Protective role of melatonin in ultraviolet radiation-induced oxidative stress in human skin photoaging

Maria Veronica Putri Suyanto† and I Gusti Ayu Widianti

ABSTRACT

The ultraviolet radiation of the sun that reaches the earth is made up of ultraviolet A (95%) and ultraviolet B (5%). Exposure to ultraviolet radiation (UVR) is the main factor in photoaging. Chronic exposure to sunlight acts as an environmental stressor, leading to oxidative damage or stress. Oxidative damage stimulates the accumulation of free radicals, such as reactive oxygen species (ROS) or reactive nitrogen species (RNS) that are responsible for premature skin aging. Photaged skin is characterized externally by irregular pigmentation, wrinkles, and reduced skin elasticity, and internally by the breakdown of dermal collagen and elastin. Free radicals can be scavenged and the skin can be protected from further oxidative damage by antioxidants. Melatonin is a hormone produced mainly by the pineal gland, as well as many other organs, including the skin. One of the functions of melatonin is exerted by the antioxidative melatonergic system to prevent ultraviolet (UV)-induced skin photoaging. The aim of this review was to study the protective effect of melatonin on skin photoaging resulting from UVR exposure. The references were tracked using various databases, such as Google Scholar and PubMed with regard to publications in English for the last 5 years (2019-2023). Melatonin inhibits UVR-induced aging in multiple ways, such as protecting skin cells, binding free radicals, accelerating the activity of antioxidant enzymes, preventing increased mitochondrial membrane permeability, and assisting electron transport efficiency in the mitochondrial respiratory chain. Exogenous application of melatonin is usually by the oral route, but for localized effects on the skin, topical administration is recommended, with consideration of preparations with a better half-life and bioavailability. Understanding the protective antioxidant function of melatonin in UV-induced skin photoaging helps to optimize its application. The protective properties of melatonin against UVR-oxidative stress-induced photoaging will be further explored in this review.

Keywords: Melatonin, ultraviolet radiation, photoaging, oxidative stress, free radicals, protective

Abbreviations

5-MTOL : 5-methoxytryptophan alcohol
5-MTT : 5-methoxytryptamine
6(OH)M : 6-hydroxymelatonin
AANAT : arylalkylamine N-acetyltransferase
AFMK : N1-acetyl-N2-formyl-5-methoxykynureninamene


*Correspondence :
Maria Veronica Putri Suyanto
Magister Program in Anti-Aging Medicine, Faculty of Medicine, Universitas Udayana, Denpasar, Bali, Indonesia
Phone: +62 81239823366
Email: suyanto.2280711049@student.unud.ac.id
ORCIDID:0009-0003-5489-9453

Date of first submission, July 6, 2023
Date of final revised submission, December 14, 2023
Date of acceptance, December 21, 2023

This open access article is distributed under a Creative Commons Attribution-Non Commercial-Share Alike 4.0 International License

AP-1 : activator protein-1
ATP : adenosine triphosphate
CPD : cyclobutane-pyrimidine dimers
JNK : c-Jun N-terminal kinase
DNA : deoxyribonucleic acid
ECM : extracellular matrix
EFGR : epidermal growth factor receptor
HEK : human epithelial keratinocytes
HDF : human dermal fibroblasts
HIOMT : 4-hydroxyindole-O-methyl transferase
IL : interleukin
IML : intermediolateral nucleus of the spinal cord
ipRGCs : intrinsically photosensitive retinal ganglion cells
m-iNOS : mitochondrial-inducible nitric oxide synthase
MAPK : mitogen-activated protein kinases
MLT-Els : melatonin elastic liposomes
mPTP : mitochondrial permeability transition pore
MMP : matrix metalloproteinase
MT : melatonin
NADPH : nicotinamide adenine dinucleotide phosphate
NAS : N-acetylserotonin
NAT : N-acetyltransferase
NF-κB : nuclear factor-κB
Nrf2 : nuclear factor erythroid 2-like
NQO : NADPH quinone oxidoreductase
PIP-C : procollagen type I C-peptide
PVN : paraventricular nucleus
RHT : retinohypothalamic tract
ROS : reactive oxygen species
RNS : reactive nitrogen species
RZR-α : retinoid Z receptor-α
SIRTs : sirtuins
SCN : suprachiasmatic nucleus
TNF-β : tumor necrosis factor-β
TGF-β : transforming growth factor-β
TIMP : tissue inhibitor of metalloproteinase
TPH : tryptophan hydroxylase
UV : ultraviolet
UVR : ultraviolet radiation
INTRODUCTION

