eVitroKhem. 2025; 4:251
doi: 10.56294/evk2025251

REVIEW

Photoaging: molecular mechanisms, clinical impact, and treatment strategies

Fotoenvejecimiento: mecanismos moleculares, impacto clínico y estrategias de tratamiento

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Cite as: Da Silva MN, Benitez Duarte J, Garlisi-Torales LD, Poletti Duarte RE. Photoaging: molecular mechanisms, clinical impact, and treatment strategies. eVitroKhem. 2025; 4:251. https://doi.org/10.56294/evk2025251

Submitted: 16-10-2024 **Revised:** 25-02-2025 **Accepted:** 23-09-2025 **Published:** 24-09-2025

Editor: Prof. Dr. Javier Gonzalez-Argote

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ABSTRACT

Introduction: cutaneous photoaging is a clinically distinguishable form of extrinsic aging caused primarily by chronic ultraviolet (UV) radiation exposure, accelerating the structural and functional degradation of the skin.
Objective: to critically synthesize scientific evidence on the molecular mechanisms, clinical manifestations, and therapeutic strategies related to photoaging.
Method: a narrative review was conducted between February and April 2025 through indexed databases (PubMed, SciELO, Scopus, ScienceDirect), using controlled MeSH terms and Boolean operators to retrieve full-text articles from 2000 to 2024 in English and Spanish.
Results: studies show that UV radiation triggers oxidative stress via excessive generation of reactive oxygen species (ROS), activates proinflammatory transcription factors (NF-κB, AP-1), and upregulates matrix metalloproteinases (MMPs), leading to degradation of collagen, elastin, and DNA damage. Clinically, this results in wrinkles, elastosis, and increased risk of skin neoplasms.
Conclusions: current therapies include topical retinoids, antioxidants, advanced photoprotection, and platelet-rich plasma. Personalized approaches and advanced delivery technologies such as nanoparticles and liposomes are needed to enhance therapeutic efficacy.

Keywords: Photoaging; Ultraviolet Rays; Reactive Oxygen Species; Retinoids and Sunscreens.

RESUMEN

Introducción: el fotoenvejecimiento cutáneo es una manifestación del envejecimiento extrínseco inducido principalmente por la exposición crónica a la radiación ultravioleta (UV), que acelera el deterioro estructural y funcional de la piel.
Objetivo: sintetizar críticamente la evidencia científica disponible sobre los mecanismos moleculares del fotoenvejecimiento, sus implicancias clínicas y las estrategias terapéuticas actuales.
Método: se realizó una revisión narrativa entre febrero y abril de 2025, utilizando bases de datos indexadas (PubMed, SciELO, Scopus, ScienceDirect). Se aplicaron términos controlados DeCS/MeSH y operadores booleanos para identificar artículos publicados entre 2000-2024, en español e inglés, con acceso completo.
Resultados: Los estudios revisados evidencian que la radiación UV induce estrés oxidativo por sobreproducción de especies reactivas de oxígeno (ROS), activa rutas inflamatorias (NF-κB y AP-1) y aumenta la expresión de metaloproteinasas de matriz (MMP), lo cual lleva a la degradación del colágeno, elastina y daño al ADN. Esto se traduce clínicamente en arrugas, elastosis y riesgo de neoplasias cutáneas.
Conclusiones: las terapias actuales incluyen retinoides, antioxidantes, fotoprotección avanzada y plasma

rico en plaquetas. Se destaca la necesidad de abordajes personalizados y sistemas de liberación avanzada como nanopartículas y liposomas para mejorar la eficacia terapéutica.

Palabras clave: Fotoenvejecimiento; Radiación Ultravioleta; Especies Reactivas de Oxígeno; Retinoides y Protectores Solares.

INTRODUCTION

Skin photoaging is a clinically distinguishable manifestation of extrinsic aging, caused primarily by chronic exposure to ultraviolet (UV) radiation. Unlike intrinsic aging, which is genetic and progressive in nature, photoaging is characterized by the accelerated structural and functional deterioration of the skin due to environmental factors, with UV radiation being the predominant etiological agent.[1,2]

At the molecular level, UV radiation induces excessive generation of reactive oxygen species (ROS), triggering severe oxidative stress that compromises the integrity of DNA, structural proteins, and membrane lipids. This cascade of cellular damage activates proinflammatory pathways, such as those mediated by the transcription factors NF-κB and AP-1. It promotes the expression of matrix metalloproteinases (MMPs), which are responsible for the degradation of collagen and elastin in the dermis.[3,4,5] As a result, there is a progressive loss of skin elasticity, the appearance of deep wrinkles, hyperpigmentation, and solar elastosis, which are distinctive clinical signs of UV-induced aging.[6]

In addition, ultraviolet radiation causes direct alterations in nuclear DNA, especially the formation of pyrimidine dimers, which interfere with cellular repair mechanisms and increase the likelihood of oncogenic mutations, including those of the p53 gene. Simultaneously, mitochondrial dysfunction with additional ROS release is reported, which amplifies tissue damage and promotes the establishment of a senescent and inflammatory cellular microenvironment, linked to an increased risk of skin neoplasms such as basal cell carcinoma and melanoma.[4,7]

In this context, the objective of this review is to critically synthesize the available scientific evidence on the molecular mechanisms underlying photoaging, its most relevant clinical manifestations, and emerging therapeutic strategies. It also aims to highlight the need for personalized approaches and advanced delivery technologies that optimize the efficacy and safety of dermatological treatments designed to counteract this process.

