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Skin Health from the Inside Out

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Abstract

The skin is the main interface between the body and the environment, providing a biological barrier against an array of chemical and physical pollutants (e.g., ultraviolet light, ozone, etc.). Exposure of the skin to these outdoor stressors generates reactive oxygen species (ROS), which can overwhelm the skin's endogenous defense systems (e.g., catalase, vitamins C and E, etc.), resulting in premature skin aging due to the induction of DNA damage, mitochondrial damage, lipid peroxidation, activation of inflammatory signaling pathways, and formation of protein adducts. In this review, we discuss how topical application of antioxidants, including vitamins C and E, carotenoids, resveratrol, and pycnogenol, can be combined with dietary supplementation of these antioxidant compounds in addition to probiotics and essential minerals to protect against outdoor stressor-induced skin damage, including the damage associated with aging.

CUTANEOUS TISSUES

The skin is the largest organ (approximately 2 m^2) in our body and is composed of two main layers: the epidermis and the dermis. The dermis consists of the stratum reticulare and stratum papillare. The stratum papillare is the upper layer, rich in thin collagen fibers. The lower layer, the stratum reticulare, consists of thick collagen fibers. Embedded within the dermis are structures such as nerve endings, sebaceous glands, hair follicles, and blood and lymphatic vessels. Fibroblasts are the principal cell type in the dermis and are involved in the secretion of collagen and elastin; other cells, such as endothelial, nervous, and dendritic cells, are also present in the dermis. The epidermis is the protective, outermost layer of the skin and consists of keratinocytes that are subsequently organized into different layers based on the differentiation status of the resident cells. The lowest layer of the epithelium is referred to as the stratum basale and contains transiently amplifying cells that can undergo differentiation. During the process of differentiation/keratinization, keratinocytes withdraw from the cell cycle and begin to express differentiation-dependent markers (i.e., keratins), eventually becoming anucleated, densely keratinized corneocytes (Fuchs 2016). These cells are held together in the multilayered stratum corneum by a lipid-laden extracellular matrix (ECM), which performs the barrier function of the skin (Feingold 2007). An essential function of the barrier is to prevent excess transepidermal water loss (TEWL). Because of its critical location, the skin is the main interface between the body and the environment and provides a biological barrier against an array of chemical and physical environmental pollutants. Because of constant exposure to oxidants, including ultraviolet (UV) radiation and other environmental pollutants such as diesel fuel exhaust, cigarette smoke, halogenated hydrocarbons, heavy metals, and ozone, the skin can be defined as our first defense against the outdoor environment.

CUTANEOUS DEFENSE SYSTEMS

The consequences of oxidative damage to the skin are believed to result in the development/exacerbation of premature skin aging, psoriasis, atopic dermatitis, and acne (Kim et al. 2016, Xu et al. 2011). Exposure of the skin to various pollutants, including UV light and ozone, generates reactive oxygen species (ROS), which can then alter DNA, cellular proteins, and the cell membrane, in addition to promoting apoptosis through inducing mitochondrial membrane depolarization (Cooke et al. 2003, Fu et al. 2012, Fuks et al. 2019, Pecorelli et al. 2019, Rinnerthaler et al. 2015). Furthermore, oxidative stress triggers the activation of redox-sensitive transcription factors AP1, NFκB, and AhR, promoting matrix metalloproteinase (MMP) production, which results in collagen breakdown (Fisher et al. 1996, Fuks et al. 2019). Because excessive amounts of ROS can have various deleterious effects on the skin, such as decreasing collagen production by dermal fibroblasts and damaging DNA (Tanaka et al. 1993), the skin utilizes various mechanisms to mitigate the harmful effects of ROS. For instance, the skin synthesizes endogenous enzymatic antioxidants like glutathione peroxidase (GPX) and uptakes micronutrients, such as vitamins E and C, to protect against oxidative damage.

REACTIVE OXYGEN SPECIES

ROS consist of both free radicals and other nonradical reactive species. Types of free radical ROS include superoxide anion ($O_2^{\cdot}$), oxygen radical ($O_2^{\cdot}$), hydroxyl radical ($OH^{\cdot}$), alkoxyradical ($RO^{\cdot}$), and peroxyl radical ($ROO^{\cdot}$) (Phaniendra et al. 2015). Nonradical ROS include hydrogen peroxide (H_2O_2), hypocholorous acid (HOCl), hypobromous acid (HOBR), ozone (O_3), singlet oxygen ($^1O_2$), organic peroxides (ROOH), and aldehydes (HCOR) (Phaniendra et al. 2015). Because of an odd number of electrons, free radicals are short-lived, unstable, and very reactive. They can

Table 1 Antioxidant gradient on the skin[a]

Endogenous enzymes	Concentration in epidermis versus dermis
Superoxide dismutase	126% higher in epidermis
Glutathione peroxidase	61% higher in epidermis
Catalase	720% higher in epidermis
Glutathione reductase	215% higher in epidermis
Nonenzymatic antioxidants	
α-Tocopherol (vitamin E)	90% higher in epidermis
Ascorbic acid (vitamin C)	425% higher in epidermis
Coenzyme Q	900% higher in epidermis
Uric acid	488% higher in epidermis

[a]Data from Shindo et al. (1994a).

achieve stability by taking electrons from other compounds, causing the attacked molecule to lose an electron and become a free radical, initiating a damaging cascade (Phaniendra et al. 2015). At moderate levels, ROS are involved in various physiological functions; however, excessive levels of ROS can deplete endogenous defense systems, resulting in overwhelming levels of ROS, which can cause DNA damage, lipid peroxidation, formation of protein adducts, and apoptosis.

Since the skin is the interface between the body and the external environment, it is in constant contact with pollutants, pathogens, and UV irradiation, which are the main contributors to ROS formation in skin. Because the epidermis is more exposed to the external environment than the dermis, it is no surprise that the ROS load is higher in the epidermis than the dermis (Rinnerthaler et al. 2015). To counteract this, endogenous defensive enzymes and micronutrients are present in higher concentrations in the epidermis than the dermis (see **Table 1**) (Shindo et al. 1994a). However, within the epidermis, there exists another antioxidant gradient, wherein low-molecular-weight compounds, such as vitamins C and E, glutathione, ubiquinol, and uric acid, as well as endogenous defensive enzymes [catalase (CAT) and superoxide dismutase (SOD)] are sometimes barely detectable in the upper stratum corneum (Thiele et al. 1998, Weber et al. 1999). Instead, they increase in concentration toward the deeper layers of the stratum corneum, leaving the upper layers of the stratum corneum vulnerable to outdoor stressors (Thiele et al. 1998, Weber et al. 1999).

