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Introduction

Stress is a state of disharmony or threatened homeostasis (Chrousos & Gold, 1992). The maintenance of homeostasis in stages of internal or external challenges, called stressors, requires constant adjustments of hormonal, behavioral, and autonomic functions (Miller & O'Callaghan, 2002). Stressors are chemicals, external stimuli, environmental conditions, or biological agents that cause stress to an individual by triggering the hypothalamic-pituitary-adrenal (HPA) axis stress response (Sato et al., 2006). The nuances of life may bring about unwanted stress to the human body. Some of the primary causes of stress in America include work, finances, relationships, and health. There are numerous physical and psychological symptoms associated with long-term "chronic" stress, which include fatigue, frustration, irritability, insomnia, frequent headaches, chest and back pain, weakness, and weight gain or weight loss ("50 Signs & Symptoms of Stress,"; Sinha, 2008). These symptoms of stress are associated with depression, anxiety, hypertension, diabetes, cardiovascular disease, stroke, and even cancer (Chrousos & Gold, 1992).

Stress causes a systemic elevation of the steroid hormone cortisol. The release of cortisol and catecholamines such as epinephrine and norepinephrine are important hormonal mediators of the body's response to stress, which is controlled by the HPA axis and sympathetic nervous system (SNS). Respectively, they have been noted to play a role in the ability of stress to promote disease (Miller & O'Callaghan, 2002). Cortisol levels, in plasma, increase within 15 minutes following acute stress but return to basal levels once effective coping is established (Grossi et al., 2005). Permanent or repeated exposure to stressors that one cannot adequately

cope with may contribute to a prolonged activation of the HPA axis (Grossi et al., 2005). The human HPA axis meets the demands of stress primarily through the synthesis and secretion of three hormones, corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol (Miller & O'Callaghan, 2002). In normal amounts cortisol, which is synthesized from cholesterol, helps to stimulate gluconeogenesis, which is the formation of glucose in an early fasting state (Lee, 2015). Cortisol also helps to suppress the immune system's inflammatory response to mediators of inflammation (Lee, 2015). However, chronic psychological and physical stress can result in elevated cortisol levels. Some of the symptoms of elevated cortisol levels include anxiety, depression, hypertension, osteoporosis, stress-related fatigue, insulin resistance, and obesity (Pawar & Shivakumar, 2012). Stress-related fatigue is a form of occupational stress, which can often induce long-term exhaustion and diminished interest, producing a condition known as burnout syndrome (Maslach, Schaufeli, & Leiter, 2001; Olsson, von Scheele, & Panossian, 2009; Weber & Jaekel-Reinhard, 2000). This syndrome is characterized by high levels of emotional exhaustion (EE) and depersonalization (DP) in relationships with a reduced level of personal accomplishment (PA) (Maslach et al., 2001). Growing evidence suggests a significant positive association between increased cortisol levels, weight gain, and enhanced secretion of proinflammatory hormones and cytokines (adipokines) by adipose tissue deposits (Kyrou & Tsigos, 2009).

Adaptogens are plants that help your body adapt or adjust to stress. These substances elicit, in an organism, a state of nonspecifically raised resistance to a variety of physical, chemical, and biological stressors, allowing them to counteract stressor signals and to adapt to exceptional strain (Chen, Liou, & Chang, 2008; Sato et al., 2006; Wagner, Nörr, & Winterhoff, 1994). The term “adaptogens” was first brought about by Russian scientist Dr. Nikolai Lazarev. He describes them

as medicinal plants that can enhance the so-called "state of non-specific resistance" of an organism to stress (Brekhman & Dardymov, 1969). True adaptogens are non-toxic, protect against stress, stimulate mental performance, and normalize body functions (Brekhman & Dardymov, 1969). Numerous previous studies have shown how these herbs have been beneficial in people experiencing chronic stress.

