Sleep Medicine 72 (2020) 28–36

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

# A randomized, double blind, placebo controlled study to evaluate the effects of ashwagandha (*Withania somnifera*) extract on sleep quality in healthy adults

Abhijit Deshpande [a, *], Nushafreen Irani [a], Ratna Balkrishnan [a], Irin Rosanna Benny [b]

[a] International Institute of Sleep Sciences (IISS), NEST Hospital, Second Floor, Behind SBI Naupada Br, Off Gokhale Road, Naupada, Thane, Maharashtra, 400602, India
[b] Amala Institute of Medical Sciences, Amala Nagar PO, Thrissur, Kerala, 680555, India

ARTICLE INFO

*Article history:*
Received 24 December 2019
Received in revised form
9 March 2020
Accepted 12 March 2020
Available online 21 March 2020

*Keywords:*
Non restorative sleep
Ashwagandha
RSQ
Actigraphy
Sleep quality

ABSTRACT

*Objective:* Non-restorative sleep (NRS) affects 10% people worldwide, leading to poor sleep quality, as well as physical and cognitive fatigue. This is the first human study in which an extract of ashwagandha (*Withania somnifera* Dunal L.) was evaluated for effects in improving overall sleep quality in subjects with NRS.

*Methods:* In this randomized, double-blind, placebo-controlled trial, 150 healthy subjects scoring high on non-restorative sleep measures were given 120 mg of standardized ashwagandha extract (Shoden®) once daily for six weeks. Subjects were evaluated using the Restorative Sleep Questionnaire-weekly version and World Health Organization Quality of Life-Bref (WHOQOL) scale. Sleep actigraphy was used to measure the onset of sleep latency, sleep efficiency, total sleep time and wake after sleep onset. Safety of the treatment was determined by testing of vitals, hematology, biochemistry and urinalysis.

*Results:* A total of 144 subjects completed the study, with no dropouts due to adverse events. A 72% increase in self-reported sleep quality was found for the treatment group, compared with 29% in the placebo group ($p < 0.001$). Based on activity monitoring data, the treatment group showed significant improvement in sleep efficiency (SE) ($p < 0.01$), total sleep time ($p < 0.001$) and sleep latency ($p < 0.01$) and wake after sleep onset (WASO) ($p < 0.05$) versus placebo after six weeks. In the ashwagandha group quality of life (QOL) scores showed significant improvement in physical ($p < 0.001$), psychological ($p < 0.001$), and environment domains ($p < 0.01$).

*Conclusions:* Supplementation with the standardized ashwagandha extract for six weeks improved the overall quality of sleep by significantly improving the NRS condition in healthy subjects. No treatment related adverse events were reported in the study.

*Trial registration:* Clinical Trials Registry-India (www.ctri.nic.in). Registration number: CTRI/2017/02/007801.



## 1. Introduction

Nonrestorative sleep (NRS) has been recently developed identified and validated as a clinical endpoint for inadequate sleep [1]. NRS is commonly associated with insomnia and lack of restful sleep, and is often a feature of medical conditions like fibromyalgia and chronic fatigue syndrome [2]. NRS increases fatigue, lowers cognitive function and reduces quality of life (QOL), making the recognition and treatment of NRS a priority for physicians in the field of sleep medicine [3].

Recently, NRS has been investigated in the absence of other disorders in healthy people, and also accompanying comorbid

*Abbreviations:* DIS, Difficulty in initiating sleep; DMS, Difficulty in maintaining sleep; ICSD, International Classification of Sleep Disorders; NRS, Non-restorative sleep; RSQ-W, Restorative Sleep Questionnaire-weekly; SE, Sleep efficiency; SOL, Onset of sleep latency; STOP BANG, The Snoring, Tiredness, Observed apnea, high blood Pressure (STOP)-Body mass index, Age, Neck circumference, and Gender (BANG); TBT, Total bed time; TST, Total sleep time; WASO, Wake after sleep onset; WHOQOL, World Health Organization Quality of Life; WG, Withanolide glycosides.

* Corresponding author.
*E-mail address:* abhijitd1965@gmail.com (A. Deshpande).

https://doi.org/10.1016/j.sleep.2020.03.012
1389-9457/

conditions [4,5]. Other studies have indicated a high degree of psychiatric comorbidity, with NRS occurring more frequently in individuals with mood disorder, anxiety, and substance abuse disorder [6].

Previous versions of International Classification of Sleep Disorders (ICSD) allowed for NRS as a sole complaint in absence of sleep onset or sleep maintenance issues to qualify for diagnosis of Insomnia. However, currently available treatments for insomnia, including psychological therapy and pharmacologic treatments are designed for difficulty in initiating or maintaining sleep. The current version (ICSD-3) has removed NRS as a sole criterion for diagnosis of Insomnia, however it does admit to the fact that further research is needed to explore the clinical significance in the context of Insomnia. Pharmaceutical treatments have shown efficacy for improving sleep, however many adverse effects are associated with these medicines. Despite recent advances in the development of newer sleeping aids and hypnotics in modern medical science, a significant number of patients with sleep disturbances, consume supplements regularly to support sleep [7]. Hence there is a need for medicines which are shown to be effective in addressing the issue of "NRS".

Many chronic Insomnia patients have thoughts about ongoing sleep difficulties through the day and may be amplified near bedtime. Often performance anxiety about "sleep" itself is present. A learned pattern of physiological arousal at bedtime is often seen. All this leads to perceived stress furthering Insomnia [8].

Ashwagandha (*Withania somnifera*), also known as Indian ginseng, is a shrub plant belonging to the Solanaceae family. Ashwagandha has been used by traditional Indian Ayurvedic medicine for thousands of years to help with sleep, inflammation, sexual issues, nerve tissue damage, stress, anxiety, insomnia and other ailments [9]. The efficacy of ashwagandha against anxiety and depression has been previously reported in clinical trials [9–13]. Ashwagandha has since long been well recognized to be a sleep inducing plant and in a recent study, efficacy and safety of ashwagandha root extract has been reported in subjects diagnosed with insomnia and anxiety [14]. While NRS is associated with stress, anxiety, depression and daytime fatigue [15], ashwagandha is shown to be effective in relieving stress and depression [12,16]. It is also effective in reducing fatigue [17] and inflammation [18]. Thus, it was proposed that ashwagandha may have beneficial effects in reducing NRS.

The primary objective of the present trial was to evaluate effect of daily supplementation of a standardized ashwagandha extract compared to placebo in healthy subjects with NRS after six weeks. The secondary objectives were to compare ashwagandha and placebo groups on change from baseline up to six weeks by activity monitoring during sleep, and quality of life scores using World Health Organization Quality of Life-Bref (WHOQOL-Bref) scale.

