# "Evaluation of efficacy and safety of TulsiOdaat™ in patients suffering from Insomnia Disorder - An Open Label, Single Arm, Multi-centric, Non-comparative, Interventional, Prospective, Clinical Study"

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**Abstract-:**
***Background-*** *Holy Basil (Ocimum sanctum) has been prescribed in Ayurvedic texts for the management of insomnia which possesses sleep-inducing and neuroprotective properties.*
***Objectives-*** *The objective of the study was to evaluate the efficacy and safety of TulsiOdaat™, a botanical ingredient extract in patients suffering from mild to moderate Insomnia Disorder.*
***Materials & Methods-*** *After ethics committee approval and subsequent registration of the study on CTRI, 31 consented patients, suffering from insomnia attending out-patient department of the three study centers were enrolled in the study. Patients were advised to take TulsiOdaat™ in a dose of 450 mg twice daily (900mg TulsiOdaat™ total) for a period of 28 days, with 7 day followup.*
*Assessment of insomnia was done on various objective and subjective efficacy parameters. Safety was assessed by clinical review of all safety parameters, including the adverse event reporting. Intra-group comparison was done by paired t-test or Wilcoxon matched-pairs signed-ranks. P-Value < 0.05 was considered significant.*
***Results-***
*TulsiOdaat™ significantly improved total sleep time and sleep efficiency as well helps provide relief in symptoms of mild to moderate insomnia with no significant rebound of insomnia. There was no significant change in safety parameters from baseline to 90 days follow up.*
***Conclusion:***
*Thus, it can be concluded that TulsiOdaat™ botanical ingredient extract is safe and effective for the treatment of primary insomnia.*
**Keywords-** *Tulsi, Insomnia, Holy Basil, Sleep disorders*

## Introduction:

The term insomnia is used in a variety of ways in the medical literature. Most often, insomnia is defined by the presence of an individual's report of difficulty with sleep, even when a person has the chance to do so. Individuals with insomnia can feel displeased with their sleep and habitually experience one or more of the symptoms like difficulty in initiating sleep, difficulty in maintaining sleep, waking up too early, and in some cases, non-restorative or poor quality of sleep.[1] Various studies worldwide have shown the prevalence of insomnia in 10%–30% of the population, some even as high as 50%–60%. It is common in older adults, females, and people with medical and mental ill health.[2,3,4]

Insomnia can be categorized as primary and secondary. Primary insomnia occurs when insomnia is the primary health concern and not regarded as secondary to another disorder. Primary insomnia can have both intrinsic and extrinsic factors involved in its etiology. Secondary forms of insomnia occur when insomnia is a symptom of a medical or psychiatric illness, another sleep disorder or substance abuse.[5]

Chronic insomnia is associated with cognitive difficulties, anxiety, and depression, poor work performance, decreased quality of life, and increased risk of cardiovascular disease. Insomnia has typically been treated with non-pharmacologic and pharmacologic therapies. Non-pharmacologic therapies include sleep hygiene, cognitive behavior therapy, relaxation therapy, multi-component therapy, and paradoxical intention.[6] Benzodiazepine receptor agonists (BzRAs), melatonin-receptor agonist, and histamine-1 antagonist, sedating antidepressants and antipsychotics are used as pharmacologic therapy for insomnia. Long-term usage of these drugs is associated with psychological dependence and tolerance, decreased daytime functioning, poor sleep quality, and rebound insomnia when medication is discontinued. There are reports of leucopenia, thrombocytopenia and increased liver enzymes with the use of doxepin; dizziness, dry mouth, and nausea with the use of trimipramine; daytime somnolence, dizziness, and weight gain with mirtazapine usage. In studies of depressed patients, side effects of trazodone include orthostatic hypotension, priapism, and cardiac

arrhythmias, and conduction abnormalities. [7-10] These negative effects of drug therapy often compel people to opt for alternative medicines to treat insomnia.

Many single herbs and polyhedral formulations have been described in Ayurveda for the treatment of insomnia. Holy Basil (*Ocimum sanctum*) is one such herb that possesses sleep-inducing, anti-stress, anti-anxiety, anti-depressant, and neuroprotective properties. Holy Basil has been evaluated for its central nervous system (CNS) relaxant activity and is used for its efficacy in the treatment of sleep disorders, including insomnia.[11-15]

Based upon the active ingredients of TulsiOdaat™, a hypothesis was postulated that this extract would be useful in the management of insomnia. To test the hypothesis, a clinical study titled "Evaluation of efficacy and safety of TulsiOdaat™, a botanical ingredient extract, in patients suffering from Insomnia Disorder- An Open-Label, Single-arm, Multi-centric, Non- comparative, Interventional, Prospective, Clinical Study" was developed and executed. The objective of the study was to evaluate the efficacy and safety of TulsiOdaat™ a botanical ingredient extract developed by Lodaat Pharma, in patients suffering from mild to moderate Insomnia Disorder.

