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The Efficacy of Prosomnial™ Compared to a Synthetic Comparator for Melatonin Absorption and a Pilot for Sleep Efficacy—A Randomised, Double-Blind, Active-Controlled, Cross-Over Study

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Abstract

Background: Recent findings have identified pistachios as a rich source of plant-derived melatonin, prompting the development of Prosomnial™, a unique natural melatonin supplement. This randomised, double-blind, active-controlled, cross-over pilot study aimed to evaluate the absorption and short-term effects on sleep of Prosomnial™ compared to synthetic melatonin. **Methods:** Twenty-six healthy adults (mean age 31.2 ± 7.5 years) with self-reported difficulty initiating sleep participated. Each received both formulations in a cross-over design with a 14-day washout. Pharmacokinetic parameters (C_{max}, T_{max}, $AUC_{0\text{-}2h}$) were assessed after a single dose. Sleep outcomes, including latency, duration, quality, and feeling rested, were recorded using validated daily sleep diaries over 7-day supplementation periods. **Results:** Prosomnial™ was shown to have comparable absorption to synthetic melatonin in $AUC_{0\text{-}2h}$, C_{max}, and T_{max}. Both interventions improved subjective sleep outcomes compared to baseline. Prosomnial™ significantly reduced sleep latency and improved total sleep time, sleep quality, and morning restfulness. No treatment-related adverse events were reported. **Conclusion:** Prosomnial™ demonstrated comparable melatonin absorption and sleep-promoting effects to synthetic melatonin, supporting its use as a natural alternative. Further studies with larger cohorts and objective sleep measures are recommended to confirm these findings and explore whether other plant-based compounds unique to Prosomnial™ may contribute additional effects.

Keywords

Prosomnial™, Synthetic Melatonin, Melatonin, Absorption, Sleep Latency, Total Sleep Time

1. Introduction

A large proportion of the population suffers from insufficient or poor-quality sleep. Prevalence estimates of insomnia symptoms range between 10% and 30% in the adult population, with certain subgroups, such as older adults, females, and individuals with comorbid physical or mental health conditions, exhibiting even higher rates [1]-[3]. As sleep health continues to gain prominence in both clinical and consumer wellness settings, there is a growing demand for effective, safe, and accessible interventions [4].

Melatonin plays a critical role in promoting the onset of sleep. Melatonin regulates circadian rhythm and responds to diverse environmental stimuli in the plant kingdom. This versatile molecule acts as an indolamine hormone primarily synthesized by the pineal gland [5]. It is commonly utilized as a drug or dietary supplement for regulating sleep patterns and circadian rhythms, with its benefits also extending beyond sleep management [6].

Sleep is a finely tuned process driven by intricate neurochemical interactions within the brain's sleep-promoting and arousal centres [7]. At the heart of this regulation lies melatonin, influencing various body systems and physiological processes that, in turn, induce immediate physiological responses such as fatigue and long-term health outcomes [8]-[10]. Melatonin exerts this influence by activating highly sensitive receptors MT1 and MT2 in response to changes in the light-dark cycles, directly affecting the synchronisation of circadian rhythm, sleep-wake cycles, and the duration and stages of sleep experienced [11]-[13].

While both MT1 and MT2 receptors are activated by melatonin, they have been reported to elicit distinct physiological responses due to unique expression patterns, signalling pathways, and pharmacological properties across various body organs. Activation of MT1 receptors reduces nerve cell activity in the suprachiasmatic nucleus (SCN), promoting sleep initiation, while MT2 receptor activation regulates the synchronisation of the circadian rhythm in response to environmental cues, such as light-dark cycles [12] [14]. The synergistic action of these receptors in regulating sleep timing, duration, and circadian rhythms underscores their potential as valuable pharmacological targets aimed at optimising sleep management and quality.

