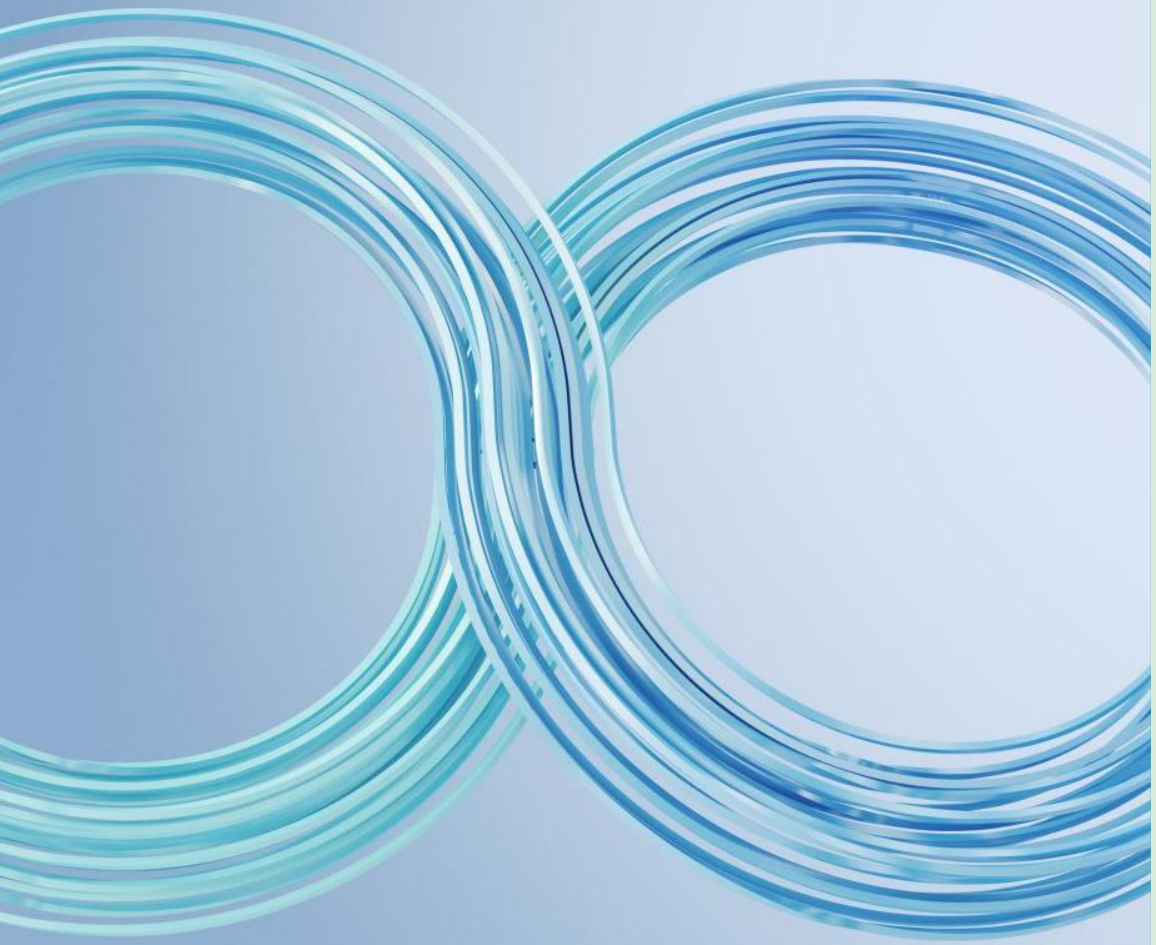
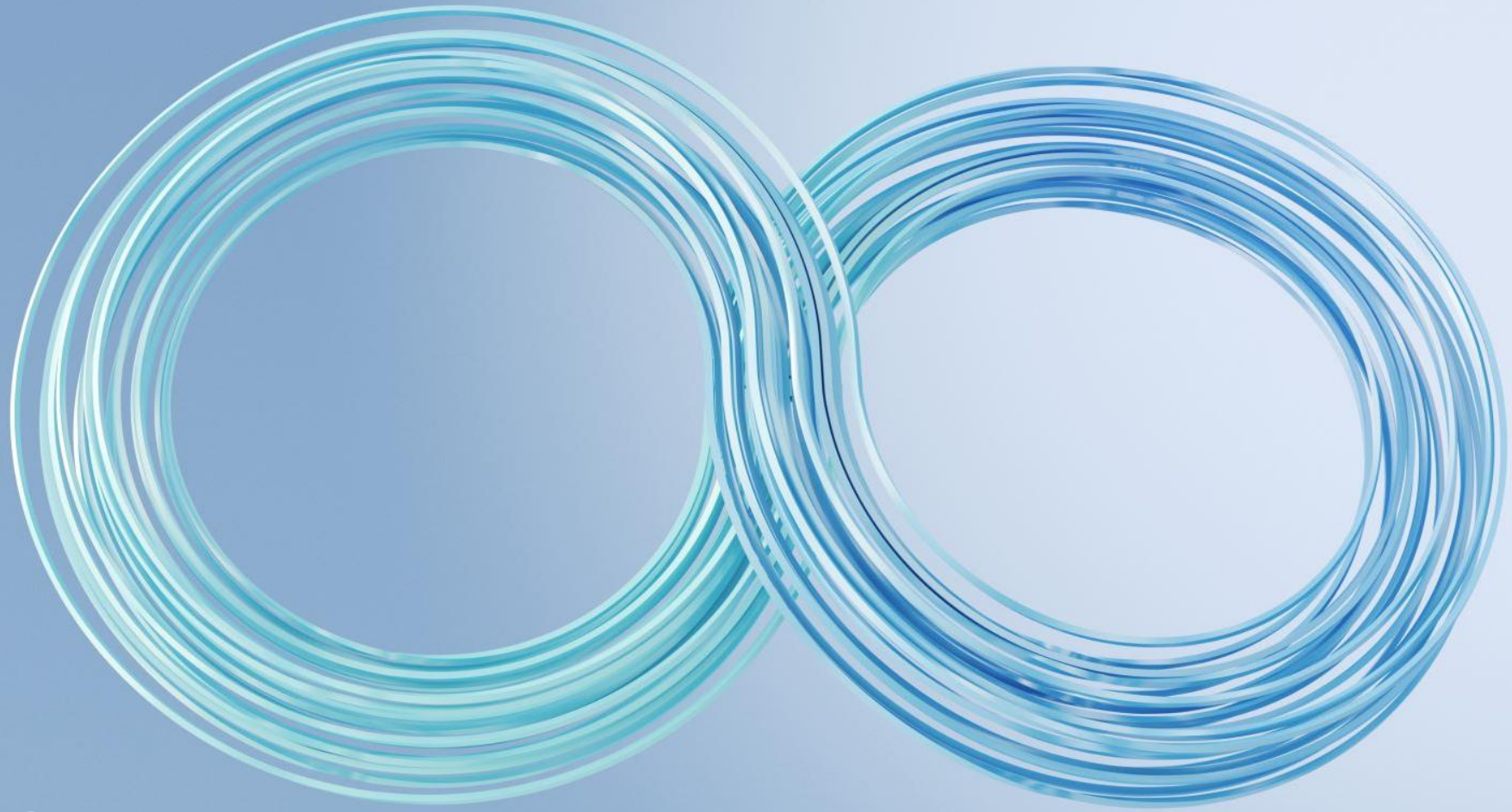


Stress, Abnormal Cortisol, and The Use of Adaptogens

Pamela W. Smith, M.D., MPH, MS

Reference

- Smith, P., What You Must Know About Women's Hormones. Garden City Park, NY: Square One Publishers, 2022.



Stress

Stress

- One study suggested that as many as 75% to 90% of visits to primary care doctors are stress related.
  - Head, K., et al., “Nutrients and botanicals for treatment of stress: adrenal fatigue, neurotransmitter imbalance, anxiety, and restless sleep,” Altern Med Rev 2009; 14(2):114-40.

Chronic Stress (Cont.)

- Chronic stress has been shown to contribute to accelerated aging and premature death in medical studies.
  - Nielsen, N., et al., “Perceived stress and cause-specific mortality among men and women: results from a prospective cohort study,” Amer Jour Epidemiol 2008; 168(5):481-91.
  - Carroll, B., et al., “Ageing, stress and the brain,” Novartis Found Symp 2002; 242:26-36.

Chronic Stress (Cont.)

- Another study revealed that chronic stress accelerated the aging process and was associated with shortened telomeres.
  - Wikgren, M., et al., “Short telomeres in depression and the general population are associated with a hypocortisolemic state,” Biol Psychiatry 2012; 71(4):294-300.

Stress (Cont.)

- Based on the type, timing and severity of the applied stimulus, stress can exert various actions on the body ranging from alterations in homeostasis to life-threatening effects and death.
- In many cases, the pathophysiological complications of disease arise from stress and the individuals exposed to stress, e.g., those that work or live in stressful environments, have a higher likelihood of many disorders.
- Stress can be either a triggering or aggravating factor for many diseases. In this study, the authors review some of the major effects of stress on the primary physiological systems of the body.
  - Yaribeygi, H., et al., "The impact of stress on body function: A review," EXCLI J 2017; 16:1057-72.

Stress (Cont.)

- One underappreciated potential mechanism that stress has on the body is related to the effects of psychological and environmental stress on micronutrient concentrations. Vitamins and minerals are essential for optimal physical and mental function, with deficiencies associated with many different diseases.
- Micronutrients identified in this review include magnesium, zinc, calcium, iron, and niacin. Overall, the bulk of evidence suggests stress can negatively affect micronutrient concentrations, often leading to micronutrient depletion.
  - Lopresti, A., "The effects of psychological and environmental stress on micronutrient concentrations in the body: A review of the evidence," Adv Nutr 2020; 11(1):103-12.

Stress (Cont.)

- Short-term stress can be protective as it prepares the organism to deal with challenges. Short-term stress is one of the nature's fundamental survival mechanisms that could be harnessed to enhance immunoprotection.
- Long-term stress causes inflammation and is related to a compromised immune system and the development or worsening of almost every major disease process from diabetes, to memory loss, to heart disease, to non-alcoholic fatty liver disease, and more.
  - Dhabhar, F., “Effects of stress on immune function: the good, the bad, and the beautiful,” Immunol Res 2014; 58(2-3):193-210.

Stress (Cont.)

- The emerging medical literature suggests that stress has a role in the etiology of type 2 diabetes mellitus both as a predictor of new onset type 2 diabetes and as a prognostic factor in people with existing diabetes.
  - Hackett, R., et al., “Type 2 diabetes mellitus and psychological stress—a modifiable risk factor,” Nat Rev Endocrinol 2017; 13(9):547-60.
  - Shiloah, E., et al., “Psychological stress and new onset diabetes,” Pediatr Endocirnol Rev 2006; 3(3):272-75.
  - Tudpor, K., et al., “Psychological stress is a risk factor for type 2 diabetes mellitus in college students,” Stud Health Technol Inform 2021; 285:296-99.

Stress (Cont.)

- This study examined the temporal relationship between perceived stress and incident type 2 diabetes in a middle-aged cohort of Australian women over 12 years. Perceived stress was a strong risk factor for type 2 diabetes.
  - Harris, M., et al., “Stress increases the risk of type 2 diabetes onset in women: A 12-year longitudinal study using causal modeling,” PLoS One 2017; 12(2):e0172126.

Chronic Stress (Cont.)

- This study suggests that 75%–90% of human diseases are related to stress.
- In addition, chronic inflammation is an essential component of chronic illnesses. Increasing evidence also suggests that excessive inflammation plays a critical role in the pathophysiology of the stress-related diseases. The authors of this article discuss the role of inflammation in stress-induced diseases and suggest a common pathway for stress-related disorders that is based on chronic mild inflammation.
  - Liu, Y-Z., et al., “Inflammation: The common pathway of stress-related diseases,” Front Hum Neurosci 2017; 11:316.

Chronic Stress (Cont.)

- Moreover, studies have shown that stress can activate an inflammatory response in the brain as well as peripherally.
  - Rohleder, N., “Stimulation of systemic low-grade inflammation by psychosocial stress,” Psychosom Med 2014; 75:181-89.
  - Calcia, M., et al., “Stress and neuroinflammation: a systematic review of the effects of stress on microglia and the implications for mental illness,” Psychopharmacology (Berl) 2016; 233:1637-50.

Stress and Disease Processes

- The most common stress-related diseases are cardiovascular diseases (CVD, i.e., hypertension and atherosclerosis), metabolic diseases (i.e., diabetes and non-alcoholic fatty liver disease), psychotic and neurodegenerative disorders (i.e., depression, Alzheimer's disease, and Parkinson's disease), and cancer.
  - Cohen, S., et al., "Psychological stress and disease," JAMA 2007; 298: 1685–87.

Stress, Inflammation, and Heart Disease

- Stress in early life, or stress as an adult, have both been linked to an increased risk of developing heart disease.
- Chronic low-grade inflammatory load may emerge as a possible link between stress and heart disease, as it is both elevated by chronic stress and contributes to early development, progression and thrombotic complications of atherosclerosis. IL-6 and CRP, the two important biomarkers of systematic inflammation, are considered indicative and potentially predictive for atherosclerosis.
- Inflammation has also been shown to correlate with endothelial dysfunction and relate to the renin-angiotensin system.
  - Li, G., et al., "Angiotensin-converting enzyme 2 activation protects against pulmonary arterial hypertension through improving early endothelial function and mediating cytokines levels," Chin Med Jour 2012; 125:1381-88.

Stress, Inflammation, and Metabolic Disease

- Stressful events commonly motivate unhealthy food choices.
  - Kuo, L., et al., “Chronic stress, combined with a high-fat/high-sugar diet, shifts sympathetic signaling toward neuropeptide Y and leads to obesity and the metabolic syndrome,” Ann NY Acad Aci 2008; 1148:232-37.
- Likewise, unhealthy foods are frequently associated with morbid obesity, type 2 diabetes mellitus, metabolic syndrome and Nonalcoholic fatty liver disease.
  - Mikolajczyk, R., et al., ”Food consumption frequency and perceived stress and depressive symptoms among students in three European countries,” Ntur Jour 2009; 8:31.

Stress, Inflammation, and Metabolic Disease (Cont.)

- Stress enhances post-meal peaks of triglycerides and delays lipids clearance.
  - Kiecolt-Glaser, J., “Stress, food, and inflammation: psychoneuroimmunology and nutrition at the cutting edge.” Psychosom Med 2010; 72:365–39.

Stress, Inflammation, and Metabolic Disease (Cont.)

- This animal trial found that insulin resistance frequently develops during acute or chronic stress. Insufficient insulin secretion to compensate for insulin resistance is also a characteristic of type 2 diabetes.
  - Tsuneki, H., et al., “Hypothalamic orexin prevents hepatic insulin resistance induced by social defeat stress in mice,” Neuropeptides 2013; 47: 213-19.

