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Role of Oral *Polypodium Leucotomos* Extract in Dermatologic Diseases: A Review of the Literature

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ABSTRACT

Polypodium leucotomos extract (PLE), derived from the tropical fern of *Polypodiaceae* family, has properties ranging from immunomodulatory and antioxidative to photoprotective. It is these multiple mechanisms of action, in combination with a favorable side effect profile, which makes PLE a promising adjunctive treatment for several dermatologic disorders. Studies are summarized on the use and potential applications of PLE in the treatment or management of photodermatoses, vitiligo, melasma, psoriasis, atopic dermatitis, and more recently, in minimizing infections in high-performance athletes. More data, however, with larger sample sizes are needed to confirm these benefits.

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INTRODUCTION

Polypodium leucotomos is a tropical fern of the Polypodiaceae family native to Central and South America. *Polypodium leucotomos* extract (PLE; Fernblock®, Ferndale Laboratories, Ferndale, Michigan, USA) is a polyphenol-enriched natural product derived from the leaves of the *Polypodium leucotomos* fern, and has long been known for its anti-inflammatory and antitumor properties.[1,2] Historically, *Polypodium leucotomos* was first introduced in Europe after the botanical expedition of Ruiz funded by the Spanish Crown, and later spread to other areas[3]. Several animal and human studies have been performed in recent years that have helped elucidate PL's mechanisms of action, which may explain its observed clinical effects of photoprotection and chemoprevention.

PLE has been used in various formulations for several years in folk medicine for treatment of a variety of inflammatory ailments including psoriasis, vitiligo, atopic dermatitis, and photosensitive disorders. Fernblock® is currently distributed in over 26 countries including the United States and Europe. It is available as a topical gel, cream, spray, and compact makeup powder as well as a systemic agent in the form of oral capsules. PL has been available as a supplement in Europe since 2001, and as a topical product since 2000. PL has been an oral dietary supplement in the US since 2006. Currently, it is marketed as an oral dietary supplement to help "protect against sun-related effects and aging", with a recommended dose of one 240 mg capsule in the

morning, and when extensive sun exposure is anticipated, to take 240 mg one hour before exposure, and another 240 mg 2-3 hours after. It is marketed as Heliocare™ by Ferndale Healthcare, Ferndale, Michigan.

In regards to future developments, research is currently underway to explore alternative extraction processes, which could further enhance PL's photoprotective and anti-oxidant activities both topically and orally, as well as to investigate PL's use in combination with other agents, which could provide synergic activity. It is hoped that this research will allow for the development of targeted formulations for specific photoprotection indications, for prevention of photoaging, and as adjuvant treatment in sunlight induced or aggravated conditions such as actinic keratosis and melasma.

PLE has been used to treat a variety of dermatologic disorders including immunologically-mediated photodermatoses, vitiligo, melasma, psoriasis, and atopic dermatitis. It has also been used to minimize the development of photoaging and skin cancers, and more recently, to decrease the development of infectious disease in athletes. In this article, we will briefly discuss its mechanisms of action as well as review its use in the treatment of dermatologic diseases.

Mechanism of Action

It is well documented that chronic unprotected or excessive ultraviolet (UV) radiation exposure induces a variety of damage responses on cellular and molecular levels, including the induction of stress proteins, indirect DNA damage due to reactive oxygen species and direct DNA damage due to formation of cyclobutane pyrimidine dimers; these lead to immunosuppression and carcinogenesis, impaired immune surveillance due to UV-induced decrease in epidermal Langer-

hans cells, and cutaneous photoaging due to disruption of the extracellular matrix.[4] Clinically, UV radiation possesses both pro-inflammatory and anti-inflammatory effects. Its pro-inflammatory effects include induction of photodermatoses and photoaggravated skin diseases, and acceleration of cutaneous photoaging, whereas the anti-inflammatory effects include increased susceptibility to photocarcinogenesis.

