Role of Oral Melatonin in the Treatment of Melasma: A Comparative Randomized Controlled Study

Nirinthya Tanaprasertphol, Boonyagorn Keattisaksri, Sunatra Nitayavardhana, and Premjit Juntongjin*

Chulabhorn International College of Medicine, Thammasat university, Pathum Thani, Thailand
*Corresponding author, Email: premjitvp@yahoo.com

Abstract

Melasma is a chronic pigmentary disorder with multifactorial pathogenesis. Oxidative stress has emerged as a significant factor in the pathogenesis of melasma, contributing to the overproduction of melanin and subsequent tissue damage. Melatonin, recognized for its potent antioxidant properties and ability to scavenge free radicals, has shown therapeutic potential in managing melasma by mitigating oxidative stress and enhancing skin repair mechanisms. This study aims to evaluate the efficacy of oral melatonin compared to a placebo in melasma patients through a prospective, randomized, placebo-controlled, evaluator-blinded clinical trial. An independent t-test was employed for statistical analysis. A total of 40 adult patients with a confirmed diagnosis were enrolled and randomized into two equal groups, with 20 patients per group. The Melatonin group received 2 mg of oral melatonin once daily, administered one hour before bedtime, while the Placebo group received an identical placebo capsule at the same time. The primary outcome measure was the reduction in pigmentation, assessed using the Modified Melasma Area and Severity Index (mMASI) at baseline and after four weeks of treatment. All participants were instructed to apply a broad-spectrum sunscreen (SPF50, PA+++) each morning and a cream base before bedtime throughout the study period. In the Melatonin group, the total mMASI score for both cheeks significantly decreased from 5.90 ± 3.06 at baseline to 5.01 ± 2.53 at week 4. The mean reduction was 0.89 points (95% CI: -1.52, -0.25; p-value = 0.009). However, no statistically significant difference was observed between the melatonin and placebo groups. Minimal side effects were reported. Nonetheless, melatonin may represent a potential therapeutic agent for melasma, offering pigmentation reduction with minimal side effects. *Limitation:* The study was limited by its small sample size and short duration.

Keywords**:** *melasma, melatonin*

1. Introduction

Melasma is a chronic pigmentary disorder characterized by the presence of irregular brown patches on areas of skin exposed to sunlight, including the forehead, cheeks, upper lip, and chin. Its development is influenced by genetic predisposition, hormonal fluctuations, and environmental triggers such as ultraviolet (UV) radiation and visible light exposure. Conventional therapeutic approaches such as hydroquinone, chemical peels, and laser treatments often demonstrate limited efficacy and may be associated with potential adverse effects.

Recent studies suggest that oxidative stress plays a significant role in the pathogenesis of melasma, as the imbalance between free radicals and antioxidant defense mechanisms contributes to excessive melanin synthesis and subsequent tissue damage. Melatonin, known for its potent antioxidant capacity, has exhibited promising effects in reducing oxidative stress, modulating melanogenesis, and enhancing skin repair processes.

Choubey et al., (2017) investigated the role of oxidative stress in patients with melasma by assessing and comparing serum levels of malondialdehyde, superoxide dismutase, and blood glutathione. The study found that these oxidative stress biomarkers were significantly elevated in melasma patients compared to the control group, thereby supporting the involvement of oxidative stress in the etiopathogenesis of melasma.

Similarly, Sarkar et al., (2020) evaluated the association between oxidative stress and serum melatonin levels in melasma patients. The findings revealed that oxidative stress levels were elevated, and a

melatonin deficiency was also observed among the affected individuals. However, no significant correlation was identified between oxidative stress levels and the clinical severity of the condition.

Melatonin, a potent antioxidant, functions as a robust free radical scavenger and stimulates the activity of other antioxidant enzymes. It has shown potential in the treatment of melasma by reducing oxidative stress, inhibiting the synthesis of tyrosinase and inducible nitric oxide synthase (iNOS), and enhancing skin repair mechanisms. Clinical trial findings by Malankar et al., (2023) indicated that the topical application of melatonin can lead to significant improvement in melasma severity, accompanied by minimal side effects.

