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MODULATION OF THE HYPOTHALAMIC–PITUITARY–ADRENAL AXIS AND NEUROENDOCRINE STRESS MARKERS BY AYURVEDIC PHARMACOTHERAPY: CURRENT EVIDENCE AND FUTURE DIRECTIONS

Dr. Priyanka Kumari[1*], Dr. Richa kumari[2], Dr. Sanju Rao[3], Dr. Komal Rathore[4]

[1]Assistant Professor, PG Department of Kriya Sharir,Post Graduate Institute of Ayurveda, DSRRAU, Jodhpur*
Email: priyankaloyal09@gmail.com
[2]Assistant Professor, PG Department of Roga Nidan EvumVikriti Vigyan, Post Graduate Institute of Ayurveda, DSRRAU, Jodhpur
Email: richa1996loyal@gmail.com
[3]Associate Professor, Department of Prasuti Tantra EvumStriroga, SBLD Ayurveda Vishwabharati, Sardarshahar, Email: sanjurao31121993@gmail.com
[4]Associate Professor, Department of Kaya Chikitsa, SBLD Ayurveda Vishwabharati, Sardarshahar
Email: Komalhukam@gmail.com

Corresponding Author: Dr. Priyanka Kumari
(priyankaloyal09@gmail.com)

ABSTRACT

The hypothalamic–pituitary–adrenal (HPA) axis constitutes the principal neuroendocrine mediator of the stress response, and its chronic dysregulation underpins a wide spectrum of psychosomatic and metabolic disorders. Ayurveda, the traditional Indian system of medicine, has long employed a class of rejuvenative and intellect-promoting herbs and formulations collectively termed Rasayana and Medhya Rasayana that exhibit striking parallels with the modern concept of adaptogens [1]. This review critically examines the preclinical and clinical evidence for the modulation of HPA axis activity and associated neuroendocrine stress markers by Ayurvedic pharmacotherapy, with particular emphasis on well-characterized botanicals including Withania Somnifera (Ashwagandha), Bacopa Monnieri (Brahmi), Centella asiatica (Mandukaparni), Ocimum sanctum (Tulsi), and classical polyherbal formulations. The available data demonstrate that these agents attenuate HPA axis hyperactivity through multimodal mechanisms: downregulation of corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) secretion, restoration of glucocorticoid receptor sensitivity, mitigation of oxidative and nitrosative stress, and preservation of hippocampal neuroplasticity [2, 6, 9]. Clinical trials consistently report significant reductions in serum cortisol, improved perceived stress scores, and amelioration of anxiety and depressive symptomatology [13, 21]. Nevertheless, the field is constrained by methodological heterogeneity, including variability in extract standardization, dosing regimens, and outcome measures, as well as a relative paucity of large-scale, long-term randomized controlled trials. Future directions must prioritize the elucidation of precise molecular targets, application of network pharmacology and systems biology approaches, and rigorous clinical

validation aligned with contemporary evidence-based standards. The integration of Ayurvedic pharmacotherapy into mainstream stress management paradigms holds considerable promise, contingent upon sustained interdisciplinary collaboration and methodological refinement.

KEYWORDS: Ayurveda; Hypothalamic–Pituitary–Adrenal Axis; Adaptogens; *Rasayana*; Cortisol; Stress; *Withania Somnifera*; *Bacopa Monnieri*; Neuroendocrinology

1. Introduction

The stress response represents a phylogenetically ancient and highly conserved physiological mechanism that enables organisms to adapt to environmental challenges and maintain internal homeostasis. At the core of this adaptive machinery lies the hypothalamic–pituitary–adrenal (HPA) axis, a complex neuroendocrine cascade that orchestrates the synthesis and release of glucocorticoid hormones, principally cortisol in humans and corticosterone in rodents. Under acute conditions, activation of the HPA axis confers survival advantage by mobilizing energy substrates, enhancing cardiovascular tone, and modulating cognitive and immune functions. However, when stress becomes chronic or the regulatory feedback loops that govern HPA axis activity are compromised, the resultant glucocorticoid excess exerts pleiotropic deleterious effects, including hippocampal atrophy, impaired synaptic plasticity, neuroinflammation, and metabolic dysregulation. This pathophysiological state, often termed allostatic overload, has been causally implicated in the etiology and progression of major depressive disorder, generalized anxiety disorder, post-traumatic stress disorder, insomnia, cardiovascular disease, and metabolic syndrome.

Contemporary pharmacotherapy for stress-related disorders relies heavily on synthetic agents such as selective serotonin reuptake inhibitors (SSRIs), benzodiazepines, and beta-blockers. While these agents provide symptomatic relief for many patients, their utility is frequently tempered by incomplete efficacy, delayed onset of action, adverse effect profiles, and, in the case of benzodiazepines, significant abuse liability. These limitations have galvanized interest in traditional systems of medicine, which offer a holistic, multi-targeted approach to restoring physiological equilibrium. Among these systems, Ayurveda—a codified medical tradition with roots extending over three millennia—provides a particularly rich repository of botanical and mineral therapeutics for the management of stress and its somatic sequelae.

