The role of adaptogens in stress management

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Stress is a normal part of everyday life but it is important to be able to use tools for its management otherwise chronic stress, if left untreated, can lead to a variety of stress related illnesses including hypertension, heart disease, anxiety, depression, memory impairment and chronic fatigue syndrome. The aim of this literature review is to summarise and critically analyse research conducted on the adaptogenic herbs *Withania somnifera, Panax ginseng, Eleutherococcus senticosus, Schisandra chinensis, Glycyrrhiza glabra, Rhodiola rosea, Bacopa monniera* and *Centella asiatica.* The mechanism of adaptogens appears to involve the hypothalamic pituitary adrenal axis with resultant decreases or normalising of nitric oxide and cortisol, which are increased during times of stress. Most adaptogens also have anxiolytic and antioxidant properties and these have been attributed to their adaptogenic effect.

Methods: The online databases PUBMED, PROQUEST, EBSCO and the Directory of Open Access Journals were searched to obtain peer-reviewed journal articles on adaptogens. The Library of the National Herbalists Association of Australia was also searched. Most studies used animal experimental models but some limited human clinical trials have been conducted. Fourteen studies using animal experimental models were identified and these have been summarised in Table 1. Twelve human clinical trials were identified and these have been summarised in Table 2.

Results and conclusions: *Withania somnifera* appears to be the most commonly used, and extensively studied, adaptogen followed closely by *Panax ginseng* and *Eleutherococcus senticosus*. *Schisandra chinensis* is an extensively used adaptogen in Traditional Chinese Medicine (TCM). Other herbs studied that show adaptogenic activity include *Rhodiola rosea, Glycyrrhiza glabra, Bacopa monniera* and *Centella asiatica*, with the latter two more specific in improving memory. Most studies on adaptogens have used animal experimental models and whilst positive benefits have been shown, more large scale human clinical trials are needed.

Introduction

It is generally regarded as virtually impossible to remove all stress from our lives; stress is a normal part of everyday life and accordingly cannot really be avoided. However it is necessary to be able to manage stress to not result in ill health. Exposure to chronic stress, if left unchecked, can lead to serious illness including cardiovascular abnormalities such as hypertension and heart disease (Porth 1998). Other stress related health problems include anxiety, depression, panic attacks, memory impairment, digestive disorders, autoimmune diseases and chronic fatigue syndrome (Gruner 2006). Hence the importance of being able to cope with stress – this is where adaptogenic herbs can help.

Adaptogens improve the response to stress (Mills 2000). They help the body to adapt by normalising physiological processes in times of increased stress (Trickey 2003). Adaptogens can be viewed as tonics and are prescribed to enhance vitality and are indicated when stress levels are high, during convalescence after surgery or illness, or during periods of challenging or difficult life changes (events) (Trickey 2003).

So how do adaptogens work? Panossian (2009) states that adaptogens exert their stress protective effect by regulating homeostasis via several mechanisms of action associated with the hypothalamic pituitary adrenal (HPA) axis, and also by controlling key mediators of the stress response such as molecular chaperons (e.g. Hsp70), stress activated c-Jun N-terminal protein kinase (JNK-1), transcription factor DAF-16, cortisol and nitric oxide (NO). He believes the key point of action of adaptogenic herbs appears to be their upregulating and stress mimetic effects on the 'stress sensor' protein Hsp70, which plays an important role in cell survival and apoptosis. Hsp70 affects circulating levels of nitric oxide and cortisol by inhibiting expression of NO synthase II gene and interacting with glucocorticoid receptors directly and via the JNK pathway (Panossian 2009). Prevention of stress induced increase in NO and the associated decrease in ATP production results in increased performance and endurance, and adaptogen induced up regulation of Hsp70 triggers stress induced JNK-1 and DAF-16-mediated pathways regulating the resistance to stress and resulting in enhanced mental and physical performance (Panossian 2009).

Research and design methods

The online databases PUBMED, PROQUEST, EBSCO and the Directory of Open Access Journals were searched to obtain peer reviewed journal articles on adaptogens. Keywords used included adaptogen, herbal medicine and stress but these did not yield great results. The use of botanical and common names of the most commonly used adaptogens yielded much more effective results. A search at the Library of the National Herbalists Association of Australia also proved quite fruitful. There are various herbs that can be used as adaptogens but the most common ones this paper will focus on are *Withania somnifera* (withania), *Panax ginseng* (Korean ginseng), *Eleutherococcus senticosus*

(Siberian ginseng), *Schisandra chinensis* (schisandra), *Glycyrrhiza glabra* (licorice), *Rhodiola rosea* (rhodiola), *Bacopa monniera* (brahmi) and *Centella asiatica* (gotu kola). It was easier to find information on withania, ginseng and rhodiola but some information was found on all the eight major adaptogens reviewed.

Results

Withania somnifera (withania)

Withania has immunomodulatory, anti-inflammatory but most significantly adaptogenic effects, which may result from the complex of the many steroidal withanolides found in the root of the herb (Mills 2000, Braun 2007). The withanolides are the major chemical constituents of withania and the plant has been the subject of considerable modern scientific attention (Mirjalili 2009).

