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1 Overview

Summary and Quick Facts for Stress Management

- Stress is meant to be an adaptive response, and in the short term, it is healthy. But chronic, low-level psychological stress, which is so common in the modern world, can cause many health problems.
- This protocol will help you understand how the body reacts to stress and how long-term stress can damage health. You will learn about lab tests that help determine if stress is affecting your health, and discover several nutrients (such as the tea compound theanine), along with dietary and lifestyle changes, that can promote a healthy stress response.

What is Stress?

Stress generally occurs when external stimuli disturb the dynamic balance of the body's physiological processes. A specialized signaling network called the HPA

axis coordinates the body's stress response.

Acute stress helps prime the body to respond to immediate, transient threats.

Intermittent mild stress, such as exercise, is healthy and promotes positive adaptive changes. Chronic stress, however, causes maladaptive responses and dysregulated HPA axis function. This can contribute to many health problems by disrupting the circadian rhythm, promoting inflammation, altering the microbiome, and causing epigenetic changes.

Natural interventions such as **adaptogens**, **L-theanine**, **B vitamins**, and **omega-3 fatty acids** may help relieve stress and restore normal HPA axis function.

How Can I Determine If Stress is Affecting My Health?

- Lab tests (including cortisol, dehydroepiandrosterone [DHEA], salivary alpha-[α] amylase, and immunoglobulin A [IgA])
- Heart rate variability

What Dietary and Lifestyle Changes Can Help Relieve Stress?

- Cognitive-behavioral therapy
- Meditation and mindfulness
- Exercise
- Maintain good sleep hygiene, sufficient sleep duration, and consistent sleep patterns
- Maintain social connections and interact with friends and loved ones frequently, even using social media platforms to do so if circumstances limit face-to-face interaction
- Maintain sex hormone balance
- Eat more fruits and vegetables
- Eat breakfast regularly

- Minimize caffeine and alcohol intake

Can Medications Help Relieve Stress?

Many cases of stress can be managed with dietary and lifestyle interventions. However, in more severe cases when stress is contributing to other conditions, such as anxiety or insomnia, medications may be appropriate for short-term use to temporarily address the stress-related condition(s). It is important to understand that medications do not eliminate stress or the causes of stress, but simply provide temporary relief from some of the symptoms caused by stress.

- Antidepressants and anti-anxiety medications such as selective serotonin reuptake inhibitors (SSRIs) (eg, Prozac and Zoloft)
- Beta-blockers (eg, propranolol)
- Sedatives such as benzodiazepines (eg, Valium and Klonopin)
- Hydrocortisone

What Natural Interventions May Help Relieve Stress?

- **B vitamins.** B vitamin deficiencies are linked with multiple neuropsychiatric disorders. Supplementation with B vitamins has been shown to relieve stress and support normal HPA axis function.
- **Vitamin C.** Low intake and circulating levels of vitamin C are correlated with symptoms of depression and anxiety. Increasing vitamin C levels via supplementation has been shown to reduce symptoms.
- **Omega-3 fatty acids.** Omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) found in fish oil, may help improve various mood- and stress-related phenomena like anxiety, depression, and aggression.

- **L-theanine.** L-theanine, an amino acid found in tea, has been shown to reduce perceived stress and physiological markers of the stress response.
- **Bioactive milk peptides.** Peptides found in milk, such as **α -lactalbumin** and **casein**, may support healthy neurological function, improve mood, and promote sleep.
- **Probiotics and prebiotics.** Probiotics and prebiotics can improve the balance of gut bacteria and have a positive impact on the stress response. Probiotics may lower stress reactivity and anxiety, and improve mood, memory, and cognition.
- **Adaptogens.** Adaptogenic herbs help support homeostasis in the body and can be used to relieve fatigue, improve cognitive function and mood, and support the immune system.
 - **Magnolia and phellodendron.** This herbal combination has been found to reduce stress and stress-related weight gain.
 - **Holy basil.** Several clinical and preclinical studies have demonstrated holy basil's ability to improve mood and cognition.
 - **Ashwagandha.** Ashwagandha has been shown to relieve stress, improve stress-related eating behaviors, and promote weight loss.
 - **Lemon balm.** Lemon balm has been found to improve mood and cognition and relieve symptoms of anxiety and insomnia.
 - Additional adaptogens that may help relieve stress include **bacopa**, **saffron**, **ginseng**, **rhodiola**, and **cordyceps**, and others.
- Other natural interventions may help relieve stress, including **phosphatidylserine**, **L-tryptophan**, **melatonin**, and **dehydroepiandrosterone (DHEA)**.

Over the course of evolutionary time, the human body has become reliant on the acute stress response to overcome short-term adversity. But human physiology is simply not adapted to the relatively modern phenomenon of unrelenting low-level stress. Consequently, we now face a plethora of health problems to which chronic stress is a contributing factor.^{1,2}

Many types of events and circumstances can be perceived as stressful. Events such as natural disasters, violence, war, and traumatic accidents are stressful to everyone they impact and are important causes of stress-related mental health problems that can affect whole communities.³⁹³ Other personal events such as divorce, job loss, critical or chronic illness, and bereavement affect people differently but are common causes of chronic stress in individuals.³⁹⁴⁻³⁹⁷

A key physiological feature of chronic stress is dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, a network of signaling centers in the brain and body that modulates our physiological response to stress. Normal activation of the HPA axis is necessary for healthy adaptive responses to stressors, but chronic activation leads to a maladaptive stress response marked by changes in the release and activity of the stress hormone, cortisol, which contributes to stress-related illness.^{2,3} Interactions between the HPA axis and the central nervous system, immune system, and gut microbiome contribute the wide-ranging effects of stress on overall health.^{4,5}

The good news is that making healthy lifestyle decisions and adhering to a healthy diet can enhance resistance to the detrimental effects of chronic stress.⁴⁻⁶ In this protocol, you will learn how chronic stress causes health problems and how you can improve your ability to cope with stress and fortify yourself against the negative health effects of our stressful modern world.

3 How Does The Body Respond to Stress?

The Fight or Flight Response

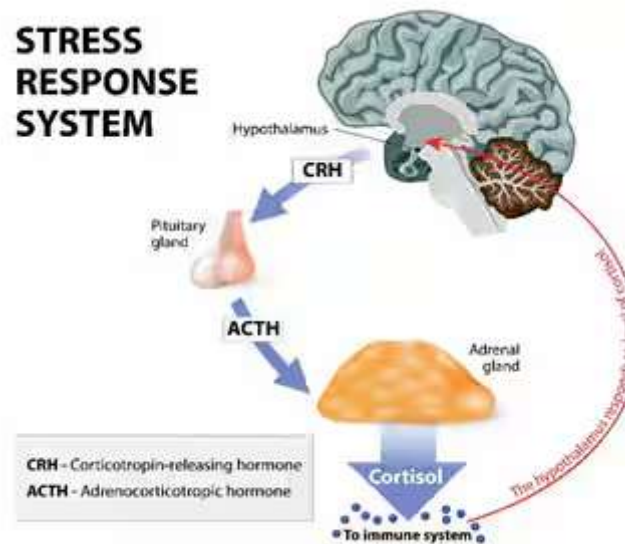
Stress generally occurs when external stimuli disturb the dynamic balance of the body's physiological processes.⁷ The stress, or “fight or flight,” response begins in the brain, where a perceived threat triggers the release of corticotropin releasing hormone (CRH) from the region called the hypothalamus. This stimulates the anterior pituitary, a gland that sits just under the hypothalamus, to increase release of adrenocorticotrophic hormone (ACTH) into the bloodstream. ACTH then acts on the adrenal cortex, raising production and release of cortisol and the less active glucocorticoid, corticosterone, as well as another adrenal hormone called dehydroepiandrosterone, or DHEA.⁸

The signaling network between the nervous system and adrenal glands, called the hypothalamic-pituitary-adrenal (HPA) axis, is regulated in part by a negative feedback mechanism, through which rising blood levels of cortisol inhibit release of both CRH and ACTH.^{3,9}

Stress also directly engages sympathetic nervous system signaling in the brain region called the locus coeruleus.

Catecholamine neurohormones

(epinephrine and norepinephrine, also known as adrenaline and noradrenaline) released by the adrenal medulla and sympathetic nerve endings have physiologic effects intended to help the body respond and adapt to stressful circumstances.



Although it tends to work in concert with the HPA axis, the sympathetic nervous system also functions independently to activate the stress response.^{3,9}

Acute Stress

As mediators of the stress response, cortisol and catecholamines have profound effects throughout the body (see Table 1). When acutely elevated, they help prepare the body to escape danger. For example, cardiac output increases to support stronger blood flow; blood sugar levels increase to meet higher energy demands; pupils dilate to allow for greater visual input; alertness and cognition are enhanced; and digestive and reproductive functions are inhibited due to their not being essential in the short term.⁹

Table 1: Hidden Causes of Acute Stress

Physiological Stressor	Acute Adaptive Stress Response
Low blood glucose level ^{10,11}	Catecholamines stimulate breakdown of carbohydrate stores and conversion of protein and fat into glucose Cortisol inhibits glucose use by non-central nervous system tissue
Low blood pressure ^{3,12}	Catecholamines stimulate constriction of blood vessels Cortisol increases sodium and water retention in the kidneys
Low oxygen saturation ^{3,13,14}	Catecholamines stimulate the respiratory center of the brain to

	increase breathing, increase heart rate and contraction strength, and selectively constrict blood vessels
Oxidative stress ¹⁵	Catecholamines and cortisol alter cell metabolism to restore reductive-oxidative balance
Inflammatory cytokines ^{1,16}	Catecholamines and cortisol modulate immune activities

Chronic Stress

The acute stress response can lead to positive adaptive effects, but when the HPA axis and locus coeruleus are chronically activated, their effects become maladaptive: the response to a chronic or repeated stress may become dull, yet, at the same time, sensitivity to new stressors may be enhanced.^{12,17} A dysregulated stress response results in altered patterns of cortisol and catecholamine production and/or receptor response to them.^{3,9} Chronic stress may even alter brain structure.¹⁸ In addition, impairment of the HPA axis due to chronic stress appears to suppress DHEA production and its release, even under acutely stressful circumstances.^{8,19} This is important because DHEA opposes some of the actions of cortisol: it protects nerves and stimulates development of neuronal connections, has immune-regulating effects that oppose and balance those of cortisol, and may prevent cortisol-induced metabolic disturbances.⁸ The exact nature of the response to chronic stress depends on individual characteristics such as personality traits, gender and age, life experiences, and genetic and epigenetic factors.³

The Stress Burden of Social Isolation and Loneliness

In January 2018, the British government announced the establishment of a Ministry of Loneliness. The decision was based on a 2017 report finding that 9 million Britons often or always feel lonely and the growing recognition that social isolation and loneliness take a toll on physical and mental health.^{20,21}

The evidence for links between loneliness, a form of psychological stress, and poor health is particularly strong for cardiovascular disease and mental health problems.²⁰⁻²³ In older adults in particular, loneliness has been linked to increased cognitive decline and dementia, health care use, nursing home admissions, and mortality.²¹ A recent review of the research noted the health effects of loneliness may be mediated by altered HPA axis and sympathetic nervous system reactivity to stress. Like the stress response itself, the reaction to social isolation appears to vary among individuals.²⁴

There is also evidence that lack of social connection may increase the risk and severity of viral respiratory infection. In one study, feeling supported and hugging were both associated with reduced stress and decreased risk of a viral cold. In those with lower levels of social support, increased stress was associated with an increased risk of infection.⁴⁰⁵ These findings highlight the importance of identifying people at highest risk of isolation and loneliness and taking steps to increase their social support without raising their risk of infection.