Within the Ayurvedic framework, stress is conceptualized as a disturbance of the tripartite humoral constitution, or *Tridosha* (specifically aggravation of *Vata* and *Pitta*), coupled with impairment of the mental faculties *Dhi* (intellect), *Dhriti* (retention), and *Smriti* (memory) [1]. This phenomenological description aligns remarkably with contemporary understanding of HPA axis dysregulation and its cognitive and affective consequences. To redress these imbalances, Ayurveda prescribes a class of therapies known as *Rasayana*, which literally translates to "the path of essence" and encompasses rejuvenative agents that promote longevity, vitality, and resistance to disease. A specialized subset, termed *Medhya Rasayana*, is specifically indicated for the enhancement of cognitive function and the mitigation of psychological distress [3, 17].

The modern concept of the "adaptogen," a term coined by Soviet scientist Nikolai Lazarev in 1947 and subsequently refined by Israel Brekhman and Igor Dardymov, refers to substances that increase the state of non-specific resistance to stress and normalize physiological function without perturbing homeostatic set points. The formal definition stipulates three cardinal criteria: (i) the agent must be innocuous and cause minimal disturbance to normal physiological function; (ii) it must exert a non-specific, broad-spectrum normalizing action; and (iii) it must enhance resistance to a wide array of physical, chemical, and biological stressors. Intriguingly, a substantial proportion of Ayurvedic *Rasayana* herbs satisfy these criteria and have been empirically employed for stress mitigation for centuries [2]. Mechanistically, adaptogens are posited to interface with the HPA axis, the sympathoadrenal system, and intracellular stress-sensing pathways involving heat shock proteins and the nuclear factor erythroid 2-related factor 2 (Nrf2)–antioxidant response element (ARE) axis [23].

The past decade has witnessed a burgeoning body of preclinical and clinical research aimed at elucidating the molecular underpinnings of Ayurvedic pharmacotherapy and its capacity to modulate neuroendocrine stress markers. This review endeavors to synthesize the extant evidence, with a specific focus on HPA axis modulation, to critically appraise the methodological quality of available studies, to identify salient knowledge gaps, and to chart a course for future investigation. The scope is restricted to primary Ayurvedic botanicals and polyherbal formulations for which substantive mechanistic and clinical data are available, with particular emphasis on *Withania somnifera* (*Ashwagandha*), *Bacopa monnieri* (*Brahmi*), *Centella asiatica* (*Mandukaparni*), *Ocimum sanctum* (*Tulsi*), and *Glycyrrhiza glabra* (*Yashtimadhu*). References are limited to publications from the last ten years to ensure contemporaneity and relevance.

2. Methods

2.1 Search Strategy and Selection Criteria

A systematic literature search was conducted across multiple electronic databases, including

PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, and Google Scholar, for articles published between January 2014 and March 2026. The search strategy employed combinations of the following keywords and Medical Subject Headings (MeSH) terms: "Ayurveda," "Ayurvedic," "*Rasayana*," "*Medhya Rasayana*," "adaptogen," "hypothalamic-pituitary-adrenal axis," "HPA axis," "cortisol," "corticosterone," "adrenocorticotropic hormone," "ACTH," "corticotropin-releasing hormone," "CRH," "stress," "anxiety," "depression," "*Withania Somnifera*," "*Ashwagandha*," "*Bacopa Monnieri*," "*Brahmi*," "*Centella asiatica*," "*Mandukaparni*," "*Ocimum sanctum*," "*Tulsi*," "*Glycyrrhiza glabra*," "*Yashtimadhu*," "*Convolvulus Pluricaulis*," "*Shankhpushpi*," "*Nardostachys jatamansi*," "Jatamansi," and "polyherbal formulation."

Inclusion criteria were as follows: (i) original research articles, systematic reviews, meta-analyses, and narrative reviews published in English-language peer-reviewed journals; (ii) studies investigating the effects of Ayurvedic herbal preparations or isolated bioactive constituents on HPA axis activity, cortisol/corticosterone levels, ACTH, CRH, or related neuroendocrine stress markers; (iii) preclinical studies employing validated animal models of acute or chronic stress, or in vitro mechanistic investigations; and (iv) human clinical trials, including randomized controlled trials (RCTs), open-label studies, and observational studies. Exclusion criteria comprised: (i) conference abstracts, editorials, and opinion pieces lacking primary data; (ii) studies focusing exclusively on non-Ayurvedic traditional medicine systems; (iii) articles not reporting quantitative outcome measures related to HPA axis function; and (iv) publications in languages other than English.

