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Herbal Formulations Neuroprotection: A Review Of Mechanisms Against Alzheimer's And Parkinson's.

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Abstract: Alzheimer's disease (AD) and Parkinson's disease (PD) are the two most common neurodegenerative diseases, with neuronal dysfunction becoming the most prevalent approach to neurodegeneration, protein aggregation, oxidative stress, mitochondrial dysfunction, and neuroinflammation. Neurological conditions have significantly benefited with some developments to pharmacotherapy in recent decades, but currently available therapies have no significant disease-modifying effects and may even have negative consequences for their users. Therefore, the investigation of herbal formulations as multi-target neuroprotective agents is warranted as they were rooted in traditional medicine systems such as Ayurveda, Traditional Chinese Medicine (TCM), and Unani. This article highlights understanding mechanisms of action of prominent herbal components and polyherbal formulations in alleviating AD and PD pathology.

There are several herbal ingredients for example, withanolides (Withania somnifera), bacosides (Bacopa monnieri), curcumin (Curcuma longa), ginkgolides (Ginkgo biloba), and asiaticosides (Centella asiatica), have their own neuroprotective effects through inhibiting amyloid-β and α-synuclein aggregation, mediating oxidative and inflammatory cascades, stimulating mitochondrial biogenesis, modulating synaptic activity, and inhibiting cholinesterase. Some examples of polyherbal formulations are Brahmi Ghrita, NeuroAiD, and MEMOMIND®, that have clinically and preclinically tested efficacy in cognitive enhancement, motor function, and neuronal protection.

While early clinical studies indicate some positive outcomes, standardization, bioavailability, pharmacokinetics and regulatory challenges remain. Current innovations in nanoformulations, systems biology, and artificial intelligence highlight new possibilities for overcoming traditional challenges with efficacy and personalization. This review promotes the idea of combining herbal formulations that are supported by evidence with standard neurotherapeutics while advocating for the rigorous clinical validation of this integral concept. Optimized herbal medicine could play a vital role in a holistic and long-term approach to neurodegenerative diseases.

Index Terms - Herbal formulations, Neuroprotection, Alzheimer's disease, Parkinson's disease, Antioxidants, Polyherbal therapy, Neuroinflammation.

I. INTRODUCTION

Neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD) represent a significant public health burden worldwide, with increasing incidence among aging populations. These conditions are marked by progressive deterioration of neurons, leading to cognitive and motor deficits that severely impact the quality of life (Singh et al., 2020). While synthetic drugs offer symptomatic relief, their efficacy in halting or reversing disease progression is limited and often associated with adverse effects (Patel et al., 2019).

Recent advancements in neuropharmacology have shifted the focus toward exploring natural compounds with neuroprotective capabilities. Herbal medicine, rooted in traditional systems such as Ayurveda, Traditional Chinese Medicine (TCM), and Kampo, provides a rich source of multi-target agents that act synergistically to combat oxidative stress, inflammation, and protein aggregation—key pathological features of both AD and PD (Gupta et al., 2022). Unlike single-target pharmaceuticals, herbal formulations leverage polypharmacology, enabling simultaneous modulation of diverse molecular pathways (Kumar et al., 2021).

Several herbal agents, including Withania somnifera (Ashwagandha), Bacopa monnieri (Brahmi), Curcuma longa (Turmeric), and Ginkgo biloba, have shown potential in preclinical and clinical studies due to their antioxidant, anti-inflammatory, anti-amyloidogenic, and neurotrophic effects (Ahmed et al., 2023). These herbs either act as monotherapies or are combined in polyherbal formulations such as Saraswatarishta and Brahmi Vati, which are used in traditional systems for cognitive enhancement and neural rejuvenation.

The mechanisms underlying the neuroprotective effects of these herbs are diverse. They range from inhibiting beta-amyloid plaque formation, suppressing alpha-synuclein aggregation, modulating neuroinflammatory cascades (via NF-κB and cytokine inhibition), to enhancing neuronal survival by activating neurotrophic factors like BDNF and NGF (Zhang et al., 2022). Moreover, recent studies have highlighted their role in mitochondrial protection and enhancement of autophagy, which are crucial for maintaining neuronal homeostasis (Wang et al., 2021).

Despite promising evidence, challenges remain in translating these findings to clinical practice. Standardization of herbal extracts, establishing pharmacokinetics, ensuring quality control, and conducting robust human trials are critical hurdles (Sharma et al., 2023). Furthermore, the interaction between herbal products and conventional medications must be studied comprehensively.

