

**Phytotherapeutic modulation of hypothalamic –pituitary adrenal (HPA) axis
in neurological disorders - preclinical evidence and clinical perspectives**

Authors

Elakiya R¹, Subhadra devi v^{2*}, Dhivya G³, Asok Kumar K³, Sriram S⁴

Affiliations

¹Department Of Pharmacology, College of Pharmacy, Sri Ramakrishna Institute Of Paramedical Sciences.

²Professor, Department Of Pharmacology, College of Pharmacy, Sri Ramakrishna Institute Of Paramedical Sciences.

³Assistant Professor, Department Of Pharmacology, College of Pharmacy, Sri Ramakrishna Institute Of Paramedical Sciences.

³Professor & Head, Department Of Pharmacology, College of Pharmacy, Sri Ramakrishna Institute Of Paramedical Sciences.

⁴Principal, College of Pharmacy, Sri Ramakrishna Institute Of Paramedical Sciences.

Corresponding author-

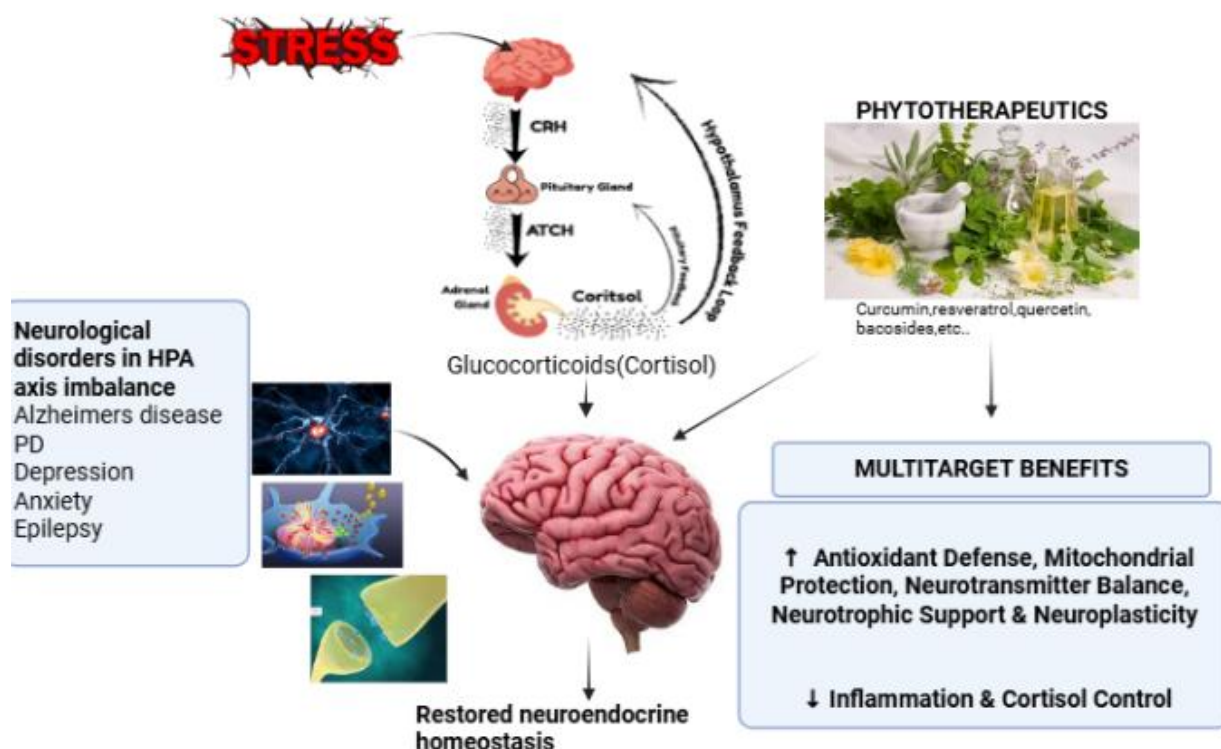
Dr.Subhadra devi V

Professor,

Department Of Pharmacology,

College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences.

Graphical abstract



Abstract

Neurological disorders, including Alzheimer's disease, Parkinson's disease, depression, anxiety, and epilepsy, involve complex pathological mechanisms such as oxidative stress, neuroinflammation, mitochondrial dysfunction, neurotransmitter imbalance, and neuronal loss. Increasing evidence indicates that dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis plays a crucial role in their pathogenesis. Chronic stress-induced HPA-axis activation results in excessive glucocorticoid release, promoting cognitive impairment, neuroinflammation, and neurodegeneration. Although conventional therapies provide symptomatic relief, their long-term efficacy is often limited by adverse effects. Consequently, phytotherapeutics have gained attention as promising complementary interventions because of their multitarget neuroprotective properties and favorable safety profiles. This review highlights the role of HPA-axis dysfunction in neurological disorders and explores the therapeutic potential of plant-derived bioactive compounds in restoring neuroendocrine homeostasis. Phytochemicals such as curcumin, resveratrol, quercetin, epigallocatechin gallate, bacosides, withanolides, and ginsenosides exhibit beneficial effects by modulating glucocorticoid signaling, reducing oxidative stress and neuroinflammation, enhancing neurotrophic factors, and regulating neurotransmitter systems. Evidence from preclinical and emerging clinical studies supports their ability to improve neurological function and stress resilience. Furthermore, advances in nano-phytomedicine may improve the bioavailability and brain-targeted delivery of phytotherapeutic agents, enhancing their therapeutic potential. Overall,

phytotherapeutics represent promising supportive strategies for managing neurological disorders associated with HPA-axis dysregulation.

Keywords

Phytotherapeutics, HPA Axis, Neurological disorders, Neuroprotection

Introduction

Neurological disorders are a diverse group of diseases affecting the brain, spinal cord, and peripheral nervous system, resulting in cognitive, motor, sensory, and behavioral impairments. Neurological disorders contribute substantially to disability worldwide and affect quality of life through cognitive, motor, and behavioral impairments. The pathogenesis of neurological disorders involves multiple interconnected mechanisms including oxidative stress, neuroinflammation, mitochondrial dysfunction, abnormal protein aggregation, impaired neurotransmission, and neuronal apoptosis. Chronic stress and dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis further contribute to neuronal damage and cognitive decline by increasing glucocorticoid secretion, inflammatory cytokines, and oxidative injury [1]. Recent studies have also highlighted the role of gut–brain axis interactions, immune dysfunction, and neuroendocrine imbalance in the progression of neurodegenerative diseases. Despite advances in pharmacotherapy, current treatments mainly provide symptomatic relief and are often associated with adverse effects during long-term use. Therefore, there is growing interest in identifying safer and more effective therapeutic approaches, including phytotherapeutic agents with antioxidant, anti-inflammatory, and neuroprotective properties for the management of neurological disorders.

Review methodology

A literature search was performed using databases including PubMed, Scopus, Web of Science, and Google Scholar to identify studies related to phytotherapeutic modulation of the hypothalamic–pituitary–adrenal (HPA) axis in neurological disorders. Relevant articles published between 2010 and 2026 were selected using keywords such as HPA axis, phytochemicals, medicinal plants, neurological disorders, cortisol, neuroinflammation and neuroprotection.

