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ORIGINAL ARTICLE

# The combination of oral and topical photoprotection with a standardized *Polypodium leucotomos* extract is beneficial against actinic keratosis

Giovanni Pellacani[1] | Ketty Peris[2] | Silvana Ciardo[3] | Claudia Pezzini[3] | Sara Tambone[2] | Francesca Farnetani[3] | Caterina Longo[4] | Camilla Chello[1] | Salvador González[5]

[1]Dermatology Clinic, University La Sapienza, Rome, Italy

[2]Dermatology Clinic, Catholic University, Rome, Italy

[3]Dermatology Clinic, University of Modena and Reggio Emilia, Modena, Italy

[4]Ospedale S. Maria Nuova – IRCCS, Reggio Emilia, Italy

[5]Department of Medicine and Medical Specialties, Alcalá de Henares University, Madrid, Spain

**Correspondence**
Giovanni Pellacani, Dermatology Clinic University La Sapienza, Rome, Italy.
Email: pellacani.giovanni@gmail.com

Caterina Longo, Ospedale S. Maria Nuova – IRCCS, Reggio Emilia, Italy.
Email: longo.caterina@gmail.com

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## Abstract

**Introduction:** This study describes a prospective, multicentre, randomized controlled, open-label study with three arms aimed at studying the differences between: [Cnt], self-administered sun protection; [T], topical treatment; and [TO], topical + oral treatment; for the management of Actinic Keratosis (AK) in a cohort of subjects of advanced age displaying severe actinic damage (SAD).

**Methods:** Treatments administered to groups [T] and [TO] had a common component, which is a botanical extract, Fernblock, with demonstrated photoprotective activity.

**Results:** In total, 131 subjects were distributed randomly in the three groups, and followed up clinically at three separate time points, beginning of the study ($t = 0$) and after 6 and 12 months. Analysis of clinical data and examination using reflectance confocal microscopy (RCM) revealed that group [T] and [TO] displayed decreased clinical AK and field cancerization parameters, including the number of new lesions, and reduced the need for additional interventions in these patients. RCM revealed normalization of the keratinocyte layer. Improvements in AK and field cancerization parameters were greatest in the group [TO], suggesting that topical and oral photoprotection improves the clinical and anatomical outcome compared to control conditions.

**Conclusions:** The combination of topical and oral immune photoprotection provides an advantage compared to topical photoprotection alone.

KEYWORDS
actinic keratosis, controlled trial, Fernblock, oral photoprotection

## 1 | INTRODUCTION

Excessive exposure to sunlight or UV radiation causes acute and chronic skin damage. Actinic damage can be acute, i.e. sunburn; chronic damage causes photoaging and cancer, including melanoma and non-melanoma skin cancer. Photoprotection helps prevent these damages. The most common strategy is the use of topical sunscreens. Sunscreens are primarily composed of chemical (also known as organic) and/or physical (also known as inorganic) filters, although some of them contain additional components such as photon quenchers and antioxidant substances, often of natural origin, which reduce UV-induced oxidative damage. The main limitation of

this approach with respect to its implementation is practical: most subjects do not apply the sunscreen correctly, or sufficiently, over time. Multiple lines of evidence indicate that an insufficient dose at first application and failure to reapply after elimination or removal of the filters from the skin due to sweating, friction, etc., are major risk factors for skin damage and the onset of cancer. This alone justifies the use of systemic (oral) photoprotectors, which complement topical photoprotection with generalized anti-oxidant activity, DNA protection and repair, protection of skin immunosurveillance, anti-aging and anti-hyperpigmentation activities. For this reason, we sought to evaluate the effects of a specific topical formulations and the potential additional protection offered by oral photoprotection in high-risk subjects.

