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Review Article

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# 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

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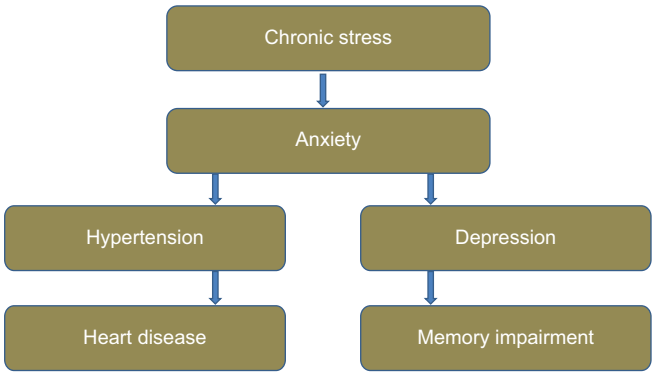


**Figure 1:** Chronic stress and its related defects

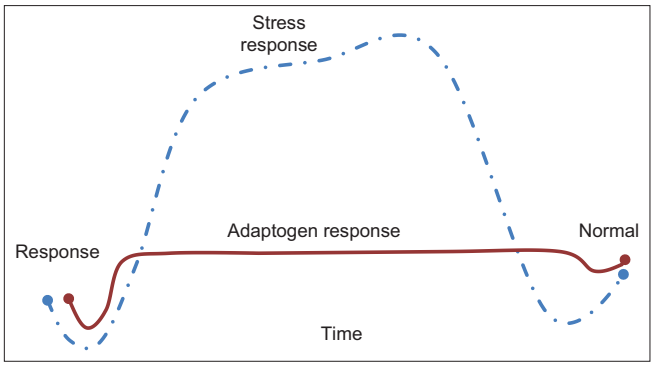


**Figure 2:** Effect of adaptogen on stress response

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 neutraceuticals 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 saponins 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, Rc, Rs3, 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, Rc, 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 (Voces *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).

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 vario0us other biochemical parameters such as creatine kinase, plasma glucose level, triglycerides, cholesterol and serum cortisterone. 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). Traditionally, *Withania somnifera* has been used to stabilize mood in patients with behavioral disturbances. Researches revealed that Withania produces anti-anxiety and anti-depressant effects in rats which are very similar to the drugs such as Lorazepam for anti-anxiety, Imipramine for anti-depressant (Archana & Namasivayam, 1998; Upadhyay *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 balb/c 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 GCLC level through Nrf2 pathway and reduces neurodgeneration (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).

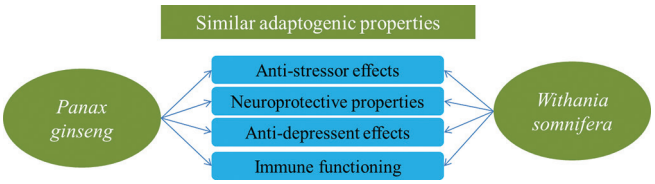


**Figure 3:** Similar adaptogenic properties between two ginseng plants

## 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 glycogen 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-constituents 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

Ali, N. A. A., Jülich, W. D., Kusnick, C., & Lindequist, U. (2001). Screening of Yemeni medicinal plants for antibacterial and cytotoxic activities. *Journal of Ethnopharmacology*, *74*(2), 173–179. https://doi.org/10.1016/S0378-8741(00)00364-0

Andrade, C., Aswath, A., Chaturvedi, S. K., Srinivasa, M., & Raguram, R. (2000). A double-blind, placebo-controlled evaluation of the anxiolytic efficacy of an ethanolic extract of *withania somnifera*. *Indian Journal of Psychiatry*, *42*(3), 295–301.

