Nutrition and Dietary Supplements

Dovepress
Taylor & Francis Group

Open Access Full Text Article

CLINICAL TRIAL REPORT

# Improving Sleep and Daytime Function with Tryptophan, Magnesium, Melissa and Lactuca Formulation: An Exploratory Study in Adults with Sleep Disturbances

Franziska Schmitt[1], Ramon Weishaupt[2], Philipp KM Katumba[3], Dominic Vogt[1], Nadin Meyer[1], Michael Feld[4], Juliane Hellhammer[1]

[1]Contract Research Organization Daacro GmbH, Trier, 54296, Germany; [2]Medical Department, A.Vogel AG, Roggwil, 9325, Switzerland; [3]SIHLMED Integrative Medicine, Zürich, 8003, Switzerland; [4]Sleep Medicine Practice, Frechen-Königsdorf, 50226, Germany

Correspondence: Franziska Schmitt, Contract Research Organization daacro GmbH, Max-Planck-Str. 22, Trier, 54296, Germany, Tel +49 651 912049, Email schmitt@daacro.de



**Purpose:** Insufficient sleep is common and under-reported, linked to increased health risks. Many individuals seek alternatives to conventional medications, which often have adverse side effects.

**Patients and Methods:** This monocentric, single-arm, open-label exploratory study (Reg. No: NCT05748574) evaluated a granulate formulation containing 75 mg extract of the fresh herb of *Lactuca sativa*, 190 mg *Melissa officinalis*,120 mg L-Tryptophan, and 60 mg Magnesium in healthy adults with sleep disturbances. Conducted in Germany in 2023, 50 subjects consumed the formula nightly for 14 days. Outcomes were assessed via diaries, questionnaires, cognitive tests, wearables, saliva samples, and polysomnography (PSG) in a 10-subject subgroup. Statistical analysis compared pre- and post-treatment differences.

**Results:** Nightly awakenings reduced by 31% ($p < 0.001$) and early morning awakenings by 16% ($p < 0.001$). PSG data indicated a 28% increase in deep sleep (N3&N4, $p > 0.05$), a 70% rise in stage N4 ($p = 0.042$) and an 18% reduction in REM sleep ($p > 0.05$). The Apnea-Hypopnea index decreased by 26% ($p = 0.11$). Sleep quality ("Sleep questionnaire" SF-B/R index, primary outcome) improved by 14% ($p = 0.003$), with a 37% improvement in highly anxious individuals ($p \leq 0.001$). Restedness increased by 22% in week 1 and 28% in week 2 ($p \leq 0.001$). Psychological tension dropped by 21% and up to 29% ($p \leq 0.001$). Daytime performance indicators included a 13% reduction in sleepiness and a 23% improvement in mood ($p \leq 0.014$). Executive function showed a 13% improvement ($p \leq 0.001$) on computerized tests (COMPASS). Findings from wearables, sleep quantity, and salivary biomarkers yielded an inconsistent picture. Adherence was high, with no serious adverse events reported.

**Conclusion:** The formulation was associated with observed improvements in subjective sleep quality—particularly among anxious individuals—as well as well-being and daytime function. Further confirmation through randomized placebo-controlled studies is warranted to further prove causality.

**Keywords:** herbal supplement, polysomnography, PSG, insomnia, sleep quality, clinical trial, anxiety-related sleep disturbance

## Introduction

Insufficient sleep has emerged as a significant public health issue in modern society, often under-recognized and under-reported.[1] Sleep disorders significantly impair physical and mental health, increasing the risk of cardiovascular disease, cognitive impairment, and metabolic dysfunction. Additionally, poor sleep correlates with a heightened risk of accidents, decreased quality of life, and greater health-care utilization.[2–4]

Alongside sleep disturbances, stress and mood disorders are escalating due to the pressures of contemporary lifestyles. The interconnection between sleep and stress is mediated by the hypothalamic-pituitary-adrenal (HPA) axis, where sleep deprivation enhances HPA axis activity, leading to neuroendocrine dysregulation.[5]

Received: 8 July 2025
Accepted: 20 July 2025
Published: 7 August 2025

Data from the German Health Interview and Examination Survey for Adults (DEGS1) reveal that approximately 25% of 8152 subjects reported poor sleep quality, with 5.7% meeting the criteria for insomnia syndrome.[6] These prevalence rates vary across gender and age groups[6] and are on the rise.[7] Insomnia is a sleep disorder characterized by persistent difficulty initiating or maintaining sleep, which often leads to significant distress and preoccupation with sleep-related issues. These challenges can substantially impair daytime functioning, manifesting as excessive sleepiness, reduced cognitive performance, and diminished quality of life. According to the ICD-10/11 (International Classification of Diseases) diagnostic criteria (F51.0/7A00), insomnia is diagnosed when symptoms occur at least three times per week for a duration of one month or longer.[8]

With the growing prevalence of sleep disturbances and stress, many individuals are exploring special diets and nutritional supplements as an alternative to conventional medication, which is often associated with adverse side effects.[9] As sleep-related disorders continue to rise and impose significant personal and societal costs, easily available over-the-counter products have become increasingly popular. Nutritional supplements present a promising, well-tolerated, and safe option for improving sleep quality and supporting overall well-being.

This study evaluated the potential of Sleep Well Granulate™, a novel formulation combining herbal extracts of fresh *Lactuca sativa* and *Melissa officinalis* with L-Tryptophan and Magnesium, over a 14-day intervention. Designed as a direct granulate for convenience, the study primarily assessed its impact on sleep quality with secondary evaluations of sleep quantity, its effects on psychological well-being and cognition in healthy adults reporting sleep complaints.

# Materials and Methods

## Study Design

This exploratory, open-label, one-armed, prospective, interventional trial was carried out in accordance with the study protocol at one study centre (daacro in Trier, Germany) from March to July 2023 strictly adhering to ICH-GCP principles, the declaration of Helsinki (2013), and local regulations. The trial was prospectively registered at clinicaltrials.gov with the identifier: NCT05748574. The study protocol was approved by the Institutional Review Board of the International Medical & Dental Ethics Commission (IMDEC) GmbH Freiburg, Germany (IRB Ref. No. 2023/103).

