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# The application of melatonin in anti-aging cosmetics. An overview of clinical efficacy and mechanisms of action

## *Zastosowanie melatoniny w kosmetykach przeciwstarzeniowych. Przegląd skuteczności klinicznej i mechanizmów działania*

ABSTRACT

Skin changes associated with aging processes are increasingly recognized as a significant dermatological and aesthetic problems. Melatonin is an endogenous hormone known for its powerful antioxidant and anti-inflammatory properties. Its topical application is gaining popularity as an effective way to slow down the aging process.

The study aimed to assess the potential effectiveness and mechanisms of action of melatonin as an anti-aging agent in cosmetics. A systematic review of studies was conducted on publications from January 1990 to April 2025 using the PRISMA guidelines, PubMed, ScienceDirect, Google Scholar, and Cochrane Library databases.

Melatonin in cosmetic preparations has been shown to reduce wrinkles, improve skin firmness, and increase hydration. This was associated with the role of melatonin as a powerful antioxidant that reduces oxidative stress, improves mitochondrial function, regulates lipid metabolism, and protects collagen and elastin fibers, preventing skin damage and promoting skin rejuvenation. Topical application of melatonin appears promising, but further clinical studies are needed to confirm its efficacy and optimize formulation strategies.

**Keywords:** skin aging, anti-aging effects, melatonin, cosmetics, topical application.

STRESZCZENIE

Zmiany skórne związane z procesami starzenia są coraz częściej uznawane za istotny problem dermatologiczny i estetyczny. Melatonina jest hormonem endogennym znanym ze swoich silnych właściwości przeciwutleniających i przeciwzapalnych. Jej miejscowe stosowanie zyskuje na popularności jako skuteczny sposób spowalniania procesów starzenia.

Celem badania była ocena potencjalnej skuteczności oraz mechanizmów działania, dzięki którym melatonina stosowana w kosmetykach może oddziaływać jako środek przeciwstarzeniowy. Przeprowadzono systematyczny przegląd badań w zakresie publikacji od stycznia 1990 r. do kwietnia 2025 r. przy użyciu wytycznych PRISMA, korzystając z baz PubMed, ScienceDirect, Google Scholar i Cochrane Library.

Wykazano, że melatonina zawarta w preparatach kosmetycznych spłyca zmarszczki, poprawia jędrność skóry i nawilżenie, co wynika z jej silnych właściwości przeciwutleniających. Melatonina ogranicza stres oksydacyjny, wspiera funkcjonowanie mitochondriów, reguluje metabolizm lipidów oraz chroni włókna kolagenowe i elastynowe. W efekcie zmniejsza uszkodzenia skóry i sprzyja jej regeneracji oraz odmłodzeniu. Miejscowe stosowanie melatoniny wydaje się obiecujące, jednak niezbędne są dalsze badania kliniczne w celu potwierdzenia jej skuteczności oraz optymalizacji strategii formułowania preparatów.

**Słowa kluczowe**: starzenie się skóry, działanie przeciwstarzeniowe, melatonina, kosmetyki, miejscowa aplikacja.

## INTRODUCTION

Skin aging is a complex process, influenced by both internal and external factors, resulting in structural and physiological alterations [1, 2]. There are a few mechanisms that are associated with skin aging, including oxidative stress, cellular senescence, and stem cell dysfunction [3, 4]. Environmental factors, especially ultraviolet (UV) radiation, are known to accelerate this process by inducing DNA damage and cellular dysfunction [5]. Other risk factors that are known are smoking, air pollution, nutrition, age, gender, and ethnicity [6]. Different forms of interventions have been developed to combat skin aging, such as topical agents (e.g., retinoids, antioxidants, peptides) and clinical procedures (e.g., chemical peels, laser resurfacing, microneedling, injectable treatments). Dietary approaches have also been explored [1, 2, 7].

