From Ancient Roots to Nano Routes: Targeted Delivery of Ginkgo and Gastrodia for Parkinson's Disease (PD) Treatment

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Preface

It is with immense pride and gratitude that I present this edited volume, *"From Ancient Roots to Nano Routes: Targeted Delivery of Ginkgo and Gastrodia for Parkinson's disease (PD) Treatment"* This book brings together the collective wisdom of researchers, clinicians, and academicians who are working at the intersection of traditional herbal medicine and cutting-edge nanotechnology, aiming to create more effective, targeted, and patient-centered therapeutic strategies for PD.

The vision behind this book is to bridge the timeless legacy of natural remedies with the transformative potential of modern nanomedicine. PD, with its complex and multifactorial pathology, demands approaches that go beyond conventional therapies. By exploring the neuroprotective properties of *Ginkgo biloba* and *Gastrodia elata*, and advancing their potential through nanocarrier-based delivery systems, this volume highlights a holistic and innovative path forward.

I also wish to express my sincere appreciation to my favorable, **Dr. Akashdeep Singh and Dr. Binita Ghosh**, whose expertise, vision, and thoughtful contributions have greatly enriched this work. Her involvement has been instrumental in shaping the book into a comprehensive and meaningful resource for researchers, clinicians, and students alike.

I extend my heartfelt gratitude to the **Department of Pharmacy, Jagannath University, Jaipur, Rajasthan**, for their continuous support, academic encouragement, and for nurturing an environment that fosters innovation and research. The department's commitment to excellence in pharmaceutical sciences has been a source of great inspiration throughout the preparation of this book.

Finally, I am thankful to all the contributors whose scholarly efforts made this compilation possible, and to the readers, for whom this book has been carefully curated. It is my hope that this volume not only serves as a valuable reference for advancing research and clinical applications but also inspires innovative ideas that take natural product–based nanomedicine "from bench to bedside and beyond."

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Chapter 1: Introduction to Nanotechnology in Parkinson's Disese (PD): Pathophysiology and Clinical Challenges

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Abstract

PD (PD) is the second most prevalent neurodegenerative disorder, characterized by the progressive loss of dopaminergic neurons in the substantia nigra, leading to motor dysfunctions such as tremors, rigidity, and bradykinesia, as well as non-motor symptoms including cognitive decline and sleep disturbances. Current pharmacological therapies, primarily levodopa and dopamine agonists, provide only symptomatic relief and are limited by poor bioavailability, off-target effects, and inability to cross the blood-brain barrier (BBB) effectively. Nanotechnology has emerged as a promising strategy to overcome these limitations by enabling targeted delivery, controlled drug release, and improved BBB penetration. Various nanosystems-including polymeric nanoparticles, lipid-based carriers, metallic nanoparticles, dendrimers, and carbon nanomaterials-have been explored for delivering anti-Parkinsonian agents, neurotrophic factors, antioxidants, and even gene-editing tools. These nanoplatforms not only enhance drug stability and reduce systemic side effects but also hold potential for disease modification by protecting neurons, reducing oxidative stress, and modulating α-synuclein aggregation. Despite encouraging preclinical results, significant challenges remain, including long-term toxicity, immunogenicity, manufacturing scalability, and regulatory uncertainties. Future directions highlight the integration of exosome-based nanocarriers, stimuli-responsive nanoparticles, and CRISPR-loaded nanoplatforms, coupled with AI-guided design, to develop personalized and multifunctional therapies. This review consolidates current advances in nanotechnology-based interventions for PD, emphasizing their potential role in transforming diagnosis, treatment, and disease monitoring, while outlining the barriers that must be addressed to enable clinical translation and improved patient outcomes.

Keywords: *PD, nanotechnology, blood–brain barrier, nanoparticles, targeted delivery, neurodegeneration*.

1. Introduction

PD (PD) is a chronic, progressive neurodegenerative disorder that primarily affects the motor system due to the gradual degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) of the midbrain. First described by James Parkinson in 1817, PD is clinically recognized by its characteristic motor symptoms bradykinesia, rigidity, resting tremor, and postural instability as well as a wide array of non-motor symptoms, such as cognitive decline, mood disorders, sleep disturbances, and autonomic dysfunction. At the molecular level, the disease is strongly associated with the pathological accumulation of misfolded alpha-synuclein protein, forming Lewy bodies within neurons.

PD is the second most common neurodegenerative disorder after AD and represents a significant global health burden. The prevalence of PD increases with age, affecting approximately 1% of the population over 60 and rising to 3% in individuals over 80. As the global population continues to age, the number of individuals living with PD is projected to surpass 10 million by 2030. Despite advances in pharmacological and surgical management, current therapies remain primarily symptomatic and do not halt or reverse disease progression. The long-term impact of PD on quality of life, combined with the increasing prevalence, underscores its clinical and public health significance. The complexity of PD pathology, including the presence of the blood-brain barrier (BBB), mitochondrial dysfunction, oxidative stress, neuroinflammation, and alpha-synuclein aggregation, poses significant challenges for effective drug delivery and disease modification. Traditional pharmacological approaches often fail to achieve adequate therapeutic concentrations in target brain regions and are associated with systemic side effects and limited bioavailability.

Nanotechnology offers a transformative platform for addressing these limitations. Nanoparticles can be engineered to cross the BBB, deliver drugs directly to affected neurons, and release therapeutic agents in a controlled and sustained manner. Moreover, nanomaterials can be functionalized with ligands to enhance target specificity, reducing off-target effects and toxicity. Beyond drug delivery, nanotechnology also enables novel approaches for early diagnosis, neuroprotection, gene therapy, and neuro regeneration. Given these capabilities, nanotechnology holds great promise in revolutionizing the treatment landscape of PD by overcoming traditional therapeutic barriers and opening new avenues for disease-modifying interventions

2 Pathophysiology of PD

PD (PD) is a multifactorial neurodegenerative disorder characterized by a progressive deterioration of motor and non-motor functions. The underlying pathophysiology is complex, involving a cascade of molecular and cellular events that culminate in neuronal death, primarily affecting dopaminergic neurons. While the exact etiology remains unclear, significant advances have identified key pathological hallmarks and contributing mechanisms. Different mechanisms involved in pathogenesis of PD are explained in the fig-1.1

2.1 Dopaminergic Neuron Degeneration

The most defining feature of PD is the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc), a region of the midbrain crucial for modulating voluntary movement. The resultant depletion of dopamine in the striatum disrupts the normal functioning of the basal ganglia circuitry, leading to the classical motor symptoms of PD bradykinesia, rigidity, resting tremors, and postural instability. The loss of these neurons is gradual but irreversible and continues throughout the disease course.

2.2 Role of α-Synuclein and Lewy Bodies

Alpha-synuclein (α-syn), a presynaptic neuronal protein involved in synaptic vesicle regulation, plays a pivotal role in PD pathology. Under pathological conditions, α-syn undergoes misfolding and aggregation, forming insoluble fibrils that accumulate within neurons as Lewy bodies and Lewy neurites hallmark pathological features of PD. These aggregates disrupt cellular homeostasis, impair vesicle trafficking, induce membrane damage, and promote mitochondrial dysfunction. Phosphorylation at serine-129 is commonly observed in aggregated α-syn and is strongly associated with neurotoxicity.

2.3 Neuroinflammation and Oxidative Stress

Neuroinflammation is a central component of PD pathogenesis. Activated microglia and astrocytes release pro-inflammatory cytokines, reactive oxygen species (ROS), and nitric oxide, creating a hostile environment that exacerbates neuronal damage. The continuous release of inflammatory mediators contributes to a vicious cycle of neuronal injury, further stimulating glial activation. Concurrently, increased oxidative stress due to dopamine metabolism, mitochondrial defects, and impaired antioxidant defense mechanisms accelerates dopaminergic neuron degeneration.

2.4 Mitochondrial Dysfunction and Apoptosis

Mitochondria play a crucial role in cellular energy metabolism, calcium homeostasis, and apoptosis regulation. In PD, mitochondrial dysfunction manifests through impaired oxidative phosphorylation, increased ROS production, and reduced ATP generation. These alterations lead to bioenergetic failure and the activation of apoptotic pathways. Additionally, mutations in mitochondrial-associated genes such as PINK1 and Parkin disrupt mitophagy the process of clearing damaged mitochondria—further contributing to neuronal loss. Mitochondrial impairment is both a cause and consequence of α-syn aggregation and neuroinflammation.

2.5 Genetic and Environmental Contributors

While most PD cases are idiopathic, approximately 10–15% are linked to genetic mutations. Genes such as SNCA (encoding α-syn), LRRK2, PARK2 (parkin), PINK1, DJ-1, and GBA have been implicated in familial PD. Mutations in these genes affect protein homeostasis, mitochondrial quality control, lysosomal function, and oxidative stress responses. Environmental factors such as pesticide exposure (e.g., paraquat, rotenone), heavy metals, and head trauma are also associated with increased PD risk. These factors may act synergistically with genetic susceptibility to trigger the disease in vulnerable individuals.

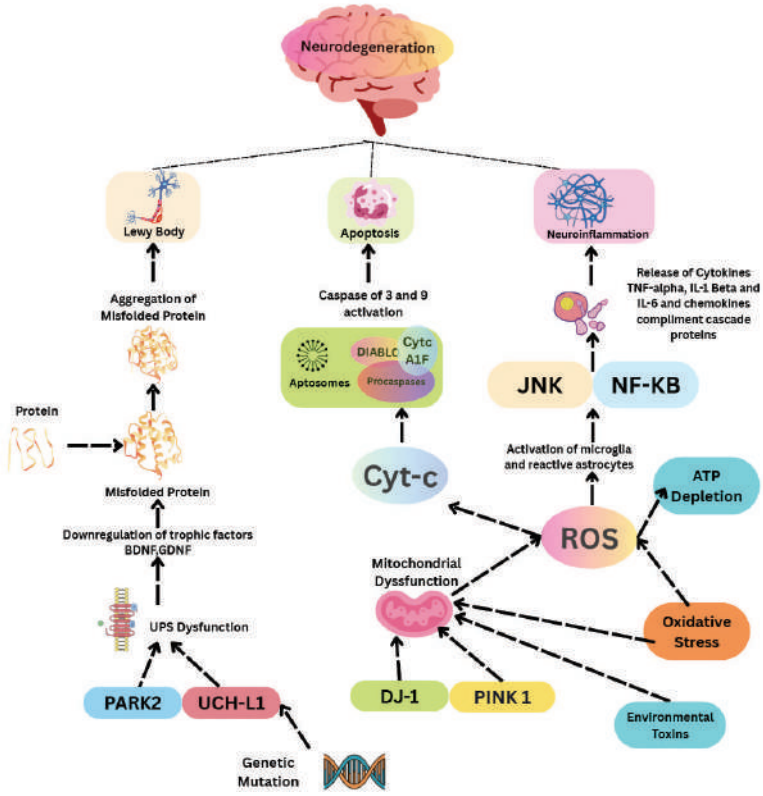

Figure 1.1: Different mechanisms involved in Parkinson disease pathogenesis.

3 Current Therapeutic Approaches and Limitations

Despite significant progress in understanding PD (PD) pathogenesis, current treatment strategies are largely symptomatic and fail to halt or reverse the neurodegenerative process. A combination of pharmacological and non-pharmacological approaches is employed in clinical practice. However, these interventions come with limitations, particularly in terms of long-term efficacy, adverse effects, and challenges in delivering drugs across the blood-brain barrier (BBB).

3.1 Pharmacological Treatments

Levodopa and Dopamine Agonists

Levodopa, the precursor of dopamine, remains the most effective and widely used medication for PD. Co-administered with a peripheral dopa-decarboxylase inhibitor (e.g., carbidopa or benserazide), levodopa replenishes dopamine levels in the striatum and significantly alleviates motor symptoms. However, chronic use is associated with motor complications such as “wearing-off” phenomena and levodopa-induced dyskinesias (LID), which often emerge after 5–10 years of therapy.

Other pharmacologic options include:

- **Dopamine agonists** (e.g., pramipexole, ropinirole) that stimulate dopamine receptors directly.

- **MAO-B inhibitors** (e.g., selegiline, rasagiline) that prevent dopamine breakdown.
- **COMT inhibitors** (e.g., entacapone, opicapone) which prolong levodopa action.
- **Amantadine**, used to manage dyskinesias, and anticholinergics, occasionally prescribed for tremor.

Although these drugs improve symptom control, they do not alter disease progression and may cause adverse effects such as hallucinations, impulse control disorders, orthostatic hypotension, and gastrointestinal issues.

3.2 Deep Brain Stimulation (DBS)

DBS is a surgical intervention used in advanced PD patients who are refractory to medical treatment or experience severe motor fluctuations. Electrodes are implanted in specific brain targets most commonly the subthalamic nucleus (STN) or globus pallidus interna (GPi)—and connected to a pulse generator. DBS modulates neural circuits to reduce motor symptoms and improve quality of life.

While DBS is effective in reducing off-time and medication use, it does not address non-motor symptoms or neurodegeneration. Furthermore, not all patients are suitable candidates. Surgical risks, cognitive decline, and hardware-related complications also pose limitations.

3.3 Challenges with Blood-Brain Barrier (BBB) Penetration

The BBB presents a major obstacle in the treatment of PD. It is a highly selective barrier that restricts the passage of most therapeutic agents, especially large or hydrophilic molecules, into the central nervous system (CNS). As a result, many potentially neuroprotective or disease-modifying agents fail to reach effective concentrations at target sites in the brain.

Current drug delivery systems often require high systemic doses to compensate for low brain penetration, leading to peripheral side effects. Attempts to bypass the BBB through invasive delivery (e.g., intracerebral infusion) are not routinely feasible due to safety concerns and patient burden. Hence, overcoming the BBB remains a critical challenge in PD drug development.

3.4 Lack of Disease-Modifying Therapies

Till date, there are no approved disease-modifying therapies (DMTs) for PD. Existing treatments only manage symptoms without addressing the underlying neurodegeneration. Efforts to target α-synuclein aggregation, mitochondrial dysfunction, oxidative stress, and neuroinflammation have shown promise in preclinical studies but have failed to translate into successful clinical outcomes.

Several factors contribute to this translational gap:

- Heterogeneity of PD pathology, making it difficult to identify universal targets.
- Late diagnosis, often after substantial neuronal loss.
- Inadequate biomarkers, impeding early intervention and tracking therapeutic response.
- Failure of clinical trials to demonstrate significant benefit in disease progression.

As a result, there is a pressing need for innovative therapeutic platforms that can go beyond symptomatic relief and alter the course of PD. In light of these challenges, nanotechnology has emerged as a promising avenue to overcome existing barriers in PD treatment. By enabling targeted drug delivery,

crossing the BBB, and enhancing bioavailability, nanomedicine holds potential to transform the future landscape of PD management.

4 Clinical Challenges in PD

Despite considerable advancements in PD (PD) research and symptomatic therapies, the clinical management of PD continues to face numerous challenges. These obstacles stem from the disease's heterogeneity, progressive nature, and complex symptomatology, all of which limit the effectiveness of current diagnostic and treatment paradigms. The following subsections address key clinical hurdles that complicate early identification, individualized treatment, and long-term disease control. Clinical challenges in PD are mentioned in table 1.1 below.

Table 1.1: Clinical Challenges in Parkinson's Disease (PD) Management

Challenge Category	Description
Early Diagnosis Difficulties	No definitive diagnostic biomarker; diagnosis relies on late-stage motor symptoms after significant neuronal loss; common misdiagnosis from other parkinsonian syndromes.
Non-Motor Symptoms	Significantly impact quality of life; often precede motor dysfunction; commonly include cognitive impairment, mood disorders, sleep disturbances, fatigue, pain, and autonomic dysfunction; poorly addressed by standard therapies.
Medication Side Effects & Tolerance	Chronic dopaminergic medication use leads to motor fluctuations ("wearing-off," dyskinesias); non-motor side effects include hallucinations and impulse control disorders; reduced therapeutic efficacy over time requiring complex regimens.
Progressive Nature & Variability	PD is relentlessly progressive with no disease-modifying therapies; highly individualized progression patterns complicate prognosis and treatment; patients transition to complex states with fluctuating responses and drug-resistant symptoms.

4.1 Early Diagnosis Difficulties

One of the most critical challenges in PD management is the difficulty of early diagnosis. At the time of clinical presentation, more than 50–60% of dopaminergic neurons in the substantia nigra have already degenerated. Early symptoms such as anosmia, REM sleep behavior disorder, depression, and constipation are non-specific and often overlooked or misattributed. There is currently no definitive diagnostic biomarker or imaging modality approved for routine clinical use that can detect PD at its prodromal stage.

Clinical diagnosis still largely depends on patient history and the presence of characteristic motor symptoms, which appear relatively late in the disease process. Misdiagnosis is common in early stages, especially when differentiating PD from other parkinsonian syndromes such as multiple system atrophy or progressive supranuclear palsy. These diagnostic limitations delay therapeutic intervention and may preclude enrollment in disease-modifying clinical trials at a time when neuroprotective strategies would be most effective.

4.2 Non-Motor Symptoms and Quality of Life

While motor symptoms are the defining features of PD, non-motor symptoms (NMS) significantly impact patients' functional status and overall quality of life. These symptoms often precede motor dysfunction by years and may persist or worsen throughout disease progression. Common NMS include:

- Cognitive impairment and dementia
- Depression, anxiety, and apathy
- Sleep disturbances (insomnia, REM behaviour disorder)
- Fatigue and pain
- Autonomic dysfunction (constipation, urinary urgency, orthostatic hypotension)

These symptoms are often underrecognized and undertreated, yet they are major determinants of disability, caregiver burden, and institutionalization. Standard dopaminergic therapies have limited efficacy in alleviating most NMS, and the pathophysiological mechanisms remain incompletely understood. Addressing these multifactorial symptoms requires multidisciplinary care and often fails to keep pace with disease progression.

4.3 Medication Side Effects and Tolerance

Chronic use of dopaminergic medications introduces several treatment-related complications. The most common of these is the development of motor fluctuations, including “wearing-off” phenomena and levodopa-induced dyskinesias (LID) involuntary, erratic, and often disabling movements. These issues emerge in nearly 50% of patients after five years of levodopa therapy.

Additionally, non-motor side effects such as hallucinations, impulse control disorders (e.g., pathological gambling, hypersexuality), and orthostatic hypotension may arise from dopaminergic overstimulation, especially in the elderly. Tolerance to medications also reduces therapeutic efficacy over time, necessitating frequent dose adjustments, polypharmacy, and complex treatment regimens that increase the risk of adverse events and drug-drug interactions.

4.4 Progressive Nature and Individual Variability

PD exhibits highly individualized progression patterns, influenced by factors such as age of onset, genetic background, environmental exposures, and coexisting medical conditions. Some patients remain stable with minimal symptoms for years, while others deteriorate rapidly, developing severe motor and cognitive impairments. This heterogeneity complicates both prognosis and treatment planning. Moreover, PD is a relentlessly progressive disease with no current therapies proven to slow or stop neurodegeneration. As the disease advances, patients often transition from medication-responsive early stages to a more complex state with fluctuating response, drug-resistant symptoms, and multidimensional disability. Tailoring therapy to individual patient needs becomes increasingly difficult, and clinical trial designs struggle to accommodate such variability in outcomes and progression rates. PD poses intricate and evolving clinical challenges that span the spectrum from early detection to advanced-stage management. The failure of current approaches to provide early diagnosis, control non-motor symptoms, maintain long-term drug efficacy, and adapt to patient variability underscores the urgent need for innovative strategies. Emerging technologies such as nanomedicine offer promising avenues to overcome these longstanding barriers in PD care.

5 Role of Nanotechnology: A New Paradigm

1.5.1. Introduction to Nanomedicine in Neurology

Nanotechnology has ushered in a transformative era in medicine, and its application in neurological disorders known as *nano neuro medicine* has particularly gained traction in recent years. Neurological diseases like PD (PD) are notoriously difficult to treat owing to the complexity of the central nervous

system (CNS), the progressive nature of neurodegeneration, and the restrictive architecture of the blood-brain barrier (BBB), which limits the entry of most therapeutics. As the traditional pharmacological armamentarium has reached a plateau in its ability to modify disease progression, nanotechnology offers a new paradigm by introducing precision-engineered nanoscale delivery vehicles that can enhance drug bioavailability, control release kinetics, target specific regions of the brain, and potentially deliver multifunctional payloads including small molecules, peptides, nucleic acids, or even imaging agents.

Nanomedicine operates at a scale of approximately 1–100 nanometers, which is comparable to biological molecules such as proteins, DNA, and cellular organelles. This scale allows for biomimicry and integration into biological systems, enabling nanocarriers to navigate intracellular compartments and cross tight junctions within the BBB. In PD, where degeneration of dopaminergic neurons in the substantia nigra leads to a cascade of motor and non-motor deficits, the ability to deliver drugs directly to the affected neuronal pathways while avoiding systemic toxicity is a key unmet need. Nanotechnology, through its advanced surface chemistry and tunable physicochemical properties, serves as a conduit for crossing this therapeutic threshold.

5.2. Potential of Nanoparticles in Drug Delivery

Nanoparticles (NPs) offer distinct pharmacokinetic and pharmacodynamic advantages over conventional drug formulations. One of the most significant features is their capacity to improve solubility and protect labile drugs from enzymatic degradation in systemic circulation. Many neuroactive compounds, including dopamine and neurotrophic factors, are unstable and rapidly metabolized. Encapsulation within nanoparticles prevents premature metabolism, facilitates transport to the brain, and ensures that an optimal therapeutic concentration reaches the target site. Different types of nanoparticulate systems for drug delivery are mentioned in below fig-1.2.

Nanoparticles also allow versatile drug loading. Depending on the physicochemical properties of the therapeutic agent, NPs can encapsulate hydrophilic compounds in their aqueous core, and hydrophobic agents within their lipid bilayers or polymeric matrix. This flexibility enables delivery of a wide range of agents, including:

- Dopamine and levodopa
- Monoamine oxidase inhibitors (e.g., selegiline)
- Neuroprotective peptides
- Gene-silencing agents such as siRNA and miRNA
- Growth factors (e.g., BDNF, GDNF)

Several types of nanoparticles have been explored in PD therapy, including polymeric nanoparticles, lipid-based systems, metallic/inorganic nanoparticles, dendrimers, carbon-based nanomaterials, and biomimetic vesicles (e.g., exosomes).

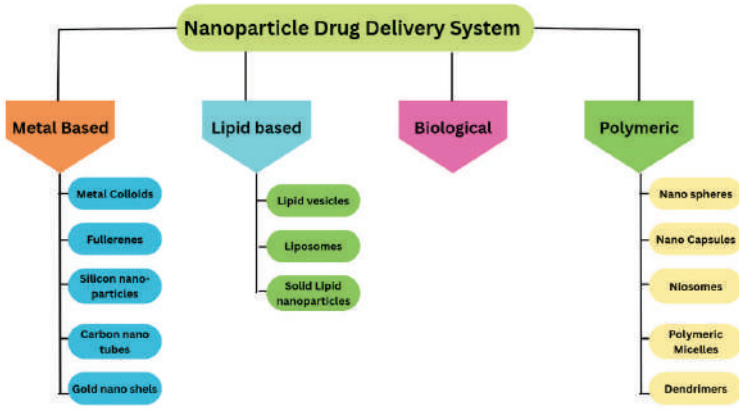

Figure-1.2 Different types of nanoparticulate systems for drug delivery

For instance, PLGA (poly(lactic-co-glycolic acid)) nanoparticles have shown promising results due to their FDA approval, controlled release properties, and ability to be surface-functionalized. Drugs like ropinirole and selegiline have been successfully incorporated into PLGA NPs, resulting in enhanced bioavailability and reduced dosing frequency. Moreover, nanoparticles can co-deliver multiple agents, such as combining levodopa with COMT inhibitors or antioxidants, which enables synergistic pharmacological effects while reducing pill burden and enhancing patient adherence.

5.3. Overcoming the Blood-Brain Barrier with Nanocarriers

The blood-brain barrier (BBB) is composed of tightly joined endothelial cells, astrocyte end-feet, and pericytes, forming a highly selective permeability barrier that prevents the entry of ~98% of small molecules and nearly 100% of large biomolecules. Overcoming this barrier is perhaps the most challenging aspect of drug delivery in neurodegenerative diseases. Different types of methods to overcome BBB are mentioned in below fig1.3. Nanoparticles have emerged as a revolutionary solution for BBB transport through several mechanisms:

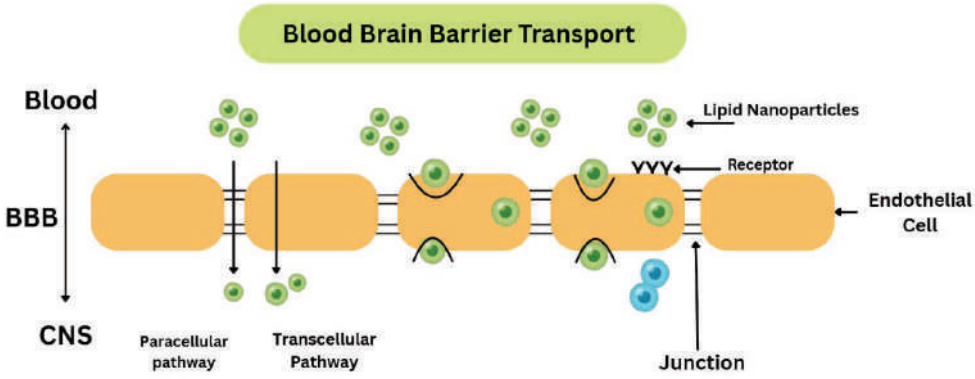

Figure-1.3: Different mechanisms involved in overcoming BBB

i. Receptor-Mediated Transcytosis (RMT)

RMT is one of the most effective strategies used by nanocarriers to cross the BBB. It involves surface modification of nanoparticles with ligands (e.g., transferrin, insulin, lactoferrin, apolipoproteins) that bind to corresponding receptors on the endothelial cells of the BBB. Once bound, the nanoparticle-receptor complex is internalized via endocytosis, transported across the cell, and released on the brain-facing side.

For example, transferrin-conjugated liposomes loaded with levodopa have shown enhanced accumulation in the brain and improved motor function in PD animal models.

ii. Adsorptive-Mediated Transcytosis (AMT)

AMT leverages electrostatic interactions between the positively charged surface of NPs and the negatively charged endothelial membrane. Chitosan and polyethyleneimine (PEI) are commonly used cationic polymers for this purpose. While AMT is less selective than RMT, it offers relatively higher transcytosis efficiency for certain formulations.

iii. Carrier-Mediated Transport (CMT)

CMT exploits endogenous solute transporters like glucose transporters (GLUT1) or amino acid transporters (LAT1). NPs mimicking these substrates or conjugated with analogs can effectively piggyback on transporter systems to gain BBB entry.

iv. Temporary Disruption of BBB

Another method is the temporary and localized opening of the BBB using focused ultrasound (FUS) combined with microbubbles. Although not a direct feature of nanoparticles themselves, this approach can significantly enhance NP delivery if applied concurrently.

v. Intranasal Delivery

This route bypasses the BBB entirely via the olfactory and trigeminal pathways. Nanoparticles administered intranasally have been shown to directly reach the CNS, offering a non-invasive and rapid delivery route. Chitosan-based mucoadhesive NPs and lipid nanoparticles are particularly effective in this application.

5.4. Targeted Therapy and Controlled Release

Targeted drug delivery is a key feature that elevates nanotechnology beyond mere drug encapsulation. Nanoparticles can be engineered to actively home to specific cells or brain regions using ligands, antibodies, or aptamers that recognize disease-specific markers. In PD, targeting the dopaminergic neurons of the substantia nigra or striatal terminals allows for spatially precise drug deposition, maximizing therapeutic efficacy and minimizing off-target toxicity.

5.5. Controlled and Sustained Drug Release

Controlled release is achieved by tuning the physicochemical properties of the nanoparticle matrix, such as:

- Polymer degradation rate (e.g., PLGA degradation through hydrolysis)
- Cross-linking density
- Diffusion coefficients of the encapsulated drug

This enables sustained plasma drug levels, avoiding the peak-trough fluctuations observed with oral levodopa therapy, which contribute to motor complications like dyskinesia. Furthermore, controlled release reduces the frequency of administration, enhancing patient compliance.

5.6. Chronotherapeutic Nano systems

Chronotherapy, aligning drug release with biological rhythms, is another frontier. NPs can be designed for time-dependent release, using pH-sensitive or enzyme-responsive materials that release the drug at optimal therapeutic windows e.g., early morning release of dopamine to counteract PD “off” periods.

5.7 Theranostic Nanoparticles: Combining Therapy and Diagnosis

Emerging research in *theranostics* a fusion of therapy and diagnostics enables real-time monitoring of drug delivery and disease progression. Iron oxide nanoparticles, for example, can be used as MRI contrast agents while also delivering therapeutic payloads. Gold nanoparticles offer both imaging and photothermal properties, making them versatile for multifunctional applications.

In PD, theranostic NPs could help:

- Visualize dopaminergic neuron integrity using MRI
- Track real-time delivery of dopamine analogs
- Monitor progression through biomarker tracking

This integration of therapy and diagnostics represents a leap toward personalized and precision medicine in neurology.

6. Clinical and Preclinical Progress

While most of the nanoparticle-based therapies for PD (PD) remain in the preclinical stage, a growing body of evidence from animal models highlights their therapeutic potential. For instance, selegiline-loaded nanoparticles have demonstrated significantly increased drug accumulation in the brain, resulting in enhanced neuroprotective effects compared to conventional formulations. Similarly, glial cell line-derived neurotrophic factor (GDNF)-loaded nanoparticles have shown the ability to promote the survival of dopaminergic neurons and support axonal regeneration, offering a promising approach to slow or reverse neuronal degeneration. Furthermore, dopamine-conjugated lipid nanoparticles have been found to improve locomotor activity and reduce neuronal apoptosis in PD models, suggesting their efficacy in restoring motor function and preventing further neuronal loss. These encouraging findings reinforce the potential of nanoparticle-mediated drug delivery systems in addressing both the symptomatic and neurodegenerative aspects of PD.

7. Challenges and Future Prospects

Despite the great potential of nanomedicine in treating PD, there are still many important challenges that need to be solved before it can be used safely and effectively in patients. One major concern is **long-term safety**. Some nanoparticles do not break down easily in the body. If these non-degradable particles build up in the brain over time, they might cause toxicity or inflammation, which could harm healthy cells.

Another issue is the **immune response**. Nanoparticles that are not properly coated—such as with materials like polyethylene glycol (PEG) may be seen as foreign by the immune system. This can lead to the particles being quickly removed from the body or cause allergic reactions. Therefore, careful surface design is needed to avoid these problems and help the nanoparticles stay in the body long enough

to work. It also limit the use of nanoparticles. Making nanoparticles with consistent size, shape, surface charge, and drug content is difficult, especially when moving from small laboratory batches to large-scale production. These differences can affect how the particles work and how safe they are, which makes it harder to get approval from health authorities. It is another barrier. Agencies like the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are still developing specific rules for nanomedicines. Without clear guidelines, it is difficult for researchers and companies to bring these new treatments to the market quickly. Looking to the future, scientists are developing **multi-functional and "smart" nanoparticles**. These nanoparticles can respond to changes in the disease environment, such as low pH, oxidative stress, or certain enzymes. This allows the drug to be released only when and where it is needed, which can make treatment more precise and reduce side effects. Another exciting area is the use of nanoparticles for **gene editing**, such as delivering CRISPR/Cas9 systems to brain cells. This could allow scientists to fix faulty genes or stop the production of harmful proteins, possibly treating the root cause of PD rather than just the symptoms. Researchers are also exploring **nanorobots** and **biohybrid systems**. These are advanced types of nanoparticles made by combining synthetic materials with living cells or membranes. They could travel through the body, find damaged areas in the brain, and release drugs exactly where needed. Some may even send feedback about disease activity or treatment effects. In summary, **nanotechnology offers a powerful new approach** to treating PD. It can help overcome problems faced by current drugs, such as poor ability to cross the blood-brain barrier, unwanted side effects, and lack of targeting to the right brain regions. Nanoparticles can carry drugs directly to affected neurons, release them slowly over time, and may even protect or repair brain cells.

Conclusion

Parkinson's disease (PD) is a progressive neurodegenerative condition characterized by oxidative stress, mitochondrial dysfunction, protein misfolding, neuroinflammation, and the loss of dopaminergic neurons. Current dopaminergic treatments only provide symptomatic relief and do not stop disease progression, often leading to long-term motor and non-motor complications. In this regard, nanotechnology has emerged as a revolutionary strategy, introducing nanocarrier systems such as liposomes, niosomes, polymeric nanoparticles, and solid lipid nanoparticles. These systems can bypass the limitations of the blood-brain barrier, improve solubility, stability, and bioavailability, and facilitate targeted and controlled delivery of drugs and bioactive compounds like *Ginkgo biloba* and *Gastrodia elata*. They not only reduce systemic side effects but also enable multi-targeted modulation of PD pathophysiology. Furthermore, their use in diagnostics and theranostics offers potential for early detection and personalized treatment. However, challenges such as large-scale production, long-term safety, immunogenicity, regulatory approval, and cost-effectiveness need to be addressed, along with the necessity for standardized models and thorough clinical validation. In summary, the incorporation of nanomedicine into the management of PD represents a significant shift from merely symptomatic treatment to precise, disease-modifying, and patient-centered approaches, providing hope for enhanced outcomes and quality of life, and potentially paving the way for progress in other neurodegenerative diseases.

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Chapter 2: Traditional Chinese Medicine (TCM) In Neurodegeneration: An Overview

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Many of the major neurodegenerative disorders including Alzheimer's, Parkinsonism, Hungtington's have similar pathological characteristics including generation of reactive oxygen species, aggregation of proteins, neuronal inflammation, increased neurotropic factors. Medications such as levodopa, donepezil for PD and AD offer only symptomatic relief rather a complete cure. Admist all the therapeutic gaps, traditional Chinese medicine (TCM) emerges as a promising complementary option. Many of the recent researches highlights the therapeutic properties of TCM herbs, formulations, decoction etc in alleviating oxidative stress, immunomodulation, neuro restoration, and neuronal regeneration. Further research is required to evaluate the safety, efficacy and long term outcomes of TCM therapy. This chapter involves the TCM concepts, neurodegenerative diseases, clinical findings, future prospectives of TCM in neurodegenerative diseases.

Keywords: *TCM, neurodegenerative diseases, Alzheimer's, Parkinsonism, oxidative stress*

1. Introduction

Neurodegenerative disorders (ND) cause progressive deterioration or death of the neuronal network components. The major causes of almost all illnesses relating to the brain is neurodegeneration[5]. Approximately 3.4 billion individuals worldwide suffer from neurological disorders, particularly neurodegenerative illnesses, which were the primary cause of disability in 2021[5]. AD, PD, multiple sclerosis, Huntington's disease, and amyotrophic lateral disease are among the commonly known neurodegenerative disorders. Series of gradual degeneration in the neuronal network acts as a significant hallmark of these disorders, which eventually results in cognitive and motor decline and behavioral abnormalities (*National Institute of Health Sciences*, n.d.). Alzheimer's disease (AD), one of the common neurological illnesses, and its frequency and severity varies with the increase in age of the patient. Although the disease's etiology is yet unknown, two primary pathological characteristics are mentioned: i) extracellular aggregates of amyloid-beta peptide and ii) hyperphosphorylated Tau protein. The second most reported neurodegenerative disease is PD[3]. Motor related symptoms, such as slowness of movement, muscle stiffness, shaking, and unstable posture, are indicative of Parkinson's disease (PD). The etiology of PD is as follows: i) loss or degeneration of dopaminergic neurons results in stiff muscles and shaking with tremors; ii) formation of Lewy bodies by the buildup of misfolded alpha-synuclein protein (α-syn); iii) inflammation in neurons and oxidative stress; iv) genetic factors; and v) dysfunction of mitochondria, resulting in energy failure[5]. According to recent statistics, millions of individuals worldwide are suffering from neurodegenerative disorders, and this number is projected to double in the next two decades. Current pharmacological treatments offer only symptomatic relief and do not address the underlying causes. Furthermore, the effectiveness of many of these medications is limited by specific adverse effects and the gradual emergence of resistance. Thus, the development of novel therapeutic approaches is imperative, including novel synthetic drugs and herbal or natural remedies. This growing demand is driving researchers to explore alternative approaches that are not only more effective, but also safer and capable of targeting the root mechanisms of neurodegeneration.