4 How Does Stress Cause Health Problems?

Prolonged stress is associated with many chronic disorders and diseases affecting all of the body's organ systems. As life's stressors take their toll on the psyche and body, chronic illness itself becomes a source of stress. The two-way relationship between stress and disease creates a downward spiral in mental and physical health that can become difficult to overcome.²

Stress and the Circadian Rhythm

The HPA axis is closely regulated by circadian signaling in the brain. This circadian signaling is affected by day and night (light and dark) cycles, patterns of eating times, and most likely other factors yet to be discovered. Normally, cortisol levels peak shortly after waking in the morning and are lowest around bedtime. By acting on receptors throughout the body, cortisol imposes diurnal (two-phase; day-night) rhythms to other physiological functions.^{17,25}

Numerous studies have shown that disruption of the circadian clock, such as due to shift work, sleep apnea, and other sleep disorders, is associated with health problems including cardiovascular disease, type 2 diabetes, obesity, and an array of age-related diseases.^{26,27} Circadian disturbances may even correlate with reduced lifespan.²⁸ Chronic stress appears to impair circadian control of the HPA axis, which can result in either excess evening levels or blunted morning levels of cortisol.²⁹ These dysfunctional patterns of cortisol release may be an underlying factor in the negative physical and mental health consequences of chronic stress and circadian rhythm disruption.³⁰

Stress and the Immune System

One important way that chronic stress affects long-term health is through dysregulated immune signaling. Although cortisol is best known for its immunosuppressive action, its effects on immunity are complex, stimulating some aspects of immunity and inhibiting others.^{1,25} A phenomenon known as glucocorticoid resistance, in which tissues and cells become less responsive to cortisol, occurs following long-term elevation of cortisol levels due to chronic stress.^{31,32}

Chronic stress-induced immune dysfunction results in reduced immune protection against infections and cancer. Chronic stress, particularly when it involves

interpersonal relationships or work, has been consistently correlated with increased risk of respiratory infections such as influenza and the common cold.⁴⁰⁶⁻⁴⁰⁸ Studies have also shown persistently high levels of perceived stress and cortisol are associated with a heightened inflammatory response to pathogens, due at least in part to glucocorticoid resistance. This heightened inflammatory response results in increased susceptibility to infection, tissue damage, and symptom severity.⁴⁰⁸⁻⁴¹⁰ In one study, participants with higher cortisol production not only had increased risk of the common cold but also more days of viral shedding, indicating longer duration of infection and possibly transmissibility.⁴¹¹

Stress has also been implicated as a contributing factor in inherently inflammatory conditions, such as allergic and autoimmune disorders, and conditions related to low-level systemic inflammation like heart disease and diabetes.^{1,33} Once inflammation is initiated, it perpetuates the stress response through the actions of cytokines (small signaling proteins of the immune system) on the hypothalamus, pituitary, and adrenal cortex.^{25,34}

Stress and the Microbiome

Chronic stress may impact health through interactions with the gut microbiome—the trillions of microorganisms that reside in the intestines. Through its relationship with nervous system signaling, often referred to as the “gut-microbiota-brain axis,” and its ability to regulate the immune system, a healthy microbiome appears to be essential for modulating stress responsiveness and preventing overstimulation of the HPA axis. Conditions associated with chronic stress have been shown to alter the composition of the gut microbial community. Microbial imbalances, in turn, can cause intestinal and systemic inflammation and abnormal neurological signaling that can trigger HPA activation.³⁵⁻³⁸

The Epigenetics of Stress

Exposure to stress early in life can alter stress responsiveness and resilience throughout life. Part of this is likely due to effects of stress on brain and adrenal gland development; another important element is epigenetics. Epigenetics refers to environmentally induced modifications to gene expression patterns (as opposed to changes in gene sequence) or factors that control how genes are used to direct protein synthesis in cells. These modifications are lasting but can be reversed by future circumstances.³⁹

The epigenetic changes induced by prenatal and early life stress result in hyperresponsiveness of the HPA axis and increased risk of neuropsychiatric problems in adulthood, such as depression, anxiety, and post-traumatic stress disorder.³⁹⁻⁴¹ Emerging research has shown that stress-induced epigenetic changes can also occur in adulthood, affecting HPA axis responsiveness and increasing vulnerability to stress-related health problems.⁴² In addition, because the epigenome is passed on to offspring by both parents, exposure to intense or unremitting stress has implications for resilience and health that may span multiple generations.^{41,43,44}

Hormesis—The Benefits of Intermittent Mild Stress

While chronic stress has toxic effects that can ultimately shorten lifespan, short-term exposure to stress can promote development of adaptive strategies, supporting health and longevity. The process of developing coping mechanisms in response to minor stressors as a means of building resilience against greater stress has been called hormesis. Another way of expressing the concept of hormesis is the common phrase, “What doesn’t kill you makes you stronger.”^{45,46}

Exercise is an example of a hormetic stressor: it causes stress by increasing body temperature, mechanical demands, nutrient and oxygen demands, and free radical production.⁴⁶ The cellular responses to the stress induced by **regular**

moderate exercise can lead to resiliency reflected in a broad spectrum of health benefits and longer life. On the other hand, extreme exercise, such as bouts lasting 18–24 hours without interruption, exhausts the body's ability to adapt, can harm health, and may shorten lifespan.^{45,46} Moderate **calorie restriction** also confers hormetic benefits: adapting to lower energy availability involves changes in metabolic, immune, and neuroendocrine function that are associated with healthy aging and may extend life.^{47,48}

5 What are the Health Consequences of Chronic Stress?

Chronic stress can exert considerable body-wide health effects. It can contribute to the onset or worsening of many types of ailments. The following discussion highlights some of the more common conditions to which chronic stress often contributes.

Cardiovascular Disease

One of the most widely recognized health effects of chronic stress is **heart disease**. Through the effects of cortisol and catecholamines, and by disrupting circadian rhythms through sleep disturbance, chronic stress has been shown to impair nervous system regulation of cardiac function,⁴⁹ and can cause high blood pressure, arrhythmia, and vascular inflammation leading to atherosclerosis and blood clots.⁵⁰ Prolonged stress at home and at work has been clearly linked to increased risk of coronary artery disease and cardiac events including heart attack and stroke.^{12,51} A recent meta-analysis highlights the influence of work stress on heart disease risk: after analyzing data from more than 740,000 men and women, researchers found that people who work 55 or more hours per week have a 12% increased risk of coronary artery disease and a 21% increased risk of stroke compared with those who work less.⁵²

Acute stress can also pose a threat to the heart. Studies have noted the incidence of heart attack increases following acutely stressful events such as earthquakes and World Cup soccer championships.⁵³ Takotsubo cardiomyopathy, a sudden weakening of the heart muscle that mimics the symptoms of heart attack or angina and is potentially fatal, is another example of the danger of acute stress to the heart. Also known as stress cardiomyopathy, broken heart syndrome, and apical ballooning syndrome, Takotsubo cardiomyopathy typically occurs a few hours after a severe physical or emotional trauma and is most common in postmenopausal women.^{54,55}

Psychiatric and Neurological Disorders

Chronic stress is closely associated with several common neuropsychiatric disorders, including **depression**, **anxiety**, dementia, and **Alzheimer disease**.

Inflammation in the brain triggered by stress-related signaling is an important factor linking stress to neuropsychiatric disorders.⁵⁷ In Alzheimer disease, stress-related immune dysfunction appears to weaken the brain's ability to clear amyloid-beta, a protein involved in Alzheimer disease development and progression.^{58,59} In addition, persistently high cortisol levels, a marker of chronic stress, can trigger changes to neuronal structure and reduce brain plasticity (the ability to make new neuronal connections).⁵⁶ Early life, repetitive, or chronic stress may also reduce the activity of nerve growth factors, especially brain-derived neurotrophic factor (BDNF), involved in the formation of new nerve connections.⁶⁰⁻⁶² Low levels of BDNF are associated with mood disorders as well as learning and memory deficits.⁶² Furthermore, these stress-related changes may be encoded epigenetically, altering nerve system plasticity and function in lasting ways.⁶³

Cancer

A growing body of evidence suggests that the neurohormones of the stress response can promote the initiation and progression of cancer.^{64,65} Furthermore, chronic stress may be associated with behaviors, such as smoking, substance abuse, overeating, and decreased physical activity, that increase the risk of certain cancers.^{66,67} Coping with a cancer diagnosis, symptoms, and treatment is inherently extremely stressful for some individuals,^{68,69} yet a high burden of stress may negatively impact response to cancer treatment and prognosis.^{64,70,71}

The mechanism by which stress influences cancer is likely to be multifaceted, but the cornerstone may be immune dysregulation, marked by decreased immune surveillance and systemic inflammation. HPA axis dysregulation suppresses immune defenses against cancer, and chronic systemic inflammation creates conditions that support cancer initiation, progression, and metastasis.^{72,73}

Inflammation may stem from other stress-induced sequelae, including weight gain and metabolic disturbance, disruption of the gut microbiome, and epigenetic alterations⁷²; in turn, inflammation can contribute to these processes.⁷⁴ In addition, stress may affect cancer development by desynchronizing circadian regulation of biological activities.^{29,75}

Metabolic Disturbance: Why Does Stress Make it Hard to Lose Weight?

