



Review Article

THE ROLE OF NOVEL HERBAL ADAPTOGENS IN TARGETING THE ANXIETY-DEPRESSION-COGNITION AXIS: PHARMACOLOGICAL MECHANISMS, THERAPEUTIC POTENTIAL, AND FUTURE PERSPECTIVES

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ABSTRACT

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Anxiety, depression, and cognitive dysfunction are closely interconnected neuropsychiatric disorders that share common pathological mechanisms, including hypothalamic-pituitary-adrenal (HPA) axis dysregulation, neurotransmitter imbalance, oxidative stress, neuroinflammation, and impaired neuroplasticity. Although conventional pharmacotherapies remain the primary treatment option, their long-term use is often limited by adverse effects, delayed therapeutic response, and incomplete symptom relief. Consequently, increasing attention has been directed toward herbal adaptogens as multitarget therapeutic agents capable of enhancing stress resilience and restoring physiological homeostasis. Emerging evidence suggests that novel herbal adaptogens exert anxiolytic, antidepressant, neuroprotective, and cognition-enhancing effects by modulating multiple molecular pathways involved in the anxiety-depression-cognition axis. This review summarizes the pharmacological mechanisms, therapeutic potential, and recent advances in novel herbal adaptogens while highlighting current challenges and future research directions for their translation into evidence-based therapies for neuropsychiatric disorders.

Keywords: Herbal adaptogens; Anxiety-depression-cognition axis; Anxiety; Depression; Cognitive dysfunction; Neuroprotection; Pharmacological mechanisms; Therapeutic potential.

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1. INTRODUCTION

Mental health disorders are among the leading causes of disability worldwide, with anxiety, depression, and cognitive dysfunction affecting millions of individuals and imposing a significant burden on healthcare systems and society. These disorders frequently coexist and share overlapping neurobiological mechanisms that contribute to emotional disturbances, impaired memory, reduced cognitive performance, and poor quality of life. According to the World Health Organization, mental disorders affect approximately one in eight people globally, emphasizing the urgent need for more effective and safer therapeutic strategies [1,2].

Recent advances in neuroscience have led to the concept of the anxiety-depression-cognition axis, which

describes the interconnected relationship between emotional regulation, stress responses, and cognitive function. Dysregulation of this axis is associated with hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis, altered monoaminergic neurotransmission, oxidative stress, neuroinflammation, mitochondrial dysfunction, and impaired neuroplasticity. These pathological changes not only contribute to anxiety and depressive symptoms but also accelerate cognitive decline [3,4].

Although conventional medications such as antidepressants, anxiolytics, and cognitive enhancers are widely prescribed, their clinical effectiveness is often limited by delayed onset of action, adverse effects, treatment resistance, and poor long-term adherence.

Consequently, there is growing interest in natural products with multitarget pharmacological actions that can simultaneously modulate multiple pathways involved in neuropsychiatric disorders [5,6].

Herbal adaptogens are a unique class of medicinal plants that enhance the body's resistance to physical and psychological stress while maintaining physiological homeostasis. Unlike conventional drugs that primarily target a single receptor or signaling pathway, adaptogens exert broad neuroprotective effects by regulating neurotransmitter systems, reducing oxidative stress, suppressing neuroinflammation, and promoting neuronal survival and synaptic plasticity [7,8]. In addition to well-established adaptogens, several novel medicinal plants have recently demonstrated promising anxiolytic, antidepressant, and cognition-enhancing activities in experimental studies, highlighting their potential as multitarget therapeutic agents.

This review provides an overview of the pharmacological mechanisms through which novel herbal adaptogens influence the anxiety–depression–cognition axis. It summarizes current evidence regarding their therapeutic potential, discusses recent advances in experimental research, and highlights future perspectives and challenges for their clinical development in the management of anxiety, depression, and cognitive dysfunction.

Concept of Herbal Adaptogens

Herbal adaptogens are a unique class of medicinal plants that enhance the body's capacity to adapt to physical, chemical, and biological stressors while maintaining physiological homeostasis. Unlike conventional pharmacological agents that generally target a single receptor or signaling pathway, adaptogens exert multitarget effects by modulating interconnected neuroendocrine, immune, metabolic, and antioxidant systems. Owing to these broad pharmacological actions, herbal adaptogens have gained considerable attention as potential therapeutic agents for the prevention and management of stress-related disorders, including anxiety, depression, and cognitive dysfunction [9,10].