ENDOGENOUS DEFENSIVE ENZYMES

To prevent the accumulation of excess ROS and disruption of redox homeostasis, the cell utilizes endogenous defensive enzymes, such as SOD, to scavenge ROS. The function of SOD is to dismutate $O_2^{\cdot}$ into H_2O_2 (Fukai & Ushio-Fukai 2011). There are three different isoforms of SOD in mammals. SOD1 utilizes Cu/Zn as cofactors and is localized to the cytosol and nucleus (Fukai & Ushio-Fukai 2011). SOD2 is localized to the mitochondria and binds to manganese (Fukai & Ushio-Fukai 2011). SOD3 is detected in extracellular spaces and utilizes Cu/Zn as cofactors as well (Fukai & Ushio-Fukai 2011). In the skin, SOD is detected primarily in the epidermis (Shindo et al. 1994a). All three human SODs have a huge impact on aging skin, as demonstrated in vivo using isoform-specific knockout mice (Murakami et al. 2009; Schriner et al. 2005; Shibuya et al. 2014; Treiber et al. 2011, 2012; Velarde et al. 2012).

However, excess levels of H_2O_2 can generate $OH^{\cdot}$ in the presence of free copper or iron via the Fenton reaction (Barb et al. 1949, Wardman & Candeias 1996). This species of ROS is the most damaging, as it is the main trigger for lipid peroxidation. Both CAT and GPX are involved

in preventing the formation of the toxic $OH^{\cdot}$ by converting H_2O_2 into water (Rinnerthaler et al. 2015).

CAT is very prominently expressed in the skin, especially in the stratum corneum. In the epidermis, the amount of CAT exceeds the amount of SODs (Hellemans et al. 2003, Shindo et al. 1994a,b). In aged skin, the activity of this enzyme is reduced in the dermis, which is also associated with an accumulation of H_2O_2 (Shin et al. 2005). In addition, the recovery of CAT activity in the stratum corneum after UV exposure is also reduced in aged subjects (Hellemans et al. 2003).

In addition to CAT, GPX also catalyzes the reduction of H_2O_2 into water and inhibits lipid peroxidation (Flohe & Schlegel 1971, Mills 1957). In humans, there are eight GPXs, and five of them contain selenium as a cofactor. Alterations in enzymatic activities in aging skin and photoaged skin have not yet been characterized; however, targeted disruption of GPX4 in mice displayed severe skin phenotypes such as hyperplasia of the epidermis, dermal inflammation, increased rates of lipid peroxidation, and higher levels of cyclooxygenase-2 (Sengupta et al. 2013).

In addition to inhibiting the accumulation of ROS, the cellular defense system also utilizes the thioredoxin system, wherein protein thioredoxins act as antioxidants by reducing oxidized cysteine residues on proteins, resulting in electron transfer and the reduction of thioredoxin (Rinnerthaler et al. 2015). Oxidized thioredoxin can then be reduced by thioredoxin reductase (TXNRD), which is an NADPH-dependent enzyme and the only known enzyme that can catalyze the reduction of thioredoxin (Rinnerthaler et al. 2015). Interestingly, both TXNRD and GPX are selenocysteine-containing flavoenzymes; therefore, the activity of both of these enzymes can be increased by dietary supplementation with selenium. In conclusion, these endogenous defensive enzymes play key roles in preventing ROS accumulation, which can result in premature aging and other skin conditions (Murakami et al. 2009; Schriner et al. 2005; Shibuya et al. 2014; Treiber et al. 2011, 2012; Velarde et al. 2012).

ANTIOXIDANT MICRONUTRIENTS

Besides the enzymatic machinery, cutaneous tissue is equipped with so-called antioxidant components such as vitamin E. This compound is synthesized by plants and obtained by humans through food intake. It is the most abundant fat-soluble antioxidant found in human skin, and the most abundant form of vitamin E found in the skin is α-tocopherol (Shindo et al. 1994a). Tocopherol is highly important because it has been suggested to be the most effective molecule involved in stopping lipid peroxidation by reducing lipid peroxyl radicals to hydroperoxides. In the course of this detoxification process, α-tocopherol loses a proton and is transformed into a nonreactive radical that can be further detoxified by ascorbate, glutathione, or enzymes (Burke 2007). Indeed, exposure to UV light or ozone depletes vitamin E levels in the skin (Thiele et al. 1997a,b; Weber et al. 1997), confirming its role in skin defense against outdoor oxidants. In addition, levels of vitamin E also decrease with age, which could be due to increased pollutant exposure over time (Rhie et al. 2001).

Another micronutrient found in the skin is vitamin C, also known as ascorbic acid. Like vitamin E, vitamin C is synthesized in plants but cannot be synthesized by humans and must be taken up with food (Telang 2013). In the skin, Vitamin C is a cofactor for prolysyl and lysl hydroxylase, which are enzymes that cross-link collagen (Burke 2007). In addition, vitamin C promotes the transcription and stabilization of procollagen mRNA (Davidson et al. 1997, Geesin et al. 1988). It is also involved in promoting keratinocyte differentiation and the barrier function of the skin (Pasonen-Seppanen et al. 2001, Ponec et al. 1997).

Vitamin C is water soluble and among the most abundant of all antioxidants. It reacts with potentially dangerous free radicals by donating an electron. In this way, vitamin C itself is

oxidized and forms semidehydroascorbic acid. Similar to tocopherol, the resulting radical is stable and comparably unreactive. This radical can either be reduced or react further to produce dehydroascorbic acid (Burke 2007). Therefore, like vitamin E, it functions in protecting the skin from oxidative stress by neutralizing free radicals and is depleted in response to UV light and ozone (Lin et al. 2003; Stewart et al. 1996; Thiele et al. 1997a,b). It has also been demonstrated that vitamin C protects against ozone-induced skin damage and inflammation in vitro and in 3D skin models (Valacchi et al. 2015, 2016). Because of similar effects on the skin, numerous studies have found that although vitamins E and C function alone as antioxidants, they function best in this capacity when used in conjunction (Lin et al. 2003; Stewart et al. 1996; Valacchi et al. 2015, 2016). Furthermore, vitamin C can reduce oxidized vitamin E (Burke 2007).