Traditional Chinese medicine (TCM) is a medical approach or practice that originated thousands of years ago in China[18]. The key components of TCM are acupuncture, herbal medicine, Tai Chi/Qigong (exercise), cupping/tuina, guasha, bone setting, and dietary therapy. Chinese Herbal Medicine (CHM), acupuncture, and physical therapy (Tai Chi, Tu-nai, and Qi-gong) are the three primary techniques used[19]. Since the early 2000s, TCM was incorporated in the treatment of neurodegenerative diseases, dementia, and age-related illnesses[14]. One of its main benefits is its high efficacy and fewer side effects while acting on several targets to improve the condition. According to the findings of several recent preclinical and clinical investigations, individuals with neurodegenerative illnesses respond well to natural products.

The TCM concepts, mechanisms of action, herbs used in TCM, recent research, integration with Western medicine, and TCM-based neurorestorative therapy in AD and PD. The challenges and future prospects of TCM in neurodegeneration are also discussed in this chapter.

2. TCM concepts relevant to neurodegenerative diseases

The phrase "complementary and alternative medicine" (CAM) refers to medical procedures and products that are not included in the conventional healthcare system[31]. Among CAM, TCM is a major branch. For over 2,000 years, the Chinese community has used TCM to address symptoms such as amnesia, disorientation, sleeplessness, loss of consciousness, cramps, and convulsions[14]. These symptoms are closely linked to aging or age-related illnesses. According to TCM, the term "health" refers to the functional interaction of entities inside the body in response to environmental factors. To restore health, a TCM practitioner seeks to attain a total dynamic balance between Yin and Yang, Qi–Xue, and Zhongs–Fus[16].

According to Chinese medicine theory, the major reasons for the deterioration of the brain/neurodegeneration or health are i) imbalance between *ying* and *yang;* ii) shortage of nutrients to the brain caused by the loss of renal function (shen jing), causing memory loss; iii) impaired function of the heart and spleen, lacking the flow of blood to the brain (Qi), resulting in anxiety, sleeplessness, and a decrease in memory; and iv) blockage and immobility in blood flow (qi) in the surrounding organs[14]. Irregularity in mitochondrial activity is a major signature of neurodegeneration. Microglial activation, oxidative stress, apoptosis, and disruption of cell signaling pathways are some of the ways where mitochondrial failure can result in neurodegeneration[22,12]. There are now several TCM decoctions that have demonstrated effectiveness in improving motor impairment in PD models and recovering memory functions in AD models, including Qingxin Kaiqiao Fang, Danggui Buxue Tang, Jia-Jian-Di-Huang-Yin-Zi decoction, and Bushen-Yizhi formula. These decoctions improve the deterioration of the brain or neurodegeneration[6,7,10,20]. Chinese medicine improves neuronal survival rates in the microenvironment and has positive effects on neurons, showing great promise for use as a treatment for neurodegenerative illnesses.

Additionally, because TCM has synergistic effects on several components, targets, and pathways, it may be further optimized to treat complicated disorders. A few examples of TCM formulations used to treat neurodegenerative diseases are listed in Table 2.1. Many of the formulations and decoctions showed reduced oxidative stress, improved mitochondrial activity, energy production, cognitive function, and anti-apoptotic properties, and reduced mitochondrial swelling.

Table 2.1 TCM formulations used to treat neurodegenerative diseases

FORMULATION	DISEASE	MODE OF ACTION
Dihuang Yinzi	AD, PD	Reduces mitochondrial swelling, increases cognitive function(1)
Da-Bu-Yin-Wan	PD	Increase in mitochondrial mass Increased cellular ATP Increased mitochondrial activity(2)
Huangpu Tongiao capsule	AD	Decreased oxidative stress Reduced mitochondrial death(3)
Yinxing Pingchan Recpie	PD	Increased mitochondrial function Increased mitochondrial enzyme activity(4).
Kaixin Powder	AD	Reduced oxidative stress Reduced mitochondrial swelling(5)
Qingxin Kaiqiao Fang	AD	Increases learning and cognitive function(6).
Wu-Tou decoction	AD,PD	Inhibits microglial activation(7)

3. Mechanism of action in TCM/ Herbal extracts for neurodegenerative diseases

TCM-based therapies for these illnesses have shown several similar positive outcomes, including enhanced neurotrophic factor (NTF) production, neurogenesis augmentation, neuroinflammation suppression, and the removal of aberrant protein aggregates.

The main mechanism includes

- Neuronal regeneration activation
- Increased amount of NTF secretion
- Control of immunomodulation and inflammation in the brain
- Clearence of abnormally aggregated proteins[5]

3.1. Activation of neuronal regeneration

Neurodegeneration is defined as the damage or loss of neurons. The alterations that occur in the brain in various neurological disorders also vary. For instance, neurodegeneration in AD refers to the gradual decrease in neuronal network in the hippocampal region and cerebral cortex, whereas in PD, it only affects dopamine depletion within the substantia nigra. TCM reverses neuronal death and activates neuronal regeneration. Recent studies have shown that TCM activates neuronal regeneration. Research using extracts from Polygonum multiflorum and tetrahydroxy stilbene glucoside in 6-OHDA-induced rats and SH-SY5Y cells with MPP+-induced damage demonstrated that DA neurons were protected[28,10]. Neural stem cells and Astragalus membranaceus-derived polysaccharides, flavonoids, and astragaloside reduce DA neuron degeneration and behavioral abnormalities in mice modelled by MPTP[6]. In mice administered MPTP, extracts from Ganoderma lucidum were shown to have comparable effects[27]. Apart from their anti-apoptotic properties, these extracts also regulated the mitogen-activated protein kinase (MAPK) signalling pathway. P38 kinase, c-Jun N-terminal kinase (JNK), and extracellular signal-regulated kinase (ERK) are components of this pathway, and they also influence downstream targets, such as those that encode the Bcl-2 protein family. The members in the Bcl-2 family regulate cell necrosis mediated by mitochondria, which is a prominent apoptotic route in mammalian cells[5]. This would account for the fact that many herbal treatments and formulations used in TCM cure the neuronal mitochondrial dysfunction.

3.2. Increased Neurotropic factor (NTF) secretion

A class of secreted proteins known as NTFs affects brain cell function in different ways. Numerous studies have examined the critical roles that NTFs play in the development, survival, and homeostasis of the central nervous system. The adult central nervous system (CNS) depends on NTFs for neuronal survival and function, leading to widespread interest in using these factors to treat neurodegenerative disorders. Several *in vitro* and *in vivo* studies have reported that elevated NTF levels reduce neuronal degeneration. The first member of the GDNF family, GDNF, also demonstrated a highly selective NTF for dopaminergic neurons in the midbrain[1,29]. According to a recent study, GDNF injections have been demonstrated to shield dopamine selective neurons within the substantia nigra (SN) of mice and nonhuman primates from axotomy and injury caused by 1 methyl-4 phenyl-1,2,3,6 tetrahydropyridine (MPTP). Likewise, Subsequent research has verified the strong effects of NGF in lesion-induced degeneration models in primates. Neurotrophin (NGF), commonly referred to as neuron survival promoting factor, is the first NTF. Further research has shown that neurotrophic factors, Wnt, Notch, Shh, and other neurogenic pathways can all be activated by TCM active ingredients. TCM-induced neurotrophic factor activation can trigger the three main pathways—MAPK/ERK, PLC, and PDK—downstream of tropomyosin receptor kinase (Trk) receptors. Genes required for neurogenesis are activated when active effector molecules move into the nucleus[1,29].

Studies have shown that Isorhamnetin present in G. biloba helps increase NGF activity and also enhances the neuronal activity in the axonal region. This states that flavones like kaempferol and quercetin including Isorhamnetin may be beneficial in preventing neuronal degeneration and also participate in the neuronal cell differentiation. Another study demonstrates the use of Astragaloside IV, also known as AS-IV, is isolated from the dried root of Astragalus membranaceus (A. membranaceus) which is commonly used in TCM due to its role as an anti- inflammatory agent having antioxidant benefits and cardiac protective properties[27]. Methanolic preparations of A. mongholicus have been shown to counteract the effects of neuronal degeneration and cognitive deficits in the hippocampal region and cerebral cortex of mice when induced with Aβ (25–35)[32]. According to the above-mentioned studies, traditional Chinese medicinal substances generally seem to have neurogenic activity[5].

Table 2.2: TCM active molecules and their effects on neurogenesis.

TCM	CONSITUENTS	ACTION
G. biloba	Isorhamnetin, flavonol aglycones	Increases the activity of NGF(8)
Glycyrrhizae radix	Liquiritin	Potentiate neural regeneration(9)(10)
Radix Puerariae	Daidzein, dihydroxyflavone	Promotes neurogenesis(11)
Astragalus membranaceus	Astragaloside IV (AS-IV)	Reverse cognitive deficits(12)
Acori tatarinowii	Asarones	Potentiates neurogenesis(13)
Rabdosia rubescens	Oridonin, diterpenoid	Activates BDNF,TrKB pathway,activating neurogenesis(14).

3.3. Control of immunomodulation and inflammation in the brain

Neuroinflammation pose a major part in the progression of neuroinflammation. Here the regulation of inflammation and immunomodulation in the brain by various steps which includes,

- In neuroinflammation, peripheral lymphocyte cells infiltrate the CNS and neuronal network thus activating the microglial cells, oligodendrocytes and astrocytes as well.
- Many illnesses, including multiple sclerosis (MS), traumatic brain injury (TBI), Parkinson's disease (PD), and Alzheimer's disease (AD), are characterized by it.
- Restoring homeostasis is the ultimate goal of immunomodulation, which is the capacity to activate or inhibit the immune system.
- The steps for regulating neuroinflammation include inhibiting the activation of microglia, inhibiting oxidative stress, and suppressing proinflammatory pathways, including JAK-STAT/MAPK[5].

Table 2.3: TCM and its effects on immunomodulation and inflammation in the brain.

TCM	EFFECTS
Scutellaria baicalensis	Inhibits proinflammatory pathway NF-κB, MAPK(9)
Ginseng	Regulates cytokine production(16)
Ginkgo biloba	Reduces oxidative stress, alleviates mitochondrial activity(8)
Rhizoma Acori Tatarinowii α/β-asarone and oil	NTF secretion increases, prevents oxidative stress (13)
Psoralea corylifolia Corylin	Reduces neuroinflammation(17)

3.4. Clearence of abnormally aggregated proteins

A significant factor in the development of neurodegeneration may be the clumping of misfolded proteins, as evidenced by the detection of inclusion bodies with aberrantly aggregated proteins in many neurological conditions. Parkinson's disease is characterized by the intraneuronal growth of inclusions called Lewy bodies that appear in the substantia nigra. These inclusions are primarily composed of misfolded α-syn protein. Tau protein, which typically strengthens microtubules exhibits hyperphosphorylation in Parkinsonism-plus disorders such Corticobasal Degeneration (CBD) and Progressive Supranuclear Palsy (PSP). In this abnormal state, it aggregates into pathological structures, including neurofibrillary tangles, tufted astrocytes in PSP, and astrocytic plaques in CBD. From the above-mentioned theories, it is understood that the elimination of abnormal protein aggregates can alleviate PD and AD. Therefore, the reduction of abnormal protein aggregates is a promising therapeutic strategy for AD and PD[21].

4. Herbs in TCM for treating neurodegenerative diseases

Herbs and herb-related formulations are involved in TCM treatments because of their efficacy and reduced adverse effects. The following herbs are recommended to help with memory retention: Gouqi (*Fructus Lycii*), Fuling (*Poria*), Gancao (*Radix Glycyrrhizae*), Shichangpu (*Rhizoma*), and Yuanzhi (*Radix Palygalae*), Renshen (*Radix Ginseng*), and Hehuanpi (*Cortex Albiziae*). Another use of Acori Tatarinowii is to enhance cognitive function. *Ginkgo biloba, Alpinia oxyphylla, Radix Notoginseng, Panax ginseng, Rhodiola spp., and Psoralea corylifolia* are among the herbs that are helpful in treating AD. PD models are treated with *Astragalus, Polygonum multiflorum, Acanthopanax, Achyranthes bidentata*, and Radix[5,14].

Table 2.4 shows examples of a few herbs involved in TCM and their actions.

Herbs	Action
Radix Notoginseng	Improves cognitive function(18)
Panax ginseng	Improves cognitive function,reduces protein aggregates(19)
Rhodiola spp	Improves cognitive function and mitochondrial activity(24)
Psoralea corylifolia	Cognitive performance is improved(17)
Radix Glycyrrhizae	Reduces protein aggregation,oxidative stress and neuronal degeneration(10).

5. TCM-Based Neurorestorative Therapy for PD

5.1. Overview of TCM in PD

Traditional Chinese Medicine (TCM) has a long history of application in chronic neurological illnesses. Unlike conventional medications that usually act on single molecular targets, TCM treatments—comprise of herbal formulas, acupuncture, and moxibustion thereby utilizing multi-target mechanisms. Unlike conventional drugs that primarily focus on symptomatic relief, TCM aims for "neurorestoration," which includes preserving dopaminergic neurons, promoting neural repair, reducing neuroinflammation, and enhancing protein clearance[24]. Zhang and colleagues emphasized that TCM interventions can protect neurons and regulate inflammation in neurodegenerative conditions. In practice, CHM is often combined with standard dopaminergic therapy. One large hospital-based analysis reported that nearly 70% of PD patients in China used CHM in conjunction with conventional treatment, demonstrating both cultural preference and perceived therapeutic benefit[48].

5.2. Herbal Formulations and Neuroprotection

Several herbal formulas have shown effective neurorestoration effects. *Buyang Huanwu Decoction*, a classic preparation designed to "invigorate Qi" and improve circulation, was shown in animal studies to enhance dopaminergic neuron survival by regulating metabolic and gene-expression pathways[41]. Another example is *Zishenpingchan granules*, a patented formula created by Professor Hu in Shanghai. A randomized controlled trial demonstrated that combining Zishenpingchan with levodopa significantly reduced dyskinesia, motor complications, and non-motor symptoms compared to placebo[46]. Systematic reviews further support improvements in motor function and gait among PD patients treated with this preparation[42]. In addition to formulas, individual herbs such as *Panax ginseng*, *Astragalus membranaceus*, *Gastrodia elata*, and *Pueraria* extracts contain bioactive molecules like baicalin, astragaloside, catalpol, and procyanidins. These compounds have been shown in preclinical models to protect midbrain neurons against toxin-induced injury, particularly in MPTP models of PD[40,45]. Notably, licorice root extract has been tested in a pilot clinical trial, where it improved motor symptoms without causing significant side effects.

5.3. Mechanisms of Neurorestoration

The therapeutic actions of TCM in PD contribute to its capability in targeting several cellular pathways. Antioxidant activity is one of the most studied mechanisms. Many herbs and formulations neutralize free radicals while enhancing endogenous defense systems such as superoxide dismutase (SOD) and glutathione. A study reported that herbal compounds, including baicalein and ginsenosides, markedly reduced oxidative stress in PD models. Similarly, procyanidins from *Vitex* species were found to prevent oxidative injury and improve neuronal survival[59]. Another major pathway is the reduction of neuroinflammation. Numerous CHM formulations suppress pro-inflammatory cytokines including TNF-α and IL-1β and prevent microglial activation. A study highlighted that these effects occur alongside inhibition of mitochondrial dysfunction, apoptosis, and protein aggregation[43]. Additionally, acupuncture and certain herbal compounds have been observed in promoting the signaling and stimulation of factors such as brain-derived neurotrophic factor (BDNF), which further supports synaptic plasticity and neuron survival[49]. TCM agents may also facilitate autophagy, promoting the clearance of toxic α-synuclein aggregates thus contributing in progression of parkinsonism[44].

Recently, research has also explored the gut–brain axis. Studies suggest that TCM formulations can alter gut microbiota composition and metabolite production, thereby strengthening the intestinal barriers and reducing gut-derived inflammation. This indirect protection of the nigrostriatal pathway offers a new perspective on how TCM contributes to PD management[17]. Altogether, TCM therapies appear to exert a combination of antioxidative, anti-inflammatory, neurotrophic, and microbiome-regulating actions, which together provide a holistic protective effect against neurodegeneration.

5.4. Preclinical and Clinical Evidence

Studies supporting the role of TCM in neurorestoration have also been found evidently. In animal experiments, herbal formulas such as *Liuwei Dihuang Wan* demonstrated neuroprotective properties by evident reduction in oxidative stress and increase in neuronal enzyme activity. Clinical trials also report encouraging findings. Study showing meta-analysis of 23 randomized controlled trials ($n \approx 1465$) showed that combining CHM with conventional medication significantly improved Unified PD Rating Scale (UPDRS) scores across motor and daily living subscales compared with medication alone[48]. Importantly, this combination therapy was well tolerated, whereas CHM monotherapy showed variable outcomes. Smaller pilot trials have also provided evidence for specific formulas. For example, *Jiawei Liu Jun Zi Tang* improved motor complications and quality-of-life measures in PD patients[45]. Adverse effects were generally mild, with safety profiles comparable to placebo. Although some studies suffer from small sample sizes and methodological heterogeneity, more recent double-blind and placebo-controlled trials continue to demonstrate the potential of TCM in improving both motor and non-motor outcomes in PD[70,42]. Collectively, the available evidence suggests that TCM-based neurorestorative therapy is a promising adjunct to conventional treatments and warrants further investigation in large-scale studies.

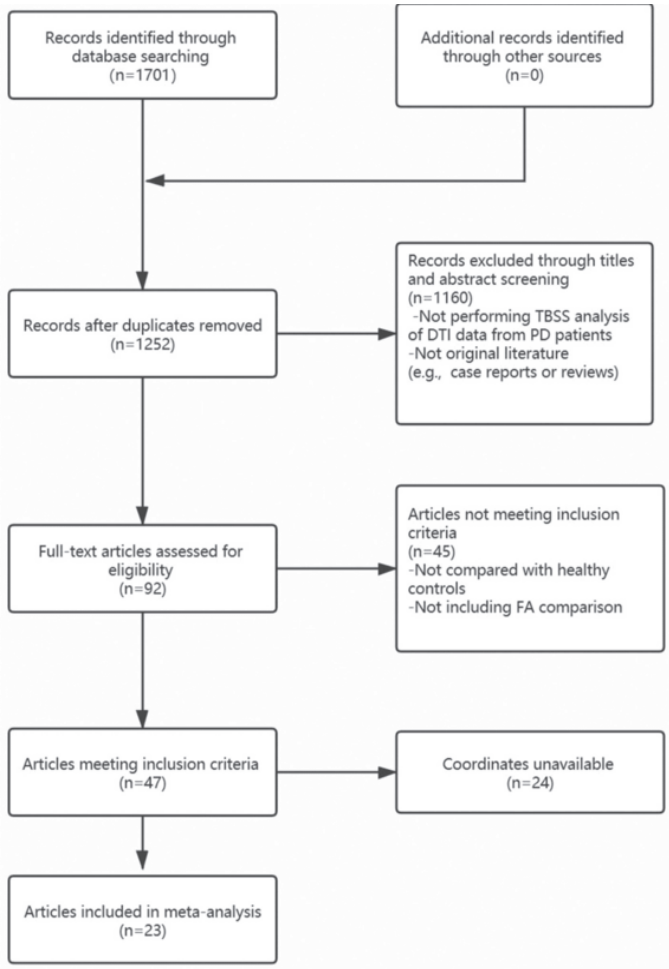

Figure 2.1. Wei, X., Yin, Z., Li, Y., Zhang, J., Zhao, J., & Li, H. (2021). *Flow chart demonstrating the various PD (PD) studies*. Figure represents, meta-analysis study performed using diffusion tensor imaging techniques by tract-based statistical techniques demonstrating white matter anomalies in Parkinson's disease patients. *Frontiers in Aging Neuroscience*, *13*, 659.

6. Acupuncture & Moxibustion

6.1. Traditional Context and Clinical Use

Acupuncture and moxibustion have been considered as one of the essential elements in Traditional Chinese Medicine (TCM) for centuries. In the context of PD (PD), these therapies are viewed as methods to “move Qi,” reduce stagnation, and nourish the liver and kidney, which are considered central to motor function in TCM theory. Acupuncture involves the insertion of thin needles into specific acupoints, while moxibustion uses the burning of dried *Artemisia vulgaris* (mugwort) near or on the skin to stimulate circulation and energy flow. In modern clinical practice, patients with PD frequently seek acupuncture as a complementary therapy, often in combination with standard medications, to provide both motor and non-motor related symptomatic relief[50].

6.2. Mechanisms of Action

Research has shed light on how acupuncture and moxibustion may exert neuroprotective effects. Animal studies suggest that acupuncture activates multiple biological pathways, including the overstimulation of neurotrophic factors such as BDNF, altering of neurotransmitters, and enhancement of autophagy[54]. Stimulation of points such as GB34 and LR3 is seen to prevent the dopamine depletion by activating the Akt–mTOR–BDNF signaling cascade, thereby improving neuronal resilience[65]. Electroacupuncture, in particular, appears to reduce neuroinflammation by suppressing pro-inflammatory cytokines and restoring synaptic balance.

Moxibustion, while less studied, has shown potential in animal models. It helps in maintain dopaminergic neurons by altering the oxidative stress levels which in turn results in limiting of iron absorption (ferroptosis) causing cell death linked to PD pathology[57]. Together, these therapies appear to act through antioxidative, anti-inflammatory, and neurotrophic mechanisms, aligning with the multifaceted pathology of PD.

6.3. Evidence for Acupuncture in PD

Clinical studies provide growing evidence that acupuncture can improve PD outcomes when used alongside medication. A systematic review, reported that acupuncture combined with dopaminergic therapy resulted in a marked increase in motor scores scaled using Unified PD Rating Scale [UPDRS] in comparison to medication alone[52]. A network meta-analysis of 17 trials found that bee-venom acupuncture produced the most notable motor improvements among the various acupuncture modalities studied[53].

Beyond motor symptoms, acupuncture has also been reported to improve non-motor related issues such as sleep disturbances, depressive actions, and anxiety[56]. In a recent randomized controlled trial, electroacupuncture combined with levodopa led to better overall motor function and improved their living than levodopa alone[55]. Importantly, adverse events were generally mild, such as mild bruises or redness along with swelling and pain at the site of injection, with no serious complications reported[51].

6.4. Evidence for Moxibustion in PD

Compared to acupuncture, research on moxibustion in PD remains limited. However, emerging findings are promising. For example, a study demonstrated in an MPTP mouse model that moxibustion reduced motor deficits by inhibiting ferroptosis and improving mitochondrial function[57]. Early clinical reports also suggest that moxibustion may improve gait and rigidity, although large-scale randomized controlled trials are still lacking[55]. Nevertheless, its long-standing use in TCM and favorable safety profile make it an appealing adjunct therapy worthy of further investigation.

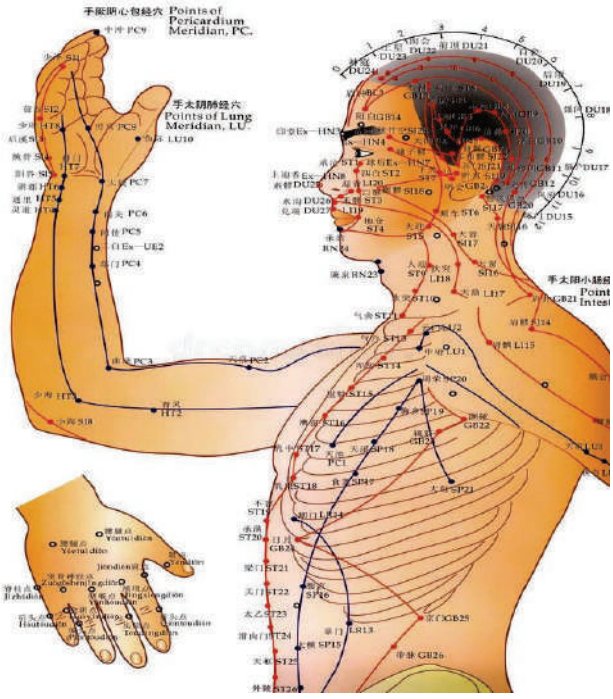

Figure 2.2: Dreamstime. (n.d.). Figure describes the meridian chart in a female body demonstrating the major acupuncture points and meridians along with its direction of stimulation [Vector illustration]. Dreamstime. Retrieved August 17, 2025, from https://www.dreamstime.com/illustration/acupuncture-chart.html .

7. Mechanistic Insights from Modern Research

7.1. Neurobiological Mechanisms of TCM in PD

Modern biomedical studies have begun to uncover the molecular and cellular mechanisms by which Traditional Chinese Medicine (TCM), acupuncture, and herbal remedies exert their effects in PD (PD). Unlike conventional drugs that often target a single receptor or pathway, TCM interventions tend to work in a multi-target manner, which may be advantageous given the multifactorial pathology of PD.

One of the most widely reported mechanisms is antioxidant activity. Compounds such as baicalin, ginsenosides, and astragaloside significantly reduce oxidative stress in dopaminergic neurons, thereby preserving mitochondrial integrity[59]. Similarly, acupuncture has been shown to increase superoxide dismutase (SOD) activity and enhance glutathione levels, which helps neutralize free radicals[62].

7.2. Neuroinflammation and Immune Modulation

Chronic microglial activation and neuroinflammation play a central role in PD pathology. TCM formulations and acupuncture both demonstrate anti-inflammatory properties by downregulating the inflammatory mediators such as TNF-α, IL-1β, and IL-6, while stimulating the release of anti-inflammatory agents[24]. For example, licorice flavones suppress NF-κB signaling, thereby reducing

neuroinflammatory cascades. This dual regulation of immune pathways contributes to a neuroprotective environment[43].

7.3. Neurotrophic and Synaptic Plasticity Pathways

Another important mechanism is the **upregulation of neurotrophic factors**. Acupuncture, particularly electroacupuncture, has been shown to enhance brain-derived neurotrophic factor (BDNF) and its receptor TrkB, which are critical for neuronal survival and synaptic plasticity[65]. Similarly, herbal extracts such as catalpol stimulate BDNF and glial-derived neurotrophic factor (GDNF), further supporting dopaminergic neuron survival

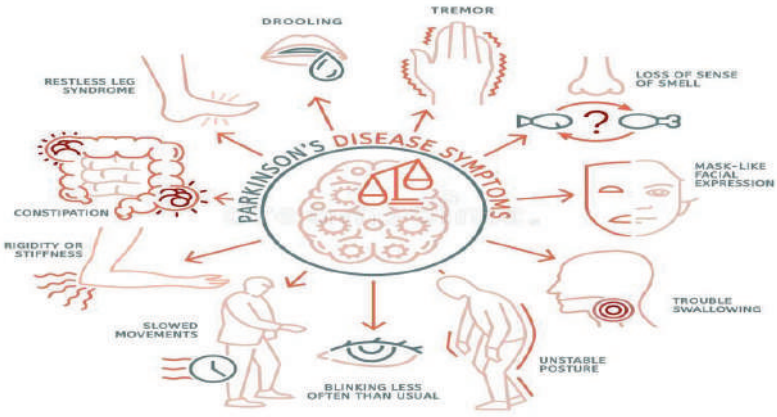

Figure 2.3. PD symptoms infographic, including mental impairment, posture instability, rigidity, and drooling. *Editable vector illustration in line style isolated on a white background.* Reprinted from *Dreamstime* (Royalty-Free), discovered via Dreamstime's "PD infographic" collection. Retrieved from https://www.dreamstime.com/illustration/parkinsons-disease-infographic.html

7.4. Protein Clearance and Autophagy

Accumulation of misfolded α-synuclein is a pathological hallmark of PD. TCM compounds like puerarin and ginsenoside Rg1 promote autophagy, thereby facilitating clearance of toxic protein aggregates[63]. Electroacupuncture has also been linked to the activation of autophagic pathways, which may help reduce Lewy body formation and restore neuronal homeostasis.

7.5. Gut–Brain Axis Regulation

Emerging research highlights the gut–brain axis as a critical target in PD. Altered gut microbiota composition has been linked to motor and non-motor symptoms. TCM herbal formulas modulate gut microbial balance, enhance formation of shorter-chain fatty acids, thereby maintaining the intestinal barrier function[42]. By influencing peripheral and central immune responses, these changes may indirectly protect the nigrostriatal pathway.

8. Research Findings and Evidence

8.1. Overview of Current Evidence

Research into the role of Traditional Chinese Medicine (TCM), acupuncture, and herbal formulations in PD (PD) has expanded significantly over the past two decades. Numerous **preclinical animal studies** and **human randomized controlled trials (RCTs)** suggest that these therapies can reduce both motor and non-motor symptoms, enhance neuroprotection, and improve overall quality of life when used alongside standard pharmacological treatments[71]

8.2. Clinical Trials and Meta-Analyses

A meta-analysis of 23 clinical trials involving more than 1,400 patients reported that patients receiving TCM-based formulas in combination with levodopa recorded significant scores in Unified PD Rating Scale (UPDRS) in comparison to the group treated with levodopa alone[71]. Similarly, another study demonstrated that Zishenpingchan granules significantly improved gait and reduced motor complications[70].

Acupuncture has also been extensively studied. Another study reviewed randomized controlled trials and found that acupuncture, especially electroacupuncture, produced measurable improvements in motor function, non-motor symptoms, and quality of life[68]. Importantly, adverse events were mild and transient, indicating that these therapies are generally safe as adjunctive treatments[66].

8.3. Emerging Evidence for Non-Motor Symptoms

Beyond motor control, non-motor symptoms such as depression, anxiety, constipation, and sleep disturbances significantly affect the daily activities in PD patients. A systematic review by Huang, showed that TCM interventions help in management of non-motor symptoms, with particular improvements in sleep quality and mood regulation[42]. These findings suggest that TCM may address aspects of PD not fully managed by conventional drugs.

8.4. Limitations and Research Gaps

Despite encouraging results, existing research has notable limitations. Many RCTs have **small sample sizes**, short follow-up durations, and methodological variability (different TCM formulas, acupuncture points, or dosages). Blinding is often difficult in acupuncture studies, raising concerns about placebo effects. Moreover, few large-scale multicenter trials have been conducted, limiting the generalizability of findings[45].

Another challenge is standardization: TCM is inherently individualized, and herbal compositions may vary across practitioners and regions. This makes it difficult to replicate studies or establish universal guidelines. Future research should focus on **multicenter RCTs with standardized treatment protocols**, long-term outcome assessments, and integration of biomarkers (e.g., imaging, microbiome profiles) to provide mechanistic validation.

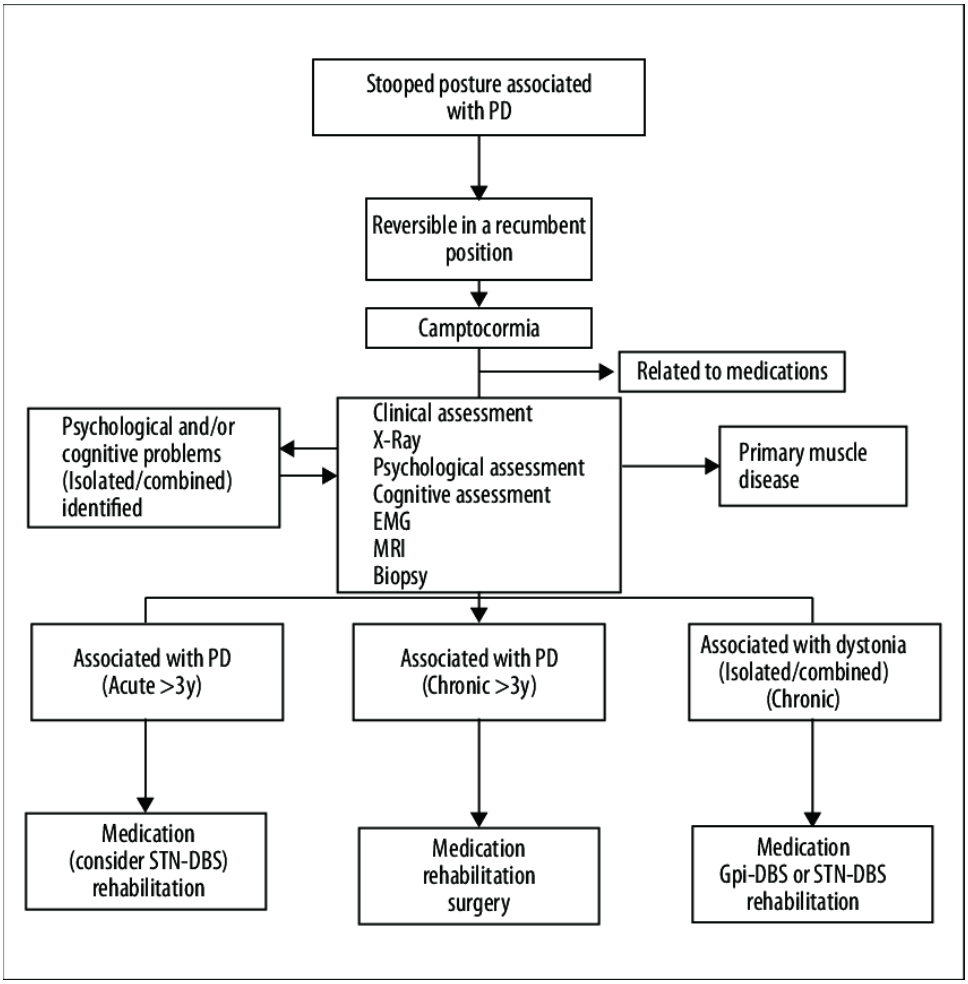

Figure 2.4. Flow diagram showing the procedures for diagnosing and treating PD–associated camptocormia. Adapted from *The Study of Subthalamic Deep Brain Stimulation for Parkinson Disease-Associated Camptocormia*, by S. Liang, Y. Yu, H. Li, & H. Yang, 2020. *Medical Science Monitor*, *26*, e923420. CC BY-NC-ND 4.0. Retrieved from ResearchGate.

9. Challenges and Future Perspectives

Traditional Chinese Medicine (TCM) has shown encouraging promise in addressing neurodegenerative diseases such as PD (PD), yet significant barriers remain before its therapies—especially herbal interventions like *Ginkgo biloba*—can be integrated into mainstream neurology. Understanding these challenges is crucial to designing a framework for future research and clinical application.

9.1. Standardization and Quality Control

One of the most pressing issues in TCM research is the lack of standardized herbal preparations. Different sources, growing conditions, and extraction techniques often lead to significant variability in the chemical composition of herbal remedies[80]. For instance, the concentration of ginkgolides and

bilobalide in *Ginkgo biloba* extracts may differ greatly depending on the preparation method, making it difficult to reproduce results across studies[74]. This lack of consistency complicates both laboratory research and clinical application, as physicians require reliable and standardized drug products adhering to patient compliance and effective treatment plans.

9.2. Safety Concerns and Herb–Drug Interactions

Another major challenge involves safety concerns, particularly herb–drug interactions. *Ginkgo biloba* is widely used as an adjuvant therapy in addition to drugs like levodopa in PD management. However, ginkgolides act as platelet-activating factor antagonists, which upon combining with anticoagulants or antiplatelet agents results in increased risk of bleeding in individuals[73]. Furthermore, long-term use of unregulated herbal mixtures can expose patients to hepatotoxic or nephrotoxic compounds. Establishing rigorous pharmacovigilance frameworks and conducting systematic safety assessments will be essential for widespread adoption of TCM-based therapies.

9.3. Limited Clinical Evidence

Despite centuries of empirical use, the scientific evidence supporting TCM interventions in PD remains limited. Many clinical studies suffer from small sample sizes, methodological inconsistencies, and lack of double-blind randomized controlled trials (RCTs)[77]. While meta-analyses have indicated potential improvements in motor and non-motor symptoms with herbal adjuncts, the heterogeneity of studies prevents drawing definitive conclusions[79]. This gap underscores the urgent need for large-scale, high-quality RCTs that assess both efficacy and safety.

9.4. Integration with Western Medicine

The addition of TCM with Western medical systems proposes both opportunities and obstacles. On one hand, combining conventional dopaminergic therapy with neuroprotective herbal interventions could make up a more promising and effective approach in PD treatment[72]. On the other hand, the biomedical community often remains sceptical due to the lack of mechanistic clarity and variability in study quality. Bridging this gap will require translational research that aligns TCM theories (such as Qi regulation) with molecular mechanisms measurable in modern neuroscience, including oxidative stress pathways, mitochondrial function, and neuroinflammation[76].

