

Oral *Polypodium Leucotomos* Extract and Its Impact on Visible Light-Induced Pigmentation in Human Subjects

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ABSTRACT

Background: Visible light (VL) has multiple effects on the skin that currently available sunscreens do not protect against. Polypodium leucotomos extract (PLE) has properties that may offer protection against VL.

Objectives: To determine the effectiveness of PLE in preventing VL-induced effects.

Methods: Twenty-two subjects with Fitzpatrick skin phototype IV-VI were enrolled. On day 0, subjects were irradiated with VL. Clinical Investigator's Global Assessment (IGA) scoring and spectroscopic evaluations were performed immediately, 24 hours, and 7 days after irradiation. Subjects then received a 28-day supply of PLE (480 mg daily). Irradiation and evaluation were repeated. Three 4-mm punch biopsies were obtained for immunohistochemistry analysis: one from normal unirradiated skin and the other two twenty-four hours after irradiation, pre- and post-PLE, from sites irradiated with highest dose of VL.

Results: All subjects had immediate pigment darkening, persistent pigment darkening, and delayed tanning both pre- and post-PLE. For the highest VL dose (480 J/cm²) spectroscopic assessments demonstrated a statistically significant decrease in persistent pigment darkening and delayed tanning post-PLE. In addition, there was a significant decrease in cyclooxygenase-2, and a trend towards decreases in the markers for cellular damage post-PLE. While there was a trend towards lower IGA scores post-PLE, statistical significance was not reached possibly due to lack of sensitivity of the visual IGA scoring system in detecting small changes.

Conclusions: Spectroscopic data and immunohistochemistry indicate an effect of PLE on visible light induced effects. As such, PLE may be used as an adjuvant to traditional means of photoprotection to protect against the effects of VL.

Clinical trial registration number: NCT02904798.

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INTRODUCTION

Approximately 44% of sunlight is composed of visible light (VL).[1] VL has been shown to have multiple biologic effects on the skin[2] including DNA damage secondary to the production of reactive oxygen species (ROS), the induction of pro-inflammatory cytokines,[3] worsening of photo-exacerbated conditions,[4] and pigmentation in melanocompetent individuals.[5,6] Pigmentation caused by VL occurs in 3 stages.[6] The first, immediate pigment darkening (IPD), occurs immediately after exposure and can last up to 2 hours. IPD is followed by persistent pigment darkening (PPD), which occurs between 2 to 24 hours after exposure. Both IPD and PPD are caused by the oxidation and redistribution of existing melanin in the skin. The final stage is delayed tanning (DT), which occurs 24 hours to several days after exposure and is caused by the new production of melanin.[6]

Disorders of pigmentation such as melasma and post-inflammatory hyperpigmentation are relatively common in those with skin of color. Affected individuals often note worsening of cutaneous hyperpigmentation after sun exposure despite appropriate application of broad- spectrum sunscreens. This is in part because currently available organic sunscreens and micronized inorganic sunscreens primarily protect against ultraviolet (UV) radiation, but are ineffective against VL.[4] Iron oxides, which are present in make-up and tinted products, are effective against VL. However, many people are resistant to the idea of wearing "make-up" for photoprotection. They are also not water or sweat resistant. Taken together, alternative, and supplementary methods of protection against VL induced effects, such as oral antioxidants, are necessary.

PLE is an over-the-counter supplement derived from a fern native to Central and South America,[7] which has multiple anti-inflammatory, immunomodulatory, chemoprotectant, and antioxidant properties.[2] One effect of PLE is that it enhances the endogenous antioxidant system, which neutralizes superoxide anions, lipid peroxides, and hydroxyl radicals.[3,8,9] PLE has also been shown to suppress UV-induced erythema, and to decrease cyclooxygenase (COX)-2, p53, cyclobutane pyrimidine dimers, epidermal proliferation, sunburn cells, and inflammatory infiltrates induced by UV radiation.[10,11] More recently, PLE was shown to decrease VL-induced cell death, matrix metalloproteinase (MMP)-1 production, and other alterations of the extracellular matrix in an in-vitro model.[12] Given the photoprotective effects of PLE and its antioxidant properties, this study was designed to quantify the effects of oral PLE on VL-induced pigmentation in human subjects.