Another necessary group of micronutrients is the carotenoids, which are a family of plant pigments that are important precursors of vitamin A that are not synthesized by humans. Therefore, they must be taken up through the diet. Their main role is to protect against ROS accumulation via quenching singlet oxygen and scavenging other species of ROS. For instance, in the skin, β-carotene is a carotenoid that inhibits lipoxygenases, which are enzymes capable of producing ROS, and scavenges free radicals. β-carotene quenches peroxyl radicals, which are directly added to its backbone, forming an epoxide that can be further decomposed (Liebler & McClure 1996).

Uric acid is derived from purine degradation and is generated by xanthine oxidase, an enzyme involved in producing endogenous ROS (Rinnerthaler et al. 2015). Uric acid is also a reductant for ROS and can quench hydroxyl radicals and singlet oxygen (Rinnerthaler et al. 2015). By taking an electron, uric acid is transformed into a nonreactive radical (Rinnerthaler et al. 2015). However, it does not play a crucial role in skin antioxidant defense because levels of uric acid are high in circulation, and cutaneous tissues do not have a large blood supply (Rinnerthaler et al. 2015). In human epidermis, uric acid is present at a concentration of ~1 μM/g skin, whereas ascorbic acid and dehydroascorbic acid are present at a combined concentration of ~7.6 μM/g skin (Shindo et al. 1994a).

Coenzyme Q_{10} (CoQ_{10}) is a type of lipid-soluble ubiquinone that contains a functional group called a benzoquinone, which can accept and donate electrons; it exists in a fully reduced form ($CoQ_{10}H_2$), a radical semiquinone intermediate ($CoQ_{10}H$), and a fully oxidized form (CoQ_{10}). In mitochondria, CoQ_{10} is part of the electron transport chain and contributes to ATP production. Although it protects against lipid peroxidation, it is not nearly as effective in protection against UV light as are vitamins E and C; however, it is also capable of reducing the oxidized form of vitamin E. In the skin, it is more concentrated in the epidermis than the dermis but is present at a much lower concentration in the skin than vitamins C and E (~7.66 nM/g skin versus ~34 nM/g skin and ~7,600 nM/g skin, respectively).

CUTANEOUS DAMAGE BY ENVIRONMENTAL INSULTS

The abovementioned cutaneous enzymatic machinery and micronutrients are of essential importance in daily life and defense of the skin from outdoor stressors such as pollution. The effects of pollutant-mediated increased oxidative stress in the skin are believed to result in the development/exacerbation of premature skin aging. Aging is characterized by the functional decline of an organism over time, resulting in increased susceptibility to diseases and death. In the skin, aging is affected by both intrinsic and extrinsic factors (Vierkotter & Krutmann 2012). Intrinsic aging is primarily controlled by genetic factors and is characterized by loss of elasticity, skin atrophy, vascular prominence, and wrinkles (Uitto 2008). In contrast, extrinsic aging is the consequence of exposure to various environmental factors, including UV light, smoking, and environmental pollution and is characterized by rough texture, telangiectasia, irregular pigmentation, and deep

wrinkles (El-Domyati et al. 2002). In fact, the exposome, which describes the totality of exposures, including UV light and air pollution, that an individual is exposed to, has been shown to potentiate skin aging (Krutmann et al. 2017). The consequence of long-term exposure to environmental pollutants in the skin-aging exposome is the depletion of micronutrients and/or vitamins in the skin, leading to an increased risk in developing the chronic diseases of aging because of the allocation of scarce micronutrients for short-term survival, according to the triage theory (Ames 2006). Skin senescence is one of the main hallmarks of aging (Toutfaire et al. 2017), and senescent cells are unable to divide, although they remain metabolically active and are capable of secreting various factors [known as senescence-associated secretory phenotype (SASP)] (Toutfaire et al. 2017). Long-term pollution exposure has been demonstrated to promote aging and induce SASP signaling (Martens & Nawrot 2016, Vierkotter et al. 2010, Vriens et al. 2019, Ward-Caviness et al. 2016). In addition to aging, exposure to pollutants, such as UV light, ozone, and diesel exhaust, is also believed to promote the development/exacerbation of inflammatory skin disorders such as psoriasis and atopic dermatitis through induction of increased oxidative stress (Kramer et al. 2009, Schafer et al. 1996, Xu et al. 2011). Although decades of work have focused on applying antioxidants topically to alleviate and/or prevent the aforementioned conditions, we believe that topical intervention alone is not enough for treating these cutaneous conditions.

IMPROVING SKIN HEALTH THROUGH TOPICAL APPLICATION

Topical Application with Natural Compounds

The role of vitamin E in protecting against oxidative skin damage has been heavily investigated. Reviewed extensively by Krol et al. (2000), topical application of vitamin E has been demonstrated to have several beneficial effects in SKH1 hairless mice, including reductions in UV-induced skin cancer, DNA damage, and photoaging. In other mouse models, topical application resulted in the reduction of free-radical formation, photoaging, and thymine dimer formation (Jurkiewicz et al. 1995, McVean & Liebler 1997, Norkus et al. 1993). However, topical formulations of vitamin E are limited by the inherent instability of the micronutrient. Thus, vitamin E conjugates have been utilized to increase the stability of topically applied vitamin E to penetrate skin layers.

