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Anti-Inflammatory and Skin-Hydrating Properties of a Dietary Supplement and Topical Formulations Containing Oligomeric Proanthocyanidins

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Key Words
Erythema · Skin hydration · Procyanidins · Oligomeric proanthocyanidins · Anti-inflammatory properties

Abstract
Background: Anti-inflammatory and skin hydration properties of a dietary supplement and 2 topical formulations (Anthogenol®) with oligomeric proanthocyanidins were investigated. ***Methods:*** Forty-two subjects were randomized into 2 groups: one taking the dietary supplement (100 mg/day) and the other without supplement. After 4 weeks, erythema was induced using UV radiation followed by treatment with topical cream or lotion. Erythema was measured for up to 72 h after irradiation. Skin hydration after 1 and 2 weeks of application of the cream and lotion was also measured in separate test fields. ***Results:*** Both topical formulations led to a significant suppression of erythema formation and the dietary supplement led to an additional slightly stronger suppression. Thus 72 h after UV exposure and compared to the control fields of patients that had not taken a dietary supplement, erythema was slightly (13.2%) lower in the subjects that had taken a dietary supplement. The cream resulted in a maximal reduction of erythema of 45.9% ($p = 0.0015$), while the lotion resulted in a maximal reduction of 53.1% ($p = 0.0002$). Both topical formulations also increased skin hydration (by nearly 20%; $p < 0.002$ for all combinations of dietary supplementation and topical treatment) and the hydration was higher in the group taking the dietary supplement. ***Conclusion:*** The regular use of Anthogenol® products may help to protect from free-radical-mediated skin inflammation and to increase skin hydration.

Introduction

Chronic exposure to UV radiation is thought to be the primary cause of photoaging and may also play an important role in more serious consequences such as skin cancers. UV light is an external oxidative stressor on the skin and the level of generated free radicals depends on the UV dose [1].

Exposure to UV radiation can deplete the skin's endogenous antioxidant system and the application of exogenous antioxidants may help to reduce free-radical-induced damage [1, 2]. Excessive exposure to UV light results in a free-radical-mediated inflammatory response in the skin (erythema). The ultimate aim of protecting the skin against sunlight is to prevent the consequences of the damaging effects of UV radiation. Providing antioxidants in the superficial skin layers by topical applica-

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Table 1. Demographic data of subjects (ITT population)

Characteristic	No dietary supplement (n = 21)	Dietary supplement, 100 mg/day (n = 21)
Age, years	33.1 (range 19–47)	37.8 (range 22–49)
Males	6	4
Females	15	17
Skin type frequencies, n		
Type I	6 (28.6%)	4 (19.0%)
Type II	13 (61.9%)	9 (42.9%)
Type III	2 (9.5%)	8 (38.1%)

tion and/or by supplementation with nutrients may support the skin's defenses, thereby protecting it against the harmful effects of UV light.

Oligomeric proanthocyanidins (OPCs) are phytonutrients that belong to the polyphenol family of antioxidants and possess a high free-radical-scavenging activity. Studies have shown that some procyanidolic oligomers are more effective at scavenging free radicals than vitamin E [3]. There is much evidence supporting the beneficial effects of dietary OPCs against free-radical-mediated conditions such as ischemia and reperfusion injury, arthritis, carcinogenesis, chronic inflammation and allergy [4–7]. In addition to their antioxidant properties, the anti-inflammatory effect of OPCs has often been attributed to their ability to increase capillary resistance [8, 9]. OPCs have also been shown to protect collagen and elastin from degradation by collagenases and elastases [10, 11].

The anti-inflammatory, antiallergic and antiaging properties attributed to OPCs are of particular interest in dermatology. Indeed, early in vivo studies in male albino guinea pigs show that the topical application of a cream containing OPCs (derived from *Vitis vinifera*) after exposure to UV radiation suppressed erythema in these animals by 34% [12]. Kapoor et al. [13] showed that the intradermal application of OPCs improved wound healing in rats. However, the skin care properties of dietary supplementation with OPCs, though often implied, have not been documented well in clinical situations [14].

Supporting the ability of the skin to cope with UV exposure would thus be a highly beneficial skin care property of any topical formulation. Exposure to UV radiation results in a free-radical-mediated inflammatory response in the skin (erythema) characterized by a reddening of the skin. The suppression of UV-induced erythema is a useful variable to indirectly evaluate the anti-inflammatory effect of dietary supplements as well as topically applied formulations.