Actinic Keratosis (AK) is a chronic, recurrent, and frequent disease caused by prolonged exposure to the Sun.[1,2] It is a high prevalent disease in Caucasians, affecting over one-third of adults over 60 year-old individuals in Europe, and up to 60% in Australia.[3,4] AKs are considered as initial forms of squamous cell carcinoma (SCC).[5] They may evolve into invasive SCC through the progressive and sequential transformation of neoplastic intraepidermal keratinocytes, identified and classified as histopathological grade I, II, and III, or through early invasion of early (grade I) lesions that evolve into invasive tumors directly.[6] Thus, the risk of developing SCC positively correlates better with the number of AK lesions than the single lesion histological grade.[7] Also, apparently unaffected sun-exposed areas in patients with AK present skin alterations similar to AK region, defining the so-called cancerization field, a wide skin area prone to develop new AKs and non-melanoma skin cancer.[8,9]

The fact that UV radiation present in sunlight is the main cause of the disease, photoprotection is necessary. In this respect, systemic photoprotection could provide useful additional protection, as suggested by a clinical trial showing that systemic photoprotection decreased the incidence of SCC.[10] However, the lack of systematic and robust data results in a lack of consensus regarding the use of sunscreens, which gives too much leeway to the criteria of the physician or dermatologist regarding the use of additional measures, such as oral photoprotectors in high-risk groups.

Here, we postulate that systemic (oral) photoprotection administered in a controlled, systematic manner, increases the efficiency of topical treatment in subjects with severe actinic damage. To address this, we follow up on a combination of clinical parameters, that constitute the basis of easy-to-use "photo score", and microscopic examination of the skin carried out by means of non-invasive technique (in vivo reflectance confocal microscopy (RCM)), for determining intensity of damage and efficacy of the intervention.[11] The hypothesis is that this photo score will improve in subjects receiving protocol-determined doses of a specific topical sunscreen containing a non-filtering botanical extract compared to control subjects that use sunscreen ad libitum; and that the addition of a regime of a systemic (oral) photoprotector in addition to the topical regime would improve the photo score even further.

We selected a photoprotector (Fernblock, also referred to as *Polypodium leucotomos* extract, abbreviated PLE) that is used both topically and orally. Fernblock (standardized PLE) is a natural substance with well-documented beneficial effects in terms of photoprotection[12–14] and systemic reduction of Cyclobutane Pyrimidine Dimer (CPD) production in the dark after UV exposure.[15] Its mechanism of action includes anti-oxidant and DNA repair ability[16,17]; inhibition of t-UCA isomerization[18]; and prevention of immune cell depletion upon UV irradiation.[14,17,19] To our knowledge, this is the first assessor-blind, controlled trial evaluating the photoprotective effect of PLE, topical or topical + oral in high-risk patients bearing severe actinic damage.

### 1.1 | Study aim

Here, we have evaluated the effects of different sun protection strategies, subjects displaying severe actinic damage (SAD) were randomly assigned to one of three groups: [Cnt] = general, non-specific photoprotection measures as decided by the patients (doctor recommendation of sun protection with SPF100, but patients' free choice of product); [T] = topical photoprotection alone (SPF100+ gel containing PLE, twice daily in sun-exposed skin areas, including face, scalp, arms and dorsal part of the hands); [TO] = topical photoprotection (SPF100) combined with oral photoprotection (oral PLE, 240 mg once daily).

## 2 | MATERIALS AND METHODS

The present study was reviewed and approved by the Ethical Committee of Modena and Reggio Emilia University and Cattolica University, then conducted in two Dermatology University Clinics, one in Modena (66 subjects) and the other in Rome (65 subjects), Italy, from 09/2017 to 12/2019.

### 2.1 | Subjects

A total of 131 subjects (84% men, mean age 74 years) with severe photoaging and history of at least 3 actinic keratosis agreed to participate in this trial, providing written informed consent. The patients were assigned randomly to the [Cnt], [T], or [TO] groups. using a randomization list created with the Stata program, statistical software release v14. StataCorp LP. There was no matching (demographic or otherwise) during the patient assignment. The inclusion criteria were: clinically relevant photodamage signs (Clinical Photoaging score > 16); with previous multiple AK located in the face and/or scalp; treated for AK and cancer site within 1 month of enrolment; displaying no need for further treatment and scheduled for just clinical follow-up according to the current guidelines; immunocompetent; age range: 60–85 years old. Exclusion criteria were: history of organ transplantation; previous skin cancer diagnosis, excluding BCC and SCC, to the face or scalp; or tumors of any nature that may result in systemic localization; previous diagnosis of dermatological

diseases that might confuse the findings of the present study, e.g., LES, high-sensitivity photosensitivity, rosacea, etc.; age outside of the 60–85 years old range; inability to comprehend and thus provide formal consent for inclusion in the study or unable to follow the instructions provided to the different treatment groups; very limited photo exposure, e.g., subjects that do not leave their house; allergies and/or adverse reactions to the active principles, or adjuvants, of the topical and oral components of the formulations used in the study.

