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REVIEW ARTICLE

Photoprotection of human skin beyond ultraviolet radiation

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J. K. serves as a consultant to companies that develop cosmetic products for photoprotection, including Stada AG (Bad Vilbel, Germany) and Skinceuticals (Clark, NJ, USA); the IUF has received financial support from both companies to assess the efficacy of antioxidants in protection against infrared radiation.

SUMMARY

Photoprotection of human skin by means of sunscreens or daily skin-care products is traditionally centered around the prevention of acute (e.g. sunburn) and chronic (e.g. skin cancer and photoaging) skin damage that may result from exposure to ultraviolet rays (UVB and UVA). Within the last decade, however, it has been appreciated that wavelengths beyond the ultraviolet spectrum, in particular visible light and infrared radiation, contribute to skin damage in general and photoaging of human skin in particular. As a consequence, attempts have been made to develop skin care/sunscreen products that not only protect against UVB or UVA radiation but provide photoprotection against visible light and infrared radiation as well. In this article, we will briefly review the current knowledge about the mechanisms responsible for visible light/infrared radiation-induced skin damage and then, based on this information, discuss strategies that have been successfully used or may be employed in the future to achieve photoprotection of human skin beyond ultraviolet radiation. In this regard we will particularly focus on the use of topical antioxidants and the challenges that result from the task of showing their efficacy.

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It is now generally accepted that ultraviolet radiation (UVB, 290–320 nm, and UVA, 320–400 nm) is causally related to photocarcinogenesis (with UVB being a complete carcinogen) and photoaging of human skin. As a consequence, photoprotection of human skin has long been synonymous with protection against UVB- and UVA-induced skin damage. Within the last decade, however, this traditional view has been challenged. Accordingly, an increasing number of independent studies from Europe, Asia and the USA have provided compelling evidence that wavelengths present in natural sunlight but beyond the UV spectrum may contribute to actinic damage of human skin (Fig. 1). From these studies it appears that wavelengths within the visible (400–770 nm) and infrared (IR) (770 nm–1 mm) spectrums, and particularly those in the near IR or IRA range (770–1400 nm), significantly contribute to photoaging of skin. From a clinical point of view, these observations suggest that photoprotection of human skin should not be limited to protection against UV but should include protection against visible and IRA radiation. Indeed, sunscreens and daily-care products claiming IRA and visible light protection have been available since 2006, first in Europe, but now at an increasing rate in other continents, including North and South America as well as Asia.

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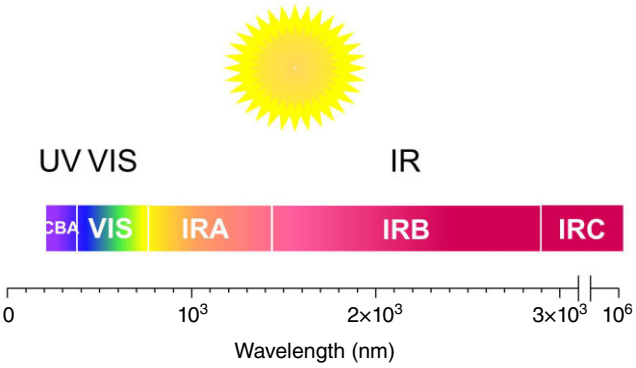

Fig. 1. Spectrum of solar radiation. VIS, visible light; IR, infrared.

Here, we would like to discuss this development from a scientific point of view, because it is of increasing importance to photodermatology as well as the consumer and might even evoke regulatory consequences. The evidence that IRA and visible radiation may damage human skin has been the topic of a number of reviews, including a very recent one from Krutmann *et al.*, and thus, we will only briefly summarize some of the key studies rather than provide a complete review of the existing literature (1, 2). Instead, we would like to use this opportunity to describe the current knowledge about the mechanisms responsible for visible light/IRA-induced skin damage and then, based on this information, discuss strategies that have been successfully used or may be employed in the future to achieve photoprotection of human skin beyond UV radiation. In this regard we will particularly focus on the use of topical antioxidants and the challenges that result from the task of showing their efficacy.