In addition to vitamin E, the effects of vitamin C topical applications to improve skin health have also been widely researched. Because vitamin C is water soluble and a charged molecule, it is repelled by the lipid barrier in the upper layers of the epithelium; however, it can be delivered as ascorbic acid when pH levels in the skin are low (Al-Niaimi & Chiang 2017). Topical application of vitamin C has been demonstrated to partially restore the anatomical structure of the epidermal–dermal junction in young skin and increases the number of nutritive capillary loops in the papillary dermis in aged skin (Sauermann et al. 2004). Although there have been numerous studies examining the beneficial effects of vitamin C on the skin in vitro and in animal models, there have been limited numbers of human clinical studies. In one clinical study, it was determined that topical application of vitamin C improved the appearance of photodamaged skin (Humbert et al. 2003). The results included an improvement in small and coarse wrinkles, firmness, smoothness, and dryness of the skin due to enhanced collagen and elastin synthesis (Humbert et al. 2003). However, many studies have demonstrated that vitamin C used in conjunction with vitamin E is more effective in protection from outdoor stressors than either micronutrient alone (Valacchi et al. 2015, 2016). Vitamins C and E can act synergistically to reduce UV damage via reducing apoptosis and the formation of thymine dimers (Burke 2007, Lin et al. 2003). This is because vitamin C can reduce oxidized vitamin E, demonstrating the need for both micronutrients in the skin (Chan 1993). Both vitamins C and E have been shown to inhibit UV damage, UV-induced photoaging, and skin cancer (Burke et al. 2000). It has also been observed in 3D skin models, ex

vivo human biopsies, and human volunteers that vitamin C and E mixtures can protect against pollutant-induced skin inflammation and collagen degradation (Valacchi et al. 2015, 2016, 2017).

Many other micronutrients, often called antioxidants, have been used for topical applications to prevent outdoor stressor-induced skin damage. For a more in-depth review, see Dzialo et al. (2016). Among necessary micronutrients are carotenoids, which are a family of plant pigments. Although there are more than 200 types, only 20 are found in human tissues (Souyoul et al. 2018). The four major types of carotenoids found in tissues are β-carotene, lutein, zeaxanthin, and lycopene, and they have all been demonstrated to protect against oxidative-induced skin damage and photoaging. Supporting this idea is a recent review by Souyoul et al. (2018) that discusses how skin concentrations of carotenoids are decreased with oxidative stress and UV exposure.

β-Carotene is a red–orange pigment found in plants and fruits. It is typically not used in topical applications due to its coloring. However, topical application of β-carotene has been shown to protect the skin of human subjects against infrared irradiation (Darvin et al. 2011). Another study demonstrated that topical application of β-carotene improved skin pigmentation in human subjects (Kar 2003). Because topical application of β-carotene protects against stressor-induced depletion of endogenous carotenoids, it is believed that future sunscreens should also utilize antioxidants in their formulations (Darvin et al. 2011).

In addition to β-carotene, lutein and zeaxanthin are also present in the skin, where they work as filters to block damaging blue wavelengths (Souyoul et al. 2018). Topical application of lutein and zeaxanthin protects keratinocytes from UV-induced photoaging, prevents ECM degradation by inhibiting MMPs, and decreases lipid peroxidation in the skin (Souyoul et al. 2018). Furthermore, although the primary carotenoid lycopene has no vitamin A activity, it is considered the best singlet oxygen quencher in the carotenoid family (Souyoul et al. 2018). Several studies have examined the effects of lycopene on the skin and found that it can be effective at reducing the effects of UV-light-induced inflammation, but this is a long-term process, as with other carotenoids (Addor 2017). Furthermore, higher skin concentrations of lycopene are associated with decreased skin roughness (Souyoul et al. 2018). To take advantage of combined antioxidant capacities, topical applications should include all of these compounds because topical application of a mixture of vitamins E, C, and carotenoids increased skin moisture and elasticity in human subjects (Lademann et al. 2016).

Along with vitamins E, C, and A, an extranutritional compound that has also been shown to influence skin repair and skin health is pycnogenol, a plant extract from the bark of *Pinus pinaster*, composed of phenolic acids, procyanidin/proanthocyanidin, and flavonoid compounds (Packer et al. 1999). Marini et al. (2012) demonstrated that twelve weeks of supplementation with this extract can increase skin elasticity, hydration, and production of protective hyaluronic acid in skin, which are also correlated with a reduction in skin wrinkles. Other studies have demonstrated that pycnogenol binds to and protects collagen and elastin from degradation by MMPs and promotes cutaneous wound healing (Belcaro et al. 2005, Grimm et al. 2004). Furthermore, Saliou et al. (2001) demonstrated that pycnogenol protected against UV-induced inflammation by inhibiting NFκB's transactivation activity (Saliou et al. 2001). Pycnogenol has also been proposed to act synergistically with vitamins E and C and increase the endogenous antioxidant enzyme system (Iravani & Zolfaghari 2011).

Despite being surrounded by controversy, resveratrol (3,5,4′-trihydroxy-*trans*-stilbene), an antioxidant natural phenol found in red grapes, peanuts, and berries, has been studied extensively for health benefits. The largest problems with using resveratrol are that it has a short half-life, exhibits poor bioavailability in vivo, has low water solubility, and is believed to be sensitive to oxidation/degradation, affecting absorption into the skin (Hung et al. 2008, Ndiaye et al. 2011). Recently reviewed by Ndiaye et al. (2011), there is currently a focus on improving resveratrol's bioavailability and stability by using analogs, hydrogel patches, and nanosuspensions for topical

application. Although clinical studies supporting the use of resveratrol in skin health are limited, there have been several in vivo and in vitro studies supporting its use to reduce UV-induced skin damage. Resveratrol treatment in an EpiDerm full-thickness model increased gene expression of SIRT1, collagen, and elastin and downregulated expression of inflammatory markers (Lephart et al. 2014). In keratinocytes, resveratrol protected against UV-induced apoptosis (Cao et al. 2009). In SKH1 hairless mice, topical application of resveratrol reduced bifold skin thickness and ear punch weight and inhibited UV-induced leukocyte infiltration (Afaq et al. 2003). It has also been demonstrated that resveratrol decreases cigarette smoke–induced ROS and protein carbonyl formation in human keratinocytes (Sticozzi et al. 2014).

Although topical applications have been widely investigated for improving skin health, the barrier function of the stratum corneum can be effective in preventing the passage of compounds/nutrients to the lower layers of the epidermis and dermis. Topical applications are also constrained by the fact that many of these compounds have short half-lives, although esterified derivatives (in the cases of vitamin C and E) can be used to increase half-lives. However, to ensure optimal delivery of nutrients/compounds to the dermis and lower epithelial layers, these therapeutics must also pass through the bloodstream, and this could be achieved through dietary modulation.