2.2 Data Extraction and Synthesis

Data were extracted from eligible studies using a standardized template that captured the following parameters: first author and year of publication, study design, sample size, participant characteristics (for human studies) or animal model (for preclinical studies), intervention (botanical species, part used, extraction method, standardization, dose, duration), comparator (placebo, active control, or untreated stress group), primary and secondary outcomes (including cortisol/corticosterone levels, ACTH, CRH, behavioral assays, and safety parameters), and key findings. Due to substantial heterogeneity in study design, interventions, and outcome measures, a formal meta-analysis was not feasible. Instead, findings are presented in a narrative synthesis format, organized by botanical agent and study type (preclinical vs. clinical), with critical appraisal of methodological strengths and limitations.

2.3 Quality Assessment

The methodological quality of included human RCTs was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool, which evaluates potential biases arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Preclinical studies were evaluated using the Systematic Review Center for Laboratory Animal Experimentation (SYRCLE) risk of bias tool. Studies with a high risk of bias were not excluded but are identified and discussed with appropriate caveats in the Results and Discussion sections.

3. Results

3.1 Overview of Ayurvedic Concepts and HPA Axis Physiology

Before detailing the specific evidence for individual botanicals, it is instructive to consider the conceptual alignment between Ayurvedic and modern stress physiology. The HPA axis comprises a hierarchical neuroendocrine cascade: stress-sensitive neurons within the paraventricular nucleus (PVN) of the hypothalamus synthesize and secrete corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), which traverse the hypophyseal portal circulation to stimulate the anterior pituitary corticotrophs to release adrenocorticotropic hormone (ACTH). ACTH, in turn, acts upon the zona fasciculata of the adrenal cortex to promote the synthesis and pulsatile secretion of glucocorticoids. Glucocorticoids exert negative feedback inhibition at the level of the hippocampus, hypothalamus, and pituitary, thereby constraining the duration and magnitude of the stress response. Chronic stress exposure engenders a maladaptive state characterized by impaired glucocorticoid receptor (GR)-mediated feedback inhibition, sustained CRH drive, and elevated basal glucocorticoid levels a profile that is mirrored in numerous neuropsychiatric and metabolic disorders.

Ayurveda does not articulate the HPA axis in biochemical terms, but its foundational principles offer a remarkably congruent framework. The concept of *Manovaha Srotas* (channels of the mind) and *Majja Dhatu* (nervous tissue) encompasses the functional domain of the central nervous system and its neuroendocrine efferents. Stress is viewed as a perturbation of *Prana Vayu* (a subtype of *Vata Dosha* governing higher nervous functions) and *Sadhaka*

Pitta (a subtype of *Pitta* governing cognition and emotion), culminating in a state of *Ojas Kshaya* (depletion of vital essence) that manifests as fatigue, anxiety, insomnia, and impaired immunity [1]. *Rasayana* therapy aims to replenish *Ojas*, pacify aggravated *Doshas*, and restore the functional integrity of *Srotas* (microcirculatory channels) [24]. This holistic, systems-level approach prefigures contemporary concepts of allostasis and resilience.

3.2 *Withania Somnifera* (*Ashwagandha*)

Withania Somnifera (L.) Dunal (family Solanaceae), commonly known as *Ashwagandha* or Indian winter cherry, is arguably the most extensively investigated Ayurvedic adaptogen [2, 25]. The root is the primary medicinal part, containing a complex array of bioactive constituents including steroidal lactones (withanolides), alkaloids (withanine, somniferine), sitoindosides, and flavonoids. Withanolides, particularly withaferin A and withanolide A, are considered the principal pharmacologically active moieties [26].

3.2.1 Preclinical Evidence

A substantial body of preclinical literature documents the capacity of *Ashwagandha* extracts to modulate HPA axis activity in animal models of acute and chronic stress. In a landmark study, rats subjected to chronic unpredictable stress (CUS) exhibited elevated plasma corticosterone and ACTH levels, which were significantly attenuated by concurrent administration of a standardized aqueous extract of *Ashwagandha* root and leaf (125–500 mg/kg) [20]. This attenuation was accompanied by restoration of adrenal gland weight and histological architecture, as well as normalization of stress-induced alterations in brain monoamine levels. Mechanistic investigations have elucidated that *Ashwagandha* downregulates CRH expression in the PVN and reduces neuronal excitability in stress-responsive hypothalamic circuits, thereby raising the threshold for HPA axis activation [2]. Furthermore, withanolides have been shown to modulate the activity of the glucocorticoid receptor and to enhance the expression of heat shock proteins (Hsp70), which function as molecular chaperones and stress sensors that protect cellular integrity during stress exposure [23].

Additional preclinical studies have demonstrated that *Ashwagandha* mitigates stress-induced oxidative damage in the hippocampus and prefrontal cortex, preserves dendritic arborization and spine density, and upregulates brain-derived neurotrophic factor (BDNF) expression—a key mediator of neuroplasticity and resilience. These neuroprotective effects likely contribute to the observed anxiolytic and antidepressant-like behavioral outcomes in rodent models, which are independent of, and likely synergistic with, direct HPA axis modulation [20].

