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Mulberry leaf extract combined with tryptophan improves sleep and post wake mood in adults with sleep complaints – A randomized cross-over study

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Abstract

Purpose: In the current study we evaluated a blend of ingredients containing mulberry leaf extract (to lower postprandial glucose of the evening meal), tryptophan (facilitator of the sleep initiation) to benefit sleep initiation and quality in adults with self-reported difficulties with sleep initiation.

Methods: Forty-three adults aged between 25 and 50 years enrolled in a randomized, crossover, double-blind, controlled trial. Participants received standardized meals with a glycemic load of 55 ± 10% and were assigned to receive treatment comprising a combination of mulberry leaf extract (750 mg), whey protein containing 120 mg tryptophan, zinc (1.35 mg), magnesium (12.6 mg), vitamin B3 (1.93 mg) and B6 (0.135 mg) and control (4 g wheat protein hydrolysate). Each intervention phase lasted 14 days separated by a washout period of 28 days. The primary outcomes were actigraphy-measured sleep onset latency and sleep efficiency. Secondary outcomes included continuous glycemic responses, mood, and cognition.

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Results: A linear mixed model intention-to-treat analysis conducted on 42 participants found that the treatment reduced sleep onset latency (actigraphy: −3.82 mins, p = 0.026; self-report: −3.09 mins, $p = 0.048$). Treatment significantly reduced evening meal's postprandial glucose response (incremental area under the curve, mmol/L*min) at 1 hour by 21% ($p < 0.001$), incremental maximum concentration by 16% (p = < 0.001) and nocturnal glucose variation over the 14-day period. Participants on treatment reported improved sleep quality (Karolinska Sleepiness Scale, −0.17, $p = 0.041$) and feeling more relaxed (Brief Mood Introspection Scale, −0.4, $p = 0.003$) the next morning compared to when taking the control. Additionally, the treatment improved the vigor dimension on the Profile of Mood Scale (0.8, $p = 0.038$). No effects were observed on the cognitive performance. Lowering postprandial glucose significantly mediated the treatment effect of lowering sleep onset latency and lower nocturnal glucose variation was also associated with improved sleep quality and next-day positive mood.

Conclusion: The evening meal supplement benefited sleep initiation and quality, and also improved post wake mood in adults.

Trial registration: Registration number of Clinical Trial - ClinicalTrials.gov NCT05372900

Keywords

Actigraphy; Continuous glucose monitoring; Mulberry leaf extract; Tryptophan; Nocturnal glycemia; Sleep quality

Introduction

There is a bi-directional relationship between sleep and glucose control [27, 36, 38, 40]. Patients with poorly-controlled type-2 diabetes mellitus (T2DM) take longer to fall asleep resulting in lower sleep efficiency [44], show greater variability in sleep duration [33] and report poorer quality sleep [26] than patients who have good glycaemic control. Larger internight variability in sleep duration has also been associated with higher glucose levels in T2DM [4]. Persons with T2DM and insomnia have higher fasting blood glucose and insulin levels [24]. Finally, high sleep variability, longer sleep onset latency (SOL) and short sleep duration are associated with higher risk of developing T2DM [19].

There is increasing evidence that poorer glucose regulation in healthy adults is also associated with poorer sleep quality and duration [36, 37, 41]. Difficulty initiating and maintaining sleep is closely linked to greater insulin resistance and glucose intolerance [4]. Glycemic variability across days (mean of daily differences) measured using continuous glucose monitoring (CGM) is negatively correlated with total sleep time (TST), and positively correlated with total wake duration, which includes both SOL and wake after sleep onset (WASO), an indicator of sleep fragmentation [20]. Targeting glucose regulation may thus be a promising intervention for improving sleep quality.

Dietary habit is a major modifiable lifestyle factor that can influence glycemic variability [13, 23, 31]. Notably, manipulating the quantity and quality of carbohydrate intake has been shown to not only affect glycemic variability but also sleep [13, 23, 31]. Diets with a high glycemic index or those rich in added sugars, starch, and refined grains have been associated with a higher prevalence of sleep problems [37]. Conversely, meals with a lower glycemic load have been linked to improvements in sleep architecture, including reduced SOL and WASO [9], [35]. Based on these findings, we posited that lowering blood glucose post meal might be a viable means of improving sleep quality.

To this end, the present study evaluated a formulation with two key active components: a mulberry leaf extract (MLE) rich in 1-deoxynojirimycin shown to reduce the postprandial glucose [13, 23, 31] by inhibiting α-glucosidase, and tryptophan [32], which can facilitate sleep initiation [43]. We hypothesized that supplementing evening meals with this formulation would benefit sleep initiation and quality, and that this might also be reflected in improvement of cognitive performance and mood.

Methods

Study design and participants

Participants for this randomized, double-blind, cross-over trial were recruited between March and July 2022 (ClinicalTrials.gov NCT05372900). Eligible persons had to be between 25 and 50 years of age, score more than 5 on the Pittsburgh Sleep Quality Index (PSQI) and have body mass index (BMI) between 18.5 and 28.0 kg/m^2. Eligible candidates underwent two weeks of actigraphy to verify that their sleep efficiency (SE) was below 85%. CGM was under-taken to exclude persons with significant hypoglycemic episodes defined as having more than 1% of readings below 3.0 mmol/L. The trial consisted of a screening period of two weeks to verify low SE, followed by two intervention phases, each lasting two weeks with an intervening washout period of 4–6 weeks. Participants were free living adults, not asked to modify their lifestyles in other ways during the study period. The study protocol received approval from the institutional review board (NUS-IRB ref. no: NUS-IRB-2021–790).

Study products, randomization, and masking

Each participant received either treatment or control, once daily for 14 days in both intervention phases in a random order. Both treatment and control products were provided as a dry powder to be reconstituted with drinking water to a volume of 200–250 mL at home and consumed within 30 min of starting the standardized evening meal (consumed approximately 4-h before bedtime). Participants were instructed to consume one unlabeled sachet containing the test product per day. Each product kit was coded by manufacturers with individual numbers. The codes were printed on the labels, otherwise the packaging and labeling is identical. The color and taste of the products were similar.

