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Review Article

Involvement of Natural Therapeutics for the Treatment of Age-Associated Neurodegenerative Disorders Through Modulation of the HPA Axis

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ABSTRACT

The pursuit of increased longevity has been a longstanding human objective. However, brain ageing undermines this objective by being strongly linked to multiple disorders. Pathological neuronal ageing significantly contributes to the onset of neurodegenerative diseases, causing progressive deterioration, cellular destruction, impairment of the structure and function of neurons, and leading to disability among older adults. As global life expectancy continues to rise, the occurrence of age-related neurodegenerative conditions is expected to grow significantly. Recent evidence indicates that altered Hypothalamic-Pituitary-Adrenal (HPA) axis signalling contributes significantly to age-associated neurodegenerative disorders by promoting chronic cortisol exposure, oxidative stress, neuroinflammation, mitochondrial dysfunction, and neuronal injury, thereby accelerating disease progression. This review examines major pathological processes associated with age-related neurodegenerative disorders, oxidative stress, chronic neuroinflammation, and protein aggregation and misfolding, while highlighting the contribution of HPA axis dysregulation to these interconnected pathological events. Over the past decade, considerable interest has focused on the application of herbal plants and natural phytochemicals as multi-target therapeutic agents capable of regulating several molecular pathways involved in neurodegeneration. The review further evaluates the potential of traditional plants such as *Withania somnifera, Panax ginseng, Curcuma longa, Bacopa monnieri, Ginkgo biloba,* and *Astragali radix,* along with their bioactive compounds, with particular emphasis on their ability to modulate HPA axis activity, attenuate oxidative stress and neuroinflammation, and preserve neuronal function during brain ageing. The collective findings suggest that herbal plants and their phytochemicals have considerable potential as a complementary strategy for managing age-associated neurodegenerative disorders by regulating HPA axis activity, influencing interconnected pathological pathways and supporting healthy brain function.

Keywords: Neuroinflammation, Neuroprotection, Oxidative stress, Pathological Mechanism, Traditional Medicine.

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INTRODUCTION

Neurodegeneration is an age-linked disorder affecting the peripheral and Central Nervous Systems (CNS), with diverse pathologies and etiologies.[1] Major pathological features include sensory dysfunction, functional loss, and neuronal degeneration caused by multiple factors, including inflammatory responses, environmental factors, locomotor impairment, genetic mutations, increased oxidative stress, deposition of aggregated proteins, and the gut microbiota.[2] Increasing age continues to be the strongest risk factor, with the most common being Parkinson's disease, Alzheimer's disease, and Huntington's disease.[3,4] Despite the growing prevalence of these disorders in ageing individuals, there remains a lack of effective therapeutic strategies. The rapid increase in the ageing population has prompted researchers globally to better understand and investigate the fundamental mechanisms and biological basis of pathogenesis, to enhance the regulation of neurological activation and increase individual longevity.

In recent studies, persistent HPA axis abnormalities have been linked to brain ageing and neurodegenerative diseases. Prolonged

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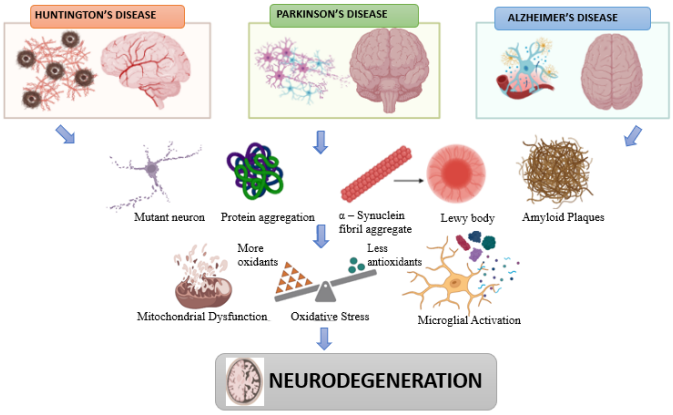


Figure 1: Schematic Illustration of the molecular mechanisms underlying major neurological disorders. Disease-specific misfolded proteins, mutations, α-synuclein, and amyloid-β undergo abnormal aggregation, leading to oxidative stress, mitochondrial dysfunction, and microglial activation. These processes result in progressive neurodegeneration. The figure was created using BioRender.

exposure to GC could play a role in oxidative stress, neuroinflammation, mitochondrial dysfunction, diminished synaptic plasticity, and neuronal vulnerability. These relationships are, however, complex and reciprocal, and not identical for each disease, and do not provide proof that modulation of the HPA axis would be sufficient to change clinical disease progression. Therefore, interventions affecting HPA axis homeostasis should be regarded as investigational and possibly complementary and not as approved disease-modifying interventions.[5]

Parkinson's Disease (PD) is a progressive disorder associated with motor and non-motor dysfunction and a progressive loss of dopaminergic neurons. There is preclinical evidence that chronic use of GC can lead to enhanced oxidative stress, microglial activation and dopaminergic neuronal vulnerability. These findings suggest continued research on stress-axis biology in PD, but do not provide clinical evidence of the effectiveness of HPA axis-acting herbs (Figure 1).[6]

Alzheimer's Disease (AD), another prevalent condition of neurodegeneration found in older individuals, is closely linked to ageing, which gradually reduces the body's capacity for cellular repair. The dominant feature of the disease is the unusual processing of the amyloid precursor protein, which is processed to generate β-amyloid peptide and tau proteins. β-amyloid peptides aggregate to form extracellular plaques, whereas the intracellular neurofibrillary tangles arise from hyperphosphorylated microtubule-associated tau proteins (Figure 1). This condition is particularly severe in the entorhinal cortex and hippocampus region of the brain.[7] In addition, increasing evidence suggests that chronic HPA axis dysregulation and prolonged glucocorticoid exposure contribute to amyloid-β accumulation, tau hyperphosphorylation, and hippocampal dysfunction, thereby accelerating disease progression and cognitive decline.

