Systemic photoprotection in 2021

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Abstract

Systemic photoprotection aims to negate the negative effects of ultraviolet radiation-induced DNA damage. Systemic supplements might be used as a monotherapy or in combination with topical sunscreens. Using the keywords ‘carotenoids,’ ‘flavonoids,’ ‘systemic photoprotection,’ ‘polyphenols’ and ‘polypodium leucotomos extract,’ we searched the databases MEDLINE and EMBASE to find relevant English-language articles. Few trials have supported the use of any of these supplements as a monotherapy, impeding the recommendation of these systemic supplements as an alternative to sunscreen for photoprotection. Nicotinamide has exhibited clinically relevant benefits in reducing non-melanoma skin cancers in trials and could be recommended as an adjunctive therapy in those most vulnerable. Further research is required that is of higher statistical power, using more clinically meaningful outcome measures with comparison to the current gold standard of care, topical photoprotection, to support the use of alternative therapies in clinical practice.

Background

Systemic photoprotection aims to reduce the damaging effects of ultraviolet 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 anti-oxidant capacities. Currently, gold standard photoprotection includes photoavoidance and topical sunscreens. We review the current evidence available to support the use of systemic photoprotective therapies. Studies included include randomised controlled trials (RCT), longitudinal and case-control studies with patients typically treated for 12 weeks. Outcomes included the UVB-induced minimal erythema dose (MED) and UVA-induced minimal pigmentation dose in many trials. In addition, trials used histological indices of photodamage and photoprotection which may be of unproven clinical significance.

Carotenoids

Carotenoids are precursors of vitamin A and are anti-oxidant micronutrients found in fruits and vegetables. The main carotenoids are β-carotene and lycopene found in carrots and
tomatoes. Other examples include lutein, zeaxanthin, xanthophylls and astaxanthin. They have a role in gene signalling and expression and are reported to augment the skin’s resistance to UV damage.2

In a double-blind RCT (n=65),3 patients were treated with a lycopene-rich tomato nutrient complex (TNC), lutein or placebo (Table 1). TNC and lutein inhibited UVA1 and UVA/B-induced upregulation of intercellular adhesion molecule-1 and matrix metallopeptidase-1 mRNA, both indicators of oxidative stress and photodamage.3

In a double-blind RCT (n=60), patients receiving a composite carotene supplement (β-carotene, α-carotene, lutein, 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 to the control group.4 This suggests daily supplementation with carotenoids protects human skin against UVR-induced erythema and pigmentation.4

A separate double-blinded RCT5 (n=60) used a similar supplement (lycopene, β-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 a 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.5

Lycopene in capsule form and tomato paste was 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.6

Carrascosa et al also found their formulation (astaxanthin, β-carotene, vitamin E, vitamin C, lutein, lycopene) imparted photoprotection against erythemal radiation in a double-blind RCT (n=43) in patients with Fitzpatrick skin types II and III.7 Further evaluation of the effects of this formulation on UVA and infrared is needed, as well as the individual effects of each component in this formulation.7 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 \((n=20)\), \(^8\) 55g tomato paste (containing 16mg 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 matrix-metalloproteinase-1 expression. Processed tomatoes elicited this response more readily than fresh tomatoes. \(^8\)

In a separate study, participants who had received tomato paste (16mg/day lycopene) had 40% lower solar-induced erythema at ten weeks compared with controls \((n=19; p=0.02)\). \(^9\)

In a 12-week open prospective single centre trial \((n=30)\), the efficacy of a food supplement containing vitamins A, C, D3, E, selenium, lycopene, lutein, green tea, polypodium and grape extracts upon MED was evaluated. \(^10\) Significant improvement was found in MED levels, skin radiance and elasticity. \(^10\) It is unclear whether these findings translate to direct clinical benefit. A large randomised 12-year primary prevention trial appeared to show no benefit of \(\beta\)-carotene supplementation on the development of non-melanoma skin cancers (NMSC) \((n=22,071)\). \(^11\) Conversely, some groups have reported benefit of \(\beta\)-carotene supplementation on symptoms of erythropoietic protoporphyria (EPP) with doses between 90-180mg due to its anti-oxidant properties. \(^12,13\)