Clinical studies have extensively explored the administration routes of melatonin, primarily focusing on oral and intravenous methods in healthy volunteers [15]-[17]. However, the findings regarding its pharmacokinetics have shown inconsistency [18] [19]. Studies have shown oral melatonin follows first-order kinetics, with absorption averaging around 15%, although it can vary significantly among individuals [15] [19]. Various factors, including age, caffeine consumption, smoking, oral contraceptive use, feeding status, and concurrent medications like fluvoxamine, influence its pharmacokinetics [19]. Despite this, it maintains a consistent half-life of approximately 45 minutes, with the peak concentration in the bloodstream occurring within 1 hour following oral dosage [19].

Studies have identified pistachios as a rich source of melatonin, with certain cultivars of pistachios containing high levels of melatonin, exceeding 12 μg/g [20]. Additionally, among other nuts, pistachios exhibited significantly higher levels of phytomelatonin, with some varieties containing up to 223 μg/g [21]. These findings highlight pistachio-derived melatonin foods as a potential therapeutic option.

Prosomnial™ is a unique botanical formulation containing plant-derived melatonin extracted from pistachios. Prosomnial™ offers a non-synthetic option for a more natural approach to sleep support. Reports suggest meaningful improvements in sleep outcomes following use of Prosomnial™. However, scientific validation comparing its efficacy to synthetic melatonin through clinical testing has yet to be conducted.

This randomised, double-blind, active-controlled, cross-over study aimed to evaluate the effects of 100 mg of Prosomnial™ (providing 1 mg of natural melatonin) on absorption and key sleep parameters compared to an equivalent dose of synthetic melatonin. We hypothesised that Prosomnial™ would provide a comparable absorption profile and comparable improvements in sleep parameters from a natural alternative to synthetic melatonin.

2. Methods

This was a randomised, double-blind, active-controlled, cross-over pilot study conducted in Brisbane, Australia, between October 2024 and February 2025. Randomisation was conducted using random allocation software (https://www.sealedenvelope.com/) by someone not involved in the conduct of the study. Product was randomised in two blocks of 13 for even distribution of product. All investigational products were packed in identical containers and labelled identically except for the product number (based on the randomisation code). The product was uniquely numbered, and as each participant was enrolled, they were given the next sequentially numbered product. Neither the trial participants nor the investigators conducting the study or the statistician analysing had access to the product allocation sequence. Unless medically necessary, only upon the completion of all sample analysis (including statistics) was the randomisation code revealed to investigators.

This study had ethics approval from The University of Queensland Human Research Ethics (2024/HE001744), with all participants providing written informed consent prior to starting the study. The primary objective of this study was to assess the absorption of melatonin from two different sources. A secondary objective was to conduct a pilot study on the effect each product may have on acute sleep disturbance.

Statistical power was calculated to detect equivalence in baseline-corrected total melatonin absorption based on area under the curve (AUC) between groups within a ±10% margin. To achieve 90% power with a significance level of 0.05, 18 participants are required to complete each product arm. To account for potential dropouts and ensure adequate power at study completion, 26 participants were recruited. Participants were eligible if they were over 18 years of age and generally healthy, with a body mass index (BMI) between 18.5 and 29.9 kg/m^2. Participants were required to provide informed consent and report difficulty falling asleep, defined as taking more than 20 minutes to do so. They had to agree not to participate in any other clinical trials during the study period, and to maintain their current diet and exercise habits without changes to frequency or intensity. Additionally, participants were required to refrain from taking any other medications, supplements, or foods intended for sleep, stress, or anxiety, aside from the test product. Female participants were required to be using a prescribed form of birth control, such as an oral contraceptive.

