

TOPICAL 0.5% MELATONIN CREAM VERSUS 3% TRANEXAMIC ACID CREAM FOR MELASMA: A RANDOMIZED DOUBLE-BLIND SPLIT-FACE STUDY

Zaw Latt YE NAUNG^{1*} and Anon PAICHITROJJANA¹

1 School of Anti-Aging and Regenerative Medicine, Mae Fah Luang University,
Thailand *Corresponding author: Zaw Latt Ye Naung

ARTICLE HISTOR

Received: 1 August 2026

Revised: 12 August 2026

Published: 28 August 2026

ABSTRACT

Melasma is a chronic acquired hyperpigmentation disorder for which safe, sustained treatment remains challenging. This study compared the efficacy and safety of topical 0.5% melatonin cream with topical 3% tranexamic acid cream. In this prospective, randomized, double-blind, intra-individual split-face study, 20 adults with melasma were enrolled and 18 completed 12 weeks of treatment. Participants applied melatonin to one randomized hemiface and tranexamic acid to the contralateral hemiface twice daily; all used broad-spectrum sunscreen. Hemifacial modified Melasma Area and Severity Index (mMASI) scores and Mexameter melanin indices were assessed at baseline and Weeks 4, 8, and 12. Satisfaction and adverse effects were also evaluated. Mean hemifacial mMASI decreased from 3.11 to 2.73 with melatonin and from 3.11 to 2.51 with tranexamic acid (within-treatment $p < 0.001$ for both). Mean melanin index decreased from 254.8 to 242.2 and 236.3, respectively (within-treatment $p < 0.001$ for both). Between-treatment differences at individual visits were not statistically significant. Satisfaction scores of 4 or 5 (ranging from 1-lowest satisfaction to 5-highest satisfaction) were reported for 11 of 18 melatonin-treated sides and 12 of 18 tranexamic acid-treated sides ($p = 1.000$). Both preparations were well tolerated, with no moderate or severe adverse events. Topical 0.5% melatonin and 3% tranexamic acid both improved melasma over 12 weeks. Since there was no statistically significant difference in efficacy between the two creams, melatonin may represent a well-tolerated alternative deserving further evaluation in larger trials.

Keywords: Melasma; Melatonin; Tranexamic Acid; Split-Face Study; Hyperpigmentation

CITATION INFORMATION: Ye Naung, Z., & Paichitrojjan, A. (2026). Topical 0.5% Melatonin Cream Versus 3% Tranexamic Acid Cream for Melasma: A Randomized Double-Blind Split-Face Study. *Procedia of Multidisciplinary Research*, 4(8), 54.

INTRODUCTION

Melasma is a chronic, acquired disorder of facial hyperpigmentation characterized by irregular brown-to-gray macules and patches on sun-exposed skin. It is particularly common in women and people with Fitzpatrick skin phototypes III-V, although it can affect any sex or phototype. Although benign, melasma can impair self-esteem, social functioning, and quality of life. Its recurrent course and sensitivity to ultraviolet and visible light make durable control difficult (Ogbechie-Godec & Elbuluk, 2017).

The pathogenesis of melasma is multifactorial. Genetic susceptibility, ultraviolet radiation, hormonal influences, oxidative stress, inflammation, vascular proliferation, basement-membrane damage, mast-cell activity, and fibroblast senescence interact to maintain a hypermelanogenic cutaneous environment (Espósito et al., 2022; Kwon et al., 2016). Accordingly, treatment generally combines rigorous photoprotection with topical depigmenting therapy and, in selected cases, oral or procedural interventions. Hydroquinone and triple-combination therapy remain important options, but irritation, post-inflammatory hyperpigmentation, exogenous ochronosis, recurrence, and concern about prolonged use encourage evaluation of non-hydroquinone alternatives (Cassiano et al., 2022).

Tranexamic acid, a synthetic lysine analogue, reduces ultraviolet-induced melanogenesis by inhibiting plasminogen activation and downstream arachidonic-acid and prostaglandin signaling. Topical concentrations of approximately 2%-5% have shown benefit with generally favorable local tolerability (Zhang et al., 2018). Melatonin is an endogenous indoleamine with antioxidant, anti-inflammatory, and photoprotective activity in the skin. It can scavenge reactive oxygen species, support DNA repair, and modulate melanogenic signaling (Fischer et al., 2008). Lower serum melatonin and increased oxidative stress have been observed in people with melasma, providing a biological rationale for therapeutic investigation (Sarkar et al., 2020).