**Polypodium leucotomos extract**

*Polypodium leucotomos* (PL) is a fern from Central America, whilst Fernblock® (IFC Group, Spain) is an extract from these leaves with anti-oxidant and photoprotective capacity. \(^14\) PL inhibits matrix metalloproteinases, whilst increasing expression of tissue inhibitors of metalloproteinases. Fernblock® when stimulated by UVR, also inhibits the transcription of activator protein-1 and nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB). Fernblock® also inhibits cyclooxygenase-2 expression. \(^14\)
In a RCT, oral PL extract (240mg twice daily for 12 weeks), given alongside sunscreen and hydroquinone, was associated with significant and expedited reduction in melasma severity and quality of life indices compared with placebo (hydroquinone and sunscreen only) (n=40) (Table 2).\textsuperscript{15}

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 history of malignant melanoma (MM) or familial MM.\textsuperscript{16} 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 melanomas. This finding could be clinically relevant to those at risk of MM in whom oral supplementation might have most benefit alongside topical sunscreens and photoavoidance.\textsuperscript{16}

**Afamelanotide**

Afamelanotide is a potent α-melanocyte stimulating hormone (α-MSH) analogue that has been used to treat EPP and solar urticaria.\textsuperscript{17} It works by increasing epidermal melanisation protecting UVR induced damage and acts locally on melanocytes unlike natural α-MSH.\textsuperscript{17} 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 melanoma, as had been reported previously.

A longitudinal study of 115 patients with EPP treated with afamelanotide 16mg implants over eight years demonstrated improved quality of life scores, high compliance, few side-effects (except nausea), and low dropout rates (dropouts were unrelated to side-effects) (Table 2).\textsuperscript{17} This observational study allowed for the evaluation of afamelanotide treatment, in a rare disease such as EPP, where a RCT would not be feasible, allowing for an estimate of clinical effectiveness. In terms of clinical significance, anecdotal evidence found that patients could resume employment and familial tasks that they previously had been unable to do before this treatment.\textsuperscript{18}

Barnetson and colleagues treated 65 Caucasian patients with subcutaneous afamelanotide 0.16mg/kg for three, ten-day cycles over three months in a RCT, finding
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.\textsuperscript{18} Five patients with solar urticaria treated with a single dose of 16mg afamelanotide implant subcutaneously in winter, demonstrated a significant increase in melanin density as well as a significant fall in wheal area found across a wide range of wavelengths (300-600nm).\textsuperscript{19} 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.\textsuperscript{20} This is clinically relevant for patients at high risk of NMSCs, including immunosuppressed patients such as organ transplant patients. In a double-blind RCT (n=61), patients given oral nicotinamide (1500 or 500mg daily) had significantly reduced UV-induced immunosuppression on irradiated skin possibly through nicotinamide’s role in cellular metabolism and DNA repair; however, nicotinamide did not protect against sunburn (Table 2).\textsuperscript{21} A phase III RCT randomised patients to receive nicotinamide 500mg twice daily 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 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.\textsuperscript{22} Nicotinamide has few significant side-effects that preclude its use, but it can cause flushing and headaches and less frequently gastrointestinal disturbances.\textsuperscript{20} At a dose of 3g/day it tends to be well-tolerated.\textsuperscript{20}

**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.\textsuperscript{23}
Oral isoflavones (100mg/day isoflavone soy extract) reduce histological features of photoaging when given for six months (Table 2).\textsuperscript{24}

**Dietary botanicals**

**Pomegranate extract**

Pomegranate extract has anti-inflammatory and anti-oxidant actions and is photoprotective with inhibition of UVR-stimulated synthesis of free radicals, erythema, DNA damage and cell proliferation.\textsuperscript{25}

In a RCT (\(n=70\)), healthy women were assigned to be treated with pomegranate extract or placebo drink for 12 weeks (Table 3).\textsuperscript{26} The treatment group had increased MED following UVB, suggesting pomegranate has photoprotective properties. 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 randomised 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 improved compared to controls (\(n=60\)) (Table 3).\textsuperscript{27}

**Cocoa extract**

Cocoa extract is a flavonoid that appears to confer dose-dependent photoprotection (Table 3).\textsuperscript{26} Twenty-four participants were treated with either high- or low-flavanol cocoa powder for 12 weeks.\textsuperscript{29} Following irradiation, UV-stimulated erythema was significantly lower in the high-flavanol participants by 25%, with no change in the low-flavanol group. Skin thickness increased, trans-epidermal 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.\textsuperscript{29} These findings were supported in a subsequent study demonstrating double the MED after consuming high-flavanol chocolate for 12 weeks.\textsuperscript{30}

**Rosemary and grapefruit**
In a randomised parallel group study, 90 volunteers were treated with a combination of rosemary and grapefruit with treated participants demonstrating a decrease in skin erythema and an improvement in signs of skin photoageing thought to be due to inhibition of UVR-stimulated oxygen damaging species and reduction in inflammatory cytokines (Table 3).  

