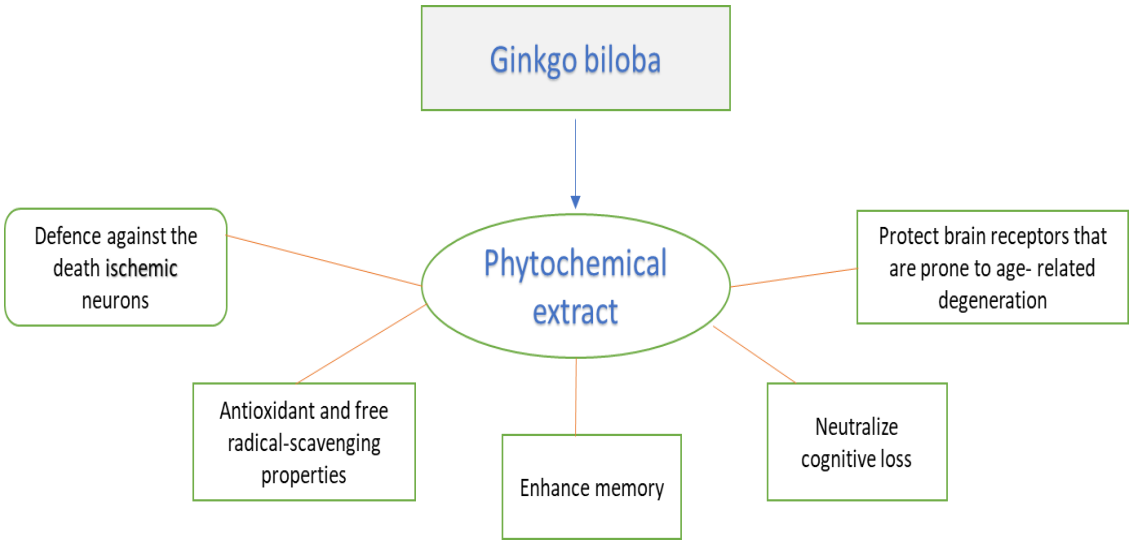


Fig 2.4- Represents the effectiveness of phytochemicals of G biloba in PD.

Chinease tree ginkgo biloba is well-known for its traditional useas a remedy for lung and heart problems. Studied on ginkgolides with parkinson's disease have showed promise. One such preparation is EGb761, which possesses antioxidant capabilities. EGb761 guards against neurotoxic effects, avoids damage to dopaminergic nerves, and prevents pesticide-induced cell death. Another substance found in G. biloba leaves, ginkgetin, controls iron levels and lowers oxidative stress in parkinson's disease models. Ginkgolide B and Bilobalide protected cells from damage caused by alpha synucelin [46].

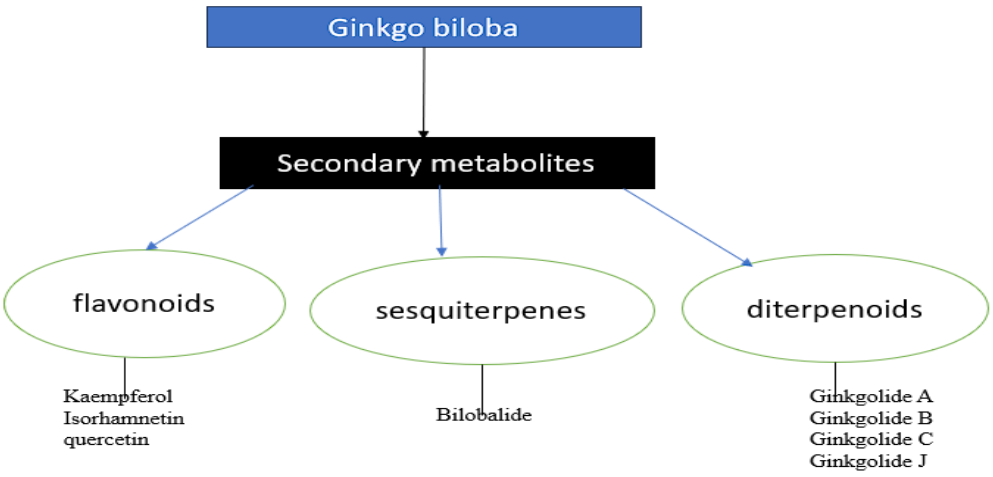


Fig 2.5- shows the different metabolites of Ginkgo biloba.

2.4.2- Metabolites of G. biloba-

Among the special substances found in ginkgo biloba that makes it useful in herbal therapy are terpene trilactones, acylated flavonol, glycoside, biflavones, ginkgotides, and ginkolic acids. More than 60 bioactive components are included in the extract, the most important of which are flavonoids and terpenoids (24% and 6%), as well as organic acids, proanthocyanidins, tannins, sitosterols, carotenoids, polysaccharides, glucose, minerals, and vitamins [47]Terpene trilactones produced by Ginkgo biloba tress, such as ginkgolides and bilobalide, have anti-inflammatory, neuroprotective, anti-tumor and anti- apoptotic properties. However, because of their sluggish development and complicated character, these chemicals are difficult to isolate. Ginkgolides and bilobalide may be successfully produced by endophytes from Ginkgo tress, offering an alternate approach of obtaning these bioactive metabolites without depending entirely on the slow development of the tree [43]. The safety and effectiveness of biloba plant extracts depend upon the quality of raw materials, extraction solvents and procedure.EGb761 is standardized to include certain quantities of ginkgo flavonoids, trepene lactones, and low levels of ginkolic acids. It produced from G biloba leaves using acetone 60% [48]

FLAVONOIDS

These are the polymers with a 15- carbon skeleton and consist of two benzene rings and a 3- carbon chain. They can exit in both glycoside- bound and free aglycone forms. G. biloba leaves contain 110 flavonoids, including flavanol glycosides, flavone glycosides, isoflavone glycosides, flavan-3-ols, biflavanoids, and biginkgosides. Common flavonal aglycones include isohamnetin, kaempferol, and quercetin [49] Young ginkgo seedlings conatin flavonoids, which offer a wide range of biological benefits, including anti-inflammatory, anti-viral, anti-cancer, anti-bacterial, and neuroprotective activities. These have been notable therapeutic benefits shown when quercetin, kaempferol, and isohamnetin aglycones are combined. But as tree become older, the quality of the extract declines, thus foliar fertilization or other alternate watering techniques are used to boost the level of flavonoids [40].