SKIN DAMAGE BY INFRARED RADIATION AND VISIBLE LIGHT

It is now generally accepted that, similarly to UVB or UVA radiation, IRA radiation may exert profound biological effects on human skin in general and the dermal compartment of skin in particular; the literature has been reviewed by Krutmann *et al.* (2). As is the case with UV radiation, IRA-induced effects may be harmful, e.g. by contributing to photoaging, but under certain conditions, they may also be beneficial, e.g. when used therapeutically to treat sclerotic skin lesions or to stimulate wound healing. As we are here primarily concerned about photoprotection of skin against IRA-induced detrimental effects, we will not discuss the potential therapeutic use of this type of radiation.

The impact of IRA radiation on human skin is best illustrated by the recent observation that this type of radiation changes the transcriptome of primary human skin fibroblasts (3). In this study, approximately 600 genes were found to be IRA-responsive, and these genes were functionally clustered into groups involved in extracellular matrix homeostasis, apoptosis, cell growth, and stress responses (3). These genes are in a broader sense related to photoaging and possibly also photocarcinogenesis. Accordingly, among the genes that were significantly up-regulated in primary human skin fibroblasts was that coding for matrix metalloproteinase 1 (MMP-1), thus confirming a previous report of IRA-induced MMP-1 mRNA expression in this cell type (4). Increased MMP-1 mRNA expression occurred in human skin fibroblasts without a concomitant up-regulation of its tissue-specific inhibitor TIMP-1, indicating the possibility that IRA radiation may cause increased MMP-1 activity and thus breakdown of collagen fibers, which would ultimately cause the formation of coarse wrinkles, a clinical hallmark of photoaged skin. In fact, it is now generally accepted that IRA radiation is causally related to wrinkle formation in skin because the original *in vitro* observation of IRA-induced MMP-1 up-regulation was shown to be of *in vivo* relevance for both human (5) and mouse (6) skin. Even more importantly, chronic exposure of hairless mice to IRA radiation caused the formation of coarse wrinkles (6), and the treatment of these animals with combined IRA and UV radiation resulted in wrinkle formation greater than that achieved by UV alone or IR alone, indicating that the two types of radiation were causing photoaging through different (photobiological and molecular) mechanisms. Increased MMP-1 expression is presumably not the only mechanism responsible for IRA-induced photoaging, because IRA exposure was also reported to reduce type 1 collagen expression (by reducing the production of procollagen-1-stimulating transforming growth factors β1, β2, and β3 in human skin) (7). Also, IRA radiation may induce angiogenesis in human skin by a mechanism involving the increased expression of vascular endothelial growth factor (8), i.e. another molecular feature of photoaged skin, which has been suggested to be of functional relevance for photoaging-associated wrinkle formation (9). In addition, IRA radiation was found to increase the number of mast cells in human skin *in vivo* (10), and this effect is also indicative of its potential to cause photoaging. As previously mentioned (2), it should be noted that the majority of these studies employed artificial irradiation devices, which do not mimic natural sunlight but preferentially or even selectively emit IRA radiation. It has therefore been argued that the findings described above are of limited relevance for natural IRA irradiation during sun exposure (11). We would therefore like to point out again (2) that

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this question has recently been addressed in a very elegant study by Cho *et al.* (12), in which the effects of natural sunlight, sunlight minus UVR, and the heat component within natural sunlight were directly compared with each other. By exposing human buttock skin to the three different qualities of natural sunlight, it was shown that UV-filtered sunlight significantly increased MMP-1 expression in exposed skin, indicating that IRA radiation contributes to natural sunlight-induced skin responses. Collectively, these independent studies provide clear evidence that IRA radiation causes photoaging.

In contrast to its role in photoaging, the role of IRA radiation in photocarcinogenesis is less well studied. Accordingly, a study by Jantschitch *et al.* showed that IRA irradiation, if provided prior to UVB radiation, may prevent UVB-induced keratinocyte apoptosis (sunburn cell formation) and might thereby contribute to the development of skin cancer (13). This assumption is further supported by a recent *in vivo* photocarcinogenesis study from the same authors, in which IRA irradiation preceding UVB irradiation did not cause earlier or more tumor growth but was associated with significantly accelerated, more aggressive tumor growth and a higher number of more malignant skin tumors (14). Further studies are clearly required to answer the question of whether exposure of skin to IRA radiation is associated with an increased risk of developing non-melanoma and/or melanoma skin cancer. In this regard, study protocols should not only assess the effects of IRA radiation alone or sequential IRA/UV irradiation but should also study the consequences of simultaneous exposure regimens, as this is what happens if human skin is being exposed to natural sunlight.