Meals were prepared by the external catering service provider and customized to meet the target nutrient composition for each participant according to gender and estimated daily energy requirements. Meals were designed to provide 50–60% energy from carbohydrates (GL of 55 ± 10%), 15–20% from proteins, and 30–40% from fats (see Supplementary Table 1 for details).

Randomization was implemented in Medidata RTMS using dynamic allocation. The treatment consisted of a single serving containing 750 mg MLE (1% 1-deoxynojirimycin) (commercially available as Reducose®; Phynova), 5.4 g whey protein containing 120 mg of tryptophan, 1.337 mg zinc, 12.39 mg magnesium, 1.96 mg vitamin B3 and 0.13 mg vitamin B6. The control consisted of 4 g wheat gluten hydrolysate containing low tryptophan (approximately 40 mg).

Study visits, clinical assessments, and measurements

A schematic of the study protocol is presented in Fig. 1; further details appear in Supplementary Table 2. The primary objective of the study was to examine the effects of the treatment on SOL and SE (SE = TST/TIB), based on objective sleep measurements acquired using the Philips Actiwatch Spectrum Plus. In addition, as secondary measures, WASO and Rise (measured by Actiwatch), self-reported sleep quality (Karolinska Sleep Diary, [3], sleepiness (Karolinska Sleepiness Scale, KSS [2],Epworth Sleepiness Scale, ESS [18]) and mood (Brief Mood Introspection Scale, BMIS [29],Profile of Mood States - Short Form 2, POMS-SF 2 [30]) were assessed daily 30–60 min from awakening via the Medidata ePRO smartphone app (Medidata Solutions Inc.). Subjective sleepiness (KSS) and Mood (BMIS) were also measured 30–60 min daily before bedtime.

Glucose levels during the intervention phase were continuously assessed using multiple measures extracted from CGM data (FreeStyle Libre PRO IQ by Abbott). Postprandial glycemic response (PPGR) following the evening meal was assessed by i) 0 to 3-h incremental area under the curve of glucose response (3h-iAUC); ii) incremental maximum concentration (iCmax); time to maximum concentration (Tmax); and time to return to baseline (TRB). Nocturnal glycemia, glucose excursion during the night from bedtime to waking up, was assessed using glucose mean, standard deviation (SD), and coefficient of variability (CV). In addition, PPGR for the next-day breakfast was also assessed using 3h-iAUC, iCmax, and Tmax. For PPGR iAUC calculations, the 40th percentile of the past 24 h of glucose measures was used as the baseline [8].

Cognitive performance was assessed 60–90 min after breakfast, lunch, and dinner (approximately 1, 6, and 12 hours after waking up) on Day 0 (baseline), Day 8 (midpoint), and Day 14 (end) of each intervention phase. The cognitive test battery, self-administered using E-PRIME software on a study laptop, comprised five tests. These assessed vigilance, attention, response inhibition, working memory, and short- and long-term memory: i) Immediate Free Recall; ii) Psychomotor Vigilance Task (PVT); iii) N-back (0- and 2-back); iv) Go/No-Go; v) Delayed Free Recall (see Supplementary Table 4 for details). After completing the cognitive test battery, participants rated their perceived performance and workload for the session using the NASA Task Load Index (NASA-TLX), which consisted of six 100-point scales assessing mental demand, physical demand, temporal demand, performance, effort, and frustration [15]. A summed score from four of six NASA-TLX items appears to most reliably measure a single overall workload [39].

As exploratory measures, fasting saliva and urine samples were collected for assessment of cortisol and melatonin respectively on the first morning (before study product consumption) and morning after last day of each intervention phase, using the Super SAL universal saliva collection kit and the BD Vacutainer® Urine Collection Kit.

Sample size, statistical analyses and compliance

The sample size calculation and statistical analysis were based on previous research by Kim *et al.*, who evaluated the effect of alpha-s1 casein hydrolysate on sleep disturbance [22]. The study aimed to recruit 45 participants, factoring a dropout rate of 20%. Linear mixed model analyses were conducted on the full analysis set, with baseline (average of the last 3 days of screening and last 3 days of washout for actigraphy variables, day before start of each intervention phase for the other study variables), treatment/control, and intervention phase as fixed effects, and participant as a random effect (based on the data availability and model fit, baseline was not included for KSS and ESS scores). Spearman correlation coefficient and partial Spearman correlation coefficient analyses were employed to determine the association between the study outcomes. Mediation analysis was conducted using a traditional regression approach, fitting three linear regressions to examine direct and indirect effects on the outcome variables. We conducted inferential tests on the indirect effect (Sobel test, and average mediated effect (indirect effect / variance of the mediator, Wald test). The significance of the indirect effect is indeed a key factor in confirming mediation.

Participants' compliance to product intake was verified by Food View by taking photos of empty IP packaging and IP beverage with the standardized evening meal before and after consumption. In addition, the evening meals were weighed with a weighing machine before and after consumption. The ePRO was also recording if product and/or standardized meal was not taken. Subjects were resupplied with investigational product between visits as required. Upon resupply, the investigator or his/her designee verified that investigational product intakes were correct and dosing information were recorded in the (e)CRFs. Participants' non-compliance was defined as either missed study product intake for at least three non-consecutive days or missed product intake for at least two consecutive days within each intervention phase.

Results

One out of 43 eligible participants withdrew after randomization before starting any intervention (Fig. 2). From those who completed the study, there were a total of 15 days of missed intake and 2 days of partial intake, resulting in an overall compliance rate of 98.55%. No significant differences were found in demographic characteristics based on the allocated intervention sequence (Supplementary Table 3). However, it was observed that the overall BMI was higher for participants who received the treatment in intervention phase 2. This difference in BMI is the result of the random allocation process and not indicative of concealment issue, as there were no differences observed in other characteristics (Supplementary Table 3).

