Safety and Efficiacy of an Ashwagandha for Body Weight Management under Stress

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Body-weight management in adults under chronic stress through treatment with Ashwagandha root extract: A double-blind, randomized, placebo-controlled trial.

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ABSTRACT

Background: Chronic stress has been associated with a number of illnesses. People living with chronic stress have a tendency toward obesity. Ashwagandha (also known as *Withania somnifera*) is a well-known herbal adaptogen that has been found to be effective in reducing stress and anxiety in humans.

Objective: The objective of the study was to evaluate the safety and efficacy of a standardized extract of Ashwagandha root in the management of body weight in patients under chronic stress.

Methods: In this single centered, prospective, double-blind, randomized, placebo-controlled trial, a total of 52 subjects with a history of ongoing, chronic stress were randomized to receive either Ashwagandha root extract (300 mg) or placebo twice daily. The primary efficacy measures were Perceived Stress Scale (PSS) and Food Cravings Questionnaire (FCQ) domain scores, whereas secondary efficacy measures were the Oxford Happiness Questionnaire (OHQ) score, Three Factor Eating Questionnaire (TFEQ) domain scores, serum cortisol levels, body weight, body mass index (BMI) and vital parameters. Each subject was assessed at the start of the trial and again at 4 and 8 weeks. During the trial, safety & tolerability of the treatment were observed, and adverse events were recorded.

Results: The treatment with Ashwagandha root extract resulted in significant improvements in primary efficacy measures, such as PSS score ($P < 0.05$) and FCQ domain scores ($P < 0.05$) compared to placebo over the course of the study. The treatment also produced significant improvement in secondary efficacy measures, including TFEQ scores, serum cortisol levels ($P < 0.005$), TFEQ scores ($P < 0.05$), body weight ($P < 0.05$) and BMI ($P < 0.05$) of the subjects, as well as, significant improvement in OHQ scores ($P < 0.05$) when compared to placebo group at the end of the study. The Ashwagandha root extract was found to be safe and tolerable with negligible adverse events.

Conclusion: The outcome of this study suggests that Ashwagandha root extract can be utilized for body weight management in adults under chronic stress.

Key words: Adaptogen, Stress, Food craving, *Withania somnifera*, Weight gain, Serum cortisol.

INTRODUCTION

Chronic psychological stress is a major health concern worldwide, and has been associated with numerous serious illnesses, including depression, cardiac disease, diabetes, hypertension, and possibly even cancer.[1] Excess stress is also associated with symptoms such as muscle tension, gastrointestinal disturbances, sleep disturbances, cognitive dysfunction, headaches and fatigue.

Psychological stress has also been linked to weight-gain and obesity.[2,3] Stress causes systemic elevation of stress hormones such as cortisol, and chronic elevation of these hormones leads to increased visceral adiposity and other metabolic syndrome.[4]

Chronic stress may also lead to changes in eating behavior.[5,6] The exacerbation of negative mood in response to external stress elements is highly correlated with increased food intake,[2] and chronic stress is also associated with reduced physical activity.[5] Both of these behaviors may have a significant impact on body weight.[2] Increased cortisol production has been shown to potentiate hunger.[7-9] Thus, there may be a physiological component to the tendency to overeat during times of stress. In addition, stress tends to elicit cravings for sweet and fried foods, soft drinks, and alcoholic beverages.[2,10]; these cravings are linked to increased caloric consumption and resultant higher body mass index (BMI).[10,11] This may be due to the fact that chronic stress increases activation of the hypothalamic–pituitary–adrenal

(HPA) axis, which has been found to increase sweet cravings in persons prone to binge-eating sweet and fried foods, soft drinks, and alcoholic beverages.[2]

In double-blind studies of various herbal extracts traditionally associated with calming and adaptogenic properties, links were found between anxiety, stress, and body weight, and patients who were treated showed marked reduction in body weight and serum cortisol levels compared to placebo.[12,13]

The root of the Ashwagandha plant (also known as *Withania somnifera*), has a long history of use as an adaptogen in the Ayurvedic system of complementary medicine, and is used to counteract the negative effects of stress. Modern research has begun to identify a number of active components in Ashwagandha that may have useful therapeutic applications.[14] The plant contains a range of bioactive constituents, including withanolides, glycowithanolides, sitoindosides, Withaferin A and other therapeutically active phytochemicals.[15] Other studies have identified anticancer, antidepressant, anxiolytic, cardioprotective, antioxidant, thyroid modulating, immunomodulating, antibacterial, neuroprotective, antifungal, anti-inflammatory, and hematopoietic activities.[16]