Studies evaluating the effects of plant-derived compounds in preclinical and clinical models were included. Review articles, duplicate publications, and studies unrelated to HPA-axis regulation or neurological disorders were excluded. Data regarding phytochemical source, study model, mechanisms involved, and therapeutic outcomes were extracted and summarized.

Dynamics and regulation of the hypothalamic–pituitary–adrenal (HPA) Axis

The hypothalamic–pituitary–adrenal (HPA) axis is the body's main stress-response system and plays an important role in maintaining homeostasis. When the body encounters stress, the hypothalamus releases corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), which stimulate the anterior pituitary gland to secrete adrenocorticotrophic hormone (ACTH). ACTH then acts on the adrenal cortex to promote the release of cortisol.

Cortisol helps regulate metabolism, immune function, cognition, emotional behavior, and adaptation to stress. It also controls its own production through a negative feedback mechanism by inhibiting the hypothalamus and pituitary gland.(Fig 1)

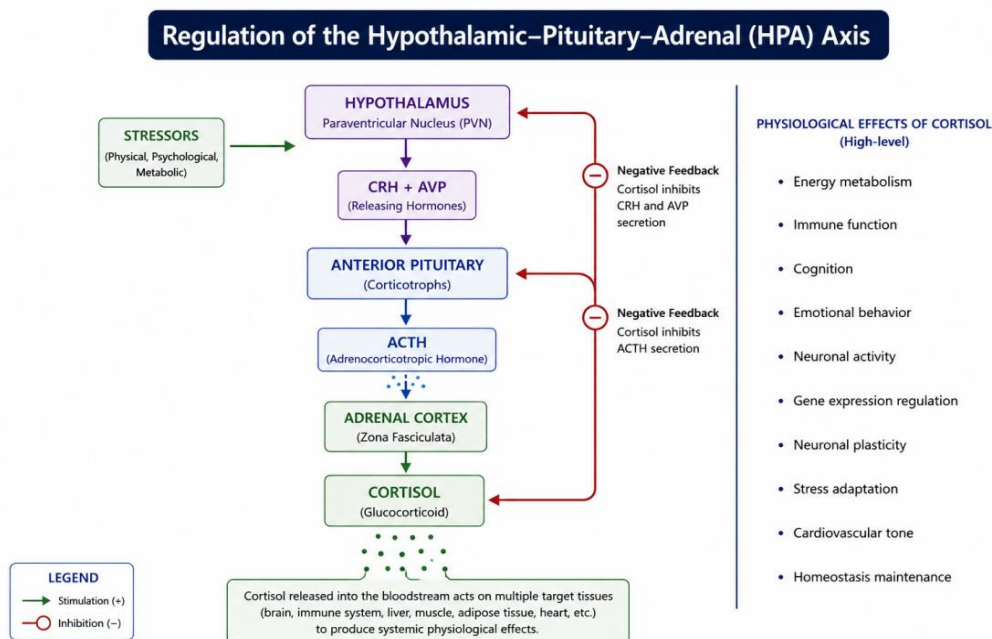


Figure 1: Schematic representation of the HPA axis. Stressors activate the hypothalamus to release CRH and AVP, stimulating pituitary ACTH secretion and subsequent cortisol production by the adrenal cortex. Cortisol acts on peripheral tissues to regulate physiological functions and exerts negative feedback on both the hypothalamus and pituitary to maintain homeostasis and prevent excessive stress responses.

The HPA axis follows a daily (circadian) rhythm, with cortisol levels peaking in the morning and gradually declining throughout the day. This rhythm is regulated by the suprachiasmatic nucleus (SCN), which synchronizes hormone secretion with the light–dark cycle[2].

During stress, activation of the HPA axis increases cortisol production, helping the body adapt to changing conditions. Cortisol exerts its effects through mineralocorticoid receptors (MRs), which are active under normal conditions, and glucocorticoid receptors (GRs), which become more active during stress. Cortisol is released in both circadian and pulsatile patterns, which are important for maintaining normal receptor function and cellular signaling. Disruption of these rhythms can contribute to stress-related disorders and impaired physiological function.

Feedback regulation of the HPA Axis

Elevated cortisol levels regulate the HPA axis through negative feedback by suppressing CRH and ACTH release from the hypothalamus and pituitary gland. This regulation occurs in the hypothalamus, pituitary, hippocampus, and prefrontal cortex.(Fig 2)

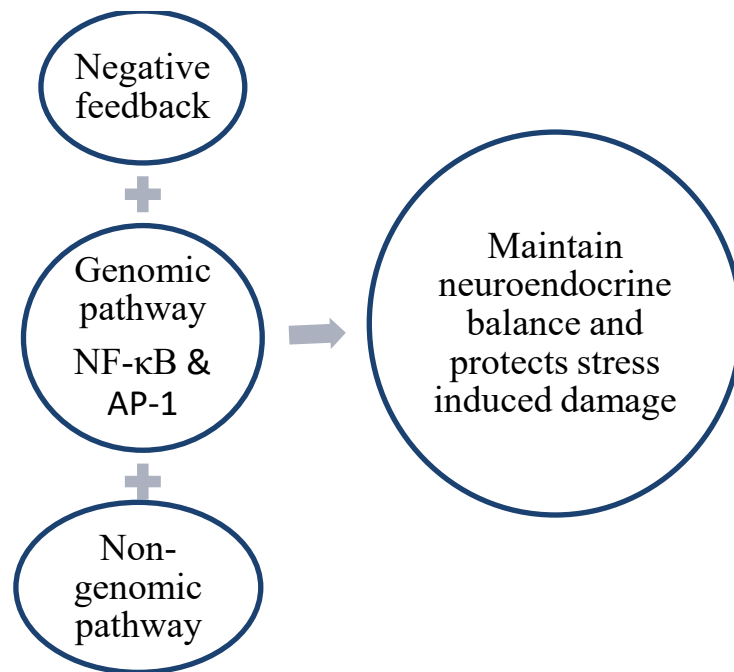


Figure 2: Schematic representation of glucocorticoid-mediated negative feedback regulation of the HPA axis. Genomic and non-genomic signaling pathways cooperate to limit excessive stress responses, maintain neuroendocrine balance, and prevent stress-induced damage.

Cortisol acts through both genomic and non-genomic pathways to control gene expression, reduce excitatory neurotransmission, and enhance inhibitory signaling. These mechanisms help maintain HPA axis homeostasis and prevent excessive stress-induced activation[3].

Top-down neural regulation of the HPA Axis

The HPA axis is extensively regulated by higher brain regions that integrate emotional, cognitive, and environmental information. Among these, the hippocampus, prefrontal cortex, amygdala, thalamus, and brainstem structures play critical roles in modulating stress responses(Fig 3).

