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REVIEW ARTICLE

Plant-based Adaptogens in Stress Management: Traditional Use and Modern Evidence

Shaik Aminabee[1*], Ramana Gangireddy[2], K. Ravi Shankar[2], Naga Venkata Chenchu Lakshmi Kollipara[3], Saritha Karnati[4], Puppala Srinivasu[2], M. Lavanya[1], M. Bala Gopi[1], M. Siva Shankar[1] and K. S. V. Shanmukh[1],

[1]Department of Pharmacology, V. V. Institute of Pharmaceutical Sciences, Gudlavalleru - 521356, Krishna District, Andhra Pradesh, India; aminaammi786@gmail.com

[2]Department of Pharmaceutics, KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada – 520010, Krishna District, Andhra Pradesh, India

[3]Department of Pharmaceutical Chemistry, KL College of Pharmacy, Koneru Lakshmaiah Education Foundation (KLEF), Vaddeswaram – 522501, Andhra Pradesh, India

[4]Department of Pharmaceutical Chemistry, KV Subba Reddy College of Pharmaceutical Sciences, Kurnool - 518218, Andhra Pradesh, India

Abstract

The assault of stress has developed into one of the biggest health issues in the world, a condition that has led to a large variety of both psychological and physiological imbalances. In this regard, herbal adaptogens, i.e., a type of natural compounds that increase the ability of the body to keep itself resistant to the pressures of stress, provide an interesting, comprehensive solution to stress management. This review explores the traditional foundations and modern pharmacological evidence supporting the use of adaptogenic medicinal plants.Based on ancient traditions like Ayurveda, Traditional Chinese Medicine (TCM), and native ethnomedicine, we point out the most important adaptogenic herbs, *Withania somnifera* (*Ashwagandha*), *Panax ginseng*, *Rhodiola rosea*, *Ocimum sanctum* (*Tulsi*) and *Bacopa monnieri* (*Brahmi*). Their phytoconstituents,such as withanolides, ginsenosides, rosavins, and bacosides,are shown to exert neuroprotective, anti-inflammatory, antioxidant, and endocrine-modulating effects, particularly through regulation of the Hypothalamic-Pituitary-Adrenal (HPA) axis and stress-related biomarkers. The review combines the outcome of preclinical and clinical studies, which show substantial threats in the mitigation of anxiety, fatigue, and enhancement of stress cognitive performance. The improvement of the delivery systems and formulation technology, including nanoformulations and phytosomes to increase bioavailability and therapeutic efficiency,is also covered. Additionally, issues of standardisation, safety, and regulatory frameworks are examined to ensure the rational use of adaptogens in integrative healthcare.This review connects the information of the previous century and before regarding the question about plant-based adaptogens and potential therapeutic uses in preventing and treating conditions caused by stress, and heralds the ways to implement them in future studies and practice.

Major Findings: Traditional solutions to stress, plant-based adaptogens have scientifically confirmed stress-protective, neuroendocrine, and antioxidant properties, whereas they are potentially promising in integrative therapy, and their overall research and regulatory development are expected to focus on their standardisation, long-term safety, and clinical trial needs.

Keywords: Adaptogens, Ayurveda, HPA Axis, Oxidative Stress, Rasayana, Stress Management

1. Introduction

Adaptogens are a term used to refer to a special category of naturally occurring substances, most derived from plants, that strengthen the body's non-specific resistance to stress or support its state of homeostasis. Adaptogens were first defined by Russian scientists N.V. Lazarev and I.I. Brekhman in the

*Author for correspondence

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mid-20th century and are characterised as substances that increase resistance to stress, fatigue, and disease, without causing harm or imbalance to the physiological system[1]. Today, adaptogens are recognised as natural metabolic regulators that improve an organism's ability to adapt to environmental, physical, and emotional stressors.

The application of adaptogenic products dates back to several ancient medical systems, including nitrates and nitrites. Guided by the understanding that nitrites are herbivores, some nitrate and nitrites can be found at rest. Similarly, TCM emphasises the use of "Qi tonics" like *P. ginseng* to strengthen the body's life force and resistance to illness. *Rhodiola rosea* and *Eleutherococcus senticosus* were traditionally included in Russian folk medicine and Siberian folk medicine as endurance-enhancing (adaptogens) withstanding extreme climatic conditions[2]. These traditional applications emphasise the cultural status and traditional empirical experience that has accumulated with adaptogens.

In the modern era, chronic stress has become a widespread issue, contributing to the pathogenesis of various disorders, including anxiety, depression, cardiovascular diseases, immune dysfunction, and neurodegeneration. The drawbacks of the traditional pharmacological interventions, including the side effects, dependency and the limited sustainability of the effect, have triggered the revival of the natural, holistic methods of treatment, like the adaptogenic treatment[3]. The complexity of adaptogenic action makes them especially applicable now, when several modes are considered, such as the HPA axis and antioxidative protection, as well as neuroendocrine control.

This review aims to comprehensively explore the traditional uses, phytochemical composition, pharmacological actions, and clinical relevance of major plant-based adaptogens. It also explores the existing formulation practices, safety profiles and regulation of adaptogenic products[4]. Through the combination of ancient scientific knowledge and modern academic discoveries, the review aims to accentuate the therapeutic value of adaptogens in the management of stress and in the promotion of general well-being.