## 2.2 | Study design

This was a multi-center prospective, randomized, parallel-group, assessor-blinded trial. A total of 3 clinical assessments (at enrolment, $t = 0$; after 6 months, 6m; after 12 months, 12 m) were performed on each subject.

## 2.3 | Ethics statement

The study was conducted in compliance with the GCP, the ethical principles deriving from the Helsinki Declaration, and the current legislation on observational studies. The EC code given to the study at EC of Modena was 312.2017 (EC approval 24/10/2017).

## 2.4 | Study outcomes

The trial outcomes include: AKASI (Actinic Keratosis Area Score Index)[20]; AK-FAS (Actinic Keratosis Field Assessment Scale)[21]; appearance of new AK lesions; need for specific AK-related interventions, such as PDT, cryotherapy, 5-FU, imiquimod, etc.

*AKASI*: Four skin areas were considered to determine the AKASI score: scalp, forehead, and both sides of the face. In each region, the percentage of the surface affected by AK, the distribution, the intensity of the erythema, and the degree of thickness of the most severe lesions were classified numerically. The sum of the four scores was multiplied by the area coefficient to obtain a partial score for each area of the head. The sum of the 4 scores determined the final AKASI score.[20]

*AK-FAS*: it was calculated as physician global evaluation of the extent of area covered by AK, and, separately, the severity of hyperkeratosis and photodamage. The AK-FAS, therefore, represented a grading of the severity of AK disease and cancerization field together, considering the whole area and not the number of lesions.[21]

Clinical evaluations were made during every follow-up visit and therefore were not blinded (patients were given additional topical or topical+oral additional products at the end of the two follow-up visits).

*RCM parameters*: Lesions were observed using RCM (Vivascope 1500) and recorded at each visit. RCM imaging involved the acquisition at each visit of 3 mosaics at different depths (Vivablock) to represent the horizontal plane of the epidermis, the dermo-epidermal junction, and the superficial dermis. At the center of each lesion, a Vivastack (corresponding to a series of 50 images from the surface at 100 μm depth spaced 2 μm each) was acquired to measure the following parameters, defined in.[22,23] Epidermal parameters studied included: Irregular honeycomb pattern scored from 0 to 4 (0 = absent, regular honeycomb pattern, 1 = <25%; 2 = 25%–50%; 3 = 50%–75%; 4 = 75%–100% of the total surface); Mottled pigmentation, scored from 0 to 4 (0 = absent, 1 = <25%; 2 = 25%–50%; 3 = 50%–75%; 4 = 75%–100% of the involved area). A junctional parameter examined was the appearance of polycyclic papillary contours, defined as elongated structures and cords, sometimes anastomosed, separated by dark areas, with an intricate texture, usually observable in solar lentigos. The presence of these structures is a marker of photo damage,[24] scored from 0 to 4 as above. Dermal parameters include: Collagen appearance, as described in,[24] including: thin reticulated; coarse (bundled); huddled (thickened); curled bright (wavy) structures. Each sub-category was scored as described elsewhere.[25]

RCM evaluations were conducted blinded from the randomization arm.

Additional parameters include: adverse events emerging during the study, related to the use of the products; skin color homogeneity at 6 and 12 months; visual assessment of the treated area and untreated areas; the degree of patient satisfaction and adherence to the study for 12 months. These last data were collected through a survey using a fillable form, which included questions regarding sun habits, photoprotection, and self-perception.

## 2.5 | Statistical analysis and sample size calculation

The hypothesis is that [T] and [TO] groups display a better clinical score of the analyzed parameters compared to the [Cnt] group. Sample size calculation was carried out using with G*Power 3.0.10 software (17695343). Sample size calculation was complicated by the fact that reports on average AKASI scores for these patients are scant, and it is difficult to predict the degree of improvement caused by the treatments. Setting up an initial AKASI score average of 4.75, we estimated that a reasonable improvement threshold could be 20% (3.75). These parameters returned the following statistical values: $\alpha = 0.025$; $\beta = 0.2$; $r$(ratio) = 1 (allocation of 1 subject to one experimental group and 1 subject to the control group). These parameters define a sample size of 44 subjects in the experimental and control groups for a total of 132 subjects.

