

A Randomized, Double-blind, Placebo-controlled, Multi-centric, Interventional, Prospective Clinical Study to Evaluate Efficacy and Safety of *Passiflora incarnata* (Aerial Parts) Extract in participants with Stress and Insomnia

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Abstract

Background: *Passiflora incarnata* is used for treating anxiety or nervousness, generalized anxiety disorder (GAD), insomnia, and other related disorders. Previous studies indicate that passion flower has a positive effect on sleep patterns. It reduces the time to fall asleep and increases the duration of sleep.

Objectives: To Evaluate Efficacy and Safety of *Passiflora incarnata* (Passion Flower) Extract in participants with Stress and Insomnia

Methods: In a Randomized, Double Blind, Placebo Controlled, Multi-centre, Interventional, Prospective Clinical Study, a total of 65 participants with stress and insomnia were screened and recruited and randomised to two groups (32 in the *Passiflora* group and 33 in the Placebo group). The participants were randomized either to *Passiflora incarnata* (Aerial Parts) Extract group or placebo group in 1:1 ratio. Subjects were asked to take given product at bed time with water for 30 days. Subjects were evaluated on Day 1, Day 15 and Day 30 on Perceived Stress Scale (PSS), subject's Quality of Life on GHQ12 Scale. Subject's insomnia was evaluated on Insomnia Severity Index. Appropriate statistical tests were applied to the data derived from the clinical study to draw inferences.

Results: Statistically significant reduction in mean score of stress on PSS and mean score of total sleep time were observed with the use of *Passiflora* extract as compared to placebo. The general psychological health significantly improved in *Passiflora* group compared to placebo group on day 15 and day 30. *Passiflora* Extract was found to be safe without producing any adverse effects.

Conclusion: *Passiflora incarnata* (aerial parts) extract was significantly effective in reducing stress and other related symptoms. It improved sleep time and quality of sleep with no adverse events.

Introduction

Stress is the physical, emotional or intellectual strain caused as a result of a response to what happens around us. In humans, stress typically describes a negative or a positive condition that can have an impact on a person's mental and physical well-being.¹ Stress can increase the risk of strokes, heart attacks, ulcers, and mental illnesses such as depression.² Excess stress can manifest itself in a variety of emotional, behavioural and even physical symptoms. Symptoms of stress vary extremely among different individuals. Common physical symptoms of excess stress include sleep disturbances or changes in sleeping habits (insomnia or excessive sleep), muscle tension, muscle aches, headache, gastrointestinal problems and fatigue.³

Insomnia or sleeplessness is a sleep disorder, where people have trouble sleeping.⁴ They may have difficulty either falling asleep or staying asleep as long as desired.⁵⁻⁷ Insomnia is typically followed by low energy, daytime sleepiness, irritability, and a depressed mood.³ Insomnia may be short-term, lasting for days or weeks, or long-term, lasting more than a month.³ Insomnia can occur independently or as a result of secondary effects of other conditions. Conditions, which cause insomnia, include psychological

stress, chronic pain, hyperthyroidism, heartburn, restless leg syndrome, menopause, certain medications, and drugs such as caffeine, nicotine, and alcohol.^{8,9} Other risk factors include working night shifts and sleep apnea.⁵ Diagnosis is based on sleep habits and an examination to look for underlying cause.³ People over the age of 65 are more affected than younger people.⁸ Females are more often affected than males.⁷ Lifestyle changes and Sleep hygiene are typically the first treatment for Stress and insomnia.¹⁰ An important step in stress management and treatment of stress-related symptoms is exercise.¹¹ Other measures include cognitive behavioural therapy (CBT), which helps us to understand our thought patterns, recognize trigger points and identify positive actions we can take, meditation and Yoga with a particular focus on reducing stress.¹²

Tranquillizers and antidepressants can help to reduce or manage some of the signs of stress and Insomnia. But these drugs may cause nausea, increased appetite and weight gain, fatigue and drowsiness, dry mouth, blurred vision and constipation.¹³

Passiflora incarnata is used for treating anxiety or nervousness, generalized anxiety disorder (GAD), insomnia, neuralgia, convulsion, spasmodic asthma, palpitations, cardiac rhythm abnormalities, hypertension etc. It has shown a calming effect, which helps to reduce stress, and can therefore be helpful in the treatment of insomnia, anxiety, and depression. Research studies indicate that passionflower has a positive effect on sleep patterns. Passionflower reduces the time to fall asleep and increases the duration of sleep.¹⁴

Looking at the activities of *Passiflora incarnata* (Aerial Parts) extract, a hypothesis was postulated that it would be useful in the management of stress and insomnia. To test the hypothesis, a clinical study titled “A Randomized, Double-blind, Placebo-controlled, Multi-centric, Interventional, Prospective Clinical Study to Evaluate Efficacy and Safety of *Passiflora incarnata* (Passion Flower) Extract in participants with Stress and Insomnia” was carried out.

Materials and Methods

- Study design, sites:

The study was a randomized, double-blind, placebo-controlled, multi-center, interventional, prospective clinical study conducted at two clinical sites in India, viz; KVTR Ayurvedic College, Boradi, Dhule and D.Y. Patil deemed to be University School of Ayurveda, Sector – 7, Nerul, Navi Mumbai, Maharashtra.

- Ethical considerations:

Ethical approvals from Institutional ethics committees of all study centers were obtained. The study was registered on Clinical Trials Registry India (CTRI) vide registration number CTRI/2022/07/043753 registered on 6th July 2022.

- Enrolment of participants:

Participants having a history of stress and insomnia attending the outpatient department of the study centers were considered for the study. The study was carried out and reported adhering to CONSORT statement. (Figure 1)

- **Study duration & Visits:**

The total duration of treatment was 1 month (30 days). Patients were asked to visit study site every 15th day for 1 month (30 days).

- **Primary and secondary Outcomes:**

The primary Outcomes of the study were to assess the change in stress using the perceived stress scale (PSS) from baseline to end of the study visit and between the two groups and Change in Patient-reported total sleep time (as per Subject diary) from baseline to end of the study visit and between the two groups.