Several preclinical studies have indicated that Ashwagandha does indeed have adaptogenic and anti-stress activities. Jain et al[17] observed that Ashwagandha extract reduced damage to hippocampal neurons in the CA2 and CA3 region by 80%. In another study, rodents pretreated with Ashwagandha *extract* showed significant attenuation of hypercortisolemia and other physiological indictors of stress. Also, the Ashwagandha component withanolide A was found to reverse the memory deficits and induce regeneration of dendritic spines & axons in mice.[18] In another study with rodents, the anti-stress potential of the Ashwagandha components sitoindoside VII and VIII was established.[19]

Additional studies have determined that extracts of Ashwagandha root have significant anxiolytic properties in humans, as measured both by patient-reported instruments and by quantitative analysis of serum biomarkers.[3,20,21] For example, due to its GABAergic activity on ionotropic GABA-A and GABA-ρ receptors, it has shown efficacy in the treatment of insomnia.[14] Chandrasekhar et al[1] evaluated the efficacy of a standardized extract versus placebo in a 60-day clinical trial. Significant differences were found for all outcome measures, including scores on the Perceived Stress Scale ($P< 0.0001$), the General Health Questionnaire ($P< 0.0001$), and levels of cortisol in the bloodstream ($P = 0.0006$).[12,13]

Based on previous work linking stress to anxiety and weight gain, the aim of the present randomized, double-blind, placebo-controlled clinical study was to assess the efficacy of a standardized extract of Ashwagandha root in improving general well-being and reducing physiological markers of stress that have been associated with obesity in adults under chronic stress. We hypothesized that treatment with this extract would yield anxiolytic and anti-stress effects, thus improving patient-reported measures of psychological and physical well-being, and normalizing serum cortisol levels, thereby reducing hunger and stress-eating behaviors and reducing weight gain.

MATERIALS AND METHODS

Patient enrollment

Study subjects were selected from several outpatient clinics in the city of Pune, India. Inclusion criteria included: Symptoms of chronic, routine work stress; age between 18 and 60 years old; ability to provide written informed consent; a Perceived Stress Scale (PSS)[22] score ≥20, and a body mass index (BMI) between 25 and 39.9 kg/m^2.

Exclusion criteria included: A diagnosable eating disorder; participation in a weight-loss program in the past three months; predisposition to weight gain due to genetic or endocrine conditions; diagnosed neurologic disorder, unstable medical condition, or known allergy/side-effects to Ashwagandha root extract; pregnancy or lactation; taking medications known to affect weight (e.g., corticosteroids, antidepressants, anti-psychotics, mood stabilizers, and anti-epileptic drugs); participation in other clinical trials during the previous three months; history of alcohol abuse or smoking; and clinically significant acute unstable hepatic, renal, cardiovascular or respiratory disease.

The study was conducted in accordance with the Declaration of Helsinki (1989) and 'Guidelines for Clinical Trials on Pharmaceutical Products in India – GCP Guidelines issued by the Central Drugs Standard Control Organization, Ministry of Health, and Government of India. Institutional Review Board approval was obtained from the study center at Chaitanya Hospital & Nursing Home, Pune, India. Ethics Committee notifications as per Good Clinical Practice Guidelines, issued by Central Drugs Standard Control Organization and Ethical

Guidelines for Biomedical Research on Human Subjects, issued by Indian Council of Medical Research, were followed.

Data collection

This eight-week prospective clinical trial was conducted using a random-assignment, parallel-group, single-centre, double-blind, placebo-controlled design to evaluate the efficacy of Ashwagandha root extract compared to placebo in reducing markers of stress, and in controlling weight gain and improving general well-being in adults under chronic stress.

The study comprised a screening visit followed by an eight-week treatment period. At the screening visit, a medical history was obtained from each subject and symptoms of chronic stress were assessed. A general physical examination was conducted, and vital parameters, baseline body weight, BMI and baseline serum cortisol levels were recorded. Each subject was then assessed using the Perceived Stress Scale (PSS).[22] A qualified psychiatrist performed a clinical psychiatric examination on each subject to check for primary psychiatric disorders that would warrant exclusion from the study. Following screening, eligible patients were randomized through a computer-based predetermined randomization (Rando version 1.0) in a 1:1 ratio to receive either Ashwagandha root extract or placebo. The investigational products were packaged in such a way that the extract and placebo medication packs identical in appearance. The packs were coded to conceal their contents, and the label contained the patient serial number (ID of the study). After the patient was enrolled, he/she was provided with the medication pack having the corresponding serial number. The randomization codes were provided in a separate sealed envelope for each patient.