Data collected, including socio-demographic and lifestyle-related information, was described as percentages for categorical and medium variables and Standard Deviation (SD) for continuous variables. Those variables were tested for association with outcome measurements as follows: comparison among the groups relied on analyzing the frequencies of the main end points using the Kruskal-Wallis test. Other binary endpoints were evaluated using the Chi framework test, while the end points measured by continuous variables were evaluated using Student's $t$ test for comparison between two groups; Kruskal-Wallis for comparison among the three groups.

Endpoint 1 = comparison of subjects' averages among the three different groups by the Kruskal-Wallis test. The primary null hypothesis H1 is that subjects in the [Cnt] group would display the highest scores, meaning the worse situation; followed by those enrolled in the [T] group; subjects in the [TO] group would display the lowest scores, i.e. the highest degree of improvement.

Endpoint 2 = Association between AKASI score and the following variables: number of sunny days; lifestyle; BMI; smoke; alcohol consumption. The H2 hypothesis is that there is an association between the score (dependent variable) and the subsequent independent variable variables, considered in a multivariate regression model, correcting for the following confounding factors: age, gender, education, professional life, etc.

## 3 | RESULTS

The study was carried out between September 2017 and December 2019 in two Dermatology University Clinics in Modena (66 subjects) and Rome (65 subjects), Italy. Subjects were originally enrolled as follows: 43 in [Cnt] group; 44 in [T] group and 44 in [TO] group. Of these, 116 (89%) came back to the 6-month follow-up, and 97 (74%) made it to the 12-month appointment. Table 1 collects the demographic data of the subjects.

Regarding clinical parameters (Tables 2–4), AKASI displayed a 3% increase ($p = .001$) in the [Cnt] group at 6 m compared to $t = 0$. There was no further modification at 12 m. When comparing the subjects in the [T] at the three time points, we found no significant difference. Interestingly, AKASI decreased 3% in the [TO] groups at 6 m, and an additional 3% from 6 m to 12 m (total improvement 7%, $p = .001$ 1 m vs. $t = 0$).

AK-FAS displayed a significant change in the evolution of hyperkeratinization. In subjects from the [Cnt] group, AK-FAS (hyperkeratosis) increased from 9.3% to 20.5% to 30% at $t = 0$, 6 m, and 12 m, respectively. In the [T] group, it decreased from 13.6% to 10.3% to 5.9% at the same time points, whereas in the [TO] group the decrease was 13.6% to 8.6% to 3%.

Relevant differences pertained to the appearance of new AK lesions and/or the need for new interventions for AK treatment (Tables 5 and 6). At 6 m, 10 [Cnt] subjects (25%) had developed at least a new AK, whereas 1 subject only did in the [T] group (2.6%) and none in the [TO] group ($p = .008$). On the other hand, 9 subjects of the [Cnt] group (23%) needed additional treatment, whereas this was the case in 4 subjects of the [T] group (10%) and only one (3%) in the [TO] group ($p = .027$). These 14 patients discontinued the study as per protocol since the field treatments have a large influence on the outcome of the rest of the study. Another two dropped from the study, resulting in the 97 patients that completed the study.

**TABLE 1** Demographical data of the subjects enrolled in this study.

| | Global value (%) | Group | | | *p*-value |
|---|---|---|---|---|---|
| | | [Cnt] | [T] | [TO] | |
| *n* | | 43 | 44 | 44 | |
| Age | 74.7 ± 6.6 | 75.2 ± 6.6 | 75.3 ± 7.1 | 73.8 ± 5.9 | .522 |
| Gender | | | | | |
| Male | 110 (84.0) | 35 (81.4) | 38 (86.4) | 37 (84.1) | .819 |
| Female | 21 (16.0) | 8 (18.6) | 6 (13.6) | 7 (15.9) | |
| Phototype | | | | | |
| I | 3 (2.3) | 0 | 1 (2.3) | 2 (4.5) | .886 |
| II | 58 (44.3) | 18 (41.9) | 20 (45.4) | 20 (45.4) | |
| III | 67 (51.1) | 24 (55.8) | 22 (50.0) | 21 (47.7) | |
| IV | 3 (2.3) | 1 (2.3) | 1 (2.3) | 1 (2.3) | |
| Smoker | | | | | |
| No | 105 (80.9) | 29 (67.4) | 37 (84.1) | 40 (90.9) | .017 |
| Yes | 25 (19.1) | 14 (32.6) | 7 (15.9) | 4 (9.1) | |
| Alcohol | | | | | |
| No | 128 (97.7) | 43 (100) | 44 (100) | 41 (93.2) | .048 |
| Yes | 3 (2.3) | 0 | 0 | 3 (6.8) | |
| Part of the workforce | | | | | |
| No | 88 (67.2) | 30 (69.8) | 28 (63.6) | 30 (68.2) | .818 |
| Yes | 43 (32.8) | 13 (30.2) | 16 (36.4) | 14 (31.8) | |
| Prior KC | | | | | |
| No | 84 (64.1) | 29 (67.4) | 29 (65.9) | 26 (59.1) | .687 |
| Yes | 47 (35.9) | 14 (32.6) | 15 (34.1) | 18 (40.9) | |

