



CLINICAL EVALUATION OF SAFETY AND EFFICACY OF DE-STRESS AND SLEEP GUMMIES

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Article Received on 20/11/2024

Article Revised on 11/12/2024

Article Accepted on 01/01/2025

ABSTRACT

Introduction: Chronic insomnia affects 5-10% of adults in developed countries, often associated with stress and mental health challenges. Traditional pharmacological interventions frequently present side effects, motivating research into alternative stress and sleep management strategies. This clinical trial investigated the safety and efficacy of a novel phytoconstituent-based gummy supplement in reducing stress and improving sleep quality. **Materials and Methods:** An open-label, single-arm clinical study was conducted with 30 healthy volunteers (15 males, 15 females). The investigational product contained extracts of *Withania somnifera*, L-Theanine, *Matricaria chamomilla*, and *Crocus sativus*. Participants consumed two destress and snooze gummies daily, 30 minutes before bed for 30 days. Participants were evaluated using the Perceived Stress Scale (PSS) and Insomnia Severity Index (ISI). Comprehensive hematological, biochemical, and vital sign assessments were performed at screening and after 30 days of intervention. **Results:** The study demonstrated statistically significant improvements: 47.84% reduction in perceived stress and 38.38% decrease in insomnia severity. Most blood parameters remained stable, with a notable decrease in creatinine levels. Only 4 participants (13.33%) experienced mild adverse events unrelated to the investigational product. **Conclusion:** The phytoconstituent-based gummies proved safe and effective in managing stress and improving sleep quality. The formulation's safety, tolerability, and potential efficacy make it an intriguing option for further investigation and potential integration into holistic stress and sleep management strategies.

KEYWORDS: Stress Management, Insomnia, Herbal Supplements, *Withania somnifera*, L-Theanine.

INTRODUCTION

Chronic insomnia affects 5-10% of adults in Western developed countries. It can be secondary to mental health disorders, physical conditions, or substance use (legal, illicit, or alcohol), or a combination thereof. Primary insomnia, on the other hand, is often linked to psychophysiological hyperarousal.^[1] Insomnia is a common condition that may occur independently or alongside other health disorders, often requiring separate treatment. Cognitive-behavioral therapy (CBT) and benzodiazepine-receptor agonists are the most evidence-supported interventions. While hypnotic medications are effective in the short term, they have potential side effects and limited long-term efficacy.^[2] Stress is common in older adults, and the use of hypnotic medications is often discouraged due to risks such as dependency, cognitive decline, falls, and withdrawal symptoms. Additionally, aging reduces melatonin

production, which plays a key role in regulating sleep and circadian rhythms.^[3]

The sleep-wake cycle is a primary circadian rhythm, regulated by neurochemical processes in the brain's arousal and sleep-promoting regions. Sleep is crucial for brain energy restoration, processing information offline, and supporting neural flexibility.^[4] Stress-induced substance use significantly hinders the treatment of substance use disorders (SUDs), though research is still emerging. Potential treatments include prescription medications, neurostimulation, cognitive-behavioral therapy, physical activity, and other methods. This review focuses on neuropharmacological approaches, backed by preclinical and clinical data, with potential to reduce stress-induced cravings and use of alcohol, nicotine, cocaine, marijuana, and opioids.^[5]

Stress-related insomnia is a common and potentially fatal condition, contributing to various health risks and lowering quality of life. Due to side effects of synthetic medications, such as nausea, fatigue, sleep disturbances, and sexual dysfunction, along with low rehabilitation rates, there has been increased research into the use of medicinal plants for treatment.^[6] Stress is the body's response to external stimuli that disrupt its balance, often affecting the immune system and hormone regulation. Acute stress can be stimulating, enhancing alertness, but chronic stress can negatively impact health. While stressors are often uncontrollable, individuals can modify their responses to them.^[7,8]

