Sunscreen-Based Skin Protection Against Solar Insult: Molecular Mechanisms and Opportunities

12

Andrea Krajisnik, Jessica Perer, and Georg T. Wondrak

Contents

12.1 Sunscreens as Skin Photoprotectants and Cancer Chemopreventive Agents

Solar ultraviolet (UV) photons are established environmental carcinogens. Sunscreens (small molecule organic filters that absorb solar UV-photons and particle-sized inorganic filters that reflect and scatter UV-photons) are important solar photoprotectants and cancer chemopreventive molecular agents. Specifically, sunscreen-based suppression of acute UV skin damage and prevention of actinic keratosis and squamous cell carcinoma have been documented and

A. Krajisnik · J. Perer · G. T. Wondrak (✉)
Department of Pharmacology and Toxicology, College of Pharmacy and University of Arizona Cancer Center, University of Arizona, Tucson, AZ, USA
e-mail: wondrak@pharmacy.arizona.edu

D. S. Alberts, L. M. Hess (eds.), *Fundamentals of Cancer Prevention*,
https://doi.org/10.1007/978-3-030-15935-1_12

reviewed extensively in the literature (Kullavanijaya and Lim 2005; Lautenschlager et al. 2007; Thompson et al. 1993; Naylor et al. 1995; Green et al. 2011; Green et al. 1999; Ulrich et al. 2009; van der Pols et al. 2006; Gallagher et al. 2000; Lee et al. 2005; Gonzaga 2009; Autier et al. 2011; Olsen et al. 2017a, 2017b; Ghiasvand et al. 2016; Goldenhersh and Koslowsky 2011; Hughes et al. 2013; Iannacone et al. 2014; Mancuso et al. 2017).

The importance of efficient skin UVB (290–320 nm) photoprotection that attenuates photomutagenic events originating from direct absorption of UVB photons by DNA bases is firmly established as reviewed (Kullavanijaya and Lim 2005; Lautenschlager et al. 2007; Mancuso et al. 2017; Bens 2008; Marrot and Meunier 2008). In addition, cumulative evidence for the involvement of chronic UVA exposure in the causation of solar skin damage including photocarcinogenesis and photoaging now dictates the necessity for additional broad-spectrum skin photoprotection that includes the UVA spectral region of sunlight (Gasparro 2000; Fourtanier et al. 2012). Indeed, solar photons in the deeply penetrating UVA region (320–400 nm) account for more than 95% of total solar UV energy incident on human skin, contributing to cutaneous photooxidative stress and redox dysregulation, photoallergic dermatoses including polymorphous light eruption, photoimmunosuppression, tumorigenic initiation and progression of nonmelanoma and melanoma skin cancer, and photoaging (Gonzaga 2009; Fourtanier et al. 2012; Tyrrell 1995; Kvam and Tyrrell 1997; Scharffetter-Kochanek et al. 1997; de Gruijl 2000; Agar et al. 2004; Bowden 2004; Wondrak et al. 2006). In addition, research indicates the relevance of photoprotective approaches that cover regions of deeply penetrating near visible UVA, blue visible, and infrared light, all of which are significant contributors to skin photooxidative (and potentially genotoxic) solar insult (Kvam and Tyrrell 1997; Wondrak et al. 2006; Haywood et al. 2003; Bissonnette et al. 2008; Schroeder et al. 2010; Liebel et al. 2012; Nakashima et al. 2017; Zastrow et al. 2009). An additional layer of mechanistic complexity underlying skin photodamage and carcinogenesis with specific relevance to melanocytes has been revealed by investigations that attribute a significant proportion of UV-induced photomutagenesis in skin cells to chemiexcitation reactions that involve the photooxidative formation of peroxide (dioxetane) and triplet carbonyl species capable of cyclobutane pyrimidine dimer formation through energy transfer long after the cessation of UV exposure, a skin-relevant scenario referred to as “photochemistry in the dark” that might contribute to melanomagenesis (Premi et al. 2015; Brash 2016).

Based on the emerging consensus that daily, year-round, broad-spectrum photoprotection is an effective key component of a sun-safe strategy to reduce cumulative lifetime exposure to UV light, much effort has been directed towards the identification, development, and optimization of topical photoprotectants that prevent and attenuate solar skin damage (Lautenschlager et al. 2007; Mancuso et al. 2017; Bens 2008; Fourtanier et al. 2012; Bissonnette 2008; Svobodova and Vostalova 2010; Marionnet et al. 2017; Bernerd and Marionnet 2017). A topic of particular relevance is the optimized use of molecular photoprotection strategies in high-risk patients such as immunosuppressed organ transplant recipients and individuals suffering from conditions associated with extreme photosensitivity such as erythropoietic

protoporphyria or cutaneous lupus erythematosus (Surber et al. 2012; Kreuter and Lehmann 2014). Generally, sunscreen development has aimed at (a) increased absorbance with broadened spectral coverage over the whole UVA/B spectrum, (b) optimized photostability of UV-active chromophores, and (c) prolonged skin residence time with minimal skin penetration and lack of systemic availability upon topical application. In addition, other aspects of drug safety including (d) lack of phototoxic reactivity as well as (e) absence of dark toxicities, originating, for example, from unwanted ligand activity towards the estrogen (ER) receptor, have been addressed by recent sunscreen development.

The SPF (sun protection factor) value is an important quality parameter that specifies potency of protection from UVB-induced erythema following a single exposure to solar simulated radiation as determined according to EC (European Commission) and United States FDA (Food and Drug Administration) regulations (Bens 2008; Fourtanier et al. 2012). The FDA defines the SPF as follows: "The UV energy required to produce an MED on protected skin divided by the UV energy required to produce an MED on unprotected skin, which may also be defined by the following ratio: SPF value = MED [protected skin (PS)]/MED [unprotected skin (US)], where MED (PS) is the minimal erythema dose for protected skin after application of 2 mg per square centimeter of the final formulation of the sunscreen product, and MED (US) is the minimal erythema dose for unprotected skin, i.e., skin to which no sunscreen product has been applied" (FDA Code of Regulations, Title 21, volume 5 (21CFR 352); revised as of April 1, 2012).

Importantly, the level of UV filtration achieved by cutaneous sunscreen application is not directly proportional to the SPF of the sunscreen product. This results from the fact that the amount of UV transmission observed upon sunscreen application equals 1/SPF. For example, an SPF of 2 allows 50% UVB photon transmission (1/2 transmitted). An SPF of 4 will block out 75% of UVB light (1/4 transmitted). An SPF of 8 will block out 87.5% of UVB light (1/8 transmitted), and an SPF of 30 will block out 97% of UVB light (1/30 transmitted). Consequently, the difference in photon transmission between high SPFs (> 30) becomes marginal. However, ongoing research interest focuses on elucidating the potential benefit provided by very high (≥50) SPF products (Diffey and Osterwalder 2017). Apart from the numeric SPF, anti-erythemal activity of a specific sunscreen product will depend on additional factors including the user's skin type, interval between prior topical application and subsequent sun exposure, amount and frequency of application, and cutaneous exposure to physical factors that influence skin residence time of the topical sunscreen including wash off during swimming or sweating.

For quantification of UVA protection suppression of persistent pigment darkening (PPD), a visual cutaneous response to UVA observed between 2 and 24 h after exposure thought to originate from photooxidation of preformed melanin and its precursors, is now the standard methodology (Sklar et al. 2012). PPD-based quantification of UVA protection conferred by topical agents assessed in vivo has now been adapted to UVA testing in vitro as specified by the European Cosmetic Industry Association (COLIPA). In analogy to SPF interpretation, a PPD rating of 5 would indicate that the applied sunscreen allows a fivefold increase in UVA

exposure before darkening occurs that equals that observed in unprotected skin (Bens 2008; Fourtanier et al. 2012). In addition, UVA photoprotection is also established by spectrophotometric determination of the "critical wavelength," a physical parameter that indicates the quality of broad-spectrum protection by specifying the wavelength below which 90% of a photoprotectant's spectral coverage (absorbance between 290 and 400 nm) occurs.

It is important to note that photoprotection products designed for broad-spectrum (UVA-I/UVA-II/UVB) protection can achieve different levels of UVA protection even though they display the same SPF. Moreover, even though erythema is considered to be primarily UVB induced, it has been demonstrated that a broad-spectrum combination sunscreen containing both UVA and UVB filters achieves superior anti-erythemogenic photoprotection as compared to a UVB-only filter displaying the same SPF as the combination sunscreen (Young et al. 2010). According to recent European Commission requirements, all sunscreen products should display photoprotection against UVB and UVA with a ratio of protection levels (SPF/UVA-protection factor) less than or equal to 3.

Given the causative involvement of UV- and visible photon-induced photooxidative stress in solar skin photodamage, a free radical protection index has been proposed as an additional quality parameter that specifies the ability of sunscreen agents to suppress photooxidative stress as assessed by electron paramagnetic resonance-based detection of free radicals (Zastrow et al. 2004; Haywood et al. 2012; Zastrow and Lademann 2016; Zastrow et al. 2017). Moreover, cumulative evidence suggests a detrimental synergism between solar photons and specific polycyclic aromatic environmental pollutants acting as sensitizers of photooxidative stress and mutagens, a molecular scenario relevant to urban areas exposed to high pollution levels around the globe (Gao et al. 2005; Soeur et al. 2017; Marrot 2017).

12.2 FDA-Approved Sunscreen Drugs

Among the member states of the European Union where UV photoprotectants are listed as cosmetics, regulations are harmonized by the European Cosmetic Toiletry and Perfumery Association (COLIPA). However, in contrast to other countries where sunscreen agents are typically commercialized as cosmetic products, the United States FDA regulates sunscreen products as over-the-counter (OTC) drugs, and approval and marketing of novel sunscreen agents in the United States (US) is a rare event, consistent with stringent requirements for safety and efficacy of molecular agents intended primarily for use on healthy skin affecting large populations (Mancuso et al. 2017). In the US, seventeen agents approved for OTC drug use are available, fifteen organic filters and two inorganic metal oxides (zinc oxide and titanium dioxide; Table 12.1) (FDA Code of Regulations, Title 21, volume 5 (21CFR 352: § 352.10, § 352.20); revised as of April 1, 2012). The organic filters belong to eight chemical groups, subdivided into either UVB-directed (aminobenzoic acid-, salicylate-, cinnamate-, benzimidazole derivatives) or UVA-directed (anthranilate-, benzophenone-, dibenzoylmethane-, benzylidene camphor derivatives) molecules (Fig. 12.1).

Table 12.1 FDA-approved organic and inorganic ingredients with photoprotective properties

Active ingredient / UV filter	Maximum allowed concentration (%)	Spectral coverage (UV)
Organic		
Aminobenzoic acid (para-aminobenzoic acid; PABA)	15	*UVB*
Avobenzone (4-tert.-butyl-4′- methoxy-dibenzoylmethane)	3	*UVA-I*
Cinoxate (2-ethoxyethyl *p*-methoxycinnamate)	3	*UVB*
Dioxybenzone (2,2′-dihydroxy-4-methoxybenzophenone; benzophenone-8)	3	*UVB, UVA-II*
Ecamsule[a] (terephthalylidene dicamphor sulfonic acid)	3	*UVA-I, UVA-II*
Ensulizole (phenylbenzimidazole sulfonic acid)	4	*UVB*
Homosalate (3,3,5-trimethylcyclohexyl 2-hydroxybenzoate)	15	*UVB*
Meradimate (menthyl anthranilate)	5	*UVA-II*
Octinoxate (octyl 4-methoxycinnamate)	7.5	*UVB*
Octisalate (octyl salicylate)	5	*UVB*
Octocrylene (2-ethylhexyl 2-cyano-3,3-diphenyl-2-propenoate)	10	*UVB*
Oxybenzone (2-hydroxy-4-methoxy-benzophenone; benzophenone-3)	6	*UVB, UVA-II*
Padimate O (2-ethylhexyl 4-(dimethylamino)-benzoate)	8	*UVB*
Sulisobenzone (benzophenone-4)	10	*UVB, UVA-II*
Trolamine salicylate [tris-(2-hydroxyethyl) ammonium 2-hydroxybenzoate]	12	*UVB*
Inorganic		
Titanium dioxide	25	*(UVB, UVA-II)*
Zinc oxide	25	*(UVB, UVA-II, UVA-I)*

[a]Limited FDA approval for specific sunscreen formulations marketed by a single manufacture.