Hippocampus

The hippocampus serves as a major inhibitory regulator of HPA-axis activity and contains abundant glucocorticoid and mineralocorticoid receptors. Through feedback mechanisms, the hippocampus contributes to the termination of stress responses and restoration of hormonal homeostasis. Impaired hippocampal function or structural damage is associated with exaggerated glucocorticoid secretion and prolonged HPA-axis activation. Neural projections from the ventral hippocampus indirectly suppress hypothalamic activity through intermediary GABAergic pathways, thereby limiting cortisol production.

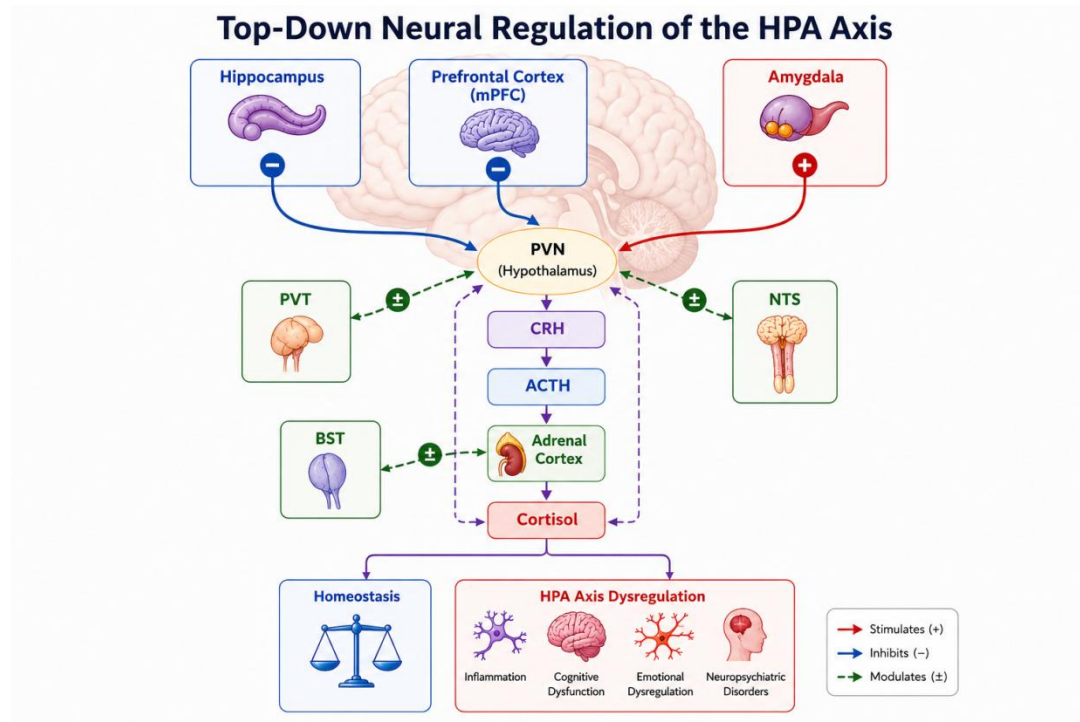


Figure 3: Schematic representation of top-down neural regulation of the HPA axis. Multiple brain regions coordinate inhibitory, excitatory, and modulatory inputs to regulate stress responses and cortisol secretion.

Prefrontal cortex

The medial prefrontal cortex (mPFC) is involved in executive function, emotional regulation, and adaptive responses to stress. Both the prelimbic and infralimbic regions contribute to inhibitory control of the HPA axis.

Chronic stress reduces glucocorticoid receptor expression within the prefrontal cortex, impairing its ability to regulate neuroendocrine activity effectively. Dysfunction of this region is therefore associated with impaired stress adaptation and heightened vulnerability to neuropsychiatric disorders.

Amygdala

In contrast to the inhibitory influence of the hippocampus and prefrontal cortex, the amygdala generally facilitates HPA-axis activation. It plays a central role in emotional processing, fear responses, and anxiety-related behaviors. Chronic stress enhances amygdala activity, increases dendritic remodeling, and promotes CRH expression, thereby amplifying stress responsiveness and sustaining glucocorticoid secretion. These changes contribute to emotional dysregulation and stress-related neuropathology.

Thalamus and brainstem regulation

The paraventricular nucleus of the thalamus (PVT) participates primarily in the regulation of chronic stress responses and stress adaptation. Through extensive connections with limbic and cortical regions, the PVT coordinates long-term neuroendocrine responses to repeated stress exposure.

The nucleus of the solitary tract (NTS), located in the brainstem, conveys visceral and physiological stress signals to the hypothalamus. It receives sensory information from peripheral organs and regulates HPA-axis responses to physiological challenges such as hypoglycemia, hypoxia, inflammation, and immune activation. Neurotransmitters and neuropeptides originating from the NTS contribute to both activation and feedback regulation of stress-responsive pathways.

Bed nucleus of the stria terminalis

The bed nucleus of the stria terminalis (BST) functions as an important relay center integrating signals from the hippocampus, amygdala, prefrontal cortex, thalamus, and brainstem. Through its complex network of excitatory and inhibitory connections, the BST coordinates behavioral, autonomic, endocrine, and emotional responses to stress. Depending on the nature and duration of the stressor, specific BST subregions may either enhance or suppress HPA-axis activity.

Overall, HPA-axis regulation involves a highly integrated neurocircuitry network that balances stress responsiveness with physiological homeostasis. Dysregulation of these regulatory pathways contributes to chronic stress, neuroinflammation, cognitive dysfunction, and the progression of neurological and neuropsychiatric disorders, highlighting the importance of therapeutic strategies aimed at restoring normal HPA-axis function[4]

Natural products and phytotherapeutics in the management of neurological disorders

The increasing prevalence of neurodegenerative diseases and the limitations of current treatments have stimulated interest in alternative therapeutic strategies. Although conventional drugs can provide symptomatic relief, they often have limited efficacy and may be associated with adverse effects. Consequently, there is a growing need for safer and more effective approaches to support neurological health.

Ayurveda offers a holistic approach that combines herbal medicines, dietary interventions, lifestyle modifications, and behavioral practices to promote brain function and overall well-being. Many medicinal plants contain bioactive compounds with antioxidant, anti-inflammatory, neuroprotective, and immunomodulatory properties. These compounds may help reduce oxidative stress, prevent the accumulation of toxic proteins, support neuronal survival, and regulate neuroendocrine-immune interactions involved in neurodegenerative diseases.

In addition, traditional rejuvenative therapies have been reported to improve memory, cognition, and healthy aging. Together with proper nutrition, lifestyle management, and psychosocial support, these approaches may contribute to the prevention and management of age-related neurodegenerative disorders, including Alzheimer's disease[5].

Natural products from plant, animal, microbial or marine origins have served as an important source for novel drugs. These naturally occurring compounds have provided useful lead molecules for drug discovery for centuries and were found to be effective in the treatment of various diseases [6,7]. Several naturally occurring compounds possess diversified bioactivity such as antioxidant, anti-inflammatory, anti-apoptotic, neuroprotective and thereby used in neurological conditions [8].