2. Pathophysiology of Stress and Mechanism of Adaptogens

Stress is a physiological and psychological response to internal or external stimuli that disrupt an organism's homeostasis. The reactions of the body to stress are organised by a chain of complex interactions that include the statistical mechanisms of the HPA axis, the SNS, and the oxidative stress pathway mechanisms, which are accountable for the pathophysiology of stress-related sicknesses[5].

2.1 Overview of Stress Biology

When a stressor is detected, the HPA axis is stimulated by the hypothalamus and the latter releases Corticotropin-Releasing Hormone (CRH); silver fox the CRH stimulates the anterior pituitary to release Adrenocorticotropic Hormone (ACTH). The ACTH will thereupon have its effects on the adrenal cortex, causing the production and release of the glucocorticoids, chiefly the cortisol in humans[6]. Concurrently, the SNS is activated, releasing catecholamines such as adrenaline and noradrenaline, which prepare the body for a 'fight or flight' response. When such pathways are chronic dozens of times, neuroendocrine imbalance, immune suppression, and oxidative stress may lead to performance anxiety, depression, metabolic syndrome, and other stress-related disorders. Additionally, elevated pro-inflammatory cytokines (e.g., IL-6, TNF-α), excessive Reactive Oxygen Species (ROS), and mitochondrial dysfunction further exacerbate cellular damage[7].

2.2 Neurotransmitters and Stress Biomarkers

The neurochemical state in stress is described by a change in neurotransmitters like serotonin (5-HT), Dopamine (DA), Gamma-Aminobutyric Acid (GABA), as well as glutamate level. Chronic stress causes high levels of cortisol, enhances adrenaline levels, as well as aggravation of pro-inflammatory cytokines, which act as vital biomarkers of stress that an adaptogenic intervention targets[8].

2.3 Mechanisms of Action of Adaptogens

The mechanisms of action of plant adaptogens are mechanisms of action of multi-target action, regulating

the stress response system, and increasing physiological adaptability. Key mechanisms include[9]:

2.3.1 HPA Axis Modulation

Adaptogens promote the normalisation of the HPA axis without extreme cortisol secretion and recovery of the homeostatic feedback. Indicatively, withanolides in *W. somnifera* and ginsenosides in *P. ginseng* have been found to stabilise cortisol to minimise the allostatic load.

2.3.2 Antioxidant and Anti-inflammatory Actions

Most adaptogen herbs have strong free radical scavenging as well as anti-inflammatory effects, which in turn shield cells when attacked by free radicals. Rosavins and curcuminoids constituents, along with bacosides, regulate the NF-κBsignalling, lowering the signs of pro-inflammatory mediators like COX-2, IL-1b and TNF-alpha[10].

2.3.3 Neuroprotection and Mitochondrial Stabilisation

Adaptogens augment the stability of neurons and heart cells, providing the preservation of cellular energy stability. They enhance the production of Adenosine Triphosphate (ATP), limit the production of oxidation reaction in nerve cells and safeguard neurons facing excitatory neurotoxicity by glutamate, which contributes to enhanced mental and emotional steadiness[11].

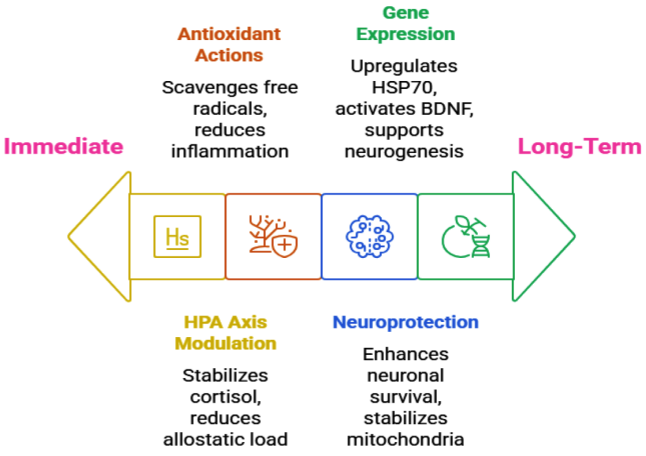


Figure 1. Adaptogen mechanisms range from immediate to long-term effects.

2.3.4 Regulation of Gene Expression

The adaptogens regulate the expression of genes in the area of cellular protection and longevity. To give some examples, stress tolerance is molecularly improved by upregulation of Heat Shock Proteins (HSP70), and neurogenesis and synaptic plasticity are facilitated by the activation of the Brain-Derived Neurotrophic Factor (BDNF). These gene-level changes confer long-term adaptive advantages (Figure 1).

3. Traditional Perspectives on Adaptogenic Herbs

3.1 *Ayurvedic Rasayanas* and Their Classification as Adaptogens

The term *Rasayana* refers to a category of longevity-enhancing herbs and preparations, thought to improve health, raise levels of immunity, and enhance longevity. *Rasayanas* are also not merely restorative; they are also prophylactic and are employed in balancing doshas, postponing age, and increasing stress and disease resistance. Classical *Rasayana* herbs such as *W. somnifera* (*Ashwagandha*), *B. monnieri* (*Brahmi*), *Emblica officinalis* (*Amalaki*), and *Tinospora cordifolia* (*Guduchi*) align closely with the modern understanding of adaptogens due to their homeostasis-regulating, immunomodulatory, and neuroprotective properties[12]. The rejuvenative effect mentioned in the texts of ancient Ayurveda is quite consistent with the stress-protecting, reparative characteristics proven today in pharmacological studies.

