



Role of Herbal Extracts in Neuroprotective Drug Development: Mechanistic Insights, Translational Potential, and Emerging Therapeutic Applications

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Abstract

Neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease, constitute an escalating global health burden, collectively affecting more than fifty million individuals worldwide with projected increases driven by demographic ageing. Current pharmacological therapies predominantly offer symptomatic relief without modifying the underlying pathological progression, underscoring the critical need for novel neuroprotective interventions capable of targeting the multifactorial mechanisms that drive neuronal degeneration. Herbal extracts and their bioactive constituents represent a scientifically compelling and historically validated source of pharmacological diversity for neuroprotective drug development. This article systematically reviews the mechanistic basis of herbal neuroprotection, encompassing antioxidant activity, modulation of neuroinflammatory signalling cascades, mitochondrial preservation, inhibition of pathological protein aggregation, and activation of endogenous neuronal survival pathways. Major bioactive classes discussed include flavonoids, alkaloids, terpenoids, polyphenols, saponins, and stilbenes, with emphasis on their specific molecular targets and demonstrated efficacy in validated preclinical models of neurodegeneration. The article further examines the preclinical-to-clinical translational landscape, evaluating current clinical evidence, challenges related to standardization and bioavailability, and the role of advanced drug delivery technologies in enhancing CNS penetration and therapeutic efficacy. Regulatory frameworks governing botanical drug development and the ethical dimensions of ethnopharmacological research are critically appraised. The article concludes by identifying precision medicine integration, network pharmacology-guided formulation strategies, and biomarker-validated clinical trial design as priority directions for translating herbal neuroprotective research into clinically deployable therapeutics.

Keywords: Herbal extracts, Neuroprotection, Neurodegenerative diseases, Phytochemicals, Drug development, Translational research

1. Introduction

The global prevalence of neurodegenerative diseases has reached epidemic proportions, with Alzheimer's disease alone accounting for approximately sixty to eighty percent of dementia cases and generating annual socioeconomic costs exceeding one trillion US dollars worldwide ^[1]. The pathophysiological complexity of neurodegenerative disorders, characterized by the convergence of oxidative stress, chronic neuroinflammation, mitochondrial dysfunction, excitotoxicity, and the aberrant accumulation of misfolded proteins, presents formidable challenges for therapeutic development ^[2]. The single-target pharmacological paradigm that has dominated drug discovery over the past three decades has yielded limited clinical success in

neurodegeneration, with numerous promising candidates failing in late-stage clinical trials despite robust preclinical efficacy data [3]. This translational deficit has catalysed renewed scientific interest in multi-target pharmacological strategies capable of simultaneously engaging the interconnected pathological networks that underpin neuronal degeneration.

Herbal medicine occupies a historically significant and scientifically substantive position within this therapeutic landscape. Approximately forty percent of currently approved pharmaceutical drugs are derived from or inspired by natural product structures, and the chemical diversity encoded within plant secondary metabolites remains an incompletely explored repository of neuroprotective pharmacological activity [4]. Ethnopharmacological traditions from Ayurvedic, Traditional Chinese Medicine, and indigenous botanical systems have historically identified plants with apparent cognitive and neurological benefits, providing leads that modern pharmacological investigation has begun to mechanistically validate. The development of Huperzine A from *Huperzia serrata* as a clinically utilized acetylcholinesterase inhibitor, and the widespread clinical deployment of Ginkgo biloba extract EGB761, exemplify the translational potential of herbal neuroprotective research [5]. The present article critically examines the mechanistic, translational, and clinical dimensions of herbal extract research in the context of neuroprotective drug development.

2. Molecular Basis of Neurodegeneration and Therapeutic Target Landscape

2.1. Oxidative Stress and Mitochondrial Dysfunction

The central nervous system is uniquely susceptible to oxidative damage by virtue of its high metabolic rate, elevated oxygen consumption, abundant polyunsaturated fatty acid content, and relatively limited endogenous antioxidant capacity compared to peripheral tissues [6]. Reactive oxygen species generated primarily within the mitochondrial electron transport chain overwhelm cellular antioxidant defences in neurodegenerative conditions, leading to lipid peroxidation, protein oxidation, and DNA strand breaks that collectively impair neuronal function and viability. Mitochondrial dysfunction, manifested as reduced complex I activity, decreased ATP synthesis, increased membrane permeabilization, and dysregulated calcium homeostasis, plays a particularly prominent role in the pathogenesis of Parkinson's disease and amyotrophic lateral sclerosis [7]. The Nrf2-Keap1 antioxidant response pathway, which coordinates the transcriptional upregulation of cytoprotective enzymes including superoxide dismutase, heme oxygenase-1, and glutathione peroxidase, represents a compelling therapeutic target for herbal neuroprotective compounds [8].