Hamadi et al., (2009) investigated the efficacy of a 5% topical melatonin cream, administered both as monotherapy and in combination with sunscreen and an oral melatonin (3 mg/day), for the treatment of melasma. Their study demonstrated a significant reduction in modified Melasma Area and Severity Index (mMASI) scores compared to baseline, thereby demonstrating the clinical efficacy and safety of oral melatonin at doses up to 3 mg/day over a 90-day period. Only mild, transient drowsiness was observed as a side effect.

More recently, Holanda et al., (2024) evaluated the therapeutic efficacy of 5-mg oral melatonin in a double-blind, placebo-controlled trial conducted over an eight-week period involving 50 women with moderate-to-severe facial melasma. The findings revealed that the participants in the melatonin group exhibited a 22% reduction in mMASI scores, compared to a 12% reduction in the placebo group, with statistically significant superiority favoring melatonin ($p = 0.014$).

Although melatonin has demonstrated potential in treating melasma due to its antioxidant properties, studies evaluating its efficacy in this context remain limited. Furthermore, there are currently no established guidelines regarding the optimal dosage or titration strategy for melatonin in the management of melasma. While some investigations have employed higher doses, ranging from 3 mg to 5 mg per day, standardized recommendations are currently lacking.

Circadin® is a prolonged-release melatonin formulation (2 mg/tablet) and is currently the only melatonin product approved by the Thai Food and Drug Administration (FDA) for the treatment of primary insomnia. The recommended dose is one tablet (2 mg) administered orally before bedtime. This dosage is associated with a favorable safety profile, with common adverse effects, such as drowsiness and dizziness, typically limited to the initial phase of treatment and resolving spontaneously. The 2 mg prolonged-release formulation was selected for this study due to its well-established safety and pharmacokinetic properties, which support sustained antioxidant activity particularly relevant in the management of chronic and relapsing conditions such as melasma.

Wade et al., (2010) conducted a six-month randomized, placebo-controlled trial in patients with primary insomnia and reported that adverse events in the melatonin group were generally mild and comparable to those observed in the placebo group. Similarly, Lemoine et al., (2007) demonstrated that prolonged-release melatonin significantly improved sleep quality and morning alertness in patients aged 55 years and older, with a low incidence of side effects and no evidence of withdrawal symptoms following treatment discontinuation.

Most prior studies on melatonin and melasma have focused on topical formulations, combinations with other oral medications, immediate-release preparations, or higher doses. Therefore, this study aims to evaluate the efficacy and safety of a 2 mg prolonged-release melatonin formulation in comparison with placebo, in conjunction with standard topical sunscreen and cream base applied by all participants. The findings will help determine whether prolonged-release melatonin represents a viable alternative treatment option for melasma, offering therapeutic benefit with fewer adverse effects than conventional therapies.

2. Objectives

1) To evaluate the efficacy of oral melatonin, compared to oral placebo in the treatment of melasma.
2) To evaluate the adverse effects associated with oral melatonin in the treatment of melasma.

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3. Materials and Methods

This study was a prospective, randomized, placebo-controlled, evaluator-blinded trial designed to assess the efficacy and safety of oral melatonin in the treatment of melasma. A total of 40 adult patients, clinically diagnosed with melasma, were enrolled and randomly allocated into two equal groups (melatonin and placebo) using a computer-generated simple randomization sequence to ensure unbiased allocation. The randomization codes were concealed until the point of the assignment.

Inclusion criteria

1) Patients aged 18 years or older.
2) Volunteers who are willing to participate.
3) Patients clinically diagnosed with melasma.