3.2.2 Clinical Evidence

The clinical efficacy of *Ashwagandha* in reducing stress and anxiety has been evaluated in numerous randomized, double-blind, placebo-controlled trials, many of which have included serum cortisol as a primary or secondary outcome measure. A 2021 systematic review of human trials examining the effects of plant-derived phytonutrients on HPA axis activity identified *Ashwagandha* as the agent with the most consistent evidence for a morning cortisol-lowering effect [8]. A meta-analysis of five RCTs (total n = 400) reported that *Ashwagandha* extract significantly improved sleep quality and reduced perceived stress scores, with concomitant reductions in serum cortisol levels.

A representative randomized controlled trial conducted by Salve et al. (2019) enrolled 60 adults with self-reported high stress and randomized them to receive either 240 mg/day of a standardized *Ashwagandha* extract (Shoden®, containing 35% withanolide glycosides) or placebo for 60 days. The treatment group exhibited a significant reduction in serum cortisol (-27.9% from baseline vs. -7.9% in the placebo group; *p* < 0.001), along with improvements in the Perceived Stress Scale (PSS-10) and Hamilton Anxiety Rating Scale (HAM-A) scores [13]. A subsequent dose-response study (2024) demonstrated that even a low dose of 125 mg/day of an aqueous *Ashwagandha* root and leaf extract produced significant reductions in chronic stress and cortisol levels in a dose-dependent manner.

More recent investigations have extended these findings to specific clinical populations. A 2025 trial examining *Ashwagandha* supplementation in adults with autism spectrum disorder (ASD) and anxiety hypothesized that the treatment group would exhibit reduced cortisol levels and improved behavioral scores, reflecting modulation of the HPA axis and anxiolytic effects [4]. Additionally, a comparative study evaluating the effects of a multi-herb formulation versus *Ashwagandha* root extract alone concluded that both interventions reduced anxiety and improved mood and sleep quality, with the mechanism of action attributed to HPA axis regulation and subsequent cortisol reduction [5].

The weight of clinical evidence supports *Ashwagandha* as an effective botanical intervention for stress reduction, with a favorable safety profile and good tolerability [21, 22]. Adverse events

reported in clinical trials are generally mild and transient, including gastrointestinal discomfort and drowsiness. However, caution is warranted in individuals with thyroid disorders, as *Ashwagandha* may influence thyroid hormone levels, and in those taking sedative or immunosuppressive medications.

3.3 *Bacopa Monnieri* (*Brahmi*)

Bacopa Monnieri (L.) Wettst. (family Plantaginaceae), known in Ayurveda as *Brahmi*, is a revered *Medhya Rasayana* herb traditionally indicated for memory enhancement, cognitive decline, epilepsy, and anxiety [3, 27]. The primary bioactive constituents are triterpenoid saponins termed bacosides, which have been shown to exert neuroprotective, antioxidant, and cholinergic modulatory effects.

3.3.1 Preclinical Evidence

The capacity of *Bacopa Monnieri* to modulate HPA axis activity has been demonstrated in several well-controlled preclinical studies. In a rat model of chronic unpredictable stress (CUS), administration of *Bacopa Monnieri* extract (BME) significantly attenuated depressive-like behaviours and normalized the elevated plasma levels of ACTH and corticosterone induced by CUS. Importantly, BME treatment also upregulated the expression of BDNF and markers of hippocampal neurogenesis (DCX and BrdU/NeuN), suggesting that HPA axis normalization is accompanied by restoration of stress-induced impairments in neuroplasticity [6].

Another study investigated the effects of prenatal stress (PNS) on rat offspring, a paradigm known to induce long-lasting HPA axis hyperactivity and cognitive deficits. Pretreatment of dams with standardized *Bacopa Monnieri* extract (CDRI-08) ameliorated PNS-induced elevations in corticosterone and prevented anxiety-like behavior and memory impairments in the offspring [7]. The antioxidant properties of bacosides, including their ability to scavenge free radicals and upregulate endogenous antioxidant enzymes, are posited to underlie, at least in part, their protective effects against HPA axis dysregulation and stress-induced neuronal injury.

3.3.2 Clinical Evidence

Relative to *Ashwagandha*, the clinical evidence for HPA axis modulation by *Bacopa Monnieri* is less robust and somewhat equivocal. A double-blind, placebo-controlled cross-over study examined the acute effects of 320 mg and 640 mg doses of a standardized *Bacopa Monnieri* extract (CDRI 08) on multitasking stress reactivity and mood in healthy adults. The study reported some positive mood effects and a reduction in cortisol levels, suggesting a physiological mechanism for stress reduction [12]. However, a more recent review concluded that while some studies suggest that *Bacopa* may help manage stress, a direct and consistent cortisol-lowering effect has not been conclusively demonstrated, and further research is needed to clarify its effects on HPA axis activity [8].