Melatonin (N-acetyl-5-methoxytryptamine) is an indoleamine that is derived from the biogenic amine serotonin, which is synthesized from the amino acid tryptophan.\(^1\)\(^-\)\(^3\) Melatonin synthesis mainly occurs in pinealocytes (melatonin-producing cells of the pineal gland), but the brain-derived melatonin is insufficient to maintain vital processes.\(^1\)\(^-\)\(^3\) Therefore, two components of the melatonin production system should be considered: the central component located in the pineal gland, and the peripheral component that consists of other light-independent cells, including cells of the skin, retina, bone marrow, cardiovascular system, and gastrointestinal mucosa.\(^1\)\(^-\)\(^5\) Various physiological activities involve melatonin, including the circadian rhythm, thermoregulation, immune responses, the oxidative process, apoptosis, and mitochondrial homeostasis.\(^6\)\(^-\)\(^7\) Melatonin produced by the skin is rapidly metabolized to maintain homeostasis against environmental stresses, including solar radiation, air pollution, and cosmetic products.\(^6\)\(^-\)\(^8\) Protecting internal homeostasis against the external environment is one of the functions of the skin as the largest organ of the human body.\(^9\)

Ultraviolet radiation (UVR) is the primary extrinsic cause of the skin’s susceptibility to damage, because ultraviolet A (UVA) and ultraviolet B (UVB) can penetrate the ozone layer.\(^1\)\(^0\)\(^-\)\(^1\)\(^1\) The accumulation of UV-induced ROS by oxidative stress as the consequence of oxidative damage to the skin is believed to result in the development or exacerbation of premature skin aging, which condition is called photoaging or photodamage.\(^1\)\(^2\)\(^-\)\(^1\)\(^3\) Evident symptoms may be seen in the formation of irregular pigmentation and wrinkles, and in the reduction in skin elasticity.\(^1\)\(^4\)\(^-\)\(^1\)\(^5\) Ultraviolet (UV) activates and inhibits various signaling pathways in the dermis and epidermis, leading to a decrease of the extracellular matrix (ECM) content and provoking an uneven skin structure or even collapse of the skin.\(^1\)\(^1\)

Melatonin is starting to be considered as a therapeutic option in photoprotection and skin aging due to its antioxidant effects, indicating its critical role in preventing damage due to deoxyribonucleic acid (DNA) repair mechanisms.\(^1\)\(^3\)\(^-\)\(^6\) However, current melatonin use in dermatology and aging indicates that it has not yet taken its place in clinical therapy despite its potential.\(^3\)

Research articles focused on the effect of melatonin in photoaging that were collected from various databases, such as Google Scholar and PubMed for the period of 2019-2023, were used for data collection, by using the term ‘melatonin’ alone or in combination. Initially, 634 articles were found to match the inclusion criteria, but in the end 628 articles were removed due to duplication, failure of access, and irrelevant topic. Finally, the writing of this review was carried out using the 6 articles that met the inclusion criteria to be written into a full paper (Figure 1).

Thus, this review will focus on the potential effect of melatonin in the prevention of photoaging by using the most recent significant data in the last five years (Table 1).