Most of the studies on withania have used rat experimental models, but in one human clinical trial the anxiolytic efficacy of an ethanolic extract of the herb was evaluated (Andrade 2000). In that double blind placebo controlled study, 20 patients suffering from anxiety disorder received an extract of withania in the form of a tablet whilst 19 people received a placebo and patients were assessed at baseline, the end of week 2 and at the end of week 6 (the treatment endpoint).

According to the authors the study demonstrated a trend for the anxiolytic superiority of withania over placebo and they concluded that withania has useful anxiolytic potential and merits further investigation (Andrade 2000). As anxiety can be one outcome of chronic or severe stress, withania may well have a role in stress management. However the study was not large enough with only 39 people involved and it was conducted over a very short period, only six weeks.

Another randomised human trial investigated the effectiveness of naturopathic care on anxiety symptoms, and withania was used in the treatment group alongside other therapies rather than on its own (Cooley 2009). The authors state that both investigators and participants were blinded during randomisation and allocation, with 41 participants in the treatment group who received dietary counselling, deep breathing relaxation techniques, a standard multivitamin and withania root standardised to 1.5% withanolides, 300 mg twice daily (Cooley 2009). The control group of 40 participants received psychotherapy, matched deep breathing relaxation techniques and placebo. The primary outcome measure was the Beck Anxiety Inventory (BAI) – 75 participants were followed for 8 weeks or more on the trial and final BAI scores decreased by 56.5% ($p<0.0001$) in the treatment group and 30.5% ($p<0.0001$) in the control group (Cooley 2009).

These scores are statistically significant given the very low p values but it would be difficult to determine what treatment was of benefit, the counselling, relaxation, multivitamin, withania or a combination.

Apart from their adaptogenic properties, withania's alkaloids (withanolides) are also considered to be sedative, hypotensive and able to reduce heart rate, accordingly the herb is also used for insomnia (Braun 2007). A study conducted on rats investigated the effect of *Withania somnifera* root extract and its possible interaction with GABAergic modulators on the sleep wake cycle (Kumar 2008). Rats were sleep deprived for 24 hours and then injected intraperitoneally with *Withania somnifera* extract (100 mg/kg) 30 minutes before electrophysiological recordings. Pre treatment with withania shortened sleep latency, decreased waking, increased non rapid eye movement and total sleep time (Kumar 2008).

The researchers used the GABAergic modulators picrotoxin and mucimol to test the sleep promoting effects of withania and found that the herb's root extract induced sleep promoting effects by involving GABAergic modulation, which was antagonised by picrotoxin but potentiated by muscimol (Kumar 2008). The results appear interesting but obviously more research is needed. Some people suffering from stress also experience insomnia so this may be another role that withania plays in stress management. A human clinical trial would be welcome.

Chronic stress depresses immune functioning and increases susceptibility to disease (Kour 2009). A recent study was conducted on Swiss albino mice to see the effect of withanolide A (isolated from *Withania somnifera* root extract) on chronic stress induced alterations on T lymphocyte subset distribution and corresponding cytokine secretion patterns (Kour 2009). Withanolide A was orally administered once daily on the stressed experimental animals and showed that it caused significant recovery of stress induced depleted T cell population causing an increase in the expression of IL-2 and IFN-gamma (a signature cytokine of Th1 helper cells) and a decrease in the concentration of corticosterone (Kour 2009). This study supports withania's role in stress management including immune function.

As previously stated, chronic stress can result in memory impairment. In another study researchers investigated the effect of withanolide A on memory deficient mice showing neuronal atrophy and synaptic loss in the brain (Kuboyama 2005). Treatment with withanolide A induced significant regeneration of both axons and dendrites, in addition to the reconstruction of pre and postsynapses in the neurons (Kuboyama 2005).

Stress has been reported to be a causative factor for male infertility and withania's ability to treat stress related infertility was assessed in a trial comprised of 60 infertile men in the treatment group and 60 fertile men in the control group (Mahdi 2009).

Treatment with *Withania* resulted in a decrease in stress, improved the level of antioxidants and improved overall semen quality in a significant number of

individuals. The treatment resulted in pregnancy in the partners of 14% of the patients (Mahdi 2009).

Panax ginseng (Korean ginseng)

One indication for prescribing Korean ginseng is to improve physical and mental performance and well being and improve general performance whist under stress (Bone 2003). The root of *Panax ginseng* has been reported to have an antistress action (Tachikawa 2004). Korean ginseng has been used for thousands of years and is traditionally known as a medicinal plant with mysterious powers particularly in regions such as Korea, China and Japan (Choi 2008). Key constituents of Korean ginseng root include a complex mixture of saponins called ginsenosides, with 38 contained in Korean ginseng as opposed to only 19 in American ginseng (Bone 2003, Choi 2008).

During periods of stress the adrenal glands secrete catecholamines and cortisol from the medulla and the cortex which can lead to disease if left unchecked for too long (Tachikawa 2004). The effects of Korean ginseng components on functions of adrenal medulla were investigated in vitro and it was found that the saponin rich fraction greatly reduced the secretion of catecholamines whereas the non saponin fraction did not affect it at all (Tachikawa 2004).