Abbreviation: KC, keratinocyte carcinoma.

TABLE 2 Clinical parameters at $t = 0$.

| | Total value (%) | Group [Cnt] | [T] | [TO] | *p*-value |
|---|---|---|---|---|---|
| AKASI | 3.9 ± 1.2 (0.6–6.2) | 3.4 ± 1.2 (0.8–6) | 3.4 ± 1.2 (0.6–5.4) | 3.3 ± 1.1 (1.2–6.2) | .929 |
| AK-FAS (area) | | | | | |
| <10% | 78 (59.5) | 28 (65.1) | 24 (54.6) | 26 (55.1) | .617 |
| 10%–25% | 44 (33.6) | 11 (25.6) | 18 (40.9) | 15 (34.1) | |
| >50% | 9 (6.9) | 4 (9.3) | 2 (5) | 3 (6.8) | |
| AK-FAS (hyperkeratosis) | | | | | |
| No | 115 (78.8) | 39 (90.7) | 38 (86.4) | 38 (86.4) | .776 |
| Yes | 16 (12.2) | 4 (9.3) | 6 (13.6) | 6 (13.6) | |
| AK-FAS (sun damage) | | | | | |
| No | 21 (16) | 8 (18.6) | 7 (15.9) | 6 (13.6) | .819 |
| Yes | 110 (84.0) | 35 (81.4) | 37 (84.1) | 38 (86.4) | |
| PGA | | | | | |
| 1 = mild | 86 (65.6) | 28 (65.1) | 26 (59.1) | 32 (72.7) | .402 |
| 2 = moderate | 45 (34.3) | 15 (34.9) | 18 (40.9) | 12 (27.3) | |

TABLE 3 Clinical parameters at 6 months.

| | Total value (%) | Group [Cnt] | [T] | [TO] | *p*-value |
|---|---|---|---|---|---|
| AKASI | 3.4 ± 1.2 (0.8–6.2) | 3.5 ± 1.2 (0.8–6) | 3.3 ± 1.2 (0.8–5.4) | 3.2 ± 1.1 (1.2–6.2) | .416 |
| AK-FAS (area) | | | | | |
| <10% | 68 (60.2) | 23 (58.9) | 23 (59.0) | 22 (62.9) | .900 |
| 10%–25% | 36 (31.9) | 12 (30.8) | 14 (35.9) | 10 (28.6) | |
| >50% | 9 (7.9) | 4 (10.3) | 2 (5.1) | 3 (8.6) | |
| AK-FAS (hyperkeratosis) | | | | | |
| No | 98 (86.7) | 31 (79.5) | 35 (89.7) | 32 (91.4) | .252 |
| Yes | 15 (13.3) | 8 (20.5) | 4 (10.3) | 3 (8.6) | |
| AK-FAS (sun damage) | | | | | |
| No | 10 (8.9) | 4 (10.3) | 5 (12.8) | 1 (2.9) | .299 |
| Yes | 103 (91.1) | 35 (89.7) | 34 (87.2) | 34 (97.1) | |
| PGA | | | | | |
| 1 = mild | 75 (66.4) | 24 (61.5) | 24 (61.5) | 27 (77.1) | .268 |
| 2 = moderate | 38 (33.6) | 15 (38.5) | 15 (38.5) | 8 (22.8) | |

Regarding the appearance of new AK at 12 m, the percentages were: 14% [Cnt]; 0% [T]; 0% [TO], $p < .001$. Multivariate analysis of these outcomes with respect to the clinical features of the subjects included in the study did not reveal any significant correlation in terms of age, skin phototype, and lifestyle.

