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# Melatonin – A Cutaneous Perspective

**Mona Sharma[1], Priyanka Hemrajani[1], Tapan Kumar Dhali[1]**

[1]Department of Dermatology, Venereology, and Leprosy, PGIMSR & ESI Model Hospital, Basaidarapur, New Delhi – 110015

## Abstract

Melatonin (MLT) is an endogenous hormone secreted from the pineal gland, located deep in the brain in the epithalamus associated with numerous biological activities. The primary function of melatonin is to regulate sleep-wake cycles. However, research over the last few years has enlightened a range of functions associated with this molecule, including anti-inflammatory, direct and indirect antioxidant activity, regenerative tissue benefits, and preservation of mitochondrial function. Melatonin's anti-inflammatory and antioxidant support, coupled with its mitochondrial modulation, makes it a vital molecule to use for skin health homeostasis. The cutaneous melatoninergic system's widespread expression and pleiotropic activity provides for a high level of cell-specific selectivity. Several skin cells, including normal and malignant keratinocytes, melanocytes, fibroblasts and hair follicles, express melatonin receptors. Melatonin also has receptor-independent effects that protect against oxidative stress and can reduce ultraviolet radiation-induced damage. Several functions of melatonin in the skin have been experimentally implicated such as hair growth cycling, fur pigmentation, melanoma control, suppression of ultraviolet-induced damage to the skin cell. Melatonin may play a role in treating several dermatoses e.g., atopic eczema, psoriasis, melasma, ulcer healing, and malignant melanoma. There is a plethora of functional melatonin properties, which still await to be fully appreciated by dermatologists. The current review emphasizes few of the established uses and few emerging potentialities that render melatonin a promising candidate for managing several diseases.

**Key words:** Anti-oxidant; Melatonin; Photoprotection; Skin

## Introduction

Melatonin, an evolutionarily ancient derivative of serotonin with hormonal properties, is the primary neuroendocrine secretory product of the pineal gland. It is an endogenous neuroendocrine hormone and is a well-known pleiotropic regulator of the circadian rhythm. The most accepted role of melatonin is its involvement in the regulation of the sleep-wakeup cycle. It is a methoxyindole (N-acetyl 5 methoxytrytamine) primarily produced by the pineal gland from tryptophan via serotonin. It is also synthesized in various extrapineal sites such as lungs, liver, kidney, brain, harderian gland, retina, cochlea, ciliary body, bone marrow, immune cells, lens, endothelial cells, thyroid, pancreas, thymus, gastrointestinal tract, spleen, placenta, gonads, and skin.[1] It is metabolized by the liver as well as peripheral organs, including the skin.

Melatonin has numerous functions, which are taxon, species and tissue specific to various bacteria, fungi, eukaryotes, plants; vertebrates, and invertebrates which produce it. In humans, melatonin orchestrates numerous complex cell responses,[1, 2] directly and indirectly, apart from sleep regulation due to its anti-inflammatory, anti-ageing, anti-oxidant, anti-

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**Address of Correspondence**
Prof. Dr. Tapan Kumar Dhali
ORCID ID: 0000-0003-0378-9003
Dept. of Dermatology, Venerology and Leprosy, PGIMSR & ESI Model Hospital, Basaidarapur, New Delhi – 110015, Phone number 9990724083,
E-mail: tapan99@gmail.com

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tumour, thermoregulatory, radioprotective and immunomodulator properties. Rather, the idea of supplementing melatonin in the advanced aged population to protect brain health arises after discovering its antioxidant properties. Similarly, research has elucidated melatonin as a protective agent against ischaemia reperfusion injury in the brain, heart, and liver.[3] Melatonin and its metabolites have emerged as indispensable for physiological skin functions and adequate protection of cutaneous health from hostile environmental factors. Its cutaneous effects are a consequence of its local concentration, metabolic consumption, and generation of metabolites with potentially diverse phenotypic activities acting through receptor-dependent and independent mechanisms. Mammalian skin transforms L-tryptophan to melatonin through serotonin and n-acetyl serotonin (NAS intermediates). Human scalp hair follicles also synthesize and secrete it in vitro, and this process is upregulated by norepinephrine. Melatonin and its metabolites act as free radical scavengers and protectors against oxidative stress. Melatonin also regulates mitochondrial functions that maintain cutaneous cellular homeostasis.

