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Mechanism of action and promising clinical application of melatonin from a dermatological perspective

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ABSTRACT

Melatonin is the main neuroendocrine product in the pineal gland. Melatonin can regulate circadian rhythm-related physiological processes. Evidence indicates an important role of melatonin in hair follicles, skin, and gut. There appears to be a close association between melatonin and skin disorders. In this review, we focus on the latest research of the biochemical activities of melatonin (especially in the skin) and its promising clinical applications.

1. Introduction

Melatonin is secreted mainly by the pineal gland [1]. The effects of melatonin on the central nervous system have been studied extensively, including the regulation of mood, sleep, reproduction, or acting as a scavenger of free radicals. However, it also has critical roles in extra-pineal organs, from the skin and gut to bone and spleen [2]. Investigations of local secretion of melatonin, its metabolites, as well as receptors on the organs stated above and some organelles [3–6] have shown that melatonin has antioxidation, oncostatic, immunoregulatory, anti-inflammatory [7], photoprotective [8], and barrier integrity-maintaining activities [9,10]. Thus, relatively high concentrations of melatonin and its metabolites are required to elicit such protective effects, which cannot be achieved by secretion from the pineal gland.

Inflammation is a complex and essential biological response to tissue injury by different stimuli. It is important for homeostasis and usually modulated delicately with regard to production of free radicals and activation of pro-oxidant enzymes. Nevertheless, inflammation can become uncontrolled and perilous for the host. Pathological inflammation has been associated with numerous diseases, and anti-inflammatory drugs are broad-spectrum or non-targeting, and can have many harmful side effects. Hence, identification of appropriate candidate agents for controlling chronic inflammation without impairment of the physiologic inflammatory response is important.

Accumulating evidence suggests that melatonin may exert antioxidant effects and combat inflammation. It is also claimed to have an important role in inhibiting malignancy, aiding tissue repair and immunoregulation. Hence, melatonin as well as its metabolites and receptors could become therapeutic targets.

2. Melatonin in the skin

2.1. Synthesis and metabolism

Skin is deemed to be the site for the production and metabolism of

Abbreviations: MT1/2, Melatonin receptor; Trp, Tryptophan; 5HT, Serotonin; MT, Melatonin; ROS, Reactive oxygen species; RNS, Reactive nitrogen species; iNOS, Inducible nitric oxide synthase; COX-2, Cyclooxygenase-2; NF-κB, Nuclear factor kappa-B; IkB, NF-κ-B inhibitor; IKK-α, IkB kinase-α; TPH, tryptophan5-hydroxylase enzymes, including dominant TPH1 and TPH2; AAD, Aromatic amino acid decarboxylase; AANAT/NAT, serotonin-N-acetyltransferase(s); HIOMT, 4-hydroxyindole-O-methyl transferase; CYP450, cytochrome P450; HSP 70, Heat Shock Protein 70; NQO1, NAD(P), quinone oxidoreductase 1; NQO2, NRH, Quinone oxidoreductase 2; Nrf2, Nuclear erythroid 2-related factor; RZR-α, Retinoid Z receptor α; HO-1, heme oxygenase-1; γ-GCS, c-glutamylcysteine synthetase; PEPT1/2, oligopeptide transporter 1/2; SOD, superoxide dismutase; GPx, Glutathione peroxidase; CAT, catalase; GSH, Glutathione; Casp-1/3, caspase 1/3; IL-1β, interleukin-1 β; IL-6, interleukin- 6; DNCB, 2,4-dinitrochlorobenzene.

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melatonin. Although the skin is relatively desiccative and nutrient-deprived, the stratum corneum of the epidermis is high in tryptophan derived from dead keratinocytes and broken keratin, which might provide abundant substrates for melatonin synthesis. Studies have shown that melatonin and its metabolites can be found in keratinocytes, melanocytes, macrophages, fibroblasts, mast cells, and skin appendages. The key enzymes for melatonin synthesis, such as tryptophan 5-hydroxylase (TPH)1, TPH2, aralkylamine N-acetyltransferase (AANAT), and 4-hydroxyindole-O-methyl transferase (HIOMT), can also be detected in the skin.