In contrast to the numerous studies that have been conducted to analyze the effects of IRA radiation on skin, the studies focusing on visible light and skin are very few. Accordingly, Zastrow *et al.*, by means of electron spin resonance, demonstrated increased free radical formation in *ex vivo* irradiated human skin as a consequence of exposure to wavelengths not only in the UV and IRA ranges but also in the visible range (15, 16). Biological consequences of visible light irradiation of human skin were shown shortly thereafter by Mahmoud *et al.* (17). By employing an artificial irradiation device with an emission mainly confined to wavelengths between 400 and 800 nm, these authors were the first to provide clear-cut evidence that wavelengths in the visible range at doses between 80–480 mW/cm^2 can cause pigmentation *in vivo* in human skin in the absence of UV radiation. Visible-light-induced skin pigmentation was apparent at the clinical level and confirmed by histopathology. Interestingly, visible-light-induced skin pigmentation was only found to occur in darker skin types, i.e. Fitzpatrick skin type 4 and darker. These observations, which have been confirmed by at least three other investigators in independent studies (personal communications to J. K.), indicate that visible light might enhance skin pigmentation and, by doing so, might contribute to the formation of melasma and other skin diseases or conditions associated with increased skin pigmentation. In another study, evidence was provided that visible light exposure might also contribute to photoaging by enhancing collagen breakdown (18). In this study, *in vitro* exposure of human epidermis models to visible light was reported to increase expression of MMP-1 and tumor necrosis factor alpha mRNA in epidermal keratinocytes. This gene-regulatory activity of visible light was associated with an increased production of reactive oxygen species (ROS) in these epidermis models, and this latter observation could be confirmed *in vivo* in human skin when ROS production was measured by detection of chemiluminescence. Experimental evidence from human *in vivo* studies that visible light possesses gene-regulatory activities and from *in vivo* animal studies that chronic exposure to visible light indeed causes wrinkle formation in skin is currently lacking. In addition, virtually nothing is known about the role of visible light in skin carcinogenesis and the interaction among the effects of UV radiation, IRA radiation and visible light. Nevertheless, the existing studies are in line with the assumption that visible light might exert biological effects on human skin that include an increase in ROS production and that are of relevance for skin pigmentation (and maybe photoaging) at least in darker-pigmented individuals.

THE ROLE OF REACTIVE OXYGEN SPECIES IN IRA- AND VISIBLE-LIGHT-INDUCED SKIN DAMAGE

The mechanistic basis underlying IRA radiation-induced gene regulation in human skin fibroblasts has been extensively studied in previous years; for detailed reviews please see Schroeder *et al.* and Krutmann *et al.* (1, 2). In brief, from these studies it appears that the generation of ROS in human skin plays a prominent role in initiating IRA-induced signaling. IRA radiation-induced ROS production has been shown to occur *in vitro* in cultured primary human skin fibroblasts, *ex vivo* in IRA-irradiated skin biopsies, and *in vivo* in human skin (5, 15, 19, 20). ROS production is not specific for IRA radiation but also occurs upon exposure of human skin cells or skin to UVB or UVA radiation. In this context, it is important to note that the three wavelengths use different chromophores, and thus

