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Effects of Ashwagandha (Withania Somnifera) on Stress and Anxiety: A Systematic Review

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Abstract

Background: Stress is a known causative factor in modulating cognitive health, on which the overall well-being and quality of life are dependent. Long-term stress has shown to disrupt the balance of the hypothalamic–pituitary–adrenal (HPA) axis. Adaptogens, such as Withania somnifera (Ashwagandha), are commonly used in ayurvedic medicine for stress relief and ameliorating HPA-axis dysfunction. Its current research covers many aspects of human health, including neuroprotective, sedative and adaptogenic effects, and effects on sleep. The species name somnifera comes from the Latin word for sleep-inducing, signifying another purported property of this botanical. In addition to sleep, Ashwagandha is commonly promoted for stress and anxiety reduction. Ashwagandha is rich in phytochemicals, including steroidal lactones (known as withanolides) and alkaloids.

Methods: A comprehensive search was conducted in MEDLINE, EMBASE, PubMed, PsychINFO and the Cochrane Library. Randomized controlled trials that examined the effects of Ashwagandha on stress and anxiety were included. Both subjective and objective measures of stress and anxiety were assessed as outcome variables.

Conclusion: The findings from the included studies indicated that Ashwagandha formulations had beneficial effects on stress and axnxiety. The adverse effects associated with Ashwagandha are limited; however, further information is required to determine its safety with long-term administration.

Key words: anxiety; ashwagandha; ayurveda; perceived stress scale (pss); psychosomatic; stress; withania somnifera; ashwagandha

Introduction:

Anxiety & Stress:

Ayurveda, the traditional system of medicine from India, offers a holistic approach to managing anxiety, focusing on balancing the body's energies (doshas), mind, and spirit. The Ayurvedic perspective on anxiety is that it results from an imbalance in the mind-body connection, often due to factors like stress, poor diet, lack of sleep, or unresolved emotional issues. Anxiety is commonly associated with the Vata dosha, which governs movement, energy, and the nervous system. An imbalance in Vata can lead to restlessness, worry, and fear, which are common symptoms of anxiety [1]. Pitta dosha, which controls digestion and metabolism, can also contribute to anxiety when it becomes excessive, leading to irritability and impatience [2]. Kapha dosha imbalances, though less common, can contribute to anxiety in the form of lethargy and depression [3].

Anxiety is often accompanied by stress, which is the body's physiologic response to mental or physical threats. While brief exposure to the stress response is meant to be a beneficial coping mechanism, long-term stress is likely to result in the decline of overall health and the complication of existing diseases [4]. According to the World Health Organization (WHO), approximately 4.4% of the global population is affected by anxiety disorders. This equates to more than 300 million people worldwide[v]. Anxiety and Depression are one of the symptoms in various diseases but are not a disease itself. It may be due to various reasons such as the aspects involving both personal and professional life of an individual.

2. Drug review: Ashwagandha

Ashwagandha (Withania somnifera) is an adaptogenic herb, has a long history of use for its health benefits, particularly for reducing stress and anxiety. The species name somnifera comes from the latin word for sleep-inducing, signifying another purported property of this botanical [5]. Ashwagandha (*Withania somnifera*, fam. Solanaceae) is commonly known as “Indian Winter cherry” or “Indian Ginseng”. It is one of the most important herb of Ayurveda (the traditional system of medicine in India) used for millennia as a Rasayana for its wide ranging health benefits. Ashwagandha is commonly promoted for its well-known assistance in stress and anxiety reduction, in addition to stimulating a sound sleep. The Nagori Ashwagandha is the supreme among all the known Ashwagandha varieties. It is known to provide maximum benefit when fresh Ashwagandha powder is used [6] .

