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Review Article

Exploring Plant Based Neuroprotective Agents in Neuropharmacognosy

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Abstract

The most relevant and comprehensive causes of morbidity and mortality across the globe include Alzheimer disease (AD), Parkinson disease (PD), Huntington disease (HD) and amyotrophic lateral sclerosis (ALS). The current pharmacotherapies are largely symptomatic in nature, which does not inhibit the slow disappearance of neurons. Many plant based natural products with long histories of ethnomedical utilization offer structurally diverse molecules, that are acting in a multitude of ways (antioxidant, anti-inflammatory, anti-apoptotic, cholinesterase inhibition, mitochondrial protection, modulated neurotrophic factors) and would therefore be excellent targets in the development of neuroprotective agents. The paper describes the concept of neuropharmacognosy, summarizes the mechanistic and preclinical evidence on personality neuroprotective phytochemicals and botanical extracts (e.g., *Bacopa monnieri, Withania somnifera, Ginkgo biloba,* curcumin, resveratrol), discusses the current strategies used to address the translational gaps (nanodelivery systems, network pharmacology, omics), regulatory issues, and sets out future research priorities. Although preclinical evidence is persuasive in the case of a number of phytochemicals, there are challenges of bioavailability, standardization and properly controlled clinical trials which hinder clinical translation. The combination of novel drug-discovery technologies with attentive pharmacognostic and clinical assessments might enable the faster pace in the development of evidence-based phytotherapeutics in neurodegenerative diseases.

Keywords: Neuropharmacognosy; Neurodegenerative Diseases; Phytochemicals; Neuroprotection; Network Pharmacology; Translational Challenges

Introduction

Neurodegenerative diseases (NDDs) such as Alzheimer disease (AD), Parkinson disease (PD), Huntington disease (HD), and amyotrophic lateral sclerosis (ALS) are diagnosed by progressive neuronal degeneration and dysfunction that result in cognitive and motor impairments. Age-related NDDs have a growing incidence across the world as the population is ageing and there are no effective disease-modifying therapies. Multi-target therapeutics that can regulate the multifaceted pathophysiology of NDDs (oxidative stress, neuroinflammation, mitochondrial dysfunction, protein aggregation, excitotoxicity) [1-4], can be achieved by current pharmacological strategies which tend to target individual

targets and simply provide symptomatic relief. Plant-based natural products are structurally versatile, and often pleiotropic in their activities, and are of interest in neuroprotection and symptomatic treatment [5-9].

Neuropharmacognosy is a term used to refer to the interdisciplinary field that aims at identifying, defining, and developing neuroactive agents by using natural sources, combining ethnopharmacology, phytochemistry, pharmacology, and the current methods of drug discovery. The interface between traditional knowledge (e.g., Ayurvedic, Traditional Chinese Medicine) and modern molecular practices (network pharmacology, metabolomics, high-throughput screening, and computational docking) is neuropharmacognosy which tries to find multi-target plant-derived agents in the treatment of neurological disorders [10,11]. This is a synthesis of mechanistic understanding, previous clinical and preclinical results, and translational solutions in neuropharmacognosy that is extensive and up-to-date [12].

Methods (Search Strategy)

In the case of this narrative review, electronic searches in PubMed, PMC, and other significant review sources were completed in order to locate the relevant recent literature (2010-2025) on the topic of plant-derived neuroprotective compounds, herbal extracts with neuroprotective evidence, the mechanisms of action, nanoformulation strategies, network pharmacology applications, and clinical trials. Systematic reviews, meta-analyses, recent preclinical research, and high quality narrative reviews were of higher priority. The most important keywords were plant-derived neuroprotective agents, phytochemicals neuroprotection, *Bacopa monnieri* neuroprotection, *Withania somnifera* neuroprotective, *Ginkgo biloba* Alzheimer, curcumin neuroprotection, resveratrol neuroprotection, nanoformulations phytochemicals and network pharmacology phytochemicals. The most relevant and up-to-date sources are mentioned.

Molecular mechanisms underpinning phytochemical neuroprotection

Phytochemicals have a multitude of mechanisms that are applicable in neuroprotection. The most important mechanisms with the help of which preclinical and translational studying works are supported are as follows.

Antioxidant activity and redox modulation

Oxidative stress plays a pivotal role in neuronal injury in neurodegenerative disease, and too much ROS can perform lipid, protein, and DNA damage, promote mitochondrial dysfunction and cell death.1 Oxidative stress can be mitigated by a wide range of phytochemicals including flavonoids, phenolic acids, stilbenes, induced by Nrf2/ARE pathway upregulation, and protects mitochondrial activity, thereby limiting oxidative damage in neurodegeneration models [13,14]. Such antioxidant activities have been well established in preclinical research with many botanicals and isolated compounds [14].

