UV light and skin aging

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Abstract: This article reviews current data about the relationship between sun radiation and skin, especially with regards ultraviolet light and the skin aging process. The benefits of sun exposition and the photoaging process are discussed. Finally, the authors present a review of photoprotection agents that are commercially available nowadays.

Keywords: photoaging; sun protection; ultraviolet (UV) exposure.

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Aging

The process of aging begins at the moment of birth, but people now live longer than ever before. This is due to the continued advancements in medicine involving new technologies for immunization, organ transplant, reduced infection (1) and equipment to support life, which have all become more available.

In many countries a demographic transition is occurring, involving aging of the population and reduced birthrates, as well as large-scale migrations. In the next 50 years, about one-third of women will be menopausal, and anti-aging medicine will gain importance (2) because no one especially wants to continue to live in a way, in which they also physically decline. Whereas cultural and technical manipulations have brought about increased longevity, this has also shaped cultural and technical manipulations so that the side effects of longevity, including wrinkled skin, are increasingly treated. The eternal desire of people around the world is to live longer, to be young longer, or at least to look younger (3).

As skin ages, keratinocytes change shape, becoming shorter and fatter; by contrast, corneocytes become bigger due to decreased epidermal turnover. Enzymatically, active melanocytes decrease at a rate of 8% – 20% per decade, resulting in uneven pigmentation in elderly skin (5).

As time goes by, skin becomes less resistant to shearing forces and presents an increased vulnerability to insult due to the flattening of the dermo-epidermal junction, which occurs as a result of the loss of dermal papillae and the reduced interdigitation between layers. This flattening begins in the sixth decade (6). The smaller contiguous surface between the two layers also creates a reduced cellular supply of nutrients and oxygen, leading to an increased risk of dermo-epidermal separation, a process that may explain the mechanism by which wrinkles form (8).

Signs of aging. Physiological changes in aged skin include structural and biochemical changes as well as changes in neurosensory perception, permeability, response to injury, repair capacity, and increased incidence of some skin diseases (5).

The skin aging process occurs in the epidermis and dermis. Although the number of cell layers remains stable, the skin thins progressively over adult life at an accelerating rate. The epidermis decreases in thickness by about 6.4% per decade on average, with an associated reduction in epidermal cell numbers (6), particularly in women. Further, dermis thickness decreases with age, and thinning is accompanied by a decrease in both vascularity and cellularity (5).

Aged skin turns dryer (7), and this can be proven by transepidermal water loss (TEWL) measurements. Baseline TEWL decreases with age, an observation believed to be due to the reduction of the water content of aged skin, which can be associated with a profound change in barrier integrity. Although the number of sweat glands does not change, sebum production decreases by as much as 60%. A reduction of the natural water and fat emulsion on the skin is also observed, as is water content in the stratum corneum. Global lipid content of the aged skin is reduced by as much as 65%. Changes in the amino acid composition in aged skin may reduce the amount of cutaneous natural moisturizing factor, thereby decreasing its capacity for water binding (5).

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Inside the dermis, many changes also occur. For example, the amount of glycosaminoglycans in the
dermis declines with old age. The amount of hyaluronic acid, elastin and collagen decreases as they are produced by fibroblasts, whose number also declines. Indeed, aging is inevitably associated with a decrease in collagen turnover (due to a decrease in fibroblasts and their collagen synthesis) as well as elastin. Elastin also has higher degree of calcification in aged skin, with an associated degradation of elastin fibers. In this case, collagen crosslinks stabilize, whereas collagen bundles become disorganized. The loss of molecular integrity of the dermis leads to increased rigidity, decreased torsion extensibility, and diminished elasticity, eroding faster in women than in men, with a concomitant increase in vulnerability to tear-type injuries (5).

Cutaneous aging is a mix of intrinsic aging (due to inherent genetics) and extrinsic aging (due to environmental conditions like solar exposure) (7, 9). However, the interactions between chronological and photo-induced aging are complex, and the quantification of only the effect of sun-exposure is difficult to obtain. Hence, a study clinically quantified the effect of sun exposure on facial aging in terms of the appearance of new specific signs or in terms of increasing the classical signs of aging. This study seems to confirm that pigmentation heterogeneity is a pure photoaging sign, whereas sagging of tissues is essentially a result of chronological aging. Vascular disorders could be considered a precursor of future photoaging. The appearance of wrinkles and skin texture are influenced by both extrinsic and intrinsic aging, depending on the behavior of the individual and the amount of sunlight to which he or she has been exposed (10).

Intrinsic aging

Intrinsic aging of the skin occurs inevitably as a natural consequence of physiological changes over time at variable yet inalterable genetically determined rates (11); it is also characterized primarily by functional alterations than by gross morphological changes (12).