Exclusion criteria

1) Any use of topical treatments, including topical hydroquinone, whitening agents, retinoids, and steroids on the affected area within 4 weeks prior to enrollment.
2) Any use of oral tranexamic acid and supplements within 3 months prior to study enrollment.
3) History of laser treatment, dermabrasion, or energy-based device within 6 months of study enrollment.
4) History of botulinum toxin and filler injection, or chemical peeling, within 3 months prior to study enrollment.
5) Pregnant or lactating women
6) History of allergy to oral melatonin.
7) Patients who are unable to comply with the follow-up schedule according to the study protocol.

All participants were instructed to take one tablet of their assigned intervention either 2 mg prolonged-release melatonin [Circadin®] or an identical placebo orally, once daily, one hour before bedtime for four weeks. **To minimize external confounding factors**, all participants were also required to apply a broad-spectrum sunscreen (SPF 50, PA+++) each morning and a standardized cream base each night throughout the study period. **Compliance with sunscreen application was monitored via self-reported daily usage logs**, which were reviewed during each weekly follow-up visit.

Outcome Measures and Statistical Analysis

The primary outcome was the change in pigmentation severity, evaluated using the Modified Melasma Area and Severity Index (mMASI) at baseline and after four weeks. An **independent samples t-test** was employed to compare mMASI scores between the two groups, while **paired t-tests** were applied for within-group comparisons (baseline vs. week 4). A p-value of less than 0.05 was considered statistically significant. All statistical analyses were conducted using SPSS software.

4. Results and Discussion

4.1 Results

Baseline patient characteristics are summarized in Table 1. A total of 40 patients, including 38 females and 2 males, were equally randomized into two groups. The mean age was 47.6 ± 10.33 in the melatonin group and 45.30 ± 6.67 years in the placebo group. A positive family history of melasma was reported in 15 patients (75%) in both the melatonin group and the placebo group. Fitzpatrick skin type III was predominant, observed in 14 patients (70%) in the melatonin group and 16 patients (80%) in the placebo group. The most common melasma pattern was the mixed type, found in 15 patients (75%) in the melatonin group and 18 patients (90%) in the placebo group. Baseline total mMASI scores, presented in Table 2. were 5.90 ± 3.06 in the melatonin group and 5.45 ± 3.00 in the placebo group. No statistically significant differences in baseline characteristics were observed between the groups ($p>0.1$).

Table 1 Baseline characteristics of participants

Characteristics	Melatonin (n = 20)	Placebo (n = 20)	p-value
Gender			
Female	19 (95.0)	19 (95.0)	1.000
Male	1 (5.0)	1 (5.0)	
Age (years)	47.6 ± 10.33	45.30 ± 6.67	0.408
Height (cm)	158.18 ± 5.44	159.55 ± 5.40	0.427
Body weight (kg)	64.46 ± 11.81	66.83 ± 18.29	0.630
Body mass index (kg/m²)	25.77 ± 4.58	26.07 ± 6.10	0.862
Duration of melasma (years)	4 (2 - 10)	4 (3 - 5)	1.000
Family history of melasma			
Yes	15 (75.0)	15 (75.0)	1.000
No	5 (25.0)	4 (20.0)	
Unknown	0 (0.0)	1 (5.0)	
Occupation			
Housekeeper	4 (20.0)	3 (15.0)	0.570
Nurse	2 (10.0)	2 (10.0)	
Freelance	0 (0.0)	0 (0.0)	
Government/State enterprise employee	3 (15.0)	6 (30.0)	
Private sector employee	6 (30.0)	5 (25.0)	
Entrepreneur	0 (0.0)	2 (10.0)	
Others	5 (25.0)	2 (10.0)	
Outdoor activities or work (per day)			
0-4 hours	16 (80.0)	17 (85.0)	1.000
4-8 hours	4 (20.0)	3 (15.0)	
Sunscreen (per week)			
Every day	13 (65.0)	13 (65.0)	1.000
5-6 days	3 (15.0)	3 (15.0)	
3-4 days	1 (5.0)	1 (5.0)	
1-2 days	0 (0.0)	1 (5.0)	
Never used	3 (15.0)	2 (10.0)	
Fitzpatrick Scale			
II	1 (5.0)	0 (0.0)	0.716
III	14 (70.0)	16 (80.0)	
IV	5 (25.0)	4 (20.0)	
Types of melasma			
Epidermal	5 (25.0)	2 (10.0)	0.407
Mixed	15 (75.0)	18 (90.0)	

Data are presented as number (%), mean ± standard deviation or median (interquartile range).
P-value corresponds to [a]Independent samples t-test, [b]Mann-Whitney U test, [c]Chi-square test or [d]Fisher's exact test.

