

IN-DEPTH REVIEW

Unveiling the Anti-Aging Potential of Topical Melatonin: A Systematic Review

Christy Angelia Budiono, MD¹, Anis Irawan Anwar, Prof.¹, Asnawi Madjid, MD¹, Khairuddin Djawad, Prof.¹, Andi Alfian Zainuddin, MD², Latifah Rahman, Prof.³

¹ Department of Dermatology & Venereology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

² Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

³ Faculty of Pharmacy, Hasanuddin University, Makassar, Indonesia

ABSTRACT

Introduction: Skin aging is driven by intrinsic and extrinsic factors that cause progressive structural, functional, and biochemical deterioration. Age-associated decline in endogenous cutaneous melatonin may weaken antioxidant defense and repair capacity. Topical melatonin is amphiphilic and may mitigate oxidative stress, photoaging, mitochondrial dysfunction, and extracellular matrix degradation via receptor-mediated and receptor-independent pathways.

Methods: A systematic search of PubMed, Google Scholar, and Science Direct was conducted for studies published between 2015 and 2025 evaluating topical melatonin and skin aging outcomes. Eligible studies included human clinical trials, ex vivo human skin research, in vitro cellular studies, and an in vivo animal model reporting anti-aging parameters (wrinkle depth/roughness, hydration, firmness, pigmentation, oxidative stress biomarkers, and extracellular matrix markers). Twelve relevant studies met inclusion criteria and were qualitatively synthesized.

Results: Across clinical studies, topical melatonin (alone or in combination) improved hydration (up to +59.5%) and firmness (up to +30%), and reduced wrinkle depth (−11% to −31%) and surface roughness (−13% to −26.5%). Ex vivo evidence showed reduced mTORC1 activity and MMP-1, alongside increased COL17A1, fibrillin-1, and mitochondrial markers (TFAM, MTCO-1, VDAC). Combined topical plus oral strategies were associated with improved lipid profiles (including ceramides and triglycerides). Animal data supported angiogenic signaling (increased VEGF) and collagen remodeling. No serious adverse effects were reported.

Discussion: Current evidence suggests short- to mid-term benefits (4–12 weeks), but longer follow-up and head-to-head formulation trials remain limited.

Conclusion: Topical melatonin demonstrates multi-targeted anti-aging effects with a favorable safety profile and promising clinical relevance for skin rejuvenation.

INTRODUCTION

Skin aging is a result of a combination of external and internal changes with ultraviolet

(UV) radiation and pollution, which increases oxidative stress, mitochondrial dysfunction, matrix metalloproteinase (MMP) activation, and the remodelling of extracellular-matrix (ECM). These interplays resulted in wrinkles,

skin laxity, dyschromia, and barrier impairment.^{1,2}

Melatonin is an indoleamine more commonly known for its role in circadian regulation; however, it also functions as a potent, amphiphilic antioxidant with receptor-mediated and receptor-independent actions in skin. Human skin expresses a melatonergic system, enabling local synthesis and responsiveness to exogenous melatonin. Topical delivery is particularly attractive: it bypasses first-pass metabolism, avoids sedative systemic effects, and achieves cutaneous levels that can outpace endogenous production, supporting DNA repair, mitochondrial resilience, and anti-inflammatory signaling in the cutaneous microenvironment.^{3,4,5}

Preclinical and translational research provides biological plausibility for the cutaneous effects of melatonin, indicating its ability to modulate oxidative stress responses, mitochondrial function, extracellular matrix turnover, inflammatory signaling, and cellular repair pathways relevant to skin aging across in vitro, ex vivo, in vivo, and clinical contexts. Accordingly, this systematic review aims to evaluate the anti-aging effects of topical melatonin on human skin by synthesizing evidence from clinical studies, supported by ex vivo human skin research, in vivo animal models, in vitro cellular experiments, and formulation-focused investigations.

METHODS

This systematic review follows PRISMA guidelines (**Figure 1**) to evaluate the potential of topical melatonin as an anti-aging compound for skin and its related anti-aging parameters.

Search Strategy

The search was conducted on three databases (PubMed, ScienceDirect, and Google Scholar) using search queries tailored to those databases.