## 2. Methods

### 2.1. Study design

This was a prospective, randomized, double blind, parallel, placebo controlled, clinical study. The study was conducted at International Institute of Sleep Sciences, NEST Hospital, Thane, Maharashtra, India. The study was conducted in accordance with the Declaration of Helsinki, the ICH-GCP E6 (R1, R2), and ICMR-National Ethical Guidelines for Biomedical and Health Research, 2006. The study protocol was approved by the institutional ethics committee and registered with Clinical Trials Registry-India (www.ctri.nic.in) (Registration number: CTRI/2017/02/007801). The clinical study protocol on the present trial has been already published [19]. Informed consent was taken from the subjects before starting any study related activity.

### 2.2. Population and inclusion/exclusion criteria

Male and female subjects 18–65 years old were recruited for this study. The inclusion criteria included subjects with RSQ-W (Restorative Sleep Questionnaire-weekly) score less than or equal to 50 [1], and have not taken ashwagandha or any sleep medicine within last one year, who were able to read/communicate in English and willing to provide written informed consent. Subjects with a medical history of heart disease, respiratory disorders, seizure disorders or other chronic health conditions requiring medication were excluded. Subjects suffering from severe intrinsic sleep related disorders such as severe sleep apnea (STOP BANG questionnaire score >5; The Snoring, Tiredness, Observed apnea, high blood Pressure (STOP)-Body mass index, Age, Neck circumference, and Gender (BANG) questionnaire) [20], moderate to severe restless leg syndrome (RLS), narcolepsy, and untreated depression (Score of 15 or more for Anxiety or Depression when measured with Hospital Anxiety and Depression Scale) were also excluded from the study. Subjects with shift work disorders and other psychiatric disorders which needed medication management were also excluded. Nursing or pregnant women were excluded. Subjects were also excluded if they met any of the following conditions: current prescription medication or herbal treatment, history of drug or alcohol addiction or abuse within the past 12 months, hepatic or renal impairment, history of hypersensitivity to ashwagandha, or prior participation in a clinical trial in the past 12 months.

### 2.3. Type, sequence and duration of study periods

The study was a parallel treatment study with two groups (See Fig. 1). The study was designed in three phases: (1) Screening phase, (2) Pre-treatment phase, and (3) Treatment phase. In the screening phase (−2 to −1 day) those subjects passing the inclusion/exclusion criteria were called for randomization (day 0). In the pre-treatment phase (day 0–8) the eligible subjects were enrolled into either the ashwagandha group or the placebo in an allocation concealed manner. The treatment phase had 42 days where days 15, 22, 29, & 43 were interviews by telephone.

In the screening phase the subjects were given the STOP BANG, RSQ-W, and WHOQOL questionnaires and blood was obtained for safety analysis. Actiwatch (Actisleep® device from Actigraph Corporation, Pensacola, Florida, USA) was given and data collected after seven days. The subjects were then followed on an outpatient basis based on the study schedule. WHOQOL and RSQ-W questionnaires were collected as baseline on day 8. Interventions were dispensed on day 8, with the final study visit on day 50. Subjects were not permitted to take any medication (allopathic or herbal preparation) without approval of study investigator approval. Medications not known to interact with study medication were permitted if necessary by the investigator. Laboratory investigations of all the efficacy and safety parameters were conducted at screening and end of the study.

### 2.4. Intervention

The ashwagandha root and leaves raw material was authenticated by a qualified botanist and voucher specimen was deposited in the Research and Development Lab of Arjuna Natural Private Limited for future reference. The treatment extract (Shoden®, Arjuna Natural Private Ltd, Kerala, India) was prepared and purified to enrich the withanolide glycosides (WG)