SKIN HEALTH IS MODULATED BY NUTRITION

It has become increasingly apparent that nutrition is important for skin health. This is exemplified by the appearance of skin conditions in response to nutrient deficiencies. For instance, scurvy is a disease caused by vitamin C deficiency and is characterized by skin fragility and impaired cutaneous wound healing (Hodges et al. 1969, 1971; Ross & Benditt 1962). Thus, consuming the right foods and nutrients is important for skin health. Although the skin contains antioxidant endogenous defensive enzymes and micronutrients (derived from circulation), these levels/activity can be depleted by exposure to the environment (Shindo et al. 1994b; Thiele et al. 1997a,b, 1998; Valacchi et al. 2000; Weber et al. 1997). As an alternative to topical application, dietary modulation has been proposed as a useful avenue for protection against skin damage. For example, in clinical trials, when comparing supplementation with the antioxidants lutein and zeaxanthin orally or topically, oral administration was more effective than topical treatment in preventing changes in lipid peroxidation (Palombo et al. 2007). This study confirms the idea that oral supplementation can improve skin health, suggesting a possible additive, if not synergistic, effect on skin health when combined with topical application. Furthermore, dietary intake of omega-3 fatty acids (FAs) and selenium contributes to inhibiting cutaneous oxinflammation (Valacchi et al. 2018).

Another way to improve skin health through diet modulation is to alter gut microbiota. Gastrointestinal disorders, such as inflammatory bowel disease and celiac disease, are characterized by dermatological manifestations such as vitiligo, erythema nodosum, and dermatitis herpetiformis (Saarialho-Kere 2004, Shah et al. 2013, Tavarela Veloso 2004, Thrash et al. 2013). In addition, skin disorders such as psoriasis, rosacea, and atopic dermatitis can be improved through altering the gut microbiome via supplementation with probiotics or antibiotic therapy (Groeger et al. 2013, Parodi et al. 2008, Salem et al. 2018). In conclusion, there is clinical evidence suggesting a relationship between intestinal dysbiosis and cutaneous inflammatory conditions. However, the molecular mechanisms involved in this relationship are just beginning to be understood because the association between the gut and the skin is multifactorial and involves communication among the skin and gut and nervous, endocrine, and immune systems (Arck et al. 2010).

Molecular Mechanisms Involved in the Gut–Skin Axis

The main player in the gut involved in the gut–skin axis is the gut microbiome, which consists of commensal bacteria, fungi, protozoa, and viruses and influences the metabolism and immunity of

the host. Multiple studies in rodent models have demonstrated a link between gut microbiota and skin health, which has been extensively reviewed by Salem et al. (2018) and O'Neill et al. (2016). In response to external stimuli, the intestinal microbiome produces neurotransmitters (dopamine, serotonin, GABA, and acetylcholine) that can cross from the intestinal epithelium into the bloodstream to regulate skin functions (**Figure 1**). For instance, multiple types of bacteria, including *Lactobacillus*, can produce neurotransmitters that are capable of altering barrier function, hair growth, and melatonin synthesis in the skin (O'Neill et al. 2016). In addition, short-chain fatty acids (SCFAs), produced by bacteria, such as butyrate, can bind to G-protein-coupled receptors (GPCRs) expressed on keratinocytes (GPR109a) and endothelial and immune cells and inhibit inflammation through regulating the activity of histone deacetylases, modulating the inflammatory NFκB signaling pathway, and promoting Treg accumulation in the skin (O'Neill et al. 2016, Salem et al. 2018) (**Figure 1**). In the skin, Tregs can promote the regeneration of epithelial stem cells via induction of Notch signaling (Ali et al. 2017). Butyrate can also stimulate collagen synthesis via increasing insulin-like growth factor signaling in fibroblasts (Karna et al. 2009). However, the effects of bacterial metabolites on the skin depend on which bacteria are present. For instance, *Faecalibacterium prausnitzii*, *Bacteroides fragilis*, and *Clostridium* and/or their metabolites can promote the accumulation of anti-inflammatory Tregs (Hornef & Pabst 2016, Round & Mazmanian 2010). In contrast, segmented filamentous bacteria can promote the accumulation of inflammatory Th17 and Th1 cells (Ivanov et al. 2009). Th17 cells are proinflammatory cells that promote the pathogenesis of inflammatory skin disorders (e.g., psoriasis), and the balance of Tregs and Th17 effector cells is regulated by the intestinal microbiota, illustrating the importance of the gut microbiome in host immunity. In addition, the gut microbiome can influence the skin microbiome, although this interaction has not been well-studied. SCFAs produced by bacteria in the gut may be able to affect the growth of cutaneous commensals on the surface of the skin (i.e., skin microbiome), such as *Staphylococcus epidermidis* and *Cutibacterium acnes*, because SCFAs can be found in the blood in concentrations ranging from 1 to 150 μM (Ohira et al. 2017). In conclusion, the gut microbiome can affect skin functions directly through the secretion of bacterial metabolites and indirectly through the regulation of immune cells.

Interestingly, the gut microbiota can also generate peptides that activate formyl peptide receptors on epithelial cells, triggering NADPH oxidase to catalyze ROS generation, which can then regulate the activity of redox-sensitive transcription factors like NFκB (Jones & Neish 2017). Because the link between the gut and the skin is well-established (O'Neill et al. 2016), as is the link between pollution exposure and alterations in the gut microbiome (Salim et al. 2014), the effects of pollution on the gut could alter skin health. To test this idea, one could alter the gut microbiota in human volunteers and/or SKH1 hairless mice through the use of dietary supplementation with probiotics and/or antibiotic therapy and exposure to pollutants and then examine whether pollution-induced skin damage is affected.

