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Mechanistic basis of adaptogenic activity: selectivity of pharmacodynamic responses to adaptogens and structurally diverse phytochemicals

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ABSTRACT
Adaptogens are substances that help organisms handle stress by improving their overall ability to adapt and maintain balance. Traditional reductionist methodologies are too limited to capture the full complexity of biological processes and cannot fully show the many different factors involved at the physiological levels or to explain the biochemical mechanisms responsible for adaptogenic effects. It can be said that the effects of adaptogens cannot be fully understood using traditional drug models that look at only one target. Instead, network pharmacology and systems biology give a better and more accurate way to explain how they work. These approaches make it possible to understand adaptogens more broadly by showing how they act on connected molecular targets and signalling pathways that help the body maintain homeostasis. Research has identified shared molecular networks among adaptogens that influence stress hormones and other key regulators of physiological stability. Their mechanisms are directly linked to stress-protective functions and improved adaptability. As a result, adaptogens have wide-ranging health benefits, including potential protection against chronic inflammation, cardiovascular disease, neurodegenerative conditions, metabolic disorders, cancer, and age-related ailments. In contemporary scientific and clinical contexts, adaptogens are widely used to help manage stress-related tiredness, cognitive dysfunction, mood disturbances, and a range of behavioural abnormalities. Given their inherently complex and multi-targeted pharmacodynamic profiles, researchers maintain that it is improbable for any single adaptogenic constituent to exert its effects through a solitary receptor. Instead, these bioactive molecules modulate a broad spectrum of mediators involved in the stress-response system, acting across multiple tiers of cellular signalling and intercellular communication to produce their overall therapeutic outcomes.

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1. INTRODUCTION:

Adaptogens work in a complex way and affect many targets, so it is unlikely that any single component acts through only one receptor. They influence multiple parts of the stress-response system and affect both cell signaling and communication between cells to produce their overall effects. Traditional drug models, which assume one receptor controls the action, do not fully explain how adaptogens work, because these compounds can also regulate receptor levels through other pathways (Brekhman, & Dardymov, 1968). Adaptogens act on a wide range of receptors, including corticosteroid, mineralocorticoid, progestin, estrogen, serotonin (5-HT), NMDA, (Wagner & Winterhoff, 1994; Panossian, Wikman & Wagner, 1999) nicotinic acetylcholine receptors, tyrosine kinases receptor, and G protein–coupled receptors. Understanding their effects requires looking

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Table 1. Plants cited in the literature with adaptogenic properties

Ajuga turkestanica (Regel) Briq.	Rostellularia diffusa (Willd.) Nees.
Emblica officinalis Gaetrn	Hippophae rhamnoides L.
Piper longum L.	Lepidium peruvianum/Lepidium meyenii Walp.
Alstonia scholaris (L.) R. Br.	Ligusticum striatum DC.
Eucommia ulmoides Oliv.	Melilotus officinalis (L.) Pall.
Potentilla alba L.	Morus alba L.
Anacyclus pyrethrum (L.) Lag.	Mucuna pruriens (L.) DC.
Evolvulus alsinoides (L.) L.	Ocimum sanctum L.
Ptychopetalum olacoides Benth.	Panax ginseng C.A.Mey.
Andrographis paniculata (Burm.f.)	Panax pseudoginseng Wall.
Firmiana simplex (L.)W.Wight	Paullinia cupana Kunth
Rhaponticum carthamoides (Willd.) Iljin	Piper longum L.
Aralia mandshurica Rupr. & Maxim	Potentilla alba L.
Gentiana pedicellata (D.Don)Wall	Ptychopetalum olacoides Benth.
Rhodiola heterodonta (Hook. f. & Thomson) Boriss.	Rhodiola heterodonta (Hook. f. & Thomson) Boriss
Argyreia nervosa (Burm. f.) Bojer	Rhodiola rosea L.
Glycyrrhiza glabra L.	Salvia miltiorrhiza Bunge
Rhodiola rosea L.	Schisandra chinensis
Argyreia speciosa (L. f.)	Scutellaria baicalensis Georgi
Heteropterys aphrodisiaca Machado	Sida cordifolia L.