A comparative study assessed the antistress effects of *Panax ginseng* and *Ginkgo biloba* (Rai 2003). In this study rats were subjected to acute stress and chronic stress resulting in adrenal hypertrophy and gastric ulceration, indicating the active involvement of the hypothalamic pituitary adrenal (HPA) axis which is highly responsive to stress (Rai 2003). Before being exposed to acute and chronic stress, the animals were treated with *Ginkgo* at 30mg/kg and with *Panax* at 100 mg/kg. After a few days the rats were sacrificed for dissection and examination of the stomach for ulceration, and for any changes in biochemical parameters such as plasma glucose, cholesterol, triglycerides, creatine kinase and serum corticosterone.

The researchers found that *Ginkgo biloba* is more effective in acute stress whereas *Panax ginseng* is a better option for chronic stress, and they concluded that both herbs possess significant antistress properties and can be used for the treatment of stress induced disorders (Rai 2003).

In a study of 90 healthy male and female volunteers exposed to a cold environment, researchers examined the effects of Korean red ginseng (*Panax ginseng*) on changes in blood pressure, heart rate and tolerability to cold stress (Kaneko 2004). The volunteers were divided into three random groups; one group received the herb, one received placebo and the other received the calcium channel blocking drug nifedipine. It was found that the herb was more effective than the drug in dilating blood vessels, increasing blood flow under cold stress and decreasing the pain from ischemia (Kaneko 2004). However the report does not specify if the trial was double blinded nor does it provide p values for all the results in the sub groups. It is also questionable whether comparing a calcium channel blocker with a crude herb is appropriate or reliable.

The effectiveness of using a combination of ginseng, Oriental Bezoar (ox gallstone) and *Glycyrrhiza* was tested in a small randomised double blind placebo controlled experiment (Zheng 2008). Only ten healthy males (mean age 27 ±1) were used and the experiment was carried out over two and a half hours. Salivary and blood measurement values of pre and post mental arithmetic stress were compared, and ECG measurement values of pre and mid mental arithmetic stress were compared.

The researchers concluded that the combination herbs used should be useful in reducing mental stress ($p<0.05$) (Zheng 2008). This study is flawed in that only ten young participants were used and the experiment lasted a very short time and it is difficult to determine which of the three medicines helped. It would be interesting to conduct such a study on at least 100 older people and for a longer period of time.

In contrast *Panax ginseng* has been used as an experimental control in a forced swimming study conducted on mice to assess the effects of the African plant *Alchornea cordifolia* (Ishola 2008). It was suggested the African herb possesses antistress properties because it prolonged the swimming time ($p<0.05$), but similar effects were observed in mice pre treated with *Panax ginseng* (Ishola 2008).

A human study comprising 16 healthy male volunteers aged 21, was conducted to determine whether fermented ginseng (FG) can improve the first night effect (FNE) during sleep recording in a laboratory (Kitaoka 2009). The results suggested that FG could improve the FNE in humans, and the improvement may be related to an anxiolytic effect of FG which acts via GABAergic modification (Kitaoka 2009). A larger scale study using volunteers of varying ages could provide more definitive results. Nevertheless it is not surprising that the FG produced anxiolytic effects; ginseng is the most famous of all Chinese medicinal plants and has a great reputation as an adaptogen (van Wyk 2004). People who are under a lot of stress usually have their sleep disturbed so perhaps this study adds weight to other studies' conclusions showing the adaptogenic potential of ginseng.

Eleutherococcus senticocus (Siberian ginseng)

Siberian ginseng has been used for over 2000 years according to Chinese medical records, and has been used to increase vitality and energy (Braun 2007). Russian cosmonauts use it to improve alertness and energy and to aid in adaptation to the stresses of life in space (Braun 2007). A paper which examined in detail the meaning of the word 'adaptogen' concluded that so far as specific pharmacological activities are concerned,

there are a number of valid arguments for equating the action of so called adaptogens with those of medicinal agents that have activities as antioxidants, anticancer, immunomodulatory and hypocholesterolemic as well as hypoglycemic and choleretic action (Davydov 2000).

The authors concluded that the chemistry of the isolated secondary metabolites of *Eleutherococcus* and their pharmacological effects support their hypothesis that the reported beneficial effects of adaptogens derive from their capacity to exert protective and/or inhibitory action against free radicals (Davydov 2000).

Key constituents of *Eleutherococcus* root include the eleutherosides, triterpenoid saponins and glycans (Bone 2003). The leaf of Siberian ginseng contains hyperoside, a flavonol glycoside, which showed remarkable activity in a forced swimming test on mice (Deyama 2001). Isofraxidin in the bark and hyperoside in the leaf are respectively reported as effective sedative components (Deyama 2001).

Stressed rats show enlarged adrenal glands, reduced thymus and spleen size and damage to the gastric mucosa (Mills 2000). *Eleutherococcus* significantly reduced this adrenal hypertrophy and adrenal ascorbic acid depletion, and the sparing effect on the adrenal cortex by the herb allows the organism to better withstand prolonged stress (Mills 2000).

Siberian ginseng can act in different ways to support the body during times of stress and this is dependent on what stage the stress response is at (Oates 2008). Research suggests that there is a threshold of stress below which the herb increases the stress response and above which it decreases the stress response, and various mechanisms have been proposed as to how *Eleutherococcus* works including inhibition of catechol-O-methyl transferase, which inactivates catecholamines (Oates 2008). As a result catecholamine levels are not depleted and release of new catecholamines from nerve synapses is decreased. Eleutherosides have also been shown to improve carbohydrate metabolism and energy provision and increase the synthesis of protein and nucleic acids (Oates 2008). In theory these factors may help prevent the exhaustion stage of the stress response. But this is just a theory and more concrete evidence is needed. As part of its adaptogenic effect Siberian ginseng may also exert neuroprotective, hepatoprotective and cardioprotective activity (Oates 2008). This is a good example of a herb's holistic characteristics; an adaptogen that also helps protect vital organs.