Altering the Gut Microbiome to Promote Skin Health

Because the gut microbiome is such a significant player in the gut–skin axis, it is no surprise that altering the composition of the gut microbiome can be used to promote skin health. For instance, mice supplemented with *Lactobacillus reuteri* demonstrated increased sebocyte production, increased dermal thickness, and enhanced folliculogenesis, which depend on the presence of IL10, suggesting that probiotics play a role in the "glow of health" (Levkovich et al. 2013). Poutahidis et al. (2013) demonstrated that oral supplementation with *L. reuteri* in drinking water decreased wound healing time in mice because of oxytocin-mediated Treg trafficking. Oral supplementation with *Lactobacillus brevis* increased cutaneous blood flow in rats and decreased TEWL, which is a

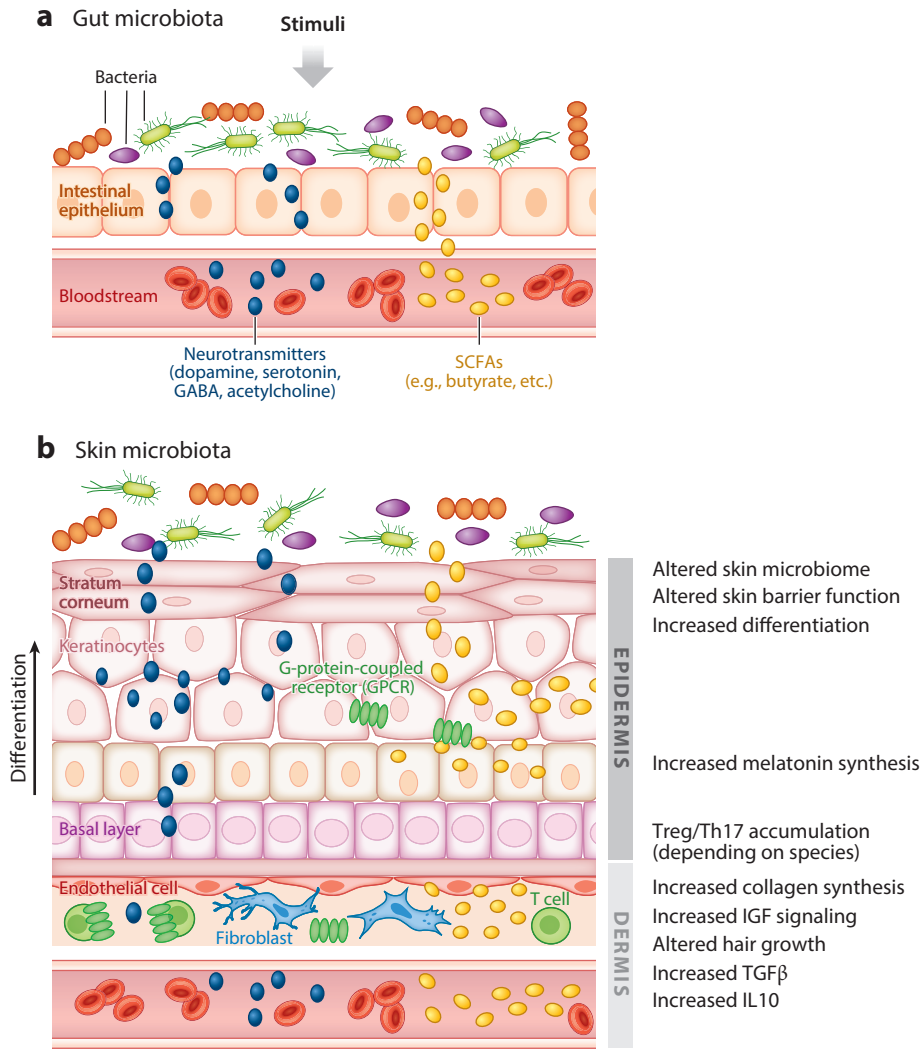


Figure 1

Gut–skin axis. (*a*) In response to external stimuli, the intestinal microbiome produces bacterial neurotransmitters (dopamine, serotonin, GABA, and acetylcholine) and short-chain fatty acids (SCFAs) such as butyrate that transport through the intestinal epithelium to reach the bloodstream to regulate skin functions (bloodstream SCFAs at 1–150 μM conc.). (*b*) In the skin, these mediators can alter hair growth and promote Treg or Th17 accumulation. Specifically, butyrate can stimulate collagen synthesis by fibroblasts via increasing insulin-like growth factor signaling. In addition, bacterial metabolites can alter melatonin synthesis and skin barrier function in the epithelium. Furthermore, the gut microbiome could potentially influence the skin homeostasis (differentiation, proliferation, and the growth of cutaneous commensals on the surface of the skin). Abbreviations: IGF, insulin-like growth factor; IL10, interleukin 10; TGFβ, transforming growth factor beta.

marker of skin health (Horii et al. 2014). In human subjects, oral supplementation with *L. brevis* resulted in decreased TEWL and increased skin hydration (Ogawa et al. 2016). Bacterial supplementation with *Lactobacillus paracasei* in humans promotes skin barrier function and decreased TEWL as well as skin sensitivity to chili pepper extract because of increased levels of circulating TGFβ,

which regulates the barrier function of the skin (Gueniche et al. 2014, O'Neill et al. 2016). Another study demonstrated that milk whey fermented by *Lactobacillus helveticus* resulted in increased levels of K10, involucrin, and profilaggrin in vitro in human keratinocytes (Baba et al. 2006). In a subsequent study, Baba et al. (2010) demonstrated that oral supplementation with *L. helveticus* decreased SDS-induced dermatitis and TEWL in hairless mice. Oral supplementation with *Lactobacillus johnsonii* protected SKH1 hairless mice against UV-induced contact hypersensitivity because of decreased Langerhans cells and increased IL10 levels in serum (Gueniche et al. 2006). In humans, *L. johnsonii* oral supplementation accelerated the recovery of skin immune homeostasis after UV radiation exposure (Peguet-Navarro et al. 2008). In addition to oral supplementation with probiotics, researchers have also investigated the effects of oral supplementation with micronutrients and/or other plant-derived compounds on skin health, primarily in the context of UV protection.

Dietary Supplementation with Micronutrients and Other Plant-Derived Compounds to Promote Skin Health

After dietary intake, vitamin C can be transported into the epidermis from blood vessels via sodium-dependent vitamin C transporters SVCT1 and SVCT2 (Pullar et al. 2017). Vitamin E is fat soluble, so it is transported by lipoproteins for tissue delivery (Traber 2007). In the liver, α-tocopherol binds to the α-tocopherol transport protein and is then incorporated into lipoproteins for tissue delivery (Niki & Traber 2012). Normally, it is provided to the skin through sebum (Thiele et al. 1999). As previously alluded to, vitamins C and E are more effective when used in combination, and this observation applies to studies using dietary supplementation as well as topical application. Oral supplementation with vitamin E alone (400 IU) has been studied in short-term (eight weeks) and long-term (six months) studies with no observable changes in photoprotection (McArdle et al. 2004, Werninghaus et al. 1994). In contrast, in SKH1 mice, oral and topical application of vitamin E protected against UV-induced skin cancer (Burke et al. 2000). Although oral supplementation with vitamin C alone (500 mg) for eight weeks in humans was unsuccessful in providing photoprotection (McArdle et al. 2002), when it was used in combination with vitamin E, human studies reported decreased UV-induced inflammation (Eberlein-Konig et al. 1998, Fuchs & Kern 1998, Placzek et al. 2005).