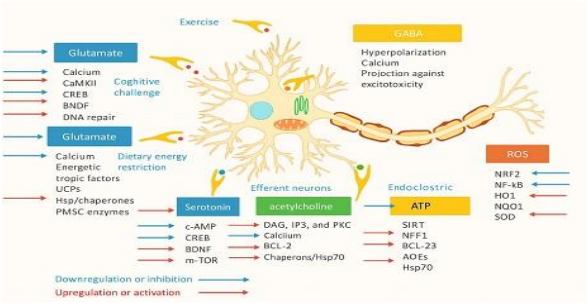

Figure 1. Adaptive stress response and effects of adaptogens. Adaptive cellular stress response signaling that mediates beneficial effects of environmental challenges (updated and adapted) (Stranahan & Mattson, 2012) and adaptogens on neuroplasticity and vulnerability to neurodegeneration. A glutamatergic hippocampal neuron integrates excitatory inputs arising from exercise, cognitively demanding activities, and dietary energy restriction, which together activate multiple adaptive stress response pathways that enhance neuronal survival and synaptic plasticity. These energetic and cognitive challenges trigger coordinated signaling through neurotransmitter receptors, redox-sensitive pathways, and inhibitory GABAergic circuits to induce a broad neuroprotective, pro-plasticity transcriptional program. At the complex interactions and feedback mechanisms in the neuroendocrine and immune systems that together shape the body's response.

1. The historical background of the adaptogen concept

An organism's resilience and survival under stress are determined by its adaptive capacity and the intrinsic thresholds that define tolerance to specific stressors. Activation of innate and adaptive defense mechanisms in response to stress involves a complex network of signaling mediators, predominantly within the neuroendocrine–immune axis, which collectively sustain allostasis in both simple and complex biological systems. Repeated exposure to mild or subthreshold stressors enhances cellular and systemic resilience, fostering an adaptive state that supports survival and long-term physiological stability. In 1936, Hans Selye pioneered the study of physiological adaptation to repeated subthreshold stressors through a series of experiments in rats. The stressors included exposure to cold, hypoxia, physical exertion, adrenaline, and morphine. The animals displayed a range of nonspecific physiological responses, including thymic atrophy, adrenal hypertrophy, gastric ulceration, and elevated secretion of cortisol and catecholamines. Selye collectively described these stress-induced changes as the general adaptation syndrome (GAS), establishing a foundational concept in stress biology (Selye, 1976; Selye, 1938). The General Adaptation Syndrome (GAS) has three stages. The first stage, the alarm reaction, happens when the body first detects a stressor, causing noticeable symptoms (Brekhman, & Dardymov, 1968; Stranahan, & Mattson, 2012; Panossian, Gabrielian & Wagner, 1999). The second stage, resistance, occurs as the body adapts, and the initial symptoms often decrease. The third stage, exhaustion, happens when the body can no longer cope with the stress, leading to the return of symptoms and, if stress continues, possible severe damage or death. In the 1950s and 1960s, Lazarev and Brekhman suggested that certain compounds and herbal extracts, called adaptogens, could help the body resist stress longer and reduce the severity of the alarm stage (Brekhman, & Dardymov, 1968; Lazarev, 1958; Lazarev, Ljublina, & Rozin, 1959; Amsterdam, & Panossian, 2016).

The adaptogens were defined as nontoxic compounds with polyvalent mechanisms of action and pharmacological effects related to adaptability and surviva (Brekhman, & Dardymov, 1968; Lazarev, 1958; Amsterdam, & Panossian, 2016). The adaptive stress reaction is a well-kept physiological mechanism detected across multiple regulatory systems, ranging from the cellular level to the total organism. At the cellular and molecular levels, both intracellular and extracellular signaling pathways are triggered during

Journal of Molecular Science
Volume 35 Issue 4, Year of Publication 2025, Page 1668-1673
DoI-10.004687/1000-9035.2025.217

the alarm phase, leading to the upregulation of antiapoptotic proteins, antioxidant enzymes, and neuropeptides (Stranahan, & Mattson, 2012).

