

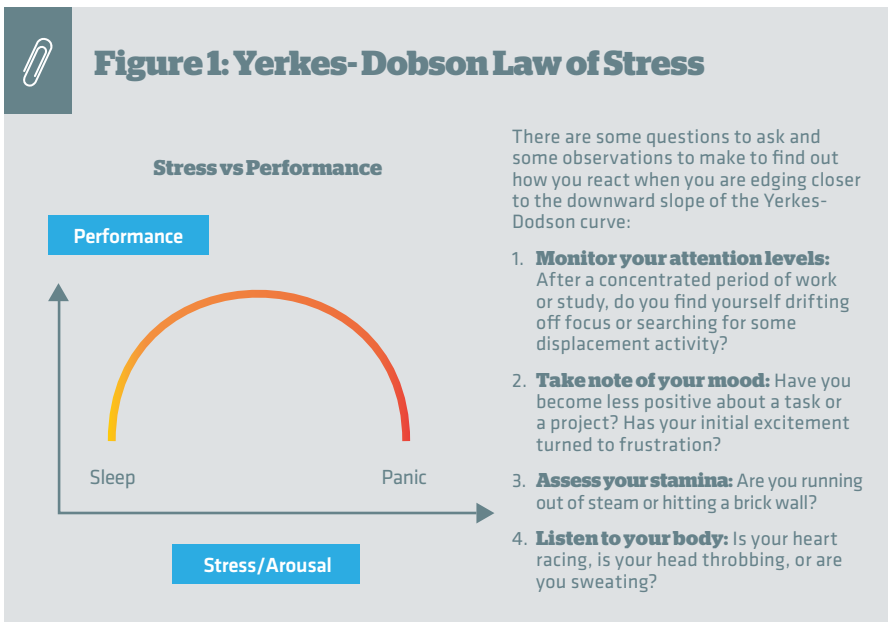
Herbal and Nutritional Solutions for Adrenal Support



Stress is a fact of life. Stress can be both good and bad. It can enhance performance and our lives, it can be the source of motivation to succeed, but it can also be the dark cloud that hinders morale, performance and relationships.

People are capable of incredible feats of sporting excellence, outstanding bravery or creative brilliance; all of which may be encouraged by healthy stress levels. Severe and prolonged distress however, has been linked to mental health issues. One in four people suffer from depression at some time in their life¹ and stress management strategies are an important component of treatment protocols. In Australia, 25% of the population reported experiencing moderate to severe stress, 40% cited work as a source of stress and 23% reported a 'strong to very strong' impact of stress on mental health.

Physiologically, stress causes disruption to endocrine and neural pathways; specifically, the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system. Stress activates the body's fight-or-flight response; heart rate and blood pressure go up and hormones, like adrenaline and cortisol, are released into the blood stream. In the short term, these can boost performance, focus, memory and creativity. More than a century ago, Harvard researchers, Robert Yerkes and John Dodson, calibrated the relationship between stress arousal and performance, finding that as stress goes up, so does efficiency and performance. But, at a certain level of stress, its benefits disappear and performance declines.³ (Refer to Figure 1).



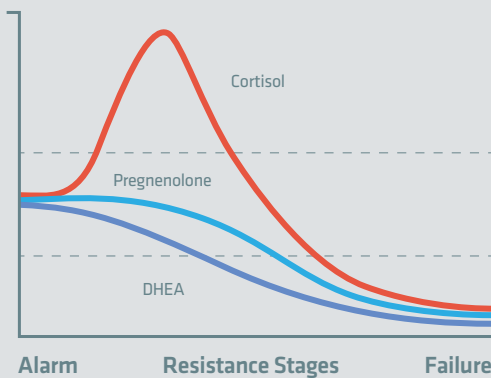
Everyone reacts to stress in different ways; a certain level of stress may energise one person, but debilitate another. The trick is to identify our own stress-response pattern and find out how to manage stress to make it work for us. Figure 2 is a simple illustration of the progression of the stress response and its effects on our hormones. Prolonged stress leads to hormonal decline and is associated with a higher prevalence of exhaustion disorder and stress-induced symptoms.⁵



Clinical Presentations of Stress⁴

- Stress and anxiety
- Adrenal exhaustion and burnout
- Fatigue
- Low stamina and poor performance
- Depression
- Headaches
- Sexual dysfunction or fertility issues
- Poor immunity
- Gastrointestinal complaints
- Advanced ageing
- Poor cognition and mental performance
- Sleep disturbances