**Melatonin**

Melatonin, or N-acetyl-5-methoxytryptamine, was initially thought to change the skin color of frogs, and thus was considered to be associated with human skin disorders,\(^4\)\(^2\)\(^2\)\(^2\)\(^3\) until its function as an antioxidant was discovered.\(^2\)\(^4\)

Melatonin synthesis occurs in pinealocytes (melatonin-producing cells) in the pineal gland, a neuroendocrine gland located in the brain. The synthesis starts with the formation of 5-hydroxytryptophan from the amino acid tryptophan with the help of the enzyme tryptophan hydroxylase, then 5-hydroxytryptophan is transformed into serotonin. The enzyme arylalkylamine N-acetyltransferase aids in the acetylation of serotonin into N-acetylserotonin (NAS), which is finally converted into melatonin.\(^5\) This process is mainly controlled by the circadian rhythm, whose activity increases at night and decreases during the day, and also by the
modulation of the hypothalamus by the suprachiasmatic paraventricular nuclei, thus rendering melatonin production sensitive to light, while variations in the light-dark cycle incredibly alter melatonin release. (23,25,26) Light inhibits melatonin synthesis by melanopsin breakdown followed by the activation of the suprachiasmatic nucleus (SCN). (25,27,28) The photopigment melanopsin in the intrinsically photosensitive retinal ganglion cells (ipRGCs) presents light information to the central nervous system which leads to melatonin suppression. (28–30) Activation of the suprachiasmatic nucleus (SCN) through the retinohypothalamic tract (RHT) inhibits the GABAergic neurons, which then reduce the activity of the intermediolateral nucleus of the spinal cord (IML), paraventricular nucleus (PVN), and superior cervical ganglion, activate the pineal gland, and suppress melatonin production. Conversely, darkness activates the pineal gland circuit through postganglionic sympathetic neurons, which enables further synthesis of melatonin and N-acetyltransferase. (3,25,27,28)

The pineal gland and melatonin act as mediators between environmental cyclical phenomena and physiological regulatory processes. (5) Melatonin is also synthesized locally at extrapineal sites, including the skin, thymus, bone marrow, cardiovascular system, eyes, and gastrointestinal tract. (1,4,5) The relevance of melatonin to human skin physiology and pathology has captured attention, resulting in a variety of studies, ranging from anti-aging, photoprotective effects, immunomodulation, anti-melanoma effects, barrier integrity-maintaining activity,
Table 1. Reports on the protective effects of topical melatonin against UVR-induced skin photoaging (16–21)

<table>
<thead>
<tr>
<th>Author</th>
<th>Research subjects</th>
<th>Interventions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldberg et al. (16)</td>
<td>103 females aged 40-65 years with Fitzpatrick type I-IV and visible crow’s feet wrinkles.</td>
<td>Melatonin-based cream for 12 weeks</td>
<td>Decreases wrinkles (-11%) and redness (-70%), increases skin firmness (+8%).</td>
</tr>
<tr>
<td>Narda et al. (17)</td>
<td>- Primary adult human epithelial keratinocytes (HEKs) and human dermal facial fibro- blasts (HDFs) - Abdominal skin explants from 2 Caucasian women aged 30 and 32 years with Fitzpatrick type II.</td>
<td>- 10 μL melatonin-based cream for 4 days - 12.5 J/cm² of UVA and 50 ml/cm² of UVB</td>
<td>Increases filaggrin and aquaporin in HEKs, collagen (I, III) in HDFs, also precursor procollagen type I and tropoelastin in skin explants. Decreases apoptotic sunburn cells in UV-exposed skin explants.</td>
</tr>
<tr>
<td>Egrilmez et al. (18)</td>
<td>HDFs from 10 fe-males aged 20-40 years old with Fitz-patrick type III and IV</td>
<td>- 1 μM melatonin - 0.1 J/cm² of UVB (311 ± 5 nm) for 6 s</td>
<td>Melatonin inhibits UVB-induced oxidative/nitrosative stress damage, downregulates UV-in-duced activation of EGFR and the c-Jun N-terminal kinase (JNK)/activator protein-1 (AP-1) signaling pathway, decreases UVB-induced activities of matrix metalloproteinase (MMP)-1 and MMP-3, increases tissue inhibitor of metalloproteinase (TIMP)-1 and procollagen type I C-peptide (PIP-C).</td>
</tr>
<tr>
<td>Hou et al. (19)</td>
<td>30 Kunming female mice (35 ± 5 g)</td>
<td>- 300 μl melatonin elastic liposomes (MLT-ELs) - 2 hours irradiation with UV lamp (223 nm) 30 cm away, for 10 weeks</td>
<td>MLT-ELs ameliorate the skin elasticity, enhance the skin hydration level, and preserve the integrity of dermal collagen and elastic fibers.</td>
</tr>
<tr>
<td>Koçtürk et al. (20)</td>
<td>HDFs from 10 fe-males aged 20-40 years with skin type III and IV</td>
<td>- 1 μmol/L melatonin-in - 20 J/cm² of UVA (320-400 nm)</td>
<td>Melatonin decreases UVA-induced oxidative/nitrosative stress damage, also suppresses phospho-rylation of epidermal growth factor receptor (EGFR), activation of mitogen-activated protein kinases (MAPK)/AP-1 signal transduction pathway, and production of MMPs.</td>
</tr>
<tr>
<td>Ma et al. (21)</td>
<td>- Human Immortal-ized foreskin keratinocytes (HaCa Ts) from 5 adult men - 21 C57BL/6 J mice aged 8 weeks</td>
<td>- 1, 2.5, and 5% melatonin - 80 ml/cm² of UVB lamp (311–313 nm) 40 cm away for 46 s at 1.5 mW/ cm² power density - 600 ml/cm² of UVB (311–313 nm) 15 cm away for 130 s at 4 mW/cm² power density.</td>
<td>Melatonin inhibits UVB-induced senescence-assoc-iated pigmentation via the p53-tyrosinase pathway in primary melanocytes and prevents pigmentation obviously in the dorsal and ear skin of C57BL/6 J mice.</td>
</tr>
</tbody>
</table>
pigmentation modulatory effects, to potential hair growth promoting effects.\(^{18,31–34}\)

