



Research Summary

Cortisol: Mediator and Inhibitor

Cortisol production is regulated by the hypothalamic-pituitary-adrenal axis (HPA axis) - a complex network integrating the endocrine, nervous, and immune systems. In response to stress, the hypothalamus secretes corticotropin-releasing hormone (CRH), a neurohormone that stimulates the anterior lobe of the pituitary gland to release adrenocorticotropic hormone (ACTH). When ACTH reaches the adrenal cortex, cortisol is synthesized and secreted into the bloodstream.¹ Only 10 percent of circulating cortisol is free; the remaining majority is bound to plasma proteins. This slows cortisol clearance and reduces concentration fluctuations.²

As the major glucocorticoid, cortisol acts both as mediator and inhibitor of the stress response. As an insulin antagonist, cortisol maintains blood glucose levels by inhibiting glucose uptake and oxidation.¹ As an enhancer of catecholamine release, cortisol improves cardiac function and blood flow. Cortisol also suppresses collagen synthesis, osteoblast activity, hematopoiesis, protein synthesis, immune responses, and kidney function.²

For the most part, the stress response is meant to be acute and self-limiting. The HPA axis is controlled by negative feedback with excess cortisol signaling the hypothalamus to suppress CRH production.^{1,2} However, if the original stimulus of the stress response is prolonged or if it is of increasing magnitude, the HPA axis may no longer respond to negative feedback. The stress response becomes chronic causing continuous cortisol synthesis. Chronically elevated cortisol levels are linked to a myriad of health disorders, including:

- Coronary artery disease
- Myocardial infarction
- Cardiomyopathy³⁻⁵
- Metabolic syndrome^{6,7}
- Insulin resistance and diabetes⁵
- Overweight and obesity⁸⁻¹²
- Polycystic ovary syndrome^{13,14}
- Sleep fragmentation¹⁵⁻¹⁷
- Major depression¹⁸⁻²¹
- Conduct disorder²¹
- Anxiety and psychosocial stress²²
- Periodontal disease, impaired wound healing^{23,24}
- Reduced mental acuity²⁵
- Chronic fatigue syndrome²⁶
- Impaired immune response²⁷⁻²⁹
- Chronic inflammatory processes^{5,30,31}
- Alopecia and facial acne vulgaris^{32,33}

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What is the most accurate method of measuring chronic cortisol elevation? Saliva tests are an easy and accurate way to detect cortisol levels. When cortisol is chronically elevated, it makes its way into various tissues, including the tongue, cheek, and soft palate of the mouth.¹ Controlled collection times allow for accurate baseline testing and the effective monitoring of treatments.² Patients can collect their own saliva samples at home or at work. The first sample is generally taken one hour after getting up in the morning, followed by three more tests spaced four hours apart.¹²

Research has consistently shown that cortisol levels are highest as the day begins, and levels decrease as the day progresses. The most consistent measures of salivary cortisol levels are in the morning taken approximately one hour after waking. While values may vary slightly among different laboratories, normal cortisol levels at 8:00 in the morning range between 6 mcg/dl to 23 mcg/dl (micrograms per deciliter).¹

What is the most effective way to manage chronically elevated cortisol levels? Research findings have shown that the best way to manage chronic cortisol production is to ensure the adrenal glands are well-nourished.^{1,2} When continuously making cortisol, nutrients crucial to adrenal health, including vitamin B6, pantothenic acid, and vitamin C, often become depleted.³⁴ The amino acids L-tyrosine and L-theanine help the adrenal glands combat stress-related fatigue and anxiety.³⁵ Adequate amounts of calcium, magnesium, potassium, manganese, and zinc are needed for effective regulation of the cortisol feedback control mechanism.³⁶

There are several plant medicines well-known for their ability to reduce cortisol levels. Ashwagandha (*Withania somnifera*), also known as Indian ginseng and winter cherry, has been an important herb in the Ayurvedic and indigenous medical systems for over 3000 years.³⁷ Clinical trials and laboratory research support its use to enhance mood, reduce anxiety, and increase energy.³⁸⁻⁴¹ Recently, ashwagandha has been shown to reduce corticosterone a glucocorticoid hormone structurally similar to cortisol.^{1, 42-43} Another well-documented cortisol-lowering agent, phosphatidylserine, significantly reduced both ACTH and cortisol levels after exposure to physical stress.^{44,45} Similar to ashwagandha, phosphatidylserine also helps promote a positive mood.^{46,47}

In a recent study, study subjects took a nutritional supplement formulated to lower cortisol levels and reduce feeling of anxiety for 45 days. The supplement combined the cortisol-lowering ingredients ashwagandha (*Withania somnifera*) and phosphatidylserine with the anxiety-relieving components magnolia and L-theanine. The subjects collected their own saliva samples at five scheduled intervals throughout the day. The results demonstrated that the nutritional supplement decreased salivary cortisol levels in relation to baseline at all five sampling times throughout the day. The effect began almost immediately and persisted on a consistent basis throughout the entire 45 day duration of the study, averaging a reduction in cortisol levels of -75% and -83% for the pooled subject data. Participants reported additional benefits associated with cortisol-lowering, including increased feelings of relaxation throughout the day (71%), improved sleep/deeper sleep (71%/64%), and reduced levels of stress (57%).⁴⁸