Within the skin, collagen production slows down and elastin has a bit less spring. Dead skin cells do not shed as quickly, and turnover of new skin cells may decrease slightly. Although these changes usually begin in the 20s, the signs of intrinsic aging are typically not visible for decades (4). The clinical manifestation of intrinsic aging includes xerosis, laxity, wrinkles, slackness, and the appearance of a variety of benign neoplasms like seborrheic keratosis and cherry angioma. At the same time, hair becomes depigmented, terminal hair converts to vellus hair, and loss of hair is increased. There are also changes in nail plate and there are fewer glands in aged skin (3).

In women, estrogen levels strongly influence skin integrity, that is, falling levels in midlife contribute to earlier signs of aging. Furthermore, intrinsic aging proceeds at different rates in all organisms at genetically determined pace; this is caused primarily by the buildup of reactive oxygen species (ROS) as a by-product of cellular metabolism. ROS, in turn, cause damage to critical cellular components like membranes, enzymes, and deoxyribonucleic acid (DNA) (5).

There is a great effect of ethnicity on aging, and it is primarily related to differences in pigmentation. High levels of pigmentation are protective with regards the cumulative effects of photoaging, with African Americans showing little cutaneous difference between exposed and unexposed sites (11). Increased innate pigmentation is related to ultraviolet (UV) damage protection, including less collagen decrease and DNA damage in darker-skinned people (13).

Extrinsic aging

Extrinsic skin aging process is characterized by striking morphologic and physiologic changes that generally lead to a premature aging of the skin. Prominent manifestations of the extrinsic skin aging process are coarse wrinkles, solar elastosis, and pigment irregularities. These signs superimpose the intrinsic skin aging signs at chronically exposed areas of the body (12).

Extrinsic factors are, to varying degrees, controllable and include exposure to sunlight, pollution or nicotine, repetitive muscle movements like squinting or frowning, and miscellaneous lifestyle components, including diet, sleeping position, and overall health (14). Repetitive facial movements actually lead to fine lines and wrinkles. When we use a facial muscle, a groove forms beneath the surface of the skin, which is why we see lines forming with each facial expression. As skin ages and loses its elasticity, the skin stops springing back to its line-free state, and these grooves become permanently etched on the face as fine lines and wrinkles. When the skin elasticity declines in middle age, the effects of gravity become evident. Gravity causes the tip of the nose to droop, the ears to elongate, the eyelids to fall, the jowls to form, and the upper lip to disappear as the lower lip becomes more pronounced. Resting your face in the same way every night for years eventually also leads to wrinkles. As a person ages, sleep wrinkles become etched on the surface of the skin and no longer disappear (4).
Environmental stressors

Terrestrial organisms are chronically exposed not only to natural environmental stress factors like UV and ozone (O₃), but also to pollutants of anthropic origin (15). Industrialization changed our lifestyle and new habits have developed that challenge the skin, including smoking, pollution, usage of tanning beds, unhealthy food and beverages, sedentary lifestyle, and insufficient sleep (16).

The major mechanism by which environmental insults exert a detrimental effect on the skin is through the generation of oxidative stress, which overwhelms the skin’s defenses by quickly depleting the enzymatic (glutathione peroxidase, glutathione reductase, superoxide dismutase, catalase) and nonenzymatic (vitamin E, vitamin C, and glutathione) antioxidant capacity. Free radicals and ROS interact with lipid-rich plasma membrane and initiate the so-called lipid peroxidation reaction cascade. ROS also stimulate the release of pro-inflammatory mediators from a variety of skin cells. Skin inflammation leads to skin infiltration by activated neutrophils and other phagocytic cells that generate further free radicals (both reactive oxygen and nitrogen species), thus establishing a vicious circle (15).

Oxidative stress initiates complex biologic processes in various layers of the skin, which can result in transient or permanent genetic damage, activation of transcription factors and signaling pathways that are involved in cell growth, as well as in differentiation and degradation of the connective tissue of the dermis (15).

Smoking

In 1969, Harry Daniell recognized that smokers look older than non-smokers, and the association between smoking and skin wrinkling was reproduced in various epidemiological studies. It has been further elucidated that smoking is an independent skin aging-inducing environmental factor (similar to the effect of sun exposure), and that smoking is multiplicative or additive (12). A study carried out on twins estimated that 10 years of smoking difference corresponds to a 2½ year-older appearance (17).

Cigarette smoke (CS) is a highly complex aerosol composed of several thousand chemical substances (gas and the particulate phase). The presence of high levels of pro-oxidants (e.g., free radicals) in smoke is well documented. It is estimated that gas-phase smoke contains more than 1014 low molecular-weight carbon- and oxygen-centered radicals per puff. In addition, CS contains up to 500 ppm nitric oxide (NO), which slowly undergoes oxidation to nitrogen dioxide (NO₂) (15).

Smoking causes skin damage primarily by decreasing capillary blood flow to the skin, which, in turn, creates oxygen and nutrient deprivation in cutaneous tissues. It has been shown that those who smoke have fewer collagen and elastin fibers in the dermis, which causes skin to become slack, hardened, and less elastic. In addition, constriction of the vasculature by nicotine may contribute to wrinkling (11).