In chronic stress, multi dose administration of Siberian ginseng engages the HPA axis which plays a primary role in the body's ability to adapt to repeated stressors (Oates 2008). Studies have demonstrated that maximal effects are achieved around four weeks but do not persist at the eight week time point, which may help explain the practice of giving Siberian ginseng for 6-8 weeks with a 1-2 week break before repeating (Oates 2008).

Numerous studies use Siberian ginseng in combination with other adaptogens, such as *Rhodiola rosea* and *Schisandra chinensis*, which may potentially act synergistically for improved effects. One such study was carried out with mice taking ADAPT-232, a fixed combination of native extracts of *Eleutherococcus senticosus, Schisandra chinensis* and *Rhodiola rosea*, for seven consecutive days followed by a forced swimming test to exhaustion (Panossian 1999).

It was found that this combination strongly increased the endurance of the mice, increasing the time taken to exhaustion in a dose dependent manner (Panossian 1999).

Schisandra chinensis (schisandra)

Schisandra chinensis is another herb viewed as an adaptogen, particularly in Traditional Chinese Medicine (TCM) where it is prescribed with other herbs to increase resistance to physical and emotional stressors (Braun 2007). Several experimental models have shown schisandra to have adaptogenic and tonic effects (Bone 2003). Renal and gonadal RNA, glycogen and enzyme levels were increased in mature animals compared with those in younger rabbits. Reproductive cell numbers were increased in both sexes and working capacity was increased in vivo, all by oral administration. Dibenzocyclooctene lignans, such as schisandrin, are key constituents of schisandra fruit (Bone 2003).

The adaptogenic effects of *Schisandra chinensis* were assessed together with the effects of the adaptogen *Bryonia alba* in a placebo controlled double blind study of several groups of athletes (Panossian 1999). Since heavy physical exercise increases the content of nitric oxide (NO) and cortisol in blood and saliva, the athletes were tested for these parameters before and after herbal treatment, as well as before and after physical exercise.

In the course of the study athletes followed the same training course and feeding regimes. Both *Schisandra* and *Bryonia* administration significantly increased the basal level of salivary NO in athletes versus athletes taking placebo, and these results correlated with higher extension of the increase of physical performance in athletes taking adaptogens versus athletes taking placebo (Panossian 1999). After treatment with the herbs, heavy physical exercise did not increase salivary NO in athletes in the treatment group whereas it did in the control group of athletes treated with placebo ($p<0.001$).

The authors suggest that Schisandra and Bryonia induced an increase in physical performance which could be due to their stimulatory effect on NO production, which adapts the organism to heavy physical exercise (Panossian 1999). Whilst the results are statistically significant because of the low p value, the study is ten years old and a more recent trial would be welcome.

Glycyrrhiza glabra (licorice)

Traditionally licorice is viewed as an adrenal tonic, most likely due to its ability to slow cortisol breakdown

(Braun 2007). It may be of benefit in patients unable to mount a healthy stress response (adrenocorticoid insufficiency) due to chronic stress (Braun 2007). Human studies on the adaptogenic effects of licorice are lacking but there are some animal studies. In one study, rabbits were treated orally with a preparation of *Glycyrrhiza glabra* for 30 days and in parallel were exposed to vibration stress for 30 days (Oganesyan 2002). The licorice preparation reduced catalase activity in the peripheral blood and increased animal resistance to vibration stress ($p<0.001$).

Licorice is chemically similar to corticosteroid hormones, producing a corticosteroid like effect. This is very important as glucocorticoids normalise metabolic processes, exerting and maintaining a physiological effect facilitating adaptation to novel conditions, thus the adaptive effect of licorice root (Oganesyan 2002). In another study conducted on rabbits, the effect of continuous vibration and treatment with licorice root on the rabbits' peripheral blood red cells was investigated (Adamyan 2005).

Active substances of licorice root accelerated metabolism in cells of the bone marrow erythroid stem, enhanced compensatory reserve of the organism and increased animal's resistance to stress (Adamyan 2005). It is not known why rabbits were used in these studies and not other animals such as mice or rats, as the reports do not give a reason.

Rhodiola rosea (rhodiola)

Rhodiola rosea has been categorised as an adaptogen by Russian researchers due to its observed ability to increase resistance to a variety of chemical, biological and physical stressors (Kelly 2001). A study conducted on rats explored the effects of *Rhodiola rosea* on the body weight and the intake of sucrose and water in depressive rats induced by chronic mild stress (Chen 2008). It was found that low dose rhodiola can increase the body weight and sucrose intake of depressive rats, making them recover to normal status.

A trial of 15 recreationally active college women found that acute rhodiola ingestion decreases the heart rate response to submaximal exercise and appears to improve endurance exercise performance (Noreen 2009). Many more than 15 participants would be required before any real credence could be placed on the results.