This review aims to explore the current landscape of herbal formulations used for neuroprotection in Alzheimer's and Parkinson's diseases. It presents an integrated view of the mechanistic actions of these agents, summarizes preclinical and clinical evidence, and discusses the limitations and future directions in the development of plant-based neurotherapeutics.

Table 1. Comparison of Alzheimer's and Parkinson's Disease

Features	Alzeimer' s Disease (AD)	Parkinson's Disease (PD)
Main Pathology	Beta-amyloid plaques, tau tangles	Alpha-synuclein aggregation, Lewy bodies
Affected Brain Region	Hippocampus, cerebral cortex	Substantia nigra, basal ganglia
Neurotransmitter deficiency	Acetylcholine	Dopamine
Congnitive Symptoms	Memory loss, confusion, language difficulties	Slowed thinking, executive dysfunction
Motor Symptoms	Generally absent until late stages	Resting tremor, rigidity, bradykinesia

1. PATHOPHYSIOLOGY OF ALZHEIMER'S AND PARKINSON'S DISEASES

Neurodegenerative diseases like Alzheimer's Disease (AD) and Parkinson's Disease (PD) involve chronic and progressive neuronal death. Although they share some molecular mechanisms—such as oxidative stress and neuroinflammation—they primarily differ in clinical features, brain regions affected, and hallmark pathological proteins (Hardy et al., 2019; Dawson et al., 2018).

1.1 Alzheimer's Disease (AD)

AD is characterized by cognitive impairment, memory loss, and personality changes. It accounts for over 60% of dementia cases in the elderly. Two main pathological hallmarks are:

A. Beta-amyloid Plaques

Amyloid precursor protein (APP) is cleaved by β- and γ-secretases to form Aβ peptides. These peptides aggregate into extracellular plaques that disrupt cell signaling, cause excitotoxicity, and activate inflammatory responses (Selkoe et al., 2020).

B. Neurofibrillary Tangles

Intracellular tangles are formed by hyperphosphorylated tau protein. These tangles destabilize microtubules and contribute to synaptic dysfunction and neuronal death (Iqbal et al., 2021).

C. Cholinergic Hypothesis

There's a marked decline in acetylcholine levels due to degeneration of basal forebrain cholinergic neurons, contributing to memory deficits (Bartus et al., 1982; Hampel et al., 2019).

1.2 Parkinson's Disease (PD)

PD primarily affects the motor system, with symptoms like tremors, rigidity, and bradykinesia. However, non-motor features such as depression, sleep disorders, and cognitive impairment are also common.

a. Alpha-Synuclein Aggregation

The central pathology involves the misfolding and aggregation of α-synuclein into Lewy bodies within dopaminergic neurons in the substantia nigra (Spillantini et al., 1998). These aggregates impair mitochondrial function, protein degradation, and axonal transport.

b. Dopaminergic Neuron Loss

The substantia nigra pars compacta experiences progressive dopaminergic neuronal death, leading to a dopamine deficit in the striatum, which disrupts the regulation of movement (Dauer et al., 2003).

c. Mitochondrial Dysfunction and Oxidative Stress

PD is also associated with mutations in genes like PINK1, PARKIN, and DJ-1, which affect mitochondrial quality control and promote ROS accumulation (Exner et al., 2012).