Subjects were recruited via the study center's database and local flyers in Trier, Germany. Interested individuals underwent telephone pre-screening and were included at their first visit (V1) upon providing written informed consent and meeting eligibility criteria. The 17-day study included a 3-day run-in phase as baseline without intervention, followed by a 14-day therapy phase starting on day 4 (Figure 1). Subjects visited the study center three times: upon inclusion to record baseline measures (day 1, V1), to receive the study product and record additional baseline and acute measures (day 4, V2), and for final close-out to assess post-treatment and acute measures (day 17, V3). At V2 and V3, subjects took one sachet under the supervision of the study staff after the completion of the pre-acute intervention assessments. The sachet was administered one hour prior to conducting the post-acute intervention assessments. Acute assessments included computerized tests to evaluate cognitive performance and the State-Trait Anxiety Inventory State questionnaire (STAI-X1) to measure acute changes in state anxiety.

A sub-collective of 10 volunteering subjects had two additional study centre visits to be equipped with the portable PSG devices (day 3 at visit V2-1, day 16 at V3-1). Portable PSG devices were utilized for home recording sleep on the

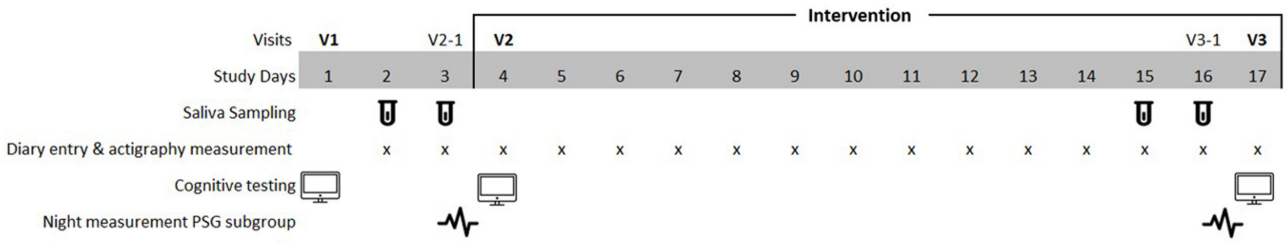


**Figure 1** Study Scheme.

nights prior V2 (baseline) and V3 (post treatment). Additionally, saliva samples for assessment of cortisol and melatonin were collected by each subject at home at baseline on days 2 and 3 and treatment days 15 and 16.

The primary objective of this exploratory study was to evaluate the effect of the intervention on subjective sleep quality, assessed via the SF-B/R questionnaire. Secondary objectives included assessments of sleep quantity (via diary, PSG, and wearables), psychological well-being (questionnaires), endocrine markers (salivary cortisol and melatonin), cognitive performance (COMPASS battery), and safety. As no formal a priori hypotheses were statistically tested, expected improvements were based on known properties of the individual ingredients.

## Subjects

Generally, healthy subjects aged 18–65 years with self-reported impaired sleep as a precursor of the S3 guideline criteria for non-organic insomnia (F 51.0), including difficulties initiating or maintaining sleep or poor sleep quality occurring regularly over the past three months. These criteria were adapted in accordance with the S3 guideline on non-restorative sleep to reflect preclinical complaints relevant to OTC interventions. Individuals with the following criteria were excluded from participation: not having habitual bedtime between 9pm-12am, BMI <18 or >30 kg/m$^2$, high systolic/diastolic blood pressure (≥159 mmHg / 99 mmHg), pregnant/lactating, any known history of organic/non-organic disorder affecting sleep (including diagnosed insomnia), serious acute/chronic disease, intake of medication influencing sleep patterns, drug misuse, excessive alcohol consumption, heavy smokers (>10 cigarettes/day), learning/behavioral difficulties, visual impairments, history of time zone travel within one month of V1, participation in another trial within the last 30 days, shift worker, not fluent in local language or having known allergies to the components of the study product. Other supplements were not permitted, and caffeine was limited to ≤10 cups/day. A complete list of applied inclusion/exclusion criteria can be found in the Supplementary Materials, Section A.

## Formulation and Dosing

The study product (Sleep Well Direct Granulate™) contains per single dose sachet 190 mg of a standardized, aqueous *Melissa officinalis* leaf extract ≥6% rosmarinic acid, 75 mg of pressed juice concentrate from freshly-harvested *Lactuca sativa* herb (10 x concentration factor from pressed juice), 410 mg Magnesium dicitrate (60 mg Magnesium, 15% NRV), 120 mg L-Tryptophan, natural orange/vanilla flavors and excipients. GMP-compliant manufacturing was performed by A. Vogel AG (Roggwil, Switzerland). Each subject was supposed to take one sachet daily 0.5–1 hour prior going to bed. The applied dosage regimen reflects common OTC intake levels and safety standards for the contained ingredients. Subjects were instructed to take the content of one sachet directly into the mouth, followed by at least 10 seconds dissolution before swallowing for 14 consecutive days. A 14-day intervention period was selected to evaluate short-term tolerability and preliminary efficacy. Subject boxes containing sufficient sachets for 14 days of intervention were identically labelled with batch number (1097005/12012024) and subject ID according to Annex 13 (ICH-GCP). Compliance with respect to study product intake was confirmed via online diaries and by counting upon return at final visit V3.

## Assessments

### Sleep Recordings

At V2 and V3, subjective sleep parameters were evaluated using the SF-B/R questionnaire, a validated tool for assessing sleep quality and difficulties (Schlaffragebogen B/Sleep questionnaire B, revised).[10] The SF-B/R comprises 31 questions across 12 scales, including: sleep quality (SQ, primary outcome), difficulty falling asleep, difficulty staying asleep, early waking, fragmented sleep, total sleep duration, feeling refreshed, pre-sleep well-being, pre-sleep exhaustion, psychosomatic symptoms, dream recall, and sleep-wake patterns in retrospective of the past 2 weeks. Items were rated on a 5-point Likert scale (1 = "never" to 5 = "very often").

Daily sleep diaries recorded the following sleep parameters continuously from days 1–17: sleep onset latency (SOL), total sleep time (TST), number of awakenings (NWAK), time in bed (TIB), and sleep efficiency. The diary also assessed physical/psychological tension, sleep enjoyment, and restedness on numeric rating scales from 0 = "very low ratings" to 10 = "very high ratings"; completed electronically by subjects each morning after waking up.

Wearable devices (Fitbit Charge 5, Fitbit, Inc., USA) recorded TIB, TST, SOL, and sleep stages (deep, REM, light, awake) continuously from days 1–17, using proprietary algorithms.