- Pubmed: ("melatonin"[MeSH Terms] OR melatonin[tiab] OR "N-acetyl-5-methoxytryptamine"[tiab])AND (topical[tiab] OR cream[tiab] OR gel[tiab] OR serum[tiab] OR "skin application"[tiab] OR derm*[tiab]) AND ("skin aging"[MeSH Terms] OR aging[tiab] OR ageing[tiab] OR anti-aging[tiab] OR antiageing[tiab] OR wrinkle*[tiab] OR photoaging[tiab] OR photoprotection[tiab]) AND (randomized controlled trial[pt] OR clinical trial[pt] OR trial[tiab] OR cohort[tiab])
- Google Scholar: ("topical melatonin" OR "melatonin cream" OR "melatonin gel" OR "melatonin serum") AND ("skin aging" OR aging OR anti-aging OR wrinkle* OR photoaging OR photoprotection)
- Science Direct: ("melatonin" AND "topical" AND "skin" AND ("anti-aging" OR "anti-ageing" OR "aging" OR "ageing"))

Inclusion Criteria

We included original research comprising randomized clinical trials, cohort studies, prospective studies, and in vivo and in vitro studies published in English between 2015 and 2025. Only freely accessible full-text articles were included.

Exclusion Criteria

We excluded review articles, case reports, non-English publications, and studies without free full-text access.

Study Characteristics

A total of 11 studies were included: 6/11 (54.5%) human clinical studies, 1/11 (9.0%)

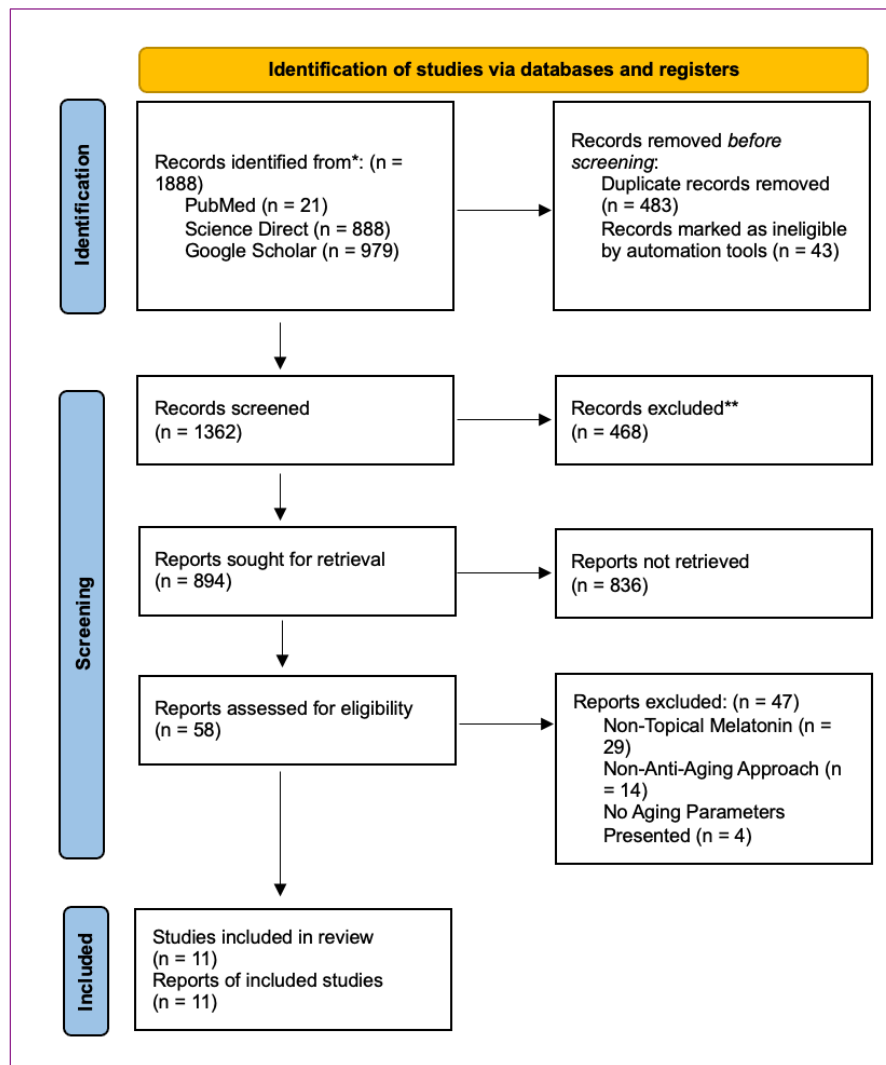


Figure 1. PRISMA Guideline Literature Search

ex vivo human skin study, 2/11 (18.1%) in vitro studies, 1/11 (9.0%) in vivo animal study, and 1/11 (9.0%) formulation/permeability study (Table 1).^{1-6, 11-12, 21-24}