TERPENOIDS

Trepenoids like ginkgolides and bilobalides, which are found in ginkgo seeds, are critical for their therapeutic and preventive benefits aginst heart and brain disorders. All portions of ginkgo seeds contain terpenoids, howeever the concentration is highest in the embryo and endosperm. In ginko extarct, ginkgolides A,B,C,J and M are the principal terpenoids [40]. Ginkgolides, particularly ginkgolide B, are extremely therapeutic substances that improve memory and learning, prevent neurol

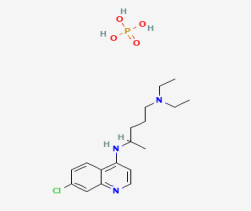
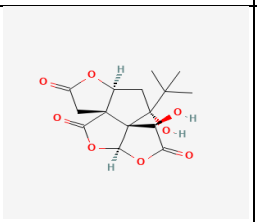
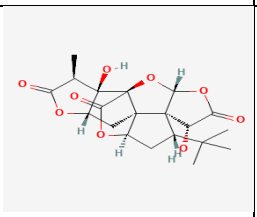
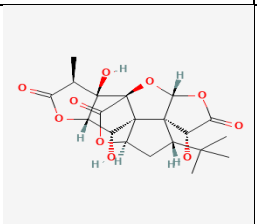
degeneration, and have anti-epileptic aactions on hippocampus neurons. They also have anti-inflammatory, anti-apoptotic, and antioxidant properties as a platelet-activating factor receptor antagonist [50]

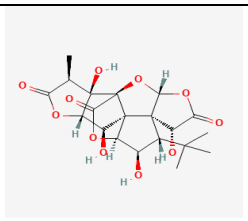
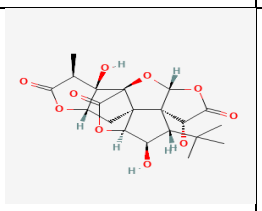
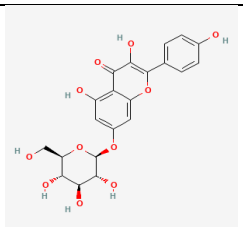
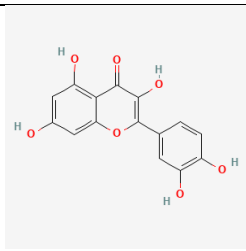
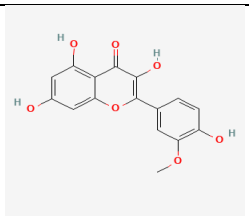
A diterpenoid called bilobalide isomerizes under moderate acylation conditions. Enzyme such as Gb LPS, which produces levopimaradiene, are involved in the biosynthesis of terpenoids such as ginkgolides and bilobalides starts with isopentyl diphosphate and dimethyl diphosphate which condenses into farnesyl precursors and geranylgeranyl diphosphate. It is a three-step process. The structure and oxidation pattern are determined by the late cuclization and oxidation stages that are catalyzed by cytochrome P450 enzymes and terpenoid synthases [40], [51].

2.5 Phytochemical of G. biloba in PD

Herbal treatment is a secure and efficient method for addressing mental health issues, with a significant global population relying on medical plants. Promising outcomes have been observed in treating psychiatric diseases like depression, schizophrenia, anxiety, sleeplessness, and Alzheimer's. investigating the potential of natural substances for Parkinson's disease treatment is promising [52]conventional treatments for PD provide only partial relief from symptoms and do not address the underlying brain problems. Nevertheless, there is potential in using natural compounds that include anti-oxidant and anti-inflammatory properties, such as polyphenols, flavonoids and trepenoids, for therapeutic purposes.these chemicals originated from plants have ability to inhibit the clustering of alpha-synuclein, a define trait of PD which have the power to activate enzymes,boost mitochondrial function, and promote cognitive performance. In light of the cost and adverse effect profiles of synthetic medications, natural treatments are a viable option for management of disease [53]. Due to their preceived health benefits, patients choose natural substances over manufactured medications for neurological illnesses. However death of well monitored clinical trials has prevented natural substances from becoming accepted therapies. In order to get broad acceptability, more thorough testing are required. Despite the fact that there are currently no therapies for PD and ADHD, natural substances show promise in controlling their development since they lower oxidative stress [54].

Table 2.1 shows the different phytochemicals of ginkgo biloba and their effects against neurodegenrative disease.

Plant	Phytochemical	Metabolite	Structure	Effect	Refrence
GINKGO BILOBA	EGb761(cloroquione monophosphate)	Standard extract		Antioxidant and neuroprotective properties, prevent loss of dopamine in PD	[40]
	Bilobalide	sequiterpenes		Not harmful, anti-inflammatory and mitochondrial-stabilizing effects in PD	[55]
	Ginkgolide A	ditrepenoids		Not harmful, immunostimulating and anti-inflammatory properties.	[56]
	Ginkgolide B	ditrepenoids		Not harmful, safeguard dopaminergic neurons favorable impact on the central nervous system's functionality	[57]

GINKGO BILOBA	Ginkgolide C	ditrepenoids		Not harmful,protects dopaminergic neurons from oxidative stress and inflammation	[58]
	Ginkgolide J	ditrepenoids		Not harmful, improved neuronal survival and function in high-stress environments.	[59]
	kamepferol	flavanoid		Antioxidant, inflammatory-reducing, and capable of scavenging free radicals	[40]
	quercetin	flavanoid		Anti-diabetic, antioxidant, antibacterial, also supporting the health of the brain and circulatory systems	[40]
	isorhamnetin	flavanoid		Positive effects on the nervous system and blood vessels, include anti-inflammatory	[60]

Although, currently there is no as such cure for PD, research is into the potential symptoms relief of phytochemicals derived from herbal plants and other natural sources is still continuing. Antioxidant and anti-inflammatory compounds such as Bilobalide, Ginkgolides, flavonoids from Chinese plant G biloba may shield neurons from harm. Furthermore, using LightBBB, the permeability of ginkgo biloba extracts across the blood- brain barrier was evaluated in order to determine their potential therapeutic effectiveness.