It is remarkable that among organic UVA filters only avobenzone and ecamsule are able to cover parts of the important spectral UVA-I (340–400 nm) region, whereas all other UVA-active agents only filter in the shorter UVA-II (320–340 nm) range, incapable of providing broad-spectrum protection if combined with UVB absorbers. Due to possible unfavorable photochemical interactions between some of these agents, the FDA restricts the choice of suitable combinations of UVB/UVA chemical filters. Importantly, some of these agents (e.g., PABA) are now considered obsolete due known insufficiencies regarding spectral coverage, photostability, phototoxicity, systemic availability, and suspected estrogenicity, fueling an ongoing controversy that questions safety and efficacy of photoprotection that is solely based on topical application of synthetic sunscreens (Mancuso et al. 2017; Bens 2008; Fourtanier et al. 2012; Haywood et al. 2003; Wolf et al. 2001; Serpone et al. 2002; Hanson et al. 2006; Burnett and Wang 2011; Krause et al. 2012).

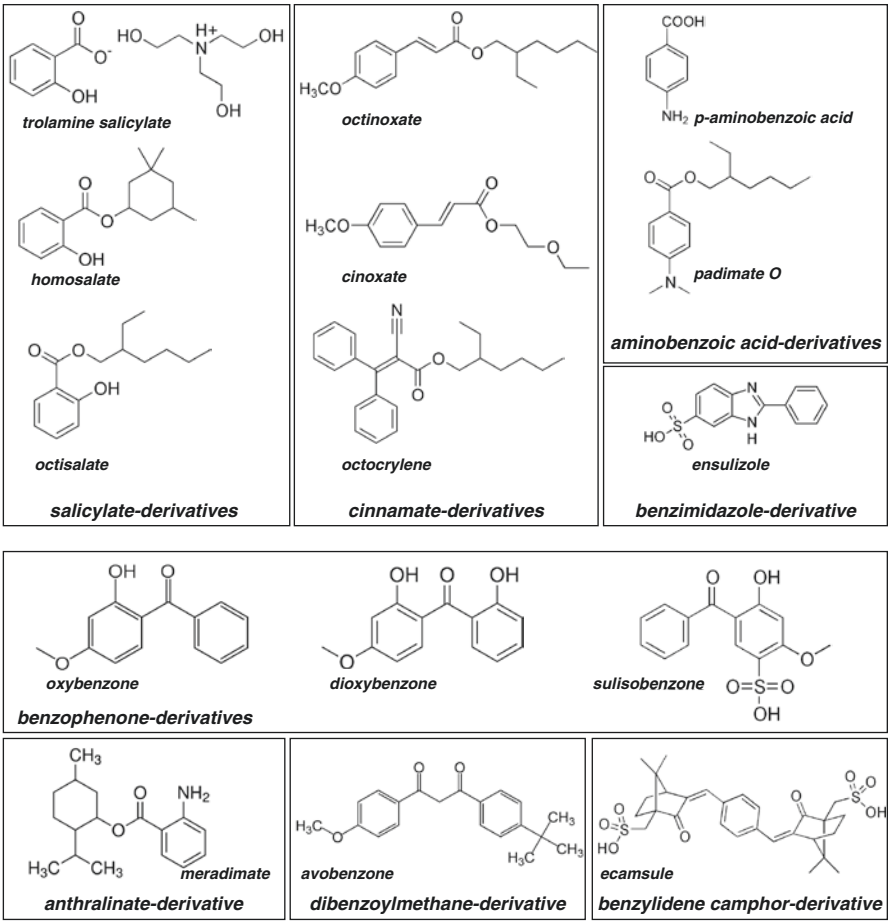

Fig. 12.1 Chemical classes of FDA-approved organic sunscreen agents

Worldwide, much research has focused on the development of more efficacious and safer sunscreen agents, their combinatorial synergistic use, and their incorporation into advanced formulations as detailed below. Out of four advanced organic filter ingredients approved by the European Commission (ecamsule, drometrizole trisiloxane, bisoctrizole, and bemotrizinol) only ecamsule has become available in the US since 2006, based on a limited FDA approval for specific ecamsule containing sunscreen formulations marketed by a single manufacturer (L'Oreal) (Fourtanier et al. 2012). FDA approval of these and other advanced UV filters remains pending as of early 2018 (Mancuso et al. 2017; Diffey 2016).

12.3 FDA New Regulations Concerning Sunscreens

In contrast to the stagnation experienced in the area of approval of new sunscreen agents, in June 2011 the FDA has finalized new regulations that establish revised standards for testing the effectiveness of sunscreen products and require product labeling that accurately reflects test results. According to the new regulations that have become effective in 2012 the "drug facts" section of the product must indicate that sunscreens labeled as both "broad spectrum" and "SPF 15" (or higher) not only protect against sunburn, but "if used as directed with other sun protection measures can reduce the risk of skin cancer and early skin aging" (Fig. 12.2a), a specific drug use not approved by the FDA in the past when sunscreen use was limited to "prevention of sunburn."

According to the revised regulations sunscreen products that are not broad spectrum and/or display an SPF lower than 15 are confined to the use indication "helps prevent sunburn" and must display the following "Skin Cancer/Skin Aging alert:

Fig. 12.2 Sunscreen labeling according to 2011 FDA final rule (21CFR, parts 201 and 310, June 17, 2011). (**a**) Labeling of products that provide broad-spectrum and SPF15 protection. (**b**) Labeling of products that do not provide broad-spectrum and/or SPF15 protection (according to FDA guidelines: http://www.fda.gov/forconsumers/consumerupdates/ucm258416.htm); for explanations see text

Fig. 12.2 (continued)

Spending time in the sun increases your risk of skin cancer and early skin aging. This product has been shown only to prevent sunburn, not skin cancer or early skin aging" (Fig. 12.2b). Only products with combined broad spectrum SPF15 and above performance display the following additional information that specifies the nature of other essential sun protection measures as follows: "Spending time in the sun increases your risk of skin cancer and early skin aging. To decrease this risk, regularly use a sunscreen with a broad spectrum SPF of 15 or higher and other sun protection measures, including: (1) limit time in the sun, especially from 10 a.m. to 2 p.m. and (2) wear long-sleeve shirts, pants, hats, and sunglasses" (Fig. 12.2a). Product labels such as "waterproof" or "sweatproof" specifying unsubstantiated water resistance are now banned by the FDA. Instead, labeling now indicates "water resistant (40 min)" or "water resistant (80 min)." In addition, due to insufficient evidence of clinical benefit for products displaying very high SPFs (>50), labels may now claim a maximum SPF value of "50+" (Mancuso et al. 2017; Diffey and Osterwalder 2017; Diffey 2016).

Obviously, these more recent FDA regulations revising sunscreen OTC product labeling are intended to facilitate a more appropriate and informed sunscreen selection and use among consumers, stressing the importance of frequent and ample application of sunscreens and their obligatory combinatorial use in conjunction with behavioral sun protection measures (e.g., sun avoidance and protective clothing) as promoted widely by many initiatives including the SunWise Program of the U.S. Environmental Protection Agency [http://www.epa.gov/sunwise/]. However, concerns remain

regarding the unspecific and broad nature of the general skin cancer protection claim now permissible according to the revised FDA regulations for broad spectrum SPF15+ OTC products. It can be argued that the FDA-approved drug claim implies a general cancer chemopreventive benefit resulting from sunscreen use that does not account for differences in the solar and nonsolar etiology of specific types of nonmelanoma and melanoma skin cancer and their respective precursor lesions. Indeed, an indiscriminate reduction of skin cancer risk by sunscreen application (expected to vary by formulation and chemical identity of molecular agents beyond categorization according to "SPF" and "broad-spectrum" coverage) is not substantiated adequately by the published scientific literature that mostly supports efficacy of topical sunscreen use for the suppression of acute UV skin damage, prevention of actinic keratosis and squamous cell carcinoma, and photoaging (Kullavanijaya and Lim 2005; Lautenschlager et al. 2007; Green et al. 1999, 2011; Ulrich et al. 2009; van der Pols et al. 2006; Gallagher et al. 2000; Lee et al. 2005; Gonzaga 2009; Autier et al. 2011; Olsen et al. 2017a, 2017b; Ghiasvand et al. 2016; Goldenhersh and Koslowsky 2011; Hughes et al. 2013; Iannacone et al. 2014; Mancuso et al. 2017). As of February 21, 2019, the US FDA has issued a proposed rule that would update regulatory requirements for most sunscreen products in the US (https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm631736.htm). The FDA is publishing this proposed rule as part of the regulatory proceeding to put into effect a final monograph for nonprescription, OTC sunscreen drug products under the OTC drug review (https://www.federalregister.gov/documents/2019/02/26/2019-03019/sunscreen-drug-products-for-over-the-counter-human-use). The proposal addresses sunscreen active ingredient safety, dosage forms, and SPF/ broad-spectrum requirements (in line with other OTC drugs). In addition, updates concerning product labeling enabling consumers to identify key product information are included and maximum SPF values on sunscreen labels are increased from 50 to 60. Importantly, of the sixteen currently marketed active ingredients, only two ingredients (zinc oxide and titanium dioxide) are designated as GRASE ('generally recognized as safe and effective') for use in sunscreens, whereas two ingredients (PABA and trolamine salicylate) are not GRASE for use in sunscreens due to safety issues. Remarkably, the FDA states that there are twelve ingredients for which there are insufficient safety data that would allow a positive GRASE determination at this time, and consequently the FDA is asking industry and other entities for additional data that would allow unequivocal GRASE designation.

12.4 Rational Molecular Design of Optimized Sunscreen Ingredients

12.4.1 General Considerations

Optimization of sunscreen compounds can be achieved by rational molecular design determining efficient photon absorption at specific wavelengths that should be followed by harmless dissipation of photon excitation energy (Fig. 12.3a) (Kullavanijaya and Lim 2005; Lautenschlager et al. 2007; Bens 2008; Fourtanier et al. 2012; Bissonnette 2008; Svobodova and Vostalova 2010; Forestier 2008). An

organic filter substance will first absorb photons (excitation energy, ΔE) leading to excitation of electrons situated in $\pi-$ and nonbinding orbitals of the molecule that undergo a transition to higher antibonding orbitals (excited singlet state formation), followed by return to the electronic ground state by thermal energy dissipation, a process referred to as internal conversion (IC). In specific cases, the excited singlet state can undergo further electronic rearrangements [referred to as intersystem crossing (ISC)] with formation of excited triplet states and biradical species (featuring unpaired electrons), highly reactive intermediates that cause photodegradation of the absorbing molecule itself and can also damage molecules in its close vicinity through energy and electron transfer reactions. In addition, singlet oxygen ($^1O_2$), a highly reactive electronically excited form of molecular oxygen, can be generated by energy transfer that occurs between the triplet state of the initial absorber and ground state triplet oxygen ($^3O_2$). Numerous sunscreen compounds including the UVA filter avobenzone have been associated with undesirable photochemical reactivities associated with photooxidation, photodegradation, and phototoxicity [Fig. 12.3a, depicting the reaction sequence for avobenzone photooxidation (tricarbonyl-formation) via UVA-driven triplet state formation] (Tarras-Wahlberg et al. 1999).

