

Sunscreen



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Systemic photoprotection in 2021

- Systemic photoprotection aims to reduce the damaging effects of ultraviolet (UV) radiation (UVR), visible light and infrared radiation on photoageing, photodermatoses, pigmentary disorders and skin cancer caused by reactive oxygen species and DNA damage.
- Systemic photoprotective agents appear to work through their anti-inflammatory and antioxidant capacities.
- Currently, the gold standard of photoprotection includes photoavoidance and topical sunscreens.



SUNSCREEN material CLASSIFICATIONS

- **Physical (inorganic, mineral)**
- **Chemical (organic, synthetic)**
- **Herbal extracts**



Physical

- Opaque formulations containing:
 - titanium dioxide
 - talc, kaolin ,Bentonit
 - zn oxide ,Mg oxide
 - Ca carbonate, Ba sulphate
 - ferric chloride
 - red petrolatum (not about Vaseline and paraffin)
- Mechanism: scatters or reflects UV (A,B) radiation due to large particle size

The forms of nano-TiO₂ used in sunscreens are mostly the rutile crystal structure or a rutile/anatase combination, rarely the anatase structure only.



Chemical

| Sunscreen | Range of protection (nm) | Maximal effect of protection (nm) |
|--|--------------------------|-----------------------------------|
| PABA and PABA esters | | |
| PABA | 260–313 | 283 |
| Padimate O | 290–315 | 311 |
| Padimate A | 290–315 | 309 |
| Glycerol aminobenzoate | 260–313 | 297 |
| Cinnamates | | |
| Octyl methoxycinnamate | 280–310 | 311 |
| Cinoxate | 270–328 | 290 |
| Salicylates | | |
| Homosalicylate | 290–315 | 306 |
| Octyl salicylate | 260–310 | 307 |
| Triethanolamine salicylate | 269–320 | 298 |
| Octocrylene | 287–323 | 303 |
| Etocrylene | 296–383 | 303 |
| Benzophenones | | |
| Oxybenzone | 270–350 | 290–325 |
| Dioxybenzone | 206–380 | 284–327 |
| Sulisobenzone | 250–380 | 286–324 |
| Menthylanthranilate | 200–380 | 336 |
| Dibenzoylmethanes | | |
| Tert-butylmethoxy dibenzoylmethane (Parsol) | 310–400 | 358 |
| 4-isopropylidibenzoyl-methane (Eusolex) | 310–400 | 345 |
| Trometrizole trisiloxane, terephthalylidene dicamphor sulfonic acid (Mexoryl XL) | 300–400 | 328 |



Herbal oils

- carrot seed, soya oil, green tea, Cotton seed oil, sesame oil, Almond oil, Olive oil, Aloe vera, sunflower oils and sandalwood
- The herbal formulation **absorbs into deeper layers** of skin and provides **better action at lesser concentration.**
- **Natural polyphenols have the ability to absorb the UVB radiation and antioxidant.**



Herbal extracts

- their UV absorption profile depends on the **presence and number of aromatic rings and cyclic or conjugated double bonds**, as well as on the stereochemistry and typology of substituents. For instance, **soluble and insoluble polyphenols absorb radiation in the range of 304-350 and 352-385 nm, respectively.**
- Phenolic or hydroxyl benzoic acids and hydroxyl cinnamic acid can be found in corn, coffee, sugar beet and others.
- We highlight ferulic, caffeic and *p*-coumaric acids and their acidic derivatives (e.g. rosmarinic and chlorogenic acids) since they can **absorb in the UVB range.**



- flavonoids, which are polyphenols with two aromatic rings (two chromophores), absorb in the region of 240-285 and 300-550 nm. Thus, their incorporation into sunscreens works as a strategy to achieve broad-spectrum protection.
- The most common flavonoid classes are:
 - flavones (catechin) and flavonols (quercetin) ($\lambda = 280-350$ nm)
 - flavanones diosmetin, anthocyanidins ($\lambda = 280-290$ nm)
 - isoflavones ($\lambda = 236-262$ nm)
 - anthocyanidins ($\lambda = 465-560$ nm)
 - Anthocyanins also have photo protective properties.