Melatonin in the skin is a potent antioxidant, because it can protect the skin from UV damage by protecting mitochondrial and cellular functions.\(^{35–37}\) The antioxidant effects of melatonin result in (i) direct scavenging of ROS/RNS; (ii) accelerating antioxidant enzyme activity; (iii) protecting against oxidative damage; (iv) synergistic effects with other antioxidants; (v) improving electron transport efficiency in the mitochondrial respiratory chain, and (vi) limiting overproduction of free radicals by reducing electron leakage.\(^{38}\) Several ROS/RNS species are involved in this process, including the following radicals: hydroxyl (OH), peroxyl, \(O_2^-\), hydrogen peroxide (H\(_2\)O\(_2\)), singlet oxygen (\(1^\text{O}_2\)), peroxynitrite (ONOO\(^{-}\)), and nitric oxide (NO).\(^{39}\)

The melatonin biosynthetic pathway of the skin begins with the hydroxylation of tryptophan by tryptophan hydroxylase (TPH) to form 5-hydroxytryptophan, which is decarboxylated by aromatic amino acid decarboxylase. Serotonin as the product is acetylated by arylalkylamine N-acetyltransferase (AANAT) or N-acetyltransferase (NAT). Finally, 4-hydroxyindole-O-methyl transferase (HIOMT) converts N-acetylserotonin into melatonin. The final metabolites of melatonin are 5-methoxytryptamine (5-MTT), 5-methoxytryptophan alcohol (5-MTOL), 2-hydroxymelatonin, N1-acetyl-N2-formyl-5-methoxykynurenamine (AFMK), N1-acetyl-5-methoxykynuramine (AMK), all of which are dominated by 6-hydroxymelatonin (6(OH)M) in epidermal cells.\(^{26}\)

The regulatory effects of melatonin in the skin are mediated via specific membrane and nuclear receptors or binding sites in mitochondria and cytoplasm, including melatonin-1 (MT1), melatonin-2 (MT2), retinoid Z receptor-\(\alpha\) (RZR-\(\alpha\)), as well as calmodulin, calreticulin, and NADPH-quinone oxidoreductase 1/2 (NQO1/2), previously known as melatonin 3 (MT3).\(^{26,40,41}\) Melatonin 1 (MT1) and MT2 belong to the G protein-coupled receptor family which is important for skin protection against aging.\(^{19,26,41}\)