The study group received 300 mg of a standardized Ashwagandha root extract (KSM-66 Ashwagandha, manufactured by Ixoreal BioMed, Los Angeles, California, USA, containing 5% withanolides) in capsule form, twice daily with water for 8 weeks. The control group received identical placebo capsules containing inert filler. At the beginning of the study and at the end of 4 and 8 weeks, patients were assessed using the outcome measures described below. In addition, body weight, BMI, serum cortisol levels and vital parameters were recorded. Data on safety and adverse effects of the investigational drug were collected at the end of 8 weeks. Patients Global Assessment of Tolerability to therapy (PGATT) was assessed on a 5-point Likert scale at the end of therapy.

Clinical safety was assessed based on the adverse events reported by the patients during the follow-up or during clinical evaluation of patients. Adverse events were recorded, along with their severity, duration and relationship to study drug. Assessment of the tolerability of the Ashwagandha root extract was done through PGATT on a 5-point scale of 'worst', 'poor', 'moderate', 'good' and 'excellent tolerability' at the end of therapy.

Outcome Measures

The primary outcome measures were the Perceived Stress Scale (PSS)[22] and the Food Cravings Questionnaire-Trait (FCQ-T).[23] Secondary outcome measures included the Oxford Happiness Questionnaire (OHQ);[24,25] the Three Factor Eating Questionnaire (TFEQ);[9,26] serum cortisol levels; initial and final body weight, and BMI.

The PSS instrument is used to measure psychological stress. This 14-item scale determines general stress experienced in the previous month, with higher scores representing higher stress and possible values ranging from 0 to 56. PSS evaluates physical and mental depressive symptoms, requirement of health services, social anxiety, and correlates with life-event scores. [22] Perceived stress was used as a continuous variable in the present analysis to determine any effect of treatment.

The FCQ-T is a 39-item, self-reported questionnaire which is used to measure stable dimensions of food cravings, with answers based on a six-point Likert scale ranging from 1(never/not applicable) to 6 (always). FCQ-T records nine domains of food cravings: (1) Planning to eat food; (2) positive reinforcement from eating; (3) relief from negative mood by eating; (4) lack of control on over-eating of food; (5) thoughts about food; (6) physiological state; (7) emotions that involvement during food cravings or eating; (8) environmental cues that may trigger food cravings; and (9) guilt experienced due to food craving. [23]

The OHQ[24,25] consists of 29 questions that are answered on a six point Likert scale (1 = strongly disagree, 6 = strongly agree). The OHQ is an effective tool to measure happiness, well-being and optimism. In general, happiness and stress are believed to be inversely proportional.[27] Therefore, reduction of the effects of stress may be expected to improve general well-being in study subjects.

As noted above, serum cortisol levels are an indicator of stress,[4] and have been shown to affect appetite.[7-9] Therefore, cortisol represents an effective parameter for measuring the anti-stress effect of Ashwagandha in subjects under chronic stress, and its impact on weight gain.[7-9]

The TFEQ utilized in this study was the Revised-TFEQ as explained and revised by Cappelleri et al[28] and Karlsson et al[26] from the original version of TFEQ by Stunkard and Messick.[29] This questionnaire is used to determine eating behavior. It is a four-point Likert response format with a three-factor structure containing 18 items. The three factor scales are *'cognitive restraint'*, *'uncontrolled eating'* and *'emotional eating'*.

Statistical Analyses

Baseline scores were compared to post-treatment scores using a Friedman test followed by post-hoc individual comparisons using a Wilcoxon test. The two groups were compared for changes from baseline in the scores using a Wilcoxon test.

All data were expressed as means with standard deviation (SD). Categorical data and discrete data were expressed as numbers with percentages. Changes in the scores from baseline were calculated and expressed as mean change and percent change from baseline. Differences at the level of $P< 0.05$ were regarded as statistically significant.

RESULTS

A total of 52 adults (38 men and 14 women) between the ages of 18 and 60 years were enrolled in the present study, and randomized to receive treatment or placebo (Figure 1).

Out of the 52 enrolled subjects, two (one each in the placebo and treatment group) were not compliant with the study protocol. The data for the remaining 50 subjects were used for efficacy analysis as per-protocol (PP) datasets. For safety analysis, intent-to-treat (ITT) datasets were used. The ITT dataset included all 52 subjects recruited for the study irrespective of their study completion status.

The efficacy of the Ashwagandha root extract with regard to weight management was evaluated using FCQ scores, body weight, BMI and TFEQ scores, while the efficacy in stress management was evaluated through PSS and OHQ scores.

Baseline occupational and illness characteristics

Occupational and baseline characteristics were comparable across treatment groups in the trial (Table 1). The majority of patients (72% in Ashwagandha group and 68% in placebo group) were found to be employed. The remaining patients were either students or housewives. All patients in the trial had chronic stress symptoms. The majority were troubled with difficulties in concentration (60% in Ashwagandha group and 44% in placebo group) and insomnia (60% in Ashwagandha group and 44% in placebo group). About 44% of the patients in Ashwagandha group and 52% in placebo group had problems with anxiety and restlessness. Other major symptoms included physical exhaustion, mental fatigue, and headaches.

