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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.[1] 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.[2] 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 RCT[5] (*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 β-carotene supplementation on the development of non-melanoma skin cancers (NMSC) (*n*=22,071).[11] Conversely, some groups have reported benefit of β-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).[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.[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.[16]

Afamelanotide

Afamelanotide is a potent α-melanocyte stimulating hormone (α-MSH) analogue that has been used to treat EPP and solar urticaria.[17] It works by increasing epidermal melanisation protecting UVR induced damage and acts locally on melanocytes unlike natural α-MSH.[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).[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.[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.[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).[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.[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).[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.[22] Nicotinamide has few significant side-effects that preclude its use, but it can cause flushing and headaches and less frequently gastrointestinal disturbances.[20] At a dose of 3g/day it tends to be well-tolerated.[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.[23]

Oral isoflavones (100mg/day isoflavone soy extract) reduce histological features of photoaging when given for six months (Table 2).[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.[25]

In a RCT (*n*=70), healthy women were assigned to be treated with pomegranate extract or placebo drink for 12 weeks (Table 3).[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).[27]

Cocoa extract

Cocoa extract is a flavonoid that appears to confer dose-dependent photoprotection (Table 3).[28] Twenty-four participants were treated with either high- or low-flavanol cocoa powder for 12 weeks.[29] Following irradiation, UV-stimulated erythema was significantly lower in the high-flavonol participants by 25%, with no change in the low-flavonol 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.[29] These findings were supported in a subsequent study demonstrating double the MED after consuming high-flavanol chocolate for 12 weeks.[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).[31]

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).[32] 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.[33]

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 erythropoeitic 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.

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Table 1. Carotenoids in systemic photoprotection

Study	Population	Intervention	Tolerability	Comparators	Duration	Outcome measures	Efficacy	Strengths	Weaknesses	Level of evidence
Grether-Beck *et al*, 2016[3]	65 healthy volunteers	5mg Lycopene-rich tomato nutrient complex (TNC) or lutein 10mg. Washout phase	Diarrhoea after lycopene in one patient for a first few days after treatment.	TNC, lutein or placebo	12 weeks	Skin was irradiated and 24 h later biopsies were taken from untreated, UVAB and UVA1 irradiated skin for reverse transcriptase polymeras	TNC and lutein inhibited UVA1 and UVA/B-induced upregulation of intercellular adhesion molecule-1 and matrix metallopeptidase-1	Large, double-blind RCT. Crossover design –large power and decreased confounders.	Weakness in crossover design with possible inappropriate washout phases in the lutein arm.	1b

		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.			
Baswan *et al,* 2020[4]	60 participants with (Fitzpatrick types II-IV)	Nutrilite™ Multi Carotene supplement (β-carotene,	None reported	Placebo	12 weeks	UVB-MED, UVA-induced minimal persistent pigmentation dose and skin	The treatment group demonstrated a significant increase in skin carotenoid levels,	Double blind RCT.	Use of a non-clinically meaningful outcome such as MED.	1b

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 measured	UVB-induced MED (p<0.000) and UVA-induced minimal pigmentation dose (from baseline 15.19±1.49 to 15.50 ± 1.55 At 12 weeks p<0.000) compared to the	

						by the Biozoom® device.	control group.			
Marini *et al*, 2014[5]	60 patients with PLE	Lycopene, β-carotene, and Lactobacillus johnsonii.	None reported	Placebo	12 weeks	PLE score. Skin biopsies were taken before and after supplementation from unexposed and exposed skin, and intercellul	After 12 weeks, the supplement significantly reduced the PLE score 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.	1b

ar adhesion molecule 1 (ICAM-1) mRNA expression evaluated by real-time polymerase chain reaction.	(p<0.001). At a molecular level, those in the treatment group had reduced expression of ICAM-1 mRNA after irradiation compared with the placebo. This difference,

							however, was not significant after two UVA1 exposures.			
Sokolos ki *et al,* 2015[6]	20 non-smoking, healthy patients aged from 20 to 40, Fitzpatri ck II or III	Synthe tic lycope ne capsul es	None reported	Tomato paste	10 week s	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 adherenc e 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.	1b

							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[7]	43 healthy volunteers, aged 18-60	The active formulation (Geno	Reduced palatability of tomato	Placebo	56 days	MED 28 and 56 days after treatment	At day 57, mean MED was 1.58	Combinations of antioxidants and carotenoi	Small sample size. Use of a non-clinically meaningful outcome	1b

with Fitzpatrick II or III	sun oral®) contained astaxanthin (4 mg), β-carotene (4.8 mg), vitamin E (6 mg), vitamin C (40 mg	paste	(SD=0.44) in the treatment group (a 20.51% increase from baseline) compared to a 1.4 (SD=0.33) in the control group (an 8.63% increase from baseline), which significantl	ds investigated. An oral therapy means do not need to rely on technique of application of topical photoprotection.	such as MED which also ignores the effect of UVA. Unclear as to the extent of effect of each element of the supplement.	