the cellular compartments in which ROS production is being initiated differ depending on the type of irradiation used. Accordingly, we and others have previously shown that the chromophores for UVB radiation include nuclear DNA as well as cytoplasmic tryptophan, whereas UVA radiation-induced intracellular signaling is initiated at the level of the cell membrane lipid rafts (21). In contrast to UV, IRA radiation was found to be strongly absorbed intramitochondrially. Accordingly, copper atoms present in complex IV of the respiratory chain are thought to serve as the major IRA chromophores (22), and this assumption is consistent with the notion that IRA-irradiated fibroblasts show an increased intramitochondrial ROS production (19). Importantly, mitochondrial ROS production is of functional relevance for IRA radiation-induced gene expression, because (i) chemical inhibition of the electron transport chain inhibited IRA-induced but not UVB- or UVA-induced MMP-1 expression in primary human skin fibroblasts, and (ii) cells lacking a functional respiratory chain (Rho^0 cells) failed to up-regulate MMP-1 mRNA expression in response to IRA irradiation, whereas (iii) fibroblasts that overexpressed peroxisome proliferator-activated receptor gamma coactivator (PGC-1) and displayed increased electron transport chain content showed the opposite behavior, i.e. hypersensitivity towards IRA-induced MMP-1 mRNA expression; last but not least, (iv) antioxidants containing a mitochondrial leader sequence were approximately a thousandfold more effective in abrogating IRA-induced MMP-1 gene expression in primary human skin fibroblasts than their cytoplasmic analogues (19). These studies indicate that intramitochondrial ROS production represents an initiating step in IRA-induced intracellular signaling. It has been proposed that IRA-induced gene expression is mainly the consequence of a retrograde signaling response (Fig. 2) that is initiated inside mitochondria, subsequently leaves the mitochondria and affects intracytoplasmic calcium levels, activates mitogen-activated protein kinases, and ultimately reaches the nucleus, where it affects gene transcription (23). This concept is strongly supported by subsequent studies of the transcriptome of IRA-irradiated primary human skin fibroblasts, which clearly showed that the vast majority of IRA-responsive genes were regulated via intramitochondrial ROS signaling responses (3). It should be noted that for a small set of IRA-responsive genes, prevention of their regulation by IRA radiation may not be achieved with mitochondrially targeted antioxidants, whereas treatment of primary human skin fibroblasts with *N*-acetylcysteine, which is known to increase endogenous glutathione levels, was able to do so. These observations indicate that IRA radiation may cause functionally relevant

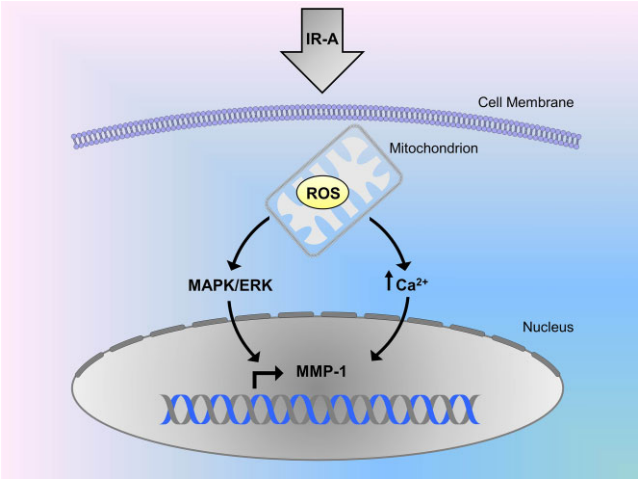

Fig. 2. Infrared A (IRA) radiation-induced retrograde signaling in human skin fibroblasts. Adapted from Krutmann *et al.* (2). ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; MMP-1, matrix metalloproteinase; ROS, reactive oxygen species.

intracellular ROS production independent of mitochondria (3) and that mitochondrial targeting of antioxidants is not always a *conditio sine qua non* for interference with IRA-induced signaling responses.

Another open question concerns the role heat might play in IRA-induced ROS production. Accordingly, it has been proposed that heat exposure might contribute to photoaging of human skin because exposure of human skin to natural sunlight through a black cloth (which absorbs UV and IR rays but generates heat) increased MMP-1 expression (although to a lesser extent than unfiltered sunlight or sunlight filtered for UV rays) (12). In fact, evidence has been provided for a process termed thermal aging (24), which is thought to involve activation of the transient receptor potential vanilloid type 1 (TRPV-1) channel (25–28). If and to what extent heat generation, TRPV-1 channel activation, and ROS generation contribute to IRA radiation-induced skin damage is currently not completely understood and is under debate (4, 11, 13, 29). On the other hand, there is compelling evidence from a constantly growing number of independent studies that generation of ROS plays a crucial role in the pathogenesis of IRA-induced skin damage, and as described in the following paragraph, this has prompted the development and use of skin-care products based on antioxidants for the prevention of IRA radiation-induced skin damage.