Air pollution

Air pollution represents another environmental threat to which millions of humans worldwide are exposed. The skin is in direct contact with various air pollutants, and thus, the association between air pollution and skin damaging effects leading to skin aging is likely (12).

A recent epidemiological study discovered a direct link between airborne particulate matter (PM) exposure and the occurrence of prominent skin aging signs, especially pigment spots and wrinkles (18). One major mechanism by which ambient PM exerts its detrimental effects is through the generation of ROS. Furthermore, particles can serve as carriers for organic chemicals and metals that are capable of localizing in the mitochondria and generating ROS directly in mitochondria leading to skin aging by mitochondrial damage (12).

Ozone

Ozone (O₃) formed from chemical reaction between UV and O₂, is a gaseous oxidant that can induce oxidative stress in cutaneous tissue. In fact, although O₃ is not a radical species per se, its effects are mediated through free radical reactions. It is generally accepted that its noxious effects are a consequence of biomolecule oxidation, with consequent ROS generation, or via a cascade of bioactive nonradical-molecules like aldehydes (lipid peroxidation products) (15).

Some studies have already investigated the effects of O₃ on murine cutaneous tissue, providing evidence that O₃ is capable of affecting the integrity of the skin as a strong oxidative agent. Furthermore, it can induce the expression of matrix metallopeptidase MMP-9 in murine skin, thus indicating a role in matrix remodeling (12).

UV radiation

UV radiation is a classical and probably the most important factor responsible for skin aging. There are many studies on this subject, some of which are presented below.
UV light and skin aging

Earth is constantly irradiated by light photons coming from the sun; 56% are infrared light photons (wavelength, 780–5000 nm), 39% is visible light (400–780 nm), and 5% is UV light (290–400 nm) (19).

Radiation in the UV region is divided into UVA (320–400 nm), UVB (280–320 nm), and UVC (100–280 nm) (20). The UVC radiation is screened out by the oxygen in the atmosphere, and most of the UVB is screened out by the ozone layer (21). However, given the human-induced damage to the protective O$_3$ layer, increasing amounts of UVB radiation have now reached the Earth’s surface (15). Many factors contribute to this phenomenon, including solar zenith angle, season, time of day, hemisphere, latitude, altitude, clouds, air pollution, surface reflections, and the stratospheric ozone (21). For every 300 m of elevation, there is an increase of 4% of UV radiation that reaches the surface, whereas for every degree of decrease in latitude, there is a 3% increase in the transmission of UVB rays (22). Moreover, each person’s UV dose varies depending on avoidance (staying indoors), seeking shade from trees and shade or protection from buildings, awnings, umbrellas, and other sources (e.g., clothing, hats and sunscreens) (21).

When light shines on the skin, several processes take place. Light can be reflected, scattered, and transmitted onto the skin and then remitted, i.e., sent back out to the surface. All of these processes have an effect on how much energy enters the skin and is able to react with the tissue (2).

Benefits of sun radiation on skin

Skin exposure to UV radiation has beneficial effects for the human body, e.g., in vitamin D3 formation, or in a curative application in combination therapy for skin diseases like psoriasis (15, 21) and endorphins production (23). Vitamin D is produced in skin by the conversion of 7-dehydrocholesterol in the epidermis to pre-vitamin D, using the energy provided by UVB radiation. Thermal conversion at body temperature creates the stable form, vitamin D (24). Approximately 90% of synthesized vitamin D is derived from casual exposure to sunlight (25).

It is already established that vitamin D plays a key role in skeletal health in young and elderly adults. An updated review of the literature emphasizes that adequate levels of vitamin D are needed to prevent osteoporosis, falls, and fractures in the elderly population (26). Emerging data also point to the role of vitamin D in cardiovascular disease, auto-immune conditions, diabetes, cancers, infections and neurodegenerative disease (27, 28).

Deleterious effects of sun radiation on skin

Meanwhile, biological research has also unveiled the deleterious effects of sun radiation on the skin (29). Biological and clinical consequences of sun exposure range from immediate sunburn reaction and tanning to long-term effects like photoaging (7, 11, 30), photocancer (19, 30), hyperpigmented lesions (19), verrucous papules, and telangiectasia (31). In these processes, two skin compartments are affected, namely, the epidermis and the dermis (30). In addition, UV light has a profound effect on the eyes. Every year, approximately, 3 million people lose their sight because of UV-related damage like cataracts, thus highlighting the need to incorporate photoprotective measures for the care of the eyes (19).

The effects of sunlight on the skin are profound, and are estimated to account for up to 90% of visible skin aging (11). In a review, Ichihashi (2009) pointed out that the photoaged characteristics appear to differ between racial phenotypes or pigmentary groups. It is commonly held that lighter-skinned people tend to manifest photoaging by wrinkles, whereas those of Asian ethnicities exhibit pigmented spots (solar lentigines) rather than wrinkles. The severity of photoaging in any case depends on cumulative sun exposure, and is usually most determined by occupation and lifestyle.

