Assessing the Potential Role for Topical Melatonin in an Antiaging Skin Regimen

Doris Day MD,[a] Cheryl M. Burgess MD,[b] Leon H. Kircik MD[c]
[a]NYU Langone Medical Center, New York, NY
[b]Center for Dermatology and Dermatologic Surgery; George Washington University School of Medicine and Health Sciences; Department of Internal Medicine/Dermatology, Georgetown University Medical Hospital, Washington, DC
[c]Icahn School of Medicine at Mount Sinai, New York, NY; Indiana Medical Center, Indianapolis, IN; Physicians Skin Care, PLLC, Louisville, KY; DermResearch, PLLC, Louisville, KY

ABSTRACT

Background: Melatonin is an endogenous hormone commonly associated with regulation of sleep. However, over the last two decades, research has elucidated a range of effects associated with the compound, including anti-inflammatory, both direct and indirect antioxidant activity, tissue regenerative benefits, and preservation of mitochondrial function. Melatonin's anti-inflammatory and antioxidant support, coupled with its mitochondrial support, make it an intriguing target for use to support skin health. Human skin and hair follicles express functional melatonin receptors. They also engage in substantial melatonin synthesis. By supporting cutaneous homeostasis, melatonin and its metabolites are thought to attenuate carcinogenesis and possibly other pathological processes, including hyperproliferative/inflammatory conditions.

The primary extrinsic driver of aging has been considered to be exposure to ultraviolet (UV) light, which is well-established to contribute to sunburn, immunosuppression, skin aging, and carcinogenesis. Topically applied melatonin has been shown to reduce markers of reactive oxygen species formation and to reverse signs of skin aging.

As the global population continues to age, photo-damage remains a significant cutaneous concern. While use of sunscreens and UV avoidance strategies are essential to mitigate skin cancer risks, the potential to protect the skin and improve the appearance of photo-damage through the use of topical antioxidant support is appealing. The evidence suggests that melatonin deserves consideration for topical use as an anti-aging and skin protective agent. It is shown to be both safe and effective when topically applied.

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INTRODUCTION

Melatonin, the main neuroendocrine product of the pineal gland, is an endogenous hormone commonly associated with regulation of the sleep cycle. Exogenous melatonin, in the form of oral supplements, has been used for many years to help regulate the sleep cycle. Research over the last two decades supports a range of additional benefits associated with melatonin, including anti-inflammatory and both direct and indirect antioxidant activity. Melatonin also has been shown to induce tissue regeneration.[1] Specifically, research has elucidated regenerative effects of melatonin on tissues of the nervous system, liver, bone, kidney, bladder, muscle, and skin.[1] The combined antioxidant, anti-inflammatory, and regenerative effects of melatonin are sufficiently potent that melatonin has been investigated as a protective agent for ischemia-reperfusion (IR) injury in brain, heart, and liver.[2] The degree of myocardial protection from melatonin following myocardial IR has been characterized as "substantial."[3]

One area of research has focused on the use of melatonin systemically for its anti-aging benefits via preservation of mitochondrial function. As mitochondrial function declines with age, impairment leads to damage to mitochondrial proteins, lipids, and DNA. One way that melatonin may preserve mitochondrial physiopathology and prevent aging is by preserving cardiolipin, a phospholipid that plays an important role in several biochemical processes of the mitochondrial function, from ROS mediated oxidation.[4]

Of particular interest, melatonin and its metabolites have been identified as integral to physiological skin functions.[5] Such functions are known to decrease with age and cumulative skin damage. In the skin, melatonin functions largely as a direct and an indirect antioxidant.