9.5. Regulatory and Ethical Challenges

Herbal medicines are subject to widely different regulatory frameworks across the world. In China, TCM is officially integrated into healthcare policy, whereas in many Western countries herbal remedies are categorized as dietary supplements, with limited oversight regarding safety and efficacy[78]. This discrepancy poses barriers to international collaboration and clinical adoption. Ethical challenges also arise when conducting clinical trials involving vulnerable populations, such as elderly patients with PD, where informed consent and cultural sensitivity must be carefully addressed.

9.6. Future Perspectives

Looking ahead, several strategies could strengthen the role of TCM in neurodegenerative disease management:

1. **Standardized Formulations:** Development of globally accepted quality-control standards for herbal extracts like *Ginkgo biloba* will be crucial for reproducibility and clinical reliability.
2. **Systems Biology and Network Pharmacology:** Emerging tools such as multi-omics analysis and computational modelling can help decode the multi-target mechanisms of TCM herbs, aligning them with modern biomedical frameworks[75].
3. **Personalized Medicine:** TCM's strength lies in individualized diagnosis based on pattern differentiation (Zheng). Integrating this with biomarker-driven stratification may enable tailored therapeutic approaches for PD patients.
4. **Collaborative Clinical Trials:** Future research should prioritize multinational RCTs with robust methodology, focusing on combined therapies (e.g., *Ginkgo biloba* plus levodopa) to evaluate both symptomatic relief and disease-modifying potential.
5. **Global Policy Integration:** Building consensus among policymakers, clinicians, and researchers is vital to harmonize regulatory systems and ensure patient access to safe, evidence-based TCM treatments.

Conclusion

Traditional Chinese Medicine (TCM) provides a comprehensive and multi-faceted strategy that effectively tackles the intricacies of neurodegenerative diseases, such as PD, AD, and similar ailments. In contrast to standard single-target treatments, TCM formulations abundant in bioactive phytochemicals and frequently used in synergistic combinationsoffer neuroprotection through their antioxidant properties, anti-inflammatory actions, stabilization of mitochondria, regulation of neurotransmitter levels, and modulation of apoptotic pathways. The information presented in this chapter highlights that TCM is not just an adjunct therapy but can also function as a strategic and scientifically validated treatment option in managing neurodegeneration. Significantly, contemporary pharmacological research and nanotechnology-driven delivery systems are starting to confirm and enhance the therapeutic potential of traditional TCM herbs like *Ginkgo biloba*, *Gastrodia elata*, Panax ginseng, and *Curcuma longa*. This fusion of traditional wisdom with modern biomedical advancements opens the door to more targeted, effective, and patient-focused neurotherapies. In summary, TCM stands as a pivotal frontier in the research and treatment of neurodegenerative diseases. Its enduring principles, when integrated with current molecular understanding and advanced delivery methods, promise to revolutionize patient care-from merely managing symptoms to achieving genuine disease modification. The future of neurotherapeutics may hinge on this integrative approach, where ancient knowledge and contemporary science unite to provide solutions "from bench to bedside and beyond."

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Chapter 3: Unveiling the Role of *Ginkgo biloba* & *Gastrodia elata* in Neurodegeneration: Pharmacognosy, Phytochemistry, and Therapeutic Insights

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Abstract

Neurodegenerative disorders, continue to challenge the limits of modern medicine due to their progressive and multifactorial nature. While existing treatments offer symptomatic relief, they often fall short of addressing the root causes or halting disease progression. In this context, traditional medicinal plants like *Ginkgo biloba* and *Gastrodia elata* have drawn significant attention for their potential neuroprotective roles. This chapter explores the pharmacognostic identity, chemical constituents, and therapeutic promise of these two herbs. *Ginkgo biloba*, known for its unique fan-shaped leaves, is rich in flavonoids (quercetin and kaempferol) and terpene lactones (ginkgolides A, B, and C, and bilobalide), compounds that protect neurons through antioxidant, anti-inflammatory, and mitochondrial-supporting actions. *Gastrodia elata*, traditionally used in Chinese medicine, contains gastrodin, vanillin, parishin, and related phenolics that help modulate neurotransmission, reduce oxidative stress, and improve neuronal function. Both plants show promising results in laboratory studies, especially in models of PD. Standardized extracts like EGb 761 from *Ginkgo* and gastrodin from *Gastrodia* are being investigated for their ability to support brain health and complement conventional treatments. Despite promising clinical findings, challenges persist in bioavailability, dosing optimization, and consistent therapeutic outcomes. Innovations like nanocarriers, phospholipid complexes, and cyclodextrin inclusion have shown potential to enhance efficacy. This chapter combines traditional knowledge and modern scientific advances to showcase the neuroprotective potential of *Ginkgo biloba* and *Gastrodia elata*.

Keywords: Bioavailability Enhancement, *Gastrodia elata*, *Ginkgo biloba*, Neurodegeneration, Neuroprotection, Phytochemistry.

1. Introduction

1.1 Global Burden & Understanding Neurodegenerative Disorders

Global Burden of Neurodegenerative Disorders (NDs): It is becoming more widely acknowledged that NDs are a major global public health concern, and over the coming decades, this burden is expected to increase. Although infectious neurological illnesses have decreased over the past 30 years, the number of deaths has risen by 39%, and the number of disability-adjusted life-years (DALYs, which are the sum of years of life lost and years lived with disability) has increased by 15%. The burden primarily falls on low-income and middle-income nations [1]. Different NDs' proportionate contributions to the total burden of neurological illnesses are displayed in figure 1. According to a significant study published in The Lancet Neurology, over 3 billion people globally suffered from a neurological disorder in 2021. Data from the Global Burden of Disease (GBD), Injuries, and Risk Factor Study (GBD) 2021 were analyzed with assistance from the World Health Organization (WHO). The most common cause of illness and impairment in the world today is neurological disorders. Since 1990, there has been an 18% increase in the total number of neurological diseases that result in impairment, illness, and premature mortality (often referred to as disability-adjusted life years, or DALYs). High-income countries have up to 70 times more neurological professionals per 1,000,000 people than low- and middle-income countries, despite the fact that over 80% of neurological deaths and health losses occur in these countries. The rate of neurodegenerative disorders has reached crisis levels. Neurological disorders now account for 9 million deaths each year, making them the largest cause of death and disability combined [2, 3].

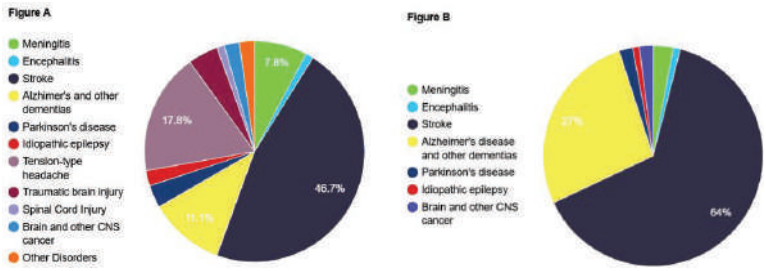

Figure 3.1: Proportions of NDs' disability-adjusted life years (A) and deaths (B) according to information from Feigin and associates.

Neurodegenerative Disorders: A wide range of chronic, progressive illnesses known as neurodegenerative disorders (NDs) are characterized by the progressive loss of neuronal structure or function, which frequently leads to the death of the affected neurons. These conditions primarily impact the brain and spinal cord, resulting in gradual deficits in a wide range of neurological processes, including mobility, cognition, and behavior [4]. The aberrant buildup of misfolded proteins in neurons and glial cells, which disrupts cellular processes and causes neuronal death, is a defining feature of the majority of NDs [5]. Huntington's disease (HD), Parkinson's disease (PD), Alzheimer's disease (AD), Prion disease, spino-cerebellar ataxia (SCA), and spinal muscular atrophy (SMA) are a few major NDs [6].

Causes of Neurodegenerative Disorders (NDs):

- **Progressive Neuronal Loss:** What sets these diseases apart from acute brain traumas or static lesions is the persistent and specific loss of neuronal populations. The loss frequently affects certain functional or anatomical systems, leading to unique clinical symptoms [4, 6].
- **Proteinopathies:** The hallmark of neurodegenerative diseases is the aberrant accumulation and aggregation of misfolded proteins like tau, α-synuclein, amyloid-beta, TDP-43, or huntingtin. These inclusions cause toxicity, interfere with cellular functions, and have the ability to propagate throughout the brain system like prion disease [7, 8].

- **Impaired Cellular Mechanisms:** Decreased energy production, oxidative stress, toxic accumulation, and decreased cell-to-cell communication are the outcomes of disturbances in important processes such as mitochondrial activity, axonal transport, autophagy, and protein clearance [9, 10].

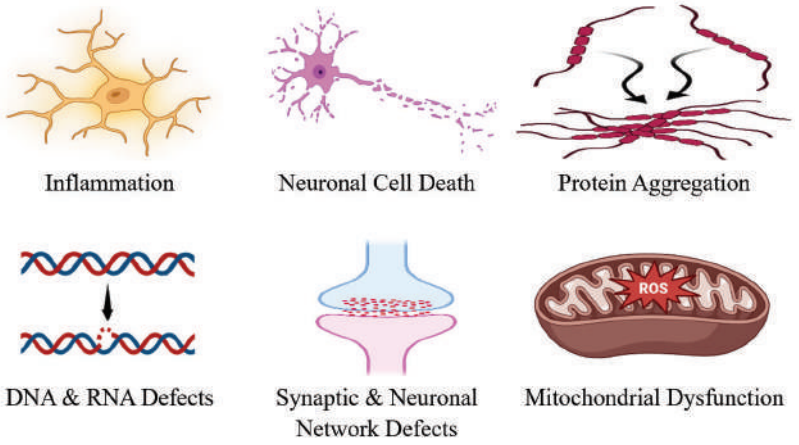

Figure 3.2: Signatures of Major Neurodegenerative Disorders. (adapted from "Hallmarks of neurodegenerative diseases", "Created with BioRender.com").

Common Types of Neurodegenerative Disorders:

- **AD (AD):** AD is a progressive, multifactorial dementia biologically defined by extracellular β-amyloid plaques and intracellular hyper-phosphorylated tau neurofibrillary tangles that drive synaptic dysfunction, neuronal loss and global cortical atrophy, leading to amnestic cognitive decline that typically begins after age 65 years [11,12].
- **PD (PD):** PD is a motor disorder characterized by loss of dopaminergic neurons in the substantia nigra pars compacta, reduced striatal dopamine, and widespread intraneuronal buildup of misfolded α-synuclein (Lewy bodies), leading to bradykinesia, rigidity, resting tremor, postural instability, and various non-motor symptoms [13].
- **Prion Disease:** Human prion diseases are rapidly progressive, invariably fatal encephalopathies caused by the misfolding of cellular prion protein into an infectious β-sheet-rich isoform that self-propagates, yielding spongiform degeneration, gliosis and neuronal loss after a long incubation and brief clinical phase [14].
- **Huntington's Disease (HD):** Huntington's disease is an autosomal dominant neurodegenerative disorder produced by CAG trinucleotide repeat expansion in the huntingtin gene (HTT), resulting in mutant polyglutamine-expanded huntingtin protein, selective striatal medium-spiny neuron loss and a triad of chorea, cognitive decline and psychiatric disturbances [15,16].
- **Spinocerebellar Ataxia (SCA):** Spinocerebellar ataxias comprise a genetically heterogeneous group of autosomal-dominant disorders most commonly polyglutamine repeat expansions that primarily damage cerebellar Purkinje neurons and interconnected brain-stem pathways, leading to progressive limb and gait ataxia, dysarthria and oculomotor abnormalities with variable extracerebellar features [17,18].
- **Spinal Muscular Atrophy (SMA):** Spinal muscular atrophy is an autosomal recessive motor-neuron disease caused by loss-of-function mutations in Survival Motor Neuron 1 (SMN1), resulting in deficient survival motor neuron protein, degeneration of anterior horn α-motor neurons, symmetrical proximal muscle weakness and, in severe infantile-onset forms, respiratory failure and early mortality [19].

1.2 Exploring the Scope of Plant-Based Therapeutics:

For neurodegenerative diseases, plant-based therapies are becoming more and more popular as supplements or substitutes for conventional drug therapies. The neuroprotective qualities of two well-known herbal remedies, *Gastrodia elata* and *Ginkgo biloba,* have been thoroughly investigated [20, 21]. While *Gastrodia elata* is still a potent neuroprotectant with potential uses in Alzheimer's and Parkinson's diseases, *Ginkgo biloba* has more well-established clinical uses, especially in dementia and cognitive decline [22, 23]. Both plants provide multi-targeted activities that reduce protein misfolding, fight oxidative and inflammatory damage, enhance mitochondrial function, and promote neurogenesis at different stages of neurodegenerative cascades. The complex nature of neurodegenerative disorders is better addressed by this comprehensive approach than by single-target synthetic drugs [21, 24]. Plant-based medications typically show higher safety profiles with fewer and milder side effects than synthetic drugs. Because of this, they are especially well-suited for long-term usage in patients with chronic neurodegenerative diseases who need ongoing care. To improve therapeutic efficacy and possibly lessen negative effects, drugs might be administered in conjunction with conventional treatments [22].

2 Traditional Roots and Modern Relevance

2.1 Historical use of *Ginkgo biloba* and *Gastrodia elata*

The foundation of ancient healing systems has traditionally been medicinal plants. Among these, *Ginkgo biloba*, a mycoheterotrophic orchid, and *Gastrodia elata*, which is frequently called a “living fossil,” are notable for their distinct biological characteristics and historical significance. Their applications range from cardiovascular health to neurological problems, and their use dates back thousands of years [25, 26].

Historical Perspectives and Pharmacological Potential of *Ginkgo biloba:* *Ginkgo biloba* is thought to be one of the oldest tree species, having originated in China more than 200 million years ago [27]. Its seeds were used to treat respiratory conditions in the *Shen Nong Ben Cao Jing* (~200 BCE), which is the earliest known medicinal application [28]. Its use for skin infections and its symbolic and therapeutic value were detailed in Li Shi-Zhen’s *Ben Cao Gang Mu* in the 16th century [29]. In order to help the species survive the Ice Age, Buddhist monks kept it alive in temple gardens [27]. Ginkgo leaf extracts (such as EGb 761) were widely used in Western medicine during the 20th century to treat vascular diseases and improve cognitive function [28]. Traditional claims of improved circulation and memory are supported by bilobalide and ginkgolides [30]. Seeds have been shown to have antibacterial action against *Streptococcus pyogenes* and *Staphylococcus aureus* [27]. Standardized preparations of *Ginkgo biloba* are now commonly used to treat peripheral artery disease, dementia, and tinnitus [31].

Historical Perspectives and Pharmacological Potential of *Gastrodia elate:* The Shennong Bencaojing is where *Gastrodia elata* initially appeared and has been used for more than 2,000 years. In Chinese, it is called “Tian Ma” [23]. Traditionally, it was administered to treat convulsions, headaches, epilepsy, and dizziness in order to “calm liver wind” [32]. It was used in Chinese, Korean, and Japanese folk medicine to treat hypertension, rheumatism, and stroke [33]. Particularly in areas like Zhaotong, Yunnan, its use and cultivation were strongly ingrained in ethnic practices [34]. Gastrodin has anti-inflammatory, anticonvulsant, and neuroprotective properties [35]. GABAergic modulation is consistent with its historical application in the treatment of convulsions [36]. *Gastrodia elata* is being studied for its potential to cure neurodegenerative disorders, and it is now licensed in China for the treatment of migraines and neurasthenia [37].

2.2 The Ethnobotanical Significance of *Ginkgo biloba* and *Gastrodia elata* in Neurological Health

The study of how plants and human cultures interact, known as ethnobotany, offers important insights into plant species that have been utilized for ages to cure a variety of illnesses, including neurological

disorders [38]. *Ginkgo bilob* and *Gastrodia elata* are notable among the extensive pharmacopeia of traditional medical systems due to their long-standing usage in the treatment of disorders associated with brain function and health [39]. The ethnobotanical relevance of these two plants is examined in this chapter, along with their historical applications and modes of action in relation to neurological health.

Traditional uses of *Ginkgo biloba:* As one of the oldest surviving tree species, *Ginkgo biloba* has a special place in botanical history and has earned the nickname "living fossil" [40]. It is renowned for its tenacity; specimens have shown incredible endurance and adaptation by surviving the Hiroshima atomic attack [41]. The Chen Noung Pen T'sao, a Chinese pharmacopeia that dates to around 2800 BCE, has the earliest known therapeutic use of ginkgo in traditional Chinese medicine [42]. In the past, TCM practitioners mostly used the seeds (called "bai guo") to treat digestive and respiratory issues, but the leaves became popular in medicine much later [43]. *Ginkgo biloba* leaves were reportedly being utilized to "benefit the brain" and enhance mental performance by the 15th century [44]. Traditional uses included the treatment of what are now known to be circulatory, memory, and cognitive decline symptoms [45]. Because of its great significance, the plant was cultivated to ensure its preservation and was eventually included in temple gardens and royal complexes [41]. The use of ginkgo in Western medicine is relatively new; it gained favor in Europe in the 1960s once standardized preparations were made accessible [46]. In contemporary scientific studies to treat neurodegenerative diseases, the most extensively studied form is the standardized extract known as EGb 761, which has a specified proportion of terpene lactones and flavonoid glycosides [47].

Traditional uses of *Gastrodia elata:* *Gastrodia elata*, a rare orchid native to high-altitude regions of China, Korea, and Japan, presents a fascinating case of co-evolution and symbiosis. This non-photosynthetic plant depends entirely on mycorrhizal fungi for nutrition, developing a parasitic relationship with fungi that themselves form symbiotic relationships with nearby photosynthetic trees [48]. Tian Ma, as it is known in Chinese, first appeared in the Shennong Bencao Jing (Divine Farmer's Materia Medica), compiled around 200 CE, where it was classified as a superior herb that could "prolong life without side effects" [49]. Traditional Chinese medical texts categorized it as an herb that "extinguishes wind and stops tremors," making it a primary treatment for conditions characterized by tremors, spasms, dizziness, and headaches [48]. In traditional Korean medicine (Hanbang) and Japanese Kampo medicine, *Gastrodia elata* was similarly valued for treating neurological symptoms, particularly those associated with what modern medicine would identify as epilepsy, stroke sequelae, and various movement disorders [50]. The dried rhizome is the primary medicinal part, typically prepared through various processing methods to enhance specific therapeutic properties [35].

3 Pharmacognostic Overview of *Ginkgo biloba & Gastrodia elata*

3.1. Botanical Identity and Morphological Features of *Ginkgo biloba*

Botanical Identity: The oldest tree species still in existence is the *Ginkgo biloba*, which originated in prehistoric periods about 300 million years ago. The name *Ginkgo biloba* was first assigned to the tree by the botanist Linnaeus in his *Mantissa Plantarum Altera* published in 1771. The Japanese word "Ginkgo" was mistranslated, and it should have been "Ginkyo." "Biloba" is a Latin term that means "two-lobed," describing the distinctive form of the leaves. The name "Ginkgo" originates from the Chinese and Japanese terms for the plant, which means "silver apricot" or "silver fruit," in reference to the Yellow colored apricot female seed structure [51, 52]. This taxon is typically placed in its own division, Ginkgophyta. It is differentiated from Coniferophyta primarily by its reproductive features, particularly the presence of multi-flagellated sperm cells, and from Cycadophyta based on differences in vegetative anatomy. However, recent molecular analyses of the ginkgo genome suggest it shares a closer

evolutionary relationship with Cycadophyta than with Coniferophyta [41, 53]. Taxonomy of *Ginkgo biloba* is given in table 1 [54].

Table 3.1: Taxonomy of *Ginkgo biloba.* [54].

Classification	Name
Botanical Name	*Ginkgo biloba* L.
Kingdom	Plantae
Division	Pinophyta
Phylum	Ginkgophyta
Class	Ginkgoopsida
Order	Ginkgoales
Family	Ginkgoaceae
Genus	Ginkgo
Species	Biloba
Plant Part	Leaf
Common Names	Fossil tree, Kew tree, Maidenhair tree

Morphological features: *Ginkgo biloba* has a sporophytic plant body and a general look similar to some conifers. The trees exhibit a distinctly excurrent growth pattern and can reach heights of up to 30 meters. Their branches are dimorphic, consisting of long shoots with indeterminate growth and scattered leaves, as well as dwarf shoots, which are short, determinate branches. A dwarf shoot measuring 2 to 3 cm in length can be several years old [55].

- **Leaves:** The leaves of *Ginkgo biloba* can vary in color, ranging from pale yellow and golden yellow to dark green. The foliar epidermis displays distinct characteristics unique to the species. The leaves are hypostomatic, meaning stomata are present only on the underside. *Ginkgo biloba* trees have both long and short branches that extend at right angles. During spring, leaves emerge alternately on the long branches. These leaves are fan-shaped, smooth, and leathery, often featuring a deep central groove that divides them into two distinct lobes, hence the name *biloba*, meaning "two-lobed" [56].
- **Trunk:** A *Ginkgo biloba* tree can grow to a height of 30 to 40 meters with a spread of approximately 8 meters. The trunk may reach a diameter of 3 to 4 meters and is typically straight, columnar, and sparsely branched. Young trees typically have a pyramid-shaped central trunk and asymmetrical, regular, ascending, and lateral branches. As the tree matures, its bark becomes rough and cracked, and deep furrows form [57].
- **Fruits:** The female Ginkgo tree produces fleshy, oval to round fruits measuring approximately 2.5 to 3.5 cm in length and 1.6 to 2.2 cm in width, similar in size to a small jujube (Chinese date). These fruits are green when immature and turn pale yellow upon ripening. The outer layer, known as the sarcotesta, has a strong, unpleasant odor. Each fruit contains a single hard-shelled seed at its center, which encases an edible embryo or kernel. The kernels are about 1.5 to 2.0 cm long and 1 cm in diameter, typically displaying a light jade-green color [58].
- **Flowers:** Female flowers of *Ginkgo biloba* bear numerous ovules arranged in pairs on stalks, each containing an egg cell. These ovules are initially bright green, gradually changing to greenish-yellow, then orange, and eventually brown as they mature. Male flowers are pollen cones (microsporangia), which resemble catkins and are ivory in color. They usually emerge in clusters of three to six on each short shoot. These cones contain boat-shaped pollen sacs with broad, open slits [59].
- **Seeds:** Ginkgo seeds are comparatively large when fully grown, with dimensions of roughly 20 to 30 mm in length and 16 to 24 mm in breadth. It is surrounded by a thick seed coat made up of three layers: a thin, membrane-like inner layer, a hard, stony middle layer, and a soft, fleshy outer layer (sarcotesta). It also contains an embryo buried within the tissue of the female gametophyte. Once the fleshy sarcotesta

is removed, the seed is commonly referred to as a Ginkgo "nut," typically ranging from 19 to 30 mm in size [60].

3.2 Morphological and Microscopic characteristics of *Gastrodia elate*

Gastrodia elata Blume commonly known as Tianma in traditional Chinese medicine, is a fully mycoheterotrophic orchid that lacks chlorophyll and depends entirely on symbiotic fungi for nutrition. It is widely distributed across East Asia and has significant medicinal value due to its neuroprotective and anti-inflammatory properties [61, 62]. *Gastrodia elata* Bl. still widely known as a medicinal plant due to its anti-inflammatory, neuroprotection, cardiovascular protection etc. Furthermore, these medicinal uses are inextricably linked to its anti-aging, antioxidant, and cell apoptosis-regulating properties, which also make it a potential functional food. It has been consumed in China for over 2,000 years [63].

Morphological characteristics:

- **Rhizome:** Elliptical, underground, measuring 8-12 cm in length and 3-5 cm in diameter, may grow up to 7 cm [64].
- **Stem:** Erect, leafless, cylindrical, orange-yellow to tan, ranging from 0.3 to 10 meters in diameter [64].
- **Flowers:** Pale olivine to orange red, with a scape length of 5-30 cm. It has lanceolate floral bracts and a slanting pot-shaped perianth tube [64].
- **Labellum:** White, circular, with three lobes and a pair of pulp calluses at the base [64].
- **Fruits and seeds:** Capsules are oval, containing upto 40,000 dust like seeds per fruits [64].
- **Growth Habit:** Grows in symbiosis with *Armillaria mellea* on decaying wood, relying on fungal hyphae to invade its root system for nutrient absorption [64].

Microscopic characteristics:

- **Rhizome:** The rhizome exhibits a single-layered epidermis without cuticle, a broad cortex filled with simple and compound starch granules and occasional calcium oxalate druses, and a central collateral vascular bundle encased in sclerenchyma [65].
- **Stem cross-sections:** It reveal a stomata-free epidermis, 4 to 6 layers of cortical parenchyma, and a single ring of collateral vascular bundles surrounding a parenchymatous pith [65].
- **Stem powder**: Shows epidermal cells, cork cells, calcium oxalate raphides, and refractive crystals [26].
- **Flower:** The floral tissue displays thick-walled perianth parenchyma with vascular septa, phenolic-laden secretory idioblasts in the labellum, and an ovary wall with densely packed vascular bundles and reduced intercellular spaces [65].
- **Flower powder:** Contains nonglandular hairs, spiral vessels, calcium oxalate raphides, and secretory canals [26].

3.3 Authentication, Collection, Quality control parameters

Ginkgo biloba and *Gastrodia elata* Blume represent two of the most significant medicinal plants in traditional herbal medicine systems. *Ginkgo biloba*, commonly known as the maidenhair tree, is a living fossil species renowned for its neuroprotective properties and standardized leaf extracts containing flavonoids and terpenoids [66, 67]. *Gastrodia elata*, known as "Tianma" in Traditional Chinese Medicine, is a saprophytic orchid valued for its rhizomes containing gastrodin and other bioactive compounds with neurological benefits [68]. The increasing global demand for these medicinal plants necessitates stringent authentication, proper collection practices, and comprehensive quality control measures to ensure therapeutic efficacy and consumer safety [69, 70].

Botanical Identification (Authentication): Proper authentication begins with accurate botanical identification using established scientific nomenclature [71]. *Ginkgo biloba* exhibits distinctive fan-shaped leaves with dichotomous venation, while *Gastrodia elata* presents as a leafless orchid with characteristic underground rhizomes [72]. Macroscopic examination involves evaluating morphological characteristics including size, shape, color, texture, and surface features of the plant materials [73].

- **Microscopic Examination:** Microscopic analysis provides definitive identification through cellular structures and diagnostic features. For *Ginkgo biloba* leaves, key microscopic markers include bifacial mesophyll structure, anomocytic stomata, and characteristic trichomes. *Gastrodia elata* rhizomes display specific anatomical features including parenchymatous cortex and distinctive vascular bundles [74, 75].
- **Organoleptic Assessment:** Sensory evaluation through organoleptic assessment helps distinguish genuine materials from adulterants. This includes evaluation of odor, taste, color, and texture characteristics specific to each species [76]

Collection Parameters:

- **Plant Parts and Timing:** Optimal collection requires harvesting specific plant parts at appropriate developmental stages [77]. *Ginkgo biloba* leaves should be collected during peak growing season when flavonoid content is maximum, typically in late summer [78]. *Gastrodia elata* rhizomes are harvested in winter when gastrodin concentrations reach optimal levels [79].
- **Sustainable Harvesting:** Collection practices must ensure species conservation and habitat preservation. *Ginkgo biloba* cultivation has been successfully established globally, while *Gastrodia elata* requires careful wild harvesting protocols due to its specialized ecological requirements [80, 81].
- **Geographic Considerations:** Source authentication includes verification of geographic origin, as phytochemical profiles can vary based on environmental conditions and genetic variations [82].

Quality Control Parameters:

- **Pharmacopoeial Standards:** Quality control adherence follows established pharmacopoeial monographs including moisture content (≤10%), total ash (≤5%), and acid-insoluble ash specifications. Extractive values for water-soluble and alcohol-soluble components provide additional quality indicators [77].
- **Phytochemical Standardization:** Chemical fingerprinting using High-Performance Thin Layer Chromatography (HPTLC) and High-Performance Liquid Chromatography (HPLC) enables quantification of marker compounds [83]. *Ginkgo biloba* standardization focuses on flavonoids (22-27%) and terpenoids including ginkgolides A, B, C, and bilobalide [84]. *Gastrodia elata* quality assessment centers on gastrodin content, typically requiring minimum 0.2% gastrodin [85].
- **Safety Testing:** Comprehensive safety evaluation includes microbial contamination testing for bacteria, yeasts, molds, and specific pathogens. Heavy metal analysis screens for lead, cadmium, mercury, and arsenic within acceptable limits. Pesticide residue testing ensures compliance with maximum residue limits for agricultural chemicals [86].
- **Storage and Stability:** Proper storage conditions maintain product integrity through controlled temperature, humidity, and light exposure. Stability testing evaluates shelf-life and degradation patterns of bioactive compounds under various storage conditions [83, 84].

4 Phytochemical Profile and Bioactive Insights

4.1 Key phytochemicals of *Ginkgo biloba*

Ginkgo biloba is a well-studied medicinal plant whose phytochemical profile centers mainly on leaf-derived constituents, featuring four key classes of bioactive phytochemicals: flavonoids, terpene trilactones, biflavonoids, and phenolic acids, [85, 86] shown in Table 2. These compounds collectively underlie the plant's diverse pharmacological properties, including antioxidant, anti-inflammatory, neuroprotective, anti-apoptotic, and vasoactive effects. *Ginkgo biloba's* broad utility in neuroprotection, cardiovascular health, and anti-inflammatory therapies, driven by its distinctive phytoconstituent composition predominantly located in leaves. Standardized extracts such as EGb 761 combine these bioactives for therapeutic applications in cognitive disorders and neurodegenerative diseases [85, 87, 94].

Table 3.2: Key phytochemicals of *Ginkgo biloba*.

4.2 Bioactivities of Key phytochemicals of *Ginkgo biloba*

- **Flavonoids:** Flavonoids from *Ginkgo biloba* exert potent antioxidant effects by scavenging reactive oxygen species (ROS) and upregulating antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx). They also inhibit pro-inflammatory signaling pathways including NF-κB and MAPK, leading to decreased levels of inflammatory cytokines like TNF-α and IL-1β. These compounds provide neuroprotection by preserving mitochondrial function and preventing excitotoxicity, contributing to improved cognitive and neurological outcomes in disease models [85, 86].

Phytochemical Class	Key Compounds	Main Bioactivities	References
Flavonoids	Quercetin-3-O-glucoside, rutin, kaempferol, isorhamnetin, luteolin derivatives	Antioxidant, anti-inflammatory, neuroprotective, mitochondrial protection, cognitive enhancement	[85], [86]
Terpene Trilactones	Ginkgolides A, B, C, J; bilobalide	PAF antagonism, neurotrophic, anti-apoptotic, mitochondrial protection	[86], [86]
Biflavonoids	Ginkgetin, isoginkgetin, amentoflavone, bilobetin	Anti-inflammatory, anti-thrombotic, antioxidant	[87], [25]
Phenolic Acids	Protocatechuic acid, ferulic acid, caffeic acid, vanillic acid	Antioxidant, anti-inflammatory, neuroprotective	[88]

- **Terpene trilactones:** Terpene trilactones are notable for their ability to antagonize platelet-activating factor (PAF), thus reducing microvascular inflammation and thrombosis. Bilobalide specifically enhances neurotrophic factors such as BDNF and activates neuronal survival pathways (e.g., PI3K/Akt), while inhibiting apoptosis markers (caspase-3, Bax). These contribute to mitochondrial protection by sustaining complex I activity and ATP production under oxidative stress [85, 86].
- **Biflavonoids:** Biflavonoids exhibit strong anti-inflammatory activity by suppressing microglial activation and downregulating inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) through NF-κB inhibition. They also have anti-thrombotic properties by inhibiting thrombin and contribute synergistically to antioxidant defenses [25, 87].
- **Phenolic Acids:** These acids scavenge ROS, enhance endogenous antioxidant defenses, and inhibit pro-inflammatory signaling via TLR4/NF-κB pathways. They protect dopaminergic neurons from toxin-induced degeneration and improve motor function in PD models, highlighting their neuroprotective potential [88].

4.3 Key phytochemicals of *Gastrodia elata*

Gastrodia elata is a renowned medicinal herb widely used for its therapeutic effects on the nervous system. The secret to its healing potential lies in its rhizome (underground tuber), which is rich in a unique combination of bioactive compounds. Primarily, the tuber contains four major classes of phytoconstituents: Phenolic glycosides, Phenolic acids/alcohols, Polysaccharides, and Sterols/organic acids, [23, 89] shown in Table 3. Together, these organic substances provide a wide variety of pharmacological actions. *Gastrodia elata* is especially known for its antioxidant, anti-inflammatory, neuroprotective, anti-apoptotic, and mitochondrial-supportive actions. Additionally, recent studies suggest it may also help regulate the gut-brain axis, which plays a vital role in overall neurological function. Due to this complex and synergistic phytochemical profile, *Gastrodia elata* holds significant promise in the prevention and management of neurodegenerative disorders, particularly PD, by supporting neuronal health and protecting against progressive neural damage [90, 91].

Table 3.3: Key phytochemicals of *Gastrodia elata.*

Phytochemical Class	Key Compounds	Main Bioactivities	References
Phenolic Glycosides	Gastrodin, Parishins	Antioxidant (ROS scavenging, ↑SOD/GPx, ↓MDA), anti-inflammatory (suppression of NF-κB/NLRP3), anti-apoptotic (↑Bcl-2/Bax, ↓caspase-3), mitochondrial protection, neuroprotection	23], [90]
Phenolic Acids/Alcohols	4-Hydroxybenzyl alcohol, vanillic acid, vanillin	Antioxidant, anti-inflammatory (inhibition of TLR4/NF-κB axis), neuroprotection (mitochondrial support), GABAergic modulation	23], [91]
Polysaccharides	Heteropolysaccharides (mannose, glucose, galactose, rhamnose, xylose)	Gut–brain axis modulation (microbiota restoration, SCFA increase), anti-inflammatory (microglial inhibition), anti-apoptotic, immune regulation	91]
Sterols & Organic Acids	β-Sitosterol, p-hydroxybenzoic acid	Antioxidant, membrane stabilization, neuroprotection	21]

4.4 Bioactivities of Key phytochemicals of *Gastrodia elata*

- **Phenolic glycosides:** Phenolic glycosides such as gastrodin and parishins (A - E) exert strong antioxidant actions by scavenging reactive oxygen species (ROS), boosting endogenous antioxidant enzymes, and protecting mitochondria, while also providing anti-apoptotic effects by upregulating the Bcl-2/Bax ratio and inhibiting caspase-3, thus preserving neuronal integrity; these compounds further attenuate neuroinflammation by inhibiting NF-κB and NLRP3 inflammasome pathways, collectively safeguarding against neurodegenerative insults [23, 90].
- **Phenolic Acids/Alcohols:** Phenolic acids/alcohols and polysaccharides extracted from *Gastrodia elata* suppress neuroinflammation by inhibiting key pro-inflammatory signaling cascades such as NF-κB, NLRP3 inflammasome, and TLR4/NF-κB pathways. This leads to decreased levels of cytokines like TNF-α, IL-1β, and IL-6 in neural tissues, reducing the inflammatory burden in neurodegenerative conditions [23, 91].
- **Polysaccharides:** Polysaccharides, composed of heteropolymers such as mannose, glucose, galactose, rhamnose, and xylose, contribute to restoration of gut microbiota balance (e.g., elevating beneficial SCFAs), strengthen the intestinal barrier, and exhibit both anti-inflammatory and anti-apoptotic properties through inhibition of microglial activation and immune regulation, ultimately supporting the gut-brain axis and neuroprotection [91].
- **Sterols:** *Gastrodia elata's* complex phytochemical network of neuroprotection is completed by sterols and organic acids (p-hydroxybenzoic acid, β-sitosterol) that strengthen antioxidant defenses and stabilize membrane integrity, hence enhancing neural stability [21].

5 Experimental and Therapeutic Evidence

5.1 Preclinical Models in PD and Observed Neuroprotective Effects

Both *Ginkgo biloba* extract (EGb 761) and *Gastia elata* phytochemicals have been systematically evaluated in established PD (PD) paradigms, 6-hydroxydopamine (6-OHDA), 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine (MPTP)/1-methyl-4-phenyl pyridinium ion (MPP^+), rotenone toxin models, and related cellular assays that demonstrating robust neuroprotection via antioxidant, anti-inflammatory, anti-apoptotic, and mitochondrial-stabilizing mechanisms [92, 93].