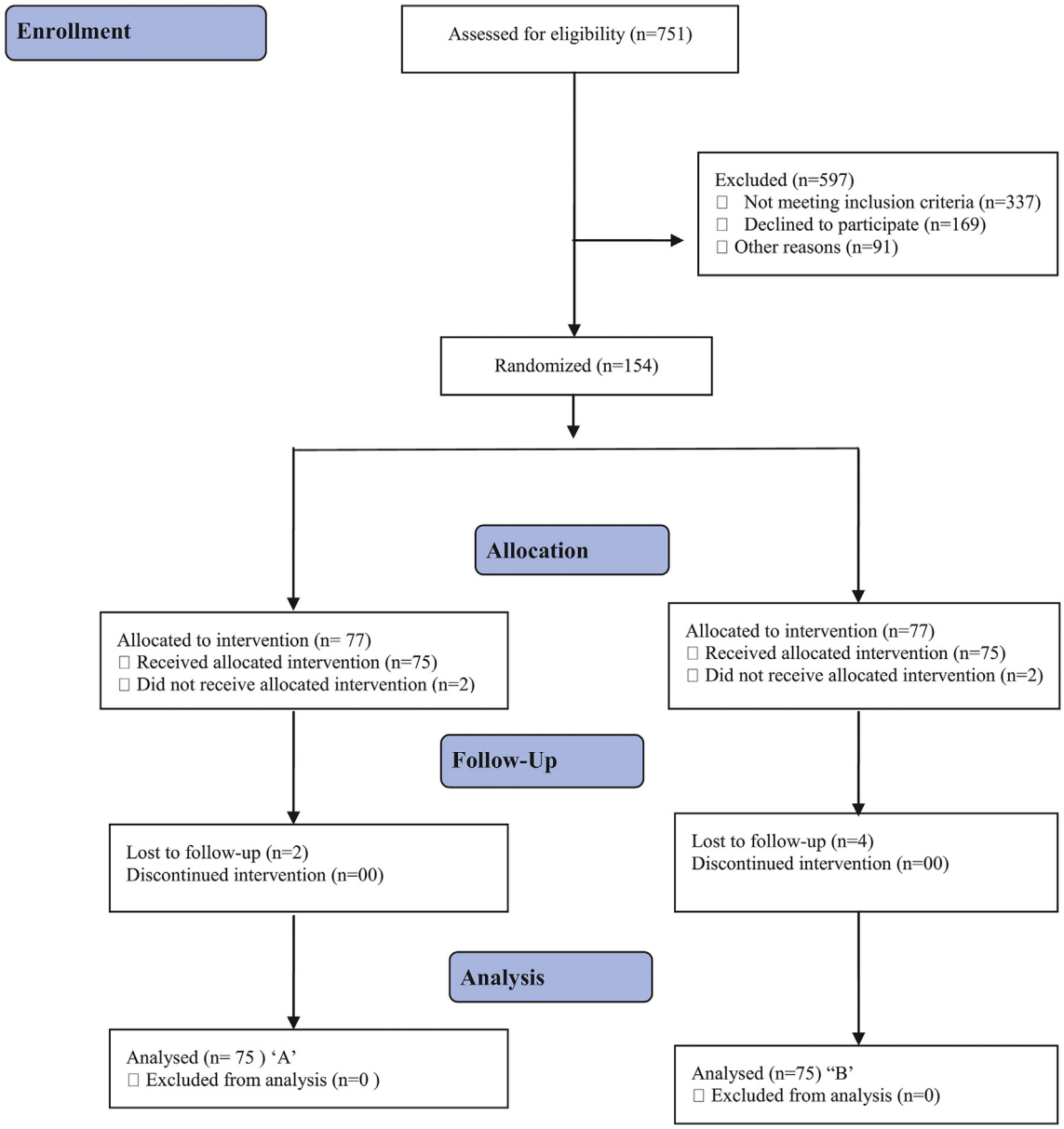


**Fig. 1.** Flow diagram of study design and intervention.

content and analyzed by high performance liquid chromatography. The dosage of ashwagandha extract in each capsule was standardized to contain 21 mg of WG. The treatment or matching placebo (rice powder) were given as two 60 mg capsules per day. To maintain blindness of study treatment, opaque capsules were used. The subjects were instructed to take two capsules with water once daily in the evening, approximately 2 h before the evening meal.

### 2.5. Randomization, blinding and unblinding

Block-randomization was performed by the independent statistician using SPSS software. The study was designed as a double blinded study such that the investigator and subject were unaware of the treatment allocated. The enrolled subjects were assigned to either of the two study groups according to the centralized computer generated randomization in a 1:1 ratio.

### 2.6. Efficacy assessment

The primary efficacy measure was mean percent change in total score of restorative sleep questionnaire-weekly (RSQ-W) at the end of six weeks between the two groups. The secondary outcome measures were mean percent change in actigraphy parameters and mean percent change in quality of life scores using WHOQOL-Bref scale [21] at the end of six weeks between the two groups. Adverse events encountered during the course of the study and subject's compliance for study treatments were also considered as secondary outcomes.

#### 2.6.1. Restorative sleep questionnaire (RSQ-W) total score

RSQ-W is one of the most common validated scales for measuring whether restful sleep occurred. The questionnaire included nine questions, with answers scaled from 1 to 5. The total RSQ-W score is based on an average from all nine questions, and presented on a scale of 0–100.

#### 2.6.2. Actigraphy parameters

Actigraphy, or activity monitoring, is a biomedical instrument capable of monitoring motor activity in order to identify the presence or absence of body motion during sleep or wakefulness. Activity monitoring by means of an actigraph is useful in detecting sleep episodes and differentiating periods of sleep and rest from periods of wakefulness. The device works on the principle that movement of the non-dominant wrist is correlated with wakefulness, whereas long, quiescent periods are associated with rest or sleep. Studies have demonstrated an 88.9 percent correlation of accuracy with polysomnographically measured sleep [22]. In this study, Actisleep® device from Actigraph Corporation, Pensacola, Florida, USA, with software algorithms of Actilife® (version 6.10) was used to calculate the sleep parameters. Actilife software uses validated algorithms developed by Cole and coworkers. During this validation, wrist worn actigraphy data was used to determine sleep and wake against gold standard nocturnal polysomnogram [23]. This protocol was further validated in 2003 by De souza et al., and was shown to have excellent correlation with polysomnogram epochs with sensitivity of actigraphy approaching 99% for accuracy [24].

The Actiwatch is worn on the wrist like a regular watch and was instructed to be worn at all times. Parameters included onset of sleep latency (SOL), sleep efficiency (SE), total sleep time (TST), total bed time (TBT), wake after sleep onset (WASO), average number of awakenings and average awakening time. SE refers to the actual time spent for sleep in comparison to overall time spent in bed. TST is referred to as the actual sleep time in a sleep period and WASO is the duration a person remains awake after the defined onset of the sleep.

#### 2.6.3. WHOQOL-Bref scores

WHOQOL-Bref is a self-administered, 26-item, cross culturally validated questionnaire measuring the following broad domains: physical health, social relationships, psychological health and environment. The scores obtained in each domain are scaled in a positive direction (ie higher scores denote better QOL). The mean score of items for each domain is used to calculate the total domain score based on a 0–100 scale. English version was used in the present study.

### 2.7. Safety assessment

A central clinical pathology laboratory (Dr. Vaidya's Laboratory, Thane, Maharashtra, India) was used for all laboratory investigations. Lab parameters analyzed were hematological parameters (hemoglobin levels, total leukocyte count, absolute neutrophil count, platelet count etc.), biochemistry (fasting blood sugar, blood urea, serum creatinine, serum bilirubin, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, c-reactive protein). The safety of the study medication was also assessed by recording the adverse events occurred during the entire course of the study.

### 2.8. Sample size

The group-sequential method was used to determine the sample size. The planned sample size of 75 in each study treatment group was required to detect a difference of 10 points in change in RSQ-W total score after six weeks from the baseline between the study treatment groups, assuming a standard deviation of 25 points and a 15% drop-out rate, to achieve 80% statistical power at 5% (two-sided) level of significance.

### 2.9. Statistical analysis

The data collected were analyzed for demographics, efficacy & safety. Descriptive statistics was used for different variables at baseline. A $p$-value of <0.05 was considered as statistically significant. Two-sample Hotelling's $T^2$ test was used to compare day 8 and day 50 data obtained for RSQ-W. Differences of 10 points and 15 points for RSQ-W total score were considered as clinically significant and clinically highly significant, respectively. Assuming standard deviation of 25 points, these differences correspond to standardized effect size of 0.4 (small-to-medium) and 0.6 (medium-to-large), respectively, as per Cohen's recommendation.

The activity monitoring data and WHO-QOL were analyzed using paired T-test or Wilcoxon Signed Rank Test for within the group data. Mann–Whitney or Equal-Variance T-Test was used to compare the variables between the groups. The normality analysis of the data was performed using the NCSS software which computes Shapiro–Wilk, Skewness, Kurtosis, & Omnibus normality. Since the sample size was large and the analysis made was normal approximation, the value of t-test was taken wherever anyone of the normality assumptions was not rejected. Where all assumptions made were rejected then Wilcoxon Sign rank test was used. The vital parameters were analyzed by multivariate analysis of variance (MANOVA).

## 3. Results

A total of 751 subjects were assessed during Mar 2017 to Sep 2018 for eligibility, from which 154 subjects met the study criteria and were randomized into two groups (77 subjects in each group) (Fig. 1). Four subjects (two from each group) withdrew before treatment exposure, thus, 150 subjects (75 in each study group) received the intervention. Study duration per subject was six weeks. Out of 75 subjects in each group, 73 subjects completed the study in placebo group and two subjects were lost to follow up. Similarly in ashwagandha group, 71 subjects completed the study and four subjects were lost to follow up. All the subjects who had received the interventional products were included in the analysis. The analyses were taken with intent to treat and all 150 subjects were included in the analysis with last observation carried forward method.