Mitochondria are important organelles for enriching and transporting melatonin into cells. In various types of tumor cells in humans, specific melatonin transporters, such as peptide transporter (PEPT)1/2 on mitochondrial membranes, have been documented [11]. Beyond that, mitochondria can synthesize and metabolize melatonin. He and colleagues found that the mitochondria in oocytes have the key enzyme AANAT/NAT, which can transform serotonin to melatonin [12]. Melatonin in mitochondria is metabolized through different metabolic pathways, including the monooxygenase (cytochrome P450 (CYP450)-dependent) pathway and peroxidase (kynuric) pathway [13]. However, melatonin is a small molecule with an amphiphilic nature, so it can "seep" into all cellular compartments, which endows it with pleiotropic bioactivities. Whether mitochondria are the major sites for melatonin synthesis and exerting functions in skin cells remains to be demonstrated.

The melatonin biosynthetic pathway in the skin is described in Fig. 1. The process begins with hydroxylation of tryptophan by TPH enzymes to obtain 5-hydroxytryptophan. TPH1 is expressed widely in all skin cells. TPH2 expression can also be detected in skin fibroblasts, melanocytes, and cultured human keratinocyte cells. 5-hydroxytryptophan is decarboxylated further by the aromatic amino acid decarboxylase. The product, serotonin, is acetylated by AANAT/NAT. The final synthetic step is completed by HIOMT, which converts N-acetylserotonin into melatonin, though CYP450 can reverse this conversion [14]. In all resident skin cells, melatonin is metabolized through classic, indole, and kynuric pathways. Its final metabolites are the products of 5-methoxytryptamine (5-MTT), 5-methoxytryptophan alcohol (5-MTOL), 2-hydroxymelatonin, N1-acetyl-N2-formyl-5-methoxykynurenamine (AFMK), and 6-hydroxymelatonin (6(OH)M). Among these metabolites, 6(OH)M is the main product in epidermal cells. In the classical pathway, melatonin is metabolized to 6(OH)M by enzymes of the CYP450 family. In the indole pathway, melatonin is transformed to 5-MTT by melatonin deacetylase, then converted to 5-methoxyindoleacetaldehyde by monoamine oxidase and, finally, metabolized by acetaldehyde dehydrogenase to 5-Methoxyindole-3-acetic acid or by alcohol dehydrogenase to 5-MTOL. The kynuric pathway involves two types: enzymatic and non-enzymatic. In the enzymatic pathway, melatonin is metabolized by indoleamine-2,3-dioxygenase to produce AFMK. AFMK is metabolized further by arylamine formamide to produce N1-acetyl-5-methoxykynuramine (AMK). Also, under irradiation with ultraviolet (UV) light, melatonin is metabolized through non-enzymatic kynuric pathways in skin cells [15]. Maharaj and colleagues demonstrated that addition of melatonin into a cell-free system and exposing melatonin to visible light produced high levels of reactive oxygen species (ROS), which oxidized melatonin to generate 6(OH)M and AFMK [16].