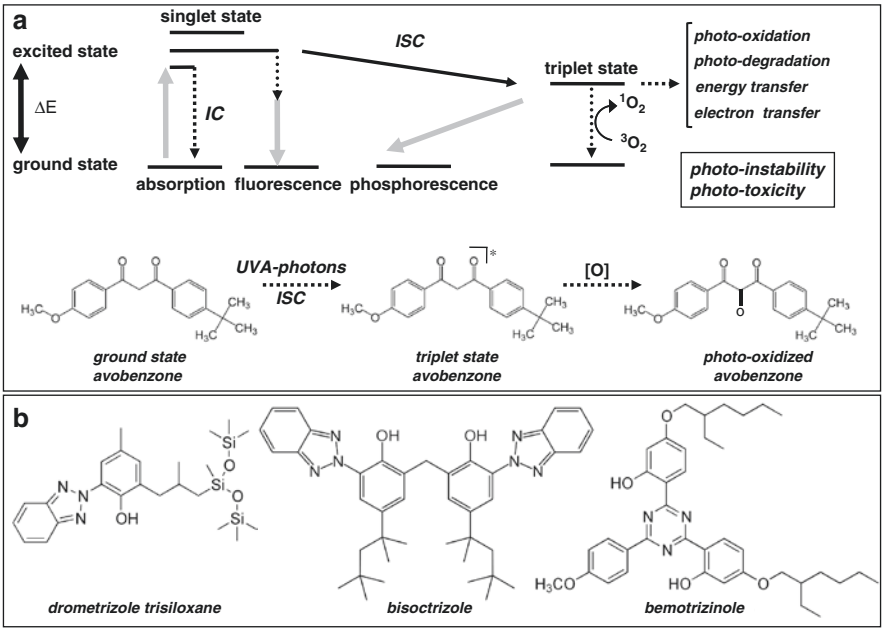

Fig. 12.3 Sunscreen excitation by solar photons followed by excited triplet state formation. (**a**) Upper section: Photochemical reactions may occur downstream of absorption of solar photons by the sunscreen chromophore. lower section: Photooxidation of avobenzone (chemical structure, left) results from excited triplet state formation (chemical structure featuring an excited triplet carbonyl group, center) followed by formation of oxidation products such as the triketo-derivative shown (chemical structure, right). (**b**) Photostable broad-spectrum sunscreen agents of the hydroxybenzotriazole and hydroxytriazine classes. For explanations see text

Rational molecular design of sunscreen chromophores has therefore aimed at the generation of improved photostable molecules capable of efficient photon absorption at specific wavelengths with minimized excited state lifetimes and absence of intersystem crossing (triplet state formation) avoiding singlet oxygen formation that would occur via energy transfer. Moreover, optimized sunscreens bear molecular moieties that facilitate harmless dissipation of photon excitation energy through reversible intramolecular reactions, such as excited state intramolecular proton transfer (ESIPT), keto-enol tautomerism, and cis-trans isomerization (Bens 2008; Forestier 2008). Moreover, research has paid increased attention to formulation-related performance parameters of sunscreens including cutaneous film thickness (Sohn et al. 2014; Sohn et al. 2016). In the context of general considerations relevant to the use and development of sunscreens, it should also be mentioned that recent concerns about environmental compatibility of specific sunscreen chemical entities (such as oxybenzone/benzophenone-3) acting as suspected environmental toxicants have been substantiated (DiNardo and Downs 2017). Likewise, the occurrence of photoallergenicity and dermal uptake from clothing have been associated with specific sunscreen compounds including oxybenzone (Nash and Tanner 2014; Benevenuto et al. 2015; Morrison et al. 2017).

12.4.2 Sunscreen Optimization by coformulation

Avobenzone [1-(4-Methoxyphenyl)-3-(4-tert-butylphenyl)propane-1,3-dione] displays extended spectral coverage that extends far into the UVA-I region (340–400 nm; λ_{max} = 357 nm) making it an important constituent of broad-spectrum formulations that filter UVA-I. However, it has been observed that UVA excitation causes generation of triplet excited states that either cause avobenzone photodegradation or initiate the formation of singlet oxygen or other reactive species (Fig. 12.3a) (Bens 2008; Fourtanier et al. 2012; Wolf et al. 2001; Serpone et al. 2002; Tarras-Wahlberg et al. 1999; Cantrell and McGarvey 2001). Avobenzone photostablilization has been achieved in OTC-marketed sunscreen products by combining it with other more photostable UV filters such as octocrylene, a hydrophobic UVB absorber that photostabilizes and potentiates other UV absorbers (Forestier 2008). Similarly, diethylhexyl 2,6-naphthalate (DEHN), an organic non-UV-screen energy transfer acceptor has shown efficacy in stabilizing avobenzone against UVA-induced degradation and is therefore an established photostabilizer additive employed in numerous formulations.

12.4.3 Sunscreen Optimization Using Nanoparticle and Encapsulation Technology

Significant advances in materials science, specifically in the areas of nanoparticle and encapsulation technology, have impacted the design of improved sunscreen ingredients. Titanium dioxide (TiO_2) and zinc oxide (ZnO) are metal oxide-based inorganic UV filters that exert photoprotection by absorbing, reflecting, and

scattering photons (Cole et al. 2016). Due to the large particle size of microsized metal oxide-based powders, photon reflection may also occur in the visible range of the solar spectrum potentially causing white cast and grainy skin feel that both limit cosmetic acceptance, problems that have been addressed by the development of nanosized TiO_2 and ZnO preparations (<100 nm), a particle size that allows transmission of visible light causing a transparent appearance while maintaining UV-blocking properties (Smijs and Pavel 2011). UV and visible photon-directed blocking properties of metal oxide-based nanoparticles are a function of particle size that inversely correlates with the wavelength of incident photons, and among metal oxides zinc oxide displays superior absorption in the long UVA. For spherical TiO_2, a particle size of 20 nm blocks UVB only, a particle size of 50 nm allows UVB and some UVAII coverage, and a particle size of 100 nm extends coverage over the entire UVA region. Thus, the cosmetically desirable size reduction of nanosized TiO_2 (and ZnO) increases UVB absorption of both particles at the expense of UVA absorption causing unbalanced UV protection. ZnO dispersions should therefore contain both small (nanosized) and large (microsized) particles to maintain a favorable balance between UVA and UVB protection.

The potential for percutaneous penetration of nanomaterials has fueled safety concerns associated with nanosized TiO_2- and ZnO-based sunscreens addressed by research (McSweeney 2016; Osmond-McLeod et al. 2016). A large number of studies suggests that nanosized TiO_2 and ZnO do not penetrate the intact stratum corneum of healthy human skin as reviewed extensively (Smijs and Pavel 2011). A consensus exists that further studies should examine the potential for nanoparticle sunscreen penetration through sunburned skin and under conditions of ultraviolet exposure (Newman et al. 2009). UVB-damaged pig skin displayed slightly enhanced TiO_2 or ZnO nanoparticle penetration from sunscreen formulations but no transdermal absorption was detected (Monteiro-Riviere et al. 2011). It has also been reported that TiO_2 nanoparticles are efficient photocatalysts potentially enhancing UVA-induced skin photooxidative stress (Jaeger et al. 2012). Remarkably, the International Agency for Research on Cancer (IARC) classifies TiO_2 as an IARC group 2B carcinogen ("possibly carcinogenic to humans") based on the finding that high concentrations of ultrafine TiO_2 dust causes respiratory tract cancer in rats (Baan et al. 2006). However, a study has reported that TiO_2 nanoparticles do not promote UVB-initiated skin carcinogenesis in rats, a lack of carcinogenicity attributed to the test particles' inability to penetrate the epidermis (Xu et al. 2011).

Advanced encapsulation and coating strategies can potentially overcome limitations associated with insufficient photostability, unwanted photoreactivity, and skin penetration of inorganic and organic sunscreen agents. For inorganic filters, commonly used nanoparticle coatings that display minimal interference with photoprotective properties and quench light-driven free radical reactivity comprise inert polymeric materials such as silicon and polymethylacrylic acid (Jaeger et al. 2012). For stabilization of organic filters, macromolecular complexation by inclusion of hydroxypropyl-beta-cyclodextrin in sunscreen formulations may enhance photoprotection reducing both skin penetration and photodecomposition of UV absorbers such as avobenzone (Yang et al. 2008).

In an attempt to further block skin permeation and systemic availability of topical photoprotectants, surface immobilization of topical sunscreens has led to the concept of "nonpermeating sunscreens" achieved either by covalent macromolecular polymerization of sunscreen chromophores (e.g., polyacrylamidomethyl benzylidene camphor) or through linkage to a macromolecular nonpermeating backbone (Touitou and Godin 2008). Additionally, a nondelivery encapsulation system has been developed based on entrapping organic UV filters in silica-based microparticles. Glass microencapsulation prevents direct physical contact between the active ingredients and skin, blocking skin permeation and enhancing sunscreen photostability, an innovative concept that has been referred to as "sunglasses for the skin."

12.4.4 Sunscreen Optimization by Designing Improved Chromophores

Apart from photostabilization by coformulation, a more UV-stable avobenzone derivative [1-(4-tert-butylphenyl)-2-decanyl-3-(4′-methoxyphenyl)-propane 1,3-dione] has been described carrying a ten-carbon aliphatic substituent at the alpha-carbonyl position of avobenzone, a modification thought to stabilize the enole form of the molecule in apolar water-in-oil emulsions attenuating photodegradation by limiting the occurrence of the keto-form of the molecule from which triplet state formation and photodegradation can occur (Fig. 12.3a); however, these molecules have not reached the stage of efficacy testing on human skin (Wetz et al. 2005).

Benzylidene camphor and its derivatives [including 4-methylbenzylidene camphor] are potent UVB chromophores contained in a number of established UVB sunscreens approved in Europe but not in the US. Benzylidene camphor is photostable and releases absorbed photon energy by internal conversion through cis-trans photoisomerization, a process characteristic of all benzylidene camphor derivatives (Beck et al. 1981). Further photochemical development aimed at shifting absorption towards longer wavelengths (allowing UVA-II coverage) and blocking skin permeation upon topical application (Forestier 2008). A blue shifted absorption spectrum can be obtained through aromatic extension of the benzylidene camphor-based chromophore, and skin penetration is antagonized by addition of charged substituents (such as anionic sulfonic acid residues). Based on these considerations, a superior photostable UVA-II sunscreen (λ_{max} = 345 nm) has been generated (ecamsule, terephthalylidene dicamphor sulfonic acid), marketed in other parts of the world since 1993 and available to US customers since 2006 (Fig. 12.1, bottom right) (Fourtanier et al. 2012; Seite et al. 1998).

