

# Oral administration of a hydrophilic extract of *Polypodium leucotomos* for the prevention of polymorphic light eruption

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**Background:** Polymorphic light eruption (PLE) is the most common idiopathic photodermatosis. Reactive oxygen species have been implicated in the pathogenesis of PLE. *Polypodium leucotomos* (PL) is a natural extract from tropical fern leaves with potent antioxidant and anti-inflammatory properties.

**Objective:** In this study we sought to evaluate whether a concentrated hydrophilic extract of PL might prevent or delay the photoinduction of typical PLE lesions by artificial ultraviolet (UV) radiation.

**Methods:** A total of 35 patients with long-standing PLE were included in this open, uncontrolled bicenter study. PLE was induced by photoprovocation with artificial UVB and UVA light, thereafter oral treatment with PL was initiated. Two weeks later a second photoprovocation was performed while the patients were still taking PL.

**Results:** Thirty patients developed PLE lesions after repeated irradiation with UVA. Of these, 18 patients also responded to UVB. After PL treatment, 9 (30%) and 5 (28%) patients, respectively, were unresponsive to repeated UVA and UVB exposure. In the remaining patients, the mean number of UVA and UVB irradiations required to elicit PLE increased significantly from 1.95 to 2.62 ( $P = .005$ ) and from 2.38 to 2.92 ( $P = .047$ ), respectively.

**Limitations:** The study was open and uncontrolled and included a relatively small number of patients.

**Conclusion:** Our data indicate that oral PL treatment might be beneficial for the prevention of PLE. (J Am Acad Dermatol 10.1016/j.jaad.2010.09.773.)

**Key words:** antioxidant; photoprovocation; polymorphic light eruption; *Polypodium leucotomos*; prevention.

**P**olymorphic light eruption (PLE) is the most common idiopathic photodermatosis.<sup>1,2</sup> The underlying pathogenesis of PLE is thought to

#### Abbreviations used:

MED: minimal erythema dose  
 PL: *Polypodium leucotomos*  
 PLE: polymorphic light eruption  
 UV: ultraviolet

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involve a T-cell–mediated immune reaction directed against a sun-induced cutaneous neoantigen.<sup>3,4</sup> According to a recent cross-sectional study PLE occurs in 18% of Europeans.<sup>5</sup> A link between polymorphisms in the glutathione-S-transferase gene and susceptibility to PLE has been demonstrated in a recent genetic study indicating that reactive oxygen species might play a crucial role in the pathogenesis of PLE.<sup>6,7</sup>

An extract of the tropical fern *Polypodium leucotomos* (PL) has been shown to exert both potent antioxidative and immunomodulatory effects. In a recent open study on 25 patients with PLE the administration of PL extract (480 mg/d) resulted in

a relevant and statistically significant reduction of skin reactions and subjective symptoms.<sup>8</sup> The current study was designed to investigate in a controlled manner whether a concentrated hydrophilic extract of the leaves of PL may inhibit the photoinduction of typical PLE lesions by repetitive irradiation with artificial ultraviolet (UV) B and UVA light.

## METHODS

### Patients and trial protocol

The study was conducted at the Division of Special and Environmental Dermatology of the Department of Dermatology, Medical University of Vienna, Austria, and the Department of Dermatology, Spedali Civili and University, Brescia, Italy. Approval of the local ethics committee was obtained in both centers and all enrolled patients gave informed consent to participate in the study.

Twenty patients with PLE were recruited in Vienna and 15 in Brescia, respectively. The diagnosis of PLE was established by an experienced photodermatologist based on the patient's medical history, the clinical presentation, and the absence of abnormally high antinuclear antibody titers (>1:80).<sup>9</sup>

Inclusion criteria were a typical history consistent with PLE and, if present, a clinical presentation of PLE. Exclusion criteria were children, pregnant or breast-feeding women, any photosensitive disorder other than PLE, and the intake of immunosuppressive drugs within 4 weeks or the topical use of corticosteroids within 2 weeks before study entry.

The study was performed between late fall and early spring and was divided into 3 sections: (1) days 0 to 7, first photoprovocation with repeated exposures to artificial UVB and UVA to induce PLE lesions; (2) days 7 to 28, daily administration of PL extract over 3 weeks; and (3) days 21 to 28, second photoprovocation.

After inclusion into the study, induction of typical PLE lesions by repeated irradiation with artificial UVB or UVA (photoprovocation) was performed in all patients. Initially, the minimal erythema dose (MED) of UVB was determined on day 0 by exposure of buttock skin to a geometric dose series of broadband UVB. On the next day the MED was read and circumscribed areas (5 × 5 cm) of previously affected skin sites (mostly the extensor surface of the upper

aspect of arms, alternatively the upper back of the trunk) were exposed to 1 MED of UVB or a skin phototype-dependent dose of UVA, respectively (day 1). The UVA irradiation dose was 60 J/cm<sup>2</sup> for skin phototype I, 75 J/cm<sup>2</sup> for skin phototype II, 85 J/cm<sup>2</sup> for skin phototype III, and 100 J/cm<sup>2</sup> for skin phototype IV, according to the Fitzpatrick skin type scale.