Corneocytes in sun-exposed areas become pleomorphic with increasing anomalies: retention of nuclear remnants, loss of lines of overlap, and roughening of border edges. In addition, UV radiation alters the skin’s immune function systemically. Epidermal thickness increases, then decreases, with an eventual loss of epidermal polarity (orderly maturation) and increased atypia among individual keratinocytes (11). Histopathologically, aged skin undergoes progressive disorientation of dermal collagen and elastic fiber bundles (32). In photoaged skin, there can be a significant increase in space between fiber bundles, thinning of fibers and increased disorganization of fiber proteins (31).

Given that the amount of energy is inversely proportional to the wavelength, UVB delivers more energy than UVA. Thus, short wavelength radiations in the UV range have higher energy and are potentially more damaging (16). However, UVA has a higher penetration rate and reaches the deepest epidermal layers, whereas UVB affects primarily epidermis and papillary dermis (33).
effects of UVA and UVB radiation of photoaging process will be presented in more details ahead.

Within the last decade, it has been reported that wavelengths beyond the UV spectrum, especially visible light and infrared radiation, contribute to skin damage in general and photoaging of human skin in particular (34). Visible light penetrates deeply into biological tissues and about 20% reaches the hypodermis. Some recent studies have revealed that visible light affects skin physiology in many ways, and this is already changing the way we are looking at light. Similar to what is seen with UVA, irradiation of skin with visible light has been reported to (16) generate ROS following photon-induced activation of endogenous photosensitizers, induce inflammatory cytokines (IL-1, IL-6, IL-8, GM-CSF), increase the expression of matrix-degrading enzymes (MMP-1 and MMP-9) in human epidermal equivalents, affect DNA through the formation of oxidized DNA bases, and induce pigment darkening in subjects with darker skin (Fitzpatrick type IV–V).

In addition, visible light is suspected of being an aggravating factor in melasma (16).

Infrared (IR) has the lowest energy but comprises around 56% of the solar spectrum reaching human skin. As UV light, IR is divided into IRA (700–1400 nm), IRB (1400–3000 nm), and IRC (3000 nm–1 mm). IRB and IRC do not penetrate the skin very deeply, but IRA does (16). Infrared A is able to penetrate through all three layers of the skin, namely, the epidermis, dermis, and subcutis (12).

IR exposure appears to have non-negligible effects on skin physiology that are mediated through various molecular mechanisms, including the generation of ROS within the skin, promotion of unbalanced gene expression of matrix metalloproteinase (MMP), decreased collagen gene expression in vitro and in vivo, angiogenesis, photoaging, promotion of carcinogenesis, and influence on mitochondrial integrity. However, it is poorly absorbed by usual skin chromophores like melanin and is too weak to directly affect DNA. Indeed, we still do not know which one is most important and to what extent these mechanisms, globally and individually, contribute to skin changes with aging. As is the case for visible light, the biological relevance of the effects of IR in relation to UV needs to be clarified (16).

Clinical and molecular aspects of photoaging

Clinical manifestation of photoaging

Clinical signs of aging are widely described in the literature. Jackson (35) has described the differences between skin changes brought on by age and skin damaged by habitual exposure to sunlight to provide a guide when examining patients, thus allowing physicians to give appropriate counsel (Table 1) (35).

Despite the fact that it is difficult to quantify the sun’s effect on skin aging, in a study by Flament et al. (10), it has been suggested that pigmentation heterogeneity and vascular disorders are more related to photoaging, whereas tissue sagging is a result of chronological aging. Wrinkles and skin texture are both influenced by intrinsic and extrinsic factors (10). However, clinical signs may vary in different parts of the world. Chung et al. (36) have suggested that wrinkling is more common than hyperpigmentation in Asians. In addition, women show more wrinkles than men. It is probably due to the fact that skin

<table>
<thead>
<tr>
<th>Structure</th>
<th>Intrinsic aging</th>
<th>Photoaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidermis</td>
<td>Thin</td>
<td>Keratosis: solar (actinic), chelitis, and disseminated superficial actinic porokeratosis</td>
</tr>
<tr>
<td>Dermis</td>
<td>Thin, inelastic, wrinkled</td>
<td>Yellowish-brown dotted and plaquelike thickening (solar elastosis), pseudocicatrix, elastotic nodules of the pinna</td>
</tr>
<tr>
<td>Hypodermis</td>
<td>Fold formation</td>
<td>Diffuse telangiecitas, erythema, brown pigmentation on side of neck, Bateman’s (solar) purpura</td>
</tr>
<tr>
<td>Blood vessels</td>
<td>Cherry angiomas, venous lakes</td>
<td>Mottled irregular areas of hypopigmentation and hyperpigmentation/Brown solar keratosis</td>
</tr>
<tr>
<td>Melanocytes</td>
<td>Solar lentigo (flat sebohrreic keratosis)</td>
<td>None</td>
</tr>
<tr>
<td>Hair</td>
<td>Gray, alopecia</td>
<td>None</td>
</tr>
<tr>
<td>Sebaceous glands</td>
<td>Senile sebaceous hyperplasia</td>
<td>Solar comedones, nodular cutaneous elastoides</td>
</tr>
<tr>
<td>Eccrine glands</td>
<td>Dry skin</td>
<td>None</td>
</tr>
<tr>
<td>Nails</td>
<td>Splitting into layers distally and linear striaions</td>
<td>None</td>
</tr>
</tbody>
</table>
collagen content decreases due to hypoestrogenism after menopause (36).