- Hesperidin and diosmin (in alkaline medium) show maximum absorbance peaks at 268 and 285 nm.
- Chalcones from *Prunus* spp., *Eucalyptus* spp. and *Juglans* spp. (bark) show a typical peak of flavanones at 280 nm;
- Among carotenoids, the representatives that contribute to UV protection are α -carotene, β -cryptoxanthin and lycopene. Carotenoids (such as α -tocopherol and β -carotene), which have long carbon chains, absorb mainly in visible light, at around 455 nm.
- Green tea extracts are commonly used in cosmetics, since they contain compounds like (-)-epicatechin-3-gallate, (-)-epicatechin, (-)-epigallocatechin, and (-)-epigallocatechin-3-gallate, that could be used as photoprotective actives.
- Resveratrol is a phenolic compound of the stilbene class with potent antioxidant activity. It is widespread in the plant kingdom in about 70 plant species and may be found in *trans* and *cis* forms. *Cis* form cannot be found after grape extraction; on the other hand, *trans* is easily found in nature.



TINTED SUNSCREENS

- Tinted sunscreens are products that combine a colored base coverage with UV filters. The tint pigments that function as visible light filters but not as UV filters.

| Variable | Color | | | |
|------------------|-------------------------|--|--|-----------------------------|
| | Iron oxide red | Iron oxide yellow | Iron oxide black | Pigmentary titanium dioxide |
| Chemical formula | Fe_2O_3 | $\text{FeO}(\text{OH}) \cdot \text{H}_2\text{O}$ | $\text{FeO} \cdot \text{Fe}_2\text{O}_3$ | TiO_2 |
| INCI name | CI 77491* | CI 77492 | CI 77499 | CI 77891 |

INCI, International Nomenclature of Cosmetic Ingredients.

*Color index (CI), a universally accepted nomenclature for pigments and dyes.

- These pigments are listed as inactive ingredients without the requirement to include the percentages by FDA.
- The difference between tinted and untinted sunscreens is the presence of absence of iron oxide/ titanium dioxide pigments. Of these pigments, very few cases of contact dermatitis to iron oxides have been reported.



- **Iron oxides** are pigments produced from ferrous sulfate. Depending on the oxidation state, they may appear yellow, red, or black. Yellow or red pigment appears as yellow or red because of reflection of the corresponding wave lengths within the visible range. Black appearance of a pigment is caused by absorption throughout the visible region, with no photons reflected in this domain.
- **Pigmentary titanium dioxide (titanium dioxide that is not nanosized)** is another pigment that can be used to provide coverage and opacity. It appears white because it reflects all photons in the visible light range.



EFFECTS OF TINTED SUNSCREENS

- Tinted sunscreens that contain iron oxides reduced transmittance of visible light more effectively than untinted sunscreens.
- The effect of particle size on the visible transmittance spectra of yellow, red, and black iron oxides. They compared iron oxide pigments of different particle sizes (200 nm, 1500 nm, 1700 nm, and 3000 nm) and found that yellow, red, and black iron oxides of 200 nm yielded better protection in the blue spectrum of visible light than iron oxides of 1500 to 3000 nm.

Tinted sunscreens have become a rapidly growing sector of sunscreen product development.



SUNSCREEN

- Sunscreen comes in many different types

- Inhalation concerns particularly on children
- Asthma and Allergy

Lotion
Gel
Spray
Cream
Stick

SPF ranges from 0 to 50+



- Using SPF 30+ instead of SPF 15+ does not mean you can safely double your time in the sun.
- Sunscreen remanence refers to its resistance to outside removal by water, sweat, or rubbing.
- A usual recommendation for sunscreen use is one **application 15– 30 min before sun exposure**.
- The product has to be reapplied earlier after activities washing out or rubbing off the sunscreen, that is, after swimming, sweating, or towel drying.
- **Reapply sunscreen every 2 hours if you are swimming or sweating a lot.**
- **Fragrances and moisturizers in sunscreen may cause allergic reaction; experiment with other brands if this is a problem.**



systemic

- **Carotenoids**
- Carotenoids are precursors of vitamin A, and are antioxidant micronutrients found in fruits and vegetables.
- The main carotenoids are b-carotene and lycopene, which are found in carrots and tomatoes.
- Other examples include lutein, zeaxanthin, xanthophylls and astaxanthin.
- They have a role in gene signaling and expression, and are reported to augment the skin's resistance to UV damage