Melatonin, commonly known as the "hormone of darkness," is primarily produced in the pineal gland but is also synthesized in peripheral tissues, including the skin. Beyond its neuroendocrine role, melatonin acts as a potent cutaneous antioxidant. It penetrates the skin's lipid barrier, scavenges free radicals, preserves mitochondrial function by maintaining membrane integrity and limiting mitochondrial reactive oxygen species (ROS) production, and reduces UV-induced oxidative and inflammatory damage. Endogenous skin melatonin declines with age, suggesting a protective role against skin aging. Through its antioxidant, anti-inflammatory, and mitochondrial-regulating actions, topically applied or locally produced melatonin contributes to maintaining skin integrity and delaying visible signs of aging [8-10].

Topical application of melatonin is becoming a promising strategy for mitigating skin aging due to the advantages over oral administration. Oral administration of melatonin faces first-pass hepatic metabolism, which reduces its availability throughout the body and skin penetration [11]. The topical application of melatonin allows direct skin penetration and localized effects that may improve its effectiveness [9, 12].

Despite growing interest, current research on topically applied melatonin is still varied across studies with different designs and outcome measures. Previous articles have mostly discussed melatonin's role in skin physiology and aging from a theoretical or narrative standpoint. This systematic review advances the field by combining only interventional clinical data on topical melatonin application and directly linking observed clinical outcomes to specific molecular mechanisms. Through the integration of clinical evidence, mechanistic insights into melatonin's cutaneous actions, and a systematic risk-of-bias assessment, this review provides a more evidence-based foundation for future topical melatonin formulation development and its clinical use in anti-aging treatments.

## AIM

This systematic review aimed to evaluate the clinical effectiveness of topical melatonin application in improving skin aging parameters and to investigate the biological mechanisms by which melatonin exerts its anti-aging effects.

## METHODS

### Search strategy

This systematic review followed the guidelines from The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). A literature search was conducted in several journal databases, including PubMed, ScienceDirect, Google Scholar, and Cochrane, from January 1990 to April 2025. Intervention studies were included, such as randomized controlled trials (RCTs), non-randomized controlled trials (non-RCTs), and cohort studies that assessed the use of topical melatonin application for skin aging. Boolean operators were used with the following keywords: "topical melatonin", "anti-aging", "skin" and "wrinkle". Outcomes of this study included the effectiveness of topically applied melatonin, which involved several different parameters.

### Data extraction

Inclusion criteria of this study were: healthy individuals with signs of aging, intervention studies, including prospective or retrospective cohort studies, case-control studies, and clinical trials, human-based studies, and patients receiving topical melatonin formulations (creams, serums, or gels) as intervention. Studies involving non-human subjects, case reports or series, narrative reviews, and articles with unavailable full texts were excluded. Duplicate records were manually removed using Microsoft Excel. The extracted data from each study included age, sample size, details of both the intervention and control, and study outcomes that measure skin aging parameters such as wrinkle severity, skin firmness, hydration, and transepidermal water loss (TEWL).

### Risk of bias analysis

The risk of bias in the included studies was assessed using the Cochrane Risk of Bias Assessment Tool 2 (RoB 2.0) for RCTs and the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool for non-RCTs.

## RESULTS

The initial search yielded 241 records for evaluation (Fig. 1). Removal of duplicates resulted in a total of 125 records. Out of these, 25 records were included after title and abstract screening. Nineteen of the 25 full-text articles were excluded because of differences in study design. Six studies were included in the review and are listed in tab. 1.

All the studies in this review concentrated on the impact of topical melatonin therapy on various skin aging parameters. In total, 205 participants were evaluated for the effects of topical melatonin application. The melatonin dosage applied varied from 0.1% to unspecified in different formulations, such as creams, serums, and balms. Commonly measured outcomes

**Tab. 1.** Characteristics and key findings of studies evaluating topical application of melatonin for skin aging. **Source:** Own elaboration.