Uneven pigmentation is one of the major changes in the gross morphologic characteristics of the aging skin and is much more marked in sun-exposed areas. In the epidermis, melanin pigments are good indicators of photoaging. UV radiation plays a major role in the induction of melanocyte aging and may severely damage the melanocyte system of the skin, resulting in both hypermelanotic and hypomelanotic lesion (37). Coelho et al. (38) have studied the effects of repetitive UV exposure on human skin, suggesting that there is great variability in the constitutive levels of skin pigmentation as well as in the ability to increase pigmentation in response to UV. The pigmentation response UV is determined to a large extent by constitutive pigmentation and is more pronounced with darker skin color. There are four distinct stages in the responses related to pigmentation: the first step termed immediate pigment darkening (IPD), which occurs after minimal UV exposure; persistent pigment darkening (PPD), which occurs after hours or days of UV radiation; delayed pigmentation (DP), which results in increased melanin; and finally, long-lasting pigmentation (LLP), which results from prolonged activation of the pigmentary system. Coelho et al. also demonstrated that melanocyte density and skin pigmentation increase after repetitive UV exposure. Furthermore, long-term effects of UV can persist for years, as complete turnover of the epidermis usually occurs every 4–5 weeks. However, the mechanism underlying how the pigmentary system remains activated for years later should be studied in more detail to provide more insights into abnormal hyperpigmentation in UV-related pigmentedary diseases (38).

Despite the studies mentioned above, the complex mechanisms that lead to pigmentation are still not fully understood; furthermore, the complex relationship between pigmentation and UV exposure remains controversial. The literature suggests that UV-induced DNA repair and damage involve initiation of signals that induce melanogenesis after UV irradiation, but the chromophores for melanogenesis have not been yet completely established. Studies have demonstrated that the spectrum that leads to tanning is the same as that which induces erythema, so that it is similar to the typical DNA photoproduct (CPD); moreover, UV-exposed melanocytes increase DNA repair and the melanin content.

It is known that a mix of carotenoids, oxy-/deoxy-hemoglobin, and different types of melanin and their distribution in melanosomes determine the skin color. Brenner and Hearing (39) have already reviewed the role of melanin in UV-exposure and described the importance of this substance in the incidence of skin cancer. Eumelanin serves as a physical barrier for UV irradiation and is a known free radical scavenger. However, the deleterious effect of melanin has also been described, as it presents toxic properties after UV exposure and reacts with DNA. Furthermore, pheomelanin may generate hydrogen peroxide and superoxide anions as well as increase histamine release (39).

Solar elastosis is considered a biomarker for cumulative UV exposure and its risk increased substantially with age. Data suggested that more men present solar elastosis than women and it is related to the exposed areas. It has been demonstrated that solar elastosis is strongly associated with cumulative lifetime site-specific UV dose; however, no link between sunburn and solar elastosis has yet to be identified (40).

Photoaging mechanisms

Photoaging refers to the mechanisms involved in sun damage superimposed on intrinsically aged skin. Molecular changes in extrinsic aging involve an augmentation of the alterations in chronological aging. Two main defense mechanisms have been developed to protect against the damaging effects of UV: epidermal thickening and the stimulation of melanin synthesis (11).

According to Pattison and Davies (41), UVR can mediate damage through direct absorption of the incident light by the cellular components and through photosensitization mechanisms; such mechanisms are related to electron transfer and hydrogen abstraction processes to yield free radicals (Type I) or energy transfer with O₂ to yield the reactive excited state, singlet oxygen (Type II) (41).

The first mechanism by which UV radiation initiates molecular responses in skin is via ROS, through endogenous enzymatic and nonenzymatic protective antioxidants. If the intracellular mechanisms (e.g., antioxidant and repair processes) are working properly, ROS usually cause little harm. However, they are responsible for oxidative stress, in which there is an imbalance between their generation and the antioxidant defense activity, leading to cell damage and death. According to the Free Radical Theory of Aging, in aged skin, endogenous antioxidative and repair mechanisms are no longer effective and ROS tend to increase (42, 43).