Archana, R., & Namasivayam, A. (1998). Antistressor effect of *Withania somnifera*. *Journal of Ethnopharmacology*, *64*(1), 91–93. https://doi.org/10.1016/S0378-8741(98)00107-X

Baitharu, I., Jain, V., Deep, S. N., Shroff, S., Sahu, J. K., Naik, P. K., & Ilavazhagan, G. (2014). Withanolide a prevents neurodegeneration by modulating hippocampal glutathione biosynthesis during hypoxia. *PLoS ONE*, *9*(10), e105311. https://doi.org/10.1371/journal.pone.0105311

Bhatnagar, M., Sisodia, S. S., & Bhatnagar, R. (2005). Antiulcer and antioxidant activity of *Asparagus racemosus* Willd and *Withania somnifera* Dunal in rats. *Annals of the New York Academy of Sciences*, *1056*, 261–278. https://doi.org/10.1196/annals.1352.027

Bhattacharya, A., Ghosal, S., & Bhattacharya, S. K. (2001). Anti-oxidant effect of *Withania somnifera* glycowithanolides in chronic footshock stress-induced perturbations of oxidative free radical scavenging enzymes and lipid peroxidation in rat frontal cortex and striatum. *Journal of Ethnopharmacology*, *74*(1), 1–6. https://doi.org/10.1016/S0378-8741(00)00309-3

Bhattacharya, A., Muruganandam, A. V., Kumar, V., & Bhattacharya, S. K. (2002). Effect of poly herbal formulation, EuMil, on neurochemical perturbations induced by chronic stress. *Indian Journal of Experimental Biology*, *40*(10), 1161–1163.

Bhattacharya, S., & Muruganandam, A. (2003). Adaptogenic activity of *Withania somnifera*: an experimental study using a rat model of chronic stress. *Pharmacology Biochemistry and Behavior*, *75*(3), 547–555. https://doi.org/10.1016/S0091-3057(03)00110-2

Braun, L., & Cohen, M. (2015). *Herbs and Natural Supplements* (Vol 2). In *Herbs and Natural Supplements: An evidence-based guide,* Chatswood, New South Wales, Australia: Elsevier.

Brekhman, I. I., & Dardymov, I. V. (1969). New substances of plant origin which increase nonspecific resistance. *Annual Review of Pharmacology*, *9*(1), 419–430. https://doi.org/10.1146/annurev.pa.09.040169.002223

Chen, J.-X., Li, W., Zhao, X., & Yang, J.-X. (2008). Effects of the Chinese traditional prescription xiaoyaosan decoction on chronic immobilization stress-induced changes in behavior and brain BDNF, TrkB, and NT-3 in rats. *Cellular and Molecular Neurobiology*, *28*(5), 745–755. https://doi.org/10.1007/s10571-007-9169-6

Chen, J., Li, Z., Hua, M., & Sun, Y. (2021). Protection by ginseng saponins against cyclophosphamide-induced liver injuries in rats by induction of cytochrome P450 expression and mediation of the l-arginine/nitric oxide pathway based on metabolomics. *Phytotherapy Research*, *35*(6), 3130–3144. https://doi.org/10.1002/ptr.6951

Chiu, P. Y., & Ko, K. M. (2004). Schisandrin B protects myocardial ischemia-reperfusion injury partly by inducing Hsp25 and Hsp70 expression in rats. *Molecular and Cellular Biochemistry*, *266*(1/2), 139–144. https://doi.org/10.1023/B: MCBI.0000049151.79238.30

Choi, K. (2008). Botanical characteristics, pharmacological effects and medicinal components of Korean Panax ginseng C A Meyer. *Acta Pharmacologica Sinica*, *29*(9), 1109–1118. https://doi.org/10.1111/j.1745-7254.2008.00869.x

Cooley, K., Szczurko, O., Perri, D., Mills, E. J., Bernhardt, B., Zhou, Q., & Seely, D. (2009). Naturopathic care for anxiety: A randomized controlled trial ISRCTN78958974. *PLoS ONE*, *4*(8), 4–13. https://doi.org/10.1371/journal.pone.0006628

Fllaketov, A. A., Bogdanova, T. S., Podvigina, T. T., & Bodganov, A. I. (2009). Role of pituitary-adrenocortical system in body adaptation abilities. *Experimental and Clinical Endocrinology & Diabetes*, *92*(05), 129–136. https://doi.org/10.1055/s-0029-1210793

Gajarmal, A. A., Shende, M. B., & Clothe, D. S. (2001). Antistress activity of ashwagandha (*Withania somnifera* Dunal) – A review. *International Ayurvedic Medical Journal*, *2*(3), 386–393.