**Materials & Methods-**

- Study design, sites – This was an Open Label, Single arm, Multi-centric, Non- comparative, Interventional, Prospective, Clinical Study conducted at three sites across India; namely, Parul Ayurveda Hospital, Parul, University, Vadodara, Gujarat, Ayurved seva sangh Ayurved Mahavidyalaya, Nashik and D. Y. Patil University School of Ayurveda Nerul, Navi, Mumbai, Maharashtra.
- Ethical considerations- Ethical approvals from Institutional Ethics Committees (IEC) of all study centers were obtained. The clinical study was registered with the Clinical Trial Registry - India (CTRI) on 05/11/2020. The CTRI number for the study is CTRI/2020/11/028939.
- Enrolment of patients- Patients, suffering from Insomnia attending out-patient department of the study centers and who consented, were considered for the study. The study was carried out and reported adhering to CONSORT statement. (Ref. Figure 1 in annexure)
- Study duration & Visits- The total duration of the study treatment was 28 days. Patients were asked to visit study site every 14$^{th}$ day for 1 month. On day 35, participants were asked to partake in a followup visit.
- Inclusion Criteria-
  Individuals of any of the genders aged 21 to 65 years (both inclusive) diagnosed with Insomnia Disorder based on DSM-5 Diagnostic Criteria for Insomnia Disorder, having Insomnia Severity Index more than 7 and less than 21 (indicative of mild-moderate insomnia) and willing to sign informed consent form and to follow the procedures as per the study protocol were included in the study.
- Exclusion Criteria-
  Individuals having history or diagnosis of any other disease resulting in another sleep disorder, history of bipolar disorder, psychotic disorder or posttraumatic stress disorder or current psychiatric disorder that requires medication on-going depression and generalized anxiety disorder, history of substance abuse or dependence and with habit of smoking were excluded from the study.
  Individuals with history or current evidence of a clinically significant cardiovascular disorder or clinically significant electrocardiogram (ECG) at screening visit or patients with known history of hepatitis b and/ or c, history of malignancy ≤ 5 years prior to study participation taking prohibited medications [opium, cannabis (marijuana) and methamphetamines] were also excluded from the study.
  Individuals having known hypersensitivity to any of the ingredients of "TulsiOdaat™ or its capsule dosage form and any other condition due to which patients were deemed to be unsuitable by the investigator for reason(s) not specifically started in the exclusion criteria were excluded too.

- **Laboratory Investigations:**
  Blood investigations i.e. CBC, Hb%, blood sugar fasting, liver function tests, renal function tests, lipid profile and HIV test (if necessary) were performed. Also, patient's ECG and X-ray chest (if necessary) were done.
- **Details of Study Intervention (Supplement) –**
  TulsiOdaat™ botanical ingredient extract developed by Lodaat Pharma administered in vegetarian capsule form. Each Vegetable capsule contains: 450mg TulsiOdaat™ (Lodaat's proprietary Holy Basil Extract (*Ocimum sanctum*)
  Patients were advised to take TulsiOdaat™ in a dose of 2 Capsules daily (900mg TulsiOdaat™ total) for a period of 28 days.

- **Sample size:**
  A total of 32 patients were screened into the study, out of which there were no screen failures. A total of 32 patients were recruited in the study and 31 of these patients completed the study. The details are presented in the CONSORT provided in the annexure.

**Assessment of Efficacy Parameters:**

Assessment of insomnia was done on subject-reported total sleep time (as per patient diary), Sleep efficiency (Total sleep time/ time in bed*100) derived from patient diary**,** Patient-reported time to sleep onset (as per patient diary), subject- reported number of awakenings (as per patient diary), Patient -reported wake time after sleep onset [Wake Time After Sleep Onset (WASO) was defined as total awakening time from falling asleep to final awakening was subjectively determined based on patient diary)], Requirement of sedatives as rescue medication during study period, Insomnia using Insomnia Severity Index **,** Fatigue using Fatigue Severity Scale (FSS)**,** Daytime mood, ability to function at work, concentration and memory on a graded scale and Quality of sleep on Pittsburgh Sleep Quality Index (PSQI). Assessment of Rebound of insomnia was done on day 35 (as per patient reported diary).