Participants were excluded if they used medications, supplements, CBD, or aromatherapy for sleep, stress, or anxiety; had diagnosed sleep disorders (e.g., insomnia, restless leg syndrome, sleep apnoea); or had serious or unstable medical conditions such as mood or neurological disorders, kidney, liver, or heart disease, diabetes, or thyroid dysfunction. Additional exclusions included current malignancy (excluding basal cell carcinoma), recent cancer treatment (within 2 years), use of anticoagulants (e.g., Warfarin, Heparin, low-dose aspirin), smoking, drug use, or high alcohol intake (>14 drinks/week). Pregnant or lactating women, those with relevant allergies, recent or concurrent clinical trial participation, or any condition deemed unsuitable by the investigator were also excluded. A serious illness was defined as a condition that carries a risk of mortality, negatively impacts quality of life and daily function, and/or is burdensome in symptoms and/or treatments. An unstable illness was classified as any illness that is currently not being treated with a stable dose (>3 months with no change in dose) of medication or is fluctuating in severity.

Once enrolled, participants were randomised to receive one of two active melatonin gummies—Prosomnial™ or a synthetic comparator (**Figure 1**). Prosomnial™ is a proprietary, plant-based melatonin extract derived from pistachio, a rich natural source of melatonin. Prosomnial™ is standardised to contain 1% melatonin, with each 100 mg gummy delivering 1 mg of melatonin. The synthetic melatonin gummy used as a comparator was a common over-the-counter melatonin supplement, formulated to deliver 1 mg of melatonin per gummy. Both gummy matrices included standard food-grade excipients and flavouring agents, serving primarily as a palatable delivery vehicle without additional bioactive compounds. Both supplements were independently assayed and found to contain 1 mg of melatonin per dose.

Enrolled participants were required to complete several procedures during the study period, including three in-person visits to the study clinic. Initial screening was conducted remotely via telephone, followed by an in-person screening and the signing of consent. Consenting participants then completed a three-day sleep diary (Baseline 1) immediately before their second visit. Visit 2 involved an absorption assessment of the investigational product conducted in-clinic.