Photoprovocation was then repeated daily until day 4 or the occurrence of typical PLE lesions in the irradiated skin sites. In the absence of an erythema reaction the irradiation dose of UVB dose was increased by 20% on subsequent exposures whereas the UVA irradiation dose was always kept constant. In case of a negative test reaction at day 4, the patients were subjected to a fourth photoprovocation and a final assessment of the test results was made on day 7.

On day 7 at the beginning of the second week of the

study, all patients with a positive phototest reaction to UVB, UVA, or both (ie, the elicitation of typical PLE lesions in the test areas) were set on a daily dose of PL extract (Fernblock, Industrial Farmaceutica Cantabria, Madrid, Spain) according to body weight: less than or equal to 55 kg, 720 mg every day; 56 to 70 kg, 960 mg every day; and more than 70 kg, 1200 mg every day.

After 2 weeks of daily treatment with PL extract a second photoprovocation identical to the first one was administered to all the patients between days 21 and 28. Test areas were in the immediate vicinity of those that had been exposed to UV at baseline. All patients continued treatment with PL until completion of the second photoprovocation.

Irradiations in Vienna and Brescia were performed using filtered metal halogen lamps emitting broadband UVB or broadband UVA (Vienna: Sellasol, Dr Sellmeier, Gevelsberg-Vogelsang, Germany; Brescia: Dr Hönle GmbH, Martinsried, Germany). In Vienna, irradiance was determined with a double spectrophotometer (Bentham Instruments Ltd, Reading, United Kingdom) and at a distance of 50 cm. Irradiance values were 2.61 mW/cm<sup>2</sup> for UVB and 9.63 mW/cm<sup>2</sup> for UVA. In Brescia, irradiance was determined with a double spectrophotometer (MACAM 9910, Macam, Livingston, United Kingdom) and at skin level. Irradiance values were 4.12 mW/cm<sup>2</sup> for UVB and 12.42 mW/cm<sup>2</sup> for UVA.

### CAPSULE SUMMARY

- Polymorphic light eruption is the most common photosensitive disorder.
- Reactive oxygen species have been implicated in the pathogenesis of polymorphic light eruption.
- *Polypodium leucotomos* is a natural extract from tropical fern leaves with potent antioxidant properties.
- Induction of typical polymorphic light eruption lesions by repetitive irradiation with artificial ultraviolet light can be prevented or delayed by oral intake of *Polypodium leucotomos*.

**Table I.** Effect of artificial ultraviolet A and B irradiation in eliciting polymorphic light eruption in patients included in study

	UVA irradiation	UVB irradiation
No. of responsive patients	30/30	18/30
No. of exposures (mean)	2.3	3.1

Note that 5 patients included in study were nonresponsive and are not included in data.  
UV, Ultraviolet.

**Table II.** Overall effect of oral treatment with *Polypodium leucotomos* on ultraviolet A- and B-induced polymorphic light eruption

	No PLE lesions	Apparent PLE lesions
PL+UVA	9/30	21/30
PL+UVB	5/18	13/18

PL, *Polypodium leucotomos*; PLE, polymorphic light eruption; UV, ultraviolet.

After the phototesting, the patients in Brescia continued the PL treatment at the same individual dosage used for phototesting during the whole summer period. In addition, the patients were using the same sunscreens as in previous years. After the summer a follow-up assessment was performed and the efficacy of PL extract in protecting from episodes of PLE was recorded.

### Statistical analysis

Data from UVA and UVB photoprovocation tests at baseline and after PL treatment were analyzed by using the Kaplan-Meier test followed by the log rank test to compare the responses. To compare MED results between both time points (before and after treatment), a paired Student *t* test and analysis of variance were used.

### RESULTS

Of all 35 enrolled patients in both institutions, 30 patients showed induction of typical PLE lesions after repeated irradiation with UVB or UVA. The remaining 5 patients with a negative response to photoprovocation were excluded from further evaluation. All 30 patients with a positive photoprovocation test were sensitive to UVA and 18 patients also reacted to UVB. Hence, a total number of 48 positive reactions was recorded in 30 patients. The mean number of UVA or UVB exposures required to elicit a positive reaction was 2.3 and 3.1, respectively (Table I).

After 2 weeks of continuous PL treatment a significant increase in the threshold for induction of PLE lesions by UVA was observed. Using the same

**Table III.** Number of ultraviolet exposures needed for elicitation in those patients showing polymorphic light eruption after oral intake of *Polypodium leucotomos*

No. of exposures	Pre-PL	Post-PL
UVA	1.95 ± 1.07	2.62 ± 1.02*
UVB	2.38 ± 1.19	2.92 ± 0.95 <sup>†</sup>

PL, *Polypodium leucotomos*; UV, ultraviolet.

\**P* = .005.