| Author, Year | Study Design | Country | Intervention | Control | Sample Size (n) | Age (years) | Parameter | Measured Value | p-value |
|---|---|---|---|---|---|---|---|---|---|
| Milani & Sparavigna, 2018 [13] | Randomized, split-face, assessor-blinded trial | Italy | 0.1% melatonin-based day & night creams | Placebo on one side of the face | 60 | 45-65 | Wrinkle Severity | -15% | p = 0.05 |
| | | | | | | | Skin Dryness | -59.5% | p = 0.001 |
| | | | | | | | Skin Tonicity | +33% | p = 0.05 |
| Milani & Puviani, 2018 [14] | Open, prospective, evaluator-blinded trial | Italy | 0.1% melatonin-based cream | None | 15 | >45 | Wrinkle Volume | -31% (coarse), -18% (fine), -17% (periorbital) | p < 0.01 |
| | | | | | | | Wrinkle Volume (Coarse) | 25.7 → 17.8 $mm^3$ (−31%) | p = 0.001 |
| | | | | | | | Wrinkle Volume (Fine) | 9.0 → 6.0 $mm^3$ (−18%) | p = 0.05 |
| Goldberg et al., 2019 [15] | Prospective, single-center, observational study | France | Night serum with melatonin, bakuchiol, and ascorbyl tetraisopalmitate | None | 39 | 40-65 | Wrinkle Depth | -11% at 84 days | p < 0.01 |
| | | | | | | | Skin Firmness | +8% at 84 days | p < 0.01 |
| | | | | | | | Skin Hydration | +44.5% at 4h (peak) | p < 0.05 |
| | | | | | | | TEWL | −7.8% at 4h; −8.5% at 6h | p = 0.047 (4h); p < 0.01 (6h) |
| Granger et al., 2020 [16] | Open-label, single-center study | Spain | Night cream with melatonin, carnosine, and *Helichrysum italicum* extract | None | 31 | 35-65 | Wrinkle Number | -11.1% (28 days), -18.9% (84 days) | p < 0.05 |
| | | | | | | | Wrinkle Volume | -8.1% (56 days), - 14.8%; (84 days) | p < 0.05 |
| | | | | | | | Wrinkle Depth | -6.9% (56 days), -7.7% (84 days) | p < 0.05 |
| | | | | | | | Skin Firmness | +9.2% (28 days), +15.3% (56 days), +22.4% (84 days) | p < 0.05 |
| | | | | | | | Skin Elasticity | +4.2% (28 days), +12.9% (56 days), +7.7% (84 days) | p < 0.05 |
| | | | | | | | TEWL | −10% after 1h | p < 0.05 |
| Puviani et al., 2020 [8] | Monocentric, open-label clinical study | Italy | NUTRIAGE Eye Balm (melatonin 0.1%, *karitè* butter, hyaluronic acid and a tetrapeptide) applied twice daily | None | 20 | Mean: 54.3 ± 7.6 | Eye contour roughness index (PRIMOS 3D) | -31% (2 months) | p = 0.001 |
| Colombo et al., 2025 [17] | Randomized, prospective study | Italy | Melatonin-based ‚In & Out' strategy (0.1% melatonin cream + 0.5 mg oral melatonin) | Topical treatment only | 40 | 55-69 | Skin Moisturization | +23.6% (Intervention), +18.3% (Control) | p < 0.05 |
| | | | | | | | Wrinkle Depth | -18.5% (Intervention), -9.4% (Control) | p < 0.05 |