Table 2.2 shows the permeability across blood-brain barrier of different extracts of medicinal plant (G biloba).

Extract	Permeable across BBB
Bilobalide	Permeable
Kamepferol	Non-permeable
Quercetin	Non-permeable
Ginkgolide A	Permeable
Ginkgolide B	Permeable
Isorhamnetin	Non- permeable
Ginkgolide C	Permeable
Ginkgolide J	Permeable

2.6 In silico approach-

Historically, the process of finding new drugs has been drawn out and expensive, requiring an average of $1.8 billion USD from lead identification to clinical trials. However, because in silico techniques such as molecular docking has the potential to speed up the process and cut costs, time and resources, interest in them has surged recently [61]. Docking is an essential technique in molecular and structural biology and computer-aided drug design. It is used to forecasting ligand-target binding. MD has advanced over the past 30 years, accelerated by computer availability and capacity, and easier access to databases [62]Techniques are crucial methods for comprehending

the atomic-level chemical interactions with proteins, hence offering valuable insights into biological systems. Blind docking, which is a strict method, has several drawbacks. Molecular modelling, an essential element of pharmaceutical research, enables the investigation of intricate biological and chemical systems. By integrating computational and experimental techniques, researchers have identified novel molecules. Docking techniques play a crucial role in drug design by evaluating the binding energy and spatial configurations of ligands inside biological targets[63]. The use of in silico methods has made it possible to screen a large number of chemicals virtually in an acceptable amount of time. As a consequence, the initial costs of

identifying potential hits have decreased, and the chances of finding the necessary medication candidates have improved [64] Furthermore, it consists of two interconnected steps: first sampling the, shape of the molecule inside the protein's active spot and then evaluating these conformations using a scoring function. Fischer's lock-and-key theory explain how the ligands fits into the receptor, while Koshland's induced-fit concept suggests that ligand interactions alter protein active sites, highlighting the inherent adaptability of both ligands and receptor [65].

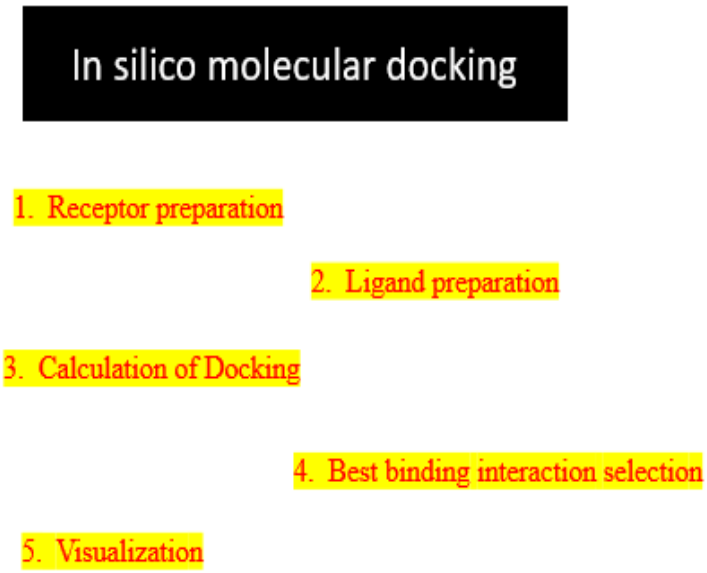


Fig 2.6- Steps involved in MD.

CHAPTER 3

METHODOLOGY

3.1 Screening of PD related genes-

By using Parkinson's disease as a keyword, searched in and Gene Cards database (https://www.genecards.org/) OMIM database (https://www.omim.org/) to find the different PD related genes. OMIM is freely available database of human genes and genetic disorder which contain detailed and referenced overview of all known genetic disorders.

Gene cards is a human gene database which contain genomic, proteomic, genetic, clinical and practical information. After analysis all the gene related to Parkinson's DJ-1(PARK7) gene is target for docking purpose. Mutations in DJ-1 gene cause early onset of Parkinsonism.

3.1.1 Construction of protein

Protein interactions- determine the degree of interaction between the protein by using STRING (string-db.org). STRING database integrate all predicted and known interaction between the protein. This shows the interaction of DJ-1(PARK7) gene with other protein which regulate the molecular function and pathways of neurodegenerative disease (PD).

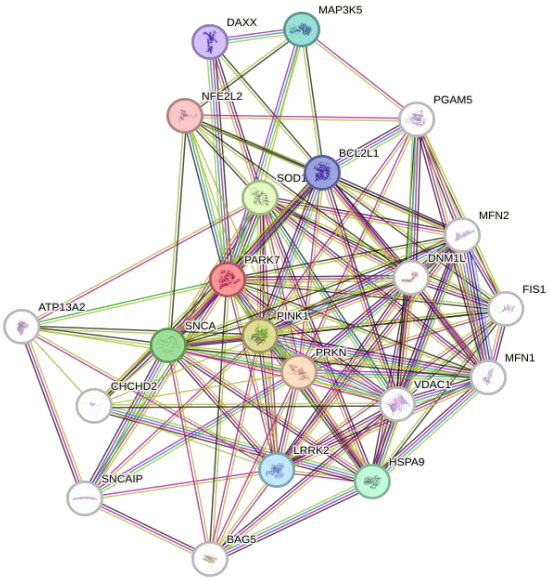


Fig 3.1- shows protein-protein interaction of PARK7(DJ-1) with other gene related to PD.

3.2 Screening and selection of drug

It is essential to take excretion, metabolism, absorption, and distribution into account while creating pharmacological substances. We take into account a few parameters, including Lipinski rule, BBB permeability, and lead resemblance, before selecting a drug. Only medications that satisfy these norms are selected for molecular docking study. We make use of many available web-based servers to evaluate the requirements for these tiny ligands.