The concept of adaptogens was first introduced by the Russian pharmacologist Nikolai V. Lazarev in 1947, who described adaptogens as substances capable of increasing the body's nonspecific resistance to adverse environmental influences. This concept was later refined by Brekhman and Dardymov, who proposed three fundamental criteria for an adaptogen: (i) it should enhance nonspecific resistance against a broad range of stressors, (ii) it should normalize physiological functions irrespective of the direction of pathological changes, and (iii) it should be safe and cause minimal disruption of normal biological processes [11,12]. These criteria continue to provide the scientific basis for identifying and evaluating adaptogenic plants.

Exposure to chronic stress activates the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system, resulting in sustained secretion of glucocorticoids and catecholamines. Although these responses are essential

for maintaining short-term physiological adaptation, prolonged activation contributes to oxidative stress, neuroinflammation, mitochondrial dysfunction, impaired neuroplasticity, and neurotransmitter imbalance, thereby increasing susceptibility to anxiety, depression, and cognitive impairment. Herbal adaptogens help restore physiological equilibrium by regulating stress-response pathways and enhancing the body's adaptive capacity [10,13].

The pharmacological activity of herbal adaptogens is primarily attributed to a diverse array of bioactive phytochemicals, including flavonoids, alkaloids, saponins, terpenoids, phenolic compounds, lignans, and glycosides. These constituents exhibit antioxidant, anti-inflammatory, neuroprotective, immunomodulatory, and endocrine-regulating properties through modulation of multiple intracellular signaling pathways. Consequently, adaptogens influence several molecular targets involved in stress adaptation, neuronal survival, neurotransmitter regulation, and cognitive function [14,15].

Based on the extent of scientific evidence, herbal adaptogens can be broadly categorized into classical and novel (emerging) adaptogens. Classical adaptogens, such as *Withaniasomnifera*, *Panax ginseng*, *Rhodiola rosea*, *Eleutherococcus senticosus*, and *Schisandra chinensis*, have been extensively investigated for their adaptogenic properties. In contrast, novel herbal adaptogens comprise less-explored medicinal plants that have recently demonstrated promising anxiolytic, antidepressant, neuroprotective, and cognition-enhancing activities in experimental studies. The exploration of these emerging plants has expanded the scope of adaptogen research and may facilitate the discovery of new phytochemicals with multitarget therapeutic potential [10,15].

Recent advances in molecular pharmacology have further clarified the mechanisms underlying the adaptogenic effects of medicinal plants. Adaptogens have been shown to regulate signaling pathways associated with oxidative stress, inflammation, apoptosis, and synaptic plasticity, including nuclear factor erythroid 2-related factor 2 (Nrf2), nuclear factor-kappa B (NF-κB), phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), mitogen-activated protein kinase (MAPK), and brain-derived neurotrophic factor/cyclic AMP response element-binding protein (BDNF/CREB) pathways. Through modulation of these interconnected pathways, adaptogens promote neuronal resilience, improve cognitive performance, and protect against stress-induced neuronal damage [14–16].

Overall, herbal adaptogens represent a promising group of natural therapeutic agents capable of enhancing stress resilience and maintaining physiological homeostasis through multitarget pharmacological actions. Their broad spectrum of biological activities provides a strong scientific rationale for investigating novel herbal adaptogens as potential interventions for anxiety, depression, and cognitive dysfunction. However, further studies focusing on phytochemical standardization, pharmacokinetics, safety evaluation, and clinical efficacy are required to support

their translation into evidence-based clinical practice [10,16].

Anxiety-Depression-Cognition Axis

Anxiety, depression, and cognitive dysfunction are closely interconnected neuropsychiatric disorders that frequently coexist and share common neurobiological mechanisms. Rather than representing isolated conditions, these disorders are increasingly recognized as components of the anxiety-depression-cognition axis, a framework that highlights the complex interactions among stress responses, emotional regulation, and cognitive function. Dysregulation of this axis contributes to the development and progression of mood disorders and cognitive impairment, emphasizing the need for therapeutic approaches that target multiple pathological pathways [17,18].