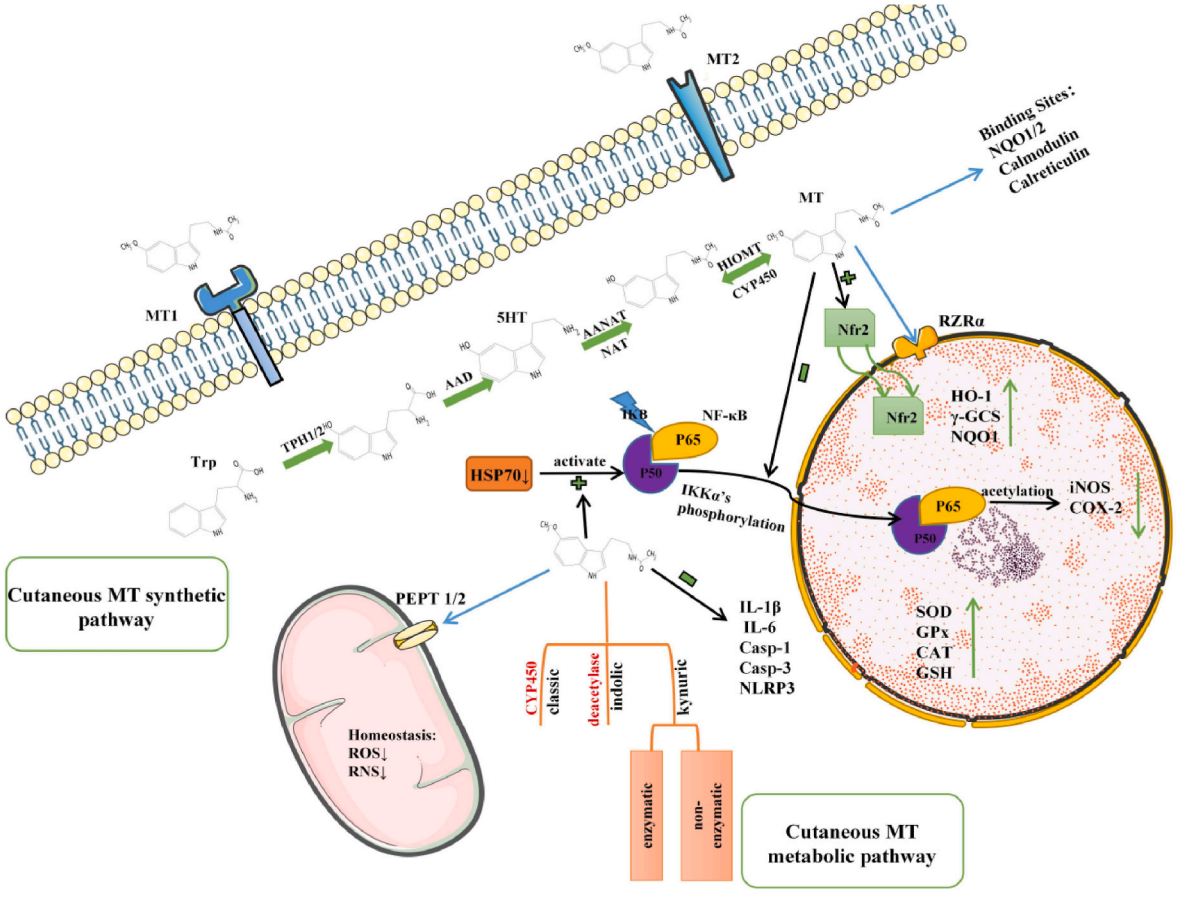

Fig. 1. The cutaneous melatonin synthetic and metabolic pathways as well as interactions with several cellular signaling pathways. Melatonin binds to membrane-bound receptor MT1 or MT2, nuclear receptor RZR-α and intracellular binding sites including NQO1/2 (previously described as MT3), Calmodulin, Calreticulin. Subsequent activation of signal transduction cascades stimulates the expression of antioxidative enzymes and inhibit inflammatory mediators. Melatonin might also be transported to mitochondria through PEPT1/2.

2.2. Melatonin receptors in the skin

Melatonin acts through membrane receptors and nuclear receptors. However, there are also binding sites for melatonin in mitochondria and cytoplasm. Melatonin receptor type 1 (MT1) and MT2 are membrane receptors and belong to a family of G protein-coupled receptors. Retinoid Z receptor-α is a nuclear receptor found in skin cells [17]. Apart from membrane receptors and nuclear receptors, binding sites for melatonin in cytoplasm and mitochondria have been reported: calmodulin, NAD(P)H:quinone oxidoreductase 1 (NQO1), dihydronicotinamide riboside:quinone oxidoreductase 2 (NQO2), and calreticulin [18–20].

