González *et al. Plast Aesthet Res* 2022;9:32
DOI: 10.20517/2347-9264.2022.04

Plastic and Aesthetic Research

Editorial

Open Access

Introduction to special issue "Recent Advances in Skin Anti-Aging Agents"

Salvador González[1], Concepción Parrado[2], Ángeles Juarranz[3]

[1]Department of Medicine and Medical Specialties, Alcalá de Henares University, Madrid 28805, Spain.
[2]Department of Histology and Pathology, Malaga Medical School, Malaga University, Málaga 29071, Spain.
[3]Department of Biology, Faculty of Sciences, Universidad Autónoma de Madrid, Madrid 28049, Spain.

Correspondence to: Dr. Salvador González, Department of Medicine and Medical Specialties, Alcalá de Henares University, Madrid 28805, Spain. E-mail:salvagonrod@gmail.com; Dr. Ángeles Juarranz, Department of Biology, Faculty of Sciences, Universidad Autónoma de Madrid, Madrid 28049, Spain. E-mail: angeles.juarranz@uam.es

How to cite this article: González S, Parrado C, Juarranz Á. Introduction to special issue "Recent Advances in Skin Anti-Aging Agents". *Plast Aesthet Res* 2022;9:32. https://dx.doi.org/10.20517/2347-9264.2022.04

Received: 18 Jan 2022 **Accepted:** 14 Feb 2022 **Published:** 6 May 2022

Academic Editor: Wen-Guo Cui **Copy Editor:** Xi-Jun Chen **Production Editor:** Xi-Jun Chen

INTRODUCTION

The skin is the main defensive barrier of our body and it protects us from physical, chemical, and biological threats from the environment. The cutaneous barrier also provides homeostatic balance maintenance. The external factors (lifestyle, occupation, pollutants, and light exposure), combined with internal factors, are responsible for cutaneous aging, which affect healthy skin and increase the risk of cancer. Skin aging is externally characterized by the appearance of wrinkles, presence of spots, loss of elasticity, or loss of skin tone, among others. The aging process produces oxidative stress, inflammatory responses, a decrease of immune functions, and disruption of the skin barrier. Several cell stressors, such as mitochondrial dysfunction, telomere shortening, activation of oncogenes, and changes in chromatin structure, are implicated in intrinsic and extrinsic skin aging. Oxidative stress plays a crucial role in both intrinsic and extrinsic aging. In the skin, oxygen is converted into reactive oxygen species (ROS) by intrinsic processes, and ROS are the primary effectors of UV-caused photoaging. More recently, research is focused on the assessment of injury that environmental factors cause to the skin. Besides sun radiation exposure, environmental factors involved in skin belong to the following major categories: air pollution (outdoor and indoor air pollution) and tobacco smoke, among others. At the same time, the components of

environmental stress can interact with ultraviolet radiation. Three major mechanisms seem to be related to the adverse effects of ambient air pollutants on skin health: the generation of free radicals, the induction of an inflammatory cascade, and the impairment of the skin barrier.

It is of critical importance that we explore the deeper knowledge of all the factors (internal and external) involved in skin aging to develop new anti-aging therapies that can keep the skin undamaged over time and improve its ability to repair.

RESEARCH SNIPPETS

Botanicals for photoprotection. Torres *et al.*[1]. Electromagnetic radiation, particularly ultraviolet radiation (UVR), exerts harmful effects on human skin, playing a role in photoaging, photoimmunosuppression, and photocarcinogenesis. The damage is mainly produced through the generation of ROS and the resulting oxidative stress. In addition to behavioral strategies against sunlight exposure and sunscreens, there is a growing interest in alternative photoprotective methods, such as oral and topical products of botanical origin. These botanical-based photoprotectors act through a variety of biologic mechanisms to counteract the adverse effects of UVR. *Polypodium leucotomos* extract is the most well studied botanical photoprotective agent. It has immunomodulatory, tumor suppressive, and anti-aging properties, which are mainly attributed to its polyphenols content (such as caffeic acid and ferulic acid). *Polypodium leucotomos* extract has been shown to minimize the oxidative damage, suppress UV-induced erythema, reduce cutaneous phototoxicity, preserve epidermal Langerhans cells, accelerate extracellular matrix turnover, and promote renewal of dermal collagen. Green tea also has antioxidant, anti-inflammatory, immunomodulatory, and chemopreventive properties, primarily due to the phenolic green tea catechins. Green tea catechins reduce photodamage and confer protection against photoinflammation and photocarcinogenesis. Pomegranate as well is rich in phenolic compounds, such as anthocyanins, catechins, and tannins, and has anti-inflammatory properties and very strong antioxidant activity. Resveratrol, a non-flavonoid polyphenol present in grapes and red wine, has also demonstrated antioxidant, anti-inflammatory, and anti-tumor effects in several *in vitro*, animal, and human studies. The active constituent of turmeric, curcumin, not only mitigates *in vitro* UVB-induced damage but also confers protection against UVA-mediated photodamage. Finally, the isoflavone silymarin contains flavonolignans, which are the polyphenols through which this botanical product exerts its antioxidant and anti-inflammatory effects. There is evidence that the use of these botanical products as photoprotective agents could be beneficial, as long as they are applied as adjunctive measures to conventional photoprotection.