In contrast, the following three advanced sunscreen agents, used throughout Europe, Australia, and other parts of the world, remain unavailable to US consumers as of early 2018 (Fig. 12.3b) (Mancuso et al. 2017). Bisoctrizole (methylene bis-benzotriazolyl tetramethylbutylphenol), a broad-spectrum photoprotectant featuring a photostable hydroxy-benzotriazole chromophore (λ_{max} = 359 nm), is

a hybrid UV absorber (Osterwalder and Herzog 2010). Produced as microfine organic particles (<200 nm) combining characteristics of an organic filter and particle-based photoprotectant, bisoctrizole exerts photoprotection through both absorption and scattering. UVA-I photoprotection is superior among available organic filters as indicated by a "critical wavelength" of 388 nm (as defined in Sect. 12.1 of this chapter). Bisoctrizole also fulfills stringent requirements of advanced photoprotectants (such as lack of skin penetration and absence of estrogenicity) (Ashby et al. 2001).

Drometrizole trisiloxane is another hydroxy-benzotriazol-based broad-spectrum photoprotectant with excellent UVA coverage and photostability. A lipophilic trisiloxane substituent allows formulation optimized for increased water resistance upon topical application (Bens 2008). Combinatorial use between drometrizole trisiloxane and ecamsule potentiates UVA photoprotection (Moyal 2004). Bemotrizinol (bis-ethylhexyloxyphenol methoxyphenyltriazine), available in the European community and Australia since 2000, is a triazine-based lipophilic broad-spectrum UV screen with exceptional photostability, attributed in part to the molecule's ability to dissipate excitation energy by internal conversion though reversible intramolecular proton transfer that occurs between the phenolic substituents and the nitrogens of the core triazine (Osterwalder and Herzog 2010). Importantly, bemotrizinol also confers photostability to other coformulated sunscreen agents known to be intrinsically photoreactive due to triplet state formation (such as avobenzone), a photostabilization effect attributed to excited state quenching representing an innovative mechanism of photoprotection (Chatelain and Gabard 2001).

12.4.5 Sunscreen Optimization Through Potential Synergism with "Non-Sunscreen" Molecular Approaches

Recent research has focused on the identification of targeted molecular interventions and agents that are expected to synergize with sunscreens and may also provide photoprotective benefit if used in stand-alone topical regimens (referred to as "non-sunscreen photoprotection") (Wondrak 2007; Dinkova-Kostova 2008; Afaq and Mukhtar 2006; Nichols and Katiyar 2010; Janda et al. 2016; Dickinson and Wondrak 2017). Moreover, development of experimental therapeutics for post-UV intervention that suppress tumorigenic progression in high risk skin presenting with extensive chronic solar damage is the subject of ongoing research activities (Justiniano et al. 2017a). Remarkably, advances in peptide-based pharmacology have facilitated the clinical availability of a potent α-MSH analogue with pronounced melanogenic properties ("melanotan I; CUV1647"), causing constitutive melanin-based tanning and photoprotection even in pheomelanocytic individuals. This pharmacological stimulation of melanogenesis may benefit patients with severe photo-hypersensitivity {e.g., erythropoietic protoporphyria (EPP), polymorphic light eruption, solar urticaria, xeroderma pigmentosum} or melanogenesis disorders (vitiligo), a medical approach approved in Europe for the treatment of EPP (Dorr et al. 2004; Langendonk et al. 2015).

12.4.5.1 Quenchers of Photoexcited States (QPES)

Compounds capable of inactivating photoexcited states by direct chemical and/or physical interaction are called quenchers of photoexcited states (Wondrak et al. 2006; Wondrak et al. 2005). As combinatorial agents used in conjunction with sunscreen compounds they limit photoreactivity and instability associated with extended photoexcitation of numerous sunscreen agents as mentioned for diethylhexyl 2,6-naphthalate (DEHN) (Chatelain and Gabard 2001). In addition, photoexcited states of endogenous skin chromophores and singlet oxygen (photoexcited oxygen formed by photosensitization) are novel molecular targets for photoprotection by quencher substances, including the xanthone-derivative gentiacaulein, the amino acid L-proline, and marine photoprotectant mycosporines as reviewed previously (Wondrak 2007; Lawrence et al. 2017a). Moreover, NRF2-directed antioxidant and photoprotective activities of the UV-absorbing mycosporine-like amino acid palythine have been documented in cultured human keratinocytes, suggesting that this and other multifunctional photoprotective mycosporines may serve as natural and biocompatible photoprotectants that may synergize with synthetic UV filters (Lawrence et al. 2017b). Recent research indicates that light-driven redox cycling of non-DNA skin chromophores [including porphyrins, riboflavin (vitamin B_2), pyridoxine (vitamin B_6), collagen crosslinks, melanin precursors, AGE-pigments (protein epitopes that form during chronological and actinic skin damage)] acting as endogenous photosensitizers is a major source of reactive oxygen species (ROS) in solar photon-exposed human skin (Scharffetter-Kochanek et al. 1997; Wondrak et al. 2006; Wondrak et al. 2004; Tonolli et al. 2017; Justiniano et al. 2017b). The causative role of photoexcited states that occur downstream of photon absorption but upstream of ROS formation in skin photodamage suggests that direct molecular antagonism of photosensitization reactions using physical and chemical quenchers represents a novel chemopreventive opportunity for skin photoprotection to be substantiated in the future (Wondrak et al. 2006; Bohm et al. 2012).

12.4.5.2 Photoprotective Phytochemicals

Molecular photochemoprevention beyond sunscreen use aims at the identification and development of topical or systemic agents capable of ameliorating the adverse effects of solar radiation on skin. Among numerous experimental and investigational agents that have been tested for photochemopreventive activity, phytochemicals of dietary and non-dietary origin have attracted much research interest (Dinkova-Kostova 2008; Afaq and Mukhtar 2006; Nichols and Katiyar 2010; Bosch et al. 2015). Impressive results documenting chemopreventive potential in mouse models of photocarcinogenesis with topical and systemic administration of phytochemicals have been obtained, including phenolic compounds (e.g., curcumin, resveratrol, tyrosol, caffeic and ferulic acid), flavonoids [e.g., (−)epigallocatechin-3-gallate, apigenin, silibinin], anthocyanidins [e.g., delphinidin] and anthocyanins (e.g., cyanidin-3-O-glucoside), and various carotinoids and xanthophylls (e.g., lutein, zeaxanthin) (Gensler et al. 1996; Singh and Agarwal 2005; Tarozzi et al. 2005). Beyond activity as antioxidants and redox modulators, efficacy of these photochemicals is related to modulation of multiple molecular pathways and targets involved in

skin solar damage [including NRF-dependent activation of the cellular antioxidant response, inhibition of inflammatory signaling (e.g., through modulation of NFκB, AP-1, and COX-2), and attenuation of UV-induced photoimmunosuppression] as expertly reviewed elsewhere (Afaq and Mukhtar 2006; Nichols and Katiyar 2010; Bosch et al. 2015).

12.4.5.3 NRF2 Activators

Recent research strongly suggests that the redox-sensitive transcription factor NRF2 (nuclear factor-E2-related factor 2) is a promising molecular target for modulation of skin barrier function, photoprotection, and cancer chemoprevention that works through pathways that do not involve photon screening (Bosch et al. 2015; Dinkova-Kostova et al. 2006; Kawachi et al. 2008; Saw et al. 2011; Tao et al. 2013, 2015; Reisman et al. 2015; Schafer et al. 2012; Schafer and Werner 2015; Knatko et al. 2016). Nrf2 transcriptional activity orchestrates major cellular antioxidant, phase-II detoxification, and anti-inflammatory pathways that protect tissue against electrophilic insult (Zhang 2006). It is well established that numerous dietary chemopreventive factors activate NRF2 through covalent adduction and/or oxidation of redox-sensitive thiol residues in Keap1 (Kelch-like ECH-associated protein 1), the negative regulator of NRF2 (Zhang et al. 2004). Inhibition of Keap1-dependent ubiquitination and subsequent suppression of proteasomal degradation of NRF2 allows NRF2 nuclear translocation, a process followed by NRF2-dependent transcriptional activation of cytoprotective target genes underlying NRF2-dependent suppression of environmental toxicity and carcinogenesis as reviewed recently (Rojo de la Vega et al. 2017). Additional functions of NRF2 with relevance to skin barrier integrity, and environmental protection and repair have recently emerged, including a role in stem cell renewal and pluripotency, mitochondrial homeostasis and energy metabolism, and autophagic and proteasomal regulation (Rojo de la Vega et al. 2018; Holmstrom et al. 2016; Hawkins et al. 2016).

The key role of NRF2 in the coordination of anti-inflammatory, antioxidant, and cytoprotective pathways is supported by extensive studies using NRF2 knockout (NRF2 KO) versus wild-type mice demonstrating that NRF2 KO mice are more susceptible to environmental electrophilic stress and inflammatory stimuli (including solar ultraviolet and ionizing radiation, arsenic, benzo[a]pyrene, hyperoxia, cigarette smoke, and diesel exhaust) as reviewed recently (Surh et al. 2005; Kundu and Surh 2010; Kensler and Wakabayashi 2010; Osburn and Kensler 2008; Nakagami and Masuda 2016).

Pharmacological intervention using dietary factors that activate NRF2 represents a promising strategy for chemoprevention of various types of cancer (Surh et al. 2005; Kundu and Surh 2010; Hayes et al. 2010). Several studies strongly suggest a role of NRF2-mediated gene expression in the prevention of epidermal chemical (TPA/DMBA-induced) and UV-induced carcinogenesis (Knatko et al. 2016; auf dem Keller et al. 2006). In cultured human skin cells, the small molecule NRF2 activator cinnamaldehyde displayed strong cytoprotective activity by suppressing reactive oxygen species (ROS)-dependent photooxidative stress, and NRF2-dependent protection against UVA-induced keratinocyte damage has

been observed (Tao et al. 2013; Wondrak et al. 2008; Tian et al. 2011). Protection against UVB-induced skin carcinogenesis by topical application of an NRF2 activator (sulforaphane-enriched broccoli sprout extract) has been demonstrated in SKH-1 mice (Dinkova-Kostova et al. 2006; Talalay et al. 2007), but the photochemopreventive activity of topical sulforaphane application has also been attributed to potent inhibition of AP-1 (Dickinson et al. 2009). Sulforaphane-based NRF2 activation confers a protective effect against UVB-induced acute inflammation and sunburn reaction, and NRF2-dependent attenuation of UVB-induced sunburn reaction and oxidative DNA damage can be observed in Nrf2 wild-type versus KO mice (Kawachi et al. 2008; Saw et al. 2011). However, no increased susceptibility towards UVB-induced skin carcinogenesis was detected in NRF2 KO mice. In contrast, UVB-induced photoaging is accelerated in NRF2 KO mice based on increased wrinkle formation, epidermal thickening, dermal deposition of extracellular matrix, lipid peroxidation, and loss of cutaneous glutathione (Hirota et al. 2011). In addition, topical NRF2 activation using a synthetic tricyclic bis(cyanoenone)-based NRF2 inducer has shown efficacy protecting against UVA-induced cutaneous photooxidative stress in a murine model of systemic immunomodulatory thiopurine therapy (Kalra et al. 2012). Importantly, a substantial body of experimental evidence indicates that NRF2 dysregulation, either due to insufficient adaptive activation in response to environmental stressors or due to constitutive hyperactivation as a result of genetic alterations that may also involve KEAP1, has detrimental effects compromising skin barrier function and stress responses. For example, seminal research has documented that hyperkeratosis in murine skin results from constitutive epidermal NRF2 over-activation through permanent genetic deletion of KEAP1 (Wakabayashi et al. 2003). Importantly, it has been demonstrated that genetic NRF2 activation protects SKH-1 murine skin against acute photodamage and photocarcinogenesis (Knatko et al. 2016; Kalra et al. 2012; Knatko et al. 2015). Consequently, pharmacological modulation of NRF2 is now explored as an innovative approach achieving sunscreen-independent molecular skin photoprotection, cancer photochemoprevention, and suppression of skin photoaging (Rojo de la Vega et al. 2017).