3.2 TCM Tonics and Their Stress-relieving Roles

In TCM, adaptogenic-like herbs are classified as Qi tonics, Yin tonics or Yang tonics depending on whether they boost, deplete or do not affect bodily energy, nutrition and vitality. Herbs such as *P. ginseng* (*Ren Shen*), *Schisandra chinensis* (*Wu Wei Zi*), and *Astragalus membranaceus (Huang Qi)* are classified as tonic herbs that strengthen vital energy (Qi), protect the organ systems, and improve tolerance to stress[13]. The effect of these tonic herbs on the body in TCM is to balance (Yin-Yang), tonify the spleen and the lungs, and calm the mind,which is the same as the effect of modern adaptogens on managing stress, boosting the immune

system, and modulating neuroendocrine functioning. TCM recipes tend to be a weaving of herbs that are specific to individual constitution and pathology, resembling the current personalised herbal medicine techniques[14].

3.3 Ethnomedicinal Practices from Tribal and Folk Systems

Local plants have provided the basis of tribal and folk medicine systems throughout the world for a long period of time: to treat stress, fight tiredness and overcome illness. Root decoctions, tonic pastes, and fermented extracts have been used traditionally in India, Africa, South America, and Southeast Asia by indigenous communities with similar modern adaptogenic uses as energy enhancers, fertility supplements, cognitive-enhancing compounds, and treatment of debilitation effects. For example, *R. rosea* has been used by Siberian tribes for increasing stamina and physical performance in cold environments, while *E. senticosus* (Siberian ginseng) has a history of use among Russian hunters and athletes as a stamina booster[15]. These ethnobotanical uses point towards a trans-cultural appreciation of adaptogenic herbs much earlier than the appearance of the term adaptogen in modern pharmacology (Table 1).

4. Key Plant-Based Adaptogens: Phytochemistry and Pharmacology

Such herbs contain adaptogenic ones, which increase resistance to stress, energy levels, and homeostasis. They are credited due to numerous bioactive phytoconstituents which can adjust the neuroendocrine, immune and oxidative pathways[16]. This part is a broad profile of variously investigated plant-based adaptogens in terms of their phytochemistry, pharmacology, and supporting both experimental and clinical data (Table 2).

5. Preclinical and Clinical Evidence

5.1 Overview of Experimental Models Used in Adaptogen Research

The pharmacological potential of adaptogenic herbs has been well researched by means of numerous preclinical experimental models aimed at mimicking physiological and psychological stress. One of the most popular ones is the Forced Swim Test (FST) that measures behavioural despair, and an abatement of immobility acquires antidepressant or adaptogenic properties[17]. The Restraint Stress Model induces acute physical and emotional stress by immobilising animals, leading to observable changes in behaviour and stress biomarkers such as cortisol, glucose, and oxidative stress markers.

Others are ACTH stimulation Test, the assessment of the sensitivity of the HPA axis response; cold restraint or immersion tests, which act like stress in the environment by provoking thermoregulation and stress tolerance levels.Behavioural paradigms like the Elevated Plus Maze and Open Field Test are used to assess anxiety and locomotor activity[18]. Besides, the levels ofROS and lipid peroxidation are measured by using models to assess the antioxidant effects of adaptogens.

5.2 Key Preclinical Findings on Adaptogenic Effects

Preclinical studies have revealed comprehensive stress-protective, neuroregulatory and antioxidative

Table 1. Correlation of traditional concepts with modern pharmacology

Traditional Concept	System of Medicine	Modern Pharmacological Equivalent	Examples
Rasayana (Rejuvenation)	*Ayurveda*	Adaptogenic, anti-ageing, cognitive enhancer	*Ashwagandha, Brahmi, Amalaki*
Qi Tonics	TCM	Energy metabolism modulator, immune enhancer	*Ginseng, Schisandra, Astragalus*
Ojas / Jing / Vitality tonics	*Ayurveda* / TCM	Endocrine regulator, antioxidant, neuroprotective	*Shatavari, Reishi, Tulsi*
Anti-fatigue / endurance tonics	Folk medicine	HPA axis modulators, mitochondrial protectants	*Rhodiola, Eleutherococcus, Gotu kola*
Calming Shen / *Medhya Rasayana*	TCM / *Ayurveda*	Anxiolytic, antidepressant, cognitive enhancer	*Bacopa, Reishi, Centella asiatica*