METHOD

This study is a narrative review of the scientific literature, prepared with the purpose of identifying, selecting, and critically analyzing the available evidence on the pathophysiological mechanisms of skin photoaging and its current therapeutic approaches. To this end, a bibliographic search was conducted between February and April 2025 in recognized international scientific databases such as PubMed, SciELO, Scopus, and ScienceDirect. Articles published between 2000 and 2024 in Spanish and English that were available in full text were selected.

The search strategy was structured using Health Sciences Descriptors (DeCS)/MeSH (Medical Subject Headings), combined using Boolean operators (AND and OR), with the following controlled terms: “photoaging,” “ultraviolet radiation,” “reactive oxygen species,” “matrix metalloproteinases,” “retinoids,” “antioxidants,” “sunscreens,” “skin neoplasms,” and “platelet-rich plasma.”

Original articles, systematic or integrative reviews, and clinical trials that directly addressed any of the following topics were considered eligible: the molecular mechanisms of photoaging, the effects of ultraviolet radiation on skin structure, and topical, antioxidant, photoprotective, or regenerative therapies aimed at treating this condition. The inclusion criteria required that the studies be available in full text, have an explicit methodology, and be published in recognized scientific journals. Duplicate articles, editorials, letters to the editor, opinions without empirical support, or those that did not offer direct evidence on the subject of study were excluded.

The selection process was carried out independently by two authors, and in case of discrepancy, it was resolved by consensus. Subsequently, the selected information was organized into four main categories: molecular mechanisms of photoaging, clinical and histological manifestations, the relationship between photoaging and skin cancer, and therapeutic interventions for photoaging. The findings were critically analyzed to provide an integrated, up-to-date, and clinically relevant overview of the therapeutic approach to photoaging.

DEVELOPMENT

Molecular Mechanisms of Photoaging

Photoaging is a process mediated by a series of complex molecular events resulting from the interaction between ultraviolet (UV) radiation and the cellular components of the skin. UV radiation, specifically UVA

and UVB rays, is mainly absorbed by chromophores such as DNA, RNA, and structural proteins, triggering the generation of reactive oxygen species (ROS). These ROS, including superoxide anions, hydrogen peroxide, and hydroxyl radicals, are products of photosensitization and mitochondrial dysfunction. The resulting oxidative damage affects membrane lipids, structural proteins, and nucleic acids, altering cellular homeostasis and promoting accelerated skin aging.[5]

A fundamental molecular aspect of the photoaging process is the activation of matrix metalloproteinases (MMPs), especially MMP-1 and MMP-3, which play a crucial role in the degradation of type I and III collagen, as well as elastin, essential components of the dermal extracellular matrix. Exposure to ultraviolet (UV) radiation induces the generation of reactive oxygen species (ROS), which activate transcription factors such as AP-1 (protein activator-1) and NF-κB. These factors regulate the expression of MMPs, promoting the progressive degradation of the extracellular matrix. This process leads to structural changes in the skin, manifesting clinically as loss of firmness and elasticity, distinctive characteristics of photoaging.[8,9]

Exposure to ultraviolet (UV) radiation induces the formation of thymine dimers in nuclear DNA, generating lesions that compromise genomic integrity and promote mutations in key genes such as p53. This gene, essential for cell cycle regulation and DNA repair, undergoes alterations that favor the accumulation of mutations and cellular senescence. Clinically, these mutations are associated with an increased risk of developing skin neoplasms, including basal cell carcinoma, squamous cell carcinoma, and melanoma.[10]

Mitochondrial dysfunction plays a key role in the pathophysiology of skin photoaging. Exposure to ultraviolet (UV) radiation causes damage to mitochondrial DNA, compromising cellular energy production and exacerbating the generation of reactive oxygen species (ROS). This increase in oxidative stress activates cellular senescence pathways mediated by regulatory proteins such as p16^INK4a^ and p21, which inhibit the proliferation of keratinocytes and fibroblasts, thus limiting the regenerative capacity of the epidermis. The accumulation of senescent cells contributes to the creation of a chronic inflammatory microenvironment, which amplifies dermal damage and accelerates skin aging.[10]