One of the central mechanisms underlying this axis is the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, the body's primary neuroendocrine system responsible for maintaining the stress response. Under normal physiological conditions, activation of the HPA axis promotes adaptation to acute stress through the controlled release of glucocorticoids. However, chronic or excessive stress results in prolonged secretion of cortisol in humans and corticosterone in experimental animals, leading to neuronal dysfunction, impaired synaptic plasticity, and structural changes in the hippocampus, amygdala, and prefrontal cortex. These alterations are strongly associated with anxiety, depression, and deficits in learning and memory [19,20].

Neurotransmitter imbalance further contributes to the pathogenesis of the anxiety-depression-cognition axis. Serotonin (5-HT), dopamine, γ -aminobutyric acid (GABA), glutamate, and norepinephrine play essential roles in regulating mood, motivation, emotional behavior, and cognitive performance. Disturbances in these neurotransmitter systems disrupt neuronal communication, resulting in anxiety symptoms, depressive behavior, and impaired cognitive function. Consequently, modulation of these neurotransmitters remains one of the principal therapeutic strategies for treating stress-related neuropsychiatric disorders [18,21].

Chronic stress also induces oxidative stress and neuroinflammation, both of which contribute significantly to neuronal injury. Excessive production of reactive oxygen species (ROS) damages cellular lipids, proteins, and DNA, while activated microglia release pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6). These pathological processes impair neuronal survival, reduce synaptic plasticity, and exacerbate emotional and cognitive dysfunction, creating a self-perpetuating cycle that accelerates disease progression [22-24].

Another important component of this axis is brain-derived neurotrophic factor (BDNF), a key regulator of neuronal survival, synaptic plasticity, and memory formation. Reduced BDNF expression has been consistently

associated with anxiety, depression, and cognitive decline. In addition, increasing evidence suggests that alterations in the gut-brain axis influence neuropsychiatric disorders through bidirectional communication between the intestinal microbiota and the central nervous system. Changes in gut microbial composition can affect neurotransmitter production, immune responses, and HPA-axis activity, thereby influencing emotional behavior and cognitive function [25-27].

Overall, the anxiety-depression-cognition axis represents a complex network of interconnected molecular and cellular mechanisms involving HPA-axis dysregulation, neurotransmitter imbalance, oxidative stress, neuroinflammation, impaired neuroplasticity, and gut-brain communication. Since these pathways interact to drive the progression of stress-related neuropsychiatric disorders, therapeutic agents with multitarget pharmacological actions are likely to provide greater clinical benefits than single-target treatments. In this context, herbal adaptogens have emerged as promising candidates because of their ability to simultaneously modulate multiple components of the anxiety-depression-cognition axis, offering a potential strategy for the integrated management of anxiety, depression, and cognitive dysfunction [17,28].

Pharmacological Mechanisms of Herbal Adaptogens

Herbal adaptogens exert their therapeutic effects through multiple molecular and cellular pathways that collectively enhance stress resistance, maintain physiological homeostasis, and protect the nervous system. Unlike conventional pharmacological agents that generally target a single receptor or signaling pathway, adaptogens influence several interconnected mechanisms involved in the pathogenesis of anxiety, depression, and cognitive dysfunction. Their multitarget pharmacological actions include regulation of the hypothalamic-pituitary-adrenal (HPA) axis, modulation of neurotransmitter systems, attenuation of oxidative stress and neuroinflammation, enhancement of neuroplasticity, and preservation of mitochondrial function. These complementary effects make herbal adaptogens promising therapeutic agents for stress-related neuropsychiatric disorders [29,10].

One of the primary mechanisms of herbal adaptogens is the regulation of the hypothalamic-pituitary-adrenal (HPA) axis, which plays a central role in the physiological response to stress. Chronic activation of the HPA axis results in excessive glucocorticoid secretion, leading to neuronal damage, impaired synaptic plasticity, and cognitive dysfunction. Adaptogenic herbs help restore HPA-axis homeostasis by regulating cortisol or corticosterone levels and improving feedback mechanisms that control stress responses. This normalization reduces the harmful effects of chronic stress and contributes to improved emotional stability and cognitive performance [31,32].

Another important mechanism involves the modulation of neurotransmitter systems. Herbal adaptogens influence the synthesis, release, and activity of neurotransmitters such as serotonin, dopamine,

norepinephrine, γ -aminobutyric acid (GABA), and glutamate, all of which are essential for regulating mood, anxiety, learning, and memory. By restoring neurotransmitter balance, adaptogens improve emotional regulation, reduce anxiety-like and depressive behaviors, and enhance cognitive function. Their ability to modulate multiple neurotransmitter pathways simultaneously distinguishes them from many conventional drugs that primarily target a single neurotransmitter system [10,33].