Probiotics
In a prospective double-blind RCT, 57 patients were treated with either synbiotics or placebo for 12 weeks and melasma severity evaluated (Table 3). 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.

Summary
At present, 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 to 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 the most susceptible individuals.

Learning points
• The main carotenoids are β-carotene and lycopene 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 ultraviolet damage.
• Afamelanotide is a potent α-melanocyte stimulating hormone analogue that has been used to treat erythropoietic protoporphyria and solar urticaria.
• *Polypodium leucotomos* extract has antioxidant and photoprotective capacity. It is thought to inhibit matrix metalloproteinases, whilst increasing expression of tissue inhibitors of metalloproteinases.
• Nicotinamide has demonstrated clinically relevant benefit in reducing NMSC in trials could be most useful as a systemic adjunct in photoprotection.
• Dietary botanicals such as flavonoids and probiotics also have a role in systemic photoprotection.
References


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<th>Study</th>
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<th>Efficacy</th>
<th>Strengths</th>
<th>Weaknesses</th>
<th>Level of evidence</th>
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<tr>
<td>Grether-Beck et al, 2016</td>
<td>65 healthy volunteers</td>
<td>5mg Lycopene-rich tomato nutrient complex (TNC) or lutein</td>
<td>Diarrhoea after lycopene in one patient for a first few days after treatment</td>
<td>TNC, lutein or placebo</td>
<td>12 weeks</td>
<td>Skin was irradiated and 24 h later</td>
<td>TNC and lutein inhibited UVA1 and UVA/B-induced upregulation of intercellular adhesion molecule-1 and matrix metalloproteinase-1</td>
<td>Large, double-blind RCT.</td>
<td>Weakness in crossover design with possible inappropriate washout phases in the lutein arm.</td>
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<td>Washout phase</td>
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<tr>
<td>Baswan et al, 2020</td>
<td>60 participants with Fitzpatrick types II-IV</td>
<td>Nutrilite™ Multi Carotene supplement (β-carotene,</td>
<td>None reported</td>
<td>Placebo</td>
<td>12 weeks</td>
<td>UVB-MED, UVA-induced minimal persistent pigmentati on dose and skin</td>
<td>The treatment group demonstrated a significant increase in skin carotenoid levels,</td>
<td>Double blind RCT.</td>
<td>Use of a non-clinically meaningful outcome such as MED.</td>
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of 2 weeks followed by 12 weeks of treatment.

* e chain reaction analysis of gene expression.

mRNA (p<0.05), both indicators of oxidative stress and photodamage.

Both indicators of oxidative stress and photodamage.
α-carotene, lutein, zeaxanthin.

Carotenoid levels measured at baseline, 4, 8, and 12 weeks of intervention. Skin colour was by colorimetry and evaluated by exports. Carotenoid levels were compared to the baseline (from 15.19 ± 1.49 to 15.50 ± 1.55 at 12 weeks, p < 0.000).
Marini et al., 2014 evaluated 60 patients with PLE and reported on the control group. None of these patients reported a Placebo effect. After 12 weeks, PLE score significantly reduced following one irradiation with UVA1 in the treatment group. Double blind RCT. The study design does not allow for identification of the extent of each ingredient in the supplement.
At a molecular level, those in the treatment group had reduced expression of ICAM-1 mRNA after irradiation compared with the placebo. This difference, (p<0.001), was evaluated by real-time polymerase chain reaction.
| Sokoloski et al, 2015 | 20 non-smoking, healthy patients aged from 20 to 40, Fitzpatrick II or III | Synthesenic | None reported | Tomato paste | 10 weeks | MED 24 hours after UVB and variation of colour a. | There was a marginally significant MED increase for the capsule compared with the tomato paste. | Good adherence of the subjects to the dietary regime due to rigorous follow up. | Small sample size. Use of a non-clinically meaningful outcome such as MED. |
Marginal significance in difference of colour after 10 weeks marginally significant ($p=0.054$), greater for capsule use ($p=0.066$).