Methods

A robust search for clinical journal articles and reviews on stress, adaptogens, and cortisol was completed on the PubMed and CINAHL (EBSCO host). Some keywords included "chronic stress AND cortisol," "adaptogens AND chronic stress," "cortisol AND adaptogens." The aim is to review the scientific literature published regarding the effects of three adaptogen herbs (Ashwagandha, Rhodiola, and Bacopa) on cortisol levels and the symptoms associated with physical and psychological stress. Another aim is to examine the effects of these adaptogens on fatigue, memory, and cognitive function. More specifically, I will be examining the active components in these herbs and the various concentrations and dosages used in the studies. These adaptogens contain active phytochemicals at specific standardization percentages, which help account for their adaptogenic functions. They include withanolides in Ashwagandha, rosavins and salidrosides in Rhodiola, and bacosides in Bacopa. In this literature review, I draw upon scholarly articles evaluating the association between these adaptogens, their phytochemicals, symptoms of stress, and levels of cortisol. The articles are mainly human clinical trials. This review will also discuss the history, alternative names, and other health benefits of these three adaptogens.

Ashwagandha

Ashwagandha, also known as, *Withania somnifera* or Indian Ginseng, is an Indian Ayurvedic herb whose plant parts have been credited with antitumor, anxiolytic, antiarthritic, GABA-mimetic, cognitive, anti-cortisol, adaptogenic, and energy benefits for over six centuries (N Singh, 2011). A prospective, randomized, double-blind, placebo-controlled study examined the safety and efficacy of a high-concentration of full-spectrum (KSM-66) extract of Ashwagandha root in reducing stress and anxiety in 64 adults with a history of chronic stress. The study demonstrated that KSM-66 Ashwagandha extract significantly decreased feelings of stress, depression, anxiety and significantly increased general well-being after 60 days based on three different extensively used sets of stress scales ($p< 0.0001$) (Chandrasekhar, Kapoor, & Anishetty, 2012). Also, there was a statistically significant decrease in serum cortisol levels after 60 days ($p< 0.0006$) (Chandrasekhar et al., 2012). There were a few reports of adverse effects in both the placebo and the treatment group such as nausea, constipation, and drowsiness. The KSM-66 Ashwagandha dosage was 600 mg standardized to at least 5% withanolides (Chandrasekhar et al., 2012).

A similar double-blind, randomized, placebo-controlled trial evaluated the safety and efficacy of a standardized root extract of Ashwagandha on body weight management in 52 adults experiencing chronic stress. KSM- 66 Ashwagandha root was effective in decreasing various psychological and physical symptoms of chronic stress (Choudhary, Bhattacharyya, & Joshi, 2016). There were statistically significant changes from baseline to four and eight weeks in primary outcome measures such as various questionnaire scores, serum cortisol levels, body weight, and body mass index (BMI). The decreased BMI and body weight may be a result of the decreased cortisol levels since diet history was not assessed. Perceived Stress Score (PSS)

reduction was 22.1% in the fourth week (p=.0025) and 32.7 % in the eighth week (p< .0001). The difference between the mean reductions in serum cortisol levels in the treatment and placebo groups were noted after the fourth week (p=.0328) and eighth week (p=.0019) of treatment. However, there were no statistically significant positive changes from baseline in blood pressure, respiratory rate, and pulse rate (Choudhary et al., 2016).

A double-blind, placebo-controlled study examined the efficacy of 500 mg of Ashwagandha in 39 patients diagnosed with ICD-10 anxiety disorder. At six weeks, several more patients met anxiolytic response criteria in the drug group (88.2%) as compared with the placebo group (50%), which was statistically significant (p< 0.026) (Andrade, Aswath, Chaturvedi, Srinivasa, & Raguram, 2000). The herb was well-tolerated and did not cause more adverse effects than the placebo (Andrade et al., 2000).

Rhodiola

Rhodiola, also known as *Rhodiola rosea*, or "golden root,*"* has been used for its antioxidant, cardioprotective, and anticancer properties, and for its resistance to physical, chemical, and biological stressors (Chen et al., 2008; Kelly, 2001). A recent study examined the antioxidant potential of three adaptogen extracts, *Rhodiola rosea*, *Eleutherococcus senticosus and Emblica officinalis*. The study found Rhodiola had the highest potential for single oxygen scavenging, hydrogen peroxide scavenging, ferric reducing, ferrous chelating, and protein thiol protection (Chen et al., 2008). These protocols and methods measure the antioxidant potential of the substance. Rhodiola also had the highest polyphenol content; polyphenols combat free radical formation and decrease the potentially detrimental effects caused by oxidative stress (Chen et al., 2008).