3. Mechanism of action of melatonin from a dermatological perspective

At the pineal level, melatonin modulates physiological processes related to the circadian rhythm in animals. Besides, melatonin plays an important part in anti-inflammation , antioxidation [21–23], anti-tumor process [24], innate immunity and adaptive immunity [25]. Given the daily variations of the immune system in organs and cells, the roles of locally produced melatonin have been noted in bone marrow, the spleen, gut, and skin [2,9]. Notably, Dong and colleagues showed that melatonin production in the skin is controlled by the circadian rhythm. Also, melatonin can dose-dependently stimulate expression of the period 1 (PER1) clock gene in fibroblasts and keratinocytes, thereby implying a feedback loop in skin cells [8]. Melatonin in the skin can augment the thickness, enhance barrier function, as well as increase sebum secretion and pH of the skin. These regulatory effects change with the time of day. For example, the effect of proliferation of inactive cells is most obvious during the day, whereas active repair of DNA as well as increases in cell proliferation, skin temperature, barrier permeability, and skin blood-flow are strongest at night. Expression of melatonin receptors also changes with cell maturation, and then affects physiological functions [8]. Locally produced melatonin also engages in anti-inflammation, antioxidation, anti-tumor processes, as well as innate immunity and adaptive immunity. Here we discuss the mechanism of the processes stated above.

3.1. Antioxidation mechanism

The antioxidant properties of melatonin involve several mechanisms. Besides scavenging free radicals such as ROS and reactive nitrogen species (RNS) directly from stimulated skin cells or mitochondrial oxidative respiration [26], melatonin can act synergistically with other antioxidants, such as vitamin C or α-tocopherol [27]. Similarly, the melatonin derivative AMK can react with carbamoyl phosphate, hydrogen peroxide, and copper-II ions from oxidation to form N-[2-(6-methoxyquinazolin-4-yl)-ethyl] acetamide [28], bur it can also react with nitrosonium ions, nitric oxide (NO), or nitroxyl radicals to produce 3-acetamidomethyl-6-methoxyoctenone, which eliminates free radicals directly.

Melatonin also regulates antioxidases to decrease the concentration of free radicals indirectly. Kilańczyk and collaborators found that melatonin augmented the activities of superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx), and increased glutathione (GSH) expression in skin fibroblasts from healthy controls and patients suffering from diabetes mellitus [29]. Fischer and colleagues discovered that melatonin-enhanced antioxidant enzymes could prevent ultraviolet (UV)B light-induced exhaustion of antioxidases in human skin, reduce ROS, and inhibit oxidative damage to DNA [30]. Kleszczyński and colleagues demonstrated that melatonin mediated the translocation of nuclear erythroid 2-related factor (Nrf2) from the cytoplasm to the nucleus, combined with antioxidant response elements in the nucleus and, ultimately, promoted production of antioxidant enzymes, including heme oxygenase-1 (HO-1), NQO1, and gamma-glutamylcysteine synthase (γ-GCS), to protect epidermal keratinocytes from UVR light-mediated oxidative stress [31].