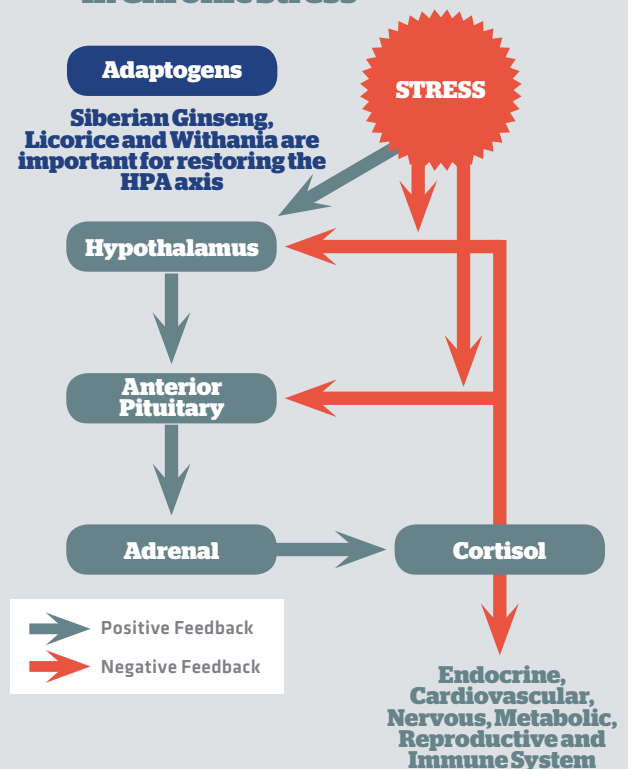
Figure 2: Hormone Stress Response⁵



Normalising Stress Hormones with Adaptogens

Adaptogens are medicinal plants that augment resistance to stress and increase concentration, performance and endurance during fatigue.⁶ Adaptogens are used as a tonic for the entire body to restore health and vitality. Acute dosing with adaptogen herbs has been shown to activate corticosteroid formation while repeat dosing normalises the levels of stress hormones, such as adrenocorticotrophic hormone (ACTH).⁷⁻¹² Adaptogens appear to increase the ability of the stress system to respond to a range of stressful stimuli in a manner that tends to preserve homeostasis, particularly by modulating the biosynthesis of eicosanoids, regulating the basal level of arachidonic acid, and most importantly, by regulating the hyperactivation of the HPA axis due to the regulation of corticosteroids in response to acute and chronic stress.^{13,14} The effect of adaptogens on the HPA axis response to chronic stress is demonstrated in Figure 3.

Figure 3: The Effect of Adaptogens on the Positive Feedback Loop in Chronic Stress¹⁵



In situations of chronic stress, the mechanism of negative feedback is lost. Adaptogens restore the functioning of the axis. The effects of adaptogens become somewhat clearer when it is recalled that stress is a defensive response to external factors, and that it stimulates the formation of endogenous “messenger” substances such as catecholamines, prostaglandins, cytokines, NO, and platelet-activating factor, which in turn activate other factors that may either counteract stress or, conversely, induce or facilitate disease. According to this concept, the “stress-executing” or “switch-on” mechanism activates the sympathoadrenal system and over the longer term also activates the HPA axis, together with various regulators of cell and organ function.^{8,16}

Counteracting this is the “switch-off” system, which protects cells and organ systems, and thus the entire organism, from damaging overreaction. This switch-off system includes antioxidant enzymes such as catalase, glutathione peroxidase, and superoxide dismutase; interleukins that downregulate various aspects of the immune response; certain corticosteroids and eicosanoids such as prostaglandin E2; and anti-inflammatory mediators. Excessive activity of the stress system is associated with increased arousal or anxiety, increased blood pressure, gastrointestinal dysfunction, and suppression of the immune response.^{17,18,19} The net result of this is adrenal exhaustion and burn-out.

Although adaptogens share the characteristic of improving resistance to stress, each adaptogen has its own unique profile and mechanism of action within the body. Many work directly on the HPA axis; modulating its function, whilst others affect receptor sensitivity, hormones, prevent the degradation of stress hormones or act directly on the biological consequences of stress within the body.^{20,21} Mechanisms of action of a selection of adaptogens is summarised in Figure 4.



Figure 4: Potential Mechanisms of Action of Selected Adaptogens

Withania



- **Modulates HPA axis and related effects:** Binds to GABA receptors, thereby acting as a GABA mimetic agent. This may explain the calming and anti-stress properties of Withania; reduces stress-induced increases in the number of dopamine receptors in the corpus striatum (within the cerebrum of the brain); has a corticosteroid-sparing effect, therefore protecting against stress-induced damage.⁴⁵
- **Secondary actions which may support stressed individuals:** Tonic, aphrodisiac, anti-inflammatory, mild sedative, neuroprotective, antioxidant, immune modulating.⁴⁶ Withania has also been shown in humans and animals to increase cortical muscarinic acetylcholine receptor capacity (which may be linked to cognitive function).

Siberian Ginseng



- **Direct HPA axis support:** Siberian Ginseng has been shown to accumulate in the adrenal gland, reduce adrenal hypertrophy and reduce adrenal depletion in response to stress.⁴⁶
- **Increases Heat Shock protein Hsp72:** In combination with other adaptogens, Siberian Ginseng has been shown to increase basal levels of Hsp72. This protein is produced in response to stress and protects the body from damage and cellular apoptosis.⁶⁵
- **Secondary actions which may support stressed individuals:** tonic, immune modulating, hormone modulating, mild stimulant.⁴⁶

Licorice



- **HPA axis potentiator:** Glycyrrhizin is a potent 11-beta hydroxysteroid dehydrogenase inhibitor (an enzyme which inhibits the breakdown of cortisol). Therefore, it can increase circulating cortisol, support the adrenal gland and potentiate the stress response.⁵²
- **Modulator of various hormones and neurotransmitters:** By interacting with hormonal receptors and inhibiting various enzymes within the body, the active constituents in Licorice have been shown to influence levels of dopamine, epinephrine, norepinephrine, oestrogen, prolactin and cortisone.
- **Secondary actions which may support stressed individuals:** anti-inflammatory, spasmolytic, immune modulation.

Herbal Support to Relieve the Symptoms of Stress

Withania somnifera (Withania)

Withania somnifera (also known as Ashwagandha or Withania) root is an important 'rasayana' herb in traditional Ayurvedic medicine where it has been used for over 3000 years to improve vitality and longevity, and to promote physical and mental health.²²⁻²⁴ Withania acts as an adaptogen, tonic, anti-anaemic, mild sedative, immune modulator, antioxidant and anti-inflammatory. Today, Withania is amongst the most widely researched adaptogens and scientific evidence supports many of these traditional actions and indications.²⁵

Withania's Clinical Indications

- Debility, fatigue, convalescence, nervous exhaustion²⁶
- Stress, anxiety and mood disorders²⁷
- Imbalanced cortisol and DHEA (high doses)²⁵
- Reduced mental or physical performance, insomnia^{25,28,29}
- Active individuals; may improve muscle strength and recovery as well as cardiorespiratory endurance
- Poor growth and anaemia, especially in children³⁰
- Fatigue, post-viral syndromes, poor immune function, adjunctive treatment for cancer²⁵
- Sexual and reproductive therapy, including impotence, male infertility, and female sexual health²⁹
- Chronic diseases, especially those marked by inflammation, such as arthritis³¹
- As a general tonic for disease prevention and for the elderly³²
- May be hepatoprotective³³
- Adjunctive therapy in chemotherapy and radiation²⁵

Advantages of Withania as KSM-66 Ashwagandha

There are many Withania extracts available and each may differ in composition, therapeutic activity, clinical validation and excipient profile. KSM-66 Ashwagandha is a clinically proven, standardised extract of Withania root. Key advantages of KSM-66 Ashwagandha are summarised in Table 1.