The main objective of this study was to evaluate the skin care properties of dietary supplementation with OPCs in combination with 2 topical formulations when applied after exposure to UV radiation. The test products – a dietary supplement, a cream and a lotion – were formulated to serve as an effective skin care regimen to combat free-radical-mediated inflammatory response following UV exposure (erythema), while also providing essential hydration to the skin.

Three different UV doses were investigated, allowing an evaluation of the range of effectiveness. In addition, the skin hydration properties of the test products were assessed by measuring skin hydration in a separate test on the same subjects.

Materials and Methods

Subjects

The realization of the study was approved by the Freiburg Ethics Commission International (Freiburg, Germany). Written informed consent was obtained from 42 healthy volunteers prior to inclusion in the study. The demographic data of the subjects are listed in table 1.

Major exclusion criteria were: acne, suntan, eczema, hyperpigmentation or tattoos within the area of the test fields; a history of photosensitivity; skin type IV–VI according to Fitzpatrick; pregnancy or nursing; any clinically relevant and significant illness; the application of cosmetic products in the treatment areas 2 weeks before or during the study; taking food supplements 4 weeks before or during the study; known allergic reactions to cosmetics or adhesive patches; the use of systemic or locally acting medications such as antihistamines or glucocorticosteroids, including treatments which increase light sensitivity.

Test Products

All test products (Anthogenol® dietary supplement, Anthogenol® cream and Anthogenol® lotion) were provided by the International Nutrition Company (Loosdrecht, The Netherlands); the cream and the lotion were provided blinded by the sponsor. Anthogenol® products contain single (monomers) and slightly

condensed (dimers up to pentamers) forms of flavan-3-ol (monomeric and oligomeric proanthocyanidins) derived from *V. vinifera*. The Anthogenol® cream components listed by the International Nomenclature of Cosmetic Ingredients (INCI) are: aqua, glyceryl stearate, glycerin, dicaprylyl ether, ceteareth-20, cetearyl alcohol, hexyldecyl laurate, ester-OPC, *Butyrospermum parkii*, tocopheryl acetate, caprylic/capric triglyceride, dimethicone, phenoxyethanol, polyacrylamide, panthenol, ceteareth-12, cetyl palmitate, C13-14 isoparaffin, methylparaben, propylparaben, laureth-7, butylparaben, ethylparaben, and isobutylparaben. The Anthogenol® lotion components are: aqua, ethylhexyl cocoate, cyclomethicone, hydrogenated polydecene, alcohol, glycerin, cetyl PEG/PPG-10/1 dimethicone, perfume, disodium phosphate, cera alba, tocopheryl acetate, phenoxyethanol, ester-OPC, cera microcristallina, methylparaben, propylparaben, limonene, linalool, hydroxy-isohexyl 3-cyclohexene carboxaldehyde, hydroxycitronellal, citronellol, citral, and α-isomethyl ionone.

Treatment with Dietary Supplement

After enrollment in the study, the subjects were randomized into 2 groups (n = 21 per group). One group received a dietary supplement (50 mg, twice daily) for a period of 6 weeks, the other group did not receive any supplement. Four weeks after starting supplementation, the UV erythema and skin hydration tests began.

UV Erythema Test

A sun simulator (Uvaspot 2000, Hönle, Martinsried, Germany), emitting UVA, UVB (16:1) and reduced visible light, was used to provide even surface lighting with an UVB intensity of 4 mW/cm^2. In order to set the required intensity, the distance of the source from the plane of the surface to be irradiated was adjusted before every irradiation series with a UVA/B meter (Waldmann, Villingen-Schwenningen, Germany).

Twenty-four hours before induction of the UV erythema, an 8-step light scale was used to determine the minimal erythema dose (MED). The UV dose was increased by 15% per step. The light scale was read 24 ± 2 h after exposure. The exposure time of the first field showing distinct erythema was taken as 1 MED.

A light-impermeable template with perforated holes (1.2 cm diameter each) corresponding to the 9 test fields was then attached to the back. All test fields were irradiated simultaneously. The 3 fields in each UV dosage group were covered simultaneously with a light-impermeable strip at the end of the individual exposure time calculated for 1.25, 1.6 and 2.0 MED. The assignment of the 3 UV doses (1.25, 1.6 and 2.0 MED) to the upper, middle or lower region of the back was permutated over all subjects. Approximately 200 μl of the topical test products were applied occlusively to the treatment fields in the Finn® chambers (18 mm) immediately following UV irradiation and after measurements at 24 and 48 h after irradiation. One control field per irradiation dose was irradiated and occluded but otherwise left untreated.