The primary outcomes of the study are presented in Table 2, which compares mMASI (modified melasma area severity index) at baseline and 4 weeks, both within and between groups, by using an independent paired t-test.

Table 2 Comparison of modified Melasma Area and Severity Index

mMASI	Melatonin (n = 20)	Placebo (n = 20)	Mean difference (95%CI)	p-value†
	Mean ± SD	Mean ± SD		
Right side of melasma				
AREA (0-6)				
Baseline	4.10 ± 1.25	4.10 ± 1.52	0.00 (-0.89, 0.89)	1.000
4 weeks	3.90 ± 1.29	4.05 ± 1.50	-0.15 (-1.05, 0.75)	0.737
Mean difference	-0.20 (-0.39, -0.01)	-0.05 (-0.16, 0.06)		
p-value	0.042*	0.330		
Darkness (0-4)				
Baseline	2.40 ± 0.75	2.25 ± 0.64	0.15 (-0.30, 0.60)	0.501
4 weeks	2.15 ± 0.75	2.25 ± 0.64	-0.10 (-0.54, 0.34)	0.651
Mean difference	-0.25 (-0.46, -0.04)	0.00 (-0.15, 0.15)		
p-value	0.021*	1.000		
mMASI (Each area)				
Baseline	3.06 ± 1.51	2.99 ± 1.60	0.08 (-0.92, 1.07)	0.879
4 weeks	2.58 ± 1.36	2.97 ± 1.64	-0.39 (-1.35, 0.57)	0.418
Mean difference	-0.48 (-0.8, -0.16)	-0.02 (-0.23, 0.20)		
p-value	0.005*	0.886		
Left side of melasma				
AREA (0-6)				
Baseline	3.65 ± 1.53	3.55 ± 1.23	0.10 (-0.79, 0.99)	0.821
4 weeks	3.65 ± 1.46	3.65 ± 1.18	0.00 (-0.85, 0.85)	1.000
Mean difference	0.00 (-0.22, 0.22)	0.10 (-0.16, 0.36)		
p-value	1.000	0.428		
Darkness (0-4)				
Baseline	2.40 ± 0.75	2.10 ± 0.79	0.30 (-0.19, 0.79)	0.226
4 weeks	2.15 ± 0.67	2.10 ± 0.72	0.05 (-0.40, 0.50)	0.821
Mean difference	-0.25 (-0.46, -0.04)	0.00 (-0.22, 0.22)		
p-value	0.021*	1.000		
mMASI (Each area)				
Baseline	2.84 ± 1.65	2.46 ± 1.46	0.38 (-0.62, 1.37)	0.452
4 weeks	2.43 ± 1.25	2.45 ± 1.36	-0.02 (-0.85, 0.82)	0.971
Mean difference	-0.41 (-0.80, -0.01)	-0.02 (-0.27, 0.24)		
p-value	0.044*	0.904		
Total mMASI				
Baseline	5.90 ± 3.06	5.45 ± 3.00	0.45 (-1.49, 2.39)	0.642
4 weeks	5.01 ± 2.53	5.42 ± 2.88	-0.41 (-2.14, 1.33)	0.639
Mean difference	-0.89 (-1.52, -0.25)	-0.03 (-0.38, 0.32)		
p-value	0.009*	0.859		

†Independent samples t-test
* Significant at p-value < 0.05

Table 2 presents a comparison of the Modified Melasma Area and Severity Index (mMASI) scores between the melatonin and placebo groups, assessed at baseline and after four weeks of treatment. At baseline, the mean total mMASI score for melasma lesions on both cheeks was 5.90 ± 3.06 in the melatonin group and 5.45 ± 3.00 in the placebo group. Following four weeks of intervention, the mean scores were 5.01 ± 2.53 and 5.42 ± 2.88, respectively. No statistically significant difference in mMASI scores was observed between the two groups at baseline or at the four-week follow-up ($p > 0.05$).