Taken together, cumulative evidence suggests feasibility of using topical NRF2 activators as novel photoprotectants and photochemopreventive agents. However, performance of these agents must be tested more rigorously as a function of solar spectral range in acute and chronic models of human skin photodamage in order to better define their efficacy as single or combinatorial photoprotective ingredients optimized for targeted topical delivery, photostability, long-term safety, and mechanistic synergism with other photoprotective agents.

12.4.5.4 Nutritional Photoprotection

The dietary origin of numerous photochemopreventive factors suggests the possibility of achieving efficient skin delivery through oral systemic administration, an emerging concept referred to as “nutritional photoprotection.” Indeed, clinical studies document feasibility of human skin photoprotection by dietary intake of lycopene from processed tomato and flavonoid-rich cocoa (Sies and

Stahl 2004; Heinrich et al. 2006; Williams et al. 2009). In addition, oral administration of non-dietary photoprotectants including aqueous extracts of polypodium leucotomos have given impressive clinical results, particularly in the context of attenuation of skin photo-hypersensitivity reactions (e.g., polymorphic light eruption) in human patients (Middelkamp-Hup et al. 2004; Gonzalez et al. 2010; Parrado et al. 2016). Photoprotective efficacy of nutritional intervention has been attributed to direct UV absorption by chromophores contained in phytochemicals such as conjugated polyenes in carotinoids or 2-phenylchromen-4-one in flavonoids (Astner et al. 2007). It should be mentioned that the degree of protection against acute solar insult achievable by nutritional intervention (as assessed by suppression of solar erythema) is generally moderate and does not reach the level of protection achieved by synthetic sunscreen agents. Moreover, safety concerns related to chronic administration of specific phytochemicals such as carotenoids at elevated oral doses have been raised. It has been demonstrated that systemic administration of the apocarotenoid bixin in SKH-1 mice, a key component of achiote (also referred to as "annatto") and FDA-approved food colorant and spice used since ancient times throughout the tropical Americas, provides significant skin photoprotection and improvement of barrier integrity as a function of cutaneous NRF2 activation. Specifically, it was reported that (a) bixin, devoid of pro-vitamin A activity, is a potent activator of the NRF2-dependent cytoprotective response in human skin keratinocytes; (b) systemic administration of bixin activates NRF2 with protective effects against solar UV-induced skin damage; and (c) bixin-induced suppression of photodamage is observable in *Nrf2*$^{+/+}$ but not in *Nrf2*$^{-/-}$ SKH-1 mice confirming the NRF2 dependence of bixin-induced antioxidant and anti-inflammatory effects that occur independent of photon absorption (Tao et al. 2015; Rojo de la Vega et al. 2017; Rojo de la Vega et al. 2018).

Importantly, molecular mechanisms beyond UV screening including excited state quenching, NRF2 activation of the cellular antioxidant response, inhibition of inflammatory signaling (NFκB, AP-1), modulation of energy metabolism and DNA repair, and attenuation of photoimmunosuppression may determine the photochemopreventive activity of diverse dietary biofactors that have shown efficacy in animal models and recent human trials (Afaq and Mukhtar 2006; Nichols and Katiyar 2010; Parrado et al. 2016; Minocha et al. 2017). Specifically, encouraging clinical data indicate the efficacy of oral nicotinamide for chemoprevention of nonmelanoma skin cancer as substantiated by a multicenter, phase 3, double-blind, randomized, placebo-controlled trial in a high-risk population ("Oral Nicotinamide to Reduce Actinic Cancer" [ONTRAC]), followed by clinical evidence indicating efficacy of nicotinamide-based skin cancer chemoprevention in renal transplant recipients (Chen et al. 2015, 2016).

More research is needed in order to substantiate feasibility and preventive benefits of dietary photoprotection aiming at an optimal cutaneous supply of specific phytochemicals and nutrients that increase constitutive skin defense against the deleterious consequences of acute and chronic UV exposure.

12.5 Future Developments Improving Skin Photoprotection: Concerns and Opportunities

Many opportunities for improved solar photoprotection and cancer chemoprevention involving the use of sunscreen agents remain to be explored. Importantly, only limited published information is available on crucial molecular interactions with obvious consequences relevant to sunscreen use in large populations, such as sunscreen/skin microbiome interactions (Rensburg et al. 2016). Areas of current interest include (a) optimization of cancer chemopreventive activity of sunscreens used in conjunction with other measures of photoprotection, (b) potential inhibition of UV-dependent skin vitamin D photosynthesis, a matter of ongoing debate based on accumulating evidence for the chemopreventive action of this solar vitamin against major types of cancer (Giovannucci 2005; Reichrath and Nurnberg 2009; Diehl and Chiu 2010; Gordon-Thomson et al. 2012; Makarova et al. 2017), (c) insufficient protection against solar photooxidative stress together with inadequate spectral coverage, particularly in the regions of near visible UVA, visible (blue) and infrared light, known to contribute to skin photoaging and photogenotoxicity (Wondrak et al. 2006; Zastrow et al. 2017; Moseley et al. 2001; Mahmoud et al. 2008; Darvin et al. 2010; Kolbe 2012), (d) photoinstability and phototoxicity due to light-induced harmful excited state chemistry of many ingredients used in current formulations (Kullavanijaya and Lim 2005; Lautenschlager et al. 2007; Bens 2008; Bissonnette 2008; Svobodova and Vostalova 2010; Maier et al. 2001), (e) systemic availability through transdermal delivery, and (f) insufficient consumer compliance (Bech-Thomsen and Wulf 1992; Autier et al. 2007; Boniol et al. 2008, 2016; Ruppert et al. 2017). Undoubtedly, current sunscreen use is inadequate and does not comply with the recommendations of the American Academy of Dermatology [http://www.aad.org/media-resources/stats-and-facts/prevention-and-care/sunscreens]. Concerns have specifically been raised regarding insufficient frequency and quantity of sunscreen application (Mancuso et al. 2017; Diffey 2001). Research suggests that sunscreen application is the single most frequently used method of sun protection across all age groups, contrary to guidelines that it should be employed in conjunction with other solar protection measures (Stanton et al. 2004). Moreover, it has been argued that, guided by the perceivable benefit of suppression of UV-induced sunburn, consumers might use sunscreens in order to massively overextend skin solar exposure time, thereby receiving high cumulative doses of solar radiation in spectral regions where photon screening by currently available photoprotectants is insufficient or completely absent (Mancuso et al. 2017; Bens 2008; Autier et al. 2007; Boniol et al. 2008). This might be of particular relevance in the regions of deeply penetrating near visible UVA, blue visible, and infrared light, all suggested to be significant contributors to skin photooxidative and potentially genotoxic solar insult (Mancuso et al. 2017; Kvam and Tyrrell 1997; Wondrak et al. 2006; Haywood et al. 2003; Bissonnette et al. 2008; Schroeder et al. 2010; Liebel et al. 2012; Zastrow and Lademann 2016; Zastrow et al. 2017).

Strikingly, toxicological concerns relating to potential systemic availability upon transdermal delivery of specific sunscreen molecular entities remain to be resolved (Gonzalez et al. 2006; Schneider and Lim 2018). Moreover, substantial ecotoxicological concerns now lead to sunscreen bans by regulatory agencies, originating from growing evidence that these chemicals, washed off swimmers or entering the ocean through sewer systems, harm coral reefs through bleaching, DNA damage, and compromised antimicrobial defenses [https://oceanservice.noaa.gov/news/nov15/sunscreen-corals.html] (Schneider and Lim 2018; Downs et al. 2016). On May 1, 2018, Hawaii became the first US state to pass a bill banning the sale of sunscreen containing chemicals believed to harm coral reefs. Beginning January 1, 2021, Hawaii will ban the sale, offer of sale, or distribution of any sunscreens containing oxybenzone (benzophenone-3) or octinoxate (octyl methoxycinnamate) without a prescription from a licensed health care provider. Likewise, in a law passed in November 2018, the Pacific nation of Palau has banned "reef-toxic" sunscreen products containing any one of ten chemicals, including oxybenzone and octinoxate, thought to damage marine environments. In addition, it is expected that the aforementioned FDA proposed rule updating regulatory requirements for most sunscreen products in the US as issued February 21, 2019 will cause a significant impact on future use and commercialization of this important class of OTC drugs (https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm631736.htm).

An informed use of modern sunscreen products remains a key component of the chemopreventive armamentarium for contemporary skin protection against carcinogenic solar insult. A concerted effort that better integrates, expands, and develops the current portfolio of regulatory, educational, behavioral, and pharmacological interventions will ensure that informed consumers can benefit from improved options for effective sun protection that reflects the current state of research.

References

Afaq F, Mukhtar H (2006) Botanical antioxidants in the prevention of photocarcinogenesis and photoaging. Exp Dermatol 15:678–684

Agar NS, Halliday GM, Barnetson RS, Ananthaswamy HN, Wheller M, Jones AM (2004) The basal layer in human squamous tumors harbors more UVA than UVB fingerprint mutations: a role for UVA in human skin carcinogenesis. PNAS 101:4954–4959

Ashby J, Tinwell H, Plautz J, Twomey K, Lefevre PA (2001) Lack of binding to isolated estrogen or androgen receptors, and inactivity in the immature rat uterotrophic assay, of the ultraviolet sunscreen filters Tinosorb M-active and Tinosorb S. Regul Toxicol Pharmacol 34:287–291

Astner S, Wu A, Chen J, Philips N, Rius-Diaz F, Parrado C, Mihm MC, Goukassian DA, Pathak MA, Gonzalez S (2007) Dietary lutein/zeaxanthin partially reduces photoaging and photocarcinogenesis in chronically UVB-irradiated Skh-1 hairless mice. Skin Pharmacol Physiol 20:283–291

auf dem Keller U, Huber M, Beyer TA, Kumin A, Siemes C, Braun S, Bugnon P, Mitropoulos V, Johnson DA, Johnson JA, Hohl D, Werner S (2006) Nrf transcription factors in keratinocytes are essential for skin tumor prevention but not for wound healing. Mol Cell Biol 26:3773–3784

Autier P, Boniol M, Dore JF (2007) Sunscreen use and increased duration of intentional sun exposure: still a burning issue. Int J Cancer 121:1–5

Autier P, Boniol M, Dore JF (2011) Is sunscreen use for melanoma prevention valid for all sun exposure circumstances? J Clin Oncol 29:e425–e426; author reply e427

Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Cogliano V (2006) Carcinogenicity of carbon black, titanium dioxide, and talc. Lancet Oncol 7:295–296

Bech-Thomsen N, Wulf HC (1992) Sunbathers' application of sunscreen is probably inadequate to obtain the sun protection factor assigned to the preparation. Photodermatol Photoimmunol Photomed 9:242–244

Beck I, Deflandre A, Lang G, Arnaud R, Lemair J (1981) Study of the photochemical behaviour of sunscreens - benzylidene camphor and derivatives. Int J Cosmet Sci 3:139–152

Benevenuto CG, Guerra LO, Gaspar LR (2015) Combination of retinyl palmitate and UV-filters: phototoxic risk assessment based on photostability and in vitro and in vivo phototoxicity assays. Eur J Pharm Sci 68:127–136