The secondary Outcomes of the study were to assess the change in general psychological health using Short General Health Questionnaire (GHQ-12) from baseline to end of the study visit and between the two groups, change in sleep efficiency (Total sleep time/ time in bed*100) derived from subject diary from baseline to end of the study visit and between the two groups, change in Patient-reported time to sleep onset (as per subject diary) from baseline to end of the study visit and between groups, change in Patient-reported number of awakenings (as per subject diary) from baseline to end of the study visit and between the two groups, change in Patient-reported wake time after sleep onset [Wake Time After Sleep Onset (WASO) is defined as the total awakening time from falling asleep to final awakening was subjectively determined based on the Subject diary)] from baseline to end of the study visit and between the two groups, change in the severity of insomnia using Insomnia Severity Index from baseline to end of the study visit and between the two study groups, post study change in serum cortisol (morning) level between the two study groups, change in daytime fatigue using Fatigue Severity Scale (FSS) from baseline to end of the study visit and between groups, change in daytime mood, ability to function at work, concentration and memory on a graded scale from baseline to end of the study visit and between the two study groups, change in quality of sleep using Pittsburgh Sleep Quality Index (PSQI) from baseline to end of the study visit and between the two study groups, assessment of requirement of rescue medications (sedatives) from baseline to end of the study and between the two study groups, assessment of adverse events and vitals including blood pressure, pulse rate, respiration rate and body temperature from baseline to end of the study visit and between the two study groups, assessment of safety by assessing safety lab parameters including CBC, Liver function tests, Renal function tests, Lipid Profile and Fasting Blood Sugar level, global assessment for overall change by participants and by physician at the end of the study and assessment of post study tolerability of study product by participants and physician.

Selection of Participants:

Inclusion criteria: Literate male & female subjects of age 18 to 55 years (both inclusive) who perceived themselves to be under stress and had a score between 14 - 24 on the Perceived Stress Scale (PSS) with an insomnia severity score of more than 7 and 21 on insomnia severity index and who were willing to follow the procedures as per the study protocol and voluntarily give informed consent were enrolled in the study.

Exclusion criteria: Subjects suffering from any chronic physical, hormonal, or psychiatric illness, using oral or systemic contraceptive medications, with uncontrolled diabetes and hypertension. subjects with substance dependence [taking prohibited medications like opium, cannabis methamphetamines, etc], chronic alcoholics, and habitual tobacco chewers, known cases of severe/chronic hepatic or renal disease, known subjects of any active malignancy, subjects giving a history of significant cardiovascular events <12 weeks prior to recruitment, subjects having known chronic, contagious infectious diseases, such as active tuberculosis, Hepatitis B or C, or HIV, known cases of active metabolic or gastrointestinal diseases that may interfere with nutrient absorption, metabolism, or excretion, excluding diabetes, subjects using any other investigational study product within 1 month prior to recruitment or subjects currently participating in any other clinical study, known hypersensitivity to any of the ingredients used in study products, pregnant and lactating females were excluded from the study. Other conditions, which in the opinion of the investigators, made subjects unsuitable for enrolment or could have interfered with his/her participation in, and completion of the study were also excluded from the study.

- **Sample size:**

A total of 65 participants were screened in the study and all of them were recruited and randomized into two groups (32 in the *Passiflora* group and 33 in the Placebo group) as there were no screen failures. All 65 participants completed the study (32 in the *Passiflora* group and 33 in the Placebo group) as there were no dropouts.

- **Treatment Groups:**

As per the computer-generated randomization list, participants were randomized either to the *Passiflora incarnata* (Aerial Parts) Extract group or the Placebo group in a 1:1 ratio. Subjects were asked to take a given product in a dose of 600 mg at bedtime with water for 30 days

- **Study drug:**

Product Name: *Passiflora incarnata* (Passion Flower) Extract Capsule

- **Ingredients:**

1. a) *Passiflora incarnata*- Extract (Flower and aerial parts) - 600 mg each.
2. b) Placebo Capsules were made using Microcrystalline Cellulose filled in similar looking capsules as *Passiflora incarnata* Capsules

- **Dosage:** As per computer generated randomization list, participants were randomized either to *Passiflora incarnata* (aerial parts) Extract group or placebo group in 1:1 ratio. Dose of Passiflora extract was 600 mg at bed time with water for 30 days.

Assessment Parameters:

1. **Efficacy Parameters:** The study involved the use of laboratory parameters and various scales for the assessment of symptoms, overall change, and safety. The investigator assisted /explained /guided/helped the subject in filling up the scores in these scales wherever required.

1.1 Assessment of change in stress using the perceived stress scale (PSS):

The perceived Stress Scale (PSS) is the most widely used psychological instrument for measuring perception of stress. It is a measure of the degree to which situations in one's life are appraised as stressful. Items are designed to tap into how unpredictable, uncontrollable, and overloaded respondents find their lives. The scale also includes a number of direct queries about current levels of experienced stress. The questions in the PSS ask about feelings and thoughts during the last visit. In each case, respondents were asked how often they felt a certain way. PSS scores were obtained by reversing responses (e.g., 0 = 4, 1 = 3, 2 = 2, 3 = 1 & 4 = 0) to the four positively stated items (items 4, 5, 7, & 8) and then summing across all scale items.

1.2 Assessment of change in Subject-reported total sleep time (as per Subject diary):

A daily diary card was given to the subjects to record total sleep time. Subjects reported daily total sleep time (as per the Subject diary). Changes observed in the subject's average reported total sleep time (as per patient diary) on daily basis over 15 days were compared to baseline visits and between the two groups.

