

Effect of Adaptogens on the Central Nervous System and The Molecular Mechanism Associated with Their Stress (Protective Activity)

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ABSTRACT

Adaptogens are natural compounds derived mainly from plants and fungi that enhance resilience against stress, fatigue, and anxiety by modulating the hypothalamic–pituitary–adrenal (HPA) axis and related neuroendocrine pathways. They protect the central nervous system (CNS) from the adverse effects of chronic stress through mechanisms involving regulation of cortisol, heat shock proteins, neurotransmitters, and intracellular signaling pathways such as PI3K/Akt and ERK1/2. Adaptogens like *Rhodiola rosea*, *Withania somnifera*, and *Eleutherococcus senticosus* demonstrate neuroprotective, anti-fatigue, antidepressant, and anxiolytic properties by balancing stress hormones, enhancing mitochondrial energy metabolism, and reducing neuroinflammation and oxidative stress. Growing evidence also highlights their role in cognitive enhancement and neuroplasticity, while market expansion and AI-driven research are driving innovation in adaptogen discovery, formulation, and quality control. However, challenges remain due to limited large-scale clinical evidence, safety concerns, regulatory inconsistencies and potential herb–drug interactions. Overall, adaptogens represent a promising but evolving domain bridging traditional medicine and modern pharmacological science.

Keywords: Adaptogens; Stress; Metabolic Syndrome; Biomarkers; HPA Axis; Insulin Resistance; Oxidative Stress

INTRODUCTION

Adaptogens are a class of natural compounds derived primarily from plants and fungi that enhance the body's resilience to stress, fatigue, and anxiety, primarily by modulating the hypothalamic–pituitary–adrenal (HPA) axis and other neuroendocrine pathways. First conceptualized in the mid-20th century, adaptogens have since gained significant attention due to their potential neuroprotective, anti-fatigue, antidepressant, and anxiolytic effects, particularly under conditions of chronic stress and central nervous system (CNS) dysfunction. [1] The central nervous system is particularly susceptible to the detrimental effects of chronic stress, which can lead to neuroinflammation, oxidative stress, and neurotransmitter imbalances. Adaptogens such as

Rhodiola rosea, *Withania somnifera* (Ashwagandha), and *Eleuthero coccus senticosus* exert stress-protective effects by influencing molecular targets involved in stress response, including heat shock proteins (Hsp70), cAMP-response element-binding protein (CREB), and key mediators of the HPA axis such as corticotropin-releasing hormone (CRH) and cortisol. [2] On a molecular level, adaptogens have been shown to regulate intracellular signaling pathways such as PI3K/Akt, JNK, and ERK1/2, which are involved in cellular adaptation, survival, and neuroplasticity. They also modulate the expression of neuropeptides, reduce cortisol release, and enhance mitochondrial function and ATP production, which are critical for maintaining CNS homeostasis during stress. [3]

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- **cAMP-response element-binding protein (CREB):** Supports neuroplasticity, memory and cell survival [5]

3. Impact on Neurotransmitters and Mood

Adaptogens modulate neurotransmitters such as:

- **Dopamine, serotonin, and norepinephrine,** leading to improved mood and cognition.
- *Withania somnifera* increases GABAergic activity, which has an anxiolytic effect.
- *Rhodiola rosea* influences the monoamine system by inhibiting monoamine oxidase and enhancing serotonin levels [6]

4. Antioxidant and Anti-inflammatory Effects

Chronic stress induces oxidative stress and inflammation, which can damage neurons. Adaptogens:

- Reduce reactive oxygen species (ROS).
- Upregulate antioxidant enzymes like superoxide dismutase (SOD), catalase, and glutathione peroxidase.
- Downregulate pro-inflammatory cytokines (e.g., IL-6, TNF- α) [7]

5. Mitochondrial Protection and Energy Metabolism

Adaptogens help preserve mitochondrial function and increase **ATP production**, thus improving cellular energy under stress conditions. They enhance:

- Mitochondrial membrane potential
- Oxidative phosphorylation efficiency
- Fatigue resistance in neurons and muscle cells [8]