3.2. Anti-inflammatory mechanism

Chronic inflammation is accompanied by an increased level of inflammatory mediators (especially free radicals), NO, and pro-inflammatory factors. Furthermore, chronic inflammation is closely related to degenerative diseases, autoimmune diseases, and even cancer. In pathological models such as tissue ischemia, aging, lipopolysaccharide-induced inflammation, diabetic retinopathy, and spinal-cord injury, melatonin can reduce translocation of nuclear factor-kappa B (NF-κB) through receding inhibitory kappa B kinase alpha (IKKα) phosphorylation and its downstream inflammatory genes, including inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2) [32–34], and other pro-inflammatory factors. Kleszczynski et al. found that in human epidermal keratinocytes, melatonin could reverse the pro-inflammatory effects induced by an excessively activated NF-κB pathway after depletion of heat shock protein 70 (HSP70), and inhibit production of the pro-inflammatory factors interleukin (IL)-1β, IL-6, caspase-1, and the pro-apoptotic protein caspase-3 [35]. In a radiation-induced model of oral mucositis, highly oxidized mitochondria generated an excess of ROS and activated the NLR family pyrin domain containing 3 inflammasome to produce the natural proinflammatory factor IL-1β, yet melatonin could reverse mitochondrial dysfunction and inhibit the process described above [36]. In addition, growing evidence shows that melatonin can alleviate ochratoxin A-induced liver inflammation [37], oxazolone-induced colitis [38], weaning stress [39], lipid dysmetabolism [40] in an intestinal microbiota-dependent manner. Zhao et al. demonstrated melatonin treatment can suppress type-2 immunity-associated ulcerative colitis [38]. Melatonin also increased the abundance of bifidobacterium (a well-known probiotic) and reduced proportions of several harmful bacterial genera [38]. However, studies exploring whether melatonin can modulate the skin microbiome are lacking.

3.3. Immunoregulatory mechanism

Melatonin modulates innate and adaptive immune responses. Melatonin can regulate the functions of cells in the innate immune system (e.g., monocytes, macrophages, eosinophils, basophils, neutrophils, natural killer cells) as well as the cytokines they secrete (e.g., IL-3, IL-4, IL-6, IL-12, interferon-γ, tumor necrosis factor (TNF)-α, IL-1β) [41]. Melatonin can enhance the chemotaxis of neutrophils and peripheral blood mononuclear cells [42]. With respect to adaptive immunity, melatonin plays an important part in the activation and proliferation, regulates the immune pathological process, and decides the fate of T cells. Studies have shown that melatonin can increase expression of cluster of differentiation (CD)69 [43], CD28, and p21 [44] on $CD4^+$ T cells, thereby promoting T-cell activation. Melatonin has been shown to upregulate expression of the cell-proliferation antigen ki67 and anti-apoptotic protein B-cell lymphoma-2, which stimulate the proliferation of $CD4^+$ T cells [44,45]. In determining the fate of T cells, melatonin promotes the T helper type 2 (Th2) response by increasing the IL-4 level, and inhibits the Th1 response by reducing the interferon-γ level. For example, in an ovalbumin-sensitized model in mice, melatonin treatment increased the IL-4 concentration significantly and reduced the interferon-γ concentration in serum, implying selective activation of the Th2 response [46]. There is also evidence supporting the importance of melatonin in modulating T regulatory cells (T_{regs}). Melatonin does not affect the T_{regs} from healthy individuals but, in patients with systemic lupus erythematosus, melatonin increases the number of $CD4^+$ $CD3^+$ forkhead box P3 $(Foxp3)^+$ cells [47].

3.4. Maintenance of the barrier

Melatonin can protect the skin barrier by inhibiting UVR-mediated apoptosis. Melatonin suppresses activation of a mitochondrial pathway-related promoter (caspase 9) by stabilizing the mitochondrial membrane potential, and inhibits activation of effectors (caspase 3 and caspase 7), thereby reducing or preventing keratinocyte apoptosis [48]. Also, melatonin can enhance expression of tight junction proteins, such as ZO-1 and occludin, in mice suffering from colitis, to attenuate intestinal permeability [38]. Given the similar tight junctions in the skin stated above, whether melatonin exerts the same function in the skin remanins to be tested. The actual mechanism involved is still to be explored.

