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Review Article

Integrated Management of Cortisol: A Multidimensional Perspective

Acharya Balkrishna[1,2], Nidhi Sharma[1], Sanu Diwakar[1], Razia Parveen[1], Ankita Kukreti[1], Bhavya Trivedi[3], Deepika Srivastava[1*] and Vedpriya Arya[1,2]

[1]Patanjali Herbal Research Department, Patanjali Research Institute, Haridwar, Uttarakhand, India; [2]University of Patanjali, Patanjali Yogpeeth, Haridwar, Uttarakhand, India; [3]School of Applied & Lifesciences, UIT, Uttaranchal University, Dehradun, Uttarakhand, India

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Abstract

Cortisol, the body's primary glucocorticoid, is central to maintaining homeostasis through its regulation of metabolism, immunity, cardiovascular tone, and neurobehavioral functions. However, chronic dysregulation of the hypothalamic–pituitary–adrenal axis, whether from persistent psychological stress, lifestyle imbalance, or circadian disruption, contributes to diverse metabolic, psychiatric, and inflammatory disorders. This comprehensive review aims to explore cortisol physiology, mechanisms of dysregulation, and emerging strategies for restoring hormonal balance through integrative management. Conventional approaches such as pharmacotherapy and surgical interventions remain essential for severe endocrine disorders like Cushing's syndrome and Addison's disease; however, they inadequately address chronic, stress-related dysfunction. Nutritional modulation, sleep optimization, moderate physical activity, and mind-body therapies, including *yoga*, meditation, and mindfulness-based stress reduction, demonstrate measurable reductions in cortisol and inflammatory cytokines. Adaptogenic botanicals such as *Withania somnifera*, *Ocimum tenuiflorum*, *Rhodiola rosea*, and *Panax ginseng* exhibit robust evidence for normalizing cortisol and enhancing resilience through hypothalamic–pituitary–adrenal axis modulation. Complementary modalities such as acupuncture, naturopathy, and homeopathy show potential in improving autonomic and neuroendocrine balance. By synthesizing biomedical, nutritional, psychological, and traditional perspectives, this review proposes an integrated model of cortisol management that harmonizes physiology and behavior. Such multidimensional frameworks offer promising, evidence-based pathways for mitigating stress-related diseases and promoting holistic well-being.

Introduction

Cortisol is a steroid hormone that plays a pivotal role in the body's metabolic, physiological, and adaptive responses to stress, whether physical (illness, injury, trauma) or psychological (emotional or cognitive strain). Often associated with the "fight-or-flight" response, cortisol equips the body to respond swiftly and effectively to perceived threats. It is synthesized and secreted by the adrenal cortex under the control of a finely tuned neuroendocrine system, the hypothalamic–pituitary–adrenal (HPA) axis, which integrates signals from the central nervous and endocrine systems to maintain homeostasis during stress.[1] In humans, cortisol (and corticosterone in rodents) is synthesized from cholesterol in the zona fasciculata of the adrenal cortex. Its production and secretion are tightly regulated by the HPA axis, which governs both circadian and ultradian rhythms to ensure physiological balance and responsiveness to stress.[2] Cortisol exhibits a well-defined 24-h circadian rhythm, peaking approximately 30 min after awakening, known as the cortisol awakening response (CAR), and gradually declining to reach its lowest point during early sleep. Chronic stress can dysregulate this rhythmicity by overstimulating the HPA axis, thereby contributing to a spectrum of stress-related, metabolic, and psychiatric disorders.[3,4]

Cortisol dysregulation manifests in two major clinical conditions. Hypercortisolism, characterized by elevated cortisol levels, underlies Cushing's syndrome, which is associated with obesity, insulin resistance, hypertension, glucose intolerance, and osteoporosis.[5,6] Conversely, hypocortisolism results from adrenal insufficiency, primary (Addison's disease), secondary, or tertiary, arising from dysfunctions of the adrenal cortex, pituitary, or hypothalamus, respectively. Typical manifestations include fatigue, hypoten-

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***Correspondence to:** Deepika Srivastava, Patanjali Herbal Research Department, Patanjali Research Foundation, Maharishi Dayanand Gram, Delhi-Haridwar National Highway, Near Bahadrabad, Haridwar, Uttarakhand 249405, India. ORCID: https://orcid.org/0000-0001-5234-4364. Tel: +91-8941088889, E-mail: deepika.srivastava@prft.in

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sion, weight loss, hyperpigmentation, and hyperkalemia.[6] Given cortisol's wide-ranging influence on metabolic, immune, and neurobehavioral systems, there is a growing emphasis on integrated therapeutic strategies that combine pharmacological, lifestyle, and mind-body approaches to restore hormonal equilibrium and optimize well-being. Increasing evidence suggests that adaptogenic herbs can modulate cortisol levels and support HPA axis function. Key examples include *Withania somnifera* (Ashwagandha), *Camellia sinensis* (green tea), *Ocimum sanctum* (Tulsi), *Ginkgo biloba*, *Glycyrrhiza glabra* (licorice), and *Elaeagnus angustifolia*.[7–9] Complementary modalities such as massage therapy and acupuncture have also demonstrated efficacy in reducing cortisol levels and alleviating HPA axis dysregulation.[10,11]

Similarly, lifestyle interventions, including adequate sleep, yoga, mindfulness, and balanced nutrition, play a vital role in maintaining cortisol homeostasis.[12–15] Integrated therapeutic frameworks combining physical, dietary, and spiritual components have shown promising results. For instance, a holistic 14-day intervention integrating yoga, dietary regulation, physical therapy, and *dhikr*-based spiritual practice was shown to significantly reduce serum cortisol levels in women with polycystic ovary syndrome, indicating improved stress regulation.[16] Dhikr, a core Islamic contemplative practice aimed at fostering mindfulness and spiritual connectedness, has also been independently associated with reduced anxiety and depression and enhanced psychological well-being, suggesting its potential role in modulating stress-related neuroendocrine responses.[17] Similarly, a 12-week yoga and meditation intervention among medical students led to a marked decrease in morning cortisol levels.[18] These findings underscore that optimal cortisol regulation emerges from the synergy of balanced lifestyle domains, where mindfulness, restorative sleep, and moderate physical activity collectively enhance stress resilience.

This review aims to synthesize current knowledge on an integrated model for cortisol regulation that aligns physiological mechanisms with behavioral interventions. It integrates evidence on mechanisms of dysregulation, assessment strategies, and therapeutic interventions and critically evaluates evidence-based approaches for cortisol regulation. Distinct from existing reviews, this work brings together traditionally fragmented domains into a single, clinically meaningful narrative and proposes a holistic, systems-level framework that transcends isolated, domain-specific treatments. By aligning modern endocrinological insights with traditional and lifestyle-based therapies, the review advances a comprehensive, cortisol-centric approach to health that supports personalized intervention and sustained hormonal balance across body, mind, and environment.

Physiological roles of cortisol

Cortisol influences nearly every organ system by regulating metabolism, immune response, brain activity, cardiovascular function, and reproductive function (Fig. 1). Beyond its role in stress adaptation, cortisol is essential for energy regulation, inflammation control, and maintaining homeostasis. Understanding its physiological roles provides insight into how the body responds to both acute and chronic challenges.

Metabolic regulation (carbohydrate, protein, lipid)

Cortisol plays a central role in regulating the metabolism of carbohydrates, proteins, and lipids to ensure a continuous supply of energy during stressful conditions, such as fasting, exercise, or the fight-or-flight response. As a potent catabolic hormone, its primary function is to maintain adequate glucose availability for the brain. In carbohydrate metabolism, cortisol raises blood glucose levels by stimulating hepatic gluconeogenesis, converting non-carbohydrate substrates like amino acids and glycerol into glucose, while simultaneously reducing glucose uptake in muscle and adipose tissue by inducing insulin resistance. Paradoxically, it also promotes glycogen synthesis in the liver, creating a glucose reserve for future energy demands.[19–21] In protein metabolism, cortisol exerts catabolic effects by promoting proteolysis in skeletal peripheral tissues. The resulting amino acids are transported to the liver to serve as substrates for gluconeogenesis, further supporting glucose production.[22] In lipid metabolism, cortisol has dual effects depending on the duration of exposure: during acute stress, it enhances lipolysis, releasing fatty acids into the bloodstream for immediate energy use; however, chronic cortisol elevation promotes lipogenesis and central fat accumulation, contributing to abdominal obesity and increasing the risk of metabolic disorders, including metabolic syndrome.[23]

Cortisol controls inflammatory and immune responses

Cortisol is a key immunomodulatory hormone that maintains immune homeostasis by regulating both innate and adaptive immune responses. As a glucocorticoid secreted by the adrenal cortex under the control of the HPA axis, cortisol exerts potent anti-inflammatory and immunosuppressive actions, essential for preventing excessive immune activation and tissue damage.[24] At the molecular level, cortisol binds to intracellular glucocorticoid receptors (GRs), which translocate to the nucleus and modulate gene transcription. This interaction inhibits pro-inflammatory transcription factors such as nuclear factor-kappa B and activator protein-1, thereby suppressing the production of cytokines, including interleukin (IL)-1β, tumor necrosis factor-alpha (TNF-α), and IL-6.[25] Cortisol also enhances the expression of anti-inflammatory mediators such as annexin-1 and IL-10, promoting the resolution phase of inflammation.[26]

In addition to cytokine modulation, cortisol influences leukocyte trafficking by reducing the migration of neutrophils and lymphocytes to inflammatory sites, while promoting apoptosis of activated immune cells to terminate immune responses.[27] During stress, transient increases in cortisol help suppress inflammation and maintain immune balance. However, chronic hypercortisolemia, seen in prolonged stress or Cushing's syndrome, can cause immunosuppression and increased infection susceptibility, while hypocortisolism, as in Addison's disease, may result in uncontrolled inflammation and autoimmune tendencies.[28] Thus, cortisol serves as a critical regulator of the immune system, ensuring that inflammatory processes remain proportionate, self-limiting, and compatible with physiological homeostasis.

Cortisol influences cognitive performance, mood, and memory consolidation

Cortisol exerts significant effects on brain function, influencing cognition, emotion, and memory through its actions on the central nervous system. GRs and mineralocorticoid receptors, which mediate cortisol's effects, are abundantly expressed in brain regions critical for cognitive and emotional regulation, particularly the hippocampus, amygdala, and prefrontal cortex.[29,30] Under physiological conditions, moderate cortisol levels facilitate optimal arousal, attention, and memory consolidation, especially for emotionally salient events. Cortisol enhances long-term potentiation in the hippocampus, supporting declarative memory formation, while tran-