RESULTS

Clinical Studies

Across six human clinical studies, topical melatonin, used alone or in combination, was consistently associated with improvements in hydration, wrinkle-related parameters, and skin firmness, with good tolerability reported

across study designs. An ex vivo plus open-label clinical program evaluating a night cream containing melatonin, carnosine, and *Helichrysum* reported rapid hydration increases, reduced TEWL, reductions in wrinkle-related measures, and less stinging.² In a randomized split-face trial, day and night melatonin creams reduced crow's feet, improved microrelief, and enhanced skin tonicity and hydration over three months with good tolerability.⁴ A multi-study clinical program evaluating a 3-in-1 night serum containing melatonin with co-actives reported improvements in wrinkles, firmness, and redness,⁵ and longer follow-up with clinical

Table 1. Characteristics of studies evaluating topical melatonin for skin aging across clinical and preclinical models

| Study Type | Author(s) | Design/ Model | Topical Melatonin Exposure | Comparator | Duration | Outcome | Key Findings |
|---|---------------------|--|--|--|-----------------------|--|--|
| Human clinical (in vivo) | Milani & Sparavigna | Randomized split-face, assessor-blinded; women with facial aging | Day + night creams containing melatonin (0.1%) | Contralateral untreated/control side | 3 months | Wrinkle grading (crow's feet), microrelief, tonicity, dryness, instrumental profiling/3D imaging | Improved crow's feet, microrelief/profilometry, tonicity and hydration; reduced dryness; good tolerability |
| Human clinical (in vivo) | Puviani et al. | Prospective pilot; periorbital application | Melatonin-based eye-contour balm (0.1%) | Baseline (within-subject) | 2 months | Antera 3D roughness/wrinkle metrics; tolerability | Reduced wrinkle roughness/skin surface roughness; well tolerated |
| Human clinical (in vivo) + ex vivo (human skin) | Granger et al. | Clinical program (open-label) + ex vivo arm | Night cream with melatonin + carnitine + <i>Helichrysum</i> | Typically baseline/within-subject (clinical) | Weeks (program-based) | Hydration/TEWL, wrinkle-related parameters, reactivity/stinging, photodamage-related outcomes | Reported rapid hydration increase, reduced TEWL, reduced wrinkle-related outcomes, less stinging/irritation; supports photodamage mitigation |
| Human clinical (in vivo) | Goldberg et al. | Multi-study clinical program | Night serum-in-oil: melatonin + bakuchiol + ascorbyl tetraisopalmitate | Mostly baseline/within-subject (varies by sub-study) | 28–84 days | Wrinkles, firmness, redness, hydration, TEWL; tolerability | Improvements in wrinkles/firmness/redness with favorable tolerability profile |

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| Human clinical (in vivo) | Goldberg et al. | Open-label clinical + histology (subset) | Same 3-in-1 serum | Baseline; some treated vs untreated biopsy comparisons | 12 weeks (+ extension to 24 weeks) | Clinical improvement indices; texture/pigmentation/erythema; histology (skin thickness/ECM markers) | Improvements sustained/extended to longer follow-up; histologic signals consistent with remodeling |
| Human clinical (in vivo) | Colombo et al. | Randomized prospective | Topical melatonin-based cream vs topical + oral supplement (melatonin + HA + apigenin) | Topical-only arm | 84 days | Moisturization, wrinkle depth (instrumental), lipidomics | Both improved; combined approach showed larger moisturization/wrinkle changes and lipidomic shifts consistent with barrier support |
| Ex vivo (human skin) | Samra et al. | Organ-cultured aged human eyelid skin | Melatonin exposure in culture | Vehicle control | Days (short-term culture) | p-S6 (mTORC1), MMP-1, COL17A1, mitochondrial markers (TFAM/MTCO-1/VDAC), VEGFA, fibrillin-1 | Downregulated mTORC1 and MMP-1; increased COL17A1, mitochondrial markers, VEGFA; improved fibrillin-1 organization; selective biomarker effects |
| In vitro (cells) | Egrilmez et al. | UVB-stressed human dermal fibroblasts | Melatonin pretreatment (cell exposure) | UVB-only and non-irradiated controls | Hours-days (post-UVB) | Oxidative stress markers; JNK/AP-1; MMP-1/MMP-3; TIMP-1; procollagen-related markers | Reduced oxidative damage signaling and collagen-degrading enzyme activity; supported collagen preservation pathways |
| In vitro (cells) | Shukla et al. | Human fibroblasts | Melatonin | Untreated/ve | Experimental | Sox2, Oct4, Nanog | Increased core transcription factors |

