Title:

Ashwagandha's Effects on Anxiety, Depression, Sleep, and Stress

Abstract:

Ashwagandha is an Indian herb commonly used as a nootropic and adaptogen that can improve stress, sleep, anxiety, depression, cognition, power output, testosterone in men, and sperm quality in men. Ashwagandha's main biologically active components are withanolides, a steroidal lactone, where more than 40 different types of withanolides have been identified in ashwagandha. This study analyzes 1 meta-analysis and 3 randomized control trials studying ashwagandha's effects on anxiety, depression, sleep and stress. The major findings of this study suggest that ashwagandha can reduce serum cortisol levels, improve self-reported perceived stress, anxiety, and depression, and improve sleep quality. The mechanism of action is unknown but ashwagandha can presumably impact GABA, serotonin, dopamine, and endogenous antioxidant levels.

Introduction:

Ashwagandha (Withania somnifera) is an herb originating from India and parts of the Middle East. It is also known as winter cherry and Indian ginseng and has been used for Ayurveda medicine, the traditional Hindu system of medicine, dating back to 6000 BC ("Ashwagandha: History and Importance of a Powerful Nootropic"). In Ayurveda medicine, it has been used for arthritis, anxiety, tumors, and respiratory ailments. Today, the herb is used for medicinal purposes, including its small red-orange fruit, but the ashwagandha roots and leaves are the most commonly used part of the plant. It is currently used as a nootropic to combat stress, improve cognition, and to improve sleep. Consuming ashwagandha extracts has been linked to reducing anxiety, stress, depression, insomnia, and fatigue. It has also been linked to increasing power output, testosterone, and sperm quality in men. This study will focus on ashwagandha's effects on anxiety, depression, stress, and sleep.

Ashwagandha's nootropic effects are presumably caused by withanolides, a steroidal lactone, where more than 40 different withanolides have been identified in ashwagandha

(Mandlik and Namdeo, 2021). Steroidal lactones have a similar structure to testosterone but contain a cyclic organic ester attached to one end. Ashwagandha's effect on reducing anxiety and depression may be related to its GABA, and dopamine stimulating effects. GABA is an important inhibitory neurotransmitter that plays an important role in anxiety and depression by inhibiting neuron transduction of fear, anxiety, and stress. Dopamine also plays an important role in anxiety and depression by upregulating the feelings of pleasure which can help manage symptoms and improve quality of life.

Ashwagandha's effect on reducing stress levels is presumably due to modulation of the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis is responsible for producing cortisol which is a good measurement of stress. Ashwagandha may also play a role on modulating the sympathetic-adrenal-medullary (SAM) axis. The SAM axis controls epinephrine and norepinephrine release which modulate factors such as breathing, heart rate, and blood pressure where ashwagandha may help reduce stress and anxiety symptoms.

Ashwagandha also contains a compound called trimethylene glycol which may give ashwagandha its sleep-inducing capacity (Speers et al. 2021). Triethylene glycol and other unidentified compounds may be contributing to ashwagandha's effect on GABAergic and serotonergic pathways where activation of GABA and serotonin receptors are well established to improve sleep.

Cases of anxiety, depression, insomnia, and chronic stress are all on the rise where these conditions are all interconnected. For example, depression may be the cause of someone's anxiety, stress, and insomnia while insomnia may be the cause of someone's anxiety, stress, and depression. Ashwagandha could be a viable treatment to help reduce symptoms of these conditions. This study will analyze the current research on ashwagandha's effects on anxiety, depression, insomnia, and chronic stress.

Discussion:

Ashwagandha is usually taken in powdered tablets of 300 – 600 mg doses and larger doses may cause side effects such as diarrhea, vomiting, drowsiness, loss of motivation, and

lethargy. There are three types of powdered ashwagandha extract: KSM-66, Sensoril, and Shoden. KSM-66 extract is made from only root extracts containing about 5% withanolides. Sensoril ashwagandha is extracted from both the leaves and the roots containing about 10% withanolides. Lastly, Shoden ashwagandha is extracted from both the leaves and the roots and contains about 35% withanolides. There is currently no research on Shoden ashwagandha in relation to stress, anxiety, depression and sleep. More research is needed to determine the optimal dosage and concentration of withanolides to elicit greater benefits.

