RESEARCH PAPER

Herbal Drugs Used For Neurodegenerative Diseases: Mechanisms, Evidence, And Future Directions

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Abstract

Background: Neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and other dementias share overlapping pathological mechanisms including oxidative stress, mitochondrial dysfunction, neuroinflammation, protein aggregation, and synaptic failure. In recent years, herbal drugs containing polyphenols, terpenoids, alkaloids, and saponins have attracted considerable attention for their multi-target neuroprotective actions, offering potential adjunctive value in managing these complex disorders.

Aim: To review major herbal drugs used in neurodegenerative diseases and summarise their bioactive constituents, mechanisms of neuroprotection, clinical evidence, limitations, and future research priorities.

Methodology: This narrative review synthesised findings from recent preclinical and clinical studies, published systematic reviews, and pharmacological evidence concerning herbal agents with neuroprotective potential. Key herbs were analysed for their active constituents, molecular targets, therapeutic mechanisms, safety profiles, and evidence from clinical trials.

Results: Herbal drugs including Ginkgo biloba, Bacopa monnieri, Withania somnifera, curcumin (Curcuma longa), resveratrol-containing plants, and Panax ginseng demonstrated antioxidant, anti-inflammatory, anti-amyloid, anti-apoptotic, neurotrophic, and cholinergic-modulating actions across multiple neurodegenerative pathways. While several exhibit promising preclinical results and modest clinical benefits, challenges remain, such as variable extract standardisation, poor bioavailability for some phytochemicals, limited large-scale randomised controlled trials, and potential herb–drug interactions.

Conclusion: Herbal drugs show significant mechanistic plausibility and preliminary clinical support as adjunctive therapies for neurodegenerative diseases. However, definitive evidence for disease-modifying effects is lacking. Future progress requires well-designed, standardised, multi-centre clinical trials alongside improved formulations and biomarker-integrated research approaches to validate long-term efficacy and safety.

Keywords: Neurodegenerative Diseases; Herbal Medicine; Antioxidants; Plant Extracts.

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1. Introduction

Neurodegenerative diseases (NDs) such as Alzheimer's disease (AD), Parkinson's disease (PD), and other dementias are major causes of disability, institutionalisation, and mortality worldwide. Ageing populations and limited disease-modifying therapies have driven growing interest in herbal drugs and natural products as adjuncts or alternatives to conventional pharmacotherapy.[1–3]

Pathologically, NDs share common mechanisms: oxidative stress, mitochondrial dysfunction, protein aggregation (Aβ, tau, α-synuclein), neuroinflammation, excitotoxicity, and synaptic failure.[1,3–5] Many herbal drugs are rich in polyphenols, terpenoids, alkaloids, and saponins that target multiple pathways simultaneously, including antioxidant effects, modulation of inflammatory cascades, inhibition of amyloidogenesis, enhancement of neurotrophic signalling, and improved cerebral perfusion.[1,4,5]

2. Pathophysiological Rationale for Herbal Therapies

NDs involve a convergence of:

- **Oxidative stress & mitochondrial dysfunction** – excess ROS and impaired mitochondrial respiration promote neuronal death.
- **Neuroinflammation** – microglial activation and pro-inflammatory cytokines amplify injury.
- **Protein misfolding & aggregation** – Aβ and tau in AD, α-synuclein in PD, huntingtin in HD.
- **Excitotoxicity & calcium dysregulation** – glutamatergic overactivity and Ca^{2+} overload.
- **Synaptic and neurotrophic failure** – reduced BDNF and impaired plasticity.[1–5]

Herbal drugs typically exert multi-target effects, for example:

- Polyphenols (curcumin, resveratrol, EGCG): strong anti-oxidant and anti-inflammatory actions; modulation of amyloid/tau pathways and synaptic signalling.[6,7]
- Terpenoids (ginkgolides, bilobalide, withanolides, ginsenosides): neurotrophic, anti-apoptotic, and anti-excitotoxic effects; modulation of neurotransmission and cerebral blood flow.[8,9]
- Saponins (bacosides): enhancement of synaptic plasticity, cholinergic modulation, and anti-oxidant effects.[10]

These multi-modal mechanisms support the concept of herbal "network pharmacology" in NDs, where complex phytochemical mixtures target multiple nodes in disease pathways.