Bens G (2008) Sunscreens. Adv Exp Med Biol 624:137–161

Bernerd F, Marionnet C (2017) In vitro skin models for the evaluation of sunscreen-based skin photoprotection: molecular methodologies and opportunities. Curr Med Chem

Bissonnette R (2008) Update on sunscreens. Skin Therapy Lett 13:5–7

Bissonnette R, Nigen S, Bolduc C, Mery S, Nocera T (2008) Protection afforded by sunscreens containing inorganic sunscreening agents against blue light sensitivity induced by aminolevulinic acid. Dermatol Surg 34:1469–1476

Bohm F, Edge R, Truscott TG (2012) Interactions of dietary carotenoids with singlet oxygen (1O2) and free radicals: potential effects for human health. Acta Biochim Pol 59:27–30

Boniol M, Dore JF, Autier P (2008) Changing the labeling of sunscreen, will we transform sun avoiders into sunscreen users? J Invest Dermatol 128:481; author reply 481–482

Borghi A, Corazza M, Battaglia Y, Maietti E, Minghetti S, Virgili A (2016) What is the key to improving renal transplant recipients' awareness of skin cancer risk? Dermatology 232: 715–720

Bosch R, Philips N, Suarez-Perez JA, Juarranz A, Devmurari A, Chalensouk-Khaosaat J, Gonzalez S (2015) Mechanisms of photoaging and cutaneous photocarcinogenesis, and photoprotective strategies with phytochemicals. Antioxidants (Basel) 4:248–268

Bowden GT (2004) Prevention of non-melanoma skin cancer by targeting ultraviolet-B-light signalling. Nat Rev Cancer 4:23–35

Brash DE (2016) UV-induced melanin chemiexcitation: a new mode of melanoma pathogenesis. Toxicol Pathol 44:552–554

Burnett ME, Wang SQ (2011) Current sunscreen controversies: a critical review. Photodermatol Photoimmunol Photomed 27:58–67

Cantrell A, McGarvey DJ (2001) Photochemical studies of 4-tert-butyl-4′-methoxydibenzoylmethane (BM-DBM). J Photochem Photobiol B 64:117–122

Chatelain E, Gabard B (2001) Photostabilization of butyl methoxydibenzoylmethane (Avobenzone) and ethylhexyl methoxycinnamate by bis-ethylhexyloxyphenol methoxyphenyl triazine (Tinosorb S), a new UV broadband filter. Photochem Photobiol 74:401–406

Chen AC, Martin AJ, Choy B, Fernandez-Penas P, Dalziell RA, McKenzie CA, Scolyer RA, Dhillon HM, Vardy JL, Kricker A, St George G, Chinniah N, Halliday GM, Damian DL (2015) A phase 3 randomized trial of nicotinamide for skin-cancer chemoprevention. N Engl J Med 373:1618–1626

Chen AC, Martin AJ, Dalziell RA, McKenzie CA, Lowe PM, Eris JM, Scolyer RA, Dhillon HM, Vardy JL, Bielski VA, Halliday GM, Damian DL (2016) A phase II randomized controlled trial of nicotinamide for skin cancer chemoprevention in renal transplant recipients. Br J Dermatol 175:1073–1075

Cole C, Shyr T, Ou-Yang H (2016) Metal oxide sunscreens protect skin by absorption, not by reflection or scattering. Photodermatol Photoimmunol Photomed 32:5–10

Darvin ME, Haag SF, Lademann J, Zastrow L, Sterry W, Meinke MC (2010) Formation of free radicals in human skin during irradiation with infrared light. J Invest Dermatol 130:629–631

de Gruijl FR (2000) Photocarcinogenesis: UVA vs UVB. Methods Enzymol 319:359–366

Dickinson SE, Wondrak GT (2017) TLR4-directed molecular strategies targeting skin photodamage and carcinogenesis. Curr Med Chem. https://doi.org/10.2174/0929867324666170828125328
Dickinson SE, Melton TF, Olson ER, Zhang J, Saboda K, Bowden GT (2009) Inhibition of activator protein-1 by sulforaphane involves interaction with cysteine in the cFos DNA-binding domain: implications for chemoprevention of UVB-induced skin cancer. Cancer Res 69:7103–7110
Diehl JW, Chiu MW (2010) Effects of ambient sunlight and photoprotection on vitamin D status. Dermatol Ther 23:48–60
Diffey B (2001) Sunscreen isn't enough. J Photochem Photobiol B 64:105–108
Diffey B (2016) New sunscreens and the precautionary principle. JAMA Dermatol 152:511–512
Diffey B, Osterwalder U (2017) Labelled sunscreen SPFs may overestimate protection in natural sunlight. Photochem Photobiol Sci 16:1519–1523
DiNardo JC, Downs CA (2017) Dermatological and environmental toxicological impact of the sunscreen ingredient oxybenzone/benzophenone-3. J Cosmet Dermatol. https://doi.org/10.1111/jocd.12449
Dinkova-Kostova AT (2008) Phytochemicals as protectors against ultraviolet radiation: versatility of effects and mechanisms. Planta Med 74:1548–1559
Dinkova-Kostova AT, Jenkins SN, Fahey JW, Ye L, Wehage SL, Liby KT, Stephenson KK, Wade KL, Talalay P (2006) Protection against UV-light-induced skin carcinogenesis in SKH-1 high-risk mice by sulforaphane-containing broccoli sprout extracts. Cancer Lett 240:243–252
Dorr RT, Ertl G, Levine N, Brooks C, Bangert JL, Powell MB, Humphrey S, Alberts DS (2004) Effects of a superpotent melanotropic peptide in combination with solar UV radiation on tanning of the skin in human volunteers. Arch Dermatol 140:827–835
Downs CA, Kramarsky-Winter E, Segal R, Fauth J, Knutson S, Bronstein O, Ciner FR, Jeger R, Lichtenfeld Y, Woodley CM, Pennington P, Cadenas K, Kushmaro A, Loya Y (2016) Toxicopathological effects of the sunscreen UV filter, oxybenzone (benzophenone-3), on coral planulae and cultured primary cells and its environmental contamination in Hawaii and the U.S. Virgin islands. Arch Environ Contam Toxicol 70:265–288
Forestier S (2008) Rationale for sunscreen development. J Am Acad Dermatol 58:S133–S138
Fourtanier A, Moyal D, Seite S (2012) UVA filters in sun-protection products: regulatory and biological aspects. Photochem Photobiol Sci 11:81–89
Gallagher RP, Rivers JK, Lee TK, Bajdik CD, McLean DI, Coldman AJ (2000) Broad-spectrum sunscreen use and the development of new nevi in white children: a randomized controlled trial. JAMA 283:2955–2960
Gao D, Luo Y, Guevara D, Wang Y, Rui M, Goldwyn B, Lu Y, Smith EC, Lebwohl M, Wei H (2005) Benzo[a]pyrene and its metabolites combined with ultraviolet A synergistically induce 8-hydroxy-2′-deoxyguanosine via reactive oxygen species. Free Radic Biol Med 39:1177–1183
Gasparro FP (2000) Sunscreens, skin photobiology, and skin cancer: the need for UVA protection and evaluation of efficacy. Environ Health Perspect 108(Suppl 1):71–78
Gensler HL, Timmermann BN, Valcic S, Wachter GA, Dorr R, Dvorakova K, Alberts DS (1996) Prevention of photocarcinogenesis by topical administration of pure epigallocatechin gallate isolated from green tea. Nutr Cancer 26:325–335
Ghiasvand R, Weiderpass E, Green AC, Lund E, Veierod MB (2016) Sunscreen use and subsequent melanoma risk: a population-based cohort study. J Clin Oncol 34:3976–3983
Giovannucci E (2005) The epidemiology of vitamin D and cancer incidence and mortality: a review (United States). Cancer Causes Control 16:83–95
Goldenhersh MA, Koslowsky M (2011) Increased melanoma after regular sunscreen use? J Clin Oncol 29:e557–e558; author reply e859
Gonzaga ER (2009) Role of UV light in photodamage, skin aging, and skin cancer: importance of photoprotection. Am J Clin Dermatol 10(Suppl 1):19–24
Gonzalez H, Farbrot A, Larko O, Wennberg AM (2006) Percutaneous absorption of the sunscreen benzophenone-3 after repeated whole-body applications, with and without ultraviolet irradiation. Br J Dermatol 154:337–340
Gonzalez S, Gilaberte Y, Philips N (2010) Mechanistic insights in the use of a Polypodium leucotomos extract as an oral and topical photoprotective agent. Photochem Photobiol Sci 9:559–563

Gordon-Thomson C, Gupta R, Tongkao-On W, Ryan A, Halliday GM, Mason RS (2012) 1alpha,25 Dihydroxyvitamin D(3) enhances cellular defences against UV-induced oxidative and other forms of DNA damage in skin. Photochem Photobiol Sci 11:1837–1847

Green A, Williams G, Neale R, Hart V, Leslie D, Parsons P, Marks GC, Gaffney P, Battistutta D, Frost C, Lang C, Russell A (1999) Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. Lancet 354:723–729

Green AC, Williams GM, Logan V, Strutton GM (2011) Reduced melanoma after regular sunscreen use: randomized trial follow-up. J Clin Oncol 29:257–263

Hanson KM, Gratton E, Bardeen CJ (2006) Sunscreen enhancement of UV-induced reactive oxygen species in the skin. Free Radic Biol Med 41:1205–1212

Hawkins KE, Joy S, Delhove JM, Kotiadis VN, Fernandez E, Fitzpatrick LM, Whiteford JR, King PJ, Bolanos JP, Duchen MR, Waddington SN, McKay TR (2016) NRF2 orchestrates the metabolic shift during induced pluripotent stem cell reprogramming. Cell Rep 14:1883–1891

Hayes JD, McMahon M, Chowdhry S, Dinkova-Kostova AT (2010) Cancer chemoprevention mechanisms mediated through the Keap1-Nrf2 pathway. Antioxid Redox Signal 13:1713–1748

Haywood R, Wardman P, Sanders R, Linge C (2003) Sunscreens inadequately protect against ultraviolet-A-induced free radicals in skin: implications for skin aging and melanoma? J Invest Dermatol 121:862–868

Haywood R, Volkov A, Andrady C, Sayer R (2012) Measuring sunscreen protection against solar-simulated radiation-induced structural radical damage to skin using ESR/spin trapping: development of an ex vivo test method. Free Radic Res 46:265–275

Heinrich U, Neukam K, Tronnier H, Sies H, Stahl W (2006) Long-term ingestion of high flavanol cocoa provides photoprotection against UV-induced erythema and improves skin condition in women. J Nutr 136:1565–1569

Hirota A, Kawachi Y, Yamamoto M, Koga T, Hamada K, Otsuka F (2011) Acceleration of UVB-induced photoageing in nrf2 gene-deficient mice. Exp Dermatol 20:664–668

Holmstrom KM, Kostov RV, Dinkova-Kostova AT (2016) The multifaceted role of Nrf2 in mitochondrial function. Curr Opin Toxicol 1:80–91

Hughes MC, Williams GM, Baker P, Green AC (2013) Sunscreen and prevention of skin aging: a randomized trial. Ann Intern Med 158:781–790

Iannacone MR, Hughes MC, Green AC (2014) Effects of sunscreen on skin cancer and photoaging. Photodermatol Photoimmunol Photomed 30:55–61

Jaeger A, Weiss DG, Jonas L, Kriehuber R (2012) Oxidative stress-induced cytotoxic and genotoxic effects of nano-sized titanium dioxide particles in human HaCaT keratinocytes. Toxicology 296:27–36

