International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 532-537 www.ijprajournal.com ISSN: 2249-7781

A Review on: Safety and efficacy of herbal medicine (ashwgandha)

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Submitted: 05-05-2023 Accepted: 15-05-2023

ABSTRACT: - Stress can have negative effects on mental and emotional health, leading to underperformance and clinical conditions. Ashwagandha, an adaptogenic herb, has been shown in Ayurvedic texts, animal studies, and clinical trials to be a safe and effective way to combat stress. This study aimed to evaluate the safety and efficacy of a high-concentration full-spectrum extract of Ashwagandha roots in reducing stress and anxiety, as well as improving general well-being in adults experiencing stress.

The study was a single-center, prospective, double-blind, randomized, placebo-controlled trial involving 64 subjects with a history of chronic stress who underwent relevant clinical examinations and laboratory tests, including measuring serum cortisol and completing standard stress-assessment questionnaires. The subjects were randomized into either the placebo control group or the treatment group and were asked to take one capsule containing 300 mg of high-concentration full-spectrum extract from the root of the Ashwagandha plant twice a day for 60 days. Follow-up telephone calls were made to all subjects on Days 15, 30, and 45 to check for treatment compliance and adverse reactions. Final safety and efficacy assessments were performed on Day 60 using t-tests and Mann-Whitney tests.

The group that received the high-concentration full-spectrum Ashwagandha root extract demonstrated a significant reduction ($P<0.0001$) in stress-assessment scores compared to the placebo group on Day 60. Serum cortisol levels were also significantly reduced ($P=0.0006$) in the Ashwagandha group compared to the placebo group. Adverse effects were mild and comparable in both groups, with no serious adverse events reported.

In conclusion, this study suggests that a high-concentration full-spectrum Ashwagandha root extract is safe and effective in improving an individual's resistance to stress, leading to an improvement in their self-assessed quality of life.

Keywords: Ashwagandha, Stress, anxiety.

I. INTRODUCTION:

Stress is a state that occurs when external physical or mental demands exceed a person's capacity to cope with them. It can cause feelings of being overwhelmed, nervousness, anxiety, and a decreased ability to respond to environmental pressures. Prolonged exposure to stress can disrupt a person's mental and physiological equilibrium, leading to other health problems such as depression, high blood pressure, heart disease, and metabolic disorders. These conditions, which have their roots in mental or emotional factors, are becoming more prevalent and are emerging as major global health concerns. As a result, an increasing number of people are seeking medical assistance to manage stress.

Adaptogens are a group of herbs that can enhance an individual's ability to cope with stress. These herbs work by normalizing the body's physiological processes during times of increased stress, enabling the body to adapt to changes. According to a recent definition, adaptogens are a class of metabolic regulators that improve the organism's capacity to adapt to environmental factors and prevent damage from such factors. To qualify as an ideal adaptogen, it should: a) reduce stress-induced damage, b) be safe and beneficial even with prolonged use, c) have no negative effects such as withdrawal symptoms, and d) not disrupt normal bodily functions beyond necessary levels. Ashwagandha is an example of an adaptogen that possesses all of these characteristics.

Ashwagandha, scientifically known as Withania somnifera Dunal, belongs to the Solanaceae family and is commonly referred to as Indian Ginseng or Winter Cherry. The name

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Volume 8, Issue 3 May-June 2023, pp: 532-537 www.ijprajournal.com ISSN: 2249-7781

"Ashwagandha" is derived from two reasons. Firstly, the fresh roots of the herb give off an odor similar to that of a horse. Secondly, it is believed that consuming extracts of the herb may impart strength and vitality similar to that of a horse. Ashwagandha holds a significant place in Ayurvedic medicine and is often referred to as a "royal herb" due to its multifaceted rejuvenative effects on the human body. It acts on various systems of the body, including the neurological, immune, energy-production, endocrine, and reproductive systems.