Rhee et al. (44) investigated the activities of four antioxidant enzymes, superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx), and glutathione reductase (GR), along with four antioxidant molecules, namely, alphatocopherol, ascorbic acid, uric acid, and glutathione during
the intrinsic aging and photoaging processes. They found that the activities of SOD and GPx did not change during the aging and photoaging processes, whereas the catalase activity became significantly higher and lower in the epidermis and dermis, respectively, of photoaged and naturally aged human skin in vivo compared with young skin. In addition, antioxidant molecule levels are decreased after UV exposure. Further, the induction and regulation of endogenous antioxidant defense mechanisms could offer a good strategy for aging and photoaging treatment and prevention (44).

Through ROS generation, UVA causes DNA photodamage, which is one of the most important acute effects of UV irradiation. UVA is related to production of superoxide anion, hydrogen peroxide and singlet oxygen, whereas UVB induces base structural DNA damage, as it is absorbed directly by DNA (45, 46).

The cellular response to UV radiation involves multiple and specific signal transduction pathways and transcription factors. López-Camarillo et al. (47) reviewed these specific signal transduction pathways and transcription factors, describing the role for p38, MAPK, JNK, ERK1/2, and ATM kinases in the response network to UV exposure, as well as the participation of NF-xB, AP-1, and NFR2 transcription factors in the control of gene expression after UV-irradiation (47).

Through ROS generation, Protein Kinase C (PKC) isoforms are also involved in skin photoaging. Bossi et al. (48) reported that the process wherein low doses of UV radiation generate ROS is regulated by PKC delta and not by PKC alpha (48).

In keratinocytes, the down-regulation of the pigmen-
tative effect of UV radiation occurs, involving increased synthesis of the cytokines interleukin-1 (IL1) and tumor necrosis factor alpha (TNF-alpha), whereas in the melanocytes, these factors decrease the proliferation and tyrosinase activity. The prostaglandins D2, E2, and F2-alpha are increased in the skin after UV radiation, whereas prostaglandins E2 and F2-alpha increase the dendricity of melanocytes, the effect of which is involved in skin pigmentation as it facilitates the transfer of melanosomes to keratinocytes.

Collagen originates from dermal fibroblasts and is regulated by the transformation of growth factor (TGF-beta) and activator protein (AP-I). TGF-beta is responsible for collagen formation, whereas AP-I acts through the up-regulation of MMPs, thus causing collagen breakdown (49).

UV irradiation changes the dermal collagen through the stimulation of collagen breakdown and inhibition of procollagen biosynthesis, causing loss of collagen content. This process is mediated by MMP expression. In normal skin conditions, MMPs are low. However, after UV exposure, the expression of MMP family is induced, leading to collagen degradation.

Fisher et al. (50) have demonstrated that at least three different MMPs in human skin are increased with UV radiation: interstitial collagenase (MMP-1), stromelysin-1 (MMP-3), and 92kDa gelatinase (MMP-9). The combined actions of these three MMPs are capable of degrading most of the proteins that comprise the dermal extracellular matrix (50). Meanwhile, Quan et al. (51) have shown that MMP-1, -3 and -9 are primarily induced in the epidermis keratinocytes after UV exposure of the skin. However, dermal cells, through the release of growth factors or cytokines, may also play a role in the epidermal production of MMPs (51).

UV irradiation decreases procollagen mRNA expression in the dermis and decreases collagen amounts, inducing wrinkle formation; however, further studies related to the impact of UV irradiation on dermal collagen protein synthesis rates are necessary (52).

Photoaging also leads to remodeling of the dermal extracellular matrix. The effect of repetitive UVB irradiation on dermal hyaluronic acid (HA) has been studied, and it involves several mechanisms, including the reduction of dermal HA, down-regulation of HA enzymes, regulation of HA expression in skin fibroblasts in vitro, suppression of TGF-beta1- and TbetaR-II expressions, and decreased fibroblast proliferation (53, 54).

Aside from all mechanisms involving inflammation, oxidation and pigmentation, a recent work has elucidated the involvement of telomere-based signaling after UV exposure. Intrinsic aging is controlled by progressive telomere shortening, and this same effect can happen after UV irradiation, damaging DNA and accelerating telomere shortening. Aging and photodamage appear to share a common final pathway, which involves signaling through p53 following the disruption of the telomere. These findings suggest the need to protect from UV damage, with telomeres as new targets for preventing photoaging (55, 56).

Overall, scientific progress in understanding the multitude of mechanisms induced by UV-irradiation could lead to specific targets for the prevention and control of UV-induced aging process.

**Photoprotection**

**Sun filters**

Recent advances in photoaging have given rise to new opportunities of preventing or treating this process.
These approaches include novel antioxidants and new compounds. To minimize the deleterious effects of UV radiation, photoprotective measures should be adopted. Currently, there are various compounds with photoprotective properties ranging from antioxidants to plant extracts to DNA repair enzymes. However, in order to permit new approaches to modulate skin pigmentation, there is a need to gain better understanding of the photoprotective properties of melanin and contributions of melanocytes to cancer.