Oxidative stress and chronic neuroinflammation are major contributors to neuronal dysfunction in anxiety, depression, and cognitive impairment. Herbal adaptogens are rich in bioactive phytochemicals, including flavonoids, phenolic acids, saponins, alkaloids, and terpenoids, which possess potent antioxidant and anti-inflammatory properties. These compounds reduce the generation of reactive oxygen species (ROS), enhance endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), and inhibit lipid peroxidation. Simultaneously, adaptogens suppress inflammatory mediators by inhibiting nuclear factor-kappa B (NF- κ B) signaling and reducing the production of cytokines, including tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6). Through these actions, herbal adaptogens protect neurons from oxidative and inflammatory damage and preserve normal neuronal function [34–36].

Herbal adaptogens also promote neuroplasticity, a fundamental process required for learning, memory, and emotional regulation. Several adaptogenic plants increase the expression of brain-derived neurotrophic factor (BDNF) and activate downstream signaling pathways such as cyclic AMP response element-binding protein (CREB), phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), and mitogen-activated protein kinase (MAPK). Activation of these pathways supports neuronal survival, stimulates hippocampal neurogenesis, strengthens synaptic connections, and improves cognitive performance. In addition, adaptogens help maintain mitochondrial function by preserving ATP production, reducing mitochondrial oxidative damage, and preventing stress-induced apoptosis, thereby ensuring adequate energy supply for neuronal activity [37–39].

The therapeutic value of herbal adaptogens lies in their multitarget pharmacological profile. Rather than acting on a single molecular target, they simultaneously regulate neuroendocrine function, neurotransmission, oxidative balance, inflammatory signaling, and neuronal plasticity. This integrated mode of action is particularly beneficial for disorders such as anxiety, depression, and cognitive dysfunction, where multiple pathological mechanisms occur concurrently. Consequently, herbal adaptogens have emerged as promising candidates for the development of safer and more comprehensive therapeutic strategies aimed at restoring both emotional and cognitive health. Nevertheless, further mechanistic studies and well-designed clinical trials are required to validate their efficacy, establish standardized formulations, and facilitate

their integration into evidence-based clinical practice [29,10,40].

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Mechanism	Therapeutic Effect
HPA-axis regulation	Reduces stress hormones
Neurotransmitter modulation	Improves mood and cognition
Antioxidant activity	Protects neurons from ROS
Anti-inflammatory activity	Reduces neuroinflammation
BDNF/CREB activation	Enhances neuroplasticity
Mitochondrial protection	Improves neuronal survival
Gut-brain axis modulation	Supports emotional and cognitive health

Therapeutic Potential of Novel Herbal Adaptogens

Herbal adaptogens have emerged as promising therapeutic agents for the management of anxiety, depression, and cognitive dysfunction because of their ability to simultaneously modulate multiple biological pathways involved in the anxiety–depression–cognition axis. Unlike conventional pharmacotherapies that often target a single mechanism, adaptogenic plants contain diverse phytochemicals capable of regulating stress responses, reducing neuroinflammation and oxidative stress, restoring neurotransmitter balance, and enhancing neuroplasticity. These multitarget effects have positioned herbal adaptogens as potential complementary or alternative interventions for stress-related neuropsychiatric disorders [41,10].

Among the well-investigated adaptogens, *Withaniasomnifera* (Ashwagandha) has demonstrated significant anxiolytic, antidepressant, and cognition-enhancing effects in both experimental and clinical studies. Its bioactive withanolides regulate the hypothalamic–pituitary–adrenal (HPA) axis, reduce cortisol levels, enhance γ -aminobutyric acid (GABA) signaling, and improve antioxidant defenses, resulting in reduced stress and improved cognitive performance [43]. Similarly, *Rhodiola rosea* has shown the ability to alleviate fatigue, improve mood, and enhance mental performance through modulation of monoaminergic neurotransmission and reduction of oxidative stress [44].