Outcome Measures

The primary and secondary outcomes of the trial are shown in Table 2. The primary outcome of the study was obtained from the PSS score. The treatment (Ashwagandha) and placebo groups were similar with respect to baseline PSS scores (P=0.759). At both subsequent time points, however, the mean PSS score of the treatment group decreased significantly (Table 2). This was a superior response compared to the placebo group (P=0.05 at 4 weeks and 0.0015 at 8 weeks). A reduction in PSS scores was observed at the end of 4th and 8th weeks for both the treatment and placebo groups. However, the treatment group experienced a significantly greater degree of reduction than the placebo group at the end of the 4th week (22.1%, $P = 0.0025$) and the 8th week (32.7% reduction at 8 weeks, $P < 0.0001$).

The scores of FCQ components are also shown in Table 2. The FCQ component 'Planning' scores for the treatment group were compared to the placebo group at baseline and at the end of the 4th and 8th weeks. No significant differences between the two groups were observed at baseline ($P = 0.366$) or 4th week ($P = 0.113$) score. However, at the end of 8th week, the mean FCQ-'Planning' score for the treatment group was significantly lower than that for the placebo group ($P = 0.0406$). A reduction of the mean FCQ-'Planning' score from baseline to 4 and 8 weeks was observed for both the treatment and placebo groups. However, the reductions of FCQ-'Planning' scores for the treatment group at the end of 4th week ($P = 0.0269$) and 8th week ($P = 0.0087$) were statistically significant compared to the placebo group. The mean FCQ-'Positive reinforcement' score of the treatment group at the 8th week was found to be significantly lower than that of the placebo group ($P = 0.0287$). The mean difference from the baseline FCQ-'Positive reinforcement' score at the end of the 4th ($P = 0.0067$) and 8th weeks ($P < 0.0001$) for the treatment group were found to be significant compared to the placebo group.

The mean FCQ -'Negative reinforcement' scores of the treatment group at the 4th and 8th weeks did not show any significant difference compared to the placebo group. However, the mean reduction from the baseline FCQ -'Negative reinforcement' score for the treatment group showed a significant difference from the placebo group at the 4th (P = 0.008) and 8th (P=0.0083) weeks. The mean FCQ scores of the treatment group showed a significant reduction from baseline compared to the placebo group for the following components: 'Lack of control' (4th week, P=0.0443; 8th week, P = 0.0097), 'Emotion' (4th week, P = 0.0352; 8th week, P = 0.0068), and 'Environment' (8th week, P = 0.039), during the study. However, the mean FCQ component scores of the treatment group for the 'Thoughts about food', 'Physiological' and 'Guilt' components did not show any significant differences compared to the placebo group.

With regard to the secondary outcomes of this study, mean OHQ scores were found to improve in both the placebo and treatment groups over the 8-week period of study. However, at the end of 8th week, the mean OHQ score of the treatment group improved significantly compared to the placebo group (P = 0.0087). At the end of the 4th (P = 0.0342) and 8th (P < 0.0001) weeks, the mean increase of the OHQ score from baseline for treatment group was significantly better than the placebo group, with an overall improvement of 19.18% .

Table 2 summarizes changes in serum cortisol levels, measured in μg/dL. Both the treatment and placebo groups had similar serum cortisol levels at baseline (P =0 .6835). However, by the end of the study (8th week), mean serum cortisol levels of the treatment group were significantly lower compared to placebo group (P = 0.0132). After 4 and 8 weeks of treatment, a reduction from baseline of 16.05% and 22.2% respectively was observed in the treatment group. The difference between the mean reductions of serum cortisol levels in the two groups after the 4th (P = 0.0328) and 8th weeks (P = 0.0019) of treatment were statistically significant.

Mean changes in body weight are shown in Table 2. The body weight for both the treatment and placebo groups was found to be reduced during the 8-week period of the study. After 4 weeks of treatment, a mean reduction of 2.14% and 1.09%, from baseline was observed in the treatment and placebo groups, respectively. However, the difference in reduction in the two groups was not statistically significant after 4 weeks (P = 0.0503). However, at the end of 8 weeks, the reduction of body weight for the treatment and placebo groups were 3.03% and 1.46% respectively. The data collected after 8 weeks of treatment suggest a significant difference in mean reduction of body weight for both groups (P = 0.0148).

The mean BMI for both groups was reduced during the study (Table 2). After 4 weeks and 8 weeks of treatment, a mean reduction from baseline of 2.08% (P=0.0429) and 2.93% (P = 0.0096) respectively was observed in the treatment group, which was statistically significant compared to the placebo group (4th week, 1.03%; 8th week, 1.4%).