Full-night polysomnography (PSG) was conducted in a subgroup of N = 10 with subjects accepting the increased effort using SOMNO HD eco (Somnomedics AG, Germany) for one night at baseline (night of day 3) and for one night post-intervention (night of day 16). PSG measured TIB, TST, SE, SOL, wake after sleep onset (WASO), sleep stages (N1, N2, N3+N4 combined, N4 exclusively, REM), apnea-hypopnea index (AHI), and oxygen desaturation (DESAT). Acknowledging AASM guidelines that combine N3+N4 into slow-wave sleep (SWS), a separate exploratory analysis of N4 was conducted to investigate potential distinctions within SWS. Data was analyzed by a blinded sleep specialist using Domino software (version 3.0.0.6, Somnomedics AG, Germany).

### Psychometric Assessments

Baseline assessments (V1) included the Trier Inventory for Chronic Stress (TICS)[11] and STAI Trait (STAI X2 scale).[12] At V2 and V3, subjects completed questionnaires assessing daytime sleepiness (ESS scale);[13] depression, anxiety and stress (DASS-21 scale);[14] general well-being (WHOQOL-BREF scale);[15] happiness (OHQ scale),[16] and state anxiety (STAI X1 scale).[12] State anxiety was assessed pre- and post-interventional during acute evaluations at V2 and V3.

### Cognitive Assessments

Cognitive performance was evaluated using the Computerized Mental Performance Assessment System (COMPASS, Northumbria University, UK). The 14-days intervention effects were assessed by comparing baseline (V2-pre) to post intervention (V3-pre) performance, while acute effects were calculated by comparing baseline (V2/V3-pre) to post dosage measurements (V2-/V3-post). Tasks included memory, executive function, and attention assessments (eg, Immediate Word Recall, Reaction Time, Serial Subtraction), alongside a 30-minute Cognitive Demand Battery (CDB) and visual analogue mood scales (VAMS) for alertness, stress, and mood. The COMPASS battery has been validated in prior studies.[17–19] Scoring and domain-specific details are provided in Supplementary Materials Section B and Figure S1.

### Laboratory Procedures

Saliva samples were self-collected at home using Salivette® tubes (Sarstedt, Germany) following staff instructions. Samples were collected at baseline (days 2–3) and post-treatment (days 15–16). For cortisol, three morning samples were taken (at awakening, +30 min, +45 min) to assess the cortisol awakening response (CAR),[20] along with one evening sample at 8 pm. Melatonin was measured from an additional single evening sample at 8 pm.

Subjects were instructed to avoid eating, drinking, or brushing teeth throughout the entire sampling period (despite drinking water until 10 minutes before each collection). Samples were refrigerated at home and stored at −20°C at the study site until analysis. Cortisol and melatonin levels were measured using ELISA kits (Salimetrics, LLC, USA), adhering to the manufacturer's protocols. Hormonal changes from baseline to post-intervention were analyzed for associations with sleep and psychometric variables.

### Safety

Safety assessments included adverse event (AE) monitoring and vital sign measurements (blood pressure and pulse). AEs were reported via daily electronic diaries and evaluated for causality, severity, and seriousness during each visit. Vital signs were assessed at each site visit.

## Sample Size Estimate

Sample size was calculated using G*Power 3.1.9.7 for within-subject repeated measures ANOVA with two time points. Assuming alpha = 0.05, power = 0.80, and a medium effect size (f = 0.3), a minimum of 39 subjects was required. To account for the potential dropouts, 40 subjects were enrolled in the non-PSG group. An additional 10 subjects were included for PSG analysis, resulting in a total of 50 subjects.

## Statistical Analysis

Analyses were performed using SPSS version 27 (IBM Corp., 2020). The intent-to-treat (ITT) population, which was identical to the safety (SAF) and per-protocol (PP) populations, included all subjects who received at least one dose of the intervention and completed all study procedures. The primary outcome was the change in sleep quality (SF-B/R sub score: SQ), while secondary outcomes included assessments of sleep quantity (PSG, diaries, wearables), daytime sleepiness, psychological well-being, endocrinological markers, and cognitive functioning.

Within-subject changes between two timepoints were analyzed using paired t-tests or Wilcoxon signed-rank tests. Repeated measures ANOVA were applied for outcomes assessed across multiple timepoints or for detecting interaction effects in subgroups (eg, time × subgroup based on anxiety level as per the STAI trait score upon inclusion). When assumptions for parametric tests were not met, equivalent non-parametric tests (eg, Mann–Whitney U) were used. All tests were two-tailed unless otherwise stated. For exploratory PSG variables, one-tailed p-values with a threshold of 0.15 were used to identify potential directional trends in this reduced sized subgroup, as is common in early-phase research. Given the exploratory nature of the study, formal corrections for multiple testing (eg, Bonferroni or FDR) were not applied to maintain sensitivity in detecting potential effects in this early phase study, while increased risk for type 1 errors is acknowledged. Data normality and variance homogeneity were assessed with Shapiro–Wilk and Levene's tests, with transformations applied as needed.

# Results

## Baseline Characteristics

Out of 138 screened individuals, 50 subjects (25 females and 25 males) were eligible, enrolled, and completed the study. There were no dropouts and only minor protocol deviations occurred; thus, the ITT collective was identical to the safety collective. Table 1 shows demographic and physiological baseline characteristics of the ITT population (N = 50).

The BMI, systolic and diastolic BP, and heart rate of the subjects were within normal ranges (Table 1). Normal ranges were defined as systolic/diastolic BP below 120/80 mmHg,[21] HR between 60 and 100 bpm,[22] and BMI between 18.5 and 24.9 kg/m².[23] Trait anxiety and chronic stress levels were moderate,[24,25] indicating that the study cohort was generally healthy with moderate psychological complaints in addition to their self-reported sleep issues (ICD-10, F 51.0 criteria). Subjects were highly compliant at 102 ± 12%, with two individuals over 120% and none below 80%.