Effects of Adaptogens on the Central Nervous System:

1. Regulating Your Stress Response (HPA Axis & Cortisol)

Adaptogens interact with the HPA axis, the system that controls stress hormone (like cortisol) release. They can help moderate and normalize cortisol levels,

reducing feelings of stress, improving mood, and enhancing focus [9]

2. Boosting Brain Protection & Repair

They can activate:

- **Antioxidants** that guard brain cells against damage
- **Anti-inflammatory pathways** that reduce harmful swelling in the brain
- **Neurotrophic factors** like BDNF, which support brain cell growth and repair [10]

3. Enhancing Mental Performance

Adaptogens have shown:

- Anti-fatigue and energizing effects
- Improved mental endurance and concentration
- Reduced anxiety and depression-like symptoms in animal and human studies [11]

4. Balancing Brain Chemicals (Neurotransmitters)

They influence key mood-related chemicals:

- Increase GABA (calming neurotransmitter)
 - Support serotonin (mood, sleep) and dopamine (focus, motivation)
- Some adaptogens may even support neuropeptide Y (NPY) a stress-reduction molecule [12]

5. Reducing Brain Inflammation (Neuroinflammation)

Studies highlight how adaptogens like; *ashwagandha*, *rhodiola*, *eleuthero* and *schisandra* can lower inflammation in the brain, potentially relieving symptoms like memory loss, anxiety, and impaired movement [13]

6. Balancing Stress Hormones (HPA Axis & Cortisol)

- Many adaptogens, like ashwagandha, rhodiola and holy basil, help regulate the HPA axis (your body's central stress response system) and reduce cortisol, the stress hormone. This may improve your mood and reduce anxiety.

For example, a human trial showed ashwagandha lowered cortisol by about 22–23% compared to placebo.

- One study with physicians on overnight shifts found that rhodiola improved mental fatigue, memory, concentration, and perception speed [14]

7. Mental Energy, Focus & Anti-Fatigue Effects

- Adaptogens like rhodiola and ginseng help your mind work better under stress—improving energy, clarity, and resistance to mental exhaustion.
- They also act at a cellular level controlling stress-related proteins and enzymes like Hsp70 and JNK1, which help your brain handle stress better [15]

8. Protecting Nerves & Supporting Long-Term Brain Health

- Some adaptogens are neuroprotective: they reduce neuron damage caused by oxidative stress or toxins, and may help prevent processes linked to neurodegeneration.
- Active compounds such as salidroside and tyrosol (from rhodiola) support cell survival, energy production, and healthy stress response. [16-17]

9. Balancing Brain Chemicals (Neurotransmitters)

- Adaptogens influence key brain chemicals boosting calming neurotransmitters like; GABA and mood-enhancers like serotonin and dopamine.
- Rhodiola specifically encourages serotonin and dopamine activity for better emotional balance [18-19]

HERBAL PLANTS AS ADAPTOGENS:

1) *Albizzia julibrissin* Durazz:

Commonly known as Persian silk tree or pink silk tree, belongs to the family Fabaceae (Leguminosae). The biological source of this plant includes the flowers, teas and bark extracts of the Persian silk tree, which have been traditionally utilized for their therapeutic benefits. Phytochemical studies have revealed that the plant is rich in triterpenoid saponins,

flavonoids or flavonol glycosides and lignans or lignan glycosides, which contribute to its diverse pharmacological properties. *Albizzia julibrissin* is widely recognized for its medicinal applications in the treatment of insomnia, irritability and anxiety, reflecting its traditional use as a natural sedative and mood stabilizer. In addition to its calming properties, the plant exhibits antioxidant, anti-inflammatory and antidepressant activities, which further enhance its therapeutic potential. These combined effects make *Albizzia julibrissin* an important herbal candidate for managing neuropsychological disorders and oxidative stress-related conditions [20].



