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Phytopharmaceutical Interventions in Neurodegenerative Disorders: Emerging Trends and Prospects

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ABSTRACT

Neurodegenerative diseases, characterized by progressive neuronal loss and dysfunction, pose significant challenges to global health. Recent advances in phytopharmaceuticals have emerged as a promising avenue for the prevention and treatment of these disorders. This review explores the current research on various plant-derived compounds, highlighting their neuroprotective effects and mechanism of action, including antioxidant, anti-inflammatory, and neurotropihic activities. We discuss specific phytochemicals such as flavonoids, phenolic acids, and alkaloids that have demonstrated efficacy in preclinical and clinical studies for conditions like Alzheimer’s, Parkinson’s, and Hungtington’s diseases. Additionally, the integration of modern approaches such as network pharmacology and herbal-based nanosystems is examined for enhancing the bioavailability and therapeutic potential of these natural products. Despite the promising findings, challenges such as limited bioavailability and standardization of herbal formulations remain. Future directions in research should focus elucidating the molecular mechanisms underlying the neuroprotective effects of phytochemicals, conducting rigorous clinical trials, and developing innovative delivery systems to optimize their therapeutic applications. By bridging traditional knowledge with contemporary scientific methodologies, phytopharmaceuticals hold the potential to significantly improve treatment outcomes for patients suffering from neurodegenerative diseases.

1. INTRODUCTION

1.1 Overview of Neurodegenerative Diseases:

Neurodegenerative illnesses, one of the leading causes of morbidity and disability worldwide, are increasing attention due to their considerable impact on an aging population. The fundamental cause of these illness is a chronic reduction in neuronal function, which causes brain shrinkage. Thefollowing are listed in this review as some of the most prevalent neurodegenerative diseases: Amyotrophic lateral sclerosis (ALS), Hungtington’s disease(HD), Parkinson’s disease (PD)’ AND Alzheimer’s disease (AD) **(Teleanu et al., 2022)**.

The primary hallmark of neurodegenerative disorders is neuronal loss. The two most prevalent neurodegenerative diseases are Parkinson’s and Alzheimer’s. While there are a number of approved medications in order to cure neurodegenerative illnesses, the vast majority of them simply address the symptoms that are connected to them**(Lamptey et al., 2022).**

Neuron loss is the primary characteristic of neurodegenerative illnesses of the nervous system.Lou Gehrig’s disease is a term used to describe neurodegenerative conditions like Alzheimer’s, Parkinson’s, Hungtington’s, Amyotrophic Lateral Sclerosis, and Multiple Sclerosis **(Vyawhareet al., 2023)**.

Age and some genetic variations are recognized risk factors for neurological disorders. Low educational attainment, endocrine diseases, smoking, head trauma, depression, infections, oxidative stress, inflammation, stroke, high blood pressure, diabetes, and gender, cancers, chemical exposure, immunological and metabolic diseases, and vitamin deficits are some of the more likely conditions that cause neurodegenerative disorders. Neurons in these disorders gradually or totally lose their structure and function.

In neurodegenerative disorders, the nervous system malfunctions as a result of the slow and progressive death of neural cells. Balance, movement, speech, respiration, and heart function are among the cellular functions that are impacted by degenerative NDs. The progressive degeneration and ultimate neuronal death in the peripheral nervous system or brain are hallmarks of an neurodegenerative disorders**(Vellingiri B., 2023)**.

Some of the most common neurodegenerative diseases include:

Alzheimer's Disease (AD): One of the most prevalent forms of dementia, the brain condition known as Alzheimer's disease mainly affects the elderly. It is typified by the development of two primary protein clusters, neurofibrillary tangles, and senile plaques, which contribute to the gradual neuronal death and degeneration. Alzheimer's disease neurodegeneration is a pathogenic state of cells rather than an accelerated form of aging **(Maccioni et al., 2001).** Alzheimer's disease's defining feature is the abnormal buildup of tau protein and amyloid--β (Aβ) peptides, which causes tangles in the neurofibrillaand the death of neuronal cells. The healthy human brain contains the 39–43 amino acid residue peptide amyloid beta, It is said to have a normal physiological role. due to cleavage from a larger precursor protein for amyloid, it exists as Aβ fibrils. In AD, the buildup of amyloid fibrils in the extracellular space of brain cells called amyloid plaques or senile plaques is intimately associated with synaptic dysfunction, neuronal loss, inflammatory reactions, and synaptic loss**(Magalingam et al., 2018)**.

Parkinson's Disease (PD): After Alzheimer's, Parkinson's disease (PD) is the second most prevalent neurological illness. Parkinson's disease is a chronic neurodegenerative disease defined by the death of dopaminergic neurons in the substantia nigra, resulting in low dopamine levels in the striatum and impaired motor function. As a complex disorder Parkinson's disease is typically caused by the interaction of several risk and protective variables, such as environmental and genetic factors.**(Teles et al., 2018)**.

Hungtington's Disease (HD): Hungtington's disease (HD) is typified by irregular involuntary movements, behavioral abnormalities, cognitive failure, and mental illness **(Frank S., 2013).**Hungtington's disease is caused by a mutation in the HTT gene, a neurological illness that progresses slowly and ultimately deadly. Cognitive impairments, emotional swings, and chorea—uncontrollable dance-like movements—are among of the signs of HD**(Cepeda et al., 2014)**.

There are three or more common characteristics among neurodegenerative diseases, including Parkinson's, Alzheimer's, and prion diseases: (i) a gradual decline in neuron function that causes cognitive decline; (ii) the disease's molecular basis, which includes metal ion (Cu^{2+}, Zn^{2+}, and Fe^{3+}) imbalances that result in oxidative damage or metalloprotein misfolding with the accumulation (amyloid beta, alpha synuclein, and prion protein); and (iii) the absence of a treatment to reverse or halt the symptoms' progression **(Rowinska-Zyrek et al., 2014)**.

Neurodegenerative illness is managed with the aid of advances in our knowledge of the different targets and intracellular and intercellular signaling pathways involved. It is imperative that future research on neurodegenerative diseases concentrate on better drug delivery techniques and a critical understanding of the pathophysiology of illnesses, highlighting the interplay between multiple elements such inflammation, genetic mutation, and other neurochemical abnormalities**(Gadhave et al., 2024)**.

1.2 Phytopharmaceuticals in Medicine: A Historical Perspective

Although the majority of dementias cannot be cured, medication (cholinesterase inhibitors), occupational therapy, complementary and alternative medicine, and other approaches can help manage symptoms **(Shoaib et al., 2023)**. For instance, galantamine, rivastigmine, and donepezil are recommended to treat Parkinson's disease, vascular dementia, and Alzheimer's disease **(Rege et al., 2021)**.