MATERIALS AND METHODS

Study Subjects

Twenty-seven healthy males and females with skin phototypes IV-VI were enrolled in this study, with 24 subjects completing the study. This study was approved by the Institutional Review Board at Henry Ford Hospital (IRB# 8385) and all guidelines from the Declaration of Helsinki were followed. Informed consent was obtained from all participants. Exclusion criteria included current or past history of skin cancer, photoaggravated conditions, photosensitizing medications in the VL range, tanning, intention to become pregnant, pregnancy, and lactation. Subjects were willing to limit direct exposure of areas being irradiated to light during the study. Urine pregnancy tests were performed for any females of child-bearing potential with a last menstrual period of over 5 weeks.

Study Design

Subjects were irradiated with 5 doses of VL on the left side of the back at 6 sites on day 0. IPD was then assessed. The doses were 40, 80, 160, 320, and 480 J/cm^2, with the dose of 480 J/cm^2 being repeated for biopsy purposes. PPD and DT did not occur at 40 and 80 J/cm^2 in the first 13 subjects, therefore, these doses were eliminated for the remaining subjects. On day 1, PPD was assessed and biopsies were performed of normal skin and 1 of the sites irradiated at 480 J/cm^2. On day 7, DT was assessed, and suture removal performed. In addition, subjects were given a 28-day supply of oral PLE (Heliocare, Cantabria Labs, Madrid, Spain) with instructions to take 2 pills (total dose 480 mg) 1 hour apart between the hours of 8 AM and noon starting on day 8. Day 0 through 7 responses are referred to as pre-PLE in the remainder of the manuscript. On day 35, subjects returned for VL irradiation of the right back at the same doses and number of sites as was performed pre-PLE. Post-PLE IPD was assessed and the number of remaining PLE pills recorded to ensure compliance. Day 36 consisted of assessment of post-PLE PPD and biopsy of the second dose of 480 J/cm^2. Post-PLE DT was assessed on day 42 in addition to suture removal.

TABLE 1.

Investigator Global Assessment Scale for Pigmentation	
IGA	Hyperpigmentation
0	Clear of hyperpigmentation
1	Almost clear of hyperpigmentation
2	Mild but noticeable hyperpigmentation
3	Moderate hyperpigmentation (medium brown in quality)
4	Severe hyperpigmentation (dark brown in quality)
5	Very severe hyperpigmentation (very dark brown, almost black in quality)

Light Sources and Irradiation

The light source used in this study was a Fiber-Lite (Dolan-Jenner Industries, Boxborough, MA) with a 150W EKE lamp. The spectral output consisted of over 97.5% VL, with less than 0.5% and 2.0% of UVA1 and infrared radiation, respectively. The UVA1 contribution in the spectral output has been shown to be insufficient to cause pigmentation on its own based on known minimal tanning doses.[13] The fluence rate was adjusted to either 250 mW/cm^2 or 200 mW/cm^2 using an Oriel thermopile (Oriel, Stamford, CT). A fluence rate of 250 mW/cm^2 was used in most subjects. As the output of the radiation source included trace amounts of UVA1, if a subject was on photosensitizing medication in the UVA1 range, a fluence rate of 200 mW/cm^2 was used instead. However, the same fluence rate was used for both pre- and post-PLE irradiation for a given subject.

Clinical and Spectroscopic Assessments

Clinical photography and Investigator Global Assessment (IGA). Clinical photographs of the back were taken at each visit. The degree of pigmentation and erythema in each site was graded using an Investigator Global Assessment (IGA) scale (Table 1). The same investigator performed IGA scoring both pre- and post-PLE.