Patients experiencing burnout syndrome from stress-related fatigue have been found to present a relatively high cortisol response to awakening stress (Grossi et al., 2005). A randomized, double-blind, placebo-controlled, parallel group study of 60 individuals examined the effects of a 3% rosavin standardized extract of SHR-5 Rhodiola at 576 mg. The post-treatment cortisol response to awakening stress was significantly reduced in the group that had received SHR-5 for 28 days than in the control group (Olsson et al., 2009).

A double-blind, placebo-controlled pilot study examined the stimulating and adaptogenic effects of 100 mg of SHR-5 Rhodiola extract on stress-induced fatigue in 40 students during an examination. The study displayed statistical significance in physical fitness, mental fatigue, neuro-motoric tests ($p < 0.01$) and general well-being ($p < 0.05$) in 20 days (Spasov, Wikman, Mandrikov, Mironova, & Neumoin, 2000). Physical fitness was measured using two parameters: physical work capacity via the veloergonomic test PWC-170 and an increase in pulse rate following the ergometric test compared with the pulse rate just before. The neuromotoric tests were the spiral maze test, where subjects moved a "pen" from the center of a spiral without touching small obstacles, and the tapping test. Mental fatigue was assessed by mental work capacity via a correction of text test.

A similar double-blind, cross-over study repeated low-dose administration of standardized extract SHR-5 Rhodiola extract, but this time at a standardized 2.6 % salidroside dosage of 170 mg. The study presented statistically significant improvement in five mental fatigue and cognitive tests taken by 56 Armenian physicians. A group comparison change of 20 % ($p < 0.01$) was seen between the treatment group in the period before the Rhodiola was administered and two weeks after the Rhodiola was administered (Darbinyan et al., 2000). Anti-fatigue effects were noted without any reported adverse reactions or side-effects in a situation of

a moderate level of stress-related fatigue (Darbinyan et al., 2000). Under chronic stress, there is often difficulty concentrating due to physical and mental fatigue. The physician's night duty working schedule was considered an abnormal stressful condition since it goes against the normal circadian rhythm.

Another study viewed the effects of SHR-5 Rhodiola extract's effect on stress and fatigue in 161 Russian military cadets. The study displayed statistically significant data based on a mean antifatigue index (AFI) using two doses of Rhodiola extract (Shevtsov et al., 2003). AFI mean values were 1.0385 for two capsules (370 mg) and 1.0195 for three capsules (555 mg), while the figure for the placebo group was 0.9046. ($p < 0.001$). There was no significant difference observed between the two dosage groups of 370 mg and 555 mg a day (Shevtsov et al., 2003).

A multicenter, non-randomized, open-label, single-arm study administered 400 mg of concentrated Rhodiola WS 1375 treatment to 101 subjects. 200 mg of Rhodiola WS 1375 (as dry extract) is equivalent to 300–1000 mg of Rhodiola roots and rhizomes (Edwards, Heufelder, & Zimmermann, 2012). The study presented a statistically significant improvement between baseline and week four body mass index and baseline scores of Perceived Stress Questionnaire (PSQ), Multidimensional Fatigue Inventory 20 (MFI-20), Multidimensional Moodstate Questionnaire (MDMQ), and Sheehan Disability Scale (SDS) ($p < 0.0001$) (Edwards et al., 2012). The positive benefits were noted in three days, with adverse events consisting of mostly of mild intensity and included nervous system disorders and gastrointestinal disorders; no serious adverse events were reported (Edwards et al., 2012). No placebo was used in the study, which may indicate selection bias. While some evidence suggests the herb may be helpful for enhancing physical performance and alleviating mental fatigue, methodological flaws limit accurate assessment of efficacy (Ishaque, Shamseer, Bukutu, & Vohra, 2012).