One of the most important functions of the stress response is to ensure that adequate energy is available to cope with stressful circumstances. During episodes of acute stress, appetite is suppressed to reserve attention for fight or flight, and extra energy in the form of glucose is freed from stored fats and carbohydrates. Under conditions of chronic stress, however, appetite is typically up-regulated and cravings for high-sugar, high-fat, high-calorie foods can intensify as a result of long-term hyperstimulation of the HPA axis and its complex interactions with appetite-regulating neurohormones such as ghrelin and leptin. For reasons that are not

entirely clear, an increased appetite as a reaction to chronic stress is more pronounced in women than men.^{10,76}

To make matters worse, chronic stress and HPA axis dysregulation are associated with insulin resistance and **type 2 diabetes**, as well as fat tissue growth and obesity.^{77,78} In one study, salivary cortisol tests showed disturbances in the diurnal rhythm of cortisol release correlated with body mass index (BMI) and waist circumference, a measure of visceral fat and one of the cardiovascular risk factors in metabolic syndrome.⁷⁹ These metabolic consequences of long-term stress then promote widespread inflammatory signaling that damages blood vessels and increases cardiovascular risk.^{80,81} Systemic inflammation also affects the nervous system, contributing to mood and cognitive disorders, and creates a vicious cycle of increased HPA axis activation.^{10,82}

Although widely believed that chronic stress can lead to weakened thyroid function, there is little evidence as of the date of this writing to support this notion. In one study, hair cortisol levels were higher in adults with overt hypothyroidism than in healthy adults, and were correlated with higher body weight and BMI; however, in participants with subclinical hypothyroidism, a condition characterized by normal to slightly abnormal lab values and possibly symptoms of hypothyroidism, hair cortisol levels were not significantly different from those of healthy participants.⁸³ Findings from preliminary studies indicate stress may contribute to the onset of autoimmune hypothyroidism; however, a review of these studies was unable to confirm the connection.⁸⁴ On the other hand, evidence from animal studies suggest hypothyroidism may trigger HPA axis dysregulation and, when chronic, reduce adrenal output.^{85,86}

Additional Health Conditions Stress Can Worsen

Virtually any health condition can be negatively affected by stress. In addition to those already discussed, the following are some of the disorders and diseases that stress may impact:

- Asthma⁸⁷
- Atopic dermatitis⁸⁸
- Autoimmune diseases⁸⁹
- Chronic fatigue syndrome⁹⁰
- Upper and lower respiratory infections⁹¹
- Infertility⁹²
- Irritable bowel syndrome⁹³
- Migraine⁹⁴
- Pain disorders^{95,96}
- Sexual dysfunction⁹⁷

6 Determining if Stress May be Affecting Your Health

Although the effects of chronic stress can vary among individuals, several laboratory and clinical assessments can help determine if stress may be contributing to health problems. Objective tests that may be helpful in assessing the extent to which stress is affecting overall health include cortisol, DHEA level, salivary alpha-[α] amylase and immunoglobulin A (IgA) levels, and heart rate variability.

Cortisol

Measuring cortisol levels can be helpful in assessing HPA axis function. Cortisol levels in saliva, blood, urine, and hair have been shown to be reliable markers of adrenal cortisol output.^{98,99} These tests are widely available and are sometimes used as indicators of HPA axis function. In general, long-term increased cortisol

output, reflecting over-activity of the HPA axis, is typical in major depression, while decreased cortisol output, reflecting under-activity of the HPA axis, is typical in chronic fatigue syndrome and post-traumatic stress disorder.¹⁰⁰

- *Salivary cortisol* is a non-invasive test that may be helpful in determining whether the circadian rhythm of adrenal gland function is intact or disturbed. Late night salivary cortisol is sometimes used to diagnose Cushing syndrome (a condition caused by excess exposure to cortisol or drugs that mimic cortisol). However, tests that measure cortisol levels at multiple times in a day, creating a curve that reflects the diurnal pattern of cortisol release, may have broader usefulness in assessing stress.^{101,102} One research review found that flatter diurnal cortisol curves are correlated with poorer health.¹⁰³

Cortisol levels rise gradually with age and are affected by gender, especially around puberty and in the elderly. Although every lab determines its own reference ranges, peak salivary cortisol levels (within the first hour after waking) in adults appear to range from 1.8 to 26 nmol/L, and evening trough levels (about 16 hours after waking) range from 0.2 to 3.5 nmol/L.¹⁰⁴

- *Hair cortisol* concentration is a novel and non-invasive method of evaluating long-term cortisol exposure over months to years. Because stress levels can fluctuate over time, cortisol is generally measured in the three centimeters of hair closest to the scalp (reflecting HPA axis activity during the previous three months).¹⁰⁵ Cortisol concentrations in scalp hair have been found to vary with psychological and physical stressors, and have been correlated with perceived stress and stress-related symptoms and illnesses, including obesity, metabolic syndrome, and cardiovascular disease.^{99,106}

Salivary Alpha [α]-Amylase and Immunoglobulin A (IgA)

Alpha [α]-amylase is a starch-digesting enzyme produced in the salivary glands as well as the pancreas. Production of salivary α -amylase increases under stimulation by the sympathetic nervous system, which triggers the “fight or flight” reaction and has a critical role in the stress response. On the other hand, production of salivary proteins like α -amylase and the antibody immunoglobulin A (IgA) is inhibited by the parasympathetic nervous system, which controls resting body functions. Therefore, salivary α -amylase and salivary IgA have been proposed as markers of the balance of nervous system regulation and objective measures of stress.¹⁰⁷⁻¹⁰⁹

Numerous studies show that α -amylase increases as a result of physical and psychological stress, and high levels have been seen in stress-related conditions such as anxiety.^{107,110} It is sometimes tested along with salivary cortisol, which reflects HPA axis activity, to provide a more comprehensive assessment of stress. Although not performed routinely, evidence suggests this combination of salivary tests may be useful for non-invasively and objectively evaluating the contribution of stress in patients with chronic conditions¹¹¹ and monitoring the effects of stress-reducing therapies.¹¹²

Salivary secretory IgA (sIgA) has also been proposed as a marker of stress. A number of studies have shown that acute stress can increase levels of this important antibody.¹¹³⁻¹¹⁵ With chronic stress, however, sIgA appears to be depleted and salivary levels drop,^{116,117} possibly increasing risk of oral, gastrointestinal, and respiratory infections.¹¹⁸ Interpretation of salivary sIgA is somewhat challenging due to its sensitivity to other factors in the oral environment.¹¹⁹

Salivary sIgA and α -amylase tests are commercially available and frequently recommended and interpreted by integrative health care providers. In general, standardization of these salivary tests and more information about factors that interfere with their interpretation, such as smoking, food and beverage

consumption, and medication use, will help increase their usefulness and acceptance.^{108,119,120}

DHEA

Dehydroepiandrosterone (DHEA) is an adrenal hormone that opposes some of the actions of cortisol in many tissues. Acute stress can increase production of both DHEA and cortisol in healthy individuals, but chronic stress has been correlated with low DHEA and high cortisol output.⁸ In one study, levels of DHEA-S (DHEA-sulfate, the form of DHEA typically measured in the blood) were 23% lower in healthy adults with the highest perceived work-related stress compared to those with the lowest work-related stress.¹²¹ The balance between cortisol and DHEA production also varies dramatically with age: DHEA release is lowest in older age, and it is thought that the unabated action of cortisol in the presence of declining amounts of DHEA may contribute to age- and stress-related diseases.^{8,122,123}

Evidence suggests blood levels of DHEA-S that generally correspond with optimal health are 350–500 µg/dL for men and 275–400 µg/dL for women. Measuring the ratio of serum cortisol to DHEA-S may also provide some insights into the function of the adrenal gland and stress resilience.⁸

Heart Rate Variability

The heartbeat is not a precisely regular rhythm but instead oscillates unpredictably over time in response to dynamic shifting in the balance of sympathetic and parasympathetic regulation. Heart rate variability is the fluctuation in the length of time between heartbeats.¹²⁴ In a healthy person at rest, when the parasympathetic nervous system is the predominant heart rhythm regulator, heart rate variability increases, but during times of stress, when the sympathetic nervous system is strongly activated, heart rate variability decreases. Like salivary α-amylase, heart rate variability at rest provides information regarding the stress-related activity of

the nervous system.¹²⁵ Greater variability in heart rate reflects more robust ability to adapt to changing conditions.¹²⁴

A growing body of evidence shows that resting heart rate variability is a meaningful reflection of cardiac and nervous system activity.^{124,125} Low heart rate variability has been noted to be closely correlated with other measures of stress and is an indicator of low stress-resilience and increased risk of heart attack and overall mortality.¹²⁵⁻¹²⁸ Furthermore, stress management strategies like exercise and mindfulness practices can improve heart rate variability.^{128,129} Taken together, the evidence suggests heart rate variability may prove helpful in predicting risk of stress-related physical and psychological disorders.^{126,130}

Heart rate variability is measured during long (24-hour), short (five-minute), or ultrashort (shorter than five-minute) monitoring periods. At this time, 24-hour data sets are considered the “gold standard” and seem to offer a better reflection of health status. Questions remain about the significance of short- and ultrashort-term heart rate variability measurements, ideal timing of data collection, frequency of oscillations, and the influence of individual factors such as gender, disease status, and medication use on heart rate variability measurements.¹²⁴ Nevertheless, devices that measure heart rate variability are increasingly commercially available.