Stress, Inflammation, and Depression

- Four-week chronic stress exposure significantly upregulates the inflammatory cytokines such as TNF alpha, IL-18, IL-1beta and inflammatory inducible NOS (iNOS) expression.
- With the increase in inflammatory cytokines, depressive-like behaviors were observed.
  - Peng, Y-L., “Inducible nitric oxide synthase is involved in the modulation of depressive behaviors induced by unpredictable chronic mild stress,” Jour Neuroinflammation 2012; 9:75.

Stress, Inflammation, and Neurodegenerative Diseases

- During the last two to three decades, increasing evidence from animal and clinical studies has implicated stress and neuroinflammation as risk factors and also may play a fundamental role in the pathogenesis of Alzheimer's disease and Parkinson's disease.
  - Kunjathoor, V., et al., "Beta-amyloid promotes accumulation of lipid peroxides by inhibiting CD36-mediated clearance of oxidized lipoproteins," Jour Neuroinflammation 2004; 1:23.

Stress, Inflammation, and Cancer

- Chronic stress has been demonstrated to account for a place in physiological and pathological disease outcomes, including several types of cancers.
  - Krizanova, O., et al., “Stress, catecholaminergic system and cancer,” Stress 2016; 419–28.
- Chronic stress is thought to correlate with the etiology of tumor growth, progression, and metastasis.
  - Thaker, P., et al., “Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma,” Nat Med 2006; 12:939-44.

Stress, Inflammation, and Cancer (Cont.)

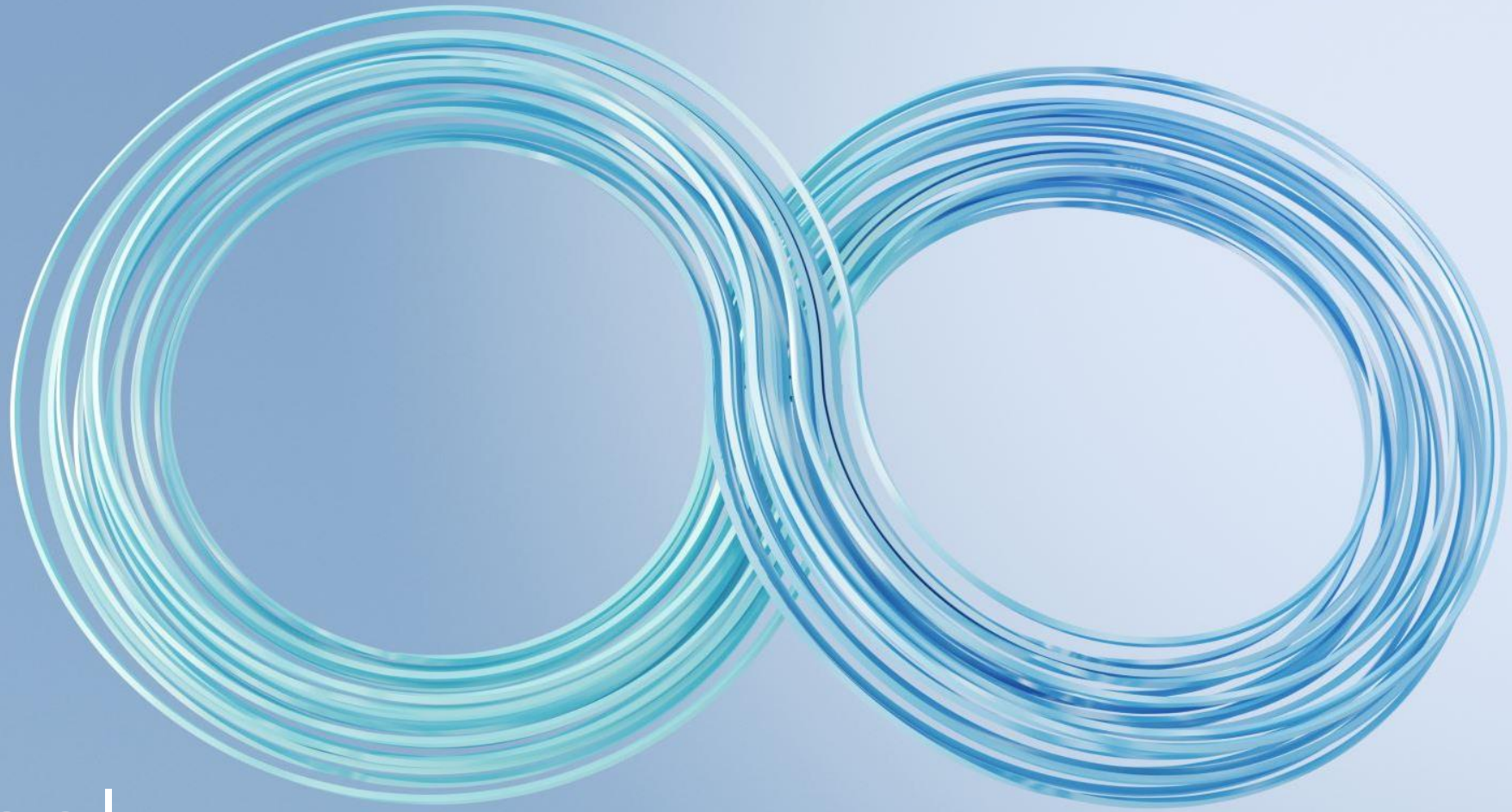
- Classic stress signal, beta-adrenergic signaling activation is considered as the main cause of pancreatic cancer, acute lymphoblastic leukemia, breast cancer progression, and invasion.
  - Lamkin, D., et al., “Chronic stress enhances progression of acute lymphoblastic leukemia via β-adrenergic signaling,” Brain Behav Immun 2012; 26: 635–41.
  - Qin, J., et al., “Adrenergic receptor β2 activation by stress promotes breast cancer progression through macrophages M2 polarization in tumor microenvironment,” BMB Rep 2015; 48:295-300.

Stress, Inflammation, and Cancer (Cont.)

- Cancer patients usually live under chronic stress, caused by diagnosis-related strong emotional experience and depression, resulting from various difficulties associated with disease progression and treatment.
- At the molecular level, stress factors induce production and secretion of stress-related hormones, such as catecholamines, glucocorticoids, and dopamine (as a part of adaptational body response), which influence both normal and transformed cells through their specific receptors.
- The effects exerted by these molecules on cancer cells have been seen in-- in vitro cultures and include changes in proliferation, apoptosis susceptibility, and migration/invasion potential.
- Consequently, it has been suggested that stress hormones may be responsible for progression of malignancy and thus accelerate the metastasis formation in cancer patients.
  - Surman, M., et al., "Stress and its molecular consequences in cancer progression," Postepy Hig Med Dosw (Online) 2017; 71(0):485-99.

Stress, Inflammation, and Cancer (Cont.)

- Primarily, chronic stress activates the classic neuroendocrine system [the hypothalamic-pituitary-adrenal (HPA) axis] and the sympathetic nervous system (SNS) and leads to a decline and dysfunction of the prefrontal cortex and the hippocampus under stress. Stress hormones produced during the activation of both the HPA axis and the SNS can promote tumorigenesis and cancer development through a variety of mechanisms.
- Chronic stress can also cause corresponding changes in the body's immune function and inflammatory response, which is significant because a long-term inflammatory response and the decline of the body's immune surveillance capabilities are implicated in tumorigenesis.
  - Dai, S., et al., “Chronic stress promotes cancer development,” Front Oncol 2020; 10:1492.



Cortisol

Cortisol

- The release of cortisol is under control of the hypothalamus-pituitary-adrenal (HPA) axis. Corticotropin-releasing hormone (CRH) is released by the paraventricular nucleus of the hypothalamus.
- It then acts on the anterior pituitary to release adrenocorticotropic hormone (ACTH), which then acts on the adrenal cortex.
- In a negative feedback loop, sufficient cortisol inhibits the release of both ACTH and CRH. The HPA axis follows a circadian rhythm. Therefore, cortisol levels will be high in the morning and low at night.

  - Ramamoorthy, S., et al., "Corticosteroids: Mechanisms of action in health and disease," Rheum Dis Clin North Amer 2016; 42(1):15-31.

Cortisol (Cont.)

- Glucocorticoid receptors are present in almost all tissues in the body. Therefore, cortisol is able to affect nearly every organ system.
  - Nervous
  - Immune
  - Cardiovascular
  - Respiratory
  - Reproductive
  - Musculoskeletal
  - Integumentary
    - Kadmiel, M., et al., “Glucocorticoid receptor signaling in health and disease,” Trends Pharmacol Sci 2013; 34(9):518-30.

Functions of Cortisol

- Balances blood sugar
- Weight control
- Immune system response
- Bone turnover rate
- Stress reaction
- Sleep regulation
- Protein synthesis
- Balances the other hormones
- Anti-inflammatory
- Participates with aldosterone in sodium reabsorption

References

- Thau, L., et al., Physiology, Cortisol. StatPearls (Internet), Sept 6, 2021.
- Oakley, R., et al., “The biology of the glucocorticoid receptor: new signaling mechanisms in health and disease,” Jour Allergy Clin Immunol 2013; 132(5):1033-44.

What Elevates Cortisol

- Stress
- Depression
- High progestin intake
- Sodium depletion
- High prolactin
- Inflammation
- Cushing’s disease
- Obesity
- Low estradiol levels in women

What Lowers Cortisol

- Chronic stress
- Addison’s disease
- Opioid use
- Chronic marijuana use
- Accutane
- Glucocorticoid use

Consequences of Elevated Cortisol

- Compromised immune system
  - Decreases the release of antibodies
  - Causes an inhibition in the proliferation of T cells
  - Increases inflammatory cytokines
  - Inhibits the release of some interleukins
  - Latent virus activation
  - Shift from Th1 to Th2 cytokine expression
    - Yaribeygi, H., et al., “The impact of stress on body functions: A review,” EXCLI Jour 2017; 16:1057-72.

Consequences of Elevated Cortisol (Cont.)

- Confusion
- Shakiness between meals
- Memory is not as sharp
- Low energy
- Night sweats
- Binge eating
- Thin skin
- Increased blood pressure
- Increased cholesterol
- Increased triglycerides
- Increase blood sugar
- Increased risk of bone loss by loss of minerals in the bones

Consequences of Elevated Cortisol (Cont.)

- Increased insulin/insulin resistance
- Increased infections
- Fatigue
- Irritability
- Sugar cravings
- Easy bruising
- Muscle weakness
- Weight gain around the middle
- Sleep disturbances
- Impaired hepatic conversion of T4 to T3
- Favors the development of leaky gut syndrome

Consequences of Elevated Cortisol (Cont.)

- There is a strong inter-relationship between activation of the hypothalamic-pituitary-adrenal axis and energy homeostasis.
- Patients with abdominal obesity have elevated cortisol levels. Furthermore, stress and glucocorticoids act to control both food intake and energy expenditure.
- In fact, glucocorticoids are known to increase the consumption of foods enriched in fat and sugar.
  - Hewagalamulage, S., et al., "Stress, cortisol, and obesity: a role for cortisol responsiveness in identifying individuals prone to obesity," Domest Animal Endocrinol 2016; 56(Suppl):S112-20.

Consequences of Elevated Cortisol (Cont.)

- In women, high-cortisol individuals eat more in response to stress than low-cortisol leading to increased food intake and reduced energy expenditure and thus, predisposition to obesity.
- Therefore, cortisol responsiveness may be used as a marker to identify individuals who are at risk of weight gain and subsequent obesity.
  - Lee, T., “High cortisol responses identify propensity for obesity that is linked to thermogenesis in skeletal muscle,” FASEB Jour 2014; 28(1):35-44.

Consequences of Elevated Cortisol (Cont.)

- Stress response
  - When a person is stressed, the sympathetic nervous system (SNS) is activated. The SNS is responsible for the fight or flight response, which causes many responses in the body. The amygdala is responsible for processing fear, arousal, and emotional stimuli to determine the appropriate response. If necessary, the amygdala sends a stress signal to the hypothalamus.
    - Hakamata, Y., et al., "Amygdala-centered functional connectivity affects daily cortisol concentrations: a putative link with anxiety," Sci Rep 2017; 7(1):8313.

Consequences of Elevated Cortisol (Cont.)

- Stress response (cont.)
  - The hypothalamus then activates the SNS, and the adrenal glands release a surge of catecholamines, such as epinephrine. This results in effects such as increased heart rate and respiratory rate. As the body continues to perceive the stimuli as a threat, the hypothalamus activates the HPA axis. Cortisol is released from the adrenal cortex and allows the body to continue to stay at a state of high alert. Moreover, acutely, cortisol's mechanisms provide energy to the body.
    - Lee, D., et al., "Technical and clinical aspects of cortisol as a biochemical marker of chronic stress," BMB Rep 2015; 48(4):209-16.

Consequences of Elevated Cortisol (Cont.)

- Glucose and protein homeostasis
  - The presence of glucocorticoids, such as cortisol, increase the availability of blood glucose to the brain. Cortisol acts on the liver, muscle, adipose tissue, and pancreas. In the liver, high cortisol levels increase gluconeogenesis and decrease glycogen synthesis.
    - Kuo, T., et al., “Regulation of glucose homeostasis by glucocorticoids,” Adv Exp Med Biol 2015; 872:99-126.

Consequences of Elevated Cortisol (Cont.)

- Glucose and protein homeostasis (cont.)
  - In the presence of cortisol, muscle cells decrease glucose uptake and consumption and increase protein degradation; this supplies gluconeogenesis with amino acids that are glucogenic.
    - Exton, J., “Regulation of gluconeogenesis by glucocorticoids,” Monogr Endocrinol 1979; 12:535-46.

Consequences of Elevated Cortisol (Cont.)

- Glucose and protein homeostasis (cont.)
  - In adipose tissues, cortisol increases lipolysis which results in the release of glycerol and free fatty acids. These free fatty acids can be used in B oxidation and as an energy source for other cells as they continue to produce glucose.
  - Lastly, cortisol acts on the pancreas to decrease insulin and increase glucagon. Glucagon is a peptide hormone secreted by the pancreatic alpha cells to increase liver glycogenolysis, liver gluconeogenesis, liver ketogenesis, lipolysis, as well as decreases lipogenesis. Cortisol enhances the activity of glucagon, epinephrine, and other catecholamines.

Consequences of Elevated Cortisol (Cont.)

- This study found that in type 2 diabetics, hypothalamic-pituitary-adrenal activity is enhanced in patients with diabetes complications and the degree of cortisol secretion is related to the presence and number of diabetic complications.
  - Chiodini, I., et al., “Cortisol secretion in patients with type 2 diabetes: relationship with chronic complications,” Diabetes Care 2007; 30(1):83-8.

