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SUNSCREENS AND ANTIOXIDANTS AS PHOTO-PROTECTIVE MEASURES: AN UPDATE

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Abstract
There are many photo-protective measures adopted for protection from the solar radiation especially the UV radiation spectrum, sunscreens being the main agents. Besides the traditional approach of topical use of sunscreens, both chemical and physical, a new approach has emerged to use systemic agents in the form of vitamins and minerals. In this review, we are describing the major aspects related to sunscreens and anti-oxidants as photo-protective measures.

Key words: photo-protective measures; sunscreens; antioxidants

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Introduction

Ultraviolet (UV) radiation spectrum is the major component of solar radiation, with multitude of effects on the skin. In order to provide protection from the deleterious effects of solar radiations, especially the UV component, various measures have been adopted since time immemorial. Besides the physical protective measures like protective clothing, shields and others, various medicinal preparations which provide a barrier between the sun and skin have been in use in the form of sunscreens. Of late, a new trend has emerged of using antioxidant preparations which increase the antioxidant defence system to cope up with the oxidative damage induced by solar radiations. We hereby present a comprehensive and precise review of sunscreens and anti-oxidants as photo-protective measures, keeping in mind the newer trends that have emerged over the years.

UV radiation spectrum

The most important biologically active functional components of UV radiation spectrum are UV A (~320-400 nm) and UV B (~290-320 nm) components.

UVB is responsible for more severe damage to skin, with acute erythematogenic effect and long term carcinogenic potential, inducing photo-aging and mutagenic damage to nucleic acids.

UVA,less absorbed by biological targets in the skin, penetrates deeper than UVB and is less erythematogenic. It promotes reactive oxygen species (ROS) accumulation and induces direct cell damage, carcinogenesis and contributes to photo-aging and many photo-dermatoses, including polymorphous light eruption [1].

Sunscreens

Most common types of sunscreens presently in use are the topical preparations, designated as physical and chemical sunscreens. Various systemic agents in the form of antioxidants, vitamins and minerals, designated as systemic sunscreens, have emerged as new photo-protective measure. The main goals of sunscreens are to protect against UVB radiation and long-wavelength UVA radiation, scavenge ROS, activate cellular repair systems, including DNA repair [2,3].

Topical sunscreens

Topical sunscreens are available as ointments, lotions, creams or sprays. In order to ensure optimal patient compliance, an ideal sunscreen would be: combination of physical and chemical agents, broad spectrum, cosmetically elegant, substantive, non-irritant, hypoallergenic, non-comedogenic and economical.

The activity of a sunscreen is judged based on sun protection factor (SPF), which measures their capacity to block UV radiation. SPF is defined as a ratio of minimal erythema dose (MED) with sunscreen application to the MED without sunscreen application and is measured using solar simulated radiation and a defined sunscreen application density (2 mg/cm-2). Higher SPF denotes higher efficacy.

High SPF sunscreens almost always contain a physical filter and at least two organic filters,one with optimal screening for UVB wavelengths and the other for UVA photons.

Due to their ease of use, topical sunscreens are the most common photo-protective measure in use [4-6].

Topical sunscreens include the following categories of preparations:

i) Those which reflect or scatter UV photons (physical sunscreens),
ii) Those which absorb them, preventing their effect on the cells of the skin (chemical sunscreens),
iii) Preparations with antioxidant properties

Inorganic (physical) sunscreens

Inorganic sunscreens are formulations containing opaque particulate particles (0.1-1mm diameter), which act by scattering, reflecting or absorbing solar radiation in the UV andvisible radiation spectrum. The factors which affect the effectiveness of inorganic sunscreen are their reflective index, particle size, dispersion in base and film thickness. Their opaque nature and `whitening effect` is an inherent disadvantage, which may be minimized by the use of micronized or ultrafine particles. Various types of inorganic sunscreen agents available include:

a) Zinc oxide (ZnO)
b) Titanium dioxide (TiO).
These are by far the two most commonphysical blockers. Micro-fine ZnO is a betterblocker than TiO7.
c) Others - iron oxide, red veterinary petrolatum, kaolin, calamine, ichthammol, talc,

Organic Sunscreens

Organic Sunscreens are active ingredients which absorb specific wavelengths of UV radiation, not allowing them to reach the viable cells of epidermis. There are more than 21 US FDA approved chemicals used as organic sunscreens. Most common ones are shown in table I.