Mean scores for the TFEQ components are shown in Table 2. During the study, the TFEQ- 'Cognitive Restraint' scores of the treatment group did not show significant differences when compared to the placebo group. However, the mean TFEQ- 'Uncontrolled eating' and 'Emotional eating' scores showed marked reduction from baseline scores for the treatment group, which was statistically significant compared to the placebo group at the end of the 4th week ('Emotional eating', P = 0.0207) and 8th week ('Uncontrolled eating', P = 0.0247; 'Emotional eating', P = 0.0135) of the study.

Vital parameters such as systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate and body temperature are summarized in Table 2. Mean systolic blood pressure, diastolic blood pressure and pulse rate were observed to change to a similar extent in both groups. Respiratory rate and body temperatures of the subjects of both groups were found to be unaltered during the 8 weeks of the trial. Therefore, it can be concluded that the treatment with Ashwagandha root extract did not produce any significant changes in vital parameters when compared with placebo.

Safety analysis

At the end of 8 weeks of treatment, patients were evaluated with the Patients Global Assessment of Tolerability to Therapy (PGATT) test, on a 5-point scale, which is done based on the ITT population. The majority of the patients in both the treatment (96%) and placebo group (96%) reported 'excellent tolerability'

Adverse events

Data on adverse events were collected and analyzed for the ITT population, considering all 52 subjects. Only two subjects (4%) out of 52 reported effects such as giddiness, heaviness of head,

blurring of vision and/or hyperacidity. The severity of these adverse events was mild and temporary. The treatment was tolerable to most of the patients in both groups.

DISCUSSION

This prospective, randomized, double-blind clinical study evaluated the safety and efficacy of a standardized Ashwagandha root extract in 50 subjects suffering from chronic stress & related disorders. The aim of the study was to analyze the impact of the extract on food cravings and body-weight management compared to a placebo. The results indicate that the treatment with Ashwagandha root extract was more effective than placebo.

Treatment with Ashwagandha root extract resulted in a marked reduction of mean scores on the Perceived Stress Scale (PSS) compared to baseline values at both 4 and 8 weeks. The treatment group exhibited significantly greater improvement than the placebo group. This result is in accordance with the findings of Chandrasekhar et al., who observed a 44% reduction of PSS score from baseline was observed at the end of a 60-day study with 64 subjects.[1] The other measures of efficacy utilized in this study also showed significantly greater improvement in the treatment group than the placebo group. These included measures of well-being and happiness, food cravings, reactive eating, serum-cortisol levels, and body weight.

Chronic stress is a common problem in modern life. Individuals experiencing prolonged stress are prone to overeating and improper diet maintenance.[2] Food cravings can be linked with higher consumption of palatable foods, thereby leading to increased BMIs. These cravings are known to mediate stress-related weight gain.[11] In the present study, mean FCQ scores for 'Planning', 'Positive reinforcement', 'Negative reinforcement', 'Lack of control', 'Emotion' and 'Environment' were reduced significantly ($P < 0.05$) after 8 weeks of treatment with Ashwagandha root extract, when compared to placebo. However, mean FCQ component scores of the treatment group for 'Thoughts about food', 'Physiological' and 'Guilt' did not show significant changes during the study. These results support the conclusion that, due to the anxiolytic and anti-stress properties of Ashwagandha, subjects rejected the use of food as a method for coping with stress. Cravings for food due to stress can lead to unconscious eating.Consequently, we can see that 'Thoughts about food', 'Physiological' and 'Guilt' parameters were not affected due to the treatment. Similar results were obtained from the TFEQ study. Scores for 'Uncontrolled eating' and 'Emotional eating' were reduced significantly ($P < 0.05$) after 8 weeks of Ashwagandha treatment, but were not reduced for 'Cognitive Restraint'. It has been observed previously that higher scores on the 'uncontrolled eating' and 'emotional eating' subscales are related to a higher preference of high energy-dense foods.[30]

The reduction of body weight and BMI observed in the present study further supports hypothesis that Ashwagandha root extract exerts anti-stress activity, resulting in reduced food cravings and better eating behaviors (as reflected in improved FCQ and TFEQ scores).

Stress-induced increases in serum cortisol leads to increased visceral fat deposition in humans. Prolonged stress also increases circulating glucocorticoid concentrations, which eventually promotes the ingestion of carbohydrates and fat and decreased energy expenditure by suppressing corticotropin-releasing hormone and stimulating neuropeptide hypothalamic secretion.[4] Low leptin levels have also been associated with increased symptoms of depression.[31] Leptin is a hormone that regulates energy balance by suppressing food intake, and thereby induces weight loss. Stress reduction restores normal leptin levels and helps to control obesity.[31] These results further support the hypothesis that treatment with Ashwagandha can be helpful in limiting stress-associated weight gain in humans.