PLE has been shown to act at the molecular and cellular levels to inhibit UV induced photodamage. Its chemical composition includes phenolic compounds such as p-coumaric, ferulic, caffeic, vanillic and chlorogenic acids, potent ROS inhibitors, which demonstrate significant antioxidant, anti-inflammatory, and photoprotective activity after systemic absorption.[5,6] Specifically, PLE inhibits Th1 proinflammatory response via Th1 cytokines IL-2, IL-6, IFN-γ, TNF-α, which may explain the use of PLE in Th-1 mediated inflammatory phenomena such as psoriasis. [7] PLE has also been shown to decrease UV-induced mast cell infiltration, leading to a reduction in neovascularization, tumor growth, and cutaneous elastosis[7].PLE also has a beneficial effect in cutaneous photoaging and sun-damaged skin[8], as it has been shown to preserve cytoskeletal structure in human fibroblasts and their proliferative capacity after exposure to UVA radiation, as well as improve cell membrane integrity, increase elastin expression, inhibit lipid peroxidation and MMP-1 expression in fibroblasts and keratinocytes.[9] Its photoprotective properties are due to its inhibition of UVA and UVB induced photoisomerization and photodecomposition of *trans*-urocanic acid (t-UCA), which is a major UV-absorbing component in the stratum corneum.[10] It also decreases the formation of sunburn cells, cyclobutane pyrimidine dimers, proliferation of epidermal cells, and preserves Langerhans cells after UV exposure.[11]

Effects of PLE on Photoaging and Skin Cancer

The studies are summarized in Table 1. It has been shown that pre-treatment with PLE may prevent UVA-induced skin photodamage by preventing UVA-dependent mitochondrial damage.[12] Results from a pilot study conducted by Villa et al,[12] suggest that pre-treatment with oral PLE may prevent the increase of common deletion (CD) following UVA exposure. CD is a 4977 base pair long mitochondrial DNA whose deletion is thought to be induced by chronic UVA radiation and is found in UVA-damaged skin, hence associated with photoaging.[13] In this study, ten healthy patients received UVA exposure (2 and 3 times each patient's MED-A values) combined with pre-treatment with either two 240mg of PLE or placebo. PLE was administered 8 and 2 hours prior to UVA exposure. The authors found that, although there was no significant histologic difference in skin after UVA exposure between the two groups, there was a difference with regard to increase in the common deletion, with the placebo group showing a higher increase in CD values than the PLE group. Specifically, the PLE group had less of an increase in CD levels compared to the placebo group as the UVA dose was increased. This effect, however, did not reach statistical significance, which could be

due to the small sample size. Another potential mechanism for protective effect of PLE in photocarcinogenesis is via activation of tumor suppressor p53 gene and inhibition of molecular marker COX-2, which is induced by UV exposure and involved in mutagenesis. Both effects have been demonstrated in a mouse model.[14]

In another study, Aguilera et al,[15] investigated the effect of PLE in patients who were at a high-risk for skin cancers; the study included patients with history of melanoma, family history of melanoma, or atypical mole syndrome. The authors assessed MED-B in these patients before and after administration of 1080 mg of oral PLE, and found a statistically significant increase in MED-B values after treatment with oral PLE, with each subject serving as its own control. Of note, 720 mg of oral PLE was administered in three doses (240 mg every 8 hours) and then single doses of 360 mg of oral PLE given 1 day and 3 hours, respectively, prior to exposure to UVB. The authors also found that an increase in MED-B was noted in patients with darkercolored eyes and in those with a lower base-line MED-B. They concluded that these two characteristics were independent factors in predicting a better response to oral PLE.

PLE and Photodermatoses

Demonstration of photoprotective properties of PLE has lead to the investigation of oral PLE for the treatment of immunologically- mediated photodermatoses, including polymorphous light eruption (PMLE), solar urticaria, chronic actinic dermatitis, actinic prurigo, and subacute cutaneous lupus erythematosus (SCLE) (Table 1).