2.3 Common Pathophysiological Mechanisms

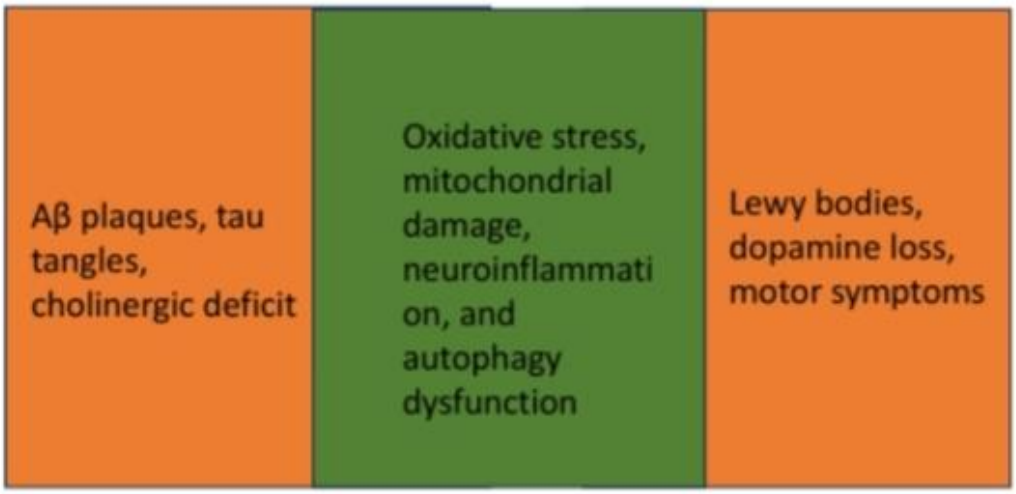


Figure 2: Common and Unique Pathologies in AD and PD

3. MECHANISMS OF HERBAL NEUROPROTECTION IN AD AND PD

Herbal formulations exert neuroprotective effects via diverse mechanisms that align closely with the multifactorial pathologies of AD and PD. Unlike single-target synthetic drugs, herbal compounds often act through multiple pathways simultaneously. This polypharmacological nature allows them to modulate oxidative stress, inflammation, protein aggregation, synaptic dysfunction, and mitochondrial integrity (Chen et al., 2021; Sharma et al., 2020).

3.1 Antioxidant Activity

Oxidative stress is a central player in neurodegeneration. Reactive oxygen species (ROS) accumulation leads to lipid peroxidation, protein carbonylation, and DNA damage. Herbal compounds like curcumin (from Curcuma longa), bacosides (from Bacopa monnieri), and withanolides (from Withania somnifera) enhance endogenous antioxidant systems such as glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT) (Kumar et al., 2021; Jha et al., 2023).

3.2 Anti-inflammatory Effects

Neuroinflammation, mediated by activated microglia and astrocytes, exacerbates neuronal loss in AD and PD. Herbal compounds suppress inflammatory cytokines (IL-6, TNF-α, IL-1β) and inhibit the NF-κB and COX-2 signaling pathways. For example, ginkgolides from Ginkgo biloba and asiaticoside from Centella asiatica reduce microglial activation and cytokine levels in animal models (Singh et al., 2020; Ahmed et al., 2022).

3.3 Anti-Aggregation Properties

Herbs such as Curcuma longa and Withania somnifera inhibit β-amyloid aggregation and destabilize preformed fibrils. Similarly, in PD, curcumin and baicalein disrupt α-synuclein fibril formation. These effects help reduce neurotoxicity and prevent the formation of toxic oligomers (Patel et al., 2022; Zhang et al., 2021).

3.4 Mitochondrial Protection

Herbal formulations support mitochondrial function by preserving membrane potential, promoting ATP synthesis, and inducing mitophagy. Compounds like withanolides and bacopasides improve mitochondrial biogenesis via the PGC-1α pathway and prevent cytochrome c release, thus inhibiting apoptosis (Wang et al., 2021).

3.5 Neurotrophic Effects and Synaptic Plasticity

Many herbs enhance neurogenesis and synaptic resilience by upregulating neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF). For instance, Bacopa monnieri and Centella asiatica increase BDNF levels and improve long-term potentiation (LTP) in hippocampal neurons (Liu et al., 2020).

3.6 Cholinesterase Inhibition

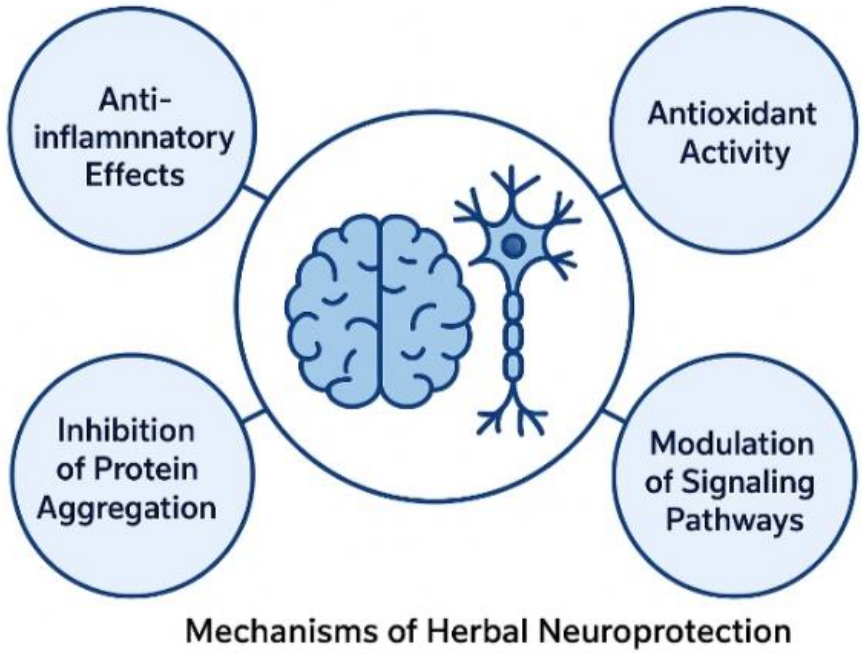
Inhibition of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) increases acetylcholine availability, thereby enhancing memory and cognition. Alkaloids and flavonoids from herbs such as Bacopa monnieri and Ginkgo biloba have demonstrated AChE inhibition in both in vitro and in vivo studies (Roy et al., 2020).