Ashwagandha demonstrates a promising effect at decreasing anxiety, stress, and depression while improving sleep quality. Most research conducted with ashwagandha uses subjective measurements such as questionnaires and limited objective measurements such as measuring cortisol levels. Because of this, the mechanism of action is unknown, but it may affect the HPA axis, SAM axis, GABA pathways, dopamine pathways, serotonin pathways, and act as an antioxidant and anti-inflammatory agent (Figure 1). From studies performed in mice, researchers found an increase in serotonin and dopamine, and a reduction of noradrenaline after treatment of ashwagandha (Speers et al., 2021). They also identified an upregulation of catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) in mice, giving ashwagandha its antioxidant and anti-inflammatory properties.

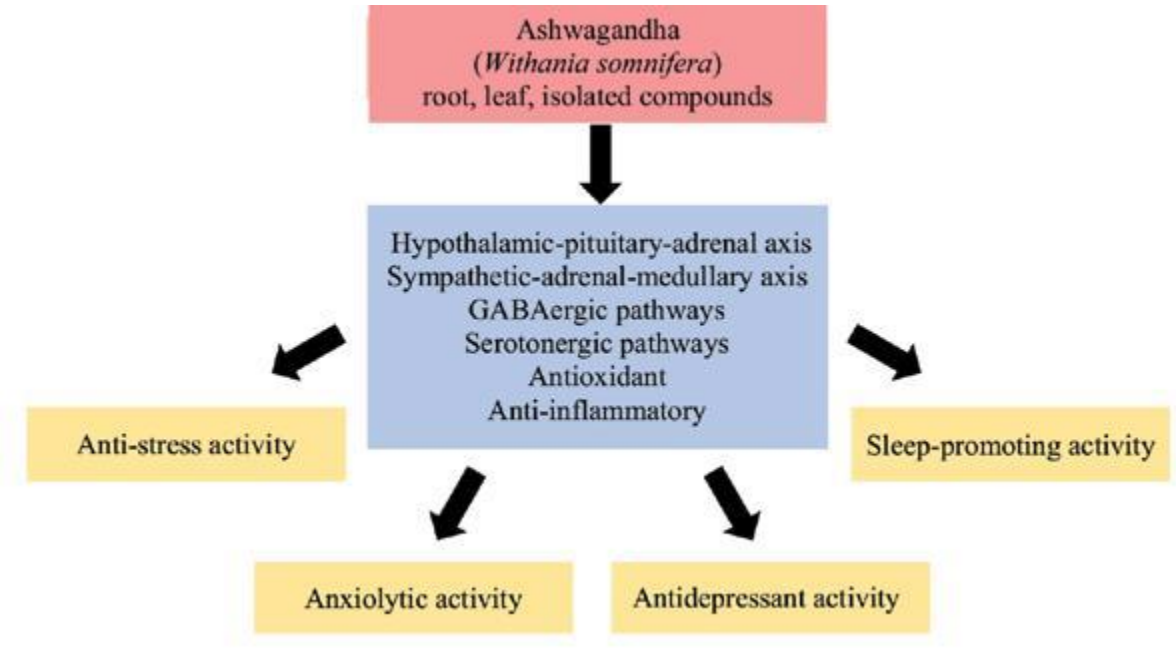

Figure 1: **Ashwagandha Mechanism of Action:** Ashwagandha may affect the HPA axis, SAM axis, GABAergic pathways, serotonergic pathways, and act as an antioxidant and anti-inflammatory agent to reduce anxiety, stress, depression and improve sleep.

Article 1 (Lopresti et al., 2019):

A randomized double-blind control trial was conducted by Lopresti et al. (2019) in India. The study included 60 stressed males and females and demonstrated that Shoden ashwagandha in a daily dose of 240 mg for 60 days has the capacity to reduce anxiety, stress/cortisol, and depression. Anxiety was assessed using the Hamilton Anxiety Rating (HAM-A) scale which is a validated self-reported 14 question survey. The survey asks questions related to the severity of perceived anxiety on a 5-point scale where higher scores indicate greater anxiety symptoms. After 60 days of Shoden ashwagandha consumption, HAM-A scores significantly reduced by 41% in the treatment group ($P<.001$) but also significantly by 24% in the control group ($P<0.001$) when compared to baseline scores. However, the difference between the two groups was significant ($P=.040$). This demonstrates that there was some placebo effect present, however, the difference between the two groups demonstrated that Shoden ashwagandha has a significantly greater effect than the placebo.