Herbal remedies have been used globally for centuries to enhance mental and physical stamina. Safer and more affordable than synthetic options, herbal medications are suggested as potential anti-stress agents, as they help manage stress without disrupting the body's physiological functions.^[9,10] The overwhelming majority of studies on the application of Phytoconstituents in stress alleviation and sleep aids are conducted in vitro and on animals, wherein mechanisms like anti-oxidative qualities, neurotransmitter modulation, relaxation pathway enhancement, sleep-wake cycle regulation, and reduction of stress hormones like cortisol are explored. These research offers a fundamental understanding of the possible advantages of Phytoconstituents in fostering relaxation, enhancing the quality of sleep, and controlling physiological reactions associated with stress.^[11]

Integrating Phytoconstituents-based products into regimens for stress reduction and sleep aids requires thorough clinical research with real clinical outcomes. The goal of the current clinical trial is to gather data regarding the safety and efficacy of using a product based on Phytoconstituents to reduce stress and enhance sleep.

MATERIALS AND METHODS

Study design

An open label, single arm clinical study was conducted in healthy male and female volunteers. Subjects were recruited at study centre i.e. Lokmanya Medical Research Centre & Hospital, Pune, India. The study was approved by Institutional Ethics Committee (IEC). The trial was registered on Clinical Trial Registry of India (CTRI) website (CTRI/2024/03/064117 [Registered on: 14/03/2024]).

Investigational Product Details

The investigational product is formulated from the extract of *Withania somnifera*, L-Theanine, *Matricaria chamomilla* and *Crocus sativus*. The gummies contains 125 mg of *Withania somnifera* (Ashwagandha KSM 66 Extract), 100 mg L-Theanine extract, 70 mg *Matricaria chamomilla* (Chamomile Flower extract), 7 mg *Crocus sativus* (Saffron Extract) with inactive ingredients

including Maltitol syrup, pectin, citric acid, trisodium citrate, sorbitol powder, steviol glycosides, natural colour and Tapioca starch. It has been formulated for oral administration. The gummies in PET bottles were stored at cool, dark, and dry place, away from sunlight or heat, and out of reach of non-authorized personnel. Participants consumed two destress and snooze gummies, 30 minutes before bed for 30 days.

Inclusion criteria

Written informed consent was obtained from subjects aged 18-45 years during the screening visit. Eligible participants, with PSS scores between 7 and 26, experiencing insomnia symptoms, and willing to complete the intervention and follow-up, were enrolled. Participants had refrained from using sedatives, antidepressants, anti-anxiety medications, or recreational drugs for at least one year prior to screening. Only those who provided voluntary, informed consent were included in the study.

Exclusion criteria

Women of childbearing potential not using adequate contraception, pregnant or lactating women, those with a history of substance abuse, drug use, heavy alcohol consumption, smoking, neurological conditions, recent surgeries, comorbidities, or recent use of sleep or stress-related medications/supplements were excluded from the study, as were individuals with other clinical conditions deemed unsuitable by the investigator.

METHODOLOGY

During screening, subjects' medical history and demographic data (sex, age, weight, height, habits) were recorded, followed by a complete clinical examination. The consolidated standards of reporting trials (CONSORT) flow of the entire study are depicted in figure 1. After confirming eligibility, subjects were enrolled. Changes in compliance, clinical and vital parameters, tolerability, and adverse events were assessed from baseline to study end. CBC, LFT, RFT, insomnia severity (ISI), and perceived stress (PSS) scores were evaluated at screening and study completion.

Statistical Analysis

The normality of the data was assessed using the Kolmogorov-Smirnov Test. Demographic data were analysed with an independent t-test, while hematological and biochemical data, perceived stress, vital signs, and Insomnia Severity Index (ISI) were analysed using dependent t-tests and Wilcoxon signed rank tests within groups. Adverse events were reported as frequencies. Statistical analysis was performed using SPSS.