1.3 Assessment of change in general psychological health using Short General Health Questionnaire (GHQ-12):

The General Health Questionnaire (GHQ-12) consists of 12 items, each assessing the severity of a mental problem over the past few weeks using a 4-point scale (from 0 to 3). The score is used to generate a total score ranging from 0 to 36, with higher scores indicating worse conditions. Assessment of general psychological health using Short General Health Questionnaire (GHQ-12) was done on baseline visit, visit 1 (day 15) and visit 2 (Day 30). Changes observed in general psychological health using Short General Health Questionnaire (GHQ-12) on Visit 1(Day 15) and Visit 2(Day 30) were compared to Baseline Visit and between the two groups.

1.4 Assessment of change in sleep efficiency (Total sleep time/ time in bed*100):

Sleep efficiency was defined as total sleep time/ time in bed*100. Subjects were given daily diary card to record sleep efficiency on baseline visit, day 15 and day 30. Changes observed in average sleep efficiency on daily basis over 15 days were compared to baseline visit and between the two groups.

1.5 Assessment of change inpatient-reported time to sleep onset (as per subject diary): Daily diary cards were given to the subjects to record time to sleep onset on baseline visit, day 15 and day 30. Changes observed in average time to sleep onset on daily basis over 15 days was be compared to baseline visit and between the two groups.

1.6 Assessment of change in patient reported number of awakenings:

Subjects were given daily diary card to record number of awakenings on baseline visit, day 15 and day 30. Changes observed in patient reported average number of awakenings on daily basis over 15 days was compared to Baseline Visit and between the two groups.

1.7Assessment of change in patient -reported wake time after sleep onset:

Wake Time after Sleep Onset (WASO) is defined, as total awakening time from falling asleep to final awakening. This was determined based on Subject diary. Average WASO was evaluated on baseline visit and further on daily basis over 15 days. Changes observed in average WASO on daily basis over 15 days was compared to baseline visit and between the two groups.

1.8 Assessment of change in severity of insomnia using Insomnia Severity Index:

The Insomnia Severity Index has seven questions. The seven answers are added up to get a total score. Last 2 weeks severity of insomnia problem was evaluated using this index. The severity of insomnia is graded as 0–7 = No clinically significant insomnia, 8–14 = Sub threshold insomnia, 15–21 = Clinical insomnia (moderate severity) and 22–28 = Clinical insomnia (severe). Severity of Insomnia was evaluated on Baseline visit, visit 1 (day 15) and Visit 2 (day 30). Changes observed in Insomnia Severity Index on day 15 and day 30 was compared to baseline visit and between the two study groups.

1.9 Assessment of post study change in serum cortisol (morning) levels:

Morning Serum Cortisol level was checked on screening visit and at visit 2 i.e. end of study visit (Day 30). Changes observed in morning serum Cortisol level on visit 2 (Day 30) was compared to baseline visit and between the two study groups.

1.10 Assessment of change in daytime fatigue using Fatigue Severity Scale (FSS):

The fatigue severity scale (appendix F) is a method of evaluating the impact of fatigue. The FSS questionnaire contains nine statements that rate the severity of fatigue. Each question is given number from 1 to 7, subject needs to circle the number that reflects his/her condition during the past week and the extent to which he/she agree or disagree that the statement applies to him/her. Severity of fatigue

was evaluated on baseline visit, visit 1 (day 15) and visit 2 (day 30). Changes observed in fatigue severity scale on day 15 and days 30 were compared to baseline visit and between the two study groups.

1.11 Assessment of requirement of rescue medications (sedatives):

As rescue medications, subjects were allowed to use sedatives during the study period if required. Record of number of sedatives and their dosage used by subject was recorded in the case record form. Number of subjects required rescue medication (sedatives) were calculated at the end of the study and were compared between the two groups.

1.12 Assessment of change in daytime mood, ability to function at work, concentration and memory on a graded scale:

Subjects were evaluated to check whether sleep problem interferes with his/her daily functioning such as daytime mood, ability to function at work, concentration, and memory on graded scale (0= Not at all Interfering, 1= A Little, 2= somewhat, 3= Much, 4= Very Much Interfering). Assessment of Daytime mood, ability to function at work, concentration and memory was done on baseline visit, visit 1 (day 15) and visit 2 (day 30). Changes observed in Daytime mood, ability to function at work, concentration, and memory on day 15 and day 30 was compared to baseline visit and between the two study groups.

1.13 Assessment of change in quality of sleep using Pittsburgh Sleep Quality Index (PSQI):

Pittsburgh Sleep Quality Index (PSQI) contains 19 self-rated questions and 5 questions rated by the bed partner or roommate. Only self-rated questions are included in the scoring. The 19 self-rated items are combined to form seven component scores each of which has a range of 0-3 points. In all cases, a score of 0 indicates no difficulty, while a score of 3 indicates severe difficulty. The seven component scores are then added to yield one global score with a range of 0- 21 points. 0 indicating no difficulty and 21 indicating severe difficulties in all areas. The Pittsburgh Sleep Quality Index (PSQI) (Appendix E) was evaluated on baseline visit, visit 1 (day 15) and visit 2 (day 30). Changes observed in quality of sleep using Pittsburgh Sleep Quality Index (PSQI) on day 15 and days 30 were compared to baseline visit and between the two study groups.

1.14 Global assessment for overall change by participants and by physician:

The CGI- I is a global assessment scale used by physician/investigator to provide a brief, stand- alone assessment of the Subject's global functioning prior to and after initiating a study medication, including a knowledge of the Subject's history, psychosocial circumstances, symptoms, behaviour, and the impact of the symptoms on the Subject's ability to function. CGI-I was recorded/ filled at the end of the study. The CGI is rated on a 7-point scale, with the severity of illness scale using a range of responses from 1 (very much improved) to 7 (very much worse). Each component of the CGI is rated separately; the instrument does not yield a global score. At the End of Study, Investigator and participant rated the total change, whether or not, it is entirely due to product compared to participant's condition at admission to the study and how much has he/she changed.