Active ingredients for photoaging, considering protection against different mechanisms and antioxidant activities, have already been described (7). Sunscreens are UV radiation-absorbing chemicals that protect the skin and attenuate the effect of UV radiation on the skin, precluding sunburns and protecting people from serious skin damage. They are selected and tested for their ability to prevent erythema. In addition, sunscreens must be photostable and must have the ability to dissipate the energy absorbed efficiently through photophysical and photochemical pathways, which rule out the ROS and other harmful reactive intermediates. They should not penetrate the skin, and should not be transported into the human cells where they can cause deleterious damage to DNA. Despite the fact that they are widely use, further data related to the safety and efficacy of sunscreens are needed.

Ideal sunscreening agents should be safe, chemically inert, nonirritating, nontoxic, photostable, and must provide complete protection of the skin against damage from solar radiation. They should be formulated in a cosmetically acceptable form and ingredients should remain on the upper layers of the skin. In the US, sunscreen production is regulated by the FDA; meanwhile, in European countries and in Brazil, among other countries, there are efforts to regulate the maximum concentration of use. Sunscreens are divided into physical and organic compounds (57).

Titanium dioxide (TiO₂) and Zinc oxide (ZnO) are the most used, as they block UVB/UVA sunlight through reflection and scattering. These mineral compounds are used extensively in cosmetics, including foundations, powders, eye shadows and pencils, due to their low potential for producing irritant reactions.

Different from TiO₂ and ZnO, organic filters are classified into either UVA (benzophenones, anthranilates and dibenzoylmethanes) or UVB filters (PABA derivatives, salicylates, cinnamates and camphor derivatives). They are used in combination in order to provide high enough sun protection factor (SPF) protection or broad-spectrum absorption (58, 59).

With the development of nanotechnology, there has been a growth in the application of nanoparticles for drug delivery systems, antibacterial materials, cosmetics, and electronics. Nowadays, almost all UV filters are available in nanoforms. As they do not have to penetrate skin in order to protect it, sunscreens have become more opaque. In order to solve this cosmetic drawback, nanotechnology for sun filters has been developed. In the case of nanomaterials, a deep physicochemical approach could help new formulations display a balance between safety and effectiveness because safety also concerns the physicochemical properties of UV filters to be taken up by the skin in both the absence and presence of light. However, there is lack of safety data concerning the toxicological properties of these compounds, and no occupational or environmental exposure limits have yet to be established (60, 61).

A sunscreen SPF measures how much the product shields the sun’s shorter-wave UVB rays (UVB radiation), which can cause sunburn. SPF varies from 8 to 100 + and it is a controversial issue. When using sunscreen, the relationship between the applied amount of sunscreen and SPF should be considered. The US FDA and Cosmetics Europe (former COLIPA) recommend 2 mg/cm² of product application, based on the observation that lower amounts reduce the homogeneity of the protective film on the skin as a result of irregularities of the skin surface (62, 63).

However, the amount of the sunscreen applied is often inadequate, and the protection achieved by the user is lower than that shown in the product label. Recent data in the literature have reinforced the need to promote the appropriate use of protection against UV radiation, considering the correct amount and frequent reapplication (64).

Osterwalder and Herzog (65) have described the relationship between high SPF values and protection against UV, meaning that higher SPF provides more protection, as the UV radiation doses are smaller in higher SPF conditions. This issue has already been under discussion, but in addition to the SPF, data on the water resistance, UVA protection, and photostability should be considered for adequate protection (57, 65).

At present, researchers are developing newer broad-spectrum chemical agents that are effective against UVA and UVB rays, including bis-ethylhexyloxyphenol methoxyphenyl triazine, methylene bis-benzotriazolyl tetramethylbutylphenol, and butyl methoxy-dibenzoyl methane. It is challenging to provide cosmetically acceptable preparations that are non-stick and water-resistant, and educate people about following the correct application instructions. Furthermore, these UV filters should be compliant to safety and regulatory requirements, so the
industry should consider sensitization reactions, especially in those with eczema or photodermatoses as well as irritation, following new directions regarding no animal testing (57).

New sunscreen properties like anti-inflammatory and antioxidant effects have also been described. Another new approach is the use of active ingredients in cosmetic formulations in order to increase SPF. Formulators are using certain ingredients with anti-inflammatory properties like a-bisabolol and 18 b-glycyrrhetinic acid. However, further data are needed to determine how the biological response of the human UV-irradiated skin might vary with the inclusion of specific anti-inflammatory ingredients in the sunscreens (66).

Osterwalder et al. (67) have reviewed the global state of sunscreens, pointing out the controversies related to high SPF as well as the relationship between UV radiation and agent protection. Global harmonization should be of concern in order to provide global access to modern UV sunscreen technology, performance measurements, and adequate criteria for good sun protection (67).

Despite all controversial aspects, the importance of sunscreen usage remains unquestionable. Many epidemiological studies have been conducted to correlate the effects of sunscreen use on skin cancer, and more recently photaging, but their findings have been mostly uninformative. Although Iannacone et al. (68) reviewed the available data on the issue, adequate evidence remains limited, especially related to the prevention of photaging. Sunscreen use alone will not reduce skin cancer and photaging, but its cosmetic benefits may be an effective strategy that can be used by dermatologists, general physicians, and public health and prevention agencies to achieve sun protection for long-term primary prevention of skin cancers (68).