Diffuse reflectance spectroscopy.

This non-invasive objective assessment technique quantifies the degree of melanin and hemoglobin in lesions, which corresponds to pigmentation and erythema, respectively. Diffuse reflectance spectroscopy was used to collect absorbance spectra at each visit within the irradiated site and at adjacent normal skin. The methodology has been described in detail in our previous publication.[5] To summarize, an average of 3 measurements was used for analysis. The difference between the absorbance spectra of irradiated and normal skin was calculated and integrated between 400-700 nm. This integrated value (area under the curve) was referred to as the relative pigment since it included contributions from both melanin and hemoglobin, corresponding to the overall darkness of the irradiated site. Higher values of relative pigment correspond to a darker lesion. The pre-PLE relative pigment was compared to post-PLE relative pigment for the corresponding time point. In addition, the ratio of pre-PLE relative pigment to that of post-PLE relative pigment was used to calculate the VL protection factor for a given assessment time point.[14]

Immunohistochemistry

The following stains were performed on the specimens biopsied: COX-2, cyclin D1, MMPs 1, 2, and 9, Fontana Masson, Melan-A/Mart 1, and B-cell lymphoma (Bcl)-2. These stains assessed inflammation, cell cycle progression, structural integrity, pigmentation, and apoptosis, respectively.

COX-2, cyclin D1, and melanoma-associated antigen recognized by T cells (MART)-1 were counted for positive cells with an Olympus BX51 microscope fitted to an Olympus DP71 digital camera (Olympus America, Inc., Center Valley, PA) at 40x magnification. Positive cells of MART-1 were counted throughout the tissue sections while the numbers of positive cells per 100 epidermal cells of COX-2 and cyclin D1 were counted at 3 different microscope fields. Each field consisted of the edges of both sides and the centre of the tissue sections by using photographs at 40x magnification. Brown nuclear staining was considered as positive for cyclin D1, while cytoplasmic staining was considered as positive for COX-2. The number of positive cells was assessed by 2 independent observers and the average number of positive cells was calculated.

MMP-1, MMP-2, MMP-9, Bcl-2, and Fontana-Masson were evaluated by intensity scores (Table 2). Keratinocytes, and dermal fibroblasts were evaluated for MMP-1, MMP-2 and MMP-9, and basal keratinocytes were assessed for Bcl-2. The intensity scores were assessed by 2 independent observers from 6 different fields at 40x magnification and the average score was calculated.

Statistical Analysis

Paired t-tests were used to compare IGA scores, relative pigment intensity, and immunohistochemistry results. When the t-test assumption of distribution normality was violated, the Wilcoxon signed rank test was performed instead. Statistical significance was set at p-values less than 0.05. Immunohistochemistry findings of day 1, referred to as pre-PLE, were compared with those on day 36, referred to as post-PLE. For IGA and relative pigment intensity, comparisons were made for each time point IPD, PPD, and DT. All analyses were done using SAS software (version 9.4, SAS Institute Inc., Cary, NC).

TABLE 2.

Intensity Scoring System for Select Stains	
Score	**Interpretation**
-4	>75% decrease in intensity when compared to control
-3	51%-75% decrease in intensity when compared to control
-2	26%-50% decrease in intensity when compared to control
-1	10%-25% decrease in intensity when compared to control
0	Unchanged when comparing to control
1	10%-25% increase in intensity when compared to control
2	26%-50% increase in intensity when comparing to control
3	51%-75% increase in intensity when comparing to control
4	75% increase in intensity when comparing to control

RESULTS

All subjects had an IPD response at the VL doses delivered, but PPD and DT were not consistently present or were subtle. As such, the results reported will focus on the highest VL dose (480 J/cm^2). Two subjects formed blisters at the dose of 480 J/cm^{2}during the post-PLE irradiation visit (day 35), which was likely secondary to fluctuations in the intensity of the lamp in the radiation source. The lamp was replaced, and the light source was recalibrated. Another course of PLE was given to 1 of the subjects who blistered, with repetition of all post-PLE visits. The subject did not form blisters post-PLE once the light source had been recalibrated, and it was concluded that PLE was not the cause of blistering. The data from the 2 subjects who blistered was excluded.