Direct clinical comparisons of topical melatonin and topical tranexamic acid are limited. This study therefore compared twice-daily 0.5% melatonin cream with 3% tranexamic acid cream over 12 weeks using a randomized, double-blind, split-face design. The primary objective was to compare changes in hemifacial mMASI. Secondary objectives were to compare Mexameter melanin indices, patient satisfaction, and adverse effects.

LITERATURE REVIEW

Melasma Pathogenesis and Therapeutic Challenges

Melasma is now understood as more than an isolated increase in epidermal melanin. Histologic and molecular studies demonstrate hyperactive melanocytes together with solar elastosis, basement-membrane disruption, increased vascularity, and altered dermal signaling. Ultraviolet radiation stimulates melanocortin and endothelin pathways, promotes reactive oxygen species, and induces paracrine signals from keratinocytes, fibroblasts, mast cells, and endothelial cells. Hormonal influences and genetic predisposition further modify this response (Espósito et al., 2022; Kwon et al., 2016). These interacting mechanisms help explain both the heterogeneity of treatment response and the frequent recurrence after apparent improvement.

Photoprotection is foundational, but monotherapy is often insufficient. Hydroquinone, retinoids, corticosteroids, azelaic acid, kojic acid, chemical peels, lasers, and energy-based devices can reduce pigmentation, yet each has limitations. Irritant dermatitis can worsen pigmentation, and procedures may precipitate post-inflammatory hyperpigmentation in darker phototypes. Current reviews therefore emphasize individualized, multimodal, and maintenance-oriented management

(Cassiano et al., 2022). A topical agent that is active, tolerable, and suitable for repeated use would be clinically valuable.

MELATONIN

Melatonin is produced by the pineal gland and locally within the skin. Cutaneous cells express melatonin receptors and possess a melatonergic antioxidant system. Melatonin and its metabolites can directly neutralize free radicals, enhance antioxidant enzymes, reduce inflammatory signaling, and limit ultraviolet-induced cellular injury (Fischer et al., 2008; Slominski et al., 2018). These properties are relevant to melasma because oxidative stress and chronic photodamage are integrated into its pathogenesis.

Clinical evidence for melatonin in pigmentation disorders remains emerging. Sarkar et al. (2020) reported lower serum melatonin and greater oxidative stress in patients with melasma than in controls, although biomarker levels did not correlate with severity. A randomized photoprotection study found a dose-dependent effect of topical melatonin against sunlight-induced erythema, with significant protection at 12.5% (Scheuer et al., 2016). Thus, 0.5% topical melatonin is biologically plausible and likely tolerable, but its depigmenting efficacy cannot be assumed from photoprotection studies and requires direct clinical evaluation.

TRANEXAMIC ACID

Tranexamic acid competitively inhibits the conversion of plasminogen to plasmin. In skin exposed to ultraviolet radiation, this can reduce keratinocyte-derived arachidonic acid and prostaglandins that stimulate melanocytes. It may also influence vascular and mast-cell components of melasma. Early experimental work demonstrated that topical trans-4-aminomethylcyclohexanecarboxylic acid suppressed ultraviolet-induced pigmentation (Maeda & Naganuma, 1998). Subsequent systematic review and meta-analysis supported tranexamic acid across oral, topical, and intradermal routes, while emphasizing heterogeneity in dose, delivery, and study quality (Zhang et al., 2018).

Topical 3% tranexamic acid is particularly relevant as a non-hydroquinone option. In a double-blind split-face trial involving skin of color, 3% tranexamic acid cream produced improvement comparable to 4% hydroquinone with favorable tolerability (Yasnova et al., 2024). A separate prospective randomized study also documented clinical improvement with 3% tranexamic acid, although topical glutathione produced a larger response in that parallel-group comparison (Bijalwan et al., 2024). These studies establish 3% tranexamic acid as an appropriate active comparator for an exploratory melatonin formulation.