## Melatonin synthesis in skin

Aaron Lerner hypothesized that melatonin release in the skin might lead to pigmentary disorders. The earliest documentation of melatonin synthesis in the skin was done by Slominski et al., wherein biotransformation of [3H] serotonin by cultured hamster skin to 3H-metabolites corresponding to N-acetylserotonin (NAS), melatonin, and 5-methoxytryptamine (5-MT) was demonstrated.[4]

Follow-up studies on rodent, and human hair follicles proved that keratinocytes, melanocytes, and melanoma cells are capable of endogenous melatonin production. Mammalian skin transforms L-tryptophan to melatonin through serotonin and n-acetyl serotonin (NAS intermediates). Skin cells express tryptophan hydroxylase type 1 (TPH1; all resident cells), TPH2 (melanocytes), as well as enzymes necessary for acetylation of serotonin such as arylalkylamine-N-acetyl- transferase/serotonin N-acetyltransferase (SNAT), arylamine-N actyltransferase (AANAT), hydroxyindole-Omethyltransferase/N-acetylserotonin methyltransferase (HOMT/NASMT). The rate-limiting enzyme of melatonin synthesis is AANAT/SNAT. Human scalp hair follicles also synthesize and secrete it in vitro, and this process is upregulated by norepinephrine. Skin expression of membrane-bound melatonin receptors MT1(in the epidermis) and MT2 (in adnexal structures) varies among species, and consequently, melatonin levels vary depending on environmental factors (UVB), underlying pathology (skin cancer), age, race, genetic background.[5] The highest melatonin concentration was found among Afro-Americans.

## Melatonin metabolism

Studies on human immortalized epidermal keratinocytes (HaCaT) have shown that both indolic and kynuric pathways metabolize melatonin, and this metabolism is stimulated by UVB. Several metabolites are generated in the epidermis, such as 6-hydroxymelatonin (major metabolite), 5-methoxytryptamine,5-methoxytryptophol, AFMK, N1-acetyl-5-methoxykynuramine (AMK). These potentially affect mitochondrial functions and consequently the skin phenotype.[6]

## Melatonin–mitochondria axis

Melatonin metabolism in mammals occurs through complex pathways associated with cytosol, endoplasmic reticulum (microsomes), and mitochondria. In mitochondria, melatonin is metabolized through monooxygenase (the cytochrome P450 dependent pathway) and peroxidase (the kynuric pathway). The kynuric pathway involves pseudo-peroxidase activity of cytochrome c in the presence of $H_2O_2$. This converts melatonin into AFMK and its secondary product, AMK, via sequential steps that generate 2-hydroxymelatonin and 2,3-dihydroxymelatonin as intermediates which not only compensate for the absence of the conventional H2O2—detoxifying enzymes (catalase, glutathione peroxidase, and peroxiredoxin III) in the intermembranous space but also contribute to the neutralization of ROS. Similarly, cytochrome P-450-dependent 6-hydroxylation and O-demethylation of melatonin provide mitochondria with target compounds that maintain mitochondrial homeostasis. It has been suggested that melatonin could donate electrons to the ETC, thus improving mitochondrial respiration and increasing ATP production. Such electron transfer in the terminal cytochrome c oxidase segment of the ETC is crucial considering age-related decline in complex II (succinate: ubiquinone oxidoreductase) activity in human skin fibroblasts. Melatonin thus plays a significant role in mitochondrial bioenergetics and homeostasis (including biogenesis, fission, fusion, mitophagy), and the skin protective activities of melatonin (both direct and indirect) are dependent on mitochondria through the reciprocal interactions with skin cell homeostasis.[7]

## Role of Melatonin In Skin

The role of melatonin, its precursors, and metabolites in the regulation of physiological functions of the skin and its attenuating effects in skin pathology has been extensively reviewed in recent times. Melatonin can regulate cutaneous adnexal, pigmentary, barrier, and oncostatic functions. Various functions of melatonin have been tabulated. (Table 1)