Ghosal, S., Lal, J., Srivastava, R., Bhattacharya, S. K., Upadhyay, S. N., Jaiswal, A. K., & Chattopadhyay, U. (1989). Immunomodulatory and CNS effects of sitoindosides IX and X, two new glycowithanolides from *Withania somnifera*. *Phytotherapy Research*, *3*(5), 201–206. https://doi.org/10.1002/ptr.2650030510

Giridharan, V. V., Thandavarayan, R. A., Sato, S., Ko, K. M., & Konishi, T. (2011). Prevention of scopolamine-induced memory deficits by schisandrin B, an antioxidant lignan from *Schisandra chinensis* in mice. *Free Radical Research*, *45*(8), 950–958. https://doi.org/10.3109/10715762.2011.571682

Han, J.-Y., Ahn, S.-Y., Oh, E.-H., Nam, S.-Y., Hong, J. T., Oh, K.-W., & Lee, M. K. (2012). Red Ginseng extract attenuates kainate-induced excitotoxicity by antioxidative effects. *Evidence-Based Complementary and Alternative Medicine*, *2012*, 1–10. https://doi.org/10.1155/2012/479016

Hwang, Y. P., & Jeong, H. G. (2010). Ginsenoside Rb1 protects against 6-hydroxydopamine-induced oxidative stress by increasing heme oxygenase-1 expression through an estrogen receptor-related PI3K/Akt/Nrf2-dependent pathway in human dopaminergic cells. *Toxicology and Applied Pharmacology*, *242*(1), 18–28. https://doi.org/10.1016/j.taap.2009.09.009

Jin, Y., Cui, R., Zhao, L., Fan, J., & Li, B. (2019). Mechanisms of *Panax ginseng* action as an antidepressant. *Cell Proliferation*, *52*(6), 1–15. https://doi.org/10.1111/cpr.12696

Khanum, F., Singh, A., & Singh, B. (2005). *Rhodiola rosea* : A Versatile Adaptogen. *Comprehensive Reviews in Food Science and Food Safety*, *4*(4), 55–62. https://doi.org/10.1111/J.1541-4337.2005.TB00073.X

Kim, D. H., Moon, Y. S., Lee, T. H., Jung, J. S., Suh, H. W., & Song, D. K. (2003). The inhibitory effect of ginseng saponins on the stress-induced plasma interleukin-6 level in mice. *Neuroscience Letters*, *353*(1), 13–16. https://doi.org/10.1016/j.neulet.2003.08.070

Kim, J.-H. (2018). Pharmacological and medical applications of *Panax ginseng* and ginsenosides: a review for use in cardiovascular diseases. *Journal of Ginseng Research*, *42*(3), 264–269. https://doi.org/10.1016/j.jgr.2017.10.004

Kim, S. H., Park, K. S., Chang, M. J., & Sung, J. H. (2005). Effects of *Panax ginseng* extract on exercise-induced oxidative stress. *The Journal of Sports Medicine and Physical Fitness*, *45*(2), 178–182.