<sup>†</sup>*P* = .047.

range of UV doses and the same number of UV exposures the phototest was negative in 30% (9 of 30) of all the UVA-sensitive patients. In the remaining 21 patients the mean number of UVA exposures required to induce PLE had increased significantly from 1.95 ± 1.07 to 2.62 ± 1.02 (*P* = .005) (Tables II and III).

The suppressive effect of PL extract on photoinduction of PLE lesions by the UVB range was very similar. Of 18 patients with a positive reaction to UVB in the first photoprovocation, 5 patients (28%) remained negative in the second. The mean number of UVB exposures required to elicit PLE also increased significantly from 2.38 ± 1.19 to 2.92 ± 0.95 (*P* = .047) (Tables II and III).

The mean MED of UVB before and after 2 weeks of treatment with PL extract was 67 ± 19 mJ/cm<sup>2</sup> and 102 ± 30 mJ/cm<sup>2</sup> (*P* = .04), respectively, thus revealing a significant increase of the threshold UVB dose for erythema induction.

Follow-up of the patients in Brescia who had continued to take PL extract during the whole summer season revealed that 7 of 15 patients (47%) did not experience additional PLE episodes, and 4 patients (27%) developed only a minor rash with a delayed onset. The remaining 4 patients reported little or no effect of PL extract in preventing PLE.

The tolerance of PL extract was excellent in all patients. No adverse events were recorded throughout the whole study period.

### DISCUSSION

PL is a natural extract from tropical fern leaves with potent antioxidant and anti-inflammatory properties, likely because of its high concentration of polyphenolics and other antioxidant moieties.<sup>10</sup> Several studies in human beings have shown that PL extract is an effective oral photoprotective agent with the capacity to reduce several aspects of UV-induced skin damage such as solar erythema, induction of sunburn cells, formation of cyclobutane pyrimidine dimers, and depletion of Langerhans cells.<sup>11,12</sup> Although the

mechanism has not been completely elucidated, it involves inhibition of UV-induced reactive oxygen species production and prevention of other UV-induced damages such as trans-urocanic acid isomerization, DNA damage leading to p53-mediated apoptosis, or degradative matrix remodeling.<sup>13-15</sup>

Several lines of evidence indicate that reactive oxygen species are involved in the pathogenesis of PLE.<sup>6,16</sup> Given its well-known antioxidant activities we hypothesized that oral intake of PL may prevent or delay the induction of PLE lesions by repetitive exposure to artificial UVB or UVA light. A positive photoprovocation result was obtained in 86% (30 of 35) of all patients. All of them (30 of 30) reacted to UVA and 60% (18 of 30) also reacted to UVB. These results are in good agreement with older studies showing that UVA is the main waveband involved in eliciting PLE.<sup>17,18</sup>

After 2 weeks of PL intake a substantial reduction in positive photoprovocation results and a significant delay in formation of PLE lesions was observed. In all, 30% and 28% of all patients who previously had developed photo-induced PLE lesions remained negative after 4 exposures to UVA and UVB, respectively. In the remaining patients there was a significant increase in number of exposures required to elicit a positive response to UVA or UVB. Despite the fact that the study presented here is an open trial with no placebo control, our data show that PL efficiently increased the cumulative threshold dose for PLE induction and reduced the number of positive photoprovocation outcomes in a significant fraction of the patients.

It is important to address the question of whether the observed effect on PLE induction with artificial UV light might also be of clinical relevance. For several reasons we do believe this might be the case.

First, it has to be emphasized that the patients included in our study represent a selected subset of severely affected patients. These patients were not or were insufficiently protected from PLE by the use of high-potency broad-spectrum sunscreens and most of them had previously required prophylactic photo-desensitization with narrowband UVB or PUVA. The fact that only patients with a positive photoprovocation result after up to 4 repetitive UV light exposures were enrolled in the study also stresses their low threshold for PLE induction. It is thus well conceivable that in the average patient with PLE the PLE-protective effect conferred by PL extract is substantially greater than in our study population of patients with severe disease.

Second, the delay in development of PLE afforded by PL extract might act synergistically with the process of natural photohardening that occurs

during exposure to ambient sunlight. Because of this combined effect the patients' tolerance to PLE induction might be enhanced and/or the rash attenuated to a tolerable extent.

Finally, evidence for the clinical benefit of PL extract in the treatment of PLE also comes from a recent Italian study on 25 patients.<sup>8</sup> After 15 days of daily treatment with 480 mg of PL extract normalization or clear improvement was reported by 9 and 4 patients, respectively, whereas slight or no improvement occurred in 9 and 3 patients each. Thus, about half of the patients experienced substantial or complete relief from PLE after PL treatment. Similar findings were also made in the open field trial that was conducted in Brescia. Continuous PL treatment during the summer period resulted in absence or marked reduction of PLE in 11 of 15 patients.

In conclusion, this study demonstrates the potential use of PL extract in the prevention of PLE in severely affected patients. Future studies will have to determine the optimum daily dose of PL extract and the required duration of the pretreatment.

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