Nevertheless, in a double-blind, randomized controlled trial, 30 subjects were assigned to either Rhodiola (SHR-5 containing 144mg Rhodiola, 2.7% rosavins) or ADAPT-232 (140 mg of a proprietary blend including Schizandra, Rhodiola, and Eleutherococcus) for one week to compare the results. Ultra-weak photon emission (UPE) was measured on the dorsal side of the hand before and after one week of supplementation. UPE is known as one type of spontaneous photon emission that can be detected with a highly sensitive single photon counting photomultiplier tube (PMT) from the surface of human bodies (Edwards et al., 2012). This test may reflect the body's oxidative cellular damage. In addition, subjects were evaluated for perceived levels of stress and fatigue. After one week, subjects in the Rhodiola group experienced a significant decrease in UPE and levels of fatigue ($p = 0.027$) ($p=0.049$) (Schutgens et al., 2009).

Bacopa

Bacopa, *Bacopa monniera*, has been used in traditional Ayurvedic medicine for various reasons including benefits regarding adaptogenic properties, memory decline, inflammation, pain, pyrexia, epilepsy and as a sedative for almost three centuries (Benson et al., 2014; Russo & Borrelli, 2005). The burnout syndrome, again, can cause physical and mental fatigue, and cognitive weariness, and is believed to be a result of ineffective coping with chronic stress (Melamed et al., 1999).

A double-blind, placebo-controlled, independent-group study assessed the chronic effects of 300 mg of Bacopa on cognitive function in 46 subjects. The study displayed significantly improved speed of visual information processing measured by the IT task, learning rate and memory consolidation measured by the Rey Auditory Verbal Learning Test (AVLT) ($p< 0.05$),

and state anxiety ($p < 0.001$) after 12 weeks (Stough et al., 2001). Adverse effects included headaches, nausea, cramps and other effects reported by both the treatment and placebo groups. The active ingredients were standardized to no less than 55% of combined bacosides A and B.

Another double-blind, randomized controlled trial assessed various memory functions and measuring anxiety levels in 76 subjects. The study exhibited no significant effect of chronic administration of Bacopa on measures of short-term memory, working memory, attention, or the retrieval of information from long-term memory acquired pre-experimentally ($p < 0.05$) (Roodenrys et al., 2002). The only measures to show significant effects were the delayed recall of word pair tasks and new information retention ($p < 0.05$), ($p < 0.01$). The dosage administered was 300 mg for subjects under 90 kg, and 450 mg for subjects over 90 kg, which is equivalent to 6g and 9g dried rhizome, respectively (Roodenrys et al., 2002).

A double-blind, randomized, placebo-controlled, non-crossover, parallel trial examined the effects of 300 mg of Bacopa, which was standardized to 11.4 % total bacosides, in 60 medical students studying in India. The study found statistically significant improvement in the tests relating to cognitive function after using Bacopa. These tests included various neuropsychological tests and computerized tests (Kumar et al., 2016). The neuropsychological measures for the efficiency of attention, freedom from distractibility, and working memory improved significantly with the use of Bacopa ($p < 0.05$) as was measured by digit span backward test. The logical memory test, known to be a measure of immediate recall of logical material and language comprehension, also significantly improved ($p < 0.05$). However, there were no results or charts pertaining to the computerized tests. Blood biochemistry also showed a significant increase in serum calcium levels ($p < 0.05$) (Kumar et al., 2016).

Conclusion

The physical and psychological symptoms of chronic stress can negatively affect aspects of an individual's life. Along with elevated cortisol levels, stress-related fatigue, burnout syndrome, irritability, weight gain, and poor concentration, chronic stress has also been associated with various chronic diseases (Chrousos & Gold, 1992). Adaptogens help the body to adjust to and positively respond to stress by normalizing cortisol, decreasing fatigue, and improving cognition. Adaptogens contain other beneficial properties such as antioxidant, cardioprotective, immune, analgesic, and energy properties (Chen et al., 2008). Therefore, Ashwagandha, Rhodiola, and Bacopa consumed at standardized dosages may be beneficial for individuals suffering from physical or psychological symptoms of chronic stress. Other stress relieving actions such as yoga, controlled breathing, exercise, and consuming a balanced diet are sometimes ineffective alone. Due to the normalizing effect of adaptogens, a combination of adaptogens may potentially be more beneficial in the reduction of the physical and psychological symptoms of chronic stress. Also, adaptogens paired with other herbs or dietary supplements may also have a potentially synergistic effect, regarding stress relief. Thus, additional clinical trials, which use various dosages and concentrations of these adaptogens in combination with other herbs or dietary supplements, should be conducted to test further this notion.

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