2.2. Neuroinflammation and Protein Aggregation

Chronic neuroinflammation, orchestrated principally by activated microglia and reactive astrocytes through the sustained release of pro-inflammatory cytokines, chemokines, and reactive nitrogen species, constitutes both a pathological driver and a consequence of progressive neuronal degeneration [9]. Activation of the NF- κ B and NLRP3 inflammasome signalling axes represents critical amplification mechanisms in neuroinflammatory cascades,

with the latter increasingly implicated in the maturation and secretion of neurotoxic interleukin-1 beta in Alzheimer's and Parkinson's disease models. Concurrent with inflammatory pathology, the aberrant aggregation of amyloid-beta peptides, hyperphosphorylated tau protein, and alpha-synuclein generates proteotoxic oligomeric species that disrupt synaptic transmission, impair axonal transport, and initiate apoptotic cell death programs [10]. The intersection of these pathological mechanisms with endogenous neuronal survival pathways, including the PI3K/Akt/mTOR axis and BDNF/TrkB signalling, defines the multi-dimensional therapeutic target landscape within which herbal bioactive compounds operate.

3. Herbal Extracts and Their Neuroprotective Bioactive Constituents

3.1. Flavonoids and Polyphenols

Flavonoids represent the most extensively studied class of herbal bioactive compounds with demonstrated neuroprotective activity. The flavone baicalein, derived from *Scutellaria baicalensis*, exerts potent anti-neuroinflammatory effects through selective inhibition of the NLRP3 inflammasome and downstream caspase-1 activation, reducing IL-1 beta secretion in lipopolysaccharide-stimulated microglial cultures and attenuating dopaminergic neurodegeneration in MPTP-induced Parkinson mouse models [11]. Quercetin, ubiquitously present in dietary plants and herbal medicines, activates the Nrf2/HO-1 antioxidant pathway, inhibits acetylcholinesterase, and reduces amyloid-beta oligomer-induced synaptic toxicity in hippocampal neuronal cultures [12]. The polyphenol curcumin, derived from *Curcuma longa*, exerts pleiotropic neuroprotective effects through simultaneous engagement of NF- κ B inhibition, SIRT1 activation, beta-secretase suppression, and direct interference with amyloid-beta fibril formation, representing one of the most pharmacologically multifaceted natural neuroprotective agents investigated to date [13].

3.2. Alkaloids, Terpenoids, and Saponins

Among alkaloids with established neuroprotective relevance, Huperzine A from *Huperzia serrata* occupies a position of particular translational significance as a reversible, selective inhibitor of acetylcholinesterase with a duration of action and safety profile that has supported its clinical use for Alzheimer's disease in China [14]. Berberine, an isoquinoline alkaloid present in multiple medicinal plants, modulates AMPK activation, reduces neuroinflammation through suppression of microglial M1 polarization, and attenuates dopaminergic neurodegeneration in multiple experimental PD paradigms [15]. Terpenoids from Ginkgo biloba, notably ginkgolides A and B, act as selective platelet-activating factor antagonists and exert anti-excitotoxic effects through modulation of NMDA receptor activity, contributing to the neuroprotective profile of standardized EGB761 extract in ischaemic and neurodegenerative experimental conditions [16]. Ginsenosides from *Panax ginseng*, particularly Rg1 and Rb1, activate neurotrophic factor expression including BDNF and NGF through CREB-mediated transcription, stimulate hippocampal neurogenesis, and confer protection against both oxidative and endoplasmic reticulum stress-induced apoptosis in neuronal populations relevant to Alzheimer's disease [17].