Huntington's disease follows autosomal dominant inheritance with a pathogenic expansion of the CAG repeats in the HTT gene. While sporadic Alzheimer's disease and Parkinson's disease are considered age-associated disorders, Huntington's disease is not. Age may, however, have some effect on clinical manifestations and disease course. In this review, therefore, the discussion of HD is done in the wider context of neurodegenerative disorders and brain ageing, while being aware of the unique genetic cause of Huntington's disease (Figure 1).[8]

A variety of herbal components have been studied for crossing into the blood-brain barrier and modulating molecular pathways associated with the survival of neurons. The blood-brain barrier penetration and mitochondrial localisation, however, are two mechanistic aspects, i.e. pharmacokinetic and intracellular distribution, respectively, that have to be confirmed by separate experiments.[9–11] The blood-brain barrier permeability does not necessarily indicate neuronal mitochondrial accumulation and therapeutic efficacy of a compound. Historical herbal texts document numerous formulations that significantly enhance drug performance by improving pharmacokinetics, facilitating intracellular uptake, strengthening therapeutic efficacy, and ensuring better localisation at the target site. For instance, phytocompounds such as celastrol, lycopene, resveratrol, flavonoids, and curcumin from Ashwagandha, Ginseng, and *Centella asiatica* have demonstrated notable anti-ageing properties along with neuronal effects. Growing evidence indicates that these herbal plants have significant potential to modulate HPA axis activity, regulate glucocorticoid signalling, attenuate oxidative stress, and manage age-associated neurodegenerative disorders.[12–14]

While several review articles have addressed the role of herbal medicines in specific neurodegenerative diseases, studies have largely concentrated on a single disease, such as Alzheimer's disease/ dementia or a specific group of phytochemicals. In addition, most current reviews focus on symptomatic management rather than the biological processes involved in brain ageing. The multiple interacting processes of ageing and the therapeutic activities of natural products are not fully addressed in the existing literature. Moreover, although accumulating evidence highlights the involvement of HPA axis dysregulation in the neuroprotective mechanisms of natural therapeutics remains insufficiently explored. Furthermore, very little research has focused on the capacity of phytochemicals to target several pathways in the pathogenesis of cancer and other diseases, and their potential to overcome BBB permeability, a major obstacle in the treatment of age-associated neurodegenerative disorders.

The present review stands out for its detailed analysis of the bioactive constituents of herbals as multi-target therapeutic agents and for using the perspective of brain ageing to provide a

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comprehensive overview of the age-related neurodegenerative disorders. This review is different from the previously published reviews, which focused on a single disease or a single pathological process, because it integrates the role of HPA axis dysregulation with major pathological mechanisms driving cellular senescence. Furthermore, it highlights how natural therapeutics can modulate HPA axis activity and its downstream molecular pathways, providing a broader understanding of their multi-target neuroprotective potential in preventing and managing age-associated neurodegenerative disorders.

This review examines the pathological mechanisms of neurodegenerative diseases and brain ageing and focuses on the possible role of HPA axis dysfunction. It also critically reviews six medicinal herbs and their bioactive components for their neuroprotective properties. Importantly, the review differentiates direct evidence of modulation of the HPA axis from indirect antioxidant, anti-inflammatory, mitochondrial, anti-amyloid and cognitive effects. *In vitro* studies, animal studies and clinical studies in humans are considered separately to prevent inappropriate translation from the preclinical to the therapeutic context.

METHODOLOGY

Review design and reporting

This review was conducted following the PRISMA 2020 reporting guidelines. The protocol was not prospectively registered, and this is recognised as a limitation. The question reviewed the evidence for six medicinal herbs and their effects on neurodegenerative disorders and brain ageing, with a special focus on direct (versus indirect) measurement of HPA axis outcomes.

Information sources, date and search fields

Articles were searched on Scopus, Web of Science Core Collection and Google Scholar databases from 1 January 2015 to 31 March 2025. The latest searches were conducted on 31st March 2025. This search was used in Scopus (TITLE-ABS-KEY), in Web of Science (Topic fields: title, abstract, author keywords, and Keywords Plus) and in Google Scholar (full-text indexing). Additionally, reference lists from eligible articles and relevant reviews were examined for any further studies.

Database-specific search strategies

The search strategy used was developed in Scopus by searching for the following terms: TITLE-ABS-KEY(”neurodegenerative disorder” OR ”brain ageing” OR ”brain aging” OR ”Alzheimer’s disease” OR ”Parkinson’s disease” OR ”Huntington* disease”) AND (”natural therapeutic” OR ”medicinal plant” OR phytochemical OR ”herbal medicine” OR ”*Withania somnifera*” OR ”*Panax ginseng*” OR ”*Ginkgo biloba*” OR ”*Curcuma longa*” OR ”*Bacopa monnieri*” OR ”*Astragali radix*”) AND (”hypothalamic-pituitary-adrenal” OR ”HPA axis” OR glucocorticoid OR cortisol OR corticosterone OR neuroprotection OR ”oxidative stress” OR neuroinflammation OR ”protein aggregation”). Web of Science: (TITLE or ABSTRACT or keywords=same disease terms) AND (TITLE or ABSTRACT or keywords=same botanical terms) AND (TITLE or ABSTRACT or keywords = same HPA axis/mechanistic terms). Google Scholar: Disease, Botanical, and HPA axis/Mechanistic terms were not combined with all in the title; combinations of the disease, botanical and HPA axis/Mechanistic terms were used, and the results were screened in order of relevance. The search histories that are exported should be saved along with the review records, as accurately as possible.

Eligibility criteria

Studies in humans (*In vitro, In vivo*, observational, interventional) using English-language journals that were peer-reviewed were accepted if they included one of the six botanicals or a defined constituent that measured an endpoint related to neurodegenerative disorders, ageing of the brain, neuroprotection, or a directly measured endpoint of the HPA axis. Contextual and citation-chaining data used reviews and meta-analyses, which were not considered as primary efficacy data. The following types of reports were not included: conference abstracts, editorials, unpublished reports, non-neurological studies, studies of other synthetic drugs, or reports lacking adequate methodological or outcome data.

Selection, extraction and synthesis

Any duplicates were removed from the records prior to screening. Two-stage screening included title/abstract screening and full-text screening to determine eligibility based on prespecified criteria. Data were plotted by herb, accepted botanical source, disease/experimental model, dose/duration, HPA axis endpoint, other molecular endpoints, principal finding and evidence level. Findings were synthesized narratively as it was not possible to meta-analyse the data due to the heterogeneity of interventions, preparations, models, and outcomes. The search identified 520 records, of which 110 were duplicates, and 410 records were screened for title/abstract. Of these, 165 full texts were evaluated, 92 studies were included, and 73 full texts were excluded. The reason-specific exclusion counts listed in Figure 2 should be checked with the screening log by the authors prior to resubmission.