Both *invitro* and *invivo* studies have also shown potential of natural products to reduce the pathological cascade of neurodegeneration [9]. Various phytoconstituents mainly polyphenols and antioxidant molecules found in medicinal herbs, fruits, vegetables, nuts and aquatic plants proved beneficial in brain health by preventing neuronal damage against oxidative stress, maintenance of cognitive functions and memory in neurodegenerative diseases. Therefore, phytocompounds could be developed as new treatment strategies for neurological diseases such as alzheimer's, parkinson's, epilepsy etc[10].

Therapeutic significance of phytotherapeutics in neurological disorders

Phytotherapeutics are promising candidates for the management of neurological disorders due to their natural origin, safety, and diverse biological activities. Many neurological disorders involve oxidative stress, neuroinflammation, mitochondrial dysfunction, and neuronal loss[11]. Plant-derived bioactive compounds, including flavonoids, alkaloids, terpenoids, and polyphenols, can help counter these pathological processes through antioxidant, anti-inflammatory, and neuroprotective actions. They may also preserve mitochondrial function and prevent apoptosis, thereby supporting neuronal survival and brain health[12].

Phytocompounds can help protect brain cells and slow the progression of neurodegenerative diseases. Medicinal plants such as *Withania somnifera*, *Bacopa monnieri*, *Curcuma longa*, *Panax ginseng*, and *Rhodiola rosea* have shown beneficial effects on memory, cognition, and brain health experimental and clinical setting.

Many plant-derived compounds also help regulate the hypothalamic–pituitary–adrenal (HPA) axis, which plays a major role in the body's response to stress. By helping to balance cortisol levels and improve stress adaptation, these compounds may support cognitive function and neuronal health. In addition, phytocompounds can influence important neurotransmitters such as serotonin, dopamine, glutamate, and GABA, which are involved in mood, memory, and brain function.

These findings indicate that phytochemicals may influence several mechanisms involved in neuronal injury and stress-related dysfunction.

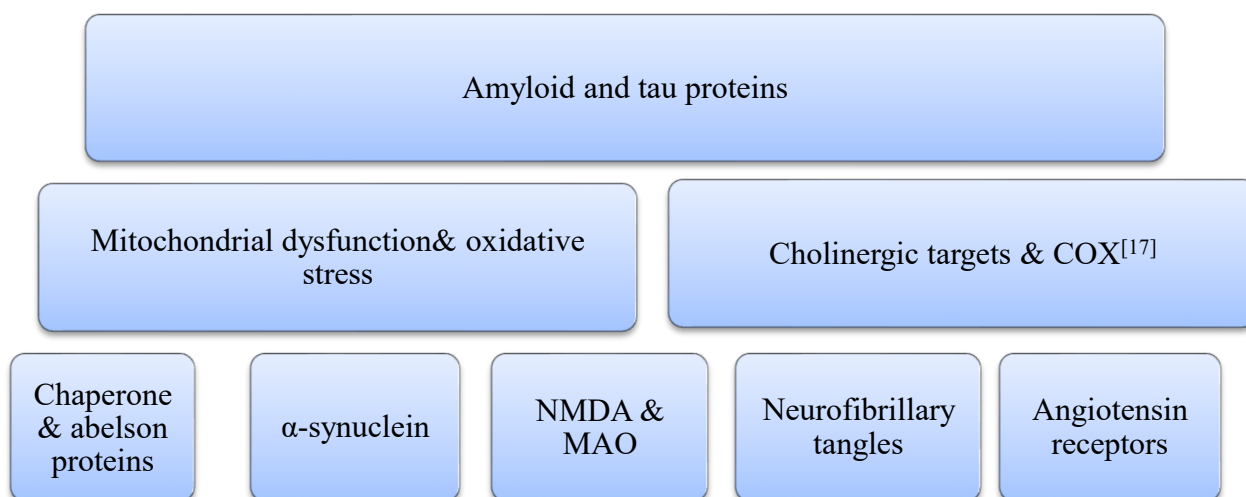
Targets of the HPA Axis in neurological disorders

The HPA axis is a major regulator of the stress response. Chronic stress and excessive cortisol production can impair brain function and contribute to cognitive, emotional, and behavioral disturbances. As HPA-axis dysregulation is closely linked to many neurological disorders, targeting this pathway has become a promising therapeutic strategy[13].

HPA-axis dysfunction is also associated with disturbances in major neurotransmitter systems, including serotonin, dopamine, glutamate, and γ -aminobutyric acid (GABA), thereby influencing mood, cognition, and neuronal survival. Furthermore, chronic glucocorticoid elevation enhances oxidative stress, mitochondrial dysfunction, and the production of pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6, leading to neuroinflammation and neuronal apoptosis. Emerging evidence also indicates that interactions between the HPA axis and the gut-brain axis contribute to immune dysregulation and disease progression.

Major therapeutic targets

Neurodegenerative disorders (NDDs) involve multiple pathological pathways, necessitating the development of multi-target therapeutic strategies. Several molecular targets have been identified for disease management and neuroprotection [14,15].



Neuroactive phytochemicals and phytotherapeutic agents in neurological disorders

Neuroactive phytochemicals and phytotherapeutic agents are plant-derived bioactive compounds that possess significant neuroprotective, antioxidant, anti-inflammatory, antiapoptotic, anxiolytic, and cognition-enhancing properties[16-18]. These compounds play an important role in the prevention and management of neurological disorders by targeting multiple pathological mechanisms such as oxidative stress, neuroinflammation, mitochondrial dysfunction, protein aggregation, neurotransmitter imbalance, synaptic dysfunction, and hypothalamic–pituitary–adrenal (HPA) axis dysregulation[19].

Chronic stress and prolonged activation of the HPA axis increase glucocorticoid secretion, leading to neuronal injury, cognitive impairment, behavioral abnormalities, and neurodegeneration. Neuroactive phytochemicals regulate stress-responsive pathways by modulating glucocorticoid receptor signaling, suppressing inflammatory mediators, and enhancing antioxidant defense systems. These compounds interact with important molecular pathways including NF- κ B, Nrf2/ARE, PI3K/Akt, ERK/CREB/BDNF, SIRT1, and PGC-1 α signaling pathways .

Curcumin, obtained from *Curcuma longa*, exhibits strong antioxidant and anti-inflammatory activities by inhibiting amyloid- β aggregation, tau hyperphosphorylation, oxidative stress, and inflammatory cytokine production in Alzheimer's disease. Curcumin also improves synaptic plasticity, learning, and memory through activation of ERK/CREB/BDNF signaling and reduction of reactive oxygen species (ROS)[20].

Resveratrol and quercetin are potent polyphenolic antioxidants that protect neurons against oxidative damage and mitochondrial dysfunction. Resveratrol activates SIRT1 signaling, enhances autophagy, maintains mitochondrial integrity, and reduces protein misfolding in Alzheimer's and Parkinson's disease[21]. Quercetin improves neuronal energy metabolism, suppresses inflammatory cytokines such as IL-6 and TNF- α , and enhances memory and cognitive performance through activation of PI3K/Akt and Nrf2/ARE pathways[22].