A primary polyphenol that has been studied in the context of dietary human supplementation and skin health is resveratrol. However, the results of these studies have varied depending on supplementation duration and concentration because of the fact it has an extremely fast half-life and is metabolized in the liver and intestine to glucuronides and sulfonates within 30–60 min (Ndiaye et al. 2011), causing poor bioavailability. Therefore, very high doses of resveratrol are needed to make an extensive systemic impact, affecting suitability for oral intake (Hung et al. 2008, Ndiaye et al. 2011).

Another dietary supplement with high polyphenolic content that has been studied in regard to skin health is cocoa. Two human studies have been conducted examining the effects of a cocoa drink containing either high (326–29 mg) or low (27 mg) levels of flavonoids (mostly epicatechin) on skin health (Heinrich et al. 2006, Neukam et al. 2007). Neukam et al. (2007) observed that short-term supplementation of the drink with high levels of flavonoids increased cutaneous blood flow, potentially affecting nutrient delivery to the skin. Heinrich et al. (2006) observed that long-term supplementation increased skin density and thickness and decreased UV-induced inflammation in the high flavanol group (12 weeks).

The mechanism behind carotenoid incorporation into the skin is well understood. Once in the gut, carotenoids are transported by lipoproteins in the bloodstream and then transported to the epidermis via scavenger receptor class B member 1 (SR-B1) (Fernandez-Garcia 2014).

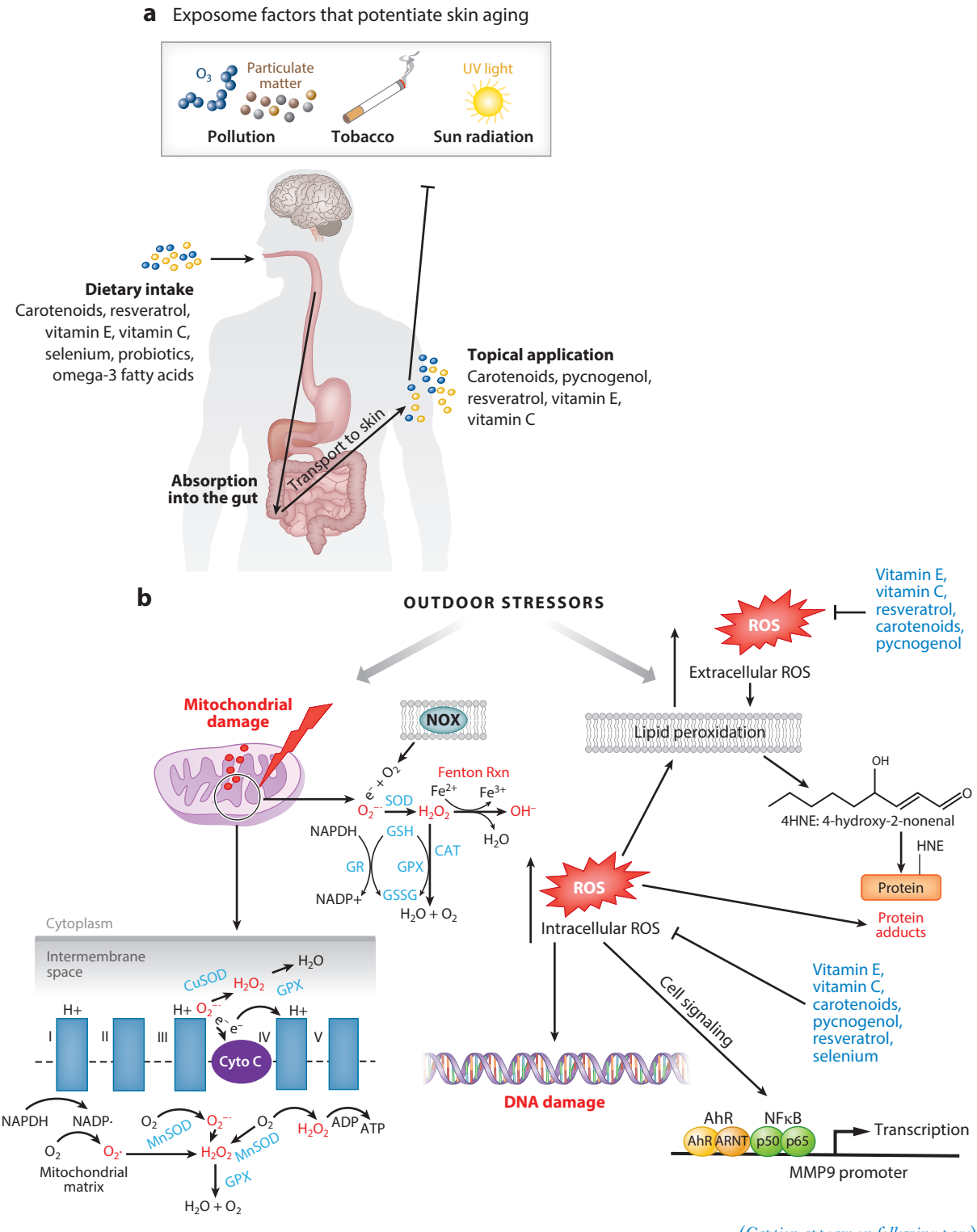
Interestingly, it has been observed that resveratrol prevents cigarette smoke–mediated loss of SR-B1 in keratinocytes (Sticozzi et al. 2014). Studies on skin health investigating dietary supplementation with carotenoids have obtained varying results. Short-term effects (less than eight weeks) have been minimal, but longer periods of supplementation resulted in decreased lipid peroxidation and UV-induced inflammation (Garmyn et al. 1995, Heinrich et al. 2003, Lee et al. 2000, McArdle et al. 2004, Stahl & Sies 2012). It has also been demonstrated that dietary supplementation with β-carotene decreases O_3-induced oxinflammation in the skin of SKH1 hairless mice (Valacchi et al. 2009). In addition, studies utilizing carotenoids in oral supplementation with other nutrients, such as selenium or vitamin E, or with the addition of a topical layer of sunscreen, have demonstrated that these combinations decrease UV-induced lipid peroxidation and inflammation (Cesarini et al. 2003, Gollnick et al. 1996, Stahl et al. 2000).