LightBBB

LightBBB (cau.ac.kr). it is an online tool for the evaluation of the barrier between the blood and brain permeability, the structure of drug entered in the form of Conical SMILIES. After searching it can predict the probability that drug can pass the blood brain barrier or not only those drugs which can permeable to the brain is selected.

SwissADME

http://www.swissadme.ch/. Molecular Modelling Group which created the online utility SwissADME. It is intended to forecast different bioavailability factors and pharmacokinetics characteristics of small molecules, especially those that resemble drugs. In this structure of selected chemicals can be entered in different forms, which include conical SMILIES which copy from PubChem database and paste into SwissADME for the analysis of drug like properties. After analysis chemicals based on pharmacokinetics characteristics were selected.

Molsoft

(https://www.molsoft.com/mprop/). This is an online bioinformatics tool for the prediction of molecular characteristics and compounds drug-likeness. in this the structure can be entered into in the form of SMILIES and then it calculates different properties of compound and give a graph of drug-likeness.

Lipinski filter

(http://scfbio-iitd.res.in/software/drugdesign/lipinski.jsp). This is an online tool available for calculation for properties of selected compounds (Lipinski rule of five). This tool will help to differentiate between drug and non-drug compound. This approach assesses a molecule's chances of becoming a medication by looking at whether it satisfied the following requirements or not:
Molecular weight of phytochemical should be less than 500 Daltons, lipid solubility should be poor (value of p should be less than 5), less than 5 and 10 donor and acceptor of hydrogen bonds respectively, and last molar refractivity in between 40 to 130.

Only phytochemical(drug) which is selected have possess these properties which is mentioned above should be selected for further molecular docking process.

3.3 Protein and Ligand preparation

3.3.1 Protein (Receptor preparation)

The 3D structure of receptor PARK7(DJ-1) is downloaded from RCBS PDB Database in PDB format (https://www.rcbs.org). RCBS PDB contain 3D structure of all proteins or gene. After downloading 3D structure open it into Biovia discovery studio for preparation. In Biovia visualization tool structural problems were identified and removed. Water molecule was removed from the targeted protein for better binding and a polar hydrogen bond added to the structure for better docking calculations. Before uploading the protein PDB file into PyRx for docking PDB file of protein is converted into PDBQT format through Open Babel.

3.3.2- Active Site prediction

To determine the function of a protein and provide potential therapeutic options. For correct binding, its active site must be predicted. Many tools like FTsite, Castp etc are available to predict protein binding site for ligand.

Castp (http://sts.bioe.uic.edu/castp/index.html). is the tool from which prediction of active site of protein takes place and detect possible binding area for ligand.

3.3.3- Ligand preparation

The 3D structure of Ginkgo biloba phytochemicals (bilobalide, Ginkgolide A, B, C and J) was obtained from the PubChem database or Zinc database but in this we use PubChem database (https://pubchem.ncbi.nlm.nih.gov/) for downloading the structure of phytochemicals. Afterward, the compounds three-dimensional conformer was retrieved in the SDF format. SDF format consists different information on molecular geometry, which is essential for accurate modelling and simulation research.

3.4 Molecular Docking

Protein-ligand docking done by using PyRx. PyRx is a software program which mostly used in drug development and computational chemistry for molecular docking purpose. It offers an easy-to-use interface for docking stimulations for predicting the ligands or the receptor preferred position when bonded together to form a stable complex.

For the molecular docking in PyRx first step is to load the receptor(protein) and ligand(phytochemicals) downloaded file into the workspace. Now, setting the docking parameters such as search algorithm, grid size, and scoring function. These parameters

determine how ligand will be positioned and oriented within the active site of the receptor.
Running docking stimulation after defining settings, PyRx starts a docking simulation utilizing algorithms such as Auto Dock or Vina, which methodically explore the conformational space of the ligand and assess interactions with the receptor.
Now, after interactions of receptor and ligand is completed than PyRx creates output files describing the anticipated binding during the docking simulation. Modes and ligand binding affinities when the docking simulation is finished.

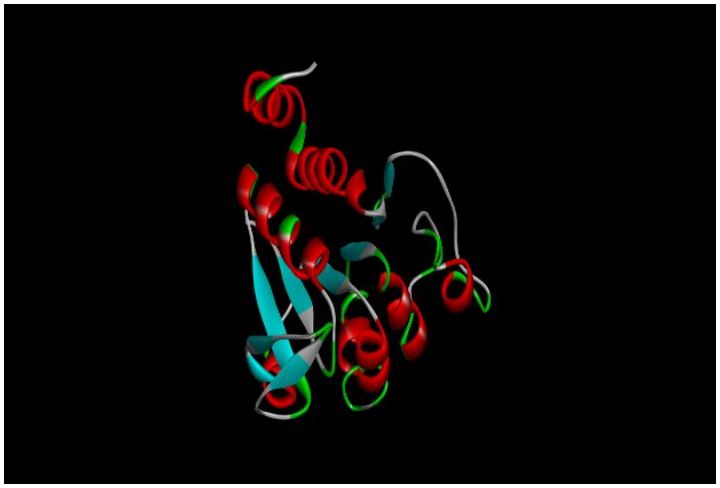
3.5 visualization of protein- ligand interactions binding

To investigate protein-ligand complexes various tools available like PyMOL, Biovia etc. To examine the results of the docking simulation, load the data into Biovia Discovery Studio, it's a software that offers comprehensive information on the interactions between the ligand and the target protein. It fastens the recognition of key interactions of different bonds associated between the ligands and the receptor protein. The visualization improved our grasp of ligand- receptor interaction and their therapeutic applications, providing awareness into the molecular recognition and binding kinetics. BIOVIA software solutions are used in various sectors where scientific research and innovation are essential, such as biotechnology, materials, medicine, and chemicals. In addition, Discovery studio used to generate both 2D and 3D confirmations of binding of targeted protein with phytochemicals.