3. Major Herbal Drugs in Neurodegenerative Diseases

3.1 *Ginkgo biloba*

Standardised *Ginkgo biloba* leaf extracts (e.g. EGb 761) contain flavonol glycosides and terpene lactones (ginkgolides A–C, bilobalide) with antioxidant, anti-inflammatory, anti-apoptotic, and vasoregulatory properties.[11] Ginkgo extracts reduce lipid peroxidation, preserve mitochondrial function, inhibit platelet-activating factor, and improve cerebral blood flow in experimental models of ischaemia, AD, and PD.[12]

Safety

Generally well tolerated, but concerns include bleeding risk (interaction with anticoagulants/antiplatelets) and rare seizures; quality control and standardisation (EGb 761 vs non-standard products) are crucial.[13]

3.2 *Bacopa monnieri* (Brahmi)

Bacopa monnieri, commonly known as Brahmi, is one of the most widely used nootropic herbs in Ayurvedic medicine, traditionally prescribed to enhance intellect, memory, and cognitive resilience. Its bioactive constituents—primarily bacoside A, bacoside B, and other bacosaponins—confer a broad spectrum of neuroprotective properties. These compounds exhibit potent antioxidant activity by scavenging free radicals and reducing lipid peroxidation, thereby protecting neuronal membranes from oxidative stress. In addition, Bacopa demonstrates significant anti-inflammatory effects through downregulation of pro-inflammatory cytokines, contributing to mitigation of neuroinflammatory cascades implicated in neurodegenerative disorders. The herb also modulates cholinergic transmission by enhancing acetylcholine synthesis and inhibiting cholinesterase activity, mechanisms that support learning and memory processes. Furthermore, bacosides promote neurotrophic actions, including increased dendritic branching, neuronal repair, and upregulation of brain-derived neurotrophic factor (BDNF), all of which are essential for synaptic plasticity and cognitive performance.[14]

Safety

Generally well tolerated; the most common adverse events are mild gastrointestinal symptoms. Long-term safety data in dementia populations remain limited.[15]

3.3 *Withania somnifera* (Ashwagandha)

The bioactive withanolides, mainly withaferin A and withanolide A, present in the roots of *Withania somnifera* (Ashwagandha), encompass wide neurotherapeutic applications. These compounds demonstrate adaptogenic properties, which help the body regulate stress responses, while their potent antioxidant and anti-inflammatory actions modulate oxidative damage and neuroinflammatory processes involved in neurodegeneration. Ashwagandha also exerts neurotrophic actions by inducing neurite outgrowth, maintaining synaptic plasticity, and enhancing neurotrophic factors such as BDNF. Due to these multiple modes of action, Ashwagandha is considered a promising herbal candidate for improving cognitive functions and preventing neurodegenerative disorders.[16] Ashwagandha is generally well tolerated but may cause gastrointestinal upset and, rarely, hepatotoxicity; caution is advised in patients with thyroid disease and those on sedatives or immunosuppressants.

3.4 *Curcuma longa* (Curcumin)

Curcumin, one of the major bioactive curcuminoids isolated from *Curcuma longa*, is a spice commonly known as turmeric. It possesses potent antioxidant and anti-inflammatory properties and inhibits amyloid aggregation and modulates multiple molecular pathways implicated in neurodegenerative diseases. This makes curcumin a promising neuroprotective agent in disorders like Alzheimer's and Parkinson's disease. However, poor oral bioavailability due to rapid metabolism, low aqueous solubility, and consequently limited blood-brain barrier penetration inhibits clinical utility despite promising biological activity, hence the development of enhanced formulations in order to improve its therapeutic effectiveness.[18]

3.5 *Resveratrol* and Related Polyphenols

Resveratrol is a stilbene phytochemical that occurs in grapes, berries, and peanuts, well-recognized for its potent antioxidant capability and its action as an activator of the sirtuin pathways, especially SIRT1. By these mechanisms, resveratrol contributes to the decrease in oxidative stress, modulation of mitochondrial function, and control of cellular survival pathways, each of which forms a core component of neuroprotection. These pleiotropic effects have positioned it as a promising candidate in neuroprotection and in the prevention and management of neurodegenerative diseases, although issues related to its bioavailability and dosing remain areas under investigation. [19]

3.6 *Panax ginseng*

Panax ginseng ginsenosides express several neuroprotective actions that include antioxidant, anti-inflammatory, neurotrophic, and cholinergic-modulating effects; these have contributed to growing interest in ginseng as a potential supportive option for cognitive decline and neurodegenerative conditions.[20] Clinical studies exploring the effectiveness of ginseng alone and within multi-herbal formulations report modest improvements in cognitive performance in disorders such as Alzheimer's disease and vascular dementia. However, given the variability in product formulations, doses, and other methodological approaches between studies, drawing consistent conclusions about its overall clinical benefit is challenging.[21]

3.7 Other Emerging Herbal Candidates

Several other herbs are under investigation:

- **Green tea polyphenols (EGCG)** – anti-amyloid, anti-oxidant, and anti-inflammatory effects in AD models.[22]
- **Centella asiatica** – enhances synaptic plasticity and exhibits neuroprotective effects in cognitive impairment models.[23]
- **Crocus sativus (saffron)** – small RCTs in AD suggest cognitive benefits comparable to donepezil, with good tolerability.[24]

Evidence for these agents remains limited but supports further controlled trials.

