Comparative adaptogenic properties of Withania somnifera and Panax ginseng

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ABSTRACT

Adaptogens are natural (herbs) or synthetic compounds (levamisole, aphobazole, etc) used to maintain stability in the human body. The plant based adaptogens were mainly used to enhance the physical endurance and mental health of patients. However, adaptogens are widely studied for their ability to protect and cope up the body against physical, chemical and biological stress and related diseases. Panax ginseng and Withania somnifera are natural adaptogens, used to attenuate stress & related disorders without increasing oxygen consumption. This review deals with a detailed description of the adaptogenic potential of Panax ginseng and Withania somnifera in improving human health. It also focuses on the similarity and mechanism of action of Panax ginseng and Withania somnifera as adaptogens on human stress induced disorders.

KEYWORDS: Adaptogen, Withania somnifera, Panax ginseng, stress

INTRODUCTION

Stress is a normal part of the modern lifestyle, which has a negative impact on one’s mental and physical well-being. Acute stress is for a short duration due to work pressure, exertion, increased physical activities or similar things. Recent studies have revealed that traditional herbal medicines may offer promising alternatives for depression treatment with high safety and tolerance (Jin et al., 2019). Chronic stress is the most serious among different stresses which may prolong for weeks, months or even for years. Chronic stress if left untreated leads to stress related defects such as hypertension, heart disease, anxiety, depression, memory impairment and chronic fatigue syndrome which is shown in Figure 1. (Provino, 2010; Salve et al., 2019).

Many natural herbs have been playing as an adaptogen in managing chronic stress and its related illness. Some of these herbs are Withania somnifera, Panax ginseng, Eleutherococcus senticosus, Schisandra chinensis, Glycyrrhiza glabra, Rhodiola rosea, Bacopa monniera, Lepidium meyenii and Centella asiatica. These adaptogens from plant extracts have been found to increase resistance against stress and stress related conditions (Khanum et al., 2005; (Panossian & Wagner, 2005; Liao et al., 2018; Todorova et al., 2021). Plant adaptogens associated with human/animal studies have shown increased cortisol level, antioxidant capacity, mental and physical performance and prevented scopolamine induced oxidative stress (Giridharan et al., 2011; Zarabi et al., 2018).

ADAPTOGEN PROPERTY

An adaptogen is a compound that increases the resistance or normalizes the influence of multiple stressors without affecting normal body functions (Oliveira & Leitão, 2016). The term ‘adaptogen’ was coined by the Russian scientist, Lazarev, in 1947 while working on dibazol (2 benzyl-benzimidazole), a synthetic compound found to stimulate nonspecific resistance of organisms (Brekhman & Dardymov, 1969; Todorova et al., 2021). The term Adaptogen was defined as “state of non-specific resistance” in stress (Brekhman & Dardymov, 1969; Panossian, 2003) a physiological condition that is linked with various disorders of the neuro endocrine–immune system (Stratakis & Chrousos, 1995). This definition has been updated as “Adaptogenic substances have the capacity to normalize body functions and strengthen systems compromised by stress. They have a protective effect on health against a wide variety of environmental assaults and emotional conditions” (Panossian et al., 2021). Lazarev defined ‘adaptogens’ as agents which allow an organism to counteract any adverse physical, chemical or biological stressor by generating nonspecific resistance and thus becoming ‘adapted’ to diverse demands imposed on it (Lazarev et al., 1959). Most of the adaptogens has antioxidant and anxiolytics property which attributes their adaptogenic property. The intake of adaptogens associated with affecting the hypothalamic pituitary adrenal axis and also affects cortisol and nitric oxide (NO) level. For instance, after consuming plant adaptogens, the level of cortisol and NO...
is not increased during physical exercise, but the adaptogens actually increases the level of messenger substance that increase NO stress decrease cortisol stress (Liao et al., 2018). Effective use of these medicinal plants is associated with mental diseases and behavioral disorders, cognitive function and stress induced diseases. Adaptogen alters the disease course and maintains good health (Panossian et al., 2021). Modern neuteuticals has a wide range of herbal adaptogens under the labels of “Anti-ageing”, “Antioxidants”, “Immunity Boosters”, “Anti-stress” formulas. Adaptogen effects on animals and cell lines exhibit neuroprotective, anti-fatigue, antidepressive, anxiolytic, nootropic, and CNS stimulating and tonic effects (Panossian & Wagner, 2005; Panossian & Wikman, 2010). The stress protective effect of adaptogens shown in Figure 2 is regulated by homeostasis via mechanisms such as stress-activated protein kinase c-Jun N-terminal protein kinase (JNK) (Panossian et al., 2007), forkhead box O (FOXO) transcription factor (DAF-16) (Wiegant et al., 2009), and molecular chaperones (Hsp70) (Panossian & Wikman, 2010), cortisol and nitric oxide (NO) (Chiu & Ko, 2004; Panossian & Wikman, 2010; Panossian et al., 2012; Lopresti et al., 2019). It was then believed that the main action of adaptogenic herbs was to up regulate and stress mimetic effects on the ‘stress sensor’ protein Hsp70 which helps in cell survival. Hsp70 affects nitric oxide and cortisol levels by inhibiting the expression of the NO synthase II gene and interacting with glucocorticoid receptors via JNK pathway. Prevention of increase NO and decrease in ATP due to stress results in increased endurance and performance. Thus up-regulation of Hsp70 with the help of adaptogen interacts with DAF-16 and JNK-1 mediated pathways, regulating the resistance to stress (Panossian et al., 2009).