Human skin expresses a strong bias toward MT1, which is located mainly in the epidermis (stratum granulosum, stratum spinosum, outer and inner root sheath of hair follicles), whereas MT2 is often found in hair follicles and blood vessels, with lower expression or absence in the epidermal cells.\(^{1,34,40}\)

The timing of MT administration is crucial as the effects appear only when the phase response curve is produced. Formulation and dose affect the half life and bioavailability, which are 1-2 hours and 1-74% respectively. The metabolism of oral MT occurs mainly in the liver (90%) and involves the enzyme CYP1A2. At present, melatonin supplements are extensively used for insomnia, in combination with other ingredients to strengthen the effect. The effective dose needs to be settled by further studies because of different recommended doses, ranging from 0.3 to 10 mg, by considering the risk of desensitization of melatonin receptors resulting from higher than physiological concentrations.\(^{23,34}\) It has been shown that topical melatonin reduces the formation of free radicals and has photoprotective properties.\(^{3,34}\) Considering the role of melatonin in antiaging, it is suggested that topical application of exogenous melatonin and/or its metabolites should be considered.\(^{23,34,41}\)

**Melatonin and aging**

Melatonin has a higher concentration in the mitochondria of melatonin-producing cells than in other parts of the cells, establishing its significant role as a mitochondrial-targeted molecule in mitochondrial processes.\(^{34,42,43}\) The beneficial effects of melatonin administration depend on mitochondrial physiology. Melatonin can easily cross the cell membrane due to its hydrophilic and lipophilic structure, which supports its protective effects on intracellular and nuclear fragments against oxidative stress.\(^{18}\)

Melatonin has a strong influence on mitochondria in maintenance function, regulation of activity, protection against possible damage due to pathologies from free radicals or accumulation.
of suprathreshold Ca\(^{2+}\) concentrations, and preventing the opening of the mitochondrial permeability transition pore (mPTP).\(^{1,34,44}\)

Mitochondrial dysfunction underlies the development of various physiological and pathological conditions, such as aging, neurodegenerative disorders, cardiovascular diseases, liver disease, skeletal muscle disorders, and diabetes. The oxidative process is associated with mitochondrial dysfunction as a result of the effects of aging. The protective effect of melatonin on aging is related to its scavenging potential in the mitochondrial matrix and in the intermembrane space.\(^{1}\) Figure 2 shows that at the mitochondrial level, melatonin directly scavenges ROS/RNS in the mitochondrial matrix and in the intermembrane space, and also inhibits mitochondrial-inducible nitric oxide synthase (m-iNOS) expression.\(^{3,34,45}\) ROS/RNS are neutralized, which also improves oxidative phosphorylation and adenosine triphosphate (ATP) production.\(^{3,45}\)

The target of melatonin in the mitochondria is management of the Ca\(^{2+}\)-induced cyclosporin A-sensitive mPTP, which is formed in the initial stage of apoptosis as a response to oxidative stress and the accumulation of threshold concentrations of Ca\(^{2+}\) in the matrix.\(^{1,44}\) Aging causes the mitochondria to become more sensitive to the opening of mPTP, thereby resulting in disconnection of respiration and phosphorylation, depolarization of the inner membrane, swelling of the mitochondria, decreased activity of the Ca\(^{2+}\) transport system, oxidative stress accumulation, increased ROS or RNS production, increased permeability of the inner mitochondrial membrane, and release of proapoptotic factors.\(^1\)

Melatonin acts as an anti-apoptotic agent on mPTP through several mechanisms, either directly by dose-dependent inhibition of mPTP opening, or indirectly by maintaining the balance in alterations of Ca\(^{2+}\) homeostasis, preventing cardiolipin peroxidation which facilitates inhibition of cytochrome C release from the mitochondria.\(^{1,44}\)