4. Summary of Mechanisms and Evidence

Table 1. Key herbal drugs for neurodegenerative diseases: mechanisms and primary targets

Herb (common name)	Major active constituents	Main mechanistic targets in NDs	Primary conditions studied
Ginkgo biloba	Flavonol glycosides, ginkgolides, bilobalide	Antioxidant; anti-inflammatory; anti-apoptotic; ↑ cerebral blood flow; platelet-activating factor antagonism	AD, vascular dementia, mixed dementia

Bacopa monnieri (Brahmi)	Bacoside A/B, bacosaponins	Antioxidant; anti-inflammatory; cholinergic modulation; ↑ synaptic plasticity & BDNF	Age-related cognitive decline, MCI, dementia
Withania somnifera (Ashwagandha)	Withanolide A, withaferin A	Antioxidant; anti-inflammatory; anti-apoptotic; promotes axonal and synaptic regeneration; modulates dopaminergic pathways	PD, AD, HD (mainly preclinical); mild cognitive impairment
Curcuma longa (curcumin)	Curcuminoids	Antioxidant; anti-inflammatory; anti-amyloid; anti-tau; mitochondrial protection	AD, PD (preclinical > clinical)
Resveratrol-containing plants (e.g. grapes, *Polygonum cuspidatum*)	Resveratrol	Antioxidant; SIRT1 activation; anti-inflammatory; anti-amyloid; enhances mitochondrial function	AD
Panax ginseng	Ginsenosides (e.g. Rg1, Rb1)	Antioxidant; anti-inflammatory; cholinergic modulation; neurotrophic effects	AD, vascular dementia

Table 2. Advantages and Limitations of Herbal Drugs in Neurodegenerative Diseases

Category	Advantages	Limitations
Mechanistic Profile	Multi-target, network-level action	Difficult to isolate single mechanism
Safety	Generally safe at recommended doses	Herb–drug interactions (e.g., anticoagulants)
Accessibility	Widely accessible, cost-effective	Variable quality of commercial preparations
Evidence Base	Rich preclinical data; some RCTs	Lack of large multicenter trials
Formulation	Multiple delivery forms	Poor bioavailability for some agents (curcumin, resveratrol)

6. Limitations and Challenges

Despite extensive preclinical data, translation of herbal neuroprotective agents into effective clinical therapies faces several challenges:

1. **Heterogeneity of preparations** (different species, parts used, extraction methods, and standardisation) leading to variability in pharmacological activity and trial outcomes.
2. **Bioavailability issues**, particularly for curcumin and resveratrol, which undergo rapid metabolism and have poor CNS penetration; nanoformulations and conjugates are being explored.
3. **Under-powered, short-duration trials** with heterogeneous endpoints, often conducted in mixed populations and without biomarker-guided stratification.
4. **Drug–herb interactions**, notably Ginkgo with anticoagulants/antiplatelets, ginseng with hypoglycaemic or antihypertensive drugs, and Ashwagandha with sedatives and thyroid-active drugs.
5. **Regulatory and quality-control issues**, as many products are marketed as dietary

supplements rather than rigorously standardised medicinal products.

7. Future Directions

Key priorities for advancing herbal drugs in NDs include:

- **Standardisation of extracts** – clear specification of active constituents (e.g. bacoside content, withanolide profile, ginsenoside composition) and batch-to-batch quality control.
- **Rigorous clinical trial design** – large, multi-centre RCTs with:
    - well-defined ND subtypes and disease stages;
    - standardised doses and durations (≥12–18 months for disease-modifying questions);
    - combined clinical, functional, and biomarker endpoints (e.g. neuroimaging, CSF/plasma biomarkers).
- **Combination strategies** – evaluating herbal drugs as **adjuncts** to standard pharmacotherapy (e.g. *Bacopa* or Ginkgo plus cholinesterase inhibitors) rather than standalone monotherapy.
- **Network pharmacology and omics approaches** to map herb–target–pathway interactions and identify synergistic phytochemical combinations.
- **Safety and pharmacovigilance systems** specific to long-term herbal use in elderly, multi-morbid populations.

8. Conclusion

Herbal drugs occupy an increasingly prominent position in the search for neuroprotective strategies against neurodegenerative diseases. Among available candidates, Ginkgo biloba, Bacopa monnieri, Withania somnifera, curcumin, resveratrol, and Panax ginseng show the most compelling mechanistic and preliminary clinical evidence. However, no herbal agent has yet demonstrated unequivocal disease-modifying effects in large, high-quality RCTs. Current data support their cautious use as adjuncts for symptom management and cognitive support, particularly when standardised preparations with known safety profiles are used under medical supervision.

Future research must move beyond small, short-term, heterogeneous trials toward robust, biomarker-integrated, multi-centre studies that can clarify efficacy, optimal dosing, and long-term safety. With such advances, herbal drugs may evolve from traditional remedies to scientifically validated components of comprehensive, multi-target therapy for neurodegenerative diseases.

Data Availability Statement

The dataset used in the current study will be made available on request from the corresponding author.

Conflicts of Interest

The authors declare no conflicts of interest.

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