- In a double-blind RCT (n = 65), patients were treated with a lycopene-rich tomato nutrient complex (TNC), lutein or placebo.
- The TNC and lutein inhibited UVA1 and UVA/B-induced upregulation of intercellular adhesion molecule (ICAM)-1 and matrix metalloproteinase (MMP)-1 mRNA, both indicators of oxidative stress and photodamage.
- In a double-blind RCT (n = 60), patients receiving a composite carotene supplement (b-carotene, a-carotene, lutein and zeaxanthin taken three times daily for 12 weeks) showed a significant increase in skin carotenoid levels, UVB-induced MED and UVA-induced minimal pigmentation dose compared with the control group.
- This suggests that daily supplementation with carotenoids protects human skin against UVR-induced erythema and pigmentation.



- A separate double-blind RCT⁵ (n = 60) used a similar supplement (lycopene, b-carotene and *Lactobacillus johnsonii*) for 12 weeks in patients with polymorphic light eruption (PLE).
- After 12 weeks, the supplement significantly reduced the PLE score following one irradiation with UVA1 in the treatment group. At the molecular level, those in the treatment group had reduced expression of ICAM-1 mRNA after irradiation compared with the placebo. This difference was not significant after two UVA1 exposures.
- Lycopene (in capsule form) and tomato paste were compared in a 10-week RCT of 20 subjects. There was a marginally significant MED increase for the capsule compared with the tomato paste, possibly due to the reduced palatability of paste after a prolonged time, possibly accounting for a higher rate of dropouts in this group. In clinical practice, this highlights the importance of selecting the most appropriate method of delivery of supplementation.



- Carrascosa et al. also found that their formulation (astaxanthin, b-carotene, vitamin E, vitamin C, lutein and lycopene) imparted photoprotection against erythema radiation in patients (n = 43) with Fitzpatrick skin types II and III in a double-blind RCT.
- Further evaluation of the effects of this formulation on UVA and infrared radiation is needed, as well as the individual effects of each component in this formulation.
- In addition, the authors did not adhere to the intention-to-treat principle, which would have allowed more rigorous analysis of their findings.



- In a single-blinded RCT (n = 20), 8–55 g tomato paste (containing 16 mg lycopene) consumed daily for 12 weeks had significant defensive properties against UVR erythema, and protection against immediate UVR-induced tissue damage, with inhibition of UVR-induced MMP-1 expression. Processed tomatoes elicited this response more readily than did fresh tomatoes.
- In a separate study, participants who had received tomato paste (16 mg/day lycopene) had a 40% reduction in solar-induced erythema at 10 weeks compared with controls (n = 19; P = 0.02).



- In a 12-week open prospective single-centre trial (n = 30), the efficacy of a food supplement containing vitamins A, C, D3 and E, selenium, lycopene, lutein, green tea, polypodium and grape extracts upon MED was evaluated. Significant improvement was found in MED levels, skin radiance and elasticity
- It is unclear whether these findings translate to direct clinical benefit.
- A large randomized 12-year primary prevention trial appeared to show no benefit of b-carotene supplementation on the development of nonmelanoma skin cancers (NMSC) (n = 22 071).
- Conversely, some groups have reported benefit on symptoms of erythropoietic protoporphyria (EPP) of bcarotene supplementation at doses of 90–180 mg, owing to its antioxidant properties.