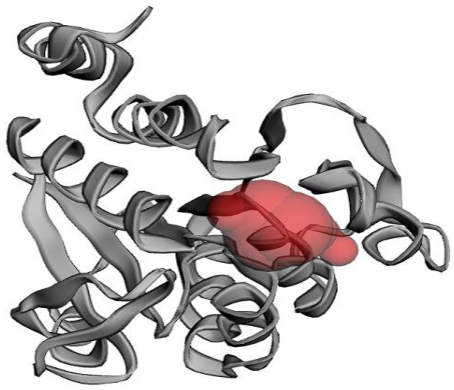
CHAPTER 4
RESULTS

4.1-3D structure, active site and Ramachandran plot visualisation-

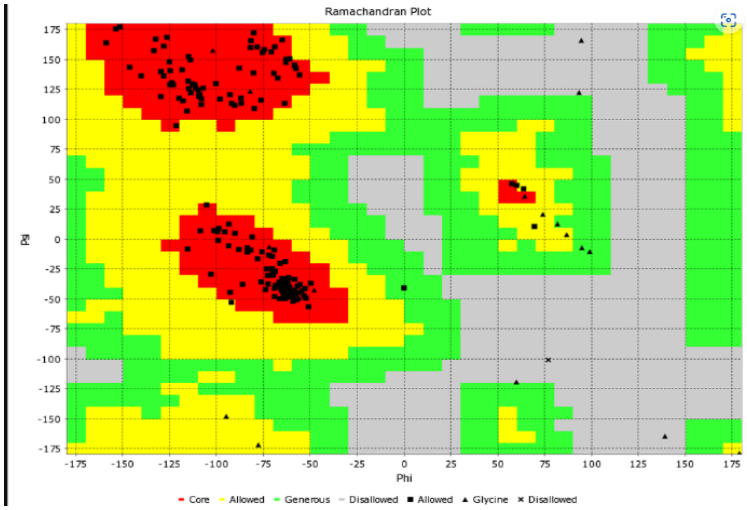
The 3D structure of PARK7 a protein that functions as a DJ-1 was extensively examined PBD ID (1P5F) obtained from PubChem, Active site is predicted using Castp tool for binding of ligand and Ramachandran plot is obtained by using VADAR tool (http://vadar.wishartlab.com/) was used to evaluate the quality of the structure, revealing a significant concentration of residues in most favourable areas. It also gives about allowed and disallowed region. In this plot of Ramachandran Red, Yellow and Green region are allowed region and rest is disallowed. All the amino acids present in allowed region except glycine; it can be present anywhere in plot.



(a) 3D structure of DJ-1(PARK7)



(b) Active site present



(c) Ramachandran plot of Dj-1

Fig 4.1- (a) 3d structure (b) active site present for ligand interaction (c) Ramachandran plot obtained for quality assessment

4.2- Calculation of Lipinski rule of five-

The compounds underwent firsts screening according to the five rules of Lipinski. The rule helps tell the difference between molecules that are like drugs and molecules that are not like drugs. It tells the chances of success or failure based on how similar the molecules are to drugs that follow two or more of the rules. The Lipinski's filter investigation revealed that all of these phytochemicals (bilobalide, ginkgolide A, B, C and J) had the capacity to have drug like property.

Table 4.1- shows the estimation of drug likeness for ginkgo biloba phytochemicals using Lipinski filter evaluation.

	Hydrogen bond acceptor	Hydrogen bond Donar	Molar refractivity	Molecular mass (Dalton)	Lipophilicity
Ginkgolide A	9	2	90.621567	408	-0.340300
Bilobalide	8	2	70.363579	326	-0.743800

Ginkgolide B	10	3	92.011360	424	-1.369502
Ginkgolide C	11	4	93.401161	440	-2.398702

4.3- Docking Calculations

The docking configurations of PARK7(DJ-1) with the screening phytochemicals (Bilobalide, Ginkgolide A, B, C and J) were determine and shown in table-. the compounds that had the most effective interactions with protein were identified based on the docking study. In addition to looking for interactions at the active site between the receptor and ligand, we also looked at other factors like binding affinity, hydrogen bonding, and hydrophobic interactions. Those compounds which had the lowest binding constants and the largest negative free energy of binding. The docking calculations of PARK7 have been provided to clarify this.

Table 4.2- shows the docking calculations of PARK7(DJ-1) with phytochemicals.

S.NO.	Phytochemicals(drug)	cluster	element	Estimated ΔG (kcal/mol)
1	Ginkgolide A	0	0	-7.3
2	Ginkgolide C	0	0	-7.6
3	Bilobalide	0	0	-6.9
5	Ginkgolide B	0	0	-7.3

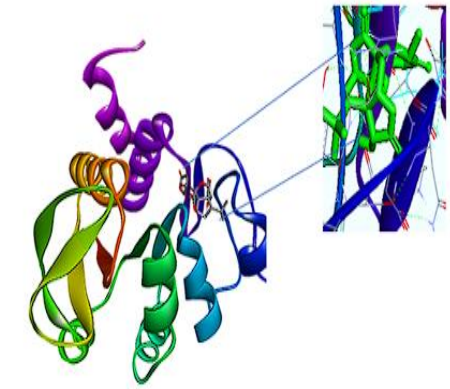
4.4-Representation of interactions

The software Biovia discovery studio was utilized to visually verify the three dimensional and two-dimensional binding interactions between Ginkgolide (A, B, C) and Bilobalide with DJ-1(PARK7). This program enables the examination of the structural analysis of how these phytochemicals, functioning as potential medicines, interacted with the specific protein. The findings revealed the four primary phytochemicals that demonstrated robust binding efficacy with targeted protein. and also, it's also visualized and analyse the molecular interactions, such as hydrogen

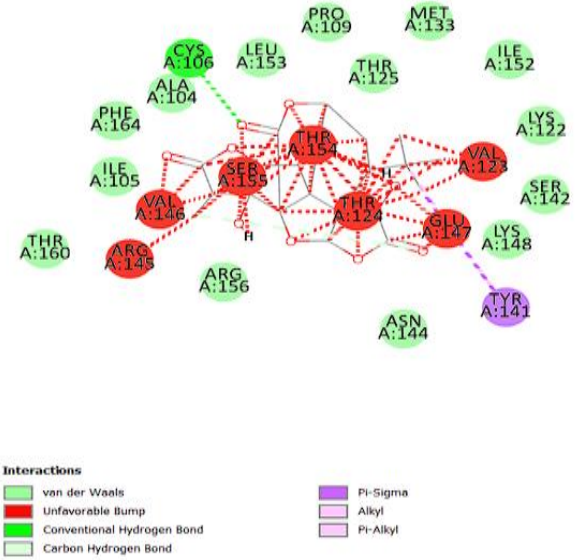
bonds, hydrophobic interactions, and electrostatic forces, with specific emphasis on interacting residues.