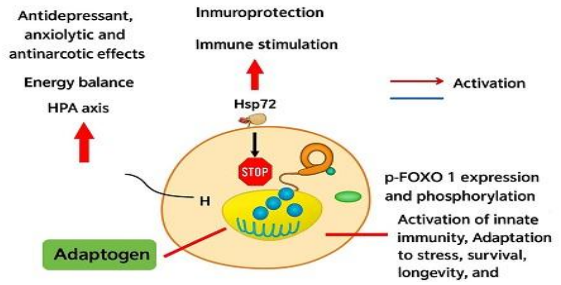

Figure 2. Hypothetical mechanism of action of adaptogens on the stress system at a cellular level. Adaptogens induce the expression and secretion of neuropeptide Y (NPY) and heat shock protein 72 (HSP72) through an HSF1-dependent pathway that involves HSF1 trimerization and nuclear translocation. NPY upregulation functions upstream of HSP72 and other stress mediators, such that HSP72 release is contingent on NPY signaling and contributes to the broader adaptogenic stress response. NPY plays a key role in modulating hypothalamic–pituitary–adrenal (HPA) axis activity, energy homeostasis, and HSP 72 secretion, thereby supporting neuroprotection and innate immune function. HSP72, once induced, negatively regulates FOXO transcription factors, a mechanism implicated in stress adaptation and longevity. Through these interconnected pathways, adaptogens exert antifatigue effects, enhance attention, and improve cognitive performance. In human neuroglial cells, activation of NPY by adaptogens triggers HSP72 expression, supporting neuronal homeostasis. The adaptogen-evoked stimulation and systemic release of NPY and HSP72 represent an innate defense reaction to mild stressors, increasing stress tolerance and promoting systemic stress-protective effects across the central nervous, sympathetic, endocrine, immune, cardiovascular, and gastrointestinal systems. Both NPY and HSP72 are critically involved in stress regulation, aging processes, and the pathogenesis of age-related disorders. Adaptogens are uniquely recognized for their ability to function as eustressors, serving as mild stress mimetics or “stress vaccines” that induce adaptive, stress-protective physiological responses (Panossian, Wikman & Wagner, 1999; Panossian, Gabrielian & Wagner, 1999; Wiegant, Limandjaja, & de Poot, 2008).

For instance, Figure 2 demonstrates the mild stressmimetic activity of diglucosyl cucurbitacin R (DCR), as evidenced by measurements of corticosterone secretion from isolated adrenocortical cells and circulating corticosterone concentrations in rats. Administration of DCR resulted in a reduction of corticosterone release in response to restraint stress in vivo and to ACTG stimulation in vitro Panossian, Wikman & Wagner,1999; Panossian, Gabrielian & Wagner,1999). A vaccination-like effect of the adaptogen in protecting against subsequent stress is clearly demonstrated by these experiments Panossian, Wikman & Wagner, 1999; Panossian, Gabrielian & Wagner, 1999; Wiegant, Limandjaja, & de Poot, 2008). A state of nonspecific resistance (SNSR) can be developed either through gradual stress conditioning or through the use of adaptogens, which act as mild stress mimetics. Regular administration of adaptogens produces a stress-protective, adaptogenic response similar to that induced by repeated exercise, leading to sustained SNSR along with enhanced stamina and resilience (Viru, 1981; Hovhannisyan, Nylander, & Panossian, 2015). The process of adaptation to stress is fundamental to the hormetic response, which manifests as a biphasic dose–response: low-level exposure to a stressor stimulates beneficial effects, while higher levels induce inhibition or toxicity (Mattson, M.P, 2008; Calabrese, Bachmann, & Bailer, 2007).

2. Pharmacodynamics and underlying mechanisms of action of adaptogens

The pharmacological efficacy of adaptogens and their stress-protective properties are typically evaluated by assessing cognitive function and physical endurance under stress conditions (Wagner, & Winterhoff, 1994; Panossian, 2003; Panossian, & Wagner, 2005). In pharmacological research, the use of validated and specific biomarkers related to pharmacological activity is widely accepted as a standard approach Panossian, (Hambardzumyan, & Hovhanissyan , 2007; Asea, Kaur & Panossian, 2013).