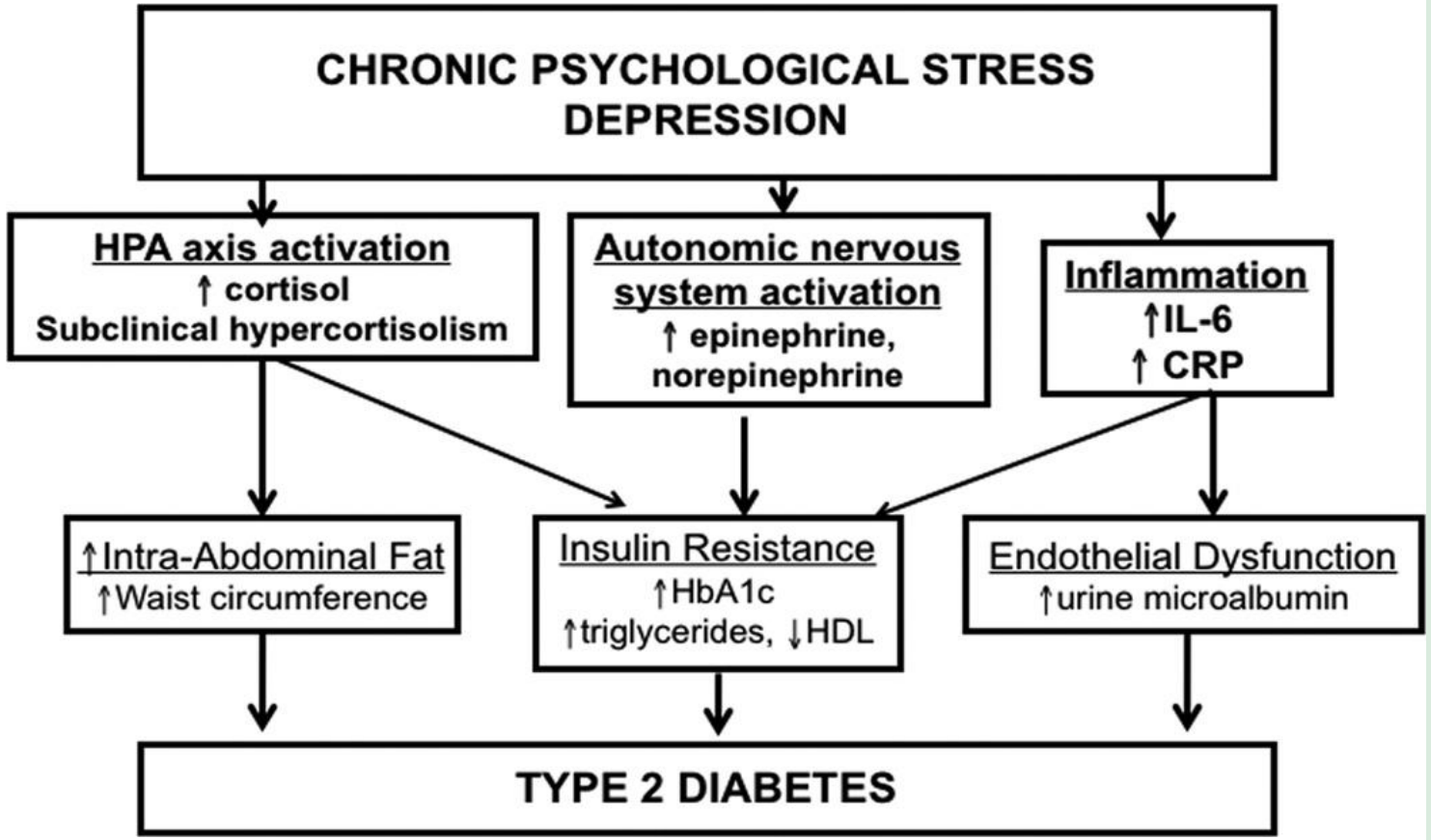
Consequences of Elevated Cortisol (Cont.)

- This trial found an association between high serum total cortisol concentrations and mortality from COVID-19. In this cohort, cortisol seemed to be a better independent predictor than were other laboratory markers associated with COVID-19.
  - Tan, T., et al., “Association between high serum total cortisol concentrations and mortality from COVID-19,” Lancet Diabetes Endocrinol 2020; 8(8):659-60.

Consequences of Elevated Cortisol (Cont.)

- This study found that depression was associated with cross-sectional and longitudinal alterations in the diurnal cortisol curve, including a blunted cortisol awakening response and flattening of the diurnal cortisol curve. Flattening of the diurnal cortisol curve was also associated with insulin resistance and type 2 diabetes mellitus.
  - Joseph, J., et al., "Cortisol dysregulation: the bidirectional link between stress, depression, and type 2 diabetes mellitus," Ann NY Acad Sci 2017; 1392(1):20-34.

Adapted from Ibid., Joseph.



Consequences of Elevated Cortisol (Cont.)

- Stressful experiences are fundamental in the provocation of major depression. Furthermore, HPA axis activation and hypercortisolemia, often seen in depressed patients, may represent increased stress hormones, CRH and ACTH secretion.
  - Capuron, L., et al., “Association of exaggerated HPA axis response to the initial injection of interferon-α with development of depression during interferon-α therapy,” Amer Jour Psychiatry 2013; 160: 1342-45.

Consequences of Elevated Cortisol (Cont.)

- In 14 studies that assessed cortisol levels in Parkinson's patients, seven showed elevation of cortisol levels. In relation to symptomatology, high levels of cortisol were associated with worst functional scores, depression, and behavior in risk preference.
  - Medeiros Soares, N., et al., "Cortisol levels, motor, cognitive and behavioral symptoms in Parkinson's disease: a systematic review," Jour neural Transm (Vienna) 2019; 126(3):219-32.

Abnormal Cortisol Levels Are Associated With

- Menopause
- Chronic fatigue syndrome
- Fibromyalgia
- Depression
- Impotence
- Anorexia nervosa
- Insulin resistance/diabetes
- Generalized memory loss
- IBS
- Exacerbations of multiple sclerosis

Abnormal Cortisol Levels Are Associated With (Cont.)

- Heart disease
- Rheumatoid arthritis
- Breast cancer
- Alzheimer’s disease
- Panic disorders
- PMS
- Infertility
- Sleep disorders
- Osteopenia/osteoporosis

References

- Wichmann, S., et al., “Cortisol stress response in post-traumatic stress disorder, panic disorder, and major depressive disorder patients,” Psychoneuroendocrinology 2017; 83:135-41.
- Thau, L., et al., “Physiology, cortisol,” StatPearls (Internet), February 8, 2021.

Hypoadrenalism

- When the patient is first stressed cortisol levels elevate, if the patient stays stressed long-term then cortisol levels become too low. This is called hypoadrenalism or hypocortisolism. The term adrenal fatigue was coined by Dr. James Wilson to also describe this phenomenon.
  - Wilson, J., “Clinical perspective on stress, cortisol, and adrenal fatigue,” Adv Int Med 2014; 1(2):93-96.

Symptoms of Hypoadrenalism

- Fatigue
- Low blood pressure
- Sensitivity to light
- Insomnia
- Digestive problems
- Emotional imbalances
- Lack of motivation
- Decreased sexual interest
- Hypo or hyperglycemia/insulin resistance

Symptoms of Hypoadrenalism (Cont.)

- Decreased immunity
- Lack of stamina
- Emotional paralysis
- Poor wound healing
- Allergies
- Increased alcoholism and drug addiction
- Unresponsive hypothyroidism (does not respond to treatment)
- Feeling overwhelmed

Causes of Hypoadrenalism

- Nutritional deficiencies
- Long-term stress
- Dysbiosis
- Chronic inflammation
- Chronic pain
- Toxic exposure
- Overly aggressive exercise
- Hypoglycemia
- Poor sleep hygiene
- Depression
- Severe allergies

Treatment of Hyperadrenalism or Hypoadrenalism

- Stress reduction techniques are key to normalizing cortisol levels. Prayer, meditation, tai chi, yoga, qigong, acupuncture, exercise, breathing techniques, and massage.
  - For example, meditation has been shown to help regulate the stress response, thereby suppressing chronic inflammation states and maintaining a healthy gut-barrier function.
    - Househam, A., et al., "The effects of stress and meditation on the immune system, human microbiota, and epigenetics," Adv Mind Body Med 2017; 31(4):10-25.

Treatment of Hyperadrenalism or Hypoadrenalism (Cont.)

- Nutrients are also very important.
  - Vitamin C
  - B vitamins
  - Calcium
  - Magnesium
  - Zinc
  - Selenium
  - Copper
  - Sodium
  - Manganese

Treatment of Hyperadrenalism or Hypoadrenalism (Cont.)

- If DHEA levels are low, then replace DHEA if the patient is a candidate for DHEA replacement.
  - Clinical pearl: When replacing DHEA, always also treat the abnormal cortisol levels if they are present, or when you repeat levels in 90 days the DHEA level will be lower, even though the patient is on DHEA.
- Adaptogenic herbs
- Calming herbs if the patient is anxious

Treatment of Hypoadrenalism

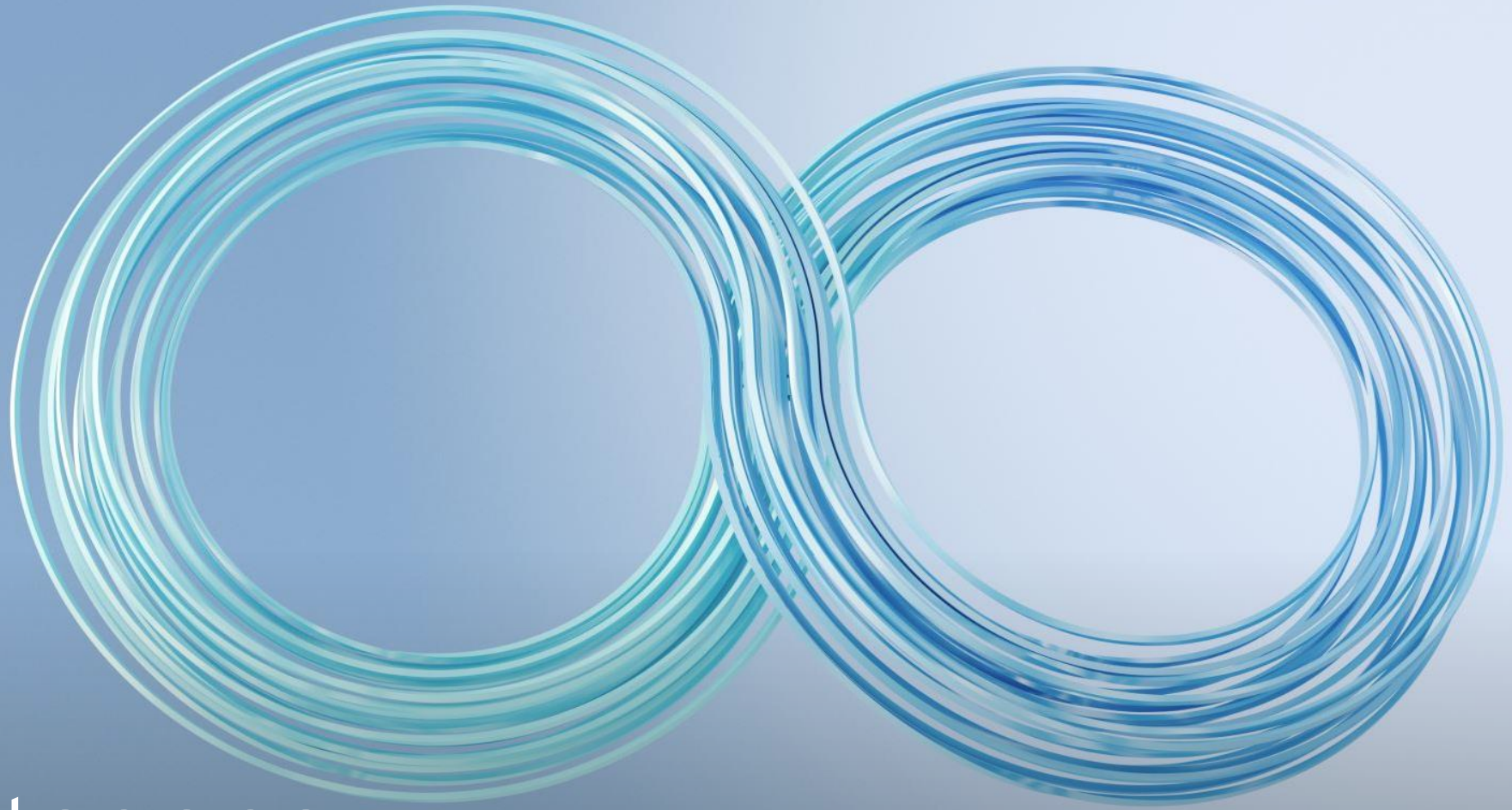
- If nutrients, stress reduction techniques, adaptogenic and calming herbs are not effective, then low cortisol levels can be treated with the following:
  - Continue stress reduction techniques, nutrients, and calming herbs.
  - Take the patient off adaptogenic herbs and instead start adrenal extracts.
  - If the cortisol levels still remain low, then add the herb licorice. Do not give licorice to patients with hypertension and if the patient develops hypertension while taking licorice then D/C.
  - Cortef® (hydrocortisone) is the treatment of last resort. When all else fails, continue the patient on adrenal extracts and add hydrocortisone for 6-9 months and then taper the patient off the hydrocortisone.
    - Dose: 7.5 mg in am, 5 mg at noon, 2.5 mg at 5 pm.

Hormones Are A Web

- If cortisol is increased, it decreases the making of progesterone and its activity.
- Cortisol competes with progesterone for common receptors.
- When cortisol is elevated, thyroid hormone is more bound and less active.
- Decreased estradiol in a women is a stressor to her body (causes decline in function of NE, serotonin, dopamine, and acetylcholine).