## Functions of melatonin

**Table 1**

| Cutaneous specific functions | Other Functions |
|---|---|
| • Photoprotective<br>• Anti-oxidant<br>• Anti-inflammatory<br>• Anti-ageing<br>• Hair growth & pigmentation<br>• Skin lightening<br>• Regulation of barrier function<br>• Thermoregulation<br>• Regulation of skin immune system<br>• Anti-vesicant action | • Circadian pacemaker<br>• Mitochondrial homeostasis<br>• DNA repair<br>• Anti-apoptotic<br>• Tissue regeneration & repair<br>• Anti-tumour<br>• Immunomodulation<br>• Radioprotective<br>• Angiogenesis<br>• Sexual maturation |

## Photoprotection

Acute exposure to UVR may cause photodamage in human skin characterized by erythema, edema, pain, pruritus, tanning, etc., whereas chronic exposure may lead to carcinogenesis and skin ageing.[7] Melatonin is a highly lipophilic molecule, which can penetrate organic membranes. It absorbs UV light in the 225-275nm wavelength range, much lower than normal UVA and UVB wavelengths. It inhibits UV-induced lipid peroxidation of membranes, thereby decreasing arachidonic acid metabolites such as prostaglandins and leukotrienes. The role of topically applied melatonin has been studied extensively in the attenuation of skin erythema in healthy human subjects exposed to either artificial UVR or natural sunlight, thus demonstrating melatonin's clinical potential as a protector against photodamage.[8-11] Melatonin is a free radical scavenger, that quenches free radicals involved in cell damage, the most notorious being nitric monoxide (NO-) and OH free radical. Several studies have confirmed the protective effects of melatonin and its metabolites:6-hydroxymelatonin, AFMK, *N*-acetyl-serotonin, and 5-methoxytryptamine against oxidative cell damage in human skin cells, namely keratinocytes, melanocytes, and dermal fibroblasts.[12-14] These also play a role in cellular defense against oxidative damage by promoting glutathione production and enhance activities of other anti-oxidant enzymes: superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (Gpx). Melatonin also prevents UVB-driven anti-oxidative enzyme depletion, including SOD1, catalase, and GPx in the human skin. Melatonin and its metabolites reduce the levels of the UVB-induced cell damage and enhance UVB-induced DNA repair in keratinocytes and melanocytes. The proposed underlying mechanism involves the stimulation of phosphorylation of tumour suppressor protein p53 and enhancement of nucleotide excision repair (NER) via interactions between damaged DNA and the NER core factors XPC and XPA. Recent studies have implicated that nuclear euthyroid 2 related factors 2 and sirtuin (sirt1) are significant regulators in oxidative stress response and skin ageing.[15,16] Melatonin or its metabolites have a crucial role in activating these nuclear factor erythroid 2-like 2 (NRF2) and upregulation of NRF2-dependent pathway in melanocytes and in activation of phase-2 antioxidant enzymes (γ-GCS, HO-1, NQO1) in ultraviolet radiation-treated normal human epidermal keratinocytes.[12,16]

## Anti Ageing

Skin ageing is due to several intrinsic and extrinsic factors, with decreased mitochondrial function as a significant underlying mechanism. UV light is a principal extrinsic agent which causes a decrease in collagen in the dermal extracellular matrix and DNA alterations (thymine-thymine dimer formation). ROS (reactive oxygen species) formation and oxidative stress cause damage to mitochondrial pathophysiology, inflammation, cytotoxicity, and resultant cell damage. Melatonin has potent, long lasting, indirect anti-oxidant action and stimulates transcription factor NRF2 (upregulation of gene expression) antioxidative enzymes in the skin such as Cu-Zn superoxide dismutase, catalase, and glutathione peroxidase (Figure 1). It also downregulates interstitial collagenase MMP-1, stromelysin 1(MMP-3), stromelysin 2 (MMP-10), aldehyde dehydrogenase 3 type A1. As 90 % of ROS is produced in mitochondria, melatonin has a significant role in anti-ageing therapy.[17,18]

The role for melatonin, vitamins D3, E, and C in the prevention and the treatment of oxidative stress-induced skin aging. (Courtesy- Bocheva G, Slominski RM, Slominski AT. Neuroendocrine Aspects of Skin Aging. Int J Mol Sci. 2019;20(11):2798**)**