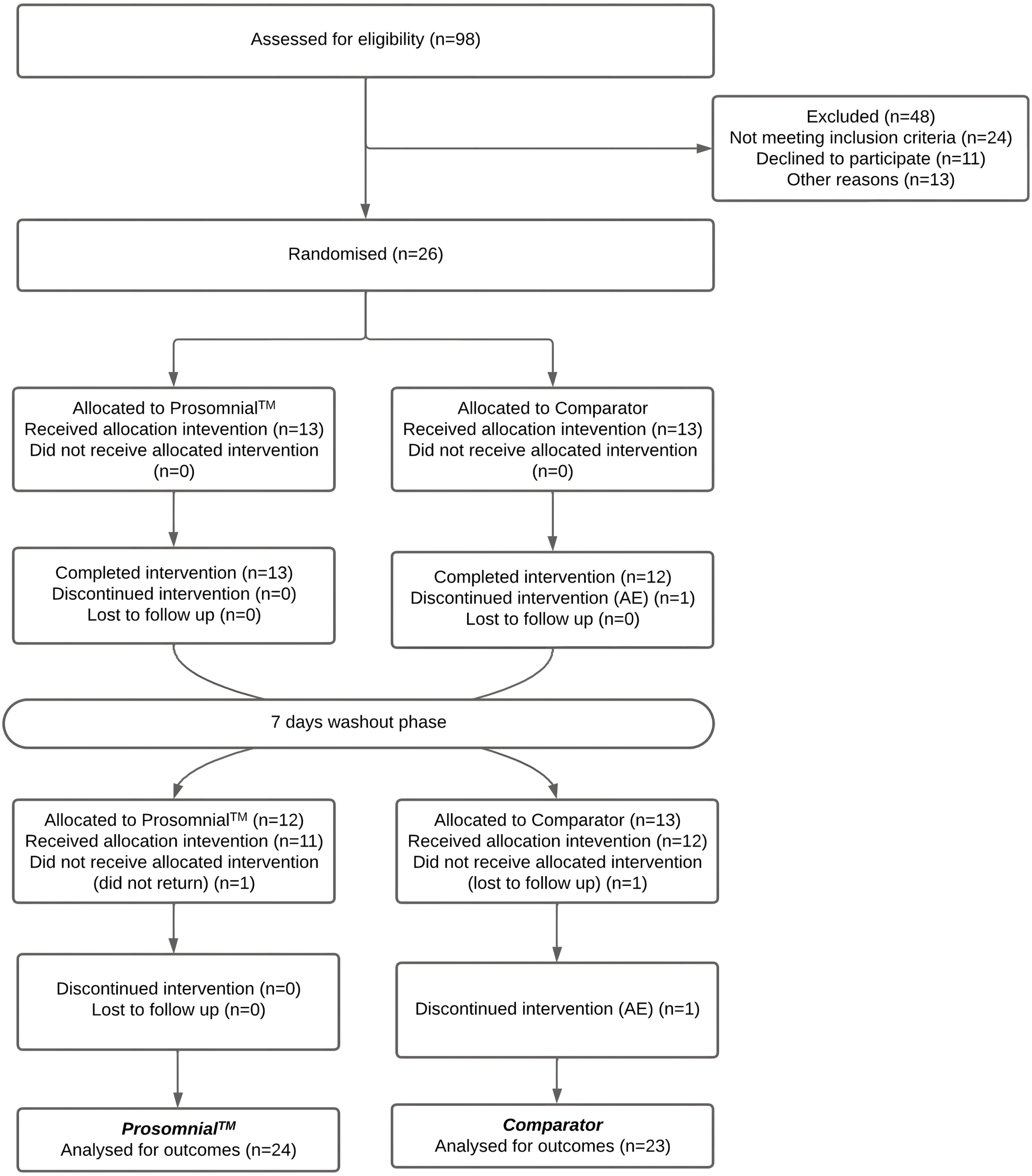

Figure 1. CONSORT flow diagram. Flow diagram of the progress through the two arms of a randomised, cross-over trial with two interventions.

During visit 2, participants were required to arrive fasted and provide a fasting blood sample via a cannula placed in the antecubital fossa. Once a baseline blood sample was obtained, participants consumed their allocated investigational product. Further blood samples were then collected from the cannula at 10, 20, 30, 45, and 60 minutes post-ingestion. A standardized breakfast meal was provided to participants following the consumption of their investigational product.

The absorption study visit was immediately followed by a seven-day supplementation phase. During this phase, participants were required to consume their allocated investigational product daily and record their sleep via a daily sleep diary as per their baseline sleep assessment. Participants were instructed to consume one gummy nightly, one hour before bedtime.

After 7 days, participants completed a washout period of 14 days, during which a second three-day sleep diary (Baseline 2) was completed before their third visit. Visit 3 included a second absorption assessment identical to Visit 2. A final seven-day supplementation phase identical to the first, but with the alternative product, followed Visit 3. At the conclusion of the 7 days of supplementation, a final phone interview was conducted to ensure no adverse events were experienced.

Adverse events were monitored throughout the study period via participant self-reporting during clinic visits and daily diaries. All reported events were recorded, assessed for severity and relationship to the intervention, and reviewed by the study investigators.

Outcome measures included melatonin absorption [area under the curve, maximum concentration reached (C_{max}), time to maximum concentration (T_{max})], sleep latency (time taken to fall asleep), total sleep time, sleep quality, and feeling of being rested upon waking. All subjective outcomes were assessed using a validated daily sleep diary completed each morning during the intervention periods.

Any participant who completed at least 75% of one arm of the study was included in the statistical analysis of the study. Any participant who consumed at least one dose of a trial product was included in the safety analysis. Statistical analysis was performed using paired t-tests or Wilcoxon signed-rank tests as appropriate to compare outcomes between baseline, Prosomnial™, and synthetic melatonin phases. Pharmacokinetic parameters (C_{max}, T_{max}, AUC) were derived using non-compartmental analysis and compared between formulations. No interim analysis was planned or conducted in this study. The study was only to be stopped for safety reasons (*i.e.*, adverse events occurring that determined the product to be unsafe).