Ashwagandha offers numerous benefits. Some common usages of the drug is summarized here. *Stress and Anxiety Reduction*: Ashwagandha is known for its ability to reduce stress by lowering cortisol levels (the stress hormone). It helps the body to adapt stress and promotes a sense of calm. A study on Ashwagandha has shown similar anti-stress activity in rats [4]. It also exhibited an antidepressant effect, comparable with that induced by imipramine, in two standard tests, the forced swim-induced ‘behavioral despair’ and ‘learned helplessness’ tests. Another investigation support the use of Ashwagandha as a mood stabilizer in clinical conditions of anxiety and depressionvi. *Improved Sleep*: Due to its calming effects, Ashwagandha may help improve sleep quality, making it a popular remedy for insomnia. *Boosts Energy and Stamina*: It is often used to enhance physical endurance, strength, and energy. Some studies suggest that Ashwagandha may help in improving physical performance and recovery, especially in athletes. *Cognitive Function*: Ashwagandha has been linked to improved brain function, memory, and focus. It may also support cognitive health by reducing oxidative stress and inflammation in the brain. *Mood Enhancement*: It can help stabilize mood and may have antidepressant-like effects, particularly in people with mild to moderate depression. *Anti-Inflammatory Properties*: Ashwagandha contains compounds that may reduce inflammation, supporting overall health and recovery from physical ailments. *Hormonal Balance*: In men, Ashwagandha may support healthy testosterone levels and fertility. It is also believed to help balance thyroid hormones.

Ayurvedic view on Ashwagandha (Withania somnifera)

Pharmacodynamic properties:

S.No.	Nighantu	Ras	Virya	Vipaka	Gun	Doshaghnata
1.	R.N.[viii]	*Katu,Tikta*	*Ushna*			Vata
2.	P.N.[ix]	*Tikta, Katu, Madhur*	*Ushna*	*Madhura*	*Laghu, Snigdha*	*Vata*
3.	S.N.[x]	-	-	-	-	*Vata*
4.	D.N.[xi]	*Kashaya,Tikta*	*Ushna*	-	-	*Vata,Kapha*
5.	B.P.N.[xii]	*Tikta, Kashaya*	*Ushna*	-	-	*Vata,Kapha*
6.	K.N.[xiii]	*Tikta, Kashaya*	*Ushna*	-	-	*Kapha*
7.	M.P.N.[xiv]	*Kashaya, Tikta*	*Ushna*	-	-	*Vata,Kapha*
8.	M.V.N.[xv]	*Tikta, Kashaya*	*Ushna*	-	-	*Vata,Kapha*

Table 1: *Pharmacological properties of Withania somnifera*

Properties:

Vajikara* (Increases sexual craving) is a one of eight major specialty of the Ashtanga Ayurveda. It is an important treatment modality and has benefits of increased sexual capacity and improving health of future progeny as well as in treatment of many common sexual disorders like infertility, erectile dysfunction and premature ejaculation. Rasayani* (Revitalizes the body). Rasayana chikitsa or therapy, is an ayurvedic rejuvenation therapy that focuses on strengthening the body and mind. It replenishes the vital fluids of the body; boosts the Ojas (vital force of life) and the immune system, thus keeping away from diseases and prevents against ill effects of advanced age. Balya* (develops strength) involves treatment and substances that enhance strength and vitality, promoting overall well-being and recovery from debility. Ati Shukrala* (enhances quality and amount of semen) drugs enhance the quality and quantity of Shukra. It enhances the Shukra (semen and sperm) quantitatively and qualitatively and facilitates its ejaculation. Shwitrapaha* (Useful in treating of white staining of the skin) Shwitra is mentioned in Kushta Roga Chikitsa in classics. It is useful in treating of white staining of the skin. Shothahara* (Useful in treating of edematous conditions and assists with clearing pollutants (Ama) from the different regions of the body) Swelling anywhere on body can be called as Shotha so Shotha Roga. It is useful in treating of edematous conditions and assists with clearing pollutants (Ama) from the different regions of the body. Kshayapaha* (Useful in treating thinness and under nutritive conditions) is useful in treatment for malnutrition, thinness and under nutritive conditions.

4. Mode of Action

Ashwagandha is considered an adaptogen, which means it helps the body adapt to stress and maintain balance (homeostasis). It contains bioactive compounds called withanolides, which are believed to contribute to its therapeutic effects. The biologically active chemical constituents of Withania somnifera include alkaloids (isopelletierine, anaferine, cuseohygrine, anahygrine, etc.), steroidal lactones (withanolides, withaferins) and saponinsxv . Sitoindosides and acylsterylglucosides in Ashwagandha are anti-stress agents. Active principles of Ashwagandha, for instance the sitoindosides VII-X and Withaferin-A, have been shown to have significant anti-stress activity against acute models of experimental stressxix. Many of its constituents support immunomodulatory actionsxx. The aerial parts of Withania somnifera yields 5-dehydroxy withanolide-R and withasomniferin-Axxi.