Table 2. Major plant-based adaptogens

Botanical Name	Common Name	Key Constituents	Pharmacological Actions	Scientific Evidence	Bioavailability
Withania somnifera	*Ashwagandha*	Withanolides, sitoindosides, alkaloids	HPA axis modulation, anxiolytic, neuroprotective, antioxidant	In vivo and clinical trials show cortisol reduction and stress relief	Moderate; improved with piperine/ liposomes
Panax ginseng	Asian Ginseng	Ginsenosides (Rb1, Rg1, Rd)	CNS stimulant, immune modulator, anti-fatigue, cognitive enhancer	Clinical evidence in fatigue, cognition, and metabolic stress	Low; nanoformulations in development
Ocimum sanctum	Tulsi / Holy Basil	Eugenol, ursolic acid, and rosmarinic acid	Anxiolytic, antioxidant, anti-inflammatory, hepatoprotective	Human trials show reduced anxiety and better stress tolerance	Good; aqueous extracts are commonly used
Rhodiola rosea	Rhodiola	Rosavins, salidroside, flavonoids	Mental alertness, mitochondrial support, anti-fatigue, antidepressant	Clinical evidence on burnout, physical and mental performance	Moderate; standardised extracts used
Glycyrrhiza glabra	Licorice Root	Glycyrrhizin, liquiritigenin, glabridin	Cortisol mimic, HPA axis stabiliser, anti-inflammatory, gastroprotective	In vivo support in fatigue, GI disorders	High caution for side effects
Eleutherococcus senticosus	Siberian Ginseng	Eleutherosides (B, E), syringin, chiisanoside	Endurance booster, immunity enhancer, antioxidant	Clinical data support work capacity and stress adaptation	Moderate; aqueous/ ethanolic extracts
Bacopa monnieri	*Brahmi*	Bacosides A and B, saponins, alkaloids	Memory enhancer, neuroprotective, antioxidant, anxiolytic	Clinical trials confirm cognitive benefits	Poor; enhanced in lipid-based systems
Curcuma longa	Turmeric	Curcuminoids (curcumin, demethoxycurcumin)	Anti-inflammatory, neuroprotective, cytokine modulator, antidepressant	Human trials show mood and antioxidant benefits	Very low; improved with piperine/nanofo

effects of many adaptogenic plants. *W. somnifera* (*Ashwagandha*) has been demonstrated to lower serum corticosterone, boost anti-oxidant enzyme action, including Superoxide Dismutase (SOD) and catalase, and augment admission into the FST. *Panax ginseng* has been shown to normalise ACTH and cortisol levels, improve learning and memory performance in maze models, and counteract fatigue[19].

Rhodiola rosea revealed itself capable of increasing the level of ATP production in mitochondria, upregulation of heat shock proteins (e.g., Hsp70) and benefits associated with endurance training under cold stress. Anxiolytic and cognitive-enhancing properties of *B. monnieri* are relevant and considerable as a result of modulation of serotonergic and cholinergic systems. Additionally, *Ocimum sanctum* and *Curcuma longa* have been shown to attenuate oxidative stress, suppress pro-inflammatory cytokines (IL-6, TNF-α), and restore physiological balance in stress-induced models[20].

These results are trial-corroboration of multimodal occurrence of adaptogens, which include modulation of the HPA axis, antioxidant-stress, neuroendocrine-regulation, and dense cellular-stress of resilience.

5.3 Clinical Trials and Human Studies

The therapeutic effects of adaptogens have also been clinically confirmed in human beings who experienced both psychological and physical stress. Several Randomised Controlled Trials (RCTs) were conducted with *W. somnifera*, which demonstrated a substantial decrease of serum cortisol levels, a reduction of anxiety level (on Hamilton and BAI scales) and an increase of

the quality of sleep and overall well-being[21]. In a 60-day study, it was found to be well-tolerated and effective in lowering stress-related symptoms.

Panax ginseng has been reported to have beneficial results as regards fatigue, cognitive stimulation and stress alleviation. Subjects indicated higher energy levels, working memory and perceived stress. Similarly, *R. rosea* has been shown to improve mental fatigue, attention, and work capacity in individuals suffering from burnout syndrome or prolonged stress exposure.

Bacopa monnieri has been researched mostly based on its cognitive and anxiolytic effects. Clinical trials have shown an increase in memory retention, processing speed and decreased signs of anxiety[22]. *Ocimum sanctum* has revealed positive influences on stress measures, such as reduced anxiety and glycemic and lipid status of people subjected to metabolic stress. *Curcuma longa*, particularly in combination with piperine, has shown mood-stabilising effects, reduced oxidative stress, and improved antioxidant status in patients with depression and chronic stress[23].

Such clinical data confirm the adaptogens as an effective and natural therapeutic reducer of stress, enhancer of cognitive abilities, and quality of life for over-stressed people (Table 3).

5.4 Meta-analyses and Systematic Reviews

The evidence on the adaptogenic efficacy has been accumulated during several systematic reviews and meta-analyses. An extensive study assessed more than 50 trials and validated the findings that adaptogens improve mental performance, reduce the level of stress, and suppress recovery after exhaustion. A meta-analysis of clinical trials on *W. somnifera* demonstrated its efficacy in reducing anxiety and serum cortisol levels with minimal adverse effects[24].

Therapeutic application of *R. rosea* in the treatment of mild to moderate depression and physical fatigue is also backed by scientific evaluations, but heterogeneity of the sources and the doses used precludesuniversal application. In general, such analyses support the clinical potential of adaptogens, but the insufficiency of standardised, large-scale trials is also identified with a well-defined endpoint[25].

5.5 Modern Evidence: Integration of In Silico Approaches

In recent years, the exploration of plant-based adaptogens has advanced beyond traditional pharmacological assays to include *in silico* approaches, which offer valuable insights into their molecular mechanisms of action. These computational methods, such as molecular docking, pharmacophore modelling, network pharmacology, and molecular dynamics simulations, help elucidate the interactions between bioactive phytoconstituents and stress-related molecular targets[26].

