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ORIGINAL ARTICLE

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Chelating Agents in Skincare: Comprehensive Protection Against Environmental Aggressors

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ABSTRACT

In addition to ultraviolet light, skin is regularly exposed to several environmental stressors that can cause damage and premature aging. Particulate matter in the environment, including transition metals, has been shown to have significant harmful effects on the skin. Therefore, the use of chelating agents in addition to sunscreen and antioxidants could represent a good strategy for preventing cutaneous damage caused by particulate matter rich in metals.

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INTRODUCTION

Although the importance of protecting the skin from sunlight is widely recognized, ultraviolet (UV) light is the main cause of skin damage and premature aging. However, many other outdoor stressors have also been shown to affect skin health and compromise its physiologic properties. It is necessary to take into account that, over the course of an individual's life, they are exposed to a wide range of non-genetic factors that can affect health. These factors, which are referred to collectively as the "exposome," can contribute to skin damage, and include infrared radiation, ozone pollution, exhaust emissions, cigarette smoke, transition metals, inadequate nutrition, psychological stress, and even lack of sleep (Figure 1).[1] Therefore, a more comprehensive approach to skin protection, extending beyond the use of sunscreen, is necessary to preserve optimal dermatologic health in the face of the diversity of environmental stressors.[2]

The Need for Comprehensive Skin Protection

Skin damage caused by sun and environmental exposure is brought about primarily by a cascade of reactions involving the generation of reactive oxygen species (ROS), which leads to peroxidation of cellular components, such as lipids, proteins, and nucleic acids.[3] Altering the lipid composition of skin can compromise the epidermal barrier, leading to serious skin damage.[2] In general, premature skin aging is characterized by visually macroscopic signs, such as rough texture, wrinkling, discoloration, and larger pores. The effects of exposure to outdoor stressors begin earlier in life than many people may realize; signs of aging can already be detected at around age 18 years to 25 years.

The inflammatory process triggered by the exposome can further contribute to skin aging through a process referred to as "inflammaging," which is directly correlated to the altered redox homeostasis of the tissue.[4] In addition, this process may also exacerbate other inflammatory conditions such as eczema, psoriasis, or acne.[5,6]

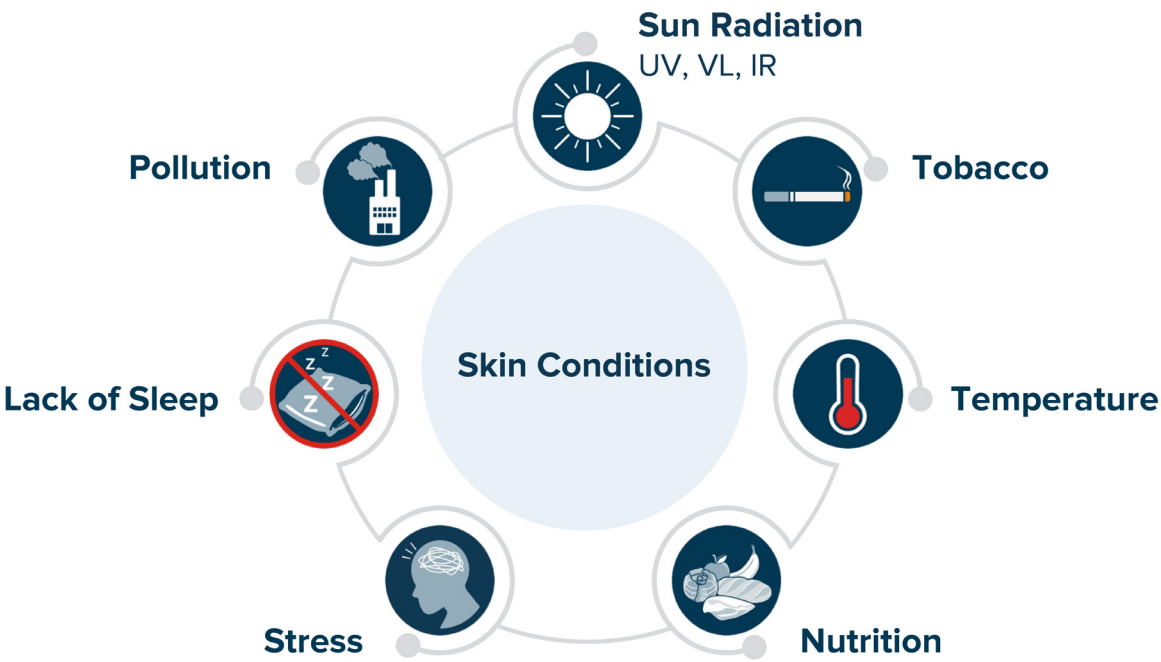
Some components of the exposome that contribute to skin aging are usually modifiable. For example, individuals can take steps to improve their nutrition or sleep hygiene, and they can even limit their exposure to direct sunlight. However, pollution in the environment presents a much more complex challenge. There are multiple environmental pollutants and they have varying chemical, biological, and physical effects that contribute to skin damage. There is little that individuals can do to avoid these pollutants and, because they have differing mechanisms of activity, their individual effects on skin tissue appear to be additive and, in some respects, synergistic.[7]