		), lutein (2.4 mg) and lycopene (2.4 mg).					y different (p=0.049).			
Rizwan *et al*. 2011[8]	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 and biopsies from unexposed and UVR-exposed	Presupplementation, UVR induced an increase in MMP-1 (baseline 12.21±1·06;	Use of mitochondrial DNA (mtDNA) as a biomarker for potential photoprotection which	Greater clarity on the clinical implications of these biomarkers is required.	1b

buttock skin pre and post supplementation	UVR16·39 ±1·12; *p*=0·01) and a reduction in fibrillin-1 (baseline, 3·42 ±0·14; UVR, 3·02±0·19 *p*=0·03). Post-supplementation, UVR-induced MMP-1	has been found to be a sensitive biomarker for cumulative UVR exposure.

						was reduced in the tomato paste compared with the. control group (15·28±1·48; *p*=0·04)			
Stahl *et al*, 2000[9]	22 healthy adults, 26-67 years old. Fitzpatri	Tomato paste (40 g) - 16 mg/d of	None reported	Olive oil alone	10 weeks	Intensity of erythema by chromatometry before	The treatment group had 40% lower solar-induced erythema	Findings are comparable to that in the literature.	Evaluation of the technique of application of the paste is warranted.	1b

	ck II	lycope ne with 10 g of olive oil.				and 24h after irradiation.	at ten weeks compared with controls (baseline erythema formation 0.37± 0.08; at 10 weeks 0.72 ± 0.07 ; *p*=0.02)			
Granger *et al*, 2020[10]	30 subjects with Fitzpatrick I-III	Food supplement containing	One subject reported difficulty in	None	12 week	Primary endpoint - MED and antioxidant capacity	The MED levels increased significantly	Secondary outcomes with clinical	The majority of subjects were female. Difficult to establish the	2b

with clinical ageing signs	vitamins A (800μg), C (40mg), D3 (5μg), E (12mg), selenium (41.5μg), lycopene (8mg), lutein (8mg),	digesting the product a second reported slight stomach burns in the last few weeks of treatment	of the skin. Secondary endpoint – tolerability and measures of skin ageing such as skin moisture, elasticity, radiance and colour of skin dark spot	compared to baseline throughout the study visits – an increase of 8.1%±2.2 at day 84, $p < 0.001$. Ferric reducing antioxidant power indicated a significant compared to	relevance.	individual effects of each ingredient. Open-study with no comparator.	

green tea (50mg), polypodium (480mg) and grape extracts (10.1mg).		baseline (22.7%±4.9 at day 84, $p < 0.01$). Skin radiance (36.1%±0.4 at day 84, $p < 0.01$), gross elasticity (13.2%±0.0139 at day 84, $p < 0.01$), net elasticity (28.0%±0.0126 at day

						84, $p < 0.01$), and moisture (13.8% at day 84, $p < 0.01$) were also significantly improved.			
Frieling et al, 2000[11]	22,071 healthy male physicians aged 40-84	Beta carotene, 50 mg, on alternate	Yellowing of the skin (1745 (15.9%) in the	Placebo	12 years	Relative risk (RR) and 95% confidence interval (CI) for a	There was no effect of beta carotene on the incidence	Large RCT with long follow-up period.	No information on previous sun exposure, skin type, or	1b

days.	treatment group compared with 1535 (14.0%) in the placebo group) and minor gastrointestinal tract symptoms-belching (275 (2.5%) in the	first NMSC, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).	of a first NMSC (RR, 0.98; 95% CI, 0.92-1.05), BCC (RR, 0.99; 95% CI, 0.92-1.06), or SCC (RR, 0.97; 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

		beta carotene compared with 124 (1.1%) in the placebo group					or harmful effects of beta carotene on NMSC by smoking status.			