Withania somnifera, also known as Ashwagandha, is the most commonly used and extensively studied adaptogen herb. A vast amount of literature is available on its properties. It has been studied for its adaptogenic, antioxidant, anticancer, anxiolytic, antidepressant, cardioprotective, thyroid-modulating, immunomodulating, antibacterial, antifungal, anti-inflammatory, neuroprotective, cognitive-enhancing, and hematopoietic effects. Ashwagandha contains various pharmacologically and medicinally important constituents such as withanolides, sitoindosides, and alkaloids that protect cells from oxidative damage and disease. Results from tests conducted to identify the anti-stress activity of sitoindoside VII and sitoindoside VIII indicate that both produce anti-stress activity. Sitoindoside IX and X were also tested in rats for immunomodulatory and central nervous system effects related to stress, memory, and learning, and they were found to reduce the incidence of stress-induced gastric ulcers significantly.

Previous trials have shown positive results for the adaptogenic and stress-reducing activity of Ashwagandha. However, most of these trials were either in-vivo or in-vitro. There is limited literature available on the stress-reducing effects of Ashwagandha root extracts on humans. The primary objective of our study was to evaluate the efficacy of high-concentration full-spectrum Ashwagandha root extract in reducing stress and anxiety and to assess its role in improving the general well-being of adults who are under stress.

In this study, we used the KSM-66 Ashwagandha extract, which is a high-concentration full-spectrum extract provided by Ixoreal Biomed, Hyderabad, India. This extract is derived solely from the roots of the Ashwagandha plant, without using any other parts like leaves. It is standardized to contain at least 5% withanolide, as measured by HPLC. Moreover, the extraction process used to produce this extract is unique and based on the principles of 'green chemistry,' meaning that it does not involve alcohol or any synthetic solvents.

II. METHODOLOGY:

For this study, a single-center, prospective, double-blind, randomized, placebo-controlled trial was conducted to assess the effectiveness of a high-concentration full-spectrum Ashwagandha root extract in reducing stress and anxiety, as well as improving general well-being among adults experiencing stress. The trial involved a total of 64 participants who reported mental stress and were observed for a period of 60 days.

The research adhered to the guidelines set by the Indian Council for Medical Research for human research (ICMR-GCP) and the Declaration of Helsinki (2008). It was granted approval by the institutional review committee at Asha Hospital in Hyderabad, India.

Participants:

To be eligible for the study, subjects had to meet the Following criteria:

1. aged between 18 and 54 years,
2. free from psychiatric conditions other than stress,
3. have a score of less than 15 on the World Health Organization–five (WHO-5) well-being index and a score Of at least 14 on the Perceived Stress Scale (PSS), and able to read and write in English. It should be noted

That lower scores on the WHO-5 well-being index indicate

Higher levels of stress.

Subjects who met any of the following criteria were excluded from the study: (1) they had a chronic physical, hormonal or psychiatric illness, (2) they were using certain hormonal birth control measures, (3) they were taking any medication regularly, (4) they were taking any herbal preparations or formulations containing Ashwagandha, ginseng, ginkgo biloba, Brahmi or related herbs, (5) they were pregnant or lactating, (6) they had substance dependence, (7) they had abnormal laboratory or ECG findings.

Interventions:

The study recruited participants through a pre-screening meeting that included an introductory lecture on stress and stress-management talks. Individuals from various sub-populations, such as

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 532-537 www.ijprajournal.com ISSN: 2249-7781

doctors, students, self-employed persons, executives, and employees of Information Technology firms, attended the meeting. The purpose of the study was explained, and interested individuals were given the WHO-5 health questionnaire to assess their stress levels. Those who had a score of 15 or lower on the WHO-5 well-being index, reported high stress levels as measured by the PSS, and were interested in participating further were invited to the research site for further evaluation.

At the research site on Day 0, the subjects' medical history was recorded, and clinical examination and laboratory assessments were conducted. The PSS questionnaire was administered, and a qualified psychiatrist performed a clinical psychiatric examination to check for primary psychiatric disorders. Subjects with a PSS score of at least 14 were enrolled in the study.