Furthermore, because of their many health advantages, plants and their bioactive chemicals have attracted a lot of interest in recent decades. Numerous studies on plants and their bioactive compounds make it abundantly evident that they have a variety of biological effects, such as neuroprotection**(Khan et al., 2021),**cardioprotection, hepatoprotection**(Yadav et al., 2020),**anti-inflammatory, antioxidant, anticancer**(Khan et al., 2019)**, antimicrobial**(Mulat et al., 2019)**, antidiabetic, and other health-promoting effects **(Sun et al., 2020)**.

The term phytomedicine was first used in 1913 by Henri Leclerc, a French physician. Phytomedicine, also known as phytotherapy, is a recognized medical technique that uses botanical raw materials, including fruiting bodies or flowers, roots, bark, seeds, and leaves, for therapeutic and medicinal purposes **(Falzon and Balabanova., 2017)**. Plants have phytotherapeutic effects that can be linked to combinations of their so-called secondary metabolites **(Guerriero et al., 2018)**.

Plant-environment interactions are mediated by secondary metabolites, often known as phytochemicals, as opposed to primary metabolites, which are directly necessary for plant growth **(Al-Khayri et al., 2023**). Plants are shielded by phytochemicals from diseases including bacteria, fungi, insects, animals, and other dangers,allowing plants to adjust and endure in their surroundings **(Ahmad Dar et al., 2017)**.Consequently, phytochemicals have developed into physiologically active substances that can have toxicological or pharmacological effects on both humans and animals **(Erb and Kliebenstein., 2020)**.

1.2.1 History of Phytotherapy:

Since the use of plants to treat human ailments is as old as humanity and has been done in almost every civilization, a comprehensive history of its use is impossible to trace.Indeed, a wealth of data from multiple sources confirms that prehistoric people employed phytotherapy**(Jin-Ming et al., 2003)**. Anthropologists and ethnobotanists have documented traditional herbal remedies that are organized and systematic in every nation and ethnic group examined globally.

The use of plants for therapeutic purposes was common in ancient Chinese, Indian, Egyptian, Native American, and European societies **(Halberstein R., 2005**).The Old Testament, Egyptian papyri, Sumerian clay tablets from 5,000 BC, the writings of the Roman authors Pliny, Dioscorides, Galen, and Theophrastus, as well as the books of the Greek physician Hippocrates, provide written proof of the use of phytotherapy **(Santic et al., 2017)**.Many ancient cultures used these concoctions as hallucinogenic substances as well as treatments for physical ailments.The discovery of how individual molecules affect an organism and the start of the extraction of phytochemicals from plants marked a breakthrough in the 19th century **(Merlin M., 2003)**.

1.2.2 Neuroprotective Activity of Bioactive Medicinal Plants: Prior to the development of modern medicine, individuals relied on traditional remedies to cure illnesses relating to the brain or central nervous system. Herbal remedies have a significant influence in western societies, and their market is growing since they are perceived as "natural" and "soft" remedies as opposed to synthetic ones.

The following mechanisms of the herbs that have been prescribed for the centuries to treat neurodegenerative diseases in Ayurvedic and Chinese medicine systems are highlighted by recent mechanistic studies: (a) rise in neurotrophic factors and nerve growth; (b) decrease in inflammation; and (c) decrease in oxidative stress damage **(Wahid et al., 2020)**.

- **Indian traditional medicine system:**
- ***Curcuma longa L.***

Cultivated throughout tropical Asia and the Indian subcontinent, *Curcuma longa L* (family: Zingiberacae, syn: C. domestica Valeton) is a perennial plant with a short stem (about 100 cm in height). It is a drug for rheumatism, sinusitis, biliary disorders, anorexia, coryza, cough, blood purifier, diabetic wounds, hepatic disorders, and hepatoprotective, according to the ancient Indian medical system, because of its antioxidant qualities **(Eigner and Scholz., 1999).** Curcumin has additional pharmacological characteristics, such as anti-inflammatory, anti-cancer, and antioxidant effects **(Hatcher et al., 2008)**.It has neuropeotectiveproperties as well**(Calabrese et al., 2008)**.

- ***Withaniasomnifera (L.) Dunal***

Also referred to as Indian ginseng or ashwagandha, Withniasomnifera(L.) Dunal is a member of the Solanumaceaefamily and is the most commonly utilized neuroprotective herb in Ayurvedic medicine. Root extract from *Withaniasomnifera*has been utilized for over 4,000 years in India's Ayurvedic system as Medhya Rasayana (nootropic) medications. The Sanskrit terms "medhya," which means "intellect or cognition," and "rasayana," which means "rejuvenation," are combined to form the word "medhyarasayanas." *Withaniasmonifera*is known to have anti-stress properties, improve memory, and have an impact on brain growth and locomotor function**(Kulkarni et al.,2012)**.

The biologically active components of ashwagandha include alkaloids (ashwagandhine, tropine, isopelletierine, pseudotropinecuscohygrine, and anaferine), steroidal compounds (ergostanesteroidalactones, dehydrowithanolide R, with anolides A to Yasomidienone, asomniferin A, withaferin A, withasomniferols A to C, and withanone), and ergostanesteroidalactones. These compounds have been shown to have neuroregeneration, adaptogenic, antistress, analgesia, immunostimulatory, immunomodulatory, antioxidant, anticancer, and cholinergic properties **(Tohda and Joyashiki., 2009)**.

- ***Convolvulupluricaulis Choisy***

Choisy's Convolvulus pluricaulis(Convolvulaceae) In the Ayurvedic system, Shankhpushpi, a plant that protects neuron, has been employed in conjunction with *B. monnieri*. *Convolvulus pluricaulisChoisy*is a perennial herb that grows all throughout India and has spreading hairs that are either sub-erect or prostrate. In the Ayurvedic system, it is traditionally referred to as the "Medhya drug," and it is recommended as a brain tonic and a remedy for mental illnesses. In India, *C. pluricaulis*is strongly advised for mental health conditions including epilepsy and insanity, as well as for enhancing and fortifying memory **(Bihaqi et al., 2009)**.

- **Chinese traditional medicine system:**
- ***Huperzia serrata (Thunb.) Tervis***

Huperzia serrate (Thunb.) Trevis, a plant in the Lycopodiaceae family with the folk name Qiancengta, has been utilized as a conventional treatment for a long time in China to cure fever, blood problems, and edema. It is used to enhance cognition, increase circulation, lessen inflammation, and treat schizophrenia in Traditional Chinese Medicine (TCM)**(Adams et al., 2007)**.