The range of potential cutaneous benefits associated with melatonin extend beyond signs of skin aging. By supporting cutaneous homeostasis, melatonin and its metabolites are thought

to attenuate carcinogenesis and possibly other pathological processes, including hyperproliferative/inflammatory conditions.[2] Reduced melatonin levels have been linked to inflammation in psoriasis, suggesting a possible therapeutic role for melatonin supplementation.[6] Topically applied melatonin has demonstrated positive effects for the management of androgenetic alopecia with a reduction in hair loss among women and a maintenance of current hair among men.[7] The benefit has been attributed to melatonin's indirect antioxidant and regenerative capacities.[8] Melatonin may also have a role in barrier function and enhance wound healing by increasing proliferative activity of keratinocytes.[9]

The range of proposed cutaneous benefits associated with melatonin are certainly intriguing. However, its role as an anti-aging agent for topical application may have both greatest promise and potential utility. A careful assessment of the indirect or direct antioxidant and anti-inflammatory effects of melatonin is therefore warranted. Additionally, it is worthwhile to review the evidence for benefit attributed to topical application of melatonin.

Skin Aging and Antioxidants

Visible signs of skin aging are the result of various intrinsic and extrinsic factors. Genetic factors may direct the rate and extent of cell senescence, the depletion of collagen stores, and structural changes, including the shifting of fat and bone.[10,11] However, extrinsic factors may significantly accelerate aging. The primary extrinsic driver of aging has been considered to be exposure to ultraviolet (UV) light. The predominant effects of UV exposure, such as sunburn, immunosuppression, skin aging, and carcinogenesis have been well-documented in the literature.[12] Exposure to UVA has been directly correlated to a reduction of collagen in human dermal extracellular matrix.[13] Relevant to both skin aging and photocarcinogenesis, the effects of UV exposure on the skin encompass DNA alterations, including induction of thymine-thymine dimers and loss of tumor suppressor gene p53.[14] More recently, focus has shifted to other extrinsic contributors to skin aging, including visible and infrared (IR) light, as well as atmospheric pollutants, such as ozone.[15-17]

The oxidative stress theory of aging is relevant to skin aging, as evidence shows that irrespective of the extrinsic agent, either solar radiation (at multiple wavelengths) or atmospheric pollutants, oxidative stress mediated formation of reactive oxygen species (ROS)[18] produces inflammation and cytotoxicity with resultant cell damage.[19] Ozone induces oxidative stress on the skin's surface via formation of lipid peroxidation (LPO) products.[17] Of note, research has shown that the mitochondria are responsible for producing 90% of ROS.

Melatonin is shown to function as an indirect antioxidant in the skin, with several of its metabolites described as potent antioxidants.[20] In addition, melatonin is also an indirect antioxidant and as such shown to stimulate the transcription factor, NRF2 and up-regulate gene expression and activity of several antioxidative enzymes, such as Cu/Zn-superoxide dismutase (CuZn-SOD), Mn-superoxide dismutase (Mn-SOD), catalase and glutathione peroxidase (GPx) in human skin explants[8,21] supporting an indirect antioxidant action of melatonin. The levels of antioxidant enzymes have been reported to stay upregulated for several hours[21] suggesting a sustained, long-lasting antioxidant protection in the skin whose benefits last through the night.[21] Its effects in supporting antioxidant activity are potent enough to inspire one group of researchers to suggest that melatonin "would improve the therapeutic ratio in radiation oncology and ameliorate skin damage more effectively when administered in optimal and non-toxic doses."[22]

While multiple antioxidants have been variously recommended—either via oral supplementation or topical application for skin protection—melatonin presents distinct potential benefits for addressing oxidative stress in the skin. Melatonin is associated with stronger antioxidant effects than vitamins C and E. Melatonin is highly lipophilic and penetrates organic membranes to protect mitochondria and DNA from oxidative damage. Mammalian skin boasts high concentrations of precursor molecules that facilitate melatonin synthesis. Therefore, topical application of melatonin is expected to provide antioxidant benefits directly at the site where ROS form in response to exposure to UV light and pollution. Melatonin applied to the skin has been shown to elevate antioxidant enzymes mRNA levels for at least 24 hours. This suggests that the upregulation of gene expression and activity of the above-mentioned antioxidative enzymes and down-regulation of interstitial collagenase (MMP-1), stromelysin 1 (MMP-3), stromelysin 2 (MMP-10), and aldehyde dehydrogenase 3 type A1 would provide important activity for protecting and repairing the skin.[21]

In a randomized, split-face, assessor-blinded, prospective three-month study, involving 22 women (mean age, 55 years) with moderate-to-severe skin aging, topical application of a melatonin cream was associated with a significant 15% reduction in the appearance of crow's feet, compared with non-treatment, at three months. Skin tone and skin dryness were also improved.[23]

Melatonin absorbs UV light at a wavelength of 225-275 nm, which is below the UVA and UVB wavelengths of 290-390 nm.[24] This has led researchers to speculate that the photoprotective benefits of melatonin are actually a direct consequence of its strong capacity to quench ROS produced as a result of radiation and of its ability to stimulate antioxidant enzymes in the skin.