UVB Absorbers	UVA Absorbers	Newer generation broad spectrum (UVA + UVB) filters
1. PABA derivatives a) Padimate O b) PABA 2. Cinnamates a) Octinoxate b) Cinoxate 3. Salicylates a) Octisalate b) Homosalate c) Trolamine d) Salicylate 4. Others a) Octocrylene b) Ensulizole	1. Benzophenones a) Oxybenzone b) Sulisobenzone c) Dioxybenzone 2. Dibenzoyl methanes a) Avobenzone or Parsol 1789 3. Anthranilates a) Meradimate	1. Ecamsule (Mexoryl SX) 2. Silatriazole (Mexoryl XL) 3. Bemotrizinol (Tinosorb S) 4. Bisoctrizole (Tinosorb M)

Table I. Most common organic sunscreen ingredients

Antioxidants

Antioxidants are commonly added in commercial sunscreen preparationsin order to reduce the photo-oxidative damage that results from UV-induced ROS production, providing a sort of non-sunscreen photo-protection and supplement the photo-protective effects of sunscreens [8]. These include several well characterized vitamins including vitamins C, E and β-carotene [9]. These substances in general help by their antioxidant, anti-inflammatory, anti-carcinogenic effects. Common compounds and effects specific to each are mentioned below.
* Hydroxicinnamic acids such ascaffeic or ferulic acids prevent UVB-induced erythema in vivo and in vitro, and decrease UV-induced oxidative damage in skin cells and lymphocytes [10-13].
* Polyphenolics such as flavonoids and phenolic acids, green tea polyphenols, resveratrol, astaxanthin have been found useful [14].
* Anthocyanins and tannins, present in several fruits such as grapes, pears act by inhibiting UVB-dependent activation of NF-kB, MAP kinase and COX-2 pathways downstream of the signalling kinases MKK4, MEK1, and Raf-1 [15,16].
* Pycnogenol, an extract of French maritime pine (Pinuspinaster Ait), prevents UV induced erythema as well as long-term effects, such as immune-suppression and tumour formation [17,18]. It also possesses regenerative skin properties, and prevents UVB-induced photo-aging [19,20].
* Fernblock, an extract obtained from the fern *Polypodium leucotomos*, inhibits UVB and PUVA therapy-induced erythema in vivo [21]. It is a potent antioxidant and has shown immune-modulating capability and inhibition of pro-inflammatory cytokines, such as TNF-α or IL-6 [22]. PL also inhibits the depletion of langerhan cells induced by irradiation with UV light and PUVA therapy [22-24] and reduces chronic elastosis and matrix metalloprotease expression [25,26].
* Dihydroxy-acetone: Photo-protective agent that provides SPF 3-4 and protects against UVA photons [27].
* Caffeine and caffeine sodium benzoate: inhibit UVB-induced apoptosis [28].
* *Polygonum multiflorum* thumb (PM): an extract that possesses antibacterial properties.
* N-(4-pyridoxylmethylene)-L-serine (PYSer): Suppresses ironcatalyzed ROS generation [29].
* Creatine: Topical use of creatine has been shown to decrease UV-induced damage in vitro and in vivo, and postulates its use to fight photo-aging [30].
* Idebenone: Clinical studies have suggested its efficacy in preventing photo-aging [31].
* COX-2 inhibitors: Topicalcelecoxib, a COX-2 inhibitor, has been shown to decrease UVBmediated erythema, inflammation and prostaglandin E2 production [32,33].
* DNA repair enzymes: Constitute an emerging approach to enhance DNA repair after UV exposure such as photolyase [34,35].

* T4 endonuclease: Assayed in patients with xerodermapigmentosum [36,37].
* DNA oligonucleotides: Enhance the cellular response to subsequent UV irradiation,regardless of the existence of previous DNA damage [38].

Systemic sunscreens

Photo-protection by oral/parentral medication is a novel approach in skin care. They complement the topical sunscreen use by preventing photo-aging and photo-carcinogenesis. They increase the basal threshold of systemic and cutaneous antioxidant systems [39]. Various biologically active compounds evaluated include:

Vitamin derivatives: Carotenoids, such as lycopene, which has been suggested to be a very efficient singlet oxygen quencher present in tomatoes, and xanthophylliccarotenoids such as lutein and zeaxanthin, exhibit beneficial photo-protective effect, singly or in combination, along with topical preparations [40,41]. Tocopheroland ascorbatealso exhibit photo-protective effect, especially when used in combination with other compounds such aslycopene, beta-carotene, selenium yeast, proanthocyanidins [42,43]. Oral use of these delays the onset of UVB induced erythema and inhibits the expression of matrixmetalloproteinases, delaying an effect on photo-aging [44].