Cortisol Testing

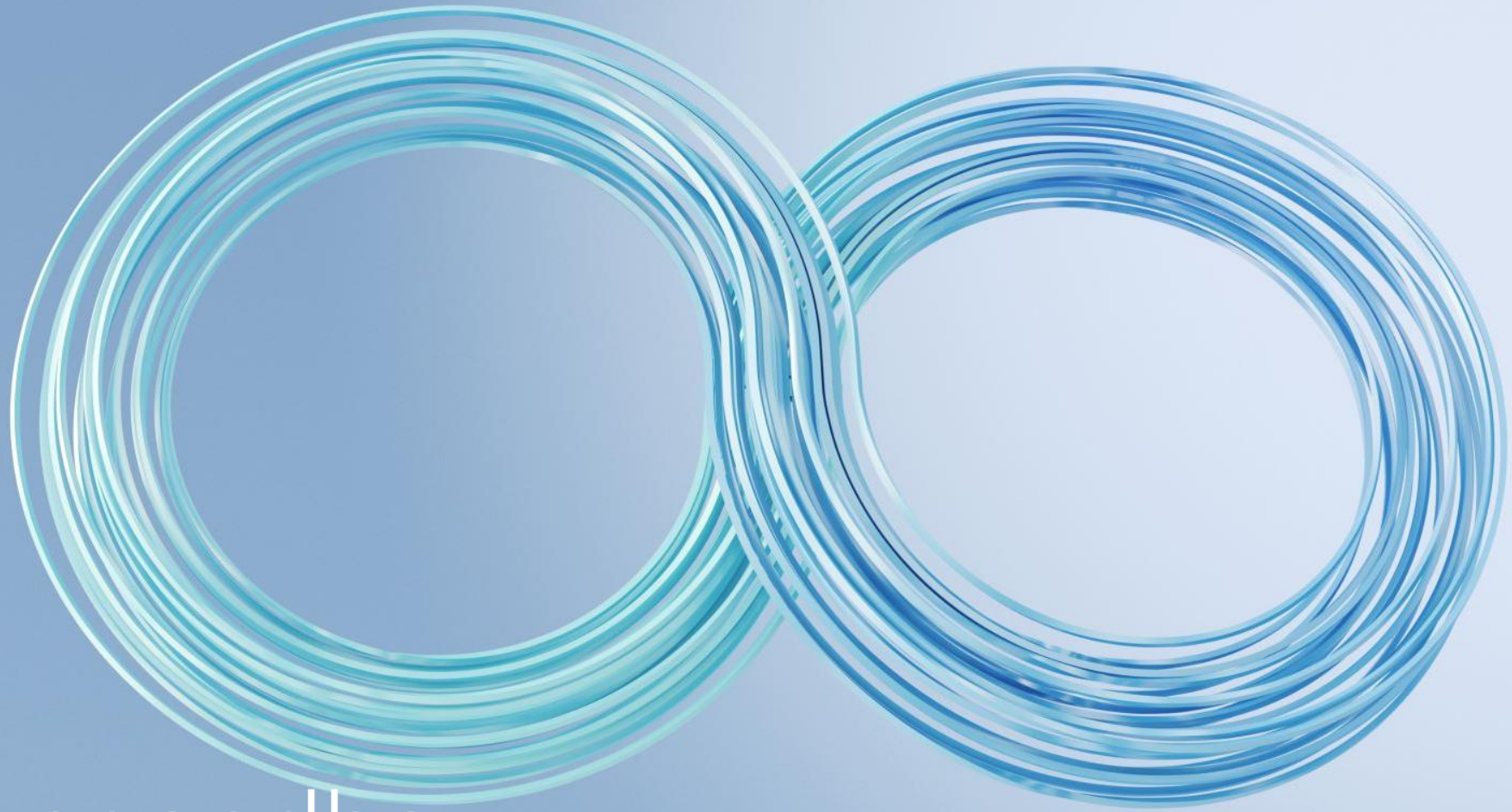
- Salivary cortisol levels are thought to correlate with the levels of free cortisol in plasma and serum.
- Therefore, salivary testing for cortisol is the gold standard for testing.
  - Ibid., Lee.
  - Bozovic, D., et al., “Salivary cortisol levels as a biological marker of stress reaction,” Med Arch 2013; 67(5):374-77.



Adaptogens

Adaptogens: Chronic Stress

- Plant adaptogens are compounds that increase the ability of an organism to adapt to environmental factors and to avoid damage from these factors. The beneficial effects of multi-dose administration of adaptogens are mainly associated with the hypothalamic-pituitary-adrenal (HPA) axis, a part of the stress-system that is believed to play a primary role in the reactions of the body to repeated stress and adaptation.
  - Panossian, A., et al., "Evidence-based efficacy of adaptogens in fatigue, and molecular mechanisms related to their stress-protective activity," Curr Clin Pharmacol 2009; 4(3):198-219.



Ashwagandha

Ashwagandha

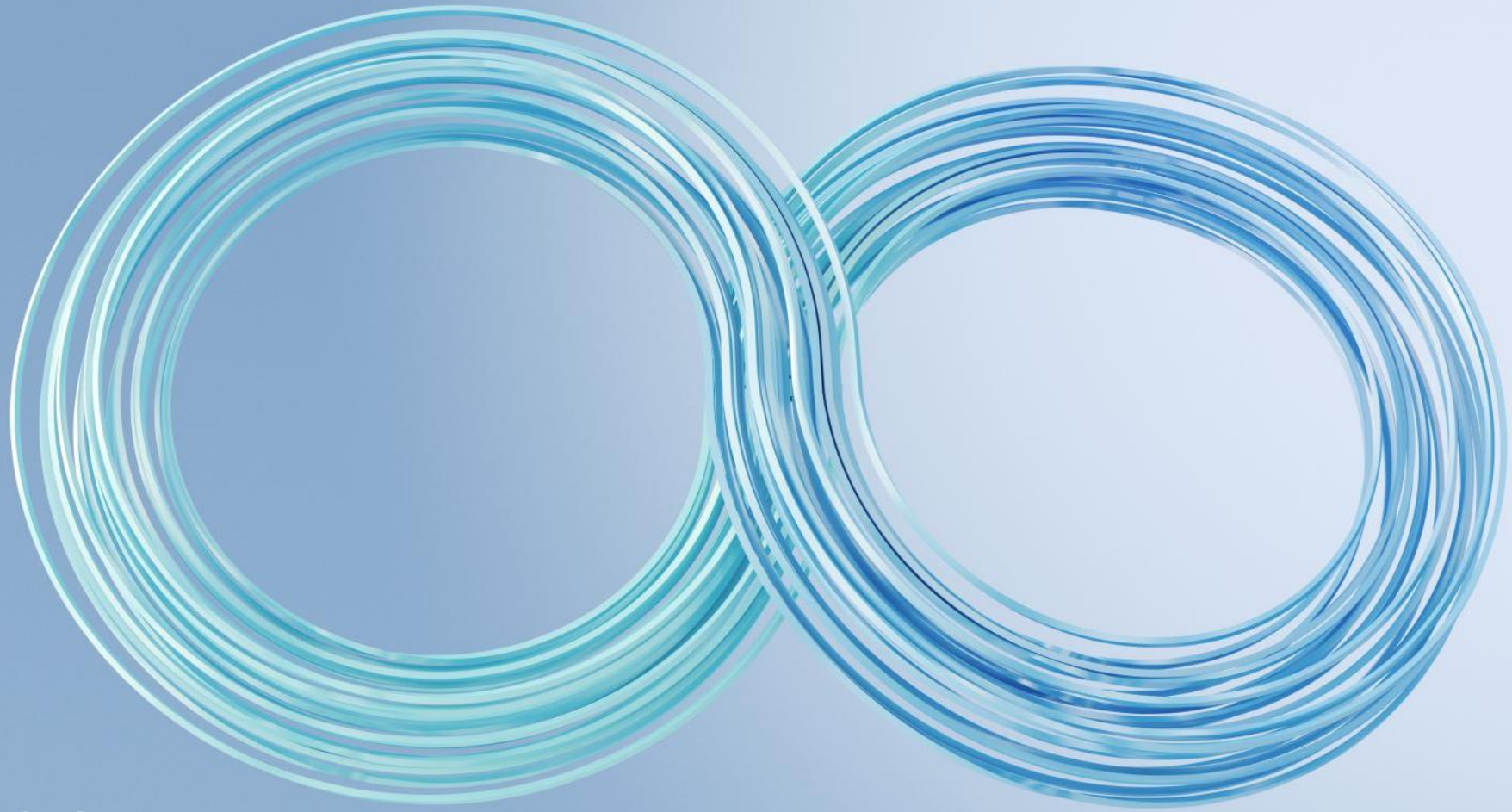
- Ashwagandha is grown in India, Pakistan, and Sri Lanka.
- Ashwagandha root (Withania somnifera) is part of the nightshade family. It is known to improve resistance to emotional and physical stress.
- Recommended daily dose:
  - Capsule form: 500 to 2,000 milligrams daily.
  - Dried root prepared in tea: 3 to 4 grams daily.
- Possible side effects and contraindications:
  - Diarrhea
  - Nausea
  - Vomiting

Functions of Ashwagandha

- Activates the immune system
- Antibacterial
- Anti-inflammatory
- Antioxidant
- Enhances endurance and strength
- Helps preserve adrenal function
- Helps with stress reduction since it is an adaptogenic herb
- Increases libido and sexual performance
- Increases muscle mass
- Lowers cholesterol
- Protects the liver
- Has cytotoxic and tumor-sensitizing actions

Yet Another Interesting Study on Ashwagandha

- A heterogeneous study population was sampled, including older adults with mild cognitive impairment and adults with schizophrenia, schizoaffective disorder, or bipolar disorder. In most instances, Ashwagandha improved performance on cognitive tasks, executive function, attention, and reaction time. It also appears to be well tolerated, with good adherence and minimal side effects.
  - Ng, Q., et al., "A systematic review of the clinical use of Withania somnifera (Ashwagandha) to ameliorate cognitive dysfunction," Phytother Res 2019; Nov 19. doi: 10.1002/ptr.6552. [Epub ahead of print]



Bacopa

Functions of Bacopa

- Anti-helicobacter pylori affect
- Regulates dopamine production
- Regulates serotonin production
- Enhances acetylcholine
- Increases the bodies utilization of nitric oxide
- Improves transmission of nerve impulses

Side Effects and Contraindications of Bacopa

- Bacopa can_intensify the activity of thyroid-stimulating drugs or inhibit the effectiveness of thyroid-suppressant drugs.
- Bacopa can have a sedative effect therefore use caution when combining it with other sedatives.
- Possible side effects particularly if taken on an empty stomach
  - Nausea
  - Cramping
  - Bloated stomach
  - Dry mouth
  - Fatigue

Therapeutic Benefits of Bacopa

- Renal protective
- Diabetic neuropathy
- Alzheimer’s disease
- Anxiety
- ADHD
- Allergies
- Irritable bowel syndrome (IBS)
- Stress
- Improves focus
- Epilepsy
- Pain relief
- Hypertension

References

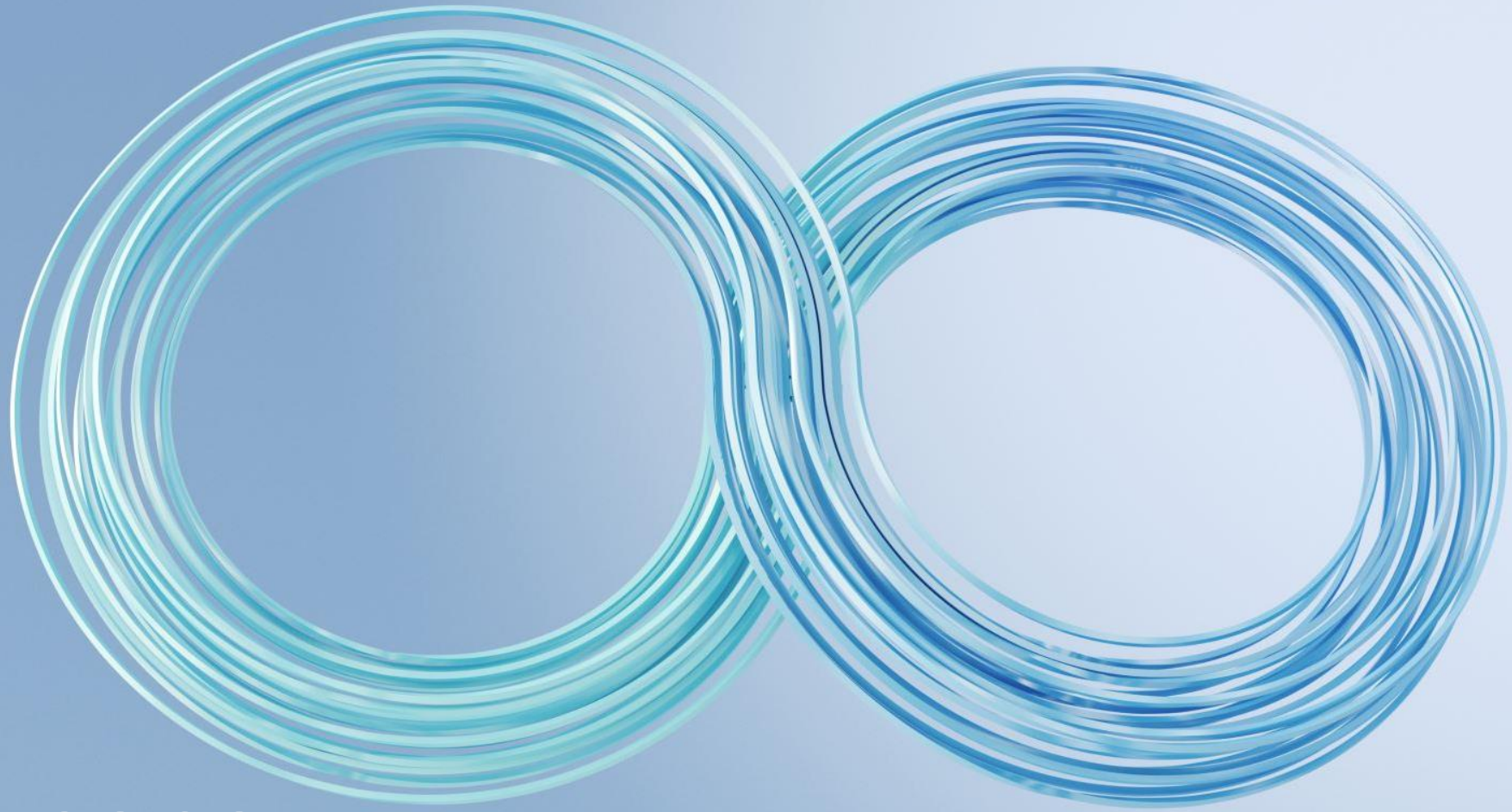
- Singh, R., et al., “Studies on the Anti-Anxiety Effect of the Medhya Rasayana Drug, Brahmi (Bacopa monniera Wettst.) - Part I,” Jour Res Ayurveda Siddha 1980; 1(1):133-48.
- Sumathy, T., et al., “Protective role of Bacopa monniera on morphine-induced brain mitochondrial enzyme activity in rats,” Fitoterapia 2002; 73(5):381-85.
- Kidd, P., “A review of nutrients and botanicals in the integrative management of cognitive dysfunction,” Altern Med Rev 1999; 4:144-61.
- Limpeanchob, N., et al., “Neuroprotective effect of Bacopa monnieri on beta-amyloid-induced cell death in primary cortical culture,” Jour Ethnopharmacol 2008; 120:112-17.
- Morgan, A., et al., “Does Bacopa monnieri improve memory performance in older persons? Results of a randomized, placebo-controlled, double-blind trial,” Jour Altern Complement Med 2010; 16:753-9.
- Stough, C., et al., “The chronic effects of an extract of Bacopa monniera (Brahmi) on cognitive function in healthy human subjects,” Psychopharmacol 2001; 156:481-84.

References (Cont.)