Epigallocatechin-3-gallate (EGCG), a major catechin present in green tea, exhibits neuroprotective effects by reducing oxidative stress, inhibiting glucocorticoid receptor overactivation, and activating endogenous antioxidant pathways. EGCG also inhibits α -synuclein aggregation, improves dopaminergic neuronal survival, and reduces mitochondrial dysfunction in Parkinson's disease[21]. Baicalein, embelin, and salidroside demonstrate significant neuroprotective activities in Huntington's disease and Parkinson's disease by reducing oxidative stress, mitochondrial dysfunction, apoptosis, and neuroinflammation. These phytoconstituents improve neuronal survival, motor function, and behavioral abnormalities[23].

Bacosides from *Bacopa monnieri* improve cognition, memory, and synaptic transmission through antioxidant and cholinergic mechanisms[24]. Withanolides from *Withania somnifera* possess adaptogenic and anti-stress properties and help regulate HPA-axis dysfunction, anxiety, depression, and neuroinflammation[25,26]. Ginsenosides from *Panax ginseng* exhibit anti-inflammatory and neuroprotective activities by regulating neurotransmitter release and mitochondrial function.

Apigenin and cannabidiol modulate γ -aminobutyric acid (GABA)-A receptor signaling and glutamate neurotransmission, thereby producing anxiolytic, anticonvulsant, and neuroprotective effects[27]. These compounds reduce seizure activity, stress-induced neuronal injury, and anxiety-related behavioral disturbances[28]. Rosmarinic acid also suppresses NF- κ B-mediated neuroinflammation, stabilizes cortisol levels, improves cholinergic neurotransmission, and enhances memory and attention in stress-related cognitive dysfunction[29].

Phytochemicals such as curcumin, hesperidin, quercetin, apigenin, EGCG regulating HPA axis by BDNF, SIRT1 upregulation, modulation of gut microbiota, GABA & monoaminergic systems, suppression of inflammation, reduction of oxidative stress[31]. Phytochemicals with Stress- and Anxiety-Modulating Properties includes Apigenin, Rosmarinic acid & EGCG modulating stress & anxiety by enhancement of GABAergic transmission, inhibition of NF- κ B & GR overactivation, HPA axis hormone modulation, activation of antioxidant pathways.

Overall, phytotherapeutic agents and neuroactive phytochemicals provide a multi-target therapeutic approach for neurological disorders by reducing oxidative stress, regulating neurotransmitter systems, improving mitochondrial function, enhancing synaptic plasticity,

suppressing neuroinflammation, and modulating HPA-axis dysfunction. Their broad-spectrum neuroprotective actions and relatively safer profiles make them promising candidates for the prevention and management of neurodegenerative and stress-related neurological disorders[30].

Preclinical studies evidence

Preclinical studies indicate that several phytotherapeutic agents can influence HPA-axis activity by modifying corticosterone levels, receptor sensitivity, and enhancing neurotrophic signaling such as BDNF. These mechanisms are particularly relevant in depression, anxiety, alzheimer's disease, parkinson's disease, and chronic stress-induced neurological disorders[31].

Experimental evidence from animal studies suggests that phytotherapeutic agents play an important role in regulating hypothalamic–pituitary–adrenal (HPA) axis function during chronic stress. Adaptogenic plants, including *Withania somnifera*, *Rhodiola rosea*, *Panax ginseng*, *Bacopa monnieri*, and *Ocimum tenuiflorum*, have been shown to mitigate stress-induced increases in corticosterone levels, regulate the secretion of corticotropin-releasing hormone (CRH) and adrenocorticotrophic hormone (ACTH), improve glucocorticoid receptor responsiveness, and support hippocampal neuronal plasticity[32](Table 1).

Phytotherapeutic	Animal Model	HPA-Axis Effects	Neurological Relevance
<i>Ashwagandha</i>	Chronic stress rats	Reduced corticosterone, normalized cortisol feedback, improved GR signaling	Anxiety, depression, cognitive impairment
<i>Rhodiola rosea</i>	Chronic mild stress mice	Reduced CRH and corticosterone secretion; improved stress resilience	Depression and fatigue
Curcumin	Chronic unpredictable stress models	Reduced corticosterone elevation and restored BDNF expression	Depression& neuroprotection
<i>Resveratrol</i>	Depression-like animal models	Reduced corticosterone and neuroinflammation	Depression and cognitive decline
<i>Schisandra chinensis</i>	Stress-induced animal models	Enhanced Hsp70-mediated stress adaptation and HPA regulation	Neuroprotection

Mangiferin	Glutamate-induced neurotoxicity in rat cortical neurons	Reduces stress-related cortisol activation indirectly by lowering oxidative stress	Protects neurons from glutamate damage, reduces oxidative stress, prevents neuronal injury and dysfunction
-------------------	---	--	--

Table 1: Preclinical evidences of phytotherapeutic modulation by neuroactive chemicals

A recent systematic review and meta-analysis by Wang *et al.*, evaluated the available preclinical evidence and underlying mechanisms of baicalein in animal models of Parkinson's disease (PD). The analysis included 20 in vivo studies and demonstrated that baicalein exerts significant neuroprotective effects, as evidenced by improvements in several behavioral and motor function assessments, including spontaneous motor activity (n = 5), pole test (n = 2), rotarod test (n = 9), apomorphine-induced rotation test (n = 4), grid test (n = 2), and tremor test (n = 2), compared with control groups. Mechanistically, baicalein was found to act through multiple signaling pathways, including modulation of neurotransmitter systems, regulation of enzyme activities, attenuation of oxidative stress, inhibition of pathological protein aggregation, and suppression of apoptotic cell death, thereby contributing to its neuroprotective potential in PD[33].

Recent advances in nanotechnology-based phytotherapeutic delivery systems have improved the therapeutic potential of natural compounds for neurological disorders. In an Alzheimer's disease (AD) model, Noor *et al.*, investigated the effects of curcumin nanoparticles in male Wistar rats subjected to intracerebroventricular administration of a sub-diabetogenic dose of streptozotocin. Treatment with curcumin nanoparticles significantly attenuated behavioral deficits and reversed several neurochemical and immunohistochemical abnormalities in the hippocampus and cerebral cortex, highlighting their potential as an effective brain-targeted therapeutic strategy[34].

Similarly, Thuraisingam *et al.*, developed a nanoemulsion formulation containing crude extract of *Centella asiatica* using a low-energy emulsification technique to enhance blood–brain barrier penetration. The formulation demonstrated promising therapeutic potential for epilepsy management by improving the delivery of neuroactive phytoconstituents to the central nervous system.

In a parkinson's disease (PD) experimental model, Junior et al. evaluated the neuroprotective efficacy of curcumin-loaded nanoemulsions compared with free curcumin. Both formulations improved motor function and reduced oxidative damage; however, the nanoemulsion system enhanced curcumin bioavailability and neuroprotective activity. Treatment was associated with decreased lipid peroxidation, improved antioxidant defense mechanisms, and inhibition of mitochondrial complex I dysfunction, suggesting a beneficial role in mitigating PD-associated neurodegeneration.

These findings collectively demonstrate that nanoformulation-based phytotherapeutics can overcome limitations such as poor bioavailability and restricted blood–brain barrier permeability,

thereby enhancing the therapeutic efficacy of plant-derived compounds in neurological disorders[35].