Figure 2: *Albizzia julibrissin* Durazz

2) *Aralia elata* (Miq) Seem:

Aralia elata (Miq.) Seem, commonly known as the Japanese angelica tree, belongs to the family Araliaceae. It is a small tree or large shrub widely distributed in East Asia and valued for its medicinal properties. The roots, bark, leaves, young shoots, and fruits of *Aralia elata* are utilized in traditional medicine and pharmacological research. The plant is known to contain a variety of bioactive constituents, including triterpene saponins, flavonoids, phenolic acids or phenolic compounds, polysaccharides, and other glycosides, along with nutritional and inorganic components such as amino acids, proteins, and minerals. In traditional East Asian medicine, *Aralia elata* has been used to treat rheumatoid arthritis, hepatitis, diabetes, gastritis, and other inflammatory or metabolic disorders. Pharmacological studies have further validated its anti-inflammatory, antioxidant, hepatoprotective, cardioprotective, and antitumor effects, particularly from the root, bark, and leaf extracts. These multifaceted biological activities make *Aralia elata* a promising medicinal plant for

developing natural therapeutic agents against chronic diseases and oxidative stress-related disorders [21].



Figure 3: *Aralia elata*

3) *Aralia schmidtii*: (Sakhalin Spikenard)

Aralia schmidtii (commonly known as Sakhalin Spikenard) is a herbaceous perennial plant belonging to the family Araliaceae. It is closely related to *Aralia cordata* and is native to the Russian Far East, Sakhalin Island, and surrounding regions. The roots, shoots, and leaves of this plant are primarily used for medicinal purposes and have been employed in traditional herbal preparations. Phytochemical investigations have shown that *Aralia schmidtii* contains a diverse range of bioactive compounds, including triterpenoid saponins, flavonoids, phenolic acids, essential oils, volatile compounds, sterols, and polysaccharides. These constituents contribute to its pharmacological properties, which are similar to those of *Aralia cordata*. Traditionally, *Aralia schmidtii* has been valued for its anti-inflammatory and antioxidant effects, and various parts of the plant particularly the roots are used in herbal medicine for promoting general health and combating oxidative stress-related conditions. Its rich phytochemical profile and therapeutic potential make it a significant species within the Araliaceae family for further pharmacological exploration [22].



Figure 4: *Aralia schmidtii*

4) *Azadirachta indica*:

Azadirachta indica, commonly known as Neem, belongs to the family Meliaceae. It is a well-known medicinal plant extensively used in traditional systems of medicine due to its wide range of therapeutic properties. The biological sources include various dried parts of the plant such as leaves, seeds (seed oil), bark, roots, flowers, fruits, and gum. Phytochemical investigations have revealed that Neem contains several bioactive compounds, including azadirachtin, nimbin, gedunin, mahmoodin, flavonoids, and sterols, which are responsible for its diverse pharmacological activities. Neem is traditionally used for the treatment of skin diseases, ulcers, wounds, fevers, intestinal parasitic infections, eye disorders, and gum diseases. It exhibits multiple therapeutic effects such as antibacterial, antifungal, anti-inflammatory, antipyretic, antiulcer, immunomodulatory, and antitumor activities, making it one of the most versatile medicinal plants. In addition to its medicinal uses, Neem also finds applications in cosmetic and skincare formulations, where neem oil and leaf extracts are incorporated into lotions, soaps, and creams for their skin-cleansing and acne-treating properties. Owing to its broad-spectrum biological activities and safety profile, *Azadirachta indica* remains an important plant in both traditional and modern herbal medicine [23].



Figure 5: *Azadirachta indica*

5) *Zingiber officinale*:

Zingiber officinale Roscoe, commonly known as Ginger, belongs to the family Zingiberaceae. The biological source of this plant is the dried rhizome, which has been widely used in both traditional and modern medicine for its remarkable therapeutic properties. The rhizome contains several bioactive chemical constituents, including gingerols, shogaols,

zingerone, volatile oils, and flavonoids, which contribute to its diverse pharmacological effects. Ginger is renowned for its ability to reduce inflammation and oxidative stress, making it beneficial in managing conditions such as arthritis and other chronic inflammatory disorders. It also plays a vital role in stimulating digestion, providing relief from nausea, bloating, indigestion, and flatulence, thereby promoting gastrointestinal health. Additionally, Ginger acts as an adaptogen, enhancing the body's resistance to stress, fatigue, and mental exhaustion by regulating stress-related biochemical pathways. Due to its potent anti-inflammatory, antioxidant, digestive, and adaptogenic properties, *Zingiber officinale* continues to be a valuable natural remedy in both traditional herbal systems and modern therapeutic applications [24].