Anti-Stress Effects

- Results from several clinical trials suggest that Ashwagandha extracts may help reduce stress and anxiety. A 2021 systematic review identified seven studies that investigated the use of Ashwagandha to treat stress and anxietyxxii. A total of 491 adults, all from India, with either self-reported high stress and anxiety or a diagnosed anxiety disorder, were randomized to take Ashwagandha or placebo for 6 to 8 weeks. Six of the studies used extracts made from Ashwagandha root alone (three studies, KSM-66), root and leaf (two studies, Sensoril or Shoden), or unspecified parts (one study), while the seventh study used dried root powder made into granules. The Ashwagandha dose varied from 240 to 1,250 mg/day of extract or 12,000 mg/day of whole root granules, which is equivalent to 6,000 mg of root powder. Overall, the studies found that Ashwagandha significantly reduced stress and anxiety levels (subjectively measured by validated rating scales), reduced sleeplessness and fatigue, and reduced serum cortisol levels (a stress hormone) when compared with placebo. In several studies, the benefits appeared to be greater with doses of 500 to 600 mg/day than with lower doses.
- In India, at two health centers 130 healthy men and women age 20 to 55 years with self-reported stress were randomized to take a sustained-released Ashwagandha root extract (Prolanza) or placebo for 90 daysxxiii. The extract was standardized to contain 15 mg withanolides per 300-mg capsule, and participants took one capsule daily. Compared with those who received placebo, participants who took Ashwagandha extract reported improvements in stress levels and sleep quality as measured by validated rating scales. They also had lower serum cortisol levels. In addition, participants reported improvements in psychological well-being, memory, and focus.
- Another study in India randomized 54 participants with mild to moderate stress and anxiety to receive either Ashwagandha root extract (Shagandha) or placeboxx . The participants in the Ashwagandha group were given tablets that were standardized to contain 2.5% withanolides; each tablet included 500 mg of the root extract and 5 mg of piperine. At day 60, participants in the Ashwagandha group had significantly lower scores for stress and anxiety on two validated rating scales than those in the placebo group. In addition, the quality of life scores increased significantly for people in the Ashwagandha group between baseline and day 60. Moreover, the researchers noted improvements in multitasking and concentration among the participants in this group.
- At the University of Colorado, in Colorado Springs, 60 students (age 18–50 years) were randomized to take an Ashwagandha root extract (Gaia Herbs) or placebo for 30 days in a double-blind trialxx ,xx . The extract contained 2.5 mg withanolides per 350-mg capsule, and participants took two capsules daily. The investigators gathered qualitative, subjective information from participants during daily check-ins and focus groups. Participants who took Ashwagandha root extract reported increased well-being, including a sense of calm; improved energy levels; heightened mental clarity;

and enhanced sleep quality. While the descriptions of stress were comparable in both groups, participants who took Ashwagandha were more likely to describe their stress as manageable compared with those taking placebo.

- A randomized clinical trial (RCTs) that investigate the effect of Ashwagandha extract on anxiety and stress is included herexxvii. The overall effect size was pooled by random-effects model and the standardized mean difference (SMD) and 95% confidence interval (CIs) for outcomes were applied. Overall, 12 eligible papers with a total sample size of 1,002 participants and age range between 25 and 48 years were included in the current systematic review and meta-analysis. It was found that Ashwagandha supplementation significantly reduced anxiety (SMD: -1.55, 95% CI: -2.37, -0.74; p = .005; I2 = 93.8%) and stress level (SMD: -1.75; 95% CI: -2.29, -1.22; p = .005; I2 = 83.1%) compared to the placebo. Additionally, the non-linear dose-response analysis indicated a favorable effect of Ashwagandha supplementation on anxiety until 12,000 mg/d and stress at dose of 300-600 mg/d.