Global assessment for overall change by investigator and by subject and Tolerability of study Product by investigator and subject were also done.

**Assessment of Safety**:

Safety was assessed by clinical review of all safety parameters, including the adverse event reporting, as applicable, Vital signs including allergic reactions etc., Laboratory parameters like Liver function tests (LFT), Renal function tests (RFT), complete blood count (CBC), ESR, Hb%, assessment of Overall Safety and Tolerability of the study product by the physician and subject on global assessment scale by the investigator and by subject himself**.**

All Adverse Events data were listed per subject including severity grading, relationship with investigational product and relationship of the adverse event to other causality, action taken and outcome of the adverse event. Any clinically significant changes in laboratory parameters were reported.

- **Statistical methods-**

All the patients who took at least one dose of the study product and who gave at least one post-baseline follow-up were considered for safety evaluation in the study. All the patients who completed the study as per the protocol were considered as "Per Protocol Population". Also, all cases who took at least one dose of the study ingredient were considered as "Safety population" and were evaluated accordingly.

The study data generated and collected was put to statistical analysis to determine final results and conclusions. The demographic data are presented in tables and graphs. The data on discrete variables has been represented as n (%). The data on continuous variables has been represented as mean (SD). GraphPad InStat Version 3.6 (www.graphpad.com) software was used for statistical analysis of data. P-Value < 0.05 was considered significant. For continuous data – Intra-group comparison, Paired t-test, Wilcoxon matched-pairs signed-ranks test were used. For discrete data (counted facts), Non -parametric test, i. e. Chi – Square test was applied.

**Demographic details:**

The average age of patients in the study was 45.88 ± 10.03 years. Most of the individuals were in the age of 41 to 50 years (41%) followed by that between the age group of 51 to 65 years (29%). There was a total of 14 (45.16%) male patients and 18 (54.83%) female patients in the study.

**A. Assessment of Primary Outcome Parameters:**

Table 1: Change in total sleep time and sleep efficiency

| Sr. No. | Parameter | Day 0 | Day 14 | Day 28 | Day 35 |
|---|---|---|---|---|---|
| 1 | **Change in patient-reported total sleep time (as per patient diary) in hours** | 5.02 ±0.75 | 5.89 ± 0.46* | 6.03 ± 0.56* | 5.69 ±0.48* |
| 2 | **Change in sleep efficiency (Total sleep time/ time in bed*100) derived from patient diary in percentage** | 72.35 ±10.12 % | 94.18 ±5.45%* | 97.77 ±5.45%* | 96.83 ±5.46%* |

*p < 0.05 compared to baseline value

**B. Assessment of Secondary Outcome Parameters:**

Table 2: Change in sleep onset, no of awakenings, severity and day time fatigue

| Sr. No. | Parameter | Day 0 | Day 14 | Day 28 | Day 35 |
|---|---|---|---|---|---|
| 1 | **Change in patient-reported time to sleep onset (as per patient diary)** | 1.18 ±0.48 | 0.69 ±0.25* | 0.63 ±0.25* | 0.63 ±0.25* |
| 2 | **Change in patient- reported number of awakenings (as per patient diary)** | 1.81 ±0.70 | 1.42 ±0.50 | 1.10 ±0.65* | 1.42 ±0.50* |
| 3 | **Change in severity of Insomnia using Insomnia Severity Index** | 14.07 ±2.89 | 9.67 ±4.73* | 6.1 ±6.08* | --- |
| 4 | **Change in daytime fatigue using Fatigue Severity Scale (FSS)** | 33.07 ±11.28 | 25.55 ±7.33* | 18.52 ±8.35* | 15.45 ± 6.80* |