Kim, S., Nah, S. Y., & Rhim, H. (2008). Neuroprotective effects of ginseng saponins against L-type Ca2+ channel-mediated cell death in rat cortical neurons. *Biochemical and Biophysical Research Communications*, *365*(3), 399–405. https://doi.org/10.1016/j.bbrc.2007.10.048

Kitaoka, K., Uchida, K., Okamoto, N., Chikahisa, S., Miyazaki, T., Takeda, E., & Séi, H. (2009). Fermented ginseng improves the first-night effect in humans. *Sleep*, *32*(3), 413–421. https://doi.org/10.1093/sleep/32.3.413

Kour, K., Pandey, A., Suri, K. A., Satti, N. K., Gupta, K. K., & Bani, S. (2009). Restoration of stress-induced altered T cell function and corresponding cytokines patterns by Withanolide A. *International Immunopharmacology*, *9*(10), 1137–1144. https://doi.org/10.1016/j.intimp.2009.05.011

Kuboyama, T., Tohda, C., & Komatsu, K. (2005). Neuritic regeneration

and synaptic reconstruction induced by withanolide A. *British Journal of Pharmacology*, *144*(7), 961–971. https://doi.org/10.1038/sj.bjp.0706122

Kumar, A., & Kalonia, H. (2008). Effect of *Withania somnifera* on sleep-wake cycle in sleep-disturbed rats: Possible GABAergic mechanism. *Indian Journal of Pharmaceutical Sciences*, *70*(6), 806–810. https://doi.org/10.4103/0250-474X.49130

Lazarev, N. V., Liublina, E. I., & Rozin, M. A. (1959). [States of non-specific increased resistance]. *Patologicheskaia Fiziologiia i Eksperimental'naia Terapiia*, *3*, 16–21.

Lee, S. E., Lee, S. W., Bang, J. K., Yu, Y. J., & Seong, N. S. (2004). Antioxidant activity of leaf, stem, and root of *Panax ginseng* C. A. Meyer. *Korean Journal of Medicinal Crop Science, 12*(3), 237–242).

Lee, S., & Rhee, D.-K. (2017). Effects of ginseng on stress-related depression, anxiety, and the hypothalamic–pituitary–adrenal axis. *Journal of Ginseng Research*, *41*(4), 589–594. https://doi.org/10.1016/j.jgr.2017.01.010

Li, N., Liu, B., Dluzen, D. E., & Jin, Y. (2007). Protective effects of ginsenoside Rg2 against glutamate-induced neurotoxicity in PC12 cells. *Journal of Ethnopharmacology*, *111*(3), 458–463. https://doi.org/10.1016/j.jep.2006.12.015

Liao, L., He, Y., Li, L., Meng, H., Dong, Y., Yi, F., & Xiao, P. (2018). A preliminary review of studies on adaptogens : comparison of their bioactivity in TCM with that of ginseng - like herbs used worldwide. *Chinese Medicine*, *13*(57), 1–12. https://doi.org/10.1186/s13020-018-0214-9

Lim, K. H., Ko, D., & Kim, J.-H. (2013). Cardioprotective potential of Korean Red Ginseng extract on isoproterenol-induced cardiac injury in rats. *Journal of Ginseng Research*, *37*(3), 273–282. https://doi.org/10.5142/jgr.2013.37.273

Lopresti, A. L., Smith, S. J., Malvi, H., & Kodgule, R. (2019). An investigation into the stress-relieving and pharmacological actions of an ashwagandha (*Withania somnifera*) extract. *Medicine*, *98*(37), e17186. https://doi.org/10.1097/MD.0000000000017186

Mahdi, A. A., Shukla, K. K., Ahmad, M. K., Rajender, S., Shankhwar, S. N., Singh, V., & Dalela, D. (2011). *Withania somnifera* improves semen quality in stress-related male fertility. *Evidence-Based Complementary and Alternative Medicine*, *2011*, 1–9. https://doi.org/10.1093/ecam/nep138

Mehta, A. K., Binkley, P., Gandhi, S. S., & Ticku, M. K. (1991). Pharmacological effects of *Withania somnifera* root extract on GABAA receptor complex. *The Indian Journal of Medical Research*, *94*, 312–315.