Dietary animal and plant extracts: Their composition is rather heterogeneous, but most contain dietary flavonoids and phenolics. Some examples include:

* Genistein, which can be used as a dietary complement as well as in topical formulations, decreases UVB induced skin photo-aging and tumour genesis in rodent models, postulating its use for cancer prevention [45].
* High doses of omega-3 polyunsaturated fatty acids from fish oil have been shown to decrease UVB induced erythema and inflammation [46].
* *Polypodium leucotomos* extract (PL) can also be administered orally with very low toxicity, in addition to its topical use as already described.Oral PL scavenges free radicals and reactive oxygen species such as superoxide anion, singlet oxygen, hydroxyl radical and hydrogen peroxide, and prevents lipid per-oxidation [47,48]. Besides the effects already mentioned, PL also prevents oxidative DNA damage (8-hydroxyguanine) and accelerates repair of thymine dimers [24,49]. In addition, it also inhibitstrans-urocanic acid photo-induced isomerization and inactivation, as well as UVA-induced cyclobutane pyrimidine dimer deletions and mitochondrial DNA damage [50,51].
* Green tea poly-phenols (GTPP), e.g. epigallocatechin-3-gallateprevents UV-induced skin tumourgenesis in mice. Several mechanisms underlie this effect, e.g. induction of interleukin 12, which prevents immune-suppression and boosts DNA repair through excision repair mechanisms, inhibition of angiogenic factors, stimulation of T cell-dependent cytotoxicity and tumour cell clearance [52]. Oral GTPPs can also decrease UV-induced expression of skin matrix metalloproteinases, postulating an effect in photo-aging [53].

Indications of sunscreen use

There are innumerable prophylactic and therapeutic indications for sun protection and potential benefits of sunscreens and antioxidants. The major ones are listed in table II [54].

Guidance for usage

Sunscreens protect the skin by absorbing and/or reflecting UVA and UVB rays. The FDA requires that all sunscreens contain a sun protection factor (SPF) label. In order to obtain maximum performance from sunscreen it is important that it is applied correctly and sufficiently with the right thickness. Application thickness has a significant effect on the amount of protection provided by a sunscreen. When not enough sunscreen is applied, the effective SPF of the product will be reduced significantly. This reduction in SPF may potentially lead to sunburn, particularly if the sunscreen used has a low or medium SPF to begin with [55].

An average size adult should apply at least one teaspoon of sunscreen to each arm, leg, frontand back of body, and at least half a teaspoon to the face (including theears and neck). Sunscreen should be applied at least 10-15 minutes before sun exposure to allow the sunscreen time to form a protective film on the skin. Sunscreen should be re-applied every two hours at minimum, even on cloudy days, and after swimming, heavy sweating, and towelling. Re-applying sunscreen doesn't extend the length of time a person is protected from sunburn. It just guarantees that the actual SPF of the product is realized [55]. While using sunscreen sprays, the product should be both sprayed on and rubbed in to ensure uniform coverage [56].

1. Sunburn
2. Freckling, discolouration
3. Photo-aging
4. Skin cancer
5. Phototoxic/ photo-allergic reactions
6. Photosensitivity diseases
   - Polymorphous light eruption (290-365 nm)
   - Solar urticaria (290-515 nm)
   - Chronic actinic dermatitis (290 nm-visible)
   - Persistent light reaction (290-400 nm)
   - Lupus erythematosus (290-330 nm)
   - Xeroderma pigmentosum (290-340 nm)
   - Albinism
7. Photo-aggravated dermatoses
8. Post-inflammatory hyper-pigmentation (post-procedure)

Table II. Main indications of sunscreen use and sun protection

Some issues of concern

The use of sunscreen as photo-protective measure is non controversial. But some concerns exist in a few special situations, as mentioned below.

* *Sunscreen use in infants:* Although not known to be hazardous, the use of sunscreens is not recommended for infants younger than 6 months. Sun protection in children plays a significant role in preventing skin cancer later in life. Research indicates that regular use of sunscreen for the first 18 years of a child's life can reduce the lifetime incidence of skin cancers by more than 70% [55].

* *Contact dermatitis:* The most common cause of contact dermatitis (photoallergy) due to sunscreens is oxybenzone [57].

