Polypodium Leucotomos Extract: A Status Report on Clinical Efficacy and Safety

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ABSTRACT

Various extracts of polypodium leucotomos (PLE) applied topically or taken orally have been shown to have several beneficial antioxidant, photoprotectant, antimutagenic, and immunoregulatory effects. Modern studies have evaluated the efficacy of PLE orally as a photoprotective agent and for use in several photo-aggravated dermatologic disorders such as polymorphous light eruption, other photodermatoses, and melasma. No articles have been published evaluating the safety of PLE. We performed a PUBMED search for any randomized clinical trials related to PLE, or anapsos, a synonym. The primary safety endpoint of the review was any mention of an adverse event, side effect, or toxicity. Overall, 19 human and 6 basic science studies were included spanning over 40 years of research. Oral PLE was administered at daily doses ranging from 120 mg to 1080 mg. No adverse effects were reported in laboratory studies. In humans, side effects (gastrointestinal complaints and pruritus) were mild to moderate and found only in very small numbers of patients overall (16/1016 [2%]). This review concludes PLE is well tolerated at all doses administered and associated with a negligible risk of side effects.

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INTRODUCTION

Polypodium leucotomos (PL) is a fern native to Central and South America historically used to treat inflammatory disorders by Native Americans.[1] Various extracts of PL applied topically or taken orally have been shown to have several beneficial properties over the last 4 decades. A specific extract of Polypodium leucotomos (PLE) is available commercially (Heliocare, Ferndale Laboratories) and has been evaluated in a variety of basic science and clinical studies. Antioxidant effects of PLE are attributed to its ability to consume superoxide anions, lipid peroxides, and hydroxyl radicals.[2,3] As a versatile photoprotectant,[4,5] PLE is believed to inhibit the photodamage process, increasing the minimal erythema dose (MED), by maintaining extracellular matrix integrity[6,7] and preventing damage to DNA repair enzymes.[5,8,9] The anti-mutagenic effects of PLE are attributed to its ability to block ultraviolet (UV) radiation-induced COX-2 expression[10,11,12] and promote p53 suppressor gene mutation.[8] Finally, PLE has been shown to have immunoregulatory effects in response to UV radiation demonstrated by inhibited infiltration of neutrophils and mast cells as well as reduced loss of antigen presenting Langerhans cells.[4]

The clinical application of PLE has been studied in order to evaluate its diverse therapeutic potential. Historically, poultices of PL were used by South Americans to treat atopic dermatitis and psoriasis.[1] Modern studies have evaluated the efficacy of PLE orally as a photoprotective agent and for use in several photo-aggravated dermatologic disorders such as polymorphous light eruption (PMLE), other photodermatoses, and melasma.

Despite decades of anecdotal evidence supporting the excellent safety profile of PL, multiple basic science and research studies evaluating PLE, and widespread exposure as a commercially available PLE capsule formulation, no articles have been published evaluating the safety of PLE. The purpose of this review of the literature is to summarize each clinically relevant study of PLE and to capture any relevant side effects associated with PLE administration in humans and animals. Studies and clinical use completed in humans treated with PLE encompass a broad range of potential indications.

METHODS

We performed a PUBMED search for any randomized clinical trials (RCTs) related to PL, PLE, or anapsos, a synonym and reviewed data on Ames and murine testing. Studies that were not randomized or placebo controlled were included if performed on a large number of patients. Considerable effort was made to find all available articles, including from less common foreign sources. The primary safety endpoint of the review was any mention of an adverse event (AE), side effect, or toxicity.

RESULTS

Basic Science Studies[13]

Two independent companies (Centro de Investigación y Desarrollo Aplicado SL, Barcelona, Spain; Biolab SL, Colmenar Viejo, Spain) performed in vitro studies to establish the carcinogenicity of PLE using the Ames test method. Reverse mutation assays were performed to evaluate the capacity of PLE to induce retromutations in several strains of Salmonella typhimurium. No significant differences were noted comparing the test product data at different assay concentrations with controls. Investigators determined that PLE substances do not exhibit mutagenic capacity.