A total of nine (6%) participants had other medical disorders. Five participants received ashwagandha and four received placebo. Out of these nine participants, four participants had diabetes and were taking oral antidiabetic medicine (Metformin), two had systemic hypertension controlled with anti-hypertensives. One participant had arthralgia without any medicines. One had elephantiasis in right leg and was not on any medicines. One had high cholesterol for which he was not receiving any medicine.

### 3.1. Demographic details

The demographic characteristics of subjects are shown in Table 1, and indicate that the study population was homogenous, with no statistically significant differences between the groups with respect to demographic variables.

### 3.2. RSQ-W

The results indicate that ashwagandha extract improved the quality of sleep as compared to placebo. Two-Sample Hotelling's $T^2$ test showed that between the groups in day 8 (before taking intervention) there was no significant difference ($p > 0.05$) whereas after the intervention (in day 50) there was significant difference between the groups ($p < 0.001$). There was 72% mean increase in

**Table 1**
Subject's demographic and baseline characteristics.

| Parameters | | Group A (Placebo) | Group B (Ashwagandha) | Significance (t-Test) |
|---|---|---|---|---|
| No. of subjects | Male | 40 (53.33%) | 32 (42.66%) | $\chi^2 = 1.3088$ |
| | Female | 35 (46.66%) | 43 (57.33%) | $p > 0.05$ |
| | Total | 75 | 75 | |
| Age (years) | Mean ± SD | 37.61 ± 10.32 | 36.8 ± 10.98 | $p > 0.05$ |
| Height (cm) | Mean ± SD | 161.83 ± 8.45 | 162.32 ± 8.1 | $p > 0.05$ |
| Weight (kg) | Mean ± SD | 66.26 ± 11.70 | 65.80 ± 12.19 | $p > 0.05$ |
| BMI (Kg/m$^2$) | Mean ± SD | 25.37 ± 4.11 | 25.03 ± 3.94 | $p > 0.05$ |

the quality of sleep in ashwagandha group as compared with 29% in the placebo group (Fig. 2).

### 3.3. Actigraphy parameters

In order to bring out a more conclusive decision on the efficacy of the intervention on the quality of sleep, the actigraph data was analyzed within the group and between the groups. The variables taken to determine the effect of intervention were SOL, SE, TST, TBT, WASO, and average awakening time (Table 2).

Within the group analysis in ashwagandha group gave very strong evidence that ashwagandha increased the TST ($p < 0.001$) and SE ($p < 0.0001$) significantly. There was statistically significant decrease in SOL ($p < 0.001$), WASO ($p < 0.0001$) and average awakening time ($p < 0.01$) in ashwagandha group compared to the corresponding initial period. Between the group analysis indicated that at baseline there was no significant difference ($p > 0.05$) between ashwagandha and placebo groups in all actigraphy parameters. At the end of the study, the ashwagandha group showed significant increase ($p < 0.001$) in TST as compared to placebo. The SOL ($p < 0.01$) and WASO ($p < 0.05$) in ashwagandha group was significantly less and SE was significantly high ($p < 0.01$) as compared to placebo group. This data indicates overall significantly better sleep quality in ashwagandha group as compared to placebo. The sequential assessment for actigraphy parameters recorded on day 15, day 22, day 29 and day 43 has been presented in Table 3. The results clearly indicate significant benefits of ashwagandha over placebo on sleep quality as duration of treatment increases. The effect size between placebo and ashwagandha indicate large effect for SE and TST, medium effect for SOL, WASO and average awakening time & small effect for awakening count (Table 4).

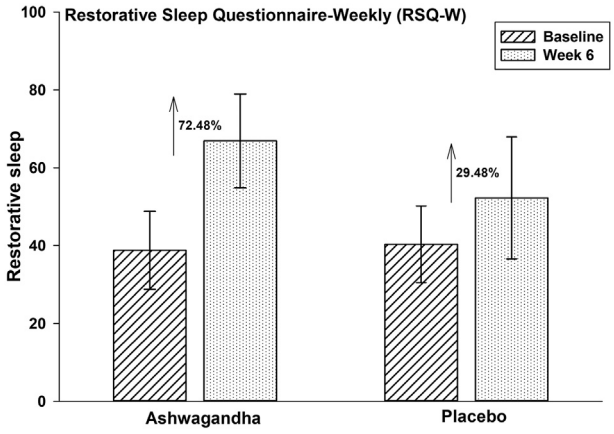


**Fig. 2.** RSQ-W score for placebo and ashwagandha groups.

There was no significant gender difference ($F_{6,129} = 1.27$, $p > 0.05$) in the overall sleep pattern as measured by the six actigraphy parameters namely SOL, SE, TST, WASO, awakening count and average awakening time and the effect size was medium.

Age contributed to a statistically significant difference ($F_{12,258} = 2.16$, $p > 0.05$) in the overall sleep pattern as measured by the six actigraphy parameters and the effect size was medium. Awakening count was the highest in the age group of 19–30 years and males had higher awakenings than females. There was no statistically significant ($p = 0.4782$) interaction between age and intervention groups (ashwagandha/placebo) and effect size was medium. Similarly, there was no statistically significant ($F_{12,258} = 1.44$, $p > 0.05$) interaction between age and gender and the effect size was medium.

### 3.4. WHOQOL-Bref scores

The summarized results (Table 5) for WHOQOL-Bref scores are presented in four domains. The ashwagandha group had significant improvement in the domains of physical ($p < 0.001$), psychological ($p < 0.001$), and environment ($p < 0.01$) dimensions. The percentage increase of score between day 8 and day 50 in each domain was better in the treatment group compared to placebo.