Table 1: Advantages of Withania as KSM-66 Ashwagandha

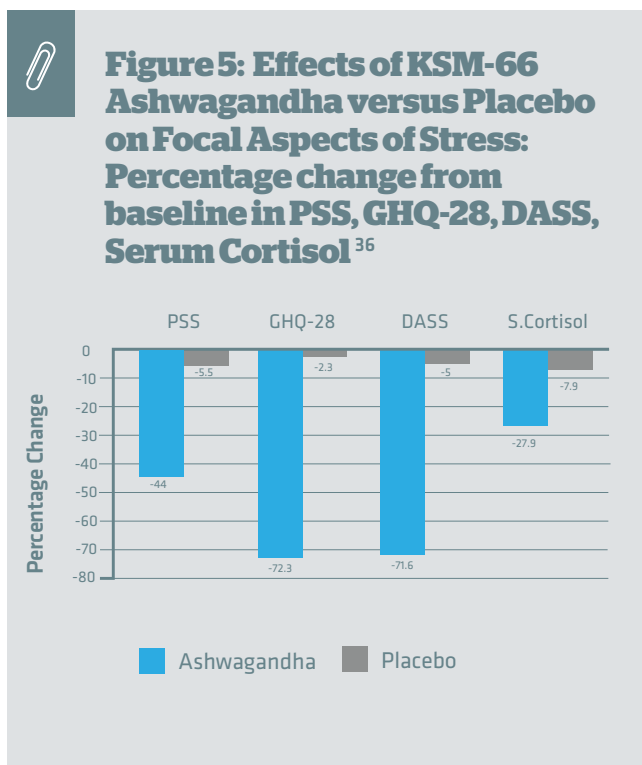
WHAT MAKES KSM-66 ASHWAGANDHA UNIQUE?	WHAT IS THE CLINICAL ADVANTAGE?
<p>Standardised: Standardised to >5% full-spectrum withanolides via HPLC</p>	Guaranteed consistent potency and dosage delivery of key active constituents
<p>Clinically Validated: Supported by numerous published human clinical studies Ongoing research and development; 6 clinical studies completed and pending publication</p>	Demonstrated therapeutic benefits
<p>Clean Processing: Unique 100% water extraction process; Free from chemical solvents</p>	Reduced exposure to chemicals
<p>Excipients: Free from carriers, fillers, dairy and lactose Withania extracts may contain lactose. In fact, KSM-66 is available in lactose-free and lactose-containing commercial grades</p>	<p>Excellent allergen profile ensures suitability for patients with dietary intolerances.</p> <p>Lactose-free foods and supplements are often sought after for stressed individuals with gastrointestinal (GIT) symptoms. Via the brain-gut axis, stress can exacerbate and contribute to several GIT disorders, including irritable bowel syndrome, which is associated with an increased prevalence in lactose intolerance.³⁴</p>

Stress and Anxiety

KSM-66 Ashwagandha was shown in a prospective double-blind, randomised, placebo-controlled trial to reduce elevated cortisol levels, improve the stress response, mild anxiety and nervous tension in healthy individuals experiencing chronic stress. 64 adult men and women (aged 18-54 years) were randomised to receive 300 mg of KSM-66 Ashwagandha or placebo twice daily for 60 days. The study assessed focal aspects of stress including:

1. The perceived stress scale (PSS);
2. The "Anxiety and Insomnia" item-subset of the general health questionnaire (GHQ-28);
3. The "Stress" item-subset of the depression anxiety stress scale (DASS);
4. The "Anxiety" item-subset of the DASS;
5. Serum cortisol levels.

Results demonstrated a significant decrease ($p < 0.0001$) in all stress-assessment scale scores (1-4) in the KSM-66 Ashwagandha group on day 60. These differences are highly statistically significant and suggest a sizable effect of KSM-66 Ashwagandha in improving well-being and focal aspects of stress. Serum cortisol reduced by 27.9% from baseline in the KSM-66 Ashwagandha group at the end of the trial, while a much smaller reduction of 7.9% was observed in the placebo group, again demonstrating a statistically significant difference ($p = 0.002$) in the two groups on day 60.³⁵



In another study, the effect of Withania on the stress response was investigated in a double-blind, randomised, placebo-controlled design in 98 chronically stressed participants over a 60-day period. Biochemical and clinical variables including the Hamilton Anxiety Scale, serum cortisol, serum C-reactive protein, pulse and blood pressure were decreased significantly in a dose-dependent manner and serum DHEAS and haemoglobin increased. The use of Withania also reduced symptoms of stress including forgetfulness and inability to concentrate, with 500 mg/day more effective than 250 mg/day. No adverse effects were reported.²⁷

Fatigue and Cancer

In a recent study researchers proposed that cancer related fatigue is a manifestation of the chronic stress induced by cancer and its associated psychological manifestations. As such the anti-stress properties of Withania, shown in previous studies in healthy people to improve physical performance and weakness as well as improving sleep patterns, responsiveness and alertness was employed in an open label study on 100 women with breast cancer in all stages, undergoing chemotherapy either with or without Withania.^{25,27,28} Patients in the intervention arm, taking 2 g of Withania every 8 hours experienced lower fatigue scores and reduced symptoms of pain and insomnia, as well as better overall physical, social and emotional functioning, supporting the use of Withania for the management of cancer related fatigue and quality of life improvement.²⁵ Significantly, in preceding studies Withania was shown not to hinder the effectiveness of chemotherapeutic agents, rather, it enhanced cell kill of such agents and as such seems to be a safe herb to use with patients during chemotherapy.²⁶

Weight Management in Chronic Stress

Chronic stress can affect eating patterns, exercise patterns and metabolism; therefore, contributing to weight gain. In a prospective double-blind, randomised, placebo-controlled trial, 52 subjects under chronic stress with a body mass index (BMI) between 25 - 39 received either KSM-66 Ashwagandha (300 mg) or placebo twice daily for 8-weeks. KSM-66 Ashwagandha resulted in significant benefits in the parameters outlined in Figure 6, when compared to placebo.³⁶

Sexual and Reproductive Health

In Ayurveda, Withania has a long history of use as an aphrodisiac, to promote fertility as well as healthy reproductive and sexual function. KSM-66 Ashwagandha has been shown in human studies to have sexual and reproductive health benefits in both men and women.