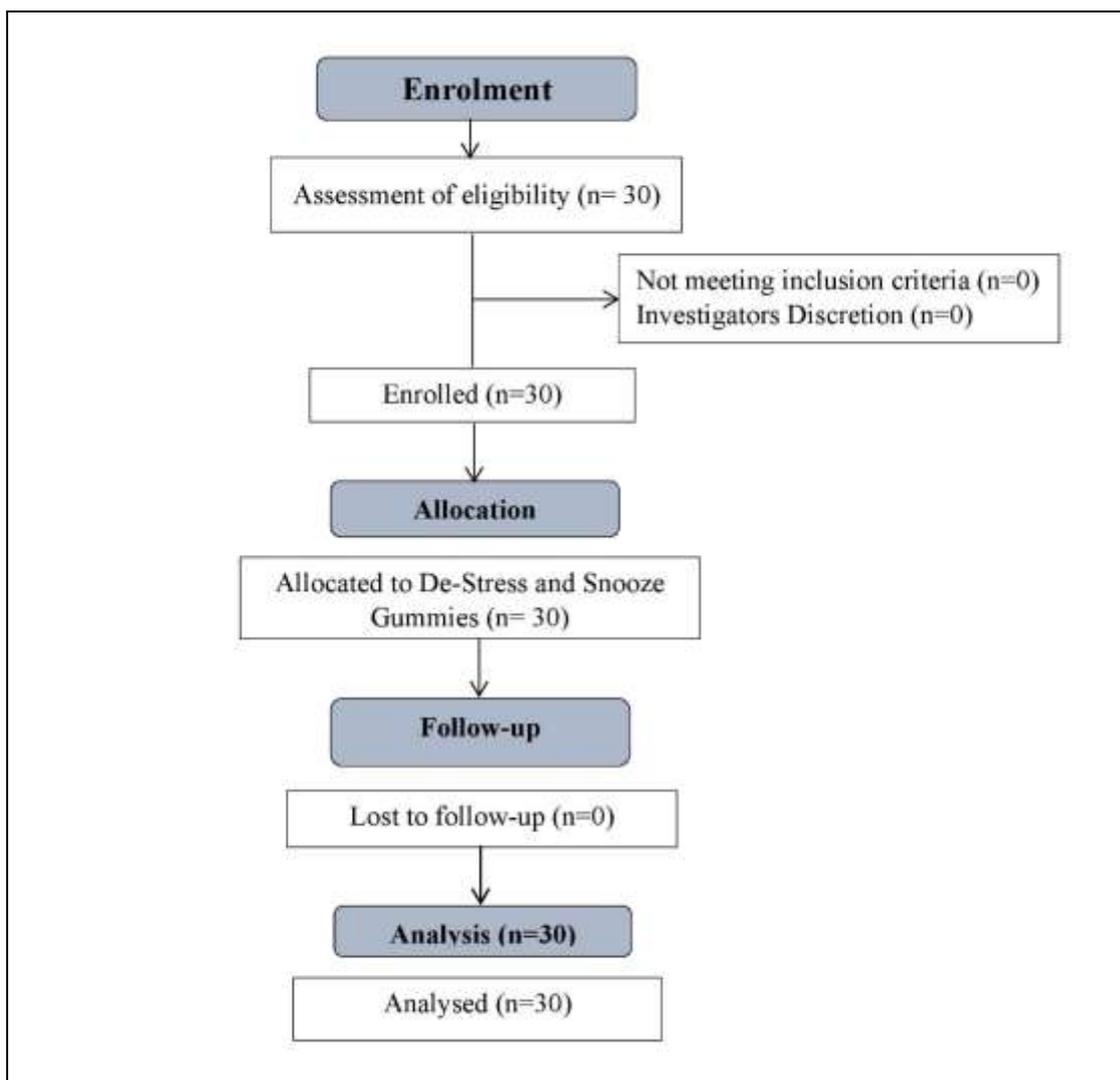


Figure 1: CONSORT flow diagram of the study.

RESULTS

Demographic characteristics

All thirty participants (15 males and 15 females) successfully completed the study. The average age of the subjects was 35.40 ± 8.08 years. Male participants had

an average weight of 66.67 kg, a height of 166.87 cm, and a BMI of 24.06 kg/m². Female participants had an average weight of 53.27 kg, a height of 162.00 cm, and a BMI of 20.36 kg/m². These demographic details are summarized in Table 1.