Therefore, a comprehensive approach to skin protection is needed to counter the damage caused by environmental stressors. In addition to daily use of sunscreen to prevent UV damage, inclusion of antioxidants and metal chelators in the routine skincare regimen is also necessary to decrease premature aging of the skin.[6]

Mechanisms of Environmental Skin Damage

The specific mechanisms by which skin damage occurs can differ among individual environmental pollutants. The mechanisms

FIGURE 1. The exposome: a diverse range of environmental stressors that can contribute to skin damage and premature aging.



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IR, infrared; UV, ultraviolet; VL, visible light.

involved in skin damage caused by pollutants can also differ from the mechanisms involved in UV damage. Understanding the specific mechanisms responsible for the damage associated with each pollutant is vital to properly plan a good defensive strategy for limiting their damage.

An example is represented by ozone, tropospheric levels of which have increased considerably over recent decades, particularly in major metropolitan areas.[3] While UV light is able to induce tissue damage by penetrating the skin, ozone cannot penetrate the skin and its effect is limited to interaction with the stratum corneum. Continuous exposure of the skin to high levels of ozone results in the accumulation of peroxidation products and induction of stress responses in the active layers of the skin, most likely due to indirect mechanisms.[3] In addition to its role in accelerating skin damage associated with aging, exposure to high levels of ozone is associated with urticaria, contact dermatitis, rash, and skin infections.[5]

Exposure to ambient particulate matter (PM) has been associated with several pathologic conditions and can impact the structure and functionality of many organs, including the heart and lungs.[8] There is also clear evidence that PM can accelerate skin aging, increase cutaneous spots, and induce skin inflammation.[3,9]

Currently, it is not known whether PM can pass through the skin. It has been suggested that some PM may enter the lower layers of the skin through hair follicles. Alternatively, rather than being permeated by the whole particle, the skin may absorb certain molecules that are attached to the particle. For example, aromatic compounds can be absorbed because they are lipid soluble and, once inside the skin, they induce inflammation.[10,11]

Nevertheless, regardless of whether PM enters the skin, evidence of its harmful effects is unequivocal.[12] Elevated levels of PM have been found to correlate with clinic and emergency department visits for urticaria.[13,14] Clear data shows that living in an urban area

where there is a high concentration of PM increases the risk of developing dark spots in the skin, wrinkles, and keratosis.[7]

Transition metals, primarily iron, and copper are a major component of PM derived from diesel exhaust. The redox potential of transition metals has for many years been explained by the Fenton reaction, in which hydrogen peroxide reacts with ferrous iron (Fe^{2+}) to generate ferric iron (Fe^{3+}) and hydroxyl radicals ($HO^{\bullet}$). The hydroxyl radical is one of the most harmful ROS due to its ability to react rapidly with lipids, inducing peroxidation and the formation of very reactive aldehydes, such as 4-hydroxy-nonenal (4HNE), which can then react with proteins and affect their physical properties.[15]

The harmful effects of PM may be amplified by UV exposure through a process called "photo-pollution." In fact, in addition to the direct damage that UV light causes, it has also been shown to stimulate the release of cellular iron.[16] If the accumulation of excess metals in skin tissue can be quenched, peroxidation and its harmful effects could be partially prevented.

Protection Against Environmental Stressors

Protecting the skin against all of these environmental pollutants is important if good dermatologic health is to be maintained. The skin plays a vital role as the first line of defense against pathogens and outdoor stressors in general, and it is well established that exposure to some solid particles in the atmosphere can bring about significant alterations to the skin.[17] If the integrity of this barrier is damaged and compromised by environmental pollutants, it may become permeable to larger and even more harmful particles or microorganisms. Therefore, a more comprehensive approach to maintaining a healthy skin barrier should be a priority in today's dermatology practice.