The potential of Ashwagandha as a natural anti-stress and anti-anxiety therapeutic has been strongly supported by previous researchers.[1,3,20,21] The results of the present study have taken this analysis a step further, and demonstrated that Ashwagandha may provide a potential additional benefit of supporting the maintenance of normal weight (or even weight loss) in people living with chronic stress.

Ashwagandha is generally considered a harmless and easily tolerated medication with few adverse effects or withdrawal symptoms. Long-term administration of Ashwagandha root extract has been found to be safe in various studies.[1,32-34] The results of the present study are consistent with those of previous studies, with Ashwagandha exhibiting a good safety profile and negligible adverse events.

Limitations

The major limitation of the present study design is the relatively small sample size. A study with a larger population involving a wider cross-section of the subjects with regard to age groups,

occupation, and socioeconomic background would provide more conclusive results. Study duration should also be increased in future research, in order to evaluate the long-term effects of Ashwagandha root extract. Also, it would be useful to measure additional parameters, such as serum leptin and ghrelin levels involved in appetite regulation. However, this preliminary study offers a useful guide for future studies with Ashwagandha root extract or other herbal medicines.

CONCLUSION

The results of this study suggest that Ashwagandha root extract reduces psychological and physiological markers of stress, improves mental well-being, and reduces serum cortisol level and food cravings and improves eating behaviors. A statistically significant reduction in body weight and BMI were observed in patients treated with Ashwagandha root extract compared to placebo. Therefore, we conclude that Ashwagandha root extract can be useful for body-weight management in patients experiencing chronic stress. However, further studies are required to bolster the potential of Ashwagandha to prevent weight gain caused by long-term chronic stress.

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Table 1. Baseline occupational and illness characteristics (ITT population)

	Ashwagandha (n=25)	Placebo (n=25)
Employment status		
House Wife	3 (12%)	4 (16%)
Employed	18 (72%)	17 (68%)
Student	4 (16%)	4 (16%)
Stress symptoms		
Difficulty in concentration	15 (60%)	11 (44%)
Physical exhaustion	7 (28%)	1 (4%)
Anxiety, restlessness	11 (44%)	13 (52%)
Insomnia	15 (60%)	11 (44%)
Headache	5 (20%)	9 (36%)
Fatigue	4 (16%)	5 (20%)
Loss of appetite	1 (4%)	0 (0%)
Mental confusion	0 (0%)	1 (4%)

Data is represented as n (%)

Table 2. Efficacy analysis: Primary and secondary outcomes (PP population)