The Issue of “Adrenal Fatigue”

An alternative medicine term that often finds its way into discussions about stress is “adrenal fatigue.” Although “adrenal fatigue” is not a recognized diagnosis in conventional medicine, the symptoms often attributed to “adrenal fatigue” may arise from multifactorial pathological processes involving, among other systems, the HPA axis.^{131,132}

On the other hand, Addison's disease, sometimes referred to as "adrenal insufficiency," is a medical condition that can be life threatening. Addison's disease is typically the result of an autoimmune disorder, but can arise due to genetic abnormalities as well. Consequences of Addison's disease are much more severe and acute than those induced by stress, and the condition should be closely monitored by a qualified healthcare professional.¹³³ Those interested in learning more about Addison's disease can do so by reviewing Life Extension's **Adrenal Disorders** protocol.

7 Medications for Temporary Stress Relief

Although there are no medications specifically indicated to treat stress, it is a major contributor in some individuals to anxiety, depression, insomnia, or other psychological or psychiatric disorders that may be treatable with antidepressants, sedatives, and anti-anxiety medications. In addition, some stress-related health problems may be responsive to treatment with the cortisol analog hydrocortisone.

It is important to note that, in most cases, these medications are not indicated for stress relief specifically and should be used only temporarily. In the majority of people suffering from chronic stress, the stress management techniques and dietary measures described later in this protocol are the best options for reducing stress-related symptoms and increasing stress resilience.

Antidepressants and Anti-Anxiety Medications

Selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) are antidepressants widely prescribed to treat depression and anxiety and are a consideration for patients with stress-related mood disorders. For example, the SSRIs paroxetine (Paxil) and sertraline (Zoloft),

and the SNRI venlafaxine (Effexor) in particular have demonstrated benefits in treating social anxiety disorder.¹³⁴ Case studies suggest the SNRI tramadol (Ultram) can effectively reduce psychological stress and may be useful taken as needed rather than daily.¹³⁵ However, these medications may cause dependence, have low success rates in achieving remission from anxiety or depression, and are associated with side effects such as nausea, sexual dysfunction, weight gain, insomnia, headache, fatigue, and anxiety.¹³⁶

Buspirone (Buspar) is an anti-anxiety medication that enhances the activation of serotonin receptors known as 5-HT_{1A} receptors. Buspirone has also been found to stimulate the HPA axis and raise catecholamine levels.¹³⁷ Results from animal research suggest it may have a role in treating stress-related anxiety and depression¹³⁸; however, buspirone can cause adverse side effects such as restlessness, nervousness, poor concentration, difficulty sleeping, drowsiness, and tiredness or weakness.¹³⁹

Trazodone (Desyrel) is classified as an atypical antidepressant. Its main adverse effect is sedation, and this has led to its use as a sleep aid.¹³⁶ Other non-FDA-approved indications for which trazodone is used include anxiety, panic disorder, and post-traumatic stress disorder, although its efficacy in these conditions has not been established.^{140,141}

Beta Blockers

Beta blockers are drugs that inhibit catecholamine receptors called beta-adrenergic receptors, thereby suppressing sympathetic nervous system signaling.¹⁴² These medications are mainly used to treat high blood pressure, arrhythmia, angina, and heart failure, and are part of post-heart-attack maintenance. Certain beta blockers are also used to treat glaucoma, migraines, essential tremor, and cardiac symptoms of hyperthyroidism.^{143,144}

Propranolol (Inderal) is a beta blocker sometimes used to prevent acute stress in individuals with situational anxiety such as exam anxiety, stage fright, performance anxiety, and fear of surgery.^{143,144} For these uses, it is typically taken intermittently and in single doses. It does not appear to be effective in treating long-term anxiety disorders such as stress-induced or generalized anxiety disorder, but controlled trials are lacking.¹⁴² Furthermore, there are concerns that long-term propranolol use, even for cardiovascular indications, may increase the risk of depression.¹⁴⁵

Sedative Medications

Benzodiazepines are a category of fast-acting sedative medications that, despite limited approved uses, are often prescribed for patients with anxiety disorders including stress-induced anxiety and insomnia.^{134,146,147} These medications enhance the action of GABA, a neurotransmitter that quiets nerve conduction and may suppress activation of the HPA axis.¹⁴⁷ Examples of benzodiazepines are diazepam (Valium), lorazepam (Ativan), and clonazepam (Klonopin). In a rat model of psychosocial stress, both lorazepam and clonazepam reduced stress-related inflammation in the central nervous system and decreased behaviors associated with stress-induced anxiety and depression.¹⁴⁸

Benzodiazepines are associated with a host of problems including confusion and falls, cognitive impairment, withdrawal symptoms, dependence, and abuse. Their use also increases pneumonia risk in older patients. In addition, they are known to interact with many medications, alcohol, and other substances. Benzodiazepines are only indicated for short-term use.^{147,149}

Non-benzodiazepine sedatives used for insomnia include zopiclone (Imovane), eszopiclone (Lunesta), zolpidem (Ambien), and suvorexant (Belsomra). While it is thought these options may be less addictive than benzodiazepines, their long-term use for insomnia may still be associated with cognitive impairment, falls,

dependence and abuse, decreased quality of life, and increased risk of pneumonia in older adults.¹⁴⁹⁻¹⁵¹

Low-Dose Hydrocortisone Replacement

Hydrocortisone (Cortef) replacement therapy is generally reserved for patients with Addison's disease, but some alternative health care practitioners prescribe low-dose hydrocortisone for those with long-term burnout related to chronic stress or chronic fatigue syndrome, a condition marked by underactivity of the HPA axis.¹⁰⁰ Chronic stress may over time lead to dysregulation of the HPA axis, which in turn can lead to reduced cortisol production in some cases. On this basis, low-dose hydrocortisone is sometimes used by integrative practitioners to counteract the HPA axis dysfunction that may arise as a consequence of long-term stress. This strategy is generally reserved for people who have not improved with other interventions such as adrenal glandulars. The hydrocortisone dosage typically ranges from 5 to 20 mg and may be adjusted according to body weight.

Results from several clinical trials suggest low-dose hydrocortisone may be beneficial as a short-term therapeutic.¹³² For example, in a crossover trial (in which all participants underwent both an active treatment phase and a control phase) of 32 participants diagnosed with chronic fatigue syndrome, low-dose hydrocortisone therapy for 28 days reduced fatigue significantly more than placebo.¹⁵² However, in a randomized controlled trial in 100 chronic fatigue syndrome patients, 5 mg hydrocortisone along with 50 mcg fludrocortisone (an analog of the adrenal hormone aldosterone) daily for six months was no better than placebo at reducing fatigue.¹⁵³ This may be due to adrenal suppression, which can occur with long-term hydrocortisone use.¹⁵⁴ Importantly, hydrocortisone replacement should only be undertaken under the supervision of

a qualified clinician because excessive cortisone replacement may lead to problems such as compromised bone integrity and impaired glucose metabolism.

8 Lifestyle and Behavioral Techniques to Relieve Stress

People experiencing high levels of stress and its health effects will undoubtedly fare better by reducing their exposure to high-stress circumstances. For many people, however, stress at home or on the job can seem unavoidable. In such cases, a healthy diet, exercise, and stress management practices can have a strong positive impact on normalizing the stress response and preventing stress-related illness.

Cognitive-Behavioral Therapy

Cognitive-behavioral therapy (CBT) refers to a group of patient-centered techniques focused on changing thought patterns associated with emotional distress and harmful behaviors. A large body of clinical studies show CBT is an effective strategy for managing general stress and relieving anxiety.¹⁵⁵ In a 2018 clinical trial, 100 subjects suffering from chronic stress were assigned to participate in a 12-week internet-based CBT intervention or be placed on a waitlist. After six months, measures of perceived stress and stress-related symptoms were lower in those who received the intervention.¹⁵⁶ CBT was found in another study to be similarly effective to mindfulness-based stress reduction (described later in this section) in reducing stress and burnout in parents of children with chronic conditions.¹⁵⁷

A recent research review showed CBT is moderately effective for treating stress- and anxiety-related psychological disorders.¹⁵⁸ CBT has also been recommended as a treatment strategy for stress-mediated chronic pain.^{159,160} In a study in 46 women

with fibromyalgia (a chronic pain condition), a six-month CBT intervention led to improved sense of control over life and increased coping behaviors, and decreased measures of depression, exhaustion, and stress behaviors; these benefits were maintained and enhanced one year after initiation of the intervention.¹⁶¹

Some stress-affected people may be more likely to benefit than others: researchers have noted that factors such as working night shifts, high burnout scores, and elevated inflammatory marker levels may reduce the efficacy of CBT.¹⁶²

Meditation and Mindfulness

Meditation helps regulate the stress response, reduce chronic inflammation, and maintain a healthy gut microbiome, and numerous studies indicate its potential benefits in treatment and prevention of diverse health disorders.⁴ Studies in veterans with post-traumatic stress disorder have shown practicing meditation not only improves patterns of cortisol release but also triggers epigenetic changes that might also contribute to its positive impacts on the stress response.^{163,164}

A review of 45 studies found that meditation lowers cortisol output, blood pressure, heart rate, triglycerides, and inflammatory marker levels, indicating its potential for protecting cardiovascular health.¹⁶⁵ The American Heart Association issued a statement in 2017 recognizing meditation's possible role, alongside smoking cessation and treatment of high blood pressure and high cholesterol, in reducing the risk of heart disease.¹⁶⁶

Mindfulness-based stress reduction is a structured program that incorporates meditation, body awareness, and gentle yoga, with an emphasis on awareness of the present moment. The benefits of mindfulness-based stress reduction on various psychological and physical health outcomes have been widely reported.⁶ For example, reviews of studies on healthcare providers and other types of workers have shown that mindfulness-based interventions can increase well-being and

reduce anxiety, depression, and burnout, and may improve work performance.¹⁶⁷⁻¹⁷⁰

In a controlled trial in overweight and obese women, a four-month mindfulness program led to reductions in stress-related eating behaviors and prevented weight gain.¹⁷¹ Mindfulness programs are usually conducted in person, but the effectiveness of online mindfulness-based stress reduction programs is gaining interest, with positive effects being reported in recent clinical trials.¹⁷²⁻¹⁷⁴

Exercise

For many people, stress reduces the desire and motivation to engage in physical activity, yet exercise can improve stress resilience¹⁷⁵ and has been shown to reduce symptoms in people with anxiety and stress-related disorders.¹⁷⁶