Carrascosa et al., 2017

| Carrascosa et al., 2017 | 43 | healthy volunteers, aged 18-60 | The active formulation (Geno Reduce) | Placebo | 56 days MED | 28 and 56 days after treatment | At day 57, mean MED was 1.58 | Combinations of antioxidants and carotenoids | Small sample size. Use of a non-clinically meaningful outcome | 1b |
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significantly
<p>| Rizwan et al. 2011 | 20 | healthy women from 21-47 years, Fitzpatrick I or II | 55 g tomato paste (16 mg lycopene) in olive oil. | None reported | Olive oil alone | 12 weeks | MED pre and post supplementation | UVR induced an increase in MMP-1 (baseline 12.21±1.06; UVR-exposed 11.58±1.12; olive oil alone 11.02±1.54), p=0.049 | Presupplementation, UVR | Use of mitochondrial DNA (mtDNA) as a biomarker for potential photoprotection which is required. | Greater clarity on the clinical implications of these biomarkers is required. |</p>
<table>
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<tr>
<th>buttock skin pre and post supplementation</th>
<th>UVR16·39 ±1·12; p=0·01</th>
<th>has been found to be a sensitive biomarker for cumulative UVR exposure.</th>
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<td></td>
<td>reduction in fibrillin-1 (baseline, 3·42 ±0·14; UVR, 3·02±0·19; p=0·03).</td>
<td>Post-supplementation, UVR-induced MMP-1</td>
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</table>
was reduced in the tomato paste compared with the control group (15.28±1.48; \( p = 0.04 \)) (Stahl et al., 2000).

22 healthy adults, 26-67 years old, received 40 g of tomato paste (40 g) - 16 mg/d of lycopene for 10 weeks. None reported adverse effects. Olive oil alone served as the control group. Erythema intensity by chromato-metry before and after the treatment was compared with the literature. The treatment group had 40% lower solar-induced erythema compared to the control group (15.28±1.48; \( p = 0.04 \)).

Findings are comparable to those in the literature. Evaluation of the technique of application of the paste is warranted.
The MED levels increased significantly compared with controls (baseline erythema formation: 0.37 ± 0.08; at 10 weeks: 0.72 ± 0.07; p = 0.02).

Granger et al., 2020

30 subjects with Fitzpatrick I-III were enrolled. One subject reported difficulty in week 12. The majority of subjects were female. Difficult to establish the clinical significance of the outcomes.
with clinical ageing signs, vitamins A (800 µg), C (40 mg), D3 (5 µg), E (12 mg), selenium (41.5 µg), lycopene (8 mg), lutein (8 mg), digesting the product a second reported slight stomach burns in the last few weeks of treatment of the skin. Secondarily endpoint tolerability and measures of skin moisture, elasticity, radiance and colour of skin dark spot compared to relevance of the skin. Secondary endpoint – tolerability and measures of skin such as moisture, reducing power and colour of skin with day 84, p < 0.001. Ferric reducing antioxidant power indicated a significant comparison to individual effects of each ingredient.

Accepted Article

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green tea (50mg), polypodium (480mg) and grape extracts (10.1mg).

baseline (22.7%±4.9 at day 84, p < 0.001). Skin radiance (36.1%±0.4 at day 84, p < 0.001), gross elasticity (13.2%±0.0139 at day 84, p < 0.001), net elasticity (28.0%±0.0126 at day 84, p < 0.001).
Frieling et al., 2000

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<th>22,071</th>
<th>Beta</th>
<th>Yellowing</th>
<th>Placebo</th>
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<th>Relative risk (RR)</th>
<th>There was no effect of beta carotene on the incidence (CI) for a large RCT with a long follow-up period.</th>
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<td>Study</td>
<td>Male</td>
<td>Healthy</td>
<td>Male, 50</td>
<td>Skin</td>
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<td>Subjects</td>
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<td>Age</td>
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<td>(15.9%)</td>
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84, p < 0.001, and moisture (13.8% at day 84, p < 0.001) were also significantly improved.
days.

There was no significant evidence of beneficial history of sunburn all known risk factors for NMSCs. Diagnosis of BCC was mainly self-reported leading to possible under-reporting.  