- Chaudhuri, P., et al., “Phytotoxic and antimicrobial constituents of Bacopa monnieri and Holmskioldia sanguinea,” Phytother Res 2004; 18(2):114-17.
- Ganguly, D., et al., “Some neuropharmacological and behavioural effects of an active fraction from Herpestis monniera, Linn (Brahmi),” Indian Jour Physiol Pharmacol 1967; 11(1):33-43.
- Jain, P., et al., “Anti-inflammatory effects of an Ayurvedic reparation, Brahmi Rasayan, in rodents,” Indian Jour Exp Biol 1994; 32:633-36.
- Singh, H., et al., “Neuropsychopharmacological effects of the Ayurvedic nootropic Bacopa monniera Linn. (Brahmi),” Indian Jour Pharmacol 1997; 29:S359-S365.
- Bhattacharya, S., et al., “Antioxidant activity of Bacopa monniera in rat frontal cortex, striatum, and hippocampus,” Phytother Res 2000; 14:174-79.

Interesting Study on Bacopa

- A study revealed that bacopa was able to provide protective effects against multitasking.
- Bacopa improved both cognitive performance and mood in 1-2 hours.
  - Dose: 320 and 650 mg
    - Benson, S., et al., “An acute, double-blind, placebo, controlled cross-over study of 320 mg and 640 mg doses of Bacopa monnieri (CDRI 08) on multitasking stress reactivity and mood,” Phytother Res 2014; 28(4):551-59.



Cordyceps

Cordyceps

- Cordyceps (Cordyceps sinsensis and Cordyceps militaris) is a mushroom that has long been used, particularly in traditional Chinese medicine. The main constituent of the extract derived from this fungus is Cordycepin (3′deoxyadenosine). Furthermore, Cordyceps, contains various types of essential amino acids, vitamins B1, B2, B12 and K, carbohydrates such as monosaccharide, oligosaccharides and various polysaccharides, proteins, sterols, nucleosides, and other trace elements.
  - Dosage depends on concentration of the active ingredient. Common dose is: 500 mg-1500 mg a day in divided doses. Some athletes take 3 grams qd.

Functions of Cordyceps

- Improves lung capacity
- Increases energy levels
- Improves kidney function
- Interferes with purine biosynthesis
- Anti-cancer
- Anti-inflammatory
- Antioxidant
- Increases cardiac output
- Lowers fibrinogen
- Anti-arrhythmic
- Interferes in mTOR signal transduction
- Provokes RNA chain termination
- Immunomodulatory
- Insecticidal
- Antimicrobial
- Hypoglycemic
- Neuroprotective
- Lipid-lowering
- Anti-bacterial
- Steroidogenic

Side Effects and Contraindications of Cordyceps

- Do not use in patients with autoimmune diseases.
- Safety has not been determined in pregnant women or women that are breast-feeding. Therefore, do not use in these patients.
- There has been couple of reports on lead poisoning in patients taking *Cordyceps*. Make sure the patient only uses pharmaceutical grade product.
- Use Cordyceps with caution in patients who are taking anti-viral or diabetic medications since this mushroom can affect the dosage of these drugs.
- Taking cordyceps might make prednisolone less effective.
- Taking cordyceps might increase the risk of bleeding in patients with bleeding disorders or patients on medications that change bleeding time. Use with caution.
- Using cordyceps might increase the risk of bleeding during surgery. Have the patient stop taking cordyceps 2 weeks before surgery.
- Instruct the patient not to take cordyceps if they are allergic to molds.

Therapeutic Benefits of Cordyceps

- Coughs, bronchitis, asthma
- Hepatic cirrhosis
- Athletes
- Hepatitis B
- Chronic kidney disease
  - Used in conjunction with conventional medicine to decrease serum creatinine, increase creatinine clearance, decrease proteinuria, and lower chronic kidney disease complications such as elevated hemoglobin and elevated serum albumin.
- Being studied as a possible anti-cancer agent
- Sexual enhancement
- Congestive heart failure
- Cardiac arrhythmias
- Infection

References

- Smith, P., What You Must Know About Vitamins, Minerals, Herbs and So Much More. Garden City Park, NY: Square One Publishers, 2020.
- Zhou, J., et al., “The scientific rediscovery of an ancient Chinese herbal medicine: cordyceps sinensis,” Jour Altern Complem Med 1998; 4:429–57.
- Rouse, J., “Herbal support for adrenal function,” Clin Nutri Insights 1998; 6(9):1-2.
- Zhang, H., et al., “Cordyceps sinensis (a traditional Chinese medicine) for treating chronic kidney disease,” Cochrane Database of Systematic Reviews 2014; Issue 12. No.: CD008353.
- Tuli, H., et al., “Pharmacological and therapeutic potential of Cordyceps with special reference to Cordycepin,” 3 Biotech 2014; 4(1):1-12.

References (Cont.)

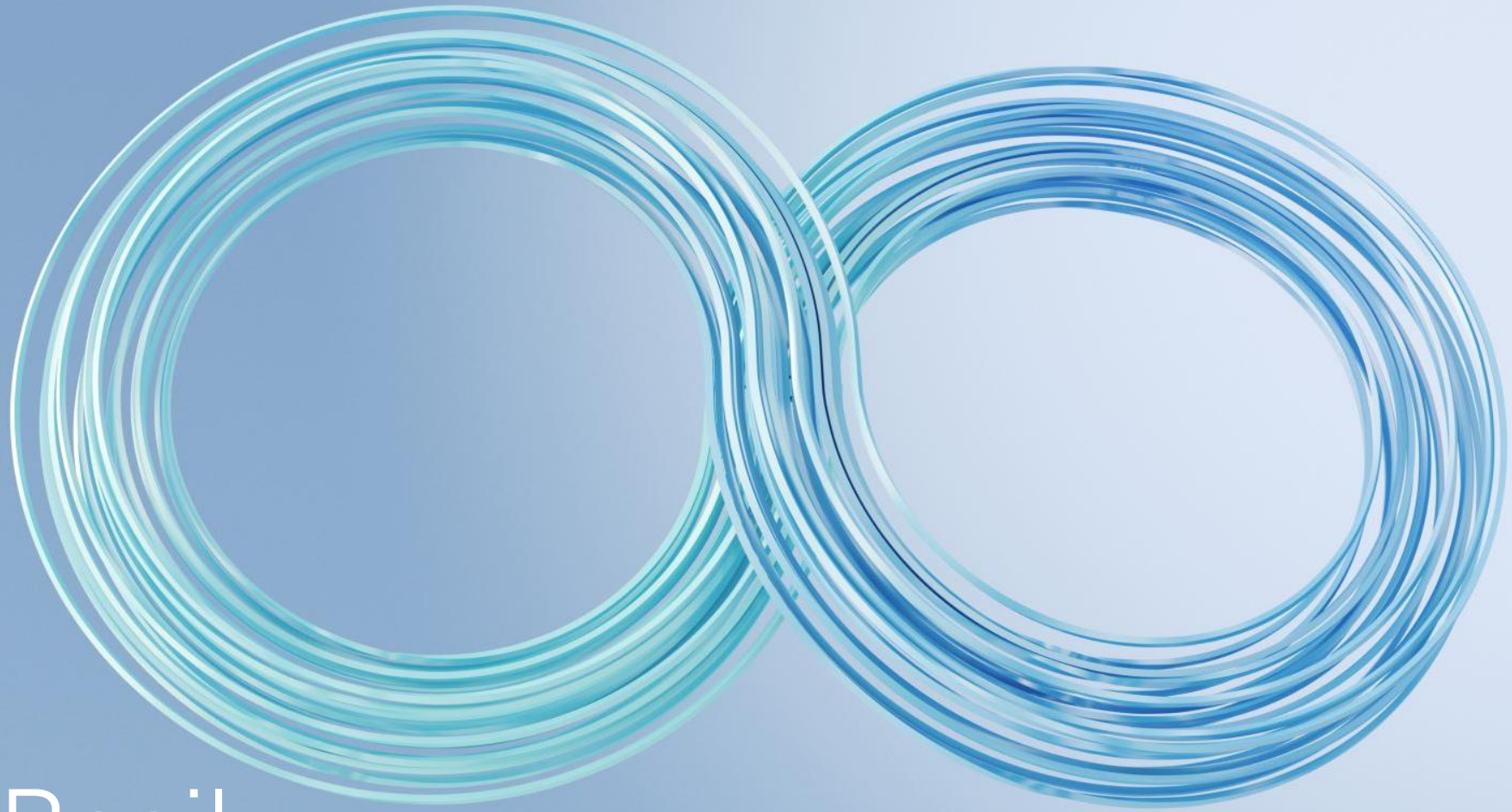
- Chen, D., “Effects of JinShuiBao capsule on the quality of life of patients with heart failure,” Jour Admin Trad Chin Med 1995; 5:40–3.
- Zhou, X., “Cordyceps fungi: natural products, pharmacological functions and developmental products,” Jour Pharm Pharmcol 2009; 61:279–91.
- Yue, K., “The genus Cordyceps: a chemical and pharmacological review,” Jour Pharm Pharmacol 2013; 65(4):474-93.
- Das, S., “Medicinal uses of the mushroom Cordyceps militaris: current state and prospects,” Fitoterapia 2010; 81:961–68.
- Huang, B., et al., “Effects of Cordyceps sinensis on steroidogenesis in normal mouse Leydig cells,” Life Sci 2001; 69:2593–2602.

References (Cont.)

- Lee, Y., et al., “Cordycepin inhibits UVB-induced matrix metalloproteinase expression by suppressing the NF-KB pathway in human dermal fibroblasts,” Exp Mol Med 2009; 41:548–54.
- Zhou, X., “Cordycepin is an immunoregulatory active ingredient of Cordyceps sinensis,” Amer Jour Chin Med 2008; 36:967–80.
- Lee, E., et al., “Cordycepin suppresses TNF-alpha-induced invasion, migration and matrix metalloproteinase-9 expression in human bladder cancer cells,” Phytother Res 2010; 24:1755–61.
- Lee, J., et al., “Anti-cancer effects of cordycepin on oral squamous cell carcinoma proliferation and apoptosis in vitro,” Jour Cancer Ther 2011; 2:224–34.
- Hyun, H., “Chemical ingredient of Cordyceps militaris,” Mycobiology 2008; 36:233–35.
- Patel, S., et al., “Recent developments in mushrooms as anti-cancer therapeutics: a review,” 3 Biotech 2012; 2:1–15.

References (Cont.)

- Rao, Y., “Constituents isolated from Cordyceps militaris suppress enhanced inflammatory mediator’s production and human cancer cell proliferation,” Jour Ethnopharmacol 2010; 131:363–67.
- Ng, T., et al., Pharmacological actions of Cordyceps, a prized folk medicine,” Jour Pharm Pharmacol 2005; 57(12):1509-19.
- Zaidman, B., et al., “Medicinal mushroom modulators of molecular targets as cancer therapeutics,” Appl Microbiol Biotechnol 2005; 67:453–68.
- Zhang, G., “Hypoglycemic activity of the fungi Cordyceps militaris, Cordyceps sinensis, Triccholoma mongolicum, and Omphalia lapidescens in streptozotocin-induced diabetic rats,” Appl Microbiol Biotechnol 2006; 72:1152–56.
- Zhu, J., “The scientific rediscovery of an ancient Chinese herbal medicine: Cordyceps sinensis: part I,” Jour Altern Complem Med 1998; 4:289–303.



Holy Basil

Holy Basil

- Holy basil (Ocimum sanctum) is also known as Tulsi. It is an aromatic plant that has been used for thousands of years. It is considered by many practitioners to be the best of the adaptogens in Ayurvedic medicine.
- Dosage
  - Can be used as a raw fresh whole herb
  - Dried leaves
    - 300-600 mg qd for prevention
    - 600-1,800 mg in divided doses as a therapy
- Side effects and contraindications
  - No reported toxicity or adverse effects and no interactions have been described.

Functions of Holy Basil

- Adaptogenic
  - Antifatigue
  - Anti-stress
- Reduction of noise stress
- Antidepressant
- Anti-anxiety
- Anti-inflammatory
- Antioxidant
- Hepatoprotection
- Cancer protection
- Helps protect from gamma radiation
- Helps protect from radioactive iodine
- Helps protect against heavy metal toxicity
- Antidiabetic activity
- Lipid lowering
- Antimicrobial:
  - Antibacterial
  - Antifungal
  - Antimalarial
  - Anti-parasitic
  - Anti-viral
- Immune enhancement
- Cognitive enhancement
- Diuretic
- Aphrodisiac
- Anti-hypotensive
- Anticoagulant
- Antipyretic

Therapeutic Benefits of Holy Basil

- Anxiety
- Cough
- Asthma
- Fever
- Malaria
- Diarrhea and dysentery
- Arthritis
- Eye diseases
- Otalgia
- Indigestion
- Hiccups
- Vomiting
- Gastropathy

Therapeutic Benefits of Holy Basil (Cont.)

- Cardiopathy
- Back pain
- Genitourinary diseases
- Skin disorders
- Leukoderma
- Ringworm
- Insect, snake and scorpion bites
- Diabetes
- Metabolic syndrome
- Ischemic heart disease
- Stroke
- Pain control

Therapeutic Benefits of Holy Basil (Cont.)

- Arthritis
- Cataracts
- Allergy
- Asthma
- Ulcers
- Wound healing
- Hand sanitizer
- Mouthwash
- Infertility
- Anti-androgenic
- Bioremediation of contaminated air and soil
- Water treatment
- Food and herb preservation

References

- Braun, L., and Cohen, M., (Eds.) Herbs and Natural Supplements. 4th Ed. Australia: Elsevier, 2015.
- Cohen, M., “Tulsi-Ocimum sanctum: A herb for all seasons,” Jour Ayurveda Integra Med 2014; 5(4):252-59.
- Gupta, P., et al., “Constituents of Ocimum sanctum with antistress activity,” Jour Nat Prod 2007; 70(9):1410-16.
- Subramanian, M., et al., “Antioxidant and radioprotective properties of an Ocimum sanctum polysaccharide,” Redox Rep 2005; 10(5):257-64.
- Mohan, L., et al., “Ocimum sanctum Linn (TULSI)—an overview,” Inter Jour Pharmaceutical Sci Rev Res 2011; 7(1):51-3.
- Pattanayak, P., et al., “Ocimum sanctum Linn. A reservoir plant for therapeutic applications: An overview,” Pharmacognosy Rev 2010; 4(7):95-105.

References (Cont.)

- Rai, V., et al., “Effect of Tulasi (Ocimum sanctum) leaf powder supplementation on blood sugar levels, serum lipids and tissue lipids in diabetic rats,” Plant Food Hum Nutr 1997; 50(1):9-16.
- Gupta, S., et al., “Validation of traditional claim of Tulsi, Ocimum sanctum Linn, as a medicinal plant,” Indian Jour Exp Biol 2002; 40(7):765-773.
- Maheshwari, R., et al., “Usage of Holy basil for various aspects,” Bull Environ, Pharmacol, Life Sci 2012; 1(10):67-9.
- Jothie, R., et al., “Anti-stress activity of Ocimum sanctum: Possible effects on hypothalamic-pituitary-adrenal axis,” Phytother Res 2016; 30(5):805-14.
- Joseph, L., et al., “Radioprotective effect of Ocimum sanctum and amifostine on the salivary gland of rats after therapeutic radioiodine exposure,” Cancer Biother Radiopharmaceuticals 2011; 26(6):737-43.
- Wani, N., et al., “Formulation and evaluation of herbal sanitizer,” Inter Jour Pharm Tech Res 2013; 591):40-43.