In contrast to IRA radiation, relatively little is currently known about the mechanisms involved in visible-light-induced skin pigmentation or MMP-1 expression. In fact, to the best of our knowledge, no study has been published on the mechanisms responsible for visible-light-induced

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skin pigmentation in darker skin types. For visible-light-induced keratinocyte gene expression, one study provides *in vitro* evidence that in human 3D epidermis models, visible-light irradiation causes the formation of ROS, and that topical treatment of these models with a sunscreen product containing a plant extract with antioxidant properties, but not with the sunscreen product alone, inhibits visible-light-induced MMP-1 expression (18). The authors also show by detection of chemiluminescence that visible light causes ROS production *in vivo* in human skin.

PHOTOPROTECTION AGAINST IRA RADIATION- AND VISIBLE-LIGHT-INDUCED SKIN DAMAGE

As outlined in the previous paragraph, numerous studies indicate that IRA radiation-induced skin damage involves the generation of ROS in dermal fibroblasts. As a consequence, photoprotection of human skin against IRA radiation-induced skin damage is currently centered around the use of topical antioxidants. In this regard it is important to emphasize that IRA photoprotection requires specific antioxidants. Accordingly, in target-driven *in vitro* screens employing IRA radiation-induced MMP-1 mRNA expression in primary human skin fibroblasts as a read-out model, we have previously shown that some but not all antioxidants are effective in providing IRA photoprotection and that efficacy of antioxidants may be further increased if an appropriate antioxidant combination is being used. Also, in 2008, we showed for the first time that topical application of an antioxidant mixture containing vitamin C, vitamin E, ubiquinone, and a grape-seed extract effectively prevented IRA radiation-induced MMP-1 mRNA expression *in vivo* in human skin (5). Although the design of this study was uncontrolled, the number of participating volunteers was limited to 9, and protection from IRA radiation-induced MMP-1 expression was far from being complete, this study is nevertheless important as proof of principle that topical application of a suitable antioxidant mixture is capable of protecting against IRA radiation-induced skin damage *in vivo* in human skin. In fact, this study pioneered the development of sunscreen products for IRA protection of human skin, which were first launched in Germany. Today, IRA photoprotection is no longer limited to the constantly growing number of sunscreen products but may be found in daily skin care products as well.

Major challenges that have to be met if cosmetic products for IRA protection of human skin are to be developed result from the fact that there is currently no biological endpoint known that reflects IRA-induced skin damage and that can be measured non-invasively (in contrast to UVB or UVA photoprotection, for which erythema and pigmentation represent easy-to-measure biological endpoints). This is particularly important when it comes to proving claims for effective IRA photoprotection of human skin, which should not only be based on *in vitro* assays but should always include *in vivo* studies in human skin employing the final product. We therefore propose a two-step strategy in which selected antioxidants are first screened *in vitro* for their capacity to inhibit IRA-induced MMP-1 mRNA expression in cultured primary human skin fibroblasts, followed by a second, clinical study in which candidate molecules that were found to be effective *in vitro* are tested as a galenic formulation representing the final skin-care product for their capacity to inhibit IRA-induced MMP-1 mRNA expression *in vivo* in human skin.

A recent example illustrating such a two-step strategy in which antioxidants for IRA photoprotection have been successfully incorporated in daily skin care products is depicted in Fig. 3. Here, *in vitro* experiments clearly demonstrated that a combination of the three antioxidants vitamin C (which has previously been shown to penetrate into skin) (31), ferulic acid and tocopherol, but not the corresponding vehicle control, significantly inhibited IRA radiation-induced MMP-1 mRNA expression in primary human skin fibroblasts in a dose-dependent manner (Fig. 3a). This *in vitro* study was then followed by an *in vivo* study in which, in a total of 25 human volunteers, it was shown that exposure of normal skin to IRA radiation caused up-regulation of MMP-1 mRNA expression by a factor of 3 to 4 and that topical application of a skin care product containing a combination of the three antioxidants mentioned significantly reduced IRA-induced MMP-1 mRNA expression (Fig. 3b).