Table 1: Global assessment for overall change by participants and by physician at the end of the study

0 = Not assessed	4 = No change
1 = Very much improved	5 = Minimally worse
2 = Much improved	6 = Much worse
3 = Minimally improved	7= Very much worse

1.15 Assessment of tolerability of study products by investigator and participants: Evaluation of adverse events/adverse drug reactions at every follow up visit and establishment of their relationship with the study product was assessed. The tolerability of study products was evaluated on following safety grades as; 1 = excellent overall safety (no adverse event/s reported); 2 = good overall safety (mild adverse events (s) reported which subside with or without medication); 3 = fair overall safety (moderate to severe adverse event(s) reported which subside with or without medication and do not necessitate stoppage of study products); and 4 = poor overall safety (severe or serious adverse event(s) which necessitate stoppage of study).

2. Assessment of Safety

Safety was assessed by clinical review of all safety parameters, including the following:

- Adverse event reporting, as applicable
- Vital signs including allergic reaction
- Lab parameters include CBC, Liver function tests, Renal function tests, Lipid Profile and Blood sugar fasting.

Safety variables were listed individually for detailed clinical review, when needed. Additional tables shall summarize adverse events by severity and relationship to study product as well as leading to SAEs and withdrawal of the subjects from the trial.

Plan for Statistical Analysis: The study data generated and collected was put to statistical analysis to reach to the final results and conclusions. The demographic data were presented in tables and graphs. The data obtained in the studies were subjected to tests of significance. The data on discrete variables has been represented as actual frequencies, i. e. n (%). The data on continuous variables has been represented as mean ($\pm$ SD). GraphPad InStat Version 3.6 (www.graphpad.com) software was used for statistical analysis of data. P value < 0.05 was considered significant.

A total of 65 subjects were screened in the study of which 65 subjects were considered as completers. All cases that completed the study as per the protocol were considered as "Per Protocol Population". Also, all

the cases who took at least one dose of the study drug were considered as “Safety population” and were evaluated.

Results

A total of 65 participants were screened in the study and all of them were recruited and randomised to two groups (32 in the Passiflora group and 33 in the Placebo group) as there were no screen failures. All 65 participants completed the study (32 in the Passiflora group and 33 in the placebo group) as there were no dropouts.

Demographic details:The average age of participants in the study in the Passiflora group was 38.63 ± 11.86 years and in the Placebo group was 40.06 ± 11.81 years ($p>0.05$, NS). The no of males and females participating in the Passiflora group was 19 and 13 respectively while in the Placebo group, it was observed to be 15 and 18 respectively ($p>0.05$, NS). This demography was similar in the two groups with no statistically significant difference.

Primary Outcomes:

Assessment of change in stress using perceived stress scale (PSS):In the Passiflora group, the mean score of stress assessed using PSS on baseline visit was 21.00 ± 3.41 , which significantly reduced ($p<0.05$) to 17.56 ± 3.56 and 15.19 ± 4.86 at the end of 15 days and 30 days respectively. In the Placebo group, the mean score of stress assessed using PSS was 19.48 ± 4.01 , which reduced significantly ($p<0.05$) to 18.64 ± 4.26 and 17.85 ± 3.93 at the end of 15 days and 30 days respectively. When compared between the group, a statistically significant reduction ($p<0.05$) in stress levels were observed with the use of Passiflora as compared to a placebo.

Table 2: Assessment of stress using perceived stress scale (PSS)

	Passiflora Group (32)			Placebo Group (33)		
	Baseline	15 Days	30 Days	Baseline	15 Days	30 Days
Mean $\pm$ SD	21.00 ± 3.41	17.56 ± 3.56	15.19 ± 4.86	19.48 ± 4.01	18.64 ± 4.26	17.85 ± 3.93
Median (Range)	22 (9 – 24)	17 (9 – 24)	15 (8 – 23)	20 (9 – 24)	19 (9 – 24)	19 (8 – 24)
p Value	–	< 0.0001	< 0.0001	–	0.0161	0.0015
15 Days	p=0.1166, not significant					
30 Days	p=0.0413, significant					

Assessment of change in subject-reported total sleep time: In the Passiflora group, the mean score of total sleep time at baseline visit was 5.25 ± 0.85 hours, which significantly increased to 5.61 ± 0.62 and 5.95 ± 0.53 hours at the end of 15 days and 30 days respectively. In the Placebo group, the mean score of total sleep time at baseline visit was 5.44 ± 0.83 hours, which non-significantly ($p > 0.05$) increased to 5.55 ± 0.83 and 5.46 ± 0.85 hours at the end of 15 days and 30 days respectively. When compared between the group, a statistically significant increase ($p < 0.05$) in total sleep time was observed in the Passiflora group at the end of 15 days and 30 days as compared to the Placebo.

Table 3: Assessment of total sleep time

	Passiflora Group (32)			Placebo Group (33)		
	Baseline	15 Days	30 Days	Baseline	15 Days	30 Days
Mean $\pm$ SD	5.25 ± 0.85	5.61 ± 0.62	5.95 ± 0.53	5.44 ± 0.83	5.55 ± 0.83	5.46 ± 0.85
Median (Range)	05 (04 – 07)	5.5 (04 – 7.5)	06 (04 – 7.5)	5.5 (04 – 7.5)	5.5 (04 – 7.5)	5.5 (04 – 7.5)
p Value	–	0.0002	< 0.0001	–	0.1099	0.1763
15 Days	p=0.9055, not significant					
30 Days	p=0.0254, significant					

Secondary outcomes:

1. Assessment of change in general psychological health using Short General Health

Questionnaire (GHQ-12): In Passiflora group, the mean score of general psychological health assessed using Short General Health Questionnaire (GHQ-12) on baseline visit was 24.13 ± 3.92 , which significantly reduced ($p < 0.05$) to 17.53 ± 2.27 and 15.47 ± 3.51 at the end of 15 days and 30 days respectively. In placebo group, the mean score at baseline visit was 22.27 ± 3.98 , which significantly reduced ($p < 0.05$) to 21.03 ± 4.13 and 20.42 ± 4.35 at the end of 15 days and 30 days respectively. When compared between the group, statistically significant reduction ($p < 0.05$) in psychological health was observed in Passiflora group at the end of 15 days and 30 days as compared to placebo.