Deschampsia antarctica extract (Edafence®) as a powerful skin protection tool against the aging exposome. Mataix *et al.*[2]. The skin is our first body barrier to face external agents and thus the totality of exposures to the environmental stressors (clustered under the term "skin exposome") are the main inductors of skin aging and skin pathologies. Among environmental agents with an impact on the organism we could highlight the next classification: air pollution, tobacco, light radiations, and other environmental agents (e.g., humidity, chemicals from daily activities, and endogenous factors). Air pollution (e.g., ionizing molecular gas species, volatile compounds, and particulate matter) have a direct impact on skin homeostasis and induce damage and stress responses in skin cells and tissues. Tobacco smoke induces generic oxidative stress and DNA damage, and it impairs the regeneration capacity of skin. Solar radiation, particularly UVR, induces DNA damage, oxidative stress, and dysregulation of homeostasis, leading to alterations that may precede to skin tumorigenesis and senescence. Additional environmental factors (e.g., temperature, cosmetics, and dietary components) can also induce adverse effects such as inflammatory infiltration, oxidative DNA damage, sensitization to UV radiation, and metabolic stress. To counteract the skin exposome, cells have developed adaptative mechanisms that are integrated with general stress responses and

repair mechanisms. Hence, the identification of compounds that specifically intervene in these mechanisms is highly relevant for the prevention of exposome-induced skin aging. The soluble extract of *Deschampsia antarctica* (a polyextremophile Gramineae), Edafence®, obtained from the leaves of the plant, has shown its capacity to protect from the detrimental effects of cutaneous environmental factors. Regarding air pollutants, Edafence® has the potential to induce endogenous antioxidant responses, confers protection against toxic compounds and dioxins, and prevents alterations to tissue architecture, skin barrier integrity, and dermal proliferation. There is also evidence that this extract reduces the impact of tobacco on cell viability, supporting its ability to maintain and enhance the tissue repair mechanisms. Moreover, exposure to Edafence® protects human skin from deleterious effects induced by UVR (e.g., senescence, oxidative damage, proapoptotic stress, and alterations on extracellular matrix remodeling enzymes) and the harmful impact exerted by visible, infrared, and blue light radiation. Finally, clinical studies conducted on the effect of topical preparations containing Edafence® support that this aqueous extract in combination with antioxidants and retinoids improves the integrity and the function of skin. In conclusion, although future studies are needed to elucidate the mechanistic basis of its activity, Edafence® confers protection against environmental aggressive factors in urban areas and prevents skin aging.

The microbiome and ageing. Abadías-Granado *et al.*[3]. The skin is colonized by an enormous variety of microbial communities (e.g., bacteria, fungi, mites, and viruses) that play a necessary role in various essential functions and are in constant interaction with both the host as well as the immune system. Thus, skin can be perceived as an ecosystem in which microbiota is determined by both internal (e.g., sex, age, genetics, and immune response) and external factors (e.g., biogeography, diet, cosmetics, and lifestyle). Under normal conditions, these communities are nonpathogenic, but its imbalance or dysbiosis, may influence the health of the host becoming an important factor for the development of numerous diseases. The physiological changes associated to aging disrupt the balance of cutaneous microbiota, so age-associated dysbiosis could be a trigger of aging. In this sense, it was suggested that skin microbiome was the most accurate indicator to predict chronological age. Accordingly, a balanced skin microbiota would offer skin additional protection against premature aging. In fact, there is increasing interest in the use of oral and topical probiotics as a therapy for regulation of microbiota balance, which would support skin barrier function and protect against environmental stressors. Different studies also suggest that dysbiosis may be involved in the genesis and progression of cancer mainly through a reaction of immune system to the microbiome imbalance. With regard to skin cancer, the excess of *Staphylococcus aureus* in actinic keratoses and squamous cell carcinomas has been described, suggesting the implication of this bacteria in the progression from actinic keratoses to squamous cell carcinomas. In contrast, other studies have proposed the skin microbiome to be a suppressor of tumor growth. Thus, microbiota may play a dual role in skin cancer, promoting it or protecting against it.