Molecular docking studies have been extensively applied to identify and predict the binding affinity of adaptogenic compounds with key stress-modulating proteins, such as heat shock proteins (HSP70, HSP90), glucocorticoid receptors, Monoamine Oxidase (MAO), Corticotropin-Releasing Factor (CRF) receptors, and GABAergic receptors. For example, withanolides from *W. somnifera* have shown strong docking affinities toward HSP90 and GABA_A receptors, suggesting their role in promoting stress resilience and neuroprotection[27]. Similarly, rosavin and salidroside from *R. rosea* have been reported to interact favorably with monoamine oxidase-B and serotonin transporters, which supports their antidepressant and anxiolytic activities.

Table 3. Clinical outcomes

Herb	Indication	Clinical Outcome
Withania somnifera	Chronic stress, anxiety	↓ cortisol, ↓ anxiety scores, ↑ quality of sleep
Panax ginseng	Fatigue, cognition, stress	↑ energy, ↑ working memory, ↓ perceived stress
Rhodiola rosea	Burnout syndrome, mental fatigue	↓ fatigue, ↑ attention and work capacity
Bacopa monnieri	Cognitive function, anxiety	↑ memory retention, ↓ anxiety symptoms
Ocimum sanctum	General stress, metabolic stress	↓ stress-related anxiety, ↑ glucose and lipid profile improvement
Curcuma longa	Depression, oxidative stress	↓ depressive symptoms, ↑ antioxidant status

In silico Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) profiling of phytoconstituents has further strengthened the selection of potent adaptogenic leads with desirable pharmacokinetic and safety profiles. Computational screening also aids in network pharmacology analysis, enabling researchers to visualise multitarget interactions and pathway modulations linked to stress response, oxidative balance, and neuroendocrine regulation[28].

These computational insights complement experimental findings, providing a rational framework for understanding the pleiotropic actions of adaptogens. By integrating *in silico* screening with *in vitro* and in vivo models, researchers can accelerate the discovery of novel adaptogenic compounds and optimise traditional formulations for enhanced efficacy and safety[29].

6. Formulation and Delivery of Adaptogens

6.1 Herbal Combinations and Synergistic Effects

Adaptogenic herbs are seldom used singly in conventional medicine perspectives, such as *Ayurveda* and TCM. Rather, they are often written as polyherbal mixtures, which are allegedly synergistic. These synergistic effects arise when multiple herbs interact to enhance therapeutic efficacy through complementary mechanisms, such as modulation of the HPA axis, antioxidant activity, neuroprotection, or immune enhancement. An example is that a combination of *W. somnifera* and *B. monnieri* has demonstrated more effects in cognitive and stress-reducing than each agent alone in animal models. Similarly, Ayurvedic preparations like *Chyawanprash* and *Ashwagandhadi lehya* incorporate several adaptogens in encouraging the rejuvenation and vitality at the systemic level[30].

Such synergistic combinations not only broaden the spectrum of therapeutic action but also may reduce the required dose of individual components, thereby minimising potential side effects. Nevertheless, there has been little scientific verification of herb-herb interactions and the mechanisms of synergy, although it is used widely through traditional practice, which needs to be explored in the future in a scientific manner[31].

6.2 Standardisation Challenges and Approaches

Lack of standardisation is one of the major challenges in the development and clinical acceptance of adaptogenic products. Plants are often extremely variable (botanical), and the growing conditions, leaf time of harvesting and methods of extraction can cause significant differences in the content of the active constituents. Without standardisation, the consistency, efficacy, and safety of adaptogen-based products cannot be guaranteed, making it difficult to replicate clinical outcomes or gain regulatory approval[32].

To avoid these problems, new phytomedicine methods include marker-based standardisation in which extracts are measured relative to major bioactive constituents, e.g., withanolides in *Ashwagandha* (< 5%), ginsenosides in *P. ginseng*, bacosides in *B. monnieri*. Chromatographic techniques such as High Performance Liquid Chromatography (HPLC), Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS), and Thin Layer Chromatography (TLC) fingerprinting are widely used to ensure quality control. Besides, DNA barcoding and spectroscopic fingerprinting are being popularised to verify plant origins and identify adulteration[33]. Such developments are important to guaranteeing batch-to-batch consistency and developing trust in adaptogenic formulations.

6.3 Novel Delivery Systems: Phytosomes, Nanoformulations, and Encapsulation

The clinical effectiveness of many phytoconstituents in adaptogens (e.g. curcuminoids, ginsenosides, and bacosides) is impaired by poor water solubility, poor intestinal absorption, and rapid metabolism. To address these pharmacokinetic challenges, a range of novel drug delivery systems have been developed[34].

Phytosomes are phospholipid complexes of plant extract, resulting in an increase in the lipophilicity and in membrane permeability of hydrophilic phytochemicals. For example, curcumin-phosphatidylcholine complexes have shown improved bioavailability and enhanced clinical outcomes in managing oxidative and inflammatory conditions. The formulations where nanotechnology, such as nanoparticles, liposomes, nanomicelles and solid lipid nanoparticles are added offer controlled release, enhance solubility and also allow targeting, especially to the central nervous system[35].

The encapsulating approaches involve the use of hydrogel, biopolymers or biodegradable matrices to prevent the destruction of sensitive compounds and also provide controlled release. These advances have greatly enhanced the pharmacological potential of adaptogens and are enabling them to become the nutraceuticals of the future and phytotherapeutics of the future (Figure 2).