Clinical investigations were conducted on its bioactive element, *Huperzine A*, an alkaloid that is regarded in Chinese literature to treat inflammation, alleviate pain, and reduce swelling following injuries. *Huperzine A* was found to enhance cognitive skills in patients with AD**(Wang et al., 2009)**

- ***Ginkgo biloba L.***

Ginkgo biloba L. (Ginkgoaceae family) A traditional Chinese tree that has long been recognized because of its health-promoting properties **(Sierpina V., 2003)**, for thousands of years, traditional Chinese medicine has utilized the leaves of the traditional *Ginkgo biloba L.* tree to cure AD, enhance memory loss, and increase cognition **(Gold et al., 2002)**.

1.3 Objective and Scope of the Review:

Herbal medications, rich in phytochemicals, have preventative and therapeutic effects for a range of conditions, including neuropsychological illnesses. Plant-derived natural compounds are increasingly being considered as potential future medications **(Farahani et al., 2014).** Numerous systematic evaluations have examined the therapeutic benefits of natural products in the cure of various psychological disorders, such as schizophrenia, generalized anxiety, Alzheimer's disease, insomnia, and depression **(Lakhan and Vieira., 2010; Bahramsoltaniet al., 2015)**.

2. MECHANISMS OF NEURODEGENERATION:

2.1 Pathophysiology of Major Neurodegenerative Diseases:

2.1.1 Mechanisms of Neurodegeneration in Alzheimer's disease:

A. **Mitochondrial Dysfunction and ROS Production:**Mitochondria produce ROS as a consequence of oxidative phosphorylation. Excessive ROS production is typically balanced by mitochondrial homeostasis **(Magalingam et al., 2018)**.

B. **Protein Oxidation:** The oxidation of key enzymes reduced ATP synthesis, disrupting ion pumps and potential gradients necessary for neuronal cell metabolism and function **(Castegna et al., 2002)**.

C. **Amyloidopathy:**Amyloidopathyrefers to the accumulation of the main ingredient of senile plaques in neurons, amyloid beta (Aβ) peptide **(Magalingam et al., 2018)**.

D. **Tauopathies:** Tauopathies are neurodegenerative illnesses characterized by intracellular abnormal aggregation of tau protein in neurofibrillary tangles **(Goedert and Spillantini., 2006)**.

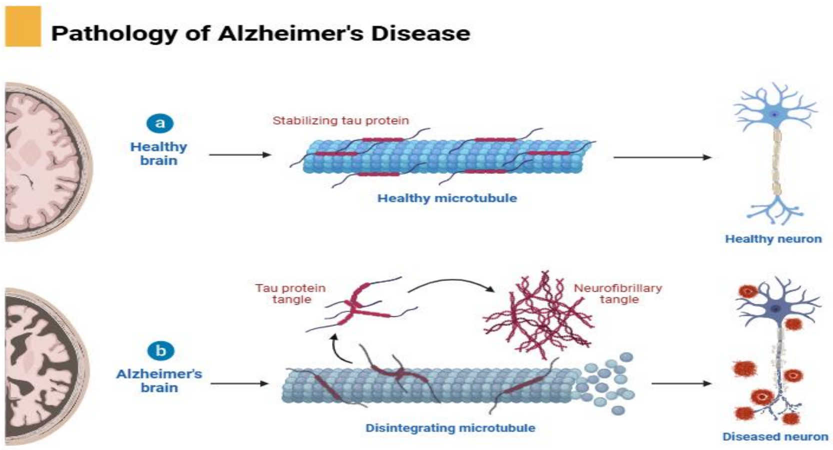
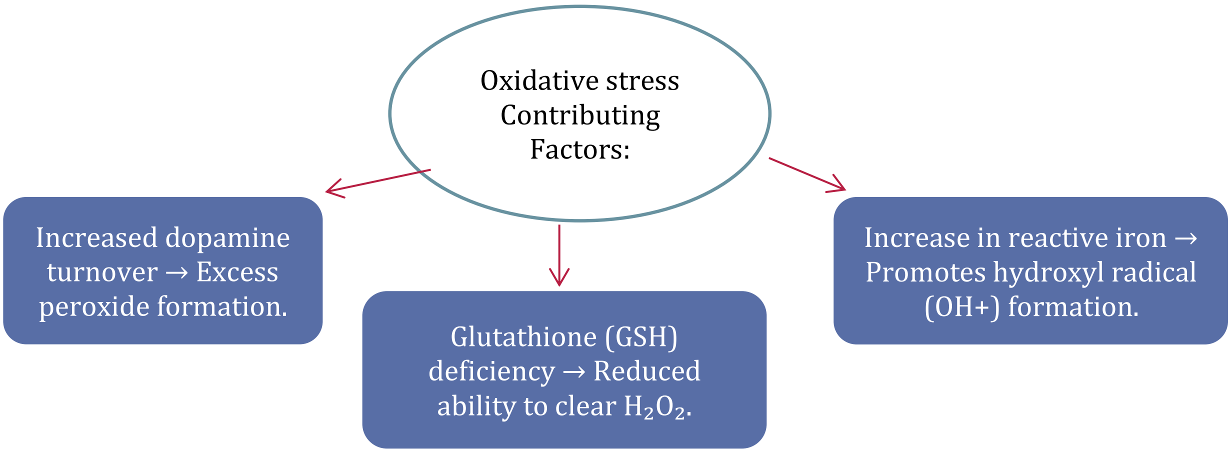


Figure 1: Mechanism of Neurodegeneration in Alzheimer's disease

2.1.2 Mechanisms of Neurodegeneration in Parkinson's disease:

A. Oxidative Stress: Because of the possibility that dopamine's oxidative metabolism could generate hydrogen peroxide (H_2O_2) and other reactive oxygen species (ROS), oxidative stress has attracted the most attention in Parkinson's disease (PD) **(Halllwell and Gutteridge., 1985)**.



B. Mitochondrial Dysfunction: Mitochondria are very oxidative, and oxidative phosphorylation produces ROS. Research indicates that mitochondrial dysfunction, namely abnormalities in complex-I of the respiratory chain, contribute significantly to the cause of Parkinson's disease **(Moore et al., 2005)**.

C. Glia Immune Modulators: TNF-α levels are higher in the neuromelanin region of Parkinson's disease, which is home to neurons or debris. When TNF-α receptors are activated, cultured dopaminergic neurons die and Nfκ-B undergoes nuclear translocation **(Hunot et al 1997)**.