On Day 0, serum cortisol levels were measured in the morning, and the subjects were administered three questionnaires: the PSS questionnaire again, the Depression Anxiety Stress Scale (DASS) questionnaire, and the 28-item version of the General Health Questionnaire (referred to as GHQ-28). After assessing the screening parameters, each subject was randomly assigned to either the study drug treatment group or the placebo control group, with a randomization ratio of 1:1 using a computer-generated randomization scheme. The subjects were provided with a blinded kit containing capsules sufficient for the entire study duration.

During the study, subjects were instructed to take one Capsule two times a day after meals, with a glass of plain Water, for a total duration of 60 days. The Ashwagandha Group received capsules containing 300 mg of high-Concentration full-spectrum Ashwagandha root extract,While the placebo-control group received capsules Containing a neutral substance. The size and form of the Capsules were identical in both groups. To ensure proper Treatment compliance and record any adverse events, Subjects were followed up with telephone calls on Day 15, Day 30, and Day 45. The results of the follow-up Calls were documented in a case report form. On Day 60, Final measurements of serum cortisol and the stress scale Responses were conducted. Safety data and information About any adverse effects of the study drug were also Collected on Day 60.

Data collection and analysis:

Physiological measures and survey responses to standard questionnaires were collected on Day 0 and Day 60 in a laboratory. Compliance and adverse reactions data were additionally collected on Day 15, Day 30, and Day 45 through a telephone call.

Assay methodology:

To evaluate the effectiveness of the high-concentration full-spectrum Ashwagandha root extract in reducing stress, data were collected on Day 0 and Day 60 through physiological measures in a laboratory and by survey responses to standard questionnaires, including the PSS, GHQ-28, and DASS. We compared the measures between the two groups on each day and assessed changes in the measures over the 60-day period for each group. This allowed us to analyze the drug's impact on different dimensions of stress. Additionally, we evaluated the safety of the Ashwagandha extract based on laboratory findings and the incidence of adverse events reported by the subjects. All adverse events were recorded, and their potential association with the study drug was assessed.

Statistical methods and analysis:

A total of 64 subjects were initially enrolled in the study, but three of them did not comply with the protocol. Thus, for efficacy analysis, only the 61 subjects who were compliant with the protocol were included. However, for safety analysis, all 64 subjects in the intent-to-treat population were considered which included all subjects who took at least one dose of either the treatment drug or the placebo.

Efficacy was assessed based on both physiological and survey measures. For each measure, we calculated the difference between the two groups on Day 0 and Day 60. We then used a t-test to determine the statistical significance of this difference. We also computed, within each group, the change in the measure over the 60 days and compared the difference in these changes across the two groups. A t-test was again used to assess the statistical significance of this difference. To ensure robustness, we also employed the non-parametric Mann-Whitney test. All these analyses allowed us to evaluate the effect of the drug on different dimensions of stress.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 532-537 www.ijprajournal.com ISSN: 2249-7781

III. RESULTS:

Background information on the subjects:

The study included a total of 64 subjects, with 41 (64%) men and 23 (36%) women, as shown in Table 1. None of the enrolled subjects had any pre-existing medical conditions related to cardiovascular, respiratory, gastrointestinal, nervous, endocrine, urogenital systems, or allergy/skin-related disorders. One subject reported a history of depression but was free from psychiatric symptoms at the time of enrollment. The remaining subjects did not have any psychiatric illnesses. During the study, two subjects from the Ashwagandha group and one subject from the placebo group were lost to follow-up. On Day 60, 61 subjects had completed the study.

Efficacy analysis

Perceived stress scale

The Perceived Stress Scale (PSS) is a widely-used psychological tool that measures an individual's self-perception of stress levels. The scale consists of ten items, each assessing the frequency or intensity of a particular stress-inducing event. Each item is scored on a scale from 0 to 4, with a score of 0 indicating the absence or non-occurrence of the event. The total PSS score is calculated by adding up the scores for each of the ten items, with a possible range of scores from 0 to 40. A score of 0 represents a complete absence of stress. Table 2 provides a summary of the data and results of statistical tests. At the end of the 60-day treatment period, the Ashwagandha group showed a significant reduction in PSS scores, with a decrease of 44.0% compared to a 5.5% decrease in the placebo group. The difference in PSS score reduction between the two groups over the 60-day period was highly statistically significant ($P<0.0001$).