Figure 6: *Zingiber officinale*

6) Curcumin:

Curcumin, commonly known as Haldi, is a natural polyphenolic compound derived from the dried rhizomes of *Curcuma longa* L., a plant belonging to the family Zingiberaceae. It is the principal bioactive constituent responsible for the characteristic yellow color and therapeutic potential of turmeric. The rhizome of *Curcuma longa* contains various chemical constituents, including curcuminoids, volatile (essential) oils constituting about 2–5% of the rhizome, sugars, proteins, resins, starch, and minerals. Curcumin is well known for its anti-inflammatory, antioxidant, and immunomodulatory properties. It exerts its anti-inflammatory action primarily by inhibiting inflammatory mediators such as cyclooxygenase-2 (COX-2) and tumor necrosis factor-alpha (TNF- α). Therapeutically, curcumin is used in the management of arthritis, joint pain, and inflammatory bowel diseases, where it helps reduce pain and swelling. Moreover, it has been reported to modulate the hypothalamic–pituitary–adrenal (HPA)

axis, thereby lowering elevated cortisol levels and helping in the management of chronic stress, anxiety, and stress-related fatigue. Due to its wide range of biological activities and safety profile, curcumin remains one of the most extensively studied natural compounds in both traditional and modern medicine [25].



Figure 7: *Curcuma longa*

FUTURES PERSPECTIVE OF ADAPTOGENS:

Market Growth & Forecasts

- The global adaptogens market was valued at around USD 10.34 billion in 2023, and is projected to reach USD 16.32 billion by 2030, reflecting a compound annual growth rate (CAGR) of ~7% from 2024–2030.
- The Asia-Pacific region is forecasted to grow at an even higher CAGR of ~12%, driven by increasing adoption in countries like India and China, rooted in their traditional medicinal practices.
- In North America, the market is expanding rapidly with a projected CAGR of around 9.1% through 2033 [26-28]

Key Trends Shaping the Adaptogens Market [29]

1. Widening Applications & Product Innovation

- **Functional Foods & Beverages:** Adaptogens are increasingly blended into teas, energy drinks, snack bars, and “mushroom coffee” an expanding category in the functional drinks space.
- **Beauty & Personal Care:** Adaptogen-enriched skincare formulations are on the rise, touted for their anti-inflammatory and antioxidant properties.

- **Convenient Formats:** There's a growing move toward ready-to-drink beverages, gummies, sachets, and capsules to cater to modern, on-the-go consumers [30-31]

2. Personalization & Clean-Label Preferences

- Customized blends targeting specific wellness goals such as; stress relief, cognitive focus, or sleep support are gaining popularity.
- Clean-label, organic, and sustainably sourced ingredients are increasingly important to consumers, with brands emphasizing transparency in sourcing and packaging [32-33]

3. Technological and Marketing Advances

- Advances in extraction and encapsulation technologies are improving bioavailability, potency and convenient delivery of adaptogen compounds.
- The shift toward D2C (direct-to-consumer) and e-commerce channels accelerates growth by increasing product access and consumer engagement [34]

4. Opportunities Ahead

- **Scientific Research & Validation:** Continued investment in R&D and clinical studies may strengthen the credibility of adaptogens and support more evidence-based marketing.
- **Emerging Markets:** There's notable potential in markets like Latin America and the Middle East/Africa, where health awareness and disposable income are rising.
- **Innovative Partnerships:** Collaborations with wellness influencers, healthcare professionals, and local distributors could accelerate adoption [35]

5. Challenges to Navigate

- **Limited Scientific Evidence:** While traditional usage is extensive, modern clinical validation remains limited, which can curb trust and regulatory approvals.