Clinical and Histological Manifestations of Cutaneous Photoaging

Cutaneous photoaging manifests clinically as the appearance of deep wrinkles, hyperpigmentation, and loss of elasticity. These signs are the result of chronic exposure to ultraviolet (UV) radiation, which induces structural and functional alterations in the skin. Histologically, solar elastosis is characterized by the accumulation of abnormal elastic fibers in the dermis, accompanied by thickening of the epidermis. This cumulative DNA damage caused by UV radiation increases the risk of developing skin cancer, such as basal cell carcinoma and melanoma.[10,11]

Relationship between Photoaging and Skin Cancer

Chronic exposure to ultraviolet (UV) radiation, both UVA and UVB, induces mutations in tumor suppressor genes such as p53, playing a crucial role in skin carcinogenesis. These mutations are a direct consequence of persistent oxidative damage and sustained activation of matrix metalloproteinases, which impair the skin's immune defenses. Numerous studies have shown that prolonged, unprotected exposure to UV radiation is one of the most significant risk factors for the development of skin cancer, including basal cell carcinoma and melanoma.[7,12,13]

Therapeutic Interventions for Photoaging

Cutaneous photoaging is the cumulative result of structural and molecular damage induced by chronic ultraviolet (UV) radiation, characterized by clinical alterations such as deep wrinkles, hyperpigmentation, loss of elasticity, and histological changes such as solar elastosis. In response to this multifactorial condition, modern therapeutic interventions focus on both preventing and repairing dermal and epidermal damage through the use of topical agents, antioxidant compounds, advanced photoprotection, and emerging regenerative therapies.[14,15]

Among the most established treatments are topical retinoids, such as retinol and tretinoin, which are derived from vitamin A. These compounds act by modulating RAR and RXR nuclear receptors, promoting keratinocyte proliferation, epidermal regeneration, and increased type I collagen synthesis by dermal fibroblasts, which partially reverses the manifestations of clinical photoaging and visibly improves skin texture.[16,17]

Likewise, the use of topical antioxidants, particularly vitamin C (ascorbic acid) and vitamin E (tocopherol), has proven effective in neutralizing reactive oxygen species (ROS) generated by UV radiation. These antioxidants act synergistically to prevent lipid peroxidation, collagen degradation, and the activation of matrix metalloproteinases (MMPs), thereby reducing dermal oxidative damage and contributing to the preservation of extracellular matrix integrity.[18,19]

Photoprotection remains the fundamental strategy in the prevention of photoaging. Broad-spectrum sunscreens, formulated with physical filters (zinc oxide, titanium dioxide) and chemical filters (avobenzone,

octocrylene), provide adequate coverage against UVA, UVB, and even visible light and infrared radiation. Recent studies have shown that continued use of photoprotectors not only prevents the appearance of new pigmented lesions and wrinkles but also allows for significant clinical improvement in patients with accumulated sun damage.[20]

In recent years, regenerative therapies such as platelet-rich plasma (PRP) have emerged as innovative options. PRP, obtained by autologous centrifugation, contains high concentrations of growth factors such as PDGF, TGF-β, and VEGF, which stimulate neocollagenesis, angiogenesis, and cell proliferation. Clinical trials have shown that its intradermal application improves skin density, hydration, and elasticity, with good safety profiles.[21]

Despite advances in these therapeutic strategies, significant clinical challenges remain. The combination of photoprotection, topical antioxidants, and regenerative therapies appears to offer a promising comprehensive approach; however, the formulation of personalized strategies, tailored to individual factors such as skin phototype, biological age, and exposome, requires further validation in high-quality methodological studies. Therefore, research into new molecules, delivery technologies (such as liposomes and nanoparticles), and combination regimens is a priority in preventive and restorative dermatology.[22,23]

CONCLUSIONS

Skin photoaging is a multifactorial biological process, mainly induced by chronic exposure to ultraviolet radiation, which causes profound molecular alterations. The most relevant mechanisms include the overproduction of reactive oxygen species (ROS), the activation of matrix metalloproteinases, cumulative damage to nuclear and mitochondrial DNA, and the dysfunction of endogenous cell repair systems. These events promote cellular senescence and contribute to the development of skin neoplasms. Clinically, this process manifests as deep wrinkles, hyperpigmentation, and loss of elasticity, reflecting a progressive deterioration of the dermal structure.

The most scientifically supported therapeutic interventions integrate the use of topical retinoids, antioxidants such as vitamins C and E, broad-spectrum photoprotectors, and emerging regenerative therapies such as platelet-rich plasma. However, current advances point to the need for more personalized approaches that consider individual factors such as skin phototype, exposome, and the patient's biological profile. In this context, advanced delivery technologies, including liposomes and nanoparticles, represent a promising strategy for optimizing the bioavailability, efficacy, and safety of therapeutic agents used in the prevention and treatment of photoaging.

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FINANCING

None.

CONFLICT OF INTEREST

None.

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