A Seminar Paper on

Application of Medicinal Plants in Neurodegenerative Diseases:

Neuroprotective Mechanism

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Application of Medicinal Plants in Neurodegenerative Diseases:

Neuroprotective Mechanism[1]

By

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ABSTRACT

In the twenty-first century, neurodegeneration—a condition in which neuronal death happens as a result of a chronic, progressive disease—is emerging as a significant public health issue. Cognitive decline, numerous neurodegenerative illnesses, including schizophrenia, depression, Alzheimer's disease (AD), dementia, cerebrovascular impairment, seizure disorders, head injury, and parkinsonism, originate from the non-replacement of degenerating neurons. Deposition of misfolded proteins, such as amyloid-(A) in Alzheimer's disease, synuclein in Parkinson's disease (PD), and transactive response DNA-binding protein 43 (TDP-43) in dementia, is a prevalent pathology of neurodegeneration. The term "neuroprotection" describes the methods and potential mechanisms that can shield the central nervous system (CNS) from neuronal damage and neurodegenerative diseases. An intense interest in herbal plants with long-term health-promoting or therapeutic properties has grown during the past ten years. Natural substances, medicinal herbs, plant extracts, and their metabolites have considerable promise as a neuroprotective agent, according to extensive research and discoveries. While the exact mechanisms of action of herbal medicines are still unknown, some of them have been shown to inhibit the brain enzymes acetylcholinesterase (AChE) and malondialdehyde (MDA) synthesis while others exhibit antioxidant activity by raising levels of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). As a result, high throughput screening for drugs to treat neurodegenerative illnesses could benefit from the use of herbal plants. This review will focus on the mechanism of action and therapeutic potential of herbal plants and their phytoconstituents in relation to neurodegenerative disorders.

Keywords: Neurodegenerative disease, Neuroprotective, Herbal Medicine.

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CHAPTER 1

INTRODUCTION

The brain is a very intricate organ with countless pathways that enable us to perform the astounding feats that we do. We rely on the efficient functioning of the brain's billions of cells every second of every day. Neurons are some of the most significant brain cells. Neurons interact with one another to carry out every mental activity, including walking, thinking about lessons learnt in school, conversing with friends, and recalling the list of groceries we need to buy. Due to the intricacy of the brain, diseases can result from very minute cell-to-cell miscommunications. Because the brain's cells are interconnected and errors in one region can affect other brain functions, brain illnesses may have a wide range of negative effects. The most complex of these conditions are referred to be neurodegenerative disorders, despite the fact that there are several diseases and conditions that can impact the brain.(Berman & Bayati, 2018).Class of progressive disorders characterized by neuronal death, neurodegenerative diseases include afflictions including Alzheimer disease (AD), Parkinson disease (PD), amyotrophic lateral sclerosis (ALS), vascular dementia, and multiple sclerosis (MS). These illnesses all exhibit overlapping but unique symptoms, such as motor dysfunction, and are each characterized by the degeneration of certain brain regions. dementia, emotional disturbances, and/or cognitive dysfunction. Initially, it was believed that neurodegeneration would lead to neuroinflammation (Blackhurst & Funk, 2023). The development of inclusion bodies and protein aggregates, or the deposition of abnormal proteins in neuronal cells, are the causes of neurodegenerative diseases like Alzheimer's disease (AD), Parkinson's disease (PD), or Huntington's disease (HD), which ultimately cause degeneration and selective neuronal vulnerability in particular brain regions. As neurons cannot regenerate or replace themselves after being harmed or dying, their structures and functions will gradually deteriorate, leading to issues with both mental and physical functions (ataxias). (dementias) (dementias) (Wu et al., 2015).Progressive destruction and dysfunction of the neurons or nerve cells are hallmarks of neurodegenerative disorders. Protein degradation, numerous environmental variables, mitochondrial problems, familial history, aberrant protein buildup in neurons, etc. are some of the causes of neurodegenerative illness. Neurodegenerative illnesses impact millions of people each year all over the world. In 2014, there were 36 million persons affected by Alzheimer's disease alone, up from 26.6 million in 2006. Among them, 5.1 million were Americans of all ages, with 200,000 of them suffering from younger-onset Alzheimer’s. Treatment for neurodegenerative diseases is exceedingly expensive; for Alzheimer's disease, annual costs exceed $100 billion (Saxena, 2015a). Due to the increased prevalence of these ailments in recent years, which is a result of longer life expectancies, families and societal economies are being severely burdened. According to a recent World Health Organization (WHO) research, neurological illnesses can impact up to one billion people worldwide, killing 6.8 million people annually. Also, developing nations have a roughly two times higher prevalence of CNS illnesses than the industrialized world (Uddin & Zidorn, 2020).Target-based treatments have been developed and put into use over the years, including neurotransmitter modulators, direct receptor agonists/antagonists, second messenger modulators, stem cell-based treatments, hormone replacement therapy, and neurotrophic factors. They have also included regulators of mRNA synthesis and their translation into disease-causing mutant proteins. While several of the NDs drug regimens that have been

licensed for use assist treat the symptoms, there are presently no treatment approaches that can stop or slow the course of NDs. but do not treat the illness directly. There is an urgent need to find more effective and safer medicines that may be used over a protracted period of NDs because many of the classic symptomatic therapies may lose their efficacy over time, induce disruptive symptoms of their own, and show severe side effects. There is a widespread notion that NPs are secure: Assuming that NPs are more efficient, secure, and non-toxic than conventional medications, many patients use them. Patients frequently consider NPs to be safer than biomedicine due to their "natural" status. The idea that botanicals are natural and "natural is good" and hence safe may be a factor encouraging the use of herbal products (Di Paolo et al., 2019).

Alkaloids and flavonoids are examples of phytomedicines, or substances produced from plants, that have been used for centuries to treat NDDS. They have the potential to be the best therapeutic and management tools for reducing the key symptoms of NDDs like AD, PD, stroke, and schizophrenia. Regular consumption of fruits and vegetables can lower the risk of numerous disorders that result in neuronal dysfunction because they include phytochemicals, also known as phytomedicines, which are bioactive plant substances present in vegetables, fruits, cereals, etc. Alkaloids are one of the most effective agents against NDDs and one of the phytochemicals with neuroprotective potential (Hussain et al., 2018) It has been claimed that several natural compounds, especially plant extracts, are utilized in traditional medicine for neuroprotective, memory-improving, and anti-aging purposes. Ginkgo biloba, Panax ginseng, Curcuma longa, Bacopa monnieri, and Salvia officinalis are a few examples of these plants. The number of persons with NDs and the related dementia also continues to rise as the global population ages and the economy develops. The hunt for new therapeutic agents for the primary, auxiliary, or tertiary prevention of these diseases has consequently attracted a significant surge in scientific attention.(Anjali Divatankar et al., 2021).