* *Nano-sized particles:* Nano-sized particles range in size from 1-100 nm. Micro-fine forms of zinc oxide and titanium dioxide have a particle size of 20-50 nm. Nanotechnology makes inorganic sunscreens more cosmetically acceptable (less whitening of skin after application). Studies show that these particles remain on the surface of the skin or in the stratum corneum, and are hence safe for human use [58].

* *Vitamin D production:* UVB radiation is responsible for more than 90% of vitamin D production in the skin. A few minutes exposure of the face, arms, and hands to mid-day summer sunlight two or three times a week is sufficient for vitamin D synthesis [59]. There have been concerns that widespread use of sunscreens, particularly those with high SPF, may lead to a significant decrease in vitamin D production. However, there is evidence that normal usage does not generally result in vitamin D insufficiency though sunscreens can significantly reduce the production of vitamin D under very strictly controlled conditions [60]. In fact, vitamin D and calcium levels have been found to be relatively normal in xeroderma pigmentosum patients, in spite of strict photo-protection [61].

* *Hormonal effects*: Some sunscreens (oxybenzone, avobenzone, octinoxate, padimate O) have been tested for their estrogenic/ anti-androgenic properties in animal studies. However, the endocrine effects of these agents remain controversial, warranting further human studies.

Sunscreen related indices

Various indices have been formulated by in vitro and in vivo methods to assess the efficacy of sunscreens with respect to specific components of the UV spectrum [1,57,58,62-64]. These are as follows:

i) Sunburn protection factor (SPF)

SPF= MED of photo-protected skin with sunscreen/ MED of unprotected skin without sunscreen.

Grading of sunscreens according to SPF:
Low: SPF 2 – 15; Medium: SPF 15 – 30; High: SPF 30 – 50; Highest: SPF >50

It is noteworthy that a sunscreen with an SPF 15 blocks about 93% of UVB radiation, while one with SPF 30 blocks about 97% of UVB radiation. This small difference of 4% in protection may make a big difference between an aesthetically pleasing sunscreen and an undesirable one, as products with higher SPF generally tend to be uncomfortable and cosmetically unpleasant due to the higher concentration of the active ingredients [65].

ii) Japanese standard (persistent pigment darkening; in vivo method)

UVA dose that induces persistent pigment darkening 2-24 hours after exposure in sunscreen protected skin/ UVA dose that induces persistent pigment darkening 2-24 hours after exposure in sunscreen unprotected skin.

iii) Australian / New Zealand standard (in vitro method)

8-µm layer of the product should not transmit more than 10% of radiation of 320 to 360 nm
OR
20-µm layer of the product should not transmit more than 1% of radiation of 320 to 360 nm

iv) European union guidelines

UVA protection factor (persistent pigment darkening method) = 1/3 of SPF
AND
Critical wavelength = 370nm

v) Boots star rating system (used in the United Kingdom)

In vitro measurement of the ratio of a product's UVA (320-400 nm) absorbance over its UVB (290-320 nm) absorbance is used to calculate its Boots star rating, shown in Table III. Products with better UVA absorbance have a higher Boots star rating.

New Sunscreen Technologies

Sun spheres

Sun-spheres are styrene/acrylate copolymers that do not absorb UV irradiation but enhance the effectiveness of the active sunscreen ingredients. The Sun-sphere polymer beads are filled with water, which migrates out of the particle, leaving behind tiny air-filled spheres, which have a lower refractive index (1.0) than the dried sunscreen film (1.4-1.5). As a result, scattering of UV radiation occurs, increasing the probability of contact with the active UV filters in the sunscreen. Sun-spheres are also available in a powder form, and can boost SPF by 50 -70% making it possible to reduce the concentration of active ingredients [66].

Microencapsulation

Active sunscreen ingredients are entrapped within a silica shell, as a result of which, allergic or irritant reactions to the active ingredient can be minimized, and incompatible sunscreen ingredients can be safely combined, without loss of efficacy [66].

Ratio of UVA:UVB absorbance		Boots star rating
Before irradiation	After irradiation	
< 0.6	< 0.56	No star
> 0.6	> 0.57	3
> 0.8	> 0.76	4
> 0.9	> 0.86	5

Table III. Boots star rating for sunscreens

Conclusion

Sunscreens are an important prophylactic and therapeutic armamentarium for dermatologists and also used as over the counter products as photo-protective measures. Sunscreens are constantly evolving and a dermatologist should be well versed with various aspects of these.

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