***Ginkgo biloba* Extract (EGb 761)**

- **6-OHDA-Lesioned Rat Model**: Rats in the 6-OHDA-Lesioned Rat Model were given 10-µg/2 µL of the drug intrastrially. EGb 761 (50–150 mg/kg i.p.) was administered daily for three weeks, beginning one

week before toxin infusion. EGb 761 decreased striatal lipid peroxidation (TBARS), restored locomotor activity and muscle coordination, lowered apomorphine-induced rotations in a dose-dependent manner, and restored decreased glutathione (GSH) levels in the substantia nigra [92].

- **MPTP-Treated Mouse Model**: C57BL/6J mice received MPTP (30 mg/kg i.p. daily for five days). EGb 761 (50–100 mg/kg i.p.) pretreatment for 17 days (starting 24 h before MPTP) preserved striatal dopamine content, maintained tyrosine hydroxylase-positive neuron counts, inhibited monoamine oxidase-B activity (thus reducing MPTP into MPP^+), and lowered malondialdehyde (MDA) accumulation in substantia nigra, resulting in improved motor performance [92].
- **Rotenone Model**: In rats exposed to rotenone (1.5 mg/kg/day s.c.), co-treatment with EGb 761 (100 mg/kg i.p.) preserved mitochondrial complex I activity, sustained ATP levels, inhibited caspase-3 activation, attenuated α-synuclein aggregation, and improved motor coordination, indicating interruption of mitochondrial-mediated apoptotic cascades [93].

***Gastrodia elata* Phytochemicals**

- **MPTP-Induced Mouse Model**: Mice received MPTP (20 mg/kg i.p. daily). *Gastrodia elata* polysaccharide (GEP; 200 mg/kg p.o.) for three weeks significantly alleviated motor dysfunction, inhibited α-synuclein accumulation, preserved tyrosine-hydroxylase$^+$ neurons, increased the Bcl-2/Bax ratio, decreased cleaved caspase-3, activated Nrf2/HO-1 antioxidant pathways, and suppressed neuroinflammation via TLR4/NF-κB and NLRP3 inflammasome inhibition [94].
- **6-OHDA-Lesioned Rat Model**: Rats received unilateral striatal 6-OHDA (10 μg). Gastrodin (50–100 mg/kg p.o.) for three weeks before and after lesioning attenuated apomorphine-induced rotations, restored mitochondrial complex I activity and membrane potential, upregulated Bcl-2, downregulated Bax and caspase-3, and reduced dopaminergic neuron apoptosis [94].
- **Gut-Brain Axis Modulation in MPTP Mice**: *Gastrodia elata* polysaccharide GEP (200 mg/kg p.o.) normalized PD-associated gut dysbiosis by increasing *Lactobacillus*, reducing *Akkermansia*, elevating colonic short-chain fatty acids, enhancing intestinal occludin expression, and indirectly promoting neuroprotection by reducing systemic inflammation and reinforcing blood–brain barrier integrity [95].

5.2 The Role of Standardized Extracts EGb 761 and Gastrodin in Neuroprotection

Standardized herbal extracts provide consistency, reproducibility, and targeted therapeutic outcomes, essential qualities in managing complex neurological disorders. Among these, EGb 761 (a standardized extract of *Ginkgo biloba*) and Gastrodin (the primary bioactive from *Gastrodia elata*) have gained significant attention for their multimodal neuroprotective properties. Their ability to target oxidative stress, neuroinflammation, mitochondrial dysfunction, and apoptosis positions them as promising candidates in the management of neurodegenerative diseases such as PD and AD [96, 97].

EGb 761 (Standardized *Ginkgo biloba* Extract): EGb 761 a quantified, standardized extract of *Ginkgo biloba* leaves containing 24% flavonoid glycosides and 6% terpene lactones (ginkgolides A, B, C, J and bilobalide) [96]. This involves several neuroprotective mechanisms as mentioned below:

- **Antioxidant and Gene-Regulatory Actions**: EGb 761 scavenges reactive oxygen species (ROS) directly and upregulates endogenous defenses (superoxide dismutase, glutathione peroxidase) via activation of the Nrf2/heme-oxygenase-1 (HO-1) pathway. In mouse models of ischemia-reperfusion injury, EGb 761 pretreatment reduced infarct volumes and improved neurological scores, effects attributed to Nrf2-mediated antioxidant gene transcription and enhanced cellular oxidative tolerance [20].
- **Anti-apoptotic and Neuritogenic Effects**: In primary neurons, EGb 761-induced HO-1 expression stabilizes the collapsin response mediator protein-2 (CRMP2) cytoskeletal pathway, preventing excitotoxic and oxidative injury. Bilobalide and ginkgolide A also inhibit caspase-3 activation and preserve mitochondrial membrane potential, collectively reducing apoptosis in models of stroke and glutamate toxicity [98].

- **Mitochondrial Protection**: Under toxin-induced stress (e.g., rotenone, MPTP), terpene trilactones in EGb 761 maintain mitochondrial complex I activity and ATP synthesis, breaking the feed-forward cycle of oxidative damage and energy failure that causes neuronal degeneration [98].
- **Anti-inflammatory Modulation**: EGb 761 antagonizes platelet-activating factor and inhibits microglial NF-κB and NLRP3 inflammasome activation, lowering pro-inflammatory cytokines (TNF-α, IL-1β). These actions attenuate neuroinflammation in models of Parkinson's and ADs [20].
- **Clinical Cognitive Benefits**: Meta-analyses and randomized trials demonstrate that 240 mg/day EGb 761 improves cognitive performance, daily living activities, and prefrontal cortical activation patterns in elderly with mild cognitive impairment and post-stroke cognitive deficits, confirming translational relevance [100].

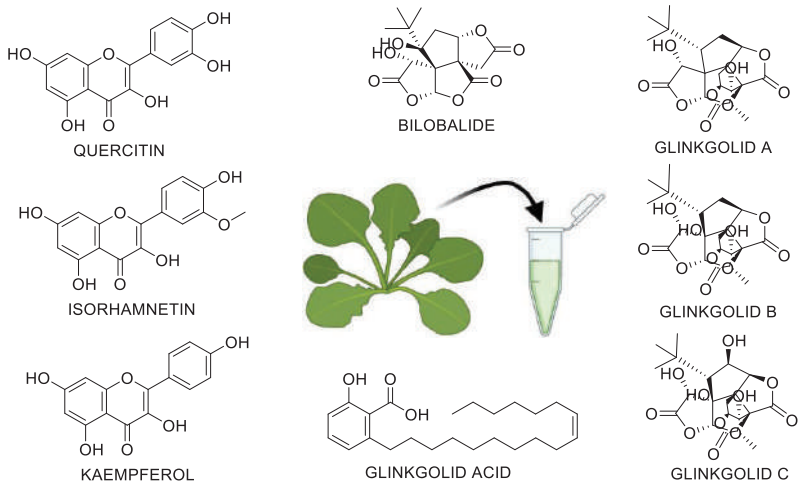

Figure 3.3: The key component of Standardized *Ginkgo biloba* Extract (EGb 761). "Created with BioRender.com."

Gastrodin (Principal Metabolite of *Gastrodia elata*): Gastrodin (4-hydroxybenzyl alcohol 4-O-β-D-glucoside) is the chief standardized constituent of *Gastrodia elata* rhizome extracts, [97] shown in Figure 4. This involves several neuroprotective mechanisms as mentioned below:

- **Antioxidant and Nrf2/HO-1 Activation**: Gastrodin upregulates Keap1/Nrf2 signaling and HO-1 expression in astrocytes and neurons, increasing glutathione peroxidase and SOD activity, reducing malondialdehyde levels, and protecting against oxidative insults in ischemia and hemorrhagic models [100].
- **Anti-apoptotic Modulation**: By increasing Bcl-2/Bax ratios and inhibiting caspase-3 and caspase -9 activation, gastrodin prevents mitochondrial mediated apoptosis in models of cerebral ischemia and PD toxins (MPTP, 6-OHDA) [101].
- **Anti-inflammatory Effects**: Gastrodin suppresses TLR4/NF-κB and NLRP3 inflammasome pathways, lowering TNF-α, IL-1β, and IL-6 in subarachnoid hemorrhage and PD models, thereby reducing microglial and astrocytic activation [21].
- **Mitochondrial Preservation**: In order to mitigate energy failure and ROS overproduction in dopaminergic neurons, gastrophin stabilizes mitochondrial membrane potential and sustains complex I activity and ATP levels during neurotoxic stress [102].
- **Gut-Brain Axis Support**: Polysaccharide-enriched gastrodin extracts (*Gastrodia elata* polysaccharides (GEP)) restore PD-associated dysbiosis (increased Lactobacillus, decreased Akkermansia), elevate short

chain fatty acids, enhance intestinal occludin expression, reduce systemic endotoxin translocation, and fortify blood brain barrier (BBB) integrity, contributing indirectly to neuroprotection [103,104].

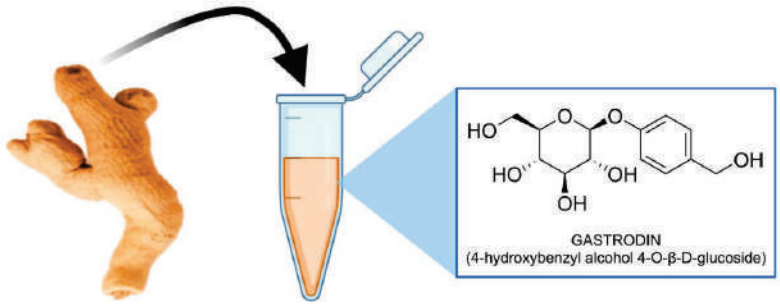

Figure 3.4: The key component of *Gastrodia elate* rhizome extracts. "Created with BioRender.com."

6. Clinical Translation, Bioavailability Issues, and Innovative Solutions

6.1 Current Clinical Findings and Limitations

Current Clinical Findings: Clinical studies and meta-analyses indicate that standardized *Ginkgo biloba* extract (EGb 761) may provide beneficial effects in neurodegenerative disorders particularly Alzheimer's disease (AD), mild-to-moderate dementia, and age-associated cognitive impairment. Clinical trials have shown that EGb 761 can improve cognitive function, activities of daily living, and neuropsychiatric symptoms in dementia, and is approved for these indications in several regions [105]. Some studies, including randomized, double-blind, placebo-controlled trials, found significant improvements in cognition and behavior in mild-to-moderate AD and multi-infarct dementia with 120 to 240 mg/day EGb 761 for at least 22 to 24 weeks [106]. Other studies reported maintained or improved cognitive scores and global function, especially when treatment begins early in disease progression. EGb 761 is generally well tolerated, with a safety profile comparable to placebo [55, 105]. Although *Gastrodia elata* has fewer extensive clinical trials than *Ginkgo biloba*, new research and a number of pilot studies show that *Gastrodia elata* has positive behavioral, cognitive, and neuroprotective effects in neurodegenerative disorders. *Gastrodia elata* and its primary bioactive, gastrodin, have shown improvements in cognitive performance and neuropsychological function in dementia, mild cognitive impairment, and Parkinson's disease in clinical and observational studies [23]. A recent human trial in middle-aged adults with cognitive complaints showed that *Gastrodia elata* extract was safe and well-tolerated, though robust evidence for efficacy in AD and PD is still under active investigation [108]. Previous studies and meta-analyses highlight gastrodin's ability to attenuate memory loss and promote synaptic plasticity, with additional benefits suggested for epilepsy and vascular dementia [23].

Table 3.4: Current Clinical Findings of *Ginkgo biloba* and *Gastrodia elata* Against Neurodegenerative Disorders.

Plant Extract	Indication	Dosing Regimen	Clinical Outcomes	Safety Profile	References
EGb 761	AD, mild-moderate dementia, cognitive decline	120–240 mg/day (22–24+ wks)	Cognitive improvement, daily function, neuropsychiatric symptoms improved; most effective early	Well tolerated, no major safety concerns	[106], [107], [55]
Gastrodia elata (GE / gastrodin)	Mild cognitive impairment, dementia, PD	300–600 mg/day (gastrodin), 200–500 mg/day (GE extract), up to 24 wks	Improved or stabilized cognition, some improvement in behavioral symptoms; mainly observational / early-phase trials	Generally safe, no mutagenicity	[23], [108]

Current Limitations of *Ginkgo biloba:*

- Clinical results remain heterogenous, with some controlled trials reporting significant benefit and others reporting equivocal or modest effects [106].
- Efficacy may depend on intervention timing: greater benefit is seen in early/mild dementia, while advanced stages show less responsiveness, likely due to irreversible pathology [55].
- Limited evidence for efficacy in PD and other neurodegenerative conditions outside the dementia spectrum [106].
- Challenges include variable extract standardization, diverse outcome measures across trials, different cognitive assessment tools, and suboptimal adherence or dosing in some studies [109].

Current Limitations of *Gastrodia elata:*

- Large-scale, double-blind, randomized controlled trials in AD and PD are still lacking; much of the supportive data comes from preclinical models or early-phase/observational clinical studies [23].
- Most trials have relatively small sample sizes, short follow-ups, and heterogeneous populations, limiting generalizability [108].
- A consistent, standardized form or dosage is not always used, and few studies compare *Gastrodia elata*/gastrodin directly to established pharmacotherapies for dementia or PD [109].
- While preclinical and pilot clinical work suggest safety and efficacy, further phase III trials are needed to determine long-term safety, efficacy, and disease modifying effects [109].

6.2 Challenges in Bioavailability and Dosing Optimization

Bioavailability Challenges in *Ginkgo biloba*:

- **Poor Gastrointestinal Absorption:** *Ginkgo biloba* extracts contain predominantly hydrophilic flavonoid glycosides and lipophilic terpene lactones with markedly different absorption characteristics. The standardized extract EGb 761 demonstrates significant interindividual variability in absorption rates, with peak plasma concentrations (Cmax) of ginkgolide B ranging from 2.3 hours post-administration across different formulations. Studies reveal that 40 mg twice daily dosing provides significantly longer half-life and mean residence time compared to single 80 mg dosing, despite the latter achieving higher peak concentrations [110].

- **Pharmaceutical Quality Impact on Bioavailability:** Comparative bioavailability studies demonstrate that pharmaceutical formulation quality critically affects therapeutic efficacy. Different *Ginkgo biloba* brands show non-bioequivalent plasma exposure profiles, with slow in-vitro dissolution of certain preparations resulting in substantial decreases in bioavailability of ginkgolides A, B, and bilobalide. Dissolution rates at pH 1 and 4.5 vary dramatically between formulations, directly correlating with reduced absorption and compromised therapeutic outcomes [111].
- **Blood-Brain Barrier (BBB) Penetration:** Despite its intended neurological applications, *Ginkgo biloba* faces considerable challenges in achieving adequate central nervous system penetration. Research indicates that significant levels of terpene trilactones and flavonoids cross the blood-brain barrier in rats after oral administration, yet human studies suggest suboptimal CNS bioavailability remains a limiting factor for consistent therapeutic efficacy in neurodegenerative conditions [112].

Bioavailability Challenges in *Gastrodia elata*:

- **Active Compounds' Low Absolute Bioavailability:** The main bioactive compound of *Gastrodia elata*, gastrodin, has a surprisingly low bioavailability of just 5–10% when taken orally [113]. Pharmacokinetic studies reveal that gastrodin reaches peak plasma concentrations (Cmax) within 2-108.5 minutes after administration, with most studies showing absorption within 30 minutes, indicating rapid absorption but extensive first-pass metabolism [114].
- **Formulation-Dependent Bioavailability:** Comparative studies reveal that the relative bioavailability of various formulations varies greatly. For example, parishin from *Gastrodia elata* extract shown bioavailability ratios of 76.06, 144.08, and 127.75% at low, medium, and high doses, respectively, in comparison to powder forms. The integrated bioavailability of parishin was calculated as only 13.84%, highlighting the need for optimized delivery systems [114].
- **Complex Metabolic Pathways:** *Gastrodia elata* constituents undergo extensive biotransformation, with gastrodin rapidly metabolized to p-hydroxybenzyl alcohol (HBA), parishin B, and parishin C. Studies identified 24 metabolites in rat plasma after administration of ethyl acetate fraction, involving glucuronidation, glucosylation, sulfation, methylation, hydroxylation, and dehydrogenation pathways. This extensive metabolism reduces the availability of parent compounds at target sites [114].

Dosing Optimization Challenges:

- **Variable Dose-Response Relationships of *Ginkgo biloba*:** Clinical trials with *Ginkgo biloba* demonstrate inconsistent dose-response patterns. Meta-analyses reveal that EGb 761 at 240 mg/day for minimum 24 weeks shows beneficial effects in mild dementia, while doses of 120-320 mg show variable efficacy depending on patient population and assessment methods. Some studies report no significant cognitive improvements with 120 mg twice daily in elderly populations with normal cognition [115].
- **Optimization Strategies for *Gastrodia elata*:** According to recent studies, bioavailability is greatly impacted by varied dosing regimens and formulations. For example, low-dose *Gastrodia elata* powder had greater relative bioavailability for gastrodin and parishin, whereas medium and high doses preferred extract formulations. Compared to single-compound study, integrated pharmacokinetic modeling indicates that comprehensive techniques that take into account several active metabolites offer superior treatment recommendations [111].
- **Patient Heterogeneity and Personalized Dosing:** Neurodegeneration patients exhibit substantial heterogeneity in disease progression, symptom severity, and drug metabolism capacity. Genetic polymorphisms affecting cytochrome P450 enzymes and drug transporters significantly influence individual responses to both *Ginkgo biloba* and *Gastrodia elata* treatments. This variability necessitates personalized dosing strategies based on genetic profiling and biomarker assessment [116].

6.3 Novel Solutions and Drug Delivery Approaches:

- **Nanotechnology-Based Enhancement:** Nanoparticle formulations have been shown to dramatically increase bioavailability in recent studies. For example, *Ginkgo biloba* extract nanoparticles made by emulsion solvent evaporation and freeze-drying demonstrated 1.81- and 1.75-fold increases in area under the curve (AUC) for flavonoids and terpene lactones, respectively, when compared to raw extract. By improving membrane permeability, these nanoformulations overcome solubility constraints [117].
- **Cyclodextrin Inclusion Complexes:** *Ginkgo biloba* extract-γ-cyclodextrin complexes demonstrate remarkable bioavailability improvements, with 5.4, 6.1, and 10.4-fold enhancements in quercetin, kaempferol, and isorhamnetin bioavailability respectively compared to conventional extracts. This approach addresses the poor solubility and stability issues of flavonoid compounds [118].
- **Phospholipid Complexation:** Studies suggest that phospholipid-based delivery systems enhance herbal drug absorption by improving lipid membrane crossing capability. These systems have shown promise for both *Ginkgo biloba* and *Gastrodia elata* compounds, addressing the fundamental challenge of hydrophilic compound absorption across lipid-rich biological membranes [119].

Conclusion

The progressive and complex nature of neurodegenerative diseases poses an increasing challenge to modern medicine. Despite advancements in symptomatic treatments, the need for disease-modifying and neuroprotective strategies remains critical. Traditional medicinal plants like *Gastrodia elata* and *Ginkgo biloba* present promising substitutes and supplementary choices in this regard. The pharmacognostic characteristics, phytochemical profiles, and medicinal significance of both plants have been thoroughly discussed in this chapter. *Ginkgo biloba* is particularly high in flavonoids and terpene lactones, such as bilobalide and ginkgolides, which have anti-inflammatory, antioxidant, and mitochondrial-supporting properties. Key bioactive components found in *Gastrodia elata*, which has long been valued in traditional Chinese medicine, include gastrodin, vanillin, and parishin. These compounds modulate neurotransmission and lower oxidative stress, which have neuroprotective benefits. Standardized extracts like gastrodin and EGb 761 have continuously shown promise in preclinical and experimental models for the treatment of neurodegenerative disorders, especially Parkinson's disease. However, issues with therapeutic consistency, dosage accuracy, and bioavailability continue with limited clinical applicability. With encouraging results, new drug delivery strategies such as phospholipid complexes, cyclodextrin inclusion systems, and nanocarriers are being investigated to overcome these limitations. Both *Gastrodia elata* and *Ginkgo biloba* have neurotherapeutic potential, as demonstrated by the integration of modern pharmacological research with traditional botanical knowledge. More research into their mechanisms, standardization, and innovative delivery methods could lead to more natural, patient-friendly, and efficient therapies for the treatment of neurodegenerative disorders in the future.

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Chapter 4: *Ginkgo biloba* and *Gastrodia elata*: Bridging Traditional Wisdom and Modern Therapy in Parkinson's Disease

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Abstract

PD (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra, leading to motor dysfunction, cognitive impairment, and reduced quality of life. While conventional pharmacotherapy offers symptomatic relief, it often presents long-term limitations and side effects. In this context, the integration of traditional medicinal approaches has gained traction. *Ginkgo biloba* and *Gastrodia elata*, revered in Traditional Chinese Medicine (TCM), have shown neuroprotective and antioxidative properties that may complement standard PD treatments. This chapter explores the historical usage, phytochemical composition, pharmacological actions, and clinical relevance of *Ginkgo biloba* and *Gastrodia elata* in the management of PD. We discuss the underlying mechanisms such as inhibition of oxidative stress, mitochondrial protection, anti-inflammatory pathways, and modulation of neurotransmitters that make these herbs promising candidates for adjunct therapy. Furthermore, recent preclinical and clinical studies are reviewed to evaluate their efficacy, safety, and potential for integration into contemporary therapeutic regimens. By bridging traditional wisdom with modern scientific validation, this chapter aims to provide a comprehensive understanding of how these botanicals could contribute to a holistic and evidence-based approach to Parkinson's disease treatment.

Keywords: *PD, Ginkgo biloba, Gastrodia elata, neuroprotection, traditional Chinese medicine, oxidative stress, phytotherapy, dopaminergic neurons, integrative medicine*

1. Introduction

PD (PD) is a progressive neurodegenerative disorder marked by a gradual loss of dopaminergic neurons in the substantia nigra pars compacta, leading to reduced dopamine levels in the striatum. The hallmark symptoms of PD include tremor at rest, bradykinesia, muscle rigidity, and postural instability. Non-motor symptoms such as depression, anxiety, cognitive decline, sleep disturbances and autonomic dysfunction are also prevalent and significantly affect patients' quality of life. The pathogenesis of PD is multifactorial, involving oxidative stress, mitochondrial dysfunction, excitotoxicity, neuroinflammation, and abnormal protein aggregation, particularly the accumulation of α-synuclein into Lewy bodies. The global burden of PD is increasing, particularly due to aging populations, with estimates suggesting that over 12 million people may be affected worldwide by 2040. (1,2)

Limitations of Current Treatments

While existing therapies offer symptomatic relief, they do not halt or reverse the progression of neuronal degeneration. Levodopa remains the most effective treatment for motor symptoms, but chronic use often results in complications such as motor fluctuations and dyskinesias. Dopamine agonists and monoamine oxidase-B inhibitors provide additional benefit but are associated with adverse effects such as impulse control disorders and hallucinations. Non-motor symptoms often remain inadequately treated, and there is currently no therapy that effectively addresses the neurodegenerative process at the core of the disease. Surgical options, such as deep brain stimulation (DBS), are effective for selected individuals but are invasive and costly. These limitations highlight the critical need for novel therapeutic strategies that offer disease modification, neuroprotection, and comprehensive symptom management. (3)

Role of Traditional Medicine in Neurodegenerative Disorders

Traditional medicine, particularly herbal formulations used in Traditional Chinese Medicine (TCM) and other ethno medical systems, has long played a role in treating neurological conditions. Medicinal plants are rich sources of bioactive compounds with antioxidant, anti-inflammatory, and Neuroprotective properties mechanisms that are highly relevant to the pathophysiology of PD. *Ginkgo biloba* and *Gastrodia elata* are two prominent herbs used in TCM for brain health, cognitive enhancement, and treatment of neurological disorders. Recent pharmacological studies have demonstrated that these botanicals may exert beneficial effects in experimental models of PD by mitigating oxidative damage, suppressing neuroinflammation, enhancing mitochondrial function, and promoting neuronal survival. As such, they represent promising candidates for integrative approaches aimed at complementing existing PD therapies.

This chapter explores the traditional use, pharmacological properties, and emerging scientific evidence supporting the use of *Ginkgo biloba* and *Gastrodia elata* in the context of PD, with a focus on bridging traditional wisdom and modern therapeutic innovation. (4,5)

Ginkgo biloba: A Historical and Pharmacological Profile

Traditional Uses

Ginkgo biloba, often referred to as a "living fossil," is one of the oldest surviving tree species, dating back over 200 million years. Native to China, it has been extensively cultivated for medicinal use and holds a revered place in Traditional Chinese Medicine (TCM). Historically, Ginkgo leaves and seeds were used to treat a wide range of conditions, including asthma, bronchitis, circulatory disorders, cognitive decline, and sexual dysfunction.

In traditional practice, Ginkgo was believed to enhance cerebral circulation and promote "brain energy." Its use for age-related memory loss and senility dates back centuries. Ginkgo is also mentioned in

ancient Chinese texts like *Ben Cao Gang Mu*, where it was recommended for its ability to "nourish the heart and brain" and alleviate dizziness, tinnitus, and cognitive impairment symptoms often associated today with neurodegenerative disorders. Over time, Ginkgo's use spread beyond Asia, gaining popularity in Europe and North America as a natural remedy for memory enhancement, dementia, and peripheral vascular disease. (6,7)

Phytochemical Constituents

Ginkgo biloba leaves contain a unique and well-characterized spectrum of bioactive compounds responsible for its pharmacological effects. The two primary classes of constituents include:

- **Flavonoids**
    - **Examples**: Quercetin, kaempferol, isorhamnetin
    - **Properties**: Potent antioxidants; scavenge free radicals and protect cellular structures
- **Terpenoids (Ginkgolides and Bilobalide)**
    - **Ginkgolides A, B, C, J**: Diterpenes with potent anti-platelet activating factor (PAF) antagonism
    - **Bilobalide**: A sesquiterpene lactone with Neuroprotective and anti-apoptotic effects

Other constituents include proanthocyanidins, organic acids, and trace minerals. Commercial Ginkgo extracts, such as **EGb 761**, are standardized to contain 24% flavone glycosides and 6% terpene lactones, ensuring consistent pharmacological efficacy and safety in clinical use. (8,9)

2. Mechanisms of Action in Neuroprotection of *Ginkgo biloba*

Ginkgo biloba demonstrates a multifaceted Neuroprotective profile, making it a valuable candidate in the management of neurodegenerative diseases, particularly PD (PD). Its Neuroprotective properties are mediated through a variety of biochemical and cellular mechanisms that address key pathological features of PD. One of the primary actions of *Ginkgo biloba* lies in its potent antioxidant activity. The plant's bioactive constituents particularly flavonoids and terpenoids act as effective free radical scavengers. These compounds mitigate oxidative stress by neutralizing reactive oxygen species (ROS), thus preventing oxidative damage to essential biomolecules such as lipids, proteins, and DNA. This is significant since oxidative stress plays a pivotal role in the progressive degeneration of dopaminergic neurons in PD. Another critical mechanism involves the protection of mitochondrial function. *Ginkgo biloba* extract has been shown to enhance mitochondrial respiration, stabilize the mitochondrial membrane potential, and support ATP synthesis, thereby preventing mitochondrial-mediated apoptosis one of the major pathways leading to neuronal loss in PD. Additionally, its anti-inflammatory properties contribute substantially to its Neuroprotective effects. The standardized extract EGb 761 has been reported to suppress the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. It also inhibits the activation of the NF-κB signalling pathway, which plays a central role in initiating and sustaining neuroinflammation.

Moreover, *Ginkgo biloba* exerts anti-apoptotic effects, particularly through the action of Bilobalide, which modulates the expression of apoptosis-regulating proteins like Bcl-2 and Bax. This modulation helps inhibit programmed cell death in neurons subjected to toxic or oxidative insults. The extract also has significant effects on neurotransmitter systems. It modulates cholinergic, serotonergic, and dopaminergic neurotransmission. In experimental models, *Ginkgo* has been observed to elevate dopamine levels in the striatum and protect against dopamine depletion induced by neurotoxins such as MPTP, which mimics PD pathology.

In addition to these effects, *Ginkgo biloba* enhances cerebral vasodilation and microcirculation. This is achieved through antagonism of platelet-activating factor (PAF) and stimulation of nitric oxide synthesis, both of which improve cerebral blood flow. Improved cerebral circulation supports optimal neuronal metabolism and function, which is particularly important in aging populations at risk for neurodegeneration. Collectively, these diverse mechanisms of action highlight the Neuroprotective potential of *Ginkgo biloba*. By targeting oxidative stress, mitochondrial dysfunction, neuroinflammation, apoptosis, neurotransmitter imbalance, and cerebral hypo perfusion, *Ginkgo biloba* presents both symptomatic benefits and possible disease-modifying properties in PD. (10,11,12)

Gastrodia elata: An Ethno pharmacological Overview

Traditional Applications

Gastrodia elata Blume (Tian Ma in Traditional Chinese Medicine) is a perennial herbaceous plant from the Orchidaceae family. It has been used in East Asian medicine for over two millennia, particularly in China, Korea, and Japan. In Traditional Chinese Medicine (TCM), *Gastrodia* is classified as a "liver-pacifying" herb, often prescribed for conditions such as:

- Dizziness and vertigo
- Epilepsy and convulsions
- Headache and migraine
- Numbness of limbs
- Wind-stroke (a TCM term for stroke-like symptoms)
- Tetanus and neuralgia

The dried rhizome is the primary medicinal part. It is frequently combined with other herbs like *Ginkgo biloba*, *Uncaria rhynchophylla*, and *Chuanxiong* in formulas designed to treat neurological or cerebrovascular disorders. Its reputed ability to "calm the liver and extinguish wind" aligns with its clinical effects on seizure control and neurovascular regulation. (13,14)

Active Compounds and Neuroactive Effects

Phytochemical analysis of *Gastrodia elata* has identified several bioactive constituents responsible for its neuropharmacological effects:

Major Active Compounds:

- **Gastrodin** – The principal bioactive component; water-soluble phenolic glycoside
- **p-Hydroxybenzyl alcohol** – A Neuroprotective phenol
- **Vanillin** – Possesses antioxidant and anti-inflammatory properties
- **Parishins A, B, and C** – Complex phenolic glycosides contributing to central nervous system effects

Neuroactive Effects:

1. **Antioxidant Effects**
   Gastrodin and its metabolites reduce oxidative stress by scavenging free radicals and enhancing antioxidant enzyme activity (e.g., superoxide dismutase [SOD], catalase).
2. **Neuroprotection in PD Models**
   In 6-hydroxydopamine (6-OHDA)- and MPTP-induced models of Parkinson's disease,

Gastrodia extracts have shown the ability to preserve dopaminergic neurons in the substantia nigra and improve motor behavior.

3. **Anti-excitotoxicity**
   Gastrodin inhibits glutamate-induced excitotoxicity, a major contributor to dopaminergic neuronal death in PD.

4. **Anti-inflammatory Action**
   Down regulation of pro-inflammatory cytokines (e.g., TNF-α, IL-1β) and suppression of the NF-κB pathway have been observed in both *in vitro* and *in vivo* models.

5. **GABAergic Modulation**
   Gastrodin increases GABA levels and GABA receptor expression in the brain, contributing to its anticonvulsant, anxiolytic, and sedative properties. This also supports regulation of dopaminergic circuits indirectly.

6. **Neurotropic and Synaptic Plasticity Effects**
   Gastrodia enhances the expression of brain-derived neurotropic factor (BDNF) and modulates pathways related to neuronal survival and regeneration. (15,16)

Clinical Trials and Human Data

A growing body of clinical research supports the potential role of *Ginkgo biloba*, particularly the standardized extract EGb 761, in improving cognitive and neurological function, with emerging evidence in the context of PD (PD). Several clinical trials and observational studies have explored its safety, efficacy, and Neuroprotective potential in human populations. In elderly patients with mild to moderate cognitive impairment or early-stage dementia conditions with overlapping features to PD *Ginkgo biloba* extract has demonstrated consistent improvements in cognitive performance, memory, attention, and daily functioning. Large-scale randomized controlled trials (RCTs), such as the GEM (Ginkgo Evaluation of Memory) study, examined EGb 761 in over 3,000 elderly individuals. While the study found no significant effect in preventing dementia, subgroup analyses suggested cognitive benefits in individuals with pre-existing neurovascular risk factors indirectly relevant to Parkinson's pathology.

Specifically related to PD, smaller-scale clinical studies have explored *Ginkgo biloba* as an adjunct therapy. In these trials, patients receiving EGb 761 alongside standard antiparkinsonian medications showed improvement in motor symptoms, cognitive performance, and quality of life compared to control groups. One pilot study reported that co-administration of EGb 761 reduced "off" periods in PD patients on levodopa therapy and enhanced dopamine availability. Another open-label trial found that long-term use of *Ginkgo biloba* extract improved mood, attention span, and reaction time in PD patients, suggesting its utility in managing non-motor symptoms such as depression and cognitive decline.

Human data also support the vascular benefits of *Ginkgo biloba*, with clinical trials demonstrating increased cerebral blood flow and oxygenation in elderly individuals. This effect may be particularly beneficial in PD patients, where cerebrovascular insufficiency is often a contributing factor to disease progression. Importantly, *Ginkgo biloba* has shown a favourable safety profile in most clinical studies, with adverse effects generally mild and infrequent commonly including gastrointestinal upset or mild headache. However, it may interact with anticoagulant medications due to its antiplatelet effects, and this warrants careful clinical monitoring.

In summary, clinical evidence supports the use of *Ginkgo biloba* particularly EGb 761 as a complementary therapeutic agent in neurodegenerative diseases. While larger, high-quality RCTs specifically targeting PD are still needed; existing human data suggest that *Ginkgo biloba* can offer

benefits in cognitive enhancement, motor function, and cerebral circulation, making it a promising adjunct in the holistic management of PD. (17,18,19)

3. Comparative and Complementary Approaches of *Ginkgo biloba* in PD Management

Ginkgo biloba offers a unique and complementary therapeutic profile when compared to conventional pharmacological treatments for PD (PD). Standard therapies, such as levodopa, dopamine agonists, MAO-B inhibitors, and COMT inhibitors, primarily aim to restore or mimic dopamine activity in the brain, thereby addressing the motor symptoms of PD. However, these medications do not halt disease progression and are often associated with long-term complications like motor fluctuations and dyskinesias. In contrast, *Ginkgo biloba* targets broader neurodegenerative mechanisms such as oxidative stress, mitochondrial dysfunction, inflammation, and impaired cerebral circulation factors that contribute not only to PD progression but also to non-motor symptoms such as cognitive decline, fatigue, and depression.

Comparatively, *Ginkgo biloba* is not a dopamine replacement therapy but rather a neuroprotective agent. Its flavonoids and terpenoids reduce oxidative stress and mitochondrial dysfunction underlying mechanisms not directly targeted by conventional PD drugs. Additionally, its anti-inflammatory and anti-apoptotic effects address the chronic neuroinflammation and neuronal death often observed in PD, which are not adequately managed by current pharmacotherapy. These mechanisms position *Ginkgo biloba* as a disease-modifying agent, potentially capable of slowing neurodegeneration when used early in the disease course.

As a complementary approach, *Ginkgo biloba* can be safely integrated with standard PD medications to enhance therapeutic outcomes. For instance, studies suggest that EGb 761 may improve cerebral blood flow and cognitive function, thereby helping manage non-motor symptoms that often persist despite optimal dopaminergic therapy. Moreover, its ability to modulate neurotransmission may enhance dopaminergic tone and reduce "off" periods in patients on levodopa. Importantly, unlike many synthetic drugs, *Ginkgo biloba* is generally well-tolerated, with a low incidence of serious adverse effects, making it suitable for long-term use as an adjunctive therapy. From a holistic or integrative medicine perspective, *Ginkgo biloba* aligns well with other complementary strategies such as physical therapy, nutritional support, yoga, and mindfulness all aimed at enhancing quality of life and preserving function in PD patients. It is particularly appealing in early or prodromal stages of PD, where Neuroprotective interventions could potentially delay the onset or progression of symptoms. (20,21,22)

In conclusion, while *Ginkgo biloba* is not a substitute for conventional dopaminergic therapies, it represents a valuable complementary approach. By addressing multiple pathophysiological pathways that underlie PD progression and by improving non-motor symptoms and overall brain health, *Ginkgo biloba* can enhance the effectiveness and tolerability of existing treatments, contributing to a more comprehensive, patient-centered management strategy for PD.