6.4 Role of Dosage, Duration, and Safety Margins

Dose, duration of administration and safety are major factors that affect the therapeutic effects of adaptogens. In contrast to synthetic drugs, adaptogens can have a biphasic dose-response, or even a hormetic dose-response; they can increase adaptive capacity in moderate doses and also lead to overstimulation or side effects in excessive doses. For example, clinical studies have shown that 300-600 mg/day of standardised Ashwagandha extract is effective in reducing stress, while higher doses may lead to gastrointestinal discomfort or sedation[36].

The majority of such adaptogens are said to be safe in the long run when taken in the usual or stated doses. Certain ones, such as *Glycyrrhiza glabra* (liquorice root), however, must be used with caution as they may cause pseudoaldosteronism or hypertension or hypokalemia when high-dose glycyrrhizin is used chronically. Therefore, careful attention must be paid to the therapeutic window, patient-specific considerations, and contraindications, especially in vulnerable populations such as pregnant women, children, or those with chronic illnesses[37].

To exploit the potential of adaptogens to their fullest in the design of modern therapeutic protocols, it is critical to develop both dosing conventions and margins of safety and duration-of-use conventions through well-designed clinical studies.

7. Safety, Toxicology, and Regulatory Aspects

Although adaptogenic herbs are traditionally used and worded as safe in general, careful evaluation is needed to guarantee their toxicological safety, misuse, and regulatory acceptability in the modern health systems[38]. This part discusses the available toxicological data, potential herb-drug interactions, and the global regulatory frameworks governing the use of adaptogens.

7.1 Toxicological Evaluations of *Adaptogenic* Plants

Most of the available adaptogens have been shown through multiple preclinical studies and some human studies to be very safe, with most showing a favourable outcome when administered at traditional or recommended doses. The non-toxic effects of *Ashwagandha*, *Tulsi*, *Bacopa*, and *Rhodiola* were evident in animals using acute and sub-chronic toxicity investigations. For example, *W. somnifera* extract did

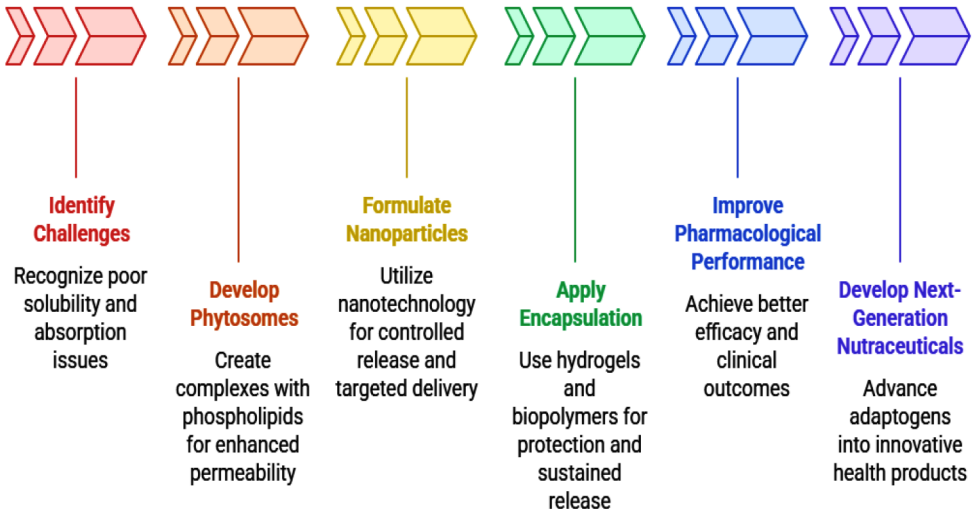


Figure 2. Novel drug delivery systems for adaptogens.

not produce significant toxic effects even at high doses in rats, and *B. monnieri* was found to be safe up to 5,000 mg/kg body weight in acute toxicity tests[39].

Nevertheless, some of the adaptogens are dangerous. Due to glycyrrhizin, large doses or prolonged use of *G. glabra* (liquorice) has the potential to display mineralocorticoid effects, including retention of sodium, hypokalemia and hypertension. *Panax ginseng* is similarly irritating to the nervous system, causing nervousness and insomnia or gastrointestinal upset when taken in very large doses[40]. Therefore, while adaptogens are broadly considered safe, systematic long-term toxicity data in humansremain limited and warrant further investigation.

7.2 Herb-drug Interactions and Contraindications

Herb-drug interactions have become a potential issue, especially between multiply medicated patients, e.g. in the elderly population or in patients with long-term diseases. Certain adaptogens might affect cytochrome P450 enzyme systems or P-glycoprotein transporters and thus interfere with the pharmacokinetics of conventional drugs[41].

For instance, *P. ginseng* has been shown to potentially interfere with warfarin, digoxin, and insulin therapy, while *C. longa* may enhance the effect of antiplatelet or anticoagulant drugs, increasing the risk of bleeding. *W. somnifera* can enhance the effect of sedatives or anxiolytics, and such medications may need dose reduction. These are usually plant-based contraindications, which consist of pregnancy and lactation, hormone-sensitive subsets, or the presenceof immunosuppressants[42].

Therefore, healthcare providers should evaluate patient history and co-medications carefully before recommending adaptogens, and future research must focus on identifying clinically significant interactions using *in vitro* and *in vivo* models (Figure 3).