The discrepancy between preclinical and clinical findings may be attributable to several factors, including differences in dosage, duration of treatment, extract standardization, and the baseline stress status of study participants. Preclinical studies typically employ higher doses relative to body weight and utilize stress-naïve or chronically stressed animal models, whereas human studies have largely been conducted in healthy volunteers with normal HPA axis function. It is plausible that *Bacopa Monnieri* exerts a more pronounced HPA-modulating effect in the context of pre-existing dysregulation, akin to the pattern observed with *Ashwagandha*. Future clinical trials should prioritize enrolment of individuals with elevated baseline cortisol or clinically significant anxiety to better elucidate the adaptogenic potential of this herb.

3.4 *Centella asiatica* (*Mandukaparni*)

Centella asiatica (L.) Urban (family Apiaceae), known as *Mandukaparni* in Ayurveda, is another prominent *Medhya Rasayana* herb with documented anxiolytic, cognitive-enhancing, and neuroprotective properties [28]. The primary bioactive constituents are pentacyclic triterpenes, including asiaticoside, madecassoside, asiatic acid, and madecassic acid.

3.4.1 Preclinical Evidence

Accumulating preclinical evidence indicates that *Centella asiatica* and its triterpenoid constituents exert significant modulatory effects on the HPA axis. In a validated model of stress-induced depression, administration of *Centella asiatica* extract consistently attenuated HPA axis hyperactivity, as evidenced by reduced serum corticosterone levels. This was accompanied by restoration of hippocampal BDNF signaling, suppression of nuclear factor kappa-B (NF-κB)-mediated neuroinflammation, and enhancement of endogenous antioxidant defenses [9]. A study investigating the effects of total triterpenes of *Centella asiatica* on corticosterone levels in a rat depression model reported significant reductions in serum corticosterone and increases in brain monoamine neurotransmitters (5-HT, dopamine, and their metabolites), leading the authors to conclude that the antidepressant effect is likely mediated by amelioration of HPA axis function

and restoration of monoaminergic tone [11].

More recent investigations have explored the role of the gut–brain axis in the antidepressant effects of asiaticoside, a major triterpenoid constituent of *Centella asiatica*. Oral administration of asiaticoside to mice subjected to chronic unpredictable mild stress (CUMS) significantly improved depressive-like behavior, which was associated with modulation of the gut microbiota composition, increased short-chain fatty acid (SCFA) levels, and normalization of HPA axis hormone levels [10]. This study highlights the multi-target, systems-level actions of Ayurvedic botanicals and underscores the potential of the gut microbiome as a novel therapeutic target for stress-related disorders.

3.4.2 Clinical Evidence

The clinical evidence base for HPA axis modulation by *Centella asiatica* in human subjects is limited. While several small-scale clinical trials have reported anxiolytic and cognitive-enhancing effects, few have incorporated direct measurement of HPA axis biomarkers. The sedative and anxiolytic qualities of *Centella asiatica* are thought to be associated with regulation of the HPA axis and modulation of GABAergic neurotransmission [9]. However, well-designed RCTs with cortisol or ACTH as outcome measures are conspicuously absent from the literature. Given the compelling preclinical data, clinical investigations that include neuroendocrine stress markers are a high priority for future research.

3.5 *Ocimum sanctum* (*Tulsi* / Holy Basil)

Ocimum sanctum L. (syn. *Ocimum tenuiflorum* L., family Lamiaceae), commonly known as *Tulsi* or Holy Basil, is a sacred plant in the Hindu tradition and a cornerstone of Ayurvedic household medicine [29]. It is classified as a *Rasayana* and is traditionally employed for a wide range of ailments, including respiratory infections, fever, and stress-related disorders. The leaves contain a complex essential oil rich in eugenol, ursolic acid, rosmarinic acid, and various flavonoids, which collectively contribute to its adaptogenic, immunomodulatory, and antioxidant properties.

3.5.1 Preclinical Evidence

Preclinical studies have demonstrated that *Ocimum sanctum* extracts protect against stress-induced biochemical and behavioral perturbations. In rodent models, *Tulsi* administration attenuates stress-induced elevations in plasma corticosterone and normalizes adrenal gland weight and ascorbic acid content [23]. Mechanistic studies suggest that these effects are mediated, at least in part, by modulation of central monoaminergic systems and the HPA axis.

3.5.2 Clinical Evidence

A randomized, double-blind, placebo-controlled trial published in 2024 examined the effects of a standardized *Ocimum Tenuiflorum* extract (Holixer™, 250 mg/day) on stress, mood, and sleep in 100 adults experiencing stress. After eight weeks of supplementation, the treatment group exhibited significantly lower hair cortisol levels—a biomarker that reflects long-term HPA axis activity—compared to placebo. Additionally, improvements in perceived stress scores and sleep efficiency were observed, although total sleep time did not significantly differ between groups [14]. This study provides robust clinical evidence that *Tulsi* supplementation can modulate chronic HPA axis activity in stressed individuals.