- **Polypodium leucotomos extract**
- Polypodium leucotomos (PL) is a fern from Central America. Fernblock (IFC Group, Madrid, Spain) is an extract from these leaves, which has antioxidant and photoprotective capacity.
- PL inhibits MMPs while increasing expression of tissue inhibitors of metalloproteinases (TIMPs). When stimulated by UVR, Fernblock also inhibits the transcription of activator protein-1 and nuclear factor kappa B. Fernblock also inhibits cyclooxygenase-2 expression



- In an RCT, oral PL extract (240 mg twice daily for 12 weeks), used in addition to sunscreen and hydroquinone, was associated with significant and expedited reduction in melasma severity and quality of life (QoL) indices compared with placebo (hydroquinone and sunscreen only) (n = 40)
- A separate study of 61 patients found that oral PL treatment significantly reduced the sensitivity of UVR, with increased MED scores in patients with a personal history of malignant melanoma (MM) or presence of familial MM.
- There was no comparator in this study, and there is a need for RCTs to support this finding and to investigate whether this would translate to fewer MMs. This finding could be clinically relevant to those at risk of MM in whom oral supplementation might have the most benefit alongside topical sunscreens and photoavoidance



- **Afamelanotide**

- Afamelanotide is a potent α -melanocyte-stimulating hormone (α -MSH) analogue that has been used to treat EPP and solar urticaria.
- It works by increasing epidermal melanization, thus protecting against UVR-induced damage, and acts locally on melanocytes unlike natural α -MSH.
- It is typically administered as a subcutaneous implant for slow delivery of the drug, reducing side-effects such as local hyperpigmentation at the injection site.
- Recent review articles have clarified that afamelanotide is unlikely to be related to MM, as had been reported previously.



- A longitudinal study of 115 patients with EPP treated with subcutaneous (SC) implants of afamelanotide 16 mg over 8 years demonstrated improved QoL scores, high compliance, few adverse effects (AEs) other than nausea, and low dropout rates (any dropouts were unrelated to AEs).
- This observational study facilitated evaluation of afamelanotide treatment in a rare disease such as EPP, for which an RCT would not be feasible, allowing for an estimate of clinical effectiveness. In terms of clinical significance, anecdotal evidence showed that patients could resume employment and family tasks that they previously had been unable to do before treatment.



- Barnettson et al. carried out an RCT on 65 Caucasian patients, treating them with SC injection of afamelanotide 0.16 mg/kg for three 10-day cycles over 3 months; they found that melanin density increased in all subjects, with the greatest increase in those with the lowest baseline melanin levels, who were the participants most at risk of sun damage.
- Five patients with solar urticaria treated with a single SC implant of afamelanotide 16 mg in winter demonstrated a significant increase in melanin density as well as a significant fall in weal area across a wide range of wavelengths (300–600 nm).
- The validity of using melanin density as a proxy for photoprotection in many of these studies might be too narrow an outcome measure, and whether this transfers clinically to photoprotection requires further exploration.



- **Nicotinamide**

- The over-the-counter supplement nicotinamide (vitamin B3) offers protection against UVR-induced immunosuppression and appears to confer protection against NMSCs.
- This is clinically relevant for patients at high risk of NMSCs, including immunosuppressed patients such as organ transplant recipients. In a double-blind RCT (n = 61), patients given oral nicotinamide (1500 or 500 mg daily) had significantly reduced UV-induced immunosuppression on irradiated skin, possibly resulting from the role of nicotinamide in cellular metabolism and DNA repair; however, nicotinamide did not protect against sunburn



- A phase III RCT randomized patients to receive twice-daily nicotinamide 500 mg or placebo for 12 months (n = 386).
- The treatment group had a statistically significant 23% relative difference in the rate of NMSCs (P = 0.302; 95% CI 4–38) and a statistically significant 11% reduction in the rate of actinic keratosis (P = 0.01).
- No safety issues were observed in this study and the authors recommended that nicotinamide might be a safe and effective treatment for renal transplant patients.
- Phase III clinical trials are needed to support this claim. Nicotinamide has few significant AEs that preclude its use, but it can cause flushing and headaches and less frequently gastrointestinal disturbances. At a dose of 3 g/day it tends to be well tolerated.