In a study by Caccialanza et al,[16] 26 patients with PMLE and two patients with solar urticaria unresponsive to other topical and systemic therapy were given a daily dose of 480 mg oral PLE, in two divided doses, starting fifteen days prior to sun exposure. Patients were then asked to rate their response to sun exposure. The authors found that 80% of participants reported a positive response with oral PLE; specifically, 49% reported improvement and 31% reported normalization of response to photoexposure after treatment with oral PLE. The two patients with solar urticaria, however, did not show any response to the PLE.

A follow-up study by Caccialanza et al,[17] with a larger sample size (53 with PMLE and 4 with solar urticaria) and identical protocol confirmed similar results.[17] They found a statistically significant (P<0.05) benefit from administration of oral PLE for treatment of PMLE. Of note, 73.68% of participants reported a positive response, of which 43.86% noted improvement and 29.82% had normalization. Three out of the four patients with solar urticaria did not show improvement. They found no adverse reactions from the use of oral PLE.

TABLE 1.

Summary of Clinical Studies

Skin Condition	Study	Subjects	Dose	Type	Outcome
Photodermatoses	1. Caccialanza M, et al (2007)	28 (26 PMLE, 2 solar urticaria)	480 mg daily in 2 divided doses (x15 days prior to UV exposure)	Open treatment trial	Statistically significant reduction of skin reaction and subjective symptoms in patients with PMLE who did not show improvement with systemic and topical drugs. The two patients with solar urticaria did not improve.
	2. Caccialanza M, et al (2011)	57 (53 PMLE, 4 solar urticaria)	480 mg daily (x15 days prior to UV exposure)	Open treatment trial	Statistically significant reduction of skin reaction and subjective symptoms in patients with PMLE who did not show improvement with systemic and topical drugs. Three of four patients with solar urticaria did not improve.
	3.Tanew et al (2012)	35 with PMLE	≤55kg→720mg/day; 56-70kg → 960mg/day; >70kg → 1200mg/day	Open, uncontrolled (no placebo)	After oral PLE treatment, 9 (30%) and 5 (28%) patients, respectively were unresponsive to repeated UVA and UVB exposure. In remaining patients, mean number of UVA and UVB irradiations required to elicit PMLE increased significantly (P=.005 for UVA, P=.047 for UVB)
	4. Breithaupt AD and Jacob SE (2012)	1 with SCLE	240 mg daily	Case report	Moderately controlled with hydroxychloroquine 200mg BID, achieved near total remission after addition of daily oral PLE
Melasma	1. Ahmed A, et al (2013)	40		Randomized, double-blinded, placebo-controlled	Oral PLE is no better than placebo as an adjunct to topical sunscreen in treatment of melasma
	2. Martin LK, et al (2012)	21	Oral PLE BID	Randomized, double-blinded, placebo-controlled	PL is effective adjunct to sunscreen SPF45 in reducing severity of melasma
Vitiligo	1. Pacifico A, et al (2009)	57	480 mg daily	Randomized prospective study	Daily oral PLE in addition to NB-UVB therapy twice weekly improves repigmentation in patients with generalized vitiligo as compared to NB-UVB therapy alone
	2. Reyes E, et al (2005)	19		Randomized, double-blind, placebo-controlled study	Oral PLE+PUVA normalizes expression of activation markers by T cells and suppresses proliferation of peripheral blood mononuclear cells versus PUVA alone; Higher rate of moderate to excellent repigmentation in PUVA+oral PLE versus PUVA alone.
	3.Middlekamp MA, et al (2006)	50	250mg PO TID, combined with NB-UVB twice weekly x25-26 weeks	Randomized, double-blind, placebo-controlled trial	Patients in PLE group showed more repigmentation in head and neck area compared to patients receiving NB-UVB alone (44% vs 27%, P=0.06)
Psoriasis	De Las Heras ME, et al (1997)	40	720mg daily, combined with three weekly PUVA sessions	Controlled, open clinical trial	Patients in PLE+PUVA group versus PUVA alone group required a lower accumulated dosage of UVA (P<0.0001) but no difference in number of UVA sessions
Atopic dermatitis	Ramirez-Bosca A, et al (2012)	105	240mg/day (<6 years), 360mg/day (6-12 years), 480mg/day (>12 years) x 6 months	Randomized, double-blinded, placebo controlled	PLE group required less oral antihistamines than placebo group (P=0.038). PLE group demonstrated a progressive reduction in topical corticosteroid use over 6 months (P=0.012).
Infectious Diseases	Solivellas BM, Martin TC (2012)	100	480mg BID x 3 months	Observational	PLE is useful in preventing infectious processes and reducing recurring episodes in athletes
Photoaging and Skin cancer	1. Villa A, et al (2010)	10	240mg, 8 and 2 hours pre-exposure to UVA	Randomized, investigator-blinded, controlled, IRB-approved	Pre-treatment with PLE may prevent increase of common deletion with increase of UVA dose.
	2. Aguilera P, et al (2012)	61	720mg + 360mg (1 day and 3 hours prior to UVB exposure): total 1080 mg	Treatment trial	PLE leads to significant decrease in sensitivity to UVR in high-risk melanoma patients