*p < 0.05 compared to baseline value

**Table 3: Assessment of Changes in daytime mood, ability to function at work, concentration, and memory:**

| Sr. No. | Parameter | No. of Patients | | | | |
|---|---|---|---|---|---|---|
| | | | No change | Little change | Somewhat change | Much change |
| 1 | **Changes in daytime mood** | **Day 14** | 03 (96.77%) | 17 (54.83%) | 10 (32.25%) | 01 (3.22%) |
| | | **Day 28** | 15 (48.38%) | 12 (38.70%) | 03 (96.77%) | 01 (3.22%) |
| | | **Day 35** | 19 (61.29%) | 10 (32.25%) | 02 (6.44%) | 00 |
| 2 | **Changes in ability to function at work** | **Day 14** | 03 (96.77%) | 19 (61.29%) | 09 (29.03%) | 00 |
| | | **Day 28** | 18 (58.06%) | 10 (32.25%) | 02 (6.44%) | 01 (3.22%) |
| | | **Day 35** | 24 (77.41%) | 05 (16.12%) | 02 (6.44%) | 00 |
| 3 | **Changes in concentration** | **Day 14** | 07 (22.58%) | 15 (48.38%) | 08 (25.80%) | 01 (3.22%) |
| | | **Day 28** | 17 (54.83%) | 11 (35.48%) | 02 (6.44%) | 01 (3.22%) |
| | | **Day 35** | 19 (61.29%) | 11 (35.48%) | 00 | 01 (3.22%) |
| 4 | **Changes in memory** | **Day 14** | 12 (38.70%) | 15 (48.38%) | 03 (96.77%) | 01 (3.22%) |
| | | **Day 28** | 20 (64.51%) | 08 (25.80%) | 03 (96.77%) | 00 |
| | | **Day 35** | 25 (80.64%) | 04 (12.88%) | 02 (6.44%) | 00 |

**Assessment of Quality of sleep on Pittsburgh Sleep Quality Index (PSQI):**
PSQI score was used to analyze the quality of life of patients using TulsiOdaat for 28 days. It was observed that the average PSQI score at baseline visit was 11.62 ±2.33 which improved to 4.36 ±3.66 at the end of 28 days. These improvements were considered significant in comparison with the baseline results.
**Assessment of Global assessment of overall change as per the investigator and the subject:**
The physician's overall assessment of the overall change on the CGI scale showed that the majority of patients showed minimal to a much-improved response by 28 days.
At the end of 28 days of study treatment, a total of 12 (39%) patients showed very much improvement while 10 (32%) patients showed much improvement in status. 7 patients (23%) demonstrated minimal improvement in status. A subject showed no change in status. One of the patients showed Minimal worsening in status. Similarly, the overall assessment of change as per the subject showed that at the end of 28 days of study treatment, a total of 12 (39%) patients showed very much improvement while 11 (36%) patients showed much improvement in status. 6 patients (19%) demonstrated minimal improvement in status. One subject presented no change in status and one subject showed much worsening in status.
**Assessment of effect of study Product on Lab Parameters:**

It was observed that there was no significant difference in the safety-related laboratory parameters such as Hematological parameters, Liver function tests, Lipid profile, and Renal function tests and the levels were within the normal range at baseline and further at the end of the study.

**DISCUSSION**:
Insomnia is one of the common ailments in adult population. According to the American Academy of Sleep Medicine's ICSD-3 manual, insomnia is defined as "persistent difficulty with sleep initiation, duration, consolidation or quality." [16] Insomnia has many potential contributing factors and symptoms, but its diagnosis

depends on two important components: sleep difficulties that occur despite adequate opportunities for normal sleep, and daytime impairment that directly results from poor sleep quality or duration. The most important aspect in evaluation of insomnia is detailed history taking and thorough physical examination. Though, non-pharmacological treatment options have favourable and enduring benefits compared to pharmacological therapy, many single herbs and poly-hebral formulations have been described in Ayurveda for the treatment of insomnia which is safe as well as effective.

Holy Basil (*Ocimum sanctum*) is one such herb that can be used in the treatment of sleep disorders, including insomnia. There is mounting evidence that Tulsi can address physical, chemical, metabolic and psychological stress through a unique combination of pharmacological actions.[17,18] The previous findings revealed that Tulsi is effective and well tolerated by all the patients suffering from insomnia.

It is seen from the results that TulsiOdaat™ botanical ingredient extract is safe and effective in subjects suffering from primary insomnia. TulsiOdaat™ significantly improved total sleep time and sleep efficiency in subjects suffering from mild to moderate insomnia. TulsiOdaat™ significantly reduced time to sleep onset, the total number of awakenings, and wake time after sleep onset and severity of insomnia. The significant effect of TulsiOdaat™ in primary insomnia started after 7 days of treatment and continued until the end of the study. TulsiOdaat™ significantly improves symptoms associated with primary insomnia such as fatigue, problems in daytime mood, ability to function at work, concentration, and memory. TulsiOdaat™ also significantly improves the quality of sleep in subjects suffering from insomnia. Even after stoppage of treatment for seven days, no significant rebound of insomnia was observed in any of the subjects suffering from primary insomnia. No significant difference in the safety-related laboratory parameters showed that TulsiOdaat™ is safe on use for continuous one month.

**CONCLUSION:**

TulsiOdaat™ was found to be a safe and effective in the management of primary insomnia. Further comparative studies with larger sample size are warranted to validate and confirm on the clinical efficacy as well as mode of action of TulsiOdaat™.

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**CONSORT Flow Diagram (Subject Details)**