The within-group analysis revealed a statistically significant reduction in mMASI scores in the melatonin group, with the mean total score decreasing by 0.89 points from baseline (95% CI: -1.52 to -0.25; $p = 0.009$). In contrast, the placebo group showed a negligible reduction of 0.03 points (95% CI: -0.38 to 0.32; $p = 0.859$), which was not statistically significant. These results suggest that, while melatonin demonstrated a significant within-group effect, it did not result in a statistically superior outcome compared to placebo over the four-week study period.

No serious adverse effects were reported in either group. One case of somnolence and one case of dizziness occurred in the melatonin group, and one case of somnolence was reported in the placebo group. All participants completed the 4-week study duration, reflecting high treatment adherence and protocol compliance.

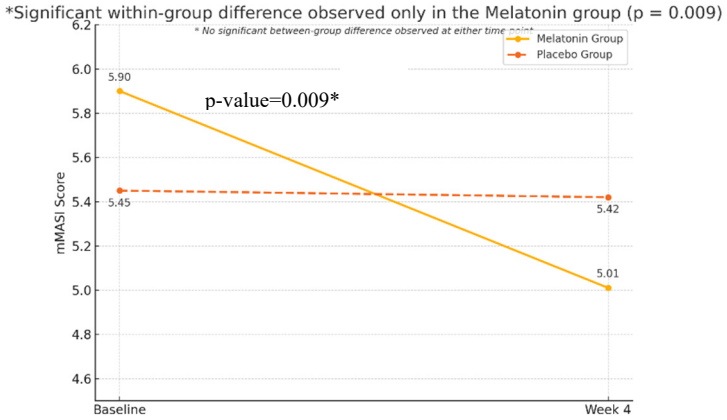

Figure 1 Comparative analysis of the modified Melasma area and severity index (mMASI) at baseline and after 4 weeks in the melatonin and placebo groups

Figure 1 illustrates the changes in the Modified Melasma Area and Severity Index (mMASI) scores over time between the melatonin and the placebo group at baseline and after four weeks of treatment. At baseline, both groups exhibit similar mMASI scores, approximately around 6. Over the four-week period, the melatonin group demonstrates a slight reduction in mMASI scores, whereas the placebo group maintains a relatively stable score. Statistical analysis indicates a significant difference between baseline and week 4 in the melatonin group, with a reported p-value of 0.009.

4.2 Discussion

Melasma is a chronic hyperpigmentary skin disorder with multifactorial etiologies, involving genetic, hormonal, environmental, and oxidative stress-related factors. Various treatment modalities, including topical agents, oral medications, and laser therapies, have been employed to manage melasma. However, each treatment presents advantages and limitations, making the management of melasma a highly challenging task. Emerging evidence points to a significant correlation between oxidative stress and the pathogenesis of melasma. Increased levels of reactive oxygen species (ROS) and dysfunctional antioxidant defense mechanisms contribute to melanocyte hyperactivity and excessive melanin production. Studies have

shown that melasma patients exhibit an imbalance between oxidative stress and antioxidant systems, including lower levels of endogenous antioxidants like melatonin

Circadin SR, a prolonged-release melatonin formulation, is currently the only product approved by the FDA for the treatment of primary insomnia for durations up to six months. It has demonstrated both short- and long-term efficacy and safety, particularly among elderly patients, with minimal side effects. Despite its established benefits in managing sleep disorders, its potential therapeutic role in dermatological conditions such as melasma remains largely underexplored (Wade et al., 2010).