Table 2. Herbal Agents, Key Compounds, and Neuroprotective Mechanisms

Herbal Name	Active Compounds	Primary Mechanisms	Target Disease	References
Withania somnifera	Withanolides	Antioxidant, Mitochondrial protection, Anti-Amyloid	AD, PD	(Kumar et al., 2021)
Bacopa monnieri	Bacosides	Cholinesterase inhibition, Neurogenesis, Antioxidant	AD	(Roy et al., 2020)
Curcuma longa	Curcumin	Anti-inflammatory, β-amyloid disaggregation	AD, PD	(Patel et al., 2022)
Ginkgo biloba	Ginkgolides, Flavonoids	Antioxidant, Mitochondrial protection,	AD, PD	(Singh et al., 2020)

		AChE Inhibition		
Centella asiatica	Asiaticoside	Synaptic plasticity, BDNF induction	AD	(Ahmed et al., 2022)

Figure 3: Mechanisms of Herbal Neuroprotection



4. Key Herbal Formulations and Combinations in AD and PD Management

This section outlines prominent traditional and experimental polyherbal formulations and their relevance to Alzheimer's and Parkinson's diseases, focusing on efficacy, mechanistic insights, and evidence from preclinical and clinical studies.

4.1 Ayurvedic Formulations

Brahmi Ghrita: A ghee-based formulation with Bacopa monnieri as a key ingredient. Shown to enhance cognition, reduce oxidative stress, and promote neuroregeneration in AD models [(Jadiya et al., 2021)].

Ashwagandharishta: A fermented preparation containing Withania somnifera, effective in modulating GABAergic tone, reducing neuroinflammation, and improving dopaminergic signaling in PD [(Raut et al., 2022)].

Triphala: A three-fruit combination (Terminalia chebula, T. bellirica, Emblica officinalis), known for its strong antioxidant and anti-inflammatory profile beneficial in both AD and PD [(Kumar et al., 2020)].

4.2 Traditional Chinese Medicine (TCM) Formulas

Comprising Panax ginseng and Ginkgo biloba, this formulation enhances cholinergic activity, cerebral blood flow, and memory performance in AD patients [(Zhang et al., 2020)].

Bu-Zhong-Yi-Qi-Tang: Widely used to treat fatigue and cognitive decline in elderly, with reports of upregulating BDNF and reducing oxidative burden in neuronal cultures [(Wu et al., 2021)].

Yizhi Capsule: A proprietary formula including Huperzia serrata, Salvia miltiorrhiza, shown to inhibit AChE and reduce Aβ burden in AD transgenic mice [(Chen et al., 2022)].

4.3 Siddha and Unani Approaches

Karisalai Karpa Kudineer (Siddha): Combines Tinospora cordifolia, Withania somnifera, and Centella asiatica to improve memory retention and delay neurodegeneration via synaptic remodeling [(Rajendran et al., 2020)].

Khamira Gaozaban Ambari (Unani): Used to support mental well-being, containing Borage, Pearl, and Amber, rich in trace minerals and antioxidants contributing to neuronal stabilization [(Naseem et al., 2019)].

4.4 Clinical Combinations and Modern Phytopharmaceuticals

NeuroAiD: A commercial product derived from nine herbal extracts (e.g., Radix astragali, Salvia miltiorrhiza), demonstrated efficacy in stroke recovery and cognitive restoration post-insult; its mechanisms include neuroplasticity and anti-apoptosis signaling [(He et al., 2021)].