A study by Tanew et al,[18] also evaluated the effect of oral PLE in PMLE. Of the 35 patients studied, 30 developed PMLE lesions after irradiation with UVA and 18 after UVB irradiation. After two-week treatment with oral weight-based dosing of daily PLE (≤55kg: 720mg/day; 56-70kg: 960mg/day; >70kg: 1200mg/day), 9(30%) patients and 5(28%) patients were unresponsive to repeated UVA and UVB exposure, respectively. The mean number of exposures required to induce PMLE lesions in remaining patients showed a statistically significant increase for both UVA (P=.005) and UVB (P=.047), demonstrating the suppressive effect of oral PLE on photoinduction of PMLE.

Oral PLE has been reported as an adjuvant therapy in SCLE. A recent publication reported a patient with biopsy-proven SCLE, moderately controlled on hydroxychloroquine sulfate 200mg BID and daily use of zinc oxide sunscreen; this patient achieved near total remission of his SCLE with addition of oral PLE 240 mg daily.[19] Within four months, the patient demonstrated clinical improvement on the face and neck as well as complete clearance of the skin on his back, and in 37 months of daily oral PLE use, he only had 3 flares, which were all in the summer months. Clearly, more studies are needed to confirm this finding.

PLE and Melasma

The ability of PLE to provide systemic photoprotection has lead to the study of PLE as an adjunctive treatment of melasma (Table 1). A study presented as a poster (but yet unpublished) by Martin et al,[20] reported that oral PLE is an effective and well-tolerated agent in reducing melasma severity. In this double-blind placebo controlled trial, 21 females were randomized to receive either placebo plus sunscreen with SPF 45 or oral PLE plus sunscreen with SPF 45 for 12 weeks, and participants rated their perceived improvement at the end of 12 weeks. The authors found a statistically significant improved mean Melasma Area and Severity Index (MASI) scores in the oral PLE group. Additionally, photographic assessment by a blinded investigator revealed mild improvement in 43% of subjects receiving PLE as compared to 17% of patients receiving placebo, and marked improvement in 14% of subjects receiving PLE as compared to 0% of patients receiving placebo.

A recently published randomized, double-blinded study by Ahmed et al,[21] found no difference in improvement of melasma in patients taking oral PLE versus placebo. In this study, forty Hispanic females were randomized to receive either placebo or oral PLE 240 mg three times daily for 12 weeks, in addition to a "standard topical sunscreen". Treatment outcomes were measured by determining melanin intensity via reflectance spectrophotometry of affected as well as adjacent normal skin, and MASI scores. Although the authors found a statistically significant improvement from baseline to week 12 in both PLE and the placebo group, there was no significant difference between the two groups using either outcome measure. They concluded that oral PLE was no better than placebo as an adjunct to topical sunscreen for the treatment of melasma.

Given limited data on treatment of melasma with oral PLE, more studies with a larger sample size are needed to further evaluate the efficacy of oral PLE for the treatment of melasma.