Several in-vivo studies have examined the short and long-term toxicity of PLE. One murine study completed by an independent company (Biolab SL, Colmenar Viejo, Spain) evaluated symptoms of toxicity after oral administration of 1g/kg PLE at 1 hour intervals. Ten orally treated Naval Medical Research Institute (NRMI) mice and 5 control mice were evaluated for 10 days. Their results revealed absence of any symptoms suggestive of toxicity.

Ten NRMI mice were assayed by an independent company (Grupo Interlab, S.L., Madrid, Spain) for acute toxicity from oral PLE. A single, weight based dose was administrated on day 1 of the experiment. After administration of PLE, the animals were examined at 4 hours and then daily over the next 14 days. All animals survived without signs of morbidity and maintained a healthy appearance with normal behavior.

Biolab SL (Colmenar Viejo, Spain) evaluated systemic PLE for signs of medium-term chronic toxicity. Repeated oral dosages (200 mg/kg) were provided for a period of 28 days in 12 NMRI mice. PLE was not associated with medium-term toxicity after 28 days of administration. Observation of treated mice was extended another 14 days to observe for any delayed toxic effects. After 42 days, none of the mice demonstrated signs of toxicity including any changes in the skin, hair, eyes, mucosa, anomalous secretions or excretions, changes in behavior, postures, and responses to hand stimulation or circular movements. Histological examination also did not reveal evidence of abnormality.

Long-term chronic oral toxicity of PLE was studied in 20 rodents via oral administration of repeat 200 mg/kg dosages for a period of 90 days. Assays were performed by Biolab S.L. (Colmenar Viejo, Spain). NMRI albino mice were observed daily to detect symptoms of toxicity, anomalous behavior, or death. Signs of toxicity were observed for changes in the skin, hair, eyes, mucosa, anomalous secretions or excretions, changes in behavior, postures, and responses to hand stimulation or circular movements. No animal died during these assays and no abnormalities developed. The study concluded PL has no toxicity in rodents after 90 days of oral administration.

Human Studies

A double-blind study by Padilla et al evaluated PLE for use in treating patients with recalcitrant psoriasis.[14] Thirty-six patients with severe psoriasis alternated between oral PLE daily for 4 weeks and oral placebo daily for 4 weeks, each in random sequence. Twenty-eight patients showed clinical and histological response to PLE, with 22 of these patients (78.6%) demonstrating a good or excellent response. No AEs were reported.

Oral PLE was also studied in patients with psoriasis by Del Pino et al. Twenty-two of 37 patients with psoriasis received 120 mg capsules of PLE.[15] Results were discordant: 9 obtained full lesion "whitening", 5 between 40% and 80% "whitening," 5 achieved <40%, and 3 had null result. An AE was reported in one patient who received PLE, described as gastrointestinal intolerance, which led to discontinuation of PLE. No other AEs were reported.

Clinical experience using PLE in 495 patients with psoriasis has been described by Alvarez.[16] He described "whitening" from 80-100% in 304 patients; and 30-80% in 46 patients, with 15 patients refractory to treatment and 11 patients experiencing relapses. The average duration of treatment was 6 months and daily doses of PLE ranged from 80 mg-720 mg depending on age, weight, and treatment phase. AEs were described in 2 patients: one with intense pruritus and another with gastric disturbances. The AEs resolved with cessation of treatment.

Jimenez et al evaluated oral PLE in patients with atopic dermatitis.[17] Seventy-six patients received daily treatment for 1 month with either PLE (n=46) or an antihistamine daily (n=30). Severity of eczematous dermatitis improved with both treatments however patients receiving PLE demonstrated a more efficacious and long-lasting response. Patients using oral PLE who also had asthma reported considerable relief from their respiratory symptoms. PLE was well tolerated and no AEs were reported in the study.

Gonzalez et al studied the photoprotective effects of PLE in 21 subjects.[18] PLE was administered orally or as a topically applied lotion. Treatment groups were divided into four categories: (a) topical PLE lotion or sunscreen without psoralen sensitization; (b) oral PLE without psoralen sensitization; c) topical PLE lotion or sunscreen with psoralen-sensitized skin and d) oral PLE with psoralen-sensitized skin. The data revealed oral and topical application of PLE was photoprotective against UV-induced sunburn reaction and UVA-induced phototoxicity in psoralen-sensitized skin. Oral and topical PLE also increased the UV dose required for immediate pigment darkening, minimal phototoxic dose and minimal melanogenic dose. No AEs were reported in any of the patients.