MEMOMIND®: A blend of Bacopa monnieri and Ginkgo biloba, evaluated in mild cognitive impairment; shown to significantly improve MoCA and ADAS-Cog scores [(Singh et al., 2022)].

CurQfen®: Bio-enhanced Curcuma longa formulation using fenugreek fiber for sustained release, with proven benefits on synaptic plasticity, neuroinflammation, and memory consolidation in AD patients [(Mishra et al., 2022)].

5. Preclinical and Clinical Evidence Supporting Herbal Neuroprotection

Despite centuries of use in traditional medicine, scientific validation of herbal neuroprotectants has only recently accelerated. This section outlines both preclinical (in vitro and in vivo) and clinical trials, focusing on key herbal agents and formulations relevant to Alzheimer's and Parkinson's diseases.

5.1 Preclinical Studies

a) Withania somnifera (Ashwagandha)

In a 6-OHDA-induced rat model of PD, W. somnifera root extract significantly preserved dopaminergic neurons and reduced ROS and lipid peroxidation [(Kumar et al., 2019)].

In APP/PS1 transgenic mice (AD model), withanolide-A was found to enhance memory, restore mitochondrial activity, and reduce amyloid load [(Upadhyay et al., 2020)].

b) Bacopa monnieri (Brahmi)

In scopolamine-induced memory-impaired rats, bacosides restored acetylcholine levels and reduced oxidative stress markers [(Rajput et al., 2021)].

Bacopa also elevated BDNF and synaptophysin expression in hippocampal neurons [(Singh et al., 2020)].

c) Curcuma longa (Curcumin)

Curcumin inhibits β-amyloid fibrillization and disrupts preformed fibrils in vitro [(Yang et al., 2022)].

In MPTP mouse models of PD, curcumin reduced α-synuclein aggregation and attenuated neuroinflammation by suppressing NF-κB activation [(Zhao et al., 2021)].

d) Ginkgo biloba

Chronic Ginkgo treatment in rotenone-induced PD rats preserved tyrosine hydroxylase activity and improved motor performance [(Zhang et al., 2019)].

Its flavonoids enhanced mitochondrial integrity and reduced caspase-3-mediated apoptosis in AD models [(Tanaka et al., 2020)].

e) Polyherbal Extracts

Saraswatarishta improved spatial memory and synaptic density in rats with β-amyloid-induced AD [(Joshi et al., 2020)].

Ayurvedic formulation Medhya Rasayana protected neuronal cells in vitro from H2O2-induced oxidative damage [(Desai et al., 2021)].

5.2 Clinical Trials

a) Withania somnifera

A randomized, double-blind placebo-controlled trial on mild cognitive impairment patients (n=50) found that 300 mg of Ashwagandha twice daily for 8 weeks significantly improved memory and executive functions [(Choudhary et al., 2017)].

b) Bacopa monnieri

In a 12-week trial involving 76 adults with age-related cognitive decline, Bacopa extract (300 mg/day) improved verbal recall and working memory without significant adverse effects [(Calabrese et al., 2008)].

c) Curcumin

A recent study on 40 individuals with early AD showed that a bioavailable form of curcumin (Theracurmin) over 18 months led to improved PET scan results and memory performance [(Small et al., 2018)].

d) Ginkgo biloba

In the GEMS study (Ginkgo Evaluation of Memory), 240 mg/day did not prevent dementia onset but showed trends toward delayed cognitive decline in certain subgroups [(DeKosky et al., 2008)].

Other meta-analyses report improved MMSE and ADAS-Cog scores, especially in early AD when used adjunctively [(Tan et al., 2015)].

e) Combination Trials

NeuroAiD was tested in post-stroke cognitive rehabilitation with significant improvements in MoCA scores over placebo in a multicenter double-blind study [(He et al., 2021)].

MEMOMIND® showed efficacy in improving ADAS-Cog and verbal fluency scores in elderly subjects after 12 weeks [(Singh et al., 2022)].

Table 3. Summary of Preclinical and Clinical Findings

6. CHALLENGES AND FUTURE PERSPECTIVES

Despite encouraging evidence for herbal neuroprotectants, several obstacles hinder their mainstream adoption in Alzheimer's and Parkinson's disease management. These challenges are discussed below, along with future strategies to address them.