To explore this potential, the present study evaluated the efficacy of 2 mg prolonged-release melatonin in the treatment of melasma over a four-week period. Given that sun exposure is a major aggravating factor in melasma, all participants were instructed to apply a broad-spectrum sunscreen (SPF 50, PA+++) each morning and a standardized cream base each night throughout the study period. This standardized photoprotection was implemented to minimize external confounding variables and maintain consistency across both treatment groups.

Our findings align with previous studies supporting the role of melatonin in the management of pigmentation disorders. For instance, Holanda et al., (2024) conducted a double-blind, placebo-controlled trial in 50 women with moderate-to-severe melasma and observed that an eight-week regimen of 5 mg oral melatonin resulted in a 22% reduction in mMASI scores, compared to a 12% reduction in the placebo group ($p = 0.014$). Likewise, Malankar et al., (2023) reported enhanced outcomes when 3 mg of oral melatonin was combined with tranexamic acid (TXA) over a three-month period, with only mild and transient drowsiness as a side effect. Additionally, Hamadi et al., (2009) demonstrated that combining oral melatonin with sunscreen resulted in greater clinical efficacy than either approach alone.

In line with these findings, the present study showed a statistically significant reduction in total Modified Melasma Area and Severity Index (mMASI) score within the melatonin group. Following four weeks of treatment, the mean mMASI score declined by an average of 0.89 points from baseline (95% CI: -1.52 to -0.25; $p = 0.009$). However, this improvement did not yield a statistically significant difference when compared with the placebo group.

The relatively stable mMASI scores in the placebo group may be attributed to the consistent application of sunscreen and the standardized cream base, both of which are essential components of melasma management. Sunscreen, in particular, remains a cornerstone in preventing exacerbation of pigmentation caused by ultraviolet and visible light. Thus, the improvements observed in both groups, though statistically significant only in the melatonin group, may represent a combined effect of photoprotection and the study interventions. These findings underscore the need for cautious interpretation of within-group changes and further highlight the importance of longer-duration studies to better distinguish the specific effects of melatonin from those of routine supportive care.

With regard to safety, only one case of somnolence and one case of dizziness was reported in the melatonin group, reinforcing its favorable safety profile. Unlike previous studies that employed higher melatonin doses or topical formulations, our study uniquely examined the effects of a 2 mg prolonged-release melatonin product (Circadin®). This approach offers insight into the potential benefits of sustained antioxidant delivery in melasma, with good patient adherence as evidenced by the high completion rate over the study period.

Nonetheless, certain limitations should be acknowledged. The relatively short intervention period of four weeks may have been inadequate to fully assess the long-term therapeutic effects of melatonin, especially given the chronic and recurrent nature of melasma. Moreover, the limited sample size may have reduced the statistical power to detect significant between-group differences. Future studies are encouraged to recruit larger and more diverse cohorts and extend treatment durations to 12–16 weeks or longer. Additionally, although this study employed a 2 mg dose of melatonin, the optimal therapeutic dose of melatonin for melasma remains undetermined. Prior studies suggest that higher doses (e.g., 3–5 mg) may confer enhanced clinical efficacy and warrant further investment.

5. Conclusion

Oral melatonin exhibits considerable promise as an adjunctive or alternative therapeutic option for melasma, demonstrating significant within-group reductions in pigmentation severity alongside a favorable safety profile. Its potent antioxidant properties offer a novel pathway for treatment, particularly suitable for patients who prefer safer and better-tolerated interventions. However, although melatonin significantly reduced pigmentation within individuals over the short term, this study did not reveal a statistically significant difference between the melatonin and placebo groups. This implies that the observed benefits may be partially attributable to concurrent photoprotection or placebo effects. Therefore, further well-controlled clinical trials involving larger sample sizes, extended treatment durations, and optimized dosing strategies are warranted to validate melatonin's therapeutic superiority and clarify its role in the clinical management of melasma.

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