2. Assessment of change in patient-reported time to sleep onset:

In Passiflora group, the mean score of patient-reported time to sleep onset at baseline visit was 72.19 ± 13.97 minutes, which significantly reduced ($p < 0.05$) to 53.91 ± 20.11 and 42.50 ± 25.21 mins at the end of 15 days and 30 days respectively. In Placebo group, the mean score of patient-reported time to sleep onset at baseline visit was 60.15 ± 16.79 mins, which significantly reduced to 56.06 ± 18.15 and 52.88 ± 21.33 mins at the

end of 15 days and 30 days respectively. When compared between the group, statistically significant reduction ($p < 0.05$) in patient-reported time to sleep onset was observed in Passiflora group at the end of 30 days as compared to placebo.

3. **Assessment of change in patient reported number of awakenings:** In Passiflora group, the mean score of patient-reported total no of awakenings as per subject's diary on baseline visit was 1.69 ± 0.69 , which significantly reduced ($p < 0.05$) to 1.25 ± 0.44 and 0.56 ± 0.72 at the end of 15 days and 30 days, respectively. In Placebo group, the mean score of patient-reported total no of awakenings as per subject's diary on baseline visit was 1.24 ± 0.44 , which non significantly ($p > 0.05$) reduced to 1.21 ± 0.42 and 1.00 ± 0.75 at the end of 15 days and 30 days respectively. When compared between the group, statistically significant reduction ($p < 0.05$) in patient-reported number of awakenings was observed in Passiflora group at the end of 30 days as compared to placebo.
4. **Assessment of change in patient-reported wake time after sleep onset:** In Passiflora group, the mean score of patient-reported wake time after sleep onset (based on subject diary) on baseline visit was 30.47 ± 14.28 minutes, which significantly reduced ($p < 0.05$) to 21.09 ± 11.96 and 10.94 ± 14.28 at the end of 15 days and 30 days respectively. In Placebo group, the mean score of patient-reported wake time after sleep onset (based on subject diary) on baseline visit was 27.58 ± 14.74 minutes, which significantly reduced ($p < 0.05$) to 25.00 ± 15.36 and 20.76 ± 19.45 at the end of 15 days and 30 days respectively. When compared between the group, statistically significant reduction ($p < 0.05$) in wake time after sleep onset (based on subject diary) was observed in Passiflora group at the end of 30 days as compared to placebo.
5. **Assessment of change in severity of insomnia assessed using Insomnia Severity Index:** In Passiflora group, the mean score of severity of insomnia assessed using Insomnia Severity Index on baseline visit was 16.25 ± 2.93 , which significantly reduced ($p < 0.05$) to 12.40 ± 2.51 and 10.63 ± 2.94 at the end of 15 days and 30 days respectively. In Placebo group, the mean score of severity of insomnia assessed using Insomnia Severity Index on baseline visit was 17.18 ± 3.25 , which non-significantly reduced ($p > 0.05$) to 16.21 ± 3.53 on day 15 and significantly reduced ($p < 0.05$) to 15.79 ± 3.87 on day 30. When compared between the group, statistically significant reduction ($p < 0.05$) in severity of insomnia was observed in Passiflora group at the end of 15 days and 30 days as compared to Placebo.
6. **Assessment of post study change in serum cortisol (morning) levels:** In Passiflora group, the mean score of serum cortisol (morning) level on baseline visit was 10.57 ± 3.35 mcg/dL, which significantly reduced ($p < 0.05$) to 8.75 ± 3.22 mcg/dL at the end of 30 days. In Placebo group, the mean score of serum cortisol (morning) level on baseline visit was 10.14 ± 4.19 mcg/dL, which significantly reduced ($p < 0.05$) to 9.02 ± 3.44 mcg/dL on day 30. Intergroup analysis showed non-significant difference between the two groups. However, a higher percentage reduction of 17.21% was observed in Passiflora group compared to 11.04% reduction in Placebo group. Serum Cortisol levels were observed to be within normal limits in both the study groups at baseline and at the end of the study.

7. **Assessment of change in daytime fatigue (Fatigue Severity Scale-FSS):** In Passiflora group, the mean score of fatigue assessed using FSS on baseline visit was 43.22 ± 7.94 , which significantly reduced ($p < 0.05$) to 31.91 ± 7.32 and 25.94 ± 9.86 at the end of 15 days and 30 days respectively. In Placebo group, the mean score of fatigue assessed using FSS on baseline visit was 40.12 ± 7.77 , which significantly reduced ($p < 0.05$) to 36.58 ± 9.42 and 36.00 ± 9.96 at the end of 15 days and 30 days respectively. Intergroup analysis showed significantly higher reduction ($p < 0.05$) in FSS levels in Passiflora group as compared to Placebo group on day 30.
8. **Assessment of requirement of rescue medications (sedatives):** None of the subjects from both the groups required rescue medication (sedatives) during the study period.
9. **Assessment of change in daytime mood, ability to function at work, concentration and memory on a graded scale:**
 - A. **Assessment of interference of sleep on daytime mood:** In Passiflora group, the mean score of daytime mood on baseline visit was 3.22 ± 0.42 , which significantly reduced to 2.19 ± 0.47 and 1.50 ± 0.84 on day 15 and day 30 respectively. In Placebo group, the mean score of daytime mood on baseline visit was 3.09 ± 0.29 , which significantly reduced to 2.64 ± 0.60 and 2.48 ± 0.83 on day 15 and day 30 respectively. Between group analysis shows significantly lesser interference of sleep on day time mood in Passiflora group as compared to Placebo group on day 15 and day 30.
 - B. **Assessment of interference of sleep on ability to function at work:** In Passiflora group, the mean score of ability to function at work on baseline visit was 3.22 ± 0.42 , which significantly reduced to 2.19 ± 0.47 and 1.50 ± 0.84 on day 15 and day 30 respectively. In Placebo group, the mean score of ability to function at work on baseline visit was 3.09 ± 0.29 , which significantly reduced to 2.64 ± 0.60 and 2.48 ± 0.83 on day 15 and day 30 respectively. Between groups analysis showed significantly lesser interference of sleep on ability to work in Passiflora group as compared to Placebo group on day 15 and day 30.
 - C. **Assessment of interference of sleep on concentration:** In Passiflora group, the mean score of concentration on baseline visit was 2.97 ± 0.18 , which significantly reduced to 2.19 ± 0.47 and 1.50 ± 0.84 on day 15 and day 30 respectively. In Passiflora group, the mean score of concentration on baseline visit was 3.00 ± 0.25 , which significantly reduced to 2.70 ± 0.64 and 2.58 ± 0.83 on day 15 and day 30 respectively. Between group analysis showed significantly lesser interference of sleep on concentration in Passiflora group as compared to Placebo group on day 15 and day 30.
 - D. **D) Assessment of interference of sleep on memory:** In Passiflora group, the mean score of memory on baseline visit was 2.97 ± 0.18 , which significantly reduced to 2.19 ± 0.47 and 1.50 ± 0.84 on day 15 and day 30 respectively. In Placebo group, the mean score of memory on baseline visit was 2.97 ± 0.17 , which significantly reduced to 2.64 ± 0.60 and 2.48 ± 0.83 on day 15 and day 30 respectively. Between group analysis showed significantly lesser interference of sleep on memory in Passiflora group as compared to Placebo group on day 15 and day 30.