The effect of PLE on cognitive performance was evaluated in patients with senile dementia by Alvarez et al.[19] Of 45 patients, 30 were randomized to receive 360 mg or 720 mg of oral PLE

daily for 4 weeks. No AEs were observed during the study. Two patients experienced pruritus, one case of which was attributed to PLE intake. Three patients were removed from the study due to an arrhythmia, dizziness, and cognitive impairment with emotional instability. Overall, study outcomes showed that ingestion of PLE 360 mg daily appeared to correlate with improved cognitive performance, brain bioelectrical activity, and blood flow of the middle cerebral arteries in patients with mild to moderate dementia.

Middelkamp-Hup et al studied 10 healthy patients to assess the effectiveness of oral PLE in decreasing oral psoralen + UVA (PUVA)-induced phototoxicity of human skin.[4] Patients were exposed to PUVA alone and PUVA with 7.5 mg/kg oral PLE. PLE-treated skin demonstrated reduced phototoxicity clinically and histologically after 48 and 72 hours. Pigmentation was also reduced 4 months later compared to PUVA alone. No AEs were reported during the study.

Middelkamp-Hup et al also investigated the photoprotective effect of oral PLE after UV radiation exposure.[5] Nine healthy subjects were exposed to UV radiation without PLE exposure and after administration of 7.5 mg/kg oral PLE. After 24 hours, skin was evaluated clinically for erythema and histologically for evidence of photo-induced effects. A significant decrease in erythema was noted clinically and histologic findings associated with photodamage were decreased. No AEs occurred during the study.

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Reyes et al performed a double-blind RCT examining the potential for PLE-induced immunomodulatory effects in patients exposed to PUVA.[20] T lymphocytes from peripheral blood were examined at baseline and after 12 weeks from 19 patients with generalized vitiligo randomized to receive PUVA plus PLE (n=10) or placebo (n=9). The percentage of subjects who achieved >50% skin repigmentation was markedly higher in the PLE group than in the placebo group. There were no AEs reported during the study.

A double-blind RCT by Middelkamp-Hup examined whether PLE improves narrow band (NB)-UVB-induced repigmentation in patients with vitiligo.[21] Fifty patients randomly received either 250 mg oral PLE or placebo three times daily. Each patient was exposed to NB-UVB twice weekly. Repigmentation was assessed initially and after 26 weeks. Repigmentation was most prominent in the head and neck area and statistically significant ($P< 0.002$) in the 18 patients receiving oral PLE who attended >80% NB-UVB sessions. Repigmentation was markedly higher in patients with Fitzpatrick II and III skin types compared to darker skin types (Fitzpatrick IV and V). Some patients (PLE, n=10 patients; placebo, n=5) experienced transient itching and dryness of the skin attributed to NB-UVB exposure. Four patients in the PLE group and 5 patients in the placebo group reported mild gastrointestinal complaints. No other AEs were reported.

Caccialanza et al studied whether the use of oral PLE could be an effective photoprotectant in patients with idiopathic photodermatoses.[22] Twenty-six patients with PMLE and two with solar urticaria were exposed to sunlight while taking oral PLE 480 mg/day. Skin response was compared to prior evaluations in the absence of PLE use. With PLE, a clinically relevant and statistically significant reduction ($P<0.05$) of the cutaneous eruption and subjective symptoms were both observed. One patient left the study due to an exacerbation of irritable bowel syndrome (IBS). However, the authors did not relate exacerbation of IBS to PLE use and indicated that the data regarding acute and chronic PLE toxicity has been very favorable and essentially devoid of AEs.

Villa et al designed a small comparative study to detect and quantify a UVA-induced photoaging marker, the CD, in both PLE-treated and placebo-treated subjects after UVA irradiation.[23] Ten subjects were selected with 5 randomly allocated to receive oral PLE 240 mg at 8 hours and at 2 hours before exposure to 2-3x MED. Biopsies were evaluated histologically for CD determination. PLE pre-treatment demonstrated a strong trend but failed to demonstrate statistical significance in preventing the rise of CD levels 24 hours after UVA irradiation. Besides the expected erythema following UVA irradiation, no treatment-related AEs were recorded.