Table 4.3- shows the presentation of binding energies and interacting residues of protein with phytochemicals

Phytochemicals	Binding energies	Interacting residues
Ginkgolide A	-7.3	CYS106, VAL146, TYR141, ARG145,
Bilobalide	-6.9	CYS106, ASN144, SER155,
Ginkgolide B	-7.3	CYS106, SER142, VAL146
Ginkgolide C	-7.6	LEU10, ALA111, PRO73, GLY74, GLY108, ASN76, ASN81

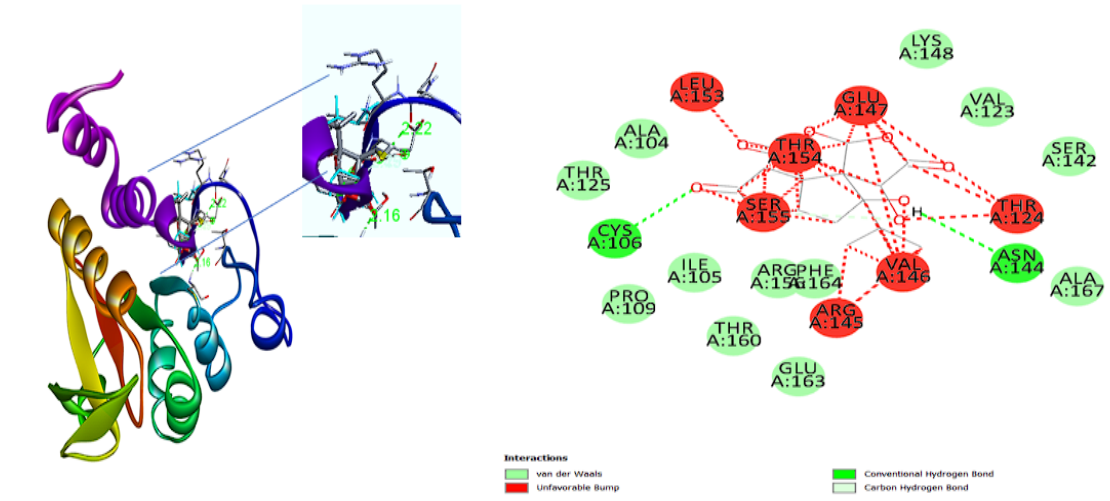


(A) 3D interaction of DJ-1 with Ginkgolide A



(B) 2D presentation of binding interaction of DJ-1 with Ginkgolide A

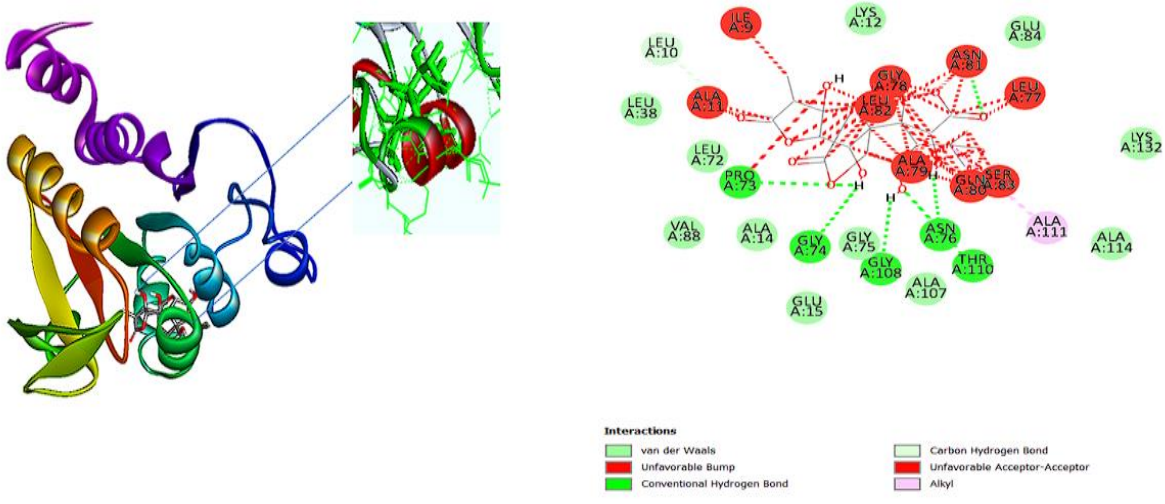
Fig 4.2- interaction of PARK7 with Ginkgolide A 3D and 2D representation is binding energy -7.3 kcal/mol