3. Results

3.1. Demographics

Twenty-six participants (19 females, 7 males) were enrolled in this study, with twenty-four participants completing the PK portion for product 1 (Prosomnial™) and twenty-three completing product 2 (Comparator) (**Figure 1**). Of the participants completing the PK portion, 21 completed the 7-day sleep diary for both product 1 (Prosomnial™) and product 2 (Comparator). As this was a cross-over study design, there was no significant difference between group demographics for either product (Table 1 and Table 2). All data were analysed per protocol, with missing data being excluded from analysis.

Table 1. Participant demographics.

	Prosomnial™ (n = 24)	Comparator (n = 23)
Height (m)	1.70 ± 0.06	1.70 ± 0.06
Weight (kg)	72.8 ± 11.5	73.5 ± 10.9
BMI (kg/m^2)	25.2 ± 3.0	25.2 ± 2.6
Waist circumference (cm)	84.2 ± 8.5	85.1 ± 9.5
Hip circumference (cm)	100.2 ± 6.9	101.7 ± 6.9

Table 2. Participant vitals at each visit.

	Prosomnial™ (n = 24)	Comparator (n = 23)
Systolic BP (mmHg)	118.8 ± 12.3	113.8 ± 11.9
Diastolic BP (mmHg)	74.1 ± 10.2	72.6 ± 8.7
Pulse (beats per minute)	73.2 ± 8.1	70.4 ± 8.8
O2 saturation (%)	97.4 ± 1.3	98.3 ± 0.8

All participants adhered to the protocol, with two participants (one in the Prosomnial™ group and one in the placebo group) withdrawing due to adverse events unrelated to the trial or trial product.

3.2. Plasma Melatonin

Overall, there was no significant difference between groups for melatonin absorption over 2 hours ($p = 0.39$, Table 3, Figure 2).

Table 3. Melatonin absorption data over 2 hours. Values are calculated from each participant's specific AUC, T_{max}, and C_{max}. Data presented are mean.

	Prosomnial™ (n = 24)	Comparator (n = 23)	p-Value
AUC_{0-2} (pg·h/mL)	5994	7425	0.39
T_{max} (min)	75	60	0.93
C_{max} (pg/mL)	64.02	95.28	0.20

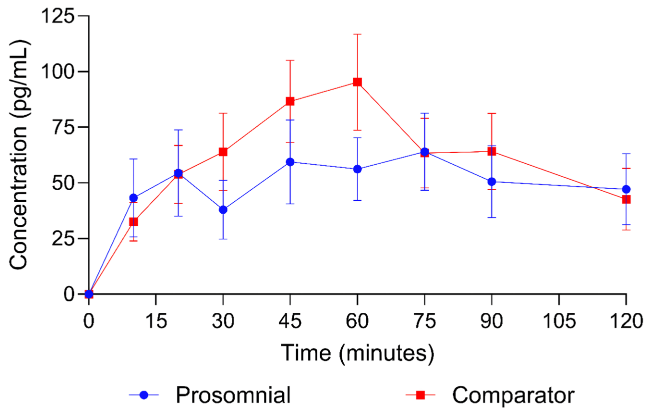

Figure 2. Melatonin absorption over 2 hours. Data presented are mean ± SEM.

3.3. Sleep Diary

There was no significant difference between groups at baseline (Table 4). When the relative change from baseline for each group was factored, there was no significant difference between groups for any sleep efficacy measure.

When within-group comparison was made, the Prosomnial™ group had a significant change in sleep latency, total sleep time, sleep quality, and feeling rested compared to baseline, whereas the comparator Melatonin had a significant change in awakenings and feeling rested compared to their baseline.

Table 4. Sleep diary data.