A follow-up study by Caccialanza et al further evaluated the photoprotective properties of oral PLE in idiopathic photodermatoses.[24] Fifty-three patients with PMLE and 4 with solar urticaria were recruited for the study. All patients exposed themselves to sunlight while consuming oral PLE 480 mg/day. About 74% of the patients experienced marked therapeutic benefit from PLE with a significant ($P<0.05$) reduction in skin eruption and subjective symptoms. Oral PLE did not appear to be effective for solar urticaria, although the number of affected subjects was very small. No AEs were observed.

Oral PLE was studied to see if daily use would reduce the need for topical corticosteroids in children and adolescents with atopic dermatitis.[25] One-hundred five patients between 2 and 17 years of age were randomized to receive oral PLE 240 mg-480 mg or placebo daily for 6 months in addition to their standard

TABLE 1.

***Polypodium leucotomos* Extract: Assessment of Studies and Reported Adverse Events**

Study	Year	N	Study Details	Adverse Events
Human Studies				
Padilla et al.[14]	1972	36	Effects of PLE on psoriasis. Uncontrolled study.	None reported
Del Pino et al.[15]	1982	37	22 patients with psoriasis receiving PLE	1 pt left study with gastrointestinal intolerance. No side effects reported otherwise.
Alvarez[16]	1983	495	Personal experience using PLE to treat psoriasis. Uncontrolled study.	1 patient with severe pruritus and another with gastric disturbances.
Jimenez et al.[17]	1987	76	46 patients with atopic dermatitis receiving PLE	Well tolerated
Gonzalez et al.[18]	1997	21	Photoprotective adjuvant to PUVA. Uncontrolled study.	None in any patient
Alvarez et al.[19]	2000	45	30 patients with senile dementia received PL to study cognitive effects	2 patients with pruritis, 3 removed from study due to arrhythmia, dizziness, and cognitive impairment
Middelkamp-Hup et al.[4]	2004	10	Photoprotective adjuvant to PUVA. Uncontrolled study	None reported
Middelkamp-Hup et al.[5]	2004	9	Photoprotection against UV radiation. Uncontrolled study	None reported
Reyes et al.[20]	2006	19	10 patients received PLE to study immunological effects with PUVA	None reported
Middelkamp-Hup et al.[21]	2007	50	Repigmentation in vitiligo with PLE. 25 patients received PLE in study.	4 patients in PLE group and 5 from placebo reported GI discomfort with oral capsule ingestion
Caccialanza et al.[22]	2007	28	Photoprotection in photodermatoses. Uncontrolled study	None attributed to PLE reported
Villa et al.[23]	2010	10	PL effects on UVA-induced marker. 5 patients received PLE	No adverse effects
Caccialanza et al.[24]	2011	57	Photoprotection in photodermatoses. Uncontrolled study	None reported
Ramírez-Bosca et al.[25]	2012	40	PLE in atopic dermatitis. Uncontrolled study.	None associated with increased risk
Tanew et al.[26]	2012	35	Prevention of PLE. Uncontrolled study	None observed
Solivellas et al.[27]	2012	100	PLE preventing infections in athletes. 50 received PLE therapy.	No adverse effects
Aguilera et al.[28]	2013	61	PLE photoprotection in high risk MM patients. Uncontrolled study	No adverse reactions included in report
Ahmed et al.[29]	2013	33	PLE in melasma. 16 patients in treatment arm.	Well tolerated
Nestor et al.[30]	2014	40	Safety of PLE and photoprotection. 20 patients received oral PLE.	4 patients reported mild episodic fatigue, bloating, and headaches
Basic Science Studies[13]				
CIDASL		n/a	Ames test for carcinogenicity	No difference to controls
Biolab SL		n/a	Ames test for carcinogenicity	No difference to controls
Biolab SL		10	Acute-term murine toxicity- hourly	Absence of toxicity
Biolab SL		10	Acute-term murine toxicity- daily	No signs of morbidity or toxicity
Biolab SL		12	Medium-term toxicity in mice	No signs of toxicity
Biolab SL		20	Chronic-term toxicity in mice	No signs of morbidity or toxicity

treatment. Oral PLE use did not significantly reduce the percentage of days on which topical corticosteroids were applied. However, a marked reduction in the percentage of days using oral antihistamines was observed in patients taking oral PLE. There were no AEs in the study associated with a perceivable increase in risk related to using PLE. The authors commented on the good safety profile of PLE and suggested that it can be prescribed safely for long-term treatment.