(A) 3D interaction of DJ-1 with Bilobalide

(B) 2D binding interaction of DJ-1 with Bilobalide

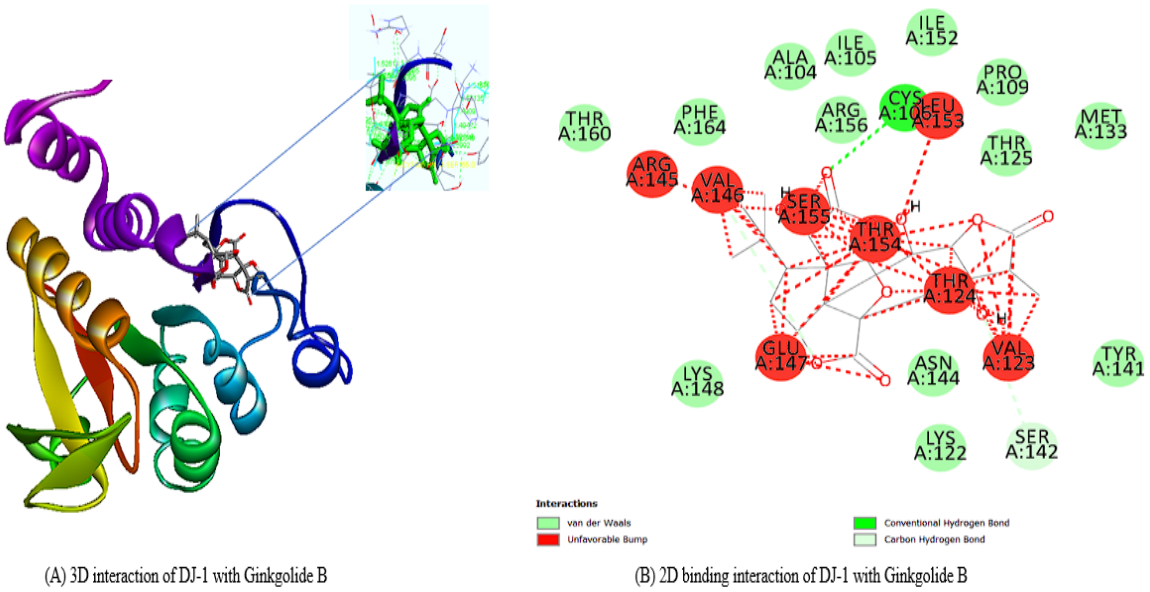
Fig 4.3- Interaction of PARK7 with Bilobalide 2D and 3D representation is binding energy -6.9 kcal/mol



(A) 3D interaction of DJ-1 with Ginkgolide C

(B) 2D binding interaction of DJ-1 with Ginkgolide C

Fig 4.4- Interaction of PARK7 with Ginkgolide C 2D and 3D representation is binding energy -7.6 kcal/mol



(A) 3D interaction of DJ-1 with Ginkgolide B

(B) 2D binding interaction of DJ-1 with Ginkgolide B

Fig 4.5- Interaction of PARK7 with Ginkgolide B 2D and 3D representation is binding energy -7.3kcal/mol

This study examined the docking interactions between PARK7 and several screening compounds, including Ginkgolide A, B, C, and Bilobalide, in order to evaluate their binding affinities. Through the examination of binding affinities and free energy data, it was shown that Ginkgolide C bound with a negative binding energy of -7.6 kcal/mol indicating a substantial interaction with PARK7. These findings indicate that Ginkgolide C had the highest binding affinity for PARK7 among the other phytochemicals tested (Ginkgolide A, B and Bilobalide). Additional examination was conducted on supplementary factors such as hydrophobic interactions, hydrogen bonding, and binding affinity. This allows for the comparison and comprehension of the mechanism by which various phytochemicals have a propensity to bind to certain proteins.

The higher binding energy of Ginkgolides C indicates that it established more robust interactions with targeted protein, which might possibly result in more significant therapeutic benefits. These suggest that it can be a promise as a potential treatment drug for PD.

DISCUSSION

One of the most common neurological diseases is Parkinson's that often shows in elderly individuals. Bradykinesia, a condition characterized by delayed movements, is often accompanied by symptoms such as stiffness or tremors when at rest. Protein known as Parkinson's disease protein 7(PARK7) as well as referred to as Protein deglycase (DJ-1) is involved in many functions like act as a positive regulator of transcription that depends on androgen receptors, redox sensitive chaperone, and acts as a sensor for cellular death and oxidative stress. If there is a problem with this gene because of an imbalance in genes or the environment, it could lead to early-onset autosomal recessive Parkinson's Disease 7.

Nevertheless, existing therapy approaches just provide partial alleviation of symptoms and have little efficacy in managing psychological side effects. Consequently, research is now focused on discovering novel chemicals that might decrease on discovering novel chemicals that might decrease psychological symptoms and perhaps improve the overall effectiveness of treatment for persons with Parkinson's disease. The extensive historical usage of medicinal plants is also having a favourable impact on the study exploring herbal drugs as a new therapy approach for PD. i.e. Ginkgo biloba was chosen. The selection on the basis of historical use in traditional medicine and the existence of secondary metabolites (flavonoids and Terpenoids) renowned for their therapeutic effects exploration of potential therapeutic use of certain phytochemicals present in plants, the anti-inflammatory and anti-oxidant activities of phytochemicals such Ginkgolide A, B, C and Bilobalide are extensively recognized. Inflammation and oxidative stress have significant roles in Parkinson's disease. This demonstrate that several diverse phytochemicals included in G biloba have the ability to provide neuroprotective advantages in PD by modulating ALD-related pathways to decrease inflammation and also mitigate oxidative stress. The investigation has also shown the extraordinary capacity of phytochemicals to eliminate this deadly neurodegenerative illness.

This work distinguishes itself from earlier investigations by using sophisticated technique: Molecular Docking Simulation, as opposed to the conventional emphasis on general antioxidant characteristics. This approach allows for the systematic analysis of interactions and docking scores, leading to better dosing judgement. Now the study indicates specific molecules derived from Ginkgo biloba that appear to have a strong affinity for Parkinson's related proteins. These findings suggest that GB phytochemicals interact to protect neurons, interact with the immune system is modulated and these agents have antioxidant properties. Importantly in PD these all are factors. Extraction of the optimal docking ligands reveal insights into interactions

within these drugs and with their target proteins. These findings are important to move forward the study efforts directed at the development of therapeutic against PD.
Moreover, it is essential for future study to include comprehensive experimentation in controlled laboratory environments and animal trails in order to authenticate these discoveries. To get a comprehensive understanding of the therapeutic advantages of these substances, we may enhance our study scope by investigating a broader array of biological targets.