Mohanty, I., Gupta, S. K., Talwar, K. K., Dinda, A., Joshi, S., Bansal, P., Saxena, A., & Arya, D. S. (2004). Cardioprotection from ischemia and reperfusion injury by *Withania somnifera*: A hemodynamic, biochemical and histopathological assessment. *Molecular and Cellular Biochemistry*, *260*(1), 39–47. https://doi.org/10.1023/B: MCBI.0000026051.16803.03

Nam, K.-Y. (2005). The Comparative understanding between red ginseng and white ginsengs, processed ginsengs (*Panax ginseng* C. A. Meyer). *Journal of Ginseng Research*, *29*(1), 1–18. https://doi.org/10.5142/JGR.2005.29.1.001

Oliveira, D. R. de, & Leitão, S. G. (2016). Introduction to Ethnobiology. In U. P. Albuquerque & R. R. Nóbrega Alves (Eds.), *Introduction to Ethnobiology*. Springer International Publishing. https://doi.org/10.1007/978-3-319-28155-1

Oliynyk, S., & Oh, S. (2013). Actoprotective effect of ginseng: improving mental and physical performance. *Journal of Ginseng Research*, *37*(2), 144–166. https://doi.org/10.5142/jgr.2013.37.144

Panossian, A. G. (2003). Adaptogens: Tonic herbs for fatigue and stress. *Alternative and Complementary Therapies*, *9*(6), 327–331. https://doi.org/10.1089/107628003322658610

Panossian, A. G., Efferth, T., Shikov, A. N., Pozharitskaya, O. N., Kuchta, K., Mukherjee, P. K., Banerjee, S., Heinrich, M., Wu, W., Guo, D. an, & Wagner, H. (2021). Evolution of the adaptogenic concept from traditional use to medical systems: Pharmacology of stress- and aging-related diseases. *Medicinal Research Reviews*, *41*(1), 630–703. https://doi.org/10.1002/med.21743

Panossian, A., Hambardzumyan, M., Hovhanissyan, A., & Wikman, G. (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*, *2*(46), 39–54. https://doi.org/10.1177/117739280700200011

Panossian, A., & Wagner, H. (2005). Stimulating effect of adaptogens: An overview with particular reference to their efficacy following single dose administration. *Phytotherapy Research*, *838*(September), 819–838. https://doi.org/10.1002/ptr.1751

Panossian, A., & Wikman, G. (2010). Effects of Adaptogens on the central nervous system and the molecular mechanisms associated with their stress-protective activity. *Pharmaceuticals*, *3*(1), 188–224. https://doi.org/10.3390/ph3010188

Panossian, A., Wikman, G., Kaur, P., & Asea, A. (2009). Adaptogens exert a stress-protective effect by modulation of expression of molecular chaperones. *Phytomedicine*, *16*(6–7), 617–622. https://doi.org/10.1016/j.phymed.2008.12.003

Panossian, A., Wikman, G., Kaur, P., & Asea, A. (2012). Adaptogens stimulate neuropeptidey and Hsp72 expression and release in neuroglia cells. *Frontiers in Neuroscience*, *6*(FEB), 1–12. https://doi.org/10.3389/fnins.2012.00006

Patel, S., & Rauf, A. (2017). Adaptogenic herb ginseng (*Panax*) as medical food: Status quo and future prospects. *Biomedicine & Pharmacotherapy*, *85*, 120–127. https://doi.org/10.1016/j.biopha.2016.11.112

Provino, R. (2010). The role of adaptogens in stress management. *Australian Journal of Medical Herbalism*, *22*(2), 41–50.