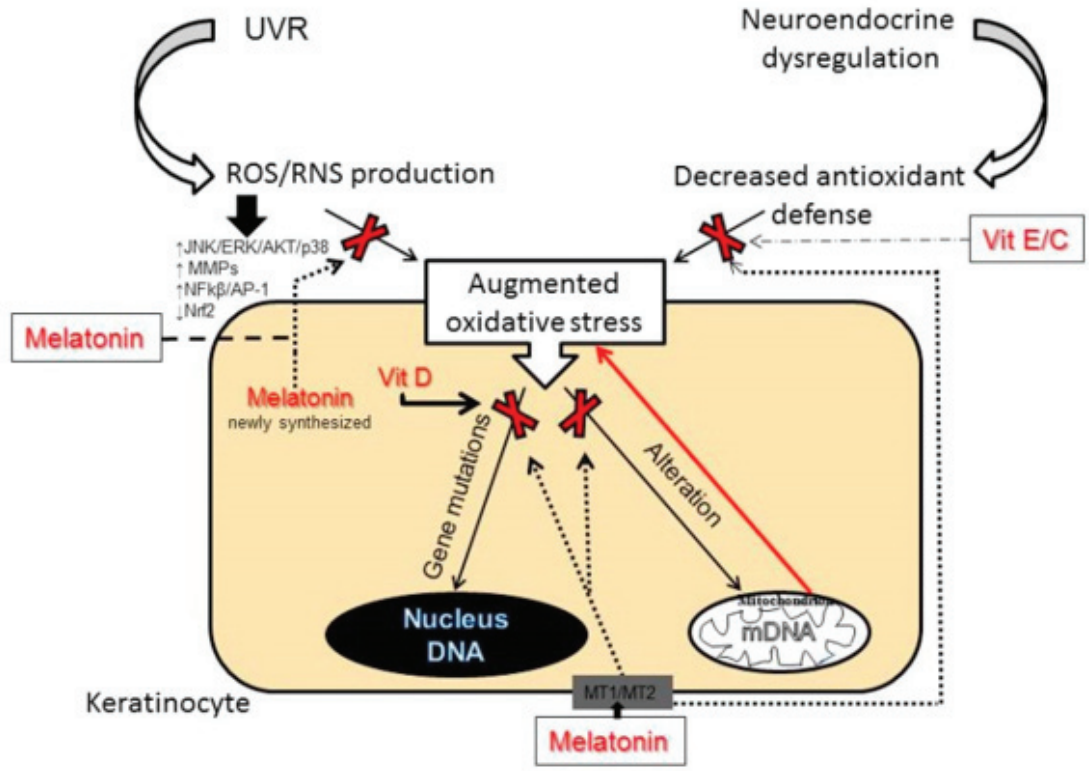


**Figure 1:** Role of Melatonin in Antiaging

## Anti-Apoptotic

Keratinocyte proliferation provides an effective epidermal barrier in the skin which is known to be depleted due to UV-mediated mitochondrial dysfunction. The terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL) assay showed the inhibition of UV-induced apoptosis in human HaCaT keratinocytes.[19] Melatonin is involved in a complex- and concentration-dependent regulation of mitochondrial homeostasis, widely known as a melatonin-mitochondrial axis in the skin as described in previous sections.[20] Melatonin was found to inhibit cytochrome c release from mitochondria and decrease activation of caspases 3, 7, and 9 suggesting inhibition of mitochondrial pathway of apoptosis.[21-22] Apart from direct scavenging of reactive oxygen species, it also helps maintain optimal mitochondrial membrane potential (Δψm). The suggested mechanism is direct, or receptor-mediated inhibition of the mitochondrial permeability transition pore (MPTP) and stimulation of uncoupling proteins (UCPs) which still requires further evaluation. It should be noted that melatonin and its metabolites would coordinate mitochondrial interactions with the skin cell to decide whether it survives or enters a precisely defined differentiation pathway, necessary for barrier formation, or dies through apoptotic pathways to prevent carcinogenesis.