Age-related mitochondrial dysfunctions are associated with oxidative stress, decreased activity of the Ca\(^{2+}\)-transporting system, increased ROS production, and increased permeability of the inner mitochondrial membrane. ROS will induce cardiolipin peroxidation to facilitate the release of cytochrome C (proapoptotic factors) from the inner mitochondrial membrane.\(^{1,46}\) Cytochrome C, an electron carrier in the mitochondrial electron transport chain, acts as a cellular life-and-death decision maker molecule that regulates cellular energy supply and apoptosis.\(^{47,48}\) Mitochondrial homeostasis is maintained by melatonin through its protective effect, which plays a critical role in the physiological processes of the cell, such that the defect in the mitochondria is considered the main cause of many pathological processes, including skin aging.\(^{1,49}\)

**Figure 2.** Melatonin as a major skin protectant
Melatonin and skin aging

Circadian rhythm homeostasis is regulated by epidermal stem cells to maintain a healthy skin by managing the energy supply and cellular conditions for optimal protection and repair. The circadian rhythm synchronizes each type of skin cell with the natural rhythm of the human body. A decline in circadian rhythm and gene expression that can contribute to oxidative stress through chronic or increased accumulation of ROS is associated with aging. Important mechanisms of the skin in maintaining homeostasis include the regulation of oxidative stress mechanisms.

The skin is a complete and independent melatonergic system, which can synthesize and metabolize melatonin on its own. Melatonin produced in the skin generates a potent protective effect against cutaneous damage caused by external factors, especially UV radiation, pollutants, and pathogens. The melatonergic antioxidative system regulates skin homeostasis and prevents UV harmful effects on the skin. Keratinocytes are considered to be a target for UV damage, while melatonin protects these cells through the prevention of UV-mediated apoptosis. The synthesis of peripheral melatonin decreases with aging.

Melatonin is metabolized in the mitochondria of skin cells. Furthermore, regarding UV solar damage, melatonin considerably counteracts the massive generation of ROS and also ameliorates mitochondrial and DNA damage that is induced by external factors penetrating into the skin and accumulating in the stratum corneum to activate antioxidant enzyme synthesis, which eliminates free radicals and repairs oxidative damage in the skin.

High concentrations of melatonin are biosynthesized in the mitochondria of the skin cells as one of the protective molecules that incapacitate ROS by electron donation and RNS by nitrosylation reactions. Melatonin diminishes MMP-1 expression and increases collagen XVII expression in HaCaT keratinocytes exposed to UVB by reducing ROS production. Nuclear factor erythroid 2-like (Nrf2) expression is also stimulated to overcome the elevated antioxidant response of keratinocytes and melanocytes against UVB-induced oxidative stress.

Unlike classical antioxidants with the ability to only scavenge a single radical species, melatonin and its derivatives (6-hydroxymelatonin, NAS, AFMK, AMK, 5-MTT) have the capacity to protect keratinocytes and melanocytes against UVB-induced cell damage by inducing the repair of DNA damaged by UVB, and also to reduce the formation of cyclobutane-pyrimidine dimers (CPDs) and 6–4 pyrimidine–pyrimidone photoproducts.

Melatonin receptor binding stimulates the expression of antioxidant enzymes to maintain skin pigmentation, given that the pigmentation process itself is cytotoxic and generates ROS and quinone compounds. Age-dependent decrease in MT1 receptor expression and reduced melatonin levels result in increased damage to the cells of the skin and physical signs of aging, which are found in aged human fibroblasts.

Melatonin and UV protection

The skin as the largest organ in the human body suffers from environmental stressors, such as UVR, poor nutrition, air pollution, and pathogens, which can lead to premature skin aging. The most significant factor in skin aging is UVR exposure, in addition to alterations in homeostatic circadian rhythm. Ultraviolet radiation (UVR) affects cutaneous biology and contributes to photodamage by stimulating the free radicals ROS/RNS, leading to chronic inflammation, impaired regenerative capacity and epidermal barrier function, skin microbiome alteration, as well as photaging. Free radicals develop in the skin cells instantly under the effect of UVR, and participate in the degradation of lipids, nucleic acids, and proteins. Chronic exposure of the skin stimulates ROS and RNS production and produces oxidative stress or direct DNA damage.
instantly, leading to apoptosis of fibroblasts and keratinocytes.\textsuperscript{(23,34)} Premature skin aging as a result of photoaging is characterized by deep coarse wrinkles, mottled irregular hyperpigmentation, thin, lax, and leathery skin texture mainly in exposed areas such as the skin of the face, neck, and hands, accompanied by lentigines, telangiectasias, and sallowness.\textsuperscript{(17,18,59,60)}