Skin collagen through the lifestages: importance for skin health and beauty. Reilly and Lozano[4]. Collagen is an essential protein arranged in networks of fibers that provide support to the skin and contribute to the maintenance of its strength, elasticity, and firmness. The synthesis and degradation of collagen are crucial processes for the development, repair, and maintenance of tissues from various anatomical and physiological systems. Fibroblasts are responsible for its production, in addition to producing other essential proteins such as elastin or glycosaminoglycans. The activation of fibroblasts by physical tension of the extracellular matrix (ECM), biochemical stimuli, or signaling pathways, results in an increase in the production of collagen. Over time, from adult stage, fibroblasts become less active, collagen production declines and collagen fibers become functionally impaired, reduced in density, and become disrupt, leading to the loss of skin firmness. In this process, known as chrono-aging, skin becomes thin, dry, and finely wrinkled. Oxidative stress resultant from the overproduction of ROS is one of the main causes of damage to

collagen integrity and content in the ECM, which lead to disruption of structure and metabolism of this protein and consequently to photo-aging, characterized by scaling, dryness, and hyperpigmentation of skin. The neutralization of free radicals through administration of antioxidants could prevent this damage, protecting cells and contributing to restore cutaneous homeostasis. Moreover, there are several targeted intervention strategies intended to stimulate the production of collagen or inhibit its degradation, such as surgical aesthetic treatments, topical treatments, or the use of oral supplements. This latter strategy, which is referred as nutricosmeceuticals, involves the administration of hydrolysed bioactive collagen peptides that are easily absorbed into bloodstream. Examples of these supplements containing collagen peptides are Pure Gold Collagen® and Gold Collagen® Forte, which have been shown to contribute to restoration of the levels of collagen and elastin in ECM leading to an increase in skin elasticity and a reduction of the visible signs of aging. It should be also noted the importance of vitamin C because of its role as a co-factor to several enzymes in the production of collagen and as an antioxidant against oxidative damage. Since fibroblasts are the main responsible of collagen production, there is a growing interest in the development of new strategies based on counteracting the replicative senescence of fibroblasts and the shortening of its telomere.

Environmental aging of the skin: new insights. Burke[5]. Protection of skin is essential for healthspan, even more when our lifestyle means we are increasingly exposed to environmental stressors, such as radiations (e.g., ultraviolet, visible, and infrared) or airborne pollution (e.g., ozone, polycyclic aromatic hydrocarbons, volatile organic compounds, and particulate matter), that cause consequences from premature aging to skin cancer. Exposure to solar UV radiation leads to an immediate pigmentary darkening and the overproduction of melanin, with the consequent generation of ROS and damaging DNA photoproducts. UVB induces persistent "fingerprint mutations" (intra-strand pyrimidine dimers) that give rise to pre-cancerous conditions (e.g., actinic keratoses) and skin cancers (e.g., basal cell carcinoma, squamous cell carcinoma, and melanoma). UVA doses to which we are usually exposed do not initiate skin cancer but inhibit the normal immune response. Individuals with pale or fair skin (phototypes I and II), are particularly sensitive to UV because of their low melanin content and their few dermal papillae. Exposure to visible light also leads to oxidative stress and inflammatory cascades that contribute to dermal matrix destruction and photoaging. Clinical cutaneous manifestations after infrared (IR) exposure (and concretely IRA) are similar than after UV, but IRA induces genes regulating apoptosis, extracellular matrix or calcium metabolism and leads to a marked elastosis. Polycyclic aromatic hydrocarbons, such as benzo[a]pyrene, present in urban environments are metabolized to quinones which generate ROS. In addition, the synergistic interaction between polycyclic aromatic hydrocarbons and UVA induce the formation of DNA adducts that also produce oxidative damage. Volatile organic compounds (e.g., nitrogen oxides, methane, carbon monoxide or sulfuric compounds) pollution in the indoor and outdoor environment, increase the ozone levels on the earth's surface, which oxidizes lipids on the skin, triggering inflammatory cascades that disrupt dermal cells and extracellular matrix and accelerate extrinsic aging. Particulate matter emitted by factories, power plants, diesel engines or traffic, also cause skin disorders through oxidation of surface lipids with the subsequent generation of ROS and inflammation process. Cigarette smoke is one of the main indoor pollutants, contains thousands of chemicals (including both particulate matter and volatile organic compounds), and can accelerate extrinsic aging through skin barrier disruption. The aryl hydrocarbon receptor present in skin cells is the main natural mechanism of binding and clearing xenobiotic pollutants and plays a crucial role in maintenance of epidermal barrier function, regulation of keratinocyte differentiation and proliferation, melanogenesis, immunity and skin inflammation. For that reason, in addition to the active study of antioxidant compounds, research on protection of skin against extrinsic damage is also focused on understanding at a cellular level aryl hydrocarbon receptor mechanism in order to find methods to modulate it.