	Ashwagandha (n=25)	Placebo (n=25)	*P* value
PRIMARY OUTCOMES			
Mean Perceived Stress Scale score (% reduction)			
Baseline	20.31(4.04)	19.96(3.99)	0.759
Week 4	15.73 (4.38)	18.50(5.33)	0.0519
Week 8	13.65(3.14)	17.83(5.16)	0.0015
Mean change from baseline:			
At 4 wks:	-4.48 (4.16)	-1.46 (2.57)	0.0025
At 8 wks.	-6.65 (4.80)	-2.12 (2.68)	<0.0001
Mean Food Cravings Questionnaire Scores - Component 1 PLANNING			
Baseline	11.54 (4.55)	12.62(3.87)	0.366
Week 4	10.12(4.14)	11.92(3.74)	0.1127
Week 8	9.35(4.18)	11.67(4.01)	0.0406
Mean change from baseline:			
at 4 wks	-1.42(1.17)	-0.71(1.04)	0.0269
at 8 wks	-2.19(1.70)	-0.96(1.49)	0.0087
Mean Food Cravings Questionnaire Scores - Component 2 POSITIVE REINFORCEMENT			
Baseline	19.12(6.45)	20.54(5.74)	0.4121
Week 4	16.65(5.82)	19.92(6.07)	0.0589
Week 8	15.92(6.16)	19.62(5.44)	0.0287
Mean change from baseline:			
at 4 wks	-2.46(1.88)	-0.62(2.58)	0.0067
at 8 wks	-3.19(1.96)	-0.92(2.10)	<0.0001
Mean Food Cravings Questionnaire Scores - Component 3 NEGATIVE REINFORCEMENT			
Baseline	10.73(3.67)	10.46(4.05)	0.805
Week 4	9.46(4.23)	10.42(4.11)	0.4218
Week 8	8.85(4.08)	10.08(4.17)	0.2947
Mean change from baseline:			
at 4 wks	-1.27(1.78)	-0.04(1.33)	0.008
at 8 wks	-1.88(2.32)	-0.38(1.47)	0.0083
Mean Food Cravings Questionnaire Scores - Component 4 LACK OF CONTROL			
Baseline	15.96(4.32)	14.50(4.49)	0.2476
Week 4	14.04(3.49)	14.08(4.20)	0.9676
Week 8	13.00(3.64)	13.83(4.31)	0.466
Mean change from baseline:			
at 4 wks	-1.92(2.83)	-0.42(2.32)	0.0443
at 8 wks	-2.96(3.49)	-0.67(2.46)	0.0097
Mean Food Cravings Questionnaire Scores - Component 5 THOUGHTS ABOUT FOOD			
Baseline	19.88 (6.87)	21.62 (5.48)	0.3253
Week 4	18.31 (6.69)	21.21 (6.06)	0.1142
Week 8	17.58 (7.27)	20.88 (5.97)	0.0851
Mean change from baseline:			
at 4 wks	-1.58 (2.94)	-0.42 (2.95)	0.1704
at 8 wks	-2.31 (3.43)	-0.75 (2.63)	0.0764
Mean Food Cravings Questionnaire Scores - Component 6 PHYSIOLOGICAL			
Baseline	11.73 (5.41)	12.33 (5.07)	0.6861
Week 4	10.96 (5.57)	12.08 (5.08)	0.46
Week 8	10.77 (5.64)	12.08 (4.94)	0.3843
Mean change from baseline:			
at 4 wks	-0.77 (1.82)	-0.25 (1.94)	0.3347
at 8 wks	-0.96 (1.89)	-0.25 (1.67)	0.1642
Mean Food Cravings Questionnaire Scores - Component 7 EMOTION			
Baseline	14.46 (5.49)	13.21 (6.39)	0.4625
Week 4	12.85 (4.89)	12.83 (6.49)	0.9938
Week 8	12.15 (4.65)	12.67 (5.87)	0.7352
Mean change from baseline:			
at 4 wks	-1.62 (2.26)	-0.38 (1.76)	0.0352
at 8 wks	-2.31 (2.65)	-0.54 (1.67)	0.0068
Mean Food Cravings Questionnaire Scores - Component 8 ENVIRONMENT			
Baseline	15.46 (4.69)	15.67 (4.86)	0.8802
Week 4	13.62 (5.35)	14.79 (5.32)	0.4401
Week 8	12.77 (5.16)	14.29 (5.36)	0.3124
Mean change from baseline:			
at 4 wks	-1.85 (2.44)	-0.88 (2.35)	0.1583
at 8 wks	-2.69 (2.33)	-1.38 (2.06)	0.039
Mean Food Cravings Questionnaire Score - Component 9 GUILT			
Baseline	8.69 (3.28)	8.04 (3.64)	0.5115
Week 4	8.12 (3.96)	7.79 (4.05)	0.7768
Week 8	7.81 (3.67)	7.58 (3.97)	0.8368
Mean change from baseline			
Change at 4 wks	-0.58 (1.65)	-0.25 (1.36)	0.4475
Change at 8 wks	-0.88 (1.42)	-0.46 (1.44)	0.299
SECONDARY OUTCOMES			
Mean Oxford Happiness Questionnaire Score			
Baseline	28.88 (5.26)	29.17 (5.83)	0.8586
Week 4	32.58 (4.62)	30.21 (7.59)	0.1949
Week 8	34.42 (4.69)	30.21(6.01)	0.0087
Mean change from baseline :			
At 4 wks.	3.69(4.43)	1.04(4.16)	0.0342
At 8 wks.	5.54(4.64)	1.04(3.06)	<0.0001
Mean Serum Cortisol Level (mcg/dl)			
Baseline	17.25 (4.41)	16.76(3.95)	0.6835
Week 4	14.47(2.94)	15.63(3.07)	0.1798
Week 8	13.41(2.17)	15.44(3.20)	0.0132
Mean change from baseline:			
at 4 wks	-2.77 (3.09)	-1.13 (2.14)	0.0328
at 8 wks	-3.83(3.18)	-1.32(2.10)	0.0019
Mean Body weight (kg)			
Baseline	76.35 (8.71)	77.16(8.46)	0.7383
Week 4	74.70 (7.81)	76.32(7.99)	0.4733
Week 8	74.03 (7.29)	76.03(7.72)	0.3523
Mean change from baseline:			
at 4 wks	-1.64(1.57)	-0.84(1.24)	0.0503
at 8 wks	-2.32(1.99)	-1.13(1.24)	0.0148
Mean Body Mass Index (BMI)			
Baseline	26.88 (1.62)	27.17(1.32)	0.4793
Week 4	26.32(1.51)	26.89(1.30)	0.1579
Week 8	26.09(1.34)	26.80(1.35)	0.0696
Mean change from baseline:			
at 4 wks	-0.56(0.51)	-0.28(0.42)	0.0429
at 8 wks	-0.79(0.65)	-0.38(0.40)	0.0096
Mean Three Factor Eating Questionnaire Score - Component 1 Cognitive Restraint			
Baseline	13.19 (4.78)	13.50 (6.15)	0.8452
Week 4	12.08 (4.96)	13.00 (6.19)	0.5656
Week 8	11.54 (4.82)	12.38 (5.33)	0.5644
Mean change from baseline:			
at 4 wks	-1.12 (2.37)	-0.50 (1.98)	0.3228
at 8 wks	-1.65 (2.17)	-1.12 (2.33)	0.4114