10. **Assessment of change in quality of sleep using Pittsburgh Sleep Quality Index (PSQI):** In Passiflora group, the mean score of quality of sleep as assessed using PSQI on baseline visit was 14.72 ± 5.02 , which significantly reduced ($p < 0.05$) to 13.47 ± 5.22 and 9.00 ± 5.11 at the end of 15 days and 30 days respectively. In Placebo group, the mean score of quality of sleep as assessed using PSQI on baseline visit was 15.09 ± 4.33 , which significantly reduced ($p < 0.05$) to 14.45 ± 5.06 and 13.15 ± 4.15 at the end of 15 days and 30 days respectively. Between group analysis showed significantly better quality of sleep ($p < 0.05$) in Passiflora group as compared to Placebo group at the end of 30 days.
11. **Assessment of vitals:** The vital parameters including pulse, respiratory rate, temperature and blood pressure remained within normal range from baseline to follow up visits and showed no significant change both within and between the groups.
12. **Assessment of laboratory parameters:** Safety related laboratory parameters including CBC, Liver function tests, Renal function tests showed no significant change from baseline to follow up visits in both the groups. The values remained within normal range at both the baseline and final visit.

Table 4: Assessment of Laboratory parameters

	Standard Group		Placebo Group	
	Baseline	30 Days	Baseline	30 Days
RBCs (mil/uL)	4.31 ± 0.56	4.32 ± 0.57	4.36 ± 0.49	4.44 ± 0.52
WBCs cells/Cumm)	6381.25 ± 1839.6	6278.13 ± 1371.5	6824.24 ± 1620.8	6318.18 ± 1002.3
Haemoglobin (g/dL)	12.79 ± 2.13	12.72 ± 2.06	12.68 ± 1.69	12.71 ± 1.53
Platelets lakh/Cumm)	2.73 ± 0.76	2.63 ± 0.71	2.79 ± 0.58	2.82 ± 0.68
ESR (mm/Hour)	17.94 ± 12.02	15.06 ± 12.07	21.12 ± 18.54	18.12 ± 15.47
Total Bilirubin (mg/dL)	0.77 ± 0.23	0.74 ± 0.22	0.75 ± 0.26	0.74 ± 0.23
Direct (mg/dL)	0.25 ± 0.07	0.24 ± 0.09	0.24 ± 0.11	0.26 ± 0.11
Indirect (mg/dL)	0.52 ± 0.17	0.50 ± 0.17	0.51 ± 0.20	0.48 ± 0.18
AST (U/L)	19.22 ± 6.07	21.27 ± 6.29	21.06 ± 5.69	20.02 ± 5.42
ALT (U/L)	28.79 ± 12.46	28.82 ± 10.62	30.81 ± 10.54	28.24 ± 11.37
Alk. Phosphatase (U/L)	104.37 ± 36.28	99.66 ± 31.07	105.50 ± 42.20	102.89 ± 36.20
Total proteins (g/dL)	7.06 ± 0.31	7.04 ± 0.37	7.07 ± 0.32	7.03 ± 0.40
Serum Albumin (g/dL)	4.04 ± 0.45	4.05 ± 0.35	3.91 ± 0.50	3.93 ± 0.34
Sr. Creatinine (mg/dL)	0.98 ± 0.17	0.95 ± 0.16	0.94 ± 0.15	0.91 ± 0.14
BUN (mg/dL)	10.33 ± 2.34	10.53 ± 2.77	10.08 ± 2.52	9.93 ± 2.68
BSL – Fasting (mg/dL)	85.36 ± 13.00	86.58 ± 11.07	93.00 ± 25.04	88.63 ± 15.57

Discussion

The present study was conducted to evaluate efficacy and safety of *Passiflora incarnata* (Aerial Parts) Extract in participants with stress and insomnia. Statistically significant reduction in the mean score of stress assessed using PSS was observed from baseline visit to all follow up visits in both the groups. When compared between the groups, statistically significant more reduction in stress was observed in Passiflora group compared to placebo group on day 30. The mean score of total sleep time derived from subject diary significantly increased from baseline visit to every follow up visit till the end of the study, however no significant increase in total sleep time was observed till the end of the study in placebo

group. When compared between the group, statistically significant increase in total sleep time was observed in Passiflora group compared to placebo group on day 15 and day 30. The general psychological health assessed using Short General Health Questionnaire (GHQ-12) significantly improved in Passiflora group compared to placebo group on day 15 and day 30.