**PANAX GINSENG AS AN ANTI-STRESSOR**

*Panax ginseng* is the first clinically used adaptogen and has been extensively investigated clinically for its stress attenuating activity (Todorova et al., 2021). *Panax ginseng* is used medicinally in most of the East Asian countries and is the most widely taken herbal product. Studies show that ginseng plays a significant role in depression and may act as potential antidepressant (Jin et al., 2019). It is used as an alternative medicine with Anti-diabetic, anti-cancer, cardioprotective, neuroprotective and anti-inflammatory properties (Patel & Rauf, 2017). The active compound of the *Panax ginseng* is the ginsenosides (Saba et al., 2018). One of the main indications for prescribing *Panax ginseng* is to improve the physical and mental status of an individual and to improve overall performance while under stress (Oliynyk & Oh, 2013). The Korean ginseng root has been reported to have a superior regulation of stress and is used to treat various ailments with its mysterious power (Choi, 2008; Lee & Rhee, 2017). It has actoprotective effect that improves physical and mental health while under stress (Oliynyk & Oh, 2013) and have been reported to have anti-stress effect (Tachikawa & Kudo, 2004; Lee & Rhee, 2017). The main constituents of *Panax ginseng* root consists of complex mixture of saponsins known as ginsenosides of 38 types (Choi, 2008; Liao et al., 2018).

The Korean red ginseng is produced by steaming which hydrolyses and converts ginsenosides into other types of ginsenosides such as Rb1, Re, Rf1, Re, Rf3, Rs4, Rh2, Rh4, Rg1, Rg3, Rg5 which play an important role in the anti-oxidant and anti-stress activities (Nam 2005; Kim, 2018). Further, Ginsenosides contains active ingredients like Protopanaxadiols: Ra1, Ra2, Ra3, Rb1, Rb2, Rb3, Re, Rd, Rg3, Rh2. Protopanaxatriols: Rg1, Rg2, Re, Rf, Rh1, Rh3 and oleanolic acid: Ro which has the following effects such as anti-cancer, anti-aging, immunomodulation, CNS regulation (Jin et al., 2019). Although studies have been demonstrated in reduction of stress in animals after ginseng administration, description on the level of factors that alter the stress levels remain unclear. On a treadmill running test, administration of ginseng increased the endurance time to exhaustion, the basal level of ACTH and the corticosteroids (Filaretov et al., 2009). Administration of ginseng also increased the superoxide dismutase, glutathione peroxidase and catalase levels and decreased malondialdehyde levels antagonistic to stress (Kim et al., 2005; Sohn et al., 2013). Ginsenoside Rg1 was found to decrease oxidative stress induced brain damage by the agent 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (Chen et al., 2008). Ginseng extract administration also prevented oxidative damage to rat muscle in response to intense exercise (Yoces et al., 2004). Administration of Rg3 and Rb1 ginsenosides decreased the polyamine compound putrescine which is an potent stress indicator and Rb2, Rg1 decreased IL-6 in the plasma level (Kim et al., 2003; Lee et al., 2004). Ginsenoside Rb1 decreased the cell death due to 6-hydroxydopamine in neuroblastome cells (Hwang & Jeong, 2010) and protected dopaminergic cells from oxidative stress (Radad et al., 2004; Kim et al., 2008).