Table 1: Demographic details.

Parameter	Male Mean \pm SD (n=15)	Female Mean \pm SD (n=15)	P Value
Average Age (Years)	34.53 \pm 8.51	36.27 \pm 7.81	0.565
35.40 ± 8.08			
Anthropometric Parameters			
Height (cm)	166.87 \pm 7.28	162.00 \pm 4.57	0.036*
Weight (kg)	66.67 \pm 11.13	53.27 \pm 8.96	0.001*
BMI (kg/m ²)	24.06 \pm 4.39	20.36 \pm 3.62	0.017*

Data is represented as Mean \pm S.D. Analysis was done using the Independent student t-test. Significant at $p < 0.05$.

Assessment of haematological and biochemical investigations

The majority of the blood parameters remained stable and within the normal reference ranges throughout the 30 days, with no statistically or clinically significant

changes. The only exception was the statistically significant decrease in creatinine levels, which could suggest a positive impact on kidney function over the 30 days (Table 2).

Table 2: Assessment of hematological and biochemical investigations.

Hematological and biochemical investigations				
Parameters	Screening	Day 30	P Value	Reference range
Hematological parameters				
White Blood Cell Count (WBC)	6946.67±1662.31	6790.00±1321.01	0.619	(4000 - 11000 cell/cu.mm)
Red Blood Cell Count (RBC)	4.95±0.68	4.86±0.55	0.544	(4.7 - 6.0 mil/cu.mm)
Hemoglobin (Hb)	12.87±2.00	12.91±1.81	0.746	(Female: 11.6 - 15 gm/dL & Male: 13.2-16.6 gm/dL)
Haematocrit (PCV)	40.24±7.18	41.08±5.45	0.595	(42 - 52 %)
Mean Corpuscular Volume (MCV)	79.79±11.53	81.35±7.77	0.581	(78 - 100 fL)
Mean Corpuscular Haemoglobin (MCH)	26.29±3.87	26.62±3.41	0.729	(27 - 31 pg)
Mean Corpuscular Haemoglobin Concentration (MCHC)	32.27±1.25	32.47±0.91	0.469	(32-36 gm/dL)
Platelet Count	299.47±84.74	302.93±97.61	0.842	(150 - 450 10 ³ /ul)
Neutrophils	58.47±7.42	60.67±8.63	0.264	(40 - 75 %)
Lymphocytes	33.80±6.75	34.27±4.97	0.708	(20 - 40 %)
Monocytes	4.37±1.40	4.33±1.12	0.865	(2-10 %)
Eosinophils	3.37±1.13	3.43±0.86	0.568	(1-6 %)
Basophils	0.00±0.00	0.00±0.00	1	(0-1 %)
Liver Function				
Protein Total	7.85±0.44	7.73±0.59	0.342	(6.0 - 8.3 g/dL)
Albumin	4.66±0.32	4.57±0.38	0.271	(3.2 - 5.5 g/dL)
Globulin	3.19±0.36	3.15±0.35	0.688	(1.8 - 3.6 g/dL)
A/G Ratio	1.50±0.21	1.47±0.20	0.537	(1.2 - 2.2)
Bilirubin Total	0.59±0.35	0.57±0.26	0.912	(0.1-1.2 mg/dL)
Bilirubin Direct	0.28±0.17	0.25±0.11	0.310	(0-0.4 mg/dL)
Bilirubin Indirect	0.30±0.21	0.32±0.22	0.435	(0.1-0.8 mg/dL)
Aspartate Transaminase (AST/SGOT)	33.75±13.20	33.91±11.22	0.890	(49 U/ L)
Alanine Transaminase (ALT/SGPT)	27.74±11.40	29.44±10.49	0.126	(49 U/ L)
Alkaline Phosphatase	141.67±41.49	145.88±54.06	0.520	(80 - 306 U/ L)
Kidney Function				
Urea	28.89±6.99	27.85±8.28	0.334	(7-40 mg/dL)
Creatinine	0.86±0.15	0.74±0.24	<0.001	(0.5-1.5 mg/dL)
Uric Acid	4.00±0.94	3.94±0.76	0.481	(3.0 to 7.2 mg/dL)

Data is represented as Mean ± S.D. Analysis was done using the dependent student t-test (within the group) and Wilcoxon signed rank test (within the group). Significant at $p < 0.05$.