In a recent study of 60 individuals (30 in treatment group, 30 in placebo group), rhodiola was used to treat stress related fatigue (Olsson 2009). It was concluded that repeated administration of *R. rosea* extract SHR-5 exerts an antifatigue effect that increases mental performance, particularly the ability to concentrate, and decreases cortisol response to awakening stress in burnout patients with fatigue syndrome (Olsson 2009). By way of comparison, in a study conducted in 2000, *Rhodiola rosea* extract SHR-5 was tested on a group of foreign students (20 in treatment group, 20 in control group) during an exam period with respect to both physical fitness and mental wellbeing and capacity (Spasov 2000). The most significant improvement in the treatment group was seen in physical fitness, mental fatigue and neuro motoric tests ($p<0.01$). The overall conclusion was that the study drug gave significant results compared with the placebo group but that the dose level probably was suboptimal (Spasov 2000).

A randomised double blind placebo controlled parallel group clinical study with an extra non treatment group was performed to measure the effect of a single dose of standardised SHR-5 *Rhodiola rosea* extract on capacity for mental work against a background of fatigue and stress (Shevtsov 2003). The study showed a pronounced antifatigue effect ($p<0.001$) but no significant difference between the two dosage groups was observed. Both groups performed significantly better compared with the placebo group (Shevtsov 2003).

In another study using rabbits, the objective was to ascertain which mediators of stress response are significantly involved in the mechanisms of action of adaptogens and to determine their relevance as biochemical markers for evaluating antistress effects (Panossian 2007). It was suggested that the inhibitory effects of *R. rosea* and *Schisandra chinensis* on phosphorylated kinase p-SAPK/p-JNK activation may be associated with their antidepressant activity as well as their positive effects on mental performance under stress (Panossian 2007).

In a study investigating the antioxidant potential of three adaptogen extracts, *Rhodiola rosea, Eleutherococcus senticosus* and *Emblica officinalis* (Indian gooseberry), it was found that rhodiola had the highest potential for singlet oxygen scavenging, hydrogen peroxide scavenging, ferric reducing, ferrous chelating and protein thiol protection over either of the other two extracts (Chen 2008). Rhodiola also had the highest polyphenol content which may not only have adaptogen properties but may decrease the risk of complications induced by oxidative stress (Chen 2008).

Bacopa monniera (brahmi)

In a study conducted on rats, *Bacopa monniera* exhibited potent adaptogenic activity by reversing chronic stress induced changes in ulcer index, adrenal gland weight, creatine kinase and aspartate aminotransferase (Rai 2003).

In another study on rats, *Bacopa* extract was found to have significant antidepressant activity in forced swim and learned helplessness models of depression and was comparable to that of the tricyclic antidepressant imipramine (Sairam 2002). As previously mentioned, depression can result from chronic stress and so *Bacopa* appears to have a role in stress management.

Chronic stress can also affect memory and this is another area where brahmi can be of use. The effects

of brahmi on human memory were tested on 76 adults aged between 40 and 65 years in a randomised double blind placebo controlled study (Roodenrys 2002). The results showed a significant effect of brahmi on a test for the retention of new information ($p<0.05$). *Bacopa* is a herb known for memory enhancement for reversal of memory deficits caused by diazepam, and this was confirmed in a recent study conducted on mice (Prabhakar 2008).

These results show promise for stressed patients who are taking diazepam or other benzodiazepines to relieve insomnia but obviously human clinical trials are needed. *Bacopa* is used as a brain tonic and its active constituents, the bacosides, have been extensively investigated confirming their nootropic action (Russo 2005). A nootropic is a chemical designed to increase brain metabolism (Mosby's 1998).

Centella asiatica (gotu kola)

Amongst other actions *Centella asiatica* is an adaptogen and nervine tonic (Bone 2003). Therefore it can be useful in stress management. Asiaticoside, one of the active constituents found in the herb's leaves, is suggested to be responsible for its pharmacological potential (Barbosa 2008).

A study conducted on rats suggests that *Centella* could be useful in some neuropsychiatric diseases as it can inhibit the phospholipase A2 group of enzymes that have abnormal activity in the central nervous system in some neuropsychiatric diseases (Barbosa 2008). Another study conducted on rats has shown that gotu kola has anxiolytic properties (Wijeweera 2006). This holds promise for stressed individuals suffering anxiety and a human clinical trial would be welcome.

Discussion

Adaptogens appear to exert their antistress effects by regulating homeostasis via the hypothalamic pituitary adrenal (HPA) axis and inhibiting or decreasing circulating levels of nitric oxide (NO) and cortisol. *Withania somnifera* (withania) seems to have received the most attention by way of animal (rat) experimental models in investigating its antistress mechanisms and potential. Limited human clinical trials have been conducted on the efficacy of withania but they are very small scale studies. Nevertheless they have shown withania to be adaptogenic but also immunomodulatory, insomnia relieving and memory enhancing. A human clinical trial showed withania to be somewhat effective in treating male stress related infertility by not only decreasing stress but also improving the level of antioxidants.

Panax ginseng (Korean ginseng) has been shown to possess significant antistress properties in animal studies using rats as subjects but a comparative study showed it to be more effective in chronic stress as opposed to *Ginkgo biloba* which was found to be more effective in acute stress. *Panax ginseng* has demonstrated anxiolytic effects in a human trial although the study was quite small. Being anxiolytic can also mean the herb is adaptogenic as chronic stress can produce feelings of anxiety.