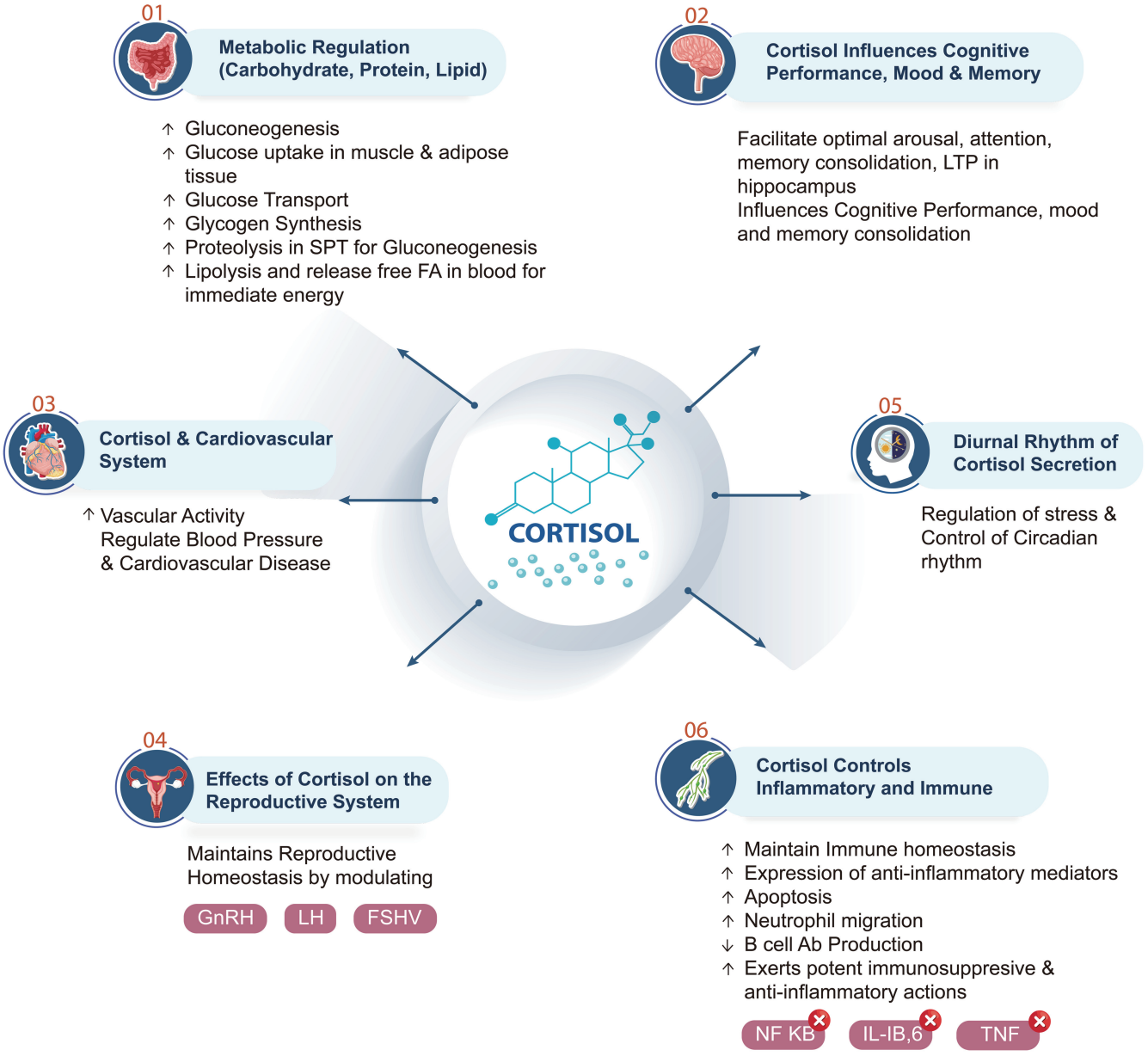

Fig. 1. Multifaceted physiological actions of cortisol across major organ systems. This figure illustrates cortisol as a central stress-responsive glucocorticoid hormone that helps the body adapt to daily demands. Cortisol mobilizes energy by regulating carbohydrate, protein, and lipid metabolism. In the brain, it supports alertness, mood regulation, and memory formation, including long-term potentiation (LTP). Cortisol contributes to cardiovascular stability by modulating vascular tone and blood pressure and supports reproductive homeostasis via effects on gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH). Its tightly regulated diurnal rhythm enables effective stress responses while maintaining circadian control. Cortisol also maintains immune balance by suppressing pro-inflammatory signaling pathways, including nuclear factor kappa B (NF-κB), interleukin (IL)-6, and tumor necrosis factor (TNF). FA, fatty acids; FSHV, follicle-stimulating hormone beta subunit; SPT, serine palmitoyltransferase.

sient increases during stress aid in encoding adaptive responses.[31] However, chronic stress or persistent hypercortisolemia disrupts hippocampal neurogenesis, impairs synaptic plasticity, and contributes to memory deficits, anxiety, and depression.[32] Excessive cortisol exposure is linked to hippocampal atrophy, cognitive decline, and increased risk of neurodegenerative disorders such as Alzheimer's disease.[33,34]

Cortisol also modulates emotional processing via its effects on the amygdala and prefrontal cortex, influencing mood and executive control. Acute elevations may improve focus and threat recognition, whereas prolonged elevations blunt emotional regulation, increase rumination, and predispose to mood disorders.[35] Conversely, hypocortisolism, often observed in chronic fatigue or post-traumatic stress disorder, is associated with emotional numbing and impaired stress resilience. Thus, maintaining balanced cortisol secretion is vital for cognitive health, emotional stability, and adaptive memory processing across varying stress conditions.

Cortisol and the cardiovascular system

Cortisol plays a vital role in maintaining cardiovascular homeostasis and regulating blood pressure through its effects on the heart, blood vessels, and hormonal pathways. It enhances vascular responsiveness to catecholamines such as epinephrine and norepinephrine, promoting vasoconstriction and sustaining systemic vascular resistance. This action involves upregulation of α-adrenergic receptors on vascular smooth muscle and modulation of endothelial nitric oxide production, thereby balancing vasoconstrictive and vasodilatory signals.[36,37] Cortisol also interacts with the renin-angiotensin-aldosterone system, influencing renal sodium and water retention by increasing the sensitivity of renal tubules to angiotensin II and inducing mineralocorticoid-responsive genes, thus maintaining circulating volume and stable blood pressure.[38]

At the cardiac level, cortisol modulates myocardial contractility, heart rate, and energy metabolism, ensuring sufficient energy substrate availability during stress. Through glucocorticoid and mineralocorticoid receptor interactions, it affects cardiac output and vascular tone, while chronic excess, as in Cushing's syndrome, can result in hypertension, arterial stiffness, and increased cardiovascular risk. Conversely, cortisol deficiency, such as in Addison's disease, leads to hypotension and impaired vascular responsiveness, underscoring its essential role in cardiovascular stability.[39,40]

Effects of cortisol on the reproductive system

Cortisol exerts profound regulatory effects on the reproductive system, primarily through its influence on the hypothalamic-pituitary-gonadal axis. Under physiological conditions, cortisol helps maintain reproductive homeostasis by modulating gonadotropin-releasing hormone (GnRH), luteinizing hormone, and follicle-stimulating hormone secretion. However, elevated cortisol levels, such as during chronic stress, can suppress reproductive function by inhibiting GnRH release from the hypothalamus and reducing pituitary responsiveness to gonadotropins.[41,42] This suppression leads to decreased secretion of sex steroids like estrogen and testosterone, impairing gametogenesis and reproductive behavior. In females, hypercortisolemia is associated with menstrual irregularities, anovulation, and reduced fertility due to impaired ovarian steroidogenesis and follicular development.[43] In males, excessive cortisol can lower testosterone synthesis, impair spermatogenesis, and cause erectile dysfunction by inhibiting Leydig cell activity and altering testicular blood flow.[44] Furthermore, cortisol interacts with glucocorticoid and mineralocorticoid receptors in reproductive tissues, influencing local gene expression and reproductive tissue integrity. Conversely, cortisol deficiency, as seen in Addison's disease, may also disrupt reproductive function due to impaired metabolic and hormonal balance. Thus, optimal cortisol levels are essential for normal reproductive physiology, while dysregulation, either excess or deficiency, can significantly compromise fertility and sexual health.

Diurnal rhythm of cortisol secretion

Cortisol secretion is tightly regulated by the HPA axis and follows a robust circadian rhythm that aligns with the body's sleep–wake cycle. Under normal physiological conditions, cortisol levels begin to rise during the late night or early morning hours (around 3–4 a.m.), peaking approximately 30–45 min after awakening, a phenomenon known as the CAR.[3,45] This early morning surge promotes wakefulness, energy mobilization, and cognitive alertness by enhancing gluconeogenesis and increasing blood glucose availability.

Following its morning peak, cortisol levels gradually decline throughout the day, reaching their lowest point (nadir) during the late evening and early sleep phases.[46] This rhythmic pattern is orchestrated by the suprachiasmatic nucleus (SCN) of the hypothalamus, which synchronizes adrenal activity with environmental light–dark cycles. Maintaining a healthy diurnal cortisol rhythm is crucial for overall homeostasis. Proper sleep hygiene, exposure to natural light, and regular daily routines help sustain this natural hormonal cycle, supporting physical vitality and psychological well-being.

Collectively, cortisol serves as a master regulator of physiological balance, influencing metabolism, cardiovascular stability, immune defense, cognition, reproduction, and circadian homeostasis. Its dynamic and context-dependent actions ensure optimal adaptation to both internal and external challenges. However, persistent dysregulation, whether hyper- or hypocortisolemia, can disrupt this equilibrium, leading to a range of metabolic, psychological, and reproductive disorders. Understanding these diverse physiological roles is therefore crucial for designing targeted interventions that promote adaptive resilience and holistic health.

Dysregulation of cortisol: Mechanisms and consequences

Cortisol dysregulation disrupts the finely balanced HPA axis, leading to significant physiological and psychological consequences. Both excess and deficiency in cortisol secretion can impair metabolic, immune, and neuroendocrine functions, contributing to a wide range of stress-related and chronic disorders. Under normal conditions, the HPA axis responds to stressors via a cascade: corticotropin-releasing hormone (CRH) from the hypothalamus stimulates adrenocorticotropic hormone (ACTH) release from the anterior pituitary, which in turn prompts cortisol synthesis in the zona fasciculata. Cortisol exerts negative feedback on the hypothalamus and pituitary via GRs, ensuring pulsatile, circadian-regulated secretion, peaking at awakening and declining nocturnally. However, dysregulation disrupts this balance, manifesting as hypersecretion, hyposecretion, or circadian misalignment, often compounded by allostatic load—the cumulative physiological toll of repeated stress adaptations that, when excessive, fosters maladaptive responses such as sustained inflammation and insulin resistance. This section elucidates these patterns, integrating biomarker insights and epigenetic programming, drawing from human and preclinical evidence to underscore clinical relevance in integrated cortisol management (Fig. 2).

HPA axis dysregulation: Allostatic load and maladaptive stress responses

The concept of allostasis describes proactive physiological adjustments to anticipated stressors, contrasting with homeostasis's reactive maintenance. Allostatic load arises when these adaptations overburden systems, particularly the HPA axis, leading to dysregulation characterized by altered cortisol trajectories: blunted awakening responses, flattened diurnal slopes, or impaired feedback. In chronic stress, persistent CRH and ACTH elevation overwhelms GR-mediated inhibition, promoting glucocorticoid resistance and visceral adiposity. This maladaptive shift is bidirectional; for instance, in type 2 diabetes mellitus (T2DM), hyperglycemia impairs hippocampal GR sensitivity, exacerbating HPA hyperactivity and perpetuating a cycle of insulin resistance and depressive symptoms. Longitudinal cohorts, such as the Multi-Ethnic Study of Atherosclerosis, reveal that higher allostatic load, quantified via multisystem biomarkers including cortisol, associates with 36%