Table 2. Polypodium leucotomos extract, afamelanotide, nicotinamide and isoflavones in systemic photoprotection

Study	Population	Intervention	Tolerability	Comparators	Duration	Outcome measures	Efficacy	Strengths	Weaknesses	Level of Evidence
Polypodium leucotomos extract										
Goh *et al,*	40 healthy adults with	Fernblock® (IFC, Madrid,	Two patients	Placebo	12 weeks	The Modified Melasma	There were statistically	Randomised, blinded	Limitations in using a	1b

2018[15]	melasma receiving treatment with hydroquinone 4% and sunscreen sun protection factor 50+	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 ($p \leq 0.01$). mMASI scores of the PL group at were also significantly lower than those of the placebo group	study with placebo comparator	skin colorimeter to measure pigmentary changes, intraindividual variability of treatment response and small sample size.

($p \leq 0.05$). At 12 weeks, a significant improvement was reached in both groups ($p \leq 0.01$), 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[16]	61 patients: 25 with familial and	Participants received the same oral	None reported	None	720 mg of oral PL	Clinical evaluation of both basal	Oral PL treatment significantly	MED – non-clinical		2b

or MM, 20 with sporadic MM and 16 with atypical mole syndrome without a history of MM	dose of a commercial form of PL (total dose 1080mg).	in three doses, (240mg every 8 hours) and 36 0 mg in a single dose, were given one day and 3 hours respecti vely, before a second MED	and post-treatment MED was performed by 2 experienced dermatologist s.	increased the MED mean in all group patients (0.123 to 0.161 J/cm^2, p<0.05). The increase in MED after PL was associated with dark eyes (χ^2=4.6 7, p<0.05) (OR 4.47, CI 95% 1.22–16.34) and a lower	meaningful outcome measure, lack of comparator.

					assess ment.		baseline MED value (χ^2=6.90, p<0.05) (OR 4.59, CI 95% 1.23–7.47).			
Afamelanotide										
Biolcati *et al*, 2014[17]	115 ambulatory patients with EPP	Afamelanotide (Scenesse®), 16 mg implant, given subcutaneously every second month	Nausea (n=146 events) . Headache (n=81events) Fatigue (n=33 events) A new	None	Up to eight years	Quality of life scores, measured by an EPP-specific questionnaire .	The quality of life scores were 31±24% prior to treatment which increased to 74%±17% (74%±17%) after treatment	Long follow-up period of eight years	Lack of a precise tool to measure things such as wavelengths of damaging visible light and air dryness at affected	2b

melanocytic 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	body areas	

			d and showed no signs of malignancy.							
Barnetson *et al*, 2006[18]	79 subjects	(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	Nausea (85% of subjects), facial flushing (74%), fatigue (44%), vomiting (26%), injectio	Placebo	3 months	Melanin density, measured by reflectance spectroscopy	Melanin density, increased significantly in all (Nle4 -D-Phe7)-α-MSH-treated subjects. The highest increases were those with the lowest	Using chromaticity measures allows for greater consistency in results giving a better representation of actual melanin change.	Care is needed in the extrapolation of the increased melanin density which might not be directly related to photo-	1b

months.	n site reactions (13%). 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 placebo) over eight skin sites compared with only 12% (from	protection.

							4.18-4.70, p<0.0001 compared with placebo) in subjects with a high-MED skin type.			
Haylett *et al,* 2010[19]	Five patients with solar urticaria	Single dose of 16mg subcutaneous afamelanotide implant in winter time	None	None	60 days	Melanin density assessed spectrophotometrically from day 0 to day 60. Monochromated light testing to geometric	Mean melanin density increased by day 7, peaked by day 15 and remained raised at day 60 (*p*=0·03, 0·01, 0·02	Use of extensive phototesting with radiation, through UVA, UVB and visible light wavelengths	Only 5 patients Included	4

dose series (increment) of wavelengths 300-600 nm was carried out at day 0, 30 and 60, with evaluation of weal and flare area and minimum urticarial dose.	vs. baseline, respectively) . Baseline phototesting revealed action spectra of 320-400 (n=1), 320-500 (n=2), 300-600 (n=1) and 370-500 nm (n=1), and upon treatment with afamelanotide, mean rises in

							minimum urticarial dose			
Nicotinamide										
Yiasemides *et al*, 2009[21]	61 volunteers	Nicotinamide 500mg or 1500mg for 7 days.	None	Placebo	5 weeks	Immunosuppression, (difference in Mantoux-induced erythema of irradiated sites compared with unirradiated control sites)	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.	Greater clarity on how the use of immunosuppression as an outcome measure will relate to clinical practice.	1b

							immunosuppression (p<0.001).			
Chen *et al*, 2015[22]	386 patients who had had at least two NMSCs in the past 5 years	Nicotinamide 500mg twice daily	No significant difference between groups	Placebo	12 months	Primary end point was the number of new NMSCs (BCC and SCC, at 6 months. Secondary end points	The treatment group had a statistically significant 23% relative difference in the rate of NMSCs	Large sample size with multiple clinically relevant outcome measures recorded.	Multiple statistical tests were performed meaning there is a greater chance that some	1b

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).	significance values were due to chance.