A major drawback of this approach is that it is invasive in nature because assessment of MMP-1 mRNA expression requires 4 mm punch biopsies to be taken from human skin that has or has not been treated with the test product of interest and exposed to IRA radiation. On the other hand, IRA radiation-induced MMP-1 mRNA expression is a biological endpoint that is directly related to IRA radiation-induced skin damage in general and skin aging in particular, and although it is difficult to assess, it may therefore be considered as ideal for the support of IRA photoprotection claims. In this regard, assessment of IRA-induced MMP-1 expression is also superior to measuring IRA-induced ROS production in human skin, which can be done non-invasively by employing Raman spectroscopy (20). This approach, however, does not measure IRA-induced ROS production directly but instead the depletion of carotenoids from skin immediately after IRA irradiation, which is thought to reflect their consumption by IRA radiation-induced ROS (5). It also focuses on IRA

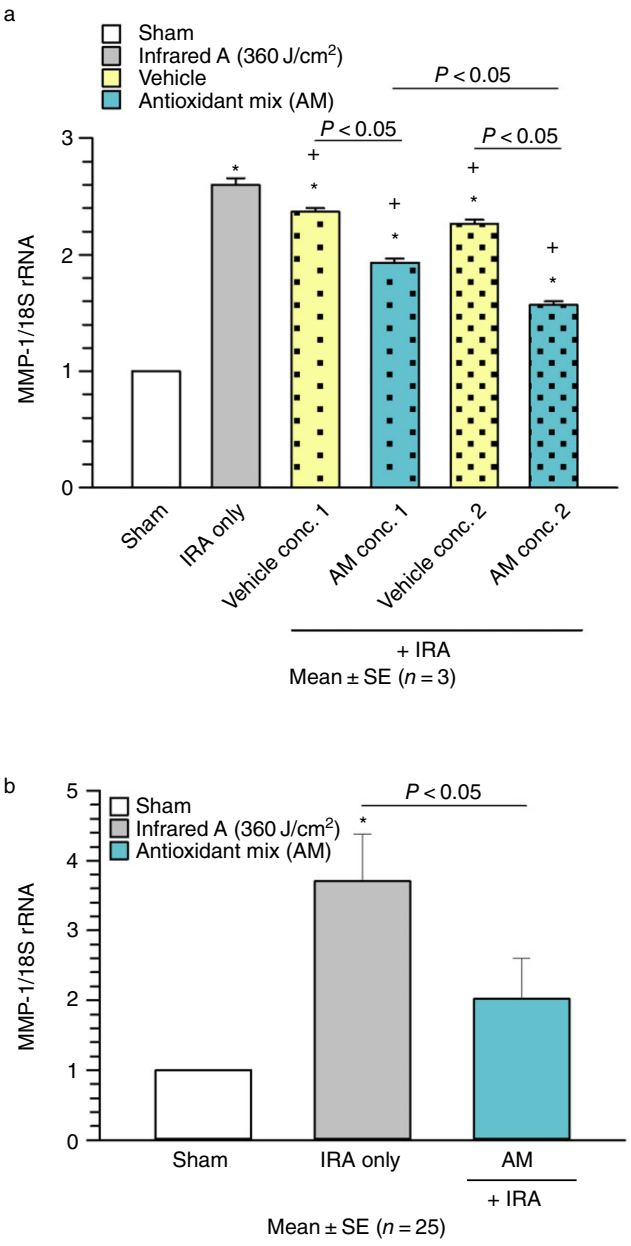

Fig. 3. (a) Dose-dependent inhibition of IRA-induced up-regulation of MMP-1 mRNA expression in primary human dermal fibroblasts by an antioxidant mix consisting of vitamin C, ferulic acid and tocopherol as compared with the vehicle (water, ethoxydiglycol, glycerine, propylene glycol, laureth-23, phenoxyethanol, triethanolamine, panthenol, sodium hyaluronate). Final concentrations were 5 μM/10 μM vitamin C, 150 nM/300 nM ferulic acid, and 136 nM/276 nM tocopherol. $^{*}P < 0.05$ versus sham; $^{+}P < 0.05$ versus IRA only; other P values as indicated (ANOVA). Culture conditions, IRA treatment and gene expression studies are described by Schroeder *et al*. (5). (b) After approval was obtained from the ethics committee of Heinrich Heine University, Düsseldorf, Germany, 25 healthy volunteers (10 female, 15 male; mean age 76.5 years, SE 1.7) were enrolled after giving written informed consent. The open-label study was performed according to the ethical rules stated in the Declaration of Helsinki, and the International Conference on Harmonisation Good Clinical Practice guideline was observed insofar as applicable. The volunteers were treated for 10 days once daily with 2 mg/cm^2 of a formulation consisting of water, ethoxydiglycol, ascorbic acid, glycerin, propylene glycol, laureth-23, phenoxyethanol, tocopherol, triethanolamine, ferulic acid, panthenol, and sodium hyaluronate. Twenty-four hours after a single IRA treatment, biopsies were taken, processed for RNA isolation, and evaluated for MMP-1 mRNA expression (30). $^{*}P < 0.05$ versus sham; other P values as indicated (ANOVA on ranks).

radiation-induced ROS formation as a biological endpoint that does not necessarily reflect IRA radiation-induced skin damage (as opposed to IRA-induced MMP-1 expression, which is directly related to skin aging). Along the same lines, protection of human skin against visible-light-induced ROS formation was reported to be reduced if a galenic formulation containing plant-derived antioxidants was applied to human skin prior to exposure (18). Whether topically applied antioxidants can provide protection against visible light-induced skin pigmentation in darker skin types is currently not known.