Several emerging herbal adaptogens have also demonstrated considerable therapeutic potential. *Centella asiatica* is rich in triterpenoids such as asiaticoside and madecassoside, which promote neuronal regeneration, improve memory, and reduce oxidative stress through activation of brain-derived neurotrophic factor (BDNF)-mediated signaling pathways [45]. Likewise, *Clitoria ternatea* possesses flavonoids and ternatins with antioxidant and neuroprotective activities that enhance

learning and memory while attenuating anxiety-like behavior in experimental models [46].

Medicinal plants relevant to the present review, including *Dioscorea wallichii*, *Ipomoea cairica*, and *Merremiadissecta*, have recently gained attention because of their diverse phytochemical profiles and promising neuropharmacological activities. These plants contain flavonoids, steroidal saponins, phenolic compounds, and alkaloids that exhibit antioxidant and anti-inflammatory properties. Experimental studies suggest that these phytochemicals may regulate neurotransmitter systems, reduce oxidative stress, and protect neuronal cells from stress-induced damage. Although current evidence is primarily derived from preclinical investigations, these findings support their potential as novel adaptogens for the management of anxiety, depression, and cognitive dysfunction [47–49].

Despite encouraging pharmacological evidence, several challenges remain before novel herbal adaptogens can be translated into routine clinical practice. Variability in phytochemical composition, lack of standardized extraction methods, limited pharmacokinetic data, insufficient toxicity evaluation, and the scarcity of well-designed clinical trials continue to limit their clinical application. Addressing these limitations through rigorous phytochemical characterization, standardized formulations, and large-scale clinical studies will be essential for establishing their efficacy and safety [10,50].

Overall, available evidence suggests that novel herbal adaptogens possess significant therapeutic potential because of their multitarget pharmacological actions and favorable safety profiles. Their ability to regulate interconnected mechanisms involved in the anxiety–depression–cognition axis makes them attractive candidates for future drug development. Continued research integrating pharmacological, phytochemical, and clinical approaches may facilitate the development of evidence-based adaptogen therapies for neuropsychiatric disorders.

Future Perspectives and Challenges

Despite encouraging preclinical evidence, the clinical application of herbal adaptogens remains limited due to several scientific and regulatory challenges. One of the major concerns is the lack of standardized herbal formulations, as variations in plant source, cultivation, extraction methods, and phytochemical composition can affect therapeutic efficacy and reproducibility. Therefore, establishing standardized quality-control measures is essential for the development of reliable adaptogen-based therapies [51,52].

Another important limitation is the scarcity of well-designed clinical trials evaluating the long-term safety, efficacy, dosage, and pharmacokinetic profiles of herbal adaptogens. Although many medicinal plants have demonstrated promising anxiolytic, antidepressant, and cognition-enhancing effects in experimental studies, additional clinical evidence is required before they can be widely recommended for neuropsychiatric disorders [53].

Future research should focus on identifying novel bioactive compounds, elucidating molecular mechanisms, and integrating advanced approaches such as omics technologies and network pharmacology to accelerate drug discovery. In addition, comprehensive toxicity studies and standardized clinical investigations will be essential to support the translation of herbal adaptogens into evidence-based therapeutic options [54,10].

2. CONCLUSION

Herbal adaptogens have gained considerable attention as promising multitarget therapeutic agents for the management of anxiety, depression, and cognitive dysfunction. By regulating the hypothalamic–pituitary–adrenal (HPA) axis, restoring neurotransmitter balance, reducing oxidative stress and neuroinflammation, and enhancing neuroplasticity, these medicinal plants help improve stress resilience and support cognitive and emotional health.

Recent studies have highlighted the therapeutic potential of both classical and novel herbal adaptogens in experimental models. In particular, emerging medicinal plants such as *Dioscorea wallichii*, *Ipomoea cairica*, and *Merremiadissecta* warrant further investigation because of their diverse phytochemical composition and promising neuroprotective properties. However, additional research is required to establish their pharmacokinetic profiles, safety, standardized formulations, and clinical efficacy.

Overall, herbal adaptogens represent a promising approach for targeting the complex mechanisms underlying the anxiety–depression–cognition axis. Future studies integrating phytochemical characterization, mechanistic investigations, and well-designed clinical trials will be essential to support their development as evidence-based therapeutic options for stress-related neuropsychiatric disorders.