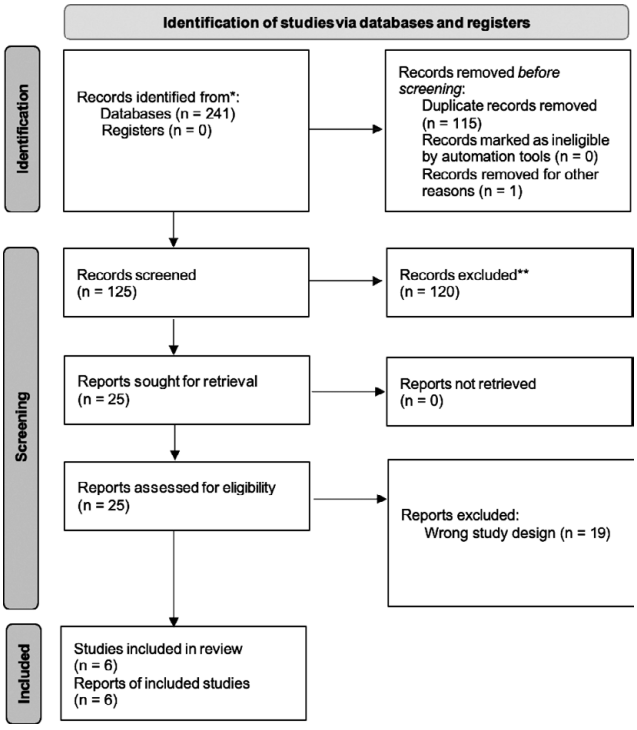


**Fig. 1.** PRISMA flow diagram illustrating identification, screening, eligibility, and inclusion of studies on topical application of melatonin for skin aging. (*): Records identified from databases were obtained through electronic database searching. No records were identified from registers. (**): Screening and exclusion of records were performed by human reviewers. No automation tools were used. **Source:** Own elaboration.

included wrinkle profile, such as number, depth, and volume, as well as skin hydration. Some studies also looked at skin firmness, tonicity, elasticity, and TEWL. Most studies reported significant improvements in skin aging parameters, such as reduced wrinkles (number, depth, volume), increased skin hydration, increased skin firmness, and decreased TEWL.

Risk of is presented in fig. 2. All four non-randomized clinical trials showed a serious risk of bias. This was mainly due to confounding, missing data, and issues in measuring outcomes. Among the RCTs, both studies were rated as having some concerns. These concerns involved the randomization process, measurement of outcomes, and selection of reported results.

## DISCUSSION

### Summary of clinical findings

Across six interventional studies involving 205 participants, topical melatonin application demonstrated consistent improvements in multiple indicators of skin aging [8, 13-17]. Clinical outcomes confirmed reductions in wrinkle depth and volume, accompanied by increases in tonicity, firmness, and elasticity, as well as enhanced skin hydration and a decrease in TEWL. These effects were observed across different formulations and application durations, suggesting that melatonin exerts a measurable and biologically meaningful impact on both structural and functional skin parameters.