Glycemic outcomes

The treatment condition reduced the 14-day average evening meal PPGR iAUC significantly compared to the control at 0–1h, 0–2h and 0–3h by 21% ($p < 0.001$), 18% ($p < 0.001$) and 11% ($p = 0.002$), respectively (Fig. 3). There was a significant reduction in the iCmax and increase in the time taken to reach Cmax by the treatment compared to the control (Table

1). During the sleeping period, treatment reduced the nocturnal glucose CV significantly by 0.58% ($p = 0.023$) compared to control (Table 1). The next morning, no significant difference between the treatment and control were observed for PPGR at breakfast (Table 1).

Sleep outcomes

There was a significant effect of treatment on SOL that resulted in a 14-day average reduction of 3.82 min compared to control ($p = 0.026$, 95% CI [− 7.17 to − 0.47]) (Fig. 4A). There was a trend for SE to be higher with treatment (0.8%, $p = 0.066$, 95% CI [− 0.05–1.65]) (Table 2). Additionally, under active treatment, participants spent 9.75 min less TIB (14-day average) compared to control ($p = 0.033$, 95% CI [− 18.69 to − 0.81]). No other actigraphy variables were significantly different between conditions (Table 2).

Self-reported SOL was significantly shorter (−3.09 min) under the treatment condition compared to the control ($p = 0.048$, 95% CI [− 6.2 to − 0.02]) (Fig. 4B). Participants also reported feeling significantly less sleepy (post wake KSS score − 0.17) under treatment compared to control ($p = 0.041$, 95% CI [− 0.33 to − 0.01]) (Fig. 4C). The treatment effect did not reach significance for the Epworth Sleepiness Scale (− 0.85, $p = 0.089$, 95% CI [− 1.84–0.13]).

Ordinal logistic regression models on Karolinska Sleep Dairy indicated significant effect of treatment on ease of falling asleep (odds ratio: 1.40, $p = 0.019$, CI [1.06–1.85]), fewer awakenings (odds ratio: 0.70, $p = 0.020$, CI [0.52–0.95], spending less time awake during period of sleep (odds ratio: 1.52, $p = 0.003$, CI [1.15–2.01]) compared to control.

Mood outcomes

Treatment effects were seen in daily mood scales the next morning, 30–60 min after awakening (Table 3). The POMS Vigor–Activity subscale score was significantly higher (0.8, $p = 0.038$, 95% CI [0.05 – 1.56]) under the treatment condition (6.63 ± 0.43) compared to the control (5.83 ± 0.41) (Fig. 5A). Total mood disturbance score was not significantly different ($p = 0.295$, 95% CI [−4.79 – 1.47]) between treatment (16.82 ± 1.52) and control (18.48 ± 1.42). Other POMS subscale scores were not significantly modulated by treatment. For BMIS, treatment (11.66 ± 0.32) was associated with significantly lower Negative–Relaxed subscale ($p = 0.003$, 95% CI [−0.67 – −0.14]) in comparison to control (12.06 ± 0.31) (Fig. 5B). The higher Overall Mood score for treatment vs control (2.61 ± 0.39 vs 2.30 ± 0.39) did not reach significance ($p = 0.082$, 95% CI [−0.04 – 0.67]).

Cognitive test battery outcomes

Treatment did not improve daytime PVT performance (averaged across all sessions at midpoint and endpoint) compared to control in terms of median reaction time (355.96 ± 5.12 ms vs 359.26 ± 5.12 ms; $p = 0.613$, 95% CI [− 16.15–9.56]), and lapses (5.05 ± 0.59 vs 5.50 ± 0.59; p=0.460, 95% CI [− 1.67–0.76]) (Table 4). There was also no significant difference in executive function (N-Back), declarative memory (Immediate and Delayed word recall), or response inhibition (Go/No-Go) tests (Table 4).

Participants' evaluation of their performance on the cognitive test battery also did not differ (NASA-TLX composite score; $p = 0.875$, 95% CI [−15.36–13.09]) between treatment (307.16 ± 7.93) and control (308.30 ± 7.93).

Association analysis

There was a consistent positive association between the CV of nocturnal glucose and the evening meal PPGR outcomes. The Spearman correlation between nocturnal glucose CV and the 3h-iAUC was $r = 0.19$ ($p < 0.001$) and remained significant after adjusting for the confounders using partial Spearman correlation ($r = 0.18$; $p < 0.001$). PPGR following the evening meal was also associated with the time taken to fall asleep, as SOL measured via actigraphy showed significant positive correlation with both 3h-iAUC ($r = 0.10$; $p < 0.001$) and iCmax ($r = 0.09$; $p = 0.002$). A relatively weak but significant correlation was observed between the nocturnal glucose CV and next-morning sleepiness reported via KSS ($r = 0.07$; $p = 0.041$). Lower sleepiness was in turn associated with better mood, as KSS was both negatively correlated with the POMS Vigor–Activity score ($r = -0.29$; $p < 0.001$) and positively correlated with the BMIS Negative–Relaxed score ($r = 0.21$; $p < 0.001$).

Mediation analysis

We evaluated whether the treatment affects SOL and sleep quality directly or indirectly through the PPGR (evening meal) and nocturnal glucose variation. There was both a direct effect of the treatment on SOL (81.5%; − 2.51 min), and a significant indirect mediation effect on SOL by the evening meal PPGR iCmax (18.5%; − 0.57 min), indicative of the partial mediation of the treatment effect on SOL through PPGR (Fig. 6A). The effect remained significant after normalization by the variability of the mediator (Sobel test $p = 0.038$, and average mediated effect Wald test statistic − 2.31, $p = 0.021$). When the PPGR 3h-iAUC was used as the mediator the direct effect of treatment on SOL remained significant (89%; − 2.66 min), but the indirect effect (11%; − 0.33 min) was not (Sobel test, $p = 0.084$). However, the average mediated effect (indirect effect divided by the variability of the mediator) was significant (Wald test statistic − 2.19, $p = 0.029$).