Herbal medicine has experienced exponential growth in recent years, and due to their natural origins and lack of side effects, these medications are becoming more and more popular in both developed and developing nations. The majority of conventional medications currently in use come from organic matter, minerals, and medicinal plants. Early people understood their reliance on nature for a healthy existence, and ever since then, humanity has relied on the variety of plant resources for food, clothes, shelter, and medicine to treat a wide range of illnesses (Agarwal et al., 2013).

Based on the above facts the objectives of this reviewed paper are

1. To identify the causes of neurodegeneration.
2. To discuss the neuropharmacological basis of medicinal plants and their bioactive components.

CHAPTER 2

MATERIALS AND METHODS

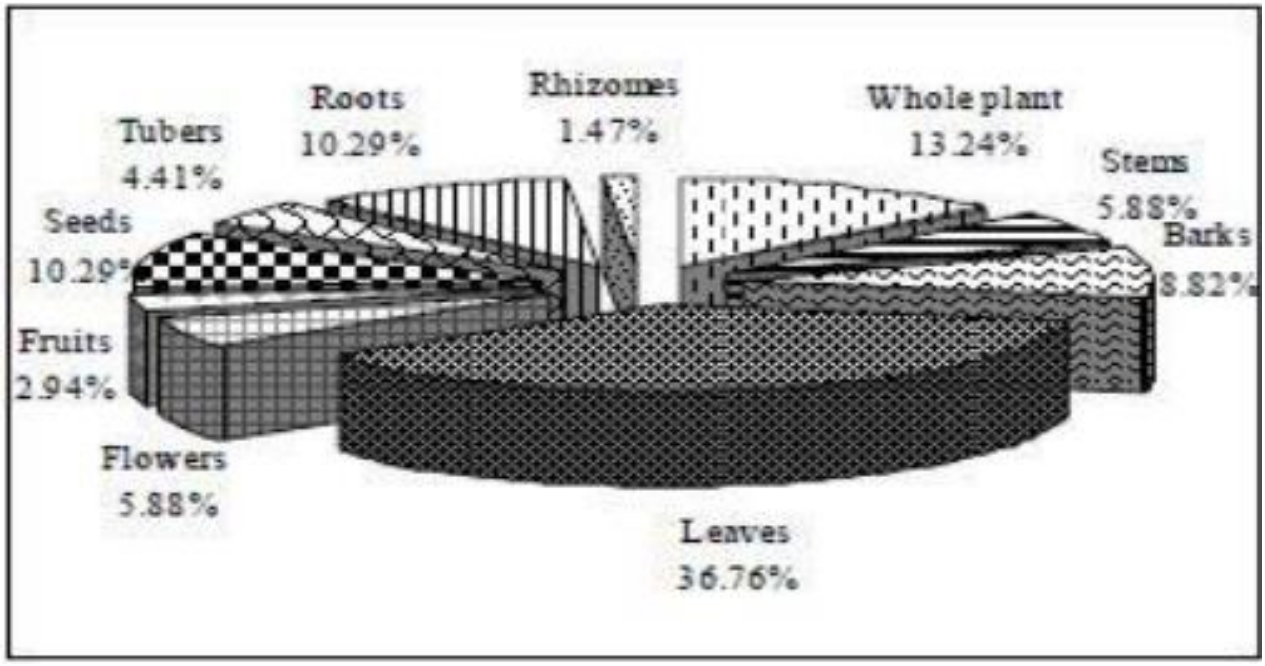
Scientific approach requires a close understanding of the subject matter. This paper mainly depends on the secondary data. Different published reports of different journals mainly supported in providing data in this paper. This seminar paper is exclusively a review paper, so all the information has been collected from the secondary sources. It is prepared by browsing internet, studying comprehensively various articles published in different journals, reports, publications, proceedings, dissertation available in the internet. The author would like to express her deepest sense of gratitude to her major professor and course instructors for their efficient and scholastic guidance, precious suggestions to write this manuscript from its embryonic stage. All the information collected from the secondary sources have been compiled systematically and chronologically to enrich this paper.

CHAPTER 3

REVIEW OF FINDINGS

3.1 Medicinal plants

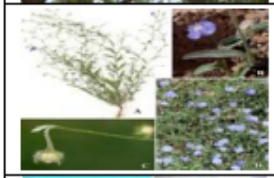
Any plant that has compounds that can be utilized therapeutically or that serve as building blocks for the production of effective pharmaceuticals is considered to be a medicinal plant. This definition enables the distinction between plants that are considered medicinal but have not yet undergone a full scientific investigation and plants whose therapeutic capabilities and ingredients have been established scientifically. Many plants have long been utilized in traditional medicine. Although there may not be enough scientific evidence (such as double-blind trials, for example) to support some of them, some do appear to work. Use of Plant Parts in Medicine People primarily employ above-ground plant parts (70.57%), followed by below-ground parts (16.17%) and complete plants (13.26%), when making therapeutic concoctions. The majority of above-ground plant parts—36.76%—are utilized for food, followed by seeds (10.29%), stems (5.88%), bark (8.82%), flowers (5.88%), and fruits (2.94%) (Figure 1).



Source: (Khan et al., 2011)

Figure 1. Graphical presentations of different parts of medicinal plant species.

Table 1. Medicinal plants against nervous disorder.

Picture	Plant Species	Parts Used	Geographical Location	Uses	Family
	*Emblica officinalis L.*	Fruit	India	Epilepsy	*Euphorbiaceae*
	*Evolvulus alsinoides L.*	Whole Plant	East Asia	Psychotropic	*Convolvulaceae*
	*Ferula asafoetidaL.*	Gum, Resin	Iran	Epilepsy	*Apiceae*
	*Valeriana*	Root	Europe	Sedative	*Caprifoliaceae*
	*Annona squamosa*	Fruit	America	Depression	*Annonaceae*

	*Cassia occidentalis L. (Link)*	Fruit Pulp	South East Asia	Hysteria	*Caesalpinaeceae*
	*Cassia fistula L.*	Fruit Pulp	South East Asia	Epilepsy	*Caesalpinaeceae*
	*Papaver somniferum L.*	Seed	Europe	Narcotic	*Papaverceae*
	*Strychnos nux vomica L.*	Seed	South East Asia	Paralysis	*Loganiaceae*
	*Hyoscyamus niger L.*	Leaves, Flower, Tops, Seeds	Europe	Hypnotic	*Solanaceae*

Source:(Mukherjee et al., n.d.)

Table 2. Medicinal plants with their bioactive components and activity.