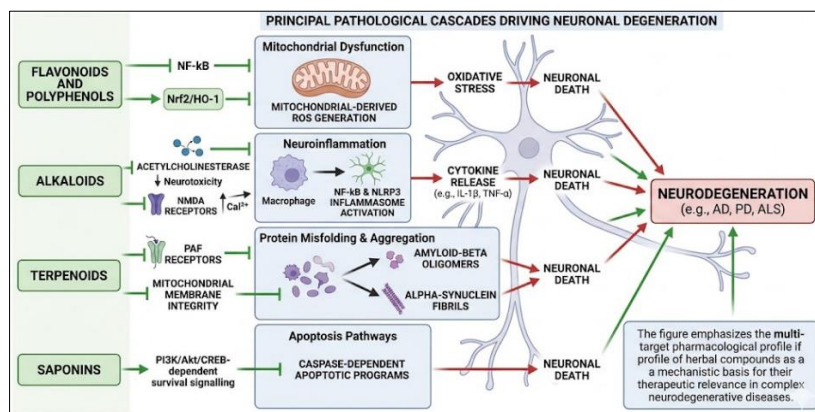


Fig 1: Major molecular pathways implicated in neurodegeneration and sites of intervention by herbal bioactive compounds

4. Mechanistic Basis of Herbal Neuroprotective Activity

4.1. Antioxidant and Anti-inflammatory Signalling

The dual capacity of herbal compounds to simultaneously activate endogenous antioxidant defences and suppress neuroinflammatory signalling cascades constitutes a mechanistic advantage over pharmacological agents targeting individual pathways in isolation. Nrf2 nuclear translocation, stimulated by electrophilic and oxidative stressors as well as by herbal compounds including curcumin, sulforaphane, and pterostilbene, drives the transcriptional induction of a coordinated battery of cytoprotective genes including heme oxygenase-1, NADPH:quinone oxidoreductase 1, and ferritin heavy chain, collectively restoring redox homeostasis in vulnerable neuronal populations [18]. Concurrently, multiple herbal bioactive compounds suppress NF- κ B activation through interference with I κ B kinase activity, proteasomal I κ B degradation, or nuclear translocation of the p65 subunit, reducing the transcription of pro-inflammatory mediators including TNF- α , IL-6, cyclooxygenase-2, and inducible nitric oxide synthase in microglial and astrocytic cells [19].

4.2. Neuronal Survival Pathways and Anti-aggregation Effects

Beyond antioxidant and anti-inflammatory mechanisms, herbal compounds modulate fundamental neuronal survival signalling cascades. Ginsenoside Rg1 and Bacopa monnieri saponins activate the PI3K/Akt/mTOR pathway, phosphorylating and inactivating the pro-apoptotic protein BAD while stimulating the anti-apoptotic Bcl-2 family members, collectively shifting the apoptotic balance towards neuronal survival under proteotoxic and oxidative stress conditions [20]. The capacity of polyphenols including EGCG and resveratrol to directly inhibit the nucleation and elongation of amyloid-beta and alpha-synuclein fibrils through hydrophobic and pi-pi stacking interactions with fibril-forming peptide sequences represents a mechanistically distinct and therapeutically significant anti-aggregation strategy [21]. Resveratrol-mediated SIRT1 activation further promotes autophagic clearance of aggregation-prone proteins through AMPK-dependent inhibition of mTORC1, enhancing proteostatic capacity in neurons under chronic protein folding stress [22].

5. Preclinical and Translational Research Frameworks

5.1. *in vitro* and Animal Model Evidence

The preclinical evidence base for herbal neuroprotective compounds spans a broad range of *in vitro* and *in vivo*

experimental paradigms. Cell-based studies employing differentiated neuronal cell lines, primary cortical and hippocampal neuronal cultures, and patient-derived pluripotent stem cell neuronal models have collectively defined the cellular pharmacology of major herbal bioactive compounds with increasing mechanistic resolution [23]. Transgenic animal models expressing disease-relevant human genes, including the 5xFAD and 3xTg-AD mouse models for Alzheimer's disease and the A53T alpha-synuclein transgenic and rotenone-infusion models for Parkinson's disease, have demonstrated significant attenuation of neuropathological hallmarks and behavioural deficits following treatment with herbal extracts including EGb761, curcumin, berberine, and baicalein [24]. Notwithstanding this substantial preclinical evidence base, systematic translation to clinical efficacy has been inconsistent, reflecting both the inherent limitations of rodent neurodegenerative models and the pharmacokinetic challenges associated with achieving therapeutically relevant CNS concentrations of many herbal bioactive compounds in human subjects.