3. Which downstream molecular effectors mediate the pharmacological actions of adaptogens, and what are the principal cellular and systemic targets through which these agents exert their stress protective effects?

Numerous human and animal studies indicate that adaptogenic plant extracts, such as Rhodiola, Eleutherococcus, Schisandra, ginseng, Bryonia, Withania, and others, exert their effects by modulating key mediators of the adaptive stress response, including cortisol, neuropeptide Y (NPY), nitric oxide, stress-activated protein kinases, heat shock proteins (HSP70 and HSP25), and the FOXO (DAF-16) transcription factor. These molecules play crucial roles in mediating the stress-protective and adaptogenic actions of these plant extracts (Wiegant, Limandjaja, & de Poot, 2008; Wiegant, Surinova & Ytsma, 2009; Panossian, Hambardzumyan, & Hovhanissyan, 2007; Asea, Kaur, & Panossian, 2013; Panossian, & Wikman, 2014; Panossian, Wikman, & Kaur, 2009; Panossian, Wikman, & Kaur; Rattan, Kryzch, & Schnebert, 2013).

These mediators collectively regulate the mechanisms

Journal of Molecular Science
Volume 35 Issue 4, Year of Publication 2025, Page 1668-1673
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underlying stress adaptation, including processes associated with aging and pathological conditions, though their individual contributions remain difficult to quantify with certainty. Numerous reviews have discussed the potential mechanisms of action of adaptogens, drawing upon findings from in vitro and ex vivo studies conducted on both human and animal cell models (Panossian, Wikman & Wagner, 1999; Panossian, 2003; Panossian, & Wikman, 2009; Panossian, &Wikman, 2010; Panossian, & Wagner, 2011; Panossian, 2013; Panossian, & Gerbarg, 2016; Lavretsky, Sajatovic, & Reynolds).

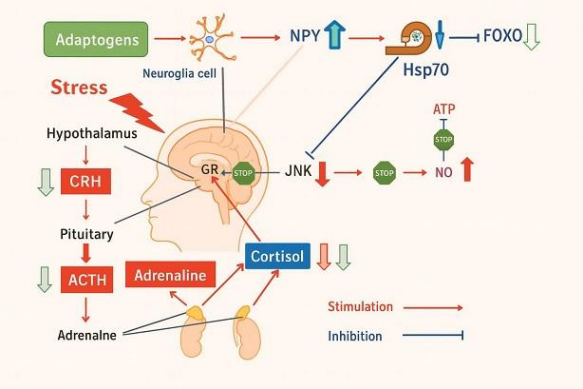

Figure 3. Hypothetical mechanism of action of adaptogens on the stress system in depression.