| | | (aged/AD vs controls) ± SH-SY5Y (per study) | exposure (cell treatment) | vehicle controls | timepoints | expression; viability-related measures | linked to cellular repair potential; supported anti-senescence plausibility |
|--------------------------|----------------|---|--|--|------------|--|---|
| In vivo (animal) | Bora et al. | Rat UV photodermatitis model | Topical sunscreen formulation fortified with melatonin (formulation-based) | UV-only, placebo/standard formulations, normal control | ~4 weeks | Skin thickness/edema, collagen-related markers, cytokines, NF-κB/COX-2 | Reduced UV-induced inflammation and signaling; preserved dermal structure-related outcomes |
| Formulation/permeability | Torrado et al. | Cream-gel system testing | Melatonin-loaded gel formulations with varying oil phase | Formulation comparisons | Lab-based | Stability, rheology, adhesiveness, skin permeability | Oil phase composition materially influenced stability and permeability trade-offs; informs optimized vehicles |

and histological assessment reported further improvements in texture, pigmentation, erythema, and overall aesthetic outcomes over 24 weeks.²⁴ In periorbital studies, melatonin-based eye-contour products reduced wrinkle volume, depth, and roughness with good tolerability.^{12,21} A randomized prospective trial comparing topical treatment alone versus a combined oral plus topical strategy reported improvements in both groups, with greater improvements in moisturization, wrinkle reduction, and lipidomic remodeling in the combined strategy.¹¹

Mechanistic and Preclinical Studies

Evidence from ex vivo human skin models, in vivo ultraviolet-exposed animal models, and in vitro human fibroblast systems consistently demonstrated antioxidant, mitochondrial-protective, and extracellular matrix-preserving effects of melatonin relevant to skin aging. In aged human eyelid skin cultures, melatonin reduced mechanistic target of rapamycin complex 1 (mTORC1) activity and MMP-1 while increasing collagen type XVII alpha 1 (COL17A1), mitochondrial markers (mitochondrial transcription factor A (TFAM), mitochondrially encoded cytochrome c oxidase I (MTCO-1), voltage-dependent anion channel (VDAC)), vascular endothelial growth factor A (VEGFA), and

fibrillin-1, suggesting dermal–epidermal anti-aging effects *ex vivo*.³ In an *in vivo* animal UV model, melatonin-fortified sunscreen reduced UV-induced inflammation, preserved collagen, and suppressed NF- κ B/COX-2 signaling.⁶ *In vitro*, melatonin reduced oxidative damage and collagen-degrading enzyme activity in UVB-stressed fibroblasts¹ and increased expression of Sox2, Oct4, and Nanog in aged and Alzheimer’s patient fibroblasts.²² A formulation study reported that oil phase composition affects melatonin stability and skin permeability in cream-gel systems.²³

DISCUSSION

Topical anti-aging agents are used to limit or combat the visible signs of aging through mechanisms that include promoting cellular turnover rate, antioxidant protection, and enhancing skin hydration.⁷ Topical melatonin may directly contribute to anti-aging by protecting the skin barrier from UV-related damage and reducing dermatitis, erythema, and sunburn.⁸ In addition, topical melatonin has been reported to reduce epidermal hyperplasia, lymphocyte infiltration, and decrease specific cytokines and chemokines levels.⁹

Specifically for anti-aging, the available evidences support a plausible molecular basis alongside measurable clinical benefits, particularly across hydration, barrier function, and wrinkle-related metrics. *Ex vivo* evidence in aged human eyelid skin shows that melatonin can modulate canonical ageing pathways in both epidermis and dermis by downregulating mTORC1 activity (reduced phosphorylated ribosomal protein S6 (pS6)), suppresses epidermal MMP-1, and increases markers of stem-cell niche integrity (COL17A1) and mitochondrial function (TFAM, MTCO-1, VDAC/porin). It also raises

VEGF-A, which has been linked to epidermal rejuvenation, and enhances dermal fibrillin-1 content and organization, without uniformly altering other biomarkers such as SIRT-1 or cyclin-dependent kinase inhibitor 2A (p16^{INK4a}).^{3,10}

Prospective clinical investigations generally support hydration-related measures, barrier function, and wrinkle-associated outcomes after topical melatonin use, including when delivered in combination formulations.^{2,4} These findings suggest consistent short- to mid-term clinical signals across commonly used anti-aging parameters, although direct comparisons between formulations and standardized outcome reporting remain limited.^{2,4}

Beyond topical-only approaches, a recent randomized prospective trial compared a melatonin-based cream alone with an “In & Out” regimen that added an oral supplement containing melatonin, hyaluronic acid, and apigenin for 84 days. Both groups improved, but the combined approach showed a larger reduction in wrinkle depth (–18.5% vs –9.4%) and a greater rise in moisturization, alongside lipidomic shifts consistent with barrier strengthening, namely, increases in triacylglycerols and multiple ceramide subclasses (EOS/NS) that support the corneocyte lipid envelope.¹¹