7.3 Regulatory Status of Adaptogens in Global Markets

Depending on their jurisdiction, adaptogens are regulated and approved differently. The adaptogenic herbs in India are governed by the Drugs and Cosmetics Act, 1940, in the form of the procedures within the AYUSH ministry and are considered as *Ayurvedic* medicines or *Siddha*, which have to adhere to the pharmacopoeial standards[43].

In the European Union (EU), adaptogens are generally categorised under botanical food supplements or Traditional Herbal Medicinal

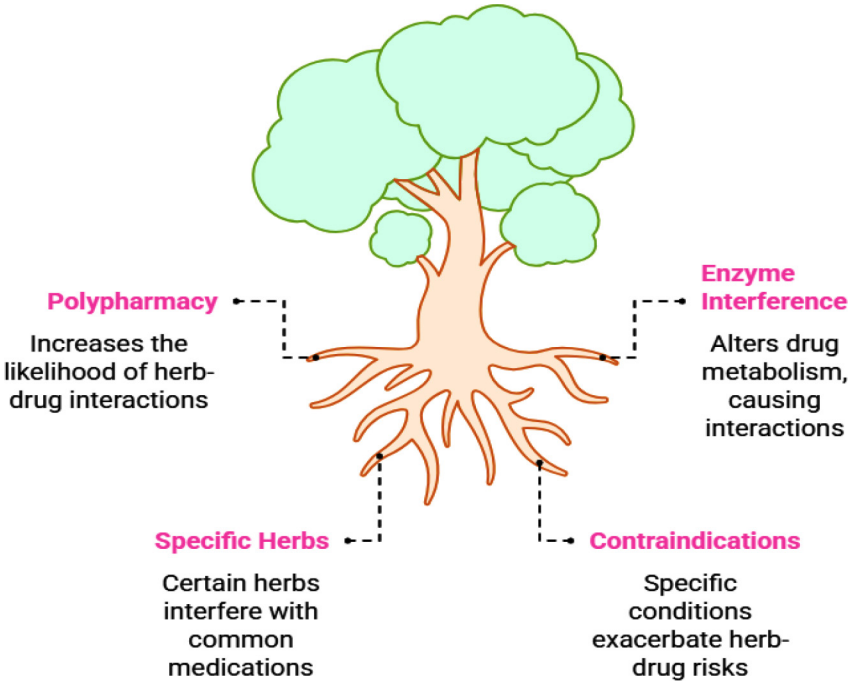


Figure 3. Risk of adverse effects from herb-drug interactions.

Products (THMPs). Products must comply with European Food Safety Authority (EFSA) safety assessments and labelling regulations. Although the European Medicines Agency (EMA) does not officially consider the term adaptogen, the European Medicines Agency accepted several herbs, such as Rhodiola and Ginseng, in terms of traditional use indication[44].

In the United States, adaptogens fall under dietary supplements regulated by the Food and Drug Administration (FDA) through the Dietary Supplement Health and Education Act (DSHEA) of 1994. Advertising is limited to structure-function claims, and the companies are bound to ensurethe Good Manufacturing Practices (GMP), though premarket approval is not obligatory except when a New Dietary Ingredient (NDI) appears[45]. Such differences indicate the absence of coordinated world meanings or categories under which adaptogens can be regulated, whichraises challenges in international trade and product development.

7.4 WHO and AYUSH Guidelines

The World Health Organisation (WHO) supports the integration of traditional medicines, including herbal adaptogens, into national health systems, provided they are safe, effective, and of assured quality. WHO monographs on some medicinal plants describe safety, dose, contraindication and preclinical information on popular herbs[46].

In India, the *Ayurveda, Yoga* and *Naturopathy, Unani, Siddha* and Homoeopathy (AYUSH) Ministry has taken active steps to standardise and promote evidence-based traditional medicine, including adaptogens. Texts such as Ayurvedic Pharmacopoeia of India (API) and Good Clinical Practice (GCP) guidelines in AYUSH research can be used to select a framework to verify clinical and safe usage[47].

Additionally, Pharmacovigilance programs under AYUSH aim to monitor adverse drug reactions and ensure post-marketing surveillance of herbal medicines. The regulatory systems are aiding in the bridging of conventional knowledge and contemporary scientific diagnostics concerning safe consumption and responsible practices of adaptogens in integrative medicine[48].

8. Current Trends and Future Directions

The therapeutic potential of adaptogens is witnessing resurgence, driven by rising global interest in natural remedies, mental well-being, and integrative health approaches. Recent technologies like personalised medicine, Artificial Intelligence (AI) and systems biology are recasting the manner adaptogens are researched and used. This addresses upcoming trends, business opportunities and research disparities which may define the future of adaptogenic therapies[49].

8.1 Role of Adaptogens in Personalised Medicine and Mental Health

As the focus of providing therapy to individuals continues to gain importance, adaptogens are taking a huge position in personalised treatment, particularly when treating stressful issues, fatigue and mood disorders. Stress responses are determined genetically and also epigenetically, which means that each different characteristicof every individual response may be determined by polymorphism of glucocorticoid transporters, serotonin transporters or inflammatory genes. Integration of adaptogens into personalised nutrition and mental health programs, guided by biomarkers such as cortisol levels, heart rate variability, and cytokine profiles, could help tailor interventions for anxiety, burnout, or cognitive decline[50].