Colorimetry

The evaluation of the test fields by colorimetry was performed prior to the irradiation of the test fields as well as 24, 48 and 72 h after irradiation. One hour before the measurement periods started, the occluding chambers were removed and test preparation residues were gently removed with a soft disposable towel.

Skin color was measured using a Chroma-Meter CR 300 (Konica Minolta, Bremen, Germany). Values were recorded in accordance with the L*a*b* system, the value on the 'red-green' axis (a*) reflecting the degree of skin reddening. Three measurements were taken from each test field in each measurement series. The a* values were expressed as arbitrary units. The test products themselves had no influence on the skin color measurements.

Skin Hydration

Skin hydration in the subjects was measured before beginning with the dietary supplementation, before the first application of the test products and after 7 and 14 days of twice daily application. Approximately 0.4 g of each test product were applied openly twice daily for 2 weeks to the test fields (5 × 5 cm^2) located on the volar side of the forearm. The assignment of the test products to the test fields was random. The hydration of the stratum corneum was assessed by measuring the electrical capacitance of the skin using a corneometer (CM 825, Courage & Khazaka, Cologne, Germany). Five measurements were made in each test field for each measurement series. The subjects rested in an air-conditioned room maintained at 20 ± 2°C and 50 ± 10% humidity for at least 30 min before measurements.

Statistics

The mean of the 3 a* values measured per test field was used to calculate the a* value differences between the irradiated test fields and the pre-irradiation values measured in the same fields. The normal distribution of the adjusted chromametric data was tested using the Kolmogorov-Smirnov test. Global differences between treatments were tested by performing an analysis of variance, using the pooled adjusted a* values from all irradiation steps in a repeated measures design. Multiple comparisons between treatments were made using the Tukey HSD test. All p values were two-tailed.

The mean of 5 skin hydration measurements per test field was used for statistical calculations. The change in skin hydration during the treatment period was tested using the Student t test. Baseline-normalized data were used to compare the study preparations at the end of the treatment period (Student t test). The baseline was defined as the corneometry value recorded immediately before the first application of the topical test products.

Results

All 42 subjects completed the study as planned. The dietary supplement and both topical formulations were tolerated well in this study.

UV Erythema Test

The course of development of the UV inflammatory reaction is a dynamic process dependent on the strength of the inflammatory stimulus. The natural course of erythema development under the experimental conditions used in the present study can be seen in the untreated ir-

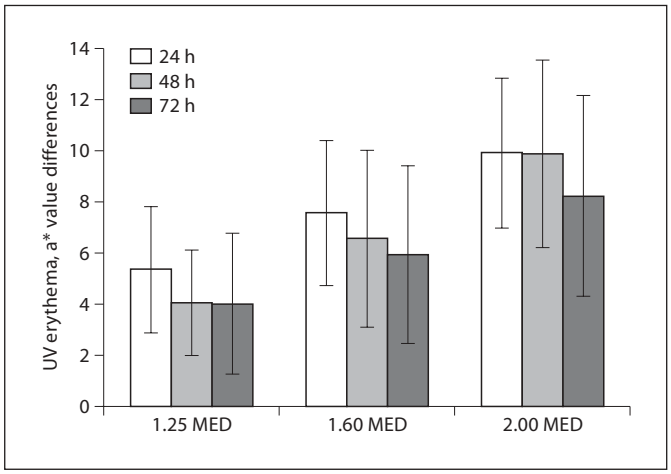

Fig. 1. Erythema (a* value differences to pre-irradiation state) after 24, 48 or 72 h following 1.25, 1.6 or 2.0 MED UV radiation. Values indicate the redness measured in untreated test fields in the subjects with no dietary supplement. Each point represents the mean ± SD; n = 21.