Siberian ginseng has also been shown to engage the HPA axis, and the herb's antioxidant activity against free radicals helps explain the overall beneficial effects of adaptogens. Rat experimental models have shown the herb's ability to significantly reduce adrenal hypertrophy as well as improve carbohydrate metabolism and energy provision. Studies demonstrated that maximal effects are achieved after four weeks but do not persist past the eight week point.

Schisandra chinensis (schisandra) is an adaptogen widely used in Traditional Chinese Medicine (TCM) and a human trial comparing it with *Bryonia alba* has suggested that schisandra works as an adaptogen by initially increasing NO production to adapt the body to physical demands placed upon it. This contrasts with the other adaptogens where it was found that NO is inhibited.

Human trials on the adaptogenic effects of licorice root are lacking but studies conducted on rabbits show that licorice produces a corticosteroid like effect thus normalising metabolic processes and enabling the organism to adapt to novel conditions. It is unclear as to why rabbits were used in place of rats, which seems to be the norm when conducting tests on animal experimental models.

Rhodiola rosea (rhodiola) is another main herb used as an adaptogen and has been extensively studied by Russian researchers. Studies show that its antistress and antifatigue effects happen even at low dose. *Bacopa* and *Centella asiatica* are also used as adaptogens but their main effect is seen on improving memory, hence they can be used in stress management as chronic stress can cause memory deficit.

Conclusion

Withania somnifera appears to be the most commonly used and extensively studied adaptogen followed closely by *Panax ginseng* and *Eleutherococcus senticosus*. *Schisandra chinensis* is an extensively used adaptogen in TCM. Other herbs used as adaptogens include *Rhodiola rosea, Glycyrrhiza glabra, Bacopa monniera* and *Centella asiatica,* with the latter two being more specific in improving memory.

Unfortunately there have been limited human clinical trials conducted to test the efficacy of adaptogens and where they do exist they are usually small scale studies. Most studies on adaptogens have used animal experimental models (particularly rats) and whilst positive benefits have been shown, more large scale human clinical trials are needed.

References

Adamyan TI et al. 2005. Effect of licorice root on peripheral blood indexes upon vibration exposure. *B Exp Biol Med* 140:2;197-200.

Andrade C et al. 2000. A double-blind, placebo-controlled evaluation of the anxiolytic efficacy of an ethanolic extract of *Withania Somnifera. Indian J Psych* 42:3;295-301.

Barbosa NR, Pittella F, Gattaz WF. 2008. *Centella asiatica* water extract inhibits iPLA2 and cPLA2 activities in rat cerebellum. *Phytomed* 15:10;896-900.

Bone K. 2003. *A Clinical Guide to Blending Liquid Herbs*. UK: Churchill Livingstone.

Braun L, Cohen M. 2003. *Herbs & Natural Supplements: an evidence-based guide*. 2nd edn. Sydney: Elsevier Australia.

Chen Q et al. 2008. Effects of *Rhodiola rosea* on body weight and intake of sucrose and water in depressive rats induced by chronic mild stress. *J Chinese Integr Med* 6:9;952-5.

Chen TS, Liou SY, Chang YL. 2008. Antioxidant evaluation of three adaptogen extracts. *Am J Chin Med* 36:6;1209-17.

Choi K. 2008. Botanical characteristics, pharmacological effects and medicinal components of Korean *Panax ginseng* C A Meyer. *Acta Pharmacol Sin* 29:9;1109-18.

Cooley K et al. 2009. Naturopathic care for anxiety: a randomized controlled trial ISRCTN78958974. *PLoS ONE* 4:8;e6628 doi:10.1371/journal.pone.0006628.

Davydov M, Krikorian AD. 2000. *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. (Araliaceae) as an adaptogen: a closer look. *J Ethnopharmacol* 72;345-93.

Deyama T, Nichibe S, Nakazawa Y. 2001. Constituents and pharmacological effects of *Eucommia* and Siberian ginseng. *Acta Pharmacol Sin* 22:12;1057-70.

Gruner, T. 2006. Stress. *J Comp Med* 5:6;12-20.

Ishola I et al. 2008. Evaluation of antistress potential and phytochemical constituents of aqueous root extract of *Alchornea cordifolia*. *Asian J Sci Res* 1:4;476-80.

Kaneko H, Nakanishi K. 2004. Proof of the mysterious efficacy of Ginseng: basic and clinical trials: clinical effects of medical ginseng, Korean red ginseng: specifically its anti-stress action for prevention of disease. *J Pharmacol Sci* 95:2;158-62.

Kelly GS. 2001. *Rhodiola rosea*: a possible plant adaptogen. *Altern Med Rev* 6;293-302.

Kitaoka K et al. 2009. Fermented ginseng improves the first-night effect in humans. *Sleep* 32:3;413-21.

Kour K et al. 2009. Restoration of stress-induced altered T cell function and corresponding cytokines patterns by Withanolide A. *Int Immunopharmacol* 9:10;1137-44.

Kuboyama T, Tohda C, Komatsu K. 2005. Neuritic regeneration and synaptic reconstruction induced by Withanolide A. *Brit J Pharmacol* 144:7;961-71.