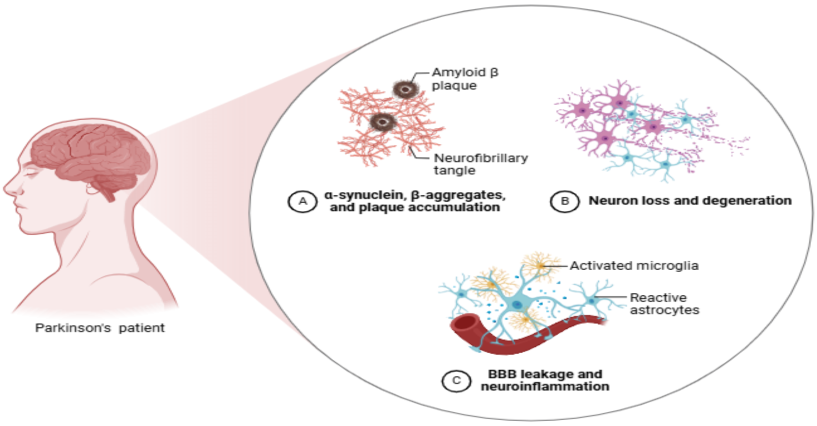


Figure 2: Mechanism of Neurodegeneration in Parkinson's disease

2.1.3 Mechanisms of Neurodegeneration in Hungtington's disease:

A. **Mitochondrial Dysfunction and Oxidative Stress**:Extended Ca2+ increase causes widespread mitochondrial depolarization, making neurons susceptible to excitotoxic stimuli. Intracellular reactive oxidative species are mostly caused by mitochondrial malfunction brought on by Ca2+ overload, extended membrane depolarization, or disruption of the electron transport chain **(Bano et al., 2011)**.

B. **Corticostriatal dysfunction and excitotoxicity:** The entire cerebral cortex provides excitatory glutamatergic inputs to the striatum, and the specific glutamate receptor typesexpressed in these cells, as well as the large number of glutamatergic inputs they get, may be the cause of the selective susceptibility exhibited by striatal neurons in HD **(Sieradzan& Mann, 2001)**.

C. **Nigrostriatal dysfunction and dopamine toxicity:** In both asymptomatic and symptomatic HD patients, cognitive function is positively connected with the loss of DA neurotransmission markers both pre- and postsynaptically **(Backman & Farde, 2001)**.

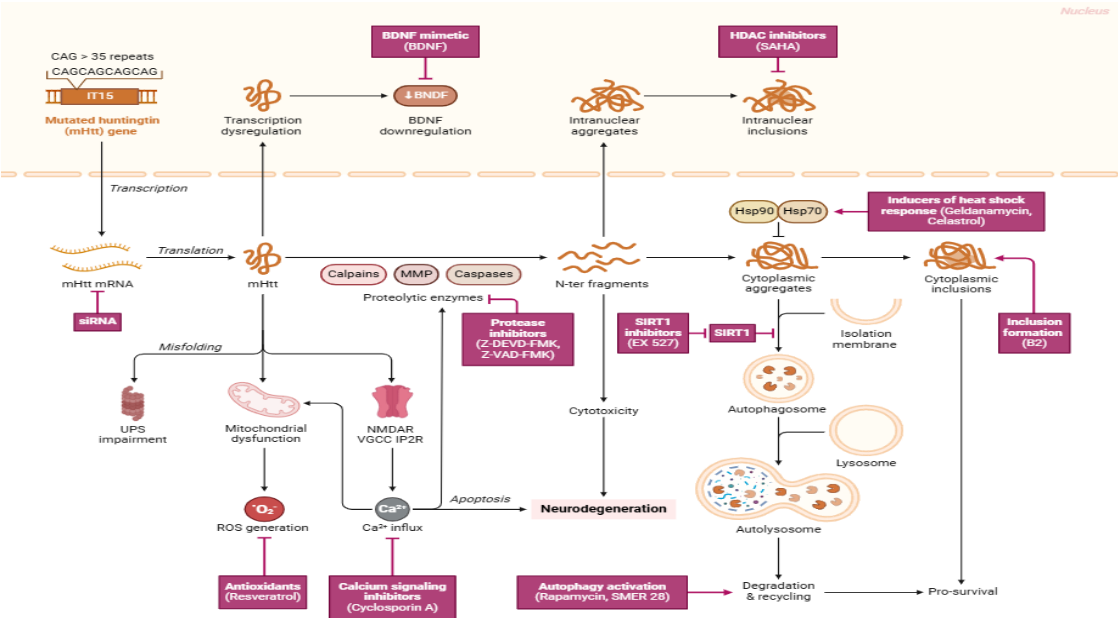


Figure 3: Mechanisms of Neurodegeneration in Hungtington's disease

2.1.4 Mechanisms of Neurodegeneration in Amyotrophic lateral sclerosis (ALS):

A. **Glutamate excitotoxicity:**Glutamates are released by presynaptic terminals and diffuse across the synaptic gap, activating particular postsynaptic receptors and initiating the action potential **(Bonafede and Mariotti, 2017).**In patients with ALS, excitotoxicitycontributes to cortical hyperexcitability and dysfunction **(Kantamneni, 2015; Diana et al., 2017; Lerskiatiphanich et al., 2022)**.

B. **Oxidative stress and mitochondrial dysfunction:**Glutamate excitotoxicity causes an increase in Ca2+ influx into cells, which in turn causes Ca2+ entrance into mitochondria. This causes mitochondrial malfunction and further ROS generation, which ultimately leads to cell death **(Sever et al., 2022)**.

C. **Neuroinflammation:**T lymphocyte infiltration, excessive inflammatory cytokine production, and activation of microglia and astrocytes are the hallmarks of neuroinflammation linked to neuronal death **(Komine and Yamanaka, 2015)**.

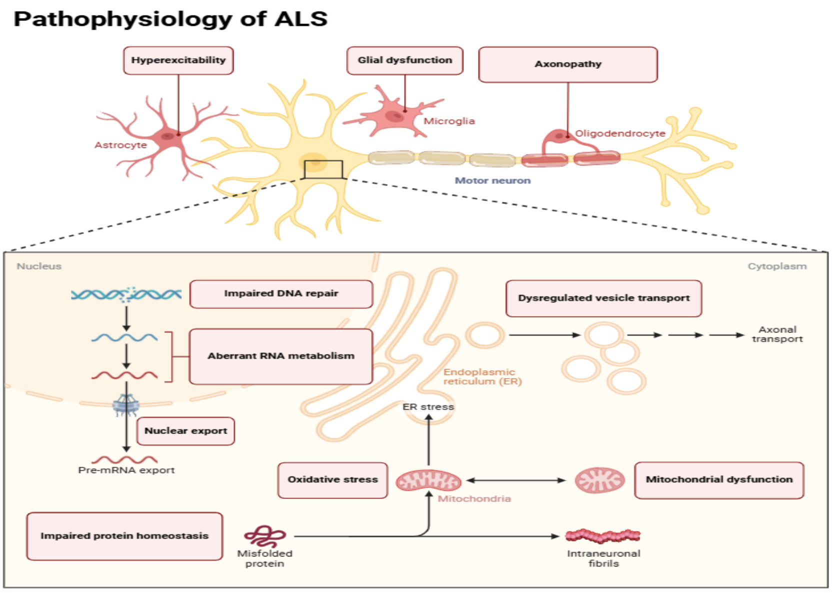


Figure 4: Mechanisms of Neurodegeneration in Amyotrophic Lateral Sclerosis (ALS) disease