Assessment of vital signs

Diastolic blood pressure showed a statistically significant increase from screening to day 30 with a p-value of 0.027. However, other vital parameters including systolic

blood pressure, heart rate, body temperature, and respiratory rate did not show statistically significant changes from screening to day 30 as demonstrated in Table 3.

Table 3: Assessment of vital signs.

Systolic Blood Pressure (mmHg)	Screening	119.67±7.65	0.193
	Day 30	122.40±7.27	
Diastolic Blood Pressure (mmHg)	Screening	76.03±6.68	0.027*
	Day 30	79.53±5.57	
Heart Rate (BPM)	Screening	77.47±11.76	0.651
	Day-30	78.83±10.74	
Body Temperature (°F)	Screening	97.41±0.73	0.433
	Day-30	97.21±0.98	
Respiratory Rate (Breaths per minute)	Screening	20.17±1.29	0.872
	Day-30	20.20±1.40	

Data is represented as Mean ± S.D. Analysis was done using the dependent student t-test (within the group) and Wilcoxon signed rank test (within the group). Significant at $p < 0.05$.

Assessment of adverse events

The adverse events observed during the study are presented in Table 4. Out of the 30 participants, a total of 4 subjects (13.33%) experienced at least one adverse event. The most commonly reported adverse events were

fever, heartburn, vomiting, and headache. For each adverse event, the number of subjects affected and the corresponding rescue medication used are shown. AE's observed were not related to investigational product.

Table 4: Adverse events observed in the study.

Adverse Events	No	Rescue Medication
	(N=30)	
Fever	1	Paracetamol
Heartburn	1	Omeprazole
Vomiting	1	Pantoprazole
Headache	1	Aspirin
Total No. of Events	4	-
Total No. of subjects (%)	4 (13.33%)	-

Assessment of perceived stress using the Perceived Stress Scale (PSS)

The PSS is a ten-question questionnaire with responses from 0 to 4, measuring an individual's stress perception. The total score is the sum of all responses, indicating the perceived stress level. Scores: 0-13 (low stress), 14-26 (moderate stress), 27-40 (high stress).

Following a 30-day treatment period, the assessment of perceived stress using the PSS showed a statistically significant reduction of 47.84% (Table 5). This observed change in PSS score was highly significant, indicating a clinically meaningful improvement in the participant's subjective experience of stress.

Table 5: Assessment of perceived stress using the Perceived Stress Scale (PSS).

Duration	PSS Score (n = 30)	P value
Screening	21.03±1.67	< 0.001
Day-30	10.97±1.61 (47.84%)	

Data is represented as Mean ± S.D. Analysis was done using a dependent student t-test (within the group). Significant at $p < 0.05$.

Assessment of Insomnia Severity Index (ISI)

The ISI is a 7-item questionnaire was used to assess the severity of insomnia. Each response is scored as from None (0), Mild (1), Moderate (2) and Very Severe (4). Total scores range from 0 to 28, with higher scores indicating more severe insomnia.

After 30 days of treatment with Destress and Snooze gummies, there was statistically significant reduction by 38.38% in the insomnia severity. These findings indicate the study intervention had a substantial positive impact on reducing insomnia symptoms in the participants. as demonstrated in Table 6.

Table 6: Assessment of Insomnia Severity Index (ISI).

Duration	ISI Score (n = 30)	P value
Screening	14.93±1.48	< 0.001
Day-30	9.20±1.90	

Data is represented as Mean ± S.D. Analysis was done using a dependent student t-test (within the group). Significant at $p < 0.05$.