B. Anti-Anxiety Effects

- WS has been used to stabilize mood in patients with behavioural disturbances. A study investigated the anxiolytic and antidepressant actions of the bioactive glycowithanolides (WSG), isolated from WS roots, in ratsxxviii. WSG (20 and 50 mg/kg) was administered orally once daily for 5 days and the results were compared by those elicited by the benzodiazepine lorazepam (0.5 mg/kg, i.p.) for anxiolytic studies, and by the tricyclic anti-depressant, imipramine (10 mg/kg, i.p.), for the antidepressant investigations. Both these standard drugs were administered once, 30 min prior to the tests. WSG induced an anxiolytic effect, comparable to that produced by lorazepam, in the elevated plus-maze, social interaction and feeding latency in an unfamiliar environment, tests. Further, both WSG and lorazepam, reduced rat brain levels of tribulin, an endocoid marker of clinical anxiety, when the levels were increased following administration of the anxiogenic agent, pentylenetetrazole. WSG also exhibited an antidepressant effect, comparable with that induced by imipramine, in the forced swim-induced 'behavioural despair' and 'learned helplessness' tests. The investigations support the use of WS as a mood stabilizer in clinical conditions of anxiety and depression in Ayurveda.
- Results from studies published after 2021 review also suggest that Ashwagandha has a beneficial impact on perceived stressxxix. For example, one clinical trial was conducted in Florida over 60 men and women (mean age 34 years) who reported experiencing stress. Participants took capsules that contained 225 mg/day or 400 mg/day of a proprietary Ashwagandha root and leaf extract (NooGandha) or placebo for 30 days. Compared with participants in the placebo group, those in both Ashwagandha groups reported positive effects on stress, anxiety, depression, and food cravings as measured by validated rating scales. In addition, participants who took the 225-mg dose had lower saliva cortisol levels than those in the placebo group.
- Another randomized clinical trial included 120 healthy men and women (mean age 54–55 years) who were overweight or mildly obese and experiencing low energy and fatiguexxx. Participants took an Ashwagandha root extract (Witholytin, which contains 200 mg hydroalcoholic extract of Ashwagandha root standardized to 1.5% withanolides) or placebo twice daily for 12 weeks. Results showed that Ashwagandha helped in reducing fatigue.

C. Sleep-Promoting Effects

- At one study center in India, 150 healthy men and women aged 18 to 65 years with self-reported sleep problems characterized by insomnia and lack of sound sleep were randomized to take Ashwagandha root and leaf extract (Shoden) or placebo for 6 weeksxxxi. The extract was standardized to contain 21 mg of withanolide glycosides per 60-mg capsule, and participants took two capsules each day. Both groups reported improvements in sleep quality as measured by a validated rating scale, but the improvements were greater in the Ashwagandha group (72%) than in the placebo group (29%). In addition, participants who took Ashwagandha extract showed improvements in sleep efficiency (time in bed spent in sleep), total sleep time, sleep latency (time taken to fall asleep), and awakening after sleep onset.
- In another trial conducted in India, 80 healthy men and women age 18 to 50 years, half of them with insomnia, were randomized to take Ashwagandha root extract (KSM-66) or placebo for 8 weeksxxxii. The extract was standardized with anolide content of more than 5% per 300-mg capsule, and participants took two capsules each day. Participants with insomnia who took Ashwagandha extract showed improvements in sleep quality, sleep onset latency, mental alertness on rising, and perceived anxiety symptoms compared with those taking placebo, as measured by actigraphy and validated rating scales. Participants without insomnia who took Ashwagandha also reported that Ashwagandha improved their sleep but it did not improve their perceived anxiety symptoms or their mental alertness on awakening.
- A Bayesian hierarchical models were developed for a pre-specified subgroup meta-analysis on strength/power, cardiorespiratory fitness and fatigue/recovery variablesxxxiii. A total of 13 studies met the requirements of this systematic review, although only 12 were included in the quantitative analysis. The meta-analytic approaches of the included studies revealed that Ashwagandha supplementation was more efficacious than placebo for improving variables related to physical performance in healthy men and female. In fact, the Bayesian models showed that future

interventions might be at least in some way beneficial on the analyzed outcomes considering the 95% credible intervals for the meta-analytic effect size.