Clinical studies

Recent clinical studies have shown that naturally derived therapeutics may provide benefits in mild-to-moderate dementia patients. However, several clinical trials were limited because of adverse effects such as hepatotoxicity. For example, berberine, a plant-derived phytoconstituent, produced gastrointestinal side effects including constipation, diarrhea, bloating, and stomach pain in patients with type 2 diabetes. Similarly, repeated doses of resveratrol were generally well tolerated, although approximately 13% of participants experienced frontal headaches[36]. Cholinesterase inhibitors such as galantamine, donepezil, and rivastigmine showed only modest memory-enhancing effects in severe Alzheimer's disease (AD) patients and were associated with side effects including nausea, vomiting, diarrhea, insomnia, muscle spasms, fatigue, and appetite loss. In addition, many anti-AD drug candidates have failed during clinical trials because of limited efficacy and toxicity concerns. Although amyloid blockers are still under clinical evaluation, their commercialization remains restricted due to safety issues. Consequently, researchers are increasingly focusing on natural compounds because of their multitarget actions, improved safety profile, and cognitive-modulating potential[37].

Several promising clinical observations have also been reported for neurodegenerative disorders. A randomized, triple-blind, placebo-controlled study evaluated curcumin as an add-on therapy in Parkinson's disease (PD) patients for 9 months and demonstrated significant improvement in motor symptoms, although mild side effects such as nausea, vomiting, and gastroesophageal reflux were observed[38]. Baicalein has also demonstrated neuroprotective activity in preclinical PD models by improving motor functions and modulating multiple pathways including neurotransmitter regulation, antioxidant defense, inhibition of protein aggregation, and suppression of apoptosis. Furthermore, cannabidiol-based formulations have shown beneficial effects in pediatric epilepsy, where a substantial reduction in seizure frequency, along with improved alertness and verbal communication, was reported, although sedation was noted in combination therapy groups.

Despite these encouraging findings, clinical evidence supporting traditional Chinese medicine systems and herbal mixtures in AD remains limited and sometimes contradictory. Problems related to reproducibility and variability continue to be major concerns. To overcome these limitations, nano-phytomedicine has emerged as a promising strategy for neurodegenerative disorders. Nanoformulations combining herbal compounds with nanoparticles improve brain drug delivery, enhance blood-brain barrier penetration, and reduce adverse effects. Nanotheranostics, which integrates diagnosis and therapy simultaneously, has gained significant attention in recent years.

Recent studies have highlighted the therapeutic potential of nano-based herbal formulations. Curcumin-loaded nanoformulations demonstrated protective effects against streptozotocin-induced AD-like alterations in the hippocampus and cortex. Similarly, nanoemulsions containing *Centella asiatica* extract showed promising blood-brain barrier penetration and antiepileptic activity. In experimental PD models, curcumin nanoemulsions improved motor function, reduced lipid peroxidation, enhanced antioxidant defense, and inhibited mitochondrial complex I

dysfunction more effectively than free curcumin. These findings suggest that nano-phytomedicine may provide a novel and safer therapeutic approach for the management of neurodegenerative diseases [39].

Clinical studies have shown promising antidepressant effects of saffron. In a randomized, double-blind, placebo-controlled trial, 54 adults aged 18–70 years were divided into two groups. The treatment group received 50 mg of dried saffron capsules twice daily, while the control group received a placebo[40]. After 12 weeks of treatment, depressive symptoms were assessed using the beck depression inventory (BDI). The saffron-treated group showed a greater reduction in depression scores compared to the placebo group, indicating a significant improvement in mood and depressive symptoms.

Another randomized double-blind study evaluated the effects of saffron in breastfeeding mothers with postpartum depression. The study included 60 women over 18 years of age who had recently delivered a healthy baby and had no history of substance abuse, psychiatric disorders, or previous use of mood-altering medications. Participants were randomly assigned to receive either 30 mg of saffron daily (15 mg twice daily) or a placebo for eight weeks (Table 2).

Depression severity was measured using the beck depression inventory-II (BDI-II), a widely used tool for assessing depressive symptoms. At the end of the study, 77% of women in the saffron group achieved remission and no longer met the criteria for clinical depression, compared with 43% in the placebo group. The results suggest that saffron may be effective in alleviating symptoms of postpartum depression. Additionally, saffron was well tolerated, with no serious adverse effects or notable discomfort reported during the treatment period, indicating good safety and tolerability[41].

Another clinical study in adults over 60 years of age evaluated the effects of lavender aromatherapy administered through massage or inhalation over eight weeks. Both treatment groups showed improvements in depressive symptoms and mood compared to the control group. In addition, participants receiving lavender therapy exhibited increased serotonin levels, suggesting a positive effect on mood regulation. These findings support the potential of lavender aromatherapy as a safe complementary intervention for reducing depressive symptoms in older adults[42].

Phytotherapeutics	HPA axis effect	Neurological relevance
Flavanoids (Quercetin, Kaempferol, Catechins)	Reduce cortisol and improve stress regulation	Reduces oxidative damage to neuronal cells, Neuroprotection, improved cognition, anti-anxiety and antidepressant effects
Curcumin	Lowers cortisol and normalizes HPA-axis overactivity	Reduces neuronal oxidative damage, stabilizes mitochondrial membranes[38].
Ginsenosides	Modulate cortisol response and improve stress adaptation	Reduces neuroinflammation, Enhances cognition, reduces fatigue, neuroprotective and mood-stabilizing effects[44].

Saffron (<i>Crocus sativus</i>)	Modulate cortisol response and reduce stress-related HPA-axis dysregulation	Antidepressant activity, improved mood, reduced depressive symptoms, neuroprotection[40]
Lavender Essential Oil	Influence serotonergic signaling involved in stress regulation	Increased serotonin (5-HT) levels, mood enhancement, anxiolytic effects[42]
St. John's Wort (<i>Hypericum perforatum</i>)	Helps normalize overactive HPA-axis responses	Reduced depressive symptoms, improved mood, enhanced emotional regulation[43]
ECCG(Epigallocatechin gallate)	Reduces stress induced cortisol levels and improves HPA-axis balance	Improves mitochondrial biogenesis, prevents apoptosis[45].
Berberine	Lowers elevated cortisol and helps normalize stress-response signaling	Reduces excitotoxicity, stabilizes neuronal function, improves memory and reduces neuroinflammation[46]

Table 2: Clinical evidences of phytotherapeutic chemicals on neurological disorders

Limitations

Although phytotherapeutic agents have shown beneficial effects on HPA-axis regulation and neurological health, some challenges still need to be addressed before their wider clinical application. Variations in plant sources, extraction procedures, and phytochemical composition can influence their activity and reproducibility. Many phytochemicals also face limitations such as poor absorption, rapid metabolism, low stability, and limited ability to reach the brain, which may affect their overall effectiveness[47]. Since most available evidence comes from preclinical studies, more clinical investigations are needed to establish their safety and therapeutic value. Recent approaches such as nanoformulations and targeted drug delivery systems may help improve the bioavailability and stability of these compounds. Further studies focusing on pharmacokinetics, dose optimization, standardization, and long-term safety are required to support their clinical use[48].