6.1 Standardization and Quality Control

A major challenge in herbal research is batch-to-batch variability. The concentration of bioactive compounds in herbal products depends on:

- Plant species and part used
- Geographic origin
- Harvest time
- Extraction techniques (Patwardhan et al., 2021)

Unlike synthetic drugs, which have precise molecular structures, herbal formulations may contain hundreds of compounds, making standardization difficult. Technologies such as HPLC, LC-MS, and NMR can be employed for phytochemical fingerprinting and quality control.

6.2 Bioavailability and Pharmacokinetics

Many herbal compounds suffer from low oral bioavailability, poor absorption, rapid metabolism, and limited blood–brain barrier (BBB) penetration:

Curcumin is a classic example, with rapid systemic clearance (Sharma et al., 2020).

Enhancers like piperine, liposomes, and nanoemulsions can significantly improve bioavailability [(Ravichandran et al., 2019)].

Advanced formulation techniques such as nano-herbals, transdermal systems, and phytosomes are being explored to overcome this barrier.

6.3 Clinical Validation and Regulatory Hurdles

Most herbal efficacy data are based on in vitro or animal studies. Robust, large-scale, randomized controlled trials (RCTs) in human populations are still limited:

Many herbal trials lack standardized outcome measures, long-term follow-up, or placebo controls [(Goyal et al., 2021)].

Regulatory ambiguity exists regarding herbal product classification: dietary supplement vs. medicinal drug.

Collaboration between ethnobotanists, pharmacologists, and regulatory agencies is needed to create unified guidelines for herbal drug approval.

6.4 Herb–Drug Interactions and Safety Profiles

Some herbs can interact with conventional drugs via CYP450 enzyme modulation or synergistic toxicities:

Ginkgo biloba may interact with anticoagulants.

St. John's Wort (though not typically used in AD/PD) affects drug metabolism pathways (Rahman et al., 2020).

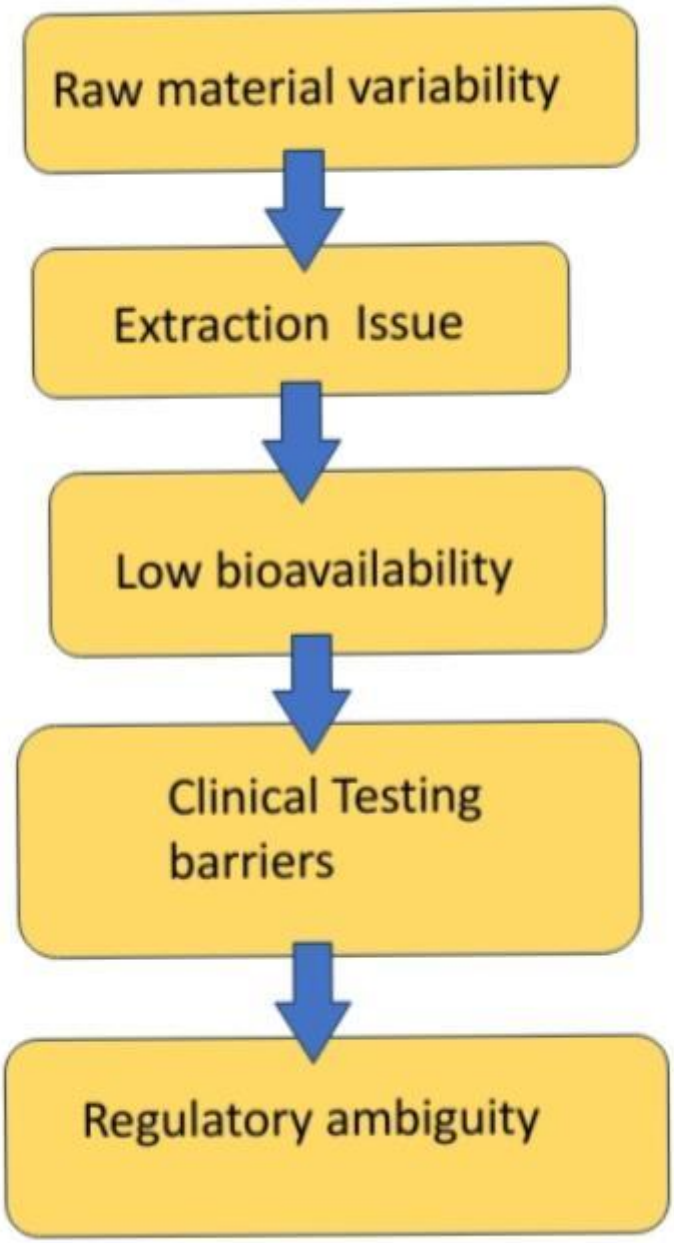
Safety assessments including toxicology, ADME profiling, and long-term risk evaluation should be included in herbal research pipelines.