Anti-aging and anti-carcinogenic effects of 1α,25-dihydroxyvitamin D_3 on skin. Philips *et al.*[6]. The biologically active form of vitamin D, 1α,25-dihydroxyvitamin D_3 or calcitriol, plays a role in a wide range of functions in the organism. Among its properties, the antiproliferative, antiangiogenic, and antiapoptotic effects stand out. These effects could give calcitriol the capacity to counteract processes such as oxidative stress, inflammation, angiogenesis or ECM remodeling, all of them involved in skin aging and carcinogenesis. The oxidative damage, mediated by an overproduction of ROS, leads to the wrinkling of the skin and also triggers mutagenic processes that give rise to skin cancer development, such as formation of 8-hydroxy-2'-deoxyguanine (8-OHdG) or cyclobutane pyrimidine dimers. The photoprotective capacity of vitamin D seems to inhibit the effects of oxidative stress, curbing the formation of 8-OHdG and cyclobutane pyrimidine dimers through the reduction of ROS production. Skin inflammatory responses involving both innate and adaptative immunity cause the release of interleukins, tumor necrosis factor, and Th2 cytokines, the activation of NF-κB and Janus tyrosine kinases, and the increased production of angiogenic factors such as vascular endothelial growth factor (VEGF) or transforming growth factor beta (TGF-β). Vitamin D is involved in the regulation of immune response and several studies suggest its potential role in the modulation of inflammatory and angiogenesis mediators, decreasing IL-1 and IL-8 or inhibiting NF-κB, VEGF, or TGF-β. The activity of ECM remodeling is enhanced when oxidative stress and inflammatory response occur. This entails a loss of collagen and an increase in the production of matrix metalloproteinases (MMPs) and elastases, which is directly associated with aging and cancer processes. According to results from various studies, vitamin D promotes the expression of collagen (through transcriptional mechanisms or stimulation of the chaperone HSP-47) and inhibits the expression of elastin and MMP-1 and MMP-2, which helps to maintain the integrity and proper functioning of the ECM. Based on the above, dietary supplementation with vitamin D (as cholecalciferol, D_3) is a key point for the maintenance of the health of our skin.

Lastly, we would like to signify that Concha Parrado passed away on October 12, 2021 in Malaga, Spain. Concha was a Full Professor and chief of the Department of Histology and Pathology at Malaga Medical School whose important contributions to Experimental Dermatology, as a scientist, teacher, and friend will be fondly remembered. She contributes as co-editor to this issue. We owe this issue to Concha's passion for skin research and creativity while applying her knowledge to experimental dermatology.

DECLARATIONS

Authors' contributions

Wrote and reviewed the article: González S, Parrado C, Juarranz A

Available of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publications

Not applicable.

REFERENCES

1. Torres AE, Luk KM, Lim HW. Botanicals for photoprotection. *Plast Aesthet Res* 2020;7:57. DOI
2. Mataix M, Rodríguez-Luna A, Gutiérrez-Pérez M, et al. Deschampsia antarctica extract (Edafence®) as a powerful skin protection tool against the aging exposome. *Plast Aesthet Res* 2020;7:69. DOI
3. Abadías-Granado I, Sánchez-Bernal J, Gilaberte Y. The microbiome and aging. *Plast Aesthet Res* 2021;8:27. DOI
4. Reilly DM, Lozano J. Skin collagen through the lifestages: importance for skin health and beauty. *Plast Aesthet Res* 2021;8:2. DOI
5. Burke KE. Environmental aging of the skin: new insights. *Plast Aesthet Res* 2020;7:59. DOI
6. Philips N, Portillo-Esnaola M, Samuel P, Gallego-Rentero M, Keller T, Franco J. Anti-aging and anti-carcinogenic effects of 1α, 25-dihyroxyvitamin D_3 on skin. *Plast Aesthet Res* 2022;9:4. DOI