**Table 2**
Actigraphy parameters for placebo and ashwagandha.

| Parameters | Placebo | | | Ashwagandha | | | Significance (p-value) between the groups | |
|---|---|---|---|---|---|---|---|---|
| | Day 8 (Baseline)[a] | Day 50 (Week 6)[a] | p-value (Day 8 Vs Day 50) | Day 8 (Baseline)[a] | Day 50 (Week 6)[a] | p-value (Day 8 Vs Day 50) | Day 8 (Placebo Vs Ashwagandha) | Day 50 (Placebo Vs Ashwagandha) |
| SOL (min) | 14.3 ± 9.9 | 12.2 ± 6.4 | >0.05; ns | 13.6 ± 8.0 | 9.9 ± 5.5 | <0.001; sig | >0.05; ns | <0.01; sig |
| SE (%) | 79.6 ± 6.8 | 78.9 ± 7.4 | >0.05; ns | 78.9 ± 8.4 | 82.6 ± 7.0 | <0.0001; sig | >0.05; ns | <0.01; sig |
| TBT (min) | 465.5 ± 52.2 | 446.6 ± 44.3 | <0.01; sig | 456.1 ± 46.4 | 457.3 ± 49.0 | >0.05; ns | >0.05; ns | >0.05; ns |
| TST (min) | 370.6 ± 46.8 | 351.7 ± 41.5 | <0.01; sig | 359.8 ± 50.4 | 377.1 ± 46.8 | <0.001; sig | >0.05; ns | <0.001; sig |
| WASO (min) | 80.7 ± 31.3 | 82.7 ± 36.2 | >0.05; ns | 82.6 ± 35.4 | 70.4 ± 32.1 | <0.0001; sig | >0.05; ns | <0.05; sig |
| Awakening count (N) | 22.0 ± 6.8 | 22.6 ± 6.6 | >0.05; ns | 22.5 ± 7.6 | 21.7 ± 1.0 | >0.05; ns | >0.05; ns | >0.05; ns |
| Average awakening time | 3.89 ± 1.38 | 3.76 ± 1.36 | >0.05; ns | 3.87 ± 1.64 | 3.35 ± 1.19 | <0.001; sig | >0.05; ns | >0.05; ns |

[a] Data presented as Mean ± SD. ns = non significant, sig = significant.

**Table 3**
Sequential assessment of actigraphy parameters for placebo and ashwagandha.

| Parameters | Day 15 | | | Day 22 | | | Day 29 | | | Day 43 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Placebo[a] | Ashwagandha[a] | Significance | Placebo[a] | Ashwagandha[a] | Significance | Placebo[a] | Ashwagandha[a] | Significance | Placebo[a] | Ashwagandha[a] | Significance |
| SOL (min) | 13.6 ± 0.5 | 12.4 ± 0.5 | $F_{1,1632} = 2.706$, $p > 0.05$; ns | 13.2 ± 0.5 | 11.9 ± 0.5 | $F_{1,1632} = 3.924$, $p < 0.05$; sig | 12.8 ± 0.5 | 11.4 ± 0.5 | $F_{1,1632} = 4.504$, $p < 0.05$; sig | 12.1 ± 0.6 | 10.3 ± 0.7 | $F_{1,1632} = 3.661$, $p > 0.05$; ns |
| SE (%) | 79.7 ± 0.4 | 80.0 ± 0.4 | $F_{1,1632} = 0.709$, $p > 0.05$; ns | 79.4 ± 0.3 | 80.5 ± 0.3 | $F_{1,1632} = 5.150$, $p < 0.05$; sig | 79.3 ± 0.3 | 81.0 ± 0.4 | $F_{1,1632} = 12.348$, $p < 0.001$; sig | 80.0 ± 0.5 | 82.0 ± 0.5 | $F_{1,1632} = 21.555$, $p < 0.001$; sig |
| TST (min) | 366.9 ± 2.4 | 367.1 ± 2.6 | $F_{1,1632} = 0.004$, $p > 0.05$; ns | 363.6 ± 2.2 | 368.3 ± 2.4 | $F_{1,1632} = 1.995$, $p > 0.05$; ns | 360.3 ± 2.3 | 369.4 ± 2.5 | $F_{1,1632} = 7.104$, $p < 0.01$; sig | 353.6 ± 3.1 | 371.7 ± 3.3 | $F_{1,1632} = 15.778$, $p < 0.001$; sig |
| WASO (min) | 81.1 ± 1.6 | 79.6 ± 1.7 | $F_{1,1632} = 0.412$, $p > 0.05$; ns | 81.6 ± 1.5 | 77.8 ± 1.6 | $F_{1,1632} = 2.938$, $p > 0.05$; ns | 82.1 ± 1.5 | 76.1 ± 1.7 | $F_{1,1632} = 7.009$, $p < 0.01$; sig | 83.0 ± 2.0 | 72.5 ± 2.2 | $F_{1,1632} = 12.195$, $p < 0.001$; sig |
| Awakening count (N) | 22.2 ± 0.3 | 22.2 ± 0.4 | $F_{1,1632} = 0.036$, $p > 0.05$; ns | 22.2 ± 0.3 | 22.1 ± 0.3 | $F_{1,1632} = 0.073$, $p > 0.05$; ns | 22.2 ± 0.3 | 21.9 ± 0.3 | $F_{1,1632} = 0.518$, $p > 0.05$; ns | 22.3 ± 0.4 | 21.5 ± 0.5 | $F_{1,1632} = 1.5211$, $p > 0.05$; ns |
| Average awakening time | 3.84 ± 0.08 | 3.75 ± 0.08 | $F_{1,1632} = 0.589$, $p > 0.05$; ns | 3.84 ± 0.07 | 3.69 ± 0.08 | $F_{1,1632} = 1.915$, $p > 0.05$; ns | 3.83 ± 0.07 | 3.62 ± 0.08 | $F_{1,1632} = 3.528$, $p > 0.05$; ns | 3.82 ± 0.10 | 3.49 ± 0.11 | $F_{1,1632} = 4.985$, $p < 0.05$; sig |

[a] Data presented as Mean ± SE. ns = non significant, sig = significant.

Pearson's correlation coefficient indicated that there is a moderate positive correlation in the domains of physical ($p < 0.0001$; r = 0.67) and psychological ($p < 0.0001$; r = 0.54) health of WHOQOL-Bref with RSQ-W in ashwagandha group and only a negligible correlation in the domain of physical health of WHOQOL-Bref with RSQ-W in the placebo group ($p < 0.05$; r = 0.26).

### 3.5. Safety assessments and adverse events

The vital parameters were analyzed by MANOVA which showed that none of the response parameters were significantly different either visit wise or group wise. All the parameters measured were in safe range. The main effects of both group and visit were not statistically significant in the model for all the analyzed parameters. All biochemistry and hematology parameters before and after the study were within the normal range, and there was no significant difference between the groups or within the group. Four adverse events were reported in placebo group whereas six adverse events were reported in the ashwagandha group. All adverse events were mild in nature, and unrelated to the treatment (Table 6).

## 4. Discussion

Many people find it hard to get restful sleep. Low sleep quality leads to chronic fatigue, daytime sleepiness, and may result in other sleep disorders [25]. Restorative sleep is considered to be an important aspect of the overall sleep experience for healthy individuals. Non-restorative sleep, as measured in this study, is one indicator of poor sleep quality that results in day time fatigue and lethargy [26]. In Ayurvedic literature and traditional practice, "*Nidrajanan*" (sleep induction) is one of the traditional clinical indications and ashwagandha is used for this purpose. Ashwagandha products are traditionally sold as sleep remedies on the Indian market [27]. The present trial was focused on the efficacy of a standardized ashwagandha extract on the quality of sleep of subjects suffering from NRS. This is the first human clinical trial on NRS with ashwagandha extract.