Janda J, Burkett NB, Blohm-Mangone K, Huang V, Curiel-Lewandrowski C, Alberts DS, Petricoin EF 3rd, Calvert VS, Einspahr J, Dong Z, Bode AM, Wondrak GT, Dickinson SE (2016) Resatorvid-based pharmacological antagonism of cutaneous TLR4 blocks UV-induced NF-kappaB and AP-1 signaling in keratinocytes and mouse skin. Photochem Photobiol 92:816–825

Justiniano R, Perer J, Hua A, Fazel M, Krajisnik A, Cabello CM, Wondrak GT (2017a) A topical zinc ionophore blocks tumorigenic progression in UV-exposed SKH-1 high-risk mouse skin. Photochem Photobiol 93:1472–1482

Justiniano R, Williams JD, Perer J, Hua A, Lesson J, Park SL, Wondrak GT (2017b) The B6-vitamer pyridoxal is a sensitizer of UVA-induced genotoxic stress in human primary keratinocytes and reconstructed epidermis. Photochem Photobiol 93:990–998

Kalra S, Knatko EV, Zhang Y, Honda T, Yamamoto M, Dinkova-Kostova AT (2012) Highly potent activation of Nrf2 by topical tricyclic bis(cyano enone): implications for protection against UV radiation during thiopurine therapy. Cancer Prev Res (Phila) 5:973–981

Kawachi Y, Xu X, Taguchi S, Sakurai H, Nakamura Y, Ishii Y, Fujisawa Y, Furuta J, Takahashi T, Itoh K, Yamamoto M, Yamazaki F, Otsuka F (2008) Attenuation of UVB-induced sunburn reaction and oxidative DNA damage with no alterations in UVB-induced skin carcinogenesis in Nrf2 gene-deficient mice. J Invest Dermatol 128:1773–1779

Kensler TW, Wakabayashi N (2010) Nrf2: friend or foe for chemoprevention? Carcinogenesis 31:90–99

Knatko EV, Ibbotson SH, Zhang Y, Higgins M, Fahey JW, Talalay P, Dawa R, Ferguson J, Huang JT, Clarke R, Zheng S, Saito A, Kalra S, Benedict AL, Honda T, Proby CM, Dinkova-Kostova AT (2015) Nrf2 activation protects against solar-simulated ultraviolet radiation in mice and humans. Cancer Prev Res (Phila) 8:475–486

Knatko EV, Higgins M, Fahey JW, Dinkova-Kostova AT (2016) Loss of Nrf2 abrogates the protective effect of Keap1 downregulation in a preclinical model of cutaneous squamous cell carcinoma. Sci Rep 6:25804

Kolbe L (2012) How much sun protection is needed?: Are we on the way to full-spectrum protection? J Invest Dermatol 132:1756–1757

Krause M, Klit A, Blomberg Jensen M, Soeborg T, Frederiksen H, Schlumpf M, Lichtensteiger W, Skakkebaek NE, Drzewiecki KT (2012) Sunscreens: are they beneficial for health? An overview of endocrine disrupting properties of UV-filters. Int J Androl 35:424–436

Kreuter A, Lehmann P (2014) Relevant new insights into the effects of photoprotection in cutaneous lupus erythematosus. Exp Dermatol 23:712–713

Kullavanijaya P, Lim HW (2005) Photoprotection. J Am Acad Dermatol 52:937–958; quiz 959–962

Kundu JK, Surh YJ (2010) Nrf2-Keap1 signaling as a potential target for chemoprevention of inflammation-associated carcinogenesis. Pharm Res 27:999–1013

Kvam E, Tyrrell RM (1997) Induction of oxidative DNA base damage in human skin cells by UV and near visible radiation. Carcinogenesis 18:2379–2384

Langendonk JG, Balwani M, Anderson KE, Bonkovsky HL, Anstey AV, Bissell DM, Bloomer J, Edwards C, Neumann NJ, Parker C, Phillips JD, Lim HW, Hamzavi I, Deybach JC, Kauppinen R, Rhodes LE, Frank J, Murphy GM, Karstens FPJ, Sijbrands EJG, de Rooij FWM, Lebwohl M, Naik H, Goding CR, Wilson JHP, Desnick RJ (2015) Afamelanotide for erythropoietic protoporphyria. N Engl J Med 373:48–59

Lautenschlager S, Wulf HC, Pittelkow MR (2007) Photoprotection. Lancet 370:528–537

Lawrence KP, Long PF, Young AR (2017a) Mycosporine-like amino acids for skin photoprotection. Curr Med Chem. https://doi.org/10.2174/0929867324666170529124237

Lawrence KP, Gacesa R, Long PF, Young AR (2017b) Molecular photoprotection of human keratinocytes in vitro by the naturally occurring mycosporine-like amino acid (MAA) palythine. Br J Dermatol. https://doi.org/10.1111/bjd.16125

Lee TK, Rivers JK, Gallagher RP (2005) Site-specific protective effect of broad-spectrum sunscreen on nevus development among white schoolchildren in a randomized trial. J Am Acad Dermatol 52:786–792

Liebel F, Kaur S, Ruvolo E, Kollias N, Southall MD (2012) Irradiation of skin with visible light induces reactive oxygen species and matrix-degrading enzymes. J Invest Dermatol 132:1901–1907

Mahmoud BH, Hexsel CL, Hamzavi IH, Lim HW (2008) Effects of visible light on the skin. Photochem Photobiol 84:450–462

Maier H, Schauberger G, Brunnhofer K, Honigsmann H (2001) Change of ultraviolet absorbance of sunscreens by exposure to solar-simulated radiation. J Invest Dermatol 117:256–262

Makarova, A., Wang, G., Dolorito, J. A., Kc, S., Libove, E., and Epstein, E. H., Jr. (2017) Vitamin D3 produced by skin exposure to UVR inhibits murine basal cell carcinoma carcinogenesis. J Invest Dermatol 137, 2613-2619

Mancuso JB, Maruthi R, Wang SQ, Lim HW (2017) Sunscreens: an update. Am J Clin Dermatol 18:643–650

Marionnet C, Nouveau S, Hourblin V, Pillai K, Manco M, Bastien P, Tran C, Tricaud C, de Lacharriere O, Bernerd F (2017) UVA1-induced skin darkening is associated with molecular changes even in highly pigmented skin individuals. J Invest Dermatol 137:1184–1187

Marrot L (2017) Pollution and sun exposure: a deleterious synergy. Mechanisms and opportunities for skin protection. Curr Med Chem. https://doi.org/10.2174/0929867324666170918123907

Marrot L, Meunier JR (2008) Skin DNA photodamage and its biological consequences. J Am Acad Dermatol 58:S139–S148
McSweeney PC (2016) The safety of nanoparticles in sunscreens: an update for general practice. Aust Fam Physician 45:397–399
Middelkamp-Hup MA, Pathak MA, Parrado C, Goukassian D, Rius-Diaz F, Mihm MC, Fitzpatrick TB, Gonzalez S (2004) Oral Polypodium leucotomos extract decreases ultraviolet-induced damage of human skin. J Am Acad Dermatol 51:910–918
Minocha R, Damian DL, Halliday GM (2017) Melanoma and nonmelanoma skin cancer chemoprevention: a role for nicotinamide? Photodermatol Photoimmunol Photomed. https://doi.org/10.1111/phpp.12328
Monteiro-Riviere NA, Wiench K, Landsiedel R, Schulte S, Inman AO, Riviere JE (2011) Safety evaluation of sunscreen formulations containing titanium dioxide and zinc oxide nanoparticles in UVB sunburned skin: an in vitro and in vivo study. Toxicol Sci 123:264–280
Morrison GC, Beko G, Weschler CJ, Schripp T, Salthammer T, Hill J, Andersson AM, Toftum J, Clausen G, Frederiksen H (2017) Dermal uptake of benzophenone-3 from clothing. Environ Sci Technol 51:11371–11379
Moseley H, Cameron H, MacLeod T, Clark C, Dawe R, Ferguson J (2001) New sunscreens confer improved protection for photosensitive patients in the blue light region. Br J Dermatol 145:789–794
Moyal D (2004) Prevention of ultraviolet-induced skin pigmentation. Photodermatol Photoimmunol Photomed 20:243–247
Nakagami Y, Masuda K (2016) A novel Nrf2 activator from microbial transformation inhibits radiation-induced dermatitis in mice. J Radiat Res 57:567–571
Nakashima Y, Ohta S, Wolf AM (2017) Blue light-induced oxidative stress in live skin. Free Radic Biol Med 108:300–310
Nash JF, Tanner PR (2014) Relevance of UV filter/sunscreen product photostability to human safety. Photodermatol Photoimmunol Photomed 30:88–95
Naylor MF, Boyd A, Smith DW, Cameron GS, Hubbard D, Neldner KH (1995) High sun protection factor sunscreens in the suppression of actinic neoplasia. Arch Dermatol 131:170–175
Newman MD, Stotland M, Ellis JI (2009) The safety of nanosized particles in titanium dioxide- and zinc oxide-based sunscreens. J Am Acad Dermatol 61:685–692
Nichols JA, Katiyar SK (2010) Skin photoprotection by natural polyphenols: anti-inflammatory, antioxidant and DNA repair mechanisms. Arch Dermatol Res 302:71–83
Olsen CM, Wilson LF, Green AC, Biswas N, Loyalka J, Whiteman DC (2017a) How many melanomas might be prevented if more people applied sunscreen regularly? Br J Dermatol
Olsen CM, Wilson LF, Green AC, Biswas N, Loyalka J, Whiteman DC (2017b) Prevention of DNA damage in human skin by topical sunscreens. Photodermatol Photoimmunol Photomed 33:135–142
Osburn WO, Kensler TW (2008) Nrf2 signaling: an adaptive response pathway for protection against environmental toxic insults. Mutat Res 659:31–39
Osmond-McLeod MJ, Oytam Y, Rowe A, Sobhanmanesh F, Greenoak G, Kirby J, McInnes EF, McCall MJ (2016) Long-term exposure to commercially available sunscreens containing nanoparticles of TiO2 and ZnO revealed no biological impact in a hairless mouse model. Part Fibre Toxicol 13:44
Osterwalder U, Herzog B (2010) The long way towards the ideal sunscreen—where we stand and what still needs to be done. Photochem Photobiol Sci 9:470–481
Parrado C, Mascaraque M, Gilaberte Y, Juarranz A, Gonzalez S (2016) Fernblock (polypodium leucotomos extract): molecular mechanisms and pleiotropic effects in light-related skin conditions, photoaging and skin cancers, a review. Int J Mol Sci 17(7)
Premi S, Wallisch S, Mano CM, Weiner AB, Bacchiocchi A, Wakamatsu K, Bechara EJ, Halaban R, Douki T, Brash DE (2015) Photochemistry. Chemiexcitation of melanin derivatives induces DNA photoproducts long after UV exposure. Science 347:842–847
Reichrath J, Nurnberg B (2009) Cutaneous vitamin D synthesis versus skin cancer development: the Janus faces of solar UV-radiation. Dermatoendocrinology 1:253–261

Reisman, S. A., Goldsberry, A. R., Lee, C. Y., O'Grady, M. L., Proksch, J. W., Ward, K. W., and Meyer, C. J. (2015) Topical application of RTA 408 lotion activates Nrf2 in human skin and is well-tolerated by healthy human volunteers. BMC Dermatol 15, 10

Rensburg JJV, Dbeibo L, Spinol SM (2016) The cutaneous microbiota as a determinant of skin barrier function: molecular interactions and therapeutic opportunities. In: Wondrak GT (ed) Skin stress response pathways: environmental factors and molecular opportunities. Springer Nature, pp 379–401