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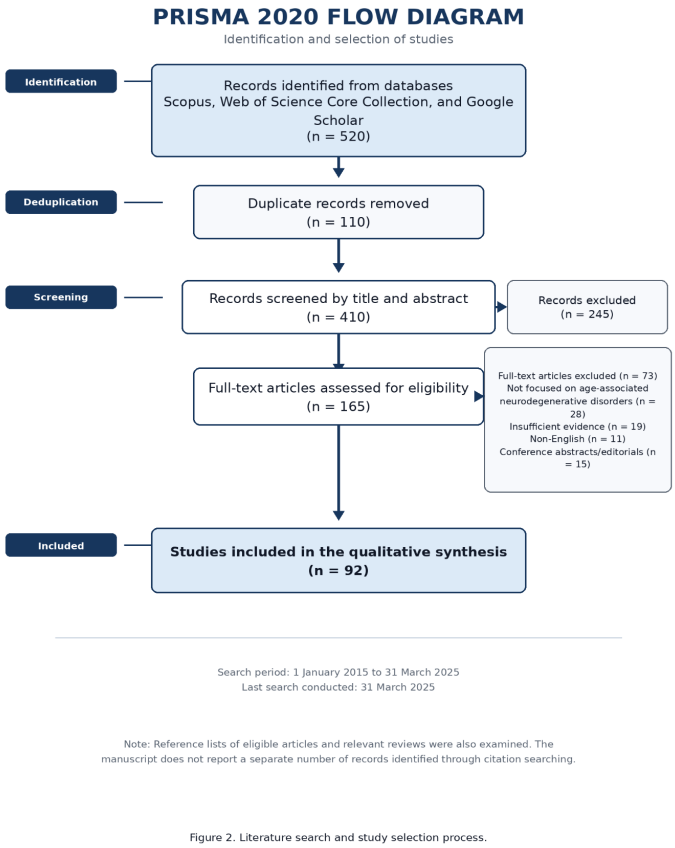


Figure 2: PRISMA 2020 flow diagram illustrating the literature search, screening, eligibility assessment, and final inclusion of studies in the qualitative synthesis.

Evidence appraisal

Evidence was rated as being presented in one of six levels: Level 1, systematic review/meta-analysis of human studies; Level 2, randomised or controlled human study; Level 3, observational human study; Level 4, *In vivo* animal study; Level 5, *In vitro*/ex vivo study; and Level 6, mechanistic inference or narrative evidence. For randomised trials, use a tool designed to assess risk of bias among trials (RoB 2). For non-randomised human studies, use a tool designed to assess risk of bias among non-randomised studies (ROBINS-I). For animal studies, use a tool designed to assess risk of bias among animal studies (SYRCLE). As the evidence covered more than one design, no pooled quality score was applied. Direct evidence from humans was given more weight, and conclusions were made explicit when derived from the results of experiments on animals, cells or inferences.

PATHOLOGICAL MECHANISMS OF AGE-RELATED NEURODEGENERATIVE DISORDERS

Age-associated neurodegenerative disorders comprise a series of progressive conditions characterised by the structural deterioration and dysfunction of neuronal cells, leading to impairments in cognition and motor abilities. While the precise mechanisms of these conditions are not completely understood. Various factors contribute to the onset of age-related neurodegenerative disorders, including oxidative stress, neuroinflammation, and protein misfolding and aggregation (Table 1). Among these interconnected mechanisms, dysregulation of the HPA axis has gained considerable attention because prolonged activation of the stress response and sustained glucocorticoid exposure can aggravate oxidative damage, neuroinflammation, and neuronal loss, thereby accelerating brain ageing and the progression of neurodegenerative disorders.[15–17]

Oxidative Stress

Oxidative stress, defined by a disruption between the production of reactive oxygen species and the efficiency of endogenous antioxidant defence mechanisms, is widely recognised as a major contributor. Reactive Oxygen Species (ROS) are known to exacerbate disease progression by inducing oxidative damage and interacting with mitochondrial function.[18,19] Excessive accumulation of free radicals damaging vital cellular macromolecules, resulting in neuronal dysfunction, structural damage, and progressive cell death. Oxygen is prone to form reactive radicals due to its electronic configuration and presence of unpaired electrons. Consequently, ROS are a group of highly reactive, oxygen-derived molecules characterised by shorter lifespan and stronger chemical reactivity. Among various forms of ROS, the hydroxyl radical (-OH) is regarded as the most reactive and is particularly potent in causing cytotoxic effects.[11,12,20] Persistent activation of the HPA axis further intensifies oxidative stress through prolonged glucocorticoid exposure, which impairs endogenous antioxidant defence systems, promotes excessive ROS generation, and increases neuronal susceptibility to oxidative damage. Endogenous and externally supplied antioxidants both play key roles in scavenging ROS and reducing oxidative damage, making them promising therapeutic candidates.[21] Current strategies increasingly focus on enhancing antioxidant defenses, mainly through modulation of pathways, for instance, the Nrf2 pathway, which regulates gene expression involved in cellular protection. Targeting these mechanisms offers significant potential in mitigating oxidative stress and slowing the progression of neurodegenerative conditions.[22]

Neuroinflammation

Neuroinflammation is a key characteristic of age-related neurodegenerative disorders and serves a vital function in neuronal damage and exacerbating cellular damage. Neuroinflammation is regarded as the immunologic response of the CNS to a cellular homeostasis disturbance. The responses include multiple cell types, including microglia and astrocytes.[23] Within the CNS, microglia act as the primary immune cells and are also regulators of inflammatory responses. Upon activation, pro-inflammatory mediators are released by microglia, such as

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Table 1: Major Pathological Mechanisms Involved in Age-Associated Neurodegenerative Disorders.

Pathological Mechanism	Key Features	Molecular Consequences	Associated Neurodegenerative Disorders	Potential Therapeutic Targets
Oxidative Stress[1]	Accumulation of excessive amounts of Reactive Oxygen Species and decreased antioxidant defence mechanism.	Lipid Peroxidation, DNA Damage, Protein Oxidation, Mitochondrial Injury, Neuronal Apoptosis	Alzheimer's Disease (AD), Parkinson's Disease (PD), Huntington's Disease (HD)	Antioxidants, Nrf2 activators, ROS scavengers, mitochondrial protestants
Neuroinflammation[13,14]	Prolonged microglial and astrocyte activation, resulting in continuous secretion of inflammatory substances.	Increased production of TNF-α, IL-1β, IL-6, activation of NLRP3 inflammasome, neuronal damage	AD, PD, HD	Anti-inflammatory agents, NLRP3 inhibitors, cytokine modulators, microglial regulators
Protein Misfolding and Aggregation[15]	Abnormal protein folding and build-up of harmful protein aggregates.	Formation of amyloid-β plaques, tau tangles, α-synuclein aggregates, impaired proteostasis	AD, PD, HD	Molecular chaperones, autophagy enhancers, proteasome activators, anti-aggregation compounds
Mitochondrial Dysfunction[16,17]	Defects in production of ATP, changes in mitochondrial dynamics and impaired mitochondrial respiration.	Defect in energy supply, generation of ROS, activation of the apoptotic pathway and neuronal degeneration	AD, PD, HD	Mitophagy inducers, mitochondrial biogenesis stimulators, antioxidants, mitochondrial-targeted therapeutics
Cellular Senescence[18]	Ageing of the cells + ageing-associated secretory phenotype [SASP]	Persistent inflammation, wound healing issues, oxidative damage, and neurological dysfunction.	AD, PD, age-related cognitive decline	Senolytic compounds, senomorphic agents, anti-inflammatory phytochemicals
HPA-axis Dysregulation[5]	Chronic activation of stress response, excessive glucocorticoid secretion, impaired negative feedback regulation	Oxidative stress, mitochondrial dysfunction, neuroinflammation, impaired synaptic plasticity, neuronal apoptosis	AD, PD, HD, Stress-associated cognitive decline	Adaptogens, glucocorticoid receptor modulators, stress-response regulators, medicinal plants