RESEARCH METHODOLOGY

Study Design, Setting, and Participants

This prospective, randomized, double-blind, intra-individual split-face comparative clinical study was conducted at Mae Fah Luang University Hospital, Bangkok. Adults aged 20-50 years with Fitzpatrick phototypes III-V and clinically diagnosed mild-to-severe melasma were eligible. Key exclusion criteria were pregnancy or lactation; use of topical or systemic depigmenting treatment within four weeks; hormone therapy or combined oral contraceptives; photosensitive disorders; relevant facial dermatoses or infection; hypersensitivity to either study product; prolonged occupational sun exposure; and use of photosensitizing medication.

Because no previous study directly comparing topical melatonin with topical tranexamic acid was available, the sample-size estimate was based on the study by Bijalwan et al. (2024), which

reported mean reductions in mMASI score of 1.34 ± 0.87 and 3.12 ± 2.08 after 90 days of treatment. These values corresponded to an estimated standardized effect size of approximately 1.12. Using a two-sided significance level of 0.05 and 90% statistical power, the minimum required sample was estimated to be 17 participants. The target enrollment was increased to 20 participants to account for possible attrition. Twenty participants were enrolled, of whom 18 completed the study and were included in the final analysis.

All participants received verbal and written study information and provided written informed consent. The study was approved by the Mae Fah Luang University Ethics Committee on Human Research on 17 November 2025 and was conducted in accordance with Good Clinical Practice. This study was registered with the Thai Clinical Trials Registry (TCTR) under registration number TCTR20260623011.

Randomization, Blinding, and Interventions

A computer-generated block-randomization schedule with blocks of four assigned 0.5% melatonin cream to either the right or left hemiface; 3% tranexamic acid cream was assigned to the contralateral side. An independent pharmacist prepared identical coded tubes. The formulations were matched for color, texture, packaging, and absence of added fragrance. Participants, the investigator, and outcome assessors remained unaware of allocation until analysis was completed.

Participants applied a thin layer of the assigned cream to each hemiface twice daily, morning and evening, for 12 weeks after cleansing. Separate hands were used for the two sides to reduce cross-contamination. All participants applied the same broad-spectrum sunscreen (at least SPF 50 with high UVA protection) to the entire face daily and were instructed to avoid other depigmenting agents and dermatologic procedures during the study. A 48-hour inner-arm application test was performed before facial use.

Outcome Assessment

Assessments were performed at baseline and Weeks 4, 8, and 12. The primary outcome was the hemifacial modified Melasma Area and Severity Index. Each hemiface was scored by multiplying area and darkness ratings within weighted forehead, malar, and chin regions, yielding a range from 0 (clear) to 12 (maximum severity). Baseline evaluation was performed by the investigator; follow-up assessments were performed by two independent physicians.

The principal secondary objective measure was the melanin index obtained with a Mexameter MX 18. The center of a representative lesion on each hemiface was marked as the measurement site. Three readings were obtained at the same site at each visit and averaged. Standardized facial images were acquired with the Canfield VISIA system under fixed positioning and lighting conditions.

At Week 12, participants independently rated satisfaction with each treated hemiface using a five-point numeric rating scale ranging from 1 (lowest satisfaction) to 5 (highest satisfaction). Scores of 4 or 5 were prespecified as satisfied. Local adverse effects were recorded at Weeks 4, 8, and 12 and graded as absent, mild, moderate, or severe. Potential reactions included erythema, pruritus, burning, desquamation, papular eruption, and increased pigmentation.

Statistical Analysis

Continuous variables were summarized using means and standard deviations; categorical variables were summarized using frequencies and percentages. Between-group p-values were calculated using independent-samples t-test at each time point. Within-group p-values were calculated using repeated-measures ANOVA test. Satisfaction (scores 4-5) and adverse-effect occurrence were compared using exact McNemar tests. Analyses used SPSS version 23.0, and two-sided p values below 0.05 were considered statistically significant.

RESEARCH FINDINGS

Participant Flow and Baseline Characteristics

Twenty participants entered the study. Two discontinued follow-up after work transfers prevented attendance at later visits; 18 participants completed the 12-week protocol and were analyzed (Figure 1). The mean age was 35.56 years (SD 4.19; range 31-43), 12 participants (66.7%) were women, and phototype IV was most common (61.1%). Baseline hemifacial mMASI values were identical for the two treatment sides.