The Role of Dietary Omega-3 and Omega-6 Fatty Acids in Skin Health

Both omega-3 and omega-6 FAs are essential polyunsaturated fatty acids (PUFAs) because mammalian cells do not express the desaturase enzyme, which creates a carbon–carbon double bond in fatty acids (Huang et al. 2018). Omega-3 FAs include eicosapentaenoic acid (EPA), which is used to produce eicosanoids that reduce inflammation. Omega-6 FAs include linoleic acid (LA). In the epidermis, LA is a constituent of ceramides, which are essential for forming the structure of the skin barrier in the stratum corneum (Feingold 2007). Therefore, a deficiency of PUFAs in the skin can increase TEWL, decreasing skin barrier function (Meguro et al. 2000), resulting in increasing levels of proliferative keratins (Ekanayake-Mudiyanselage et al. 1998). Nagata et al. (2010) compared the diet of 716 women and concluded that intake of fat (both saturated and unsaturated) was associated with increased elasticity, especially in those that consumed higher omega-3 FAs. Similar studies have observed that a higher intake of omega-3 PUFAs was able to ameliorate the effects of photoaging in both men and women (Latreille et al. 2012, 2013). In the context of pollution, interactions between omega-6 PUFAs and pollutants in the skin result in oxidation of membrane phospholipids, triggering proinflammatory cascades (Magnani et al. 2016, Valacchi et al. 2005). However, supplementation with omega-3 PUFAs protects against pollutant-induced damage in various ways, such as increasing the activity of SOD (Huang et al. 2018).

Diet Regulates the Activity of Endogenous Enzymes

Many endogenous enzymes involved in protection against ROS require the presence of cofactors for activity that can only be derived from the diet. In particular, selenoproteins, such as members of the GPX and TXNRD families, utilize selenium as a cofactor to trap H_2O_2. For selenium to be incorporated into polypeptide chains in vertebrates, it must be taken up through the diet (Zoidis et al. 2018). Plants can absorb selenium through the soil (selenate or selenite) and synthesize selenomethionine (SeMet) (Zoidis et al. 2018). Vertebrates can obtain dietary selenium as selenomethionine and other Se amino acids, although the ability of the organism to metabolize and absorb selenium depends on the form of selenium and site of absorption. For instance, SeMet is actively absorbed and requires a transport mechanism to pass through the enterocyte (Zoidis et al. 2018). In contrast, sodium selenite is passively absorbed in the intestine (Zoidis et al. 2018). Because both GPX and TXNRD play a critical role in protecting the cell against oxidative stress, a diet lacking in selenium can lead to the accumulation of ROS and oxidative stress–induced damage. In the skin, this can result in conditions such as premature aging. Furthermore, modest Se deficiency is prospectively associated with age-related diseases such as cancer, heart disease, and immune dysfunction (McCann & Ames 2011).



(Caption appears on following page)

Figure 2 (*Figure appears on preceding page*)

Combining diet modulation with topical application to prevent pollution-induced skin conditions resulting from altered redox homeostasis. (*a*) Dietary intake of antioxidants, including resveratrol, micronutrients vitamin E and vitamin C, carotenoids, and selenium in combination with topical application of carotenoids, vitamin E, vitamin C, pycnogenol, and resveratrol should help prevent skin damage and aging due to exposure to environmental exposome factors. Topical application of these compounds can increase the antioxidant capabilities of the upper layers of the epithelium, and dietary intake can increase antioxidant levels in the lower layers of the epithelium. (*b*) Preventing altered redox homeostasis is vital to prevent the development/exacerbation of exposome-induced skin conditions because exposure of the skin to exposome factors, including UV light, ozone, and particulate matter, can result in the formation of intracellular and extracellular reactive oxygen species (ROS), which can overwhelm the skin's endogenous defense system. Using both topical application and dietary intake of antioxidants can supplement the skin's natural defense system and prevent DNA damage, lipid peroxidation, protein modifications, and the activation of inflammatory signaling pathways that can negatively impact skin structure and function. For instance, activation of redox-sensitive transcription factors such as AP1, NFκB, and AhR can result in the transcription of matrix metalloproteinases, which function to break down collagen, leading to premature aging.

CONCLUSION

Skin health depends on both extrinsic and intrinsic factors. Intrinsic aging of the skin is a natural consequence of physiological changes over time due to genetic predisposition, whereas extrinsic aging is controllable and the consequence of exposure to environmental factors. The exposome, first defined by Christopher Wild in 2005, describes the totality of exposures to which an individual is subjected (Wild 2005). Exposome factors that can potentiate skin aging include sunlight, pollution, and tobacco, and exposure to these factors can result in skin damage and premature aging (Krutmann et al. 2017). In this review, we have focused on how compounds or probiotics obtained through the diet and/or topically applied can affect skin health to prevent ROS-associated skin damage because it is believed that the accumulation of ROS over time is a main contributor to skin aging (Rinnerthaler et al. 2015).

Unfortunately, dietary intervention alone is inadequate to prevent/treat skin conditions, primarily due to skin biology. As previously mentioned, the outermost layers of the epidermis are removed from the blood supply and ensuing nutrient delivery. Furthermore, the barrier function of the skin resides in the outer layers of the skin, which can prevent diffusion of molecules from the underlying dermis. Thus, it is likely that a two-pronged approach, utilizing both topical applications and dietary intervention, is needed for optimal nutrient delivery to the skin. For example, in clinical trials, combinatory oral and topical supplementation with lutein and zeaxanthin provided the highest degree of antioxidant protection (Palombo et al. 2007). We believe that utilizing this two-pronged approach to optimize antioxidant protection will decrease environmentally induced oxinflammation and the development/exacerbation of premature aging (**Figure 2**).

DISCLOSURE STATEMENT

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