Patient-reported time to sleep onset was significantly reduced in Passiflora group compared to placebo group on day 15 and day 30. In Passiflora group, the mean score of patient-reported total no of awakenings as per subject's diary significantly reduced on day 15 and day 30, however in placebo group, the reduction in patient-reported total no of awakenings was non-significant on day 15 and day 30. In both the groups, the mean score of patient-reported wake time after sleep onset (based on subject diary) significantly reduced on day 15 and day 30. When compared between the groups, statistically significant reduction in wake time after sleep onset (based on subject diary) was observed in Passiflora group on day 30.

Severity of insomnia assessed using Insomnia Severity Index reduced significantly in Passiflora group compared to Placebo group on day 15 and day 30. No significant difference was observed in serum cortisol (morning) level between the two groups, however, a higher percentage reduction of 17.21% was observed in Passiflora group compared to 11.04% reduction in Placebo group. Serum Cortisol levels remained within normal range in both the groups at both baseline and at the end of the study.

Statistically significant higher reduction in fatigue was observed in Passiflora group compared to Placebo group on day 30. Significantly lesser interference of sleep on day time mood, ability to function at work, concentration and memory was observed in Passiflora group as compared to Placebo group on day 15 and day 30. None of the subjects from both the groups required rescue medication (sedatives) during the study period. Significantly better quality of sleep as assessed using PSQI was observed in Passiflora group as compared to Placebo group on day 30.

Passion flower has been used in the management of neurotic disorders, stress, anxiety, insomnia, opioid withdrawal symptoms, morphine dependence, convulsions, and neuralgia with low addiction potential.^{15–}

¹⁸ Various research studies have shown that *Passiflora incarnata* is useful in the management of sleep disorders. Studies revealed that *Passiflora incarnata* modulates gamma-aminobutyric acid (GABA) neurotransmission system and helps to improve sleep quality.¹⁵ *Passiflora incarnata* possesses tranquillizing and calming activities. In an animal study, *Passifloraincarnata* modulated the aggressive and abnormal behaviours of animals, and lowered the salivary cortisol level.¹⁶ *Passiflora incarnata* also possesses antistress activity. In a clinical trial, 12 weeks treatment with a dried ethanolic extract of passion flower showed significant improvements in stress resistance (resilience) and quality of life in patients suffering from nervous restlessness.¹⁷ Also, in an experimental study, it has been shown that *Passiflora* reduced the stress level in the memory test in rats; consequently, increased motivation to act and improved motor activity during swimming test.¹⁸ No post treatment statistically significant change in any of the safety lab parameters was observed in both the groups suggesting safety of both the study products.

Conclusion

It can be concluded that *Passiflora incarnate* (aerial parts) extract was significantly effective in reducing stress and other related symptoms. It improved sleep time and quality of sleep. It was found to provide sound sleep with lesser disturbance. Associated symptoms like mood, ability to work, concentration and memory were also found to improve with the use of *Passiflora incarnata*. *Passiflora incarnata* (Aerial Parts) Extract was found to be safe and without producing any adverse effects too.

Declarations

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RAW DATA IN SUPP FILE

References

1. Simandan D. On how much one can take: relocating exploitation and exclusion within the broader framework of allostatic load theory. *Health Place*. 2010 Nov;16(6):1291–3. doi: 10.1016/j.healthplace.2010.08.009. Epub 2010 Aug 13. PMID: 20813575.
2. Yaribeygi H, Panahi Y, Sahraei H, Johnston TP, Sahebkar A. The impact of stress on body function: A review. *EXCLI J*. 2017 Jul 21;16:1057–1072. doi: 10.17179/excli2017-480. PMID: 28900385; PMCID: PMC5579396.
3. Medic G, Wille M, Hemels ME. Short- and long-term health consequences of sleep disruption. *Nat Sci Sleep*. 2017 May 19;9:151–161. doi: 10.2147/NSS.S134864. PMID: 28579842; PMCID: PMC5449130.
4. Bhaskar S, Hemavathy D, Prasad S. Prevalence of chronic insomnia in adult patients and its correlation with medical comorbidities. *J Family Med Prim Care*. 2016 Oct-Dec;5(4):780–784. doi: 10.4103/2249-4863.201153. PMID: 28348990; PMCID: PMC5353813.
5. Roth T. Insomnia: definition, prevalence, etiology, and consequences. *J Clin Sleep Med*. 2007 Aug 15; 3(5 Suppl):S7-10. PMID: 17824495; PMCID: PMC1978319.
6. Golub, R. M. "Insomnia". *JAMA*. 307 (24): 2653–2653.
7. Kumar S, Kumari A, Manasa RV, Das SC, Ghoshal V. Insomnia among Attendants of Patients in a Tertiary Care Hospital at Visakhapatnam. *Natl J Community Med [Internet]*. 2018 Sep. 30 [cited 2023 May 22]; 9(09):709–13.
8. Mausumi Basu, Sita Chatterjee, Abhishek De, Debasish Sinha, Afifa Ahamed, Raghunath Misra. A Study on Prevalence of Chronic Insomnia and its Association with Medical Co morbidities among Patients Attending General Out Patient Department (OPD) of a Tertiary Care Hospital of Kolkata,