Rojo de la Vega M, Krajisnik A, Zhang DD, Wondrak GT (2017) Targeting NRF2 for improved skin barrier function and photoprotection: focus on the achiote-derived apocarotenoid bixin. Nutrients 9:1371

Rojo de la Vega, M., Zhang, D. D., Wondrak, G. T. (2018) Topical bixin confers NRF2-dependent protection against photodamage and hair graying in mouse skin. Front Pharmacol 9, 287

Ruppert L, Koster B, Siegert AM, Cop C, Boyers L, Karimkhani C, Winston H, Mounessa J, Dellavalle RP, Reinau D, Diepgen T, Surber C (2017) YouTube as a source of health information: analysis of sun protection and skin cancer prevention related issues. Dermatol Online J 23

Saw CL, Huang MT, Liu Y, Khor TO, Conney AH, Kong AN (2011) Impact of Nrf2 on UVB-induced skin inflammation/photoprotection and photoprotective effect of sulforaphane. Mol Carcinog 50:479–486

Schafer M, Werner S (2015) Nrf2—a regulator of keratinocyte redox signaling. Free Radic Biol Med 88:243–252

Schafer M, Farwanah H, Willrodt AH, Huebner AJ, Sandhoff K, Roop D, Hohl D, Bloch W, Werner S (2012) Nrf2 links epidermal barrier function with antioxidant defense. EMBO Mol Med 4:364–379

Scharffetter-Kochanek K, Wlaschek M, Brenneisen P, Schauen M, Blaudschun R, Wenk J (1997) UV-induced reactive oxygen species in photocarcinogenesis and photoaging. Biol Chem 378:1247–1257

Schneider SL, Lim HW (2018) Review of environmental effects of oxybenzone and other sunscreen active ingredients. J Am Acad Dermatol Dermatol 18:32189–32193

Schroeder P, Calles C, Benesova T, Macaluso F, Krutmann J (2010) Photoprotection beyond ultraviolet radiation—effective sun protection has to include protection against infrared: a radiation-induced skin damage. Skin Pharmacol Physiol 23:15–17

Seite S, Moyal D, Richard S, de Rigal J, Leveque JL, Hourseau C, Fourtanier A (1998) Mexoryl SX: a broad absorption UVA filter protects human skin from the effects of repeated suberythemal doses of UVA. J Photochem Photobiol B 44:69–76

Serpone N, Salinaro A, Emeline AV, Horikoshi S, Hidaka H, Zhao J (2002) An in vitro systematic spectroscopic examination of the photostabilities of a random set of commercial sunscreen lotions and their chemical UVB/UVA active agents. Photochem Photobiol Sci 1:970–981

Sies H, Stahl W (2004) Nutritional protection against skin damage from sunlight. Annu Rev Nutr 24:173–200

Singh RP, Agarwal R (2005) Mechanisms and preclinical efficacy of silibinin in preventing skin cancer. Eur J Cancer 41:1969–1979

Sklar LR, Almutawa F, Lim HW, Hamzavi I (2012) Effects of ultraviolet radiation, visible light, and infrared radiation on erythema and pigmentation: a review. Photochem Photobiol Sci

Smijs TG, Pavel S (2011) Titanium dioxide and zinc oxide nanoparticles in sunscreens: focus on their safety and effectiveness. Nanotechnol Sci Appl 4:95–112

Soeur J, Belaidi JP, Chollet C, Denat L, Dimitrov A, Jones C, Perez P, Zanini M, Zobiri O, Mezzache S, Erdmann D, Lereaux G, Eilstein J, Marrot L (2017) Photo-pollution stress in skin: traces of pollutants (PAH and particulate matter) impair redox homeostasis in keratinocytes exposed to UVA1. J Dermatol Sci 86:162–169

Sohn M, Heche A, Herzog B, Imanidis G (2014) Film thickness frequency distribution of different vehicles determines sunscreen efficacy. J Biomed Opt 19:115,005

Sohn M, Herzog B, Osterwalder U, Imanidis G (2016) Calculation of the sun protection factor of sunscreens with different vehicles using measured film thickness distribution—comparison with the SPF in vitro. J Photochem Photobiol B 159:74–81

Stanton WR, Janda M, Baade PD, Anderson P (2004) Primary prevention of skin cancer: a review of sun protection in Australia and internationally. Health Promot Int 19:369–378

Surber C, Pittelkow M, Lautenschlager S (2012) Photoprotection in transplant recipients. Curr Probl Dermatol 43:171–196

Surh YJ, Kundu JK, Na HK, Lee JS (2005) Redox-sensitive transcription factors as prime targets for chemoprevention with anti-inflammatory and antioxidative phytochemicals. J Nutr 135:2993S–3001S

Svobodova A, Vostalova J (2010) Solar radiation induced skin damage: review of protective and preventive options. Int J Radiat Biol 86:999–1030

Talalay P, Fahey J, Healy Z, Wehage S, Benedict A, Min C, Dinkova-Kostova AT (2007) Sulforaphane mobilizes cellular defenses that protect skin against damage by UV radiation. Proc Natl Acad Sci U S A 104:17500–17505

Tao S, Justiniano R, Zhang DD, Wondrak GT (2013) The Nrf2-inducers tanshinone I and dihydrotanshinone protect human skin cells and reconstructed human skin against solar simulated UV. Redox Biol 1:532–541

Tao S, Park SL, de la Vega MR, Zhang DD, Wondrak GT (2015) Systemic administration of the apocarotenoid bixin protects skin against solar UV-induced damage through activation of NRF2. Free Radic Biol Med 89:690–700

Tarozzi A, Marchesi A, Hrelia S, Angeloni C, Andrisano V, Fiori J, Cantelli-Forti G, Hrelia P (2005) Protective effects of cyanidin-3-O-beta-glucopyranoside against UVA-induced oxidative stress in human keratinocytes. Photochem Photobiol 81:623–629

Tarras-Wahlberg N, Stenhagen G, Larko O, Rosen A, Wennberg AM, Wennerstrom O (1999) Changes in ultraviolet absorption of sunscreens after ultraviolet irradiation. J Invest Dermatol 113:547–553

Thompson SC, Jolley D, Marks R (1993) Reduction of solar keratoses by regular sunscreen use. N Engl J Med 329:1147–1151

Tian FF, Zhang FF, Lai XD, Wang LJ, Yang L, Wang X, Singh G, Zhong JL (2011) Nrf2-mediated protection against UVA radiation in human skin keratinocytes. Biosci Trends 5:23–29

Tonolli PN, Chiarelli-Neto O, Santacruz-Perez C, Junqueira HC, Watanabe IS, Ravagnani FG, Martins WK, Baptista MS (2017) Lipofuscin generated by UVA turns keratinocytes photosensitive to visible light. J Invest Dermatol 137:2447–2450

Touitou E, Godin B (2008) Skin nonpenetrating sunscreens for cosmetic and pharmaceutical formulations. Clin Dermatol 26:375–379

Tyrrell RM (1995) Ultraviolet radiation and free radical damage to skin. Biochem Soc Symp 61:47–53

Ulrich C, Jurgensen JS, Degen A, Hackethal M, Ulrich M, Patel MJ, Eberle J, Terhorst D, Sterry W, Stockfleth E (2009) Prevention of non-melanoma skin cancer in organ transplant patients by regular use of a sunscreen: a 24 months, prospective, case-control study. Br J Dermatol 161(Suppl 3):78–84

van der Pols JC, Williams GM, Pandeya N, Logan V, Green AC (2006) Prolonged prevention of squamous cell carcinoma of the skin by regular sunscreen use. Cancer Epidemiol Biomarkers Prev 15:2546–2548

Wakabayashi N, Itoh K, Wakabayashi J, Motohashi H, Noda S, Takahashi S, Imakado S, Kotsuji T, Otsuka F, Roop DR, Harada T, Engel JD, Yamamoto M (2003) Keap1-null mutation leads to postnatal lethality due to constitutive Nrf2 activation. Nat Genet 35:238–245

Wetz F, Routaboul C, Denis A, Rico-Lattes I (2005) A new long-chain UV absorber derived from 4-tert-butyl-4′-methoxydibenzoylmethane: absorbance stability under solar irradiation. J Cosmet Sci 56:135–148

Williams S, Tamburic S, Lally C (2009) Eating chocolate can significantly protect the skin from UV light. J Cosmet Dermatol 8:169–173

Wolf R, Wolf D, Morganti P, Ruocco V (2001) Sunscreens. Clin Dermatol 19:452–459

Wondrak GT (2007) Let the sun shine in: mechanisms and potential for therapeutics in skin photodamage. Curr Opin Investig Drugs 8:390–400

Wondrak GT, Roberts MJ, Jacobson MK, Jacobson EL (2004) 3-hydroxypyridine chromophores are endogenous sensitizers of photooxidative stress in human skin cells. J Biol Chem 279:30009–30020

Wondrak GT, Jacobson MK, Jacobson EL (2005) Identification of quenchers of photoexcited states as novel agents for skin photoprotection. J Pharmacol Exp Ther 312:482–491

Wondrak GT, Jacobson MK, Jacobson EL (2006) Endogenous UVA-photosensitizers: mediators of skin photodamage and novel targets for skin photoprotection. Photochem Photobiol Sci 5:215–237

Wondrak GT, Cabello CM, Villeneuve NF, Zhang S, Ley S, Li Y, Sun Z, Zhang DD (2008) Cinnamoyl-based Nrf2-activators targeting human skin cell photo-oxidative stress. Free Radic Biol Med 45:385–395

Xu J, Sagawa Y, Futakuchi M, Fukamachi K, Alexander DB, Furukawa F, Ikarashi Y, Uchino T, Nishimura T, Morita A, Suzui M, Tsuda H (2011) Lack of promoting effect of titanium dioxide particles on ultraviolet B-initiated skin carcinogenesis in rats. Food Chem Toxicol 49:1298–1302

Yang J, Wiley CJ, Godwin DA, Felton LA (2008) Influence of hydroxypropyl-beta-cyclodextrin on transdermal penetration and photostability of avobenzone. Eur J Pharm Biopharm 69:605–612

Young AR, Boles J, Herzog B, Osterwalder U, Baschong W (2010) A sunscreen's labeled sun protection factor may overestimate protection at temperate latitudes: a human in vivo study. J Invest Dermatol 130:2457–2462

Zastrow L, Lademann J (2016) Light—instead of UV protection: new requirements for skin cancer prevention. Anticancer Res 36:1389–1393

Zastrow L, Ferrero L, Herrling T, Groth N (2004) Integrated sun protection factor: a new sun protection factor based on free radicals generated by UV irradiation. Skin Pharmacol Physiol 17:219–231

Zastrow L, Groth N, Klein F, Kockott D, Lademann J, Renneberg R, Ferrero L (2009) The missing link—light-induced (280-1,600 nm) free radical formation in human skin. Skin Pharmacol Physiol 22:31–44

Zastrow L, Meinke MC, Albrecht S, Patzelt A, Lademann J (2017) From UV protection to protection in the whole spectral range of the solar radiation: new aspects of sunscreen development. Adv Exp Med Biol 996:311–318

Zhang DD (2006) Mechanistic studies of the Nrf2-Keap1 signaling pathway. Drug Metab Rev 38:1–21

Zhang DD, Lo SC, Cross JV, Templeton DJ, Hannink M (2004) Keap1 is a redox-regulated substrate adaptor protein for a Cul3-dependent ubiquitin ligase complex. Mol Cell Biol **24**:10941–10953