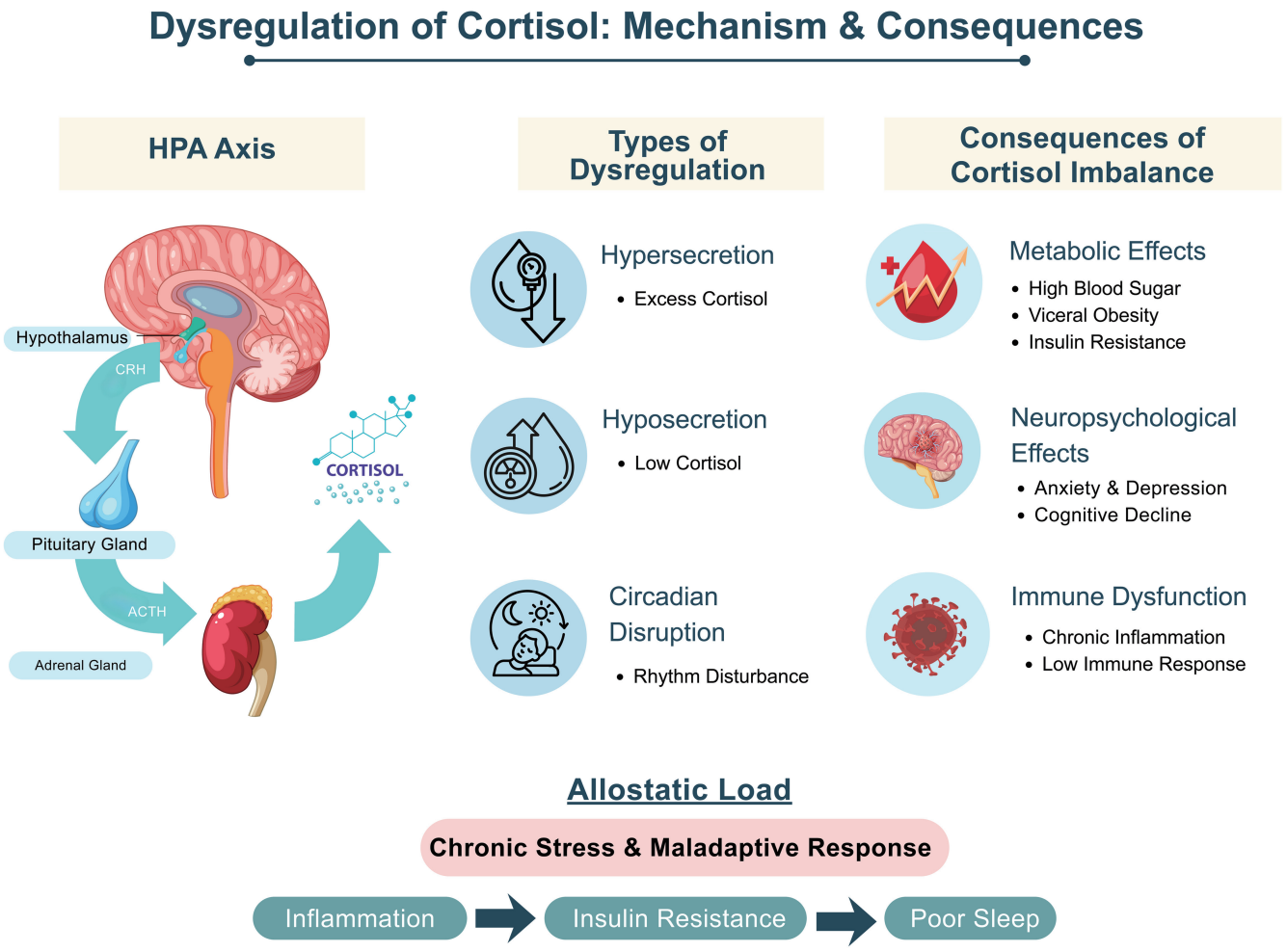

Fig. 2. Mechanisms of cortisol dysregulation and their systemic consequences. This figure summarizes how disruption of the hypothalamic–pituitary–adrenal (HPA) axis alters cortisol regulation and contributes to disease risk. Under normal conditions, cortisol is released through coordinated signaling between the hypothalamus (corticotropin-releasing hormone, CRH), pituitary gland (adrenocorticotropic hormone, ACTH), and adrenal glands. Chronic stress can lead to hypercortisolism (excess cortisol), hypocortisolism (insufficient cortisol), or circadian rhythm disruption, each representing distinct patterns of HPA axis dysregulation. These alterations are associated with adverse metabolic outcomes (e.g., hyperglycemia, visceral obesity, insulin resistance), neuropsychological effects (anxiety, depression, cognitive decline), and immune dysfunction (chronic inflammation and impaired immune responses). Persistent cortisol imbalance increases allostatic load, promoting maladaptive stress responses and reinforcing a vicious cycle linking inflammation, insulin resistance, and poor sleep quality.

greater salivary cortisol output during stress in diabetics, alongside poorer recovery in heart rate and blood pressure.[47–49]

Maladaptive responses vary by stressor chronicity and demographics. Acute stress elicits adaptive cortisol surges for energy mobilization, but chronic psychological strain (e.g., job strain) flattens decline slopes, correlating with higher evening cortisol and T2DM incidence (hazard ratio 1.33). Racial/ethnic differences emerge: discrimination predicts steeper slopes in African Americans but flatter curves in other minorities, highlighting intersectional vulnerabilities. In depression, HPA dysregulation manifests as elevated morning area-under-the-curve (AUC) cortisol, with blunted CAR forecasting recurrence. Preclinical models reinforce this; chronic corticosterone exposure in rodents reduces *Fkbp5* methylation, amplifying GR sensitivity and anxiety-like behaviors. Clinically, selective serotonin reuptake inhibitors normalize AUC cortisol, improving glycemic control in comorbid cases. Thus, allostatic overload unifies HPA perturbations across metabolic and psychiatric domains, advocating for multimodal interventions targeting feedback loops.[49,50] The characteristic patterns and consequences of HPA axis dysregulation, encompassing allostatic load, maladaptive cortisol feedback, and demographic variability, are summarized in Table 1.[48,50–52]

Hypersecretion of cortisol: Clinical syndromes and metabolic links

Hypercortisolism, or excessive glucocorticoid exposure, underlies a spectrum from subclinical states to overt Cushing's syndrome, affecting approximately 2–8 cases per million people annually, with a clear female predominance (about 70–75% of cases) and a female-to-male ratio of nearly 3–4:1.[53,54] Endogenous Cushing's syndrome arises in 80–85% from ACTH-dependent sources (e.g., pituitary adenomas in Cushing disease) or 15–20% from ACTH-independent adrenal pathologies (e.g., adenomas, carcinomas).[55] Exogenous iatrogenic forms dominate, stemming from glucocorti-

Table 1. Key aspects of HPA axis dysregulation and their associated physiological and clinical outcomes

Aspect of HPA dysregulation	Key features	Associated outcomes	Example evidence	References
Allostatic load	Cumulative "wear and tear" from chronic activation; multisystem involvement (HPA, autonomic, immune)	Insulin resistance, hippocampal atrophy, T2DM risk	MESA cohort: 36% higher cortisol output in diabetics during stress	48
Maladaptive response	Flattened diurnal curve, impaired GR feedback	Depression recurrence, visceral obesity	Whitehall II Study: Higher evening cortisol predicts incident T2DM (OR = 1.18)	50
Demographic variability	Sex/race differences in slope steepness	Heightened risk in women/minorities under discrimination	Flatter slopes in non-African American minorities	51,52

GR, glucocorticoid receptor; HPA, hypothalamic–pituitary–adrenal; MESA, Multi-Ethnic Study of Atherosclerosis; OR, odds ratio; T2DM, type 2 diabetes mellitus.

coid therapy, while pseudo-Cushing states mimic via physiologic surges in obesity, alcoholism, or depression.[56]

Classically, Cushing's syndrome presents with central obesity ("buffalo hump," moon facies), proximal myopathy, wide purple striae (>1 cm), hypertension, and hyperglycemia—features driven by cortisol's promotion of lipolysis, gluconeogenesis, and sodium retention. In obesity and metabolic syndrome, functional hypercortisolism exacerbates visceral adipogenesis; 11β-hydroxysteroid dehydrogenase type 1 regenerates active cortisol in adipose tissue, linking to dyslipidemia and insulin resistance. Depression intersects via HPA hyperactivity: 50–81% of Cushing's syndrome patients develop major depressive disorder, with elevated CAR and evening cortisol mirroring chronic stress patterns. Chronic stress itself induces subclinical hypercortisolism, graded by intensity; for example, work strain doubles T2DM risk in women via sustained ACTH. Untreated, hypercortisolism triples cardiovascular mortality through endothelial damage and hypercoagulability, underscoring urgency in screening adrenal incidentalomas (prevalence 1–9%).[57–59]

Hyposecretion of cortisol: Adrenal insufficiency and fatigue syndromes

Hypocortisolism, conversely, reflects adrenal cortex underproduction, spanning primary (Addison's disease), secondary (pituitary ACTH deficiency), and tertiary (hypothalamic CRH loss) forms. Primary adrenal insufficiency, or Addison's, affects 100–140 per million, primarily autoimmune (90% via anti-21-hydroxylase antibodies), with insidious onset: fatigue (universal), weight loss, hypotension, and salt craving from aldosterone deficit. Hyperpigmentation (due to elevated ACTH/MSH) distinguishes primary from secondary/tertiary, where mineralocorticoids remain intact. Infections (e.g., tuberculosis, HIV), hemorrhage, or metastases account for 10–20% of cases; congenital adrenal hyperplasia predominates in pediatrics (1:14,200 births).[60,61]

Fatigue-related syndromes, including chronic fatigue syndrome, overlap with secondary insufficiency post-glucocorticoid withdrawal or Sheehan syndrome, manifesting as orthostatic intolerance, anorexia, crisis, hypotension, hyponatremia, hyperkalemia, and hypoglycemia, triggered by infection or surgery (mortality 5–10% if untreated). Mechanisms involve disrupted energy metabolism and stress unresponsiveness; hypocortisolism impairs catecholamine sensitization, worsening autonomic instability. In chronic fatigue syndrome, subtle HPA blunting correlates with symptom severity, though not all cases confirm frank insufficiency. Lifelong hydrocortisone replacement normalizes prognosis, but "sick day rules" are critical to avert crises.[62]

Circadian disruption: Lifestyle factors and disease risks

Disruption of the physiological circadian rhythm of cortisol, characterized by a ~50% CAR occurring 30–45 min post-awakening followed by an approximately 75% decline by evening, has wide-ranging metabolic, cardiovascular, immune, and neurocognitive consequences. Chronic stress, night-shift work, jet lag, and sleep deprivation impair SCN-mediated synchronization of ultradian and circadian cortisol oscillations, resulting in flattened diurnal slopes and elevated nocturnal cortisol levels.[63,64] For instance, Leproult *et al*.[65] demonstrated that a single night of restricted sleep caused a significant rise in evening cortisol concentrations, indicating an acute stress response. Similarly, chronic partial sleep deprivation in healthy adults disrupted the cortisol nadir and prolonged nocturnal secretion, leading to reduced recovery and heightened stress reactivity. These findings highlight the sensitivity of the HPA axis to sleep quality and duration.[66] Large-scale epidemiological studies have confirmed the long-term implications of poor sleep on cortisol regulation. A landmark cohort study involving 3,314 participants assessed the association between recurrent short sleep (≤5 h), chronic insomnia, and diurnal cortisol rhythm.[67] Individuals with persistent sleep disturbances exhibited a flatter diurnal cortisol slope—marked by a steeper morning rise and elevated evening levels—compared to those with adequate sleep. This pattern signifies chronic HPA axis activation and impaired physiological recovery. Such dysregulation predisposes individuals to fatigue, anxiety, depression, and cardiometabolic diseases.