On the contrary, evaluation of the RCM examination revealed that, at 12 m, the percentage of subjects with normal or almost normal honeycomb pattern as seen by RCM was 26% in [Cnt] subjects, which represented no significant variation between time points; 45% in [T] subjects; and 50% in [TO] subjects ($p = .04$ [T] and [TO] vs. [Cnt]). This result is in accordance with the clinical results observed. The rest of the measured RCM parameters did not display any significant difference (not shown).

Finally, self-assessment of the subjects revealed differences in terms of self-perception ($p < .001$) and modification of photoprotection habits ($p = .03$).

## 4 | DISCUSSION

The present study represents an initial characterization of the benefit of topical + oral supplementation in the management of AK. Evaluation of objective parameters, such as AKASI, revealed an expected worsening of the condition in subjects of the control group, sunscreen use ad libitum, whereas improvements were observed in the group receiving specific topical treatment, and especially in

**TABLE 4** Clinical parameters at 12 months.

| | Total value (%) | Group [Cnt] | [T] | [TO] | *p*-value |
|---|---|---|---|---|---|
| AKASI | 3.3 ± 1.2 (0.6–6.2) | 3.5 ± 1.3 (0.8–6.0) | 3.3 ± 1.2 (0.6–5.4) | 3.1 ± 1.1 (1.2–6.2) | .427 |
| AK-FAS (area) | | | | | |
| <10% | 59 (60.8) | 17 (57.7) | 19 (55.9) | 23 (69.7) | .614 |
| 10%–25% | 30 (30.9) | 10 (33.3) | 13 (38.2) | 7 (21.2) | |
| >50% | 8 (8.2) | 3 (10.0) | 2 (5.9) | 3 (9.1) | |
| AK-FAS (hyperkeratosis) | | | | | |
| No | 85 (87.6) | 21 (70.0) | 32 (94.1) | 32 (97.0) | .002 |
| Yes | 12 (12.4) | 9 (30.0) | 2 (5.9) | 1 (3.0) | |
| AK-FAS (sun damage) | | | | | |
| No | 10 (10.3) | 4 (13.3) | 5 (14.7) | 1 (3.0) | .235 |
| Yes | 87 (89.7) | 26 (86.7) | 29 (85.3) | 32 (97.0) | |
| PGA | | | | | |
| 1 = mild | 66 (68.0) | 19 (63.3) | 20 (58.8) | 27 (81.8) | .105 |
| 2 = moderate | 31 (32.0) | 11 (36.7) | 14 (41.2) | 6 (18.2) | |

**TABLE 5** New lesions and need for retreatment at 6 months.

| | Total Value (%) | Group [Cnt] | [T] | [TO] | *p*-value |
|---|---|---|---|---|---|
| New AK | | | | | |
| 0 | 102 (90.3) | 29 (74.4) | 38 (97.4) | 35 (100) | .008 |
| 1 | 9 (7.9) | 8 (20.5) | 1 (2.6) | 0 | |
| 2 | 1 (0.9) | 1 (2.5) | 0 | 0 | |
| 3 | 1 (0.9) | 1 (2.5) | 0 | 0 | |
| Retreatment | | | | | |
| No | 99 (87.6) | 30 (76.9) | 35 (89.7) | 34 (97.1) | .027 |
| Yes | 14 (12.4) | 9 (23.1) | 4 (10.3) | 1 (2.9) | |

the specific topical treatment + oral photoprotection group. While differences are expectedly small (the conditions of the experimentation predicted a 20% improvement at best, which is the actual dynamic range of the experimental outcome), the data are robust and adhere well to the hypothesis under study, especially because of blind evaluation. However, we believe that the most interesting data pertains to the number of new AK and the need for additional management at 6 m. Only one subject of the [TO] group developed a new AK and needed additional therapy. These data demonstrate that this type of approach can prevent the onset of further lesions in sun-exposed areas of the skin. This observation may influence future clinical approach. In fact, since many years Guidelines recommend both treatment of AKs and cancerization field in the expectation that this approach is capable of reducing AK lesion recurrence and squamous cell carcinoma development, based on data showing that treatment options are superior to placebo regarding lesion clearance.[8] However, most studies focus on short-term clearance evaluated within 3 to 6 months after treatment. A recent pooled analysis of randomized controlled trials found that these results were not maintained in the long term, showing recurrence rates similar to most active interventions and were not superior to placebo.[26] Thus, an effective approach requires lesion and field treatment, followed by intervention intended to reduce lesion recurrence and, likely, squamous cell carcinoma development.