PLE and Vitiligo

Oral PLE has also been studied as a treatment for repigmentation in vitiligo. PLE's antioxidant effects as well as a shift from a Th1 T-cell cytokine profile to a Th2 T-cell cytokine profile—namely a decreased production of IL-2, IFN-γ and TNF-α and increased production of anti-inflammatory cytokine, IL-10 - are thought to play a role in its use in vitiligo.[7] A poster presentation by Pacifico et al,[22] at the American Academy of Dermatology meeting in 2009 suggests that oral PLE 480 mg daily in combination with NB-UVB was more effective in repigmentation of patients with generalized vitiligo than treatment with twice weekly NB-UVB alone (40% vs 22%, $P<0.0005$). The authors concluded that oral PLE in conjunction with NB-UVB can improve response to treatment both in terms of extent and rapidity of repigmentation.

Another study by Reyes et al,[23] compares PUVA alone to PUVA plus oral PLE as a treatment for generalized vitiligo. In this randomized, double-blinded clinical trial, nineteen patients underwent randomization to receive either PUVA alone or PUVA with oral PLE, and repigmentation rates were assessed by independent dermatologists. The authors found a higher rate of moderate to excellent repigmentation in the PUVA and oral PLE group compared to the PUVA alone group. They also demonstrated that oral PLE+PUVA normalizes expression of activation markers by T cells and suppresses proliferation of peripheral blood mononuclear cells versus PUVA alone. This study underscores the immunomodulatory effects of oral PLE as an adjuvant to phototherapy in treatment of vitiligo.

Another study by Middlekamp et al,[24] investigated the effect of oral PLE and NB-UVB in repigmentation in patients with vitiligo. Fifty patients were randomized to receive either PLE 250mg orally TID or placebo, both in conjunction with NB-UVB treatments twice weekly for 25-26 weeks, with the primary outcome measure being percentage of repigmentation at week 26. Although they did not find a statistically significant difference, they observed higher repigmentation rates in PLE group, specifically in the head and neck areas (44% vs 27%, $P=0.06$). They also found that lighter skin types (Fitzpatrick skin types II and III) showed significant increased repigmentation in the head and neck areas compared to placebo group (47% vs 21%, $P=0.01$).

Secondary outcome measures included quality of life changes measured with Skindex 29; there were no significant differences between the PLE group and placebo group. Moreover, patient self-assessment at week 26 indicated no differences between PLE group and placebo group.

Taken together, the above studies suggest that treatment with oral PLE together with NB-UVB may improve repigmentation in patients with vitiligo; however, larger trials are warranted to confirm these observations.

"In regards to future developments, research is currently underway to explore alternative extraction processes, which could further enhance PL's photoprotective and anti-oxidant activities both topically and orally, as well as to investigate PL's use in combination with other agents, which could provide synergic activity."

PLE and Psoriasis Vulgaris

De las Heras et al,[25] in 1997 sought to evaluate the effect of oral PLE as an adjuvant treatment to PUVA for patients with plaque psoriasis; they found that patients who received PLE in addition to PUVA had a statistically significant decrease in cumulative dosage of PUVA required for clearance ($P<0.0001$), whereas there was no difference regarding the number of UVA sessions required. Histochemically, they observed the preservation of epidermal CD1a+ dendritic cells in patients who had been treated with oral PLE in addition to PUVA. These results suggest that the addition of oral PLE to PUVA could potentially minimize the adverse effects seen with PUVA photochemotherapy, namely local immunosuppression and photocarcinogenesis.

Additionally, Middlekamp-Hup et al,[26] demonstrated that oral PLE significantly decreased the acute PUVA-induced phototoxic reaction and also diminished the subsequent cutaneous pigmentary response. By reducing the hyperpigmentation, the need for increasing the UVA dose was also reduced, thus leading to a lower cumulative UVA dose for clearance of psoriasis. Histologically, they showed that in patients treated with oral PLE and PUVA, there was a significantly lower number of sunburn cells ($P=0.05$) and less depletion of Langerhans cells ($P\leq0.01$) when compared to skin treated with PUVA alone, confirming oral PLE's effectiveness as a chemopreventative agent against PUVA-induced phototoxicity.