Another scale, Depression, Anxiety, Stress Scale-21 (DASS-21), was used to assess depression, anxiety, and stress. This is a self-assessed survey that asks 21 questions on a 4-point scale about symptoms of stress, anxiety, and depression where a higher score indicates more experienced symptoms. After 60 days, this study found a 30% reduction in DASS-21 scores in the treatment group ($P<0.001$) while an insignificant reduction was seen in the placebo group ($P=0.12$) when compared to baseline measures. The difference between the groups was not significant ($P=0.96$). This data demonstrates that there was a significant reduction in anxiety, stress, and, depression compared to baseline measurements from Shoden ashwagandha. However, there was not a significant difference when comparing DASS-21 scores of the

treatment group to the placebo group. This indicates that there may be some placebo effect from Shoden ashwagandha.

After 60 days, the treatment group experienced a 23% reduction in serum cortisol levels ($P<0.001$) while the placebo group experienced an increase by 0.5% ($P=0.800$) when compared to baseline scores. The difference between the groups was significant ($P<0.001$). This indicates that Shoden ashwagandha was able to decrease cortisol levels which is a good measurement of stress levels.

The insignificant DASS-21 between groups may suggest that ashwagandha can reduce anxiety, and stress, but may not significantly impact depression. Shoden ashwagandha was able to reduce anxiety scores and serum cortisol levels but this data suggests that it was not able to significantly lower depression levels. Sleep was not assessed in this article, but lower stress and anxiety can be associated with better sleep. This article demonstrates that Shoden ashwagandha can lower cortisol levels and improve anxiety based on self-assessed questionnaires.

Article 2 (Salve et al., 2019):

A randomized double blind control trial by Salve et al. (2019) was conducted in India. This study included 58 stressed male and female adults and demonstrated that KSM-66 ashwagandha root extract appears to have a dose dependent effect on self-reported stress, serum cortisol levels, self-reported anxiety, and self-reported sleep quality, where 600 mg is more effective than 250 mg.

The perceived stress scale (PSS) was used to analyze stress. This 10-item scale asks questions about lack of control, negative affective reactions, and the ability to cope with existing stressors. A higher score indicates a higher stress level. In this study, the difference between baseline PSS scores and scores after 8 weeks, were barely significant in the ashwagandha 250 ($P = 0.05$), and ashwagandha 600 group ($P = 0.05$) but not significant in the placebo group. Reductions in PSS scores were significantly higher compared to the placebo in the ashwagandha 250 group ($P = 0.05$) and in the ashwagandha 600 group ($P = 0.001$) after 8 weeks. These results demonstrate that KSM-66 ashwagandha is effective at reducing stress and has a dose-dependent effect.

Stress was also analyzed objectively by measuring serum cortisol levels. After 8 weeks, mean cortisol levels were 16.5% lower within the ashwagandha 250 ($p < 0.05$) group and 32% lower in the ashwagandha 600 group ($p < 0.05$) but not statistically different than in the placebo group (4% reduction). The differences compared to the placebo group were 12.3% lower in the ashwagandha 250 group ($p < 0.05$) and 30.0% lower in the ashwagandha 600 group ($p < 0.0001$). This data suggests that KSM-66 ashwagandha can reduce serum cortisol levels where 600 mg has a more significant effect than 250 mg.

HAM-A scores were also analyzed in this study. After 8 weeks, the ashwagandha 600 group demonstrated a significant 16.3% reduction ($p < 0.05$) compared to baseline measures and a significant 6% reduction compared to the placebo ($p < 0.0001$). However, ashwagandha 250 did not show any significant changes. This data demonstrates that 600 mg of KSM-66 ashwagandha has statistically significant results, however, a 6% reduction in anxiety may not improve quality of life.

Sleep quality was analyzed using a 7-point standard sleep quality questionnaire where a higher score indicates better sleep quality. After 8 weeks, sleep quality scores were 35% significantly higher in the ashwagandha 250 group ($p < 0.05$), 46% higher in the ashwagandha 600 group ($p < 0.05$) and an insignificant 16.5% increase in the placebo. Compared to the placebo, scores were 22.4% significantly higher in the ashwagandha 250 group ($p < 0.05$) and a significant 37.6% in the ashwagandha 600 group ($p < 0.0001$). This demonstrates that KSM-66 ashwagandha increases sleep quality where 600 mg doses are more effective than 250 mg.