5.2. Translational Challenges and Bridging Strategies

The translational gap between herbal neuroprotective preclinical findings and clinical validation is multidimensional, encompassing pharmacokinetic inadequacies, model validity limitations, and methodological heterogeneity in the preclinical literature [25]. Curcumin, despite its compelling preclinical mechanistic profile, exemplifies the translational challenge, with multiple Phase II clinical trials in Alzheimer's disease yielding equivocal results attributable in substantial part to its extremely poor oral bioavailability, rapid first-pass metabolism, and limited CNS penetration under conventional oral dosing regimens [26]. Nanoformulation strategies, including lipid-based nanoparticles, polymeric nanocarriers, liposomal encapsulation, and phospholipid complex technologies, have demonstrated marked improvements in curcumin bioavailability and brain exposure in preclinical pharmacokinetic studies, providing a rational technological basis for the reformulation of clinical development programs [27]. The application of physiologically based pharmacokinetic modelling to herbal bioactive compounds, incorporating human metabolic enzyme activity data and BBB transport parameters, increasingly supports the design of clinical dosing regimens that achieve pharmacodynamically relevant CNS target engagement.

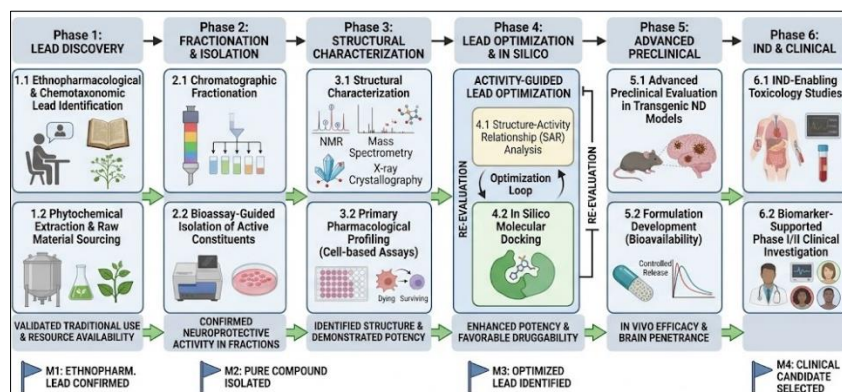


Fig 2: Workflow for the identification, isolation, and development of neuroprotective bioactive compounds from herbal sources

6. Clinical Research: Current Evidence and Limitations

Clinical evidence for herbal neuroprotective agents is most substantial for Ginkgo biloba extract EGb761, which has been investigated in over forty randomized controlled trials encompassing cognitive impairment, dementia, and vascular-related neurological disorders [28]. A Cochrane systematic review and subsequent meta-analyses have demonstrated consistent but modest effects of EGb761 on cognitive outcomes, neuropsychiatric symptoms, and activities of daily living in patients with mild-to-moderate Alzheimer's disease and vascular dementia, with an acceptable safety profile and evidence of anti-dementia biological activity including modulation of amyloid precursor protein processing [29]. Huperzine A has demonstrated significantly greater acetylcholinesterase inhibitory potency and longer duration of action compared to synthetic cholinesterase inhibitors in comparative pharmacodynamic studies, and multiple randomized trials in Chinese populations have reported cognitive benefits in both Alzheimer's disease and age-associated memory impairment [30]. Nevertheless, the broader clinical evidence base for herbal neuroprotective agents is constrained by methodological heterogeneity, inadequate trial duration, absence of validated biomarker endpoints reflecting neuroprotective mechanisms, and insufficient regulatory-grade pharmacokinetic and pharmacodynamic characterization.

Standardization of herbal extracts for clinical research represents a persistent methodological challenge, as the therapeutic activity of complex botanical preparations reflects the integrated pharmacological contribution of multiple co-occurring phytochemical constituents whose relative proportions vary with botanical origin, cultivation conditions, and extraction methodology [31]. The development of standardized extract specifications employing quantitative HPLC fingerprinting and marker compound content thresholds, as exemplified by the internationally recognized EGb761 specification requiring 24% flavone glycosides and 6% terpene lactones, provides a scientifically rigorous template for botanical drug quality assurance that supports meaningful across-study comparability and regulatory acceptance [32].