Scientific Evidence and Therapeutic Potential

Preclinical Studies

Extensive preclinical research has demonstrated that both *Ginkgo biloba* and *Gastrodia elata* possess potent Neuroprotective effects that are highly relevant to the pathophysiology of PD (PD). These effects have been extensively studied in various *in vitro* and *in vivo* models using well-established neurotoxins such as MPTP, 6-hydroxydopamine (6-OHDA), and rotenone, which mimic the progressive degeneration of dopaminergic neurons characteristic of PD.

In the case of *Ginkgo biloba*, studies utilizing the MPTP-induced mouse model have shown that treatment with the standardized extract EGb 761 effectively protects dopaminergic neurons in the

substantia nigra. This preservation of neuronal integrity was accompanied by significant improvements in motor function and a marked reduction in oxidative stress markers. Similarly, in rotenone-treated rat models, EGb 761 was found to stabilize mitochondrial function, suppress neuroinflammation particularly through the down regulation of pro-inflammatory cytokines such as TNF-α and IL-1β and enhance neuronal survival. Mechanistically, these protective actions were attributed to *Ginkgo biloba*'s robust antioxidant activity, inhibition of apoptotic pathways via the modulation of Bcl-2 and Bax proteins, stabilization of mitochondrial membrane potential, and activation of pro-survival PI3K/Akt signalling pathways.

Gastrodia elata, another traditional herbal medicine, has also shown significant Neuroprotective effects in PD models. In 6-OHDA-lesioned rats, its active compound gastrodin preserved dopaminergic neurons and improved behavioural deficits. Furthermore, in *in vitro* models subjected to glutamate-induced excitotoxicity, gastrodin prevented neuronal death by enhancing GABAergic neurotransmission and reducing excitotoxic damage. The Neuroprotective mechanisms of *Gastrodia elata* involve strong antioxidant properties evidenced by increased levels of superoxide dismutase (SOD) and glutathione (GSH) as well as anti-inflammatory actions via the suppression of nuclear factor kappa B (NF-κB) and interleukin-6 (IL-6). Additionally, *Gastrodia elata* has been shown to promote neuronal survival through the up regulation of neurotrophic factors such as brain-derived neurotrophic factor (BDNF). Notably, studies investigating the combined use of *Ginkgo biloba* and *Gastrodia elata* extracts in rodent models of PD have demonstrated enhanced neuroprotective efficacy compared to either agent alone. This synergistic effect is believed to result from the complementary mechanisms of action *Ginkgo biloba*'s antioxidant and mitochondrial-protective roles combined with *Gastrodia elata*'s anti-excitotoxic and neurotrophic-enhancing properties. Together, these herbs effectively target multiple pathogenic pathways of PD, including dopaminergic neuron preservation, inflammation modulation, oxidative stress reduction, and neurotransmitter balance.

Overall, these preclinical findings strongly support the therapeutic potential of both *Ginkgo biloba* and *Gastrodia elata*, individually and in combination, as promising neuroprotective agents in the context of PD. Their multifaceted actions offer a foundation for further translational research and eventual clinical application in disease modification and symptomatic management. (23,24,25)

Recommended Dosage Ranges

Although human clinical trials in PD remain limited, standard dosage ranges have been established based on pharmacological, toxicological, and clinical use data.

Ginkgo biloba (Standardized Extract EGb 761)

- **Preclinical dose**: 50–150 mg/kg/day (rodents)
- **Human equivalent dose (HED)**: 120–240 mg/day
- **Formulations**: Tablets, capsules, liquid extract
- **Standardization**: 24% flavone glycosides, 6% terpene lactones

Gastrodia elata (Gastrodin)

- **Preclinical dose**: 50–100 mg/kg/day (gastrodin); 0.5–1.5 g/kg/day (crude extract)
- **Human equivalent dose**:
    - Gastrodin extract: 300–600 mg/day
    - Crude rhizome: 3–6 g/day (TCM use)

- **Formulations**: Capsules, decoctions, injectable solutions (used in China)

  Dosage may be adjusted depending on the patient's age, comorbidities, concurrent medication use, and clinical goals (e.g., motor vs. non-motor symptom relief). (26,27)

Interaction with Conventional PD Medications

Both herbs may interact pharmacodynamically and pharmacokinetically with conventional PD treatments, particularly **levodopa** and **dopaminergic adjuncts**.

Ginkgo biloba Interactions

- **Levodopa**: May enhance dopaminergic activity and cerebral blood flow. Monitor for dyskinesias or fluctuations.
- **Monoamine oxidase-B inhibitors (e.g., selegiline)**: Mild MAO-inhibitory effect may potentiate drug action; watch for serotonergic effects.
- **Anticoagulants (e.g., warfarin, aspirin)**: Ginkgo inhibits platelet-activating factor (PAF), increasing bleeding risk.
- **SSRIs/SNRIs**: Theoretical risk of serotonin syndrome when combined.

Gastrodia elata Interactions

- **Levodopa**: May improve levodopa efficacy via neuroprotection and GABAergic support.
- **CNS depressants or benzodiazepines**: Gastrodin enhances GABAergic tone and may potentiate sedative effects.
- **Anticonvulsants**: May interact synergistically, potentially requiring dose adjustment. (28,29,30)

Clinical Considerations

- **Polypharmacy** is common in PD, especially among older adults. Regular monitoring for herb-drug interactions is essential.
- **Start Low and Go Slow**: It is advisable to initiate herbal therapy at the lower end of the dosage spectrum and adjust based on patient response and tolerance.
- **Monitoring Parameters**: Watch for signs of over-sedation, bleeding risk (with Ginkgo), or altered PD symptom control.

Preclinical studies strongly support the therapeutic potential of *Ginkgo biloba* and *Gastrodia elata* in PD through Neuroprotective, anti-inflammatory, and antioxidant pathways. Dosage ranges established through clinical use in other neurological disorders provide a foundation for integration into PD care. However, careful consideration of drug-herb interactions is essential to ensure safety and efficacy in clinical settings. These agents represent promising **complementary options** that warrant further investigation through high-quality clinical trials. (31)

Mechanisms of Neuroprotection

The neurodegenerative process in PD (PD) involves a complex interplay of oxidative stress, neuroinflammation, mitochondrial dysfunction, and neurotransmitter imbalance. *Ginkgo biloba* and *Gastrodia elata* exert Neuroprotective effects by targeting these critical pathways. Their combined activity offers a multi-mechanistic approach to slow disease progression and improve neurological function.

Antioxidant Activity

Oxidative stress is a central driver of dopaminergic neuron degeneration in PD, primarily due to excessive production of reactive oxygen species (ROS), impaired mitochondrial function, and dopamine metabolism itself.

Ginkgo biloba

- Rich in flavonoids (quercetin, kaempferol) and terpenoids (ginkgolides, bilobalide).
- Neutralizes ROS, reduces lipid peroxidation, and protects cellular proteins and DNA.
- Enhances endogenous antioxidant enzymes like superoxide dismutase (SOD) and catalase.
- In MPTP-treated mice, EGb 761 significantly reduced malondialdehyde (MDA) levels, a marker of lipid peroxidation.

Gastrodia elata

- Gastrodin and 4-hydroxybenzyl alcohol scavenge free radicals and upregulate antioxidant enzymes.
- In 6-OHDA and glutamate-induced toxicity models, gastrodin reduced ROS levels and prevented neuronal apoptosis.
- Increases intracellular levels of glutathione (GSH), preserving redox balance in dopaminergic neurons.

Combined Impact: When co-administered, Ginkgo and Gastrodia synergistically reduce oxidative load and promote neuronal resilience against toxin-induced oxidative injury. (32,33)

Anti-inflammatory and Mitochondrial Protection

Chronic neuroinflammation contributes to PD progression through activation of microglia and increased release of pro-inflammatory cytokines, which impair mitochondrial energy production and trigger apoptotic pathways.

Anti-inflammatory Effects

- ***Ginkgo biloba*** inhibits activation of nuclear factor-kappa B (NF-κB), suppressing the transcription of inflammatory cytokines such as TNF-α, IL-1β, and COX-2.
- ***Gastrodia elata*** downregulates inducible nitric oxide synthase (iNOS), NF-κB, and prostaglandin E2 (PGE2) in activated microglia.
- Both herbs inhibit microglial activation, reducing neuroinflammatory damage in the substantia nigra.

Mitochondrial Protection

- **Ginkgo** stabilizes mitochondrial membranes, prevents cytochrome c release, and restores ATP synthesis. Bilobalide is especially noted for preserving mitochondrial integrity.
- **Gastrodin** protects mitochondrial potential (Δψm), decreases mitochondrial ROS, and prevents calcium overload.
- In cellular models, co-treatment with both herbs preserved mitochondrial function under oxidative and inflammatory stress.

Combined Impact: Dual protection of mitochondria and inhibition of neuroinflammation reduces apoptosis and promotes energy homeostasis in dopaminergic neurons. (34,35)

Neurotransmitter Regulation

Dysregulation of neurotransmitter systems, especially dopamine and gamma-aminobutyric acid (GABA), is a hallmark of PD. Ginkgo and Gastrodia influence multiple neurotransmitter pathways.

Ginkgo biloba

- Increases dopamine availability by protecting dopaminergic neurons.
- Enhances dopaminergic transmission in the striatum and prefrontal cortex.
- Also influences serotonergic and cholinergic pathways, which may benefit mood and cognition in PD.

Gastrodia elata

- Modulates GABAergic transmission by increasing GABA levels and enhancing GABA receptor sensitivity.
- Reduces excitotoxic glutamate activity, protecting neurons from overstimulation-induced apoptosis.
- May indirectly support dopaminergic balance through neurotrophic and anti-glutamatergic actions.

Combined Impact: Ginkgo supports dopaminergic signalling, while Gastrodia enhances GABAergic stability, together improving motor coordination, reducing tremors, and alleviating non-motor symptoms such as anxiety or insomnia.

The Neuroprotective mechanisms of *Ginkgo biloba* and *Gastrodia elata* span critical pathogenic pathways in PD:

- **Antioxidant activity** protects against oxidative injury.
- **Anti-inflammatory and mitochondrial actions** preserve neuronal energy and prevent cell death.
- **Neurotransmitter regulation** restores dopaminergic and GABAergic balance.

This multimodal activity forms the pharmacological basis for their combined therapeutic potential in PD, particularly as adjuncts to conventional therapy. (36,37)

Safety, Dosage, and Drug-Herb Interactions

Toxicological Considerations

Ginkgo biloba and *Gastrodia elata* both have long-standing reputations for safety in traditional medicine systems, and modern toxicological assessments largely affirm their tolerability when used at therapeutic doses. However, like all active pharmacological agents, their safety profiles must be evaluated within the context of dosage, treatment duration, individual variability, and particularly in polypharmacy settings such as those involving PD (PD) patients, who are often on multiple medications.

Ginkgo biloba

General Safety Profile:
Ginkgo biloba, especially in its standardized form EGb 761, is widely used across Europe and Asia. It is generally well-tolerated, with most reported adverse effects being mild and transient. These commonly include gastrointestinal discomfort, headache, dizziness, and occasionally, mild allergic skin reactions. These effects are typically dose-dependent and reversible upon discontinuation.

Toxicological Data:
Preclinical studies indicate that very high doses of *Ginkgo biloba* (greater than 1,500 mg/kg/day) can lead to hepatotoxic and genotoxic effects in animals. However, such levels are vastly higher than typical therapeutic doses in humans. The U.S. National Toxicology Program (NTP) raised concerns about a possible link between long-term, high-dose Ginkgo administration and carcinogenicity in rodents, though such findings have not been replicated in human clinical settings using standard dosages. Thus, current data support the relative safety of clinical use when confined to recommended dosing regimens.

Specific Caution:
A major safety concern with *Ginkgo biloba* is its effect on blood clotting. As an inhibitor of platelet-activating factor (PAF), it may increase bleeding risk, especially when combined with anticoagulants (e.g., warfarin, aspirin), antiplatelet agents, or in patients with bleeding disorders. It is also advisable to discontinue Ginkgo supplementation before surgical procedures to reduce the risk of perioperative bleeding.

Gastrodia elata

General Safety Profile:
Gastrodia elata is also regarded as highly safe, with centuries of use in traditional East Asian medicine and formal approval as an over-the-counter remedy in China, including injectable forms for neurological and cerebrovascular conditions. Its principal bioactive compound, gastrodin, is known for its neuroprotective and anticonvulsant properties, with a high therapeutic index and minimal side effects.

Toxicological Data:
Toxicological studies have shown no evidence of mutagenicity, teratogenicity, or reproductive toxicity in standard laboratory models. The LD_{50} (lethal dose for 50% of the population) for gastrodin exceeds 10 g/kg in rodents, indicating very low acute toxicity. Moreover, chronic administration at doses higher than the human equivalent did not result in significant organ toxicity or behavioral abnormalities in animal studies, further supporting its safety in long-term use.

Specific Caution:
While *Gastrodia elata* is generally well-tolerated, its pharmacological action on the GABAergic system can lead to mild sedation. At higher doses, it may enhance the effects of sedative medications and cause drowsiness. Additionally, rare instances of mild hypotension have been reported, though these effects are not typically clinically significant. (38,39,40)

Synergistic Potential with *Ginkgo biloba*

Combining *Ginkgo biloba* and *Gastrodia elata* offers a **synergistic therapeutic profile** for neuroprotection in PD, with no evidence of toxicological antagonism. Their overlapping yet complementary mechanisms target multiple aspects of PD pathophysiology.

Table 4.1 Synergistic Potential with *Ginkgo biloba*

Mechanism	***Ginkgo biloba***	***Gastrodia elata***	**Synergistic Effect**
Antioxidant Defense	Flavonoids, Bilobalide	Gastrodin, vanillin	Enhanced ROS scavenging
Mitochondrial Support	Bilobalide enhances ATP	Gastrodin stabilizes $\Delta\psi m$	Improved energy metabolism
Anti-inflammatory	Inhibits NF-κB, cytokines	Inhibits microglia, NO	Broad-spectrum inflammation control
Neurotransmission	Enhances dopamine, acetylcholine	Enhances GABA, reduces glutamate	Balanced excitatory/inhibitory tone

Cognitive and Mood Effects	Improves memory, blood flow	Reduces anxiety, improves sleep	Improved quality of life in PD
Drug Tolerance	Generally well tolerated	Highly safe	Suitable for long-term co-administration

Formulation Examples:

- Traditional Chinese medicine formulas such as *Tianma Ginkgo Capsule* and *Ginkgo Gastrodin Tablets* are clinically used for cognitive decline, stroke recovery, and PD-like symptoms.
- Combination therapy may allow **lower doses** of dopaminergic drugs, potentially reducing side effects like dyskinesia and motor fluctuations.

Summary and Recommendations

Table 4.2 Summary and Recommendations

Herb	Standardized Dose (Humans)	Known Risks	Cautions With
Ginkgo biloba	120–240 mg/day (EGb 761)	Bleeding, GI upset	Warfarin, aspirin, SSRIs
Gastrodia elata	300–600 mg/day (gastrodin); 3–6 g/day (crude)	Sedation (mild), hypotension (rare)	CNS depressants, alcohol

Clinical Recommendation: Co-administration is generally safe in appropriate doses, but regular monitoring is advised in elderly patients, those on anticoagulants, or polypharmacy regimens. (41,42,43)

Integration into Modern Therapy

4. Challenges and Opportunities

The incorporation of traditional herbal medicines such as *Ginkgo biloba* and *Gastrodia elata* into modern therapeutic strategies for PD (PD) presents a compelling yet complex opportunity. These botanicals offer a multifaceted approach to neuroprotection and symptomatic management, potentially addressing gaps left by conventional pharmacotherapies. Their ability to modulate oxidative stress, neuroinflammation, mitochondrial dysfunction, and neurotransmitter balance makes them particularly well-suited to the intricate and progressive nature of PD. However, despite this promise, several challenges hinder their widespread clinical adoption. One of the primary barriers is the limited availability of high-quality clinical trials. Most existing human studies are small, open-label, or observational in nature, lacking the rigorous methodology of randomized controlled trials (RCTs) required to establish definitive efficacy and safety in PD populations. This scarcity of robust clinical data weakens the case for regulatory approval and formal integration into treatment guidelines. Another significant issue lies in the variability of herbal preparations. Differences in cultivation, extraction techniques, phytochemical composition, and formulation lead to inconsistencies between products, complicating reproducibility and standardization an essential requirement for evidence-based clinical use.

Additionally, the potential for herb-drug interactions is a legitimate concern. Both *Ginkgo biloba* and *Gastrodia elata* possess active constituents that may influence cytochrome P450 enzymes or platelet aggregation, raising concerns about interactions with key PD medications such as levodopa, anticoagulants, or central nervous system agents. Without careful monitoring, these interactions could compromise treatment efficacy or patient safety. Furthermore, skepticism remains prevalent in conventional medical communities, where many clinicians lack formal training in herbal or integrative medicine. This often results in hesitancy to recommend or co-manage patients using herbal therapies. Despite these challenges, notable opportunities support the integration of these botanicals into PD care. Their multi-targeted mechanisms of action align well with the complex pathology of PD, offering the

potential to address both motor and non-motor symptoms areas where standard treatments may fall short. For instance, *Gastrodia elata*'s GABAergic effects can help manage sleep disturbances and anxiety, while *Ginkgo biloba*'s vascular and antioxidant properties may support cognitive function and cerebral perfusion. Patient interest in natural and holistic therapies continues to grow, especially among those seeking alternatives to Polypharmacy or relief from non-motor symptoms such as fatigue, depression, and insomnia. These herbs also hold promise as adjunctive therapies. When used alongside conventional PD medications, they may enhance therapeutic efficacy, reduce required drug dosages, and mitigate side effects. Preliminary data suggest that such combinations could lead to improved quality of life and treatment outcomes. Moreover, their Neuroprotective properties open avenues for early intervention in prodromal PD potentially delaying disease onset or slowing progression in high-risk individuals or those with early, subtle symptoms.

In conclusion, while the integration of *Ginkgo biloba* and *Gastrodia elata* into PD management faces notable scientific and clinical hurdles, the potential benefits warrant further exploration. Strategic investments in high-quality research, standardized formulations, clinician education, and patient-centered care models could transform these traditional herbs into valuable components of a modern, integrative approach to PD. (44,45)

Regulatory and Standardization Issues

The effective incorporation of *Ginkgo biloba* and *Gastrodia elata* into mainstream healthcare systems necessitates the resolution of significant regulatory and quality control challenges. Despite their long-standing use in traditional medicine and growing scientific support for their Neuroprotective roles, especially in neurodegenerative diseases like PD (PD), inconsistencies in standardization and regulatory oversight hinder their broader acceptance and clinical application.

Standardization is a critical prerequisite for ensuring safety, efficacy, and reproducibility in herbal therapies. *Ginkgo biloba* stands as a relative success story in this regard. The extract EGb 761 comprising 24% flavone glycosides and 6% terpene lactones is a well-characterized, pharmaceutical-grade preparation that has been extensively studied and is widely used in Europe. It is recognized as an over-the-counter (OTC) supplement in the United States, although not formally approved for the treatment of specific diseases. In contrast, *Gastrodia elata* has not achieved the same global standardization. While gastrodin, its primary active compound, is widely used in China and included in the Chinese Pharmacopoeia in both oral and injectable forms, internationally harmonized standards for *Gastrodia elata* remain underdeveloped. (48)

Regulatory gaps present another layer of complexity. Herbal medicines lack uniform global regulation, leading to significant variability in how products are categorized as food, dietary supplements, or medicinal agents depending on the country. This inconsistent classification creates confusion among healthcare providers and patients, and complicates the process of obtaining regulatory approval. The situation becomes even more challenging when dealing with combination botanical products, such as formulations that include both *Ginkgo biloba* and *Gastrodia elata*, which must meet stringent criteria for quality, consistency, and synergistic efficacy requirements that are often difficult to fulfill under current regulatory frameworks. Moreover, Pharmacovigilance systems for herb-based therapies are generally underdeveloped or inconsistently implemented, limiting the ability to monitor long-term safety and efficacy in real-world settings.

To address these challenges, several recommendations can be proposed. First, there is a need for harmonized international guidelines that clearly define the regulatory pathway for herbal medicines, including combination products. This would provide a more predictable framework for manufacturers and facilitate integration into evidence-based clinical practice. Second, investment in advanced

phytochemical fingerprinting techniques and robust quality control measures is essential to ensure batch-to-batch consistency, verify bioactive content, and detect potential contaminants or adulterants. These measures will strengthen the scientific credibility of botanical products and enhance patient and clinician confidence. Third, there should be greater emphasis on post-market surveillance and the generation of real-world evidence through registries, observational studies, and patient-reported outcomes. This data can complement randomized clinical trials and provide a fuller picture of safety and effectiveness in diverse patient populations. (49,50)

In conclusion, while *Ginkgo biloba* and *Gastrodia elata* hold substantial therapeutic promise for neurodegenerative conditions such as PD, their successful integration into modern medicine hinges on overcoming regulatory and standardization hurdles. Through international collaboration, investment in scientific validation, and the development of unified policies, these traditional botanicals can be more effectively and safely utilized in contemporary healthcare settings.The integration of *Ginkgo biloba* and *Gastrodia elata* into modern clinical neurology represents a forward-thinking, patient-centered approach that harmonizes traditional medicinal wisdom with the principles of evidence-based care. PD (PD), with its multifactorial pathology and complex array of motor and non-motor symptoms, requires a comprehensive treatment model. An integrative strategy that includes these botanicals offers unique therapeutic value by addressing diverse symptom domains and underlying neurodegenerative mechanisms.

One of the primary benefits of an integrative approach is its ability to deliver holistic patient care. While conventional therapies like levodopa primarily manage motor symptoms, *Ginkgo biloba* and *Gastrodia elata* can additionally support cognitive function, mood stabilization, and sleep quality critical aspects of quality of life that are often inadequately addressed in standard regimens. Moreover, this approach enables personalized medicine, wherein herbal prescriptions can be tailored to reflect individual patient profiles, symptom severity, and comorbidities, enhancing therapeutic responsiveness and minimizing side effects. (51,52) Another significant advantage lies in the potential to reduce the burden of Polypharmacy, a common challenge in PD management. By targeting multiple pathological pathways oxidative stress, neuroinflammation, mitochondrial dysfunction, and neurotransmitter imbalances these herbs may reduce reliance on multiple synthetic agents, thereby simplifying treatment regimens and improving patient adherence. Additionally, the integrative model has strong cross-cultural relevance, particularly for patients from Asian backgrounds where traditional herbal practices are culturally ingrained. Incorporating these therapies respectfully can foster greater trust, acceptance, and cultural competence in clinical care. To effectively implement such an integrative model, several strategic steps are required. Firstly, it is essential to educate healthcare professionals, including neurologists, pharmacists, and general practitioners, in the basics of herbal pharmacology and integrative medicine principles. This foundational knowledge will help them evaluate safety, efficacy, and potential interactions in a clinical context. Secondly, evidence-informed protocols should be developed to guide the co-administration of herbal agents with conventional PD medications, ensuring therapeutic synergy while minimizing adverse effects. (53)

Additionally, collaborative care models must be established, bringing together neurologists, integrative practitioners, clinical pharmacologists, and traditional medicine experts. Such interdisciplinary teams can create individualized care plans that balance innovation with safety. Lastly, future clinical trial designs should move beyond the reductionist focus on isolated phytochemicals and instead evaluate whole-herb formulations, reflecting the way these botanicals are traditionally used and capturing the synergistic interactions among their multiple constituents. Despite existing regulatory and scientific challenges, the integration of *Ginkgo biloba* and *Gastrodia elata* into the therapeutic landscape of PD holds considerable promise. Their well-documented pharmacological actions, long-standing use in

traditional medicine, and emerging supportive clinical evidence justify their inclusion as adjunctive therapies in a modern, patient-centered, and multi-targeted treatment paradigm. Realizing their full clinical utility will require continued research, regulatory evolution, and a commitment to integrative, culturally respectful, and individualized care. (46,47,54,55)

Conclusion and Future Directions

PD (PD) is a progressive disorder with limited treatment options, where conventional drugs mainly provide temporary relief. *Ginkgo biloba and Gastrodia elata* show promise as adjunct therapies due to their antioxidant, anti-inflammatory, neuroprotective, and neurotransmitter-modulating effects, offering multi-pathway support in PD. Their safety profiles and potential to complement standard medications make them valuable candidates, but robust clinical trials are urgently needed to confirm efficacy, safety, and optimal dosing. Standardized formulations, mechanistic studies using advanced molecular tools, and integrative care models are essential for translation into practice. Future directions should also emphasize personalized medicine, early intervention, and clinician education to optimize their role in PD management.

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Chapter 7: Next-Generation Formulation and Delivery Innovations in Herbal Neurotherapeutics

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Abstract

This chapter critically examines the evolution of herbal neurotherapeutics, emphasising the transition from traditional remedies to advanced formulation and delivery technologies suitable for modern clinical application. Herbal medicines, while historically significant in managing neurological disorders, are often limited by poor solubility, low bioavailability, and challenges in crossing the blood-brain barrier, which restrict their therapeutic efficacy. Recent innovations such as nanotechnology-based systems (including nanoemulsions, liposomes, nanogels, and solid lipid nanoparticles) have demonstrated significant improvements in drug stability, targeted delivery, and central nervous system penetration, thereby enhancing the pharmacological potential of plant-derived neuroprotective agents. The chapter also explores smart, stimuli-responsive delivery platforms and the integration of polyherbal combinations, leveraging systems biology and network pharmacology to achieve multi-targeted effects. Advances in artificial intelligence and bioinformatics are highlighted for their roles in predicting blood-brain barrier permeability and optimising herbal drug discovery. Regulatory, ethical, and commercial considerations are discussed, with a focus on global harmonisation and the responsible use of traditional knowledge. Looking forward, the chapter addresses frontier trends such as exosome-mediated delivery, personalised neurotherapeutics, and digital health integration, underscoring the necessity of interdisciplinary approaches for future research, policy, and commercialisation in herbal neurotherapeutics

Keywords: *Herbal neurotherapeutics, novel drug delivery systems, nanotechnology, phytoconstituents, blood-brain barrier, neuroprotection, bioavailability, targeted delivery, polyherbal combinations.*

1. Introduction to Herbal Neurotherapeutics

(1.1) Definition and Scope of Herbal Neurotherapeutics

Herbal Neurotherapeutics represents a specialized field that encompasses the use of medicinal plants and plant-derived compounds to prevent, manage, and treat neurological disorders and symptoms affecting the central and peripheral nervous systems. This field integrates natural products, secondary metabolites, and bioactive molecules derived from plants, animals, and microorganisms that have been demonstrated to possess neuroprotective, anti-inflammatory, antioxidant, and neuroregenerative properties (1) .

The scope of neurotherapeutics extends across a wide spectrum of neurological conditions, including neurodegenerative diseases such as AD, Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis, as well as neuropsychiatric disorders including epilepsy, depression, anxiety, schizophrenia, and memory-related problems (1) . These therapeutic approaches target multiple pathways simultaneously, including modulation of amyloid and tau proteins, cholinergic systems, oxidative stress pathways, mitochondrial function, and neuroinflammation (1) .

Herbal neurotherapeutics encompasses various phytoconstituents such as polyphenolic antioxidants found in herbs, fruits, nuts, and vegetables, as well as marine and freshwater flora. These compounds, including flavonoids, alkaloids, terpenoids, and glycosides, are thought to play key roles in preventing neurodegeneration and improving brain memory and cognitive abilities(1) .

(1.2) Importance of Traditional Medicine in Neurological Disorders

Traditional medicine systems play a crucial and fundamental role in managing neurological disorders, particularly in developing countries where access to modern healthcare services and specialists remains limited (2). The World Health Organization reports that approximately 75-80% of the population in developing countries, predominantly in Africa, consult traditional healers and rely on traditional medicine for their primary healthcare needs, including neurological conditions as shown in Figure 1(2) .

Traditional holistic approaches, particularly the Indian Ayurvedic system, offer comprehensive management strategies for neurological disorders. These systems provide polyherbal formulations that function as antioxidants, reduce amyloid deposits, and act as neuroprotective, anti-inflammatory, and immunomodulating compounds that alter neuroendocrine-immune activities, enhance memory, activate neurofunctions, and improve quality of life (2) . The Ayurvedic approach emphasizes a balanced lifestyle, proper nutrition, socio-psychological support, Rasayanas (rejuvenative therapies), and psychotherapies as effective methods to prevent and treat Alzheimer's disease and other neurodegenerative disorders (2) .

The importance of traditional medicine is particularly evident in regions like Cameroon, where neurological disorders represent 20% of hospitalization cases, with epilepsy and headaches being the most prevalent conditions. In such settings, traditional medicine serves as an alternative and accessible option due to inadequate access to modern medicine, high costs of conventional treatments, and side effects associated with synthetic drugs (2). The traditional approach is especially valuable because it provides affordable healthcare to the poorest patients and utilizes the plant extracts that are perceived to have fewer side effects compared to conventional pharmaceuticals (2). In addition, the medical traditions also play the important role of drug discovery since about the twenty-five percent of medicines prescribed in the world are plant-based. This highlights the ongoing importance of and possibilities of traditional knowledge in achieving the creation of novel therapeutic applications to continue looking towards neurological disorders (2) .

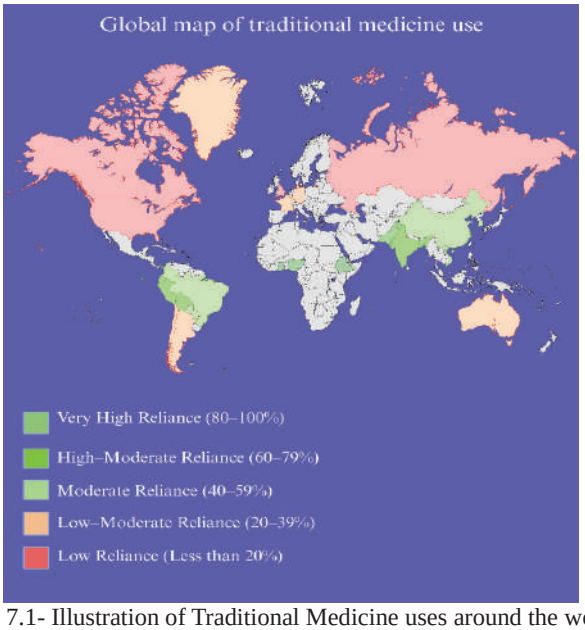

Fig 7.1- Illustration of Traditional Medicine uses around the world

(1.3) Limitations of Conventional Herbal Therapies

Despite the promising potential of herbal neurotherapeutics, several significant limitations and challenges constrain their widespread clinical application and integration into modern healthcare systems.

- One of the greatest limitations is the absence of standardization and consistency. Unlike synthetic drugs, herbal medicines do not have the same concentration of active components and universal biological chemical signature. Such changes occur because of the different species of plants, plant growth, harvesting and preparation practices, thus it is difficult to reproduce therapeutic effects in a benchmarked fashion (3) .
- Efficacy of the herbals is also restrained by poor bioavailability and pharmacokinetics. Most of the herbal compounds have low solubility, permeability, and stability, particularly those that have to survive the blood-brain barrier (BBB), limiting their access to the central nervous system. To illustrate, quercetin and other phytochemicals demand new modes of delivery such as nanoparticles to optimize drug delivery and therapeutics outcomes (3) .
- Safety issues and bad interactions are also tough challenges. The herbal supplements may severely affect the organism with neurotoxicity, and they can become unfavorably combined with other medications. As an example, St. Johns Wort (SJW) has the potential to either block the activity of monoamine oxidase or increase neurotransmitter amounts because of the harmful effect on the antidepressants that could be in use. *Ginkgo biloba* has the potential of interacting with anticoagulants and enhancing chances of bleeding and Panax ginseng has capability of lowering warfarin activity (3)
- Another notable limitation is that there is a paucity of rigorous clinical evidence. They include many of the herbal treatments done in a not so well designed randomized controlled trials needed to approve a conventional drug. This scientific sloppiness and unproven pharmacodynamic data impedes mainstream medicine acceptance of them (3) .

- There are issues regarding the design and regulatory framework of clinical trial development and authorization since it is difficult to design an effective placebo that would meet the sensory properties of the herbal products and provide a homogenous effect between different batches. In addition, new drug delivery mechanisms that can enhance the bioavailability of herbs need to pass regulations like getting FDA approvals which is a challenge (3). In summary, while herbal neurotherapeutics hold promise, overcoming these limitations through standardization, advanced delivery technologies, rigorous safety and efficacy studies, and regulatory frameworks is essential to fully realize their clinical potential (3) .

2. Fundamentals of Herbal Neurotherapeutics

Herbal Neurotherapeutics encompasses the study and application of plant-derived compounds to support, protect, and modulate the central and peripheral nervous systems. Drawing on centuries of traditional use, particularly in Ayurveda, Traditional Chinese Medicine, and other herbal systems, modern research has identified several botanicals with robust evidence for cognitive enhancement, neuroprotection, and mitigation of neuroinflammation as shown in Figure 7.2. Three exemplar herbs – **Bacopa monnieri**, **Withania somnifera** (Ashwagandha), and ***Ginkgo biloba*** – demonstrate how phytochemicals such as triterpenoid saponins, steroidal lactones, flavonoids, and terpene lactones can:

- Enhance neuronal resilience by scavenging reactive oxygen species and upregulating endogenous antioxidant defences.
- Preserve synaptic function and neurotransmitter balance through cholinergic, dopaminergic, serotonergic, and GABAergic modulation.
- Attenuate neuroinflammatory signalling via inhibition of NF-kB, MAPK, and cytokine release pathways.
- Cross the blood-brain barrier effectively, exhibiting favorable pharmacokinetic profiles that ensure central nervous system penetration.

(2.1) Common herbs used in Neurology

Bacopa monnieri,

Bacopa monnieri is a well-established perennial herb in the Indian Ayurvedic system, recognized for its extensive use as a neural tonic and cognitive enhancer. The primary bioactive compounds responsible for its neurological effects are bacosides, specifically bacoside A, along with other saponins, including bacopasides and bacosaponins.

Clinical studies have demonstrated that Bacopa monnieri extract exhibits significant neuroprotective properties through multiple mechanisms. The herb has shown efficacy in treating various neurological conditions, including AD, PD, and epilepsy. Research indicates that BME (Bacopa monnieri Extract) produces both neuroprotective and neurorescue effects in dopaminergic neurons, with studies showing improved behavioural parameters and reduced inflammation in animal models.

Bacopa monnieri contains bacopasides, which are absorbed through the gastrointestinal tract and are sufficiently lipophilic to cross the blood-brain barrier, allowing them to exert direct effects on the central nervous system. These compounds are primarily metabolized in the liver and excreted via urine (4).

Bacopa's neurotherapeutic actions stem primarily from its bacosides, which:

- Scavenge reactive oxygen species and induce endogenous antioxidants (SOD, Hsp70)
- Inhibit acetylcholinesterase and enhance choline acetyltransferase, improving cholinergic transmission
- Reduce β-amyloid-induced neuronal toxicity and enhance cerebral blood flow

- Modulate neurotransmitters (acetylcholine, serotonin, dopamine)

Bacopa monnieri has demonstrated a strong safety profile in both animal and human studies. Acute toxicity studies in rats, using a single oral dose as high as 5000mg/kg, revealed no significant adverse effects or mortality. Chronic administration for up to 270 days at doses ranging from 30 to 1500mg/kg also did not produce toxic effects, with parameters such as behaviour, organ weight, hematology, and histopathology remaining within normal ranges. Some minor changes in organ weights were observed, but without associated pathological findings, indicating no clinically significant toxicity. Human studies further support this safety, as clinical trials administering 300-450 mg daily for 30 days reported no alarming changes or toxicity in participants. Subchronic and genotoxicity studies with standardized extract (e.g., Bacognize®) confirm tolerability up to 1000 mg/kg in animal models without significant adverse effects.

Preclinical and clinical trials have demonstrated improvements in memory, attention, and learning in both healthy adults and those with mild cognitive impairment (4) .

Ashwagandha (Withania somnifera),

Ashwagandha is a prominent adaptogenic herb in Ayurvedic medicine, extensively studied for its neurological applications. The primary bioactive constituents include withanolides (particularly withaferin A and withaferin B), sitoindosides VII-X, withanosides IV, and anaferine. These compounds demonstrate significant neuroprotective effects across multiple brain disorders, including anxiety, depression, Alzheimer's disease, Parkinson's disease, and schizophrenia.