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**Figure 1**: Chronic stress and its related defects

**Figure 2**: Effect of adaptogen on stress response
A comparative study was done on rats to investigate the anti-stress effect of *Ginkgo biloba* and *Panax ginseng*. In this the rats were subjected to acute and chronic stress and were treated with both the herbs. The animals were sacrificed at the end of the study to check stomach ulcer and various other biochemical parameters such as creatine kinase, plasma glucose level, triglycerides, cholesterol and serum corticosterone. It was assessed that the *Panax ginseng* has the ability to treat chronic stress and its related effects whereas the *Ginkgo biloba* was able to treat only acute stress (Rai et al., 2003). In another study, 90 males and females were divided into three groups and were exposed to cold environment stress. Then the three groups were allocated to receive *Panax ginseng* extract, placebo and a standard drug nifedipine which blocks calcium channels. The herb seems to be more effective than the drug in dilating the blood vessels followed by increase in the blood flow in the cold condition (Kaneko, 2004).

Ginsenosides attenuates excitotoxicity induced by kainic acid in hippocampal neurons. From this study, researchers suggest that the ginseng may have anticonvulsant activity (Shin et al., 2009; Han et al., 2012). Ginsenoside, Rg2 found to protects adrenal phaeochromocytoma cells from glutamate induced neurotoxicity (Li et al., 2007), and hippocampal neural cells exposed to oxygen-glucose depleted state (Ye et al., 2009). Ginseng also suppressed gastric ulcer formation against long term stress and effectively maintained creatine kinase, cholesterol, plasma glucose and triglyceride level after exposure to stress (Rai et al., 2003; White et al., 2016). Ginseng total saponins were found to protect against oxidative stress induced by cyclophosphamide in bone marrow cells, peripheral lymphocytes in mice and liver injuries in rats (Zhang et al., 2008) through induction of cytochrome P450 expression and regulation of NO pathway in the liver of rats (Chen et al., 2021).

*Panax ginseng* was studied in various *in vitro* models and was found that saponins rich fraction greatly reduced cortisol and catecholamine secretion from adrenal glands (Tachikawa & Kudo, 2004). People under a lot of stress usually have less REM and disturbed sleep. Fermented ginseng was found to improve an individual’s sleep by anxiolytics effect via GABAergic modification (Kitaoka et al., 2009). *Panax ginseng* stands at the top of all Chinese medicinal plant and has a great reputation as an adaptogen (Wyk & Wink, 2004).

**WITHANIA SOMNIFERA AS A POTENT ANTI-STRESSOR**

*Withania somnifera* (Ashwagandha) has been used for thousands of years as a popular remedy for many conditions. Perhaps its main use, as described in Ayurvedic literature, is as a “rasayana” or rejuvenating drug. The word Ashwagandha indicates the equine (of horses) odour of the plant. Another name Avarada suggests the application of this plant for enhancing longevity. Ashwagandha was found to act as a potent anti-oxidant and counteract stress to promote wellness (Singh et al., 2011). Withania has the most significant adaptogenic effects which mainly results from the complex steroidal withanolides found in the roots (Braun & Cohen, 2015; White et al., 2016).