7. Technological Advancements in Herbal Neuroprotective Drug Delivery

The inherent physicochemical limitations of many herbal bioactive compounds, including low aqueous solubility, pH-dependent instability, rapid hepatic first-pass metabolism, and restricted CNS penetration due to efflux transporter activity at the blood-brain barrier, have motivated substantial innovation in advanced drug delivery system development for this compound class [27]. Lipid-based nanocarrier systems, including solid lipid nanoparticles, nanostructured lipid carriers, and self-emulsifying drug delivery systems, have demonstrated two- to fifteenfold improvements in oral bioavailability for poorly soluble herbal compounds including curcumin, resveratrol, and quercetin in pharmacokinetic studies, with corresponding enhancements in brain tissue concentration and pharmacodynamic effect in preclinical neurodegenerative models [28]. Nose-to-brain delivery via intranasal nanoformulations, exploiting the olfactory and trigeminal neural pathways to bypass the blood-brain barrier, represents a particularly promising strategy for herbal compounds with compelling central pharmacology but restricted systemic CNS penetration, with preclinical demonstrations of significantly enhanced hippocampal drug exposure following intranasal administration of curcumin nanoparticles and berberine lipid carriers [33].

Computational approaches, including molecular docking, molecular dynamics simulation, network pharmacology analysis, and machine learning-based ADMET prediction, are increasingly integrated into herbal neuroprotective research to accelerate target identification, optimize lead structures, and predict optimal delivery system parameters [34]. Network pharmacology platforms that map the interactions between herbal compound databases and neurodegeneration-relevant protein-protein interaction networks have proven particularly valuable for the systematic identification of bioactive constituents responsible for the observed pharmacological effects of complex herbal preparations, providing mechanistic rationales for extract standardization decisions and regulatory target product profiles [26].

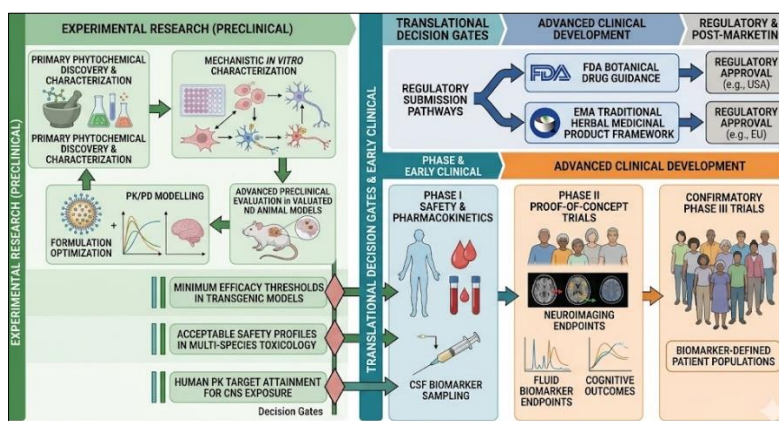


Fig 3: Translational pathway from experimental herbal neuroprotection research to clinical application

8. Regulatory, Safety, and Ethical Considerations

The regulatory framework governing herbal-derived neuroprotective drug development reflects the fundamental tension between recognition of the long historical use of medicinal plants and the rigorous evidence standards required for modern pharmaceutical approval [35]. In the United States, the FDA Botanical Drug Guidance, most recently updated in 2023, provides a regulatory pathway specifically designed for complex botanical drug substances, permitting the use of traditional use and ethnobotanical evidence to supplement clinical safety data in early development phases, with confirmatory efficacy demonstrated through conventional randomized controlled trials for full approval [34]. The approval of Veregen, a sin catechin preparation derived from green tea extract for external genital warts, established an important regulatory precedent for complex botanical drugs and demonstrated the viability of the FDA botanical drug pathway for plant-derived complex mixture pharmaceuticals. Within the European regulatory framework, the Committee on Herbal Medicinal Products at the European Medicines Agency administers both traditional herbal registration and herbal medicinal product authorization pathways, with the latter requiring full pharmacological and clinical evidence documentation analogous to conventional drug development requirements [35].