9. Daniel J. Buysse. Chronic Insomnia. *Am J Psychiatry*. 2008 June; 165(6): 678–686.
10. Suzuki K, Miyamoto M, Hirata K. Sleep disorders in the elderly: Diagnosis and management. *J Gen Fam Med*. 2017 Mar 30;18(2):61–71. doi: 10.1002/jgf2.27. PMID: 29263993; PMCID: PMC5689397.
11. Stults-Kolehmainen MA, Sinha R. The effects of stress on physical activity and exercise. *Sports Med*. 2014 Jan;44(1):81–121. doi: 10.1007/s40279-013-0090-5. PMID: 24030837; PMCID: PMC3894304.
12. Igu NCN, Ogba FN, Eze UN, Binuomote MO, Elom CO, Nwinyinya E, Ugwu JI, Ekeh DO. Effectiveness of cognitive behavioral therapy with yoga in reducing job stress among university lecturers. *Front Psychol*. 2023 Jan 5;13:950969. doi: 10.3389/fpsyg.2022.950969. PMID: 36687866; PMCID: PMC9849775.
13. Santarsieri D, Schwartz TL. Antidepressant efficacy and side-effect burden: a quick guide for clinicians. *Drugs Context*. 2015 Oct 8;4:212290. doi: 10.7573/dic.212290. PMID: 26576188; PMCID: PMC4630974.
14. Janda K, Wojtkowska K, Jakubczyk K, Antoniewicz J, Skonieczna-Żydecka K. *Passiflora incarnata* in Neuropsychiatric Disorders-A Systematic Review. *Nutrients*. 2020 Dec 19;12(12):3894. doi: 10.3390/nu12123894. PMID: 33352740; PMCID: PMC7766837.
15. Janda K, Wojtkowska K, Jakubczyk K, Antoniewicz J, Skonieczna-Żydecka K. *Passiflora incarnata* in neuropsychiatric disorders-A Systematic Review. *Nutrients*. 2020 Dec 19;12(12):3894.
16. Pastorelli G, Serra V, Turin L, Redaelli V, Luzi F, Barbieri S. Tranquillizing effect of *Passiflora incarnata* extract: outcome on behavioral and physiological indicators in weaning pigs with intact tails. *Animals* 2022; 12:203.
17. Gibbert J, Kreimendahl F, Lebert J, Rychlik R, Trompetter I. Improvement of stress resistance and quality of life of adults with nervous restlessness after treatment with a passion flower dry extract. *Complement Med Res* 2017; 24:83–89.
18. Jawna-Zboińska K, Blecharz-Klin K, Joniec-Maciejak I, Wawer A, Pyrzanowska J, Piechal A, et al. *Passiflora incarnata* l. improves spatial memory, reduces stress, and affects neurotransmission in rats. *Phytother Res* 2016; 30:781–789.

Appendices

The Appendices are not available with this version

Figures

CONSORT DIAGRAM

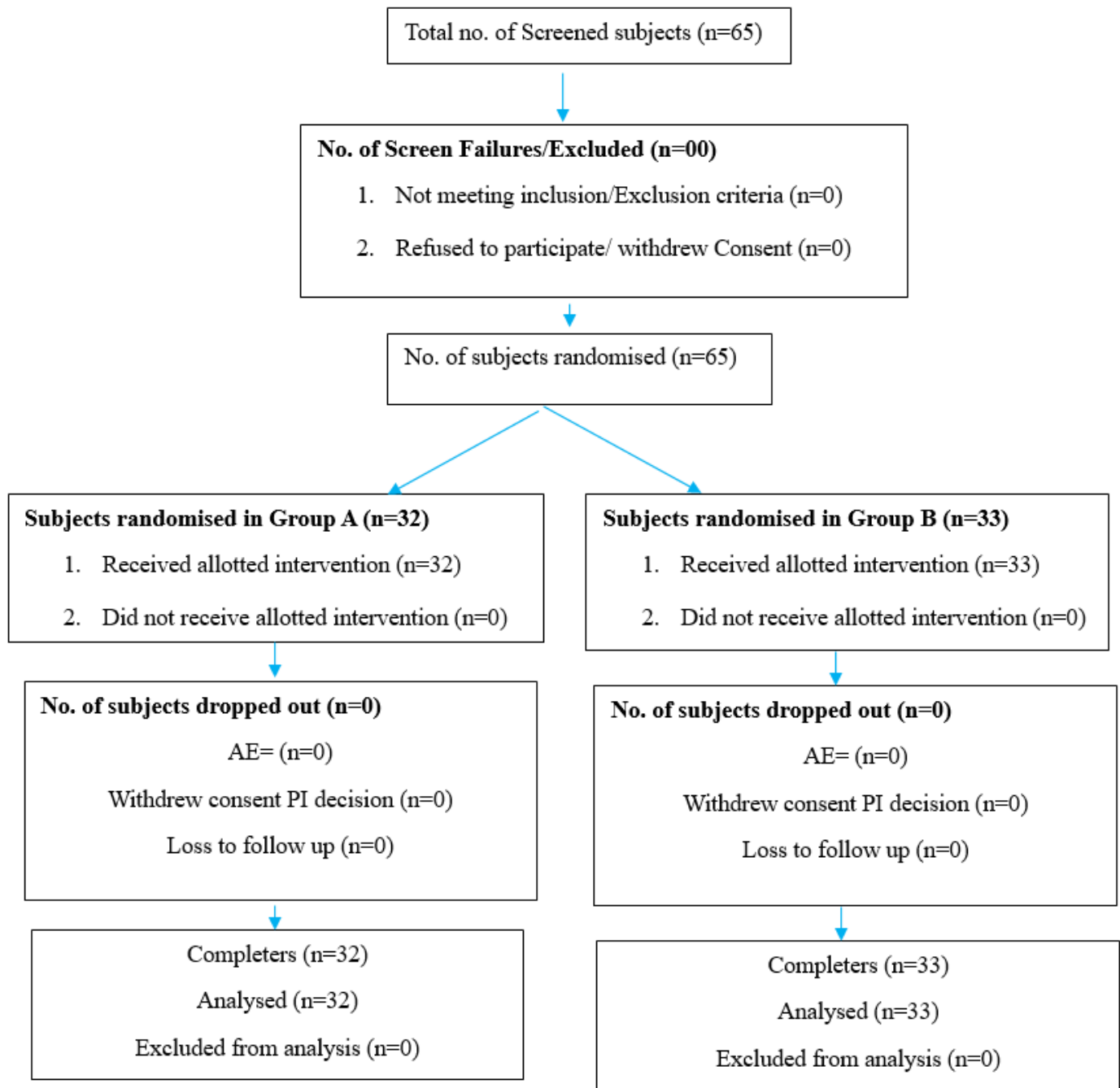


Figure 1

CONSORT DIAGRAM

Group A: *Passiflora incarnate* extract capsule

Group B: Placebo group

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [RawDataPassifloraStudyData.docx](#)