Another study of photodermatoses by Tanew et al evaluated whether oral PLE might prevent or delay the photoinduction of typical polymorphic light eruption (PMLE) lesions induced by

artificial UV radiation.[26] Thirty-five patients with long-standing PMLE were included in an uncontrolled study in which PMLE skin lesions were initially induced by UVB and UVA light. After two weeks, a second photoprovocation was performed while patients had been taking from oral PLE 720 mg-1200 mg daily. Interestingly, 30% (n=9) and 28% (n=5) of patients were unresponsive to UVA and UVB exposure, respectively. In the remaining patients, the mean number of UVA and UVB irradiations required to elicit PMLE increased significantly from 1.95 to 2.62 (P=0.005) and from 2.38 to 2.92 (P=0.047), respectively. No AEs were recorded throughout the duration of the study.

Solivellas et al evaluated the reduction of infectious processes in athletes taking oral PLE.[27] One-hundred subjects were observed over an 8 month period for the onset or relapse of infectious illness. Fifty athletes were selected to ingest PLE 480 mg twice daily for the first 3 months. The onset of infectious illness was lower for patients taking PLE compared with controls (14% vs. 56%). Relapse was only noted in 1 patient taking PLE and in 10 patients from the control group. No AEs were reported in the study.

The possible role of PLE as a photoprotectant in high-risk melanoma patients was studied by Aguilera et al.[28] Sixty-one patients (25 with familial and/or multiple melanomas; 20 with sporadic melanoma; 16 with atypical mole syndrome without history of melanoma) were exposed to artificial UVB radiation both without and after oral administration of PLE 1080 mg. PLE significantly increased the MED mean in all groups (0.123 to 0.161 J/cm2, P<0.05). No AEs noted.

Ahmed et al assessed the effectiveness of oral PLE as an adjuvant to daily sunscreen application for the treatment of melasma in a double-blinded RCT.[29] Thirty-three Hispanic women with moderate to severe melasma were enrolled. Subjects were randomized to apply SPF 45 sunscreen every morning and receive either oral PLE 240 mg or oral placebo three times a day. Change in melanin index was assessed at the onset of the study and after weeks 6 and 12. Although 29% and 14% improvement was noted between PLE and placebo groups between weeks 0 and 12, the results were not statistically significant (P=.14). Both groups tolerated the treatments well.

The primary objective of a more recent double-blinded RCT by Nestor et al was to examine the safety of oral PLE in 40 patients.[30] The secondary objective was to see the efficacy of PLE in increasing MED or reducing UV-associated damage. Twenty subjects received oral PLE twice daily for 2 months. Safety was assessed at days 14, 28, and 56. No treatment-related adverse effects were reported during the study although 4 treatment group subjects reported mild episodic fatigue, bloating, and headaches. Subjects taking PLE showed statistically significant reduction of sunburns and UV damage (P<0.01). Authors concluded that oral PLE is a safe and effective photoprotectant.

CONCLUSION

Overall, 19 human and 6 basic science studies were included in this review spanning over 40 years of research from 1972 to 2014. Oral PLE was administered at daily doses ranging from 120 mg to 1080 mg. This review of the literature has demonstrated that PLE is well tolerated at all doses administered. Adverse effects were not reported from any murine study. In humans, side effects (gastrointestinal complaints and pruritus) were mild to moderate and found only in very small numbers of patients overall (16/1016 [2%]). These symptoms disappeared with drug cessation and there were no long-term sequelae. Major AEs were not reported in any of the clinical trials referenced in this review.

Years of anecdotal use and multiple studies as reviewed in this article strongly support that oral PLE is associated with a negligible risk of side effects. The current level of evidence suggests oral PLE is safe and can be prescribed confidently for long-term use.

DISCLOSURES

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