Mean Three Factor Eating Questionnaire Score - Component 2 Uncontrolled Eating			
Baseline	23.69 (5.36)	22.75 (5.42)	0.5399
Week 4	19.92 (6.10)	20.83 (5.66)	0.5867
Week 8	18.85 (4.67)	20.17 (6.13)	0.399
Mean change from baseline:			
at 4 wks	-3.77 (3.28)	-1.92 (3.35)	0.0542
at 8 wks	-4.85 (3.78)	-2.58 (3.11)	0.0247
Mean Three Factor Eating Questionnaire Score- Component 3 Emotional Eating			
Baseline	9.46 (2.28)	9.46 (2.38)	0.9961
Week 4	8.27 (2.49)	9.21 (2.19)	0.1623
Week 8	7.96 (2.65)	9.08 (2.08)	0.1011
Mean change from baseline:			
at 4 wks	-1.19 (1.55)	-0.25 (1.22)	0.0207
at 8 wks	-1.50 (1.86)	-0.38 (1.17)	0.0135
Vital parameters			
Mean Systolic BP			
Baseline	120.88 (8.04)	122.80 (7.42)	0.385
Change at 4 wks	-0.96 (6.83)	-2.08 (7.99)	0.597
Change at 8 wks	-2.24 (13.62)	-4.56 (6.42)	0.445
Mean *Diastolic BP*			
Baseline	74.72 (4.96)	75.60 (4.83)	0.528
Change at 4 wks	2.00 (6.63)	-0.16 (5.51)	0.216
Change at 8 wks	0.08 (5.90)	-0.96 (5.45)	0.521
Mean *Pulse rate*			
Baseline	76.16 (4.20)	76.64 (3.82)	0.674
Change at 4 wks	-0.80 (4.65)	0.08 (4.14)	0.484
Change at 8 wks	-1.76 (4.70)	-2.08 (4.67)	0.810
Mean *Respiratory rate*			
Baseline	15.92 (0.64)	16.00 (0.29)	0.572
Change at 4 wks	0.08 (0.64)	0.04 (0.35)	0.785
Change at 8 wks	0.24 (0.66)	0.16 (0.37)	0.602
Mean Body *Temperature*			
Baseline	98.08 (0.09)	98.09 (0.07)	0.481
Change at 4 wks	0.03 (0.11)	0.00 (0.08)	0.390
Change at 8 wks	-0.04 (0.11)	-0.04 (0.10)	1.000

Data is represented as mean (SD)

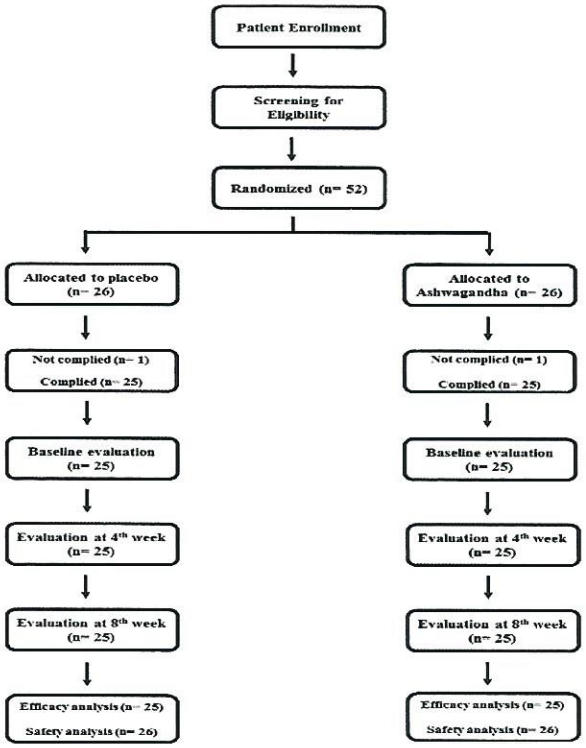

Figure 1. Patient distribution and study design