Common name	Significant Constituents	Activity
Brahmi or waterhyssop	Bacopaside and bacoside	Redox stabilization, improves mitochondrial function, attenuate a-synuclein aggregation, attenuate apoptosis improves cognition
Green tea	Polyphenols, catechins [epicatechin (EC), epicatechin gallate (ECG), epigallocatechin (EGC) and epigallocatechin gallate (EGCG)]	Redox stabilization, inhibit ROS-NO pathway, metal chelation, Protects DA neurons in a nigral region
Java bean or Sicklepod	CSE supplementation, MPP+, MPTP's neurotoxic metabolite	reduce cell damage and attenuate ROS generation and mitochondrial membrane depolarization in 6-OHDA mediated pc12 cells., causes dopaminergic neuronal loss by inhibiting respiratory complex 1 activity in dopaminergic neuronal mitochondria
Arabica and Robusta coffee	Caffeine	exerts neuroprotective effects against dopaminergic neuronal failure induces motor deficiency reversal in models of PD mice
Turmeric	Curcumin	Improves striatal dopamine level, mitochondrial Complex I activity, Reduces oxidative stress, up-regulate SOD and GPx activity, acetylcholine level, replenish mitochondria membrane potential and ATP production, inhibit a-synuclein fibrillization

Jadwar	A diterpenoid alkaloid, vilmorrianone, denudatine, panicutine, condelphine, and isotalatizidine.	reduced 3,4-Methylenedioxyamphetamine (MDA) levels, increased glutathione (GSH) content, Superoxide dismutase (SOD), catalase (CAT) activities and increased dopamine levels
Black cardamom	Essential oils, Terpenes, Diary 1heptanoids, Flavones, Nucleobases and nucleosides, Steroids.	Restores dopaminergic (DA) neuron degeneration,
Maidenhair tree	EGb 761, Ginkgolide B	Improve DA level, behavior function, and muscle coordination, redox stabilization, uplift mitochondria Function and ATP production
Walnut	Caffeic acid, a phenethyl ester derivative	Inhibits the MAO-B activity, protects against 6-hydroxydopamine-induced neuronal degeneration
Velvet bean	Glycoside, gallic acid, glutathione, Levodopa	Improves locomotor & behavior function, alleviate oxidative stress, metal chelation, mitochondrial and Synaptic function, TH expression
Milkworts or snakeroots	xanthones, saponins, and esters of oligosaccharides	Neuroprotective effect on dopaminergic neurons.
Japanese knotweed	Resveratrol (RES)	Neuroprotective, antioxidant reduction and antiapoptotic capabilities are exerted
Asian ginseng	ginsenosides	Rescuing dopaminergic neurons from degeneration increase antioxidant defenses and shields against neurotoxicity.

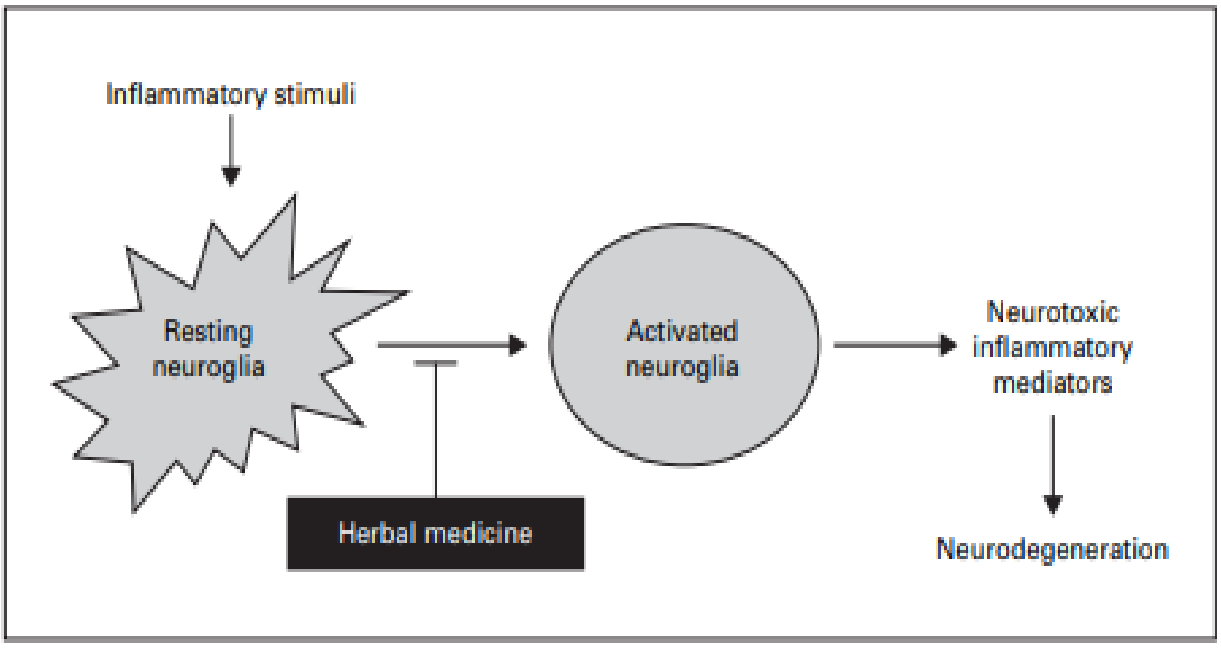
Source: (Jothilin Subitsha et al., 2021)

3.2 Neuroprotective mechanism of plants medicine

3.2.1 Neuroprotective targets of natural products

- Mitochondrial dysfunction
- Apoptosis
- Excitotoxicity
- Inflammation
- Oxidative stress and
- Protein misfolding

As a neuroprotector that specifically targets neuroglial activation, herbal medicine. LPS, IFN, and TNF are examples of inflammatory stimuli that can activate resting neuroglia. Many inflammatory mediators, such as ROS, nitric oxide, TNF, and IL-1, which result in neuronal damage, are secreted by activated neuroglia (thereby resulting in neurodegeneration). By inhibiting the inflammatory activation of neuroglia, herbal medication may protect against neurodegeneration (Figure 2).