Exercise appears to stimulate anti-inflammatory and anti-stress reactions in the body.¹⁷⁷ Engaging in regular exercise improves the body's ability to adapt to stress and has been correlated with better recovery from illness and surgery.¹⁷⁵ Exercise is associated with better sleep,¹⁷⁸ less anxiety and depression,^{179,180} and lower stress reactivity in the nervous and cardiovascular systems.¹⁸¹ A review of the research concluded that approximately 50 minutes per day of moderate intensity exercise is associated with the greatest mental health benefits compared with lower or higher doses; however, sedentary hours erode some of physical activity's positive mental health effects.¹⁸² Clinical evidence also suggests strength training may improve anxiety, depression, and sleep.^{183,184}

Exercise may mitigate stress-related eating behaviors: a number of trials have indicated that even 15-minute bouts of brisk walking can reduce stress-eating in the short term.¹⁶¹ In addition, regular exercise can help prevent or reverse the metabolic, inflammatory, and neurological consequences of chronic stress,^{66,185,186} and numerous studies support the current World Health Organization

recommendation to engage in at least 150 minutes per week of moderate-intensity physical activity as an effective means of reducing death from all causes.¹⁸⁷

Activity tracking tools may be useful and effective in incorporating exercise into a stress management protocol.^{188,189} In a 2016 preliminary study, 35 sedentary overweight participants were enrolled in a 12-week walking program in which they used pedometers to count the number of steps taken each day. The 30 participants who successfully achieved the goal of 10,000 steps per day not only lost weight and decreased their waist circumference, they also had lower scores on tests of anxiety, depression, fatigue, confusion, anger, and overall mood distress than at the beginning of the study.¹⁹⁰ In another trial, increasing physical activity by using a step-counting activity tracker plus a goal setting intervention reduced depressive symptoms in female participants.¹⁹¹

Social Support

A strong social support network can buffer perception of stress and is one of the key factors for maintaining stress resilience throughout life.^{424,425} As a characteristic of resilience, social support helps protect against the negative impacts of stress on immune function and inflammation.⁴²⁵ Although individuals differ in the amount and type of social interaction they benefit from, studies have consistently shown that social integration through contact with friends and family and membership in a religious community and other groups improves physical and mental health and extends lifespan.⁴²⁶ In mothers with stressful occupations, building social networks has been found to improve mental health and cortisol levels.⁴²⁷ In family caregivers of dementia patients, strong social support was linked to lower sense of burden and increased resilience.⁴²⁸ Studies in first responders and intensive care unit nurses have shown that perception of strong social support is associated with reduced symptoms of post-traumatic stress disorder.⁴²⁹⁻⁴³¹ In a study examining the

effects of a formal social connection program, those who provided social support reported experiencing similar increases in well-being to those receiving support during a period of stress.⁴³²

The Stress-relieving Nature of Pets

Researchers have long been interested in the relationships between humans and their companion animals and the effects of such relationships on health. In general, findings suggest pet ownership is associated with less depression and loneliness, better social interaction, and reduced anxiety and stress.¹⁹²

Several studies have noted that pet owners have lower blood pressure, cholesterol, and triglyceride levels, and are less likely to suffer fatal cardiac events (heart attack and stroke) compared with non-pet owners.¹⁹³⁻¹⁹⁵ While some of these benefits may be due in part to increased physical activity associated with dog ownership, cat owners too have a lower risk of cardiovascular death, leading researchers to propose that having pets may also impact cardiovascular health by improving mood and reducing stress reactivity.¹⁹⁵⁻¹⁹⁷

Studies of dog-assisted interventions suggest even the presence of an unfamiliar dog may lower stress during inherently stressful circumstances, such as during dental procedures.¹⁹⁸ In a laboratory setting, the presence of an unfamiliar dog mitigated stress-induced increases in cortisol and heart rate more than the presence of a friend.¹⁹⁹ In another study, participants with pets had lower baseline blood pressure and heart rate, and lower cardiovascular reactivity to physical and mental stress tests, than participants without pets. In addition, the presence of their pet during stress testing reduced stress reactivity even

further, while the presence of a friend had no effect and presence of their spouse increased stress reactivity.²⁰⁰

Maintain Sex Hormone Balance

The physiologic stress response is strongly influenced by sex hormones (testosterone, estrogen, and progesterone), and gender-related differences in reactions to stress have been widely documented. Although the relationship is complex, stress-induced activation of the HPA axis, in general, is stronger in women than men. Evidence from animal research suggests this may be due to opposite effects of testosterone and estrogen on HPA axis sensitivity: estrogen increases HPA axis responsiveness while testosterone decreases it.^{201,202} In addition, progesterone appears to suppress sensitivity of the HPA axis and downregulate anxiety.^{203,204} Furthermore, while acute stress appears to increase progesterone production,²⁰⁴ chronic stress inhibits release of all sex hormones.²⁰² Higher progesterone levels in the second half of the menstrual cycle have been associated with lower levels of premenstrual aggression, irritability, and fatigue in another study.²⁰⁵

In postmenopausal women, whose estrogen and progesterone levels are naturally low, hormone therapy has been shown to affect regulation of the stress response and may enhance some aspects of cognitive function during stress. In one study, 15 sedentary postmenopausal women who had used long-term hormone replacement therapy were compared with 15 similar women who had never used hormone therapy. Those who had never used hormone therapy were found to have abnormal diurnal salivary α -amylase patterns, while hormone therapy users had normal α -amylase patterns. In addition, hormone therapy non-users had less of a rise in salivary α -amylase concentration in response to exercise than hormone therapy users. This suggests long-term hormone therapy may help maintain normal

tone of the sympathetic nervous system.²⁰⁶ On the other hand, another trial found that postmenopausal women using estradiol therapy had a reduced cortisol response and less reduction in working memory after exposure to physical stress compared with women receiving placebo.²⁰⁷

In a preliminary study in 94 postmenopausal women under chronic stress due to caring for a family member with dementia, hormone therapy was correlated with better psychosocial function: those using hormone therapy reported less hostility and fewer negative interactions with members of their support teams than those not using hormone therapy; the greatest benefit was seen in those using both estradiol and progesterone.²⁰⁸

Progesterone therapy alone can help perimenopausal women with symptoms including hot flashes, breast pain, and sleep problems.^{209,210} Because these symptoms may be a source of stress, progesterone therapy may have anti-stress benefits in peri- and postmenopausal women. Furthermore, animal research suggests progesterone may protect the brain from harmful stress-induced inflammation.²¹¹

Taken together, these findings suggest that maintaining balanced sex hormone levels throughout life may be important for regulating stress responsiveness and promoting resilience. Men and women with possible hormone imbalances should review Life Extension's **Male Hormone Restoration** and **Female Hormone Restoration** protocols.

Non-Hormonal Option for Menopause-Related Stress

Although there is compelling evidence that hormone replacement therapy may help ease symptoms of stress associated with menopause and hormonal imbalance in aging women, hormone replacement does not appeal to everyone.

A plant-based phytoestrogen formulation derived from Siberian rhubarb has been shown to offer relief from menopause-related anxiety and improve general well-being.^{436,437}

In a multicenter, prospective, randomized, placebo-controlled trial, 109 perimenopausal women took either 4 mg of a standardized Siberian rhubarb extract or a placebo for 12 weeks. The women who took the Siberian rhubarb extract experienced a significant reduction in anxiety compared with those who took a placebo. Moreover, the women taking the extract more frequently reported improvements in general well-being than those taking placebo.⁴³⁶

9 Food and Stress-How Does Diet Affect Stress?

Stress is well known to trigger changes in eating behaviors, often increasing appetite for unhealthy “comfort” foods like those high in sugar and fat.²¹² One reason may be that stress alters levels of appetite-regulating hormones, ghrelin and leptin, producing more hunger signaling.²¹³ Although not everyone eats more in response to stress (about 40% of individuals eat more, 40% eat less, and 20% eat the same number of calories when under stress), a stress-induced rise in preference for high-sugar foods has been consistently observed and may be partly due to a dampening effect of sugar on the stress response.²¹⁴⁻²¹⁷ Compounding the problem, stress appears to increase susceptibility to diet-related metabolic disturbances like abdominal obesity and insulin resistance.²¹⁸

Countering stress-related appetite changes and food cravings is challenging; however, eating a healthy diet may be even more important during times of stress. Healthy eating habits can help ensure adequate intake of vitamins, minerals, protein, complex carbohydrates, anti-inflammatory fats, fiber, and phytochemicals

needed to combat the negative health effects of chronic stress and interrupt the cycle of stress and stress-related behaviors.^{219,220}

Eat More Fruits and Vegetables

Increasing fruit and vegetable intake can help combat stress. A study in young adults showed that increasing fruit and vegetable intake by two servings per day for two weeks resulted in enhanced psychological well-being, vitality, flourishing, and motivation.²²¹ A Mediterranean-style diet, which emphasizes olive oil, whole grains, fruits, vegetables, fish, and nuts and seeds, may improve the stress response and has been associated with better regulation of HPA axis activity. This dietary pattern may also mitigate the effects of stress by reducing systemic inflammation and the risk of many chronic health problems.²²²⁻²²⁴

Eat Breakfast Regularly

Eating breakfast may help build stress resilience. Compared to breakfast skipping, habitual breakfast eating was associated with lower levels of perceived stress, better cognitive function, and fewer job injuries and accidents in a study that included more than 800 nurses.²²⁵ In another study in 65 female participants, habitual breakfast skippers had blunted diurnal cortisol variation, increased overall cortisol output, and higher blood pressure compared with habitual breakfast eaters, suggesting a morning meal may be important for maintaining normal circadian regulation of the HPA axis.²²⁶

Minimize Caffeine and Alcohol Intake

Caffeine may seem attractive to those affected by stress-related fatigue, but its effects may aggravate symptoms such as anxiety and poor sleep in susceptible people.^{227,228} Caffeine stimulates the sympathetic nervous system, and in this way may activate the stress response.²²⁹ Even with daily consumption, its intake can raise cortisol levels and has been found to increase the cortisol response to mental

stress.^{230,231} Caffeine can also prolong the effects of physical stress on heart rate and blood pressure.²³² In one study, habitual coffee drinking was associated with greater increases in heart rate and vascular inflammation in response to mental stress.²³³ On the other hand, drinking coffee appears to promote healthy metabolism and may protect against type 2 diabetes, liver cancer, and cognitive decline.²³⁴ While sensitive individuals may fare better eliminating caffeine during times of stress, moderate intake may be reasonable for others.²²⁷

Alcohol is often used as a relaxant during times of stress^{235,236}; however, excessive intake raises cortisol levels and long-term use leads to dysregulated HPA axis signaling and disrupts the normal function of the stress response.²³⁷⁻²³⁹ Individuals experiencing stress-related insomnia frequently turn to alcohol as a form of self-medication, but because alcohol erodes sleep quality and quantity, it may actually exacerbate sleep difficulties.²⁴⁰ In addition, people with a history of early life stress and people who experience intense life stress are more vulnerable to developing problematic drinking habits.^{239,241} Therefore, it is especially important to avoid stress-related alcohol use.