Future perspectives and challenges

Although current findings are encouraging, additional well-designed studies are needed to confirm the clinical relevance of HPA-axis-targeted phytotherapy. Unlike conventional pharmacological interventions that often target a single molecular pathway, phytotherapeutics exhibit multitarget actions by simultaneously regulating oxidative stress, neuroinflammation, mitochondrial dysfunction, neurotransmitter imbalance, and neuroendocrine dysregulation. This pleiotropic nature may provide advantages in the management of complex neurological diseases characterized by multifactorial pathogenesis.

Despite encouraging preclinical and clinical findings, several challenges limit the translation of phytotherapeutics into routine clinical practice. Variability in phytochemical composition,

differences in extraction methods, poor bioavailability, lack of standardization, and limited large-scale clinical trials remain major obstacles. Furthermore, the precise molecular interactions between phytoconstituents and HPA-axis signaling components, including glucocorticoid receptors, corticotropin-releasing hormone pathways, and stress-responsive transcription factors, require further investigation.

Recent advances in nanotechnology-based drug delivery systems, metabolomics, transcriptomics, and systems pharmacology may facilitate the development of standardized phytotherapeutic formulations with improved efficacy and bioavailability. Future studies should focus on well-designed randomized controlled trials, biomarker-based patient stratification, and mechanistic investigations to establish the therapeutic value of phytotherapeutics in neurological disorders associated with HPA-axis dysfunction.

Conclusion

Current evidence indicates that HPA-axis imbalance contributes to neuronal damage and stress-related changes observed in several neurological disorders. Phytotherapeutic compounds offer a promising natural approach to address these underlying mechanisms through their neuroprotective, antioxidant, anti-inflammatory, and stress-regulating properties. Findings from both preclinical and emerging clinical studies indicate that these plant-derived agents may help improve neurological function and support brain health. Although the results are encouraging, further well-designed clinical studies are needed to establish their long-term efficacy and safety. Overall, phytotherapeutics hold considerable potential as complementary therapeutic options for managing neurological disorders associated with HPA-axis dysregulation.

Acknowledgments

The authors sincerely thank the Department of Pharmacology and their institution for providing the necessary academic support and facilities to complete this review. The authors also acknowledge the researchers whose published work contributed to the preparation of this manuscript.

The authors used a generative artificial intelligence (AI) tool solely to improve the language, grammar, and readability of the manuscript. All scientific content was independently reviewed, verified, and approved by the authors, who take full responsibility for the accuracy and integrity of the final manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest related to this work.

References

1. Feigin VL, Vos T, Nichols E, Owolabi MO, Carroll WM, Dichgans M, *et al.* The global burden of neurological disorders: translating evidence into policy. *Lancet Neurol.* 2020;19(3):255-65. doi:10.1016/S1474-4422(19)30411-9.

2. Xu DP, Li Y, Meng X, Zhou T, Zhou Y, Zheng J, *et al.* Natural antioxidants in neurological diseases. *Oxid Med Cell Longev.* 2022;2022:3759874.
3. Herman JP, Nawreen N, Smail MA, Cotella EM. Brain mechanisms of HPA axis regulation: neurocircuitry and feedback in context Richard Kvetnansky lecture. *Stress.* 2020 Nov;23(6):617-632.
4. de Kloet ER, Joëls M, Holsboer F. Stress and the brain: from adaptation to disease. *Nat Rev Neurosci.* 2005;6(6):463-75.
5. Puri V, Kanojia N, Sharma A, Huanbutta K, Dheer D, Sangnim T, *et al.* Natural product-based pharmacological studies for neurological disorders. *Front Pharmacol.* 2022;13:1011740.
6. Sharma R, Singla RK, Banerjee S, Sinha B, Shen B, Sharma R. Role of Shankhpushpi (*Convolvulus pluricaulis*) in neurological disorders: an umbrella review covering evidence from ethnopharmacology to clinical studies. *Neurosci Biobehav Rev.* 2022;140:104795. doi:10.1016/j.neubiorev.2022.104795.
7. Miranda M, Morici JF, Zanoni MB, Bekinschtein P. Brain-derived neurotrophic factor: a key molecule for memory in the healthy and pathological brain. *Front Cell Neurosci.* 2019;13:363.
8. Ratcliffe C, Wandschneider B, Baxendale S, Thompson P, Koepp MJ, Caciagli L. Cognitive function in genetic generalized epilepsies: insights from neuropsychology and neuroimaging. *Front Neurol.* 2020;11:144.
9. Mendonça-Junior FJ, Scotti MT, Muratov EN, Scotti L, Nayarissieri A. Natural bioactive products with antioxidant properties useful in neurodegenerative diseases. 2020. *Oxid Med Cell Longev.* 2021;2021:6262316.
10. Sharifi-Rad M, Lankatillake C, Dias DA, Docea AO, Mahomoodally MF, Lobine D, *et al.* Impact of natural compounds on neurodegenerative disorders: From preclinical to pharmacotherapeutics. *J Clin Med.* 2020;9(4):1061.
11. Jayaraman M, Dutta P, Krishnan S, Arora K, Sivakumar D, Raghavendran HRB. Emerging promise of phytochemicals in ameliorating neurological disorders. *CNS Neurol Disord Drug Targets.* 2023;22(9):1275-1301.
12. Sarris J, McIntyre E, Camfield DA. Plant-based medicines for anxiety disorders. *CNS Drugs.* 2022;36(1):37-60. doi:10.1007/s40263-021-00893-3.
13. Hinds JA, Sanchez ER. Glucocorticoids, stress, and their relation to test anxiety and neurocognitive function. *Stresses.* 2022;2(2):150-155.
14. Kent SA, Spires-Jones TA, Durrant CA. The physiological roles of tau and A β : Implications for alzheimer's disease pathology and therapeutics. *Acta Neuropathol.* 2020;140:417-447.
15. Martins M, Silva R, Pinto MM, Sousa E. Marine natural products, multitarget therapy and repurposed agents in Alzheimer's disease. *Pharmaceuticals (Basel).* 2020;13(9):242
16. Mannan A, Singh TG, Singh V, Garg N, Kaur A, Singh M. Insights into the mechanism of the therapeutic potential of herbal monoamine oxidase inhibitors in neurological diseases. *Curr Drug Targets.* 2022;23:286-310
17. Chinraj V, Raman S. (2022). Neuroprotection by resveratrol: A review on brain delivery strategies for alzheimer's and Parkinson's disease. *J Appl Pharm Sci.* 2022;12:1-17.
18. Moise G, Jijie AR, Moacă EA, Predescu IA, Dehelean CA, Heghes A, *et al.* Plants' impact on the human brain:exploring the neuroprotective and neurotoxic potential of plants. *Pharmaceuticals* 2024;17(10):1339.