Actigraphy, also known as activity monitoring, represents a useful diagnostic tool for the sleep medicine practitioner, allowing for assessment of sleep over extended periods of time in the natural sleep environment. Studies suggest that actigraphy may be superior to other methods like self-reported average nightly sleep duration or sleep log-recorded average nightly sleep duration for documenting sleep habits in clinical settings [28]. In the present study, the actigraphy data was consistent with self-rated sleep and quality of life scores. The subjects on ashwagandha group showed significant improvement in actigraph endpoints, including SE, TST and significant reduction in onset of SOL, WASO and average awakening time.

Improving sleep may be related to a reduction in stress and specifically a reduction in the stress hormone cortisol, which can disrupt the natural balance of the body [10]. Previous studies have found that ashwagandha can reduce cortisol levels [10]. In this study, the treatment could have improved sleep quality by decreasing cortisol and stress levels, although these measures were not included in the study.

Previous pilot studies on ashwagandha have found that quality of sleep to be improved in healthy volunteers [29]. However, previous studies were very small, and did not measure nonrestorative sleep or quality of life. In a recent study by Langade et al., [14]; efficacy and safety of ashwagandha root extract was studied in subjects diagnosed with insomnia and anxiety. Although the authors concluded that sleep quality was improved for subjects supplementing with 600 mg ashwagandha root extract daily for 10 weeks, WASO was not significantly reduced in ashwagandha group

**Table 4**
Effect size between placebo and ashwagandha at the end of the study (week 6) for various parameters.

| Response variable | Partial eta-square | Effect size measured as Cohen's f | Status | Criteria of f for small, medium and large effect |
|---|---|---|---|---|
| Sleep latency | 0.04762 | 0.22361 | Medium | $0.1 < f \leq 0.25$ |
| Sleep efficiency | 0.06906 | 0.27236 | Large | $0.25 < f \leq 0.4$ |
| Total sleep time | 0.07093 | 0.27630 | Large | $0.25 < f \leq 0.4$ |
| Wake after sleep onset | 0.03597 | 0.19317 | Medium | $0.1 < f \leq 0.25$ |
| Awakening count | 0.00350 | 0.05922 | Small | $f \leq 0.1$ |
| Average awakening time | 0.02765 | 0.16862 | Medium | $0.1 < f \leq 0.25$ |

**Table 5**
WHO-QOL-Bref domain.

| Parameters | Placebo | | | | Ashwagandha | | | |
|---|---|---|---|---|---|---|---|---|
| | Day 8 (Baseline) (Mean ± SE) | Day 50 (Week 6) (Mean ± SE) | % change | p-value | Day 8 (Baseline) (Mean ± SE) | Day 50 (Week 6) (Mean ± SE) | % change | p-value |
| Physical | 67.9 ± 1.4 | 71.2 ± 1.4 | ↑4.9 | <0.05[a] | 65.5 ± 1.6 | 74.1 ± 1.3 | ↑13.1 | <0.001[a] |
| Psychological | 66.2 ± 1.5 | 68.6 ± 1.2 | ↑3.6 | >0.05[a] | 63.8 ± 1.6 | 71.3 ± 1.4 | ↑11.8 | <0.001[a] |
| Social relationships | 65.9 ± 2.4 | 66.6 ± 2.2 | ↑1.0 | >0.05[b] | 63.9 ± 2.4 | 66.0 ± 2.3 | ↑3.2 | >0.05[a] |
| Environment | 69.1 ± 1.5 | 71.6 ± 1.2 | ↑3.6 | <0.05[a] | 71.0 ± 1.2 | 74.0 ± 1.1 | ↑4.3 | <0.01[a] |

[a] T-test.
[b] Wilcoxon signed rank test.

**Table 6**
Adverse events in placebo and ashwagandha groups.

| Indication | Serious | Expected/Unexpected | Severity | Relation to medication | Action taken | Outcome |
|---|---|---|---|---|---|---|
| **Placebo group** | | | | | | |
| Aphthous ulcer | No | Unexpected | Mild | Unlikely | None | Resolved |
| Runny nose | No | Unexpected | Mild | Unlikely | None | Resolved |
| Throat infection and cough | No | Unexpected | Mild | Unlikely | MIR[a] | Resolved |
| Allergic dermatitis | No | Unexpected | Mild | Unlikely | None | Resolved |
| **Ashwagandha group** | | | | | | |
| Viral fever | No | Unexpected | Mild | Unlikely | MIR[a] | Resolved |
| Headache | No | Unexpected | Mild | Unlikely | MIR[a] | Resolved |
| Acid reflux | No | Unexpected | Mild | Unlikely | None | Resolved |
| Acid reflux | No | Unexpected | Mild | Unlikely | None | Resolved |
| Allergic dermatitis | No | Unexpected | Mild | Unlikely | MIR[a] | Resolved |
| Allergic dermatitis | No | Unexpected | Mild | Unlikely | None | Resolved |

[a] MIR – Medical Intervention Required.

($p > 0.05$) as compared to placebo group. Similarly, TST was not significantly increased in ashwagandha group ($p > 0.05$) as compared to placebo after 10 weeks. In our study, a statistically significant reduction in WASO ($p < 0.05$) was observed compared to placebo after six weeks. WASO refers to periods of wakefulness occurring after defined sleep onset. This parameter is a better reflection of sleep fragmentation and one of the important parameters in assessment of sleep quality [30]. Similarly in our study TST was significantly increased in ashwagandha group as compared to baseline ($p < 0.001$) and as compared to placebo ($p < 0.001$). Unintended or intended sleep restriction is associated with feeling of fatigue and daytime sleepiness. Although our population did not have overt complaints about sleep duration, there was a significant increase in total sleep time with reduction in WASO. This has played a role in improving NRS scores.

Many sleep disorders can affect sleep duration. Patients with insomnia typically report short sleep duration at night, although recent studies have shown that sleep duration in insomnia patients is very similar to people without a complaint of insomnia. Disorders that affect the quality of nocturnal sleep may lead to a change in sleep duration. Increase in TST in the treatment group indicates its efficacy against sleep disorders and improvement in the normalization of sleep. Previous studies on melatonin supplementation also found an improvement in non-restorative sleep. The current study found a magnitude of effect similar to those reported with melatonin [31].