NMSC, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).  

BCC (RR, 0.98; 95% CI, 0.84-1.13). There was no significant evidence of beneficial history of sunburn all known risk factors for NMSCs.

Diagnosis of BCC was mainly self-reported leading to possible under-reporting.  

NMSC, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).
beta carotene compared with 124 (1.1%) in the placebo group or harmful effects of beta carotene on NMSC by smoking status.

<table>
<thead>
<tr>
<th>Study</th>
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<tbody>
<tr>
<td>Polypodium leucotomos extract</td>
<td>Goh et al., 40 healthy adults with Fernblock® (IFC, Madrid, 2 patients)</td>
<td>Placebo</td>
<td>12 weeks</td>
<td>The Modified Melasma</td>
<td>There were statistically significant differences, blinded, in using a</td>
<td>Randomised, blinded, in using a</td>
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Table 2. Polypodium leucotomos extract, afamelanotide, nicotinamide and isoflavones in systemic photoprotection
Melasma receiving treatment with hydroquinone 4% and sunscreen with sun protection factor 50+ in Spain). From the PL group and one from the placebo group reported mild itching and stinging sensation with hydroquinone cream.

Area and Severity Index (mMASI); melanin and erythema indexes; VISIA® photography (Canfield Scientific, Parsippany, New Jersey, USA); and the Melasma Quality of Life (MelasQoL) questionnaire.

Significant differences between the mMASI scores of both groups as compared with the baseline scores (p≤0.01). mMASI scores of the PL group at were also significantly lower than those of the placebo group.

Skin colorimeter study with placebo comparator to measure pigmentary changes, intraindividual variability of treatment response and small sample size.
(p ≤ 0.05). At 12 weeks, a significant improvement was reached in both groups (p ≤ 0.01), with no significant differences between them. The scores of the melanin and erythema indices demonstrated a slight improvement.
in both groups, without significant differences between groups. MelasQoL score showed an improvement in the PL group compared with the placebo group.

Aguilera et al, 2012

61 patients: 25 with familial and 36 without. Participants received the same oral treatment (720 mg of oral PL) and were evaluated clinically. Oral PL treatment significantly improved MED – non-clinical.
or MM, 20 with sporadic MM and 16 with atypical mole syndrome without a history of MM.

A dose of a commercial form of PL (total dose 1080mg) was given in three doses, (240mg every 8 hours) and 360 mg in a single dose, were given one day and 3 hours respectively, before a second MED and post-treatment MED was performed by 2 experienced dermatologists. The increase in MED after PL was associated with dark eyes ($\chi^2=4.67, p<0.05$) (OR 4.47, CI 95% 1.22–16.34) and a lower meaningful outcome measure, lack of comparator.
<table>
<thead>
<tr>
<th>Afamelanotide</th>
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<tr>
<td><strong>Biolo et al., 2014</strong></td>
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<tr>
<td><strong>115 ambulatory patients with EPP</strong></td>
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<td>Afamelanotide (Scenesse&lt;sup&gt;®&lt;/sup&gt;) 16 mg implant, given subcutaneously every second month</td>
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<tr>
<td><strong>Nausea (n=146 events)</strong></td>
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<td><strong>Headache (n=81e vents)</strong></td>
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<td><strong>Fatigue (n=33 events)</strong></td>
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<td><strong>A new</strong></td>
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<td><strong>Up to eight years</strong></td>
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<td><strong>Quality of life scores, measured by an EPP-specific questionnaire</strong></td>
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<tr>
<td><strong>The quality of life scores were 31±24% prior to treatment which increased to 74%±17% (74%±17%) after treatment</strong></td>
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<tr>
<td><strong>Long follow-up period of eight years</strong></td>
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<td><strong>Lack of a precise tool to measure things such as wavelength of damaging visible light and air dryness at affected</strong></td>
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</table>

**Assessment**

**baseline MED value**

\( (\chi^2 = 6.90, p < 0.05) \) (OR 4.59, CI 95% 1.23–7.47)
melanoctytic naevus (n=2 patients), appearing 2.5 and 5 years after the first afamelanotide dose, respectively. One was removed and remained at this level during the entire observation period.
Barnetson et al., 2006