## Anticancer

Melatonin is nontoxic and exhibits a range of beneficial effects against cancer via apoptotic, anti-angiogenic, anti-proliferative, and metastasis-inhibitory pathways. Combining of melatonin with conventional drugs improves the drug sensitivity of cancers, including solid and liquid tumours.[23-24]

The anti-tumour property of melatonin has been well documented in several in vitro and in vivo models.[25-27] Melatonin and its metabolites have been shown to inhibit cultured human melanoma cell growth,[28-31] and attenuation of benzo(a)pyrene-induced cutaneous sarcomas, squamous cell carcinomas, and papilloma in mice models.[32-34] Gadheri et al. found that patients with basal cell and squamous cell carcinomas had lower urinary indicators of systemic melatonin production than controls.[35] Research has proved that melatonin inhibits melanoma growth and also melanin dispersion by reducing the levels of cyclic adenosine monophosphate (cAMP) and α-melanocyte-stimulating hormone (MSH) apart from its antioxidant action against UV-induced free radicals.[11] This activity depends on the level of expression of MT1 and MT2 receptors and melatonin-binding quinone reductase NQO2 in both skin cell lines as well as melanoma cell lines.[36-37] Melatonin and its precursor *N*-acetylserotonin

bind to several regulatory proteins including quinone reductase 2.[38-39] Quinone reductase 2, protects cells against oxidative stress in dimethylbenz(a)anthracene-induced skin cancer and is required for tumour necrosis factor-α-induced apoptosis in keratinocytes.[40-41]

Clinical trials have suggested the role of melatonin and its metabolites as an adjuvant in non-resectable lentigo maligna and mucosal melanomas. Melatonin has radioprotective effects, secondary to its action on the mitochondria or/and mitochondrial melatonin metabolism to a biologically active metabolite. This property may be used in chemotherapy, either to reduce its side effects or enhance its efficacy and in post lymph node resection disease-free survival period. Systematic clinical trials for the use of melatonin in cancer prevention and oncological therapies are the need of the hour as it is cost-effective, has favourable toxicological profile, and less adverse effects.

## Wound Healing

Melatonin as a regulator of epidermal homeostasis has a positive impact on the proliferation of keratinocytes and also on the expression of involucrin, keratin-10, and keratin-14.[42] According to a proposed novel melatonin-mitochondrial axis; melatonin regulates cell survival, terminal differentiation, and also apoptosis as a part of epidermal barrier function. This regulation of epidermal cell density and ROS scavenging action together helps in tissue repair and regeneration, thereby wound healing. Melatonin can regulate angiogenesis differently under different pathological and physiological conditions. In tumours, age-related ocular diseases, and in a hypoxic environments, melatonin inhibits neovascularization. This property can be utilized in the prevention of the initiation and development of atherosclerosis.

In contrast to this, it promotes angiogenesis in gastric ulcers, skin lesions, and some physiologic processes through regulation of vascular endothelial growth factor and its receptors and other specific regulatory mechanisms, thereby opening prospects of the therapeutic use of melatonin in gastroesophageal reflux disease (GERD) and peptic ulcer disease.[43] Recent studies have also demonstrated the role of melatonin in wound healing.[44-47] Further research on the beneficial role of melatonin and its metabolites on epidermal barrier formation and wound healing is warranted.

## Skin Pigmentation

Skin pigmentation is due to several mechanisms that lead to increased melanin production /deposition and is influenced by age, hormonal imbalance, endocrine diseases, inflammatory diseases, photodamage, etc. Melatonin and its metabolites regulate circadian rhythm, melanogenesis, and melanocyte activities in the human epidermis. The use of melatonin in defined circadian windows has shown its effectiveness in skin lightening. Topical melatonin has a protective action in vitiligo due to the amelioration of oxidative stress environment.[48-49] Since melatonin plays a role in the reproductive cycle of other animals by modulation of estrogen and progesterone, it may also help reduce hyperpigmentation seen in diseases where a hormonal component is involved in the pathophysiology, such as melasma. Topical melatonin alone, and combined with 4% hydroquinone and oral melatonin, were shown to significantly decrease the pigmentation in all melasma patients. It was found that combining topical melatonin 5% with oral melatonin 3g daily for 120 days decreases MASI significantly when compared to placebo.[50-51] It also caused an increase in glutathione levels and a decrease in malondialdehyde levels, showing alleviation in oxidative stress.