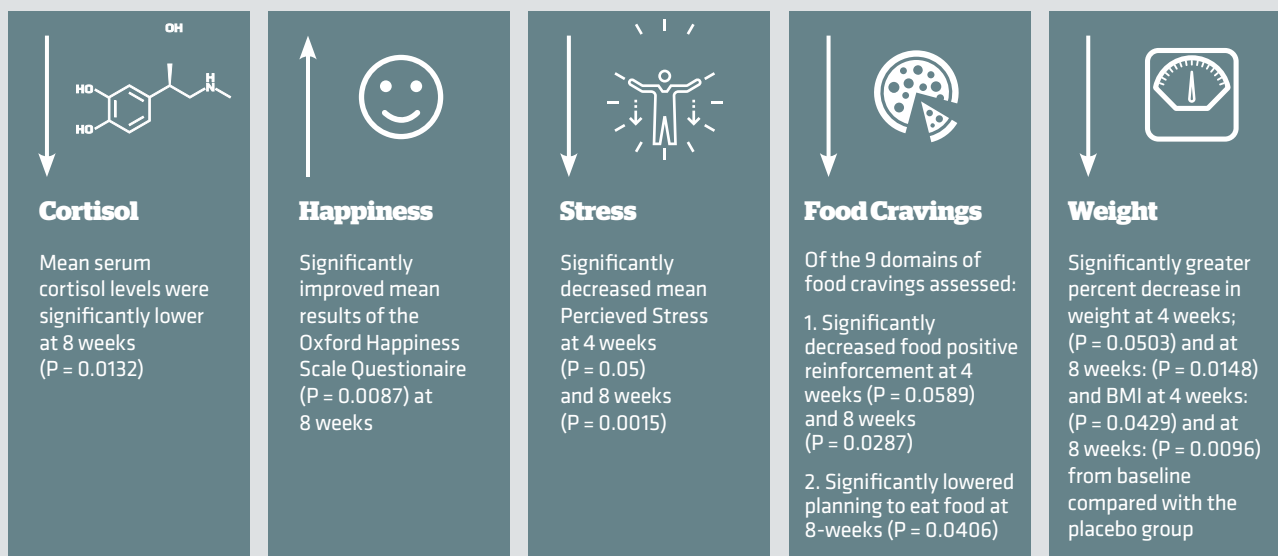
In a randomised placebo controlled pilot study, 46 men with oligospermia (sperm count < 20million/mL semen) were randomised to receive KSM-66 Ashwagandha (675mg /day) or placebo for 90 days. At 90 days, compared to baseline there was a 167% increase in sperm count (P < 0.0001), 53% increase in semen volume (P < 0.0001), and 57% increase in sperm motility (P < 0.0001). Testosterone (17%; P < 0.01) and Luteinising Hormone (34%; P < 0.02) levels increased significantly in the KSM-66 Ashwagandha group compared to baseline.³⁷

In 50 women (aged 21-50, in a relationship for > one year), KSM-66 Ashwagandha was investigated for its effects on sexual function. In this randomised, placebo controlled pilot study, 300mg KSM-66 Ashwagandha twice daily resulted in significant improvement, relative to placebo, in the Female Sexual Function Index (FSFI) Total score (P < 0.001), FSFI domain score for "arousal" (P < 0.001), "lubrication" (P < 0.001), "orgasm" (P < 0.004), and "satisfaction" (P < 0.001). Furthermore, Female Sexual Distress Scores (P < 0.001) and the number of successful sexual encounters (P < 0.001) significantly improved in the active treatment at 8-weeks.³⁸

Eleutherooccus senticosus (Siberian Ginseng)

The root of Siberian Ginseng was introduced into traditional practice in the Soviet Union in the mid-1950s.³⁹ Soviet researchers were the first to establish that certain plants had the ability to support the body's normal adaptive responses. Siberian Ginseng, is one of the most well researched of the adaptogenic herbs. Repeated studies show anti-stress, antifatigue and tonic effects with the use of Siberian Ginseng. These include; enhanced quality and quantity of work performance; increased resistance to illness (including reduced incidence of influenza and general illness); an increased sense of well-being; a deeper more restful sleep in patients experiencing irritability, anxiety, insomnia or extreme exhaustion. Other studies illustrate increased physical

Figure 6: Benefits Associated with KSM-66 Ashwagandha when compared to Placebo³⁶



endurance in athletes with increased resistance to cold weather. Siberian Ginseng has also been shown to normalise blood pressure in either hyper or hypotension and to normalise blood sugar in some cases of diabetes. Eleutherosides B+E (also known as syringin and syringaresinol diglucoside respectively) are characteristic active constituents of Siberian Ginseng found in highest concentrations in the root of the herb.^{44,48}

Stress and Anxiety

Cardiovascular stress responses in 45 healthy adults were assessed before and after treatment with Siberian Ginseng. To measure stress responses participants were submitted to a stressful cognitive task. Reduction in heart rate in response to stress and overall stress response were only seen in the treatment group however it was noted that modification of blood pressure rise was apparent in female but not male participants. The study demonstrated that treatment with Siberian Ginseng can reduce cardiovascular responses to stress in healthy young volunteers; thereby supporting stress adaptation.⁴⁰