10 Nutrients

A variety of natural, integrative interventions have been shown to help balance HPA axis function and counteract the detrimental effects of chronic stress.

Multivitamins and B-Complex Vitamins

Deficiencies of B vitamins are associated with neuropsychiatric disorders such as depression, Alzheimer disease, schizophrenia, and other types of psychosis and dementia, and adequate amounts of all B vitamins are needed for healthy nervous system function.^{242,243}

The ability of multivitamins to reduce perceived stress and fatigue has been demonstrated in a number of trials.²⁴⁴⁻²⁴⁸ In one randomized controlled trial in 60 working adults, those receiving a high-dose B-complex vitamin daily for 12 weeks reported lower levels of stress, confusion, and depressed mood compared with those receiving placebo.²⁴⁹ A review of the research concluded that multivitamins, and B-complex supplements in particular, can be effective for lowering perceived stress, reducing mild psychiatric symptoms, and improving everyday mood in healthy individuals.²⁵⁰

B vitamins may also support normal HPA axis function. In a placebo-controlled trial with 138 subjects, 16 weeks of supplementation with a multivitamin containing B vitamins increased the cortisol awakening response. The cortisol awakening response, which occurs about 30 minutes after waking and generally results in the highest cortisol level of the day, is considered a marker of healthy HPA axis tone and has been associated with lower distress levels during the rest of the day.²⁵¹ Another randomized controlled crossover trial examined the effect of one week of treatment with a multivitamin supplement in 240 Chinese military personnel who underwent intense physical stress. The multivitamin was associated with better recovery of normal HPA axis function and improvements in psychological symptoms.²⁵²

Vitamin C (Ascorbic Acid)

The adrenal glands have the highest concentration of vitamin C in the body.²⁵³ In addition to its well-known function as a free radical scavenger, vitamin C is a cofactor in the synthesis of catecholamines—neurohormones involved in the stress response—and may help modulate central nervous system activities.²⁵³⁻²⁵⁵ Levels of vitamin C in the blood and white blood cells drop quickly during times of stress or

infection,²⁵⁶ and symptoms of depression and anxiety have been correlated with low intake and low circulating levels of vitamin C.²⁵⁴

In a controlled clinical trial, patients with stress-induced anxiety and depression had lower levels of vitamin C, as well as vitamins E and A, than healthy subjects, and the addition of these nutrients (1,000 mg per day vitamin C, 800 mg per day vitamin E, and 600 mg per day vitamin A) to antidepressant therapy led to greater reductions in symptoms of anxiety and depression compared with antidepressant therapy alone.²⁵⁷ Another controlled trial found that supplementing with 500 mg per day of vitamin C reduced anxiety levels and lowered average heart rate in healthy high school students.²⁵⁸ In addition, a review of research indicated high doses of vitamin C may reduce anxiety and mitigate stress-related increases in blood pressure.²⁵⁹

Omega-3 Fatty Acids

Omega-3 fatty acids (primarily EPA [eicosapentaenoic acid] and DHA [docosahexaenoic acid] from fish oil) may help prevent and treat stress, anxiety, and depression.²⁶⁰⁻²⁶² Low blood levels of EPA and DHA have been correlated with several biological indicators of stress: elevated markers of inflammation, dysregulated nervous system signaling, and HPA axis hyper-reactivity.^{263,264} Conversely, omega-6 fatty acids, mainly obtained through eating animal fats and processed vegetable oils, promote inflammation and can thereby induce stress signaling and contribute to stress-related illnesses.²⁶¹

In a randomized controlled trial in participants with high triglyceride levels, taking 3,400 mg of combined EPA and DHA for eight weeks increased heart rate variability, indicating lower stress-related nervous system signaling; however, a lower dose of 850 mg per day had no effect.²⁶⁵ Another controlled trial found that three weeks of treatment with 60 mg EPA and 252 mg DHA daily improved perceived stress and anxiety and reduced cortisol levels in alcoholic subjects in a residential treatment

program.²⁶⁶ Evidence from trials in patients with depression suggest omega-3 fatty acids can correct HPA hyperactivity, mitigate symptoms, and may improve responsiveness to antidepressant therapy.^{264,267}

A meta-analysis published in late 2024 evaluated 29 randomized controlled trials that included 35 independent samples comprising 3,918 subjects on omega-3 supplementation to reduce aggression. The study found that omega-3 supplementation led to modest short-term reductions in aggression, regardless of age, gender, and diagnosis. On average, the studies included in the meta-analysis used a dosage of about 1,200 mg of omega-3 fatty acids per day and a treatment duration of about 16 weeks. The study found that omega-3 supplementation was effective in reducing proactive and reactive types of aggression, especially when it was based on subjective reports. The authors concluded “...there is now sufficient evidence to begin to implement omega-3 supplementation to reduce aggression... irrespective of whether the setting is the community, the clinic, or the criminal justice system.”⁴⁶⁰

L-theanine

L-theanine is an amino acid found in tea that has demonstrated anti-stress effects. Numerous studies have found that tea and theanine reduce perceived stress and physiologic markers of the stress response, including blood pressure, heart rate, cortisol levels, and patterns of brain activity.²⁶⁸ In one trial that included 20 pharmacy students, taking 200 mg L-theanine twice daily for one week decreased morning salivary α -amylase levels more than placebo. Moreover, subjects taking L-theanine reported significantly less subjective stress than those taking placebo.²⁶⁹ A separate study found that L-theanine promoted a calming effect by increasing alpha wave (ie, a type of brain wave associated with wakeful relaxation and alertness) power. Sixteen individuals ranging in age from 19 to 60 years were

randomized to receive a single dose of 200 mg L-theanine (as AlphaWave L-theanine) or placebo prior to a mental arithmetic test that elicited increased heart rate, blood pressure, stress, and anxiety. Those in the L-theanine group displayed significantly increased alpha brain wave power and reduced salivary cortisol levels compared with placebo.⁴⁶¹

The short-term effects of L-theanine were confirmed in another randomized controlled trial in 36 healthy participants age 18 to 40 years. A single 200 mg dose of L-theanine decreased subjective stress one hour after administration and the cortisol response to a cognitive stressor three hours after administration. In addition, in a subset of participants whose scores on a test of tendency to experience anxiety were high, L-theanine increased brain wave activity associated with relaxation.²⁷⁰ A longer study randomized 30 healthy adults to receive 400 mg L-theanine (as AlphaWave L-theanine) or placebo daily for 28 days. The L-theanine group reported a significant decrease in perceived stress at 28 days compared with baseline. No difference was observed in salivary cortisol levels and L-theanine was well-tolerated with no adverse events reported by the end of the study or upon follow-up.⁴⁶² In a study of 30 individuals ranging in age from 20 to 69 years, 200 mg L-theanine daily for 28 days significantly improved stress-related symptoms, sleep quality, and executive cognitive function compared with placebo.⁴⁶³ A series of small trials conducted by researchers in Japan found that L-theanine supplementation prevented heart rate elevation in response to stress-inducing arithmetic tests in the lab. Salivary immunoglobulin A (s-IgA) levels were also reduced in response to the stressful tasks in those who took L-theanine. The researchers concluded that reductions in heart rate and s-IgA in subjects taking L-theanine were likely attributable to attenuation of sympathetic nervous system activity.⁴³⁸

Theanine has also been shown to counter the stress-inducing effects of caffeine and enhance focused attention,²⁷¹ and a two-month clinical trial noted that theanine, in combination with a vitamin/mineral/herbal supplement, lowered perceived stress scores and improved cognitive function in elderly subjects.²⁷²

Phosphatidylserine

The phospholipid phosphatidylserine is found in cell membranes and helps facilitate healthy cellular communication. It modulates the tissue response to inflammation and can reduce oxidative stress.²⁷³ Several studies have shown that phosphatidylserine can balance HPA axis signaling and may limit the negative consequences of over-activation of the adrenal glands.