In this study, we showed two main points which could help in future AK management direction:

1. Sun-protection recommendation ad libitum (leaving the patient free to decide sunscreen quantity and quality) is not strongly effective in AK recurrence prevention, whereas a greater benefit is given by specific product recommendations and specific usage indications.
2. Combination of topical + oral photoprotection is significantly reducing AK recurrences and the need for further treatment.

AK-FAS displayed very significant differences in terms of the evolution of hyperkeratosis. This correlates well with the improved self-perception of the subjects in the [T] and [TO] groups of the

**TABLE 6** New lesions and need for retreatment at 12 months.

| | | Group | | | |
|---|---|---|---|---|---|
| | Total value (%) | [Cnt] | [T] | [TO] | *p*-value |
| New AK | | | | | |
| 0 | 93 (95.9) | 26 (86.7) | 34 (100) | 33 (100) | .054 |
| 1 | 3 (3.1) | 3 (10.0) | 0 | 0 | |
| 2 | 1 (1.0) | 1 (3.3) | 0 | 0 | |
| Retreatment | | | | | |
| No | 89 (92.7) | 26 (86.7) | 30 (90.9) | 33 (100) | .112 |
| Yes | 7 (7.3) | 4 (13.3) | 3 (9.1) | 0 | |

study. In addition to the positive effect seen in sun-exposed skin, these data reinforce the observation that adjuvant treatment with topical and oral photoprotectors may be beneficial in patients undergoing phototherapy.[27]

Why topical + oral photoprotection resulted more effective than photoprotection alone could be related to the combination of the protection of keratinocyte from UV direct cell damage during sun exposure and the extended cell protection and homeostasis maintenance given by oral supplementation. In this regard, oral treatment with PLE has been shown to prevent UV-induced depletion of antioxidant enzymes in blood and epidermis in a murine model.[17] This is also likely underlying the normalization of the keratinocyte layer observed by RCM[28] and in line with our results which showed higher frequencies of regular keratinocytes in the treatment groups. What we can assert is that the effects are not due to additional emollients in the PL-containing cream. In fact, members of the [C] and [T] groups were exposed to additional emollients, those in the "normal" sunscreens and those in the PLE-containing cream. However, the effects were much more noticeable in the [TO] group than in the [T], indicating that the observed differences are not due to emollients in the sunscreens or the PLE-containing cream.

Another interesting aspect of the present study is the effect on the attitude of the subjects toward photoprotection. Those in the [T] and [TO] groups were more prone to be less forgetful following sunscreen usage and maintain proper hydration (corresponding to less spots and occurrence of dry skin). This indicates that self-education plays an important role in photoprotection. Another important component of education is the general knowledge that, while sunscreens are an essential component of photoprotection, additional measures such as limitation of sun exposure by actively seeking shades, wearing photoprotective clothing, and use of brimmed hats and sunglasses are key elements of an effective photoprotective strategy.

It is important to acknowledge that the present study has some limitations. First, the groups are large enough to provide statistical power, but not sufficiently to make wider predictions. Another possible limitation of this approach is that, based on the design of the study, there is no formal proof that the ad libitum group followed the suggested application pattern with fidelity comparable to the other groups, which could affect skin hydration and hyperkeratosis. Also, skin phototype and other variables (specific lifestyle, additional dietary supplementation and unrelated medical treatments and procedures that could affect the outcome of the present protocol) would need to be taken into consideration. It is worth mentioning that the present study was impacted by the SARS-CoV-2 pandemic, which limited access to follow-up consultations and had some effect on the sun exposure of some patients due to lockdowns. Despite these issues, the present study showed that specific topical and topical + oral treatment with Fernblock (a biological non-filtering active principle endowed with protective activity when used topically or orally) of subjects already treated for AK and cancerization field (therefore at risk of recurrence), improved the control of AK and prevented new occurrences.

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## CONFLICT OF INTEREST STATEMENT

Salvador González is a consultant for Cantabria Labs, which produces Fernblock.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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