Shift work disrupts circadian rhythms and may elevate the risk of metabolic disorders. A cohort study of 1,499 oilfield workers found a higher prevalence of T2DM among shift workers (6.56%) compared with day workers (4.21%). After adjusting for confounders, shift work remained a significant risk factor for T2DM (odds ratio = 1.91, 95% confidence interval: 1.17–3.14). Additionally, shift workers exhibited significantly higher retinol-binding protein-4 levels, suggesting its potential role as an early biomarker for T2DM risk in this population.[68] Poor sleep hygiene further compounds these effects by reducing sleep efficiency and increasing sympathetic tone, while artificial light exposure at night suppresses melatonin and sustains HPA axis activation; age-related melatonin decline exacerbates this vulnerability.[69] Importantly, chronotherapeutic strategies, such as timed light exposure and melatonin supplementation, have demonstrated potential to partially restore circadian alignment and mitigate cardiometabolic and neurocognitive risk, underscoring the central role of lifestyle-based prevention. A summary of key behavioral and environmental dis-

Table 2. Major behavioral and environmental disruptors of the HPA axis: their cortisol-related impacts, associated metabolic and cardiovascular risks, and evidence-based mitigation strategies

Disruptor	Cortisol impact	Associated risks	Mitigation strategies	References
Shift work	Flattened slope, elevated evening levels	Diabetes (HR 1.09/5 yrs), CVD (20–40% ↑)	Rotating forward schedules, napping	70,71
Jet lag	Acute desynchronization, blunted CAR	Transient metabolic inflexibility	Melatonin 0.5–5 mg pre-flight	72,73
Poor sleep hygiene	Sustained hypercortisolism	Neurodegeneration, inflammation	Consistent bedtime, blue-light avoidance	74,75

CAR, cortisol awakening response; CVD, cardiovascular disease; HPA, hypothalamic–pituitary–adrenal; HR, hazard ratio.

ruptors, their cortisol-related impacts, associated health risks, and mitigation strategies is presented in Table 2.[70–75]

Epigenetic influences: Programming by early-life stress and trauma

Early-life stress, including abuse, neglect, or separation, epigenetically "programs" HPA reactivity during neurodevelopmental windows via DNA methylation, histone acetylation, and non-coding RNAs at stress-related genes. The dual-activation hypothesis posits concurrent HPA and sensory network priming: Early-life stress hypermethylates hippocampal GR (Nr3c1 exon 1F), reducing expression and feedback, yielding lifelong hypercortisolism. Rat models of low maternal care replicate this, with *Avp* hypomethylation in the paraventricular nucleus amplifying CRH/AVP synergy; human analogs in suicide victims confirm GR hypermethylation post-maltreatment.[76]

Trauma specificity emerges: sexual abuse thins somatosensory cortices via *BDNF* hypermethylation, impairing neuroplasticity, while verbal trauma thickens auditory regions. *FKBP5* demethylation heightens the risk of post-traumatic stress disorder, with allele-specific effects; sex dimorphism favors male hypersensitivity. Transgenerational echoes appear in *FKBP5* patterns of Holocaust survivors' progeny. Long-term, this fosters psychopathology (depression odds 2–3×) and metabolic sequelae, but plasticity persists; mindfulness reduces GR methylation. Epigenetic clocks thus inform trauma-informed care, prioritizing early screening.[77,78] Altogether, cortisol dysregulation encapsulates a nexus of endocrine, environmental, and genetic factors, demanding integrated approaches: pharmacotherapy for acute states, chronobiology for rhythms, and epigenome-targeted therapies for resilience. Future research should prioritize longitudinal, diverse cohorts to refine predictive models.

Biomarkers of dysregulation

The assessment of cortisol dysregulation necessitates precise and reliable biomarkers that reflect both acute and chronic alterations in HPA axis activity. Since cortisol secretion follows a distinct circadian rhythm and is modulated by stress reactivity, diverse biomarker modalities are employed to capture its dynamic and integrated physiological expression across different timeframes. Serum cortisol remains the most widely used clinical indicator for evaluating adrenal function and acute stress responses. However, its diagnostic utility is limited by substantial diurnal variation, rapid responsiveness to transient stressors, and approximately 95% protein binding to corticosteroid-binding globulin, which restricts its reflection of biologically active cortisol.[79,80] Further, salivary cortisol provides a non-invasive and accurate measure of unbound cortisol, directly representing free hormone concentrations. It is particularly useful in determining the CAR and diurnal slope, key indicators of HPA axis rhythmicity and feedback sensitivity.[81,82] The CAR is typically assessed through saliva samples collected at awakening and at 30- and 60-min intervals post-awakening, quantifying the anticipatory surge that reflects hippocampal–SCN interplay. A blunted CAR is indicative of chronic stress vulnerability and has been associated with recurrent major depressive disorder, impaired cognitive function, and reduced memory performance. Flexibility in CAR dynamics, rather than magnitude alone, better predicts psychological resilience and emotional adaptability.[3,83] Standardized CAR assay kits and AUC analyses enhance reproducibility and distinguish total hormonal output from response kinetics.

Urinary free cortisol, quantifying unbound cortisol excreted over a 24-h period, offers an integrated estimate of total daily secretion. It remains the gold standard in diagnosing hypercortisolism, particularly in Cushing's syndrome, and provides a less time-sensitive measure compared to serum or saliva.[84,85] The dexamethasone suppression test assesses negative feedback sensitivity of the HPA axis by measuring the suppression of endogenous cortisol after administration of exogenous dexamethasone. Impaired suppression reflects feedback resistance, commonly observed in major depression, chronic stress, and other neuroendocrine disorders.[35,86] Further, hair cortisol concentration (HCC) has emerged as a robust biomarker reflecting long-term systemic cortisol exposure, integrating cumulative secretion over weeks to months. Unlike plasma or saliva, which capture momentary snapshots, HCC offers retrospective insights into chronic stress physiology via cortisol diffusion from capillary blood into growing hair shafts. Typically, 3 cm of proximal scalp hair corresponds to approximately three months of cortisol accumulation.[87] Accurate assessment demands reliable biomarkers beyond plasma assays, given that traditional measures capture transient cortisol levels and overlook long-term exposure. HCC levels generally increase with age (ranging from 21–40 pg/mg in adults above 50 years) and exhibit positive correlations with body composition and cardiovascular risk.[88] Its methodological advantages include non-invasiveness (single ~50 mg snip of hair), cost-effectiveness (~$50 per assay), and superior adherence compared to multi-day saliva protocols, particularly in elderly or community settings. Epidemiological studies show that elevated HCC predicts incident T2DM and cardiovascular events, while also serving as a longitudinal biomarker to track intervention efficacy.[89,90] However, external factors such as cosmetic hair treatments or bleaching can confound cortisol recovery and should be controlled for during sampling.

Together, HCC and CAR provide a multidimensional perspective on cortisol physiology, with HCC indexing chronic exposure and CAR reflecting dynamic reactivity, enabling comprehensive profiling of HPA axis function. These biomarkers not only enhance

understanding of stress-related pathophysiology but also guide personalized management strategies by identifying individuals at heightened risk of stress-induced disorders. Collectively, the integration of multiple biomarkers, i.e., serum, salivary, urinary, hair, and dynamic suppression tests, offers a holistic framework for assessing cortisol regulation and dysregulation across temporal domains, improving both diagnostic precision and therapeutic monitoring in clinical and research contexts.

In summary, cortisol dysregulation embodies a complex interplay of neuroendocrine, metabolic, and psychosocial determinants, where sustained allostatic load progressively shifts adaptive stress responses into maladaptive physiological states. From hypercortisolism driving cardiometabolic and psychiatric morbidity to hypocortisolism underlying fatigue syndromes and adrenal insufficiency, the spectrum underscores the bidirectional crosstalk between stress biology and systemic health. Modern lifestyles, characterized by disrupted circadian rhythms, chronic psychological stress, and environmental disturbances, further exacerbate these alterations, heightening disease vulnerability. Epigenetic programming through early-life stress adds a transgenerational layer of risk, reinforcing the need for preventive and restorative strategies. The multidimensional biomarker landscape spanning serum, salivary, urinary, and hair cortisol, along with suppression tests, provides valuable tools for decoding both acute reactivity and chronic exposure, thus enabling individualized stress profiling. Understanding these dysregulatory mechanisms not only deepens insight into the pathophysiology of stress-related disorders but also establishes a scientific foundation for exploring adaptogenic and herbal interventions that restore HPA homeostasis and promote resilience.

Conventional medical approaches for cortisol balancing

Conventional medical approaches for cortisol balancing integrate pharmacological, diagnostic, and psychological strategies aimed at restoring HPA axis homeostasis. Pharmacological interventions are determined by the underlying pathology. In adrenal insufficiency, physiological glucocorticoid replacement remains the cornerstone of therapy, typically with hydrocortisone (15–25 mg/day in divided doses) or prednisone as a longer-acting option. For primary adrenal insufficiency, fludrocortisone is added to replace mineralocorticoid activity and maintain electrolyte balance.[91] In contrast, hypercortisolism or Cushing's syndrome is primarily managed through surgical removal of ACTH- or cortisol-secreting tumors. When surgery is not feasible or is incomplete, pharmacologic therapies such as ketoconazole, metyrapone, mitotane, or osilodrostat are used to inhibit adrenal steroidogenesis and reduce cortisol synthesis.[92,93] Pituitary surgery is considered the first-line treatment for Cushing's disease, achieving remission in about 78% of cases, although nearly one-third experience relapse, necessitating second-line therapies such as pituitary radiotherapy, bilateral adrenalectomy, or long-term medical therapy. The therapeutic goal is to normalize cortisol levels, reverse the clinical manifestations of hypercortisolism, and minimize recurrence risk.[94–96] Medical therapy has gained increasing importance as an adjunct or alternative to surgery, particularly in severe or inoperable cases. Adrenal steroidogenesis inhibitors, such as ketoconazole, metyrapone, mitotane (Lysodren), etomidate, and mifepristone (Korlym, Mifeprex), act by blocking key enzymatic pathways of cortisol biosynthesis, though they do not correct underlying pituitary dysfunction.[97,98] The approval of osilodrostat by the U.S. Food and Drug Administration (FDA) in 2020 represents a significant advancement, offering a potent oral option for cortisol control in Cushing's disease.[99] In adrenal insufficiency, treatment focuses on lifelong glucocorticoid and mineralocorticoid replacement, supplemented by androgen therapy when indicated. Patient education, stress-dose adjustments, and crisis prevention strategies are vital components of management. In cases of adrenal crisis, prompt administration of intravenous fluids and glucocorticoids is lifesaving.[100,101]

Accurate diagnostic evaluation is essential for effective therapy. Serum cortisol, especially morning levels, assists in detecting adrenal insufficiency, while late-night salivary cortisol is a sensitive, noninvasive marker for Cushing's syndrome, identifying loss of the normal nocturnal nadir. Twenty-four-hour urinary free cortisol quantifies total cortisol production and is often used as a confirmatory test. The dexamethasone suppression test remains a cornerstone diagnostic tool for differentiating physiological from pathological cortisol elevation.[102] Expanding diagnostic frontiers now include saliva, urine, interstitial fluid, sweat, and hair cortisol analysis, offering temporal insights into short- and long-term cortisol dynamics.[103] Emerging electrochemical sensors and wearable biosensing platforms allow point-of-care cortisol monitoring, while mass spectrometry and immunoassays remain the gold standards for laboratory-based quantification.[104] In addition to pharmacological and diagnostic strategies, psychological therapies play a key role in modulating cortisol dynamics, particularly in stress-related dysregulation. Cognitive-behavioral therapy, stress-management counseling, and biofeedback have shown efficacy in reducing salivary and plasma cortisol in individuals under chronic psychological or occupational stress.[105] Mindfulness-based interventions and relaxation techniques further support HPA axis regulation by attenuating stress reactivity and enhancing adaptive recovery. Overall, the integration of precision pharmacotherapy, advanced diagnostics, and behavioral modification forms a comprehensive, evidence-based framework for maintaining cortisol balance. Such an approach not only addresses endocrine dysfunction but also promotes holistic well-being by harmonizing physiological, psychological, and environmental factors governing HPA axis activity.

Nutritional and lifestyle interventions for cortisol management

Cortisol, the primary stress hormone, regulates metabolism, immunity, and cardiovascular function, maintaining homeostasis during stress. However, its chronic imbalance leads to metabolic, psychological, and immune disorders, making nutritional and lifestyle strategies vital for restoring balance and overall well-being.