Kumar A, Kalonia H. 2008. Effect of Withania somnifera on sleep-wake cycle in sleep-disturbed rats: possible GABAergic mechanism. *Indian J Pharm Sci* 70:6;806-10.

Mahdi AA et al. 2009. *Withania somnifera* improves semen quality in stress-related male fertility. *Evid Based Complement Alternat Med eCAM*; doi:10.1093/ecam/nep138.

Mills S, Bone K. 2000. *Principles and practice of phytotherapy*. UK: Churchill Livingstone.

Mirjalili M, Moyano E et al. 2009. Steroidal lactones from *Withania somnifera*, an ancient plant for novel medicine. *Molecules* 14:7;2373-93.

Mosby. 1998. *Mosby's Medical, Nursing & Allied Health Dictionary*. USA: Mosby-Year Book Inc.

Noreen E, Buckley J, Lewis S. 2009. The effects of an acute dose of *Rhodiola rosea* on exercise performance and cognitive function. *J Int Soc Sports Nutr* 6;14.

Oates L. 2008. Siberian ginseng *Eleutherococcus senticosus*. *J Comp Med* 7:4;44-7.

Oganesyan KR. 2002. Antioxidant effect of licorice root on blood catalase activity in vibration stress. *B Exp Biol Med* 134:2;135-6.

Olsson EM, von Scheele B, Panossian AG. 2009. 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* 75:2;105-12.

Panossian A, Wikman G. 2009. Evidence-based efficacy of adaptogens in fatigue, and molecular mechanisms related to their stress-protective activity. *Curr Clin Pharmacol* 4:3;198-219.

Panossian A et al. 1999. Effects of heavy physical exercise and adaptogens on nitric oxide content in human saliva. *Phytomed* 6:1;17-26.

Panossian A et al. 2007. The adaptogens *Rhodiola* and *Schizandra* modify the response to immobilization stress in rabbits by suppressing the increase of phosphorylated stress-activated protein kinase, nitric oxide and cortisol. *Drug Target Insights* 1;39-54.

Panossian A et al. 2009. Adaptogens exert a stress-protective effect by modulation of expression of molecular chaperones. *Phytomed* 16:6-7;617-22.

Porth C. 1998. *Pathophysiology: concepts of altered health states.* 5th ed. Philadelphia: Lippincott-Raven.

Prabhakar S et al. 2008. *Bacopa monniera* exerts antiamnesic effect on diazepam-induced anterograde amnesia in mice. *Psychopharmacol* 200;27-37.

Rai D et al. 2003. Adaptogenic effect of *Bacopa monniera* (Brahmi). *Pharmacol Biochem Behav* 75:4;823-30.

Rai D et al. 2003. Anti-stress effects of *Ginkgo biloba* and *Panax ginseng*: a Comparative Study. *J Pharmacol Sci* 93;458-64.

Roodenrys S et al. 2002. Chronic effects of Brahmi (*Bacopa monnieri)* on human memory. *Neuropsychopharmacol* 27:2;279-81.

Russo A & Borrelli F. 2005. *Bacopa monniera*, a reputed nootropic plant: an overview. *Phytomed* 12:4;305-317.

Sairam K et al. 2002. Antidepressant activity of standardized extract of *Bacopa monniera* in experimental models of depression in rats. *Phytomed* 9;207-11.

Shevtsov VA et al. 2003. A randomized trial of two different doses of a SHR-5 *Rhodiola rosea* extract versus placebo and control of capacity for mental work. *Phytomed* 10:2-3;95-105.

Spasov AA et al. 2000. A double-blind, placebo-controlled pilot study of the stimulating and adaptogenic effect of *Rhodiola rosea* SHR-5 extract on the fatigue of students caused by stress during an examination period with a repeated low-dose regimen. *Phytomed* 7:2;85-89.

Tachikawa E, Kudo K. 2004. Proof of the mysterious efficacy of ginseng: basic and clinical trials: suppression of adrenal medullary function in vitro by ginseng. *J Pharmacol Sci* 95:2;140-44.

Trickey R. 2003. *Women, hormones & the menstrual cycle.* 2nd ed. Sydney: Allen & Unwin.