Clinical trials have substantiated Ashwagandha's efficacy in managing neuropsychiatric conditions, with studies showing improved cognitive function, reduced anxiety, and enhanced stress resilience. The herb's safety profile appears favourable, with literature surveys indicating minimal toxic effects when used appropriately.

Ashwagandhas principal bioactive molecules, the withanolides, are well absorbed orally and reach therapeutic plasma concetrations at standard doses. These compounds are also able to cross in to the brain, where they modulate neurotransmitter systems, particulary by normalizing dopamine and GABA levels (5) .

Ashwagandha's withanolides confer:

- Activation of the Nrf2 pathway, upregulating heme oxygenase-1 and reducing microglial oxidative stress
- Suppression of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) via NFkB and MAPK inhibition
- Enhancement of amyloid clearance through upregulation of lipoprotein receptor-related protein
- Normalization of GABAergic and dopaminergic signalling, improving stress resilience, anxiety, and depressive symptom

Withania somnifera (Ashwagandha) is genrally regarded as safe when used at recommended doses. Preclinical studies report a high no-observed-adverse-effect level (NOAEL), and clinical trials in humans have found minimal adverse effects, even with daily use for several weeks. Most reported side effects are mild and include gastrointestinal discomfort or drowsiness. However, Ashwagandha may potentiate the effects of sedatives or immunosuppressive drugs due to its adaptogenic and immunomodulatory properties. Caution is advised in patients taking CNS depressants or those with autoimmune disorders, as herb-drug interactions may enhance sedative or immunosuppressive effects (inferred from established pharmacology and clinical experience).

Pharmacokinetic studies indicate good oral bioavailability at 100-600mg/day, with central nervous system penetration confirmed by behavioural and biomarker outcomes (5) .

Ginkgo biloba,

Ginkgo biloba extract (EGb761) represents one of the most extensively researched herbal neurotherapeutics. The standardized extract contains 24% flavone glycosides

(primarily quercetin, kaempferol, and isorhamnetin) and 6% terpene lactones (ginkgolides A, B, C, and bilobalide). Studies have demonstrated that *Ginkgo biloba* supplementation produces notable neuromodulatory effects, with significant up-regulation of genes associated with neuroprotection, including transthyretin, neuronal tyrosine/threonine phosphatase 1, and microtubule-associated tau. *Gingko bilobas* main active constituents – flavone glycosides and terpene lactones – are rapidly absorbed, with a high degree of oral bioavailability. These molecules rapidly cross the blood-brain barrier and are distributed within the central nervous system (6) .

Standardized Ginkgo extract (EGb761) contains flavonoids and terpene lactones that:

- Chelate redox-active metals and scavenge free radicals, protecting mitochondria from oxidative injury
- Antagonize platelet-activating factor (PAF) to reduce neuroinflammation
- Enhance cerebral blood flow and maintain ATP synthesis via mitochondrial stabilization
- Module gene expression of neuroprotective factors (e.g., transthyretin) and influence multiple neurotransmitter systems

Ginkgo biloba is widely used and generally considered safe when taken at standard doses. However, its antiplatelet activity can increase the risk of bleeding, particularly in patients taking anticoagulant or antiplatelet drugs. Ginkgo may also interact with medications metabolized by cytochrome P450 enzymes, potentially altering their efficacy. Rare side effects include gastrointestinal upset, headache, and allergic reactions. The risk of herb-drug interactions is most significant with anticoagulants (e.g., warfarin) and selective serotonin reuptake inhibitors (SSRIs), where Gingko may increase bleeding risk or alter drug metabolism (based on clinical and pharmacological data). Clinical and preclinical studies support its use in age-related cognitive decline, vascular dementia, and parkinsonian models, though large-scale clinical efficacy remains under investigation (6) .

Table 7.1- Key neurotherapeutic herbs, phytoconstituents, mechanisms, and traditional uses

Herb	**Phytoconstituents**	**Targets and Pathways**	**Pharmacokinetics and dosage**	**Traditional uses**	**References**
Bacopa monnieri	Bacosides A–B, bacopasaponins	↑ACh via AChE inhibition; Nrf2→↑SOD/Hsp70; CREB/BDNF synaptic plasticity	Tmax 1–2 h; t½ ≈ 4 h; 300 mg/day standardized extract	Memory enhancer; neural tonic	(7)
Withania somnifera	Withanolides A–Y, sitoindosides VII–X	Nrf2→HO-1 antioxidant; NF-κB/MAPK inhibition; ↑LRP1-mediated Aβ clearance; $GABA_a$ & D_2 receptor modulation	C_{max} 1–2 µg/mL at 300 mg/day; crosses BBB; 250–600 mg/day extract	Adaptogen; anxiolytic; cognitive resilience	(8)
Ginkgo biloba	Quercetin, kaempferol, isorhamnetin;	PAF antagonism; MAO-A/B inhibition; PI3K/Akt→↑transthyretin	BA ≈ 80%; Tmax 1.5 h; t½ ≈ 6 h; 120–240 mg/day EGb 761	Cognitive support; vascular insufficiency	(7)

	ginkgolides A–C; bilobalide	/AMPA-2; mitochondrial stabilization			
Panax ginseng	Ginsenosides Rb_1, Rg_1	PI3K/Akt, ERK1/2; ↑NGF/BDNF; Nrf2-mediated antioxidant	Oral BA low; 200–400 mg/day extract; $t_{½} \approx 3–6$ h	Cognitive enhancement; fatigue reduction	(7)
Centella asiatica	Asiaticoside, madecassoside, asiatic acid	Nrf2→HO-1; ERK1/2 & PKB signaling; dendritic arborization; anti-Aβ	$C_{max} \approx 2$ h; 250–500 mg/day extract	Memory enhancer; anxiolytic	(7)
Nardostachys jatamansi	Jatamansone, sesquiterpenes	$GABA_a$ modulation; Nrf2-mediated antioxidant; NF-κB inhibition	$t_{½} \approx 5$ h; 200–400 mg/day extract	Epilepsy; anxiety	(8)
Valeriana officinalis	Valerenic acid, valepotriates	$GABA_a$ positive modulation; sedative via ↓glutamate	Tmax ≈ 30 min; $t_{½} \approx 1–2$ h; 400–900 mg as tea or extract	Insomnia; anxiety	(7)
Scutellaria baicalensis	Baicalein, wogonin	Nrf2→HO-1; NF-κB inhibition; MAO-B inhibition; anti-Aβ aggregation	Low BA; 200–400 mg/day extract; active metabolites cross BBB	Neuroprotection; cognitive support	(7)
Uncaria rhynchophylla	Rhynchophylline, isorhynchophylline	NMDA antagonism; anti-inflammatory via ↓MAPK	$t_{½} \approx 4$ h; 100–300 mg/day extract	Epilepsy; neuroprotection	(8)
Curcuma longa	Curcumin, demethoxycurcumin	Nrf2 activation; ↑BDNF; NF-κB inhibition; anti-Aβ fibrillation	BA < 1%; 500–1000 mg/day with piperine	Cognitive enhancement; anti-neurodegenerative	(7)
Camellia sinensis	EGCG, catechins	Nrf2→↑antioxidants; ↓Aβ oligomerization; PI3K/Akt neurotrophic	Tmax ≈ 1–2 h; 300–500 mg EGCG/day	Neuroprotection; mood support	(7)
Hypericum perforatum	Hypericin, hyperforin, flavonoids	Monoamine reuptake inhibition; MAO-A/B inhibition	Tmax ≈ 4 h; $t_{½} \approx$ 24 h; 300 mg/day extract	Depression; anxiety	(8)
Melissa officinalis	Rosmarinic acid, flavonoids	ACh receptor modulation; ↓GABA-T; antioxidant	Tmax ≈ 1 h; 300–600 mg/day extract	Anxiety; cognitive support	(7)
Rosmarinus officinalis	Carnosic acid, rosmarinic acid	Nrf2 activation; NMDA antagonism; ↑BDNF	$t_{½} \approx 2–4$ h; 200–400 mg/day extract	Memory enhancement; mood support	(7)
Salvia officinalis	1,8-Cineole, rosmarinic acid	AChE inhibition; ↑ACh; antioxidant	Tmax ≈ 1 h; 300–600 mg/day extract	Cognitive support; memory enhancement	(8)
Zingiber officinale	6-Gingerol, shogaols	NF-κB inhibition; ↑BDNF; Nrf2-mediated antioxidant	Tmax ≈ 1–2 h; 500–1000 mg/day ginger	Anti-inflammatory; cognitive support	(7)
Piper nigrum	Piperine	↑BA of co-administered phytochemicals; ERK1/2→↑BDNF	5–20 mg/day as adjuvant	Cognitive enhancement;	(7)

				neuroprotection	
Coriandrum sativum	Linalool, flavonoids	AChE inhibition; antioxidant; anti-Aβ aggregation	500–1000 mg/day extract	Memory support; anxiety relief	(7)
Allium sativum	Allicin, alliin	Nrf2 activation; ↓neuronal apoptosis; ↑NO for cerebral blood flow	600 mg garlic extract/day	Neuroprotection; mood support	(8)
Convolvulus pluricaulis	Kaempferol glycosides, triterpenoids	↑ACh; dendritic arborization; Nrf2-mediated antioxidant	t½ ≈ 3 h; 200–400 mg/day extract	Memory enhancement; stress relief	(7)
Hericium erinaceus	Erinacines, hericenones	↑NGF expression; PI3K/Akt→neurogenesis; ↓Aβ plaques	1000–3000 mg/day extract; moderate BA	Mild cognitive impairment; neuroregeneration	(7)
Panax quinquefolius	Ginsenosides Rb_1, Re	↑NO; PI3K/Akt; Nrf2-mediated antioxidant	200–400 mg/day extract	Cognitive enhancement; fatigue reduction	(8)
Glycyrrhiza glabra	Glycyrrhizin, liquiritigenin	↑NMDA activity; NF-κB inhibition; Nrf2-mediated antioxidant	200–400 mg/day extract	Cognitive support; stress relief	(7)
Scutellaria lateriflora	Baicalin, scutellarein	AChE inhibition; $GABA_a$ modulation; MAPK inhibition	200–400 mg/day extract	Anxiety; memory support	(8)
Eleutherococcus senticosus	Eleutherosides B, E	↑AKT/ERK signaling; Nrf2-mediated antioxidant; neurite outgrowth	200–400 mg/day extract	Adaptogen; cognitive support	(7)
Salvia sclarea	Linalool, sclareol	AChE inhibition; GABA modulation	200–400 mg/day extract	Memory enhancement	(7)
Zanthoxylum bungeanum	Hydroxy-α-sanshool	TRPV1 modulation; ↑BDNF	100–300 mg/day extract	Cognitive support	(8)
Camellia sinensis (Decaf)	Decaffeinated catechins	As per Camellia sinensis minus caffeine effects	100–300 mg/day extract	Cognitive support	(7)
Centella asiatica (Leaf)	Asiaticoside-rich fraction	As per Centella asiatica	100–300 mg/day extract	Cognitive support	(7)
Rosmarinus officinalis (EO)	High 1,8-cineole concentration	As per Rosmarinus officinalis	Aromatherapy/inhalation	Cognitive enhancement	(8)

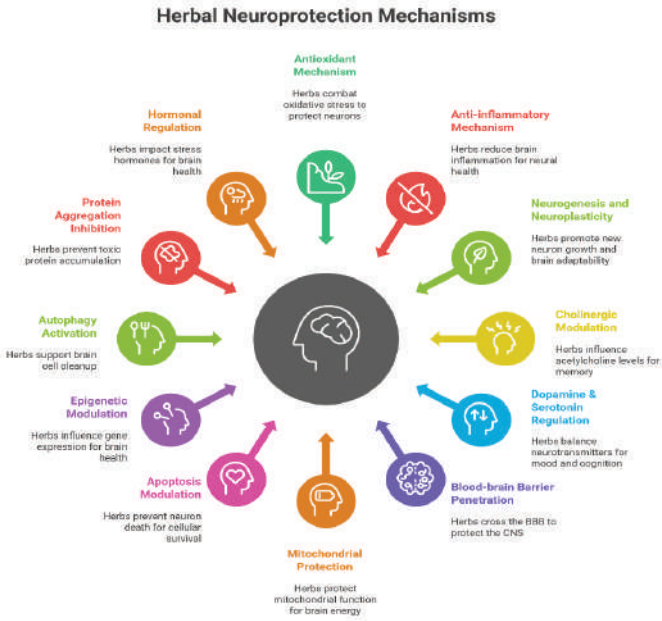

Fig 7.2- Illustration of different mechanisms of Herbal Neuroprotection

3. Conventional Formulations: Foundations and Limitations

(3.1) Oral Decotions, Powders, Capsules, and Teas

Traditional Decoctions,

Traditional oral decoctions represent one of the oldest and most fundamental forms of pharmaceutical preparation. The decoction process involves boiling herbal materials in water to extract active compounds, typically requiring that the original volume be reduced to one-fourth through sustained heating. The preparation follows a standardized four-step process: soaking the raw materials for 1 hour, conducting the first water decoction by boiling for 2 hours, filtration, and a second decoction followed by concentration. This method has been used across various traditional medicine systems, including Traditional Chinese Medicine (TCM), Ayurveda, and indigenous healing practices (9) .

However, decoctions face significant limitations. The extensive heating process can degrade thermolabile compounds, reducing therapeutic efficacy. The preparation is labour-intensive and time-consuming, making it impractical for routine clinical use. Furthermore, the resulting liquid formulations have poor stability and must be consumed within 72 hours when refrigerated, limiting their shelf life and storage convenience (10) .

Powders and Granules,

Powder formulations represent a versatile dosage form that can accommodate large doses of active ingredients and allow for easier dosage adjustments. They offer faster dissolution and onset of action compared to solid dosage forms, making them economically attractive to produce. In pharmaceutical manufacturing, powder formulations for capsules typically consist of the active pharmaceutical ingredient (API) and at least one excipient, with the formulation and filing method significantly influencing drug release rates (11) .

Despite these advantages, powder formulations present considerable challenges. Poor taste masking is a major concern, as powders are difficult to mask for bitter or offensive-tasting drugs. They require mixing with liquids before administration, creating inconvenience for patients. Additionally, powders are incompatible with hygroscopic, oxidizing, and deliquescent materials, limiting their formulation flexibility. The potential for dosage inaccuracy and the inconvenience of travel also reduce patient compliance (11) .

Capsules and Tablets,

Conventional oral solid dosage forms, including tablets and capsules, remain the most common pharmaceutical delivery systems. Hard gelatine capsules provide high patient acceptability and convenience, effectively masking taste and odour while delivering exact doses. They are generally easier to swallow than tablets and can be formulated for various release profiles. Tablets offer advantages in terms of manufacturing efficiency, stability, and cost-effectiveness (12) .

However, solid dosage forms have inherent limitations. They cannot be used for unconscious patients or those with swallowing difficulties, representing a significant barrier for paediatric and geriatric populations. The delayed onset of action due to dissolution requirements makes them unsuitable for emergencies. Manufacturing challenges include achieving uniform weight distribution, preventing brittleness and delamination, and addressing sticking and surface issues during production (12) .

(3.2) Challenges in Stability, Dosing, and Patient Compliance

Stability Issues,

Stability represents one of the most critical challenges in conventional formulations. Herbal products are particularly susceptible to degradation during storage, leading to loss of active components and production of inactive or potentially toxic metabolites. The complex nature of herbal extracts, which may contain thousands of different compounds, makes stability assessment extremely challenging (13) .

Environmental factors significantly impact stability, including temperature, light, air (oxygen, carbon dioxide, and water vapours), and humidity. Moisture is often perceived as the most common cause of drug degradation through hydrolysis and other facilitated reactions. For herbal formulations, the presence of enzymes like glycosidases, esterases, and oxidases plays a crucial role in the breakdown of secondary plant metabolites(13) .

Chemical instability manifests through various mechanisms including oxidation, hydrolysis, crystallization, emulsion breakdown, and enzymatic degradation. The monitoring of bioactive constituents is vital as it affects quality, efficacy, and shelf-life, with content variation during storage not exceeding ± 5% of initial assay values unless justified (13) .

Dosing Challenges,

Dosing accuracy represents a fundamental challenge in conventional formulations. For powder formulations, achieving consistent dosing is difficult due to flow properties, segregation, and measurement variability. Decoctions face particular challenges as the extraction efficiency varies based on raw material quality, preparation conditions, and operator technique (14).

The complexity of multi-component formulations, particularly common in traditional medicine systems, creates additional dosing challenges. Individual variations in metabolism, absorption, and therapeutic response require personalized dosing approaches that are difficult to achieve with

conventional formulations. Tablet manufacturing faces specific dosing challenges, including weight variation, which can lead to dosage errors and compromise treatment efficacy (14).

Patient Compliance Barriers,

Patient compliance represents a critical limitation of conventional formulations. Medication non-adherence occurs in approximately 50% of patients, with rates varying significantly across different formulations and therapeutic areas. The complexity of medication regimens, including multiple medications with varying dosing schedules, significantly impacts compliance (15) .

Swallowing difficulties affect a substantial proportion of patients, with prevalence ranging from 10% to 34.2% in healthcare settings. This challenge is particularly pronounced in paediatric and geriatric populations, where alternative formulations or modification of existing dosage forms becomes necessary. The bitter taste of many medications, especially herbal preparations, severely impacts compliance, particularly in children and elderly patients (15). Physical factors also contribute to compliance challenges. Large tablet size, multiple daily dosing requirements, and the need for special administration conditions (with or without food) create barriers to adherence. Cost considerations and access barriers further compound compliance issues, particularly for chronic conditions requiring long-term medication (15) .

(3.3) Bioavailability and Blood-Brain Barrier (BBB) Constraints

Bioavailability Limitations,

Bioavailibility represents a fundamental challenge in conventional pharmaceutical formulations, with over 70% of new chemical entities exhibiting poor aqueous solubility. The bioavailability of oral drugs depends on multiple factors including aqueous solubility, gastrointestinal permeabilty, first-pass metabolism, and efflux transport mechanism (16) .

Poor solubility leads to inadequate bioavailability due to low dissolution rates and limited solubility in gastrointestinal fluids. This is particularly problematic for BCS Class II drugs, where dissolution rather than permeability becomes the rate-limiting factor. The negative impact includes reduced therapeutic efficacy, increased dosing frequency, and higher treatment costs (16) .

Gastrointestinal absorption faces numerous barriers, including the mucous layer, tight junctions, efflux transporters, and enzymatic degradation. The intestinal environment presents additional challenges through pH variations, enzymatic activity, and the presence of food that can affect drug absorption. These factors create significant inter-individual and intra-individual variability in drug absorption and therapeutic response (16) .

First-Pass Metabolism Constraints,

First-pass metabolism represents a major constraint for orally administered drugs, significantly reducing the amount of active drug reaching systemic circulation. This phenomenon occurs through hepatic metabolism, where drugs absorbed from the gastrointestinal tract are metabolized by liver enzymes before reaching the systemic circulation (17) .

The extent of first-pass metabolism can be substantial, with some drugs experiencing up to 90% metabolism during the first pass through the liver. Notable drugs experiencing significant first-pass effects include morphine, propranolol, lidocaine, and many others. This necessitates higher oral doses to achieve therapeutic plasma levels, potentially increasing the risk of adverse effects (17) .

Cytochrome P450 enzymes, particularly CYP3A4, play crucial roles in first-pass metabolism, affecting the bioavailability of numerous drugs. The variability in enzyme expression between individuals contributes to significant differences in drug response and therapeutic outcomes. Environmental factors, genetic polymorphisms, and co-administered medications can further influence first-pass metabolism (17) .

Blood-Brain Barrier Challenges,

The blood-brain barrier presents unique challenges for drug delivery to the central nervous system. This semi-permeable barrier restricts the passage of most pharmaceuticals, with more than 98% of small-molecule drugs and virtually all macromolecular therapeutics being excluded from brain access (18). The BBB allows only passive diffusion of lipid-soluble drugs with molecular weights below 400-600 Da, while highly hydrophobic compounds below 400-600 Da can cross through transcellular pathways. The presence of efflux transporters, particularly P-glycoprotein, actively pumps drugs back into the bloodstream, further limiting brain penetration (18) .

Strategies to overcome BBB constraints include structural modifications to increase lipophilicity, prodrug approaches, and the use of specialized delivery systems. However, increasing lipophilicity is not universally applicable as it may reduce biological activity or increase peripheral side effects. The development of effective CNS drug delivery methods remains a significant challenge in pharmaceutical development (18). The preferred pathway of drugs entering the brain is the transcellular one which takes an advantage of carrier-mediated and receptor-mediated transcytosis. Learning about these means of transport is important in the development of efficient treatment options of neurological diseases as well as in the administration of drugs in the right amounts within the brain (18).

Table 7.2- Comparison of conventional formulations and their limitations in CNS applications

Formulation Type	**Mechanism**	**Key Limitations**	**References**
Small-molecule drugs	Passive diffusion across BBB	Very low brain uptake (<2%); efflux transporters limit penetration; systemic side effects	(19)
Prodrugs	Bioreversible modification to enhance lipophilicity	Poor bioactivation in CNS; unpredictable conversion rates; potential peripheral toxicity	(20)
Colloidal nanoparticles (e.g., niosomes)	Diffusion or intranasal delivery	Rapid mucociliary clearance; limited payload loading; poor controlled release	(21)
Lipid nanoparticles (solid lipid, liposomes)	Passive or receptor-mediated endocytosis	Low BBB crossing efficiency; opsonization and RES uptake; formulation-dependent toxicity risks	(22)
Micelles	Self-assembled amphiphiles	Instability upon dilution; rapid disassembly in blood; limited CNS targeting	(22)
Chimeric peptides (e.g., OX26 mAb conjugates)	Receptor-mediated transcytosis	Complex production; low yield; potential immunogenicity; limited permeability	(22)
Direct intracerebral/intraventricular injection	Local infusion bypassing BBB	Highly invasive; risk of tissue damage and infection; limited distribution volume	(22)
Focused ultrasound–enhanced delivery	Transient BBB disruption	Risk of uncontrolled BBB leakage; potential neurotoxicity; limited spatial precision	(22)

4. Innovations in Formulation Technologies

(4.1) Nanotechnology-Based Delivery Systems

Delivery systems based on nanotechnology are a radically new way of overcoming basic limitations of conventional pharmaceutical formulations. Such systems make use of the exceptional nature of nanomaterial to build more advanced drug delivery systems, which can overcome biological barriers, extending drug lifetime, in addition to delivering therapeutic drugs that are target-specific. Nanoparticle carriers have been gained but the field has matured into the complex multifunctional systems bringing diagnostic capability, targeted delivery, and controlled release with it.(23) .

Development of nanotechnology based-delivery systems has been informed by the necessity to solve some of the critical problems in drug delivery which include poor bioavailability, reduced tissue penetration and rapid clearance as well as lack of target specificity. The systems provide foundational opportunities to maximize the therapeutic efficacy and minimize systemic toxicity by controlling the drug pharmacokinetics and biodistribution in precise ways (23) .

Nanoemulsion, Liposomes, and Phytosomes

Nanoemulsions,

Nanoemulsions can be defined as an advanced drug delivery technology where emulsion droplets have a size of less than 1 micron that are commonly between 20 to 200 nanometres. These systems are dispersions of oil and water phase that are thermodynamically stable due to the presence of surfactants and co-surfactants. Small size of the droplets produces high interfacial area between drug and water and enhances the dissolution remarkably, increasing the solubility and the bioavailability of the poorly water-soluble drugs (24) .

The other benefit of nanoemulsions is its capability to entrap both the hydrophilic and hydrophobic drugs in a single form of delivery. This versatility endears them to drugs that have varied physicochemical properties. The increased surface area offered by the nanosized droplets enable quicker dissolution and absorption thus results in quicker onset action when compared with the conventional formulations (24) .

Nanoemulsions may be formulated in many ways into different dosage forms, such as gels, creams, foams, aerosols, and sprays and can be delivered by many routes, including oral, topical, intravenous, intrapulmonary, intranasal and intraocular delivery. This flexibility in formulation and administration routes makes nanoemulsions highly versatile platforms for drug delivery across different therapeutic applications(24) .

The stability profile of nanoemulsions is particularly noteworthy. These systems demonstrate excellent thermodynamic stability, with minimal creaming or sedimentation during storage. The small droplet size reduces gravitational forces and enhances Brownian motion, contributing to the overall stability of the system. Additionally, nanoemulsions protect encapsulated drugs from environmental degradation factors such as pH changes, oxidation, and enzymatic breakdown (24) .

Nanoemulsions have found extensive applications in various therapeutic areas. In parenteral delivery, they provide sustained drug release and improved bioavailability for drugs with poor aqueous solubility. For topical applications, nanoemulsions enhance skin penetration and provide controlled drug release at the site of action. In ophthalmic delivery, they increase drug residence time and improve bioavailability while reducing the frequency of administration (24).

Despite their advantages, nanoemulsions present certain formulation challenges. The requirement for high concentrations of surfactants and co-surfactants (typically 3-10%) for stabilization can raise safety concerns. The limited solubilization capacity for high-melting-point substances and sensitivity to temperature and pH variations s also present formulation constraints (24) .

Liposomes,

Liposomes are among the most extensively studied and clinically successful nanoparticle drug delivery systems. These spherical vesicles, typically ranging from 50 to 500 nanometers in diameter, are composed of phospholipid bilayers that spontaneously form when phospholipids are dispersed in aqueous media. The unique structural similarity to cellular membranes makes liposomes inherently biocompatible and biodegradable (25). The fundamental architecture of liposomes consists of a hydrophilic aqueous core surrounded by one or more phospholipid bilayers. This structure enables the encapsulation of both hydrophilic drugs (in the aqueous core) and hydrophobic drugs (within the lipid bilayers), providing exceptional versatility in drug loading. The phospholipid composition can be tailored to control membrane permeability, stability, and drug release characteristics (25).

Liposomes can be classified into several categories based on their structural characteristics. Conventional liposomes consist of neutral or charged phospholipids and cholesterol, providing basic drug encapsulation capabilities. Sterically stabilized liposomes, commonly PEGylated, exhibit prolonged circulation times and reduced clearance by the reticuloendothelial system. Ligand-targeted liposomes incorporate specific targeting moieties for enhanced cellular uptake and tissue specificity (25) .

The clinical success of liposomes is demonstrated by numerous FDA-approved formulations, including Doxil® (PEGylated liposomal doxorubicin) and AmBisome® (liposomal amphotericin B).There is a high level of therapeutic outcome improvement and improvement in the safety profile observed with these formulations as opposed to the conventional formulations of drugs. Doxil inhibits cardiotoxic effects of regular doxorubicin and preserves its healing effect (25).

Recent developments in the field of liposomes technology have revolved around efficiency aspects like stimuli- responsive and active target delivery. Such next-generation liposomes are designed to target a designated physiological state or even to be responsive to certain external stimuli to release the drug in a controlled manner at the targeted location. The combination of nanotechnology and the design of liposomes has resulted in hybrid systems that make use of the biocompatibility of the design of liposomes and the unusual properties of the inorganic nanoparticles (25) .

Liposome loading of drugs can be by passive or active loading. Passive loading is whereby the drugs are incorporated in the course of preparation of liposomes whereas active loading employs transmembrane gradients to induce the uptake of drug into pre-made liposomes. Active loading methods typically achieve higher encapsulation efficiencies (>90%) and provide better control over drug loading (25). The therapeutic applications of liposomes span multiple medical fields, including oncology, infectious diseases, and inflammatory conditions. In cancer therapy, liposomes enable targeted drug delivery to tumour tissues while minimizing systemic toxicity. The enhanced permeability and retention effect allows liposomes to preferentially accumulate in tumour tissues (25) .

Phtosomes,

Phytosomes are an innovative method to deliver drugs that were developed just for phytochemicals and herbal extracts. These vesicular systems are made up of phospholipid complexes that bond with plant-based molecules to make a "phyto-phospholipid complex." "Phytosome" is a

combination of "phyto" (plant) and "some" (cell-like), which describes how these delivery systems look like cell membranes (26).

The fundamental concept behind how phytosomes form is that polar phytochemicals and phospholipids, especially phosphatidylcholine, come together to form molecular complexes. Hydrogen bonding and van der Waals forces cause this complexation, which makes a stable molecule that keeps both parts' identities while making the phytochemical more available to the body. The phospholipid part has two jobs: it carries things and adds nutrients that are good for your health (26). Phytosomes have a number of benefits over traditional phytochemical formulations. The phospholipid envelope keeps fragile phytochemicals safe from digestive enzymes and harsh conditions in the stomach and intestines. This protection greatly improves the stability and bioavailability of water-soluble phytochemicals, which are usually not well absorbed when given in their natural form. Better absorption means that lower doses are needed for the same therapeutic effect (26) .

Several well-established techniques, such as solvent evaporation, thin film hydration, and anti-solvent precipitation, are used in the production of phytosomes. The most widely used method is solvent evaporation, which forms the phytosome complex by dissolving phospholipids and phytochemicals in organic solvents and then removing the solvent. The thin film hydration method entails forming a thin lipid film and then hydrating it with an aqueous solution that contains the phytochemical (26) .

Numerous phytochemicals, such as flavonoids, polyphenols, alkaloids, and terpenoids, can be delivered by phytosomes. For instance, quercetin phytosomes exhibit substantial increases in therapeutic efficacy and high encapsulation efficiencies (98.4%) with particle sizes of about 70 nm. When compared to free quercetin, these systems exhibit higher levels of antioxidant activity, better skin protection, and improved bioavailability (26) .

Commercial phytosome products, such as Sabalselect® (saw palmetto extract), Greenselect® (green tea extract), and Leucoselect® (grape seed extract), have found success in the market. These goods show that using phytosome technology to deliver herbal medicines is both feasible and profitable (26) .

The development of phytosomes for particular medicinal uses, such as tyrosinase inhibition for skin whitening, anti-inflammatory effects, and hepatoprotection, has been the focus of recent research. Because of its adaptability, phytosome technology can be tailored to meet particular therapeutic needs and intended uses (26) .

Solid lipid Nanoparticles and Nanostructured lipid Carriers

Solid Lipid Nanoparticles (SLNs),

The very first generation of lipid-based nanocarriers, solid lipid nanoparticles were created as an alternative to liposomes and traditional polymeric nanoparticles. These spherical particles, which are usually between 50 and 1000 nanometres in diameter, are made of lipids that are stabilized by surfactants and stay solid at body temperature. Compared to liquid-based systems, the solid lipid matrix offers better stability and a controlled release platform for encapsulated medications (27) .

A solid lipid core encircled by a layer of surfactants makes up the basic structure of SLNs. Fatty acids, triglycerides, partial glycerides, or waxes that are solid at body temperature and room temperature usually make up the lipid core, These are colloidal stability and prevention of the particle aggregation that is provided by the layer of the surfactant which is usually formed of lecithin, poloxamers, or other biocompatible emulsifiers (27) .

SLNs can be better in many aspects than conventional drug delivery. With respect to encapsulated drug, the solid lipid matrix provides better protection against enzymatic and chemical degradation. The lipid constituents are non-toxic and have fewer chances of reflecting negative effects since they are biocompatible and biodegradable. Moreover, the fabrication of SLNs can easily be scaled into production level by employing well-established pharmaceutical manufacturing procedures as well as through sterilization processes which are standardized (27).

Therapeutic agents are incorporated into the solid lipid matrix using a variety of models as part of the drug loading mechanism in SLNs. Drug-rich outer layers are produced when drug precipitation takes place before lipid solidification, according to the drug-enriched shell model. When lipid solidification occurs before drug precipitation, drug-concentrated interior regions are created, forming the drug-enriched core model. Uniform drug distribution across the lipid matrix is a feature of the homogeneous matrix model(27) .

SLNs have certain drawbacks in spite of their benefits. Solid lipids' highly ordered crystalline structure may limit their ability to load drugs and increase the risk of drug expulsion during storage. Drug release properties and stability may alter as a result of polymorphic transitions that take place during storage. Furthermore, controlled release performance may be jeopardized by the initial burst release that is frequently seen with SLNs (27) .

Applications for SLNs have been discovered in a wide range of therapeutic domains and delivery methods. They offer sustained release profiles and shield medications from severe gastrointestinal disorders when taken orally. SLNs improve skin penetration and offer localized drug delivery for topical applications. They provide reduced systemic toxicity and controlled release when administered parenterally(27) .

Nanostructured Lipid Carriers (NLCs),

The second generation of lipid-based nanocarriers, known as nanostructured lipid carriers, were created to get around the drawbacks of solid lipid nanoparticles. These sophisticated systems are made up of a blend of liquid and solid lipids, which results in an imperfect crystalline matrix that improves stability and increases drug loading capacity. Higher drug payloads can be accommodated by the structural flaws created when liquid lipids are incorporated into the solid matrix (27) .

The strategic integrating of liquid and solid lipids to produce a less ordered lipid matrix is the basic idea behind NLC design. Solid to liquid lipid ratios typically fall between 70:30 and 99.9:0.1; the precise ratio is determined by the drug's characteristics and the desired release characteristics. The liquid lipid component, which is typically made up of oils or fatty acid esters, stays distributed throughout the solid matrix, forming nanoscale voids that improve drug accommodation (27).

Based on their structural arrangement, NLCs can be divided into three different categories. Drug molecules are able to form amorphous clusters in Type I NLCs (imperfect crystal models), which have a highly disordered matrix with lots of voids and spaces. Liquid lipids separate into distinct phases within the solid matrix of Type II NLCs (multiple type), which have oil-in-lipid-in-water structures. Certain lipids that form solid but non-crystalline particles are used to formulate Type III NLCs (amorphous model) (28) .

NLCs have significant advantages over SLNs. When compared to SLNs, the imperfect crystalline structure frequently achieves 2-3 times higher drug payloads, greatly increasing drug loading capacity. Liquid lipids improve long-term stability by reducing drug expulsion during storage. Drugs with

different physicochemical characteristics can be accommodated more effectively thanks to the flexible matrix structure (28).

When it comes to stability, release kinetics, and drug loading, NLCs perform exceptionally well. The increased solubility of drugs in liquid lipids and the extra space that the imperfect crystal structure provides lead to the higher drug loading capacity. By modifying the solid-to-liquid lipid ratio and the choice of particular lipid components, the controlled release properties can be optimized (28) .

High-pressure homogenization, solvent emulsification-evaporation, microemulsion, and phase inversion techniques are among the methods used to prepare NLCs. The most popular technique is high-pressure homogenization, which creates a hot, uniform mixture and then allows it to cool to room temperature. To precipitate the NLC particles, the microemulsion method entails creating a microemulsion and then diluting it with cold water (28) .

NLCs have proven adaptable in a range of medical settings. They offer sustained release profiles and improve the bioavailability of poorly soluble medications when administered orally. NLCs enhance skin penetration and offer regulated drug release at the intended location for topical applications. They provide longer circulation times and less reticuloendothelial system clearance when administered parenterally (28) .

Targeting approaches and surface modification have been the main topics of recent developments in NLC technology. To accomplish precise tissue targeting, surface-modified NLCs can be functionalized with proteins, polymers, or targeting ligands. Triggered drug release in response to particular physiological conditions is made possible by the addition of stimuli-responsive components (28) .

Improved BBB penetration, Targeted Delivery, and Stability

Blood-Brain Barrier Penetration Mechanisms,

One of the most significant barriers to drug delivery is the blood-brain barrier, which effectively blocks the majority of medications from entering the central nervous system. Tightly packed endothelial cells make up this selective barrier, which restricts paracellular transport and transcellular passage to small, lipophilic molecules. Delivery systems based on nanotechnology have shown promise in overcoming these obstacles through a variety of improved penetration mechanisms, as illustrated in Figure 3 (29) .

Numerous studies have examined the size-dependent permeability of nanoparticles across the blood-brain barrier, identifying the ideal size ranges for maximum brain penetration. Studies reveal that when compared to larger particles, nanoparticles with diameters between 10 and 30 nm exhibit improved BBB crossing. Because they balance permeation ability and circulation time, medium-sized nanoparticles (about 15 nm) frequently exhibit the highest delivery efficiency. The competition between renal clearance and BBB penetration, where smaller particles enter the bloodstream more easily but are quickly removed, leads to this ideal size (29) .

Surface charge is a key factor in BBB penetration; research indicates that highly negative nanoparticles (-40 mV) accumulate more in the brain than neutral or positively charged particles. Anionic nanoparticles' increased penetration is explained by their interactions with particular BBB transport proteins, such as basigin, afamin, and apolipoprotein E. Through receptor-mediated transcytosis, these proteins help negatively charged nanoparticles cross the barrier by forming a protein corona around them (29) .