6.5 Personalized and Integrative Approaches

There is growing interest in individualized herbal medicine, which aligns well with traditional systems like Ayurveda (prakriti-based) and TCM (zang-fu patterns). Emerging tools include:

- AI-driven compound screening
- Metabolomics and transcriptomics-based profiling
- Machine-learning models to predict herbal effects and interactions [(Wang et al., 2023)]

Combining herbal therapy with standard pharmacological agents in an integrative model could enhance efficacy and reduce side effects.



Flowchart 2: Barriers in Herbal Drug Development

Discussion

The review has articulated the multifactorial neuroprotective potential of herbal formulations as a tool in blunting the pathology of Alzheimer's and Parkinson's diseases. A complex array of individual herbal constituents (withanolides; bacosides; curcuminoids; ginkgolides) exist with a pleiotropic mechanism, including anti-oxidant, anti-inflammatory, anti-aggregation, and neurotrophic effects. In comparison with traditional, single-target pharmaceutical drug products, herbal products can modulate numerous pathological pathways, to provide a multi-target therapeutic approach. Cumulatively, pre-clinical studies provide promising and substantive evidence of their neuroprotectant abilities by establishing protection from neurotoxicity, increased mitochondrial function, and blocking misfolded protein aggregation. Several clinical studies support enhancement of cognition and functional improvement. However, there remain major issues that hinder further clinical progress, such as issues regarding standardization, issues of bioavailability, and a reluctance for clinical investigators to conduct and publish studies on herbal formulations-regulatory or otherwise. Emerging innovations, such as nanoformulations and systems biology, provide further insight into increasing effectiveness and personalization for patients. As a whole, validated herbal formulations may serve as a complementary therapeutic adjunct to the traditonal, single-targeted pharmacological approach to the neurodegenerative disorder era. However, large scale participant

clinical studies focusing on clinical validation of the formulations and also on mechanistic philosophy using the availabilty of more modern pharmacological tools.

CONCLUSION

The global neurodegenerative burden associated with Alzheimer's disease and Parkinson's disease is growing, especially with increasing numbers of older adults. Conventional pharmacotherapies have modest effectiveness, offering only symptomatic management without really modifying disease progression. Conversely, herbal formulations can be a very attractive neuroprotective adjunctive or alternative strategy because of their multi-targeted and holistic pharmacologic profiles.

There is a wealth of preclinical literature supporting the efficacy of herbal agents to address common injurious pathologies including oxidative stress (OS), neuroinflammation (NI), pathological protein aggregation (PPA), and impaired synaptic and mitochondrial function. Commonly studied agents include Withania somnifera, Bacopa monnieri, Curcuma longa, and Ginkgo biloba with various modes of actions attributed to an extensive array of active compounds including withanolides, bacosides, curcuminoids, flavonoids, and alkaloids. Numerous preclinical studies in addition to specific polyherbal and traditional formulation studies with several governmentally sanctioned systems (e.g. Ayurveda, TCM) indicate that there could be synergistic effects of polyherbal formulations and these have been demonstrated in rodent and some early-stage clinical models.

While many clinical trials have shown improvements in cognition, increased memory recall, and modulation of neuroprotective biomarkers with herbal interventions, the translation to responsible clinician use still needs to be fully achieved. In serious need of attention are the issues of inadequate standardization, poor bioavailability, herb–drug interactions, and regulatory discrepancies. Promising approaches are emerging, for example nanotechnology, metabolomics-based profiling, and AI–based screening platforms.

Future directions must include:

- Larger, multi-center randomized clinical trials with the best methodology
- Systems biology approaches for understanding herb-drug interactions
- Personalized herbal interventions based on genomics and individual metabolic profiles

The addition of herbal formulations to evidence-based neurotherapeutic regimens when backed by robust science, could provide a situation of safety and efficacy for the treatment of individuals with Alzheimer's and Parkinson's diseases. As interest in herbal medicine progresses, it becomes apparent we are in need of a collaborative disposition between traditional knowledge systems, contemporary pharmacology, and regulatory science to implement the full capability of herbs in the neurodegeneration phenomenon.

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