**Table 1** Demography and Baseline Characteristics of the ITT Collective

| | Mean | Median | SD | SEM | N |
|---|---|---|---|---|---|
| Age (years) | 34.46 | 32.5 | 12.26 | 1.73 | 50 |
| Body mass (kg) | 73.32 | 73.05 | 12.73 | 1.80 | 50 |
| Height (m) | 1.74 | 1.74 | 0.09 | 0.01 | 50 |
| BMI (kg/m$^2$) | 23.96 | 23.5 | 2.84 | 0.40 | 50 |
| Heart rate (bpm) | 71.44 | 68.5 | 11.58 | 1.64 | 50 |
| Sys. blood pressure (mmHg) | 119.6 | 121 | 14.15 | 2.00 | 50 |
| Dias. blood pressure (mmHg) | 78.28 | 78 | 8.93 | 1.26 | 50 |
| STAI trait anxiety scores (a.u.) | 40.06 | 39.50 | 9.90 | 1.40 | 50 |
| TICS scores - Work overload (a.u.) | 14.56 | 15.00 | 6.14 | 0.87 | 50 |
| TICS scores - Social overload (a.u.) | 10.06 | 9.50 | 4.45 | 0.63 | 50 |

**Abbreviations**: N, sample size; SD, standard deviation; SEM, standard error of mean; STAI trait, State-Trait-Anxiety Inventory questionnaire subscale for trait anxiety (STAI X2) ranging from 20–80; TICS, Trier Inventory for Chronic Stress.


https://doi.org/10.2147/NDS.S550592

## Efficacy Analysis

The primary outcome was the change in sleep quality, assessed by the SF-B/R Sleep Quality (SQ) score. Secondary outcomes included sleep quantity (online sleep diaries, PSG, wearable), daytime sleepiness, psychological state (validated questionnaires), endocrinological markers, and cognitive function.

### Sleep Quality Assessments

Figure 2A shows SQ scores from the SF-B/R questionnaire. The supervised completion during study visits ensured high data quality. Baseline scores averaged 4.05 ± 0.20. After the 14-day intervention, scores increased significantly to 4.61 ± 0.19 (±SEM, N = 50), representing a 13.8% improvement ($p = 0.003$).

About 32% of all subjects (N = 16) experienced a ≥30% improvement in their SQ scores, while 26% (N = 13) showed no change. For trait anxiety, a median split categorized subjects into two groups: low baseline trait anxiety (0–49$^{th}$ percentile; N = 25) and high baseline trait anxiety (50–100$^{th}$ percentile; N = 25). A significant interaction effect for time × subgroup indicates that the temporal trajectory differs between individuals with high and low anxiety levels ($F_{1, 44} = 9.53$, $p = 0.003$): Those with high baseline trait anxiety showed a significantly greater improvement by 37.2% (N = 25, ±10.9%SEM), compared to those with low baseline trait anxiety 13.1% (N = 25, ±9.7%SEM as depicted in Supplementary Section A and Table S3).

The majority of SF-B/R subscales improved significantly, except for "total sleep time", "feeling exhausted before sleep", "dream recall", and "sleep-wake pattern" (see Supplementary Section A and Table S1).

E-diary entries (see Figure 2B and Supplementary Section A, Table S2) confirmed these observations with positive effects on sleep quality measures. Physical tension scores decreased on average from 4.12 ± 0.20 to 3.2 ± 0.18 score points (±SEM, −22.3%, $p < 0.001$) after 1 week, and to 2.82 ± 0.18 (±SEM, −31.6% $p < 0.001$) after 2 weeks, and psychological tension decreased from 4.15 ± 0.24 to 3.28 ± 0.19 after 1 week (±SEM, −21.0, $p < 0.001$), and to 2.94 ± 0.2 after 2 weeks (±SEM, −29.2%, $p < 0.001$). Sleep enjoyment scores increased from 4.69 ± 0.2 to 5.52 ± 0.17 (±SEM, +17.7%, $p < 0.001$) resp. to 5.75 ± 0.19 (±SEM, +22.6%, $p < 0.001$), and feeling of restoration from 4.32 ± 0.19 to 5.26 ± 0.19 (±SEM, +21.8%, $p < 0.001$), resp. to 5.55 ± 0.19 (±SEM, +28.5%, $p < 0.001$) after 1 and 2 weeks.

Sleep quality improvements occurred within ≤1-week intervention, with further gains during the subsequent period.

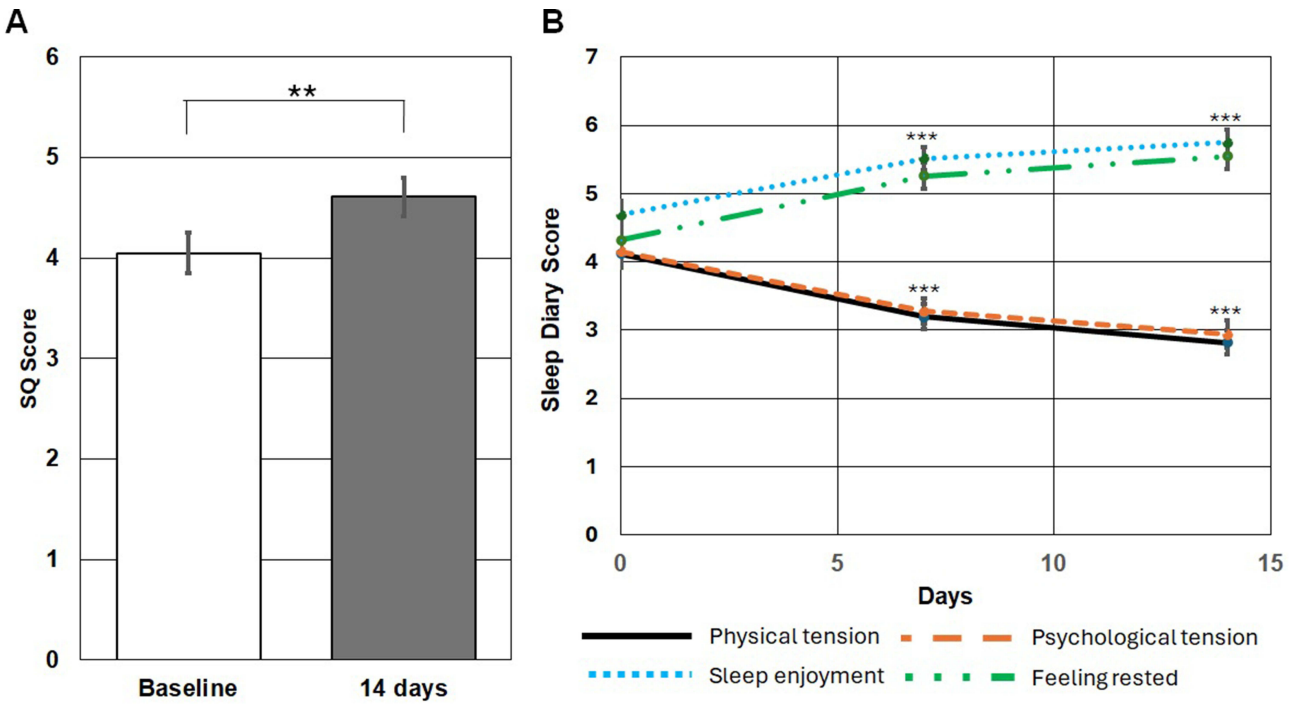


**Figure 2** Sleep quality scores during the 2-week intervention. (**A**) Sleep Quality (SQ) scores measured by the SF-B/R index (primary outcome) in retrospective of the past 2 weeks; (**B**) Sleep quality ratings recorded per e-sleep diaries in retrospective of the last night.**p < 0.01, ***p < 0.001 vs baseline. Error bars denote standard error of the mean (±SEM). Number of subjects contributing to the measure N = 50.