Clinical Photography and Investigator Global Assessment (IGA)

At the DT assessment time point, 7 out of 22 (32%) subjects had a decrease in IGA scores post-PLE (Figure 1). Although there was a trend towards lower IGA scores post-PLE, statistical significance was not reached (p = 0.07) (Figure 2).

Diffuse Reflectance Spectroscopy

At a dose of 480 J/cm^2, post-PLE there was a statistically significant decrease in the amount of relative pigment when comparing PPD and DT (P<0.05) (Figure 3). In addition, PLE exhibited a VL protection factor of 1.3, 1.5 and 1.5 at the IPD, PPD and DT time points, respectively.

FIGURE 1. Clinical photography and IGA scoring of a subject pre- and post-PLE. Abbreviations: IGA, Investigator Global Assessment; PLE, *Polypodium leucotomos* extract.

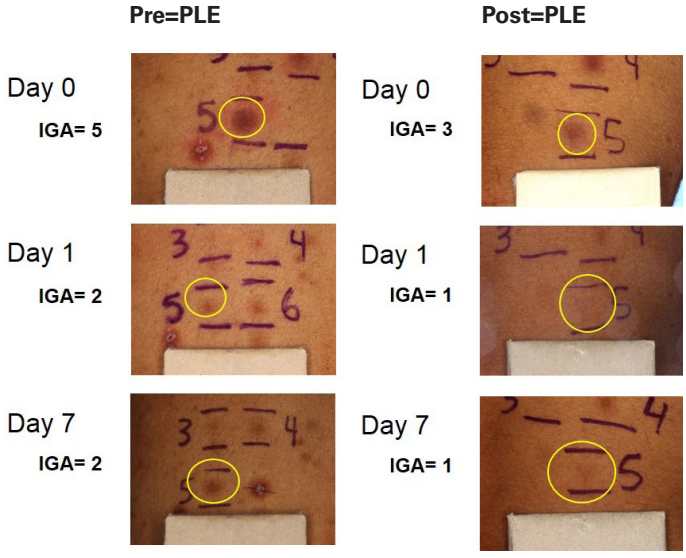


FIGURE 2. Pre-PLE and post-PLE average IGA scores for pigmentation as a function visit number at a visible light dose of 480 J/cm². Abbreviations: IGA, Investigator Global Assessment; PLE, *Polypodium leucotomos* extract.

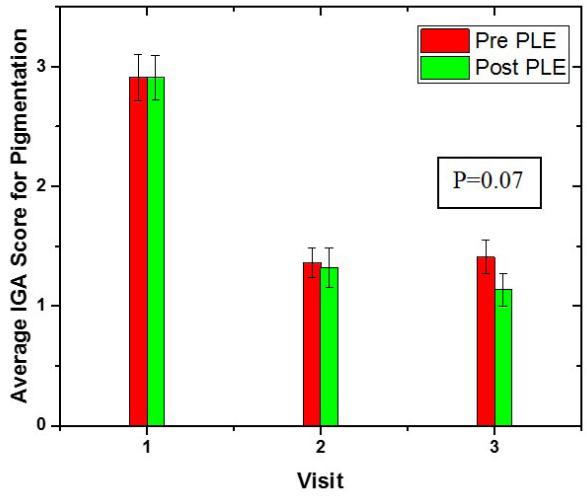
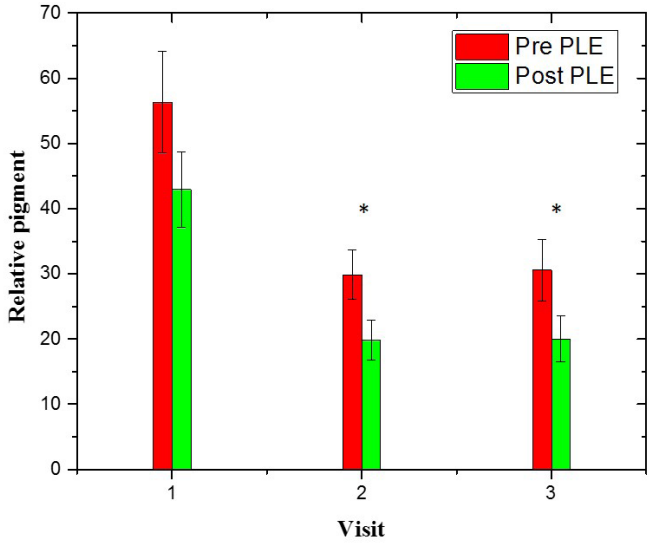


