Acta Scientific NUTRITIONAL HEALTH (ISSN:2582-1423)

Volume 10 Issue 4 April 2026

Review Article

Role of Herbal Adaptogens in Stress Modulation Cognition and Mental Health

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DOI: 10.31080/ASNH.2026.10.1616

Received: February 16, 2026

Published: March 31, 2026

Abstract

Adaptogenic substances are natural substances that are derived out of plants and have traditionally been used to enhance the ability of the body to withstand stress and related conditions as well as improve cognitive and emotional well-being. Their mechanisms of action, especially how they interact with hypothalamic-pituitary adrenal (HPA) axis, have been subjected to increasing scientific interest, and clinical studies have provided evidence to support its effects on stress, cognition, anxiety and mood. The paper is a synthesis of current preclinical and clinical evidence on major herbal adaptogenics, *Withania somnifera* and *Rhodiola rosea*, *Bacopa monnieri* (Brahmi), and more, and will identify mechanisms, clinical efficacy, safety profile, and gaps in research.

Keywords: Adaptogens; Stress Regulation; HPA Axis; Stress Response Regulation; Anxiety

Introduction

Stress is a widespread phenomenon in the contemporary society and is more and more beginning to be seen as a leading cause of cognitive impairment and mental illnesses such as anxiety, depression, burnout, and neurodegenerative disorders. Stress of prolonged physical, psychological, or environmental origin is a cause disrupting physiological homeostasis, which is mostly done by dysregulation of the hypothalamic pituitary adrenal axis (HPA) and the sympathoadrenal axis, leading to over secretion of glucocorticoids, like cortisol. The sustained increase in stress hormones has negative impact on neuronal plasticity, hippocampal, memory consolidation, emotional regulation, and mental well-being in general [1-3].

Traditional pharmacological methods in the management of stress-related mental health problems such as antidepressants, anxiolytics and psychostimulants are at times symptomatic, but are linked to other inhibitions such as side effects, slowness in their effects, tolerance and dependence. The challenges have prompted increased interest in complementary and integrative styles of treatment that put a premium on safety, multitarget action and restoration of physiological balance [4]. In that regard, herbal adaptogenic substances have come into the limelight as potential natural compounds that can increase the stress resilience as well as promote cognitive and emotional wellbeing.

Adaptogenic concept Lazarev introduced the concept of adaptogens in 1947 and was later scientifically defined by

Brekhman and Dardymov in 1969. The adaptogens, according to their criteria, are natural substances, which (i) are not toxic at the usual therapeutic doses, (ii) increase non-specific resistance to a wide range of stress, and (iii) have a normalizing effect on physiological functions, regardless of the pathological orientation [5,6]. Adaptogens, unlike stimulants or sedatives, are known to regulate stress-response pathways, as well as induce homeostasis, and have long-term effects that do not disrupt normal physiological functions.

Adaptogens act at the molecular and neuroendocrine scales through effecting their actions by controlling the HPA axis, cortisol release and stress-activated signalling pathways. They have an effect on the main mediators of heat shock proteins (Hsp70), c-Jun N-terminal kinase (JNK), nitric oxide, and cellular stress adaptation transcription factors [7,8]. Besides that, adaptogens regulate central neurotransmitter networks, such as serotonergic, dopaminergic, noradrenergic, and γ-aminobutyric acid (GABAergic) networks that are important in cognition, mood, motivation and emotional maintenance [9].

Neuroinflammation and oxidative stress are currently known as among the most significant connections between the chronic stress and cognitive as well as psychiatric disorders. Overproduction of reactive oxygen species and pro-inflammatory cytokines causes neuronal damage, loss of synaptic plasticity and cognitive failure. Adaptogenic plants are good sources of bioactive phytochemicals including flavonoids, phenolic acids, alkaloids, terpenoids, and steroidal lactones which have strong antioxidant, anti-inflammatory, and neuroprotective properties. The properties have the effect of aiding in better neuron survival, better memory and learning, and shielding against the effects of neurotoxicity caused by stress [10,11].