In a trial in 75 healthy male volunteers, taking a supplement providing 400 mg each of phosphatidylserine and its precursor phosphatidic acid for 42 days diminished the HPA axis response to acute stress in a subset of men reporting high levels of chronic stress.²⁷⁴ In other clinical research, this same combination was noted to dampen the stress response to mental stress,²⁷⁵ and 300 mg per day of phosphatidylserine alone reduced perceived stress and improved mood in healthy young adults prone to negative emotions like anxiety, worry, and fear.²⁷⁶

Phosphatidylserine has also been found to lower cortisol levels overall and reduce the cortisol response to acute exercise in men, an effect that may help prevent harmful outcomes of overtraining, such as decreased performance, injury, immune suppression, and deterioration of psychological well-being.²⁷⁷

Curcumin

Curcumin is a pigment from turmeric root responsible for its characteristic yellow-orange color. As a polyphenol, curcumin has strong free radical-quenching and anti-inflammatory actions, and has been used historically to treat a range of inflammatory disorders, including musculoskeletal problems, neurological

disorders, heart disease, and diabetes.⁴³⁹ Numerous clinical studies indicate curcumin's potential to reduce the effects of chronic and repetitive stress on cognitive function and mood.⁴⁴⁰⁻⁴⁴⁴ Furthermore, preclinical evidence suggests curcumin's anti-stress effects may be related to its ability to reduce neuro-inflammation and preserve neuroplasticity.⁴⁴⁵⁻⁴⁴⁷

Multiple randomized controlled trials and three meta-analyses have shown curcumin can reduce depressive and anxiety symptoms in individuals with depression.⁴⁴⁸⁻⁴⁵⁰ A clinical trial in 60 participants with occupational stress-related anxiety compared a combination of highly absorbable curcumin plus fenugreek, at a dose of 1,000 mg per day, to the same dose of standard curcumin or placebo. After 30 days, participants taking the curcumin/fenugreek combination reported greater reductions in stress, anxiety, and fatigue, as well as greater improvement in quality of life, compared with those taking ordinary curcumin or placebo.⁴⁵¹ In another placebo-controlled trial in 80 participants with diabetic neuropathy, taking 80 mg per day of a different highly-absorbable form of curcumin for eight weeks led to reductions in depression and anxiety symptom scores compared with placebo.⁴⁵² In patients with major depressive disorder, those receiving up to 1,500 mg curcumin daily for 12 weeks had greater improvement in depression compared with those receiving placebo. Moreover, the benefit was still measurable four weeks after the end of the trial.⁴⁵³ Curcumin supplementation was also found to lower perceived stress levels better than placebo in athletes during endurance training.⁴⁵⁴

L-tryptophan

L-tryptophan is an amino acid precursor to the neurotransmitter serotonin. Serotonin has a complex relationship with the stress response.²⁷⁸ Stress-induced inflammation appears to cause excessive breakdown of tryptophan, which may decrease serotonin production and increase risk of depression²⁷⁹; in addition,

tryptophan depletion has been shown to increase stress sensitivity.²⁸⁰ Studies in healthy adults suggest tryptophan supplementation, ranging from 800 to 2,800 mg per day, may reduce the cortisol response to stress, mitigate stress-related negative moods, and prevent stress eating in some individuals.²⁸¹⁻²⁸³ In a randomized controlled trial, a tryptophan-rich hydrolyzed protein supplement increased positive mood and lowered cortisol release in response to acute stress.²⁸⁴

Bioactive Milk Peptides

Upon ingestion, milk proteins are broken down into peptides (shortened amino acid chains) by enzymes. Some of the resulting peptides can be absorbed intact and exert biological activities.²⁸⁵ For example, α -lactalbumin is a bioactive milk peptide that has a high tryptophan content and has been found to support healthy neurological function, improve mood, and promote sleep.²⁸⁶ An enzyme-treated form of the milk protein, casein, has also demonstrated anti-stress and relaxing properties in animal studies, and appears to work by increasing signaling via receptors for GABA—a neurotransmitter that generally inhibits nervous system activity.²⁸⁷⁻²⁸⁹

One randomized, controlled, crossover trial included 63 women with stress-related symptoms such as anxiety, sleep problems, and fatigue. Thirty days of treatment with 150 mg per day of α -S1 casein hydrolysate (a form of bioactive milk peptides) was more effective than placebo at relieving symptoms.²⁹⁰ In healthy volunteers, a 200 mg dose of α -S1 casein hydrolysate was found to mitigate increases in blood pressure, heart rate, and cortisol release induced by experimental stress.²⁹¹

Probiotics and Prebiotics

The gut microbiome, nervous system, and HPA axis are closely connected. Probiotics and prebiotics (indigestible dietary carbohydrates that support the growth of beneficial bacterial colonies) can improve the balance of gut bacteria,

and a growing body of evidence points to their potential to have a positive impact on the stress response.^{35,37,260} Research indicating probiotics may lower stress reactivity and anxiety, and improve mood, memory, and cognition have led some researchers to call probiotics with these effects psychobiotics.²⁹²

Fermented milk products made with *Lactobacillus casei* strain Shirota have been found in several trials to suppress cortisol elevations in response to stress and reduce stress-related health concerns such as depressed or anxious mood, digestive upset, and cold symptoms in healthy medical students.²⁹³⁻²⁹⁵ In a randomized controlled trial, 10 days of supplementation with 10 billion colony forming units (CFUs) of *L. plantarum* 299v per day decreased salivary cortisol levels in students facing an upcoming exam.²⁹⁶ In other controlled trials, taking a combination of *L. helveticus* R0052 and *Bifidobacterium longum* R0175, at a dose of 3 billion CFUs per day, for 30 days lowered scores on scales of perceived stress as well as urinary cortisol levels in healthy volunteers,²⁹⁷ and supplementing with 1 billion CFUs per day of *B. longum* 1714 for four weeks suppressed the cortisol rise and subjective anxiety associated with an acute stressor.²⁹⁸

Prebiotics are also demonstrating positive effects in clinical research: in a trial in 45 healthy adults, taking 5.5 grams of a prebiotic supplement containing galacto-oligosaccharides for three weeks resulted in lower early-morning cortisol levels and more balanced processing of positive and negative emotional stimuli.²⁹⁹

Melatonin

The hormone melatonin, which is released from the small gland at the base of the brain called the pineal gland, is known for its relationship with the sleep cycle. Melatonin plays a central role in circadian regulation of body systems, including the HPA axis.³⁰⁰ Stress can reduce melatonin levels and destabilize the body's

biological rhythms.³⁰¹ Chronic disruption of the brain's internal clock, such as through shift-work or insomnia, harms mental and physical health.^{302,303}

Melatonin supplementation can improve sleep quantity and quality and help restore normal circadian processes,^{304,305} which may lead to reduced stress and prevention of stress-related deterioration of health.³⁰⁶ In one study, 2 mg of melatonin taken in the evening for six months improved sleep and increased DHEA-S levels in a group of elderly female volunteers.³⁰⁷

Dehydroepiandrosterone (DHEA)

Dehydroepiandrosterone (DHEA) is an adrenal hormone that, like cortisol, is secreted in response to acute stress, but chronic stress has been associated with low levels.⁸ The effect of stress on DHEA may be one of the factors linking stress to poor health and accelerated aging.¹²¹ Low DHEA-S levels have been correlated with conditions such as osteoporosis, cognitive decline and dementia, cardiovascular disease, mood disorders, and sexual dysfunction.¹²³ Findings from preclinical and clinical research suggest DHEA replacement therapy may have a role in protecting aging bone and vasculature and may help in the treatment of depression and sexual disorders.^{122,123}

In a randomized, placebo-controlled, crossover trial that enrolled 13 men and 17 women between ages 40 and 70 years, treatment with 50 mg DHEA daily for six months led to significant improvements in physical and psychological well-being. Subjects in this study reported a better ability to handle stress, improved mood, and being generally relaxed.³⁰⁸ In a different study, 24 healthy young men took high-dose DHEA (150 mg twice daily) for seven days. Subjects reported improved mood, and DHEA treatment led to reduced levels of cortisol on evening measures.³⁰⁹

Supplemental doses of DHEA typically range from 10–25 mg daily for women and 25–75 mg daily for men, but should be based on DHEA-S blood levels. More

information is available in Life Extension's **DHEA Restoration Therapy** protocol.

Lychee and Green Tea

A supplement that combines polyphenols from lychee (*Litchi chinensis*) fruit and catechins from green tea, called Oligonol, has been found to have strong free-radical quenching and inflammation-suppressing capacity.⁴³³ It may also have stress-mediating effects. A pilot study in 19 healthy sedentary men compared 100 mg Oligonol per day for four weeks to placebo. Those receiving Oligonol experienced decreases in levels of cortisol and certain inflammatory markers during the study. In addition, the Oligonol-treated men had a lower cortisol response to exercise compared with placebo.⁴³⁴ In a study of the acute effects of Oligonol in 13 healthy men, a single 100 mg dose reduced the rise in cortisol, as well as inflammatory markers, triggered by a physical stressor.⁴³⁵

Magnesium Acetyl Taurate

Magnesium is an essential mineral that acts as a cofactor in hundreds of biochemical processes, including those involved in the stress response. Magnesium can inhibit glutamate receptors to attenuate excitatory transmission and promote GABA and serotonin activity.⁴⁵⁵

Preclinical and clinical studies have observed that magnesium levels are negatively affected by stressful stimuli, and that magnesium supplementation can reduce stress.^{456,457} Low levels of magnesium can further exacerbate stress, as magnesium indirectly reduces cortisol secretion.⁴⁵⁵

Magnesium acetyl taurate, an organic salt of magnesium, has demonstrated improved bioavailability in the brain compared with other forms of magnesium.⁴⁵⁸ In an unpublished clinical study including 19 women with stress-like symptoms related to premenstrual syndrome and inadequate magnesium intake from their diet, magnesium acetyl taurate (770 mg/day, providing approximately 45 mg

elemental magnesium) was found to decrease stress-like symptoms including anxiety, nervous tension, irritability, headache, fatigue, and depression.⁴⁵⁹

Adaptogens

Adaptogenic herbs have multi-faceted beneficial effects that support the body's intrinsic resilience to stressful conditions. They work by regulating biological networks in ways that support homeostasis. For example, adaptogens can raise energy levels, yet also support sound sleep. Some typical reasons adaptogens are used include to relieve fatigue, improve cognitive function and mood, and support the immune system.³¹⁰⁻³¹²

Magnolia and phellodendron. Magnolia (*Magnolia officinalis*) is an important plant in traditional Chinese herbal medicine. Its active constituents, magnolol and honokiol, have been found in preclinical and clinical trials to have a variety of beneficial effects, including stress reduction.³¹³ In rodents exposed to chronic stress, both magnolol and honokiol, as well as their combination, have been found to normalize serotonin and HPA axis activity, increase levels of a brain growth factor (brain-derived neurotrophic factor, or BDNF), reduce neuroinflammation and brain oxidative stress, and prevent behaviors indicative of depression.³¹⁴⁻³¹⁷

A combination of magnolia and phellodendron (*Phellodendron amurense*, a tree also known as Amur cork tree and often used in traditional Chinese medicine) has been studied for anti-stress effects as well. In one controlled clinical trial, 56 healthy subjects with moderate stress levels received either a supplement providing 250 mg of magnolia plus phellodendron or placebo twice daily for four weeks. Participants underwent three (morning, noon, and night) salivary cortisol tests and answered mood questionnaires at the beginning and end of the trial. Those receiving the supplement had lower total cortisol exposure and better mood scores than those receiving placebo.³¹⁸