References (Cont.)

- Bhattacharyya, D., et al., “Controlled programmed trial of Ocimum sanctum leaf on generalized anxiety disorders,” Nepal Med Coll Jour 2008; 1093):176-9.
- Ahmad, A., et al., “Restraint stress-induced central monoaminergic and oxidative changes in rats and their prevention by novel Ocimum sanctum compounds,” Indian Jour med Res 2012; 135(4):548-54.
- Ahn, Y., “Adrenal exhaustion and fatigue due to chronic stress,” Jour Korean Med Assoc 2011; 54(1):81-7.
- Sampath, S., et al., “Holy basil (Ocimum sanctum Linn.) leaf extract enhances specific cognitive parameters in healthy adult volunteers: A placebo-controlled study,” Indian Jour Physiol Pharmacol 2015; 59(1):69-77.
- Annes, A., “Larvicidal activity of Ocimum sanctum Linn. (Labiatae) against Aedes (L.) and Culex quinquefasciatus (Say.),” Parasitology Res 2008; 103(6):1451-53.
- Amber, K., et al., “Anticandidal effect of Ocimum sanctum essential oil and its synergy with fluconazole and ketoconazole,” Phytomedicine 2010; 17(12):921-25.

References (Cont.)

- Chatterjee, M., et al., “Evaluation of ethanol leaf extract of Ocimum sanctum in experimental models of anxiety and depression,” Pharmaceutical Biol 2011; 49(5):477-83.
- Gupta, S., et al., “Antidiabetic, antihypercholesterolemic and antioxidant effect of Ocimum sanctum (Linn) seed oil,” Indian Jour Exp Biol 2006; 44(4):300-04.
- Dharmani, P., et al., “Evaluation of anti-ulcerogenic and ulcer-healing properties of Ocimum sanctum Linn,” Jour Ethnopharmacology 2004; 93(2-3):197-206.
- Megesh, V., et al., “Ocimum sanctum induces apoptosis in A549 lung cancer cells and suppresses the in vivo growth of Lewis lung cancer cells,” Phytotherapy Res 2009; 23(10):1385-91.
- Maheshwari, R., et al., “Usage of Holy basil for various aspects,” Bull Environ, Pharmacol Life Sci 2012; 1(10):67-9.

References (Cont.)

- Pai, P., et al., “Evaluation of diuretic activity of ethanolic extract of Ocimum sanctum (l.) in Wistar albino rat,” Res Jour Pharmaceutical, Biological, Chem Sci 2013; 4(1):533-38.
- Pande, M., et al., “Effect of ethanolic extract of Ocimum sanctum (ram Tulsi) on sexual behaviour in male mice,” Inter Jour Pharm Tech Res 2009; 1(3):468-73.
- Kaur, G., et al., “Exploring the potential of Ocimum sanctum in vincristine-induced neuropathic pain in rats,” Jour Brachial Plexus Peripheral Nerve Injury 2010; 5(1).
- Mahajan, N., et al., “A phytopharmacological overview on Ocimum species with special emphasis on Ocimum sanctum,” Biomed Preventive Nutr 2012.
- Singh, S., et al., “Biological activities of Ocimum sanctum L. fixed oil—an overview,” Indian Jour Exper Biol 2007; 45(5):403-12.
- Sood, S., et al., “Chronic oral administration of Ocimum sanctum Linn. augments cardiac endogenous antioxidants and prevents isoproterenol-induced myocardial necrosis in rats,” Jour Pharmacy and Pharmacol 2005; 57(1):127-33.

References (Cont.)

- Sridevi, G., et al., “Pharmacological basis for antianaphylaxis, antihistamine and mast cell stabilization activity Ocimum sanctum,” Internet Jour Pharmacol 2009; 7(1).
- Zaffer Ahmad, M., et al., “Anti-diabetic activity of Ocimum sanctum L. roots and isolation of new phytoconstituents using two-dimensional nuclear magnetic resonance spectroscopy,” Jour Pharmacognosy Phytotherapy 2012; 4(6):75-85.
- Singh, S., et al., “Effect of fixed oil of Ocimum sanctum against experimentally induced arthritis and joint edema in laboratory animals,” Pharmaceutical Biol 1996; 34(3):218-22.
- Suanarunsawat, T., et al., “Lipid-lowering and antioxidant activities of aqueous extracts of Ocimum sanctum L. leaves in rats fed with a high-cholesterol diet,” Oxidative Med Cell Longevity 2011; 2011:962025.
- Sood, S., et al., “Effect of Ocimum sanctum Linn. on cardiac changes in rats subjected to chronic restraint stress,” Jour Ethanopharmacol 2006; 108(3):423-27.

Adaptogens: Immediate Stress

- In contrast, the single dose application of adaptogens is important in situations that require a rapid response to tension or to a stressful situation. In this case, the effects of the adaptogens are associated with another part of the stress-system, namely, the sympatho-adrenal-system (SAS), that provides a rapid response mechanism mainly to control the acute reaction of the organism to a stressor.
- SAS-mediated stimulating effects of single doses of adaptogens derived from Rhodiola rosea, Schizandra chinensis and Eleutherococcus senticosus.
- Furthermore, single administration of these adaptogens effectively increases mental performance and physical working capacity in humans. R. rosea is the most active of the three plant adaptogens producing, within 30 min of administration, a stimulating effect that continues for at least 4-6 hours.

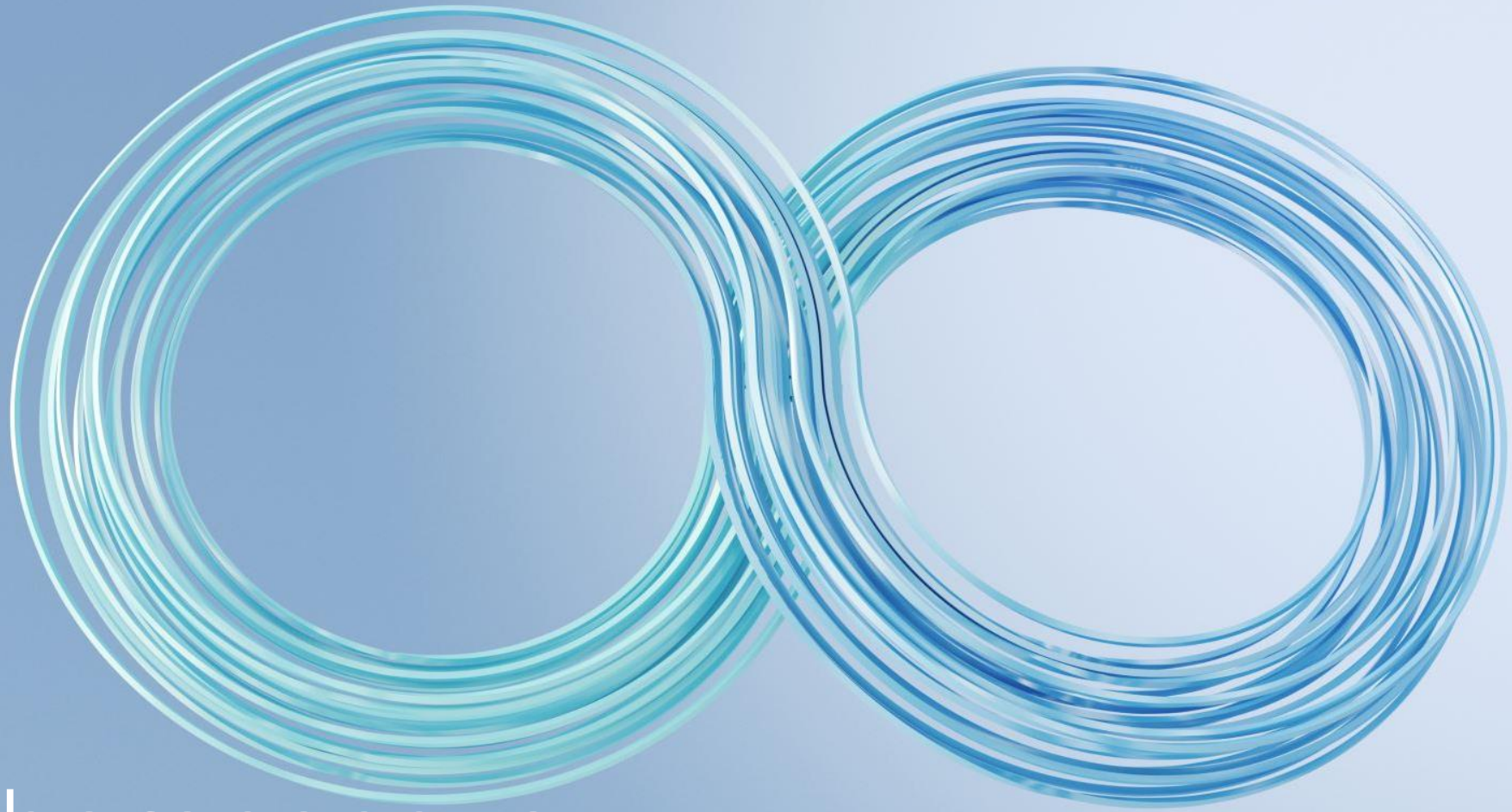
Reference

- Panossian, A., et al., “Stimulating effect of adaptogens: an overview with particular reference to their efficacy following single dose administration,” Phytother Res 2005; 19(10):819-38.

Best Adaptogens To Treat Immediate Stress

- Eleutherococcus
- Rhodiola
- Schisandra
- Combination therapies

- Each of these herbal therapies has a different mechanism of action.



Eleutherococcus

Eleutherococcus

- Eleuthero (Eleutherococcus senticosus) is an herb that is commonly used to increase energy. For many years, it was called Siberian ginseng. That name is now not used as much in the United States because it implies that the herb is part of the Panax genus (like the American and Asian ginseng), while it actually belongs to the genus Eleutherococcus. Regardless of the controversy over its name, this herb is used to treat a variety of ailments. The active ingredient is called eleutherosides which may stimulate the immune system.
  - Dose: 500 to 1,000 milligrams daily. Eleuthero can be taken for 3 months, followed by 3 to 4 weeks off.

Functions of Eleutherococcus

- Acts as a stimulant
- Acts as an adaptogen (strengthens the body’s resistance to stress)
- Aids the immune system (increases T-cell and natural killer cell activity)
- Decreases inflammation
- Improves endurance
- Improves learning ability
- Increases mental awareness
- Increases physical performance and stamina
- Increases tolerance to excess heat, noise, and workload
- Is an antioxidant
- Promotes healing
- Suppresses excessive nitric oxide production

Side Effects and Contraindications of Eleutherococcus

- Patients may experience any of the following symptoms:
  - Confusion
  - Drowsiness
  - Headache
  - Agitation
  - Hypertension
  - Insomnia
  - Irregular heart rhythm
  - Nosebleed
  - Vomiting
- Do not use eleuthero if the patient has a history of heart disease, hypertension, sleep apnea, narcolepsy, mania, schizophrenia, are pregnant or breastfeeding. Use with caution in patients with autoimmune diseases. It may interact with steroids.

Side Effects and Contraindications of Eleutherococcus (Cont.)

- Women who have a history of estrogen-sensitive cancers or uterine fibroids may not want to use eleuthero since it has mild estrogenic effects.
- Eleuthero may increase the risk of bleeding, especially if the patient is already taking blood-thinners such as aspirin, warfarin, or clopidogrel. Therefore, use with caution.
- Eleuthero may increase blood levels of digoxin.
- It may lower blood sugar levels, raising the risk of hypoglycemia.
- Eleuthero could make it harder for the body to eliminate lithium.
- Eleuthero can boost the immune system and may interact with drugs taken to treat an autoimmune disease or drugs taken after organ transplant.
- Eleuthero may make the effects of sedatives stronger, especially barbiturates.

Therapeutic Benefits of Eleutherococcus

- Anxiety
- Common cold/flu
- Diabetes
- Exhaustion
- Fibromyalgia
- Kidney disease
- Inflammation
- Insomnia
- Hypercholesterolemia
- Hypertension

Therapeutic Benefits of Eleutherococcus (Cont.)

- Joint pain
- Liver disease
- Memory loss
- Low energy (chronic fatigue)
- Osteoarthritis
- Rheumatoid arthritis
- Premenstrual syndrome (PMS)
- Stress
- Improves quality of live
- Herpes simplex type 2 infection

References

- Smith, P., What You Must Know About Vitamins, Minerals, Herbs and So Much More. Garden City Park, NY: Square One Publishers, 2020.
- Cicero, A., et al., “Effects of Siberian ginseng (Eleutherococcus senticosus maxim.) on elderly quality of life: a randomized clinical trial,” Arch Gerontol Geriatr Suppl 2004; 9:69-73.
- Hartz, A., et al., “Randomized controlled trial of Siberian ginseng for chronic fatigue,” Psychol Med 2004; 34(1):51-61.
- Bucci, L., “Selected herbals and human exercise performance,” Amer Jour Clin Nutr 2000; 72(Suppl):624S-636S.
- Dasgupta, A., et al., “Effect of Asian and Siberian ginseng on serum digoxin measurement by five digoxin immunoassays. Significant variation in digoxin-like immunoreactivity among commercial ginsengs,” Amer Jour Clin Pathol 2003; 119(2):298-303.

References (Cont.)