Some of the herbal adaptogens undergo various researches on their positive impacts on stress, cognition, and mental well-being. Ashwagandha (*Withania somnifera*) has shown anxiolytic and an anti-stress effect in randomized controlled trials such as perceived stress scores, anxiety scale, and serum cortisol levels [12,13]. *Rhodiola rosea* is known to have tradable use against fatigue and improved mental performance in stressful situations, and clinical studies have found it useful in improving attention, cognitive flexibility, and mood [14]. *Bacopa monnieri* (Brahmi) has been known to have a memory-enhancing, neuroprotective, and antioxidant activity, especially concerning any situation that involves chronic stress and deterioration of the cognitive process [15,16].

Although adaptogenic herbal preparations are gaining clinical and scientific attention, the lack of standardization is still present because of variation in the sources of plants, extraction techniques, dosages, and research design. In addition, most of the literature deals with outcomes in isolation, e.g., stress or cognition, instead of determining the combined impact of adaptogens on stress, mental performance and mental health as interrelated. There is thus a need to synthesize traditional knowledge, mechanistic insights as well as clinical evidence to help comprehend the therapeutic potential of herbal adaptogens to neuropsychological health in a better way.

The current review will critically analyze herbal adaptogens in terms of their application in stress regulation, cognitive, and mental health. Combining pharmacological mechanisms, preclinical results, and clinical evidence, this review aims to allow a scientific explanation of the rational use of adaptogens, as well as to determine the new directions of research in this area of rapid growth.

Mechanisms of action

The action mechanisms of herbal adaptogen

Herbal adaptogens have multitarget systems of action, which improve adaptive capacity and physiological homeostasis by exerting a beneficial effect on stress, cognition and mental health. Contrary to standard single-target drugs, adaptogens regulate feedback neuroendocrine, molecular, and cellular processes that mediate the stress responses, neuronal activity, and mental resilience.

Hypothalamic pituitary adrenal (HPA) axis modulation

The control of hypothalamic-pituitary-adrenal (HPA) axis, the main stress response system, is one of the main adaptogenic mechanisms. The long-term effects of chronic stress are continued activation of the HPA axis and over secretion of glucocorticids, especially cortisol, which has negative effects on cognition, mood, neurogeneration of hippocampus and regulating emotions. The adaptogenic agents promote the normalization of the HPA axis activities by regulating corticotropin-releasing hormone (CRH),

adrenocorticotropic hormone (ACTH) and cortisol secretions and thus, avoiding hyper and hypo-cortisolism [17,18].

Clinical and experimental investigations have shown that adaptogens like *Withania somnifera* and *Rhodiola rosea* have a significant effect of decreasing levels of cortisol, caused by stress, which results in stress tolerance, decrease in anxiety, and clarity of mind. This two-way process helps homeostasis without inhibiting the normal responses to stress [19,21].

Neurotransmitter systems regulation

The adaptogenic agents affect various neurotransmitter systems that affect cognition, mood, motivation and emotional balance. These are serotonergic, dopaminergic, noradrenergic and γ-aminobutyric acid (GABAergic) pathways. Alterations in the regulation of these systems are directly associated with anxiety disorders, depression, and cognitive impairment and fatigue [22].

A number of the adaptogenic herbs increase the serotonergic and dopaminergic neurotransmission that is involved in better mood, motivation, and cognitive flexibility. As an illustration, *Rhodiola rosea* has been reported to suppress the activity of monoamine oxidase and alter serotonin and dopamine concentrations to contribute to its antidepressant and anti-fatigative effects [23]. GABA-mimetic activity is also found in *Withania somnifera*, and it adds to the anxiogenic and relaxing effect but not sedative effects of this plant [24].

Cellular stress response pathways activation

At the molecular level, the adaptogens stimulate universal cell stress response mechanisms that guard cells against physical, chemical, and biological infections. The major ones are heat shock proteins (Hsp70), stress-activated protein kinases (SAPKs), nitric oxide signaling, and cell defence and survival transcription factors [25].