Nutritional strategies for optimal cortisol balance

Diet is a key modulator of HPA axis activity. Fluctuating blood glucose levels are a potent physiological trigger for cortisol release; hence, maintaining glycemic stability is crucial. Research indicates that high-glycemic diets elevate cortisol secretion compared to low-glycemic diets due to rapid glucose absorption and subsequent hypoglycemia-induced stress responses.[106,107] Therefore, consuming balanced meals with complex carbohydrates, lean proteins, and healthy fats, such as whole grains, legumes, nuts, and seeds, helps to stabilize glucose and prevent cortisol spikes. A controlled dietary intervention study involving adults on a high-glycemic index (GI) diet for three weeks reported significantly higher salivary cortisol levels and lower subjective energy compared to a low-GI group.[107] Participants who switched to low-GI foods, such as oats and lentils, experienced improved energy and reduced fatigue, highlighting that diet composition directly influences cortisol patterns. Incorporating such findings into dietary planning, especially for individuals under chronic stress, can mitigate HPA

axis hyperactivity.

In addition to macronutrient quality, micronutrients such as magnesium, vitamin C, and B vitamins play crucial roles in adrenal function and neurotransmitter synthesis. Magnesium acts as a natural relaxant, and studies have demonstrated that magnesium supplementation reduces cortisol and anxiety in individuals with stress-related fatigue.[108] Vitamin C, abundant in citrus fruits and amla, modulates cortisol responses to psychological stress.[109] Therefore, nutrient-dense diets rich in leafy greens, fruits, and whole foods support both adrenal and nervous system health.

Chronic inflammation amplifies cortisol production via cytokine-mediated HPA activation. Omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), exert anti-inflammatory and neuroprotective effects, and their supplementation has been shown to lower basal cortisol levels. In a randomized controlled trial, university students receiving 2.5 g/day of omega-3 for 12 weeks exhibited a 20% reduction in salivary cortisol and improved mood compared to placebo.[110] The researchers concluded that omega-3 intake buffered stress-induced cortisol surges, possibly by dampening pro-inflammatory cytokines. Such findings reinforce the value of including fatty fish, flaxseed, and walnuts in a cortisol-conscious diet.

The emerging science of the gut–brain axis provides another promising dietary pathway. Gut microbiota communicate bidirectionally with the HPA axis through immune, neural, and metabolic signaling.[111] A study investigated the impact of prebiotics on stress and emotional regulation in healthy adults. Forty-five participants received either fructooligosaccharides (FOS), Bimuno®-galactooligosaccharides (B-GOS), or placebo for three weeks. B-GOS supplementation significantly reduced the salivary CAR and shifted attention toward positive emotional cues, while FOS showed no effect. These findings suggest that B-GOS may beneficially modulate the gut–brain axis and stress response, supporting its potential role in managing stress-related disorders.[112]

Sleep and circadian rhythm optimization

Restoring circadian alignment through consistent sleep-wake schedules, morning sunlight exposure, and limiting late-night screen time has been shown to be beneficial.[113,114] Light exposure, particularly blue-wavelength light, directly influences the SCN, the brain's circadian pacemaker, thereby affecting cortisol and melatonin rhythms. Excessive blue light at night delays melatonin onset and suppresses nocturnal cortisol decline, worsening sleep latency and quality.[115] Interventions targeting both behavioral and light-related factors have demonstrated synergistic benefits. Janků *et al*.[116] investigated the combined effect of Cognitive Behavioral Therapy for Insomnia (CBT-I) and blue-light-blocking glasses in 30 adults with chronic insomnia. Participants using blue-light-filtering glasses 90 min before bedtime showed greater improvements in anxiety, depression, and hyperarousal scores compared to placebo. Additionally, subjective total sleep time increased while sleep latency shortened. These results suggest that blocking short-wavelength light in the evening enhances CBT-I outcomes by facilitating melatonin release and reducing HPA axis overactivation.[116]

Further, occupational studies revealed that disrupted circadian rhythms, such as in shift workers, distort cortisol and melatonin cycles. Brum *et al*.[117] compared fixed night-shift and day-shift hospital staff and found that night-shift workers experienced reduced nighttime sleep, higher social jet lag, and attenuated cortisol rhythms during work and rest days. Although both groups maintained a normal circadian cortisol pattern, night-shift workers exhibited lower amplitude and slower recovery of the HPA axis.[117] Overall, optimizing sleep and circadian rhythm through structured bedtime routines, light management, and cognitive–behavioral interventions is vital for maintaining healthy cortisol regulation. These strategies not only normalize HPA axis function but also enhance emotional resilience, cognitive performance, and overall well-being.

Physical activity: The dual role of exercise

Physical activity plays a dual role in cortisol regulation, exerting both acute and long-term effects. Intense physical exertion temporarily raises cortisol levels to mobilize energy, while consistent moderate exercise helps lower baseline cortisol and enhances overall stress resilience.[118] A meta-analysis assessing the relationship between physical activity and HPA axis regulation found that higher physical activity was modestly associated with a steeper diurnal cortisol slope (r = –0.043), reflecting improved cortisol rhythm and adaptive stress response, although it did not significantly affect the CAR.[119] A 12-week intervention study on young men from Peshawar demonstrated a significant reduction in serum cortisol levels (from 142.98 to 106.88; $P < 0.000$) and perceived stress scores (from 32.76 to 23.71; $P < 0.000$), confirming the potential of aerobic exercise to lower stress and support balanced cortisol regulation in healthy adults.[120] Further, a systematic review following PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines examined the impact of physical activity on cortisol regulation and sleep quality in adults. Ten intervention studies with low-to-moderate bias showed that physical activity significantly reduced cortisol levels (standardized mean difference = –0.37, $P < 0.001$) and improved sleep quality (standardized mean difference = –0.30, $P = 0.02$). However, most trials involved breast cancer patients, with limited male and older adult participants. Findings suggest that regular physical activity may enhance both stress regulation and sleep, particularly in individuals with poor health, though further research is needed for broader generalization.[121] Regular and moderate exercise fosters adaptive HPA axis functioning and psychological well-being. Integrating structured physical activity into daily routines can thus serve as an effective non-pharmacological strategy for maintaining optimal cortisol balance and long-term health.

Mind-body therapies and stress reduction

Psychological stress is the most potent activator of the HPA axis, making mind-body interventions integral to cortisol regulation. Meditation, yoga, deep breathing, and mindfulness-based stress reduction (MBSR) have all demonstrated measurable effects on cortisol reduction. In a landmark study, breast and prostate cancer outpatients participating in an eight-week MBSR program showed decreased salivary cortisol and improved quality of life compared to controls.[122,123] A 10-day yoga-based lifestyle intervention further highlighted these benefits in patients with chronic inflammatory diseases. Among 86 participants, cortisol levels decreased significantly (149.95 → 129.07 ng/mL; $P = 0.001$), accompanied by reductions in inflammatory cytokines IL-6 and TNF-α and an increase in β-endorphins. These findings indicate that even a short-term, structured yoga program can effectively alleviate stress and inflammation, supporting its potential as a complementary therapy in chronic disease management.[124] Similarly, an open-label clinical study on 54 patients with depression compared yoga alone, yoga combined with antidepressants, and antidepressant medication alone. After three months, participants in both yoga groups exhibited greater reductions in serum cortisol and Hamilton Depression Rating Scale scores than those receiving only medication. The decline in cortisol levels correlated with mood improvement,

suggesting that yoga may exert antidepressant effects through modulation of the HPA axis and reduction of stress hormones.[125] Further a systematic review and meta-analysis of 42 randomized controlled trials evaluated yoga asanas with or without mindfulness components on physiological stress markers. The analysis revealed notable decreases in waking and evening cortisol, blood pressure, and resting heart rate, alongside improvements in heart rate variability—signifying better autonomic and HPA axis regulation. These findings reinforce yoga's role in restoring balance to the body's stress response systems across varied populations.[126]

In adults with insomnia, 12 weeks of Classical Yoga combined with Naturopathy supplements significantly reduced Pittsburgh Sleep Quality Index scores and cortisol levels versus active rest, demonstrating improved sleep regulation and diminished stress burden.[127] Yoga and meditation programs for medical students also induced significant reductions in serum cortisol and optimized heart rate variability indices, reflecting greater autonomic resilience to chronic stress.[128] Self-care strategies such as transcendental meditation further support stress regulation, with reductions in urinary cortisol linked to relaxation behavior, suggesting a role for cortisol as a potential biomarker in stress-related therapeutic monitoring.[129]

Mind-body interventions also hold promise for younger populations. A 10-week classroom-based yoga program conducted among second- and third-grade students demonstrated that regular yoga practice could significantly reduce baseline cortisol in second graders and lower stress reactivity in both grades. Teachers observed improvements in emotional regulation, attention, and classroom behavior, underscoring the potential of school-based yoga in fostering stress resilience from an early age.[130] Together, these findings provide compelling evidence that mind–body therapies—whether practiced in clinical settings or educational environments—promote balanced cortisol rhythms, reduce stress-related inflammation, and enhance psychological well-being. They underscore the therapeutic promise of integrating yoga and mindfulness into holistic approaches for both physical and mental health management.

Herbal and nutritional supplements: Evidence and caution

Among herbal interventions, *Withania somnifera* remains the most extensively studied adaptogen for cortisol regulation. A double-blind, placebo-controlled trial involving 64 adults with chronic stress showed that 300 mg of high-concentration Ashwagandha root extract twice daily for 60 days reduced serum cortisol by 27.9% and improved anxiety and sleep quality.[131] This trial demonstrates the potential of standardized adaptogens in normalizing HPA activity. However, experts advise caution due to variable product quality and rare reports of adverse reactions with prolonged unsupervised use.[132] Other emerging supplements with promising evidence for cortisol regulation include phosphatidylserine, L-theanine, and vitamin C, although further well-controlled trials are needed to confirm their efficacy. Phosphatidylserine supplementation (300 mg/day for one month) has been shown to reduce stress and improve mood among young adults with high neuroticism scores, suggesting its potential to blunt cortisol responses and support emotional balance.[133] Similarly, a single 200 mg dose of AlphaWave® L-theanine significantly increased frontal alpha brain activity and lowered salivary cortisol, reflecting enhanced relaxation and reduced stress in healthy, moderately stressed adults; the supplement was found to be safe and well tolerated.[134] Moreover, daily intake of 1,000 mg vitamin C (ascorbic acid) for two months effectively reduced elevated cortisol and DHEA-S levels in women with functional hypercortisolemia, highlighting its role in restoring hormonal balance under stress.[135]

Inclusively, nutritional and lifestyle strategies provide a multifaceted yet practical framework for cortisol regulation. In metabolic dysfunction-associated steatotic liver disease, exercise combined with diet, particularly high-intensity interval training, significantly lowered cortisol while improving hepatic and metabolic health markers.[136] Balanced, low-glycemic diets rich in omega-3s and micronutrients stabilize blood sugar and reduce inflammation; probiotics and fermented foods support gut–brain communication; consistent sleep restores circadian rhythm; moderate exercise enhances resilience; and mind–body practices improve psychological adaptability. Carefully selected adaptogenic herbs may further enhance these benefits under clinical guidance. Together, these interventions not only normalize cortisol secretion but also promote holistic physical and mental health.

Traditional and integrative medicine approaches for management of cortisol

Managing cortisol dysregulation is vital, as chronic stress disrupts metabolic, immune, and neurological balance. Traditional and integrative approaches aim to naturally restore HPA axis harmony. Ayurvedic adaptogens such as *Withania somnifera*, *Ocimum sanctum*, and *Glycyrrhiza glabra*, along with Traditional Chinese herbs like *Rhodiola rosea* and *Panax ginseng*, help regulate cortisol and enhance resilience. Complementary practices including yoga, pranayama, meditation, acupuncture, and MBSR further lower cortisol and promote emotional stability, offering a holistic, evidence-based approach to restoring endocrine balance and overall well-being.