Anti-inflammatory effects

In neurodegenerative pathologies, neuronal death is worsened by chronic neuroinflammation that is mediated by the activation of microglial cells and pro-inflammatory transcriptional programs (e.g., NF- 80000signaling). Experimental models have demonstrated the ability of phytochemicals such as curcumin and resveratrol to inhibit the activation of NF-kB and the generation of pro-inflammatory factors (cytokines, iNOS and COX-2) thus having neuroprotective anti-inflammatory actions [15]. Ginkgolides and allied terpenoids in *Ginkgo biloba* also suppress NF- -signaling and reduce the expression of inflammatory cytokines in cellular and animal models, and may help to suppress microglial activation and inflammation [16].

Anti-apoptotic and pro-survival signaling

Numerous natural compounds regulate pro- and anti-apoptotic proteins (including Bax/Bcl-2 ratio), the caspase cascade, and survival signaling pathway (PI3K/Akt and MAPK/ERK) and suppress neuronal apoptosis in response to toxic insults (including excitotoxicity or ischemia). Preclinical literature indicates that *Bacopa monnieri* extracts have the capacity to induce pro-survival signaling such as ERK/MAPK and PI3K/Akt and regulate apoptosis-relevant signaling in neuron-like cells, which has led to a decrease in cell death in oxidative or toxic models [17].

Modulation of neurotransmission and synaptic plasticity

Other phytochemicals balance monoaminergic and cholinergic systems e.g. huperzine A and galantamine are acetylcholinesterase inhibitors that stimulate cholinergic neurotransmission and synaptic plasticity to support learning, memory, and resistance to neurodegenerative changes [18].

Anti-amyloid and anti-aggregation effects

Some plant extracts and phytochemicals act on pathological protein aggregation (amyloid-2 in Alzheimer disease and 2-synuclein in Parkinson disease) by inhibiting aggregation, promoting disaggregation or by altering aggregate clearance (autophagy or proteasomal degradation) paths [19,20].

Prominent plant-derived neuroprotective agents and evidence

The following is a review of the most common botanicals and phytochemicals whose effects have been examined and studied to have neuroprotective effects.

Bacopa monnieri (Brahmi) — bacosides and cognitive effects

Bacopa monnieri is a traditional Ayurvedic nootropic that has a long history of preclinical and growing clinical research on cognitive enhancement and neuroprotection due to the action of its principle active constituents, bacosides (especially bacoside A), and antioxidant activity, cholinergic transmission modulation, anti-amyloid effects, and activation of neurotrophic signaling pathways of relevance to synaptic plasticity [21,22]. Bacopa extracts have been reported to have reduced amyloid burden, improved synaptic markers, mitigated oxidative stress and behavioral benefits in animal models of Alzheimer and Parkinson diseases [1]. Randomized controlled trials on humans have shown to have modest yet significant effect on memory acquisition, memory retention, and cognitive performance in healthy adults and select clinical groups [22]. In clinical research, safety profiles tend to be good with primarily mild gastrointestinal reactions; nonetheless, standardization of extract composition (e.g. content bacoside) and maximized dose appear to be paramount to standardization and translational applicability [21,22].

Withania somnifera (Ashwagandha) — withanolides and neuronal resilience

Withania somnifera (Ashwagandha) has bioactive steroidal lactones called withanolides which exhibit neuroprotective effects by antioxidant, anti-inflammatory, anti-amyloid, and neurogenesis-stimulating action. Preclinical studies have revealed amyloid-B toxicity attenuation, replenishment of synaptic structure, overcoming of oxidative stress, and increased hippocampal neurogenesis in the experimental neurodegeneration models [23,24]. Mechanistically, withanolides have been shown to act as NF- 0 signaling, pro-inflammatory cytokines, neurite outgrowth, and synaptic plasticity [23]. There is some evidence of an improvement in cognitive performance, stress resiliency and mood parameter through early clinical and pilot testing, but to establish efficacy in neurodegenerative diseases, larger and well-designed randomized controlled trials are needed [24].

Ginkgo biloba — ginkgolides and cognitive disorders

Among the most extensively studied herbal preparations in neurocognitive studies is standardized *Ginkgo biloba* extract EGb 761.1 Antioxidant activity, platelet-activating factor inhibition, augmentation of cerebral microcirculation, mitochondrial protection, and anti-inflammatory effects through cytokine and NF-kB signaling modulation represent the proposed mechanisms of action [25,26].

Curcumin (from *Curcuma longa*) — polyphenol with pleiotropic activity

Curcumin is a polyphenol that has a pleiotropic activity.