REFERENCES

- [1]. Organization. World mental health report: Transforming mental health for all. Geneva: WHO; 2022.
- [2]. Ferrari AJ, Santomauro DF, Herrera AMM, et al. Global, regional, and national burden of mental disorders. *Lancet Psychiatry*. 2022;9(2):137–150.
- [3]. McEwen BS, Akil H. Revisiting the stress concept: implications for affective disorders. *J Neurosci*. 2020;40(1):12–21.
- [4]. Duman RS, Sanacora G, Krystal JH. Altered connectivity in depression: from synapses to circuits. *Neuron*. 2019;102(1):75–90.
- [5]. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs. *Lancet*. 2018;391:1357–1366.
- [6]. Krystal JH, Abdallah CG, Sanacora G, et al. Ketamine: a paradigm shift for depression research and treatment. *Neuron*. 2019;101(5):774–778.

- [7]. Panossian A, Wikman G. Effects of adaptogens on the central nervous system and molecular mechanisms associated with their stress-protective activity. *Pharmaceuticals (Basel)*. 2010;3(1):188–224.
- [8]. Panossian AG. Understanding adaptogenic activity: specificity of the pharmacological action of adaptogens. *Ann N Y Acad Sci*. 2017;1401(1):49–64.
- [9]. Panossian AG, Wikman G. Effects of adaptogens on the central nervous system and the molecular mechanisms associated with their stress-protective activity. *Pharmaceuticals (Basel)*. 2010;3(1):188–224.
- [10]. Panossian AG. Understanding adaptogenic activity: specificity of the pharmacological action of adaptogens. *Ann N Y Acad Sci*. 2017;1401(1):49–64.
- [11]. Lazarev NV. General state of the problem of action of biologically active substances on resistance. In: *Proceedings of the Conference on Pharmacology of Adaptation*. Leningrad; 1947.
- [12]. Brekhman IL, Dardymov IV. New substances of plant origin which increase nonspecific resistance. *Annu Rev Pharmacol*. 1969;9:419–430.
- [13]. McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med*. 1998;338(3):171–179.
- [14]. Panossian A, Seo EJ, Efferth T. Novel molecular mechanisms for the adaptogenic effects of herbal extracts. *Pharmacol Res*. 2021;168:105599.
- [15]. Sarris J, McIntyre E, Camfield DA. Plant-based medicines for anxiety disorders, depression, and cognition. *CNS Drugs*. 2020;34:1–25.
- [16]. Nabavi SF, Sureda A, Daglia M, et al. Natural products and phytochemicals in neuroprotection: current perspectives and future directions. *Phytomedicine*. 2022;98:153931.
- [17]. McEwen BS, Akil H. Revisiting the stress concept: implications for affective disorders. *J Neurosci*. 2020;40(1):12–21.
- [18]. Duman RS, Sanacora G, Krystal JH. Altered connectivity in depression: from synapses to circuits. *Neuron*. 2019;102(1):75–90.
- [19]. de Kloet ER, Joëls M, Holsboer F. Stress and the brain: from adaptation to disease. *Nat Rev Neurosci*. 2005;6(6):463–475.
- [20]. Herman JP, McKlveen JM, Ghosal S, et al. Regulation of the hypothalamic–pituitary–adrenocortical stress response. *Compr Physiol*. 2016;6(2):603–621.
- [21]. Belmaker RH, Agam G. Major depressive disorder. *N Engl J Med*. 2008;358(1):55–68.
- [22]. Miller AH, Raison CL. The role of inflammation in depression. *Nat Rev Immunol*. 2016;16(1):22–34.
- [23]. Troubat R, Barone P, Leman S, et al. Neuroinflammation and depression: a review. *Eur J Neurosci*. 2021;53(1):151–171.
- [24]. Salim S. Oxidative stress and psychological disorders. *Curr Neuropsychopharmacol*. 2014;12(2):140–147.
- [25]. Castrén E, Monteggia LM. Brain-derived neurotrophic factor signaling in depression and antidepressant action. *Biol Psychiatry*. 2021;90(2):128–136.
- [26]. Cryan JF, O’Riordan KJ, Cowan CSM, et al. The microbiota–gut–brain axis. *Physiol Rev*. 2019;99(4):1877–2013.
- [27]. Maes M, Galecki P, Chang YS, Berk M. A review on the oxidative and nitrosative stress pathways in major depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011;35(3):676–692.
- [28]. Panossian A, Seo EJ, Efferth T. Novel molecular mechanisms for the adaptogenic effects of herbal medicines. *Pharmacol Res*. 2021;168:105599.
- [29]. Panossian A, Seo EJ, Efferth T. Novel molecular mechanisms for the adaptogenic effects of herbal medicines. *Pharmacol Res*. 2021;168:105599.
- [30]. Herman JP, McKlveen JM, Ghosal S, et al. Regulation of the hypothalamic–pituitary–adrenocortical stress response. *Compr Physiol*. 2016;6(2):603–621.
- [31]. McEwen BS, Akil H. Revisiting the stress concept: implications for affective disorders. *J Neurosci*. 2020;40(1):12–21.
- [32]. Sarris J, McIntyre E, Camfield DA. Plant-based medicines for anxiety disorders, depression, and cognition. *CNS Drugs*. 2020;34:1–25.
- [33]. Nabavi SF, Sureda A, Daglia M, et al. Natural products and phytochemicals in neuroprotection: current perspectives and future directions. *Phytomedicine*. 2022;98:153931.
- [34]. Miller AH, Raison CL. The role of inflammation in depression. *Nat Rev Immunol*. 2016;16(1):22–34.
- [35]. Troubat R, Barone P, Leman S, et al. Neuroinflammation and depression: a review. *Eur J Neurosci*. 2021;53(1):151–171.
- [36]. Castrén E, Monteggia LM. Brain-derived neurotrophic factor signaling in depression and antidepressant action. *Biol Psychiatry*. 2021;90(2):128–136.
- [37]. Park H, Poo MM. Neurotrophin regulation of neural circuit development and function. *Nat Rev Neurosci*. 2013;14(1):7–23.
- [38]. Wallace DC. Mitochondria and neurodegenerative diseases. *Nat Rev Genet*. 2018;19(11):719–735.
- [39]. Sharma A, Cooper R, Bhattacharya K. Herbal adaptogens in neurological disorders: recent advances and future opportunities. *Biomed Pharmacother*. 2023;165:115230.
- [40]. Panossian AG, Wikman G. Effects of adaptogens on the central nervous system and the molecular mechanisms associated with their stress-protective activity. *Pharmaceuticals (Basel)*. 2010;3(1):188–224.
- [41]. Lopresti AL, Smith SJ, Malvi H, Kodgule R. An investigation into the stress-relieving and