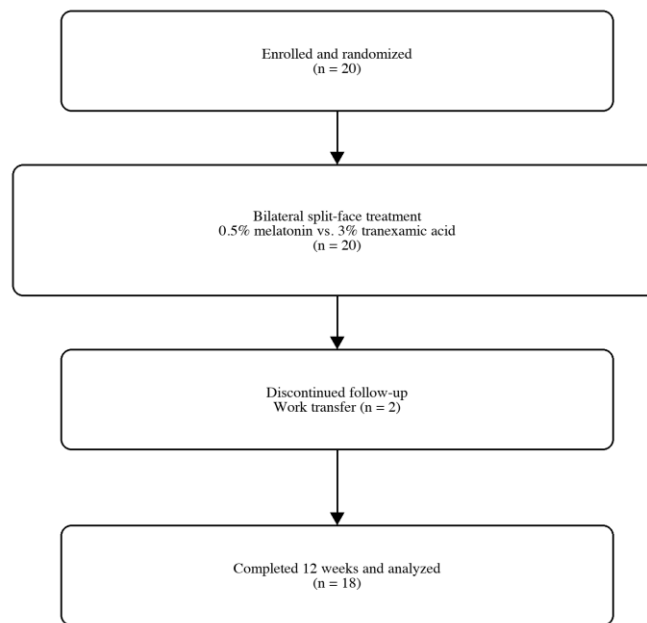


Figure 1 Participant flow through the 12-week split-face study.

Table 1 Baseline demographic and clinical characteristics (n = 18)

Characteristic	Value
Age, mean (SD), years	35.56 (4.19)
Age range, years	31-43
Female, n (%)	12 (66.7)
Male, n (%)	6 (33.3)
Fitzpatrick phototype III, n (%)	5 (27.8)
Fitzpatrick phototype IV, n (%)	11 (61.1)
Fitzpatrick phototype V, n (%)	2 (11.1)
Baseline hemifacial mMASI, mean (SD)	3.11 (1.41)

Note. SD = standard deviation; mMASI = modified Melasma Area and Severity Index.

Clinical and Instrumental Outcomes

Both treatments produced progressive improvement in hemifacial mMASI (Table 2 and Figure 2). On the melatonin-treated side, the mean score fell from 3.11 (SD 1.41) at baseline to 2.73 (SD 1.28) at Week 12, an absolute decrease of 0.38 (12.2%). On the tranexamic acid-treated side, the score fell from 3.11 (SD 1.41) to 2.51 (SD 1.24), an absolute decrease of 0.60 (19.3%). Change over time was statistically significant for both treatments ($p < 0.001$). Between-treatment differences at individual visits were not statistically significant.

Melanin indices also decreased over time (Table 2 and Figure 3). The mean index decreased from 254.8 (SD 67.7) to 242.2 (SD 61.0) with melatonin and to 236.3 (SD 62.9) with tranexamic acid. These correspond to absolute decreases of 12.6 (4.9%) and 18.5 (7.3%), respectively. The overall within-treatment time effect was significant for both sides ($p < 0.001$), whereas between-treatment differences at each visit were not significant.

Table 2 Hemifacial mMASI and Mexameter melanin-index outcomes (n = 18)

Outcome and visit	0.5% melatonin, mean (SD)	3% tranexamic acid, mean (SD)	Between- treatment p
Hemifacial mMASI, baseline	3.11 (1.41)	3.11 (1.41)	1.0000
Hemifacial mMASI, Week 4	3.01 (1.36)	2.97 (1.39)	0.9329
Hemifacial mMASI, Week 8	2.86 (1.31)	2.68 (1.31)	0.6869
Hemifacial mMASI, Week 12	2.73 (1.28)	2.51 (1.24)	0.6002
Melanin index, baseline	254.8 (67.7)	254.8 (67.7)	1.0000
Melanin index, Week 4	250.7 (65.0)	251.4 (66.7)	0.9760
Melanin index, Week 8	246.1 (62.9)	240.1 (64.0)	0.7763
Melanin index, Week 12	242.2 (61.0)	236.3 (62.9)	0.7774

Note. Between-group p-values were calculated using independent-samples t-test at each time point. Within-group p-values were calculated using repeated-measures ANOVA.

p-value < 0.05 was considered statistically significant.

SD = standard deviation.