Psychometric scales vary in their suitability for ratio-scale interpretations and conversion of changes into percentages. However, in this study, all the psychometric scales employed are regarded as ratio-scaled according to the research literature. These scales possess a critical characteristic that permits us to convert changes into percentages, namely that the minimum score corresponds to zero and signifies a state with hardly any stress signals. Hence, every value on the scale can be construed as an absolute measure of self-reported stress level. This approach is aligned with the common practice in stress research, where similar scales are frequently used.

Depression anxiety stress scale:

The DASS questionnaire, created by Lovibond and Lovibond in 1995, comprises three subsets of items that evaluate stress related to "depression," "anxiety," and "stress" separately. Each item in the scale measures the frequency or severity of stress-related events. Scores range from 0 to 42 for each subset, with a score of 0 indicating the absence or non-occurrence of stress-related events in the respective category. In addition, we report a total score that reflects overall stress across all three item-subsets. Table 4 summarizes the data and key statistical results. Baseline scores for all three DASS subsets were similar in both treatment groups ($P>0.05$). However, by Day 60, the scores in the Ashwagandha group were significantly lower compared to the placebo group ($P<0.0001$ for each item-subset and total). The Ashwagandha group showed greater reductions in scores compared to the placebo group for all three subsets ($P<0.0001$), with reductions of 77%, 75.6%, and 64.2% for the "Depression," "Anxiety," and "Stress" subsets respectively. In contrast, the placebo group showed only small reductions, with scores decreasing by 5.2%, -4.3%, and 10.4% for the corresponding subsets. The placebo group also showed a slight increase in the "Anxiety" subset and small decreases in the "Depression" and "Stress" subsets.

Serum cortisol levels:

Serum cortisol is a commonly utilized biological marker to evaluate stress. Hence, it may be beneficial to examine the impact of the treatment on cortisol levels. Table 5 presents a summary of the data and the key statistical findings. Serum cortisol levels are measured in µg/dL. At baseline, both groups exhibited similar serum cortisol levels ($P>0.05$). However, at the end of the study period, the average serum cortisol levels of the two groups differed significantly ($P=0.006$).

Following 60 days of treatment, a decrease of 27.9% from the baseline was observed in the Ashwagandha group, while the placebo-control group exhibited a reduction of only 7.9%. The contrast in the reduction of serum cortisol levels between the two groups on Day 60 was statistically significant ($P=0.002$).

Safety analysis:

Laboratory assessments:

Following 60 days of treatment, aside from the changes in the effectiveness measures noted earlier, no significant changes in laboratory

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Volume 8, Issue 3 May-June 2023, pp: 532-537 www.ijprajournal.com ISSN: 2249-7781

parameters were detected from the baseline visit to the final visit in both groups, except for the levels of serum globulin and serum triglycerides. Nevertheless, these disparities were clinically insignificant.

Adverse events:

Adverse event data were available for only 61 participants, as three were lost to follow-up. In the Ashwagandha group, six adverse effects were reported, while five were reported in the placebo group [see Table 6]. The Ashwagandha group experienced nasal congestion (rhinitis), constipation, cough and cold, drowsiness, and decreased appetite. The placebo-control group exhibited dry mouth, fatigue, fever, headache, abdominal pain and diarrhea, and leg tremors during examination. The incidences of adverse events were comparable in both groups, and the difference was not statistically significant. Additionally, all adverse events were mild in nature, and there were no known mechanisms linking these adverse events to the study drug.