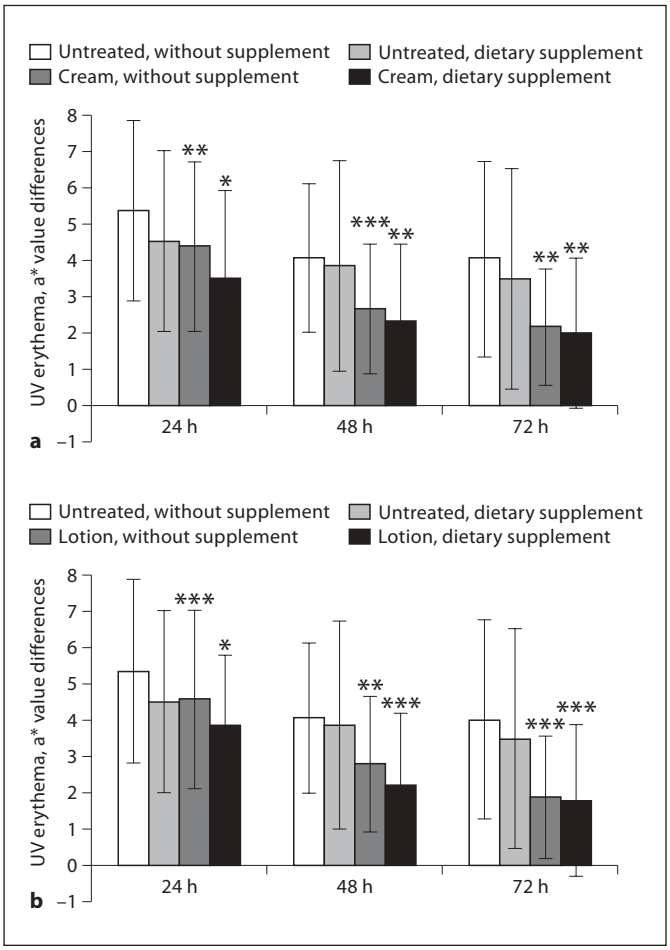

Fig. 2. Erythema (a* value differences to pre-irradiation state) measured in the test fields with and without dietary supplementation or topical application of cream (**a**) or lotion (**b**) after irradiation with 1.25 MED. Each bar represents the mean ± SD, n = 21. For comparison with the untreated group without supplement: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

radiated fields (fig. 1). A relation between UV dose and response was observed for the fields irradiated with 1.25, 1.6 and 2.0 MED, with higher mean a* value differences to the baseline in those fields that were treated with higher UV doses. In the fields irradiated with 1.25 and 1.6 MED, maximal redness was measured 24 h after irradiation, with a continuous regression of redness after 48 and 72 h. In the fields treated with 2.0 MED a decline of the maximal erythema was only seen after 72 h.

The effects of the dietary supplement and the 2 topical formulations on the development of the UV erythema following a dose of 1.25 MED are shown in figure 2. In the group receiving the dietary supplement Anthogenol, a slightly lower skin redness was measured in the untreated fields. The difference was most visible 24 h after UV exposure (15.7%; difference after 48 h: 5.2%, after 72 h: 13.2%; p = n.s.). After 24 h, the topical application of the cream (fig. 2a) and lotion (fig. 2b) resulted in similar reductions in erythema. Treatment with the cream led to a reduction of 18.1% in erythema in the group without dietary supplement (p = 0.0020) and of 23.0% in the supplemented group (p = 0.0239). The effect of the lotion was 14.9% (p = 0.0241) and 14.3% (p = 0.0215) in the groups without and with supplement, respectively. In general, the suppression of erythema was maximal in the group that took the dietary supplement and applied the cream or the lotion (fig. 2).

The use of the food supplement did not further suppress the development of erythema. However, for both topical applications, the suppression of erythema continued to increase over time and it was maximal 72 h after UV exposure (fig. 2). Thus, 72 h after UV irradiation the topical application of cream resulted in a 45.9% (p = 0.0015) maximal reduction of erythema while the lotion resulted in a 53.1% (p = 0.0002) maximal reduction.

Similar effects were observed at all the other UV irradiation doses tested (data not shown). For all 3 irradiation doses the effect of the cream and the lotion increased from 24 to 72 h. Calculated over all test points and UV doses, the effect of both topical formulations compared

to the untreated control was highly significant (cream and lotion: $p \leq 0.0001$). The suppression of erythema in both groups (with or without dietary supplement) and in the fields treated with the cream and lotion was maximal at 1.25 MED and minimal at 2.0 MED (data not shown).

Skin Hydration

Most subjects had dry skin in the test fields prior to treatment. The mean corneometer values at the baseline ranged from 39.65 to 42.06 (p = n.s.) in the fields to be treated with the cream or the lotion and the untreated control field (table 2). Corneometer values lower than 50 on the arms are generally considered indicative of dry skin (information from Courage & Khazaka).