Overall, converging evidence suggests that melatonin-centric regimens may shift ageing skin toward a more youthful phenotype, characterised by reduced oxidative and proteolytic stress, improved epidermal bioenergetics, reinforced dermal microfibrils, improved hydration and barrier lipids, and visible softening of wrinkles, particularly when formulation and combination partners are thoughtfully selected.^{12,13} These effects align with melatonin’s antioxidant properties, which extend beyond UV protection to

include free radical scavenging and enhancement of antioxidant enzyme activity.¹⁴ On this basis, topical melatonin applied over extended periods may provide meaningful benefits for skin health and may help slow or partially reverse intrinsic and extrinsic signs of aging.¹⁵

In addition to topical anti-aging effects, melatonin is capable of modulating the immune system in the context of aging and skin damage. It can penetrate the skin effectively and increase antioxidant levels, thereby protecting against free-radical damage and potentially reducing skin cancer risk while supporting skin homeostasis and mitigating photoaging.¹⁶⁻²⁰

Recent clinical investigations reinforce the potential of melatonin as a topical anti-aging agent, including applications to sensitive facial regions. These studies support feasibility for both broader facial rejuvenation and localized periorbital outcomes, but longer follow-up and comparative trials are still needed to confirm durability and optimize product selection.^{12,21}

Mechanistically, cellular evidence suggests that melatonin may exert anti-senescence activity. In human dermal fibroblasts and SH-SY5Y human neuroblastoma cells, melatonin increased expression of Sox2, Oct4, and Nanog, transcription factors critical for cellular pluripotency and repair, suggesting effects that extend beyond antioxidant defense toward preservation of regenerative capacity in ageing-associated contexts.²²

Formulation research supports translation into practice by highlighting delivery and stability constraints. Melatonin-loaded cream-gel systems demonstrated that rheology, permeability, and adhesiveness depend on the oil-to-water ratio, while Quality by Design (QbD) analyses underscore that

excipient selection can influence melatonin stability.²³

Longer-term clinical support has also been reported for combination products. A 24-week open-label study with histological assessment of a 3-in-1 night facial serum containing melatonin, bakuchiol, and ascorbyl tetraisopalmitate reported clinical improvements alongside histological findings consistent with structural remodeling.²⁴ These findings further emphasize the importance of formulation strategy and objective measurement tools in substantiating melatonin's role as a dermatological active.²⁴

In terms of biological mechanisms relevant to anti-aging, melatonin has been linked to mitigation of oxidative stress and protection of mitochondrial function.²⁵ Reported pathways include activation of SIRT1–Nrf2 signaling, alongside interactions with inflammatory signaling such as NF- κ B.²⁶ Additional mechanistic work has implicated modulation of TGF- β 1–Smad2/3 signaling and inhibition of fibrogenic cytokine activity in other tissue contexts.^{27,28}

Melatonin's established role in circadian regulation is also plausibly connected to cellular resilience and ageing-associated decline, given known links between sleep disruption, oxidative stress, inflammation, and mitochondrial dysfunction.²⁹⁻³¹ These effects have been discussed alongside parallels to other endocrine regulators relevant to antioxidant defense and cellular energy metabolism.³² Moreover, melatonin has been described as influencing extracellular matrix synthesis and VEGF-related pathways in regeneration-associated contexts.³³

Beyond skin, regenerative evidence has been reported across multiple systems,

including nerve regeneration through MT1 receptor-associated mechanisms,³⁴ osteogenic differentiation via mesenchymal stem cell regulation,³⁵ and adjuvant effects in bone repair models when combined with osteoinductive factors such as rhBMP-2.^{36,37} While these findings extend beyond topical dermatology, they provide additional biological plausibility for melatonin's broader pro-repair and homeostatic roles.^{38–40}

CONCLUSION

Topical melatonin demonstrates multi-targeted anti-aging effects in human skin, improving biomechanical, structural, and biochemical markers of aging with an excellent safety profile. Its integration into dermatologic and cosmetic regimens offers a promising, evidence-based strategy for skin rejuvenation.

Conflict of Interest Disclosures: None

Funding: None

Corresponding Author:

Christy Angelia Budiono, MD
 Jl. Perintis Kemerdekaan Km.10 Tamalanrea,
 Makassar, Sulawesi
 Phone: +6285173332233
 Email: christyangelia.ca@gmail.com

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