<table>
<thead>
<tr>
<th>Subjects</th>
<th>(Nle4-D-Phe7-α-MSH (Nle4-D-Phe7-α-MSH) delivered by subcutaneous injection into the abdomen at 0.16 mg/kg for three 10-day cycles over 3 months)</th>
<th>Nausea (85% of subjects), facial flushing (74%), fatigue (44%), vomiting (26%), injection</th>
<th>Placebo 3 months</th>
<th>Melanin density, measured by reflectance spectroscopy</th>
<th>Melanin density, increased significantly in all (Nle4-D-Phe7-α-MSH-treated subjects. The highest increases were those with the lowest.</th>
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<td>79 subjects</td>
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</tr>
</tbody>
</table>

Care is needed in the extrapolation of the increased melanin density which might not be directly related to photo-
Nine withdrew due to nausea and two withdrew due to bruising at injection site.

Baseline skin melanin levels in subjects with low MED skin type, melanin increased by an average of 41% (from 2.55-3.59, p<0.0001 compared with only 12% (from 2.55-3.59, p=0.001) compared with placebo) over eight skin sites compared with only 2

Nine (13%) withdrew due to nausea and two withdrew due to bruising at injection site.

Baseline skin melanin levels in subjects with low MED skin type, melanin increased by an average of 41% (from 2.55-3.59, p<0.0001 compared with only 12% (from 2.55-3.59, p=0.001) compared with placebo) over eight skin sites.
Haylett et al., 2010

<table>
<thead>
<tr>
<th>Patients</th>
<th>Single dose of</th>
<th>None</th>
<th>None</th>
<th>60 days</th>
<th>Melanin density</th>
<th>Mean melanin density increased by day 7, peaked by day 15 and remained raised at day 60 (p=0.03, 0.01, 0.02)</th>
<th>Use of extensive phototesting with radiation, through UVA, UVB and visible light</th>
<th>Only 5 patients Included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Five patients with solar urticaria</td>
<td>16mg subcutaneous afamelanotide implant in winter time</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
dose series vs. baseline, (increment ) respectively) of wavelengths. Baseline phototesting revealed action spectra of 320-400 nm (n=1), 320-500 nm (n=2), 300-600 nm (n=1) and 370-500 nm (n=1), and upon treatment with afamelanotid, mean rises in
<table>
<thead>
<tr>
<th>Nicotinamide</th>
<th>Yiasemides <em>et al.</em>, 2009&lt;sup&gt;21&lt;/sup&gt;</th>
<th>volunteers</th>
<th>Nicotinamide</th>
<th>None</th>
<th>Placebo</th>
<th>5 weeks</th>
<th>Immunosuppression, (difference in Mantoux-induced erythema of irradiated sites compared with unirradiated control sites)</th>
<th>Oral nicotinamide had no effect on the volunteers’ sunburn thresholds. Oral nicotinamide, at doses of either 1500 or 500 mg daily, significantly reduced UV Placebo comparator used.</th>
<th>Greater clarity on how the use of immunosuppression as an outcome measure will relate to clinical practice.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>61</td>
<td>Nicotinamide</td>
<td>500mg or 1500mg for 7 days.</td>
<td></td>
<td></td>
<td></td>
<td>minimum urticarial dose</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Chen et al., 2015

386 patients who had had at least two NMSCs in the past 5 years

Nicotinamide 500mg twice daily

No Placebo

12 months

Primary end point was the number of new NMSCs (BCC and SCC, at 6 months.

Secondary end points

Large sample size with multiple clinically relevant outcome measures recorded.

Multiple statistical tests were performed

The treatment group had a statistically significant 23% relative difference in the rate of NMSCs compared to the placebo group. (p<0.001).

Multiple clinically relevant outcome measures were recorded.

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were new BCCs, new SCCs, AK counts 6 months after the intervention and safety. (p=0.302; 95% CI 4-38) and a statistically significant 11% reduction in actinic keratosis (p=0.01).
| Isoflavones | 30 | 100 mg/day of an isoflavones-rich, concentrated soy extract | None | None | 6 months | Skin punch in the gluteal area before and immediately after the | A 9.46% increase in the epidermal thickness was found in 23 patients. The papillary index was reduced in | Use of clinically significant measurements of skin ageing. | No comparator used to compare treatment. |

*Accorsi-Neto et al., 2009*
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Amount of dermal collagen in 25 women (7.6 ± 1.5%; p &lt; 0.01)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>in the dermis was increased</td>
</tr>
<tr>
<td>Papillary</td>
<td>In 22 women</td>
</tr>
<tr>
<td>Index</td>
<td>elastic fiber numbers (18.8 ± 4.8%; p &lt; 0.01)</td>
</tr>
<tr>
<td>Index, and</td>
<td>collagen fibers and number of blood vessels increased. The</td>
</tr>
<tr>
<td>Amount of</td>
<td>vessels dermal blood was vessel numbers</td>
</tr>
</tbody>
</table>
recorded. significantly increased in 21 women (20.2 ± 5.9%; p < 0.01).