	Prosomnial™ Baseline (n = 21)	Prosomnial™ After 7 days (n = 21)	Comparator Baseline (n = 21)	Comparator after 7 days (n = 21)
How long did it take you to fall asleep? (minutes)	38.0 ± 22.0	28.3 ± 23.4*	34.8 ± 20.8	28.3 ± 50.6
How many times did you wake up, not counting the final awakening?	1.8 ± 0.9	1.4 ± 1.0	1.8 ± 1.1	1.2 ± 0.6*
In total, how long did these awakenings last (minutes)?	27.1 ± 27.6	26.9 ± 29.2	37.6 ± 34.7	25.3 ± 21.4
In total, how long did you sleep? (minutes)	380.9 ± 65.7	405.5 ± 46.8*	378.9 ± 64.8	404.8 ± 74.3
How would you rate the quality of your sleep?	3.0 ± 0.8	3.4 ± 0.6*	3.0 ± 0.7	3.4 ± 0.7
How rested or refreshed did you feel when you woke up for the day?	2.7 ± 0.7	3.0 ± 0.6*	2.6 ± 0.8	3.1 ± 0.9*
How many times did you nap or doze?	0.3 ± 0.4	0.2 ± 0.4	0.3 ± 0.4	0.3 ± 0.3
In total, how long did you nap or doze? (Minutes)	25.8 ± 25.4	21.5 ± 79.7	34.6 ± 47.8	20.4 ± 25.8

*Significant difference from baseline.

4. Discussion

This randomised, double-blind, active-controlled crossover study was designed to compare the absorption and short-term sleep-related effects of two melatonin formulations: Prosomnial™, a natural plant-derived melatonin gummy (1 mg melatonin), and a synthetic melatonin gummy (1 mg melatonin). Both products were delivered in an identical format (gummy) and melatonin dosage (1 mg), allowing for a direct comparison between natural and synthetic sources. The findings of this study indicate that melatonin absorption from Prosomnial™ was comparable to that of synthetic melatonin, with no statistically significant difference in key absorption parameters over two hours, including area under the curve (AUC), time to maximum plasma concentration (T_{max}), and maximum plasma concentration (C_{max}).

These results are consistent with prior absorption studies that have demonstrated wide inter-individual variability in melatonin absorption regardless of source or format [19] [22]. For example, Harpsoe *et al.* (2015) found Cmax values ranging between 30 - 100 pg/mL following a 1 - 2 mg oral melatonin dose, with Tmax occurring between 20 and 90 minutes across subjects [19]. Similarly, a 2012 study by Waldhauser *et al.* reported Cmax levels between 35 - 117 pg/mL with 1 mg of synthetic melatonin, closely aligning with the current findings [22].

The equivalence in Cmax between natural and synthetic melatonin is particularly noteworthy given the potential appeal of plant-derived alternatives. Consumers increasingly seek naturally sourced supplements, particularly those aligned with vegetarian, halal, gluten-free, soy-free, and non-petrochemical-derived preferences—all criteria met by the Prosomnial™ formulation. While both products in this study adhered to these dietary preferences, Prosomnial™ may appeal more strongly to individuals with concerns surrounding synthetic compounds, or petrochemical or animal-derived products.

Subjective sleep outcomes assessed using daily sleep diaries showed that Prosomnial™ significantly improved sleep latency, total sleep time, sleep quality, and feeling rested compared to baseline. The synthetic melatonin product also led to improvements, particularly in the number of awakenings and feelings of being rested. Importantly, no significant difference was observed between the two products when changes from baseline were compared, further supporting their equivalence. These findings echo a recent systematic review by Ferracioli-Oda *et al.* (2013), which concluded that exogenous melatonin modestly improves sleep latency and duration in both primary and secondary insomnia [23].

Despite the comparable findings between groups, several limitations must be acknowledged. First, the sample size was relatively small (n = 26), which may have limited the ability to detect subtle differences between the two formulations, especially in pharmacokinetic outcomes where variability is inherently high. Second, the study used a two-hour window for absorption analysis. While this is reasonable given the short half-life of melatonin (~30 - 60 minutes), longer monitoring periods might capture additional differences in extended absorption or clearance dynamics. Third, sleep outcomes were based on subjective self-reporting through sleep diaries. Although validated, these measures are inherently less precise than objective measures like polysomnography or actigraphy. Lastly, while the crossover design strengthens internal validity by allowing within-subject comparisons, potential carryover effects cannot be entirely ruled out despite the 14-day washout.