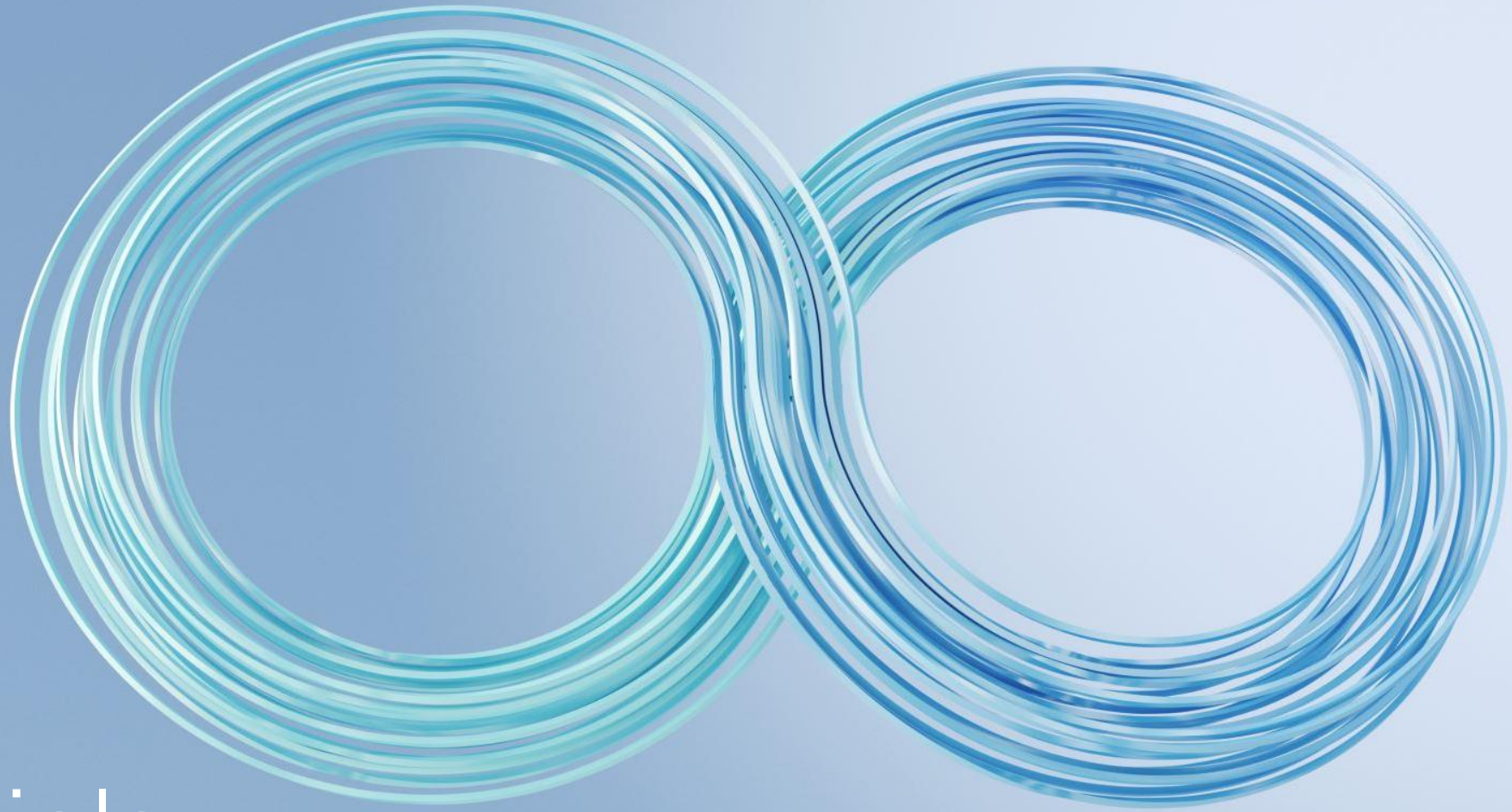
- Eschbach, L., et al., "The effect of Siberian ginseng (Eleutherococcus senticosus) on substrate utilization and performance," Int Jour Sport Nutr Exerc Metab 2000; 10(4):444-51.
- Fugh-Berman, A., "Herb-drug interactions," Lancet 2000; 355:134-38.
- Gabrielian, E., et al., "A double blind, placebo-controlled study of Andrographis paniculata fixed combination Kan Jang in the treatment of acute upper respiratory tract infections including sinusitis," Phytomedicine 2002; 9:589-97.
- Glatthaar-Saalmuller, B., et al., "Antiviral activity of an extract derived from roots of Eleutherococcus senticosus," *Antiviral Res* 2001; 50(3):223-28.
- Goulet, E., et al., "Assessment of the effects of eleutherococcus senticosus on endurance performance," Int Jour Sport Nutr Exerc Metab 2005; 15(1):75-83.

References (Cont.)

- Gyllenhaal, C., et al., Efficacy and safety of herbal stimulants and sedatives in sleep disorders," Sleep Med Rev 2000; 4(2):229-51.
- Hartz, A., et al., "Randomized controlled trial of Siberian ginseng for chronic fatigue," Psychol Med 2004; 34(1):51-61.
- Melchior, J., et al., "Double-blind, placebo-controlled pilot and phase III study of activity of standardized Andrographis paniculata Herba Nees extract fixed combination (Kan jang) in the treatment of uncomplicated upper-respiratory tract infection," Phytomedicine 2000; 7:341-50.
- Panossian, A., et al., "Evidence-based efficacy of adaptogens in fatigue, and molecular mechanisms related to their stress-protective activity," Curr Clin Pharmacol 2009; 4(3):198-219.
- Braun, L., and Cohen, M., (Eds.) Herbs and Natural Supplements. 4th Ed. Australia: Elsevier, 2015.
- Roxas, M., et al., "Colds and influenza: a review of diagnosis and conventional, botanical, and nutritional considerations," Altern Med Rev 2007; 12(1):25-48.

References (Cont.)

- Williams, M., “Immuno-protection against herpes simplex type II infection by Eleutherococcus root extract,” Int Jour Alt Complement Med 1995; 13:9-12.
- Sinclair, S., “Male infertility: nutritional and environmental considerations,” Alt Med Rev 2000; 5(1):28-38.
- Winther, K., et al., “Russian root (Siberian ginseng) improves cognitive functions in middle-aged people, whereas Ginkgo biloba seems effective only in the elderly,” Jour Neurological Sci 1997; 150:S90.
- Lin, Q., et al., “Inhibition of inducible nitric oxide synthase by Acanthopanax senticosus extract in RAW 264.7 macrophages,” Jour Ethnopharmacol 2008; 118(2):231-36.
- Lee, Y., et al., “The effects of A. senticosus supplementation on serum lipid profiles, biomarkers of oxidative stress, and lymphocyte DNA damage in postmenopausal women,” Bio Chem Bio Physico Res Comm 2008; 375(1):44-8.



Rhodiola

Rhodiola

- Rhodiola (Rhodiola rosea) is an herb used to modulate the stress response. It is a plant in the Crassulaceae family that grows in cold, mountainous regions such as the Arctic, central Asia, the Alps, Pyrenees, and Carpathian mountains. It contains 140 compounds including monoterpene alcohols and their glycosides, cyanogenic glycosides, aryl glycosides, phenylethanoids, phenylpropanoids and their glycosides, flavonoids, flavonolignans, proanthocyanins and gallic acid derivatives.
  - Dose: 200-600 mg qd in divided doses of standardized 3% rosavin and 1% salidroside

Functions of Rhodiola

- Adaptogen
- Improves physical performance
- Improves mental function
- Decreases depression
- Immunomodulation
- Antibacterial
- Cardioprotective
- Antioxidant
- Anti-inflammatory
- Lowers blood sugar
- Hepatoprotective
- Anti-cancer activity (anti-mutagenic, anti-proliferative, anti-metastatic)
- Neuroprotective
- Anti-anxiety

Functions of Rhodiola (Cont.)

- Catechol-O-methyltransferase (COMT) inhibitor
- Positive impact on hypothalamic-pituitary-adrenocortical (HPA) axis activity
- Modulates the central stress response via its effect on central biogenic amine neurotransmission and by enhancing blood brain barrier permeability to dopamine and serotonin precursors
- Increases β-endorphin levels to protect against stress-induced endorphin elevation
- Modulates release of HPA axis peptides
- Increases central neurotransmission by reducing or modulating excessive HPA axis activity

Side Effects and Contraindications For Rhodiola

- The following are possible mild side effects: allergy, irritability, insomnia, and fatigue at high doses.
- The following are some of the possible drug interactions that are associated with rhodiola.
  - Rhodiola has been shown to decrease the possible liver side effects associated with Adriamycin.
  - Rhodiola has been shown to have a synergistic effect with cyclophosphamide’s anti-tumor effect and decreases the risk of developing hepatotoxicity.
  - It alters the pharmacokinetic properties of the drug Losartan in animals. Therefore, do not use rhodiola with Losartan until more studies are completed.

Therapeutic Benefits for Rhodiola

- Normalizes cortisol and helps the patient deal with stress
- Insulin resistance/diabetes
- Cognitive function
- Sports performance enhancement
- Depression
- Anxiety
- Reward deficiency syndrome
- Nicotine dependence
- Improves work performance
- Altitude sickness

References

- Smith, P., What You Must Know About Vitamins, Minerals, Herbs and So Much More. Garden City Park, NY: Square One Publishers, 2020.
- Braun, L., and Cohen, M., (Eds.) Herbs and Natural Supplements. 4th Ed. Australia: Elsevier, 2015.
- Olsson, E., et al., “A randomised, double-blind, placebo-controlled, parallel-group study of the standardised extract shr-5 of the roots of Rhodiola rosea in the treatment of subjects with stress-related fatigue,” Planta Med 2009;75(2):105-12.
- Cropley, M., et al., “The effects of Rhodiola rosea L. extract on anxiety, stress, cognition and other mood symptoms,” Phytother Res 2015; 29(12):1934-39.
- Panossian, A., et al., “Rosenroot (Rhodiola rosea): traditional use, chemical composition, pharmacology and clinical efficacy,” Phytomed 2010; 17(7):481-93.

References (Cont.)

- Mao, J., et al., “Rhodiola rosea therapy for major depressive disorder: a study protocol for a randomized, double-blind, placebo-controlled trial,” Jour Clin Trials 2014; 4:170.
- Brown, R., et al., “Rhodiola rosea: a phytomedicinal overview,” HerbalGram 2002; 56:40–52.
- Kelly, G., “Rhodiola rosea: a possible plant adaptogen,” Altern Med Rev 2001; 6(3):293–302.
- Panossian, A., et al., “Stimulating effect of adaptogens: an overview with particular reference to their efficacy following single dose administration,” Phytother Res 2005; 19(10):819–38.
- Amsterdam, J., et al., “Rhodiola rosea L. as a putative botanical antidepressant,” Phytomed 2016; 23(7):770-83.

References (Cont.)

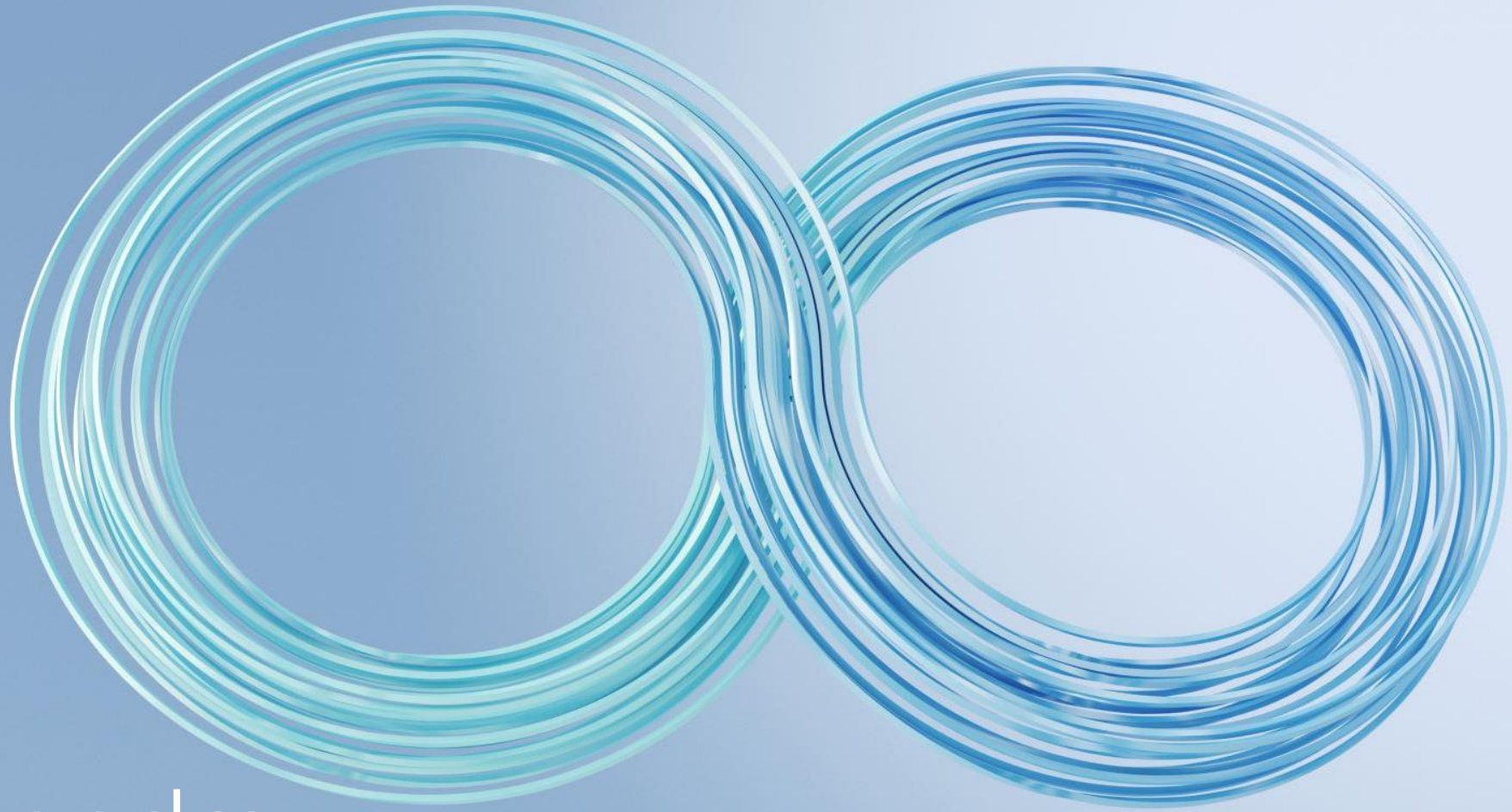
- Darbinvan V., et al., “Rhodiola rosea in stress induced fatigue--a double blind cross-over study of a standardized extract SHR-5 with a repeated low-dose regimen on the mental performance of healthy physicians during night duty,” Phytomed 2000; 7(5):365-71.
- Edwards, D., et al., “Therapeutic effects and safety of Rhodiola rosea extract WS 1375 in subjects with life-stress symptoms--results of an open-label study,” Phytother Res 2012; 26(8):1220-25.
- Noreen, E., et al., “The effects of an acute dose of Rhodiola rosea on endurance exercise performance,” Jour Strength Cond Res 2013; 27(3):839-47.
- Parisi, A., et al., “Effects of chronic Rhodiola Rosea supplementation on sport performance and antioxidant capacity in trained male: preliminary results,” Jour Sports Med Phys Fitness 2010; 50(1):57-63.
- Walker, T., et al., “Does Rhodiola rosea possess ergogenic properties?” Int Jour Sport Nutr Exercise Met 2006; 16(3):305-15.

References (Cont.)

- Abidov, M., et al., “Effect of extracts from Rhodiola rosea and Rhodiola crenulata (Crassulaceae) roots on ATP content in mitochondria of skeletal muscles,” Bull Exp Biol Med 2003; 136(6):585-87.
- De Bock K., et al., “Acute Rhodiola rosea intake can improve endurance exercise performance,” Int Jour Sport Nutr Exerc Metab 2004; 14(3):298-307.
- Shevtsov, V., et al., “A randomized trial of two different doses of a SHR-5 Rhodiola rosea extract versus placebo and control of capacity for mental work,” Phytomedicine 2003; 10(2–3): 95–105.
- Abidov, M., et al., “Extract of rhodiola rosea radix reduces the level of C-reactive protein and creatinine kinase in the blood,” Bull Exp Biol Med 2004; 138(1):63–64.
- Anon, “Rhodiola rosea,” Monograph. Altern Med Rev 2002; 7(5):421–423.
- Kelly, G., “Rhodiola rosea: a possible plant adaptogen,” Altern Med Rev 2001; 6(3):293– 302.