Adaptogens are mild stress mimetic compounds that elicit a hormetic reaction that improves the resilience of cells. The consequence of this is enhanced energy metabolism, functioning of mitochondria and resistance to stress induced cellular damage. Panossian and colleagues have shown that adaptogens control the expression of the genes related to the protection of stress, aging and survival, enhancing the general adaptability to stress [26].

Antioxidant and anti-inflammatory effects

Oxidative stress and chronic low-grade inflammation are the main factors of cognitive deterioration, neurodegeneration, and mental illness. The effects of prolonged stress are the rise of reactive oxygen species (ROS) and pro-inflammatory cytokines, which cause neuronal degeneration and loss of synaptic plasticity. Bioactive phytochemicals that are rich in adaptogenic plants include flavonoids, phenolic acids, terpenoids and alkaloids with high antioxidant and anti-inflammatory properties [27].

Adaptogens may protect the neuronal structures as well as aid in cognitive and emotional well-being by removing free radicals and decreasing the levels of endogenous antioxidant enzymes and inflammatory agents (e.g., TNF- 6). An example of such is the bacopa monnieri which has shown a great antioxidant effect in the brain leading to better memory and learning during stressful conditions [28].

Neuroprotection and cognitive enhancement

The adaptogens play a role in neuroprotection, maintaining neurons, promoting plasticity of synapses, and neurogenesis especially in the hippocampus- a brain area that is more sensitive to stress. Those effects go through better mitochondrial functioning, less excitotoxicity, and neurotrophic factor modulation including the brain-derived neurotrophic factor (BDNF) [29].

Better cerebral blood flow, better cholinergic transmission, and defense against stress-induced neuronal apoptosis combine to increase attention, learning, memory, and executive functions. The cognitive-enhancing properties of such adaptogens as Bacopa monnieri and Panax ginseng in healthy and stressed individuals are explained by these mechanisms [30,31].

Immunomodulatory action and stress resilience

Chronic stress down-regulates immune activity and induces neuroimmune dysregulation that is also gaining more and more implication in mood and cognitive disorders. Adaptogens are immunomodulators which do not stimulate or suppress immunity in a random manner but rather regulate immune responses. This leads to better stress-resistance, less fatigue and better mental and physical functioning generally [32].

Certain single herbal adaptogens

Panaxa ethiopica (Ashwagandha)

Ashwagandha, or *Withania somnifera* (L.), is one of the most popular adaptogenic herbs in Ayurveda that is used to strengthen stress-resistance, well-being, and improve mental health. Ashwagandha, as an adaptogen, increases the non-specific response to physical, psychological and environmental stresses besides re-establishing a physiological balance. The adaptogenic effect of it is mainly related to withanolides, steroidal lactones that affect the hypothalamic-pituitary-adrenal (HPA) axis and inhibit cortisol secretion under stress. Reported clinical research has shown that there were major decreases in perceived stress, anxiety levels, and serum levels of cortisol after taking Ashwagandha supplement. Anxiolytic and neuroprotective effects of the herb are also demonstrated through the modulation of the GABAergic neurotransmission and the decrease of the oxidative stress and neuroinflammation. Moreover, Ashwagandha was reported to enhance cognitive abilities, sleep patterns and moods of stressful people. Due to its multitarget mechanism of action and good safety profile, *Withania somnifera* is progressively emerging as a useful natural adaptogen to stress management and support of mental health [33–36].

Rhodiola rosea

Rhodiola rosea L. is a famous adaptive herb that has been used long before in order to boost the physical and mental stamina during stress. It enhances non-specific response to stress through HPA axis control and the regulation of secretion of cortisol to stress. Its neuroprotective, anti-fatigue, and mood-enhancing effects are due to the major bioactive constituents, i.e. rosavins and salidroside. Clinical trials have shown that *R. rosea* enhances attention, cognitive functioning and mental fatigue as well as alleviating stress and mild depression symptoms. These effects are partially achieved by the mediation of the effects of monoaminergic neurotransmitters, including serotonin and dopamine, antioxidant and anti-inflammatory processes. *Rhodiola rosea* employs a multitarget effect, which is an aspect that adds to its positive safety profile, and is extensively utilized as a natural adaptogen in stress management and cognitive support [37,39].