The safety evaluation of herbal neuroprotective candidates demands particular attention to herb-drug interaction potential, hepatotoxicity risk associated with concentrated phytochemical preparations, and long-term safety implications of chronic administration in elderly neurodegenerative disease populations [36]. Ginkgo biloba at high doses demonstrates clinically relevant interactions with anticoagulant and antiplatelet agents through inhibition of platelet-activating factor and cytochrome P450 modulation, necessitating careful pharmacokinetic interaction characterization as a prerequisite for clinical co-administration studies. Ethical dimensions of herbal neuroprotective drug development extend to the equitable sharing of benefits arising from the commercial development of compounds derived from traditional knowledge systems, principles codified in the Nagoya Protocol on Access and Benefit-Sharing, and to the responsible conduct of ethnopharmacological research with indigenous communities

that requires prior informed consent and culturally respectful collaboration frameworks [37].

9. Conclusion

Herbal extracts and their bioactive phytochemical constituents represent a scientifically compelling frontier in neuroprotective drug development, offering mechanistic diversity, multi-target pharmacological activity, and a historical validation framework that collectively distinguish them from purely synthetic pharmaceutical approaches to neurodegeneration. The accumulation of mechanistic evidence across flavonoids, alkaloids, terpenoids, polyphenols, and saponins has defined a sophisticated understanding of how plant-derived compounds engage the intersecting pathological networks of oxidative stress, neuroinflammation, protein aggregation, and neuronal survival signalling that characterize the major neurodegenerative diseases [38]. The principal translational barriers of pharmacokinetic inadequacy, model validity limitations, and clinical evidence heterogeneity are increasingly amenable to resolution through nanoformulation innovation, humanized preclinical models, and biomarker-integrated clinical trial design.

Future research priorities of critical importance include the systematic application of network pharmacology and systems biology methodologies to define the mechanistic pharmacology of complex herbal preparations at a precision medicine level, enabling biomarker-guided patient stratification in clinical trials analogous to that employed in precision oncology [26]. The integration of single-cell transcriptomic and proteomic profiling of herbal compound-treated neuronal models will provide unprecedented mechanistic resolution for the identification of responsive neuronal subpopulations and predictive biomarkers of therapeutic response. Collaborative international frameworks for the standardization of herbal extract quality, harmonization of regulatory requirements across major jurisdictions, and equitable benefit-sharing with communities of traditional knowledge origin are equally essential prerequisites for the responsible and scientifically rigorous translation of herbal neuroprotective research into accessible clinical therapeutics [37, 38].

Table 1: Comparative Overview of Major Herbal Bioactive Compound Classes: Sources, Mechanisms, and Neuroprotective Evidence

Compound Class	Representative Agents	Primary Herbal Sources	Neuroprotective Mechanisms	Key Experimental Evidence
Flavonoids	Quercetin, Luteolin, Apigenin, Baicalein	Ginkgo biloba, Scutellaria baicalensis, green tea (Camellia sinensis)	Inhibition of NF-κB and MAPK signalling; reduction of ROS; modulation of Nrf2/HO-1 pathway [5, 6]	Reduced Ab aggregation and tau hyperphosphorylation in AD murine models; dopaminergic neuron protection in PD models [7]
Alkaloids	Berberine, Huperzine A, Vincamine, Galantamine	Berberis vulgaris, Huperzia serrata, Vinca minor	Acetylcholinesterase inhibition; NMDA receptor modulation; mitochondrial membrane stabilization [8, 9]	Huperzine A approved in China for AD; berberine attenuates MPTP-induced dopaminergic neurodegeneration [10]
Terpenoids	Ginkgolides A/B, Ursolic acid, Asiaticoside, Andrographolide	Ginkgo biloba, Centella asiatica, Andrographis paniculata	PAF antagonism; suppression of neuroinflammatory cytokines (TNF-α, IL-1β, IL-6); promotion of neurite outgrowth [11, 12]	Ginkgolide B reduces ischaemic neuronal death; asiaticoside promotes hippocampal neurogenesis <i>in vivo</i> [13]
Polyphenols	Resveratrol, Curcumin, EGCG, Rosmarinic acid	Vitis vinifera, Curcuma longa, Camellia sinensis, Rosmarinus officinalis	SIRT1 and AMPK activation; inhibition of NLRP3 inflammasome; mitophagy induction; suppression of α-synuclein aggregation [14, 15]	Curcumin reduces amyloid plaque burden in transgenic AD mice; resveratrol activates neuroprotective autophagy in Parkinson models [16]
Saponins	Ginsenosides Rg1/Rb1, Astragalosides, Saikosaponins	Panax ginseng, Astragalus membranaceus, Bupleurum falcatum	Upregulation of BDNF and NGF; activation of PI3K/Akt survival pathway; reduction of ER stress markers [17, 18]	Ginsenoside Rg1 attenuates cognitive deficits and hippocampal neuronal loss in D-galactose-induced aging models [19]
Stilbenes	Pterostilbene, Piceatannol, Oxyresveratrol	Pterocarpus marsupium, Vaccinium myrtillus, Artocarpus lakoocha	Epigenetic modulation via SIRT1/SIRT3; attenuation of oxidative mitochondrial damage; Nrf2 nuclear translocation [20]	Pterostilbene demonstrates superior BBB permeability versus resveratrol; neuroprotective in stroke and TBI experimental models [21]