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Table 1: (Continued)

Pathological Mechanism	Key Features	Molecular Consequences	Associated Neurodegenerative Disorders	Potential Therapeutic Targets
Impaired Autophagy and Lysosomal Dysfunction[1,15]	Failure to remove damaged organelles and aggregated proteins	Accumulation of toxic proteins, mitochondrial dysfunction, cellular stress	AD, PD, HD	Autophagy activators, lysosomal enhancers, mTOR modulators
Blood-Brain Barrier Dysfunction[1,15]	A decrease in barrier integrity and an increase in permeability	Increased neuroinflammation, decreased removal of neurotoxic molecules, increased vulnerability of neurons	AD, PD, vascular dementia	BBB-protective agents, anti-inflammatory therapies, neurovascular modulators
Age-Related Cellular and Molecular Changes[1]	Telomere shortening, epigenetic changes, loss of stem cells, changes in intercellular communication	Lower capacity for regeneration, higher risk of degeneration of nerve cells	Multiple age-associated neurodegenerative disorders	Anti-ageing therapeutics, epigenetic modulators, regenerative medicine approaches

Tumour α-Necrosis Factor (TNF-α), Interleukins-1β (IL-1β), and IL-6, which contribute to disease progression.[14] Microglia are key regulators of maintaining CNS homeostasis, including synaptic remodelling and clearance of toxic aggregates. Advanced studies have highlighted the involvement of inflammasome complexes, mainly the NLRP3 inflammasome, in driving microglia activation and amplification of neuroinflammatory responses.[24] Chronic dysregulation of the HPA axis further influences this process by disrupting glucocorticoid-mediated immune regulation, resulting in persistent microglial activation and sustained production of pro-inflammatory cytokines that contribute to progressive neuronal injury. The most promising approaches in managing these disorders are regulating microglial activity, suppressing cytokine production, and targeting inflammasome pathways.[25]

Neuroinflammation is closely interdependent with oxidative stress, mutually amplifying each other during disease progression. The activation of inflammatory cells generates Reactive Nitrogen Species (RNS) and reactive oxygen species. The reactive molecules stimulate intracellular signalling pathways that enhance pro-inflammatory gene expression, creating a self-perpetuating cycle. During normal physiological conditions, redo balance supports a controlled and protective inflammatory response (Figure 3). However, in an individual with a neurodegenerative condition, this balance is disrupted, leading to chronic and dysregulated inflammation within the CNS. At the molecular level, oxidative stress is largely driven by mitochondrial dysfunction and Electron Transport Chain (ETC) activity, while the neuroinflammatory oxidative processes are primarily mediated by enzymes such as NADPH oxidase.[13] Persistent neuroinflammation also promotes activation of NF-κB, which further amplifies inflammatory signalling and contributes to neuronal dysfunction, highlighting NF-κB as an important therapeutic target in age-related neurodegenerative disorders.

Protein Misfolding and Aggregation

Neurodegenerative disorders are marked by abnormal protein folding, causing aggregation and accumulation of proteins such as tau and β-amyloid. This condition disrupts cellular function, impairs synaptic communication, and gradually leads to progressive brain damage. Protein aggregation is a dynamic, multi-step process in which abnormally folded proteins assemble into various intermediate forms before forming inclusion layers.[26] Unique proteins are involved in different age-related neurodegenerative disorders, and notable similarities are evident in the fundamental molecular mechanism, including protein misfolding and aggregation.[9] Advancements in research have shown that misfolded protein aggregation can propagate in a self-templating manner, spreading pathological changes between cells in a series, like prion-like transmission.[27]

Under a normal physiological state, the accumulation of misfolded proteins is prevented by healthy neurons through cellular quality-control mechanisms. These protective systems preserve proteostasis by recognizing, refolding, or eliminating damaged proteins before they become toxic. In neuronal conditions, cells' protective mechanisms are compromised, thereby promoting the buildup of toxic protein aggregates in and around the

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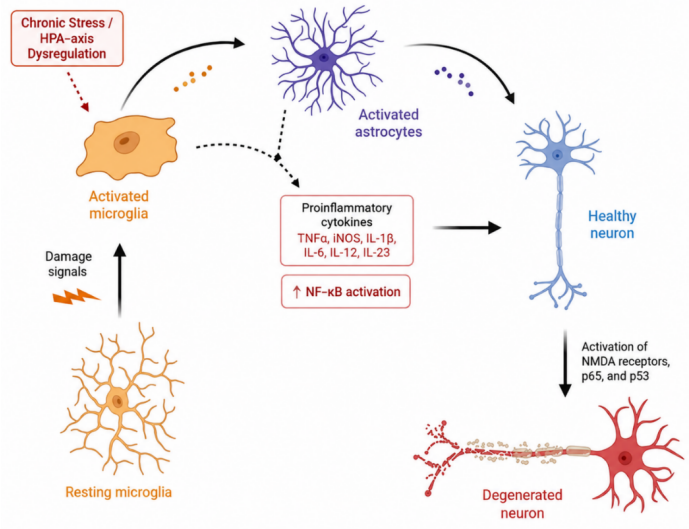


Figure 3: Model of the neuroinflammation-neurodegeneration cycle. Resting microglia are highly sensitive to signals of cellular stress or tissue damage, which trigger their activation. Chronic exposure to such stimuli leads to sustained microglial activation and a dysregulated inflammatory response. Activated microglia continuously release cytotoxic mediators, contributing to neuronal damage and promoting the advancement of disorders. HPA axis disruption further amplifies this inflammatory cascade by promoting persistent activation of microglia and enhancing the secretion of inflammatory cytokines, thereby accelerating neuronal injury and neurodegeneration. Figure was created using BioRender.