2.2 Common Mechanisms Underlying Neurodegeneration in Alzheimer’s, Parkinson’s, Hungtington’s Diseases and Amyotrophic Ltaeral Sclerosis (ALS):

A. Oxidative Stress: It has been demonstrated thatdemonstrated that oxidative stress and the generation of free radicals, which are catalyzed by redox metals, are essential for controlling redox reactions in vivo, which contribute to RNS and ROS, the primary causes of neurodegeneration **(Emerit et al., 2004).** The imbalance between pro-oxidant and antioxidant homeostasis leads to oxidative stress, which in turn contributes to the production of ROS and free radicals**(Uttara et al., 2009)**.

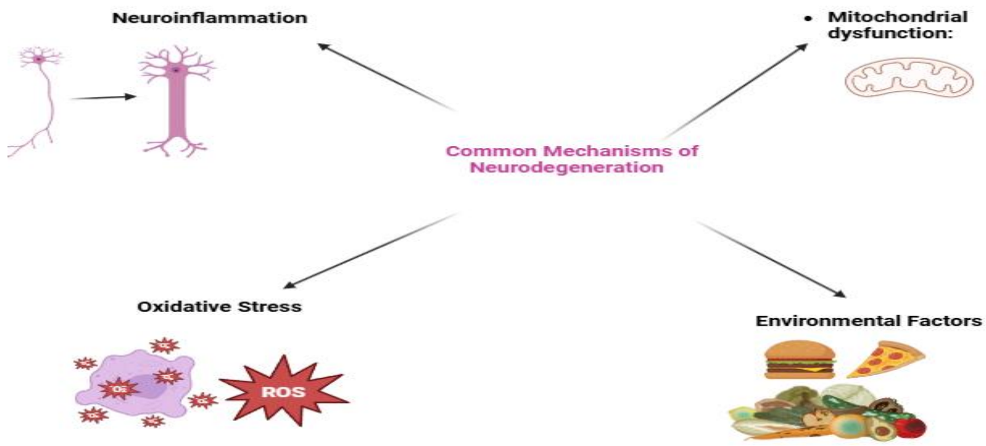


Figure 5:Common Mechanisms Underlying Neurodegeneration in Alzheimer's, Parkinson’s, Hungtington’s Disease and Amyotrophic Lateral Sclerosis (ALS)

B. Neuroinflammation: CNS-influencing inflammatory events have multifaceted outcomes, which, depending on its location, timing, and duration, can be neuro-protective, neuro-regenerative, or neurodegenerative **(Williams et al., 2017; Wareham et al., 2022)**.Theneuroinflammation in neurodegenerative diseases is just the body's reaction to other pathophysiological occurrences **(Rasheed et al., 2021; Holbrook et al., 2021; Han et al., 2021)**.

C. Mitochondrial dysfunction: Cell viability is negatively impacted when normal mitochondrial function is disrupted. Due to their heightened reliance on mitochondria for ATP synthesis and calcium buffering, neurons are particularly vulnerable to mitochondrial abnormalities **(Liu et al., 2018)**.

3. PHYTOPHARMACEUTICALS IN NEURODEGENERATIVE DISEASES

Neurodegenerative activity	Whole Plant/ parts used	Active components	Conclusion
Alzheimer’s Disease	*Camellia sinesis*Leaf	Polyphenols mainly Flavonoids	Memory impairments in the rat model of AD are improved by green tea extract's ability to prevent the synthesis of amyloid fibrils and lysozyme fibrillation**(Lee et al., 2015)**.
Alzheimer’s Disease	*Withaniasomnifera*	Withaferin A	By reducing oxidative damage brought on using streptozotocin in a cognitive impairment paradigm, WS has a positive impact on cognitive deficit **(McMurray C., 2001)**.

Parkinson's Disease	*Bacopa monnieri*	Bacosides A & B	Decrease in the baseline concentrations of oxidative indicators in different parts of the brain, including hydroperoxides (HP), malondialdehyde (MDA), and reactive oxygen species (ROS). In addition to restoring striatal DA levels, BM supplementation also restored cholinergic enzyme activity**(Parveen et al., 2015)**.
Parkinson's Disease	*Trigonella foenum-graevcum*Seeds	Trigonelline	The extract reverses motor symptoms in an animal model of Parkinson's disease, most likely as a result of its neuroprotective properties. **(Jadiya et al., 2011)**.
Amyotrophic Lateral Sclerosis	*Withaniasomnifera* Root	Sitoindosides VII-X, Withaferin A	When misfolded SOD1 is involved, WS extracts may be a viable therapy for the treatment of ALS **(Sandhu and Rana., 2011)**.
Huntington disease	*Ginkgo biloba* Leaves	Ginkgolides A and B, bilobalide	According to results, ginkgo biloba leaf extract leaf may have a neuroprotective role in the current HD paradigm, which could be connected to enhanced energy metabolism, antiapoptotic actions, and antioxidant qualities**(Bigham et al., 2021)**.
Huntington disease	*Ficus religiosa* Leaves	Campestrol, stigmasterol, α-amyrin, lupeol, tannic acid, arginine, aspartic acid	Ficus religiosa may be used as a preventative medication for Huntington's disease as the study shown that it shields the brain from oxidative stress **(Pinto et al., 2015)**.

4. CHALLENGES IN DEVELOPMENT OF PHYTOPHARMACEUTICALS:

Plant parts, either alone or in combination, are typically used in pharmaceutical dose forms to make herbal medications. Herbal remedies have the same therapeutic or preventative qualities as manufactured pharmaceuticals. Its multi-component chemicals interact to produce poly-pharmacological effects, also referred to as multi-target effects. The thorough assessment of chemical content and bioactivity is necessary for the use of this approach in the creation of phytopharmaceuticals **(Tarkang et al., 2016)**.