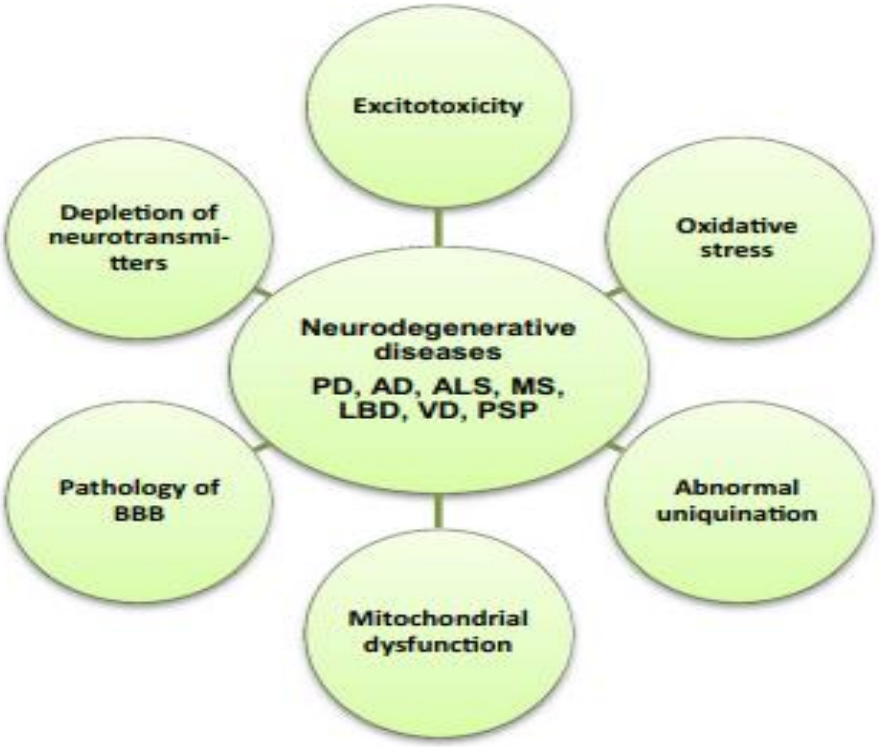


Source:(Suk, 2005)

Figure 2. Neuroprotective targets of natural products.

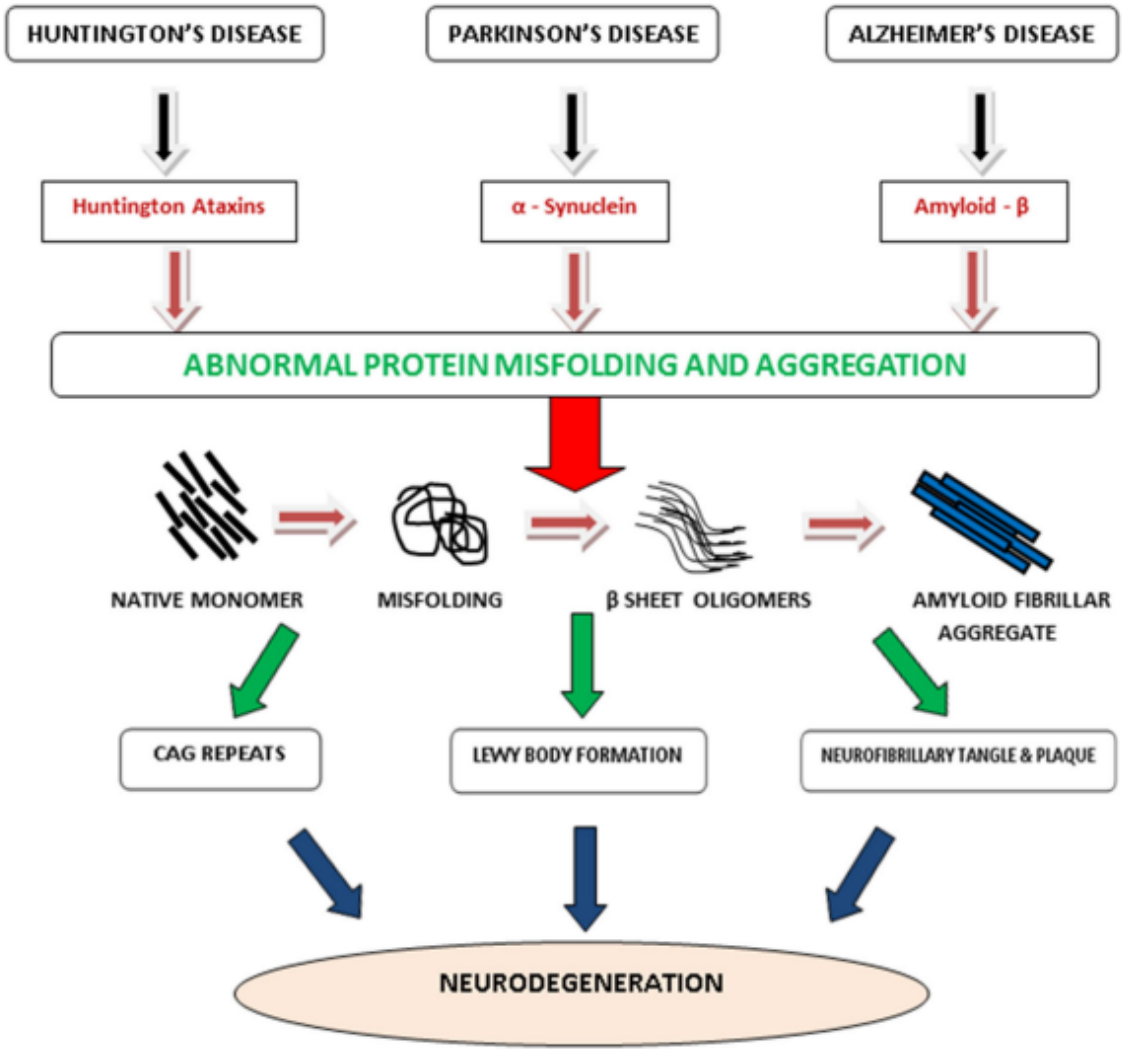
3.3 Causes of neurodegeneration:

From the molecular to the systemic levels of neural circuitry, neurodegeneration can be seen in the brain. These illnesses are regarded as incurable because there is no known mechanism to stop the ongoing destruction of neurons; nonetheless, research has revealed that inflammation and oxidative stress are the two main contributors to neurodegeneration (Pereira et al., 2021). Atypical protein assembly (like proteinopathy) and triggered cell death are two examples of the many commonalities between these disorders that have been found in biomedical research at the subcellular level (Bredesen et al., 2006).