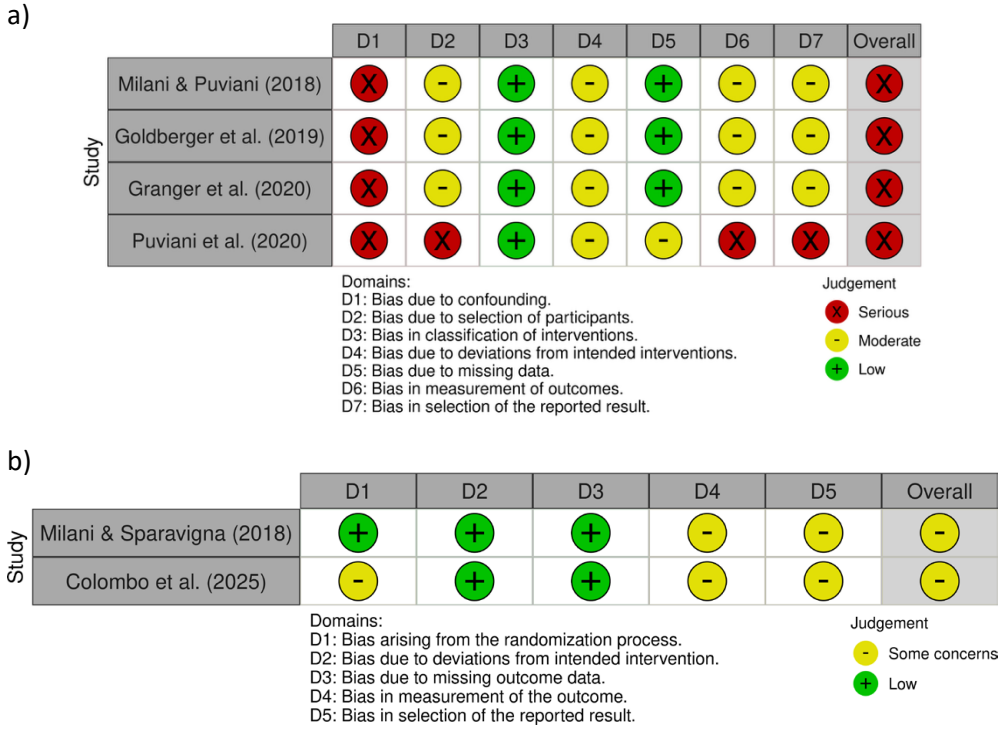


**Fig. 2.** Risk of bias of included studies: a) ROBINS-I for non-randomized studies; b) RoB 2.0 for randomized studies. **Source:** Own elaboration.

### Interpretation of risk of bias and evidence strength

While the included studies consistently reported favourable outcomes with topically applied melatonin, the overall strength of evidence should be interpreted with caution due to methodological limitations. Most non-randomized trials demonstrated a serious risk of bias, particularly related to confounding factors, lack of control groups, and incomplete outcome reporting. These limitations reduce confidence in the generalizability of the findings. Even among RCTs, concerns were noted in randomization procedures, assessor blinding, and selective reporting. As a result, although the direction of effect is consistent across studies, the magnitude of benefit may be overestimated. Strengthening future research design through standardized outcome measures, blinded assessment, and adequately powered RCTs would be essential to validate the clinical relevance of topical melatonin application in skin aging.

### Melatonin chemical structure and composition

Melatonin is an indoleamine hormone mainly produced in the pineal gland. It controls circadian rhythms and sleep-wake cycles. It also acts as a strong antioxidant and anti-inflammatory agent. Additionally, it has various therapeutic functions beyond just sleep regulation. Melatonin is chemically classified with the molecular name N-acetyl-5-methoxytryptamine [18-20]. This pleiotropic molecule possesses amphiphilic properties, allowing it to cross cellular membranes readily and access various intracellular compartments [19].

Recent studies have identified several active metabolites of melatonin, such as $N^1$-acetyl-5-methoxykynuramine (AMK) and $N^1$-acetyl-$N^2$-formyl-5-methoxykynuramine (AFMK), which contribute to melatonin's overall biological activity [21, 22]. These metabolites have been shown to exhibit neuroprotective properties and may play important roles in melatonin's anti-aging effects [21].

### Potential of melatonin as an anti-aging agent

Recent studies indicate that topical melatonin application is a promising anti-aging agent for skin. Melatonin's cytoprotective, anti-inflammatory, and antioxidant properties enable it to reduce key indicators of skin aging [23]. Melatonin's amphiphilic properties help it pass easily through cellular membranes, including the blood-brain barrier and the layers of the epidermis, allowing it to access intracellular compartments where it can exert its protective action [24]. Melatonin's protective properties against skin aging extend even to the prevention of UV-induced damage, an essential variable leading to photoaging. Melatonin effectively regulates the production of ROS while also reducing mitochondrial and DNA damage associated with UV exposure radiation [25].

### Mechanism of action of topical melatonin application

Oxidative stress plays a key role in skin aging and damage, making the body's antioxidant defence system essential for maintaining skin health. Primary antioxidant enzymes are responsible for directly detoxifying ROS, while phase II antioxidant enzymes help synthesize glutathione and other molecules that further neutralize ROS and repair oxidative damage [25]. Melatonin substantially enhances the expression of essential primary antioxidant enzymes, including superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase, by activating the Kelch-like ECH-associated protein 1–nuclear factor (erythroid-derived 2)-like 2 (Keap1-Nrf2) signalling pathway [26, 27]. It also works by activating the Nrf2 pathway, which boosts the skin's natural antioxidant defence system and encourages the expression of phase II antioxidants enzymes [28]. By activating the Nrf2/Antioxidant Response Element (ARE) pathway, melatonin promotes the nuclear translocation of Nrf2 and increases the expression of phase-2 enzymes such as γ-glutamylcysteine synthetase (γ-GCS), heme oxygenase-1 (HO-1), and NAD(P)H:quinone oxidoreductase-1 (NQO1), which boost the cell's antioxidant capacity and maintain protection after the initial scavenging event [25].