Curcumin acts as an antioxidant, anti-inflammatory, anti-amyloid, and metal-chelating agent and regulates signaling (Nrf2, NF-kB, BDNF). The key challenges to translational delivery involve poor oral bioavailability, high metabolism, and CNS bioavailability, yet novel formulations (nanoencapsulation, liposomes, adjuvants such as piperine) enhance pharmacokinetics and have demonstrated greater preclinical efficacy. The result of clinical trials in AD and cognitive impairment has been mixed, which is in part due to bioavailability factors and heterogeneity in formulations [27,28].

Resveratrol (stilbene) — sirtuins, anti-inflammatory and anti-amyloid effects

Resveratrol is a sirtuin agonist, an antioxidant, anti-inflammatory and has also been shown to reduce the amyloid burden and increase mitochondrial activity in models. Human trial effectiveness has been patchy and sample; experiencing metabolic unsteadiness and low bioavailability has been a negative side advantage in investigation [29,30].

Translational Strategies: Overcoming key barriers

Some of the issues associated with research to clinic translation are lack of bioavailability, probability of blood-brain barrier

(BBB), extract standardization and absence of homogeneity of the preclinical models. Current solutions to address these issues are high-tech delivery systems, network pharmacology and omics-based approaches [31].

Nanoformulations and targeted delivery

Nanotechnology can enhance solubility, stability and CNS of phytochemicals delivery. Better bioavailability and BBB penetration is achieved with liposomes, solid lipid nanoparticles, polymeric nanoparticles, nanoemulsions, and surface-modified carriers (e.g. receptor-targeted ligands). Research indicates that there is enhanced brain absorption and effectiveness of curcumin, resveratrol, and other phytochemicals using nanocarriers. Safety, scalability and regulatory acceptability are promising and still need to be developed further [32,33].

Network pharmacology and systems approaches

Since the NDD pathologies and phytochemical actions are multi-target, network pharmacology is a logical approach to map compound-target-pathway interactions and predict synergistic combinations. Network analyses coupled with molecular docking and in vitro validation facilitates the discovery of promising multi-component herbal formulations and elucidates mechanisms. Integrated network pharmacology with experimental validation has been used in recent studies to rank phytochemicals against targets of neurodegenerative disease [34,35].

Omics and metabolomics for active constituent profiling

High-resolution mass spectrometry and metabolomics can allow in-depth analysis of crude extracts, which can be used to standardise and detect active metabolites. Pathway modulation by botanicals in cellular/animal models, identified by transcriptomics and proteomics, supports mechanistic assertions and informs the choice of biomarkers in clinical trials [36,37].

Rational polyherbal design and synergy testing

Most of the conventional curative agents are polyherbal; systematic combination screening, isobolographic analysis, and mechanism-based synergy testing could determine the formulations that have an additive or synergistic neuroprotective effect and minimum levels of toxicity. Network pharmacology can guide rational choice of combinations that can be subjected to downstream preclinical tests [38].

Safety, toxicology, and pharmacovigilance

The herbal products are usually considered as being naturally safe, but there is the risk of drug-herb interactions, batch disparities, adulteration, and contamination. There are some examples, such as Ginkgo can also react with antiplatelet or anticoagulant drugs; some of the herbal components can influence the cytochrome P450 enzymes resulting in the change of the drug metabolism. Strict safety profiling, standardisation of preparations and pharmacovigilance systems on herbal neurotherapeutics are critical especially in the comorbid and polypharmacy populations [39,40].

Regulatory and standardization challenges

Among the obstacles, there is the uneven jurisdictional regulatory status of botanical products (dietary supplement vs. prescription drug) that defines the requirements in terms of quality control, clinical evidence, and manufacturing standards. Standardization of botanical extracts (quantification of active markers), Good Manufacturing Practices (GMP), and presentation of extract composition in a transparent form are predetermined with reproducible clinical research and ultimate therapeutic approval. Regulatory policies and incentives that are balancing botanical neurotherapeutic clinical validation would aid in the proceeding [41,42].

Conclusion

Plant-based natural products present a superior, historically informed, source of chemically diversified molecules with multi-purpose mechanisms which also find applications in neuroprotection. The preclinical evidence of the majority of botanicals is good and biologically pertinent and compelling yet the transfer to clinical evidence is hampered by bioavailability, standardization, and experiment heterogeneity. To accelerate the ethnobotanical leads to evidence-based neurotherapeutics, incorporating new technologies, including nanotechnology, network pharmacology, omics, and strict clinical practices can accelerate the process.

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Conflicts of Interest

The authors have declared that they have no potential conflicts of interest.

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