Table 3. Dietary botanicals in systemic photoprotection

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Tolerability</th>
<th>Comparators</th>
<th>Duration</th>
<th>Outcome measures</th>
<th>Efficacy</th>
<th>Strengths</th>
<th>Weaknesses</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pomegranate extract</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2b</td>
</tr>
<tr>
<td>Li et al, 2018</td>
<td>74 healthy women</td>
<td>Pomegranate extract (PomX) or juice (PJ)</td>
<td>Two patients from the PL group and one</td>
<td>Placebo</td>
<td>12 weeks</td>
<td>MED was assessed after exposure of the inner arm to UVB</td>
<td>MED was increased significantly in both PomX and PomJ</td>
<td>Investigated the pathogenesis is possible</td>
<td>MED used – greater clarity needed on how this</td>
<td>2b</td>
</tr>
</tbody>
</table>
from the placebo group reported mild itching and stinging sensation with hydroquinone cream.

Baseline and after 12 weeks of pomegranate consumption compared to placebo groups,

At the genus level the amount of 6 and 4 genera was altered significantly by PomX and PJ respectively compared with placebo.

Circulating cytokine and chemokine were not affected by the intervention.

Photoprotection with pomegranates using a wide range of outcomes transfers to clinically significant outcomes.
| Flavonoids                                      | Heinrich et al., 2011 | 60 female volunteers | A drink with green tea polyphenols with 1402 mg total catechins/day | Placebo beverage | 12 weeks | Skin photoprotection, structure, and function were measured at baseline (week 0), week 6, and week 12 | Skin structural characteristics that were positively affected included elasticity (21% increase; \( p<0.05 \)), roughness, scaling (decrease -16 and -25% respectively; \( p<0.05 \)), density (7.7% increase), and water | Use of clinically significant outcome measures related to photoaging. | Poor compliance in the study and a 40% attrition rate in the green tea group – no explanation offered for this high attrition rate. |
homeostasis. Skin thickness was not affected. Intake of the green tea polyphenol beverage for 12 week increased blood flow and oxygen delivery to the skin (29% increase by week 12; \( p<0.05 \)).

| Calzavara-Pinton et al, 2019 | 10 | Oral daily supplementation of 1g of high-flavanol cocoa | High dose vs low dose | One week | Phototesting with solar simulated radiation was performed at | Oral daily supplementation of 1g of high-flavanol cocoa | Use of crossover period allowed for monitoring | Small sample size. | Short follow-up period. | Unclear how | 4 |
cocoa (n=6), followed by all 10 taking 4–6g of cocoa for one week baseline and after cocoa supplementation. MED and spectrophotometric measurement of the a parameter 24h after irradiation. cocoa was not effective. A one-week administration of 4–6g of cocoa produced a statistically significant increase in the MED (0.051 (IQR 0.034–0.051) J cm⁻²) compared with 0.051 (IQR 0.043–0.051) J cm⁻²; [p < 0.05] and a significant decrease in the of effect in same patients reducing confounding variables. MED translates into a clinical significant outcome.
Heinrich et al., 2006

24 female healthy subjects, aged 18-65, Fitzpatrick II skin

High flavanol (HF)cocoa powder (326 mg/day) dissolved in 100 mL water. Epicatechin (61 mg/day) and catechin (20 mg/day) were the 490

Low flavanol (LF) (27 mg/day) cocoa powder - 6.6 mg epicatechin and 1.6 mg catechin as the

12 weeks UV-induced erythema and indicators of skin condition were measured before and during the intervention UV-induced erythema was significantly decreased in the HF group, by 15 and 25%, after 6 and 12 weeks of treatment respectively, no change was found in the low flavanol group.

Clinically significant outcomes were measured through examination of skin condition after treatment.