### Sleep Quantity Assessments

Data from electronic sleep diaries revealed modest effects in sleep quantity over the intervention period. After two weeks, time in bed (TIB) increased from 8.06 ± 0.14 hours to 8.36 ± 0.10 hours (±SEM, N = 50, +3.4%, $p = 0.035$), total sleep time (TST) increased from 6.92 ± 0.14 hours to 7.35 ± 0.09 hours (±SEM, N = 50, +6.2%, $p = 0.005$) and the number of awakenings (NWAK) decreased from 2.57 ± 0.22 events to 1.78 ± 0.14 events (±SEM, N = 50, −30.7%, $p < 0.001$). Sleep onset latency (SOL) and sleep efficiency did not change significantly ($p > 0.05$).

In the PSG subgroup (N = 10), no significant pre-post changes were observed for PSG measurements of SOL, TIB, TST, WASO, SE, light sleep stages (N1, N2) or Desaturation index (DESAT). However, directional trends were noted using one-tailed analysis ($p < 0.15$), including a reduction in REM sleep from 55.9 ± 22.5 min to 44.1 ± 25.1 min (−18% ratio change, $p = 0.111$) and an increase in deep sleep (N3+N4) from 62.3 ± 44.9 min to 73.3 ± 44.3 min, (+27.8% ratio change, $p = 0.116$). Notably, N4 sleep significantly increased from 15.7 ± 22.4 min to 24.6 ± 24.1 min (+70.3% ratio change, $p = 0.042$). The Apnea-hypopnea index (AHI) declined from 2.22 ± 2.08 to 1.65 ± 1.53 (−25.7% ratio change, $p = 0.110$). No significant changes were found in wearable-derived metrics.

### Psychological and Endocrinological Assessments

Significantly improved psychological well-being was observed following the 14 days' intervention. Daytime sleepiness (Epworth Sleepiness Scale) decreased from 8.84 ± 3.58 to 7.72 ± 3.67 (−12.7%, $p = 0.006$). State anxiety (STAI-X1) dropped from 36.52 ± 8.38 to 33.18 ± 7.39 (−9.2%, $p < 0.001$) after two weeks. Depression (DASS) scores fell from 3.08 ± 2.78 to 2.38 ± 2.66 (−22.7%, $p = 0.014$), anxiety (DASS) from 2.46 ± 2.42 to 1.84 ± 2.22 (−25.2%, $p = 0.018$), and stress (DASS) from 6.36 ± 3.64 to 5.22 ± 3.36 (−17.9%, $p = 0.014$). Quality of life (WHOQOL-BREF) improved slightly, from 74.25 ± 14.60 to 77.75 ± 13.19 (+13.8%, $p = 0.008$), while social happiness (OHQ) increased modestly from 4.48 ± 0.58 to 4.58 ± 0.59 (+2.2%, $p = 0.033$).

Endocrine outcomes showed no overall changes; exploratory subgroup trends suggest anxiety-related variation, warranting further investigation (see Supplementary Materials Section C, Tables S8–S10).

### Cognitive Function Assessments

Tasks addressing executive function improved modestly over 14 days (+13.2% on average, $p < 0.001$), particularly in reaction time and calculation accuracy. Memory performance also improved post-intervention. While acute assessments showed transient declines in certain memory tasks (eg, delayed recall, picture/word recognition), these were paralleled by improvements in executive function tasks and attention (eg, serial subtraction and peg-and-ball tasks) and reduced subjective stress (VAS scale), suggesting a more refined acute response (see Supplementary Materials Section B, Tables S4–S7).

## Clinical Safety Outcomes

During the 14-day intervention, 39 adverse events (AEs) were reported by 25 subjects via daily diaries and reviewed by the principal investigator. Of these, 69% were mild and 31% moderate in severity. Most AEs (79%) were deemed unrelated or unlikely related to the intervention, while 21% (8 events in 5 subjects) were classified as possibly related, including headaches, stomach aches, and circulatory complaints. Of these, mild cases accounted for 13% and moderate for 8% of events, of which all were self-limited and resolved spontaneously.

No severe or serious adverse events (SAEs) occurred nor were any follow-ups required. Vital signs remained stable throughout the intervention, indicating good overall tolerability of the formulation.

# Discussion

*Lactuca sativa* (common lettuce) has long been a calming agent, with sesquiterpene lactones (eg, lactucin, lactucopicrin) shown to be bioavailable and active for up to six hours after ingestion.[26,27] Mature, freshly harvested plants offer significantly higher concentrations of these compounds.[28,29] Clinical studies report improvements in insomnia symptoms, including reduced PSQI scores.[30,31] *Melissa officinalis* (lemon balm) has demonstrated sleep-enhancing and anxiolytic effects.[32–35] L-Tryptophan, a precursor of serotonin and melatonin, has shown benefits for sleep and mood,[36–38] while magnesium supports sleep regulation via NMDA and GABAergic modulation.[39,40] The Sleep Well granulate combines

these ingredients into a multi-modal formulation intended to support sleep and mental performance. The combination of Melissa (potentially GABAergic), magnesium (with anti-inflammatory and neuromodulatory effects), and L-Tryptophan (a precursor to both serotonin and melatonin) is hypothesized to act synergistically via complementary antioxidant, neurotransmitter, and circadian-regulating pathways—supporting broader sleep—wake stabilization than single agents.

This exploratory study suggests that 14 days of supplementation improved sleep quality, especially in anxious subjects, with supporting effects on well-being and cognitive function.