Acute stress activates the hypothalamic–pituitary–adrenal (HPA) axis, leading to corticotropin-releasing hormone (CRH) secretion from the hypothalamus, adrenocorticotropic hormone (ACTH) release from the pituitary, and subsequent adrenal secretion of glucocorticoids and neuropeptide Y (NPY) to facilitate adaptation to the stressor. Cortisol released from the adrenal cortex then engages glucocorticoid receptors (GR) in the brain, establishing a negative-feedback loop that terminates further stress-hormone release and returns circulating cortisol concentrations toward baseline. Under conditions of severe or prolonged stress, excessive production of reactive oxygen and nitrogen species, including nitric oxide, can occur and is associated with inhibition of ATP synthesis and vulnerability to stress-related disorders such as depression. Stress-activated c-Jun N-terminal kinase (JNK) signaling can inhibit GR function, thereby disrupting feedback inhibition and resulting in persistently elevated cortisol levels in depressive states, which correlate with cognitive impairment, reduced concentration, fatigue, and related symptoms. Heat shock protein 70 (HSP70) and its regulator HSF1 are considered important targets for anti-aging treatments. However, most chemical inducers of HSP70 are toxic, making them unsafe for vulnerable groups like the elderly. In contrast, plant-based adaptogens are generally safe even at high doses (up to 3000 mg/kg in rats) and during long-term use. Adaptogens such as Rhodiola, Schisandra, and Eleutherococcus, as well as the combination ADAPT-232 containing salidroside, have been shown to increase HSF1 and HSP72 in neuroglial cells, boost HSP72 secretion, and enhance HSP70 levels in living organisms (Perez, Moinuddin,& Ulain , 2012; Panossian, & Gerbarg, 2016; Chiu,& Ko, 2004; Lee, Kuo, & Liou, 2006; Li, L, Zhang, & Zhou,2014; Herna´ndez-Santana, Pe´rez-Lo´pez,& Zubeldia). Chronic administration of Rhodiola rosea has been shown to markedly reduce swimming-induced fatigue by enhancing glycogen reserves, stimulating energy production through lipogenic enzyme activity, and strengthening cellular defense systems, including those involving HSP70 (Lee, Kuo,& Liou, 2006). Extracts from R. rosea roots significantly elevate HSP70 mRNA expression and confer protection to skeletal muscle cells against chemically induced oxidative stress. 42 Similarly, pretreatment with schizandrin B elicits a time-dependent upregulation of HSP25 and HSP70 expression in rat cardiac tissue, providing protection against myocardial ischemia–reperfusion injury Chiu, & Ko, 2004; Li, L, Zhang, & Zhou, 2014).

4. What are the chemical scaffolds of the key bioactive constituents in adaptogenic plant extracts, and how do their structural features underpin their biological activities and adaptogenic mechanisms?

Currently, systematic studies exploring the structure–function relationships of purified adaptogens and their interactions with specific molecular targets are limited. However, the primary active constituents of plant adaptogens can be broadly classified into two major chemical groups:

4.1 Terpenoids with a tetracyclic backbone, such as ginsenosides, sitoindosides, cucurbitacins, and withanolides.

4.2 Aromatic compounds related to catecholamines or tyrosine, including lignans (e.g., eleutheroside E from *Eleutherococcus senticosus* and schizandrin B from *Schisandra chinensis*), phenylpropane derivatives (e.g., syringin from *E. senticosus* and rosavin from *Rhodiola rosea*), and phenylethane derivatives (e.g., salidroside from *R. rosea*).

These chemical classes provide the foundation for the diverse biological activities attributed to adaptogenic plants. Evidence suggests that ginsenosides can directly interact with corticosteroid and estrogen receptors. Adaptogens enriched in tetracyclic or pentacyclic terpenoids—such as ginseng, *Withania*, *Rhaponticum*, and *Bryonia*—appear to exert their effects predominantly through modulation of the hypothalamic–pituitary–adrenal (HPA) axis. Conversely, adaptogens primarily composed of phenolic compounds—including phenylpropanoids, phenylethanoids, and lignan dimers, as found in

Journal of Molecular Science
Volume 35 Issue 4, Year of Publication 2025, Page 1668-1673
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Rhodiola and *Schisandra* species—are proposed to act via the efferent sympathoadrenal system (SAS), reflecting distinct mechanisms aligned with their chemical composition. Neuropeptide Y (NPY) contains five tyrosine residues, each bearing a p-hydroxylmethylene group similar to those present in tyrosol and salidroside. Tyrosine moieties are known to play a key role in receptor binding in the brain and in mediating the biological activity of NPY. It has been hypothesized that the p-hydroxylmethylene group in NPY, as well as the p-hydroxyethylene groups in tyrosol and salidroside, may compete for the same receptor binding sites, potentially modulating downstream signaling outcomes. The efferent sympathoadrenal system (SAS) and the hypothalamic–pituitary–adrenal (HPA) axis are closely interconnected both anatomically and functionally, enabling reciprocal regulation during stress responses at multiple levels. For example, catecholamines released by the SAS can activate the HPA axis via corticotropin-releasing hormone (CRH), while HPA axis hormones can, in turn, influence SAS activity under stress. The SAS primarily provides a rapid response to acute stressors, but both sympathetic and parasympathetic branches of the autonomic nervous system also release neuropeptides, ATP, and nitric oxide, forming a complex regulatory network that fine-tunes the body's overall stress response. Some plants, like Eleutherococcus senticosus, contain both terpenoid and aromatic (phenolic) compounds, which give them complex effects on the stress response.