Adaptogens arouse the rising interest in the field of mental health as supplements to pharmacotherapy without side effects that reduce the neuroprotective, anxiolytic, and antidepressant effects that synthetic medication can produce. This opens possibilities for developing herb-based nootropics and mood stabilisers, especially for patients with stress-related disorders or medication intolerance[51].

8.2 AI and Systems Biology in Adaptogen Research

AI, machine learning (ML), and systems biology are the latest advances that are changing the course of adaptogenic research. Large datasets on genomics, proteomics and metabolomics can be processed by AI to select active phytoconstituents and predict herb-drug interactions and model the effects on biological networks. Systems biology helps map the multi-target interactions of adaptogens across pathways such as

the HPA axis, immune regulation, and mitochondrial function[52].

This may be easier using such integrative methods to identify new adaptogenic preparations, aid in elucidating mechanisms, and even streamline clinical trials. There is increased utilisation of *silico* approaches to modelling the network pharmacology and bioinformatics tools to minimise the trial-and-error and prioritisation of leads, as well as providing a background on the complex biological activities of adaptogens[53].

8.3 Patents and Commercial Prospects

The adaptogen business is expanding at a rapid rate with increased interest in nutraceuticals and cosmeceutical markets, as well as functional foods. A lot of patents have been registered about the adaptogen-based formulations, extraction methods, delivery methods (e.g. nanocarriers, liposomes), and synergetic formulas. For example, standardised extracts of *W. somnifera, R. rosea*, and *P. ginseng* are now incorporated in energy drinks, cognitive enhancers, stress-relief capsules, and skincare products[54].

The world is experiencing a rise in demand for natural stress reduction products that promote physical and emotional resilience in consumers. This will require regulatory validation of this with scientific data to make the market sustainable and to gain consumer trust. Companies investing in clinical validation and IP protection stand to benefit from long-term commercial opportunities.

8.4 Gaps in Research and Opportunities for Future Exploration

There are still large gaps in the activity of adaptogen studies, even though the interest has been increasing in that regard. Most clinical trials have no standardised extracts, a huge sample size, a placebo control, or follow-up, which constrains the evidence[55]. Additionally, herb-herb and herb-drug interaction data remain insufficient for informed clinical decision-making.

Further opportunities exist in:

- Defining molecular targets and signalling pathways for specific adaptogens.
- Conducting biomarker-based, stratified clinical trials.
- Investigating age-related applications, that is, pediatric Attention Deficit Hyperactivity Disorder (ADHD), menopause, or post-COVID exhaustion.
- Researching on unexploited local adaptogens of ethnomedicine, particularly on biodiversity-rich landscapes such as the Eastern Ghats and Himalayas.

9. Conclusion

Adaptogens, historically highly valued by traditional systems including *Ayurveda*, TCM and native healing therapies, are a special group of botanical substances, described as increasing the body's capacity to resist physical, emotional and environmental stresses[52]. They are called *Rasayanas*, tonics, or rejuvenators. This is due to very traditional knowledge, which has beenproven to be effective throughout the ages. In recent decades, this ancient wisdom has found growing support from modern pharmacological and clinical research, validating the adaptogenic potential of several plant-based remedies such as *W. somnifera*, *R. rosea*, *P. ginseng*, and *O. sanctum*.

Their mechanisms of action are explained by scientific studies as modulation of the HPA axis, antioxidation and anti-inflammatory processes, neuroprotection and regulation of genes. Preclinical and clinical data indicate their effectiveness in alleviating stress, boosting cognition, enhancing mood, and promoting healthy physiological homeostasis. Innovations in formulation science and delivery systems have further improved their therapeutic potential by enhancing bioavailability and patient compliance[56].

Within contemporary therapeutics, adaptogens have an important potential in terms of their application as complementary and integrative modalities, especially in chronic stress, burnout, mood disorders and neurodegenerative diseases. Their broad-spectrum activity, low toxicity, and cultural acceptability make them attractive candidates for inclusion in personalised medicine, preventive health programs, and integrative mental health strategies[57].

Nevertheless, more standardised, toxicology-screened, and properly conducted clinical trials are needed to standardise the implementation of adaptogens in general clinical practice due to their safety and efficacy and their ability to fit within the regulatory scheme. Harmonisation of traditional knowledge with modern research frameworks will be key to unlocking their full therapeutic potential[58].

To sum up, one may say that adaptogens are at the crossroads between convention and modernity. They can change our 21st-century understanding of stress resiliency and whole body wellness by integrating contemporary research-based medicine and the wisdom of the ages.

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11. Author Contribution

Shaik Aminabee conceptualised the review, designed the structure, and supervised the overall manuscript development. Ramana Gangireddy and K. Ravi Shankar contributed to the literature review and critical analysis of pharmacological mechanisms. Naga Venkata Chenchu Lakshmi Kollipara and Saritha Karnati gathered and curated ethnobotanical and traditional medicine data. Puppala Srinivasu compiled the phytochemical and pharmacokinetic profiles of key adaptogens. M. Lavanya, M. Bala Gopi, and M. Siva Shankar contributed to drafting the clinical and preclinical evidence sections. K.S.V. Shanmukh assisted in preparing tables, figures, and final editing. All authors have read and agreed to the published version of the manuscript.

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