The use of external stimuli to momentarily compromise barrier integrity is one of the more sophisticated BBB penetration techniques. Enhancing the delivery of nanoparticles to the brain has been demonstrated to be possible through focused ultrasound-induced BBB opening. By temporarily rupturing the blood-brain barrier, this method permits nanoparticles to enter the brain parenchyma while preserving the barrier's overall functionality. A promising strategy for brain-targeted medication delivery combines external stimuli with optimized nanoparticle characteristics (29) .

Another cutting-edge strategy for BBB penetration is magnetic guidance. Magnetic nanoparticles can be directed to specific areas of the brain using external magnetic fields; it has been demonstrated that magnetic directing can enlarge the accumulation in the brain, up to 63 %. Combined static and alternating magnetic fields produce even higher targeting efficiency, meaning magnetic drug delivery has the potential to be applied in the neurological field as well (29) . BBB penetration is enhanced upon surface functionalization with specific ligands through the receptor-mediated transport. Using appropriate modifications of the nanoparticles, it is possible to target transferrin receptors, glucose transporters, and other BBB specific receptors. These targeting strategies assist nanoparticles in translocating across the barrier through exploitation of the body natural transport processes (29).

Advanced Targeting Mechanism,

To provide specific drug delivery, new-aged nanotechnology-based drug deliveries involve complicated targeting systems, in which there is a combination of passive and effective methods. Passive targeting is based on the enhanced permeability and retention (EPR) effect where abnormal blood vessels and poor lymphatic drainage lead to an accumulation of nanoparticles in the diseased tissue. The benefit of this system, in the case of solid tumours, is that the leaky vessels enable nanoparticles to extravasate and concentrate in the tumour microenvironment (30).

Active targeting is achieved by including specific ligands to the nanoparticle surface, which can target specific receptors on the surface of a target. The common targeting moieties include antibodies, peptides, aptamers, small molecules and carbohydrates. The particular disease state, target tissue, and therapeutic needs all influence the choice of targeting ligands. Targeted molecular markers include transferrin receptors, folate receptors, and other tumour-associated antigens (30) .

Several targeting techniques are combined in multifunctional targeting strategies to improve efficacy and specificity. To improve drug delivery, these systems can target multiple receptors at once or take advantage of several biological pathways. Real-time tracking of medication delivery and therapeutic response is made possible by the combination of imaging and targeting capabilities (30). Stimuli-responsive targeting is a cutting-edge strategy in which nanoparticles react to particular physical or biological stimuli. pH-responsive systems take advantage of the inflammatory tissues and tumours' acidic microenvironment. When certain enzymes are overexpressed in diseased tissues, enzyme-responsive nanoparticles are made to release medication. Either endogenous temperature changes or external heating can activate temperature-responsive systems (30) .

The effectiveness of nanoparticle targeting and biological interactions are influenced by their mechanical characteristics. Compared to rigid particles, soft nanoparticles exhibit improved tissue penetration and decreased phagocytic cell clearance. The ability of nanoparticles to pass through biological barriers and enter target tissues is influenced by their flexibility (30). Cell membrane-derived targeting techniques improve the biocompatibility and targeting of nanoparticles by utilizing naturally occurring biological membranes. Nanoparticles coated with red blood cell membranes exhibit longer half-lives and decreased immune recognition. Nanoparticles coated with cancer cell membranes can increase tumour accumulation by taking advantage of homotypic targeting.(30)

Stability Enhancement Strategies,

The clinical translation and therapeutic efficacy of delivery systems based on nanotechnology depend heavily on their stability. There are several facets of stability, such as chemical stability, biological stability, and colloidal stability. Over time, colloidal stability preserves size distribution and inhibits particle aggregation. Drugs that are chemically stable are shielded from deterioration and retain their therapeutic effects. In biological settings, biological stability guarantees that nanoparticles continue to function https://www.hhs.gov/open/public-access-guiding-principles/index.html (13) .

One essential tactic for improving the stability and circulation time of nanoparticles is stealth coating. The most widely used stealth coating is polyethylene glycol (PEG), which forms a hydrophilic layer that inhibits protein adsorption and decreases reticuloendothelial system clearance. PEGylation can significantly increase the effectiveness of drug delivery by extending the circulation half-life from minutes to hours or days(13) .

PEG coatings' surface density and molecular weight have a big impact on how effective they are. PEG with a higher molecular weight (5–10 kDa) offers better stealth qualities than versions with a lower molecular weight. Achieving the brush conformation required for efficient protein repulsion requires optimizing the surface density. Generally speaking, ideal PEG densities fall between 0.1 and 1.0 molecules per nm^2 (13)To overcome PEGylation's drawbacks, substitute stealth coatings are being created. Potential benefits over PEG may be provided by hydrophilic polymers such as poly(2-oxazoline), zwitterionic polymers, and others. These substitutes might offer enhanced functionality, decreased immunogenicity, and better biocompatibility (31)

Through a variety of methods, surface modification with particular functional groups improves nanoparticle stability. Stable surface coatings can be made with carboxyl, amino, and thiol groups. The particular application and desired surface characteristics determine which functional groups are used (32) .

Given that controlled release mechanisms shield medications from deterioration and sustain therapeutic levels over time, they help to promote stability. Formulations with sustained release decrease the frequency of doses and increase patient adherence. Surface modification, particle design, and material selection can all be used to customize the release kinetics (33).

Dynamic stability control is provided by intelligent responsive systems that adjust to shifting biological conditions. Enzyme activity, temperature fluctuations, pH shifts, and other biological stimuli can all affect these systems. Improved therapeutic efficacy and optimal drug release are made possible by the responsiveness (34).

The stability of nanoparticles and biological interactions are significantly influenced by surface chemistry. The way that nanoparticles interact with biological systems is determined by their surface energy, charge distribution, and chemical makeup. Stability can be improved while preserving biological activity through optimized surface chemistry (13)

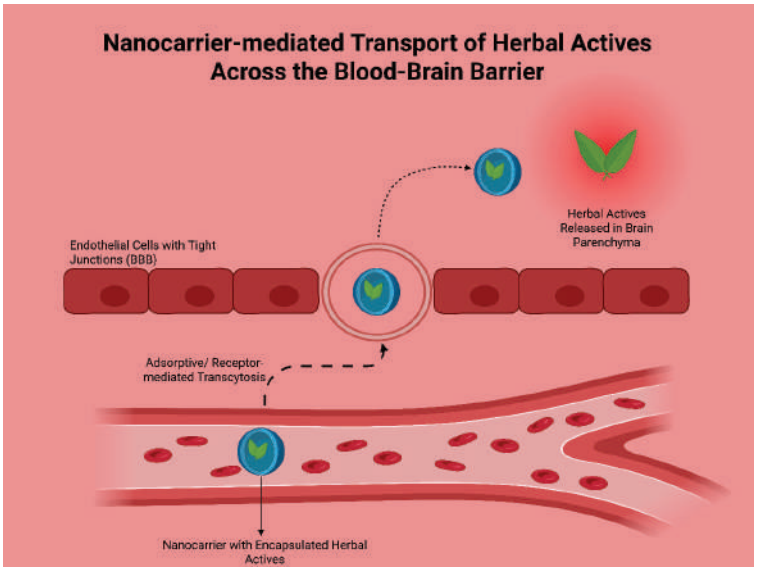

Fig 7.3- Nanocarrier-mediated transport of herbal actives across BBB

(4.2) Smart and Responsive Delivery Platforms

Through intelligent design and adaptive functionality, smart and responsive delivery platforms surpass the limitations of traditional drug delivery systems, marking the next evolutionary step in pharmaceutical science. These platforms combine cutting-edge manufacturing techniques, complex triggering mechanisms, and advanced materials science to produce delivery systems that can react dynamically to environmental stimuli and biological cues. The urgent need to attain exact spatiotemporal control over drug release, improve therapeutic efficacy, and reduce side effects through targeted intervention has led to the development of smart delivery platforms (35)(36).

Systems that can identify particular biological conditions and react appropriately by adjusting their physical attributes, drug release characteristics, or targeting behaviour are included in the notion of "smart" drug delivery. To accomplish selective drug activation and release, these platforms take advantage of the physiological conditions that naturally differ between healthy and diseased tissues, such as pH, temperature, and enzymatic activity levels as shown in figure 7.3. By incorporating responsive components, these systems can selectively activate at specific locations and stay dormant during circulation, optimizing therapeutic benefit and reducing systemic exposure (37) .

The market for smart drug delivery systems has grown significantly, reaching $12 billion in 2024 and expected to grow at a compound annual growth rate of 17% through 2034. This growth is fueled by the rising incidence of chronic illnesses, which, according to World Health Organization data, cause almost three-quarters of all deaths worldwide each year. Advances in materials science and nanotechnology, along with the pressing clinical need for more effective therapeutic interventions, have opened up previously unheard-of possibilities for smart delivery platform innovation.

Stimuli-Responsive Systems (pH, Temperature, Enzymes)

pH-Responsive Delivery Systems,

One of the most advanced and clinically applicable smart delivery platforms is pH-responsive drug delivery, which uses the body's natural pH fluctuations to achieve targeted drug release. From the extremely acidic gastric environment (pH 1.2-2.0) to the neutral to slightly alkaline small intestine conditions (pH 6.5-7.4), as well as the noticeably acidic tumor microenvironment (pH 6.0-6.8) in comparison to normal tissue (pH 7.4), the human body exhibits a wide variety of pH environments (38) .

The incorporation of ionizable functional groups that undergo protonation or deprotonation in response to environmental pH changes is the basic mechanism behind pH-responsive systems. The delivery matrix may swell, shrink, or dissolve as a result of these chemical changes that cause conformational changes in polymer chains. Commonly used pH-sensitive polymers with unique pH transition points for particular uses include poly(acrylic acid), poly(methacrylic acid), chitosan, and different polymethacrylate derivatives like the Eudragit® series (38). The pKa values of ionizable groups in relation to the target pH environment are carefully taken into account when designing pH-responsive nanoparticles. In acidic environments, polymers containing carboxylic acid groups (pKa ~4.5-5.0) remain protonated and hydrophobic; however, at neutral to basic pH, they become deprotonated and hydrophilic, resulting in polymer swelling and drug release. Enteric-coated formulations that shield acid-labile medications during gastric transit while permitting release in the intestinal environment are a successful example of this principle in action (38) .

The development of dual and multiple pH-responsive platforms that can react to successive pH changes along the gastrointestinal tract or take advantage of the acidic microenvironment of tumors has been the main focus of recent advancements in pH-responsive systems. To fine-tune the pH transition points and attain more exact control over drug release kinetics, these systems frequently include pH-buffering components. Multi-responsive systems with improved selectivity and therapeutic efficacy have been created by combining pH-responsive components with other stimuli-responsive mechanisms (38) .

Temperature-Responsive Delivery Systems,

Temperature-responsive drug delivery systems use either external heat or the natural temperature fluctuations in the human body to initiate system activation or drug release. With a lower critical solution temperature (LCST) of about 32°C, or near body temperature, poly(N-isopropylacrylamide) (PNIPAM) is the most extensively researched temperature-responsive polymer. Phase separation and possible drug release result from PNIPAM chains' adoption of an extended, hydrophilic conformation below the LCST and their collapse into a compact, hydrophobic state above the LCST (39)

The equilibrium between hydrophobic and hydrophilic interactions within the polymer chains is what gives these systems their temperature responsiveness. The extended conformation is maintained at temperatures lower than the LCST by hydrogen bonding between the polymer and water molecules. Polymer collapse and dehydration result from hydrophobic interactions becoming more favorable as the temperature rises above the LCST. Drug release rates can be regulated by taking advantage of this thermodynamic transition; higher temperatures tend to result in faster release (39) .

By adding new comonomers or modifying the composition of polymers, sophisticated temperature-responsive systems with adjustable LCST values have been created. For example, adding hydrophilic monomers like acrylamide can raise the LCST, whereas adding hydrophobic monomers like butyl

methacrylate can lower it. Systems that react to particular temperature ranges, such as mild hyperthermia (40–45°C), which is used in cancer treatment, can be designed thanks to this tunability (39).

Combining passive and active heating techniques is a common practice in the clinical use of temperature-responsive systems. By releasing doxorubicin in response to localized heating, thermosensitive liposomes—like ThermoDox®—have been created to improve drug accumulation in heated tumor tissue while lowering systemic exposure. Remote heating via alternating magnetic fields is made possible by the incorporation of magnetic nanoparticles into temperature-responsive matrices, offering exact temporal and spatial control over drug release (39) .

Enzyme-Responsive Delivery Systems,

By taking advantage of the altered enzymatic activity found in diseased tissues, enzyme-responsive drug delivery systems offer a sophisticated method for achieving highly specific drug release. These systems include substrates or linkages that can be broken down by certain enzymes, resulting in structural alterations and the release of drugs. Enzyme expression varies between healthy and pathological tissues, which gives enzyme-responsive systems their selectivity and enables targeted drug activation (40) .

Enzyme-substrate pairs must be carefully chosen for the design of enzyme-responsive systems depending on the target tissue and the particular pathological condition. Because matrix metalloproteinases (MMPs) are overexpressed in a number of cancers, inflammatory diseases, and wound healing processes, they are among the most researched enzyme targets. Peptide sequences that act as substrates for particular MMP enzymes are commonly included in MMP-responsive systems; cleavage of these sequences results in the release of the drug or the activation of the system (40) .

Proteases, such as cathepsin, chymotrypsin, and trypsin, have also been used extensively as enzyme-responsive system triggers. In a number of disease states, including cancer, where cathepsins are frequently overexpressed in lysosomes and the extracellular milieu, these enzymes show changed expression and activity. Protease-cleavable peptide linkers allow prodrug systems to be created, which are inactive until the active drug moiety is released by enzymatic cleavage(40) .

Developing multi-enzyme responsive platforms that can react to different enzyme combinations for improved selectivity has been the main focus of recent advancements in enzyme-responsive systems. For full drug release, these systems frequently include several cleavable linkages or necessitate successive enzymatic reactions. Multiple simultaneous condition systems have been developed; this is a result of integration of enzyme-responsive elements with other types of stimuli-responsive systems based on Boolean logic efect Justification Because of the integration of enzyme-responsive elements into other stimuli-responsive systems, Boolean logic-based systems that demand multiple simultaneous conditions in order to be activated have been developed.(40) .

The differences between patients in terms of enzyme expression and the potentiality of off-target enzyme activation complicate clinical translation of enzyme-responsive systems. The two solutions to circumventing these limitations are with the use of enzyme-specific inhibitors to prevent premature activation and the generation of systems with many levels of selectivity. The ability to monitor real-time enzymatic activity, as well as system activation, may be due to integrating the imaging capabilities which help to optimize and customize dosage and treatment through enhancing the depth of tissue information and depth of targeting (40) .

Hydrogel and Injectable Systems

Hydrogel-Based Smart Delivery Platforms,

The smart drug delivery has been entirely transformed by hydrogels, which is a type of versatile material due to their unique combination of properties; a high water content, biocompatibility, and variable mechanical properties. The three dimensional crosslinked polymer networks are ideal in this sustained drug release application since they can absorb and retain huge quantities of water and this ability does not compromise their structure. The mechanical properties and the water content of hydrogels resemble the same properties of natural tissues, resulting in their enhanced biocompatibility and reduced inflammatory responses following the implantation process (41) .

Some of the methods that can be used to control the nature of drug release out of hydrogels could include diffusion-controlled release, chemically-controlled release, and swelling-controlled release. The drug's molecular size in relation to the mesh size determines the release kinetics of diffusion-controlled systems, which use the hydrogel's mesh structure to control drug diffusion rates. In swelling-controlled release, the hydrogel matrix expands in response to external stimuli, resulting in bigger pores and easier drug release (41). Stimuli-responsive components found in smart hydrogels allow for controlled drug release in response to particular environmental factors. Ionizable groups used in pH-responsive hydrogels experience changes in protonation or deprotonation, which causes the gel matrix to swell or contract. Thermally-triggered drug release is made possible by temperature-responsive hydrogels, which are frequently based on PNIPAM or related polymers and show volume phase transitions at particular temperatures (41) .

Hydrogels can encapsulate and deliver a variety of therapeutic agents, including large proteins, small molecules, and even living cells, demonstrating their versatility. Sensitive therapeutics' biological activity is preserved by the gentle gelation conditions commonly used in hydrogel formation. In order to improve control over drug release profiles, recent developments have concentrated on creating multi-responsive hydrogels that can react to different stimuli (41) .

Injectable Hydrogel Systems,

A combination of the special benefit of minimally invasive administration and long-lasting therapeutic effects, injectable hydrogels have become a ground-breaking development in drug delivery. At room temperature, these systems are low-viscosity solutions or sols, but at body temperature, they gel, making it simple to inject using standard needles and allowing for in situ gel formation. This method offers localized drug delivery with controlled release properties without requiring surgical implantation (42).

Sol-gel transition can be caused by several processes like ionic interactions, temperature, pH change, or enzymatic crosslinking, which can take place in injectable hydrogels. Temperature-sensitive injectable hydrogels exemplified by those derived using Pluronic copolymers are the most studied of them due to their thermoreversible gelation behaviour. These are simple to use and manage, they are also in liquid states at storage temperature and injection temperature and at physiological temperature they gel (42) .

The optimization of gelation kinetics in the optimization of injectable hydrogel is a more complex phenomenon since it requires ensuring a satisfactory time window of injection and a fast gelation process starting after injection. The gelation time ought to be long such that a complete injection has taken place but short enough such that the diffusion process does not cause loss of the drug before gel

is formed. Viscosity measurements provide data on previous injectability and gelling behavior, and the rheological characterisation is imperative in optimising these parameters (42) .

For improved functionality, sophisticated injectable hydrogel systems with two or more responsive mechanisms have been created. These systems offer more accurate control over gelation and drug release because they can react to combinations of stimuli, such as pH and temperature. When nanoparticles or microparticles are added to injectable hydrogels, hybrid systems with altered release kinetics and increased drug loading capacity are produced (42) .

On-Demand Drug Release Systems,

The pinnacle in smart delivery technology are on-demand drug release systems, which allow for precise temporal control over drug release via internal biological signals or external triggers. When therapeutic intervention is needed, these systems can be remotely activated. They stay dormant during storage or circulation. Controlling the timing of drug release allows for individualized dosing plans and unheard-of flexibility in treatment regimens (42) .

Due to the deep tissue penetration of NIR light and the availability of biocompatible NIR-absorbing materials, near-infrared (NIR) responsive systems have attracted a lot of attention. Plasmonic nanoparticles, like gold nanorods or nanoshells, are commonly used in these systems. When exposed to near-infrared radiation, these particles produce heat, which causes temperature-triggered drug release. The precise spatial and temporal control of drug release is made possible by the combination of thermosensitive carriers and NIR responsiveness (42) .

Magnetic nanoparticles that can produce heat through magnetic hyperthermia or experience mechanical deformation when exposed to applied magnetic fields are used in magnetic field-responsive systems. These systems are appropriate for targeted drug delivery to particular anatomical locations because they provide the benefit of non-invasive activation with precise spatial control. A single system can have two functions thanks to the combination of magnetic targeting and magnetically triggered release (42)

Smart pills and implantable devices with programmable release profiles are the result of the incorporation of electronic components into drug delivery systems. Sensors for physiological condition monitoring and microprocessors for drug release control based on preset algorithms or real-time feedback can be included in these systems. More complex on-demand release systems have been made possible by the development of wireless communication and miniature electronics (42) .

3D-Printed Herbal Drug Delivery Devices

Foundations of 3D Printing in Pharmaceutical Applications,

Pharmaceutical manufacturing has undergone a revolution thanks to three-dimensional printing technology, which makes it feasible to produce intricate, personalized drug delivery systems that would be impossible to make with traditional manufacturing techniques. The technology creates three-dimensional structures with exact control over geometry, composition, and internal architecture by using computer-aided design (CAD) files to direct the layer-by-layer deposition of materials. On-demand production of customized medications is made possible by this additive manufacturing technique, which provides previously unheard-of formulation design flexibility (43) .

After the FDA approved the first 3D-printed prescription drug, Spritam® (levapiracetam), in 2015, the use of 3D printing in pharmaceutical manufacturing started to pick up speed. This innovation cleared the path for in-depth study into different 3D printing technologies for drug delivery applications and proved the clinical feasibility of 3D-printed medications. Spritam®'s success demonstrated the special

benefits of 3D printing, such as its capacity to produce extremely porous structures that facilitate quick drug release and disintegration (43) .

Pharmaceutical manufacturing has effectively used a number of 3D printing technologies, each with unique benefits and drawbacks. Thermoplastic filaments are heated and extruded through a nozzle in fused deposition modeling (FDM) to produce solid structures. By fusing powder particles with laser energy, selective laser sintering (SLS) makes it possible to create intricate geometries without the need for support structures. High resolution and smooth surface finishes are provided by stereolithography (SLA), which uses photopolymerization to cure liquid resins layer by layer (43).

The physicochemical characteristics of the drug and its excipients, the intended release profile, and the manufacturing needs all influence the choice of 3D printing technology. FDM printing works well with thermostable medications and polymers with the right melting properties because it requires materials that can tolerate high processing temperatures. Temperature-sensitive materials can be printed using SLS, but it needs powder formulations with particular flow and sintering characteristics (43) .

Herbal Medicine Applications in 3D Printing,

When herbal medicines are integrated with 3D printing technology, there are unique opportunities to discourage the otherwise inherent challenges with conventional herbal formulations, all the whilst retaining the herbal medicines therapeutic benefits. Although there is reputation of herbal extracts to possess therapeutic potential, very often they possess disadvantages of instability, low bioavailability, non-standard dosage, and low uniformity of quality. 3D printing has solutions to these issues, by enabling correct dosage adjustment and enhanced stability via encapsulation, as well as tailored formulation methodologies (44) .

Plant extracts, essential oils, or purified phytochemicals are used as various components of herbal medicines in a printable form by utilizing a variety of excipient mixtures and matrix substances as components in the 3D printing process. Due to their non-toxicity and ability to form stable matrices to incorporate herbal component, natural polymers, including chitosan, alginate, gelatin, and cellulose derivatives, are found to be particularly applicable in this application. These materials have controlled release functionality and are able to entrap fragile phytochemicals (44) .

Current research experiments have demonstrated that successful 3D printing herbal formulations can be carried out with a range of plants extracts and their traditional medical components. To address diabetic ulcers, scientists have combined an extract of roots of snakegourd, a common element of traditional Chinese medicine, and astragalus, another commonly used component of traditional Chinese medicine, into 3D-printed hydrogel matrices. The possibilities of combining traditional knowledge with new methods of manufacturing are proven by the complex of these bioproducts with modern 3D printing technology (44). The compatibility of herbal extracts with printing materials must be carefully considered when developing 3D-printed herbal formulations. Because many phytochemicals are sensitive to changes in pH, light, and heat, it is necessary to use protective excipients and mild processing conditions. Choosing the right printing technologies becomes essential. For temperature-sensitive herbal compounds, pressure-assisted microsyringe (PAM) printing is frequently chosen because it can process materials at room temperature or slightly above (44) .

Advanced 3D Printing Strategies for Herbal Delivery,

The goal of advanced 3D printing techniques for herbal drug delivery is to develop complex delivery systems that preserve the integrity and bioactivity of herbal compounds while offering exact control over drug release kinetics. To create genuinely intelligent delivery devices, these methods

frequently incorporate complex geometries, multi-material printing, and stimuli-responsive components (44) .

Multiple herbal extracts can be combined or incompatible compounds can be separated within a single dosage form thanks to multi-compartment 3D-printed devices. This method has made complex herbal formulas, which would otherwise be hard to come up with using the conventional production process, easy to formulate. Sequential and simultaneous release of different therapeutic agents can be achieved by individual compartments having different set of characteristics of release (44) .

3D printing has been integrated into the microencapsulation technology, thus came up with hybrid systems that are more functional. Microencapsulated herbal extracts can be evenly dispensed in matrices of 3D-printing materials providing a controlled release and an added barrier to environmental factors. This strategy has been demonstrated in the 3D-printed denture base materials by using antifungal phytochemicals, which have reported prolonged release and prolonged antimicrobial effect characteristics (44). 3D printing and hot melt extrusion (HME) is a recent complex manufacturing strategy that creates the possibility to create drug-loaded filaments suitable to FDM-printing. This procedure has been employed successfully in many of the herba l extracts like curcumin extract, cocoa extract, and *Ginkgo biloba* extract. Biopharmaceutical enhancement of herbal compounds can be achieved in the HME process with the help of formation of solid dispersions or amorphous system increasing the stability and bioavailability of herbal compounds (44) .

A further breakthrough in the field of 3D-printed herbal delivery is the production of bioinks which are dedicated to herbal requirements. Herbal extracts could be added to these extra-ordinary printing materials and still have the desired rheological properties in printing. The design of the herbal bioink formulation is an exact task of balancing release properties, the drug loading ability and the printability (44) .

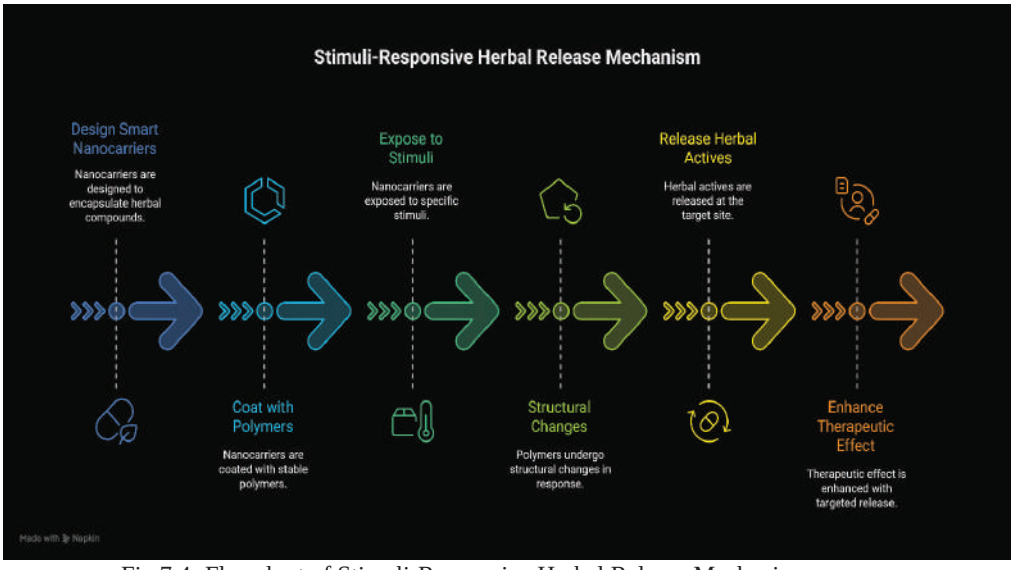

Fig 7.4- Flowchart of Stimuli-Responsive Herbal Release Mechanism

5. Synergistic and Systems-Based Innovations

Herbal medicine research is very different now that systems-based medicine and the concept of synergistic interactions that underlie the therapeutic action of conventional combinations are coming into common use. Such shift of thought would be a departure of reductionist trend that has

traditionally been accepted in pharmaceutical science. Rather it has an embracing concept that is closely related to the simple notions of the traditional medicine systems found in every corner of the globe. There is a convergence of new computer sciences with the old knowledge that is a resultant effect of the emergence of the synergistic and system-based innovations in a manner that has never occurred before. This provides a new avenue of conceptualizing, authenticating, and enhancing the herbal medicines.

The range of potential synergistic interactions via molecular mechanisms are broad in herbal medicine and beyond the scope of additivity. These can be a pharmacodynamic boost, pharmacokinetic retraction, decrease in poisonousness, and multi-target medical prescriptions. Such interactions are relevant within the philosophies of traditional medicine systems which hold that the combining of a variety of herbs in well-measured proportions can lead to actions that are more important than the sum of the parts. With the development of systems biology, network pharmacology, and the use of artificial intelligence, scientists are now able to determine molecular bases of traditional medical practices.

A great step towards drug discovery and development is the integration of traditional knowledge with modern systems biology. It addresses the issues which are associated with single-target methods prevalent in contemporary pharmaceutical research. System-based innovations enable us to better comprehend the multimodal roles and multitargets on which the herbal medicines act concomitantly. They accomplish by employing the network-level interventions striking the various pathophysiological pathways simultaneously. The approach is also in line with the new realization that complex diseases require a variety of therapy modalities that cannot be adequately embraced with single-molecule drugs.

Polyherbal Combinations for Multi-targeted Effects

Foundations of Polyherbal Synergy,

Polyherbal formulations are complicated medicinal frameworks that optimise the therapeutic superiority but diminish the side effects by using the synergistic consequences of some plant derived mixings. These formulations are based on the concept that therapeutic effect of herbs is more synergistic as compared to combination of their individual effects. A huge amount of pharmacological research has been conducted in support of this idea, demonstrating that there are many synergy mechanisms. Both pharmacodynamic synergy where different compounds act on complementary biological pathways, and pharmacokinetic synergy where some compounds improve the bioavailability and effectiveness of others, have become part of the scientific knowledge about polyherbal synergy (45)
.
The mechanistic role of polyherbal synergy is through a set of distinct pathways that sum to overall better therapeutic outcomes. In cases where active compounds of multiple herbs target different but shaped biological mechanisms, pharmacodynamic synergy occurs, which leads to a bounded therapeutic effect that treats many aspects of pathology. Anti-inflammatory plant materials and immunomodulatory herbs, such as herbs, may be used to formulate the treatment for inflammatory conditions at present. This multi-target approach proves particularly effective when it comes to complex diseases where a number of pathophysiological pathways are involved (45). The other key aspect in the efficaciousness of polyherbal drugs is pharmacokinetic synergy, which entails enhancement of the processes of absorption, distribution, biological conversion, and excretion of drugs by interaction between various herbs. Among the most renowned illustrations is the one involving curcumin and black pepper piperine that has extremely amplified the absorption of curcumin by hampering the rapid degradation and advancing intestinal up-take. The ability to transform therapeutically can be increased when seemingly inactive compounds are used since combinations are created that are optimised (45)

Multi-Target Treatment Approaches,

The multi-target basis of polyherbal formulation has a strong advantage over a single compound therapy in treating multiple patho-mechanisms complex diseases. Research has shown that polyherbal preparations may have the potential to deal with the multiple aspects of the disease process, at the levels of causes of the disease such as metabolic disorders, immune displacement, and oxidative stress. The overall approach is in line with the theories of traditional medicine, where more weight is given to treating causes of sickness rather than its symptoms (46)

. The combinatorial polyherbal formulas have been affirmed to be multi-target efficacious in various treatment areas through recent researches. Some of the combinations of herbs, such as ashwagandha, green tea, garlic, and turmeric, have been proven in the field of oncology to block various pathways of cancer, including prevention of metastasis, angiogenesis, and apoptosis. These blends enhance the anticancerous impacts and reduction of the convention chemotherapy toxicity. The simultaneous approach on several cancer hallmarks is a significant invention in the methods of integrative oncology (46)

. A further example of polyherbal combinations being shown more effective than single-herb formulation has been with cardiovascular health. Concentrating on various pathways of cardiac functionality, such as inflammatory, oxidative stress, lipid metabolism, and vascular health, the formulation that comprises herbs such as Radix Salviae Miltiorrhizae, Carthamus tinctorius, and Fructus Cartaegi has shown greater potential in the context of cardiovascular disease management. These herbs act together to be comprehensive cardioprotective to address the complexity of the cardiovascular disease (46)

Advanced Techniques for Polyherbal Development

Modern strategies of designing polyherbal formulations integrate traditional medicine with analytical and computational tools in order to maximise the therapeutic outcomes. Network pharmacology methods can be used to map the interconnective relations among herbal constituency, biological targets and pathways devoted to disease, providing a structured approach to designing combination agents that harmonize with each other. Successful polyherbal combinations often act on hub proteins within biological networks and result in a wide-range of therapeutic effects propagating on a multiplicity of interconnecting pathways because such solutions have proven to be effective against biological networks connecting the hub proteins (47) .

The active constituents, interactions, and how they collectively act pharmacologically should be strongly characterised in the endeavour to produce standardised polyherbal products. The advanced analytical procedures like nuclear magnetic resonance spectroscopy, mass spectrometry as well as high performance liquid chromatography make precision quantification of the bioactive components and their metabolites feasible. This basis of analysis is important to ensure that polyherbal products provide consistent batch-to-batch results and can deliver confounding therapeutic effects on a repeated basis (47)

Due to the complexity of multi-component systems and the potential of variability of raw materials quality control and standardisation can be especially challenging in the development of polyherbal formulations. These issues can be solved by implementing comprehensive quality assurance practice which involves stability testing, bioactivity analysis, quantity of the active compound and authentication of raw material. The newer approaches to polyherbal development now demand that standardised extracts be made and that biomarkers be applied to control quality (47) .

Combining Systems Biology and Traditional Knowledge
Connecting Ancient Knowledge with Contemporary Science

Understanding the molecular mechanisms behind centuries-old therapeutic practices is made possible through the revolutionary integration of systems biology and traditional knowledge. The integration recognises that traditional medical systems, which have been refined over thousands of years of clinical practice and empirical observation, offer important insights into the management of complicated illnesses that can be verified and improved using contemporary scientific techniques. In order to translate empirical knowledge into therapeutic interventions that are mechanistically understood, systems biology offers the analytical framework required to unravel the multi-component, multi-target nature of conventional formulations (48) .
The human body is viewed as an integrated system rather than a collection of separate organs and pathways in traditional knowledge systems, which are based on holistic principles. Approaches to systems biology, which stress comprehending biological processes through their network interactions rather than their individual components, are remarkably compatible with this viewpoint. The philosophical similarities between systems biology and traditional medicine have opened up previously unheard-of possibilities for the development of integrative research approaches that fuse the analytical prowess of contemporary computational sciences with the practical knowledge of traditional practices (48)

Because it makes it possible to analyse large amounts of traditional medical data in a methodical manner, digitising traditional knowledge has emerged as a crucial element of integration initiatives. This strategy is best demonstrated by India's innovative Traditional Knowledge Digital Library (TKDL), which uses artificial intelligence to arrange and evaluate traditional formulations, making this knowledge available to scholars everywhere while guarding against unauthorised use. The basis for extensive computational analysis of conventional therapeutic principles is provided by this digital infrastructure (48).

Methodologies for Computational Integration

With the use of computational methods, researchers can now identify patterns and links in traditional medical knowledge that they would otherwise not be able to do manually. Machine learning models are able to analyse large databases of current classical formulations and provide forecasts of their therapeutic activity, which can be similar to their area of their use, and suggest new combinations of herbs according to classical wisdom. This has demonstrated that the overall network properties of conventional formulations often give the best properties of the biological pathways of disease association (49)

Some of the techniques that have been effectively used to understand the mechanism of traditional medicine include systems biology that can be applied at the level of physiological reactions to molecular interactions. Network analysis enables scientists, by visualising the connection between herbs, compounds, targets, and diseases, to make clear maps of their relationship and reveal the logic behind the conventional treatment regimens. These network representations reveal that even traditional designs often focus on pathway modules and protein complexes associated with disease, resulting in a conceptual backing of empirical-based therapeutics (49).

The combination of traditional knowledge and omics data has opened up new possibilities for traditional-principles personalised medicine. Analyses of conventional formulations using transcriptome, proteome, and metabolome techniques show how these intricate mixtures alter biological pathways and cellular functions. This molecular-level knowledge makes it possible to optimise

formulations for unique patient characteristics and create biomarkers for the effectiveness of traditional medicine (49)

.**Traditional Medicine and Artificial Intelligence**

Research and clinical practice in traditional medicine are being advanced by artificial intelligence, a game-changing technology. Applications of AI in traditional medicine cover a wide range of topics, such as mechanism prediction, formulation optimisation, herb identification, and diagnostic support. Traditional medicine practitioners can benefit from decision support from machine learning models trained on clinical data and traditional medical texts, which can improve treatment selection and diagnostic accuracy (50)

Deep learning techniques have demonstrated special promise in deciphering the intricate patterns found in data from traditional medicine. Traditional diagnostic techniques like tongue diagnosis and pulse analysis can be analysed by convolutional neural networks, which can produce objective measurements to support subjective evaluations. These AI-powered diagnostic tools offer standardised and repeatable tests with accuracy levels on par with those of skilled professionals (50)

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The automated extraction and analysis of therapeutic knowledge from classical texts has been made possible by the application of natural language processing to traditional medical literature. AI systems are capable of extracting preparation techniques, analysing therapeutic principles, and identifying herb-disease associations from enormous databases of traditional medical literature. This ability has sped up the analysis of traditional knowledge and made it possible to conduct thorough, systematic reviews of conventional therapeutic approaches (50)

Mapping Herb-Target-Disease Interactions with Network Pharmacology
The Basics of Network Pharmacology,

The multi-component, multi-target nature of herbal medicines is ideally suited to network pharmacology, a paradigm-shifting approach to understanding drug action. A framework for comprehending how herbal compounds interact with biological targets to produce therapeutic effects is provided by this methodology, which views biological systems as intricate networks of interconnected molecules, pathways, and processes. With the help of network pharmacology, scientists can abandon the conventional "one drug, one target" paradigm and adopt more thorough "network target" strategies that more accurately capture the complexity of biological systems (50)

The idea that biological systems display network characteristics like modularity, hierarchy, and robustness that can be used for therapeutic intervention forms the theoretical basis of network pharmacology. Network-based interventions may be more successful than single-target strategies because disease states frequently involve disruptions of biological networks rather than single molecular targets. Because herbal medicines can simultaneously modulate multiple network components, their complex mixtures of bioactive compounds make them ideally suited to network pharmacology approaches (50).