CONCLUSION

This highlights the potential of plants compounds in tackling Parkinson's and paves the way for clinical tools to be developed. Neurodegenerative diseases like Parkinson's are challenging to uncover because a complex interplay of genetic and environmental factors. Proteins like PARK7 (also called DJ-1 or protein Deglycase) are essential to decipher the complex molecular pathways behind Parkinson's disease. The compounds derived from medicinal plant GB also serves as efficient therapies. The current experiment aims to explore the herbal medicine as a new therapy for PD through an advanced computational molecular docking study. Because phytochemicals present in GB can act against dopamine modulation, decrease inflammation and oxidative stress, increase the antioxidant defences among other physiologic mechanisms that together suggest they are useful as a therapeutic approach in developing potential new treatments.
By doing molecular docking studies, we have shown that phytochemicals derived from Ginkgo biloba show great potential as candidates for fighting PD. These chemicals have neuroprotective characteristics and show possible interactions with crucial proteins linked to Parkinson's disease, such as DJ-1. Phytochemicals such as Ginkgolide A and C have strong affinity for DJ-1, resulting in significant binding interactions. The notable binding affinity of Ginkgolide C, which is -7.6kcal/mol, indicates that it should be further examined in Parkinson's research, namely via in vitro investigations. One thing that should be remembered is that the effectiveness and the safety of these drugs should be evaluated beforehand in human trials. Moreover, understanding how these alterations might relate to specific Parkinson's disease relevant proteins i.e. DJ-1 themselves may open up new therapeutic avenues in PD.

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Spirulina as neuroprotective supplement in parkinsonism; A review

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ABSTRACT

Parkinson disease is a progressive disorder that impacts the central nervous system and the component that are controlled by nerves. Major pathological hallmark of Parkinsonism is the presence of anomalous aggregates of α-Synuclein protein. Several experimental and pathological studies explain the other key involvement in PD pathogenesis like; loss of dopaminergic neurons is mid brain, Chronic microglial and astrocyte's activation, mitochondrial dysfunction, brain inflammation and oxidative stress. Parkinsonism indicates the several motor and non-motor symptoms like bradykinesia (slowness and stiffness in movement), tremor and resting tremor. There is no known permanent treatment of Parkinson disease, yet certain drugs are effective on symptoms. Blue green algae such as spirulina is a unicellular species and economically distributed as nutritive food supplements. Spirulina is one the influential source of natural nutrient and many experimental studies informed about the antioxidant and anti-

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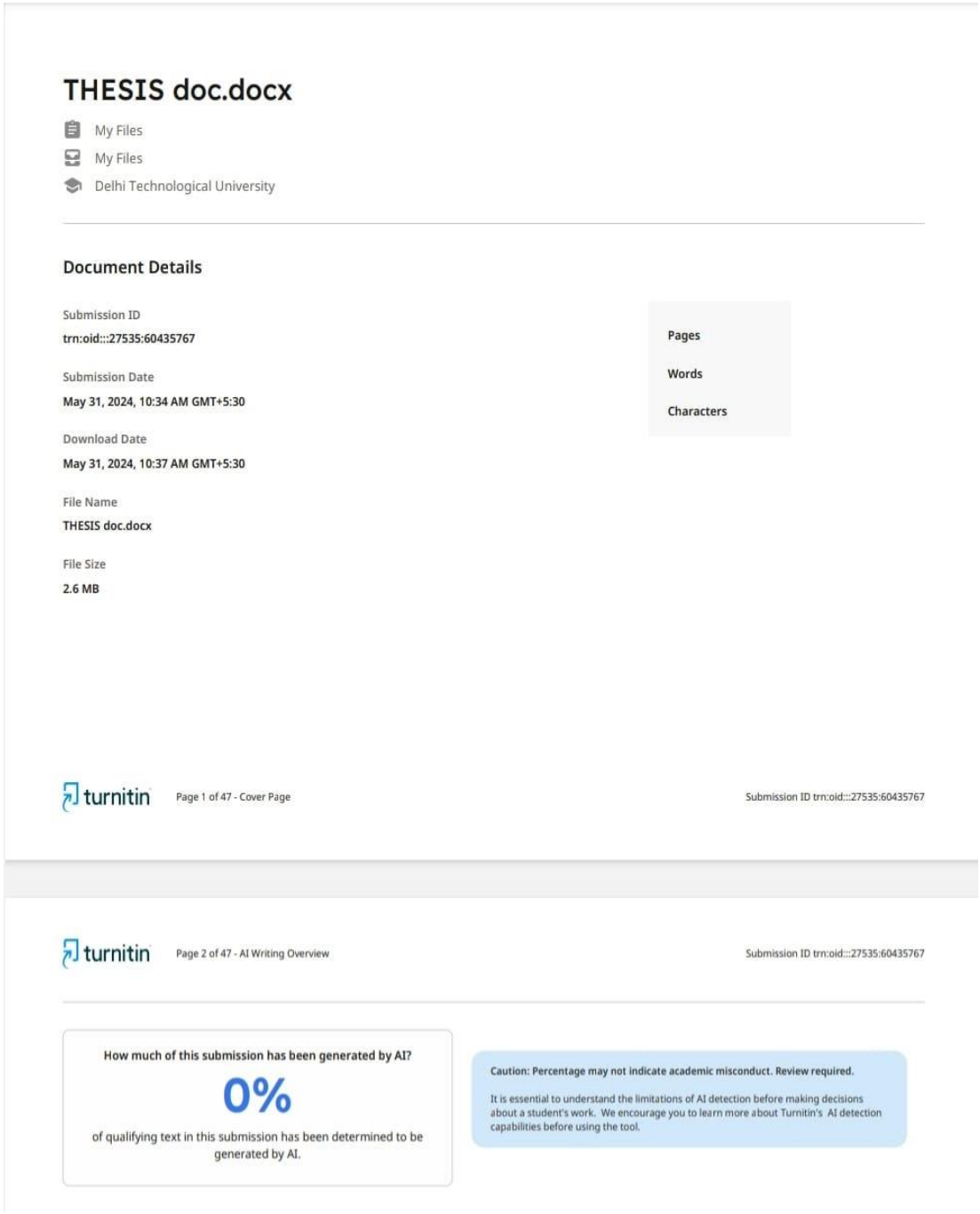

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