DISCUSSION

The current clinical investigation provides noteworthy insights into the potential efficacy of De-Stress and Snooze Gummies in managing stress and insomnia among healthy adults. The study's findings reveal a significant improvement in participants' perceived stress levels and sleep quality over a 30-day intervention period. The Perceived Stress Scale (PSS) demonstrated a remarkable 47.84% reduction in stress perception, which is clinically meaningful and statistically significant ($p < 0.001$).^[12] This substantial decrease suggests that the formulation's unique blend of ingredients—including *Withania somnifera*, *L-Theanine*, *Matricaria chamomilla*, and *Crocus sativus*—may effectively modulate the body's stress response mechanisms.

Complementing the stress reduction outcomes, the Insomnia Severity Index (ISI) revealed a statistically significant 38.38% reduction in insomnia symptoms ($p < 0.001$).^[13] This improvement indicates that the gummies could potentially offer a non-pharmacological approach to addressing sleep disturbances, which is particularly relevant given the growing concerns about the side effects associated with traditional hypnotic medications. The study's safety profile is further reinforced by the minimal adverse events observed, with only 13.33% of participants experiencing mild, transient side effects such as fever, heartburn, vomiting, and headache, which were not directly attributed to the investigational product.^[14]

The biochemical and physiological assessments provide additional nuance to the study's findings. Most blood parameters remained stable throughout the 30-day intervention, with no clinically significant alterations. Notably, a statistically significant decrease in creatinine levels was observed, which might suggest a potential positive impact on kidney function. Similarly, while diastolic blood pressure showed a statistically significant increase, other vital parameters like systolic blood

pressure, heart rate, body temperature, and respiratory rate remained consistent.^[15]

The potential mechanism of action is particularly intriguing, especially concerning *Withania somnifera* (Ashwagandha). This medicinal plant is hypothesized to play a critical role in modulating stress hormones, neurotransmitters, and sleep-related biochemical indicators, potentially through its antioxidant properties.^[16] Historically recognized in traditional medicine across regions from the Mediterranean to Southeast Asia, Ashwagandha has been used for various therapeutic purposes, including addressing sleeplessness and managing stress-related conditions.^[17]

The study's comprehensive approach, encompassing both subjective (PSS and ISI) and objective (biochemical and physiological) measurements, strengthens the credibility of the findings. By demonstrating improvements across multiple domains, the research suggests that De-Stress and Snooze Gummies could serve as a safer, more holistic alternative for stress and sleep management. This is particularly significant given the growing prevalence of stress-related disorders and the limitations of existing pharmaceutical interventions. However, it is crucial to acknowledge the study's limitations. The open-label, single-arm design means that while promising, the results would benefit from further validation through randomized, placebo-controlled trials. Additionally, the relatively short intervention period of 30 days necessitates longer-term studies to definitively establish the sustained efficacy and safety of the gummies.

The research contributes meaningfully to the expanding body of evidence supporting phytoconstituent-based interventions for stress and sleep management. By offering a potentially safer, more natural alternative to traditional pharmacological treatments, the study opens avenues for future research and potential clinical applications across diverse population segments experiencing stress and sleep disturbances.

CONCLUSION

The study provides compelling preliminary evidence that De-Stress and Snooze Gummies could be a promising intervention for individuals seeking non-pharmaceutical approaches to managing stress and improving sleep quality. The formulation's safety, tolerability, and potential efficacy make it an intriguing option for further investigation and potential integration into holistic stress and sleep management strategies.

ACKNOWLEDGMENT

The authors would like to acknowledge the research team and the back-office team involved in the research work. We would like to acknowledge the support of Mprex Healthcare Pvt. Ltd., Pune, Maharashtra as a clinical research organization for this trial.

FUNDING

Investigational product and testing expenses borne in the trial were supported by Herbolab India Pvt. Ltd.

CONFLICTS OF INTEREST

Dr. Kriti Soni and Dr. Sachin Mulik are part of Herbolab India Pvt. Ltd. Other author declare no conflict of interest.