In order to capture the relationships between herbal ingredients, their molecular targets, and related diseases, network pharmacology methodologies usually entail building extensive herb-compound-target-disease networks. Data from various sources, such as chemical databases, target prediction algorithms, databases of protein-protein interactions, and repositories of disease-gene associations, are used to build these networks. A systems-level perspective of how herbal formulations interact with biological systems to produce therapeutic effects is offered by the resulting networks (50).

Predicting Computational Targets and Building Networks,

By making it possible to systematically identify molecular targets for thousands of herbal compounds, the development of advanced computational approaches for target prediction has completely transformed the field of herbal medicine research. These methods combine several computational techniques, such as chemical similarity analysis, machine learning-based prediction, molecular docking, and pharmacophore modelling. Combining these techniques yields thorough target profiles for herbal compounds, exposing their possible modes of action and medicinal uses (51) .

Researchers can find possible targets for herbal compounds throughout the human proteome by using high-throughput virtual screening techniques. Numerous herbal compounds have been found to have polypharmacological profiles, interacting with several targets to produce their therapeutic effects, as a result of these systematic screening efforts. The discovery of these multi-target profiles directs the creation of optimal formulations and offers mechanistic explanations for the wide range of therapeutic uses of many herbal medicines (51).

Effective tools for comprehending the connections between herbal compounds, their targets, and disease processes are provided by network analysis techniques. The network-level mechanisms behind therapeutic effects can be revealed by using protein-protein interaction networks to pinpoint the biological pathways and processes that herbal remedies alter. These analyses frequently show that herbal compounds target pathway bottlenecks and hub proteins, producing therapeutic effects that spread across various biological networks (51)

Systems-Level Knowledge of Herbal Processes

Unprecedented insights into the mechanisms of action of conventional herbal formulations have been made possible by the application of network pharmacology techniques. Scientific validation for traditional formulation principles has been provided by these studies, which have shown that effective herbal combinations frequently exhibit optimal network properties for targeting disease-associated pathways. Synergistic herb combinations that target complementary pathways or improve each other's therapeutic effects through network-level interactions can be found using network analysis (52)

In herbal medicine research, the idea of "network targets"—groups of related molecules that work together to produce therapeutic effects—has become a key organising principle. Network targets are appealing sites for therapeutic intervention because they frequently match biological modules or pathways that are dysregulated in disease states. When compared to single-compound approaches, herbal formulations that successfully modulate network targets exhibit superior therapeutic efficacy (52).

Researchers can comprehend the effects of herbal medicine at various biological scales, ranging from molecular interactions to physiological responses, by using multi-layer network analysis techniques. These methods combine information from various biological levels, such as phenotypic results, metabolic pathways, protein-protein interactions, and regulatory networks. The multi-layer networks that are produced offer thorough insights into how herbal remedies alter biological systems to achieve therapeutic outcomes (52).

Personalised medicine and clinical translation,

The creation of useful tools and procedures for applying network-based approaches in clinical settings is necessary to convert network pharmacology insights into clinical applications. This includes the

creation of companion diagnostics that can identify patients who are likely to benefit from particular herbal interventions, the development of biomarkers that reflect network-level changes brought about by herbal treatments, and the development of decision support tools that can direct the prescription of customised herbal medicines (53)

Network pharmacology-based precision medicine techniques have the potential to improve herbal medicine treatments for specific patients. Clinicians can determine which herbal interventions are best for each patient by comparing target profiles of herbal compounds with patient-specific molecular profiles. This method offers a scientific basis for customised herbal medicine and is a major step forward from conventional empirical prescribing techniques (53).

Predictive models for the safety and effectiveness of herbal medicines have been made possible by the combination of network pharmacology and clinical data. Based on individual molecular profiles, these models can predict possible side effects and identify patients who are likely to respond to particular herbal treatments. By reducing trial-and-error prescribing, the application of these predictive approaches in clinical practice promises to improve the safety and effectiveness of herbal medicine treatments (53) .

Advanced Methods for Network Analysis,

Complex herb-target-disease relationships can now be better understood thanks to recent developments in network analysis methodology. Deep learning techniques and graph neural networks can accurately predict new herb-target interactions and capture non-linear relationships in biological networks. These sophisticated computational techniques have uncovered novel mechanisms of action for conventional formulations and previously unidentified therapeutic targets for herbal compounds (54).

Diverse data types can be integrated into network pharmacology analysis through the use of multi-modal learning techniques. Comprehensive models of herb-target-disease relationships can be produced by combining data on chemical structure, biological activity, gene expression profiles, and clinical outcomes. Target prediction accuracy has increased thanks to multi-modal learning, which has also given researchers a more sophisticated understanding of the workings of herbal medicines (54).

Researchers can comprehend how herb-target interactions vary over time and in response to various conditions by using dynamic network analysis techniques. These temporal analyses show that herbal remedies frequently cause biological networks to change over time, with distinct effects seen at acute and long-term time points. Optimising dosage schedules and treatment plans for herbal medications requires an understanding of these temporal dynamics (54).

Prospects and Difficulties for the Future

Future developments in artificial intelligence, data integration, and computational methodology will influence synergistic and systems-based innovations in herbal medicine. More advanced network analysis and prediction will be made possible by the creation of bigger, more thorough databases of knowledge about herbal medicine. Unprecedented insights into the clinical effects of herbal treatments in a variety of patient populations will be possible through the integration of empirical data from wearable technology and electronic health records.

Standardising research methods for herbal medicine and creating regulatory frameworks for network pharmacology-based drug development are still difficult tasks. It is challenging to determine causal relationships and make definitive clinical outcome predictions due to the complexity of herb-target-

disease networks. It will take ongoing cooperation between practitioners of traditional medicine, systems biologists, computational scientists, and regulatory bodies to address these issues.

One significant area for future development is the customisation of herbal medicine according to the unique characteristics of each patient. Prescriptions for herbal medicines will become genuinely personalised when network pharmacology is combined with pharmacogenomics, metabolomics, and other omics techniques. However, substantial investments in diagnostic infrastructure and healthcare provider training will be necessary to put these strategies into clinical practice.

Table 7.3- Examples of synergistic polyherbal formulations and their combined mechanisms

Formulation	Major Herbs	Combined Mechanism	Ref.
Turmeric–Black Pepper	*Curcuma longa* + Piper nigrum	**Pharmacokinetic synergy:** Piperine inhibits curcumin glucuronidation and efflux transporters, increasing curcumin bioavailability by ~20-fold	(55)
Antidiabetic Triherbal	*Curcuma longa*, Emblica officinalis, Trigonella foenum-graecum	**Multi-target metabolic synergy:** Curcumin improves insulin sensitivity; amla provides antioxidant support; fenugreek slows carbohydrate absorption	(56)
Antimicrobial Triple Herb	Ocimum sanctum, Azadirachta indica, Allium sativum	**Pharmacodynamic synergy:** Flavonoids, alkaloids, and organosulfur compounds disrupt microbial membranes, inhibit nucleic acid synthesis, and efflux	(56)
Anti-Inflammatory Quad herbal	*Curcuma longa*, Zingiber officinale, Boswellia serrata, Withania somnifera	**Multi-pathway immunomodulation:** Curcumin and boswellic acids inhibit COX/LOX; gingerols block NF-κB; withanolides reduce pro-inflammatory cytokines	(56)
Antinociceptive Duo	Rosmarinus officinalis, Syzygium aromaticum	**Isobolographic synergy:** Carvacrol and eugenol act on opioid and inflammatory pathways, lowering EC_{50} for analgesia and anti-inflammatory effects	(57)
Brahmi Nei (Cognitive Nutraceutical)	Bacopa monnieri, Convolvulus pluricaulis, Centella asiatica, others	**Network pharmacology synergy:** Multiple bioactives enhance mitochondrial bioenergetics, up-regulate neurotrophic genes, and reduce neuroinflammation.	(57)

6. Regulatory, Ethical, and Commercial Perspectives on Herbal Nanoformulations

Herbal nanoformulations—advanced delivery systems that integrate plant-derived compounds with nanotechnology—are emerging the intersection of traditional medicine and cutting-edge pharmaceuticals. While promising enhanced bioavailability, targeted delivery, and synergistic therapeutic effects, these formulations encounter a fragmented global regulatory landscape, significant scientific and manufacturing hurdles, complex ethical considerations surrounding traditional knowledge, and formidable commercial barriers. A comprehensive, structured approach is essential to navigate these challenges and accelerate the safe, equitable, and economically viable translation of herbal nanoformulations from bench to market.

Global Regulatory Frameworks

United States (FDA)

In the U.S., herbal nanoformulations fall under existing FDA authorities and are reviewed case by case. When classified as drugs, they may follow the 505(b)(1) pathway—requiring complete safety and

efficacy reports—or the 505(b)(2) pathway—permitting reliance on prior literature or third-party data. Conversely, those labeled as dietary supplements evade premarket authorization, subjecting them to post-market monitoring only. The unique behaviors of nanoparticles—deep tissue penetration and potential accumulation—challenge traditional toxicology protocols. Moreover, limited FDA nanotechnology expertise and extended patent office review times further complicate product approval and commercialization(58) .

European Union (EMA)

The European Medicines Agency treats herbal nanoformulations as Novel Bioactive Compound Delivery Systems (NBCDs), employing a rigorous, case-by-case conformity assessment. Applicants must submit full quality dossiers detailing botanical sourcing, Good Agricultural and Collection Practice (GACP) compliance, and advanced analytical characterization. The Committee on Herbal Medicinal Products (HMPC) issues scientific opinions guiding national authorities. In practice, the EMA's stringent data requirements often result in restricted authorizations unless manufacturers provide robust evidence of safety, efficacy, and reproducibility (58).

India (Ministry of AYUSH)

India's AYUSH Ministry, supported by the Department of Biotechnology and the Food Safety and Standards Authority (FSSAI), is developing nanotechnology guidelines for traditional medicines. The Ayurgyan scheme promotes R&D in nano-enabled AYUSH products. Existing statutes—the Fertilizer Control Order of 1985 and the Insecticides Act of 1968—have been extended to nano-fertilizers and nano-pesticides, while FSSAI adopts FDA-inspired criteria for nano-foods. Although these initiatives represent progress, a dedicated, coherent regulatory pathway for herbal nanoformulations remains nascent (58) .

Challenges in Clinical Translation and Standardization

Scientific and Biological Complexities,

Herbal nanoformulations face intrinsic complexity: multi-component plant extracts vary in active compound concentrations, exhibit low water solubility, and suffer physicochemical instability. Traditional formulation-driven approaches—designing nanocarriers first, then matching them to diseases—yield unpredictable *in vivo* behavior, as nanoparticle–tissue interactions, biodistribution, and pharmacokinetics differ markedly between animal models and humans. The lack of mechanistic understanding of how disease pathophysiology influences nanoformulation performance impedes reliable dose-response predictions (58) .

Manufacturing and Quality Control,

Scaling laboratory-scale nanoformulations to industrial production poses steep barriers: low yields, high raw-material costs, and poor batch-to-batch reproducibility inflate manufacturing expenses. Comprehensive quality control demands advanced analytical tools—mass spectrometry, chromatography, DNA barcoding—to ensure consistency in botanical identity, nanoparticle size distribution, and payload encapsulation. The absence of universally accepted reference materials for herbal nanoformulations further complicates inter-laboratory comparisons and regulatory acceptance (58) .

Regulatory and Infrastructure Constraints,

Existing pharmaceutical regulations lack specific provisions for nanomedicines, leaving sponsors to navigate ambiguous guidelines. Specialized toxicology studies are required to assess nanoparticle fate, structural stability in vivo, and long-term safety. Infrastructure gaps—limited access to pilot-scale facilities, toxicology cores, and skilled personnel—hamper translational efforts, particularly for small- and medium-sized enterprises that cannot self-fund extensive development pipelines. (58)

Ethical Use of Traditional Knowledge and Intellectual Property

Biopiracy and Benefit Sharing,

The ethical exploitation of indigenous herbal knowledge underpins controversies in patenting nanoformulations. Biopiracy—misappropriating traditional remedies without fair compensation—erodes trust between researchers and source communities. Although many blockbuster drugs (aspirin, artemisinin) trace roots to folk medicine, modern nano-enhancements risk repeating historical inequities if benefit-sharing mechanisms are not implemented (58) .

Intellectual Property Challenges,

Western IP systems demand novelty and identifiable authorship, criteria often unmet by age-old traditional knowledge. Consequently, patent disputes arise when companies patent nano-enhanced herbal extracts (e.g., curcumin, ginseng) without recognizing communal contributions. International instruments—WIPO's Intergovernmental Committee and the Nagoya Protocol—seek to create equitable frameworks, but operationalizing these agreements at the commercialization stage remains a practical challenge (58) .

Ethical Frameworks and Best Practices,

The EU's Directive 2004/24/EC exemplifies the integration of traditional knowledge into regulatory evaluation. Ethical best practices include transparent licensing agreements, community engagement in R&D, and shared-IP or patent pools that ensure originators of traditional knowledge receive fair royalties and recognition (58) .

Conclusion

In summary, the field of herbal neurotherapeutics stands at a transformative crossroads, bridging centuries-old traditional wisdom with next-generation formulation science and cutting-edge delivery technologies. While conventional herbal approaches have long demonstrated promise in managing neurodegenerative and neuropsychiatric conditions, challenges such as poor bioavailability, lack of standardization, and limited blood-brain barrier permeability have constrained their full therapeutic potential. Innovations in nanotechnology-based carriers, stimuli-responsive systems, phytosomes, solid lipid nanoparticles, and 3D-printed delivery devices are now overcoming these barriers by enhancing stability, targeting efficiency, and controlled release profiles. Furthermore, the integration of systems biology, network pharmacology, and synergistic polyherbal combinations provides a powerful framework for multi-targeted intervention against complex neurological diseases. Moving forward, rigorous scientific validation, standardization, and regulatory harmonization will be critical to translating these advanced herbal neurotherapeutic strategies from bench to bedside. Through such multidisciplinary progress, herbal medicines can continue to evolve as effective, safe, and accessible options for improving neurological health worldwide.

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Chapter 8: Preclinical and clinical studies: Evidence Supporting Efficacy in PD

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Abstract:

PD (PD) is a neurodegenerative disorder that mainly occurs due to the degeneration of dopaminergic neurons and can be easily characterized by motor and non-motor deficits. Various pharmacological treatments have been used to manage PD but they do have major side effects hence interest is getting shifted to herbal regimens for managing PD, *Gingko biloba* and *Gastrodia elata* are such herbal regimens which have been found to be effective in managing PD. Various animal models have demonstrated the efficacy of *Gingko biloba* in Parkinson by reducing Monoamino oxidase (MAO) activity, improvement in motor function. Not just animal models, Gingko biloba extract has shown effectiveness in Parkinson in clinical trials as well. Similarly, *Gastrodia elata* has this important phytoconstituent named gastrodin which is found to be effective in Parkinson mainly by modulating oxidative stress, and improvement in neurobehavioral impairments. This plant has been found to be effective in Parkinson as demonstrated by various clinical and preclinical studies. Thus, *Gingko biloba* and *Gastrodia elata* has shown efficacy in Parkinson and more research is ongoing. This chapter provides a comprehensive overview of preclinical and clinical studies conducted over years to demonstrate the efficacy of *Gingko biloba* and *Gastrodia elata* in PD. It also shows the basic phytochemistry and mechanism of action of *Gingko biloba* and *Gastrodia elata* in PD.

Keywords: *Gingko biloba*, *Gastrodia elata*, Preclinical study, Clinical trial, Efficacy.

1. Introduction

PD (PD) is one of the most common and continuously increasing neurodegenerative disorder around the globe and is mainly characterised by the degeneration of the dopaminergic neurons, having classic motor symptoms such as tremor, rigidity, and dyskinesia [1-3]. Many genetic and environmental factors can be responsible for the occurrence of PD but the major pathogenesis involved is the role of oxidative stress, dysfunction in the mitochondria [4-6].

Role of neuroinflammation and aggregation of abnormal protein known as α-synuclein, is also known to be playing important role in the pathogenesis of PD [7,8]. All these leads to the loss of dopaminergic neurons in the substantia nigra and ultimately to the progression of PD [9]. Many pharmacological treatment regimens such as L-DOPA, dopaminergic agonists and MAO-B inhibitors have been explored over years to manage the patients with PD but these do not possess long-term effectiveness and is also associated with various serious side effects such as fluctuations in the motor symptoms, dyskinesia etc [10-12]. These shortcomings observed with conventional pharmacological treatment has led to shift the focus towards natural compounds [13].

Natural compounds are often found to possess signature molecule responsible for pharmacological action and do not have side effects as are commonly associated with conventional pharmacological treatments [14-16]. Many plants have been explored to find the efficacy for PD, *Gingko biloba* and *Gastrodia elata* have been found to effective in reducing the symptoms associated with PD [17,18]. *Gingko biloba* standardised extract known as EGb761 has demonstrated effectiveness in managing symptoms of PD [19], similarly, gastrodin, an important phytoconstituent of *Gastrodia elata* blume has shown significant neuropharmacological activities [20]. There are several mechanisms by which these two plants act in PD, the major mechanism involved is preservation of mitochondrial function, inhibition of MAO-B activity, and reduction in dopamine metabolism. These mechanisms were found to be effective in various *in vitro* cell line models and *in vivo* animal models [21,22].

Clinical trials related to *Gingko biloba* has shown that it is effective in managing drug-induced parkinsonism (DIP) by improving motor and behavioural symptoms [40,41]. This chapter provides a comprehensive overview of preclinical and clinical studies conducted over years to demonstrate the efficacy of *Gingko biloba* and *Gastrodia elata* in PD. It also shows the basic phytochemistry and mechanism of action of *Gingko biloba* and *Gastrodia elata* in PD. Figure 8.1 shows the graphical abstract of the chapter showing *Gingko biloba* and *Gastrodia elata* in PD.

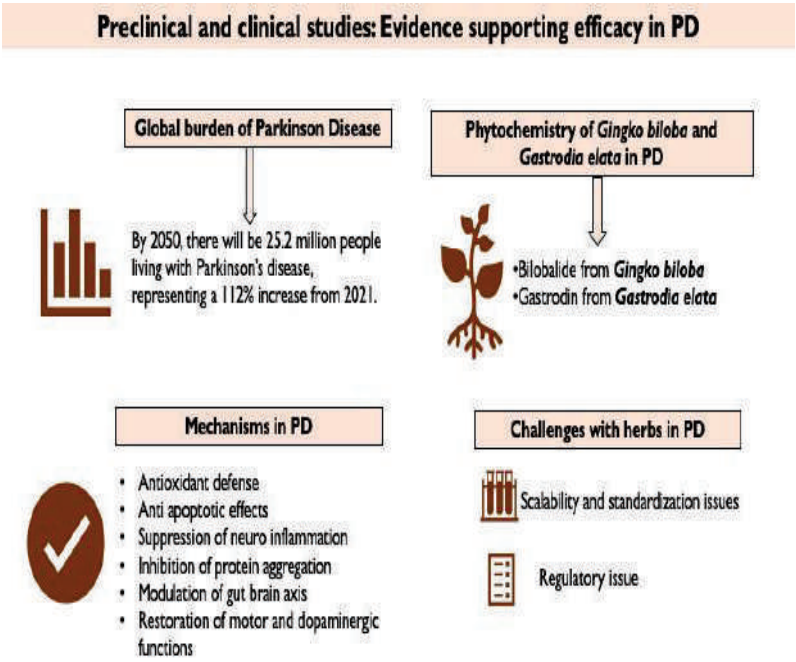

Figure 8.1: Graphical abstract

2. Phytochemistry of *Gingko Biloba* and *Gastrodia elata*

Gingko biloba has been found to show effect in PD, it comprises of a wide array of phytoconstituents including flavonoids such as quercetin, kaempferol, isorhamnetin, triterpene trilactones such as ginkgolides A, B, C, J, and bilobalide [42-44]. Bilobalide is one of the most important phytoconstituent found to be useful in PD. Various studies have demonstrated the effectiveness of *Gingko biloba* in PD due to the presence of triterpene trilactone, Bilobalide [45,46].

The widely used standardized extract of *Gingko biloba*, EGb 761 also encompasses these phytoconstituents and has been found to demonstrate action in PD [47,48]. *Gastrodia elata* is another major plant found to demonstrate action in PD, the main phytoconstituent responsible for action in PD is gastrodin, which is a phenolic compound. Other important phytoconstituents of *Gastrodia elata* includes vanillin, polysaccharides and parishin derivatives [23,24]. Gastrodin is known for its neuroprotective and antioxidant action. Some studies have also shown the importance of vanillin and polysaccharides in managing PD [49].

3. Mechanism of Action relevant to Parkinson Disease

There are several mechanisms by which *Gingko biloba* and *Gastrodia elata acts* in PD. This includes antioxidant action, inhibition of protein aggregation etc. Detailed mechanisms by which *Gingko biloba* and *Gastrodia elata* acts in PD are discussed below.

3.1. *Gingko biloba* in PD

Gingko biloba helps in scavenging reactive oxygen species (ROS) and stabilizes mitochondrial functions which leads to antioxidant action [51]. Another mechanism involved in the action of *Gingko biloba* in PD is by downregulation of inflammatory cytokines such as TNF-α and IL-6. Inhibition of

apoptosis is mainly done by reducing levels of caspase-3 and modulation of Bcl-2/Bax ratio. MAO-B is also involved in the metabolism of dopamine hence, MAO-B inhibition remains an important mechanism for action of *Gingko biloba* in PD [52].

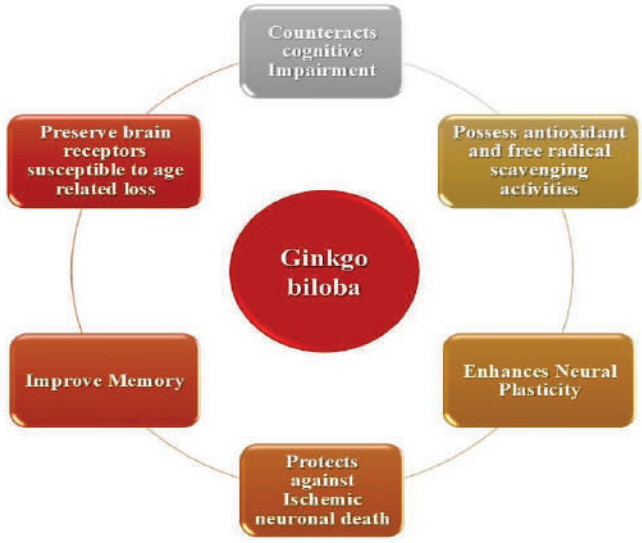

Figure 8.2: Benefits associated with the action of *Gingko biloba* in PD

3.2. *Gastrodia elata* in PD

Gastrodia elata has a significant phytoconstituent, gastrodin which exerts its action in PD. It mainly produces action by upregulating antioxidant enzymes such as SOD and catalase, this mechanism is mainly responsible for antioxidant action [53,54].

For anti-apoptosis, it regulates Bcl-2/Bax ratio. Inhibition of various inflammatory markers such as TNF-α, IL-1β, and IL-6 leads to anti-inflammatory modulation by the plant [55]. *Gastrodia elata* contains polysaccharide which helps in inhibition of protein aggregation responsible for the progression of PD [56]. Figure 8.3 shows the various beneficial mechanisms responsible for action of *Gastrodia elata* in PD.

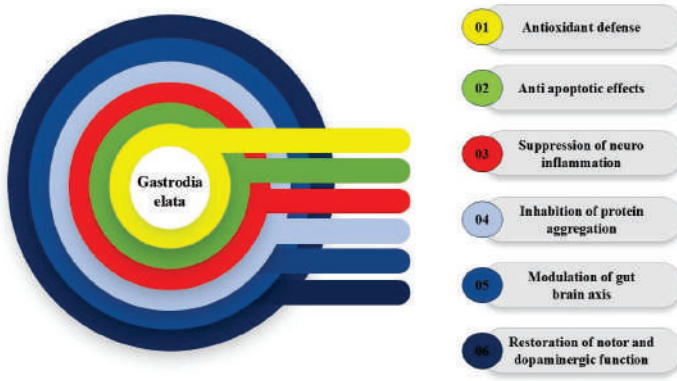

Figure 8.3: Mechanisms responsible for action of *Gastrodia elata* in PD

4. Preclinical Evidence

Preclinical evidence includes *in vitro* and *in vivo* studies which shows that any molecule shows effectiveness in a particular condition. Various research have been conducted on *Ginkgo biloba* and *Gastrodia elata* in PD, these studies include *in vitro* studies on various cell lines and *in vivo* studies on various animal models such as mice, rats, and zebrafish. The *in vitro* and *in vivo* studies of *Gingko biloba* and *Gastrodia elata* on various cell lines and animal models have been summarized in tables given below.

4.1. *In vitro* studies

Gingko biloba extract and an important phytoconstituent of *Gastrodia elata*, gastrodin have shown effectiveness in PD in various *in vitro* studies conducted on cell lines. Table 8.1 shows the *in vitro* studies of *Gingko biloba* and *Gastrodia elata* in PD in various cell lines.

Table 8.1: *In vitro* studies of *Gingko biloba* and *Gastrodia elata* in PD

Name of extract	Cell line model	Concentration	Mechanism	Main findings	Ref.
Gingko biloba leaf extract	Human neuroblastoma SH-SY5Y cells	15, 30, 60, 90, 120, and 150 µg/mL	Prevention of dopaminergic neuronal loss	Neuroprotective effect in PD	[26]
Gingko biloba extract (EGb 761)	SK-N-BE neuroblastoma cells	250 mg/mL	Protection of neuroblastoma cells	Significant protection against apoptotic cell death	[50]
Gingkolides or bilobalide	Human neuroblastoma cell line	NA	Reduction in cell apoptosis	Neuroprotective effect in PD	[57]
Gastrodin	SH-SY5Y cells	1, 5, and 25 μM	Dopaminergic neuron protection by regulating free radicals	Protective effect in PD in cell lines	[39]
Gastrodin	SH-SY5Y cells	NA	Reduction in oxidative	Synergistic action of	[58]

			stress	gastrodin and Isorhynchophylline in PD	
Gastrodia elata blume	BV-2 cells	1, 10 and 100 μg/mL	Downregulation of neuroinflammatory pathways	Potent anti-inflammatory action	[59]

4.2. *In vivo* studies

Gingko biloba extract and an important phytoconstituent of *Gastrodia elata*, gastrodin have shown effectiveness in PD in various *in vivo* studies conducted on animal models. Table 8.2 shows the *in vivo* studies of *Gingko biloba* and *Gastrodia elata* in PD in various animal models.

Table 8.2: *In vivo* studies of *Gingko biloba* and *Gastrodia elata* in PD

Name of extract	Animal model	Dosage and Duration	Mechanism	Main findings	Ref.
Gingko biloba leaf extract	Zebrafish	125, 250, and 500 μg/mL	Prevention od dopaminergic neuronal loss	Neuroprotection	[26]
Gingko biloba leaf extract	Male C57BL/6 mice	30 mg/kg/day for 5 days	Prevention of neuronal damage	Neuroprotection in PD	[26]
Gingko biloba extract	Rats	50 and 100 mg/kg	Reduction in dopamine neuron loss	Significant neuroprotection in PD	[27]
Gingko biloba supplement	Mice	NA	Increase in Nrf2 expression	Potential cortico-cerebellar protection	[28]
Gingko biloba extract	Male albino rats	150 mg/kg b.w./day	Reduction in oxidative stress markers	Neuroprotection and antioxidant action	[29]
Gingko biloba extract	α-synuclein A53T transgenic mice	40 and 60 mg/kg	Improvement in locomotor activity and inhibition of methane dicarboxylic aldehyde	Inhibition of development of PD	[30]
Gingko biloba extract	Rats	50, 100, and 150 mg/kg for 3 weeks	Increased level of generation of TBARS	Prevention of neuronal loss	[31]
Ginkgetin abd bilobalide	Mice	Ginkgetin (5, 10, 20 mg/kg), bilobalide (10, 20 mg/kg)	Reduction in GFAP levels and increase in BDNF levels	Effective in protecting dopaminergic neurons	[32]
Gingko biloba supplement	Mice	NA	Increase in Caspase-3 and reduction in Nrf2	Prevention of dopaminergic neural loss	[33]
Gingko biloba extract	Rats	100 mg/kg	Less number of Nissl's cells in levodopa group	Effective in decreasing the	[34]

				efficacy of levodopa	
Bilobalide	Rats	5, 10, and 20 mg/kg once a day for 7 days	Inhibition of neuronal loss	Due to inhibition of dopaminergic neuronal loss, significant neuroprotective action	[35]
Gastrodia elata blume	Mice	200, 400 and 800 mg/kg	Reduction in abnormal locomotor movement	Reduction in L-DOPA induced dyskinesia	[36]
Gastrodia elata polysaccharide	Mice	NA	Inhibition of accumulation of α-synuclein, inhibition of increase of GFAP	Neuroprotective effect	[37]
Water extract of *Gastrodia elata*	*LRRK2-G2019S* transgenic mice	NA	Activation Nrf2 inhibited loss of dopaminergic neurons	Potential effect in parkinson	[38]
Gatrodin	Mouse	1, 5, and 25 μM	Amelioration of bradykinesia, regulation of free radicals	Prevention of neuronal apoptosis	[39]

5. Clinical Evidence

Gingko biloba extract and an important phytoconstituent of *Gastrodia elata*, gastrodin have shown effectiveness in PD in various in clinical trials conducted on various kind of population in various study designs. Table 8.3 shows the clinical evidence of *Gingko biloba* and *Gastrodia elata* in PD.

Table 8.3: Clinical evidence of *Gingko biloba* and *Gastrodia elata* in PD

Study design	Intervention	Sample size	Dose	Duration	Main findings	Conclusion	Ref.
Randomized	*Gingko biloba* extract	63	80 mg thrice a day	3 months	Reduction in intensity of tremors,	Effective in the management of drug induced parkinsonism	[40]
Retrospective	Nimodipine combined with Gingko biloba extract	551	30 to 120 mg	3 months	Higher activity of daily living score	Improvement in cognitive function	[41]
Case study	*Gingko biloba* cocktail	1	NA	3 months	Improvement in cognitive scores	Potential alternative to PD treatment regimens	[60]

Randomized trial	*Gingko biloba* extract	356	8 pills three time a day	180 days	Ongoing	Ongoing	[63]

6. Safety Profile

Among the various *in vitro* and *in vivo* conducted to assess the safety and efficacy of *Gastrodia elata* and *Gingko biloba* in PD, no toxic effects or mutagenicity has been found. One study conducted by [15] no side effects or any kind of toxicity was observed with *Gastrodia elata* in mice model, the study was conducted for 28 days. Various clinical trials have also demonstrated the safety of *Gastrodia elata* and *Gingko biloba* in humans, a study conducted by [40] demonstrated that *Gingko biloba* helps in ameliorating symptoms of PD, no toxicity, mutagenicity or carcinogenicity was observed. Also, very low-profile side effects observed were headache and gastrointestinal discomfort which are very less as compared to conventional pharmacological treatments. But there is need of robust data to demonstrate the safety of these plants in humans when exposed to prolonged period.

7. Limitations

Although *Gingko biloba* and *Gastrodia elata* have shown efficacy in preclinical and clinical studies, yet there are certain challenges which remains in the way of using these natural plants as alternative of conventional pharmacological treatments [23-25].

First limitation is the ambiguity of mechanistic pathways involved in PD. *In vitro* and *in vivo* studies have demonstrated the effectiveness of *Gingko biloba* and *Gastrodia elata* in PD yet the fundamentals changes when it comes to humans, because there is difference in the physiological mechanism of human body (Kim et al., 2012). Another major limitation is the sample size of trials, although there are many trials that offers the effectiveness of *Gingko biloba* and *Gastrodia elata* in PD but these trials have small sample size and also trials have been conducted for shorter duration, hence it becomes difficult to assume that these will show same efficacy and safety in larger sample size when they will be exposed to prolonged period of time [62].

Another limitation is directly comparing the efficacy of these botanicals against standard pharmacological treatments, these can be used as adjuncts to increase the efficacy of conventional pharmacological treatments, but they cannot completely replace them as plants molecules are complex in nature and phytoconstituents works through different pathways which makes it difficult to understand the complete mechanism of action. Various challenges associated with the use of botanicals in disease management is also there, this includes, standardization, quality control and many more.

8. Future Directions

To integrate the therapeutic effectiveness of *Gingko biloba* and *Gastrodia elata* in PD, research is very much needed in the future as current available trials have some limitations such as small sample size and less trial duration. So, there is dire need of large scale randomized clinical trials to demonstrate the safety and efficacy of *Gingko biloba* and *Gastrodia elata* in PD in large population. Also, the extract used for trials should be standardised to get reproducible results and direct comparison between trials can be done. Focus should also be there on increasing the CNS penetration, as bioactive constituents may encounter several limitations during CNS penetration. Also, there is need for network pharmacology approaches to understand the herb-drug and polyherbal interactions. Focus should be made towards nanotechnology systems to effectively deliver these phytoconstituents to the brain for

managing PD. By addressing these points, *Gingko biloba* and *Gastrodia elata* can be more effectively deliver to manage PD.

Figure 8.4 shows the summary of preclinical and clinical studies that supports the evidence of *Gingko biloba* and *Gastrodia elata* in PD.

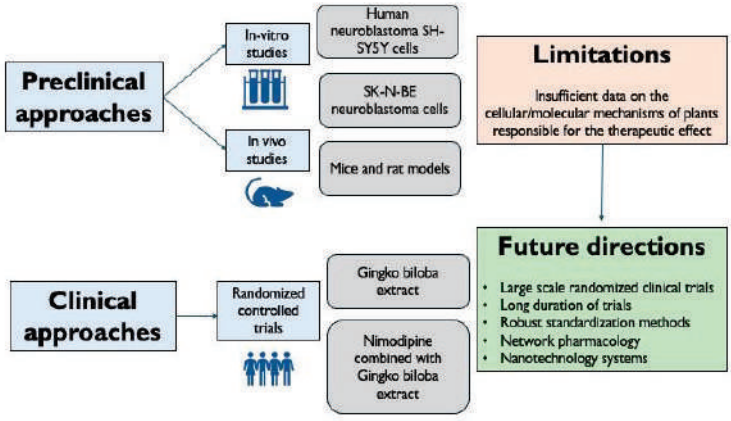

Figure 8.4: Summary description of Preclinical and clinical studies: Evidence Supporting Efficacy in PD

Conclusion

From the research done over years related to the safety and efficacy of *Gingko biloba* and *Gastrodia elata* in PD, it has been found that both these herbal regimens have demonstrated effectiveness in PD via antioxidative and anti-inflammatory pathways. *Gingko biloba* extract, EGb 761, has been found to be effective in Parkinson by reducing dopaminergic neuron loss and by modulation of oxidative stress. Gastrodin, an important phytoconstituent of *Gastrodia elata* have also shown effectiveness in PD by mitigating oxidative injury and reducing neuroinflammation. Preclinical and clinical studies conducted on *Gingko biloba* and *Gastrodia elata* in PD have shown strong evidence, still research needs to be sounder. The clinical trials conducted till now are limited to small population and for short duration. Hence, there is need of randomized trials on many populations for longer period so the effectiveness of *Gingko biloba* and *Gastrodia elata* in PD can be demonstrated on a larger level.

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