FIGURE 3. Diffuse reflectance spectroscopy measured relative pigment pre-PLE and post-PLE as a function visit number at a visible light dose of 480 J/cm². Abbreviations: PLE, *Polypodium leucotomos* extract.



Immunohistochemistry

There was a statistically significant decrease in COX-2 staining post-PLE. In addition, there was a strong trend towards reductions in MMP-2, and a weak trend towards reductions in MART-1, MMP-1, MMP-9, and Bcl-2 post-PLE. No change in pigmentation was detected with Fontana Masson among control, pre-, and post- PLE sites likely because tissue specimens were obtained 24 hours after irradiation, but new pigment formation takes longer (approximately 5-7 days). As such, histologically, difference in pigmentation could not be assessed. A post-PLE trend towards an increase in cyclin D1 was observed (Tables 3 and 4).

Adverse Events

Two consecutive subjects in this study blistered at a dose of 480 J/cm² during the post-PLE irradiation visit. However, this was unlikely to be related to PLE as when one of these patients was given a second course of PLE and re-irradiated, no blister was observed. Of note, re-irradiation was performed after lamp replacement and recalibration of the light source. Three subjects experienced intermittent gastrointestinal upset, 3 experienced pruritus, and 1 subject complained of dry mouth.

DISCUSSION

In this study, a real-world relevant dose of 480 J/cm² VL was used, which is equivalent to approximately 160 minutes of sunlight exposure.[15] This study demonstrated that at this VL dose, the administration of oral PLE prior to irradiation led to a de-

TABLE 3.

Staining Results for the Change from to Pre-PLE to Post-PLE					
IGA	N	Mean	SD	Median	*P*-value
COX post-PLE minus pre-PLE	22	-2.20	4.33	-2.833	0.027[1]
Cyclin post-PLE minus pre-PLE	22	3	7.43	3.67	0.072
MART post-PLE minus pre-PLE	22	-0.39	9.70	1.50	0.85

COX, cyclooxygenase; MART, melanoma-associated antigen recognized by T cells; PLE, *Polypodium leucotomos* extract; SD, standard deviation
[1] $P < 0.05$

TABLE 4.

Other Staining Results for the Change from Pre-PLE to Post-PLE (Post - Pre)					
Variable	N	Mean	SD	Median	*P*=value
Change from pre-PLE to post-PLE for Fontana Masson	22	0.00	0.98	0.00	1.00
Change from pre-PLE to post-PLE for MMP 1	22	-0.27	0.93	0.00	0.18
Change from pre-PLE to post-PLE for MMP 2	15	-0.60	1.06	-1.00	0.07
Change from pre-PLE to post-PLE for MMP 9	22	-0.27	0.90	0.00	0.16
Change from pre-PLE to post-PLE for Bcl-2	22	-0.27	1.07	0.00	0.24

Bcl, B-cell lymphoma; MMP, matrix metalloproteinase; PLE, *Polypodium leucotomos* extract; SD, standard deviation
$P<0.05$

crease in pigmentation at all time points, as assessed clinically via IGA scoring, though not statistically significant (Figure 2). Diffuse reflectance spectroscopy (DRS) demonstrated a statistically significant decreases in PPD and DT based on relative pigment intensity (Figure 3). As IGA is a visual assessment, while DRS is an objective, instrument-based measurement, these results clearly demonstrate the limitations of IGA, even when performed by experienced evaluators.