Ayurveda: Rasāyana herbs for HPA axis modulation

Ayurveda emphasizes Rasāyana therapy to restore psychophysiological balance and improve resilience against stress-induced disorders. Rasāyana is one of the eight clinical specialties of classical Ayurveda, concerned with health preservation, rejuvenation, and longevity. It encompasses rejuvenative formulations, dietary regimens, and health-promoting conduct (*Ācāra Rasāyana*) that enhance the quality and circulation of rasa *dhātu*, thereby strengthening immunity, delaying aging, improving physical and cognitive functions, and preventing disease recurrence. Rasāyana therapies act as nutritional and antioxidant interventions that counter oxidative stress and support systemic resilience, contributing to sustained physiological balance and vitality.[137–139] Among these, *Withania somnifera* is one of the most extensively validated adaptogens for HPA axis modulation. Multiple randomized, double-blind, placebo-controlled clinical trials consistently demonstrate its ability to reduce perceived stress levels, normalize cortisol secretion, and enhance sleep and overall well-being. A 60-day clinical trial using standardized Ashwagandha extract (240 mg/day; Shoden) significantly reduced HAM-A anxiety scores ($P = 0.040$), morning cortisol ($P < 0.001$), and DHEA-S ($P = 0.004$) in stressed adults, with excellent tolerability.[140,141] Dose-dependent improvements in stress markers, including serum cortisol, perceived stress, and sleep quality, were observed with 300–600 mg/day administration over eight weeks,[142] and reduced stress-related weight gain was further reported.[143] Additional studies show significant decreases in cortisol accompanied by improved mood, cardiovascular function, biochemical markers of inflammation and oxidative stress, and cognitive performance.[131,144–147] Preclinical findings corroborate strong adaptogenic potential through protective effects

against acute stress–induced biochemical disruptions.[148] Together, these findings establish Ashwagandha as a potent Rasāyana herb that helps regulate the HPA axis and enhance stress resilience.

Other classical Rasāyana plants also demonstrate cortisol-modulating potential. *Ocimum tenuiflorum* supplementation for eight weeks significantly reduced hair and salivary cortisol, blood pressure, stress biomarkers, and improved sleep and perceived stress scores in adults experiencing stress (Holixer™ extract; randomized controlled trial), while showing good safety. *Bacopa monnieri* (Brahmi) has shown stress-buffering properties, as observed in clinical trials reporting reduced salivary cortisol and improvements in emotional well-being, sleep-related fatigue, and other stress-associated biomarkers.[149,150] These Ayurvedic herbs contribute to restoring HPA axis balance and mitigating chronic stress burden through multifactorial neuroendocrine mechanisms.

Traditional Chinese medicine (TCM): Adaptogens for cortisol normalization

TCM conceptualizes stress-related neuroendocrine imbalance in terms of *Qi* deficiency and disruption of *Shen*, reflecting reduced physiological vitality and impaired mental-emotional regulation. *Qi*, the vital life force supporting integrated mind-body function, becomes deficient due to factors such as poor nutrition or digestion, constrained respiration, chronic stress, illness, or constitutionally weak inherited reserves, leading to diminished adaptive capacity.[151–153] *Shen*, regarded as the governor of life, governs consciousness, emotion, cognition, and perception; its disturbance manifests as altered awareness and stress reactivity.[154] Within this framework, TCM employs adaptogenic botanicals and restorative practices to strengthen resilience and buffer the neuroendocrine stress response (Table 3).[7,131,140,142–147,149,150,155–159] *Panax ginseng* has been widely studied for such effects. Although clinical trials in chronic fatigue and psychological stress have shown mixed outcomes, subgroup analyses indicate greater benefits in individuals ≥50 years old, demonstrating reductions in fatigue and stress-related symptoms with favorable safety.[155,160]

Beyond ginseng, several TCM adaptogens show promise for cortisol regulation. *Rhodiola rosea* supplementation (200–400 mg/day) consistently attenuated fatigue, burnout, and anxiety symptoms while improving concentration and reducing CAR, with effects emerging as early as week 1 and excellent tolerability.[156,161–163] *Eleutherococcus senticosus* also enhanced stress resilience and quality of life in individuals with stress-related asthenia, with reductions in CAR observed within two weeks.[164] Additionally, *Eurycoma longifolia* (Tongkat ali), used in Southeast Asian traditional medicine with overlap in TCM practice, significantly reduced salivary cortisol (−16%) and improved negative mood parameters after four weeks,[165] while *Lepidium peruvianum* (Maca) demonstrated hormonal homeostasis, including improved ACTH and cardiometabolic indicators in perimenopausal women.[157] Overall, adaptogenic herbs commonly employed in TCM exhibit promising stress-modulating actions through regulation of the HPA axis and cortisol dynamics. However, response variability across populations highlights the need for personalized-medicine-based clinical evaluations and long-term mechanistic studies to validate therapeutic consistency.

Altogether, herbal adaptogens and stress-response modulators provide a promising complementary strategy to regulate cortisol dynamics, improve overall stress resilience, and restore neuroendocrine balance. Evidence from clinical studies suggests that plants such as *Withania somnifera*, *Ocimum tenuiflorum*, *Rhodiola rosea*, and *Bacopa monnieri* most consistently reduce cortisol levels while enhancing psychological and physiological recovery. However, inconsistencies remain in dosage standardization, sampling time, and study duration, along with marked inter-individual variability in cortisol reactivity. Continued research incorporating robust biomarkers, long-term follow-up, and multi-herb formulations is essential to translate these benefits into optimized therapeutic protocols for stress-related health issues.

Acupuncture: Restoring autonomic and HPA axis balance

Acupuncture is increasingly being explored as a complementary strategy to reduce stress-related disorders by normalizing autonomic function and the HPA axis. Anxiety disorders affect over 301 million people globally, and nearly one-third of patients remain unresponsive or intolerant to conventional therapies, driving interest toward alternatives. Electro-acupuncture and Bioelectric Meridian Therapy activate specific acupoints to enhance parasympathetic activity, regulate heart rhythms, and reduce cortisol levels, thereby helping restore autonomic balance. These modalities may further modulate vagal tone, brain wave activity, and neurotransmitter release, although larger confirmatory trials are needed.[166]

Clinical findings support acupuncture's potential in different stress-associated conditions. In mild to moderate bronchial asthma, daily 20-min acupuncture sessions over one month significantly improved pulmonary function and favorably modulated inflammatory and stress markers: cortisol, TNF-α, and salivary alpha-amylase decreased, while IL-10 and DHEA-S increased, highlighting improved immune and adrenal balance.[167] In mildly stressed university students, 30-min stimulation at ST36 reduced systolic blood pressure and heart rate, suggesting autonomic relaxation, although reductions in salivary cortisol were not statistically significant, indicating the need for larger trials.[168]

Following total knee arthroplasty, acupuncture modestly reduced postoperative stress: cortisol levels on day 2 were significantly lower in the acupuncture group than in controls ($P < 0.05$), with a trend toward reduced analgesic consumption.[169] Likewise, a randomized double-blind sham-controlled trial in dysthymic patients with opioid use disorder undergoing methadone maintenance therapy showed that four weeks of auricular acupuncture significantly reduced salivary cortisol levels and suicidal ideation ($P < 0.01$).[170] Auricular acupuncture has shown benefits in major depressive disorder, dysthymia, and suicidal ideation, with single-case studies reporting significant decreases in salivary cortisol and improvements in affective symptoms,[171,172] supporting potential HPA axis regulation. In chronic nonspecific lower back pain, laser acupuncture combined with cupping therapy significantly reduced plasma cortisol and pain intensity, indicating both stress-buffering and anti-inflammatory effects.[173]

Together, these studies indicate that acupuncture may modulate cortisol-related pathways across stress, pain, respiratory, and psychiatric disorders. However, standardized treatment protocols, long-term follow-ups, and head-to-head comparisons with established therapies are necessary to strengthen clinical recommendations.

Homeopathy: Modulation of cortisol and stress pathways

Homeopathy is increasingly investigated for its potential role in regulating stress physiology and HPA axis activity. Evidence, though limited, suggests possible reductions in cortisol and improvements in stress-linked symptoms. In ACTH-dependent Cushing's disease, individualized homeopathic treatment with *Mercurius* 50M was associated with symptomatic improvement, weight reduction, and normalization of elevated plasma and urinary cor-

Table 3. Summary of human clinical studies evaluating adaptogenic herbs on cortisol regulation

Study design	Participants' characteristics	Age	Adaptogenic substance	Groups (number of subjects in the group)	Duration	Outcomes measured*	Sampling time	Key findings	References
Double-blind, crossover RCT	Healthy adults exposed to multitasking stress	18–44 years	*Bacopa monnieri* extract (BME)	1. BME 320 mg (17) 2. BME 640 mg (17) 3. Placebo (17)	Single dose with 1-week washout	SaC, BLVAS, STAI	Before noon	640 mg BME significantly reduced cortisol	149
Double-blind RCT	Poor sleepers with stress	18–70 years	*Bacopa monnieri* extract (BME)	1. BME 300 mg/day (44) 2. Placebo (45)	28 days	SaC, DASS	Morning & evening	Emotional well-being improved; however, cortisol increased	150
Double-blind, crossover RCT	Healthy perimenopausal women	41–50 years	Pre-gelatinized dried and pulverized hypocotyls of *Lepidium peruvianum* (PG-LP)	1. PG-LP 2,000 mg/day (9) 2. Placebo (9)	60 days	SC, sACTH	–	ACTH ↑; cortisol ↑ but not significant	157
Double-blind RCT	Healthy adults experiencing stress for longer than a month, and currently experiencing sleep problems	18–65 years	*Ocimum tenuiflorum* extract (OTE)	1. OTE 350 mg/day (43) 2. Placebo (38)	56 days	HC, PSS, MAST	–	Subjective stress improved; cortisol excretion decreased	7
Double-blind RCT	Healthy male subjects	18–30 years	*Ocimum tenuiflorum* extract (OTE)	1. OTE 300 mg/day (20) 2. Placebo (20)	30 days	SaC, STAI	–	Significant reduction in salivary cortisol	158
Double-blind RCT	Healthy adults suffering from at least 3 symptoms of stress	18–65 years	*Ocimum tenuiflorum* whole plant extract (OTE)	1. OTE 1,200 mg/day (71) 2. Placebo (79)	42 days	Symptom scores of stress	–	1.6 times or 39 % greater stress reduction vs. placebo	159
Double-blind RCT	Adults with chronic fatigue	19–65 years	*Panax ginseng* powder (PGP)	1. PGP 3.0/day (24) 2. Placebo (23)	42 days	SaC - AUC, F-VAS, BDI, CFSQ, FSI, SRI	4 times during the day from within 30 min after awakening till 12AM	Fatigue improved; cortisol levels increased	155

(continued)