The effect of the test products on skin hydration is shown in figure 3. There was an increase in skin hydration in the groups with (7.2%) and without (9.7%) dietary supplementation during the 4-week supplementation period prior to the testing of the topical products (data not shown). One week after the start of the topical application, there was a further increase in skin hydration in the untreated fields in both groups, slightly larger in the group with dietary supplementation (6.8%) compared to the group without the supplement (1.7%; p = n.s.). During the last week of dietary supplementation, skin hydration increased more substantially in the group with supplementation (11%) than in the group without supplementation (2.7%, increase compared to the start of the topical treatment; p = n.s.).

Twice daily application of the cream or lotion resulted in a significant increase in skin hydration over the 2-week period (fig. 3 and table 2). The skin-hydrating effect was already apparent after 1 week of twice daily application with an approximate increase of 20% in skin hydration

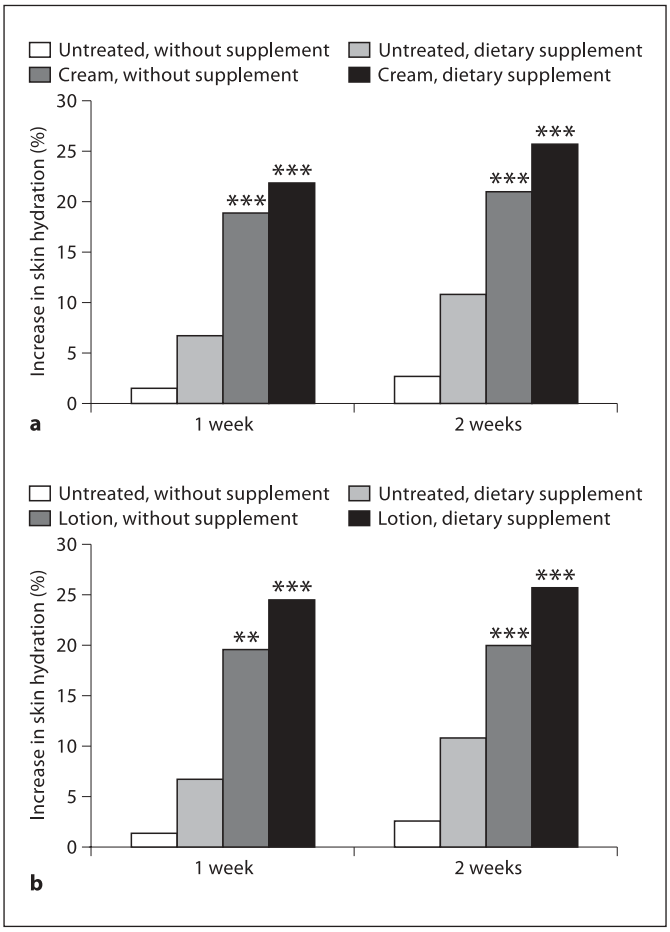

Fig. 3. Each bar represents the mean increase in skin hydration, n = 21. Subjects in the supplement group took an OPC supplement for 4 weeks prior to the start of the topical application of cream (**a**) and lotion (**b**) and continued to take the supplements for the 2-week application period. The cream and lotion were applied twice daily. For comparison (paired t test) with the start of the topical treatment: ** $p < 0.01$, *** $p < 0.001$.

Table 2. Skin hydration data (ITT population)

	Baseline (n = 21)	1 week (n = 21)	p	2 weeks (n = 21)	p
Untreated, without supplement	42.06 (6.14)	42.76 (10.83)	n.s.	43.20 (8.01)	n.s.
Untreated, dietary supplement	39.90 (8.32)	42.60 (10.07)	n.s.	44.30 (8.91)	n.s.
Cream, without supplement	39.65 (8.08)	47.16 (8.79)	<0.001	47.99 (7.93)	<0.001
Cream, dietary supplement	40.52 (8.35)	49.40 (9.48)	<0.001	50.99 (7.55)	<0.001
Lotion, without supplement	40.46 (7.77)	48.51 (7.67)	<0.01	48.58 (8.37)	<0.001
Lotion, dietary supplement	39.67 (7.41)	49.45 (10.79)	<0.001	49.93 (8.43)	<0.001

Comparison to baseline, means with SD in parentheses.