IV. DISCUSSION:

This study stands out from other studies due to the comprehensive set of measures used to assess stress levels. Unlike most studies that rely on a limited set of measures, our study used three different widely accepted stress scales along with serum cortisol level, a biochemical marker of stress, to evaluate an individual's stress, depression, anxiety, and overall well-being. The graphical representation of these results is presented in Figure 1. This collection of measures allows us to not only analyze the core aspects of stress but also to evaluate the antecedents and consequences of stress. Our findings suggest that high-concentration full-spectrum Ashwagandha root extract has a significant impact on both the aspects related to stress.

Effect of Ashwagandha on focal aspects of stress

In this study, several aspects of stress were measured using different sets of scales, including the GHQ-28, DASS, and PSS. The results presented above indicate that the group of subjects taking Ashwagandha experienced significant reductions in all four measures of stress, with reductions of 69.7%, 64.2%, 75.6%, and 44.0%, respectively. In contrast, the placebo group only saw reductions of 11.6%, 10.4%, -4.3%, and 5.5%. These differences were highly statistically significant, indicating that Ashwagandha has a significant effect in improving the well-being of individuals with respect to these focal aspects of stress. These findings support the notion that Ashwagandha possesses strong anti-stress adaptogenic properties, as demonstrated in previous in-vivo studies [4,9] and consistent with the results reported by Andrade et al. in anxiety patients.[14]

Effect of Ashwagandha on antecedents and Consequences of stress:

This study employed measures that assessed not only the focal aspects of stress, but also the antecedents and consequences of stress. These measures included the "Somatic" and "Social Dysfunction" item-subsets of GHQ-28, the "Severe Depression" and "Depression" item-subsets of GHQ-28 and DASS, and the level of serum cortisol. The results showed that the Ashwagandha group experienced significant reductions in all five measures, ranging from 27.9% to 79.2%. In contrast, the placebo group only saw reductions ranging from -10.6% to 7.9%. Of particular interest in this study is the measurement of serum cortisol, a commonly used indicator of stress. Acute stress triggers an increase in cortisol levels, which is associated with physiological responses such as increased heart rate, blood pressure, and glucose levels. The study found that the high-concentration full-spectrum Ashwagandha root extract was able to decrease the levels of serum cortisol, which suggests that it may have a direct effect on the body's stress response.

Taken together, the results suggest that high-concentration full-spectrum Ashwagandha root extract may be able to mitigate not only the focal aspects of stress, but also some of the precursors, consequences, and associated symptoms of stress. This indicates that Ashwagandha may have the potential to improve overall well-being in individuals. Previous studies have also reported similar findings in patients with stress.

Safety:

The safety of high-concentration full-spectrum Ashwagandha root extract was thoroughly evaluated in this study, and the results indicate that it is well-tolerated and safe for use. No serious adverse events were recorded, and any side effects observed were mostly mild in nature. Furthermore, there were no known causal mechanisms linking these side effects to the study drug, and the side effects observed in both groups were similar. Laboratory values showed no

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 532-537 www.ijprajournal.com ISSN: 2249-7781

significant changes in either group. These findings are consistent with previous studies on Ashwagandha, which have also reported no adverse events leading to dropouts or withdrawal symptoms. Animal studies have also demonstrated the safety of long-term administration of Ashwagandha root. However, it is important to note that individuals who are allergic to herbs in the Solanaceae family should not use this herb.

V. LIMITATIONS:

Although the sample size of the study was sufficient to demonstrate statistical significance, a larger study using a more diverse population would be beneficial. Additionally, the study only enrolled subjects who were under stress and did not have any psychological or systemic illnesses. Conducting studies on individuals with a broader range of clinical backgrounds would provide further insights. Furthermore, longer-duration studies are needed to gain a better understanding of the long-term effects of Ashwagandha on stress resistance.

VI. CONCLUSION:

The study's results provide evidence that the use of high-concentration full-spectrum Ashwagandha root extract can enhance an individual's ability to cope with stress, leading to an improvement in their overall quality of life. Moreover, the study also suggests that the use of this extract is safe and well-tolerated by adults who are experiencing stress. Therefore, high-concentration full-spectrum Ashwagandha root extract can be considered a viable adaptogen for managing stress in adults.

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