Source: (Kamal et al., 2019)

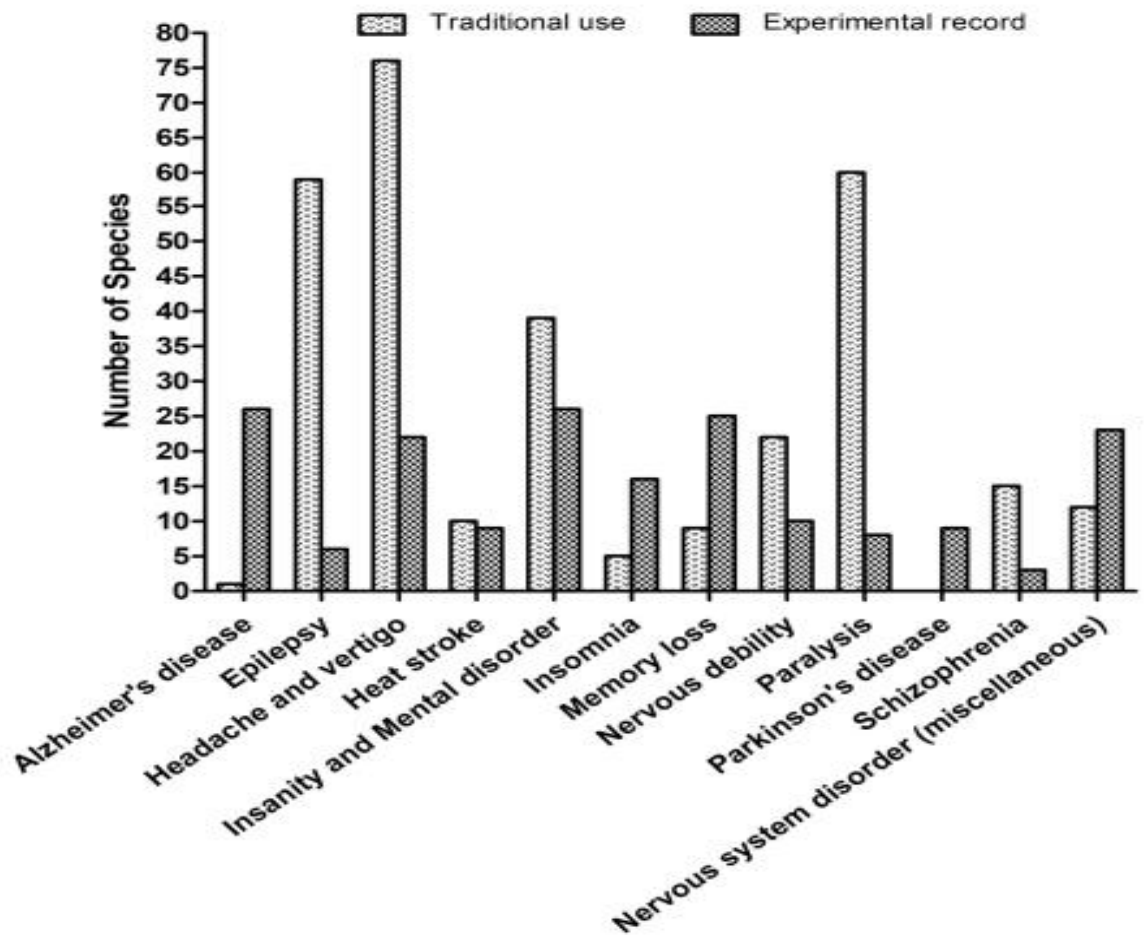
Figure 3. Various biological mechanisms contributing to neurodegenerative diseases.



Source: (Saxena, 2015b)

Figure 4. Molecular pathogenesis in neurodegenerative diseases.

3.4 Application of medicinal plants and their bioactive compound in major neurodegenerative diseases:

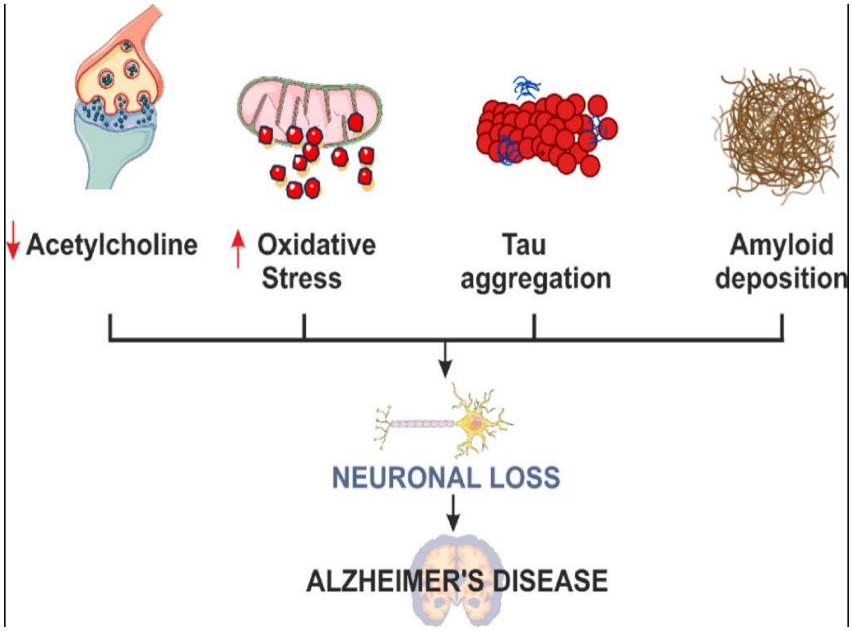


Source:(Uddin & Zidorn, 2020)

Figure 5. Comparison of the documented plant species with traditional use and experimental evidence over categorized CNS disorders.

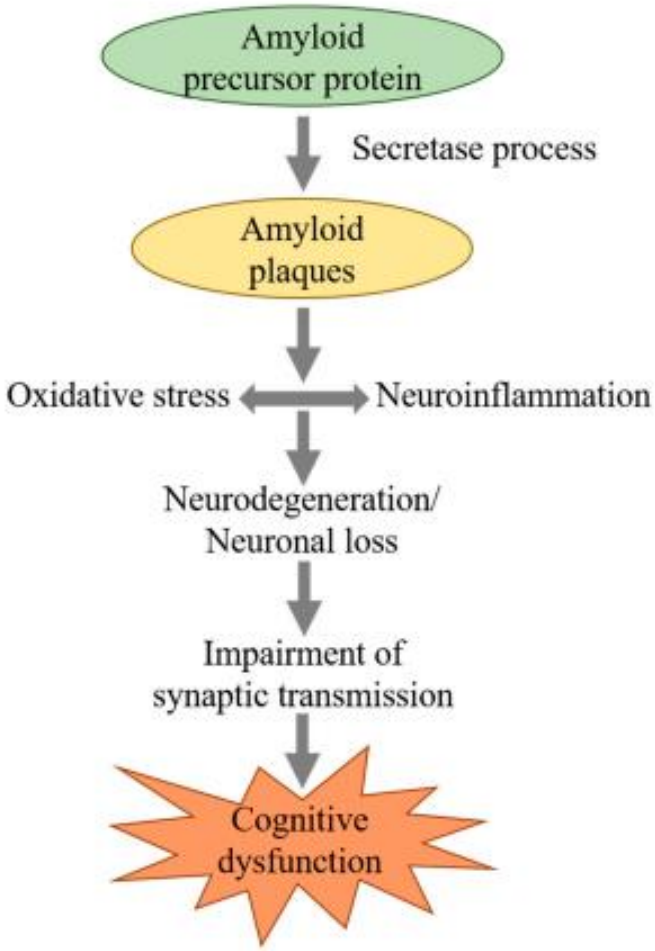
3.4.1 Alzheimer's disease (AD)