This article demonstrates that ashwagandha has a dose-dependent effect. From the previous article, Shoden ashwagandha at 240 mg improves HAM-A scores by 17% and reduces cortisol levels by 23.5% compared to the placebo. In this article, KSM-66 ashwagandha at 250 mg, improves HAM-A scores by 5% and reduces serum cortisol levels by 12.3% compared to the placebo. This suggests that the higher withanolide content in Shoden ashwagandha may cause a greater effect on anxiety and stress levels.

Article 3 (Chea et al., 2019):

A meta-analysis by Chea et al. (2021) included 5 randomized control trials studying ashwagandha's effects on sleep, and anxiety. The findings from self-reported sleep surveys demonstrated that ashwagandha significantly improves overall sleep (SMD -0.59; 95% CI -0.75 to -0.42; I2 = 62%; p <0.001; five trials) including improved sleep onset latency (SMD -0.53; 95% CI -0.77 to -0.29; I2 = 0%; p <0.001; 3 trials), total sleep time (SMD -0.45; 95% CI -0.69 to -0.21; I2 = 0%; p <0.001; 3 trials), wake time after sleep onset (SMD -0.39; 95% CI -0.62 to -0.15; I2 = 0%; p = 0.002; 3 trials), and sleep efficiency (SMD -0.68; 95% CI -1.07 to -0.29; I2 = 55%; p <0.001; 3 trials). Additionally, participants with insomnia demonstrated a significant improvement in sleep after treatment (SMD -0.69; CI -1.10 to -0.58; I2 = 59%; p <0.001; 2 trials). This meta-analysis is strong evidence that ashwagandha improves sleep quality which could be due to its stress-reducing capacity or because of the triethylene glycol.

This meta-analysis also demonstrated that ashwagandha treatment improves anxiety levels (MD -2.19; 95% CI -3.39 to -1.00; I 2 = 0%; p <0.001; 3 trials) from self-reported surveys. This data and other studies discussed suggest that ashwagandha can significantly reduce anxiety levels. The study also assessed quality of life measures which were reported using a World Health Organization Quality of Life (WHOQOL-BREF) self-administered questionnaire composed of questions about psychological health, social relationships, and physical health. It is important to note that this study did not identify any significant results in quality-of-life scores from two studies. Quality of life scores were higher after ashwagandha treatment but not statistically significant. Overall, this meta-analysis demonstrates that ashwagandha may be effective at improving anxiety and sleep, but may not significantly improve quality of life.

Article 4 (Kapoor and Anishetty, 2012):

A randomized control trial performed by Kapoor and Anishetty (2012) was performed in India. Sixty-one chronically stressed participants consumed 600 mg/day of KSM-66 ashwagandha for 60 days and quality of life and serum cortisol levels were assessed. In this study, the PSS was used to assess self-reported stress. After 60 days, the control group experienced an insignificant 5.5% reduction in baseline PSS scores, and the ashwagandha group experienced a 44.0% reduction (P<0.0001) compared to baseline scores. The difference between

the two groups after 60 days was statistically significant (P<0.0001). The ashwagandha group demonstrated a serum cortisol reduction of 27.9% from baseline and the control group demonstrated an insignificant reduction of 7.9%. The difference between groups was statistically significant (P=0.002). This demonstrates that ashwagandha is effective at reducing both subjective and objective measures of stress.

The General health questionnaire-28 (GHQ-28) was used to assess quality of life. This questionnaire has four distinct item-subsets categorized as “somatic”, “anxiety and insomnia”, “social dysfunction” and “severe depression.” This is a 21-point scale measuring the frequency of certain stress-signaling events where a higher score indicates a greater frequency of stressors. In this study, the ashwagandha group demonstrated a significant reduction in GHQ-28 questionnaire scores in the following: 76.1% for the “Somatic,” 69.7% for the “Anxiety and Insomnia” 68.1% for the “Social Dysfunction,” and 79.2% for the “Severe Depression.” In contrast, the placebo control group had corresponding reductions in scores of 4.9%, 11.6%, –3.7% and –10.6%, respectively. The differences between groups were significant (P< 0.0001 for all subsets). The meta-analysis discussed earlier reported no significant differences on quality of life but this study demonstrates ashwagandha significantly improves physical health, anxiety and insomnia, social dysfunction, and depression in chronically stressed individuals.