The treatment effect on next-morning KSS (total effect − 0.10) was not significantly mediated by nocturnal glucose CV (direct effect − 0.09; indirect effect − 0.01) (Fig. 6B) or SOL (direct effect − 0.11; indirect effect 0.00). In addition, PPGR iCmax (total effect − 0.51; indirect effect − 0.25; Sobel test $p < 0.001$; average mediated effect Wald test $p < 0.001$) significantly mediated the effect of treatment on the nocturnal glucose CV (Fig. 6C).

Salivary and urine markers

No significant differences were found in linear mixed models for morning salivary cortisol levels (− 0.064 mcg/dL; $p = 0.183$; 95% CI [− 0.16–0.03]) between treatment (0.47 ± 0.04 mcg/dL) and control (0.54 ± 0.04 mcg/dL) after 14-day consumption of respective study products. In addition, the ratio of melatonin-sulfate to creatinine, a marker of melatonin metabolism, also did not differ significantly (−2.86 ng/mg; $p = 0.242$; 95% CI [− 7.73–2.01]) between treatment (42.59 ± 4.39 ng/mg) and control (45.45 ± 4.42 ng/mg).

Discussion

In the current study, we demonstrated that supplementation of MLE combined with a natural source of tryptophan and other co-factors (B3, B6, Zn, Mg) at the evening meal lowered SOL both objectively and subjectively. Treatment resulted in reduced sleepiness, and improvement on the ‘relaxed’ and ‘vigor’ mood scales the next morning. In addition to the expected reduction in the evening meal’s PPGR by treatment, nocturnal glucose variability was also lowered. PPGR was found to be a significant mediator of the treatment effect on SOL, while nocturnal glucose variation was associated with subjective sleep quality ratings.

The objective SOL reduction (3.8 min) with treatment is relatively higher than nutraceutical sleep aids like valerian (1.3 min) [6], albeit lower than melatonin supplementation (5.5 min) [11]. However, as this result was over a two-week period, its functional relevance is promising, particularly when also aligned with subjective reduction in sleep latency and sleepiness. Meta-regression of the benefit of melatonin on sleep latency, suggest that a longer period of evaluation may yield larger benefit [11, 17, 28]. As commonly observed in patients with insomnia, participants overestimated their SOL compared to objective actigraphy assessment (41.5 vs 25.3 min) during the screening phase, here, the treatment effect in SOL reduction were similar in magnitude for both self-reports and objective assessments (3.1 min vs 3.8 min). In general, it’s less common to obtain a positive result for objectively measured sleep than subjectively measured sleep.

While it is beyond the scope of the current study to examine the mechanisms by which the treatment resulted in SOL reduction. The mediation analyses suggest that this benefit could be mediated by the lowering of the evening meal PPGR. Significant reductions were seen in both 3h-iAUC and iCmax, likely attributable to MLE, which was included in the treatment for lowering PPGR [13, 23, 31]. In addition, the reduction in Cmax (PPGR) also mediated the treatment effect on nocturnal glucose variation. To our knowledge, these findings are novel in demonstrating an interventional effect of PPGR on the SOL reduction. Tryptophan as a precursor to the production of the sleep regulating hormone melatonin, together with cofactors in this conversion process, B6, Zn and Mg, likely also contributed to reducing SOL. Consistent with the current study, a similar dose of tryptophan (in cereals) has previously been shown to significantly lower SOL [5]. Further research is warranted to elucidate the individual contributions, mechanisms of actions, and optimal dosage of the different ingredients in reducing SOL.

Compared to control, participants reported being less sleepy (KSS) on the following mornings. Next day sleepiness serves as an indicator of the impact of reduced sleep quality [1]. Prior studies have not targeted glycemia (postprandial and nocturnal) to improve sleep quality. Both postprandial glucose and nocturnal glucose variation have been shown to be associated with poor sleep quality, consistent with a possible role of glucose homeostasis in maintenance of good sleep quality. In the current study, we observed a significant reduction in both postprandial glucose and nocturnal glycemic variation following the treatment, compared to control. In addition, nocturnal glucose variation was positively associated with poor self-reported sleep quality. The recent review by St-Onge et al. [36] highlights the possibility that poor glycemic control may be particularly relevant during slow wave sleep or nonrapid eye movement sleep. [7, 12, 36]To date, nocturnal CV has been reported to be associated with poor sleep quality and next day mental functioning (such as attention) only in studies of people with T2DM [36]. Further evaluation is warranted to determine whether nocturnal blood glucose fluctuations are also associated with sleep quality in non-diabetic populations.

The treatment also resulted in positive mood the next morning, compared to control. Even though the glycemic effects of the treatment were no longer detected at breakfast, participants reported higher vigor, and being more relaxed, less negative. These results are consistent and of similar magnitude to the effects of other nutritional supplements such as soy lecithin [16], A recent systematic review highlighted the reciprocal relationship between daily sleep (sleep quality, sleep duration and SOL) and mood states (positive and negative) over the short term [21]. 15 out of 17 clinical trials, suggest a relationship between daily sleep and mood. In line with these clinical trials, we found similar associations between subjective sleep quality and mood ratings (negative association with POMS Vigor-Activity subscale, and positive association with BMIS Negative-Relaxed subscale). Therefore, the treatment benefits on mood could be partly attributable to the improvements in the sleep quality with the treatment.

The importance of sleep quality on cognition is corroborated by studies in young students [14] and community dwelling healthy adults [42], where subjective sleep quality was correlated to better sustained attention, emotional memory, visual working memory, as well as memory recall, and verbal fluency. In addition, a recently published meta-analysis also demonstrates an association between the objectively measured sleep parameters (sleep duration, continuity, and stages) with cognitive tests (global cognition, memory, executive function, attention and processing speed) [34]. In particular, lower SOL was associated with better executive functioning [34]. Despite statistically significant improvements in self-reported sleep quality with the treatment, this study did not detect significant benefits of the treatment on cognitive task performance.

This study had a randomized blinded cross-over trial design combining subjective and objective measurements, the latter using wearables for continuous sleep and glucose monitoring under natural living conditions. Although we could assess the impact of PPGR on sleep parameters using mediation analyses, the contribution of individual ingredients on sleep and mood could not be distinguished. Hence, further research is required to evaluate their respective contributions on sleep onset and sleep quality. The requirement for having evening meal within a fixed time window may have affected usual dinner and sleep timings for some individuals in study.