Small sample size. Only Fitzpatrick II skin – unclear how if this treatment will have the same effect on those with
In the HF cocoa group there was increases in blood flow to cutaneous and subcutaneous tissues, and to increases in skin density and skin hydration. Skin thickness was elevated from 1.11 ± 0.11 mm at week 0 to 1.24 ± 0.13 mm at week 12; transepidermal water loss was diminished from 8.7 ± 3.7 to 6.3
± 2.2 g/(h.m²) by week 12. No change was found in the LF group. A significant decrease of skin roughness and scaling was found in the HF group compared with the LF group.
<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Subjects</th>
<th>Intervention</th>
<th>Control</th>
<th>Duration</th>
<th>MED Assessment</th>
<th>Change in MED</th>
<th>Intervention Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Williams et al., 2009&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Healthy subjects</td>
<td>HF 20 g</td>
<td>None</td>
<td>LF 20 g</td>
<td>12 weeks</td>
<td>MED was assessed at baseline and after 12 weeks</td>
<td>No significant change in MED was found in the LF group. In the HF chocolate group, the mean MED more than doubled from 0.109 J/cm&lt;sup&gt;2&lt;/sup&gt;±0.011 at baseline to 0.223 J/cm&lt;sup&gt;2&lt;/sup&gt;±0.019 after 12 weeks (p&lt;0.005).</td>
</tr>
<tr>
<td>Nobile et al., 2016&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Females, Fitzpatrick I-III showing skin redness</td>
<td>A mixture of rosemary and citrus extracts (Nutroxsun™)</td>
<td>Placebo (100% maltodextrin)</td>
<td>UVB-induced skin redness, erythemal response</td>
<td>72 hours or 2 months</td>
<td>UVB-induced skin redness, erythemal response after UVB exposure</td>
<td>The intervention group showed a decrease in the UVB- and UVA-induced skin photodama clinically significant measures of clinically significant outcomes.</td>
</tr>
</tbody>
</table>

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mild to moderate chrono- or photoageing leaves and grapefruits, respectively 100 or 250 mg. 5–30 min before UVB exposure to 1 MED. Two supplementary doses were given 24 and 48h after UV (short or long term study) (290–320 nm), and basal and UVA-stimulated (320–400 nm) skin LPO content (redness and lipoperoxides) alterations (decreased skin redness and lipoperoxides) and an improvement of skin wrinkledness and elasticity. No differences were found between the 100 and 250 mg doses. Skin horny layer MDA content four hours after UVA decreased by 9.7, 16.2 and 20.1% after 0.5, respectively.

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exposure (short term study). In the long-term study, subjects received 100 mg Nutroxsun™, 250 mg Nutroxsun™, 1, and 2 months treatment, respectively (p=0.0000) in the 100 mg dose group, 24 hours after UVA the MDA content decreased by 8.7, 13.4, and 15.1% after 0.5, 1, and 2 months treatment, respectively (p=0.0000). In the 250 mg MDA, four hours after UVA, was decreased by 10.2, 16.4, and
21.7% after 0.5, 1, and 2 months treatment, respectively ($p=0.0000$); 24 hours after UVA the MDA content was decreased by 9.1, 13.3, and 15.8% after 0.5, 1, and 2 months treatment, respectively ($p=0.0000$).
| Piyavati et al., 2021 | 57 participants, aged 30-50 | Oral synbiotics, TS6, a combination of 50 billion CFUs of 6 probiotics strains: *Lactococcus lactis*, *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium longum*, with Fitzpatrick skin type III–VI | Placebo | 12 weeks | mMASI of the synbiotics group was 7.54±0.79, 7.36±0.80, 7.16±0.73, and 6.98±0.72 at baseline, weeks 4, 8, and 12, respectively, and 7.5±0.86, 7.52±0.88, 7.54±0.86, and 7.54±0.89 at baseline, weeks 4, 8, and 12, respectively, in | Use of standardised melasma scoring system allowing for comparability of findings between studies. Randomised controlled study with a placebo used. | Participants were aged between 30-50 only meaning the results might be harder to extrapolate to the general population. | 1b |
Bifidobacterium infantis, Bifidobacterium bifidum

The melasma score in the synbiotics group was significantly lower than that in the placebo group by week 12 ($p=0.008$). Outcomes of photodamage such as skin elasticity are missing.