Table 1
Summary of studies on effects of adaptogens using human subjects

Herb	Reference	Study design and study period	Intervention and dose	Outcomes	Significant difference (P value)	Comment
Withania somnifera	Andrade C et al 2000	6 week double blind placebo controlled 20 subjects in treatment group 20 in placebo group	250mg *Withania somnifera* or placebo	*Withania* demonstrated anxiolytic superiority over placebo	p=0.062	Small scale study and participants were not randomised. P value is high, cannot confidently rely on results. Not statistically significant
Withania somnifera	Cooley et al 2009	12 week randomised double blind placebo controlled 75 participants	300 mg *Withania somnifera* bid placebo, deep breathing exercises, multivitamin, psychotherapy	Final Beck Anxiety Inventory (BAI) scores decreased by 56.5% in treatment group and 30.5% in the control group	p<0.0001	Statistically significant but difficult to determine which therapy helped
Withania somnifera	Mahdi et al 2009	3 month study of 60 infertile men to assess withania's ability to treat stress related infertility 60 fertile men in control group	Single daily dose at 5 g per day of *W. somnifera* root powder taken orally	Decrease in stress, improved level of antioxidants, improved overall semen quality. Pregnancy resulted in the partners of 14% of the patients	p<0.05	The study was not a randomised double blind placebo controlled trial and therefore this needs to be taken into account when evaluating the results
Panax ginseng	Kaneko & Nakanishi 2004	90 healthy male and female volunteers exposed to a cold environment	Herb dose not specified Nifedipine	Herb more effective than nifedipine in dilating blood vessels, increasing blood flow and decreasing the pain from ischaemia	p=0.003	Report does not specify if the trial was double blinded. Trial flawed because only healthy volunteers used therefore effect on unwell subjects not assessed. Dose of herb was not specified
Panax ginseng	Zheng & Moritani 2008	Test effectiveness of using a combination of *Panax ginseng*, Oriental bezoar and *Glycyrrhiza glabra* 10 health males (mean age 27±1) Randomised double blind placebo controlled	Treatment capsule contained 250 mg powdered ginseng, 50 mg powdered oriental bezoar and 50 mg powdered licorice. Placebo capsules contained corn starch	Researchers concluded that the combination herbs used should be useful in reducing mental stress	p<0.05	Study is flawed in that only 10 participants were used and experiment lasted a very short time. Difficult to determine which of the 3 herbs helped
Panax ginseng	Kitaoka et al 2009	A human study comprising 16 healthy male volunteers aged 21, to determine whether fermented ginseng can improve the first night effect during sleep recording in a laboratory	1,845 mg of fermented ginseng daily for 8 days or placebo double blind sleep recordings	Fermented ginseng can improve the first night effect in humans. The improvement may be related to an anxiolytic effect of fermented ginseng which acts via GABAergic modification	p<0.05	Very small study, very short period and not randomised therefore cannot place reliance on results
Schisandra chinensis	Panossian et al 1999	Adaptogenic effects of *Schisandra* assessed together with *Bryonia alba* in a placebo controlled double blind study of several groups of athletes	*Schisandra chinensis* 91.1 mg/tablet *Bryonia alba* standardised equivalent to 1 mg cucurbitacin Salivary nitric oxide	*Schisandra* and *Bryonia* induced an increase in physical performance which could be due to their stimulatory effect on nitric oxide production, thus adapting the organism to heavy physical exercise	p<0.001	Study is 10 years old – a more recent trial would be welcome

Herb	Reference	Study design and study period	Intervention and dose	Outcomes	Significant difference (P value)	Comment
Rhodiola rosea	Noreen, Buckley & Lewis 2009	Double blind random crossover study of 15 recreationally active college women	Acute oral dose of *Rhodiola rosea* 3 mg/kg Placebo	Acute *Rhodiola rosea* ingestion decreases the heart rate response to submaximal exercise, and appears to improve endurance to exercise performance	p<0.001	Statistically significant result although study was very small with only 15 participants. Much larger trial would be welcome
Rhodiola rosea	Olsson, von Scheele & Panossian 2009	*Rhodiola* used to treat stress related fatigue Randomised double blind placebo controlled parallel group study 60 participants: 30 in treatment group 30 in placebo group	576 mg of *Rhodiola* SHR-5 extract in divided doses daily for 28 days Placebo	*R. rosea* extract SHR-5 exerts an antifatigue effect that increases mental performance, particularly the ability to concentrate, and decreases cortisol response to awakening stress in burnout patients with fatigue syndrome	p<0.01	Statistically significant result
Rhodiola rosea	Spasov et al 2000	Randomised double blind placebo controlled pilot study 40 participants: 20 in treatment group 20 in control group	50 mg *Rhodiola rosea* bid for 20 days Placebo	Treatment group showed improvement in physical fitness, mental fatigue and neuromotoric tests compared with placebo group but dose was suboptimal	p<0.01	Statistically significant result but suboptimal dose finding contrasts with low dose effectiveness in animal studies
Rhodiola rosea	Shevtsov et al 2003	Randomised double blind placebo controlled parallel group clinical study with an extra non treatment group 161 cadets aged from 19 -21 years	*Rhodiola* dry extract 185 mg up to tds Placebo up to tds	The study showed a pronounced antifatigue effect but no significant difference between the two dosage groups. Both groups performed significantly better than the placebo group	p<0.001	Statistically significant result
Bacopa monniera	Roodenrys et al 2002	Randomised double blind placebo controlled study of 76 adults aged between 40 and 65 years	*Bacopa monniera* 300 mg for persons under 9 0kg 450 mg for persons over 90 kg daily for 3 months	Significant effect of brahmi on a test for the retention of new information	p<0.05	Statistically significant result

A summary table of studies on the effects of adaptogens using animal experimental models is available from the NHAA office.

Van Wyk B, Wink M. 2004. *Medicinal plants of the World*. South Africa: Briza Publications.

Wijeweera P et al. 2006. Evaluation of anxiolytic properties of gotu kola (*Centella asaiatica*) extracts and asiaticoside in rat behavioural models. *Phytomed* 13:9-10;668-76.

Zheng A, Moritani T. 2008. Effect of the combination of ginseng, oriental bezoar and *Glycyrrhiza* on autonomic nervous activity and immune system under mental arithmetic stress. *J Nutr Sci Vitaminol* 54:3;244-9.