Conclusions

In persons with self-reported poor sleep, an evening meal supplement, designed to blunt postprandial glycemic response and enhance sleep propensity, had positive impact on sleep quality and next day positive mood. These findings support a novel approach to improve sleep and encourage further research using PPGR modulation as an intervention on utilizing this approach to improving sleep in persons with subjective sleep complaints.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of interest

ACM, VCC, PL, JJS, CC, LL, MH, MBL, EDL, JH, CD are employed by Société des Produits Nestlé SA. RT, LO, FPM, KM, GMTL, FMS were employed by Société des Produits Nestlé SA during the period of this work. MWLC received an honorarium for the time contributed to manuscript development. MPS is supported by R01HL142648; R01DK128154; R35HL155670.

Abbreviations

BMI	Body-mass index
BMIS	Brief mood introspection scale
CGM	Continuous glucose monitor
iAUC	Incremental glucose area under the curve
iCmax	Incremental maximum concentration
KSS	Karolinska sleepiness scale
MLE	Mulberry leaf extract
NASA-TLX	NASA task load index
PPGR	Postprandial glycemic response
POMS	Profile of mood states
PVT	Psychomotor vigilance task
SOL	Sleep onset latency
SE	Sleep efficiency
Tmax	Time to maximum concentration
TRB	Time to return to baseline

TST	Total sleep time
WASO	Wake after sleep onset

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Day	Screening 1 – 14	23	Intervention 1 24 – 37	Washout 38 – 64	65	Intervention 2 66 – 79	Follow-up 80 – 87
Primary Outcome							
Actigraphy	→		→			→	
Secondary Outcome							
CGM	→		→			→	
Sleep quality[a]	X X		→			→	
Mood outcomes[b]			→			→	
Cognition outcomes[c]		X	X X		X	X X	
Exploratory Outcome							
Biomarkers[d]			X	X		X	X

Fig. 1.

Overview of study visits and home procedures, Solid arrows indicate continuous measurements of the outcomes. X indicates single time point assessments. [a]Epworth Sleepiness Scale, Karolinska Sleepiness scale, [b]Profile Of the Mood States, Brief Mood Introspection Scale, [c]Psychomotor Vigilance Task, Go/No-Go, N-back, [d]Urine (melatonin metabolite) and saliva (cortisol)