Table 2: Advantages, Limitations, and Clinical Considerations of Herbal Extracts in Neuroprotective Drug Development

Domain	Advantages	Limitations	Clinical Considerations and Progress
Pharmacological Mechanisms	Multi-target activity; simultaneous modulation of oxidative, inflammatory, and apoptotic pathways reduces selective pressure for resistance	Mechanistic complexity complicates target deconvolution and regulatory attribution of therapeutic effects	Network pharmacology and systems biology approaches increasingly employed to map multi-target profiles for regulatory submissions [26]
Bioavailability and BBB Penetration	Lipophilic terpenoids and stilbenes exhibit moderate BBB penetrance; intrinsic antioxidant properties protect CNS targets	Many polyphenols (e.g., curcumin) demonstrate poor oral bioavailability due to rapid metabolism and low aqueous solubility	Nanoparticle encapsulation, phospholipid complexes (phytosomes), and solid dispersions markedly improve CNS delivery in preclinical studies [27, 28]
Preclinical Evidence	Substantial <i>in vitro</i> and animal model evidence for multiple compound classes across AD, PD, stroke, and TBI models	Translational failure rate remains high; rodent models incompletely replicate human neurodegenerative pathophysiology	Adoption of patient-derived iPSC neuronal models and humanized AD/PD murine systems improving translational validity [29]
Standardization and Quality Control	Established HPLC and mass spectrometry fingerprinting methods available; international pharmacopoeial monographs exist for major herbs	Batch-to-batch variability in phytochemical composition; seasonal, geographical, and agronomic factors affect potency	WHO guidelines for herbal quality assessment and ICH Q14 framework for analytical procedure development increasingly applicable [30]
Clinical Trial Evidence	Ginkgo biloba and Huperzine A possess the most extensive clinical trial datasets; positive signals in early-phase cognitive studies	Many trials underpowered; heterogeneous patient populations; short follow-up durations; lack of validated biomarker endpoints	Growing use of CSF biomarkers (Ab42/40 ratio, phospho-tau) and neuroimaging endpoints in herbal neuroprotection trials [31, 32]
Safety and Toxicity	Long historical use of many herbal agents provides preliminary safety data; generally favourable acute toxicity profiles	Herb-drug interactions (e.g., Ginkgo with anticoagulants); genotoxic pyrrolizidine alkaloids in some species; hepatotoxicity risk with chronic high-dose use	ICH S7A/S7B safety pharmacology studies required for CNS agents; regulatory agencies increasingly requiring full toxicological characterization [33]
Regulatory Pathway	Traditional use dossiers accepted in EU (THMPD) and WHO frameworks; botanical drug guidance available from FDA	Absence of single active ingredient paradigm complicates IND/NDA submissions; complex mixture characterization challenging	FDA Botanical Drug Guidance (2016, revised 2023) permits traditional use evidence to supplement clinical data; Veregen (sinecatechins) as approved botanical precedent [34]

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