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Table 3. *(continued)*

Study design	Participants' characteristics	Age	Adaptogenic substance	Groups (number of subjects in the group)	Duration	Outcomes measured*	Sampling time	Key findings	References
Double-blind RCT	Stress-induced fatigue	20–55 years	*Rhodiola rosea* extract (RRE)	1. RRE 576 mg/day (30) 2. Placebo (30)	28 days	SaC, PBS, MADRS	0–60 min after awakening	Cortisol level decreased, fatigue improved	156
Double-blind RCT	Anxiety (HAM-A 24–42)	18–60 years	*Withania somnifera* extract (WSE)	1.WSE 125 mg/day (19) 2. WSE 250 mg/day (30) 3. WSE 500 mg/day (34) 4. Placebo (15	60 days	SC, mHAMA	9–11 AM	Cortisol level decreased significantly, stress and anxiety improved	144
Double-blind RCT	Chronic stress, PSS ≥14	18–54 years	*Withania somnifera* extract (WSE)	1. WSE 600 mg/day (30) 2. Placebo (31)	60 days	SC, PSS, DASS-S	Morning	Cortisol level decreased significantly, stress perception improved	131
Double-blind RCT	Routine work stress, PSS ≥20, BMI 25–39.9	18–60 years	*Withania somnifera* extract (WSE)	1. WSE 600 mg/day (25) 2. Placebo (25)	56 days	SC, PSS, OHQ	–	Cortisol level decreased significantly, stress perception improved	143
Double-blind RCT	Healthy adults, PSS 14–24	20–55 years	*Withania somnifera* extract (WSE)	1. WSE in Sustained Release (SR) capsule 300	90 days	SC, PSS, OHQ	9–11 AM	Significant reductions in cortisol & PSS	146
Double-blind RCT	Anxiety (HAM-A 6–17)	18–65 years	*Withania somnifera* extract (WSE)	1. WSE 240 mg/day (30) 2. Placebo (30)	60 days	SC, HAM-A, DASS	~at 8AM	Cortisol level decreased significantly, anxiety improved	140
Double-blind, crossover RCT	Healthy male individuals exposed to experimental mental stress directly prior to sample taking	Mean age: 25.10 ± 2.29 years	*Withania somnifera* extract (WSE)	1. WSE 1,000 mg/day (10) 2. Placebo (10)	14 days	SC	–	Serum cortisol decreased significantly	145
Double-blind RCT	Chronic stress, PSS ≥14	18–54 years	*Withania somnifera* extract (WSE)	1. WSE 225 mg/day (19) 2. WSE 400 mg/day (19) 3. Placebo (19)	30 days	SaC	Morning	Significant reduction in cortisol levels	147
Double-blind RCT	Healthy adults with a PSS score above 20	18–55 years	*Withania somnifera* extract (WSE)	1. WSE 250 mg/day (19) 2. WSE 600 mg/day (20) 3. Placebo (19)	56 days	SC, PSS, HAM-A	Morning	Cortisol level decreased significantly, stress improved	142

BLVAS, Bond-Lader Visual Analogue Scale; DASS, Depression Anxiety Stress Scales; F-VAS, Fatigue Visual Analog Scale; HC, hair cortisol; MADRS, Montgomery–Åsberg Depression Rating Scale; MAST, Mood and Stress Questionnaire; mHAM-A/HAM-A, Hamilton Anxiety Rating Scale (modified); OHQ, Oxford Happiness Questionnaire; PBS, Psychological Battery Scores; POMS, Profile of Mood States; PSS, Perceived Stress Scale; RCT, randomized clinical trial; SaC, salivary cortisol; sACTH, serum adrenocorticotropic hormone; SC, serum cortisol; STAI, State-Trait Anxiety Inventory.

tisol, indicating supportive endocrine benefits when conventional therapeutic options are limited.[174] In a 12-week intervention involving adults with chronic stress, homeopathic remedies such as *Ignatia amara* and *Arsenicum album* resulted in lowered salivary cortisol and improved oxidative and inflammatory markers (MDA, SOD, IL-6, TNF-α), suggesting HPA axis modulation.[175] Homeopathy has also been tested in sleep disturbances: *Nux vomica* notably reduced cortisol levels and sleep-related symptoms in healthy volunteers, whereas effects on melatonin remained minimal, indicating selective neuroendocrine influence.[176]

Traditional and integrative medicine approaches offer a comprehensive framework for managing cortisol dysregulation by addressing both physiological and psychological aspects of stress. Evidence from Ayurveda, TCM, acupuncture, homeopathy, naturopathy, yoga, and other mind–body interventions highlights their effectiveness in modulating the HPA axis and restoring hormonal balance. Herbal adaptogens such as *Withania somnifera*, *Ocimum tenuiflorum*, *Rhodiola rosea*, and *Panax ginseng* have demonstrated consistent efficacy in lowering cortisol and enhancing resilience, while practices like yoga, meditation, acupuncture, and naturopathy promote neuroendocrine and emotional stability. These integrative modalities complement conventional therapy by targeting the root causes of HPA axis imbalance and fostering holistic well-being. Continued interdisciplinary research integrating systems biology, personalized medicine, and long-term clinical validation will be crucial to solidify their role in sustainable cortisol regulation.

Emerging evidence suggests that cortisol regulation extends beyond the classical HPA axis and is shaped by integrated circadian and systemic signals. In particular, interactions between neuroendocrine rhythms and gut-derived metabolic cues are increasingly recognized as critical modulators of glucocorticoid signaling and stress physiology. Recent work indicates that cortisol is significantly regulated by the interactions of circadian (pineal melatonin) and systemic (gut-derived butyrate) factors.[177] Both melatonin and the gut microbiome–derived short-chain fatty acid butyrate suppress the nuclear translocation of the GR-α from its cytoplasmic complex, thereby attenuating cortisol/GR-α–mediated transcriptional effects.[178,179] In addition to suppressing adrenal cortisol production,[180] melatonin plays a key role in maintaining gut barrier integrity and preventing dysbiosis. Consequently, age-related and disease-associated reductions in pineal melatonin, observed in conditions such as T2DM and chronic stress, can disrupt cortisol/GR-α regulation.[181] These interactions warrant further investigation, particularly in relation to how traditional interventions discussed in this review may modulate circadian–microbiome–endocrine crosstalk. Moreover, given the existence of multiple GR subtypes (GR-α, GR-β), haplotypes, and distinct subcellular localizations, including cytoplasmic, plasma membrane, and mitochondrial compartments, each with unique functional consequences,[182] it is essential to explore how traditional therapeutic approaches influence this broader complexity of cortisol signaling. Taken together, these insights underscore the need for future research frameworks that integrate circadian biology, gut–brain interactions, and GR heterogeneity. Such an integrative perspective may provide a more comprehensive understanding of cortisol modulation and enhance the scientific grounding of traditional and lifestyle-based therapeutic strategies.

Strength of evidence and clinical interpretation of traditional and integrative interventions for cortisol regulation

Given the growing integration of traditional medical systems into stress and endocrine management, it is critical to clearly distinguish the strength of clinical evidence supporting individual interventions to ensure accurate interpretation and responsible application. The traditional and integrative therapies discussed in this review exhibit substantial heterogeneity in evidentiary quality, necessitating a structured and transparent grading framework to avoid misrepresentation of therapeutic credibility. Accordingly, interventions were systematically categorized based on study design, sample size, reproducibility, and robustness of cortisol-related outcomes.

Grade A evidence includes *Withania somnifera* and yoga-based practices, supported by multiple large, randomized, double-blind, placebo-controlled trials consistently demonstrating significant reductions in cortisol levels and improvements in stress-related outcomes.[131,140,142,144,146] Grade B evidence encompasses *Ocimum tenuiflorum*, *Bacopa monnieri*, *Rhodiola rosea*, *Panax ginseng*, acupuncture, mindfulness/meditation practices, and Rasāyana formulations overall, which are supported by small-to-moderate randomized trials or controlled observational studies reporting generally favorable but occasionally heterogeneous cortisol responses.[149,150,156,160,167] Grade C evidence includes homeopathy and certain individualized or non-standardized traditional interventions that currently rely on case reports, pilot studies, or small uncontrolled trials and therefore require further rigorous validation prior to broad clinical generalization.[171,172,174,176] Clear evidence stratification is essential to prevent false equivalence across therapeutic modalities, strengthen scientific rigor, and guide clinicians, researchers, and policymakers toward evidence-informed integration. By balancing respect for traditional knowledge systems with transparent acknowledgment of current evidentiary limitations, this framework supports ethical clinical translation while clearly identifying priorities for future high-quality, standardized research in cortisol regulation.

Towards an integrated model for cortisol management

Cortisol, the principal glucocorticoid secreted by the adrenal cortex, plays a pivotal role in maintaining homeostasis by modulating metabolism, immune function, cardiovascular tone, and stress responses. However, chronic dysregulation of the HPA axis, whether through persistent psychological stress, inflammatory conditions, or disrupted circadian rhythms, leads to pathological states such as metabolic syndrome, depression, immunosuppression, hypertension, and reproductive dysfunction.[183,184] This underscores the need for an integrated, multidimensional model of cortisol management that combines biomedical, behavioral, and traditional healing perspectives.

An integrated model begins with the recognition that cortisol balance is both a physiological and psychosocial construct (Fig. 3). Effective regulation involves lifestyle optimization—adequate sleep, balanced nutrition, regular physical activity, and stress reduction—to stabilize circadian rhythm and autonomic function.[185] Nutritional strategies emphasizing complex carbohydrates, omega-3 fatty acids, vitamins C and B5, and polyphenol-rich foods can modulate HPA-axis activity and lower oxidative stress.[186,187] Mind-body interventions such as yoga, meditation, and MBSR have demonstrated efficacy in normalizing diurnal cortisol patterns and enhancing resilience against chronic stress.[126]

Pharmacological and complementary approaches can further support this model. Adaptogenic botanicals, such as *Withania somnifera*, *Rhodiola rosea*, *Panax ginseng*, and *Bacopa monnieri*,