Radad, K., Gille, G., Moldzio, R., Saito, H., & Rausch, W. D. (2004). Ginsenosides Rb 1 and Rg 1 effects on mesencephalic dopaminergic cells stressed with glutamate. *Brain Research*, *1021*(1), 41–53. https://doi.org/10.1016/j.brainres.2004.06.030

Rai, D., Bhatia, G., Sen, T., & Palit, G. (2003). Anti-stress effects of *Ginkgo biloba* and *Panax ginseng*: A comparative study. *Journal of Pharmacological Sciences*, *93*(4), 458–464. https://doi.org/10.1254/jphs.93.458

Saba, E., Kim, S.-H., Kim, S.-D., Park, S.-J., Kwak, D., Oh, J.-H., Park, C.- K., & Rhee, M. H. (2018). Alleviation of diabetic complications by ginsenoside Rg3-enriched red ginseng extract in western diet-fed LDL–/– mice. *Journal of Ginseng Research*, *42*(3), 352–355. https://doi.org/10.1016/j.jgr.2017.04.004

Salve, J., Pate, S., Debnath, K., & Langade, D. (2019). Adaptogenic and anxiolytic effects of ashwagandha root extract in healthy adults : A double-blind, randomized, placebo-controlled clinical study. *Cureus*, *11*(12), 1–12. https://doi.org/10.7759/cureus.6466

Seenivasagam, R., Sathiyamoorthy, S., & Hemavathi, K. (2011). Therapeutic impacts of Indian and Korean ginseng on human beings – a review. *International Journal of Immunological Studies*, *1*(3), 297. https://doi.org/10.1504/ijis.2011.041727

Shin, E. J., Jeong, J. H., Kim, A. Y., Koh, Y. H., Nah, S. Y., Kim, W. K., Ko, K. H., Kim, H. J., Wie, M. B., Kwon, Y. S., Yoneda, Y., & Kim, H. C. (2009). Protection against kainate neurotoxicity by ginsenosides: Attenuation of convulsive behavior, mitochondrial dysfunction, and oxidative stress. *Journal of Neuroscience Research*, *87*(3), 710–722. https://doi.org/10.1002/jnr.21880

Shukla, K. K., Mahdi, A. A., Ahmad, M. K., Shankhwar, S. N., Rajender, S., & Jaiswar, S. P. (2009). Mucuna pruriens improves male fertility by its action on the hypothalamus-pituitary-gonadal axis. *Fertility and Sterility*, *92*(6), 1934–1940. https://doi.org/10.1016/j.fertnstert.2008.09.045

Singh, N., (Mrs.) Nath, R., (Miss) Lata, A., Singh, S. P., Kohli, R. P., & Bhargava, K. P. (1982). *Withania somnifera* (ashwagandha), a rejuvenating herbal drug which enhances survival during stress (an adaptogen). *Pharmaceutical Biology*, *20*(1), 29–35. https://doi.org/10.3109/13880208209083282

Singh, N., Bhalla, M., De Jager, P., & Gilca, M. (2011). An Overview on Ashwagandha: A Rasayana (Rejuvenator) of Ayurveda. *African Journal of Traditional, Complementary and Alternative Medicines*, *8*(5S), 208–213. https://doi.org/10.4314/ajtcam.v8i5S.9

Sohn, S.-H., Kim, S.-K., Kim, Y.-O., Kim, H.-D., Shin, Y.-S., Yang, S.-O., Kim, S.-Y., & Lee, S.-W. (2013). A comparison of antioxidant activity of Korean White and Red Ginsengs on H 2 O 2 -induced oxidative stress in HepG2 hepatoma cells. *Journal of Ginseng Research*, *37*(4), 442–450. https://doi.org/10.5142/jgr.2013.37.442

Stratakis, C. A., & Chrousos, G. P. (1995). Neuroendocrinology and Pathophysiology of the Stress System. *Annals of the New York Academy of Sciences*, *771*(1 Stress), 1–18. https://doi.org/10.1111/j.1749-6632.1995.tb44666.x

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. *Journal of Pharmacological Sciences*, *95*(2), 140–144. https://doi.org/10.1254/jphs.FMJ04001X2