The loss of neurons and synapses in the cerebral cortex and some subcortical structures caused by Alzheimer's disease (AD), a chronic neurodegenerative illness, causes severe atrophy of the temporal lobe, parietal lobe, and portions of the frontal cortex and cingulate gyrus. The most prevalent neurodegenerative condition is it (Erkkinen et al., 2018).There are currently no viable treatments for Alzheimer's disease, despite billions of dollars being spent on research. Yet, several substances have been produced through clinical trials that may alter how Alzheimer's disease is treated in the future. A 99.5% failure rate for consistent and efficient AD treatment methods has been observed in clinical trials. This failure rate can be attributed to ineffective drug dosages, poor participant and target selection, and a lack of understanding of the pathophysiology of AD. For numerous elements of clinical diagnoses, better approaches must be used because Alzheimer's disease diagnosis is now substandard. 20% of Alzheimer's cases are misdiagnosed (Archer et al., 2017)



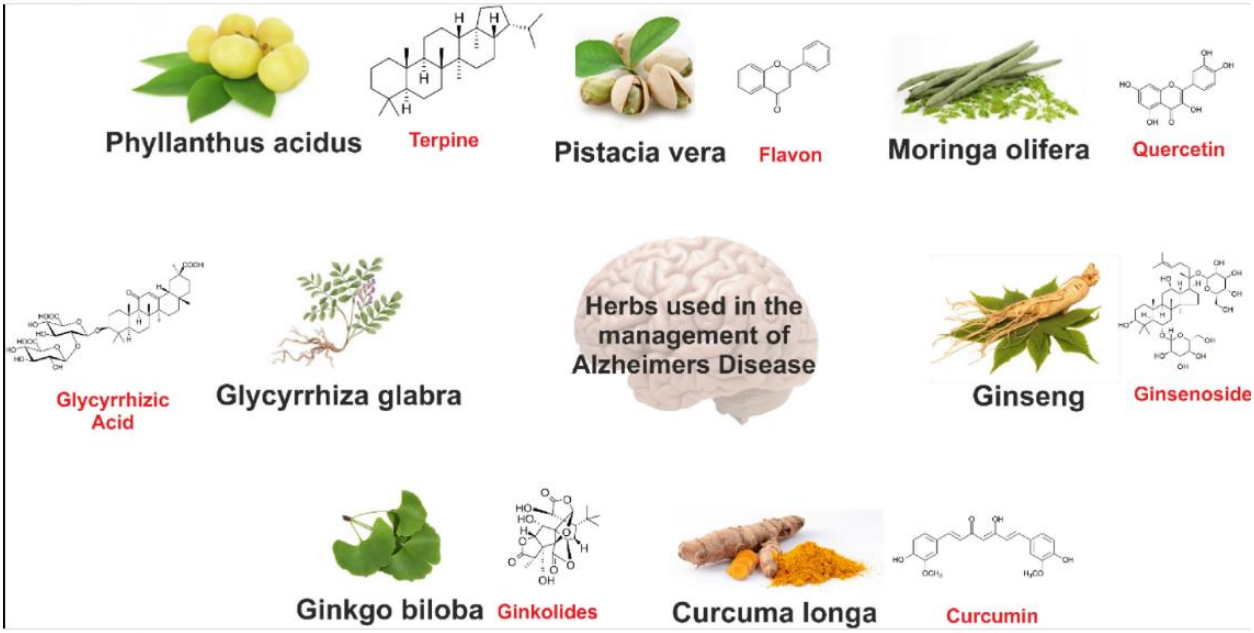
Source:(John et al., 2022)

Figure 6. Pathophysiology of Alzheimer's disease.



Source:(Mehla et al., 2020)

Figure 7. General pathogenesis of Alzheimer's disease (APP, amyloid precursor protein).



Source:(John et al., 2022)

Figure 8. Different herbs and their chemical composition used in the management of Alzheimer's disease.

Table 3. Medicinal plans and Alzheimer's disease (plant- derived cholinergic drugs).

Type	Chemical	Plant species	
Cholinesterase inhibitors	Physostigmine	*Physostigma venenosa*	Calabar bean
	Galanthamine	*Galanthus nivalis*	Snowdrops
		Narcissus pseudonarcissus	Daffodil
	Huperzine	*Huperzia serrata*	Fern
Muscarinic agonists	Arecoline	*Areca catechu*	Betel nut
	Pilocarpine	*Pilocarpus jaborandi*	
	Muscarine	*Amanita muscaria*	Fly agaric
Muscarinic antagonists	Atropine	*Atropa belladona*	Deadly nightshade
	Hyoscamine	*Hyoscamus niger*	Henbane
	Scopolamine (or hyoscine)	*Mandragora officinarum*	Mandrake
		Datura (numerous species)	e.g. thorn apple
		Scopalia carniolica	
Nicotinic agonists	Nicotine	*Nicotiniana tabacum*	Tobacco
	Lobeline	*Lobelia inflata*	Indian tobacco
	Cytisine	*Laburnum anagyroides*	Laburnum
Nicotinic antagonists	Tubocurarine	*Chondrodendron tomentosum*	
	Sparteine	*Cytisus scoparius*	Broom
	Dihydro-β-erythroidine	*Erythrina* (several species)	
	Methyllycaconitine	*Delphinium brownii*	Delphinium

Table 4. Plant species and phytochemicals relevent to cholinergic therapy in Alzheimer's disease.