In a less recent yet significant placebo-controlled study, 80 subjects with a history of neurosis (for 1-5 years) were given Siberian Ginseng for a period of 3 to 4 weeks. When compared to placebo, the herb significantly improved sleep, well-being, appetite, stamina, cognitive function, and mood. No side effects were noted.⁴¹

Animal model studies show Siberian Ginseng may have neuroprotective potential and thus help to maintain working memory for longer. In one study, Siberian Ginseng extract delayed neuronal death in the hippocampus and protected against cerebral ischaemia.⁴² In other animal models, Siberian Ginseng has been shown to prevent hypertrophy of the adrenal gland, and the resulting depletion of adrenal vitamin C levels.⁴³

Blood Sugar Control

The therapeutic potential of Siberian Ginseng in the management of patients with type 2 diabetes was evaluated in a study comparing the effects of Siberian Ginseng to Korean Ginseng or placebo when taken in combination with oral anti-diabetic medication. Compared to the Korean Ginseng and placebo arms, Siberian Ginseng intake resulted in a significant decline of fasting blood sugar and postprandial blood sugar level as well as lowered HbA1c, total cholesterol and triglyceride levels after a 12-week period. Patients taking Siberian Ginseng also demonstrated some recovery of sensory awareness to an electrical stimulus; an indication of the degree of peripheral neuropathy.⁴⁴

Immune Support

Several preclinical and clinical studies have demonstrated the immune-modulating activity of Siberian Ginseng. It may be particularly useful in immune deficiency associated with chronic stress. In a controlled trial, 36 subjects were randomised to receive Siberian Ginseng root extract (10ml TDS) or placebo. After four weeks of therapy, those in the active group had a significant increase in total lymphocyte ($p < 0.0001$), T helper ($p < 0.00001$), T-suppressor ($p < 0.0001$), natural killer ($p < 0.1$), and B-lymphocyte ($p < 0.05$) cells compared to placebo.⁴⁴

Glycyrrhiza glabra (Licorice)

Licorice root has a long history of medicinal use in Europe and Asia, reputedly dating back to 2500 BC.⁴⁵ In traditional Western Herbal Medicine, Licorice is specifically indicated as a tonic to support adrenal gland function and to address adrenal insufficiency.^{46,47} Its marked effect on endocrine and adrenal function is largely attributed to its

effects on steroid hormone metabolism. By inhibiting the metabolism of corticosteroids, Licorice can potentiate the effects of cortisol and other steroid hormones, thus supporting endogenous corticosteroid requirements.^{47,48}

Licorice root is also used traditionally for immune and digestive health; as a soothing demulcent and anti-inflammatory to relieve symptoms of dyspepsia. Preliminary studies have shown potential for its use in cognition, fatigue and stress induced depression. These additional actions of Licorice may further benefit individuals exposed to chronic stress.^{49,50} 1-4g of dried Licorice root is recommended to address adrenal insufficiency and chronic stress.^{43,51}



Licorice Safety^{41,45}

Licorice contains saponins, flavonoids, sterols, polysaccharides and other active constituents. Glycyrrhizin (GL) is a saponin found in Licorice which has established therapeutic activity but also safety implications when used in high doses and long term.

GL at doses $>100-400$ mg/ day may have an aldosterone-like effect, elevate blood pressure and disrupt salt and water balance; thereby leading to fluid retention.

Therefore, when using Licorice in the management of chronic stress, it may be prudent to ensure the GL content is standardised to a controlled level providing <100 mg/ day. Practitioners should also be aware of the following cautions and considerations:

- 1. Caution in hypertension and other heart problems.**
As GL-containing Licorice may increase blood pressure in susceptible individuals (particularly in those prescribed anti-hypertensives), blood pressure should be monitored where indicated.
- 2. Caution in use alongside diuretics, insulin, stimulant laxatives, corticosteroids, cardiac glycosides, blood-thinning medications and other medications which may influence electrolyte imbalance.** These medications are contraindicated in conjunction with high-dose GL-containing Licorice.
- 3. Consider a high potassium / low sodium diet.**



GL at doses $>100-400$ mg/ day may have an aldosterone-like effect, elevate blood pressure and disrupt salt and water balance; thereby leading to fluid retention. Therefore, when using Licorice in the management of chronic stress, it may be prudent to ensure the GL content is standardised to a controlled level providing <100 mg/ day.

Nutrients for Adrenal Support

B-vitamins are widely used as anti-stress vitamins due to their essential role in the functioning of the adrenal cortex, where they are required for steroid hormone biosynthesis. Research has shown that deficiencies of Riboflavin (B2), Pantothenic acid (B5), Pyridoxine (B6) and Nicotinamide (B3) are signs of adrenal hypo-function and an increased response to stress.⁵² Collectively, B vitamins, Vitamin C and Zinc support healthy mood, cognition, immune function and energy levels; all of which can be impaired during prolonged stress.

Vitamin B5 (Pantothenic Acid)

As an essential part of Coenzyme A, Pantothenic Acid (B5) is necessary for proper adrenal cortex function, the synthesis of steroid hormones (including cortisol), the synthesis of neurotransmitters (including acetylcholine), as well as energy production.^{41,53,54}

Vitamin B6 (Pyridoxine, Pyridoxal 5'-phosphate)

Pyridoxal 5'-phosphate (P5P), the metabolically active form of Vitamin B6 supports a healthy stress response and healthy mood due to its role in the synthesis of many neurotransmitters, including serotonin, dopamine, adrenalin, noradrenaline and gamma-aminobutyric acid (GABA). Although frank deficiency is rare, marginal deficiency has been shown to be very common.^{41,46, 55}

Vitamin C (Ascorbic Acid)

Ascorbic Acid (Vitamin C) is a cofactor in the synthesis of the adrenal hormones adrenalin and noradrenalin.^{56,57} The importance of vitamin C in adrenal function is evident through the high concentration found in the adrenal gland.^{52,58} Evidence suggests that supplementing with high levels of Vitamin C can support adrenal function and decrease high cortisol levels.⁵⁹

Vitamin E

Vitamin E is known as one of the most important lipid-soluble antioxidants, as well as an immune-stimulating and anti-inflammatory vitamin. It has been shown to increase humoral antibody production, resistance to bacterial infections, cell-mediated immunity, the T-lymphocyte response, and more.^{43,60} Like Vitamin C, it protects the body from stress-induced oxidative damage and immune disruption.