5. Do phytochemicals have explicit pharmacodynamics effects?

Plant-derived drugs used in clinical practice often lack strict specificity, interacting with multiple protein targets and producing diverse, dose-dependent pharmacological and toxic effects. Alkaloids such as morphine, atropine, pilocarpine, ephedrine, reserpine, lobeline, strychnine, berberine, and vinblastine exemplify this, affecting several biological systems through multiple receptors and enzymes. Likewise, medicinal plants like cannabis have traditionally been employed to treat a wide range of conditions—including pain, neurological disorders, autoimmune diseases, metabolic imbalances, and inflammation—reflecting their multifaceted activity. Even isolated plant compounds, including curcumin, plumbagin, and salidroside, display multitarget and pleiotropic effects. Reviews of medicinal plants consistently highlight their influence on immune, endocrine, and nervous system functions, in line with the protective roles of biologically active secondary metabolites, particularly terpenoids and phenolics, in plants. This polypharmacology allows plant-derived agents to modulate complex disease networks, potentially enhancing therapeutic efficacy and safety compared with single-target drugs, while also posing challenges related to adverse effects and regulatory approval. Cortisol, produced by the adrenal cortex, functions as a primary stress hormone that limits overactivation and inflammation through negative feedback on the HPA axis via hypothalamic glucocorticoid receptors. Elevated cortisol levels are commonly observed in conditions such as clinical depression and psychological stress, often triggered by hypoglycemia, illness, trauma, surgery, fear, pain, physical exertion, or extreme environmental factors. Persistent activation of the HPA axis and the sympathoadrenal system (SAS) occurs in disorders including melancholic depression, panic anxiety, obsessive–compulsive disorder, anorexia nervosa, chronic alcoholism, withdrawal syndromes, excessive exercise, and malnutrition. Adaptogens have been reported to restore elevated cortisol and corticosterone levels in humans and animals, likely through direct interactions with glucocorticoid receptors (GRs). For instance, ginsenoside Rg1 acts as a partial GR agonist by directly binding to its ligand-binding domain, while ginsenoside Rb1 functions as a ligand for the estrogen receptor (ER), particularly the β isoform, indicating potential benefits in stress-related conditions. Other mediators affected by adaptogens—including nitric oxide, JNK, SAPK, HSP70, HSP25, and FOXO (DAF-16)—play key roles in controlling chronic inflammation, which underlies many age-associated diseases such as sarcopenia, Alzheimer's disease, atherosclerosis, cardiovascular disorders, hypertension, osteoarthritis, type 2 diabetes, and obesity. These findings emphasize the complex, multi-targeted mechanisms through which adaptogens exert their protective effects. However, additional randomized clinical trials using standardized botanical extracts are required to confirm their efficacy and safety for specific clinical applications.

6. CONCLUSIONS:

Adaptogens are regulators of the stress response that nonspecifically enhance an organism's resilience to diverse stressors, hence facilitating adaptation and survival. Adaptation to environmental challenges and aging are multifaceted processes that entail several mechanisms and interactions. Numerous molecular networks are engaged in coordinating both intracellular and extracellular stress signals. Several targets which involves the metabolic modulation of homeostasis by adaptogens at both cellular and systemic levels. When trying to comprehend the mechanism of action of adaptogens, the traditional reductionist approach, which assumes a particular receptor/drug interaction, is inadequate and inappropriate. When trying to figure out the mechanism of action of adaptogens, the conventional reductionist strategy which implies a particular receptor/drug interaction, is inadequate and inappropriate (Amsterdam, & Panossian, 2016; Panossian, & Wikman, 2009; Panossian, 2013).

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7. Competing interests:

The authors declare no competing interests.

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