This study also used the data analysis for depression–anxiety stress (DASS) scale which is a 42-point scale where higher scores indicate a higher presence of stress signaling events. In the DASS questionnaire, the ashwagandha group demonstrated a significant reduction in the following scores: 77% for the “Depression,” 75.6% for the “Anxiety,” and 64.2% for the “Stress” category. In contrast, the placebo-control group had corresponding reductions in scores of 5.2%, – 4.3% and 10.4%, respectively. The differences between the control and the placebo were significant (P<0.0001 for all subsets). This study demonstrates very large reductions in anxiety, depression, and stress compared to previous studies which could indicate that KSM-66 ashwagandha acts better at reducing symptoms for chronically stressed individuals than in healthy adults.

Conclusion:

In conclusion, one study using 240 mg of Shoden ashwagandha did not demonstrate an improvement in depression and anxiety from the DASS-21, but demonstrated an improvement in anxiety from the HAM-A scores, and a reduction in serum cortisol levels. Another study using KSM-66 ashwagandha in doses of 250 mg and 600 mg/day demonstrated improvements in self-reported stress, anxiety from HAM-A scores, sleep quality and cortisol levels where 600 mg/day was more effective than 250. The meta-analysis discussed demonstrated insignificant quality of life improvements in healthy adults from two studies, and significant improvements in sleep and anxiety. Lastly, a study using 600 mg/day of KSM-66 ashwagandha in chronically stressed individuals demonstrated improvements in sleep, stress, anxiety, depression, and quality of life.

This data demonstrates that both KSM-66 and Shoden ashwagandha appear to be an effective treatment for improving sleep, depression, anxiety, cortisol, and stress. Shoden ashwagandha appears to have a greater effect on anxiety and cortisol levels when compared to KSM-66. Ashwagandha appears to have a dose-dependent response where higher dosages elicit greater effects. The difference of effectiveness between the type of ashwagandha is still not well understood. Future research can compare the efficacy of Shoden, Sensoril, and KSM-66 ashwagandha at different doses to identify the optimal dosage and optimal type of ashwagandha.

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Quality Draft Checklist, NFSC 345W

Completed?	Comments	Item
Title Page and Abstract		
		Listed "Title" above the paragraph
		Include a descriptive title, your name, date, and NFSC 345
		Student to teacher memo reflects on changes made to the Quality Draft based on the Writing Center tutor's recommendations.
		abstract (250-400 words) is optional for the Quality Draft
Introduction and background (1 to 2 pages)		
		Listed "Introduction"
		Benefit(s) of DS/FF and importance in terms of nutrition and health. This can include unfounded benefits that people believe. Please let the reader know.
		Background information about the DS/FF (historical use, ethnobotany)
		Objective of the term paper: Why did you choose this DS/FF? What is the focus of the paper? This part of the paper may use the personal perspective, "I".
Discussion (4 to 6 pages)		
		Listed "Discussion"
		Evidence for efficacy with findings that support this/these benefit(s). This is brief here.
		Proposed/actual physiologic mechanism, if known. Talk with me if you need help with this.
		Forms of DS/FF available (e.g., capsule, food ingredient, tincture), with recommended dose. See DS label homework.
		The population(s) who may benefit and/or who currently uses the DS/FF, based on the condition you are discussing.
		Discuss the quality of available research (strengths and weaknesses of research that supports and/or refutes purported benefit(s), including any conflicting research results and/or contradictory perspectives. This will be the bulk of the discussion. See your annotated bibliography.
		Safety concerns and risks, including contraindications with medication, other DS/FF, health status.
		Brief discussion of other purported benefits.

Conclusion (1 page)		
		Typed “Conclusion)
		State your professional recommendation based on the scientific evidence by integrating your interpretations of the literature into a sound conclusion, including the appropriate recommendations for use, if any, and suggestions for further research. You may use “I” for this part of the paper.
		Summarize the key findings about this/these primary benefit(s) and the support or lack of evidence.
References		
		Used “References” at top of page.
		Used at least 5 references; four must be scientific studies.
		At least 1 of the scientific studies is a meta-analysis.
		References cited and citations. Use APA (American Psychological Association) format. https://owl.english.purdue.edu/owl/resource/560/07/
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		Signed form from the Writing Center Form. http://www.csuchico.edu/slc/writing-center.shtml
		On a separate sheet submitted in class, Write a response to the recommended revisions in paragraph form. What changes did you make based on the tutor’s comments on your writing? Where were these changes made?
		Posted the Quality Draft on Google Docs.
		Invited instructor, plus two randomly assigned peers.
		Citing in the body of the paper should include the first author’s name and year of publication, such as (Smith and others, 2009).