$N^1$-acetyl-$N^2$-formyl-5-methoxykynuramine (AFMK) and 6-hydroxymelatonin are major metabolites of melatonin produced in human skin through both enzymatic and non-enzymatic pathways, especially under environmental stressors like UV exposure. Recent research shows that AFMK forms through the oxidation of melatonin, especially when ROS are present or during exposure to ultraviolet C (UVC) light. The formation of AFMK is significantly enhanced by UVC light, alkaline pH, and the presence of molecular oxygen and superoxide radicals, indicating that AFMK production is a typical autoxidation reaction of melatonin in its electronically excited state. It is generally recognized that 6-hydroxymelatonin is produced through the hydroxylation of melatonin, often mediated by cytochrome P450 enzymes in mammals [29, 30]. These metabolites are phylogenetically conserved and act as part of the skin's primordial defence system. AFMK and 6-hydroxymelatonin exhibit potent antioxidant properties against oxidative stress, which are key contributors to skin aging. This antioxidant activity is particularly important since aging is associated with increased free radical production and decreased tissue antioxidant capacity [30].

Melatonin has been shown to raise the concentrations of essential skin lipids, especially triacylglycerols and ceramides, which play important roles in maintaining skin structure and hydration [17]. From a mechanistic perspective, melatonin has been demonstrated to facilitate triacylglycerol accumulation through activation of the MT2 melatonin receptor. This activation increases important fat-related transcription factors like PPARγ and C/EBPα/β. This process helps precursor

cells turn into fat-rich adipocytes. Melatonin also raises the levels of fat-breaking enzymes and antioxidant defences. This reduces oxidative stress and helps with lipid metabolism. The positive effects on lipid accumulation and redox status are reversed by MT2 receptor antagonists, confirming the receptor-mediated pathway [31]. In mouse models, melatonin supplementation also modulates genes involved in lipid metabolism, inflammation, and mitochondrial function, further supporting its role in maintaining healthy skin lipid profiles, especially under stressors like aging or high-fat diets [32].

At the dermal level, melatonin significantly increases fibrillin-1 protein expression and improves fibrillin structural organization, indicating enhanced collagen and elastic fiber networks. Fibrillin-1 is the main structure for building elastic fibers. It also controls the bioavailability of growth factors that are vital for maintaining and remodelling skin. Melatonin also upregulates vascular endothelial growth factor A (VEGF-A), a key regulator of angiogenesis and tissue repair in the epidermis, which is required for inducing human skin rejuvenation [25, 33, 34]. Additionally, melatonin enhances collagen synthesis through its anti-inflammatory properties and stimulation of fibroblast activity [35].

Melatonin exerts protective effects on mitochondrial function, which is crucial for skin health and aging prevention. It maintains mitochondrial membrane potential, reduces ATP synthesis decline, and prevents cytochrome c release, thereby protecting against UV-induced cellular damage and apoptosis [36]. This mitochondrial protection is essential for maintaining cellular energy production and preventing age-related cellular dysfunction, especially for skin cells, which face constant oxidative stress from environmental factors. Importantly for cutaneous physiology, melatonin preserves mitochondrial function, which maintains membrane potential and ATP synthesis while limiting mitochondrial ROS production. It reduces the source of oxidative stress and prevents downstream oxidative damage in keratinocytes and fibroblasts [37, 38].