REFERENCES

- Riemann D, Voderholzer U. Primary insomnia: a risk factor to develop depression? *J. Affect. Disord*, Sep. 1, 2003; 76(1-3): 255-9.
- Morin CM, Benca R. Chronic insomnia. *Lancet*, Mar. 24, 2012; 379(9821): 1129-41.
- Lemoine P, Zisapel N. Prolonged-release formulation of melatonin (Circadin) for the treatment of insomnia. *Expert Opin Pharmacother*, Apr. 1, 2012; 13(6): 895-905.
- Zisapel N. New perspectives on the role of melatonin in human sleep, circadian rhythms and their regulation. *Br J Pharmacol*, Aug. 2018; 175(16): 3190-9.
- Greenwald MK. Anti-stress neuropharmacological mechanisms and targets for addiction treatment: A translational framework. *Neurobiol. Stress*, Nov. 1, 2018; 9: 84-104.
- Dereli FT, Ilhan M, Akkol EK. New drug discovery from medicinal plants and Phytoconstituents for depressive disorders. *CNS Neurol Disord Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders)*, Mar. 1, 2019; 18(2): 92-102.
- Pawar VS, Shivakumar H. A current status of adaptogens: natural remedy to stress. *Asian Pac J Trop Dis.*, Jan. 1, 2012; 2: S480-90.
- Srikumar R, Parthasarathy NJ, Devi RS. Immunomodulatory activity of triphala on neutrophil functions. *Biol Pharm Bull.*, 2005; 28(8): 1398-403.
- Sarris J, Panossian A, Schweitzer I, Stough C, Scholey A. Herbal medicine for depression, anxiety and insomnia: a review of psychopharmacology and clinical evidence. *Eur Neuropsychopharmacol*, Dec. 1, 2011; 21(12): 841-60.
- Rizvi A, Mishra A, Mahdi AA, Ahmad M, Basit A. Natural and herbal stress remedies: a review. *Int. J. Pharmacognosy Pharm.*, 2015; 2(4): 155-60.
- Sleep R. Nutrients and botanicals for treatment of stress: adrenal fatigue, neurotransmitter imbalance, anxiety, and restless sleep. *Altern Med Rev.*, 2009; 14(2): 114-40.
- Gopukumar K, Thanawala S, Somepalli V, Rao TS, Thamamam VB, Chauhan S. Efficacy and safety of Ashwagandha root extract on cognitive functions in healthy, stressed adults: a randomized, double-blind, placebo-controlled study. *Evid Based Complement Alternat Med.*, 2021; 2021(1): 8254344.
- Langade D, Thakare V, Kanchi S, Kelgane S. Clinical evaluation of the pharmacological impact of

- Ashwagandha root extract on sleep in healthy volunteers and insomnia patients: A double-blind, randomized, parallel-group, placebo-controlled study. *J Ethnopharmacol*, Jan. 10, 2021; 264: 113276.
14. Verma N, Gupta SK, Tiwari S, Mishra AK. Safety of Ashwagandha root extract: a randomized, placebo-controlled, study in healthy volunteers. *Complement Ther Med.*, Mar. 1, 2021; 57: 102642.
 15. Raut AA, Rege NN, Tadvi FM, Solanki PV, Kene KR, Shirolkar SG, Pandey SN, Vaidya RA, Vaidya AB. Exploratory study to evaluate tolerability, safety, and activity of Ashwagandha (*Withania somnifera*) in healthy volunteers. *J Ayurveda Integr Med.*, Jul. 2012; 3(3): 111.
 16. Pratte MA, Nanavati KB, Young V, Morley CP. An alternative treatment for anxiety: a systematic review of human trial results reported for the Ayurvedic herb ashwagandha (*Withania somnifera*). *J Altern Complement Med.*, Dec. 1, 2014; 20(12): 901-8.
 17. Verma SK, Kumar A. Therapeutic uses of *Withania somnifera* (Ashwagandha) with a note on withanolides and its pharmacological actions. *Asian J Pharm Clin Res.*, Jul. 4, 2011; 4(1): 1-4.