Chronic stress affects immune functioning and increases the susceptibility to diseases (Kour et al., 2009). Withania role in normal immune functioning against such kinds of stress was confirmed by a study conducted on albino mice to observe the effect of withanolide A from the root extracts of *Withania somnifera* on chronic stress induced alterations on cytokine secretion pattern and T lymphocyte subset distribution. It showed significant recovery of stress induced decrease in the T lymphocyte count resulting in the decreased corticosterone concentration and increased expression of IL-2 and IFN-gamma (Kour et al., 2009). It was found that the Withania also has the ability to improve human’s innate and adaptive immunity without any side effects by increasing the levels of immunoglobulins, cytokines and TBNK cells (Tharakan et al., 2021). *Withania somnifera* have been found to protect against leukopenia (decreased WBC count) and bone marrow suppression caused due to cyclophosphamide. Administration of *Withania somnifera* root extract was also found to stimulate immunological activity in albino mice. Withania can also be used to treat memory loss due to chronic stress. The effect of withanolide A on memory deficient mice showed significant regeneration of axons and dendrites and also reconstruction of presynapses and postsynapses in the damaged neurons (Kuboyama et al., 2005). Further, Withanolide A increases glutathione biosynthesis in rat neuronal cells by up regulating Nrf2 pathway and reduces neurogeneration (Baitharu et al., 2014).

Withania possesses an anti-stressor effect and is said to decrease stress induced changes. This antistress property of *Withania somnifera* have been investigated in a study of cold-water swimming stress test using adult Wistar strain albino rats. The results indicated that the drug treated animals show better stress tolerance (Gajarmal et al., 2001). Ashwagandha’s withanolides have been researched in a variety of animal studies examining their effect on numerous conditions, including immune function and even cancer (Ali et al., 2001; White et al., 2016). The extracts of seeds of *Withania somnifera* given to albino rats improved the protection against stomach ulcer caused due to stress (Singh et al., 1982; White et al., 2016). *Withania somnifera* suppressed stress induced gastric ulcer more effectively compared to the standard drug Ranitidine (Bhatnagar et al., 2005). Stress induced stomach ulcer was hindered by pre-treatment with sitoindosides VII and VIII and the forced swimming stress decreased the duration of the immobility after giving sitoindosides VII and VIII (Ghosal et al., 1989; Singh et al., 2011). In a research the animals received a mild electric foot shock for a period of 21 days and the stress effects on animals produced glucose intolerance, hyperglycemia, gastric ulceration, immunosuppression, mental depression and...
male sexual dysfunction (Bhattacharya & Muruganandam, 2003; Salve et al., 2019). Animals treated with Withania somnifera everyday one hour before the foot shock treatment experienced a reduced level of stress and its effects. This confirms Ashwagandha as a significant anti-stress adaptogen (Bhattacharya et al., 2001). Department of Pharmacology, University of Texas Health Science centre conducted research on Ashwagandha plant extracts and found that it produces GABA like activity which accounts for the herbs anti-stress effects (Mehta et al., 1991). Gamma amino butyric acid (GABA) is an inhibitory neurotransmitter and decreases the neuron activity from over firing, thus producing a calming effect. Rats were protected from stress induced stomach ulcer and also showed improvement in both short range and long range memory after oral application of sitoindosides IX and X (Ghosal et al., 1989). These results show that sitoindosides VII, VIII, IX and X represent adaptogenic substances of Withania somnifera (Singh et al., 2011).

A study on the effect of chronic electric shock for 14 days showed a significant decrease in the nor-adrenaline (NA) and Dopamine (DA) levels and increased 5-hydroxytryptamine (5HT) in regions of brain (Bhattacharya et al., 2002). EuMil is a polyherbal formulation which consist Withania somnifera as its key ingredient was administered on 14 days treatment and was found to normalize the level of NA, DA, 5HT induced by chronic stress (Bhattacharya et al., 2002). Treatment with Withania somnifera for two weeks was found to reverse both Ibotenicacids (IA) induced cognitive deficit and the reduction of cholinergic markers thus promoting the learning and memory capacity. In a human clinical trial of 20 patients suffering from anxiety disorder, the anxiolytics potential of Withania somnifera has been significantly evaluated (Andrade et al., 2000). Since anxiety is the outcome of chronic stress, Withania has a role in stress management (White et al., 2016).