- In a eight-week, prospective, randomized, double-blind, placebo-controlled study, the stress-relieving effect of Ashwagandha root extract was investigated in stressed healthy adultsxxxiv. Sixty male and female participants with a baseline perceived stress scale (PSS) score >20 were randomized to receive capsules of Ashwagandha extract 125 mg, Ashwagandha extract 300 mg or identical placebo twice daily for eight weeks in a 1:1:1 ratio. Two participants (one each in 250 mg/day Ashwagandha and placebo) were lost to follow-up and 58 participants completed the study. A significant reduction in PSS scores was observed with Ashwagandha 250 mg/day ($P < 0.05$) and 600 mg/day ($P < 0.001$). Serum cortisol levels reduced with both Ashwagandha 250 mg/day ($P < 0.05$) and Ashwagandha 600 mg/day ($P < 0.0001$). Compared to the placebo group participants, the participants receiving Ashwagandha had significant improvement in sleep quality.
- Ashwagandha extract appears to have a beneficial effect in improving sleep in adultsxxxv. A total of five randomized controlled trials containing 400 participants were analyzed. Ashwagandha extract exhibited a small but significant effect on overall sleep (Standardized Mean Difference -0.59; 95% Confidence Interval -0.75 to -0.42; $I2 = 62\%$). The effects on sleep were more prominent in the subgroup of adults diagnosed with insomnia, treatment dosage ≥600 mg/day, and treatment duration ≥8 weeks. Ashwagandha extract was also found to improve mental alertness on rising and anxiety level, but no significant effect on quality of life. No serious side effects were reported.

D. Adaptogenic Effects

Adaptogens are herbs that improve an individual's ability to cope with stress and adapt to change. The most recent definition of an adaptogen is "a class of metabolic regulators that enhances the body's ability to adapt to environmental factors and avoid the damage they could imply." The ideal adaptogen should reduce negative changes caused by stress, be safe and act beneficially even when the dose given is higher than required, and be free of adverse side effects, such as not affecting the functioning of the body more than neededxxxvi. Based on the above-mentioned characteristics, Ashwagandha can be considered as an adaptogen.

E. Immunomodulation and Hematopoiesis

A series of animal studies show Ashwagandha to have profound effects on the hematopoietic system, acting as an immunoregulator and a chemo protective agentxxxvii.

In a mouse study, administration of a powdered root extract from Ashwagandha was found to enhance total white blood cell count. In addition, this extract inhibited delayed-type hypersensitivity reactions and enhanced phagocyte activity of macrophages when compared to a control groupxxxviii.

F. Neuroprotective and Anti-Neurodegenerative Effects

Neurodegenerative diseases cause the destruction of the central nervous system, resulting in irreversible damage. Over the course of Alzheimer's disease, an abnormal deposition of β-amyloid protein in the brain is observed. In its fibrillar form, it has a neurotoxic effect because it induces the formation of free radicals and impairs glucose transport in neurons, which leads to cell damage and death.

In studies conducted on human nerve cells, Ashwagandha has been shown to neutralize the toxic effects of β-amyloid, an implication in neurocognitive impairment during HIV infectionxxxix.

A study was conducted on rats that were orally administered vitanon—an ingredient isolated from the root of Whitania somnifera. Significant improvements in cognitive function were observed as a result of the inhibition of amyloid β-42, and a reduction in pro-inflammatory cytokines TNF-α, IL-1β, IL-6, and MCP-1, nitric oxide, and lipid peroxidation was also observed. There was also a decrease in the activity of β and γ-secretase, enzymes responsible for the formation of insoluble neurotoxic aggregates of β-amyloid.

4. Discussion:

This meta-analysis provides the first comprehensive evaluation of Ashwagandha effects on stress, anxiety, and cortisol levels. The findings demonstrate statistically significant improvements in overall stress and anxiety, with a notable reduction in serum cortisol levels. These results suggest that Ashwagandha may be a promising natural intervention for the stress and anxiety management.