3.5. Oncostatic mechanism

In skin tumors, melatonin has inhibitory effects on melanoma *in vitro* and *in vivo*. Fischer et al. found that the oncostatic effect of melatonin was related to its concentration and co-culture duration with melanoma cells, but was also relevant to the specific melatonin receptors expressed on the membranes and nuclei of cells. Cells expressing nuclear receptors exhibited stronger growth inhibition, whereas cells expressing MT2 receptors on cell membranes were more sensitive to the inhibitory effect of melatonin [49]. Reiter and colleagues found that mice with knockout of *NQO2* (which encodes melatonin-binding sites in the cytoplasm) increased their susceptibility to carcinogens and were more likely to develop skin tumors [27]. Lv et al. analyzed RNA-sequencing data from The Cancer Genome Atlas. They found the melatonin system in the tumor microenvironment to have predictive value for the prognosis of skin melanoma. Patients with a high melatonin synthesis/metabolic index had a better prognosis and fewer patients were at an advanced stage of disease, whereas patients with a low melatonin synthesis/metabolic index had higher immunogenicity, which suggested a stronger response to immunotherapy. In the group with a low melatonin synthesis/metabolism index, the enrichment of genes related to hypoxia, inflammation, proliferation, metastasis, and DNA damage implied that melatonin could inhibit tumors through these processes, but the detailed mechanism has yet to be elucidated. Lv et al. demonstrated that the melatonin synthesis/metabolism index was an independent predictor after including disease stage for adjustment in multivariable models, which suggested that melatonin might affect the prognosis through biological mechanisms other than inhibiting carcinogenesis and proliferation [50]. Melatonin also modulates melanin synthesis. Alvarez-Artime et al. found that in a murine melanoma cell line (B16–F10), melatonin could alter the cytoskeleton, reduce the level of cyclin-dependent kinase-1, and slow-down mitosis to leave tumor cells in the G2/M cycle for a long time, thereby inhibiting proliferation of B16–F10 cells [51]. Studies have demonstrated that in melanoma, melatonin can reduce production of the antioxidant enzyme SOD in tumors [52]. Those reports suggest that melatonin may be a candidate drug to treat skin cancer by producing ROS. However, Ozben and colleagues stated that melatonin also produced ROS and caused tumorigenesis [53]. Therefore, the anti-tumor properties of melatonin through the production of free radicals need to be studied further. Bonmati-Carrion et al. showed that melatonin induced the apoptosis of melanoma cells [54]. In that study, melatonin (millimolar range) reduced the viability of melanoma cells significantly. This effect was shown to be related to activation of an apoptotic pathway triggered by an increased level of ROS, but the mechanism was not clarified. Perdomo et al. found that melatonin could regulate the phosphorylation of glycogen synthase kinase-3β and activate the microphthalmia transcription factor, which regulated melatonin synthesis. Glycogen synthase kinase-3β could increase ROS and melanin by itself or by inhibiting the Nrf2 signaling pathway [55]. However, contrary evidence suggests that melatonin can reduce melanin production [56], which suggests that melatonin exerts anti-tumor effects by influencing melanin production.

4. Involvement of melatonin in skin dermatoses

Scholars have explored the interaction between the skin and brain through immune and neuroendocrine systems. Given that melatonin is produced locally, the important immunomodulatory actions that melatonin may have in some skin disorders are being revealed.

4.1. Atopic dermatitis (AD)

The advantageous effects of melatonin in AD have been indicated [57]. Park et al. investigated mice in which AD had been induced by 2,4 dinitrochlorobenzene or corticosterone. They discovered that melatonin relieved atopic symptoms and reduced neurotoxicity through inhibiting neuroinflammation *via* modulation of the hypothalamic–pituitary–adrenal axis [58]. As with AD patients who benefit from melatonin supplementation administered orally, they demonstrated that melatonin in plasma improved sleep and behavioral disturbances. Also, reduced serum levels of total immunoglobulin (Ig)E were reported. However, a clinical trial with a small study cohort did not show a significant association between amelioration of the Scoring Atopic Dermatitis index and decrease in sleep-onset latency. Furthermore, melatonin did not improve the efficiency, architecture, or fragmentation of sleep. Thus, the effects of melatonin on AD might be attributed to its immunomodulatory or antioxidative properties instead of its effects upon sleep [59]. Surprisingly, Gao et al. found that melatonin was suppressed if intestinal-barrier dysfunction and gut-microbiota dysbiosis occurred. Importantly, they observed changes in the melatonin level in colonic tissue to be similar to the changes observed in plasma, which implied that this process involved local production of melatonin in the intestine [9]. The gut and skin have common features (e.g., rich vascularization/perfusion, massive colonization with different microbial communities, and dense innervation) and they serve as critical interfaces through which the host communicates with his/her environment. Besides, they are versatile organs that are fully integrated into immune and endocrine systems. The normal function of the skin and gut is crucial for homeostasis and survival of the host [60]. Gut-produced melatonin can influence intestinal-barrier dysfunction and gut-microbiota dysbiosis. Hence, one wonders whether skin-induced melatonin will exert similar effects on skin-barrier dysfunction or microbiota dysbiosis, especially in AD patients.