Tharakan, A., Shukla, H., Benny, I. R., Tharakan, M., George, L., & Koshy, S. (2021). Immunomodulatory Effect of *Withania somnifera* (Ashwagandha) Extract—A randomized, double-blind, placebo controlled trial with an open label extension on healthy participants. *Journal of Clinical Medicine*, *10*(16), 3644. https://doi.org/10.3390/jcm10163644

Todorova, V., Ivanov, K., Delattre, C., Nalbantova, V., & Karcheva-Bahchevanska, D. Ivanova, S. (2021). Plant adaptogens — History and future perspectives. *Nutrients*, *13*, 1–21. https://doi.org/10.3390/nu13082861

Upadhyay, G., Khoshla, S., Kosuru, R., & Singh, S. (2016). Anxiolytic, antidepressant, and antistress activities of the aqueous extract of *Cinnamomum tamala* Nees and Eberm in rats. *Indian Journal of Pharmacology*, *48*(5), 555. https://doi.org/10.4103/0253-7613.190752

van Wyk, B.-E., & Wink, M. (2004). Medicinal plants of the world. In *South Africa: Briza Publications*. https://doi.org/10.1515/9781400857555.43

Vegh, C., Wear, D., Okaj, I., Huggard, R., Culmone, L., Eren, S., Cohen, J., Rishi, A. K., & Pandey, S. (2021). Combined ubisol-q10 and ashwagandha root extract target multiple biochemical mechanisms and reduces neurodegeneration in a paraquat-induced rat model of parkinson's disease. *Antioxidants*, *10*(4). https://doi.org/10.3390/antiox10040563

Voces, J., Cabral de Oliveira, A. C., Prieto, J. G., Vila, L., Perez, A. C., Duarte, I. D. G., & Alvarez, A. I. (2004). Ginseng administration protects skeletal muscle from oxidative stress induced by acute exercise in rats. *Brazilian Journal of Medical and Biological Research*, *37*(12), 1863–1871. https://doi.org/10.1590/S0100-879X2004001200012

White, P. T., Subramanian, C., Motiwala, H. F., & Cohen, M. S. (2016). Natural Withanolides in the treatment of chronic diseases. *Advances in Experimental Medicine and Biology*, *928*, 329–373. https://doi.org/10.1007/978-3-319-41334-1_14

Wiegant, F. A. C., Surinova, S., Ytsma, E., Langelaar-Makkinje, M., Wikman, G., & Post, J. A. (2009). Plant adaptogens increase lifespan and stress resistance in C. elegans. *Biogerontology*, *10*(1), 27–42. https://doi.org/10.1007/s10522-008-9151-9

Ye, R., Li, N., Han, J., Kong, X., Cao, R., Rao, Z., & Zhao, G. (2009). Neuroprotective effects of ginsenoside Rd against oxygen-glucose deprivation in cultured hippocampal neurons. *Neuroscience Research*, *64*(3), 306–310. https://doi.org/10.1016/j.neures.2009.03.016

Zarabi, L., Arazi, H., & Izadi, M. (2018). The effects of *Panax ginseng* supplementation on growth hormone, cortisol and lactate response to high-intensity resistance exercise. *Biomedical Human Kinetics*, *10*(1), 8–14. https://doi.org/10.1515/bhk-2018-0002

Zhang, Q. H., Wu, C. F., Duan, L., & Yang, J. Y. (2008). Protective effects of total saponins from stem and leaf of Panax ginseng against cyclophosphamide-induced genotoxicity and apoptosis in mouse bone marrow cells and peripheral lymphocyte cells. *Food and Chemical Toxicology*, *46*(1), 293–302. https://doi.org/10.1016/j.fct.2007.08.025

Zhou, T., Zu, G., Zhang, X., Wang, X., Li, S., Gong, X., Liang, Z., & Zhao, J. (2016). Neuroprotective effects of ginsenoside Rg1 through the Wnt/β-catenin signaling pathway in both in vivo and in vitro models of Parkinson's disease. *Neuropharmacology*, *101*, 480–489. https://doi.org/10.1016/j.neuropharm.2015.10.024