- **Regulatory & Quality Issues:** Inconsistent regulations across regions can lead to varying product standards, mislabeling, and quality concerns.

- **Market Saturation:** As the landscape becomes crowded, new entrants may struggle to stand out in a sea of similar products, leading to price competition and consumer confusion.

- **Supply Chain Risks:** Dependence on specific geographic sources (e.g., ashwagandha, reishi) exposes the industry to environmental, geopolitical, and crop-related disruptions [36]

Role of AI in Adaptogens Research & Development:

1. AI-Powered Exploration of Traditional Texts & Reverse Pharmacology

AI facilitates the digitization and semantic exploration of ancient Ayurvedic and herbal medicine texts. Techniques like natural language processing (NLP) and optical character recognition (OCR) help convert Sanskrit and classical manuscripts into machine-readable formats, building ontological databases and knowledge graphs for drug discovery and reverse pharmacology. Likewise, similar AI-driven strategies are applied to Traditional Chinese Medicine (TCM) literature text-mining and knowledge graph approaches uncover pharmacological insights and enable syndrome classification and new therapeutic lead identification [37]

2. Rapid Drug Discovery & Virtual Screening of Bioactive Compounds

AI significantly accelerates the identification of adaptogenic compounds through:

- **Machine Learning (ML) and Deep Learning (DL)** algorithms that sift through large-scale chemical, pharmacology, and metabolomics datasets to predict compound efficacy and therapeutic potential [38]
- The **Insilico Medicine** platform, which creates novel chemical structures using generative AI (e.g., GANs, reinforcement learning),

exemplifying how deep learning aids bioactive discovery although not yet specific to adaptogens, the approach is directly translatable.

- In Indonesia's traditional medicine system (Jamu), AI leverages **pharmacophore modeling**, **molecular docking**, and ML-based ADMET predictions to systematically unearth promising bioactive herbal candidates [39]

3. Mechanistic Insights via Network Pharmacology & Graph AI

AI enhances understanding of adaptogenic mechanisms through:

- **Network pharmacology** models that elucidate multi-component, multi-target interactions in herbal formulas. These map how herbs work in synergy and affect biological pathways.
- **Graph Neural Networks (GNNs)** utilized in TCM research to quantitatively assess compatibility within multi-herb formulas and link traditional theory with modern biological targets [40]

4. Precision Formulation & Personalized Therapeutics

Advances in AI are enabling targeted adaptogen formulations:

- **AI-driven nutraceutical formulation** platforms analyse bioactive ingredient profiles and consumer data to optimize the timing, dosage, and combination of adaptogens like ashwagandha and rhodiola for sustained stress relief.
- Market reports indicate the rise of AI adaptogen blend formulation services, which offer brands the ability to design personalized supplement products particularly popular in North America, with growing adoption in Asia-Pacific [41]

5. Clinical Decision Support, Safety, and Pharmacovigilance

AI enhances safety and clinical efficacy through:

- **Clinical Decision Support Systems (CDSS)** that assist practitioners in diagnosis, herbal prescription, and monitoring herb drug interactions augmenting, not replacing, clinician judgment.
- **Adverse Drug Reaction (ADR) prediction** using AI models on clinical and public health data to proactively identify safety issues in Ayurvedic treatments [42]

6. Agriculture & Supply Chain Optimization

AI improves raw material quality and sustainability by:

- Monitoring and optimizing herb cultivation (soil, climate, disease, yield), ensuring high-quality adaptogenic crop production.
- Enhancing **quality control** via image recognition and spectral analysis (e.g., near-infrared spectroscopy), enabling rapid herb authentication and detecting adulteration.
- Ensuring **batch consistency** through ML models that track production variables, streamlining standardization in adaptogenic product manufacturing [43-44]

7. Quality Control & Safety Monitoring

AI tools ensure that adaptogen-based products meet high safety and quality standards.