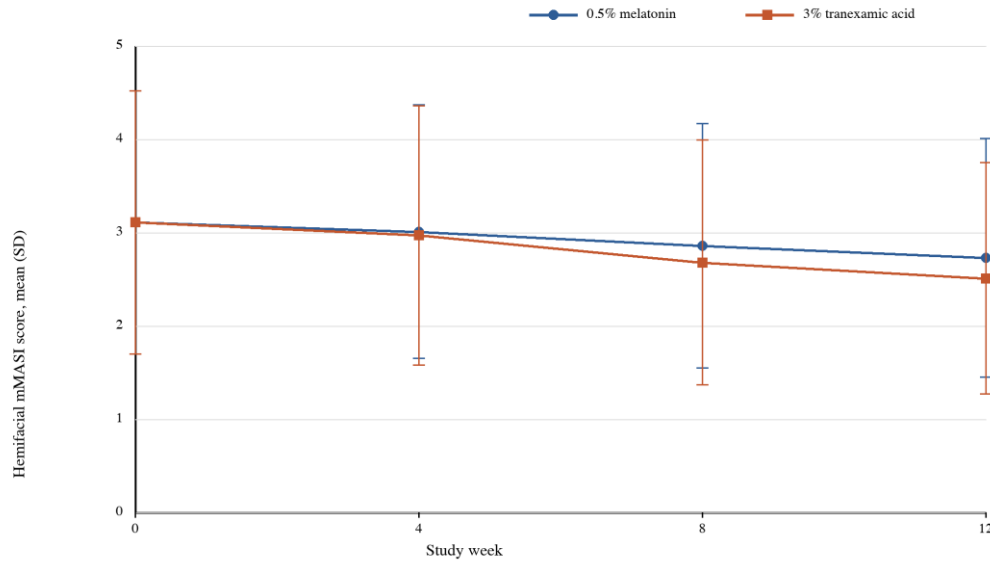


Figure 2 Mean hemifacial mMASI scores during treatment. Error bars indicate standard deviations.

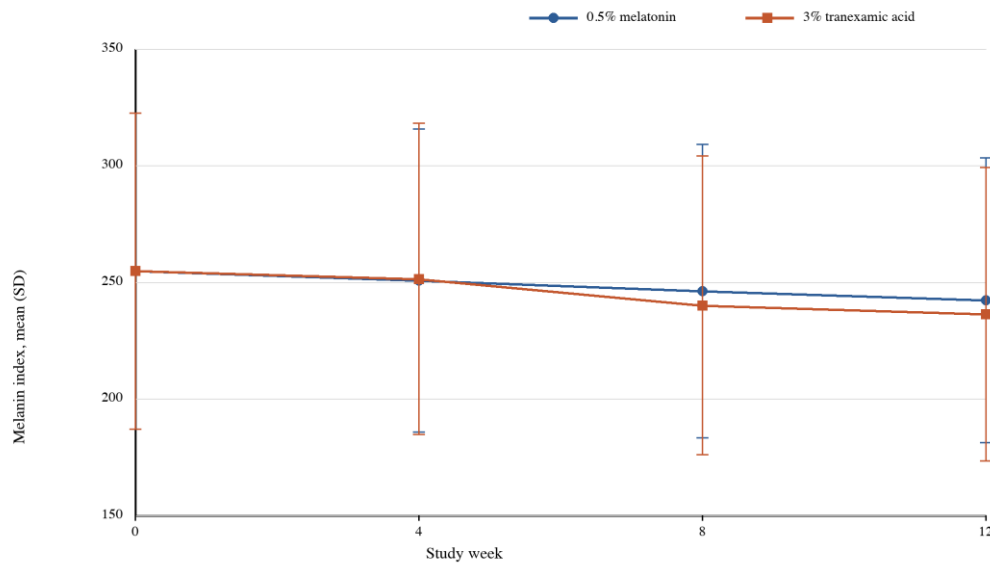


Figure 3 Mean Mexameter melanin indices during treatment. Error bars indicate standard deviations.

Satisfaction and Safety

At Week 12, 11 of 18 participants (61.1%) assigned a satisfaction score of 4 or 5 (ranging from 1-lowest satisfaction to 5-highest satisfaction) to the melatonin-treated side, compared with 12 of 18 (66.7%) for the tranexamic acid-treated side. The paired difference was not significant (McNemar $p = 1.000$). Adverse effects were described as infrequent and mild. No moderate or

severe adverse event occurred, and the occurrence of adverse effects did not differ between treatment sides ($p = 1.000$).