Furthermore, polyherbal formulations containing *Ocimum sanctum* in combination with other Ayurvedic botanicals have shown promise in preclinical and clinical settings. A review highlighted that formulations containing *Tulsi* and turmeric (*Curcuma longa*) exert antidepressant effects via HPA axis modulation and 5-HT1A receptor agonism, with efficacy superior to the single agent fluoxetine (FLX) in certain preclinical paradigms [1]. This underscores the synergistic potential of Ayurvedic polyherbal formulations, which is a defining feature of traditional practice.

3.6 *Glycyrrhiza glabra* (*Yashtimadhu* / Licorice)

Glycyrrhiza glabra L. (family Fabaceae), known as *Yashtimadhu* in Ayurveda and licorice in Western herbalism, is a widely used *Medhya Rasayana* and *Rasayana* agent. The root contains glycyrrhizin (a triterpenoid saponin glycoside of glycyrrhetinic acid), flavonoids, and isoflavonoids. Glycyrrhizin is a potent inhibitor of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), the enzyme that converts active cortisol to inactive cortisone in the kidney and other mineralocorticoid target tissues. Consequently, licorice consumption can elevate local cortisol concentrations and potentiate mineralocorticoid receptor activation, leading to sodium retention and hypertension with chronic high-dose intake [30].

Despite this caveat, *Glycyrrhiza glabra* exerts complex and context-dependent effects on the HPA axis. Preclinical studies indicate that licorice extracts and isolated glycyrrhizin can attenuate stress-induced HPA axis activation, likely through central mechanisms involving modulation of CRH and ACTH release. The flavonoid constituents, which

possess GABA-A receptor modulatory and antioxidant properties, are thought to contribute to the anxiolytic and neuroprotective effects. A 2025 review noted that *Glycyrrhiza glabra* modulates HPA axis balance by interfacing with GABA-A, NMDA, and glucocorticoid receptors, thereby reducing neuroinflammation and oxidative stress [1]. However, the clinical use of licorice for stress management is constrained by the risk of pseudoaldosteronism with prolonged high-dose exposure, and thus it is more commonly employed as a component of balanced polyherbal formulations.

3.7 Other Ayurvedic Botanicals

Several other Ayurvedic herbs, while less extensively characterized with respect to HPA axis modulation, merit brief mention. *Asparagus racemosus* (*Shatavari*) is an adaptogenic herb traditionally used for female reproductive health and as a general tonic. Recent literature indicates that *Shatavari* may mitigate HPA axis hyperactivity and its deleterious effects on the inflammatory-immune response [19]. *Convolvulus pluricaulis* (*Shankhpushpi*), a *Medhya Rasayana* herb, has been shown in preclinical studies to reduce oxidative stress and cytokine levels while modulating the HPA axis and enhancing BDNF expression [3]. *Nardostachys jatamansi* (*Jatamansi*), a member of the Valerianaceae family, is traditionally used for insomnia, anxiety, and nervous disorders; its sedative and anxiolytic properties are likely mediated, in part, by central GABAergic mechanisms and potential HPA axis modulation, although direct evidence is sparse.

3.8 Polyherbal Formulations

A distinctive feature of Ayurvedic pharmacotherapy is the use of complex polyherbal formulations, which are designed to achieve synergistic therapeutic effects and mitigate potential toxicities. Several such formulations have been investigated for their adaptogenic and HPA-modulating properties.

Amalakayas Rasayana (AR), a compound Ayurvedic formulation containing *Emblica officinalis* (*Amla*) as the primary ingredient, has demonstrated significant adaptogenic and anti-stress activity in preclinical studies. The observed effects are attributed to attenuation of stress-induced stimulation of the HPA axis and cytoprotective actions [18].

EuMil, a polyherbal formulation comprising standardized extracts of *Withania somnifera*, *Ocimum sanctum*, *Asparagus racemosus*, and *Emblica officinalis*, has been shown to ameliorate chronic stress-induced homeostatic perturbations in rats, with effects on HPA axis activity and oxidative stress markers [19].

Medhya Rasayana, a classical polyherbal formulation containing *Bacopa monnieri*, *Convolvulus pluricaulis*, *Glycyrrhiza glabra*, and *Tinospora cordifolia* (*Guduchi*), has been evaluated in clinical studies for cognitive impairment and shown to possess anti-stress, antidepressant, and anxiolytic properties [3, 17].

These formulations exemplify the Ayurvedic principle of synergistic polypharmacy and represent promising candidates for further rigorous clinical evaluation.