-
- pharmacological actions of *Withaniasomnifera* (Ashwagandha): a systematic review. *Medicine (Baltimore)*. 2019;98(37):e17186.
- [42]. Amsterdam JD, Panossian AG. *Rhodiola rosea* L. as a putative botanical antidepressant. *Phytomedicine*. 2016;23(7):770–783.
- [43]. Gray NE, Alcazar Magana A, Lak P, et al. Centella asiatica: phytochemistry and mechanisms underlying its cognitive-enhancing and neuroprotective effects. *Molecules*. 2018;23(2):383.
- [44]. Mukherjee PK, Kumar V, Kumar NS, Heinrich M. The Ayurvedic medicine *Clitoria ternatea*: from traditional use to scientific validation. *J Ethnopharmacol*. 2008;120(3):291–301.
- [45]. Kaur R, Sharma A, Kumar S, et al. Phytochemical and pharmacological potential of *Dioscorea wallichii*: a review. *J Ethnopharmacol*. 2023;314:116612.
- [46]. Prasad K, Singh R, Verma P, et al. Phytochemistry and pharmacological activities of *Ipomoea cairica*: an updated review. *Biomed Pharmacother*. 2022;152:113232.
- [47]. Sharma P, Gupta N, Singh A, et al. Pharmacological potential of *Merremiadissecta*: phytochemistry and therapeutic perspectives. *Front Pharmacol*. 2024;15:1356248.
- [48]. Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. *Front Pharmacol*. 2014;4:177.
- [49]. Panossian AG. Understanding adaptogenic activity: specificity of the pharmacological action of adaptogens. *Ann N Y Acad Sci*. 2017;1401(1):49–64.
- [50]. Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. *Front Pharmacol*. 2014;4:177.
- [51]. Sarris J, McIntyre E, Camfield DA. Plant-based medicines for anxiety disorders, depression, and cognition. *CNS Drugs*. 2020;34:1–25.
- [52]. Hopkins AL. Network pharmacology: the next paradigm in drug discovery. *Nat Chem Biol*. 2008;4(11):682–690.