If phytopharmaceuticals can demonstrate that they are safe and effective, they can be incorporated into the healthcare system. Nevertheless, ensuring the efficacy, safety, and quality of phytopharmaceuticals remains difficult to this day. Every step of the production process, including culviation, harvesting, post-harvest processing, manufacturing, packaging, and product distribution, requires the application of quality assurance. Every stage of quality assurance is meant to guarantee the safety and efficacy of the product can be replicated **(Hussain et al., 2009; Zhang et al., 2012; Pferschy-Wenzig et al., 2015)**.

4.1 Authentication of raw material:

Medicinal plants are now a significant agricultural commodity due to the recent rise in the usage of phytopharmaceuticals. It is impossible to authenticate morphology since many medicinal plants are supplied in many dosage forms, including extracts, dried substances, fresh ingredients, and dry powdered materials. This is because these materials have lost their properties. Growing demand for medicinal plants has led to unethical commercial transactions, such as substituting similar but less effective products for genuine raw resources. The health and safety of consumers will be impacted by the act of counterfeiting or combining inferior herbs, so determining the authenticity and quality of herbal raw materials of is essential to ensuring the quality of medications**(Fadzil et al., 2018; Yu et al., 2018)**.

A guarantee of adherence to tthe necessary requirements is provided by authentication. Identification, measurement of distinctive components, adulteration, pollutants, and quality verification in accordance with standards are only a few of the many facets that make up authentication. A medicinal plant raw material's specification includes its botanical or geographic origin as well as the manufacturing or processing methods used to prepare it **(Folashade et al., 2012; Cuadros-Rodríguez et al., 2016)**.

The capacity of ancient healers to identify the components of their medicinal herbs is exceedingly high. However, the capacity to recognize therapeutic plants has diminished as civilization has progressed and people have lost touch with nature. There are several plants with the same name and one plant with a different name since ancient books regarding herbal medicine are frequently translated and understood differently. Due to linguistic diversity and regional dialects, this problem is becoming more complex**(Rivera et al., 2014; Ganie et al., 2015)**.

Herbal raw materials might be mistaken for one another due to the physical similarities of plant parts. Defective raw materials may be the result of deliberate or inadvertent actions. When it comes to the material's economic value, adulteration typically takes the form of substituting other plant species that are comparable to the original raw material. The primary source of unintentional errors is workers' negligence when gathering wild plants for raw materials **(Joharchi and Amiri.,2012; Wang and Yu., 2015; Bittner et al., 2016)**.

Misidentification frequently happens as a result of nomenclature issues. Plants with local names are frequently mentioned because of their historical applications. Additionally, the local name frequently leads to errors in raw materials and becomes hazardous, particularly when toxic species are used in its place. For instance, the root of Stephania tetrandra S. Moore (Menispermaceae) is referred to as "Fangji" in Traditional Chinese Medicine (TCM). The northern region of China is where this species first appeared. "Hanfangji" is the official name according to the Chinese Pharmacopoeia. The name "Fangji" is also used for the roots of Aristolochiafangchi YC Wu ex LD ChoW and SM Hwang (Aristolocjiaceae) originating from the southern region. It contains nephrotoxic and carcinogenic acid derivatives and is known as "Guangfangji" in pharmacopeia **(Joharchi and Amiri.,2012)**.

Different plant species with the same local name can potentially be misidentified. Because the pharmacological actions of the two species differ, using them will not meet therapeutic goals. Mesua ferrea is a herb used as a heart tonic, cardiotonic, emenagogue, hypotensive, antispasmodic, antianaphylactic, and antiasthmatic. It is known as "Nagasari" in Indonesia and "Nagakeshara" in India. However, the local names "Nagasari" or "Nagakeshara" are also used to sell Calophylluminophyllum. This herb is typically used to treat psoriasis and reduce inflammation **(Asif et al., 2017; Ghosh D., 2018)**

Secondary metabolites like phytoprotein and phytoalexin are produced by plants to protect themselves from environmental factors like insects, other plants, and plant microbes.Through genetic engineering, the secondary metabolites of plants can be changed to produce more of the desired molecules and less of the unwanted ones. Due to the well-established biosynthetic pathway, the production of flavonoids and anthocyanins is the first effective genetic engineering operation. Changes in blossom color indicate the outcomes **(Rastegari et al., 2019)**.

4.2.2 Extrinsic Factors:

The types, amounts, and proportions of active chemicals in the common species are influenced by external factors such as the environment and habitat. Plant-environment interactions during a protracted evolutionary process lead to the biosynthesis of a plant's active ingredients. According to the study on Eucommia ulmoides Oliv., the location's height and the average yearly temperature had a substantial impact on the amounts of flavonoids and chlorogenic acid. The amount of sunlight received each year had a negative correlation with geniposidic acid levels but a positive correlation with a them. In traditional Chinese medicine, Potentilla fruticosa L. is used to treat scabies, hepatitis, diarrhea, and rheuma as well as to aid in detoxification. In the high, chilly areas of the northern subarctic highlands, P. fruticosa thrives. Liu et al proved that altitude has negatively correlated with tannin content, whereas the length of annual sunlight and altitude has positively correlated with flavonoid levels and antioxidant activity. Altitude has a positive correlation with total phenolic levels, whereas the average annual temperature has a negative correlation **(Liu et al., 2016)**.

The growth, development, reproduction, behavior, and spread of plants can all be impacted by ecological elements like climate, geography, land, and topography. Plants can control thesynthesis of secondary metabolites to counteract these effects.

Variations in plant quality from the original area are caused by many ecological factors. One of the traditional Chinese medicinal herbs, Dendrobium officinale, is used as a tonic, to nourish the stomach, to reduce inflammation in the neck, to enhance vision, and to encourage bodily fluids. D. officinale is primarily composed of flavonoids, alkaloids, and polysaccharides. According to the study's findings, in order to satisfy consumer demand and preserve the original plant, this plant's cultivation must satisfy requirements for soil pH, humidity, temperature, sunlight duration, and the amount of nitrogen and phosphorus the plant needs **(Yuan et al., 2020)**.

Variations in the composition and production of specific secondary metabolite "classes" are caused by interactions between plants and their surroundings. Based on qualitative and quantitative study of its chemical constituents, the composition of constituents can be employed as chemical identifiers for plants that grow from specific geographic areas and are harvested at specific times of the year or at specific ages. Mexican sunflower, or *Tithonia diversifolia (Hemsl.) A. Gray*, is a member of the *Asteraceae*family and generates essential oils that are widely distributed. The findings of Sampaio and Da Costa's study demonstrated that the geographical origin of the sample influences the chemotypes of *T. diversifolia*species.