Solar UVR consists of electromagnetic wavelengths between 100 and 400 nm that reach the terrestrial surface and has a direct effect on human health and terrestrial and aquatic ecosystems, as well as material degradation.\textsuperscript{(61–64)} It is divided into three components, depending on its transmission capability in the atmosphere and its biological effects: UVA (315–400 nm) makes up most of the UVR received on the terrestrial surface; UVB (280–315 nm) which is partially absorbed into the atmosphere, and UVC (100–280 nm) which is completely absorbed by stratospheric ozone.\textsuperscript{(34,64)} Both UVA and UVB wavelengths have been shown to contribute to photoaging, by imbalanced ROS/RNS production and/or by direct DNA damage.\textsuperscript{(34)} In Figure 3, it is stated that approximately 95% of UVA reaches the earth’s surface and penetrates up to 10 times deeper into the reticular dermis, such that UVA plays a major role in the UVR-induced oxidative damage and the aging process of the skin.\textsuperscript{(18,34,65)} Ultraviolet A (UVA) affects several functions of the skin as it is absorbed by the dermis, while UVB is absorbed by the epidermis.\textsuperscript{(23)}

![Figure 3. The role of melatonin in the prevention and treatment of skin aging](image-url)
Ultraviolet A penetrates deeper into the reticular dermis, deteriorates the ECM by increasing MMP transcription, especially the collagenolytic enzyme MMP-1 in dermal fibroblasts, to produce collagen degradation and procollagen inhibition. Imbalance of TIMP1 and MMPs contributes to wrinkle formation. On the other hand, UVB has a greater destructive effect despite its lesser penetration into the skin as it is absorbed by DNA and RNA directly to form photoproducts in keratinocytes, such as cyclobutane pyrimidine dimers (CPDs). Photolesions in DNA trigger gene mutations, including tumor suppressor gene p53. Accumulation of p53 activates gene transcription responsible for cell cycle arrest, which finally may provoke cell apoptosis.\(^{(18,34,66)}\)

The accumulation of free radicals interferes with cell signaling pathways while cytokine release leads to inflammation. Overproduction of ROS activates MAPKs and transcription factors, including Nrf2, nuclear factor κB (NF-κB), and JNK. Nuclear factor erythroid 2-like (Nrf2) is crucial for cutaneous protection during skin aging.\(^{(34)}\) Ultraviolet A (UVA) has a longer wavelength and can reach the dermal fibroblasts to stimulate Nrf2-mediated antioxidant gene expression. On the other hand, UVB indirectly activates Nrf2 through the products of its action, namely vitamin D3 derivatives.\(^{(34,67)}\) Ultraviolet B (UVB) increases AP-1 and NF-κB.\(^{(34)}\) Activator protein-1 suppresses the transformation of growth factor-β (TGF-β) receptors, and inhibits procollagen synthesis, stimulates collagen breakdown by MMP, and triggers NF-κB as the main activator of the inflammatory response.\(^{(34,68)}\) Nuclear factor-κB (NF-κB) elevates proinflammatory cytokines such as interleukin-1 (IL-1), IL-6, tumor necrosis factor-β (TNF-β) and MMPs, and decreases TGF-β and collagen type I synthesis.\(^{(34)}\)