PLE and Atopic Dermatitis

A study by Ramirez-Bosca et al,[27] sought to investigate whether daily treatment with PLE would reduce the use of topical corticosteroids in children and adolescents with moderate atopic dermatitis, in which disease severity was evaluated using the Scoring Atopic Dermatitis (SCORAD) index. They enrolled 105 participants, aged 2-17 years, to a randomized, double-blinded, placebo-controlled trial. The patients were randomized to receive, in addition to their standard treatment, either PLE or placebo for 6 months. Patients were divided into 3 treatment groups according to age, such that children aged 6 years or younger received 240mg daily of PLE, children aged 6 to 12 years received 360mg daily (120 mg in the morning and 240 mg at night), and children over 12 years old received 480mg daily in 2 divided doses. The authors found that subjects in the PLE group demonstrated a reduction in topical corticosteroid use from the first month to second month, and from the fourth month to the fifth month ($P=0.012$). More notably, they found an overall decrease in oral antihistamine use in the PLE group after the first month of treatment, and this finding became statistically significant after the third month of treatment with PLE ($P=0.038$). Clinically, the authors found a reduction in the number of flares reported by PLE group, however this was not statistically significant. These results indicate that long-term administration of oral PLE, in addition to standard first-line therapy, may have a beneficial effect in the treatment of atopic dermatitis. Again, more studies are needed, however, to confirm these benefits.

PLE and Infectious Diseases

PLE has also been investigated for its effect on infectious processes, particularly in athletes regularly engaged in rigorous physical activity (volleyball, football, athletics, cycling) who may be predisposed to a window of immunosuppression after strenuous activity. In 2012, Solivellas et al,[28] conducted an observational study in which they enrolled two groups of patients, of which one group received 480mg PLE twice daily for 3 months and the other did not receive PLE. They subsequently compared the onset of respiratory infection and relapse infection rates in both groups. The participants were followed for a total of 8 months. The authors found that symptomatic improvement was reached quicker, was more favorable in the PLE group, and fewer relapse cases were found in this group as well. The authors attributed this effect to the

anti-inflammatory and immunomodulatory properties of PLE; specifically, its ability to stimulate peripheral blood mononuclear cells and its effect on cytokines such as an increase in interleukin-2 (IL-2), IL-10, and interferon-α secretion, and a decrease in tumor necrosis factor (TNF) γ levels.[29] Additionally, PLE regulates the expression of adhesion molecules on monocytes and lymphocytes and increases membrane antigen expression on T cells and natural killer cells.[30] These changes suggest possible augmentation of cell-mediated immunity, especially against viruses.

CONCLUSION

Oral PLE has been used in the treatment of dermatologic disease with promising results and no reported side effects. It has multiple mechanisms of action, ranging from anti-inflammatory and immunomodulatory to antioxidative and photoprotective.

Given these multiple mechanisms of action and impacts on the effects of immune responses, PLE may provide a new adjunctive option for safe maintenance or additional approach to difficult chronic diseases such as photodermatoses, melasma, psoriasis, and vitiligo. Further studies with larger sample sizes are needed, however, to confirm these beneficial effects.

DISCLOSURES

Samreen Choudhry MD has no relevant conflicts to disclose; Neal Bhatia MD is affiliated with Bayer, Dusa, Ferndale, Galderma, Genentech, Leo, Medicis, Onset, PharmaDerm, Promius, Quinnova, and Valeant; Roger Ceilley MD is a consultant for Ferndale Labs; Firas Hougier MD has served as a consultant for Ferndale; Robert Lieberman MD is affiliated with Ferndale and Medicis; Iltefat Hamzavi MD serves as a consultant for Daavlin, and has received research grants from Clinuvel, Estée Lauder, and Johnson and Johnson; Henry W. Lim MD has served as consultant for Ferndale, La Roche-Posay, Uriage, and Pierre Fabre, and has received research grants from Clinuvel and Estée Lauder.

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