19. Bellavite P. Neuroprotective potentials of flavonoids: experimental studies and mechanisms of action. *Antioxidants* 2023;12(2):280.
20. Sivanantharajah L, Mudher A. Curcumin as a holistic treatment for tau pathology. *Front. Pharmacol.* 2022;13:903119
21. Amin MA, Zehravi M, Sweilam SH, Shatu MM, Durgawale TP, Qureshi MS, *et al.* Neuroprotective potential of epigallocatechin gallate in Neurodegenerative Diseases: Insights into molecular mechanisms and clinical Relevance. *Brain Res.* 2025;1860: 149693
22. Costa LG, Garrick JM, Roqué PJ, Pellacani C. Mechanisms of neuroprotection by quercetin: counteracting oxidative stress and more. *Oxidative Med Cell Longev.* 2016;2016:2986796.
23. Song Q, Peng S, Zhu X. Baicalein protects against MPP+/MPTP-induced neurotoxicity by ameliorating oxidative stress in SH-SY5Y cells and mouse model of Parkinson's disease. *Neurotoxicology* 2021;87:188-194.
24. Zaazaa AM, Daoud NN, El-Gendy OA, Al-Shafei AI. Neuroprotective role of *Bacopa monnieri* extract in modulating depression in an experimental rat model. *J Affect Disord.* 2022;308:229-235.
25. Mikulska P, Malinowska M, Ignacyk M, Szustowski P, Nowak J, Pesta K, *et al.* Ashwagandha (*Withania somnifera*)—Current research on the health-promoting activities: a narrative Review. *Pharmaceutics*. 2023;15(4):1057.
26. Jiang N, Wang H, Li C, Zeng G, Lv J, Wang Q, *et al.* The antidepressant-like effects of the water extract of *Panax ginseng* and *Polygala tenuifolia* are mediated via the BDNF-TrkB signaling pathway and neurogenesis in the hippocampus. *J. Ethnopharmacol.* 2021;267:113625
27. Alghamdi A, Almuqbil M, Alrofaidi MA, Burzangi AS, Alshamrani AA, Alzahrani AR, *et al.* Potential antioxidant activity of apigenin in the obviating stress-mediated depressive symptoms of experimental mice. *Molecules*. 2022;27(24):9055.
28. Gray RA, Whalley BJ. The proposed mechanisms of action of CBD in epilepsy. *Epileptic Disord.* 2020;22:10-15.
29. Priya V, Srinivasan D, Priyadarsini S, Dabaghzadeh F, Rana SS, Chengaiyan JG, *et al.* anxiolytic, antidepressant and healthy sleep-promoting potential of rosmarinic acid: mechanisms and molecular targets. *Neuropsychiatr Dis Treat.* 2025;21:641–661.
30. Kruk-Slomka M, Budzynska B, Slomka T. Neuroactive phytochemicals and their molecular mechanisms in neurological and stress-related disorders. *Int J Mol Sci.* 2025;26(17):8907.
31. Gołyszny, M.J.; Obuchowicz, E. Medicinal plant materials in the treatment of anxiety disorders: neurobiological aspects. *Altern Ther Health Med.* 2018;24:44–57.
32. Such S, Puchalski C, Kogut Ł, Zagula G. System-level, molecular and cellular mechanisms of selected plant adaptogens—a review. *Nutrients.* 2026;18(6):931. doi: [10.3390/nu18060931](https://doi.org/10.3390/nu18060931).
33. Wang Y., Wei N., Li X. Preclinical evidence and possible mechanisms of baicalein for rats and mice with Parkinson's disease: a systematic review and meta-analysis. *Front Aging Neurosci.* 2020;12:277.
34. Noor NA, Hosny EN, Khadrawy YA, Mourad IM, Othman AI, Aboul Ezz HS, *et al.* Effect of curcumin nanoparticles on streptozotocin-induced male wistar rat model of Alzheimer's disease. *Metab Brain Dis.* 2022;37:343-357

35. Thuraisingam S, Salim N, Azmi ID, Kartinee N. Development of nanoemulsion containing *Centella asiatica* crude extract as a promising drug delivery system for epilepsy treatment. *Biointerfac Res Appl Chem*. 2023;13:17.
36. Shaito A, Posadino AM, Younes N, Hasan H, Halabi S, Alhababi D, *et al*. Potential adverse effects of resveratrol: a literature review. *Int J Mol Sci*. 2020;21:2084.
37. Cummings J, Lee G, Zhong K, Fonseca J, Taghva K. Alzheimer's disease drug development pipeline: 2021. *Alzheimers Dement. (N Y)*. 2021;7:e12179.
38. Ghodsi H, Rahimi HR, Aghili SM, Saberi A, Shoeibi A. Evaluation of curcumin as add-on therapy in patients with Parkinson's disease: a pilot randomized, triple-blind, placebo-controlled trial. *Clin Neurol Neurosurg*. 2022;218:107300
39. Picheta N, Piekarz J, Daniłowska K, Mazur K, Pieciewicz-Szczęśna H, Smoleń A. Phytochemicals in the treatment of patients with depression: a systemic review. *Front Psychiatry*. 2024;15:1509109.
40. Mazidi M, Shemshian M, Mousavi SH, Norouzy A, Kermani T, Moghiman T, *et al*. A double-blind, randomized and placebo-controlled trial of Saffron (*Crocus sativus* L.) in the treatment of anxiety and depression. *J Complement Integr Med*. 2016;13:195–199.
41. Omidkhoda SF, Hosseinzadeh H. Saffron and its active ingredients against human disorders: a literature review on existing clinical evidence. *Iran J Basic Med Sci*. 2022;25(8):913-933. doi: 10.22038/IJBMS.2022.63378.13985.
42. Xiong M, Li Y, Tang P, Zhang Y, Cao M, Ni J, *et al*. Effectiveness of aromatherapy massage and inhalation on symptoms of depression in Chinese community-dwelling older adults. *J Altern Complement Med*. 2018;24:717-724.
43. Nicolussi S, Drewe J, Butterweck V, Meyer zu Schwabedissen HE. Clinical relevance of St. John's wort drug interactions revisited. *Br J Pharmacol*. 2020;177:1212-1226.
44. Nemetchek MD, Stierle AA, Stierle DB, Lurie DI. The Ayurvedic plant *Bacopa monnieri* inhibits inflammatory pathways in the brain. *J Ethnopharmacol*. 2017;197:92-100.
45. Naoi M, Wu Y, Shamoto-Nagai M, Maruyama W. Mitochondria in neuroprotection by phytochemicals: bioactive polyphenols modulate mitochondrial apoptosis system, function and structure. *Int J Mol Sci*. 2019;20(10):2451.
46. Lin X, Zhang N. Berberine: pathways to protect neurons. *Phytother Res*. 2018;32(8):1501-10.
47. Lopresti AL, Smith SJ and Drummond PD. Modulation of the hypothalamic–pituitary–adrenal (HPA) axis by plants and phytonutrients: a systematic review of human trials. *Nutr Neurosci*. 2022;25(8):1704-1730. doi:10.1080/1028415X.2021.1892253.
48. Wang S, Ma J, Zeng Y, Zhou G, Wang Y, Zhou W, *et al*. Icariin, an up-and-coming bioactive compound against neurological diseases: network pharmacology-based study and literature review. *Drug Des Devel Ther*. 2021;15:3619-3641.