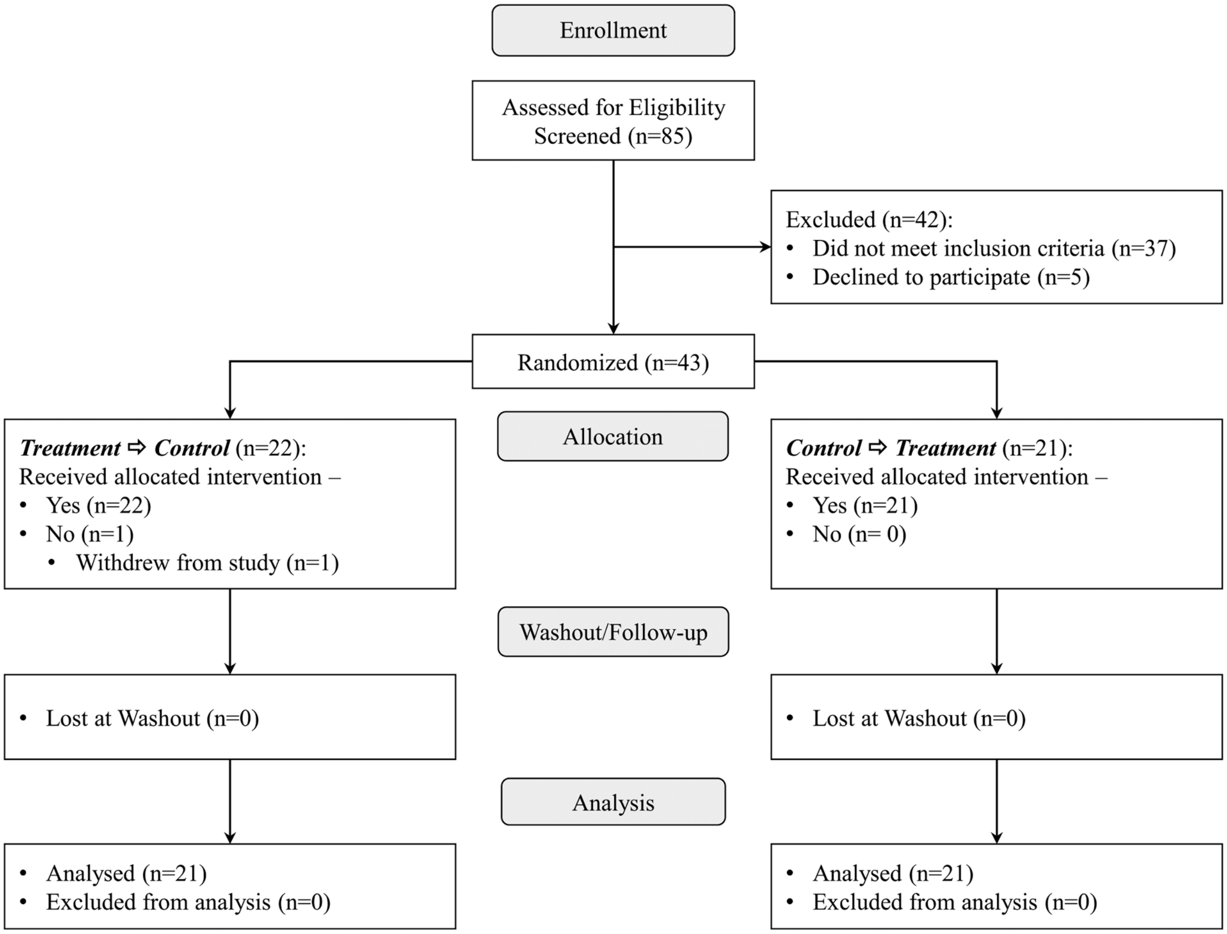

Fig. 2.
CONSORT study flow diagram

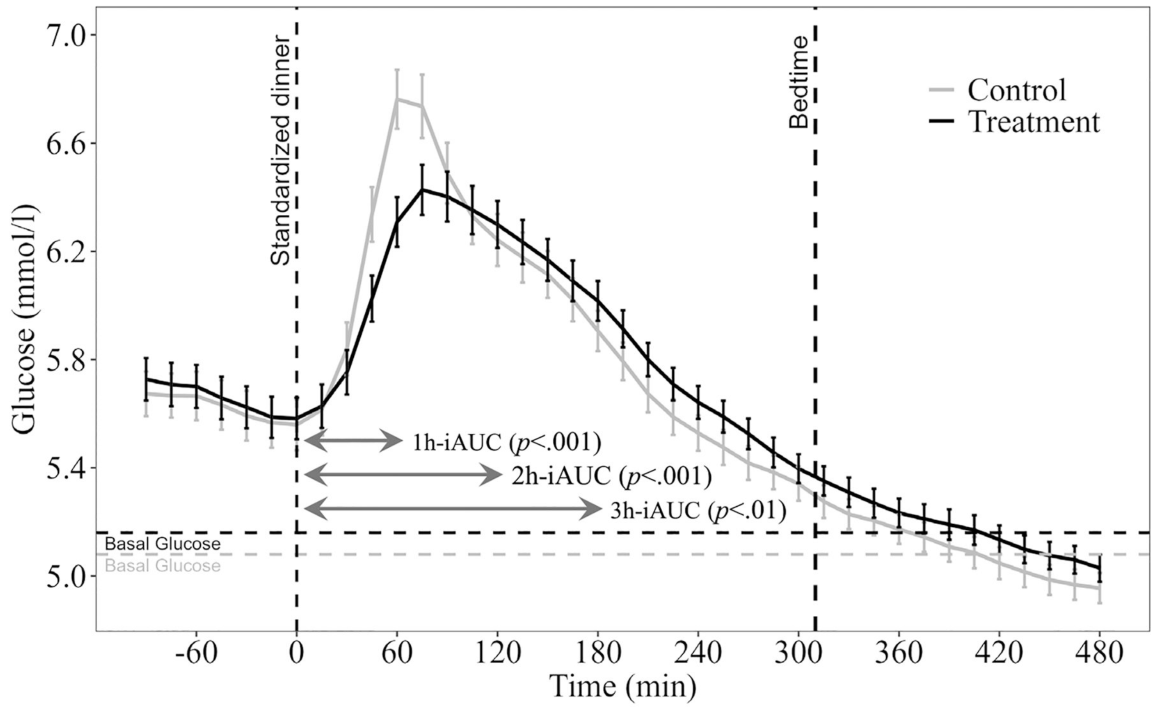

Fig. 3.

Effects of study products on postprandial glucose response to standardized evening meal. Curves show least square mean value ± SE of 14-day average postprandial glucose response to standardized evening meal, relative to meal start time. The p-values show significance of differences between treatment and control for incremental area under the curve (iAUC) from meal start to 1, 2, and 3 hours later

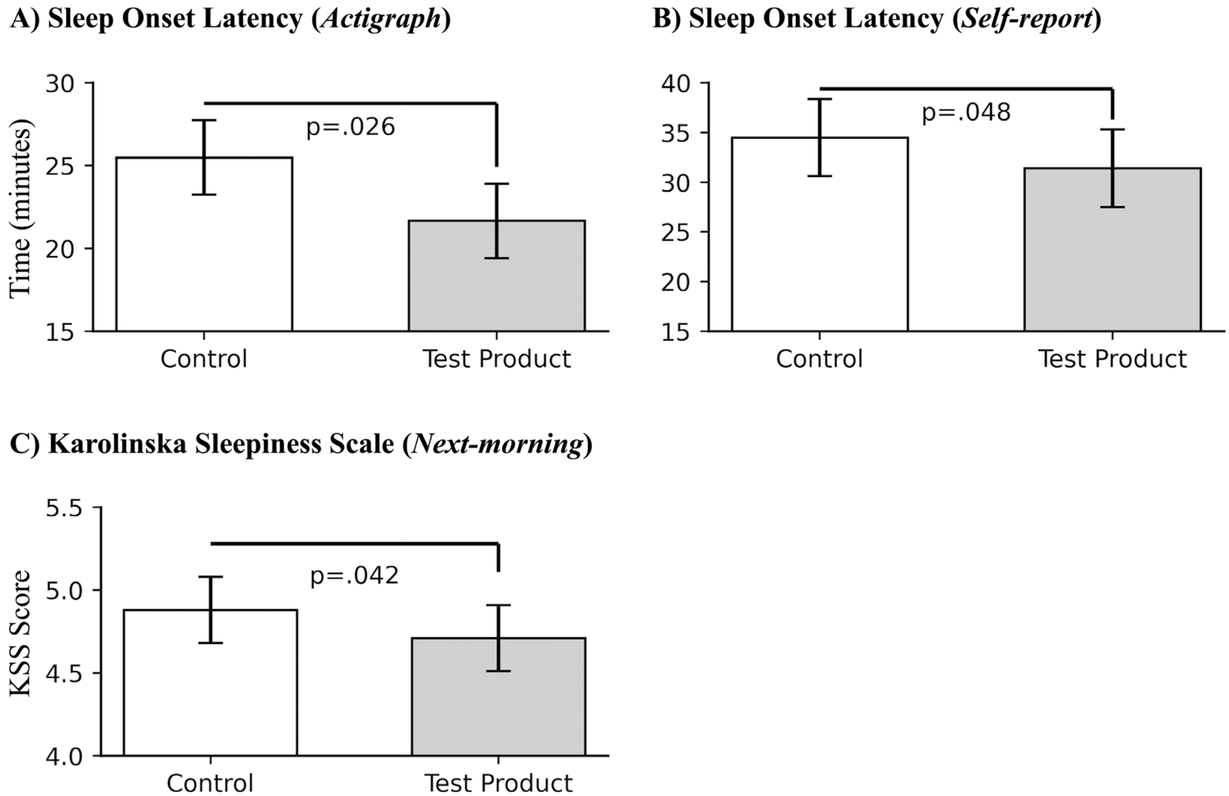

Fig. 4.