The mechanism of action for ashwagandha and sleep is not well understood. A number of animal studies have been reported with ashwagandha confirming its neuroprotective role in acute stress of sleep deprivation in rats [32], protective effect on the behavioral and biochemical alterations in sleep-disturbed mice [33], anxiolytic and immunomodulatory activity in acute sleep deprived female rats [34] and sleep promoting effects in sleep disturbed rats by GABAergic mechanism [35]. Sleep promoting effects of aswagandha and herbal preparation containing ashwagandha (BR-16A; Mentat®) were investigated in pentobarbitone induced hypnosis in mice [36]. The authors found that ashwagandha shortened the SOL and prolonged the sleep time as compared to control [36]. Interaction of ashwagandha with GABAergic drugs used in the treatment of sleep disorders was also studied. Ashwagandha significantly potentiated the effects of triazolam (a GABAergic hypnotic drug) by decreasing the SOL and increasing the total sleep time (duration). The authors concluded that dosage of GABAergic drugs can be reduced if used along with ashwagandha. In our study also there was decrease in SOL and increase in TST in the treatment group. Ashwagandha does not have sedative effects, but may help the body adapt to stress related conditions [37]. A study by Candelario et al. [38], provide evidence indicating that key constituents in

ashwagandha may have an important role in the development of pharmacological treatments for neurological disorders associated with GABAergic signaling dysfunction such as general anxiety disorders, sleep disturbances, muscle spasms, and seizures. In addition, the differential activation of GABA receptor subtypes may be another potential mechanism by which ashwagandha accomplishes its reported adaptogenic properties.

There are a few compounds reported to improve sleep. Inhalation of lavender aroma has been systematically reviewed as a possible self-care intervention to improve sleep architecture (initiation, maintenance and quality) but the authors concluded that lavender oil may be of small to moderate benefit [39]. Similarly, the use of melatonin by healthy adults shows improvements in insomnia, but to a limited extent. It was reported that, for the initiation of sleep and sleep efficacy, melatonin may not provide a consistent benefit [40]. In our study, ashwagandha extract significantly improved in sleep quality as compared to placebo, suggesting it is one of the promising dietary supplements to get sleep related benefits.

The World Health Organization (WHO) defines QOL, as individuals' perception of their position in life, in the context of culture and value systems in which they live, and in relation to their goals, expectations, standards, and concerns [41]. This conceptual framework is translated into patient-reported ratings of the degree of satisfaction one has with health, social, occupational status, and other life involvements. Hence, high QOL ratings are reflective not only of symptom reduction but also an overall improvement in the self-evaluation of one's own health. The literature reveals that quality of life is severely impaired in individuals with insomnia, comorbid conditions significantly affects quality of life negatively, and sleep restoration techniques, including cognitive behavioral therapy and medications, are successful at improving quality of life [42]. In the present trial, the ashwagandha group had significant improvement in the QOL over placebo group.

On an average a change in the score for more than “15” is considered clinically relevant and score difference of more than 20 is very significant in clinical practice (personal communication with Dr. Hays who was an author in paper on validation of NRS scale). Ashwagandha showed an average increase of 25 points compared to placebo thus proving a clinical utility.

## 5. Conclusion

Supplementation with 120 mg of ashwagandha extract improved the overall quality of sleep in healthy individuals by significantly improving NRS condition, by reducing the SOL, WASO, average awakening time and significantly improving TST, SE, and QOL. The ashwagandha extract used in this study can be considered as a useful supplement to promote healthy sleep patterns, and restful sleep.

## CRediT authorship contribution statement

**Abhijit Deshpande:** Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Nushafreen Irani:** Investigation, Methodology, Project administration, Writing - review & editing. **Ratna Balkrishnan:** Resources, Software, Supervision, Writing - review & editing. **Irin Rosanna Benny:** Validation, Visualization, Writing - review & editing.

## Acknowledgement

The authors acknowledge the gracious help of Arjuna Natural Private Ltd., Kerala for providing ashwagandha extract (Shoden®) and placebo capsules to conduct the study. The study was partially sponsored by Arjuna Natural Private Ltd., Kerala. The sponsors had no role in study design, conduct of the study, data collection, analysis, decision to publish, or preparation of the manuscript.

## Conflict of interest

The authors declare that they have no conflict of interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2020.03.012.

## References

[1] Drake CL, Hays RD, Morlock R, et al. Development and evaluation of a measure to assess restorative sleep. J Clin Sleep Med 2014;10(7):733–41. https://doi.org/10.5664/jcsm.3860.
[2] Cesta A, Moldofsky H, Sammut C, et al. The sensitivity and specificity of the Sleep Assessment Questionnaire (SAQ) as a measure of nonrestorative sleep. Sleep 1999;22:S14.
[3] Wilkinson K, Shapiro C. Nonrestorative sleep: symptom or unique diagnostic entity? Sleep Med 2012;13(6):561–9.
[4] Roth T, Zammit G, Lankford A, et al. Nonrestorative sleep as a distinct component of insomnia. Sleep 2010;33:449–58.
[5] Ohayon M, Riemann D, Morin C, et al. Hierarchy of insomnia criteria based on daytime consequences. Sleep Med 2012;13:52–7.
[6] Roth T, Jaeger S, Jin R, et al. Sleep problems, comorbid mental disorders, and role functioning in the National Comorbidity Replication Survey. Biol Psychiatr 2006;60:1364–71.
[7] Ancoli-Israel S, Roth T. Characteristics of insomnia in the United States: results of the 1991 national sleep foundation survey. I. Sleep 1999;22:S347–53.
[8] AASM. American Academy of Sleep Medicine. International classification of sleep disorders. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014. p. 25–6.
[9] Chandrasekhar K, Kapoor J, Anishetty S. A prospective, randomized double-blind, placebo-controlled study of safety and efficacy of a high-concentration full-spectrum extract of ashwagandha root in reducing stress and anxiety in adults. Indian J Psychol Med 2012;34:255–62.
[10] Lopresti AL, Drummond PD, Smith SJ. A randomized, double-blind, placebo-controlled, crossover study examining the hormonal and vitality effects of ashwagandha (Withania somnifera) in aging, overweight males. Am J Men's Health 2019;13. https://doi.org/10.1177/1557988319835985. 1557988319835985.
[11] Andrade C, Aswath A, Chaturvedi SK, et al. A double-blind, placebo controlled evaluation of the anxiolytic efficacy of an ethanolic extract of Withania somnifera. Indian J Psychiatr 2000;42:295–301.
[12] Biswajit A, Jayaram H, Achintya M, et al. A standardized Withania somnifera extract significantly reduces stress-related parameters in chronically stressed humans: a double-blind, randomized, placebo controlled study. JANA 2008;11:50–6.
[13] Cooley K, Szczurko O, Perri D, et al. Naturopathic care for anxiety: a randomized controlled trial ISRCTN78958974. PloS One 2009;4:e6628. https://doi.org/10.1371/journal.pone.0006628.
[14] Langade D, Kanchi S, Salve J, et al. Efficacy and safety of ashwagandha (Withania somnifera) root extract in insomnia and anxiety: a double-blind, randomized, placebo-controlled study. Cureus 2019;11(9):e5797. https://doi.org/10.7759/cureus.5797.
[15] Sarsour K, Van Brunt D, Johnston J, et al. Associations with nonrestorative sleep with insomnia, depression, and daytime function. Sleep Med 2010;11:965–72.
[16] Lopresti AL, Smith SJ, Malvi H, et al. An investigation into the stress-relieving and pharmacological actions of an ashwagandha (Withania somnifera) extract: a randomized, double-blind, placebo-controlled study. Medicine (Baltim) 2019;98(37):e17186. https://doi.org/10.1097/MD.0000000000017186.
[17] Shenoy S, Chaskar U, Sandhu JS, et al. Effects of eight-week supplementation of Ashwagandha on cardiorespiratory endurance in elite Indian cyclists. J Ayurveda Integr Med 2012;3(4):209–14. https://doi.org/10.4103/0975-9476.104444.
[18] Bhandari CR. Ashwagandha (*Withania somnifera*) “Vanaushadhi Chandroday” (An encyclopedia of Indian herbs)vol. 1. Varanasi, India: CS Series of Varanasi Vidyavilas Press; 1970. p. 96–7.
[19] Deshpande A, Irani N, Balakrishnan R. Study protocol and rationale for a prospective, randomized, double-blind, placebo-controlled study to evaluate the effects of Ashwagandha (Withania somnifera) extract on nonrestorative sleep. Medicine (Baltim) 2018;97:e11299. https://doi.org/10.1097/MD.0000000000011299.
[20] Chung F, Abdullah HR, Liao P. STOP-bang questionnaire: a practical approach to screen for obstructive sleep apnea. Chest 2016;149(3):631–8. https://doi.org/10.1378/chest.15-0903.