Immunohistochemistry results showed a statistically significant decrease in inflammation, and a trend toward decreases in markers for certain collagen remodelling markers post-PLE. There was also a weak trend towards a decrease in melanocytes, other collagen remodelling markers, and apoptotic markers post-PLE. These were consistent with PLE's previously proven antioxidant and anti-inflammatory characteristics. Therefore, while clinical improvements were not noted in all subjects, effects by PLE were observed as demonstrated by spectroscopy and immunohistochemistry. In this study, a total daily dose of 480 mg of PLE was used. PLE has been shown to have no observable side effects even at daily doses as high as 1080 mg.[16] Therefore, it is possible with higher doses of PLE, an even more noticeable protective effect against VL-induced changes would be observed. The non-significant increase in cyclin D1, which indicates cell cycle progression, requires further investigation.

VL has multiple effects on the skin, including erythema, DNA damage secondary to ROS, pigmentation, and the induction of pro-inflammatory cytokines, as well as MMPs 1 and 9.[1,3,4,6,9,17] Because PLE has antioxidant as well as anti-inflammatory properties, it is likely that these mechanisms could contribute to downregulation of the deleterious effects of VL by quenching ROS and reducing inflammation. It should be noted that while multiple formulations of PLE exist, all the published studies to date have been done with PLE sourced from a single source (Heliocare, Cantabria Lab, Madrid, Spain), the preparation used in this study. In a recent in vitro study comparing the photoprotective properties of different PLE preparations, preparation sourced from the referenced lab was shown to have the most potent property.[18]

While down-regulating pigmentation induced by VL is important, especially in people with skin of color, the potential for carcinogenesis induced by VL is also a concern. Oxidative damage caused by irradiation with wavelengths ranging from 312-434 nm, which partially fall into the VL spectrum, have been shown to potentially cause both melanoma and non-melanoma skin cancer in human skin cells.[17] The availability of high SPF, broad-spectrum sunscreens allows people to spend greater amounts of time in direct sunlight with decreased risk of sunburn. This leads to greater exposure to VL, and possible increased DNA damage secondary to ROS contributing to the formation of skin cancer.

Currently available sunscreens are either ineffective against VL, or for those that protect on the VL spectrum, cosmetically unacceptable to most patients. While PLE is not a substitute for sunscreen, it could serve as an oral adjuvant to provide protection against VL. PLE has previously been shown to down-regulate the biologic effects of UVB and UVA.[6,10,11,19,20] As such, PLE can potentially offers broad-spectrum protection that can supplement sunscreens and phototprotective clothing, especially in those with photo-exacerbated conditions.

CONCLUSION

VL has multiple potential deleterious effects on the skin. The administration of oral PLE prior to light exposure offers some protection against pigmentation, inflammation, and cellular damage caused by VL. As an over-the-counter supplement with an excellent safety profile, it can be used in patients as an adjuvant to, but not a substitute for, sunscreen, and other photoprotective measures.

DISCLOSURES

Drs. Lim, Hamzavi, Kohli, Mohammad, Nicholson, Nahhas, and Braunberger are investigators for Ferndale, Allergan, Unigen, and Estee Lauder. Drs. Hamzavi and Kohli have also served as investigators for Bayer and Johnson and Johnson. Dr. Kohli has served as an investigator for Pfizer and Drs. Lim and Hamzavi have served as an investigator for Incyte. All grants paid to institution. Dr. Lim has participated as a speaker in an educational session sponsored by Pierre Fabre. Drs. Treyger and Chaowattanapanit have no disclosures to report. *Funding:* This study was funded by Ferndale Laboratories.

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