Although the skin is equipped with defense systems to counteract oxidative damage induced by environmental exposure, depletion of this system can also contribute to premature skin aging.[18] Topical application of protective agents, including antioxidants, can help limit oxidative damage to skin tissue and reduce the subsequent inflammation that occurs. Ingredients of skin care preparations that can be helpful in this regard include vitamins A, C, and E; niacinamide (vitamin B); coenzyme Q; and caffeine.[2,19,20] Natural plant extracts such as polyphenols, and especially flavonoids, have been increasingly used in recent years due to growing awareness of their antioxidant and anti-inflammatory properties.[21,22]

A newer approach to preventing skin damage caused specifically by transition metals present in PM is the use of chelating agents that can directly neutralize them. Chelating agents typically bind with metal ions in skin tissue to prevent them from participating in the Fenton reaction, and thereby attenuate the production of free radicals and ensuing lipid peroxidation that can occur due to accumulation of these metals.[21]

Several molecules are able to chelate iron, and a number have been studied for dermatologic use. Perhaps the most prominent example would be kojic acid, which is a natural metabolite produced by fungi. Kojic acid and its derivatives have a wide range of applications in health care and cosmetics, such as inclusion in some creams and lotions as a skin-lightening agent. They have also been shown to effectively bind excess iron and aluminum.[23,24]

Deferoxamine is a molecule produced by the bacterium *Streptomyces pilosus* that binds free plasma iron and excess iron inside cells with high affinity. It is, therefore, a highly potent iron chelator, and it has been administered systemically for more than 3 decades to treat acute or chronic iron overload. Once deferoxamine is bound to iron, it forms ferrioxamine, a highly water-soluble complex that is excreted by the kidneys.[25] In addition to its ability to chelate transition metals, deferoxamine can also directly quench ROS, including $HO^{\bullet}$ and superoxide ($O2^{-}$), and it, therefore, has additional antioxidant properties.[2]

Iron-chelating activity has also been observed with some botanical agents, including baicalein and baicalin, flavonoids and other polyphenols, phytic acid, and chlorogenic acid.[24,26-28] Some of these phytochemicals, such as flavonoids, also protect the skin by activation of the endogenous antioxidant system involving the transcription factor Nrf2, which is considered to be a crucial regulator of the innate cellular antioxidant defense.[29]

Metal Chelators in Skincare Products

The ability of chelating agents to protect the integrity of the skin has been examined in several scientific studies. Because iron-induced peroxidation contributes to the wrinkling that occurs as a result of chronic photodamage to the skin, topical administration of kojic acid was expected to have antiwrinkling activity. This theory was tested by exposing hairless mice to chronic UV radiation. After irradiation of the mice over a period of 20 weeks, mice that had been pretreated with topical kojic acid prior to UV irradiation were found to have much less wrinkling, hyperplasia of the epidermis, and fibrosis of the lower dermis, and an increase in extracellular matrix components in the upper dermis.[30] In human skin, however, achieving adequate absorption of kojic acid has been a challenge and the use of novel delivery technology has been explored.[31,32]

More recently, the use of a chelating agent to protect the skin specifically against environmental pollutants was measured.[33] Healthy human Caucasian skin explants were assigned to 4 different preventive regimens: no treatment, a commercially available cosmetic antioxidant alone, the chelating agent deferoxamine alone, or both the antioxidant and deferoxamine. The explants were then exposed to diesel engine exhaust (DEE) for up to 4 days. DEE is not only one of the most abundant pollutants, but also the most noxious to human health; in addition to oxides of nitrogen, sulfur dioxide, and various hydrocarbons, DEE contains significant levels of metals that can induce oxidative stress and inflammation.

The beneficial effects of topical deferoxamine were demonstrated by improvement in several measures of skin integrity. In the stratum corneum, DEE exposure leads to the formation of several lipid oxidation products, of which 4HNE is one of the most harmful. The combined application of antioxidant and deferoxamine was found to have an additive effect, reducing 4HNE levels to a greater extent than either treatment alone.[33]

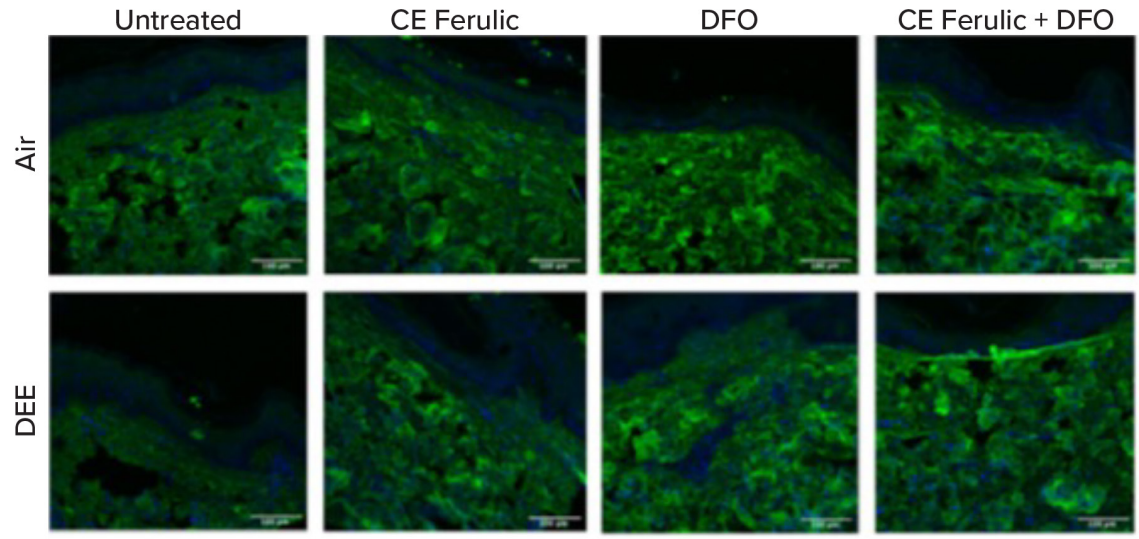
Type I collagen is an interstitial matrix collagen that is essential for the competence of the skin. Depletion of type I collagen, which is one of the most evident signs of skin aging, has been linked with premature aging due to various factors, including pollution exposure. Whereas levels of type I collagen in untreated skin fell by more than 40% following DEE exposure, no decrease at all was seen in skin that had been treated with antioxidant and/or deferoxamine (Figure 2).[33]