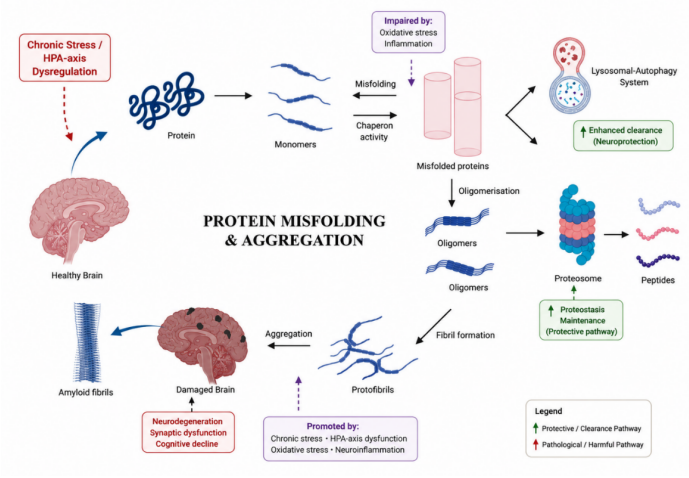


Figure 4: Protein misfolding and aggregation model. Soluble protein monomer undergoes misfolding, leading to the formation of intermediate species such as oligomers and protofibrils. These assemble into amyloid fibrils. Both genetic predisposition and environmental factors can accelerate the process of misfolding. In contrast, cellular control mechanisms, including chaperones, the ubiquitin-dependent proteasomal degradation system, and the autophagic-lysosomal degradation pathway, are involved in preventing or reducing the aggregation of misfolded proteins and in maintaining proteostasis. Chronic stress-induced HPA axis dysregulation may further impair proteostasis by disrupting protein quality control mechanisms, thereby facilitating the build-up of neurotoxic protein aggregates and accelerating neurodegenerative pathology. The figure was created using BioRender.

neurons. Molecular chaperones are crucial in maintaining protein integrity by regulating proper protein folding, preventing cross-interactions, and facilitating the refolding of abnormal proteins. Intracellular protein quality control pathways, including the Ubiquitin-Proteasome System (UPS) and autophagy-lysosomal mechanisms, eliminate defective proteins. Disruption of these degradation pathways, together with chronic stress-associated glucocorticoid signalling, further reduces the efficiency of protein clearance, thereby accelerating the accumulation of pathogenic proteins and neuronal degeneration. In unsuccessful conditions during chaperone repair, the aggregated proteins are tagged with ubiquitin chains and directed towards proteasomal degradation (Figure 4). Genetic mutations cause dysfunction of the UPS, resulting in impaired chaperone activity and leading to progression of age-related neurodegenerative disorders.[28]

Mitochondrial Dysfunction

Mitochondrial dysfunction is widely recognised as a key characteristic of both ageing and age-associated neurodegenerative disorders.[1] The high metabolic needs and limited cell regeneration capacity of neurons make them rely extensively on mitochondrial function to generate energy and preserve cellular homeostasis. Alterations in mitochondrial DNA impair oxidative phosphorylation, reduce ATP generation, and excessive ROS production collectively disrupt neuronal function and contribute to neuronal damage during ageing.[1,29] Impaired mitochondria induce apoptosis, oxidative stress and neuroinflammatory responses, which in turn result in neuronal loss.[17,29] Sustained activation of the HPA axis further compromises mitochondrial integrity, as prolonged glucocorticoid exposure disrupts mitochondrial bioenergetics, alters mitochondrial dynamics, and reduces ATP synthesis, thereby increasing neuronal vulnerability to age-related degeneration. While impaired mitochondrial dynamics and altered bioenergetics and defective mitochondrial transport are associated with impaired synaptic function and progressive cognitive decline in AD, Complex I deficiency is frequently observed and is regarded as an important factor contributing to dopaminergic neuronal degeneration in Parkinson's disease.[16,17] Thus, antioxidants, induction of mitophagy, mitochondrial biogenesis and mitochondrial quality-control recovery represent a promising therapeutic strategy for mitigating age-associated neurodegenerative disorders.[1,9,17]

Cellular Senescence and Brain Ageing

Cellular senescence is characterised by a persistent and irreversible arrest of the cell cycle together with the release of pro-inflammatory mediators.[30] While cellular senescence is a pivotal protective process against malignant transformation and tissue injury, Senescent cells have been found to build up in the ageing brain, which leads to chronic inflammation, impaired neuronal function and diminished regenerative capacity.[31,32] The gradual decline in the ability of neural cells to maintain cellular homeostasis and adapt to prolonged physiological stress further accelerates senescence, limiting neuronal plasticity and

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regenerative capacity during ageing. Senescent astrocytes, microglia, oligodendrocyte precursor cells, and neural stem cells have been identified as players in the progression of several age-related neurodegenerative disorders.[32,33] Senescent cells also release inflammatory cytokines, chemokines, growth factors and proteases, which in turn exacerbate oxidative stress and neuroinflammation and thus generate a detrimental microenvironment, thereby contributing to neuronal impairment and accelerating disease progression.[31] In recent studies, targeted elimination of senescent cells has demonstrated beneficial effects in reducing neuroinflammation and enhancing cognitive function in experimental models, positioning senolytic agents and natural phytochemicals as potential novel therapeutic strategies for slowing brain ageing and dementia.[9,18]

ROLE OF HPA AXIS DYSREGULATION IN AGE-ASSOCIATED NEURODEGENERATIVE DISORDER

The HPA axis is the principal neuroendocrine regulatory system that maintains physiological homeostasis in response to stress. It comprises the hypothalamus, pituitary gland, and adrenal cortex, which function in a coordinated manner to regulate the synthesis and release of glucocorticoids. During normal physiological stress, the hypothalamus releases corticotropin-releasing hormone, which in turn stimulates the anterior pituitary to release Adrenocorticotropic Hormone (ACTH). ACTH subsequently promotes glucocorticoid production by the adrenal cortex, resulting primarily in cortisol secretion in humans and corticosterone in rodents. These hormones regulate metabolism, immune responses, neuronal plasticity, cognition, and emotional behavior through a tightly controlled negative feedback mechanism involving the hippocampus, hypothalamus and pituitary gland. Maintenance of this regulatory feedback is essential for preserving neuronal function and protecting the brain against prolonged stress-induced damage. Dysregulation of glucocorticoid signalling also alters microglial function, shifting these cells towards a sustained pro-inflammatory state characterised by excessive secretion of cytokines and chemokines that perpetuate neuronal injury rather than resolving tissue damage. These pathological events reinforce one another, creating a feed-forward cycle in which mitochondrial dysfunction, oxidative stress, neuroinflammation, and progressive neuronal loss further compromise HPA-axis feedback regulation. This bidirectional interaction explains why elevated cortisol concentrations have consistently correlated with progressive cognitive decline, hippocampal atrophy, and disease progression in both PD and AD. Consequently, restoration of HPA axis homeostasis has emerged as a significant therapeutic strategy, as modulation of glucocorticoid signalling has the potential to simultaneously influence multiple pathological pathways instead of targeting a single downstream mechanism.[33]