- AI-based image analysis for plant authentication and contaminant detection.
- Monitors supply chain integrity for adulteration or mislabelling.
- Supports post-market surveillance using AI-driven pharmacovigilance systems. [45-46]

Safety and Limitations Of Adaptogens:

1. Scientific Validity & Regulatory Status

- The concept of "adaptogen" remains vague and not accepted in mainstream pharmacology. It's not a recognized term in the US or EU, and the FDA has issued multiple warning letters over unapproved marketing claims related to adaptogens.

- Many claims about their effectiveness are based on anecdotal evidence or small-scale studies. Research is often limited in scope or poorly controlled [47-48]

2. Common Side Effects & Contraindications

Adaptogens are generally well-tolerated, but side effects can vary:

- Digestive issues, such as nausea, diarrhea, abdominal discomfort, or dry mouth.
- Headaches, insomnia, or fatigue, depending on the herb for example, ginseng may cause insomnia or nervousness.
- Allergic reactions: mild (rash, itching) to severe (anaphylaxis) in rare cases [49]

Specific Herbs of Concern

- **Ashwagandha (Withania somnifera):** Mild side effects like sedation, gastrointestinal upset, headache, nausea; **rare cases of liver injury**, especially in people with preexisting liver issues; not advised during pregnancy or in hormone-sensitive conditions.
- **Ginseng (Panax ginseng/quinqefolius):** Can cause insomnia, digestive disturbance, headache, blood pressure fluctuations, mood changes, and rare gynecomastia; may interact with warfarin, sedatives, phenelzine, imatinib (hepatotoxicity) and lamotrigine.
- **Others:**

- **Rhodiola:** dizziness, dry mouth, gastrointestinal discomfort.
- **Eleuthero (Siberian ginseng):** elevated blood pressure, cramps, fatigue.
- Broad caution: People with autoimmune, hormonal, cardiovascular, liver, or kidney issues should be especially wary [50-51]

3. Drug Interactions & Clinical Risks

- Adaptogens can interfere with medications, e.g., warfarin, diabetes drugs, blood pressure meds, immunosuppressants, antidepressants, and thyroid treatments.
- A retrospective analysis highlighted serious interactions between adaptogens and antidepressants, including gastrointestinal bleeding, myalgia, serotonin-related effects, and others [52]

4. Long-Term Use & Psychological Considerations

- Long-term safety data are scarce. Prolonged use could alter hormonal balance or possibly blunt natural stress responses.
- Some users may develop psychological dependency on perceived benefits.
- Military sources warn that while adaptogens may offer short-term relief, they do not address underlying health issues and may include prohibited or contaminating ingredients. [53]

Table 2: Summary of Risks

Issue	Details
Regulatory status	Not officially recognized; many claims unapproved
Evidence reliability	Mostly small trials or anecdotal; more research needed
Common side effects	Digestive upset, headache, insomnia, allergies
Specific herb risks	Liver issues (ashwagandha), mood/hormone changes (ginseng), etc.
Drug interactions	Warfarin, antidepressants, immunosuppressants, etc.
Long-term & psychological	Hormone disruption, dependency, masks underlying issues
Product quality risks	Unregulated, contaminated, or contain banned substances

CONCLUSION:

Adaptogens represent a promising class of natural compounds with the potential to support the central nervous system (CNS) under stress, fatigue, and

anxiety by modulating the HPA axis, reducing oxidative stress, balancing neurotransmitters, and enhancing cellular resilience. While traditional use and emerging scientific studies highlight their neuroprotective, anti-inflammatory, and mood-

stabilizing effects, especially in herbs like Ashwagandha, Rhodiola, and Eleuthero, the field still faces significant limitations. These include vague definitions, limited clinical validation, inconsistent regulations, and potential safety concerns like herb-drug interactions and long-term hormonal effects. However, advancements in AI, personalized medicine, and sustainable cultivation practices are opening new frontiers in adaptogen research and product development. With proper scientific scrutiny and regulatory oversight, adaptogens could play a complementary role in stress management and holistic CNS support in the future.

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