Zinc

As an antioxidant and immune-stimulant,⁶¹ Zinc further guards against stress-induced insult on our endogenous antioxidant and immune defences. Zinc also plays a role in reproductive health, fertility, neurotransmission and neurological function; all of which may be impaired by chronic stress.^{43,62,63,64,65}

Diet and Lifestyle Recommendations

Dietary and Lifestyle Interventions to Tackle Your Stress

Eat Nourishing Food



Many people feel at their most stressed when their blood-sugar levels are low. Never eating breakfast, or skipping lunch are two of the easiest traps to avoid and subsequently prevent blood sugar dips. Preparing healthy, balanced snacks can help you operate smoothly throughout the day.

Get Enough Sleep



A lack of quality sleep can aggravate chronic stress. Studies have shown a direct correlation between rest and the ability to cope with stress. Wind down before bed and use evening rituals to promote a restful sleep.

Exercise



Exercise is important for everyone, whether it is a lunchtime walk, or competitive sport. Even a bit of stretching and a stroll around the office counts. Incorporate some form activity into your daily life.

Address Addictions



Limiting alcohol, caffeine and nicotine reduces stress and improves overall health. Addictions to technology should also be considered. Limit night-time stimulation from television, phones, computers or tablet devices to assist with relaxation and sleep quality.

Use Relaxation Techniques



Explore various relaxation methods such as meditation, pilates or yoga, listen to the radio, your favourite music or read a book. Do whatever works for you, the key is to do it consistently for maximum benefit. Relaxation techniques differ for everyone. Generally, doing something you love and finding hobbies can be great relaxation techniques.

Build Strong Relationships



It always helps to have people to talk to, but a social circle may provide a welcome distraction, and supportive friendships are vital for creating a productive, rounded life. Investing time in strong intimate and family relationships is also key to happiness, mood and stress levels.

Manage Your Time



Good time-management gives you better control over your schedule, however busy, and is a skill everyone should acquire. Better organisation leads to less pressure and increased efficiency, allowing more time to relax properly. Learning to say "no" is another critical skill which can prevent over committing and building stress levels.

Summary

Stress and anxiety are common psychiatric manifestations of the modern world and how our minds and bodies adapt to this stress will determine our life experience. In small quantities, stress and anxiety positively enhance our life and our performance; they can motivate and help one be more productive. However, too much stress, or a strong negative response to stress, is harmful. It can set up for general poor health, as well as specific physical or psychological illnesses like infection, heart disease, or depression.

Persistent and unrelenting stress often leads to anxiety and unhealthy behaviours. Adaptation to change is key to enhancing our experience and perception of the world around us. Natural therapy with a combination of clinically trialled KSM-66 Ashwagandha extract, Siberian Ginseng, Licorice as well as nutritional support including Zinc, Vitamin B3, Vitamin B6, Vitamin B5 and Vitamin C can help us along the way and improve our quality of life while we navigate our way through the kaleidoscope of stimulus we are called upon on a daily basis. If your patients require additional support, we recommend the following co-prescriptions to ensure effective personalised management for their individual health needs.

Endocrine Balance

- Vitamin C with bioflavonoids and cofactors
- Thyroid support with Rhodiola, Rehmannia, Tyrosine and Iodine

Brain & Nervous System Health

- Brain support with Ginkgo and Bacopa
- Herbal Anxiety & Insomnia Relief with Lavender, Kava and Withania
- Healthy Mood Balance with St Johns Wort, Saffron and Nutrients
- High Potency Magnesium Powder with activated B vitamins, Glutamine and Taurine

Multivitamin & Mineral Support

- Activated B Vitamin with Multinutritionals including 5-MTHF, Methyl B12, P5P
- Energy Multivitamin- Multinutritionals, Rhodiola and L-Acetyl-carnitine