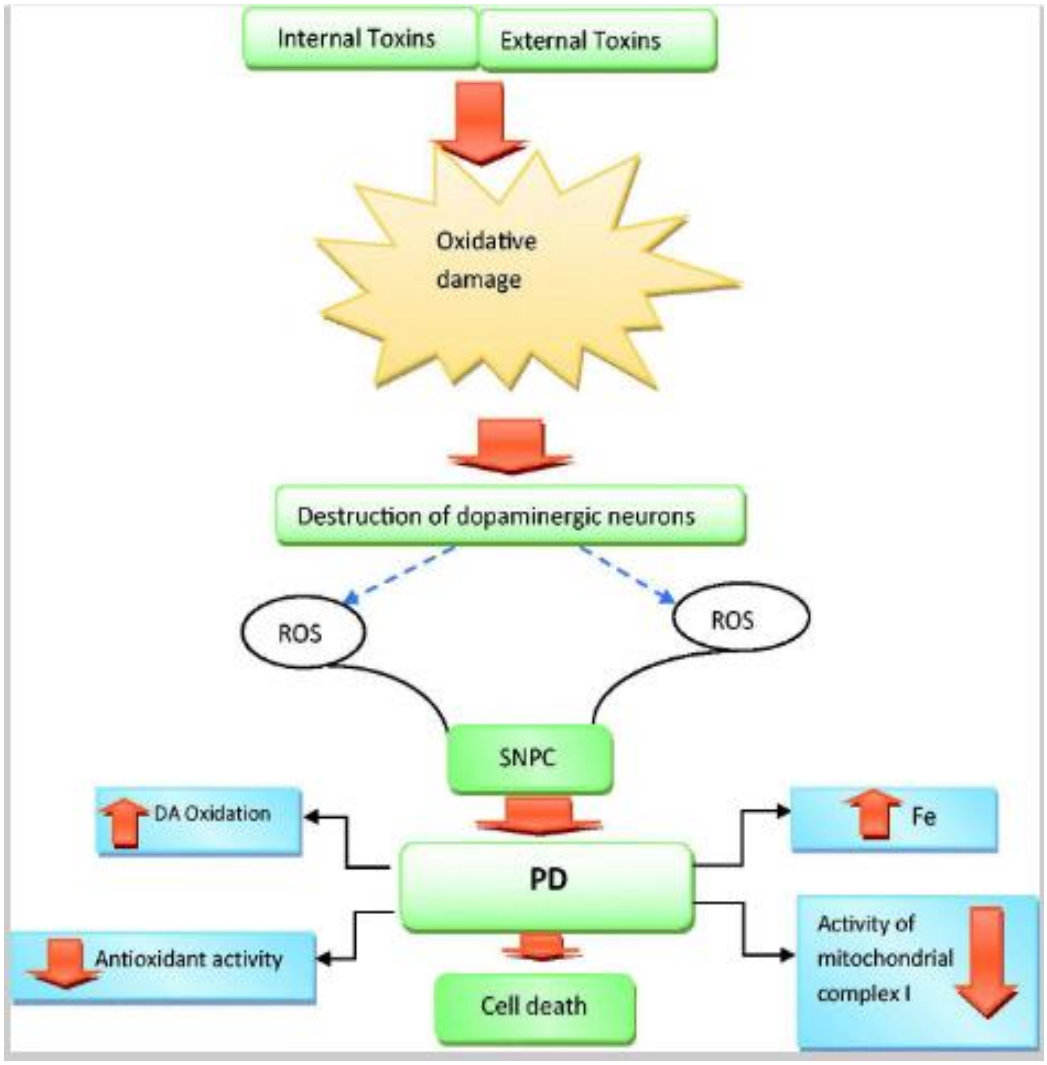
Species[a]	Active chemical	Ethnic evidence[b]	Bioactivity in model systems	Efficacy in controlled clinical trials[c]
Angelica sinensis	?	Yes	Yes	No
Evodia rutaecarpae	Dehydroevodiamine hydrochloride	Yes	Yes	No
Ginkgo biloba	Ginkgolides	Yes	Yes	Yes
Huperzia serrata	Huperzine	No	Yes	Yes
Melissa	?	Yes	Yes	No
Narcissus	Galanthamine	No	Yes	Yes
Nicotiana tabacum	Nicotine	Yes	Yes	No
Panax ginseng	?	Yes	Yes	Yes
Paeonia suffruticosa	Paeoniflorin	Yes	Yes	No
Physostigma venenosa	Physostigmine	No	Yes	Yes
Rosmarinus	?	Yes	No	No
Salvia	Monoterpenoids?	Yes	Yes	No

Source:(Perry et al., 2010)

3.4.2 Parkinson's disease (PD)

The second most common neurodegenerative ailment is Parkinson's disease (PD). Typically, bradykinesia, stiffness, resting tremor, and posture instability are the symptoms. According to reports, the incidence of PD ranges from 15 per 100,000 to 12,500 per 100,000, and its crude prevalence rate is between those numbers. The disease is less prevalent in Asian nations.

Dopaminergic neuron loss in the substantia nigra, a midbrain area, is the primary feature of Parkinson's disease (PD). It is unknown what causes this particular type of cell death. Importantly, afflicted neurons show an accumulation of alpha-synuclein-ubiquitin complexes and aggregates in Lewy bodies. It is believed that deficiencies in the machinery and regulation of protein transport, including RAB1, may contribute to the pathogenesis of this illness. Alpha-synuclein buildup in Lewy bodies may possibly be caused by impaired axonal transport of the protein. Studies have shown that both wild-type and two mutant alpha-synucleins linked to two family forms of Parkinson's disease move more slowly across the axons of cultured neurons. Another Parkinson's disease mechanism that alpha-synuclein may be responsible for is membrane damage.(Varkey et al., 2010) .