Withania somnifera’s naturopathic care on anxiety symptoms when compared to other usual therapies was assessed in a study where the participants were randomly divided into two. They received the regular therapies with one group alone receiving Withania root standard (Cooley et al., 2009). In a study, the rats were sleep deprived for 24hours and then were injected with Withania somnifera extract. This resulted in shortened sleep latency, increased non rapid eye movement and sleep time, decreased waking and total sleep time (Kumar & Kalonia, 2008). Thus proved the effect of Withania somnifera root extracts possible interaction with GABAergic modulators which plays an important role in sleep wake cycle. This was clearly assessed by the antagonistic mechanism against GABAergic modulators picrotoxin and mucimol (Kumar & Kalonia, 2008). Withania ability to treat male infertility due to stress was proved in a trial comprising of 60 fertile men in control group and 60 infertile men in the treatment group (Shukla et al., 2009). Withania treatment decreased stress and increased the antioxidant level and overall semen quality in individuals. Added to this, the treatment resulted in the pregnancy of the partners of 14% of the patients (Mahdi et al., 2011).

SIMILARITIES BETWEEN WITHANIA SOMNIFERA AND PANAX GINSENG

Withania somnifera especially the root consists of secondary metabolite compound known as withanolides which is found to have extraordinary therapeutic and medicinal properties. Withanolides are steroidal alkaloids and steroidal lactones which resembles both in their appearance and action to the active constituents of Korean ginseng (Panax ginseng) known as ginsenosides. Studies have shown that Withania somnifera provides cardio protection in ischemic rats which is similar to the adaptogens in Panax ginseng (Figure 3). Heart weight and glycoegen in myocardium is found to significantly increase intensifying the anabolic process and enhancing the contractile duration (Mohanty et al., 2004; Lim et al., 2013). The extracts of both the Withania somnifera and Panax ginseng were compared for some of the therapeutic properties which also includes chronic stress (Bhattacharya & Muruganandam, 2003; Seenivasagam et al., 2011). It showed that both Ashwagandha and Panax ginseng reversed the chronic stress and its other related effects such as Ulcer, stress induced inhibition of sexual behavior, retention of learned tasks and immune suppression. Withania somnifera had very similar activity to that of Panax ginseng except that Withania somnifera had some extra advantages on increasing the peritoneal macrophage activity and exclude the appearance of ginseng-abuse syndrome characterized by water retention, muscle tension, insomnia and high blood pressure (Bhattacharya et al., 2000; Gajarmal et al., 2001). Further, the neuroprotective effects of Withania somnifera and Panax ginseng was studied in Parkinson’s induced rat models. The inhibition of oxidative stress and anti-inflammatory effects were found to be significantly decreasing the progression of PD in rats (Zhou et al., 2016; Vegh et al., 2021).

CONCLUSION

Plants have been used as adaptogen since ancient times. In traditional medical systems such as Ayurveda, Siddha and traditional Chinese medicines celebrated the ginseng family plants as a potent adaptogen, efficient Rasayana herb and heath tonic to rejuvenate the entire heath. Further, the adaptogens are commonly used to maintain homogeneity in human/animal body via regulations of certain metabolites. Stress induced disorders like neuro-endocrine disorders, immunomodulatory diseases could be reduced using herbal adaptogens. Among them, phyto-consituents such as withanolides and ginsenosides are widely used and studied for its apoptogenic properties. These are also believed as an adjuvant that increases the quality of life of humans in post recovery of diseases, surgical and traumatic accidents.
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ABBREVIATIONS

NO–Nitric oxide; CNS–Central nervous system; JNK–Jun N-terminal kinase; FOXO–Forkhead box O transcription factor; HSP–Heat shock protein; ATP–Adenyl tri phosphate; ACTH–Adrenocorticotropic hormone; REM–Rabid eye movement; GABA–Gamma amino butyric acid; IFN–Interferon; IL–Interleukin; TBNK–Lymphocyte subset (T, B, NK cells); GCLC–Glutamate-cysteine ligase catalytic subunit; NRF2–Nuclear factor erythroid 2; HT–Hydroxytryptamine.

REFERENCES