Another important limitation is the omission of a placebo control group. While the crossover design with two active comparators allowed for a direct head-to-head comparison of natural versus synthetic melatonin, it did not enable clear differentiation between true treatment effects and improvements attributable to placebo responses. This consideration is especially relevant for sleep outcomes, which are inherently subjective and highly susceptible to expectancy effects. Placebo interventions have been shown to meaningfully influence perceived sleep latency, sleep quality, and restfulness, even in the absence of active pharmacological agents [24] [25]. By excluding a placebo condition, this pilot study was not designed to quantify the magnitude of any placebo contribution to the observed changes, limiting the strength of causal inferences regarding efficacy. The decision to prioritize an active comparator design was based on the primary objective of assessing pharmacokinetic equivalence between natural and synthetic melatonin, with subjective sleep measures included as a secondary, exploratory outcome. Future studies incorporating a placebo arm alongside natural and synthetic melatonin would therefore be essential to fully delineate treatment-specific effects from placebo-driven improvements in sleep parameters.

Despite the use of a randomized and double-blinded design, some potential biases cannot be entirely excluded. While blinding was maintained throughout, complete masking of taste, texture, or subtle differences in gummies cannot be guaranteed. Additionally, there was no placebo arm, which may have limited the ability to isolate treatment effects from placebo-related improvements in sleep quality.

The inclusion and exclusion criteria, while appropriate for safety and internal validity, limit the generalizability of the findings. Participants were healthy adults with mild sleep disturbances, excluding individuals with diagnosed sleep disorders, comorbid conditions, or those using medications/supplements that affect sleep. As such, the results may not be applicable to some populations.

From an absorption perspective, synthetic and plant-derived melatonin are structurally identical, and the present study supports the hypothesis that their absorption and efficacy are comparable. However, emerging discussions highlight the need for future studies to examine whether other plant-based compounds present in extracts used to produce natural melatonin may contribute synergistic effects or indirectly influence absorption [26]. Beyond absorption, consumer preference, perceived safety, and sustainability are key differentiators. Natural melatonin may be viewed as more "holistic" or aligned with clean-label trends, which could enhance adherence or acceptability in certain populations.

5. Conclusion

In summary, this study demonstrates that a single 1 mg dose of plant-derived melatonin (Prosomnial™) is absorbed similarly to an equivalent dose of synthetic melatonin and is equally effective in improving sleep parameters over a short-term supplementation period. These findings offer early support for the use of natural melatonin as a viable alternative to conventional synthetic formulations. Future research involving larger sample sizes, longer intervention durations, and objective sleep measurement techniques is warranted to confirm these findings and further explore the potential benefits of plant-derived melatonin.

Ethics Approval and Consent to Participate

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by The University of Queensland Human Research Ethics Committee B, approval number 2024/HE001744, approval date: 30 September 2024. All participants provided written informed consent prior to participating in the study.

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are not publicly available due to intellectual property rights but are available from the corresponding author upon reasonable request.

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Authors' Contributions

Conceptualization, A.R. and D.B.; Methodology, A.R. and D.B.; Software, A.R. and D.B.; Validation, A.R. and D.B.; Formal Analysis, A.R.; Investigation, A.R. and D.B.; Resources, A.R. and D.B.; Data Curation, A.R. and D.B.; Writing—Original Draft Preparation, D.B.; Writing—Review & Editing, A.R. and D.B.; Visualization, A.R. and D.B.; Supervision, A.R. and D.B.; Project Administration, A.R.; Funding Acquisition, A.R. and D.B.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

SCN—suprachiasmatic nucleus

AUC—area under the curve

BMI—body mass index

C_{max}—maximum concentration reached

T_{max}—time to maximum concentration