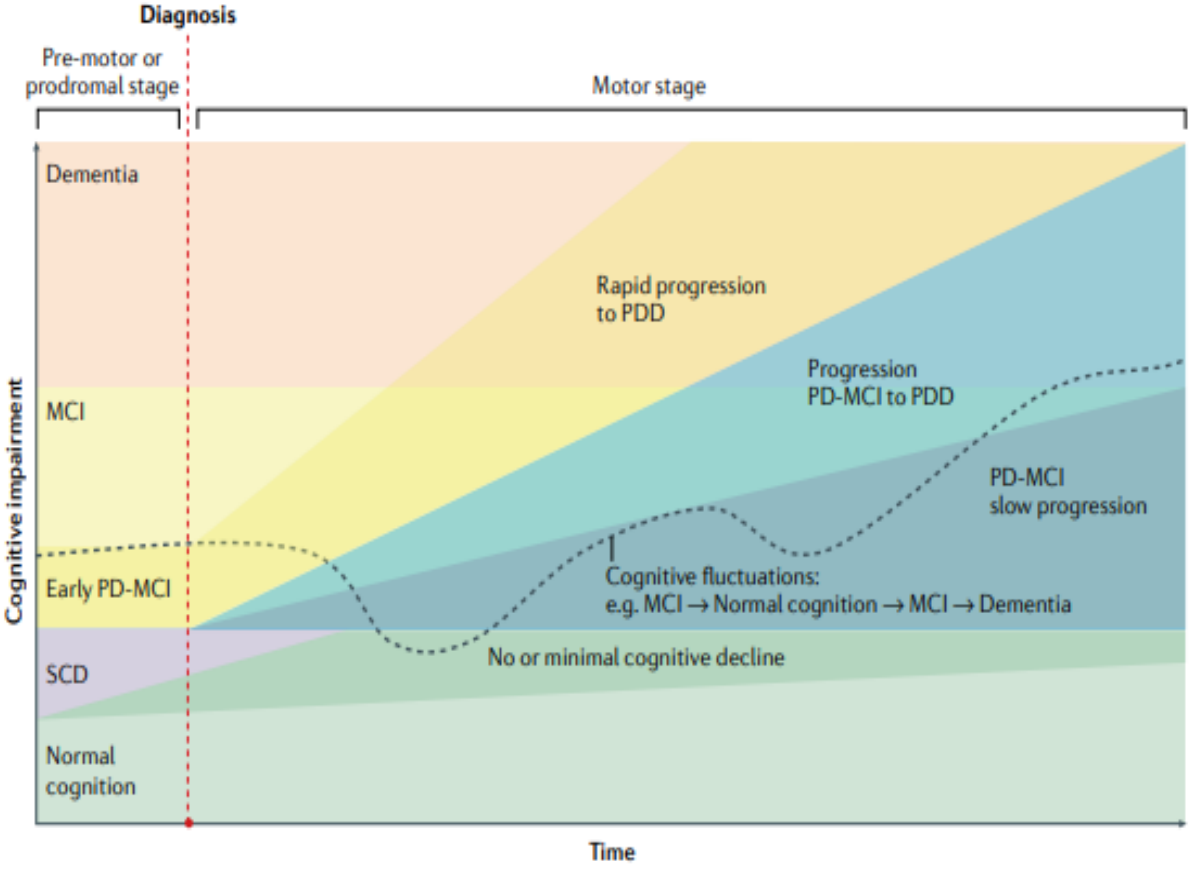


Source:(Rabiei et al., 2019)

Figure 9. Factors that contribute to oxidative stress and ultimately neuronal cell death in PD.

3.4.2.1 The range of cognitive abilities and the variety of cognitive impairment progression in Parkinson disease

Prior to or at the time of the diagnosis of Parkinson disease (PD), or even decades later, cognitive abnormalities, primarily in the form of subjective cognitive decline (SCD) or mild cognitive impairment (MCI), can develop. The rate of progression is highly variable. Additionally, there may be cognitive fluctuations, such as when some people with PD-associated MCI (PD-MCI) revert to normal cognition before later developing cognitive impairment. These cognitive fluctuations are typically accompanied by the progression of the disease's motor symptoms as well as the emergence of other non-motor symptoms. Parkinson disease dementia, or PDD (Figure 10).

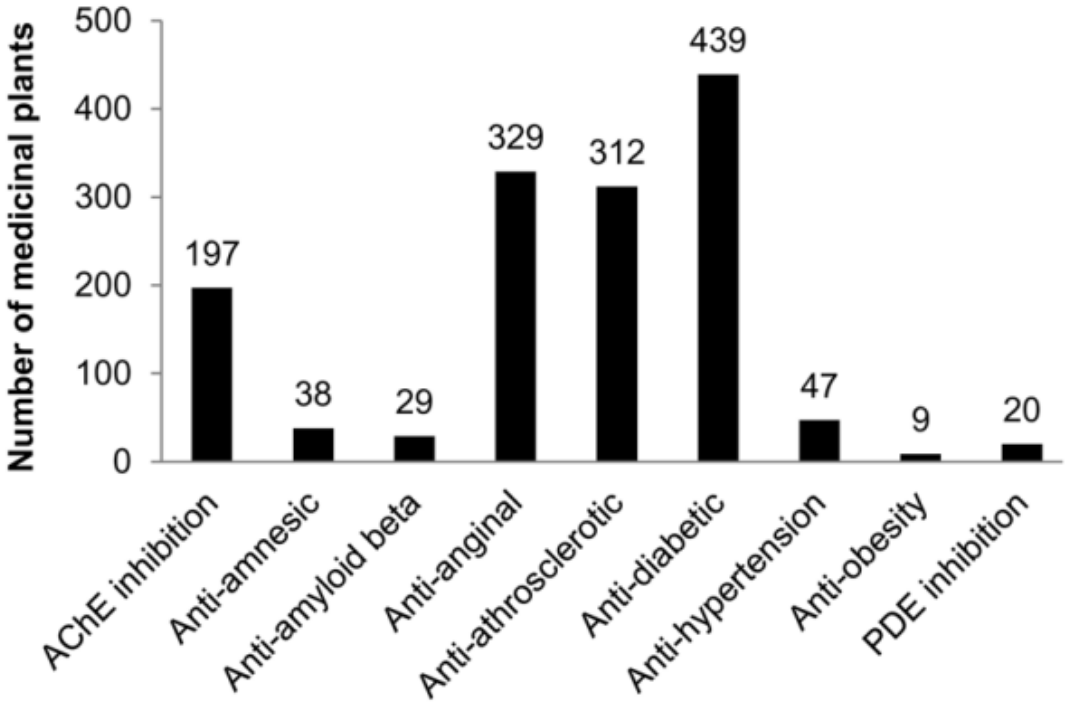


Source: (Aarsland et al., 2021)

Figure 10: The range of cognitive abilities and the variety of cognitive impairment progression in Parkinson disease.

Source: (Yin et al., 2021)

Figure 11: Representative of Chinese herbal medicine for Parkinson's disease.



. Source:(Lagunin et al., 2020)

Figure 12: Number of medicinal plants related to dementia treatment and associated diseases. AChE – acetylcholinesterase; PDE – phosphodiesterase.

CHAPTER 4

CONCLUSION

The cause of the majority of neurodegenerative illnesses is not well understood. The majority of these disorders are assumed to be brought on by a confluence of genetic and environmental variables, such as prolonged exposure to poisons and specific chemicals. Several lifestyle variables contribute to the nervous system's poor health by placing a slight strain on its neural cells.

However, additional clinical investigations are required to prove their safety and efficacy. Because of their anti-inflammatory, antioxidant, and anti-cholinesterase properties, phytochemicals will be a viable treatment for neurodegenerative diseases. The poor pharmacokinetic properties of herbal medicine and natural substances severely limit their potential The herbal medication has been integrated into a number of drug delivery formulations to get around these restrictions. Phytotherapeutic compounds are in greater demand, but before they can be widely used, they must first have scientific approval. acceptance and use. Hence Products marketed as "natural" could be a new source of helpful neuropsychotropic medications. Due to their complex pathophysiology, managing neurodegenerative disorders remains difficult in modern medicine.

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