## Hair Growth and Pigmentation

Hair follicles in the human scalp produce melatonin, and this synthesis is stimulated by noradrenaline. Melatonin is known to stimulate nuclear erythroid 2 related factor 2, which protects against oxidative stress-induced hair damage.[52,53] Kobayashi et al. found that melatonin renders human hair follicles ex vivo less susceptible to chemotherapy-induced damage.[54] Studies have shown that topical melatonin has the potential to inhibit androgenetic alopecia in females as it downregulates expression of intrafollicular estrogen receptors and thus modulates human hair follicle responses to estrogens. Circadian clock proteins have been known to be involved in the control of human hair follicle cycling and hair cum skin pigmentation.[55,56] Further research needs to be done on the impact of melatonin in hair growth and pigmentation through modulation of peripheral circadian activity in the skin.

## Inflammatory Dermatoses

Melatonin has been known to have both immunostimulatory and anti-inflammatory actions. Key cells involved in innate immunity, such as mast cells, express melatonin receptors, and melatonin has a crucial role in T-cell-based immune pathologies.[57,58] Skin disorders such as atopic dermatitis are accompanied by infiltration and activation of mast cells, releasing vasoactive and proinflammatory

mediators. Melatonin inhibits the development of atopic eczema and reduces serum total IgE and IL-4. Disturbances in serum melatonin levels have been reported in patients with psoriasis,[59] and beneficial effects of melatonin have been seen in atopic dermatitis, seborrhoeic dermatitis.[60-61] Apart from the skin, several studies have proved that melatonin has a beneficial therapeutic value in the treatment of several inflammatory diseases, such as Alzheimer's, Amiotrophic Lateral Sclerosis, Multiple Sclerosis and Huntington's disease as well as other related disorders of mitochondrial dysfunction.[62-63]

## Thermoregulation

Melatonin is important for skin homeostasis and can modify vasoconstrictor response to cooling and vasodilator response to heat. Through its circadian activity and even directly, it regulates the core body temperature and skin temperature.[64]

## Anti-Vesicant Action – Theory In Pipeline

Vesicants or blistering agents are chemical warfare agents (CWAs) which cause blistering lesions in the skin and mucous membranes. These include sulphur mustards, nitrogen mustards, and lewisite. These cytotoxic alkylating agents were initially developed as chemical weapons to induce ocular, dermal, and respiratory damage. Melatonin has been proposed as a feasible agent to counteract the induced toxic damage and possible long-term effects of the most representative blister agents. It is a well-characterized antioxidant with anti-inflammatory and scavenger action, and recent studies have shown its ability as a promising epigenetic modulator suggesting its use as a therapeutic agent for the treatment against vesicant CWAs.[65]

## Role of Melatonin in Covid-19

The potential role of melatonin in various viral infections such as Respiratory syncytial virus infection, Venezuelan equine encephalitis virus infection, viral hepatitis, viral myocarditis, Ebola virus, West Nile virus, Semliki Forest virus has been well documented. Recently, the COVID-19 pandemic has necessitated research for potential molecules. Cytokines, hyper-inflammatory state, and lymphopenia play crucial roles in COVID-19 pathogenesis. The efficacy of melatonin in the regulation of the immune system has been shown in both *in vivo* and *in vitro* studies. Reiter et al. proposed that melatonin may be given consideration for prophylactic use or treatment alone or in combination with other drugs to combat Covid-19 owing to its multiple actions as an anti-inflammatory, anti-oxidant, and anti-viral (against other viruses) agent.[66] Melatonin, like other immunomodulatory agents, may be used as an effective adjuvant besides vaccination to boost the vaccine's effectiveness in patients with both compromised and healthy systemic and cutaneous immune systems.[67, 68]

## Conclusion

Melatonin is a unique, essentially nontoxic, readily available molecule whose multifunctional aspects still lie unexplored. However, there is plenty of literature related to the beneficial actions of melatonin and its application in numerous diseases. Melatonin displays a significantly high antioxidative capacity, anti-inflammatory actions, and recent studies have shown its ability as a promising epigenetic modulator. There is a need to reinstate the role of melatonin as a potential agent in various dermatological conditions, particularly those associated with substantive oxidative damage. Topical and transepidermal delivery of melatonin is a promising area for full exploration in future dermato-therapy and preventive cutaneous medicine.

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