Table 3 Patient satisfaction and safety at Week 12 (n = 18)

Outcome	0.5% melatonin	3% tranexamic acid	p
Satisfaction score 1, n	0	0	-
Satisfaction score 2, n	2	1	-
Satisfaction score 3, n	5	5	-
Satisfaction score 4, n	6	7	-
Satisfaction score 5, n	5	5	-
Satisfied (scores 4-5), n (%)	11 (61.1)	12 (66.7)	1.000
Moderate or severe adverse events, n	0	0	-

Note. Satisfaction and adverse-effect occurrence were compared using exact McNemar tests.

CONCLUSION & DISCUSSION

Principal Findings

In this randomized split-face study, twice-daily topical 0.5% melatonin and 3% tranexamic acid both produced statistically significant reductions in clinical severity and instrumentally measured pigmentation over 12 weeks. The between-treatment comparisons at individual visits were not statistically significant. Satisfaction and tolerability were similar. These findings support activity of both formulations but do not establish equivalence or noninferiority.

Interpretation in Relation to Previous Evidence

The improvement observed with 3% tranexamic acid is consistent with its established effect on the plasminogen-plasmin pathway. By reducing plasmin activity, tranexamic acid can limit ultraviolet-induced arachidonic acid and prostaglandin release and may reduce vascular signals that sustain melanogenesis (Maeda & Naganuma, 1998; Zhang et al., 2018). The magnitude and tolerability observed here are directionally consistent with the split-face comparison by Yasnova et al. (2024), in which 3% tranexamic acid was an effective alternative to hydroquinone in skin of color.

The melatonin response is clinically noteworthy because direct evidence for topical melatonin in melasma is limited. Melatonin has broad antioxidant and anti-inflammatory actions within the skin, and melasma is associated with oxidative imbalance (Fischer et al., 2008; Sarkar et al., 2020). Nevertheless, mechanistic plausibility does not establish clinical equivalence. The present study suggests that 0.5% melatonin can reduce pigmentation over 12 weeks, but the modest sample size warrant cautious interpretation. Furthermore, photoprotection research found suppression of sunlight-induced erythema effective at 12.5% melatonin (Scheuer et al., 2016). Concentration, vehicle, endpoint, and application schedule may therefore materially influence topical melatonin effects.

The steady decline in outcomes across visits suggests cumulative rather than transient benefit. For a chronic relapsing disorder, gradual improvement with acceptable tolerability may be more

useful than an early response accompanied by irritation. Both sides also received standardized photoprotection, which is essential care and may have contributed to improvement on both hemifaces. Applying the same sunscreen bilaterally and comparing the two hemifaces within each participant reduces its confounding effect on the relative treatment comparison. However, because the study lacked vehicle-only and photoprotection controls, the absolute contribution of each active ingredient cannot be separated from sunscreen use, behavioral modification, vehicle effects, or regression to the mean.

Clinical Implications

Topical 3% tranexamic acid remains the better-supported option when a non-hydroquinone topical therapy is desired. Topical 0.5% melatonin may be considered investigational but potentially useful for patients seeking an antioxidant-based approach or for future combination regimens. The current evidence is insufficient to recommend melatonin as a replacement for established therapy. Daily broad-spectrum photoprotection should remain central regardless of the selected depigmenting agent.

Strengths and Limitations

The split-face design is a major strength because each participant served as their own control, reducing confounding from phototype, hormonal factors, genetics, and shared environmental and sunscreen exposure. Random allocation, blinding, standardized formulations, repeated assessments, independent evaluation, and the combination of clinical and device-based outcomes further strengthened internal validity.

This study was limited by the absence of vehicle-only and photoprotection control groups, which precluded separating the active-ingredient effects from vehicle and sunscreen effects. Future three-arm randomized trials should include an appropriate vehicle or photoprotection control to isolate these contributions. Additionally, as a single-center study, the findings may have limited generalizability to other populations and clinical settings.

CONCLUSION

Topical 0.5% melatonin cream and topical 3% tranexamic acid cream both improved hemifacial mMASI and melanin index over 12 weeks and were well tolerated. The between-treatment differences at individual visits were not statistically significant to establish equivalence or noninferiority. Topical melatonin is a promising investigational alternative.