Melatonin inhibits matrix metalloproteinase-1 (MMP-1) production by interfering with key cellular signalling pathways that regulate MMP-1 expression. In human dermal fibroblasts and periodontal ligament cells, melatonin decreases oxidative and nitrosative stress, which in turn downregulates the activation of the epidermal growth factor receptor (EGFR) and the mitogen-activated protein kinase (MAPK) pathways, especially the c-jun N-terminal kinase (JNK) and activator protein-1 (AP-1) signalling cascades. This suppression results in lower transcription and activity of MMP-1. It also raises levels of tissue inhibitors of metalloproteinases (TIMP-1), which further reduces MMP-1 activity. By inhibiting these pathways, melatonin helps protect tissues from inflammatory and UV-induced damage, limiting extracellular matrix degradation and promoting tissue integrity [39, 40].

## Effects of topical melatonin on skin aging

Across six clinical trials combined in this study, melatonin consistently improved multiple parameters of skin aging in adults [8, 13-17]. The key biological pathways through which topical melatonin influences skin aging are summarized in fig. 3. Melatonin reduced wrinkles of different types and locations. It improved skin hydration and strengthened the skin barrier, which was shown by decreased TEWL. Improvements in skin firmness, elasticity, and tonicity were also observed, along with reductions in surface roughness.

Wrinkles develop from both internal aging and external factors, especially due to long-term exposure to UV light. This exposure leads to oxidative stress, inflammation, and damage to the skin's extracellular matrix. UV light generates ROS that activate matrix metalloproteinases, particularly MMP-1. These enzymes break down collagen and elastin fibres, which increases the depth, volume, and number of wrinkles and causes a loss of skin elasticity and moisture. Inflammatory pathways, such as NF-κB and COX-2, are also activated, which speeds up tissue damage and wrinkle formation. Topical melatonin counteracts these processes through several mechanisms. It acts as a potent antioxidant, directly scavenging ROS and inhibiting MMP-1, thereby preserving collagen and preventing dermal matrix degradation [28, 41, 42]. Melatonin also suppresses inflammatory mediators (NF-κB, COX-2, ERK) and hedgehog signalling (SHH/GLI1), which are implicated in wrinkle formation and skin inflammation. Additionally, melatonin improves mitochondrial function and triggers mitophagy. This process boosts proline and collagen production, which supports skin structure and reduces the formation of wrinkles [41, 43].

Topical application of melatonin improves skin hydration mainly through its strong antioxidant, anti-inflammatory, and lipid-modulating effects. Melatonin penetrates the stratum corneum and acts directly on skin cells. It neutralizes ROS and reduces oxidative stress, which is a key factor that contributes to skin barrier dysfunction and dehydration. By activating melatonin receptors present in various skin cell types, it also modulates signalling pathways that enhance collagen synthesis, mitochondrial function, and the skin's natural defence systems [9, 44, 45]. From a mechanistic perspective, melatonin improves the skin's lipid profile, particularly by increasing ceramides and triglycerides, which are essential for maintaining the skin barrier and water retention [17].

The topical use of melatonin has also been shown to reduce TEWL by improving the skin barrier and lowering oxidative stress. This effect comes from the strong antioxidant properties of melatonin. These properties help fight oxidative damage caused by environmental stressors like UV radiation and pollution. By neutralizing free radicals and supporting skin repair, melatonin helps maintain the integrity of the stratum corneum. This process reduces water loss through the skin. Additionally, improved skin hydration was seen alongside decreased TEWL,