Ashwagandha, the Indian Ginseng, is an important herb in Ayurveda that has been used for its various health benefits including, management of stress and anxiety, improving sleep pattern, boosting stamina and energy level, improving brain function and stimulating antidepressant-like effects, thereby enhancing mood. 6-8 week treatment of over 491 individuals in India with different extracts of the herb namely, root, root & leaf and other with unspecified part indicated lowering of stress and anxiety level. Quality of life scores increased significantly with much improvement in multitasking and concentration level in the individuals taking Ashwagandha for over 60 days. One double blind study in Colorado showed that the herb induced a sense of calmness; improved energy levels; heightened mental clarity; and enhanced sleep quality.

A study in rats was performed to investigate the anxiolytic and antidepressant actions of Ashwagandha. This study showed that this drug exhibited an antidepressant effect, comparable with that induced by imipramine. This supports the use of WS as a mood stabilizer in clinical conditions of anxiety and depression in Ayurveda. Positive effects on stress, anxiety, depression, and food cravings as measured by standards in clinical trails conducted in Florida over 60 men and women experiencing stress. It has also reduced fatigue and increase energy level in 120 healthy men and women with overweight or mildly obese physique.

In another studies, Ashwagandha has shown improvement in sleep problems characterized by insomnia and lack of sound sleep. Moreover, it has shown far better results than placebo in terms of sleep efficiency, total sleep time, sleep latency, and awakening after sleep onset. It has been shown in studies that Ashwagandha demonstrates improvement in mental alertness on rising, and perceived anxiety symptoms compared with placebo, as measured by actigraphy and validated rating scales. Bayesian hierarchical model developed for meta-analysis on strength/power, cardiorespiratory fitness and fatigue/recovery variables proved the efficacy of Ashwagandha supplementation. A eight-week long, randomized, double-blind, placebo-controlled study on sixty male and female participants receiving Ashwagandha displayed significant improvement in sleep quality. Another controlled trials on 400 participants with Ashwagandha dosage over eight weeks showed improvement in sleep quality, mental alertness on rising and anxiety levels.

Ashwagandha can therefore be considered as an adaptogen as it reduces negative changes caused by stress, is safe and acts beneficially even when the dose given is higher than required, and is free from any adverse side effects. Ashwagandha is found to be immunoregulator, as it enhances total white blood cell count in addition to inhibiting delayed-type hypersensitivity reactions. Considering the human nervous system, Ashwagandha has shown to neutralize the toxic effects of β-amyloid in brain caused during the course of Alzheimer's disease. It shows significant improvement in cognitive functions as a result of inhibition of amyloid β-42, inflammatory cytokines TNF-α, IL-1β, IL-6, and MCP-1, nitric oxide, and lipid peroxidation. Finally, we examined the physiological impact of Ashwagandha supplementation in stressed adults and identified several changes in hormones associated with the adrenal and steroidal system.

In this article, the effects of Ashwagandha were examined so many times, which is consistent with most studies. Longer studies should be undertaken to examine the safety and efficacy of Ashwagandha supplementation over a longer period. Follow-up after intake cessation will also be helpful to identify if there are any withdrawal issues and whether positive changes are sustained over time once supplementation is ceased.

Conclusion:

Rasayana, a subfield of Ayurvedic medicine, seeks to prevent aging, boost intelligence and vigor, and strengthen the body's resilience to illness. One of the best examples of the Rasyana medicinal plant, Withania somnifera, has biological qualities such as immunomodulation, anti-cancer, anti-depressant, and neuroprotective. The drawbacks of contemporary conventional medications include elevated resistance, inevitable adverse effects, diminished effectiveness from extended usage, and exorbitant expense. Therefore, it becomes necessary to concentrate on herbal and natural medications like Withania that can offer general protection for the health of the brain and neurons. Ashwagandha contains a wide variety of bioactive substances, including phenols, flavonoids, steroids, and alkaloids. The potential of WS extract to treat a number of pathological disorders has been the subject of extensive research. The findings from the included studies indicate that Ashwagandha formulations have beneficial effects on stress and anxiety. The adverse effects associated with Ashwagandha are limited; however, further information is required to determine its safety with long-term administration.

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