Variations in the production of specific classes of secondary metabolites, including terpenes, and differences in the accumulation of ß-pinene in essential oils appear to be direct responses to various abiotic environmental conditions. Additionally, this study demonstrates that issue-specific alterations that result in secondary metabolism are environmental adaptations **(Sampaio and Costa., 2018)**.

4.2.3 Harvesting:

Choosing the right harvest time is essential to obtaining high-quality raw materials.For raw materials to be of reproducible quality, post-harvest operations like transportation, storage, and processing into dry raw materials must also be completed under ideal circumstances. Since the wild is the main source of medicinal plants, overuse may harm the environment and lead to the extinction of some species. There are issues with the homogeneity of quality in plants that are harvested from the wild. The chemical makeup and medicinal qualities will be impacted by the agroclimatic conditions.Terminalia chebula is a common medicinal plant in India that comes from different sections of the country and is known to have a variety of therapeutic uses **(Pandey A. K., Savita., 2017)**.

The chemical makeup of plants will change depending on when they are harvested. Thus, it is important to harvest at the appropriate period. It is well recognized that a plant's chemical composition is directly tied to its developmental stage. Andrographis paniculata, also known as Kalmegh, is utilized as a hepatoprotective in Ayurveda. At 18 months of age, the amount of Rauwolfia serpentine root alkaloid reaches its maximum.Withaniasomnifera (ashwagandha) plants reach their peak maturity at the root 130–180 days after planting, but Tinospora cordifolia (giloe) stems reach their peak maturity at 15 months. Vasicine is found on the leaves of Adhatodavasica, also known as Addusa or Vasaca, which is used as a bronchodilator in Ayurveda. March is when this plant blooms fully, and September is when it flowers partially. Levels of these chemicals were 3.0 in March and 1.4% in September during the flowering period. However, vasicine levels are extremely low during the vegetative stage **(Sampaio and Costa., 2018**).

One of the essential oils that is frequently utilized in the beverage, cosmetic, perfume, and pharmaceutical industries as an aromatic and antibacterial is lemongrass oil, which is derived from Cymbopogon citratus. One indicator of the quality of lemongrass oil is its citral concentration. Only 13 of the 65 chemicals found in lemongrass oil are consistently found in oil that has been harvested at various ages. Harvesting lemongrass at different stages of maturity also results in varying citral levels. Harvesting lemongrass between 6.5 and 7.0 months of age yields the oil's optimal citral concentration **(Bekele et al., 2019)**.

4.2.4 Post-harvesting process:

One element that affects the chemical and physical characteristics of plant components is water.

Drying plants reduces their moisture content, which prolongs their shelf life by inhibiting the action of microorganisms and enzymes. Dry raw materials make storage and transit easier.

The drying process is influenced by numerous factors. Consequently, it is necessary to select a drying technique that preserves or increases the phytochemical content **(Ganie et al., 2015; Bekele et al., 2019)**.

The most widely consumed beverage in the world, Camellia sinensis, also known as C. assamica, comes in green and black varieties. Green tea has a wide range of a significant pharmacological effects. However, because of the chemical content's volatility, the drying method's capacity to preserve its quality is severely limited. Vitamins, flavonoids, chlorophyll, and polyphenols—all of which have antioxidant properties—are chemical components of green tea. The recovery of taxol from Taxus baccata is impacted by the drying process. While the yield of taxol from leaves will rise as the drying temperature rises, the yield from stems is unaffected by drying temperature. A low yield will result from drying at low temperatures since it takes longer for the enzyme activity to break down the taxol**(Yuan et al., 2020)**.

4.2.5 Storage

Medicinal plants must frequently be preserved for a sufficient amount of time after harvesting in order to be utilized as raw materials for different products. In order to prevent physical, chemical, and microbial alterations, the storage technique must be appropriate. The purpose of storage is to prevent quality degradation. Certain techniques, such regulating humidity and airflow, are employed to stop metabolic processes that could harm the chemicals' composition. Another strategy is to stop mice, insects, and microbes from attacking **(Rocha et al., 2011; Roshanak et al., 2016)**.

A medicinal herb with immunostimulatory and anti-inflammatory properties, Echinacea purpurea (Asteraceae) is particularly effective at reducing the symptoms of colds. The amount of cichoric acid and alkamide in E. purpurea root is influenced by the storage technique, and vice versa. While cichoric acid levels decreased by 70% after 60 days in the dark at 500C, alkamide levels remained unchanged. The alkamide level decreased by 65% while the cichoric acid level remained same after being stored in light at 2000C. Light and temperature have an impact on E. purpurea's chemical composition**(Tanko et al., 2005; Lisboa et al., 2018)**.

When Thymus daenensisCelak aerial portions were stored in a freezer at-20°C, the chemical composition of the essential oils did not alter. Because thymol and carvacrol levels rise when stored at room temperature (25°C), its quality is also unaffected. **(Manayi et al., 2015)**.

Biological activity will alter as a result of changes in chemical composition that take place during storage. The antibacterial activity of nine African medicinal herbs remained unchanged, while their anti-inflammatory (COX-1) activity decreased **(Street et al., 2008)**The chemical composition of the raw materials used to keep medicinal plants will also be influenced by the type of packaging employed throughout the storage procedure. Numerous studies demonstrate that the packaging has a significant impact on the composition and concentration of chemicals in essential oils, as well as the stability of polyphenol groups and color stability**(Tanko et al., 2005)**.

4.3 Complex mixture of the pharmacologically active constituent

For proper growth, development, and reproduction during its initial life, the plant produces primary metabolites. Growth and development require primary metabolites like sugar, protein, vitamins, lipids, and starches, while metabolic processes like photosynthesis, respiration, and nutrient absorption require chlorophyll, amino acids, nucleotides, and carbs.

However, plants will produce secondary metabolites to defend themselves against possible threats from the environment or other species. The substrate for the primary metabolite or a change in the primary metabolite's synthetic pathway is employed to create this secondary metabolite. Secondary metabolites will build up throughout growth and are not directly required for it. Because of its biological function, this chemical may one day be employed as a human medication **(Kabera et al., 2014; Devi and Krishnakumari., 2015)**.

Controlling the quality of herbs is difficult due to their complicated chemical composition.

Therefore, isolates of active compounds derived from the separation and purification procedure supervised by bioassays are preferred for developing novel medications. Aspirin, which is made from salicylic acid that is taken from willow bark, was created in 1897. This led to a period of mono-drug therapy dominance and the creation of synthetic medications, as well as a decline in the use of natural materials in drug discovery **(Carmona and Pereira., 2013)**.