Effects of study products on sleep outcome measures. Bar charts represent least square mean ± SE. The p-values show significance of differences between Treatment and Control

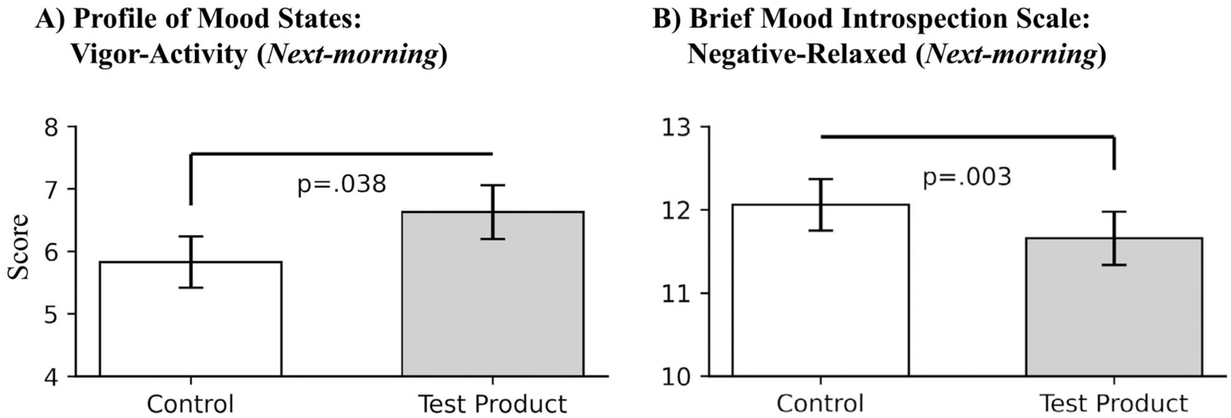

Fig. 5.

Effects of study products on next-morning mood scales. Bar charts represent least square mean ± SE. The p-values show significance of differences between Treatment and Control

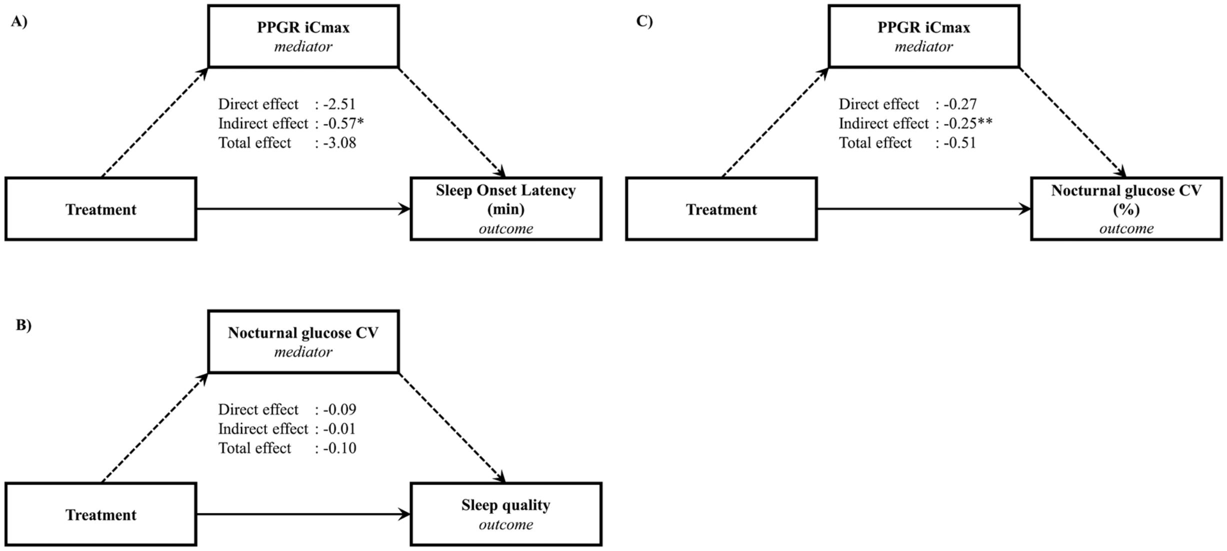

Fig. 6.

Mediation effects of postprandial glucose and nocturnal glucose variation on sleep onset and sleep quality. Direct, indirect and total effects on the outcome variables are derived from the linear regression models. Significant indirect mediation effects: *p-value < 0.05; **p-value < 0.01

Table 1

Effect of study products on postprandial (dinner and breakfast) and nocturnal glucose outcomes

Measures	Factor	Treatment	Control	*p*
Postprandial glucose (Evening meal)	1h-iAUC (mmol/L*min)	32.75 ± 2.39	41.44 ± 2.39	**<0.001**
	2h-iAUC (mmol/L*min)	101.99 ± 6.14	124.69 ± 6.13	**<0.001**
	3h-iAUC (mmol/L*min)	163.95 ± 8.83	183.90 ± 8.81	**0.002**
	iCmax (mmol/L)	1.88 ± 0.09	2.24 ± 0.09	**<0.001**
	Tmax (min)	96.54 ± 2.43	84.50 ± 2.48	**<0.001**
	TRB (min)	167.05 ± 6.67	153.47 ± 6.69	0.065
Nocturnal glucose	CV (%)	8.50 ± 0.33	9.08 ± 0.33	**0.023**
	Mean	5.11 ± 0.06	5.19 ± 0.06	**0.006**
	Sd	0.47 ± 0.02	0.44 ± 0.02	0.066
Postprandial glucose (Next-day breakfast)	1h-iAUC (mmol/L*min)	49.98 ± 3.43	50.64 ± 3.45	0.769
	2h-iAUC (mmol/L*min)	101.38 ± 7.63	104.08 ± 7.65	0.510
	3h-iAUC (mmol/L*min)	134.11 ± 9.26	134.02 ± 9.28	0.987
	iCmax (mmol/L)	1.99 ± 0.11	2.00 ± 0.12	0.867
	Tmax (min)	69.83 ± 2.96	68.40 ± 3.01	0.626