References

1. World Health Organisation. *Mental disorders affect one in four people*. 2001. Available at: http://www.who.int/whr/2001/media_centre/press_release/en/
2. Australian Psychological Society. *Stress and wellbeing in Australia survey 2014*
3. Yerkes R, Dodson J. The relation of strength of stimulus to rapidity of habit-formation. *Journal of Comparative Neurology and Psychology*. 1908; 18: 459-82.
4. Sarris J, Wardle J. *Clinical Naturopathy*. An evidence-based guide to practice. Churchill Livingstone, Sydney, 2010.
5. Selye H. Stress and the general adaptation syndrome. *British Medical Journal*. 1950; 1.4667: 1383-92.
6. Panossian A, Wikman G, Kaur P et al. Adaptogens exert a stress-protective effect by modulation of expression of molecular chaperones. *Phytomedicine*. 2009; 16(6-7): 617-22.
7. Dardimov I. *Ginseng, Eleutherococcus*. On the mechanism of biological activity. 1976; 184. Moscow, Nauka.
8. Panossian A, Gabrielian E, Wagner H. On the mechanism of action of plant adaptogens with particular references on cucurbitacin R diglucoside. *Phytomedicine*. 1999; 6(3): 147-55.
9. Panossian A, Wikman G, Wagner H. Plant adaptogens III: Earlier and more recent aspects and concepts on their modes of action. *Phytomedicine*. 1999; 6(4): 287-300.
10. Panossian A, Dadayan M, Gabrielian E. Cucurbitacin R glucoside as a regulator of steroidogenesis and production of prostaglandin E₂-A specific modulator of the hypothalamic-pituitary-adrenal cortex system. *Bulletin of Experimental Biology and Medicine*. 1987; 53: 456-7.
11. Filaretov A, Bogdanova T, Mitiushov M et al. Effect of adaptogens on the activity of the pituitary adrenocortical system in rats. *Biulleten' eksperimental' noi bidogii i meditsiny*. 1986; 101(5): 573-4.
12. Hiai S, Yokoyama H, Oura H et al. Stimulation of pituitary adreno-cortical system by ginseng saponin. *Endocrinologia Japonica*. 1979; 26(6): 737-40.
13. Panossian A, Pashinian S. Effect of tonic compounds from Bryonia alba L. roots on arachidonic acid content in adrenals and thymus of mice at the physical fatigue. In: *New Data about Eleutherococcus and Other Adaptogens*. Vladivostok. Dalne Vostochniy Filial Sibirskogo Onteleniya Akademii Nauk SSSR. 1981; 143-8.
14. Panossian A, Dadayan M, Gevorkian G. The effect of stress and adaptogene cucurbitacin R diglucoside on arachidonic acid metabolism. *Problemy endokrinologii*. 1989; 35: 58-61.
15. Engelmann M, Landgraf R, Wotjak C. The hypothalamic- neurohypophysial system regulates the hypothalamic-pituitary- adrenal axis under stress: an old concept revisited. *Frontiers in Neuroendocrinology*. 2004; 25(3-4): 132-49.
16. Panossian A, Oganessian A, Ambartsumian M et al. Effects of heavy physical exercise and adaptogens on nitric oxide content in human saliva. *Phytomedicine*. 1999; 6(1): 17-26.
17. Chrousos G, Gold P. The concept of stress system disorders: Overview of behavioral and physical homeostasis. *JAMA*. 1992; 267: 1244-52.
18. Stratakis C, Chrousos G. Neuroendocrinology and pathophysiology of the stress system. In: Chrousos NP, McCarty R, Pacak K et al (eds): *Stress. Basic Mechanisms and Clinical Implications*. *Annals of the New York Academy of Sciences*. 1995; 771: 1-18.
19. Friedman E, Irwin M. A role for CRH and the sympathetic nervous system in stress-induced immunosuppression. In: Chrousos GP, McCarty R, Pacak K et al. (eds.): *Stress. Basic Mechanisms and Clinical Implications*. *Annals of the New York Academy of Sciences*. 1995; 771: 396-418.
20. Panossian A, Wikman G. Evidence-based efficacy of adaptogens in fatigue, and molecular mechanisms related to their stress- protective activity. *Current Clinical Pharmacology* 2009; 4: 198-219.
21. Mendes F. Tonic, fortifier and aphrodisiac: adaptogens in the Brazilian folk medicine. *Revista Brasileira de Farmacognosia* 2011; 21(4).
22. Kapoor L. *CRC Handbook of Ayurvedic Medicinal Plants*. 1990. CRC Press, Boca Raton.
23. Thakur R, Puri H, Husain A. *Major Medicinal Plants of India*. 1989. Central Institute of Medicinal and Aromatic Plants, Lucknow.
24. Frawley D, Lad V. *The Yoga of Herbs: An Ayurvedic Guide to Herbal Medicine*. 1988; 2. Lotus Press, Santa Fe.
25. Kulkarni SK, Dhir A. *Review article - Withania somnifera: An indian ginseng*. *Progress in Neuro-Pharmacology & Biological psychiatry*. 2008; 32: 1093-1105
26. Biswal B, Sulaiman S, Ismail H et al. Effect of Withania somnifera (Ashwagandha) on the Development of Chemotherapy- Induced Fatigue and Quality of Life in Breast Cancer Patients. *Integrative Cancer Therapies*. 2012; 12: 312.
27. Auddy B, Hazra J, Mitra A et al. A standardized Withania somnifera extract significantly reduces stress-related parameters in chronically stressed humans: a double-blind, randomized, placebo-controlled study. *Journal of the American Nutraceutical Association*. 2008; 11: 50-6.
28. Roy A, Acharya S, De A et al. Mountain medicine: effect of Withania somnifera on the changes of psychophysiological status of trainee mountaineers by altitude gain. *International Seminar on Traditional Medicine; Calcutta, India*. 1992; 161: 7-9. In: Khare CP. *Indian Herbal Remedies*. 2004, Springer-Verlag, Berlin, Germany.