The same combination supplement was studied for its effect on stress-induced appetite and weight gain. In one controlled trial, magnolia plus phellodendron, at a dose of 250 mg three times daily for six weeks, reduced weight gain compared with placebo in overweight but otherwise healthy premenopausal women who reported stress eating and above-average levels of anxiety.³¹⁹ In another similarly designed trial, magnolia plus phellodendron reduced temporary anxiety, but did not affect longstanding depression or anxiety, appetite, sleep, or levels of salivary cortisol and amylase.³²⁰

Holy basil. Holy basil (*Ocimum sanctum*, also known as tulsi basil) is an adaptogenic herb from the Ayurvedic tradition. In Hindu spirituality, holy basil is considered a sacred plant and an incarnation of the goddess Tulsi.³²¹ A number of clinical and preclinical studies have demonstrated holy basil's anti-stress potential by providing evidence that it improves mood and cognition, normalizes metabolism, regulates immune function, reduces oxidative stress, and prevents toxic damage in various tissues by supporting detoxification.^{321,322}

In a randomized controlled trial with 40 participants, 300 mg of holy basil extract per day for 30 days resulted in reduced anxiety symptoms and improved cognitive test scores compared with placebo.³²³ Findings from another randomized controlled trial, in which 150 participants received 1,200 mg holy basil per day or placebo, indicated that holy basil lowered stress-related symptoms such as anxiety, fatigue, sleep difficulties, and sexual dysfunction.³²⁴ A pilot trial in which 35 patients with anxiety were treated with 500 mg holy basil twice daily found that treatment led to reductions in symptoms of anxiety, stress, and depression.³²⁵

Ashwagandha. Ashwagandha (*Withania somnifera*) is another important herb in the Ayurvedic herbal pharmacy, in which it is used as a general tonic and aphrodisiac.³²⁶ Numerous preclinical studies show ashwagandha prevents oxidative damage,

supports normal mitochondrial activity, modulates central nervous system signaling, and contributes to immune regulation, suggesting it may be useful in the treatment of chronic stress-related, inflammatory, metabolic, cardiovascular, and neurodegenerative disorders.³²⁷⁻³²⁹

Several clinical trials further indicate that ashwagandha is effective for relieving stress and anxiety.³³⁰ For example, in a trial with 64 participants, 300 mg ashwagandha extract twice daily was more effective for reducing perceived stress scores and lowering blood cortisol levels than placebo after 60 days of treatment.³³¹ Another trial noted the possible beneficial effects of ashwagandha on weight management in people with chronic stress. Fifty-two chronically stressed participants received either 300 mg ashwagandha twice daily or placebo for eight weeks; those receiving ashwagandha had greater reductions in perceived stress and serum cortisol levels, more improvements in food cravings and eating behaviors, and greater weight loss than those receiving placebo.³³²

Bacopa. Bacopa (*Bacopa monnieri*) has been used historically in Ayurvedic medicine to support healthy cognitive function.³³³ A number of animal studies have demonstrated its adaptogenic potential, noting its ability to normalize stress hormone levels and neurotransmitter balance,³³⁴ reduce oxidative stress,³³⁵ protect against neurodegeneration,³³⁶ and prevent or reverse other negative physiologic and behavioral consequences of stress.³³⁷⁻³³⁹ Furthermore, in rodent models of chronic stress, bacopa and an active constituent (bacopaside I) have been found to reduce depressive behavior, normalize HPA axis function, reduce brain oxidative stress, and prevent a drop in BDNF and other changes in the brain environment.³⁴⁰⁻³⁴² Bacopa has also been found to increase stress resilience and lifespan in another laboratory animal model.³⁴³

In a preliminary trial in 17 healthy adults, a standardized extract of bacopa, taken in single doses of 320 mg and 640 mg, improved cognitive performance one to two hours later on multitasking mental tests while also reducing cortisol levels, suggesting that part of its cognitive benefits may be related to stress-reducing effects.³⁴⁴ In a randomized controlled trial in 54 elderly subjects, 300 mg per day of bacopa for 12 weeks led to improved cognitive performance, lower depression and anxiety scores, and reduced heart rate compared with placebo.³⁴⁵

Lemon balm. Lemon balm (*Melissa officinalis*) is a plant in the mint family used in herbal medicine as a relaxing and uplifting nervous system tonic.^{346,347} Consumed in food or drink, lemon balm was found to generally improve mood and cognitive performance in healthy young adults.³⁴⁸ In healthy subjects exposed to experimental stress, individual doses of lemon balm had acute anti-stress and cognitive-enhancing effects, and increased self-reported calmness and alertness.³⁴⁹

In a pilot trial in 20 stressed volunteers with mild-to-moderate anxiety and insomnia, 15 days of treatment with 300 mg lemon balm extract twice daily led to symptom improvement in 19 (95%) of the participants. In addition, 14 participants had a complete remission of anxiety, 17 had remission of insomnia, and 14 had remission of both anxiety and insomnia.³⁵⁰ In a placebo-controlled clinical trial in 80 patients with stable angina, 3 grams per day of lemon balm for eight weeks reduced anxiety, depression, and stress, and improved sleep.³⁵¹ In animal research, lemon balm decreased stress-induced symptoms of irritable bowel syndrome.³⁵²

Saffron. Saffron (*Crocus sativus*) is a yellow spice prized for its color and flavor. It also has a long history of use in herbal medicine for its sedative, adaptogenic, and other properties. Several clinical trials have shown that saffron is helpful in treating mild-to-moderate depression.^{353,354} Saffron and its active constituent crocin have also demonstrated anti-stress and anti-anxiety effects in animal studies, and

preclinical evidence suggests it may exert its benefits in part by moderating HPA axis responsiveness.³⁵⁵⁻³⁵⁸ In addition, crocetin, another active compound from saffron, was found to prevent stress-induced depressive behavior in rats.³⁵⁹

In a randomized controlled trial, subjects without depression but reporting low mood who received treatment with 28 mg per day of saffron extract for four weeks had greater improvement in mood and reductions in symptoms of stress and anxiety than those receiving placebo.³⁶⁰

Ginseng. Ginseng is a common name for a group of similar plants, including Asian ginseng (*Panax ginseng*), American ginseng (*Panax quinquefolius*), and Chinese ginseng (*Panax notoginseng*). These plants all contain active compounds called ginsenosides. *Panax ginseng* and its unique ginsenosides have been widely studied for their effects on disease prevention and overall well-being.³⁶¹ This herb has been used for thousands of years to enhance vitality and longevity, and numerous studies show it has a broad range of actions such as immune-modulating, anti-inflammatory, anti-cancer, free radical scavenging, neuroprotective, and cardioprotective.³⁶²⁻³⁶⁵ With regard to stress physiology, a fermented ginseng extract was found to reduce oxidative stress and HPA axis signaling in response to exercise stress.³⁶⁶

Although unrelated to the *Panax* species of ginseng, Siberian ginseng (*Eleutherococcus* or *Acanthopanax senticosus*) is another popular adaptogenic herb. It contains active compounds called eleutherosides and has demonstrated a range of anti-stress properties.³⁶⁷

Rhodiola. Rhodiola (*Rhodiola rosea*, also known as roseroot or golden root) is an adaptogenic herb that grows in Arctic regions and is used around the world to enhance physical and mental stamina and relieve stress.³⁶⁸ Rhodiola appears to

modulate HPA axis function, reduce oxidative stress, and regulate immune activity.^{369,370}

Pilot trials in patients with chronic fatigue symptoms, burnout, and mild anxiety have found that 400 mg rhodiola extract daily is associated with improvements in measures of energy level, mood, sleep, cognitive function, and general well-being.³⁷¹⁻³⁷³ Rhodiola has also been found to help patients with stress-induced depression.³⁷⁴ This effect may be due in part to its promotion of new connections in the brain.³⁷⁵

Amla. Amla (*Phyllanthus emblica*), an adaptogen also known as Indian gooseberry, is used in Ayurvedic medicine to restore strength and good health.³⁷⁶ Some of its active constituents have demonstrated strong oxidative stress-reducing capacity.³⁷⁷ In a preliminary trial in 12 healthy volunteers, 500 mg of a standardized amla extract twice daily for 14 days mitigated acute stress-induced increase in arterial stiffness and decrease in cardiac blood flow.³⁷⁸ Research in animals suggests amla may reduce brain oxidative stress, prevent chronic stress-related damage to testicular tissue, improve stress resilience in general, and lengthen lifespan.³⁷⁹⁻³⁸¹

Schisandra. Schisandra (*Schisandra chinensis*) has been used for centuries in the treatment of depression, anxiety, and insomnia, as well as a wide range of health problems related to fatigue and weakness.^{382,383} Schisandra and its active constituents have also demonstrated liver-protecting, anti-inflammatory, immunomodulating, anti-proliferative, and cognitive enhancing effects. Schisandra also holds promise as a cardiac and neurological protectant.³⁸²⁻³⁸⁴ Findings from animal research suggest Schisandra may help regulate HPA axis activity and relieve the negative effects of stress.³⁸⁵⁻³⁸⁷

Cordyceps. Cordyceps (*Ophiocordyceps* [formerly *Cordyceps*] *sinensis*) is a fungal/insect complex used in traditional Chinese medicine to treat fatigue and as

a promoter of health, longevity, and physical performance.^{388,389} Many active compounds from cordyceps have been identified and studies have shown them to possess anti-inflammatory, immune-modulating, and oxidative stress reducing actions.³⁹⁰ Furthermore, preclinical research suggests it has potential as an anti-aging, anti-fatigue, neuroprotective, and aphrodisiac agent.³⁸⁹ In an animal model of chronic stress, cordyceps supplementation alleviated depression-like behavior induced by unpredictable and repeated mild stress. Furthermore, cordyceps treatment reduced some markers of inflammation and upregulated expression of BDNF.³⁹¹ Preliminary clinical evidence suggests cordyceps may improve athletic performance and suppress the exercise-induced rise in cortisol release, which may help prevent the harmful effects of overtraining.³⁹²

Update History



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