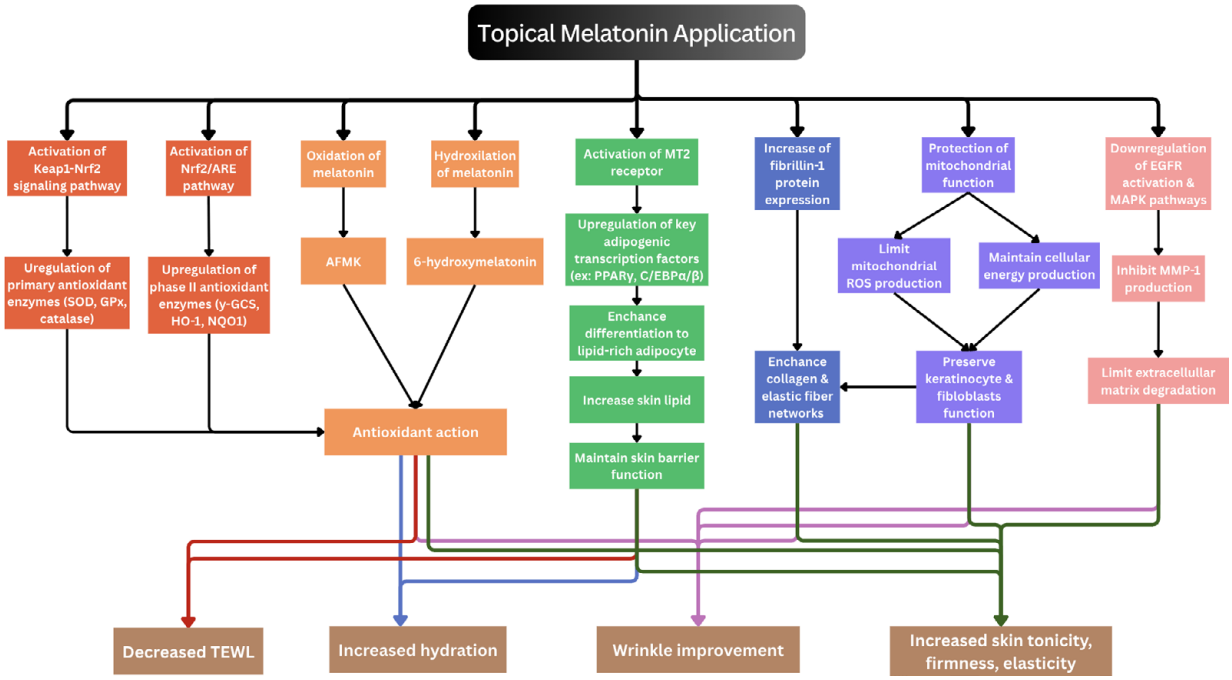


**Fig. 3.** Mechanisms by which melatonin applied topically improves different parameters of skin aging. **Source:** Own elaboration.

further supporting melatonin's role in strengthening the skin barrier and preventing moisture loss [16].

Skin tonicity refers to the overall tension and tone of the skin, firmness describes its resistance to deformation, and elasticity refers to the skin's capacity to stretch and then revert to its original shape. These properties are mainly determined by the composition and organization of the extracellular matrix, especially collagen and elastin fibers. Collagen provides structural support and firmness. In contrast, elastin fibers are crucial for elasticity and help the skin return to its original shape after stretching [16, 46, 47]. Topical application of melatonin improves skin tonicity, firmness, and elasticity through several connected mechanisms. By protecting skin cells from oxidative damage, melatonin helps maintain the structural integrity of the dermal matrix. Additionally, it stimulates collagen synthesis by upregulating mitochondrial function and promoting proline production, a critical amino acid for collagen formation, thereby directly improving skin firmness and elasticity [43, 44]. Melatonin also helps restore the skin's lipid balance, especially by boosting ceramides and triglycerides. These components are vital for preserving skin structure and hydration, which further support skin firmness [17].

## CONCLUSIONS

Topical melatonin application shows consistent potential as an anti-aging agent based on improvements in wrinkles, tonicity, firmness, elasticity, hydration, and TEWL, supported by mechanistic evidence involving antioxidant activation, mitochondrial protection, lipid regulation, and preservation of the extracellular matrix. However, current studies are limited by small sample sizes, short follow-up periods, and methodological variability, which introduces a notable risk of bias, particularly in non-randomized designs.

Given its favourable safety profile and mechanistic plausibility, topical application of melatonin may be considered as an adjunctive option in dermatological anti-aging regimens, particularly for patients seeking antioxidant-based interventions. Future research should focus on larger, well-controlled trials with standardized outcome measures, formulation optimization, and direct comparison with established anti-aging agents to better define its therapeutic relevance and long-term benefits.

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