References

29. Sandhu J, Shah B, Shenoy S et al. Effects of *Withania somnifera* (ashwagandha) and terminal Arjuna (*Arjuna*) on physical performance and cardiorespiratory endurance in healthy young adults. *International Journal of Ayurveda Research*. 2010; 1(3): 144-9.
30. Ahmad M, Mahdi A, Shukla K et al. *Withania somnifera* improves semen quality by regulating reproductive hormone levels and oxidative stress in seminal plasma of infertile males. *Fertility and Sterility*. 2009; 94(3): 989-96.
31. Sumantran V, Chandwaskar R, Joshi A et al. The relationship between chondroprotective and antiinflammatory effects of *Withania somnifera* root and glucosamine sulphate on human osteoarthritic cartilage in vitro. *Phytotherapy Research*. 2008; 22(10): 1342-8.
32. Mishra L. Scientific basis for the therapeutic use of *Withania somnifera* (ashwagandha): a review. *Alternative Medicine Review*. 2000; 5(4): 334.
33. Harikrishnan B, Subramanian P, Subah S. Effect of *Withania Somnifera* Root Powder on the Levels of Circulatory Lipid Peroxidation and Liver Marker Enzymes in Chronic Hyperammonemia. *Journal of Chemistry*. 5(4): 872-7.
34. Konturek PC1, Brzozowski T, Konturek SJ. Stress and the gut: pathophysiology, clinical consequences, diagnostic approach and treatment options. *J Physiol Pharmacol*. 2011 Dec;62(6):591-9.
35. Chandrasekhar K, Kapoor J, Anishetty S. A prospective, randomized double-blind, placebo-controlled study of safety and efficacy of a high-concentration full-spectrum extract of ashwagandha root in reducing stress and anxiety in adults. *Indian Journal of Psychological Medicine*. 2012; 34(3): 255-62.
36. Choudhary D et al. Body Weight Management in Adults Under Chronic Stress Through Treatment With Ashwagandha Root Extract: A Double-Blind, Randomized, Placebo-Controlled Trial. *J Evid Based Complementary Altern Med*. 2017 Jan;22(1):96-106.
37. Ambiye VR, Langade D, Dongre S, et al. Clinical Evaluation of the Spermatogenic Activity of the Root Extract of Ashwagandha (*Withania somnifera*) in Oligospermic Males: A Pilot Study. *Evidence-Based Complementary and Alternative Medicine*. 2013
38. Dongre S, Langade D, Bhattacharyya S. Efficacy and Safety of Ashwagandha (*Withania somnifera*) Root Extract in Improving Sexual Function in Women: A Pilot Study. *BioMed Research International Volume*. 2015.
39. Baranov A. Medicinal uses of ginseng and related plants in the Soviet Union: recent trends in the Soviet literature. *J Ethnopharmacol*. 1982; 6: 339.
40. Facchinetti F, Neri I and Tarabusi M. Eleutherococcus senticosus reduces cardiovascular stress response in healthy subjects: a randomized, placebo-controlled trial. *Stress and Health*. 2002; 18(1): 11-7.
41. Panossian A. Adaptogens in Mental and Behavioral Disorders. *Psychiatric Clinics of North America*. 2013; 36(1): 49-64.
42. Lee D. Neuroprotective effects of Eleutherococcus senticosus bark on transient global cerebral ischemia in rats. *Journal of Ethnopharmacology*. 2012; 139(1): 6-11.
43. Thorne Research. Eleutherococcus senticosus Monograph. *Alternative Medicine Review*, 2005;11(2):151-155.
44. Enno F, Gleske J. Siberian Ginseng Results in Beneficial Effects on Glucose Metabolism in Diabetes Type 2 Patients: A Double Blind Placebo-Controlled Study in Comparison to Panax Ginseng. *International Journal of Clinical Nutrition*. 2013; 1(1): 11-7.
45. Braun L, Cohen M. *Herbs & Natural Supplements - An evidence-based guide*. 4th Edition, Volume 2, Churchill Livingstone, Sydney, 2015.
46. Bone K, Mills S. *Principles and Practice of Phytotherapy*. Licorice. 2nd edition, Churchill Livingstone, Sydney, 2013.
47. British Herbal Medicine Association's Scientific Committee. British Herbal Pharmacopoeia. *Glycyrrhiza glabra*. *British Herbal Medicine Association*. Bournemouth, 1983.
48. Hoffmann D. *Medical Herbalism*. The Science and Practice of Herbal Medicine. Licorice. Healing Arts Press, Vermont, 2003.
49. Health Canada. *Licorice Monograph*. 2008. Available at: www.hc-sc.gc.ca.
50. European Medicines Agency. Community Herbal Monograph on *Glycyrrhiza glabra* L. and/or *Glycyrrhiza inflata* Bat. and/or *Glycyrrhiza uralensis* Fisch., radix. Committee on Herbal Medicinal Products (HMPC), 2012.
51. Mills S. The A-Z of Modern Herbalism. *A Complete Guide to Practical Herbal Therapy*. Licorice. Thorsons / Harper Collins Publishers, London, 1989.
52. Anderson DC. Assessment and Nutraceutical Management of Stress-induced Adrenal Dysfunction. *Integrative Medicine*. 2008; 7(5):23.
53. Kelly GS. Pantothenic acid. Monograph. *Altern Med Rev*. 2011;16(3):263-74.
54. Head KA & Kelly GS. *Nutrients and Botanicals for Treatment of Stress: Adrenal Fatigue, Neurotransmitter Imbalance, Anxiety and Restless Sleep*. *Alternative Medicine Review*, 2009;14(2):114-140.
55. Kaplan BJ et al. *Vitamins, minerals, and mood*. *Psychol Bull*. 2007 Sep;133(5):747-60.
56. Patak P, Willenberg HS, Bornstein SR. Vitamin C is an important cofactor for both adrenal cortex and adrenal medulla. *Endocr Res*. 2004 Nov;30(4):871-5.
57. Harrison FE, May JM. Vitamin C function in the brain: vital role of the ascorbate transporter SVCT2. *Free Radic Biol Med*. 2009 Mar 15;46(6):719-30.
58. Kohlmeier M. *Nutrient Metabolism*. Vitamin C. Academic Press, London, 2003.

References

59. Kelly GS. Nutritional and botanical interventions to assist with the adaptation to stress. *Altern Med Rev.* 1999 Aug;4(4):249-65.
60. Health Canada. *Vitamin E Monograph.* 2009. Available at: www.hc-sc.gc.ca.
61. Natural Medicines. *Zinc Professional Monograph.* 2016. Available at: <https://naturalmedicines.therapeuticresearch.com/>
62. Prasad AS. Zinc: role in immunity, oxidative stress and chronic inflammation. *Curr Opin Clin Nutr Metab Care.* 2009;12(6):646-52.
63. Roxas M, Jurenka J. Colds and Influenza: A Review of Diagnosis and Conventional, Botanical, and Nutritional Considerations. *Alternative Medicine Review.* 2007;12(1):35.
64. Maggini S et al. Selected vitamins and trace elements support immune function by strengthening epithelial barriers and cellular and humoral immune responses. *British Journal of Nutrition* (2007), 98, Suppl. 1, S29–S35.
65. Wintergeist ES, Maggini S, HornigDH. Immune-Enhancing Role of Vitamin C and Zinc and Effect on Clinical Conditions. *Ann Nutr Metab.* 2006;50(2):85-94.
66. Friedman E, Irwin M. A role for CRH and the sympathetic nervous system in stress-induced immunosuppression. In: Chrousos GP, McCarty R, Pacak K et al. (eds.): *Stress. Basic Mechanisms and Clinical Implications.* *Annals of the New York Academy of Sciences.* 1995; 771: 396-418.