NATURAL THERAPEUTIC HERBS TARGETING THE HPA AXIS IN NEURODEGENERATIVE DISORDERS

Medicinal herbs have the potential to affect multiple pathways that are relevant to neurodegeneration, such as oxidative stress, inflammatory signalling, mitochondrial function, protein aggregation, synaptic plasticity and stress responsivity. In the six herbs reviewed here, however, the direct evidence of modulation of the HPA axis is spotty and limited. The changes in CRH, ACTH and cortisol/corticosterone should be measured changes, as should be the neuroendocrine feedback regulation or the glucocorticoid-receptor signalling, and these changes should support the direct modulation. The effects of antioxidants, anti-inflammatories, mitochondrial, anti-amyloid or cognitive effects should not be viewed as independent evidence of regulation of the HPA axis (Table 2).[34]

Withania somnifera

Withania somnifera (Ashwagandha) is a well-established medicinal herb in Ayurveda, recognised for its broad spectrum of therapeutic properties. The therapeutic properties include anti-inflammatory, antioxidant, antiproliferative, neuroprotective, muscle-strengthening, and lipid-lowering effects, as well as adaptogenic activity that supports the regulation of the HPA axis and improves resilience to chronic stress.[35] Research on the safety evaluation showed that the daily dosage below 1250 mg is generally well tolerated.[35] Preliminary findings indicate that *Withania somnifera* may have a stress-responsivity effect and some selected glucocorticoid-mediated endpoints.[35] But the direct modulation of the HPA axis in patients with neurodegenerative diseases has been limited to some extent. This means that its antioxidant, anti-inflammatory and neurotrophic properties should be separated from direct neuroendocrine regulation.

The bioactivity of ashwagandha is attributed to its active compounds, particularly various withanolides (such as withanolide A, withanolide VI, and withanolide IV). These compounds have the potential to promote neuronal repair by reconstructing synaptic structures (pre- and post-synapses) and by regenerating axons and dendrites. Furthermore, it has exhibited growth-inhibitory effects in multiple cancer cell lines, including lung, breast, and central nervous system malignancies.[35] Dietary intake of withanolides has also been suggested to suppress tumour growth. Besides these pharmacological activities, Ashwagandha has been extensively investigated for its adaptogenic properties, where it attenuates stress-induced HPA axis hyperactivity by lowering circulating cortisol levels and improving glucocorticoid homeostasis, thereby protecting neurons against prolonged stress-induced damage. Wistar rats demonstrated ashwagandha's potential to modulate chronic stress and stress-related pathways by reducing NADPH-diaphorase activity, inhibiting anxiety, and supporting serotonin levels in the hippocampus.[36] The ability

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Table 2: Evidence hierarchy for medicinal plants with a beneficial role in the homeostasis of the HPA axis.

Herb	Disease model	Dose	HPA endpoint	Other molecular endpoints	Main findings	Evidence level
Withania somnifera	Stress-related and neurodegenerative animal models	Report exact dose, route and duration	Corticosterone or other stress-response measurements in selected studies	Antioxidant enzymes, neurotransmitters, BDNF and synaptic outcomes	Preclinical evidence suggests stress-responsive and neuroprotective effects; clinical HPA axis efficacy remains unconfirmed.	*In vivo*/preclinical
Ginseng radix—*Panax ginseng*	Ageing and cognitive models	Study-specific	Direct HPA endpoints inconsistently reported	Ginsenosides, BDNF/CREB, oxidative stress and inflammatory markers	May influence stress-responsive pathways, but direct HPA axis modulation requires confirmation.	Mainly preclinical
Ginkgo biloba	APP/PS1 and amyloid-induced models	Specify EGb 761 or extract dose	Generally, not directly measured	Amyloid clearance, tau phosphorylation, cytokines, mitochondrial apoptosis and oxidative stress	Effects are predominantly non-HPA; an HPA axis mechanism should not be inferred.	*In vitro*/*In vivo*; limited clinical evidence
Curcuma longa	Amyloid and stress-related models	Specify curcumin formulation and dose	Corticosterone in selected rodent studies	Amyloid aggregation, cytokines, oxidative stress and neurotransmitters	Preclinical evidence suggests multiple actions, but translation to human HPA axis regulation remains uncertain.	Mainly preclinical
Bacopa monnieri	Rotenone and cognitive/stress models	Specify extract or bacoside dose	Direct HPA endpoints infrequently reported	GSH, glutathione reductase, Hsp70, mitochondria and neurotransmitters	Antioxidant and adaptogenic effects may contribute, but direct HPA axis evidence remains limited.	*In vitro*/*In vivo*; limited human evidence
Astragali radix—*Astragalus membranous*	Ischaemic and neuroinflammatory models	Specify APS or astragaloside IV dose	Generally, not directly measured	BDNF-TrkB, mitophagy, ROS, apoptosis and cytokines	Evidence is predominantly preclinical and indirect with respect to the HPA axis.	*In vitro*/*In vivo*

of Ashwagandha to regulate both neuroendocrine and neuronal signalling highlights its therapeutic potential in mitigating HPA axis dysregulation associated with age-related neurodegenerative disorders. Therefore, both crude and purified forms of *Withania somnifera*, the extracts highlighted their significance in managing neuronal conditions.

Panax ginseng

P. ginseng, an ancient herb in Chinese medicine, is derived from *Panax ginseng*, which carries a therapeutic history for over two millennia. Bioactive compounds of ginseng, particularly ginsenosides, are extensively recognised for their anti-ageing properties and their beneficial effects on age-related neurodegenerative disorders. Through their adaptogenic activity and ability to regulate stress-responsive neuroendocrine pathways, including the HPA axis.[37]

Ginsenosides exhibits multiple remedial activities, including antioxidant, anti-inflammatory, and anti-apoptotic effects. These phytochemicals help control cognitive decline and age-associated neuronal loss. Rg1, a specific ginsenoside, modulates pathways associated with amyloid-β production and causes a delay in cognitive impairment. These compounds also enhance signalling mechanisms such as protein kinase A/cAMP response element-binding protein while enhancing brain-derived neurotrophic factor. Experimental studies have further demonstrated that Ginsenosides can attenuate stress-induced HPA axis hyperactivity by regulating corticosterone secretion and restoring glucocorticoid receptor-mediated feedback, thereby protecting

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neuronal function under chronic stress conditions. Varied forms of ginsenosides, including Re, Rb, and Rd, have exhibited strong neuroprotective and regulatory effects, supporting their potential as multi-target agents against HPA axis-associated neurodegenerative changes. These findings highlight *Panax ginseng* as a significant herb in the avoidance and treatment of age-related neurodegenerative disorders during ageing.[38]