The aging suppressor hormone klotho also reduces UV-induced inflammation.\(^{(34)}\) Klotho can inhibit the pro-inflammatory NF-κB pathway by preventing NF-κB translocation.\(^{(34,69)}\) Sirtuins (SIRTs) were discovered to have the ability to modulate the expression of genes affected in the oxidative stress process,\(^{(34,70)}\) SIRT1 expression, which can be stimulated by melatonin, is found to be reduced after UVB irradiation which leads to an increase in proinflammatory NF-κB activity and MMPs, especially MMP-1 and MMP-3.\(^{(34,71)}\) Photoaged skin is characterized intrinsically by massive loss of dermal collagen as a result of decreased type I and III procollagen synthesis and increased degradation of mature collagen by MMPs, leading to increased type I procollagen (PIP-C) biosynthesis, in response to UV exposure.\(^{(17,18)}\) Type I collagen imparts strength and resiliency to the skin, being the essential structural component of the dermal extracellular matrix. The disturbed balance between collagen synthesis and matrix collagen degradation by UV-induced oxidative stress upregulates the activities of MMP-1 (interstitial collagenase) and MMP-3 (stromelysin-1) in the skin, leading to collagen breakdown. Loss of balance between MMPs and TIMP contributes to skin connective tissue damage related to photoaging.\(^{(18,72)}\) Ultraviolet radiation exposure also reduces elastin synthesis and increases elastic fiber degradation. Accumulation of non-functional elastic fibers within the dermis produces yellow-colored and leathery photoaged skin. Collagen and elastin breakdown reduces the elasticity and tensile strength of the skin, resulting in wrinkling and sagging. It also disturbs the structural integrity of the epidermis (stratum corneum), alters hydration and lipid properties, also skin color, thickness, and light absorbing properties.\(^{(17)}\)

Optimal intracellular levels of melatonin can prevent damage from UV irradiation because of its antioxidant properties by stimulating endogenous enzymes to bind free radicals of all types to reduce p53 expression and the toxic effects of ROS/RNS, restoring antioxidant enzyme activity, avoiding an increase in mitochondrial membrane permeability, as well as enhancing DNA repair.\(^{(12,35,65)}\) The p53 protein is a multi-functional protein that plays many roles in determining cell fate in response to cellular stress, including as a central regulator of the DNA
damage response that impacts aging. Activation of p53 in response to DNA damage induces senescence and apoptosis when DNA damage cannot be repaired. In addition, melatonin inhibits UV-induced erythema, and protects keratinocytes, fibroblasts, and melanocytes against UV-induced photoaging. Melatonin stimulates antioxidant enzymes to bind free radicals, then reduces p53 expression and the toxic effects of ROS/RNS, and also enhances DNA repair.

**CONCLUSION**

There have been numerous studies conducted using melatonin-based cream on either animals or humans, and a recent study has compared the effects of melatonin on skin in various percentages. All of these studies are significant because the protective effect of melatonin against UV-induced skin photoaging was verified to have been derived from its role in melatonin antioxidative systems through several signaling pathways, such as JNK/AP-1, MAPK/AP-1, and p53-tyrosinase. Melatonin reduces apoptotic sunburn cells (keratinocytes), UVB-induced senescence-associated pigmentation, and MMPs, while increasing the integrity of procollagen precursors, collagen, and elastic fibers. By understanding these systems, the application of melatonin in dermatological therapy is expected to be adjusted according to its potential. The ultimate outcome will be seen phenotypically as reduced signs and symptoms of aging.

**CONFLICT OF INTEREST**

The authors declare that they have no conflict of interest.

**FUNDING**

No funding was received for conducting this study.

**ACKNOWLEDGEMENTS**

The authors would like to thank Magister Program Anti-Aging Medicine, Faculty of Medicine, Universitas Udayana, for giving the opportunity to conduct this study and facilitating the writing of this manuscript.

**AUTHOR CONTRIBUTIONS**

MVPS searched, analyzed, and wrote the journals. IGAW supervised all the process and gave suggestions. All authors contributed to revisions and approved the final version.

**DATA AVAILABILITY STATEMENT**

The data presented in this study are available within the article.

**REFERENCES**

7. Mendes C, Gomes G, Belpiede LT, et al. The effects of melatonin daily supplementation to aged rats...


27. Mure LS, Vinberg F, Hanneken A, Panda S. Functional diversity of human intrinsically...