It has already been established that UVA measurements in vivo are linked to SPF assessment, and UVA protection should follow what is recommended by the European commission, which states that UVA-PF/SPF ≥ 1/3. In addition, the available in vitro UVA methods are currently being harmonized. Other UVA categories like the Boots 5-star rating with a UVA/UVB ratio > 0.9 go beyond the EU recommendation and are thus closer to uniform UVB/UVA protection, which may be regarded as the ideal sunscreen performance (67).

Clothing and glasses

Clothing and glasses are the most basic photoprotective tools and, in many aspects, seem to be more effective than sunscreens because they offer balanced and uniformed protection for both UVA and UVB, which remain constant while using the clothes. Furthermore, the degree of protection offered by sunscreens depends on the application of the correct amount of the product. Finally, clothing and hats are less costly than sunscreens, and they are devoid of any complications like contact or photoallergic dermatitis (22).

The World Health Organization (WHO) mainly recommends photoprotection by means of clothing for children (69).

A French study analyzed the photoprotection of clothes of different types, color, and thicknesses. Concerning townwear, jeans, tracksuits, sweatshirts, pullovers and tights turned out to be very photoprotective. They are able to reach a ultraviolet protection factor (UPF) higher than 500. The thickness of the fabric is of great importance, so the lowest protection factors (PF < 12) have been obtained for the Tex baby blouse and the Domyos T-shirt. These two fabrics are both made of 100% cotton and are light-colored (white and pale green, respectively) and are of very different thicknesses (the blouse is practically twice as thick as the T-shirt); however, their photoprotective effect in the UVB field is the same, which explains the importance of how the fabric is woven (69).

Sun-protective clothing lines exist and are widely available in sporting goods stores and on the Internet. These clothing lines offer hats, long-sleeved clothing, etc. and are geared towards patients who work outdoors and are avid outdoor enthusiasts for whom sunscreens might be less practical to use. The fabrics used in these lines are highly engineered and sophisticated materials that confer high levels of sun protection and protect against both UVA and UVB. For example, Solumbra, manufactured by Sun Precautions, offers an SPF 30+ and reportedly blocks 97% of UVA and UVB. Coolibar is another brand of sun-protective clothing and hats, which provide UPF of 50+ and reportedly blocks 98% of UVA and UVB. UPFs are similar to SPF, but are typically used for devices like clothing and fabrics rather than for sunscreen. Clothing lines and other sun-protective devices endorsed by the Skin Cancer Foundation are listed on their website (14).

UV exposure can also damage the cornea, conjunctiva, lens, and retina, resulting in a number of conditions collectively named “ophthalmohelioses” (22). Acute injury in the eye presents similar features to those on the skin and includes photoconjunctivitis (“pink eye”), solar keratitis, and in severe cases, transient loss of vision. Chronic exposure, on the other hand, may result in cataracts and macular degeneration the leading causes of loss of vision (19).

Sunglasses can protect the eye from UV damage. Aside from the cosmetic quality, an ideal pair of sunglasses
should block all UV rays but should not sacrifice the transmission of visible light. Currently in the US, a standard guideline of Z80.3 2008 by the American National Standards Institute (ANSI), is issued to categorize the different types of sunglasses according to the degree of shading and UV absorption profile. ANSI is a nongovernmental and consensus body. Recently, therapeutic sunglasses have been made available, providing protection against UV and blue light. Coloring must be dark enough to prevent dazzling but must not affect color and contrast perception (19).

**Food and photoprotection**

Recently, several oral sunscreens that provide full-body coverage have been commercialized. These products contain several active principles that enable different mechanisms to prevent cutaneous sun damage. Most of them possess antioxidant activities, which replenish the normal antioxidant capability of the body after systemic loss of endogenous antioxidants during UV exposure. These products include the following: carotenoids, combination of antioxidants (vitamins C and E), selenium, proanthocyanidins, and dietary botanicals (flavonoids and phenolics). Nevertheless, the efficacy of oral sunscreens to prevent photoaging in humans has not been assessed in long-term clinical trials (19).

Probiotics (live microorganisms that confer a health benefit on the host) are most commonly administered orally, with the goal of maintaining healthy gut flora by populating the gut with symbiotic bacterial species. Strains of the genera *Lactobacillus* and *Bifidobacterium* are the most widely used probiotic bacteria. Orally ingested *Lactobacilli* have been shown to protect against UVR-induced cutaneous immunosuppression in mouse models through protection against the suppression of contact hypersensitivity, decreased epidermal Langerhans cell density and increased IL-10 serum levels, which may reduce the development of skin tumors. Although no similar human studies have been published, the use of probiotics offers a promising new direction in sun protection, and this should attract future research (70).

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