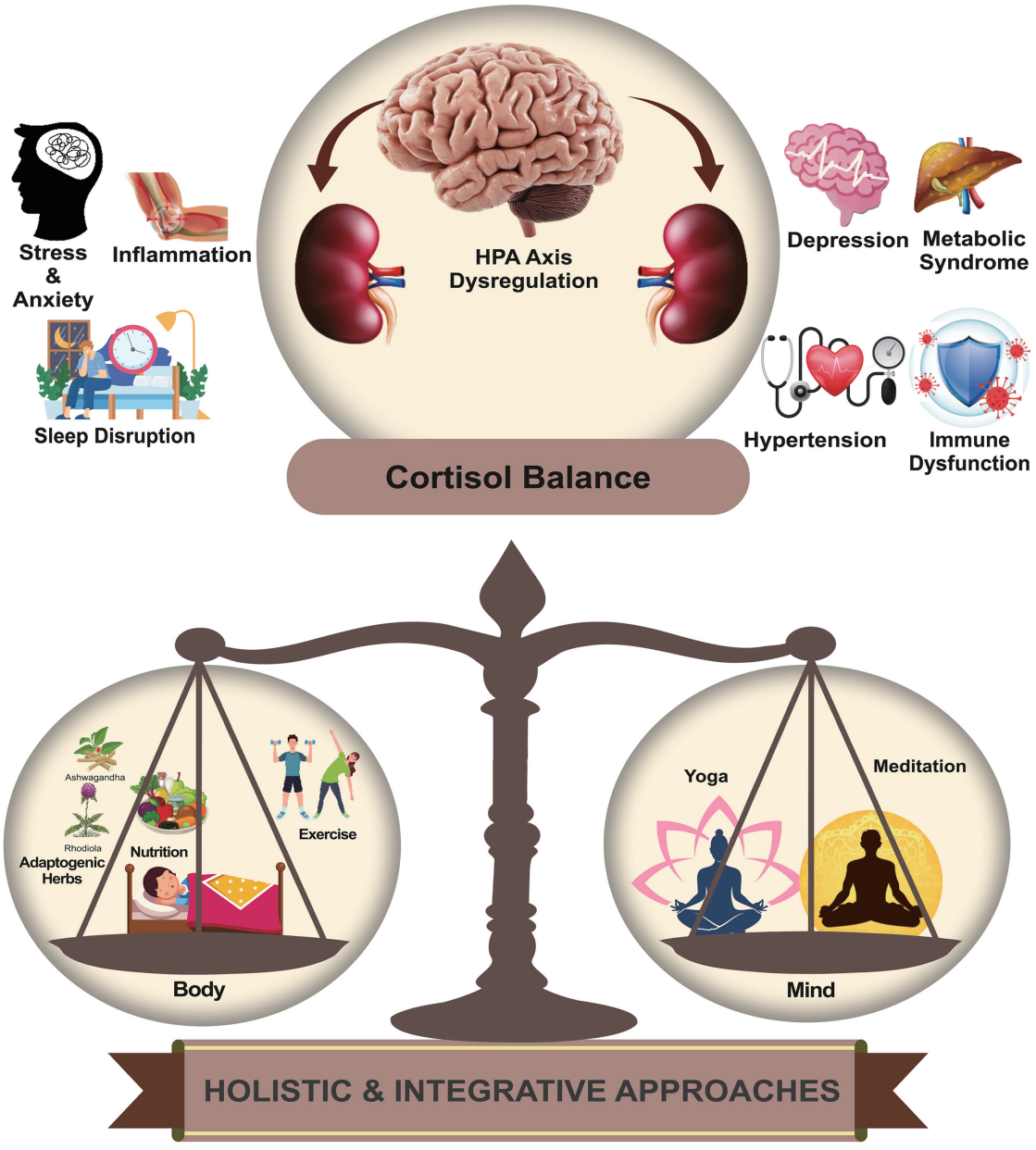

Fig. 3. Integrated mind–body approaches for restoring cortisol balance. This figure depicts how hypothalamic–pituitary–adrenal (HPA) axis dysregulation driven by chronic stress and inflammation disrupts cortisol balance, contributing to sleep disturbance, anxiety, depression, metabolic syndrome, hypertension, and immune dysfunction. The lower panel highlights a holistic strategy for cortisol regulation, integrating body-based interventions (adaptogenic herbs, nutrition, and exercise) with mind-based practices (yoga and meditation). Together, these approaches act synergistically to reduce allostatic load, improve stress resilience, and restore adaptive neuroendocrine balance.

have shown clinical potential in mitigating stress-induced hypercortisolemia and improving energy metabolism, cognitive function, and mood.[140,188,189] Integrative endocrinology also advocates monitoring cortisol rhythms via salivary or serum assays, aligning therapeutic interventions with the body's circadian patterns. Importantly, psychosocial interventions addressing emotional regulation, social support, and work-life balance are essential for long-term success. An integrated cortisol management framework, therefore, blends biomedical monitoring, psychoneuroendocrine regulation, lifestyle transformation, and traditional healing wisdom, reflecting a holistic and sustainable approach to stress adaptation and overall well-being.

Safety considerations, contraindications, and potential risks of traditional interventions

Traditional, lifestyle-based, and integrative interventions show promise in enhancing stress resilience and regulating cortisol, but their use must be grounded in careful assessment of safety and contraindications. As cortisol is essential for metabolic, immune, and cardiovascular homeostasis, indiscriminate suppression, espe-

cially in vulnerable populations, may cause adverse effects. Hence, a balanced benefit-risk evaluation is crucial for responsible clinical integration. Nutritional and lifestyle interventions, although generally safe, are not without physiological boundaries. Dietary strategies aimed at stabilizing blood glucose and reducing inflammation may become counterproductive when implemented in extreme forms. Prolonged fasting, severe caloric restriction, or very low-carbohydrate regimens can paradoxically activate stress pathways, elevating cortisol through hypoglycemia-induced neuroendocrine responses.[190,191] Clinical evidence further indicates that unsupervised caloric restriction or intermittent fasting may disrupt thyroid and reproductive hormone balance, particularly in women, thereby impairing overall endocrine homeostasis.[192,193] Omega-3 fatty acids exert anti-inflammatory and stress-modulating effects; however, excessive supplementation may increase bleeding risk and interact with anticoagulant therapy.[194,195] The Institute of Medicine recommends an acceptable macronutrient distribution range for omega-3 fatty acids (as alpha-linolenic acid) of 0.6–1.2% of total energy intake, with limited derivation from EPA and DHA. While intakes up to 5 g/day of EPA + DHA are considered safe by European Food Safety Authority and the FDA, higher or prolonged doses may increase bleeding tendency, modestly elevate atrial fibrillation risk, suppress immune responses, and cause gastrointestinal discomfort.[195]

Sleep optimization and circadian alignment remain foundational to cortisol regulation and are broadly safe when behaviorally driven. However, chronic or high-dose use of exogenous melatonin (>5 mg/day) may cause next-day somnolence, headache, or hormonal interactions, particularly in individuals with autoimmune disorders or those receiving antidepressants or antihypertensive medications.[196,197] Gradual circadian entrainment through light exposure, sleep hygiene, and behavioral modification is therefore preferable to long-term pharmacological reliance. Moderate physical activity consistently improves HPA axis resilience; nevertheless, excessive high-intensity training without adequate recovery may induce chronic cortisol elevation, immune suppression, and overtraining syndrome.[198] Exercise prescriptions should thus be individualized based on baseline fitness, age, and clinical status. Herbal adaptogens, despite their widespread perception as inherently safe, contain pharmacologically active constituents capable of producing clinically significant effects and interactions. *Withania somnifera* has demonstrated efficacy in stress reduction and cortisol modulation; however, it may increase thyroid hormone levels and should be avoided or closely monitored in individuals with hyperthyroidism or those receiving thyroid hormone replacement therapy.[199,200] *Glycyrrhiza glabra* presents well-documented risks due to its mineralocorticoid-like activity. Glycyrrhizin inhibits 11β-hydroxysteroid dehydrogenase type 2, leading to sodium retention, potassium loss, hypertension, edema, and hypokalemic metabolic alkalosis—effects that may exacerbate cardiovascular disease and directly counter cortisol-lowering objectives.[201,202] *Glycyrrhiza glabra* is therefore contraindicated in hypertension, chronic kidney disease, pregnancy, and in patients using diuretics or corticosteroids. *Panax ginseng* and *Rhodiola rosea* are generally well tolerated; however, adverse effects such as insomnia, agitation, headache, and gastrointestinal upset have been reported, particularly at higher doses or when combined with stimulants, antidepressants, or antihypertensive drugs.[203,204]

Mind-body therapies and procedural interventions exhibit favorable safety profiles when appropriately administered. Yoga, meditation, and MBSR are associated with minimal adverse effects; nonetheless, musculoskeletal strain, dizziness, or psychological distress may occur during intensive or unsupervised practice, particularly in individuals with trauma histories or severe psychiatric illness.[205] Trauma-informed, graded, and professionally supervised approaches are therefore recommended. Acupuncture is generally safe when performed by trained practitioners following established safety guidelines. Minor adverse effects such as bruising, pain, or transient dizziness are relatively common, while serious complications, such as infection or pneumothorax, are rare and typically associated with improper technique.[206,207] Patients with bleeding disorders, those receiving anticoagulant therapy, or immunocompromised individuals require additional caution.

Homeopathy, contrary to the assumption of inherent safety from extreme dilutions, may carry risks. Commonly prescribed classical, tincture-based, and proprietary homeopathic formulations can contain concerning levels of ethanol, heavy metals, undisclosed bioactive compounds, or industrial/pharmaceutical residues. An additional major risk is the delay or substitution of evidence-based care. These findings highlight serious safety and transparency concerns and reinforce the need for stricter regulation, quality control, and cautious, evidence-based clinical decision-making.[208,209] Despite being largely non-invasive, therapies such as heat and water carry risks, including burns and allergies. Implementation of NABH-mandated incidence monitoring in an accredited yoga and naturopathy hospital enabled systematic reporting of adverse events, treatment errors, and near-misses among over 27,000 patients. The findings highlight that structured quality and safety frameworks are essential to improve patient safety, clinical governance, and the credibility of using these natural therapies.[207]

Herb-drug interactions can significantly affect drug safety and efficacy by altering absorption, metabolism, and receptor activity, most commonly via CYP450 enzymes and transporters. Widespread herbal use, underreporting, and limited patient-physician communication increase the risk of unrecognized adverse effects. Greater awareness and evidence-based monitoring are essential to ensure patient safety.[210] Clinical implications and risk mitigation require a personalized, evidence-informed, and clinically supervised approach. Given the heterogeneity of cortisol physiology and individual stress reactivity, integrative interventions should be applied cautiously in patients with endocrine disorders, cardiovascular disease, autoimmune conditions, pregnancy, or polypharmacy. Clear differentiation between high-quality evidence and low-quality or exploratory evidence is essential to prevent therapeutic misinterpretation. Conclusively, traditional and integrative strategies for cortisol modulation offer meaningful benefits when applied judiciously, but they are not devoid of risk. Future research should prioritize long-term safety data, standardized formulations, interaction studies, and robust evidence-grading frameworks to support the safe, ethical, and sustainable integration of these interventions into stress and endocrine care.

Limitations and scope of the review

While this review provides a comprehensive and integrative perspective on cortisol regulation, certain limitations should be interpreted as reflections of its broad, translational scope rather than methodological shortcomings. First, the review adopts a narrative and conceptual approach, which allows synthesis across diverse disciplines including endocrinology, psychoneuroimmunology, and integrative medicine. Although this approach does not permit quantitative comparison of effect sizes, it enables a systems-level understanding that would not be achievable through narrowly focused systematic reviews. This integrative breadth represents a key

strength, particularly for emerging, interdisciplinary fields. Second, the diversity of evidence sources, ranging from randomized controlled trials to observational and traditional knowledge-based studies, introduces heterogeneity in study design and outcome measures. Rather than diminishing validity, this heterogeneity reflects the real-world complexity of cortisol dysregulation, which spans biological, behavioral, and environmental domains. The review therefore emphasizes conceptual coherence and clinical relevance over strict methodological uniformity. Third, some traditional and complementary interventions discussed remain supported by early-stage or limited clinical evidence. This limitation is acknowledged to avoid overinterpretation and is presented intentionally to highlight research gaps and future investigative priorities, rather than to equate all therapies in terms of evidentiary strength. Fourth, cortisol biomarkers such as the CAR and diurnal slope are influenced by multiple contextual factors, which may limit their standalone diagnostic precision. However, the review frames these measures within integrated assessment models, reinforcing their value when interpreted alongside clinical symptoms and lifestyle context. Overall, the proposed integrated model of cortisol regulation is conceptual rather than prescriptive. While not yet validated in large-scale clinical trials, it serves as a theoretical scaffold to guide hypothesis generation, interdisciplinary collaboration, and future translational research.

Conclusions

Cortisol serves as the body's master regulator of stress and metabolic adaptation, yet its chronic dysregulation represents a critical link between lifestyle stress and systemic disease. This review underscores that effective management extends beyond pharmacological correction to embrace integrative, preventive, and restorative strategies. Evidence from both modern and traditional systems demonstrates that balanced nutrition, restorative sleep, structured physical activity, and mind-body practices are fundamental for maintaining HPA axis homeostasis. Herbal adaptogens such as *Withania somnifera*, *Ocimum tenuiflorum*, *Rhodiola rosea*, and *Bacopa monnieri* further strengthen resilience by modulating neuroendocrine and immune pathways. When combined with complementary modalities like acupuncture and naturopathy, these approaches form a synergistic network that supports endocrine stability and emotional well-being. Future directions should focus on large-scale, longitudinal studies employing validated biomarkers, such as salivary, urinary, and hair cortisol, to personalize interventions and measure therapeutic efficacy. Ultimately, the integration of biomedical precision with traditional wisdom provides a sustainable model for cortisol regulation, advancing the model of holistic health and stress resilience in modern medicine.

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Author contributions

Conceptualization, resources (AB), data curation, formal analysis, writing–original draft, incorporation of the recent tabulated and figurative database (AK, SD, RP, BT), data correction, visualization, final analysis, review of original draft (DS, NS), project administration, supervision, guidance, suggestive measures, and final correction (VA). All authors have made significant contributions to this study and have approved the final manuscript.

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