Animal experiments have implied that melatonin suppresses AD and reduces serum levels of total IgE and IL-4. Maldonado and colleagues demonstrated that pre-processing of exogenous melatonin in hyperactive mast cells improved cell viability and decreased levels of endogenous melatonin, TNF-α, and IL-6. Those effects were correlated directly with the exogenous concentration of melatonin [61] and suggested that melatonin could prevent inflammation by reducing activation of mast cells, thereby aiding treatment of allergic inflammatory diseases. As with the hypothesized “indole-aminic theory”, melatonin (a neuroendocrine factor) may play a part in AD pathogenesis. This theory suggests an association between indole-aminic activity, reduced synthesis of melatonin, and hypersensitivity to environmental stimulators. Simultaneously, immunological dysfunction in AD leads to low levels of indolamine and melatonin in plasma. Hence, indolamine derivatives might be useful to maintain a functional skin barrier through the weakness of lipid peroxidation [29] and anti-apoptotic properties [62,63]. Some studies have demonstrated that topical melatonin can inhibit inflammation in 2, 4-dinitrochlorobenzene (DNCB)-stimulated AD mice, but the mechanism is not known [64,65].

4.2. Skin photoaging

Melatonin or its derivatives might impede skin aging because of their counteraction of oxidative stress *via* Nrf2 [66] and sirtuin-1. The link between UV light and ROS production is established. A randomized, placebo-controlled, double-blind study demonstrated the

dose-dependent sun-protective effect of melatonin applied topically. Application of melatonin cream (12.5%) protected against natural sunlight-induced erythema, whereas there was no significant difference between placebo and melatonin-cream concentrations of 0.5% and 2.5% [67]. That observation was in accordance with data from another study which found melatonin and melatonin-like molecules countered pre- and post-UVB radiation-induced damage in human skin and porcine skin *ex vivo* [31,68]. Such protection contributed to improvement of genomic, cellular, and tissue integrity against UVB-induced carcinogenesis, especially if treatment was administered before provision of UV radiation. That protection involved counteracting UVB-induced 8-Oxo-2′-deoxyguanosine formation and apoptosis, with a further increase in $p53^{ser15}$ expression and upregulation of expression of antioxidative enzymes. Topically applied melatonin (or its derivatives) is a potential candidate for impeding UVB-mediated damage and DNA impairment. Kleszczynski demonstrated that melatonin countered UVR-induced damage in keratinocytes by upregulating gene expression of the phase-2 antioxidative enzymes γ-GCS, HO-1, and NQO1, which were induced by activation of the Kelch-like ECH-associated protein 1/antioxidant response element pathway. Additional effects included production of adenosine triphosphate and reduced formation of free radicals. Melatonin also scavenged ROS directly and triggered activation of phase-2 antioxidative enzymes, thereby disclosing a new mechanism that promotes the ability of keratinocytes to exempt themselves from UVR-induced damage. Kim and collaborators demonstrated that melatonin exerted “anti-wrinkle” effects on keratinocytes. By suppressing ROS production and expression of matrix metalloprotease-1, melatonin could increase expression of collagen XVII in hairless mice, as well as lessen water loss, after UVB exposure [69].