Numerous investigations have demonstrated that its pharmacological effects were diminished or even eliminated throughout the separation and purification process.Compared to the entire extract of Artemusua annua L., artemisinin has less antimalarial activity.The lack of pharmacokinetic synergy between elements upon purification of herbal extracts is closely linked to this reduction in impact. The isolation of Aconiti (aconitum carmichaeliiDebx), gentiopicroside (Gentiana manshuricaKitag), liquiritigenin and isoliquiritigenin (Glycyrrhiza uralensis Fisch), ginsenoside Re (Panax ginseng C. A. Mey), cryptotanshinone and tanshinone (Salvia miltiorrhiza), and schizandrin (Schisandra chinensis) also showed a decrease in activity. The pharmacokinetic synergy effect between constituents in herbal extracts can occur during absorption, distribution, metabolism, and excretion**(Zhao et al., 2020; Sun et al., 2019)**.

5. FUTURE DIRECTIONS

- **Phyto-phospholipid complexation technique for improving pharmacokinetic profile of plant actives:**
- One of the most effective methods for enhancing the pharmacokinetic and pharmacodynamic profiles of plant elements with significant therapeutic promise but low bioavailability is the complexing of herbal medicine molecules with dietary phospholipids.Originally created for cosmetic purposes, the phytophospholipid complex has since undergone substantial study and development to become a new medication carrier with systemic action. Although a lot of research has been done in this area, more needs to be done to address the problems with the preparation method, stability, and true clinical superiority of these drug delivery systems **(Yue et al., 2010)**.

The potential of the phyto-phospholipid complexes for clinical applications has increases as a result of the widespread replacement of the conventional methods for creating them with hydrophilic solvents like ethanol and hazardous organic solvents like tetrahydrofuran and dichloromethane. One common conventional method for creating phyto-phospholipid complexes is the solvent evaporation technique. However, the procedure requires a number of time-consuming processing steps, and the method used to dry the residue—which hasn't been optimized in any of the studies been—often determines the quality of the final product in terms of particle size, morphology, and hygroscopicity **(Yue et al., 2009)**.

Numerous studies indicate that a medication to phospholipid ratio other than 1:1 produces a better product with respect to its pharmacological and physiological characteristics. Different formulation factors, such as the drug to phospholipid ratio, temperature, and processing time, have been found to affectthe yield of the carrier system. These factors have been responsible for the significant variation in the yield of the phyto-phospholipid complexes across various studies, ranging from roughly 25% to over 90% **(Yue et al., 2010; Yue et al., 2009).**

Future research projects must take this formulational factor into account in order to produce the highest-quality formulation possible. To achieve optimal entrapement efficiency and a superior drug release profile, the molar ratios of drug candidates with phospholipids, as well as temperature and other variables, can be optimized using additional statistical methods such as factorial design and spherical symmetric designing. There aren't many studies showing a link between the pharmacological effectiveness of drug molecules in their phospholipid complexed forms and improvements in *in vitro* and *in vivo* pharmacokinetic characteristics.**(Yue et al., 2010)**.

Without delving into the therapeutic aspects of produced formulations, more focus has been placed on the characterisation and assessment of phyto-phospholipid complex pharmacokinetic parameters. To close this gap and link the increase in bioavailability to clinical efficacy, more thorough research is needed **(Zaidi et al., 2011).**

Future studies may consider the need to adjust the drug's dosage in order to get the desired therapeutic response due to improved clinical efficacy and prolonged release pattern. More research and attention are needed in the area of concern regarding the stability of the phyto-phospholipid complexes. Regarding the phyto-phospholipid complexes' market usefulness and survivability, there is inadequate evidence to establish their stability during storage. When stored, these preparations run the danger of aggregating and degrading chemically. More than 90% pure phospholipid preparations are thought to be more vulnerable to oxidative alterations, which could be a deciding factor in the end product's stability. Both the temperature-related hygroscopicity of the formulations and the zeta potential are important factors in regulating the stability of solid dispersions and inter-particle interactions. When compared to pure drugs, experimental study has shown that phytophospholipid complexes have a considerable capacity to absorb moisture. Additionally, the formulation has been shown to become more viscous when stored in free air **(Qin et al., 2010)**.

In order to develop and enhance the stability of the phyto-phospholipid complexes and to further support the formulation as a successful new carrier system, these parameters—which have largely stayed unchanged in the majority of studies—need to be given more attention in the future. The precise process of drug-phospholipid complex absorption from the gastrointestinal tract, or more precisely from the small intestine, is rarely discussed in reports, which may present a challenge for future studies **(Narayana et al., 2001)**.

By adjusting the complexes' particle size, it is possible to alter the phyto-phospholipid complexes' ability to act as targeted carriers for the reticuloendothelial system and inflammatory locations. The product's size can be adjusted to a variety of small ranges by utilizing more recent methods, such as supercritical fluid systems, and adjusting temperature, pressure, and other factors.Because of their increases penetrability and retention, these size-controlled products will be useful in more accurately targeting different pathogenic areas, such as inflammation and tumors**(Rezende et al., 2009)**.

By attaching to cellular structures with particular ligands and antigens, phyto-phospholipid complexes can be be excellent candidates for active targeting in addition to passive targeting.This will increase the range of conditions for which phyto-phospholipid complexes can be used to treat debilitating conditions such as cancer, osteoarthritis, and rheumatism **(Maiti et al., 2007)**.[118-174]

6. CONCLUSION

Advances in phytopharmaceuticals for neurodegenerative diseases represent a promising frontier in the quest for effective treatments. The current body of research highlights the potential of various plant-derived compounds, including phenolic compounds, flavonoids, and alkaloids, to exert neuroprotective effects through multiple mechanisms such as antioxidant activity, anyti-inflammatory properties, and modulation of neurotrophic factors. These natural products not only show promise in slowing the progression of diseases like Alzheimer’s, Parkinson’s, and Hungtington’s but also offer preventive capabilities that could mitigate the onset of these debilitating conditions.

Despite the encouraging findings, several challenges remain in translating these phytochemicals into clinical practice. Issues such as bioavailability, optimal dosing, and potential interactions with conventional therapies must be addressed to maximize their therapeutic potential. Recent advancements in network pharmacology and nanotechnology provide innovative approaches to enhance the efficacy and delivery of phytopharmaceuticals, paving the way for more effective treatment strategies.

Looking ahead, future research should focus on elucidating the precise molecular mechanisms underlying the neuroprotective effects of these compounds. Additionally, comprehensive clinical trials are necessary to validate their safety and efficacy in human populations.

In conclusion, while phytopharmaceuticals hold great promise for addressing the challenges posed by neurodegenerative disorders, ongoing research and development are crucial to fully realize their potential in clinical settings. The integration of traditional knowledge with comtemporary scientific inquiry will bethekey to advancing our understanding and application of these natural products in neuroprotection.

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