The primary outcome sleep quality, assessed via the SF-B/R questionnaire, improved by 13.8% overall and by +37.2% in anxious individuals—comparable to interventions like Valerian or Oxazepam,[41] reporting 23.6% and 29.2% improvements in sleep quality (reported with the identical SF-B/R questionnaire) over 2 weeks. Unlike single-agent preparations such as melatonin or Valerian, which primarily target circadian rhythm or GABAergic pathways, respectively,[36,37,42] the Sleep Well formulation combines ingredients acting via complementary mechanisms. Notably, L-Tryptophan serves as a precursor to both serotonin and melatonin—two neurotransmitters essential to sleep regulation—thereby offering broader neurochemical support than, eg, melatonin alone. E-diary ratings in our study further showed up to a 29% increase in restoration and 32% reduction in tension, aligning, for example, with findings from saffron trials requiring a longer duration of one month, where saffron supplementation improved sleep quality by 21.5% compared to placebo (reported with the PSQI questionnaire).[43]

Sleep diary data showed modest increases in sleep duration (TIB and TST) and fewer awakenings, while wearable and PSG data showed no significant changes in duration. However, PSG results suggested trends to increased deep sleep, which could explain improvements in perceived subjective sleep quality. Subjective-Objective Discrepancies (SOSD) between subjective and objective data are well documented and may reflect perceptual and psychological shifts, especially in anxious individuals.[44–46] Technical limitations, such as limitation in the wearable algorithm sensitivity and small PSG sample size may also contributed.[47,48] Nevertheless, interpretations are supported by theories emphasizing sleep quality over quantity in restorative outcomes.[49–52]

Psychological outcomes improved consistently over the 14-days period and across measures, with reductions in daytime sleepiness (ESS), stress and anxiety (DASS), and increases in quality of life (WHOQOL-BREF) and happiness (OHQ)—consistent with literature linking better sleep to enhanced psychological states.[53,54] Though no group-level endocrine changes were observed, a higher melatonin-to-cortisol ratio was found in anxious individuals' post-treatment (see Supplementary Materials Section C), suggesting possible subgroup-specific neuroendocrine effects, warranting further investigation.

Cognitive performance improved modestly, particularly in executive function and memory recall. These effects may relate to increased deep sleep, which has been linked to mental and physical recovery.[42,55–57] Minor fluctuations after acute dosing were transient and likely reflect task fatigue. Since study site visits were conducted depending on scheduling availability, but not at a uniform time for all participants, variability in mood or cognitive performance is acknowledged, but also supports generalizability to everyday settings.

The intervention demonstrated a favourable safety profile, with no serious adverse events and high tolerability. Most of the daily assessed AEs were mild and unrelated to the intervention. Importantly, the observed AE rate is consistent with expectations in exploratory studies where proactive daily monitoring tends to increase reporting frequency.[58,59] The absence of SAEs and no significant changes in vital signs further underscore the intervention's safety. Long-term safety should be monitored in future studies to confirm these preliminary findings.

## Limitations of the Study

The open-label, single-arm design limits causal inference and necessitates cautious interpretation. The absence of a control group and the small PSG sample reduce generalizability and objective power. No light-controlled conditions were applied during salivary melatonin sampling, and neither the timing nor caffeine or food intake were controlled for the administration of the cognitive test battery. Future trials should adopt randomized, placebo-controlled designs with larger samples and longer follow-up to validate and extend these findings.

## Conclusion

This exploratory study suggests potential for the Sleep Well granulate formulation to improve sleep quality, psychological well-being, and cognitive performance—particularly among individuals with elevated anxiety; however, confirmatory evidence from placebo-controlled trials is warranted.

## Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics Approval and Consent to Participate

The Independent Review Board IMDEC GmbH, Schillerstrasse 34, 79102 Freiburg, Germany, info@imdec.org/www.imdec.org, represented by Dr. med Dieter Wetzerl, MBA/Chairman authorized the study protocol (Version F2.0 of February 9, 2023, 2023) with the IRB (institutional review board) Ref. No. 2023/103. No amendments to the study protocol were generated that required additional ethics approval. The clinical study has been registered at Clinicaltrials.gov (identifier: NCT05748574).

Written informed consent was obtained from all subjects' prior any study procedures were applied in the study. The study was performed in accordance with the ethical principles originating in the Declaration of Helsinki and consistent with the Good Clinical Practice (GCP) guidelines of the International Conference on Harmonization (ICH) and applicable regulatory requirements on bioethics and data protection were ensured permanently.

## Acknowledgments

We wish to extend our gratitude to all the study participants who made this study possible.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This study was funded by the study sponsor A. Vogel AG, Roggwil, Switzerland. Further, the sponsor provided the study products and covered the funding of the article publication fees.

## Disclosure

R.W. is an employee of A. Vogel AG, the study sponsor. F.S., N.M., J.H., D.V., M.F. work for the contract research organization performing the study for the sponsor. P.K. received honorary funds from the study sponsor for lectures on separate occasions but has contributed voluntarily to this study and has no further financial involvement. The authors indicate that they have no other competing interests to declare regarding the content of this article.

## References

1. Chattu VK, Manzar MD, Kumary S, Burman D, Spence DW, Pandi-Perumal SR. The global problem of insufficient sleep and its serious public health implications. *Healthcare*. 2018;7(1):1–6. doi:10.3390/healthcare7010001
2. Lee M, Choh AC, Demerath EW, et al. Sleep disturbance in relation to health-related quality of life in adults: the fels longitudinal study. *J Nutr Health Aging*. 2009;13(6):576–583. doi:10.1007/s12603-009-0110-1
3. Roth T. Insomnia: definition, prevalence, etiology, and consequences. *J Clin Sleep Med*. 2007;3(5 Suppl):S7–S10. doi:10.5664/jcsm.26929
4. Sivertsen B, Hysing M, Harvey AG, Petrie KJ. The epidemiology of insomnia and sleep duration across mental and physical health: the SHoT study. *Front Psychol*. 2021;12:662572. doi:10.3389/fpsyg.2021.662572
5. Hirotsu C, Tufik S, Andersen ML. Interactions between sleep, stress, and metabolism: from physiological to pathological conditions. *Sleep Sci*. 2015;8(3):143–152. doi:10.1016/j.slsci.2015.09.002