Values shown are 14-day average least square mean ± SE (n=42)

iAUC incremental area under the curve, *iCmax* maximum concentration, *Tmax* time to reach maximum concentration, *TRB* time to return to baseline, *CV* coefficient of variation, *Sd* Standard deviation

The p-values show significance of linear mixed model tests adjusted for covariates between Treatment and Control

Table 2

Effects of study products on sleep outcomes

Measure	Factor	Screening	Treatment	Control	*p*
Actigraphy (*Actiwatch Spectrum Plus*)	SE (%)	80.18 ± 0.69	81.87 ± 0.68	81.07 ± 0.69	0.066
	SOL (min)	25.26 ± 2.14	21.67 ± 2.25	25.49 ± 2.26	**0.026**
	TIB (min)	468.18± 6.81	453.27 ± 5.51	463.02 ± 5.54	**0.033**
	TST (min)	376.3 ± 6.76	369.73 ± 4.86	375.19 ± 4.89	0.186
	WASO (min)	47.35 ± 2.39	44.86 ± 2.34	44.70 ± 2.35	0.906
	Rise (min)	19.27 ± 1.73	16.71 ± 1.30	17.86 ± 1.32	0.350
Self- report (*Karolinska Sleep Diary*)	SOL (min)	41.45 ± 7.21	31.39 ± 3.91	34.48 ± 3.90	**0.048**
	TST (min)	475.53 ± 40.36	448.05 ± 11.77	433.88 ± 11.77	0.395

Values for screening are 14-day average mean ± SE (n=42). Values for treatment and control are 14-day covariate-adjusted least square mean ± SE from linear mixed models

SE sleep efficiency, *SOL* sleep onset latency, *TIB* time in bed, *TST* total sleep time, *WASO* wake after sleep onset

The p-values show significance of linear mixed model tests between treatment and control

Table 3

Effects of study products on mood

Measure	Factor	Treatment	Control	*p*
30–60 min Before Bed-time				
Brief Mood Introspection Scale	Pleasant-Unpleasant	41.43 ± 0.62	40.84 ± 0.62	**0.014**
	Arousal-Calm	24.43 ± 0.38	24.45 ± 0.38	0.907
	Positive-Tired	15.14 ± 0.30	14.95 ± 0.30	0.147
	Negative-Relaxed	11.83 ± 0.34	12.06 ± 0.34	0.053
	Overall Mood	2.68 ± 0.40	2.39 ± 0.40	0.057
30–60 min After Awakening				
Brief Mood Introspection Scale	Pleasant-Unpleasant	42.37 ± 0.78	41.88 ± 0.78	0.123
	Arousal-Calm	25.15 ± 0.34	25.3 ± 0.34	0.374
	Positive-Tired	16.14 ± 0.38	16.07 ± 0.38	0.706
	Negative-Relaxed	11.66 ± 0.32	12.06 ± 0.31	**0.003**
	Overall Mood	2.61 ± 0.39	2.30 ± 0.39	0.082
Profile of Mood States	Anger-Hostility	3.12 ± 0.29	3.03 ± 0.28	0.761
	Confusion-Bewilderment	4.54 ± 0.42	4.88 ± 0.40	0.341
	Depression-Dejection	2.71 ± 0.36	2.57 ± 0.34	0.664
	Fatigue-Inertia	8.12 ± 0.48	8.90 ± 0.44	0.141
	Tension-Anxiety	4.86 ± 0.48	5.04 ± 0.45	0.633
	Vigor-Activity	6.63 ± 0.43	5.83 ± 0.41	**0.038**
	Friendliness	8.92 ± 0.41	8.05 ± 0.39	**0.036**
	Total Mood Disturbance	16.82 ± 1.52	18.48 ± 1.42	0.295

Values shown are 14-day average least square mean ± SE (n=42). Values for treatment and control are 14-day covariate-adjusted least square mean ± SE from linear mixed models

The p-values show significance of linear mixed model tests between treatment and control

Table 4

Effects of study products on cognitive performances (multi-session average)

Cognitive Test	Outcome	Treatment	Control	*p*
Word Recall	Immediate Recall	8.54 ± 0.34	8.24 ± 0.34	0.448
	Delayed Recall	6.26 ± 0.39	6.52 ± 0.39	0.590
Psychomotor Vigilance Task	Median Reaction Time	355.96 ± 5.12	359.26 ± 5.12	0.613
	Lapses	5.05 ± 0.59	5.50 ± 0.59	0.460
	Anticipatory Errors	2.81 ± 0.27	2.72 ± 0.27	0.679
N-Back (0-Back)	Hit	6.72 ± 0.13	6.52 ± 0.13	0.263
	Miss	1.16 ± 0.14	1.28 ± 0.14	0.452
	Correct Reject	22.79 ± 0.27	23.1 ± 0.27	0.370
	False Alarm	0.45 ± 0.06	0.39 ± 0.06	0.492
N-Back (2-Back)	Hit	6.67 ± 0.13	6.69 ± 0.13	0.906
	Miss	1.17 ± 0.11	1.14 ± 0.11	0.784
	Correct Reject	22.22 ± 0.33	22.12 ± 0.33	0.801
	False Alarm	1.09 ± 0.18	1.06 ± 0.18	0.798
Go / No-go	Hit	174.99 ± 2.20	172.09 ± 2.20	0.242
	Miss	5.01 ± 2.20	7.91 ± 2.20	0.242
	Correct Reject	51.44 ± 0.47	50.90 ± 0.47	0.311
	False Alarm	8.56 ± 0.47	9.10 ± 0.47	0.311

Values shown are multi-session least square mean ± SE (n=42)

The p-values show significance of linear mixed model tests adjusted for co-variates between treatment and control