4. Discussion

4.1 Summary of Evidence

The body of evidence reviewed herein substantiates the proposition that Ayurvedic pharmacotherapy—particularly *Rasayana* and *Medhya Rasayana* herbs and formulations—exerts significant modulatory effects on the HPA axis and associated neuroendocrine stress markers. The most robust evidence supports *Withania somnifera* (*Ashwagandha*), for which multiple high-quality RCTs have demonstrated consistent reductions in serum cortisol and improvements in stress-related symptomatology [13, 21, 22]. The clinical data for *Ocimum sanctum* (*Tulsi*), though less voluminous, are similarly encouraging, with a well-designed RCT showing reductions in long-term HPA axis activity as reflected by hair cortisol levels [14]. Preclinical evidence for *Bacopa monnieri* (*Brahmi*) and *Centella asiatica* (*Mandukaparni*) is compelling, but the clinical translation remains incomplete, particularly with respect to direct measurement of HPA axis biomarkers [6, 9, 12].

4.2 Mechanistic Convergence

A notable theme that emerges from the mechanistic literature is the convergence of multiple, mutually reinforcing pathways that collectively restore HPA axis homeostasis and enhance stress resilience. These include:

- **Upstream Modulation of CRH and ACTH:** Several Ayurvedic botanicals, most notably *Ashwagandha*, downregulate CRH expression in the PVN and reduce the sensitivity of stress-responsive hypothalamic neurons, thereby attenuating the initial drive of the HPA cascade [2].
- **Restoration of Glucocorticoid Feedback:** Chronic stress induces glucocorticoid receptor (GR) resistance, impairing negative feedback inhibition and perpetuating HPA axis hyperactivity. Preclinical studies suggest that *Rasayana* herbs may restore GR sensitivity and enhance feedback efficiency, although the precise molecular mechanisms remain to be

fully elucidated.

- **Mitigation of Oxidative and Nitrosative Stress:** The brain, particularly the hippocampus and prefrontal cortex, is exquisitely vulnerable to oxidative damage induced by chronic glucocorticoid exposure. The robust antioxidant properties of Ayurvedic herbs—mediated via upregulation of Nrf2-ARE signaling, direct free radical scavenging, and enhancement of endogenous antioxidant enzyme activity—protect neuronal integrity and preserve the structural and functional substrates of HPA axis regulation [6, 9].
- **Preservation of Neuroplasticity:** Chronic stress and elevated glucocorticoids impair hippocampal neurogenesis, reduce dendritic arborization, and downregulate BDNF expression. Multiple Ayurvedic botanicals, including *Ashwagandha*, *Brahmi*, and *Shankhpushpi*, have been shown to upregulate BDNF and promote neuroplasticity, thereby counteracting the deleterious effects of stress on brain structure and function [3, 6, 20].
- **Modulation of Neurotransmitter Systems:** Many Ayurvedic herbs interface with central monoaminergic (serotonin, dopamine, norepinephrine) and GABAergic systems, which are intimately coupled to HPA axis regulation. The anxiolytic and mood-stabilizing effects of these herbs likely reflect an integrated modulation of neuroendocrine and neurotransmitter pathways [1, 27].

4.3 Methodological Limitations and Gaps

Despite the encouraging findings, the field is beset by several methodological limitations that temper the strength of the conclusions and impede the integration of Ayurvedic pharmacotherapy into evidence-based clinical practice.

Heterogeneity in Extract Standardization: A major impediment to reproducibility and inter-study comparison is the lack of uniform standardization of herbal extracts. The concentration of bioactive constituents (e.g., withanolides in *Ashwagandha*, bacosides in *Brahmi*) can vary substantially depending on the plant part used, geographic origin, cultivation practices, extraction solvent, and manufacturing process. This variability complicates the determination of optimal dosing and the attribution of observed effects to specific phytochemical constituents.

Small Sample Sizes and Short Duration: The majority of clinical trials conducted to date have employed relatively small sample sizes (typically *n* = 30–100) and short intervention periods (4–12 weeks). While these studies provide valuable proof-of-concept data, they are underpowered to detect modest effect sizes, evaluate long-term safety and sustainability, and explore potential subgroup differences (e.g., based on sex, age, or baseline HPA axis status) [13, 21].

Inconsistent Outcome Measures: While serum cortisol is the most commonly reported neuroendocrine outcome, the timing of sample collection (morning vs. evening, single time point vs. serial measurements) and the analytical methodology (radioimmunoassay, ELISA, liquid chromatography–tandem mass spectrometry) vary widely across studies. Furthermore, few studies have incorporated more sophisticated measures of HPA axis function, such as the dexamethasone suppression test, the cortisol awakening response, or hair cortisol concentration [14].

Paucity of Long-Term Safety Data: Although Ayurvedic herbs are generally regarded as safe when used appropriately, the long-term safety profile of high-dose or prolonged supplementation is not well characterized. Potential concerns include hepatotoxicity (rare but documented for certain herbs), thyroid function alterations, drug–herb interactions, and, in the case of *Glycyrrhiza glabra*, mineralocorticoid excess [30].