[21] Gholami A, Jahromi LM, Zarei E, et al. Application of WHOQOL-BREF in measuring quality of life in health-care staff. Int J Prev Med 2013;4(7):809–17.
[22] Esbensen AJ, Hoffman EK, Stansberry E, et al. Convergent validity of actigraphy with polysomnography and parent-reports when measuring sleep in children with Down syndrome. J Intellect Disabil Res 2018;62(4):281–91. https://doi.org/10.1111/jir.12464.
[23] Cole RJ, Kripke DF, Gruen W, et al. Automatic sleep/wake identification from wrist activity. Sleep 1992;15:461–9. https://doi.org/10.1093/sleep/15.5.461.
[24] De Souza L, Benedito-Silva AA, Pires ML, et al. Further validation of actigraphy for sleep studies. Sleep 2003;26(1):81–5. https://doi.org/10.1093/sleep/26.1.81.
[25] Slater G, Steier J. Excessive daytime sleepiness in sleep disorders. J Thorac Dis 2012;4(6):608–16. https://doi.org/10.3978/j.issn.2072-1439.2012.10.07.
[26] Brochu EF, Beaulieu-Bonneau S, Ivers H, et al. Relations between sleep, fatigue and health-related quality of life in individuals with insomnia. J Psychosom Res 2010 Nov;69(5):475–83. https://doi.org/10.1016/j.jpsychores.2010.05.005.
[27] Vaidya BG. In: Nighantu A, editor. Kantakaryaadi varg. 2nd ed. Varanasi: Chowkhamba Bharati Acadamy; 1999. p. 134–41.
[28] Bradshaw DA, Yanagi MA, Pak ES, et al. Nightly sleep duration in the 2-week period preceding multiple sleep latency testing. J Clin Sleep Med 2007;3:613–9.
[29] Raut AA, Rege NN, Tadvi FM, et al. Exploratory study to evaluate tolerability, safety, and activity of Ashwagandha (Withania somnifera) in healthy volunteers. J Ayurveda Integr Med 2012;3(3):111–4. https://doi.org/10.4103/0975-9476.100168.
[30] Shrivastava D, Jung S, Saadat M, et al. How to interpret the results of a sleep study. J Community Hosp Intern Med Perspect 2014;4(5). https://doi.org/10.3402/jchimp.v4.24983.
[31] Lemoine P, Nir T, Laudon M, et al. Prolonged-release melatonin improves sleep quality and morning alertness in insomnia patients aged 55 years and older and has no withdrawal effects. J Sleep Res 2007;16:372–80. https://doi.org/10.1111/j.1365-2869.2007.00613.x.
[32] Manchanda S, Mishra R, Singh R, et al. Aqueous leaf extract of Withania somnifera as a potential neuroprotective agent in sleep-deprived rats: a mechanistic study. Mol Neurobiol 2017;54(4):3050–61. https://doi.org/10.1007/s12035-016-9883-5.
[33] Kumar A, Kalonia H. Protective effect of Withania somnifera Dunal on the behavioral and biochemical alterations in sleep-disturbed mice (Grid over water suspended method). Indian J Exp Biol 2007;45(6):524–8.
[34] Kaur T, Singh H, Mishra R, et al. Withania somnifera as a potential anxiolytic and immunomodulatory agent in acute sleep deprived female Wistar rats. Mol Cell Biochem 2017;427(1–2):91–101. https://doi.org/10.1007/s11010-016-2900-1.
[35] Kumar A, Kalonia H. Effect of Withania somnifera on sleep-wake cycle in sleep-disturbed rats: possible GABAergic mechanism. Indian J Pharmaceut Sci 2008;70(6):806–10. https://doi.org/10.4103/0250-474X.49130.
[36] Kumar A, Kulkarni SK. Effect of herbals on sleep and their interactions with hypnotic drugs. Indian J Pharmaceut Sci 2005;67:391–3.
[37] Bobade MT, Thorwat VK. Ashwagandha in treatment of insomnia: a Review. Ayurlog Natl J Res Ayurved Sci 2019;3(2):1–6. Retrieved from, http://www.ayurlog.com/index.php/ayurlog/article/view/329.
[38] Candelario M, Cuellar E, Reyes-Ruiz JM, et al. Direct evidence for GABAergic activity of Withania somnifera on mammalian ionotropic GABAA and GABAρ receptors. J Ethnopharmacol 2015;171:264–72. https://doi.org/10.1016/j.jep.2015.05.058.
[39] Fismer KL, Pilkington K. Lavender and sleep: a systematic review of the evidence. Eur J Integr Med 2012;4(4):e436–47. https://doi.org/10.1016/j.eujim.2012.08.001.
[40] Costello RB, Lentino CV, Boyd CC, et al. The effectiveness of melatonin for promoting healthy sleep: a rapid evidence assessment of the literature. Nutr J 2014;13:106. https://doi.org/10.1186/1475-2891-13-106.
[41] The World Health. Organization quality of life assessment (WHOQOL): position paper from the World health organization. Soc Sci Med 1995;41:1403–9. https://doi.org/10.1016/0277-9536(95)00112-k.
[42] Ishak WW, Bagot K, Thomas S, et al. Quality of life in patients suffering from insomnia. Innov Clin Neurosci 2012;9(10):13–26.