In order to show Melatonin's impact as a direct and indirect antioxidant, researchers undertook a systematic database review, with 20 studies evaluating melatonin's protective effect against UVR-induced erythema in humans, with results indicating a

protective effect against UVR-induced erythema when topical melatonin was applied before exposure rather than after. All the studies used artificial UVR-sources and did not investigate possible side effects.[25]

Most recently, an in-vitro study was performed to evaluate the relative expression of genes associated with antioxidant activity for a melatonin-containing topical night-time formulation. The formulation was evaluated undiluted and topically applied on medaka eleutheroembryos (ME). Topical application of melatonin-containing formulation significantly increased gene expression of SOD1, CAT, Nrf2 and GPx1, as demonstrated via real-time quantitative PCR (Polymerase Chain Reaction) to quantify mRNA levels. Findings confirm that topically applied melatonin behaves as an indirect antioxidant by up-regulating the gene expression of Nrf2 and antioxidant enzymes.[26]

Considerations for Topical Application

Although oral melatonin supplements are widely available, topical formulations are far less common. Oral administration is thought to deliver the active compound to the bloodstream via the gut. But what is the mechanism for topical delivery? Topically applied melatonin is a practical option for topical application only if it can be safely and effectively delivered to the skin with minimal systemic effect. Human skin and hair follicles express functional melatonin receptors in addition to being engaged in substantial melatonin synthesis.[27] Topically applied melatonin has been shown to be safe, even with full body application, showing no effect on cognition, including measures of sleepiness. [25]

Melatonin synthesis in the human body peaks in the evening hours,[21] perhaps not surprising, given its association with regulating circadian rhythms. Since cutaneous repair processes are also thought to take place overnight, and skin permeability is at its highest at night, topical application of melatonin at nighttime may optimize the wound healing and anti-aging benefits of the compound while mimicking its endogenous effects.

CONCLUSION

There is now substantial evidence that topical melatonin, a naturally occurring hormone long used as an oral supplement to support sleep, may have important benefits for the skin. The compound is a strong direct antioxidant as well as an indirect antioxidant with demonstrated anti-aging benefits. Within the skin, melatonin behaves as an indirect antioxidant by upregulating the gene expression of antioxidant enzymes. It accomplishes this by upregulating the transcription factor, NRF2, which after translocating to the nucleus can induce the transcription of antioxidant enzymes, such as SOD1, GPX-1, and CAT by binding to the antioxidant response element (ARE) promoter region.

As the global population continues to age, photodamage remains a significant cutaneous concern. In fact, the $46.93 Billion (USD) global cosmeceuticals market is driven primarily by demand for anti-aging skincare.[28] While use of sunscreens and UV avoidance strategies are essential to mitigating skin cancer risks as well as photoaging, the potential of topical melatonin to provide anti-aging benefits through an indirect and direct antioxidant effect is appealing.

With its unique antioxidant effects, melatonin should be considered for topical use as an anti-aging and skin protective agent. Although the available in-vitro and in-vivo studies have demonstrated that topical melatonin is an effective anti-aging option for night-time application, more clinical studies are needed to understand the full potential of topical melatonin.

DISCLOSURES

Doris Day MD has been a consultant for ISDIN.

Cheryl M. Burgess MD FAAD has served on the advisory board for Aclaris Therapeutics, Inc, Revance Therapeutics, Inc., The Merz Institute of Advanced Aesthetics, Merz Pharmaceuticals, and ISDIN.

Leon H. Kircik MD is a consultant and advisory board member for ISDIN.

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AUTHOR CORRESPONDENCE

Leon H. Kircik MD
E-mail:.....wedoderm@yahoo.com