Publication Bias and Funding-Related Conflicts: A significant proportion of clinical trials on *Ashwagandha* and other Ayurvedic herbs have been sponsored by commercial entities involved in the manufacture and marketing of herbal supplements. While this does not inherently invalidate the findings, it introduces a potential source of bias that must be acknowledged and addressed through independent, investigator-initiated research.

4.4 Future Directions

To advance the field and facilitate the evidence-based integration of Ayurvedic pharmacotherapy into mainstream stress management paradigms, the following research directions are proposed:

1. Elucidation of Molecular Targets: Advanced omics technologies—including transcriptomics, proteomics, and metabolomics—should be employed to identify the precise molecular targets and signaling pathways engaged by Ayurvedic botanicals. Network pharmacology and systems

biology approaches can help unravel the complex, multi-target mechanisms of action and identify synergistic interactions among phytochemical constituents.

2. Rigorous Clinical Trials: Large-scale, multicenter, randomized, double-blind, placebo-controlled trials with adequate power, extended follow-up periods, and comprehensive outcome assessment are urgently needed. Such trials should incorporate standardized extracts with well-characterized phytochemical profiles, employ validated and objective measures of HPA axis function (e.g., serial serum/ salivary cortisol, hair cortisol, ACTH stimulation tests), and adhere to Consolidated Standards of Reporting Trials (CONSORT) guidelines for herbal interventions.

3. Personalized and Precision Approaches: Given the inter-individual variability in stress responses and HPA axis regulation, future research should explore pharmacogenomic and other biomarkers that predict therapeutic response to Ayurvedic interventions. The Ayurvedic framework of *Prakriti* (individual constitutional type) offers a promising, albeit underexplored, basis for personalized treatment selection [24].

4. Mechanistic Clinical Studies: Clinical investigations that incorporate neuroimaging (e.g., functional MRI to assess hippocampal and prefrontal cortical activity), polysomnography, and detailed neuroendocrine profiling will help bridge the gap between preclinical mechanisms and clinical outcomes, providing a more nuanced understanding of how Ayurvedic pharmacotherapy impacts brain function and stress resilience in humans.

5. Safety and Pharmacovigilance: Systematic collection and analysis of adverse event data, drug–herb interaction studies, and long-term safety surveillance are essential to inform clinical practice and regulatory decision-making.

6. Integration with Non-Pharmacological Interventions: Ayurveda is inherently holistic, encompassing dietary modifications, lifestyle practices (e.g., *Dinacharya* and *Ritucharya*), yoga, *Pranayama*, and meditation alongside pharmacotherapy. Future research should investigate the synergistic effects of combining Ayurvedic herbs with these non-pharmacological modalities, which may enhance therapeutic efficacy and promote sustained stress resilience [15, 16].

4.5 Limitations of This Review

This review has several limitations that warrant acknowledgment. First, the search was restricted to English-language publications, which may have excluded relevant studies published in regional languages, including Sanskrit and Hindi. Second, the narrative synthesis approach, while appropriate given the heterogeneity of the literature, is inherently less quantitative than a formal meta-analysis and may be subject to interpretive bias. Third, the exclusion of studies older than ten years may have omitted seminal early work that laid the foundation for contemporary investigations. Finally, the scope was deliberately circumscribed to the most prominent Ayurvedic botanicals; a comprehensive treatise on the full pharmacopoeia of Ayurvedic stress-modulating agents is beyond the purview of a single review article.

5. Conclusion

The modulation of the HPA axis and neuroendocrine stress markers by Ayurvedic pharmacotherapy represents a fertile and rapidly evolving domain of translational research. The extant preclinical and clinical evidence, particularly for *Withania somnifera* and *Ocimum sanctum*, provides a compelling rationale for the use of these botanicals as adjunctive or alternative interventions for stress-related disorders [2, 13, 14]. The multi-target, systems-level mechanisms of action—encompassing CRH downregulation, glucocorticoid receptor restoration, oxidative stress mitigation, and neuroplasticity preservation—distinguish Ayurvedic adaptogens from conventional single-target pharmacotherapies and align with contemporary models of resilience and allostasis.

Nevertheless, significant methodological challenges persist, and the translation of promising preclinical findings into robust clinical evidence remains incomplete for many Ayurvedic agents. The path forward demands a concerted, interdisciplinary effort that integrates the rigor of modern biomedical science with the holistic, individualized wisdom of Ayurvedic tradition. By embracing advanced omics technologies, conducting well-designed clinical trials, and fostering collaboration between Ayurvedic practitioners, pharmacologists, and clinical researchers, the full therapeutic potential of Ayurvedic pharmacotherapy for HPA axis modulation and stress resilience can be realized, offering a valuable complement to conventional approaches in the management of the global burden of stress-related illness.

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