6. Schlack R, Hapke U, Maske U, Busch M, Cohrs S. Frequency and distribution of sleep problems and insomnia in the adult population in Germany: results of the German health interview and examination survey for adults (DEGS1). *Bundesgesundheitsbl*. 2013;56(5–6):740–748. doi:10.1007/s00103-013-1689-2
7. BARMER. BARMER-Analyse zur Zeitumstellung – massiver Anstieg bei Schlafstörungen. Available from: https://www.barmer.de/presse/presseinformationen/presse-archiv/barmer-analyse-zur-zeitumstellung-massiver-anstieg-bei-schlafstoerungen-1288544. Accessed January 17, 2025.
8. World Health Organization. International classification of diseases for mortality and morbidity statistics (10th revision). Available from: https://icd.who.int/browse10/2019/en#/F51.0/. Accessed June 2025.
9. Morin CM, Benca R. Chronic insomnia. *Lancet*. 2012;379(9821):1129–1141. doi:10.1016/S0140-6736(11)60750-2
10. Görtelmeyer R. *SF-A/R und SF-B/R - Schlaffragebogen A und B - Revidierte Fassung. PSYNDEX Tests Info*. Göttingen: Hogrefe; 2011.
11. Schulz P, Schlotz W, Becker P. *Trierer Inventar zum chronischen Stress (TICS)*. Göttingen, Germany: Hogrefe; 2004.
12. Laux L, Glanzmann P, Schaffner P, Spielberger C. *Das state-trait-angstinventar*. Weinheim: Beltz; 1981.
13. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. 1991;14(6):540–545. doi:10.1093/sleep/14.6.540
14. Lovibond PF. Long-term stability of depression, anxiety, and stress syndromes. *J Abnorm Psychol*. 1998;107(3):520–526. doi:10.1037/0021-843X.107.3.520
15. World Health Organization. *WHOQOL-BREF: Introduction, Administration, Scoring and Generic Version of the Assessment*. WHO; 1996.
16. Hills P, Argyle M. The oxford happiness questionnaire: a compact scale for the measurement of psychological well-being. *Pers Individ Dif*. 2002;33(7):1073–1082. doi:10.1016/S0191-8869(01)00213-6
17. Kennedy D, Wightman E, Khan J, Grothe T, Jackson P. The acute and chronic cognitive and cerebral blood-flow effects of Nepalese pepper (Zanthoxylum armatum DC.) extract—A randomized, double-blind, placebo-controlled study in healthy humans. *Nutrients*. 2019;11(12):3022. doi:10.3390/nu11123022
18. Wightman EL, Jackson PA, Forster J, et al. Acute effects of a polyphenol-rich leaf extract of Mangifera indica L. (Zynamite) on cognitive function in healthy adults: a double-blind, placebo-controlled crossover study. *Nutrients*. 2020;12(8):2194. doi:10.3390/nu12082194
19. Dodd F, Kennedy D, Wightman E, et al. The chronic effects of a combination of herbal extracts (Euphytose®) on psychological mood state and response to a laboratory stressor: a randomised, placebo-controlled, double-blind study in healthy humans. *J Psychopharmacol*. 2022;36(11):1243–1256. doi:10.1177/02698811221112933
20. Stalder T, Kirschbaum C, Kudielka BM, et al. Assessment of the cortisol awakening response: expert consensus guidelines. *Psychoneuroendocrinology*. 2016;63:414–432. doi:10.1016/j.psyneuen.2015.10.010
21. Whelton PK, Carey RM. The 2017 clinical practice guideline for high blood pressure. *JAMA*. 2017;318(21):2073–2074. doi:10.1001/jama.2017.18209
22. Bickley LS. *Bates' Guide to Physical Examination and History Taking*. 12th ed. Wolters Kluwer; 2017.
23. World Health Organization. BMI classification. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed June 2025.
24. Do Nascimento B, Franco K, Franco Y, Nunes Cabral C. Can psychological factors be associated with the severity of pain and disability in patients with fibromyalgia? A cross-sectional study. *Physiother Theory Pract*. 2020;38(3):431–440. doi:10.1080/09593985.2020.1765439
25. Stute P, Anker M, Hollenstein L, et al. Measuring chronic stress exposure incorporating the active and healthy ageing (AHA) concept within the cross-sectional Bern cohort study 2014 (BeCS-14). *BioPsychoSocial Med*. 2019;13(1):2. doi:10.1186/s13030-019-0143-6
26. Matos MS, Anastácio JD, Allwood JW, et al. Assessing the intestinal permeability and anti-inflammatory potential of sesquiterpene lactones from chicory. *Nutrients*. 2020;12(11):3547. doi:10.3390/nu12113547
27. Weng H, He L, Zheng J, et al. Low oral bioavailability and partial gut microbiotic and phase II metabolism of Brussels/Witloof chicory sesquiterpene lactones in healthy humans. *Nutrients*. 2020;12(12):3675. doi:10.3390/nu12123675
28. Yang X, Gil MI, Yang Q, Tomás-Barberán FA. Bioactive compounds in lettuce: highlighting the benefits to human health and impacts of preharvest and postharvest practices. *Compr Rev Food Sci Food Saf*. 2022;21(1):4–45. doi:10.1111/1541-4337.12877
29. Assefa AD, Choi S, Lee JE, et al. Identification and quantification of selected metabolites in differently pigmented leaves of lettuce (Lactuca sativa L.) cultivars harvested at mature and bolting stages. *BMC Chem*. 2019;13(1):1–15. doi:10.1186/s13065-019-0570-2
30. Pour ZS, Hosseinkhani A, Asadi N, et al. Double-blind randomized placebo-controlled trial on efficacy and safety of Lactuca sativa L. seeds on pregnancy-related insomnia. *J Ethnopharmacol*. 2018;227:176–180. doi:10.1016/j.jep.2018.08.001
31. Yakoot M, Helmy S, Fawal K. Pilot study of the efficacy and safety of lettuce seed oil in patients with sleep disorders. *Int J Gen Med*. 2011;4:451–456. doi:10.2147/IJGM.S21529
32. HMPC. Community herbal monograph on Melissa officinalis L. folium. EMA/HMPC/196745/2012. 2013;1–7.
33. Cases J, Ibarra A, Feuillère N, Roller M, Sukkar SG. Pilot trial of Melissa officinalis L. leaf extract in the treatment of volunteers suffering from mild-to-moderate anxiety disorders and sleep disturbances. *Mediterr J Nutr Metab*. 2011;4(3):211–218. doi:10.3233/s12349-010-0045-4
34. Soltanpour A, Alijaniha F, Naseri M, Kazemnejad A, Heidari MR. Effects of Melissa officinalis on anxiety and sleep quality in patients undergoing coronary artery bypass surgery: a double-blind randomized placebo controlled trial. *Eur J Integr Med*. 2019;28:27–32. doi:10.1016/j.eujim.2019.01.010
35. Haybar H, Javid AZ, Haghighizadeh MH, Valizadeh E, Mohaghegh SM, Mohammadzadeh A. The effects of Melissa officinalis supplementation on depression, anxiety, stress, and sleep disorder in patients with chronic stable angina. *Clin Nutr ESPEN*. 2018;26:47–52. doi:10.1016/j.clnesp.2018.04.015
36. Sutanto CN, Loh WW, Kim JE. The impact of tryptophan supplementation on sleep quality: a systematic review, meta-analysis, and meta-regression. *Nutr Rev*. 2022;80(2):306–316. doi:10.1093/nutrit/nuab027
37. Binks H, Vincent GE, Gupta C, Irwin C, Khalesi S. Effects of diet on sleep: a narrative review. *Nutrients*. 2020;12(4):936. doi:10.3390/nu12040936
38. Martínez-Rodríguez A, Rubio-Arias JA, Ramos-Campo DJ, Reche-García C, Leyva-Vela B, Nadal-Nicolás Y. Psychological and sleep effects of tryptophan and magnesium-enriched Mediterranean diet in women with fibromyalgia. *Int J Environ Res Public Health*. 2020;17(7):2227. doi:10.3390/ijerph17072227
39. Abbasi B, Kimiagar M, Sadeghniiat K, Shirazi MM, Hedayati M, Rashidkhani B. The effect of magnesium supplementation on primary insomnia in elderly: a double-blind placebo-controlled clinical trial. *J Res Med Sci*. 2012;17(12):1161.