Ginkgo biloba

Ginkgo biloba, often called *Ginkgo folium*, is a tree species whose leaf extract has been extensively used for the management of CNS and cardiovascular conditions. The bioactive compounds of *Ginkgo biloba* are categorised into two standard formulations, including EGb761 and *Ginkgo biloba* Extract (GBE).[39] EGb761 has been highlighted for significant neuroprotective properties by inhibiting mitochondrial-mediated apoptotic pathways, reducing tau protein hyperphosphorylation, enhancing the clearance of phosphorylated tau, promoting anti-inflammatory cytokine expression while suppressing inflammatory mediators, and managing dementia, including both Alzheimer-type and multi-infarct Conditions. These neuroprotective effects may also help minimize neural damage associated with chronic stress and dysregulated glucocorticoid signalling.[40]

Bilobalide has been recognised as a potential neuroprotective agent with significant anti-apoptotic activity among its other constituents. Experimental studies have further demonstrated that *Ginkgo* extracts can mitigate neurotoxicity induced by harmful agents, such as Sodium arsenite, across various regions of the brain and spinal cord. Recent studies have identified novel compounds, such as YY1224, that exhibits protective effects against Amyloid-β (Aβ)-induced toxicity by inhibiting pro-inflammatory microglial activation. *Ginkgo biloba* primarily acts through indirect modulation of the HPA axis; its ability to attenuate oxidative stress, neuroinflammation and mitochondrial dysfunction complements therapeutic strategies aimed at restoring stress-induced neuronal homeostasis. *Ginkgo biloba* is a practical and scalable resource for pharmaceutical development due to its widespread availability, high yield, and cost- effectiveness.[41]

Evidence suggests that the primary action of *Ginkgo biloba* is through antioxidant, anti-inflammatory, mitochondrial, anti-apoptotic and anti-amyloid mechanisms. It acts mainly indirectly, through effects that have not yet been explicitly demonstrated in the modulation of the HPA axis. Therefore, if there is an association between *Ginkgo biloba* and HPA axis regulation, this should be referred to as an indirect association or possibly mediated by related stress and neuroinflammatory pathways, unless CRH, ACTH, glucocorticoids and/or glucocorticoid-receptor signalling were directly measured.

Curcuma longa

Curcuma longa is a widely used spice and is a well-established component of Ayurvedic medicine. *C. longa* is rich in essential nutrients, including dietary fire, vitamins, and minerals such as potassium, magnesium, and iron. Curcumin, a major bioactive compound, exhibited diverse pharmacological properties, including anti-inflammatory and immunomodulatory effects, regulation of transcription factors, antioxidant effects, and modulation of enzymes and cytokines involved in inflammatory and cellular signalling pathways. Curcumin has also been reported to alleviate chronic stress-induced neuronal dysfunction by modulating glucocorticoid signalling and restoring neuroendocrine homeostasis associated with HPA axis dysregulation.[42] In accordance with AD, curcumin has shown promising therapeutic potential. One of the key mechanisms involves enhancing macrophage-mediated clearance of amyloid-β (Aβ) plaques, thereby improving the elimination of amyloid plaques from the brain into the peripheral circulation.[43]

Normalisation of cortisol and/or therapeutic efficacy in humans cannot be confirmed in humans based on the selected rodent studies that reported changes in corticosterone. There is still limited direct clinical evidence of the regulatory effect of *Curcuma longa* on the HPA axis in neurodegenerative diseases. Research has demonstrated that exposure to curcumin improves the capacity of macrophages to internalise and degrade amyloid deposits when compared with untreated cells. Additionally, curcumin has been reported to inhibit the formation of Aβ oligomers and fibrils, thereby reducing plaque accumulation.[34]

Turmeric plays a role in improving cerebral microcirculation and managing hypertension. In experimental models, studies have shown that curcumin administration reduces blood pressure, enhances blood flow, and improves vascular function by increasing capillary perfusion and modulating vascular stress. Beyond neuroprotective effects, *Curcumin* also demonstrates antidepressant-like effects in animal models by modulating neurotransmitter levels, including dopamine, noradrenaline, and serotonin, as well as their metabolites, in the hippocampus and frontal cortex of the brain. These neuroprotective and neuroendocrine effects collectively support the capacity of curcumin in reducing neural damage associated with chronic stress and age-related neurodegenerative disorders.[44]

Bacopa monnieri

Bacopa monnieri, generally recognised as Brahmi, is a well-known Ayurvedic herb recognised for its cognitive-enhancing effect. Over the last few years, studies have increasingly explored the potential of *Bacopa monnieri* in treating neuronal disorders. The reported health benefits are primarily antioxidant defence, neurotransmitter regulation, protection of mitochondria and cognitive benefits. Changes in these mechanisms could affect

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the physiology of chronic stress, but there is limited evidence for specific endpoints of the HPA axis in humans. The key active compounds of *B. monnieri* are primarily attributed to its bioactive saponins, particularly bacosides A and B. These compounds consist of aglycones such as bacogenins (A1-A4), along with other constituents like betulinic acid and alkaloids. Among these, bacoside A is significantly associated with memory enhancement and cognitive improvement. In addition to its nootropic effects, *Bacopa monnieri* exhibits adaptogenic properties that contribute to the regulation of stress-responsive neuroendocrine pathways, primarily the HPA axis.[45]

These phytochemicals exhibits a substantial domain of biological actions, such as antioxidant, anti-stress, anti-inflammatory, antimicrobial, and smooth muscle relaxant activity. *Bacopa monnieri* has been shown to improve endogenous antioxidant systems by increasing the levels of Glutathione (GSH) and the activity of Glutathione Reductase (GR).[45] Furthermore, studies have shown that saponins present in *Bacopa monnieri* can activate stress-response proteins and enzymes such as Hsp70. Cytochrome P450 and Superoxide Dismutase (SOD), which collectively enhance the brain's resilience to stress and neurotoxicity.[45] Studies have further demonstrated that *Bacopa* attenuates stress-induced elevations in corticosterone and improves glucocorticoid receptor-mediated signalling, thereby preserving hippocampal neuronal integrity and cognitive function. These findings support its therapeutic potential in alleviating HPA axis dysregulation associated with age-associated neurodegenerative disorders.