ACKNOWLEDGEMENTS

The authors thank Professor Thamthiwat Nararatwanchai and Associate Professor Anon Paichitrojjana for academic guidance, Associate Professor Wongdyan Pandii for statistical guidance, the faculty and staff of the School of Anti-Aging and Regenerative Medicine, Mae Fah Luang University, the independent dermatology evaluators and pharmacist, and all study participants for their contributions.

REFERENCES

- Bijalwan, S., Randhawa, G. K., & Kaur, T. (2024). A prospective, randomized and open label study to compare efficacy, safety and quality of life impact of topical glutathione (2%) in comparison to topical tranexamic acid (3%) in adult melasma patients. *JK Science*, 26(3), 149-154.

- Cassiano, D. P., Espósito, A. C. C., da Silva, C. N., Lima, P. B., Dias, J. A. F., Hassun, K., Miot, L. D. B., Miot, H. A., & Bagatin, E. (2022). Update on melasma-Part II: Treatment. *Dermatology and Therapy*, 12(9), 1989-2012. <https://doi.org/10.1007/s13555-022-00780-4>
- Espósito, A. C. C., Cassiano, D. P., da Silva, C. N., Lima, P. B., Dias, J. A. F., Hassun, K., Bagatin, E., Miot, L. D. B., & Miot, H. A. (2022). Update on melasma-Part I: Pathogenesis. *Dermatology and Therapy*, 12(9), 1967-1988. <https://doi.org/10.1007/s13555-022-00779-x>
- Fischer, T. W., Slominski, A., Zmijewski, M. A., Reiter, R. J., & Paus, R. (2008). Melatonin as a major skin protectant: From free radical scavenging to DNA damage repair. *Experimental Dermatology*, 17(9), 713-730. <https://doi.org/10.1111/j.1600-0625.2008.00767.x>
- Kwon, S. H., Hwang, Y. J., Lee, S. K., & Park, K. C. (2016). Heterogeneous pathology of melasma and its clinical implications. *International Journal of Molecular Sciences*, 17(6), 824. <https://doi.org/10.3390/ijms17060824>
- Maeda, K., & Naganuma, M. (1998). Topical trans-4-aminomethylcyclohexanecarboxylic acid prevents ultraviolet radiation-induced pigmentation. *Journal of Photochemistry and Photobiology B: Biology*, 47(2-3), 136-141.
- Ogbechie-Godec, O. A., & Elbuluk, N. (2017). Melasma: An up-to-date comprehensive review. *Dermatology and Therapy*, 7(3), 305-318. <https://doi.org/10.1007/s13555-017-0194-1>
- Sarkar, R., Devadasan, S., Choubey, V., & Goswami, B. (2020). Melatonin and oxidative stress in melasma-An unexplored territory; a prospective study. *International Journal of Dermatology*, 59(5), 572-575. <https://doi.org/10.1111/ijd.14827>
- Scheuer, C., Pommengaard, H. C., Rosenberg, J., & Gögenur, I. (2016). Dose dependent sun protective effect of topical melatonin: A randomized, placebo-controlled, double-blind study. *Journal of Dermatological Science*, 84(2), 178-185. <https://doi.org/10.1016/j.jdermsci.2016.08.007>
- Slominski, A. T., Zmijewski, M. A., Semak, I., Kim, T. K., Janjetovic, Z., Slominski, R. M., & Zmijewski, J. W. (2018). Melatonin as a key player in skin functions. *International Journal of Molecular Sciences*, 19(2), 366. <https://doi.org/10.3390/ijms19020366>
- Yasnova, N., Sirait, S. P., & Rahmayunita, G. (2024). The effectiveness and safety of 3% tranexamic acid cream vs. 4% hydroquinone cream for mixed-type melasma in skin of color: A double-blind, split-face, randomized controlled trial. *Acta Dermatovenereologica Alpina, Pannonica et Adriatica*, 33(2), 83-88. <https://doi.org/10.15570/actaapa.2024.16>
- Zhang, L., Tan, W. Q., Fang, Q. Q., Zhao, Y., Chen, C. Y., Zhang, M. X., Ni, J. D., & Wu, L. H. (2018). Tranexamic acid for adults with melasma: A systematic review and meta-analysis. *BioMed Research International*, 2018, 1683414. <https://doi.org/10.1155/2018/1683414>

Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.



Copyright: © 2026 by the authors. This is a fully open-access article distributed under the terms of the Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0).