Another strategy to achieve protection against IRA radiation-induced skin damage might be the use of antioxidant-containing nutritional supplements. The authors of this article strongly believe that oral photoprotection against IRA radiation-induced skin damage represents a very attractive strategy because IRA radiation-induced skin damage has been shown to occur preferentially in the dermal rather than the epidermal compartment of skin (5); thus, supplementation of human skin with the appropriate antioxidants from the inside, i.e. via the dermal vessels, might represent an attractive alternative because it circumvents the need for epidermal followed by dermal penetration. At least for UV irradiation, systemic photoprotection by means of oral application of antioxidants has been shown in several independent studies to be a feasible and effective strategy that might be used in addition to the topical application of sunscreens; for a recent review, see Gonzales *et al.* (32). Whether such a complementary approach will also work for IRA photoprotection of human skin remains to be shown.

Last but not least, it will be of interest to see if, in comparison to antioxidants, classical sun protection of human skin, which is usually based on physical or chemical filters, has any benefit for IRA photoprotection of human skin. In this regard we are not aware of any published chemical UV filters that are capable of absorbing in the IRA range and thus might be able to provide protection against IRA radiation-induced skin damage. On the other hand,

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inorganic pigments with IR-reflecting properties are well known, indicating the possibility that physical filters might be used for IRA protection of human skin. From a cosmetic point of view, however, a major disadvantage is that all these inorganic molecules, which are widely used as, e.g., roof coatings, are pigments (reviewed by Bendiganavale *et al.*) (33) and thus would be visible to the consumer after topical application to human skin. Alternatives that might pose less or no compliance problems to the consumer may be represented by fumed silica (34). Further studies are required to assess the capacity of conventional sunscreen products containing physical filters for IRA photoprotection of human skin.

CONCLUDING REMARKS

The discovery that wavelengths beyond the UV spectrum, in particular IRA radiation and, under certain conditions, visible light, might contribute to solar radiation-induced skin damage has prompted the development of novel products for photoprotection of human skin. Clearly, topically applied antioxidants are a mainstay of such products, and by combining *in vivo* and *in vitro* strategies, it has been possible to unequivocally demonstrate their effectiveness. It should be noted, however, that there is still room for improvement because published studies indicate that the protection achieved by these products is not yet complete. Also, in contrast to protection against UVB or UVA radiation, for which indices such as the sun protection factor (SPF) for UVB have been defined to indicate the degree of protection provided by a given product, IRA protection claims are not yet regulated and are thus difficult to judge for the consumer.

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