Astragali radix

Astragali radix has obtained considerable attention over the last few years for its vital role in the management of age-related neurodegenerative disorders. The polysaccharides, astragalosides, flavonoids and saponins in *Astragali radix* provide health benefits. The neuroprotective activities attributed to it are mainly the antioxidant, anti-inflammatory, anti-apoptotic, neurotrophic and mitophagy pathways. These effects can overlap with other effects induced by chronic stress but cannot be considered direct HPA axis modulation. *A. radix* is an herb that contains a diverse range of bioactive constituents, including *Astragalus* Polysaccharides (APS), astragalosides, flavonoids, saponins, and alkaloids.[46] The primary phytoconstituents that show neuroprotective effects are APS and astragaloside IV. Among these, the *Astragalus* polysaccharide modulates neuroinflammatory responses by suppressing astrocyte proliferation and microglial activation. They also promote the autophagic process that helps eliminate damaged cellular components and contributes to mitochondrial protection by reversing structural damage and enhancing cellular defence mechanisms.[47]

It also contributes significantly to the removal of impaired mitochondria and, in turn, limits the accumulation of mitochondrial ROS by promoting mitophagy. In addition, this herb has been associated with multiple regulatory effects, including regulation of neurotransmitter activity, suppression of amyloid accumulation, and stimulation of myelin repair. Emerging evidence also suggests that *Astragali radix* supports neural homeostasis under chronic stress by attenuating glucocorticoid-mediated neural injury and reinforcing endogenous antioxidant defence mechanisms. In conclusion, *Astragali radix* regulates age-related neurodegenerative diseases through anti-neurotoxic, anti-inflammatory, stress-modulating, and antioxidant properties.[48]

FUTURE DIRECTIONS

Future studies should focus on clarifying how natural therapeutics influence the HPA axis in age-associated neurodegenerative disorders. Although several herbs discussed in this review show stress-regulating, antioxidant, and anti-inflammatory effects, direct evidence connecting their active compounds with specific HPA axis components is still limited. Further experimental studies should examine changes in CRH, ACTH, cortisol or corticosterone, and glucocorticoid receptor signalling alongside oxidative stress, neuroinflammation, mitochondrial dysfunction, and cellular senescence. This could provide a clearer understanding of whether HPA axis regulation is a direct mechanism of neuroprotection or occurs as part of broader neuronal recovery. It is important to note a species-specific difference with regard to glucocorticoid results. In humans, cortisol is the major glucocorticoid, while corticosterone is the major glucocorticoid that is measured in most rodents. Both hormones are markers of activity of the HPA axis in their own species but should not be used as a replacement for each other as a clinical endpoint. A decrease in corticosterone in an experimental rodent model may indicate modulation of a stress response, but cannot prove that it normalises cortisol levels, has clinical efficacy or might change the disease process in humans.

Another important area is the translation of these findings into clinically useful therapies. Future research should address the bioavailability, blood-brain barrier penetration, dosage, safety, and long-term effects of promising phytochemicals using well-characterised preparations. The potential of combining complementary herbal agents also deserves systematic investigation, particularly where multiple pathological pathways are involved. Well-designed animal and clinical studies will be important for validating these mechanisms and determining whether HPA axis modulation by natural therapeutics can contribute meaningfully to healthy brain ageing and the management of age-associated neurodegenerative disorders.

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CONCLUSION

Ageing is an inevitable life process characterised by the gradual aggregation of senescent cells. Brain ageing and neurodegenerative disorders are associated with multifactorial mechanisms such as oxidative stress, neuroinflammation, mitochondrial dysfunction, altered proteostasis and cellular senescence. The evidence for potentially relevant neuroprotective effects of the six herbs reviewed here is mostly preclinical in nature. There is limited, heterogeneous, and not evenly distributed direct evidence for modulation of the HPA axis for the six botanicals. So, HPA axis regulation should not be automatically given as evidence for antioxidant, anti-inflammatory, mitochondrial, anti-amyloid or cognitive findings. Findings at this time could help develop mechanistic hypotheses and future translational studies but cannot yet prove clinical efficacy or be used to replace existing treatments, which contribute significantly to the advancement of age-linked neurodegenerative disorders. Despite the rising incidence of neurological conditions, effective therapeutic interventions remain limited. However, compounds derived from traditional herbal medicine have demonstrated potential in slowing the ageing process and preventing neurodegeneration. Increasing evidence also indicates that modulation of the HPA axis represents an important therapeutic strategy, as chronic HPA axis dysregulation accelerates oxidative stress, neuroinflammation, mitochondrial dysfunction and cognitive decline associated with ageing. Multifaceted mechanisms, including the inhibition of amyloid-β production and accumulation, prevention of tau protein hyperphosphorylation, reduction of neurotoxicity, mitochondrial function restoration, and attenuation of oxidative damage through redo imbalance, together with the restoration of neuroendocrine homeostasis, contribute to the neuroprotective effects of medicinal plants.

The chemical composition of these herbal medicines is highly diverse, with saponins and polysaccharides frequently identified as primary constituents that contribute to the anti-ageing effect. Furthermore, the complexity of herbal formulations complicates the understanding of interactions among different compounds. However, combining multiple herbal agents may enhance therapeutic outcomes through synergistic effects. Further research should priorities understanding the molecular pathways underlying HPA axis modulation, identifying specific phytochemicals responsible for neuroendocrine regulation, and validating these findings through well-designed preclinical and clinical studies. Comprehensive investigations are needed to optimism their use and design effective therapeutic strategies for ageing and age-associated neurodegenerative disorders.

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ABBREVIATIONS

Aβ: Amyloid-beta; **ACTH**: Adrenocorticotropic hormone; **AD:** Alzheimer's disease; **APP:** Amyloid precursor protein; **ATP:** Adenosine triphosphate; **BBB:** Blood-brain barrier; **BDNF:** Brain-derived neurotrophic factor; **CNS:** Central nervous system; **CRH:** Corticotropin-releasing hormone; **EGb761:** *Ginkgo biloba* extract EGb 761; **ETC:** Electron transport chain; **GSH:** Glutathione; **HD:** Huntington's disease; **HPA:** Hypothalamic-pituitary-adrenal; **IL-1β:** Interleukin-1 beta; **IL-6:** Interleukin-6; **NADPH:** Nicotinamide adenine dinucleotide phosphate; **NF-κB:** Nuclear factor kappa B; **NLRP3:** NOD-, LRR- and pyrin domain-containing protein 3; **PD:** Parkinson's disease; **ROS:** Reactive oxygen species; **RNS:** Reactive nitrogen species; **SASP:** Senescence-associated secretory phenotype; **TNF-α:** Tumour necrosis factor-alpha; **UPS:** Ubiquitin-proteasome system.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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AUTHORS CONTRIBUTION

Manjula Kannasandra Ramaiah: Conceptualisation, editing of the manuscript. **Zoya Muskan Sheikh:** Drafting of the manuscript. **Radha Mallarajapatna Janardhan:** Formal analysis. **Myrene Roselyn Dsouza:** Editing of the manuscript. **Nethravathy V:** Administrative and technical support.

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