- **Isoflavones**

- Isoflavone phytoestrogens are found in soybeans and clover, with most research investigating genistein (a soybean isoflavane), which has been proposed to have clinically significant photoprotective effects.
- Oral isoflavones (isoflavone soy extract 100 mg/day) reduced the histological features of photoageing when given for 6 months



- **Dietary botanicals**

- Pomegranate extract
- Pomegranate extract has anti-inflammatory and antioxidant actions and is photoprotective with inhibition of UVR-stimulated synthesis of free radicals, erythema, DNA damage and cell proliferation.
- In an RCT of healthy women (n = 70), volunteers were assigned to be treated with pomegranate extract or placebo drink for 12 weeks
- The treatment group had increased MED following UVB, suggesting that pomegranate has photoprotective properties. The clinical implications of this photoprotective effect needs to be studied further.



- **Flavonoids**

- Green tea polyphenols
- Dietary flavonoids from green tea might offer photoprotection. In a 12-week double-blind RCT, participants randomized to receive a drink with green tea polyphenols exhibited a significant 25% reduction of UV-induced erythema.
- Skin elasticity, roughness, scaling density and water homeostasis were also improved compared with controls (n = 60)



- Cocoa extract
- Cocoa extract is a flavonoid that appears to confer dose-dependent photoprotection.
- In a study by Heinrich et al. participants were treated with either high- or low-flavonol cocoa powder for 12 weeks.
- Following irradiation, UV-stimulated erythema was significantly lower by 25% in the highflavonol participants, with no change in the lowflavonol group. Skin thickness increased, transepidermal water loss decreased and there was a significant diminution in roughness and scaling by Week 12. It was posited that dietary flavonols confer photoprotection through augmentation of dermal blood vessels.
- These findings were supported in a subsequent study demonstrating doubling of the MED after consuming high-flavonol chocolate for 12 weeks.



- **Rosemary and grapefruit**
- In a randomized parallel-group study, 90 volunteers were treated with a combination of rosemary and grapefruit. Treated participants demonstrated a decrease in skin erythema and an improvement in signs of skin photoageing, thought to be due to inhibition of UVR-stimulated damaging oxygen species and reduction in inflammatory cytokines



- **Probiotics**

- In a prospective double-blind RCT, 57 patients were treated with either synbiotics or placebo for 12 weeks and melasma severity evaluated
- At 12 weeks, the melasma score was significantly lower in the treatment group ($P = 0.008$). It is possible that synbiotics have anti-inflammatory action, protecting the skin from reactive oxygen species as well as from UVR through inhibition of tyrosinase.



- To date, various systemic supplements have been investigated for their use in photoprotection as an adjunctive treatment in combination with topical sunscreens.
- Nevertheless, few trials have shown efficacy of any treatments compared with sunscreens, precluding the recommendation of these oral supplements as an alternative to sunscreens for photoprotection.
- Nicotinamide has demonstrated clinically relevant benefit in reducing NMSC in trials and could be most useful as a systemic adjunct in photoprotection.



- The other possible beneficial systemic photoprotection supplement is afamelanotide; however, there are limited studies comparing afamelanotide to established treatments to change clinical guidelines.
- Evidence supporting the other supplements is also currently inadequate to change clinical practice.
- It is unclear whether the use of MED as an outcome measure throughout the studies directly relates to UVB (as one would expect), UVA or visible light and further clarity is therefore needed to establish the clinical impact of any findings related to this outcome.
- Larger, more statistically powered trials, which use clinically meaningful outcome measures are required to support the use of any of these supplements in the most susceptible individuals.



- The main carotenoids are b-carotene and lycopene, which are found in carrots and tomatoes; they have a role in gene signalling and expression with evidence supporting their use for photoprotection by augmenting the skin's resistance to UV damage.
- Afamelanotide is a potent α -MSH analogue that has been used to treat erythropoietic protoporphyria and solar urticaria.
- *P. leucotomos* extract has antioxidant and photoprotective capacity. It is thought to inhibit MMPs while increasing expression of TIMPs.
- Nicotinamide has demonstrated clinically relevant benefit in reducing NMSCs in trials, and could be most useful as a systemic adjunct in photoprotection.
- Dietary botanicals such as flavonoids and probiotics also have a role in systemic photoprotection.



THANK YOU FOR YOUR ATTENTION



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