References (Cont.)

- Sarris, J., “Herbal medicines in the treatment of psychiatric disorders: a systematic review,” Phytother Res 2007; 28(1):703-16.
- Kim, S., et al., “Antioxidative effects of Cinnamomi cassiae and Rhodiola rosea extracts in liver of diabetic mice,” Biofactors 2006; 26(3):209-19.
- Bystritsky, A., et al., “A pilot study of Rhodiola rosea (Rhodax) for generalized anxiety disorder (GAD),” Jour Alter Complement Med 2008; 14(2):175-80.
- Iovieno, N., et al., “Second-tier natural antidepressants: review and critique,” Jour Effect Disord 2011; 130(3):343-57.
- Spanakis, M., et al., “Pharmacokinetic interaction between Losartan and Rhodiola rosea in rabbits,” Pharmacology 91(1-2):112-16.



Schisandra

Schisandra

- Schisandra chinensis is a phytoadaptogen that exerts effects on numerous systems in the body.
- Recommended daily dose
  - Dried fruit: 1.5-6 grams daily
  - Liquid extract: (1:2): 3.5-8.5 mL/day or 25-60 mL/week
  - Commonly used in combination with other adaptogens

Functions of Schisandra

- Increases endurance and accuracy of movement
- Increases mental performance
- Increases working capacity
- Generates alterations in the basal levels of nitric oxide
- Improves cortisol levels in the saliva and in the blood with subsequent effects on the blood cells, vessels, and central nervous system
- Antioxidant activity
- Hepatoprotective activity
- Anti-inflammatory actions
- Immunomodulatory
- Anti-diabetic
- Anti-obesity
- Nephroprotective
- Cardioprotective effects

Functions of Schisandra (Cont.)

- Anti-allergic
- Anti-cancer activity
- Neuroprotective
- Anti-spasmodic activity in the GI tract
- Antibacterial
- Lipid lowering
- Inhibits leukotriene formation
- Enhances exercise endurance
- Improves bone mineralization
- Platelet-activating factor antagonist
- Anxiolytic agent
- Improves erectile function
- Modulates neurotransmitter function: noradrenergic, dopaminergic, GABAergic and glutamatergic systems

Side Effects and Contraindications For Schisandra

- Possible adverse reactions are related to mild gastrointestinal discomfort.
- Little information is available on toxicity.
  - There may be an interaction between drugs that are metabolized by CYP3A4 system. Therefore, use with caution with drugs that are metabolism through this system. Do not use medications that have a narrow therapeutic index with Schisandra in order to avoid drug toxicity.
  - Do not use Schisandra with drugs metabolized by UGT1A3 system. There may be an herb-drug interaction.
  - There may be an elevation of serum levels of drugs that are P-glycoprotein substrates when taken with this herb. Therefore, use Schisandra with caution with these medications. In addition, if the drug has a narrow therapeutic range, then do not use with Schisandra.

Therapeutic Benefits of Schisandra

- Asthenia
- Neurosis
- Depression
- Schizophrenia
- Alcoholism
- Impaired visual function
- Hypotension
- Cardiotonic disorders
- Influenza
- Chronic sinusitis

Therapeutic Benefits of Schisandra (Cont.)

- Memory maintenance
- Otitis
- Neuritis
- Otosclerosis
- Pneumonia
- Allergic dermatitis
- Acute gastrointestinal diseases
- Gastric hypo- and hyper-secretion
- Chronic gastritis
- Stomach ulcers
- Duodenal ulcers

Therapeutic Benefits of Schisandra (Cont.)

- Wound healing
- Liver dysfunction
- Mediterranean fever
- Chronic cough
- Palpitations
- Insomnia
- Night sweats
- Dyspnea
- Irritability
- Asthma

References

- Braun, L., and Cohen, M., (Eds.) Herbs and Natural Supplements. 4th Ed. Australia: Elsevier, 2015.
- Panossian, A., et al., “Pharmacology of Schisandra chinensis Bail.: an overview of Russian research and uses in medicine,” Jour Ethnopharmacol 2008; 118(2):183-212.
- Yan, T., et al.,” The effect of Schisandra chinensis extracts on depression by noradrenergic, dopaminergic, GABAergic and glutamatergic systems in the forced swim test in mice,” Food Funct 2016; 7(6):2811-19.
- Liu, C., et al., “Chemical composition and antioxidant activity of essential oil from berries of Schisandra chinensis (Turcz.),” Bull Natural Product Res 2012; 26(23):2199-203.
- Pu, H., et al., “Correlation between antistress and hepatoprotective effects of schisandra lignans was related with an antioxidative actions in liver cells,” Evid-Based Complement Altern Med 2012; 2012: 161062.

References (Cont.)

- Park, S., et al., “Schisandra chinensis a-iso-cubebenol induces heme oxygenase-1 expression through P13K/Akt and Nrf2 signaling and has anti-inflammatory activity in Porphyromonas gingivalis lipopolysaccharide-stimulated macrophages,” Int Immunopharmacol 2011; 11(1):1907-15.
- Chen, X., et al., “Chemical composition and antioxidant activity of the essential oil of Schisandra chinensis fruits,” Natural Product Res 2012; 26(9):842-49.
- Park, J., et al., “Antihypertensive effect of gomisin A from Schisandra chinensis on angiotensin II-induced hypertension via preservation of nitric oxide bioavailability,” Hypertens Res 2012; 35(9):928-34.
- Jo, S., et al., “In vitro and in vivo antihyperglycemic effects omija (Schisandra chinensis) fruit,” Inter Jour Mol Sci 2011; 12(2):1359-70.
- Jeong, E., et al., “The effects of lignan-riched extract of Schisandra chinensis on amyloid-B-induced cognitive impairment and neurotoxicity in the cortex and hippocampus of mouse,” Jour Ethnopharmacol 2013; 146(1):347-54.

References (Cont.)

- Hwang, D., et al., “A compound isolated from Schisandra chinensis induces apoptosis,” Bioorganic and Medicinal Chem Lett 2011; 21(20):6054-57.
- Kim, M., et al., “Antiplatelet aggregation activity of lignans isolated from Schisandra chinensis fruits,” Jour Korean Soc Applied Biological Chem 2010; 53(6):740-45.
- Yang, J., et al., “Relaxant effects of Schisandra chinensis and its major lignans on agonists-induced contraction in guinea pig ileum,” Phytomedicine 2011; 18(13):1153-60.
- Lee, T., et al., “Neuroprotective effects of Schisandrin B against transient focal cerebral ischemia in Sprague-Dawley rats,” Food Chem Toxicology 2012; 50(12):4239-45.
- Pan, S., et al., “Schisandrin B from Schisandra chinensis reduces hepatic lipid contents in hypercholesterolemic mice,” Jour Pharm Pharmacol 2008; 60(3):399-403.
- Wang, H., et al., “Anti-diabetic effect of a traditional Chinese medicine formula,” Food Function 2012; 3(11):1161-69.

References (Cont.)

- Kim, H., et al., “The role of the lignan constituents in the effect of Schisandra chinensis fruit extract on penile erection,” Phytotherapy 2011; 25(12):1776-82.
- Lin, S., et al., “Molecular mechanism of apoptosis induced by schizandrae-derived lignans in human leukemia HL-60 cells,” Food Chem Toxicol 2008; 46(2):590-97.
- Caichompaoo, W., et al., “Optimization of extraction and purification of active fractions from Schisandra chinensis (Turcz.) and its osteoblastic proliferation stimulating activity,” Phytother Res 2009; 23(2):289-92.
- Gurley, B., et al., “Pharmacokinetic herb-drug interactions (Part 2): drug interactions involving popular botanical dietary supplements and their clinical relevance,” Planta Medica 2012; 78(13):1490-514.
- Choi, I., et al., “Antimicrobial activity of medicinal herbs against Salmonella gallinarum and Staphlococcus epidermis,” Korean Jour Poultry Sci 2009; 36(3):231-38.

References (Cont.)

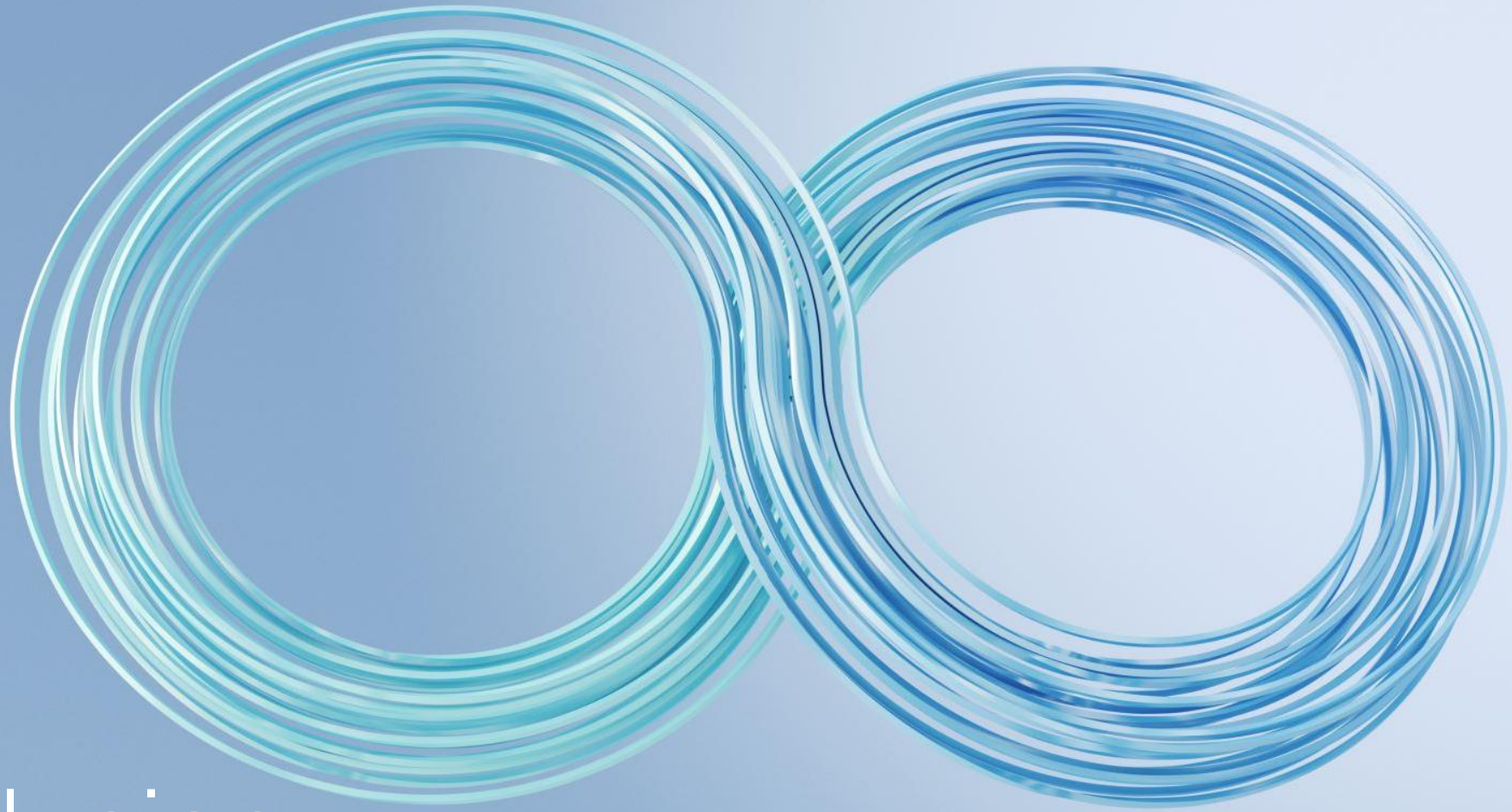
- Fan, L., et al., “Effect of Schisandra chinensis extract and Ginkgo biloba extract on the pharmacokinetics of talinolol in healthy volunteers,” Xenobiotica 2009; Fate of Foreign Comp Biol Syst 2009; 39(3):249-54.
- Tsi, D., et al., “Evalution on the combined effect of Sesamin and Schisandra extract on blood fluidity,” Bioinformation 2008; 2(6):249-52.
- Aslanyan, G., et al., “Double-blind, placebo-controlled, randomised study of single dose effects of ADAPT-232 on cognitive functions,” Phytomedicine 2010; 17(7):494-99.
- Narimanian, M., et al., “Impact of Chisan (ADAPT-232) on the quality-of-life and its efficacy as an adjunct in the treatment of acute non-specific pneumonia,” Phytomedicine 2005;12(10):723-29.
- Liu, C., et al., “Strong inhibition of deoxyschizandrin and schisantherin A toward UDP-glucuronosyltransferase (UGT) 1A3 indicating UGT inhibition-based herb-drug interaction,” Fitoterapia 2012; 83(8):1415-19.

Combination Therapies

- An animal study showed that S. chinensis and R. rosea exert an anti-stress effect in rats subjected to stress by balancing the HPA axis, and possibly by reducing the expression of c-Fos in the hypothalamus.
  - Xia, N., et al., “Schisandra chinensis and Rhodiola rosea exert an anti-stress effect on the HPA axis and reduce hypothalamic c-Fos expression in rats subjected to repeated stress,” Exp Ther Med 2016; 11(1):353-59.

Art of the Practice of Medicine and Pharmacy

- A study showed that Panax ginseng, Rhodiola rosea, and Schisandra chinensis were adaptogens that had numerous functions and their effects were found to be very different in patients depending on circumstances such as age, gender, environment, diet etc.
- Thus, in most cases, the art of the practice of medicine and pharmacy is to suggest these herbs after a complete evaluation of overall health status of the patient has been completed.
  - Chan, S., “Panax ginseng, Rhodiola rosea and Schisandra chinensis,” Int Jour Food Sci Nutr 2012; 63(Suppl 1):75-81.



Conclusion

Conclusion

- Stress is an inevitable part of life.
- Stress management is essential for both healthy people as well as individuals with major disease processes.
- For example, this study suggests that psychological stress plays a significant role in the onset and progression of diabetes and cancer.
  - Afrisham, R., et al., "The influence of psychological stress on the initiation and progression of diabetes and cancer," Int Jour Endocrinol Metab 2019; 17(2):e67400.
- The great news is that the identification of the pathways triggered by stress open a new avenue for the understanding of molecular mechanisms by which major diseases can be managed or even prevented.
- Stress reduction techniques, nutrients, adaptogens, calming herbs, and other therapeutic modalities have been shown to positively influence the stress response.

Thank You!

Questions?