4.3. Psoriasis

Psoriasis is an inflammatory skin condition mediated by Th1/Th17 cells. It is associated with melatonin and depression. Neuroimmunological investigations have suggested that melatonin may be a mediator that influences psoriasis and depression. Patients suffering from psoriasis tend to have lower levels and disrupted secretion of melatonin as compared with those in healthy controls [70]. Those results suggest a potential correlation between psoriasis and melatonin. Kartha and collaborators demonstrated that low levels of melatonin were linked significantly to psoriasis without association with depression symptoms [71].

4.4. Skin cancer

Accumulating evidence has shown that melatonin has anti-tumoral properties, but also exerts anti-inflammatory and antioxidation effects by controlling tumor augmentation. In melanoma, melatonin can induce apoptosis through several pro-apoptotic proteins, such as HSP70 and Nrf2. Furthermore, it exerts anti-inflammatory effects through the NF-κB pathway and phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin pathway, which could be sites for therapeutic intervention [72]. The anti-cancer property of melatonin makes it a promising candidate for adjuvant therapy in melanoma. Also, compared with other chemical products, the natural metabolism of melatonin in human cells has lower toxicity. Hao et al. demonstrated melatonin synergistically strengthened vemurafenib-induced inhibition of proliferation, colony formation, migration, invasion, apoptosis, cell-cycle arrest, and “stemness” weakening in melanoma cells. Melatonin inhibited nuclear translocation of NF-κB p50/p65 and their binding to iNOS and human telomerase reverse transcriptase (hTERT) promoters, thereby suppressing expression of iNOS and hTERT [73]. Scholars have elucidated that melatonin can inhibit angiogenesis in tumor tissues by complex mechanisms, thereby restraining growth and migration of tumorous gastric, breast, and ovarian cells [74]. In melanoma, angiogenesis is an important indicator of tumor aggressiveness and poor clinical outcome, but studies investigating this role of melatonin in melanoma are lacking.

4.5. Application of melatonin: good results

Melatonin has lipophilic properties. It can penetrate cell membranes and act as a scavenger of free radicals, and may have synergistic therapeutic effects against several diseases. Human skin expresses functional melatonin receptors, which inspires investigation of how the melatonin system can be used in skin conditions and preventative medicine. Topical use of melatonin and its derivatives AFMK and Nacetyl serotonin (NAS) has been shown to protect the skin barrier against UVR damage [67], to have anti-aging effects [68], and to treat alopecia [75] and AD [64,65]. Topical application of melatonin alleviates hydropenia, roughness, and wrinkles in skin, as well as increasing hair density/-thickness and decreasing hair loss. In AD-model mice, topical melatonin can suppress local inflammation, infiltration of mast cells, and epidermal hyperplasia. Those effects are achieved by increasing expression of anti-apoptotic proteins, antioxidant enzymes [68], and reducing secretion of pro-inflammatory cytokines. Meanwhile, orally administrated melatonin achieves first-pass elimination by the liver, and its content and efficacy in the skin are restricted. Topical application of melatonin could be a way to circumvent this problem.

5. Prospects

The anti-inflammatory mechanism of action of melatonin is incompletely understood, and the long-term effects of melatonin application have not been studied extensively. Given the daily rhythm of physiological processes, the relationship between the local concentration of melatonin and circadian rhythm merits attention. Moreover, the fact that melatonin regulates the microbiome may provide hints about AD therapy. Therefore, identification of the mechanisms linking melatonin with the circadian rhythm, microbiome, and peripheral immune system could aid development of targeted interventions to prevent the onset of peripheral inflammatory diseases and reverse established pathological inflammation.

Credit author statement

Shan Zhang : Conceptualization , Writing- Original draft preparation, **Xu Yao** : Writing-Review & Editing , Supervision , Funding acquisition.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could influence the work reported in this manuscript.

Data availability

Data will be made available on request.

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