40. Chollet D, Franken P, Raffin Y, Malafosse A, Widmer J, Tafti M. Blood and brain magnesium in inbred mice and their correlation with sleep quality. *Am J Physiol Regul Integr Comp Physiol*. 2000;279(6):R2173–R2178. doi:10.1152/ajpregu.2000.279.6.R2173
41. Ziegler G, Ploch M, Miettinen-Baumann A, Collet W. Efficacy and tolerability of valerian extract LI 156 compared with oxazepam in the treatment of non-organic insomnia: a randomized, double-blind, comparative clinical study. *Eur J Med Res*. 2002;7(11):480–486.
42. Abourashed EA, Koetter U, Brattström A. In vitro binding experiments with a valerian, hops and their fixed combination extract (Ze91019) to selected central nervous system receptors. *Phytomedicine*. 2004;11(7–8):633–638. doi:10.1016/j.phymed.2004.03.005
43. Lopresti AL, Smith SJ, Malvi H, Kodgule R. Effects of saffron on sleep quality in healthy adults with self-reported poor sleep: a randomized, double-blind, placebo-controlled trial. *J Clin Sleep Med*. 2020;16(6):937–943. doi:10.5664/jcsm.8376
44. Hinterberger A, Eigl ES, Schwemlein RN, Topalidis P, Schabus M. Investigating the subjective and objective efficacy of a cognitive behavioural therapy for insomnia (CBT-I)-based smartphone app on sleep: a randomised controlled trial. *J Sleep Res*. 2024;33(4):e14136. doi:10.1111/jsr.14136
45. Van Den Berg JF, Van Rooij FJ, Vos H, et al. Disagreement between subjective and actigraphic measures of sleep duration in a population-based study of elderly persons. *J Sleep Res*. 2008;17(3):295–302. doi:10.1111/j.1365-2869.2008.00638.x
46. Harvey AG, Tang NKY. (Mis) perception of sleep in insomnia: a puzzle and a resolution. *Psychol Bull*. 2012;138(1):77–101. doi:10.1037/a0025730
47. Cook JD, Prairie ML, Plante DT. Utility of the fitbit flex to evaluate sleep in major depressive disorder: a comparison against polysomnography and wrist-worn actigraphy. *J Affect Disord*. 2017;217:299–305. doi:10.1016/j.jad.2017.04.030
48. De Zambotti M, Cellini N, Goldstone A, Colrain IM, Baker FC. Wearable sleep technology in clinical and research settings. *Med Sci Sports Exerc*. 2019;51(7):1538. doi:10.1249/MSS.0000000000001947
49. Feige B, Al-Shajlawi A, Nissen C, et al. Does REM sleep contribute to subjective wake time in primary insomnia? A study comparing polysomnographic and subjective sleep in good sleepers and insomnia patients. *Sleep*. 2008;31(10):1499–1506. doi:10.1093/sleep/31.11.1499
50. Feige B, Baglioni C, Spiegelhalder K, et al. The microstructure of sleep in primary insomnia: an overview and extension. *Int Rev Psychiatry*. 2013;25(2):210–218. doi:10.3109/09540261.2013.776522
51. Feige B, Nissen C, Voderholzer U, Hornyak M, Riemann D. The microstructure of sleep in primary insomnia: an overview and extension. *Int Rev Psychiatry*. 2011;22(2):210–218.
52. Feige B, Nissen C, Voderholzer U, Hornyak M, Riemann D. The microstructure of sleep in primary insomnia: an overview and extension. *Int Rev Psychiatry*. 2010;22(2):210–218.
53. Hamilton NA, Gallagher MW, Preacher KJ, et al. Insomnia and well-being. *J Consult Clin Psychol*. 2007;75(6):939–946. doi:10.1037/0022-006X.75.6.939
54. Vgontzas AN, Tsigos C, Bixler EO, et al. Chronic insomnia and activity of the stress system: a preliminary study. *J Psychosom Res*. 1998;45(1):21–31. doi:10.1016/S0022-3999(97)00302-4
55. Eugene AR, Masiak J. The neuroprotective aspects of sleep. *MEDtube Sci*. 2015;3(1):35. doi:10.1126/science.1245798
56. Underwood E. Sleep: the brain's housekeeper? *Science*. 2013;342(6156):301. doi:10.1126/science.342.6156.301
57. Kryger MH, Roth T, Dement WC. Principles and practice of sleep medicine. *Elsevier Health Sci*. 2010.
58. van Hunsel FPAM, van der Kooi D, van de Koppel S, et al. Analysis of reports on adverse drug reactions related to herbal medicinal products and herbal supplements in the Netherlands received by the national pharmacovigilance centre lareb. *Drug Saf*. 2022;45(6):651–661. doi:10.1007/s40264-022-01180-5
59. Ioannidis JP, Evans SJ, Gotzsche PC, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med*. 2004;141(10):781–788. doi:10.7326/0003-4819-141-10-200411160-00009