Isoflavones

Accorsi-Neto *et al*, 2009[25]	30 postmenopausal women	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.	2b

treatment. Morphometric determination of epidermal thickness, the papillary index, and amount of dermal elastic, collagen fibers and number of blood vessels was	21 women - inversely proportional to skin wrinkling. Amount of dermal collagen in the dermis was increased in 25 women (7.6 ± 1.5%; $p<0.01$) In 22 women (18.8 ± 4.8%; ($p<0.01$) elastic fiber numbers increased. The dermal blood vessel numbers

						recorded.	significantly increased in 21 women (20.2 ± 5.9%; p <0.01).			

Table 3. Dietary botanicals in systemic photoprotection

Study	Population	Intervention	Tolerability	Comparators	Duration	Outcome measures	Efficacy	Strengths	Weaknesses	Level of evidence
Pomegranate extract										
Li *et al,* 2018[26]	74 healthy women	Pomegranate extract (PomX) or juice (PJ)	Two patients from the PL group and one	Placebo	12 weeks	MED was assessed after exposure of the inner arm to UVB at	MED was increased significantly in both PomX and PomJ	Investigated the pathogenes is of possible	MED used – greater clarity needed on how this	2b

from the placebo group reported mild itching and stinging sensation with hydroquinone cream.	baseline and after 12 weeks of pomegranate consumption	consuming groups compared to placebo 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[27]	60 female volunteers	A drink with green tea polyphenols with 1402 mg total catechins/day	None	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 photoageing.	Poor compliance in the study and a 40% attrition rate in the green tea group – no explanation offered for this high attrition rate.	1b

							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[28]	10 healthy subjects, Fitzpatrick I-II	Oral daily supplementation of 1g of high-flavanol	None	High dose vs low dose cocoa	One week	Phototesting with solar simulated radiation was performed at	Oral daily supplementation of 1g of high-flavanol	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.

							a parameter (6.98±1.59 compared with 5.63 ± 1.47 at baseline; p< 0.05).			
Heinrich *et al,* 2006[29]	24 female healthy subjects, aged 18-65, Fitzpatrick II	High flavanol (HF)cocoa powder (326 mg/day) dissolved in 100 mL water. Epicatechin (61 mg/day) and catechin (20 mg/day) were the	None	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	1b

major flavanol monomers	daily dose.	In the HF cocoa group there was increases in blood flow tocutaneous 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	different skin types

± 2.2 g/(h.m^2) 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.

Williams *et al,* 2009[30]	30 healthy subjects	HF 20 g	None	LF 20g	12 weeks	MED was assessed at baseline and after 12 weeks	No significant change in MED was found in the LF group. In the HF chocolate group, the mean MED more than doubled from 0.109J/cm^2±0.011 at baseline to 0.223J/cm^2±0.019 after 12 weeks (p<0.005).	Double-blind randomised controlled trial.	MED used – greater clarity needed on how this transfers to clinically significant outcomes.	1b
Nobile *et al,* 2016[31]	90 females, Fitzpatrick I-III showing	A mixture of rosemary and citrus extracts (Nutroxsun™	None	Placebo (100% maltodextrin)	72 hours or 2 months	UVB-induced skin redness, erythemal response after UVB exposure	The intervention group showed a decrease in the UVB- and UVA-induced skin	Clinically significant measures of photodama	Small sample size and high standard deviation	1b

mild to moderate chrono- or photoageing	) from dried rosemary (*Rosmarinus officinalis*) leaves and grapefruits (*Citrus paradisi*), 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,	ge recorded. Investigation of both short and long-term effects. The study was conducted on various ages and skin types meaning it is easier to extrapolate its findings to the general population.	warrant the need for further studies investigating rosemary in photoprotection.

	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)

Piyavatin *et al*, 2021[32]	57 participants, aged 30-50 with Fitzpatrick skin type III–VI	Oral synbiotics, TS6, a combination of 50 billion CFUs of 6 probiotics strains: *Lactococcus lactis*, *Lactobacillus acidophilus, Lactobacillus casei*, *Bifidobacterium longum*,	None	Placebo	12 weeks	mMASI score	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. Other clinically significant secondary	1b

	Bifidobacterium infantis, *Bifidobacterium bifidum*	the placebo group 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.