Filaggrin and involucrin are key proteins involved in skin structure. Levels of these proteins in untreated skin also fell by approximately 40% to 50% following DEE exposure. The antioxidant and deferoxamine both protected tissues from depletion of these proteins and, in skin that had been treated with both agents, levels of filaggrin and involucrin increased (Figure 3).[33]

SUMMARY

The importance of regular use of sunscreen to protect the skin from the harmful effects of UV radiation is now universally accepted. However, other environmental stressors, including ozone and PM, also cause damage to the skin and promote premature aging. Transition metals, in particular, compromise the integrity of the

FIGURE 2. Fluorescence staining showing levels of type I collagen in human skin explants that were either untreated or pretreated with antioxidant and/or deferoxamine, and exposed to air or DEE for 4 days.[33]



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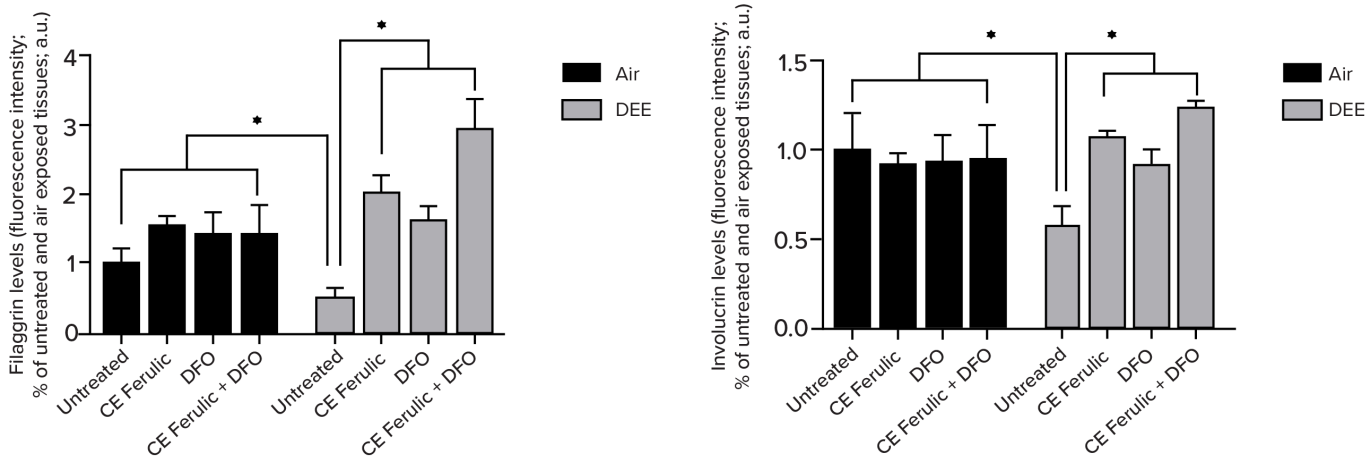
CE, L-ascorbic acid (vitamin C) and alpha tocopherol (vitamin E); DEE, diesel engine exhaust; DFO, deferoxamine.

FIGURE 3. Levels of structural proteins filaggrin and involucrin in human skin explants that were either untreated or pretreated with antioxidant and/or deferoxamine, and exposed to air or DEE for 4 days.[33]



Data are expressed as arbitrary units; *P<.05

CE Ferulic, vitamin C and E with L-ascorbic acid; DEE, diesel engine exhaust; DFO, deferoxamine.

skin via the formation of ROS. Good scientific data show that topical antioxidants and chelating agents can help protect the skin from these environmental stressors. Therefore, to preserve good skin health, adults should be advised not only to regularly use sunscreen, but also to apply an antioxidant and chelating agent every morning and every night.

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