($p < 0.002$ for all combinations of dietary supplementation and topical treatment). As shown in figure 3, the improvement in skin hydration was similar in the fields treated with cream or lotion. At the end of the second week of treatment, a slight additional increase in skin hydration was seen but the untreated reference field increased comparably. The increase in moisturizing effect from the baseline to the end of study (2 weeks) compared to the untreated control was highly significant for both the cream and the lotion ($p \leq 0.0001$). At both test points (after 1 and 2 weeks), the increase in skin hydration after the application of cream or lotion was slightly higher in the group that took the dietary supplement compared to the group that did not take any supplement, although this difference was not statistically significant.

Discussion

The present results indicate the good anti-inflammatory and skin hydration properties of 2 topical formulations – a cream and a lotion. Additionally, the results of this study suggest that a dietary supplementation with OPCs might further support skin care.

Studies investigating the effect of dietary supplementation with antioxidants on the protection of the skin against free-radical-induced injury, e.g. injury triggered by UV radiation, have reported mixed results. The oral administration of a combination of vitamin C and vitamin E for a period of 3 months significantly reduced the UVB-induced epidermal damage and protected against DNA damage following UVB challenge [15]. Saliou et al. [16] demonstrated that supplementation with a procyanidin-rich pine bark extract for up to 8 weeks protected the skin against UV-induced erythema. In contrast, other investigators have observed no UV protection in terms of the sensitivity of the skin to light upon dietary supplementation with antioxidants. Chow et al. [17] reported that a 4-week intake of green tea polyphenols (800 mg/day of epigallocatechin gallate) did not affect the MED of the subjects. Similarly, McArdle et al. [18] found that supplementation with vitamin E or β-carotene did not affect the skin's sensitivity to UV light.

In this study, the degree of erythema which developed 24 h after UV exposure with 1.25 MED was 15% lower in the group with dietary supplementation with OPCs. However, this effect was not statistically significant. Clinical studies investigating the anti-inflammatory and antiallergic properties of OPCs have usually used higher doses of OPCs and/or a longer duration [19, 20]. Considering that the supplementation period in the present study was relatively short with supplementation only for 4 weeks prior to the UV erythema test, a longer duration of supplementation or a higher dose of OPCs might be necessary to conclusively establish their role in countering the inflammatory response in UV-induced erythema. Future studies using higher doses and/or a longer duration of supplementation will further clarify the effect of this phytonutrient in the protection against UV-induced erythema.

The suppression of UV erythema following the topical application of products is very well known. The photoprotective effects of topically applied antioxidants – including the vitamins E and C, melatonin and the green tea constituent (–)-epigallocatechin-3-gallate – when applied before UV radiation, have been reported [21–23]. However, when formulations are applied prior to UV irradiation, sunscreen effects resulting from UV absorption by the formulation may contribute to the reduction of erythema development. The effect of antioxidant formulations applied after irradiation is less clear. Dreher et al. [24] were unable to demonstrate a significant protective effect of vitamin E, vitamin C or melatonin when applied after irradiation. In contrast, clear suppression of UV erythema was seen for cosmetic formulations with hamamelis that were applied after irradiation with 1.2–1.7 MED [25, 26].

In this study, the tested cream and lotion led to a significant suppression of erythema when applied after irradiation with 1.25–2.0 MED. After 24 h an effect was apparent which increased at the later test points and was highly significant after 48 and 72 h. Both topical formulations were applied to the test field only after UV exposure. This indicates that these formulations have a true anti-inflammatory effect and not only a sunscreen effect.

The mechanism by which these products protect against the development of erythema is not known. However, both these formulations contained OPCs. The topical application of exogenous antioxidants may lessen the deleterious effects of free radical damage triggered by UV exposure [2]. The beneficial effects of the topical products used in this study might thus be the result of the antioxidant effects of OPCs present in these formulations. However, further investigation is necessary to determine if the OPCs present in the formulations played a key role in the beneficial effects.

In addition to the anti-inflammatory effects, the cream and lotion also demonstrated significant skin-hydrating effects. An increase in hydration of nearly 20% in subjects

with predominately dry skin was seen after 1 week of regular use. The effect persisted with continued use. Dietary supplementation with OPCs on its own resulted in a minor but nonsignificant increase in skin hydration.

In conclusion, the results of this study demonstrate significant anti-inflammatory and skin-hydrating properties of the tested cream and lotion. The combination of the dietary supplement with the tested topical skin care products resulted in additional effects greater than either of the products used alone. The regular use of these products may thus be beneficial in skin care, especially as a defense against the development of erythema from UV exposure.

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