Bacopa monnieri (Brahmi)

Bacopa monnieri (L.) Wettst., also referred to as Brahmi, is a well-known Ayurvedic herb that is widely known to possess adaptogenic and nootropic elements. It increases the ability of the body to resist stress besides increasing cognitive ability and mental performance. It has been proposed that adaptogenic action of *B. monnieri* is primarily due to bacosides, which mediate the cholinergic transmission, decreasing the stress-induced cortisol levels, and neuroprotecting by antioxidant and anti-inflammatory effects. The clinical research has shown enhancement of memory, learning, attention, and decrease of anxiety after use of standardized Bacopa extracts. Also, *B. monnieri* enhances neuronal plasticity and prevents cognitive impairment caused by stress. Because of its multitarget and positive safety profile, *Bacopa monnieri* is regarded as a promising natural adaptogen to use in cognitive and mental health [40,42].

Ocimum sanctum L

Ocimum sanctum L. is an adored medicinal plant in the traditional Indian medicine and has adaptogenic, anti-stress, and neuroprotective effects. It increases resistance to physical and psychological stress by balancing the hypothalamic-pituitary-adrenal (HPA) axis and controlling the amount of cortisol. Eugenol, ursolic acid and flavonoid are phytoconstituents that have antioxidant, anti-inflammatory, anxiolytic and cognitive-supporting properties. According to clinical and experimental studies, there could be advantages in terms of stress and anxiety reduction, as well as the increase in mental clarity and emotional balance [43,44].

Panax ginseng

Panax ginseng C.A. Meyer is an old established adaptogenic herb that has been traditionally utilized in improving physical endurance, cognitive abilities, and resistance to stress. These adaptogenic effects of ginseng are explained by the presence of ginsenosides that is able to regulate the hypothalamic-pituitary-adrenal (HPA) axis, regulate the release of the stress hormone, and enhance the neuronal energy metabolism. It has been clinically documented that it has led to mental performance improvement, attention, mood and less fatigue. Furthermore, the P. ginseng has neuroprotective, antioxidant, immunomodulatory effects, which, in addition, make it effective in managing stress and mental well-being [45,46].

Eleutherococcus senticosus

The classical adaptogenic herb is *Eleutherococcus senticosus* (Siberian ginseng) that is employed to boost resistance against

physical and psychological stress. Its adaptogenic properties can be explained by the effect of eleutherosides, stress-response-modulating substances, which decrease fatigue, improve cognitive and physical performances during stressful situations [47].

Centella asiatica

Centella asiatica (L.) Urban, also referred to as Gotu kola, is an adaptogenic herb that has been traditionally utilized to promote cognitive ability and resiliency to stress. It has triterpenoids, asiaticoside and madecassoside, which play a role in neuroprotective, antioxidant, anxiolytic, and cognitive-enhancing effects in the stressful conditions [48].

Adaptogenic effect of *Lepidium meyenii*

Lepidium meyenii Walp. (Maca) is an adaptogenic herb used in order to boost stress resilience, energy and brain activity. Its macamides and macaenes play the role of neuroprotective, antioxidant and mood modulating effects which are important in supporting cognitive performance and stress resistance [49,50].

Conclusion

Adaptogens found in herbs (*Withania somnifera*, *Rhodiola rosea* and *Bacopa monnieri*) show good effects on stress control, cognition and mood. They are clinically supported as complementary interventions in the management of stress-related cognitive and emotional wellbeing, but further clinical studies, with larger, rigorously designed studies, are necessary to bring therapeutic recommendations into solid ground. Their multi-target processes are consistent with the neurobiology intricacy of stress and cognition regulation, and they are expected to be useful in integrative mental health interventions.

Funding Sources

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest

The author(s) do not have any conflict of interest.

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