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 ORIGINAL ARTICLE

The Utility of Oral *Polypodium Leucotomos* Extract for Dermatologic Diseases: A Systematic Review

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ABSTRACT

Background: *Polypodium leucotomos* extract (PLE), a fern plant product with strong anti-inflammatory and immunomodulatory properties, has been employed to reduce photoaging and skin cancer. PLE may also serve as an adjuvant treatment for psoriasis, vitiligo, atopic dermatitis, photodermatoses, and melasma. This systematic review synthesizes the current data on PLE usage to manage dermatological diseases.

Methods: This systematic review followed the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA) guidelines. PubMed/MEDLINE, Embase, and Cochrane Library were queried using keywords. Articles were screened for inclusion and subsequently grouped by dermatological condition.

Results: Twenty-one of the 152 identified articles met inclusion criteria, including 11 randomized controlled trials and 5 treatment trials. Implicated dermatological conditions were photoaging/skin cancer (9 studies), actinic keratosis (3), photodermatoses (3), melasma (2), vitiligo (3), and atopic dermatitis (1). A thorough article review revealed several potential applications of PLE.

Conclusion: PLE exhibits strong therapeutic potential with an encouraging safety profile. It has photoprotective and immunomodulatory properties, underscoring its potential as an adjuvant therapy for multiple dermatological conditions.

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INTRODUCTION

Polypodium leucotomos is a South American fern rich in antioxidants that produces *polypodium leucotomos* extract (PLE) from its leaves. PLE exhibits immunomodulatory and anti-inflammatory properties, making it beneficial for treating psoriasis, vitiligo, atopic dermatitis, and melasma.[1-3] PLE also inhibits ultraviolet (UV) induced generation of radical oxygen species, decreasing photoaging and skin cancer development.[4] PLE formulations include topical gels, creams, powders, and oral capsules. The most prominent commercially available oral PLE supplement is Heliocare, (Heliocare®, Ferndale Healthcare®, Ferndale, Michigan).

Numerous applications of PLE have been studied. In 2014, Choudry et al completed a literature review of PLE summarizing its indications for dermatological conditions.[1] Multiple studies supporting its efficacy have since been published. This updated systematic literature review synthesizes the emerging data on PLE's role in managing dermatological diseases.

MATERIALS AND METHODS

This systematic review followed the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. On May 8, 2023, PubMed/MEDLINE, Embase, and Cochrane Library were queried using "polypodium leucotomos" as keywords. Results were limited to full text, English-language articles, with humans as the study subject.

RESULTS

The literature search yielded 152 unique articles, which were screened by 2 independent reviewers (MPZ and DZ). Fifty-two articles underwent full text review and 21 studies met inclusion criteria, 11 of which were randomized controlled trials (RCTs). Articles were grouped by dermatologic condition: photodermatoses, photoaging and skin cancer, vitiligo, melasma, psoriasis, and atopic dermatitis. The findings are summarized in Table 1.

TABLE 1.

Clinical Studies Summary

Skin Condition	Study	Subjects	Dose	Type	Outcome
Photoaging and Skin Cancer	Aguilera P et al (2012)	61	720+360 mg (total 1080 mg) 1 day and 3 hr before UVB exposure	Treatment trial	PLE significantly decreased UVR sensitivity in high-risk melanoma.
	Emanuele E, et al (2017)	40	PLE/pomegranate combination 480 mg daily (n=20) or PLE 480 mg daily alone (n=20) for 3 months	RCT	PLE and PLE/pomegranate improved photoaging skin parameters. The combination yielded a greater improvement than PLE alone.
	Kohli I, et al (2017)	22	240mg 2 hours and 1 hour (480 mg total) before irradiation with UVA1, UVB, and visible light	Open Treatment trial	PLE exhibited significant chemoprotective and anti-inflammatory properties against UVB-induced damage.
	Middelkamp-Hup MA, et al (2004)	10	7.5 mg/kg oral PLE+PUVA at various intervals	Open Label study	PLE decreased clinical and histological indicators of phototoxic damage, indicating it is an effective chemophotoprotector against PUVA-induced phototoxicity.
	Middelkamp-Hup MA, et al (2004)	9	7.5 mg/kg oral PLE+UV Radiation at various intervals	Open Label study	PLE-treated skin had a significant decrease in erythema, sunburn-cell formation, DNA damage, epidermal hyperproliferation, and dermal mast cell infiltration. PLE has chemophotoprotective properties, against UV radiation.
	Mohammad TF, et al (2019)	22	480 mg daily x 28 days + visible light irradiation	Open Label study	PLE administration before visible light decreased pigmentation. There was a statistically significant reduction in persistent pigment darkening, delayed tanning, and decreased inflammation on immunohistochemistry.
	Nestor MS, et al (2015)	40	240 mg BID x 60 days	Randomized, double-blinded, placebo-controlled	PLE group showed a decreased likelihood of sunburn, an increased minimal erythema dose, and a greater likelihood of decreased ultraviolet-induced erythema intensity. PLE (240 mg BID for 60 days) was safe and effectively reduced damaging effects of ultraviolet radiation.
	Villa A, et al (2010)	10	240 mg 8 and 2 hours before UVA exposure	Randomized, investigator blinded, controlled trial	PLE pretreatment showed a strong, but not significant, trend towards preventing increased CD levels 24 hours after UVA irradiation and with increasing UVA doses.
	Gonzalez S, et al (1997)	21	1080 mg oral PLE vs topical PLE in psoralen-sensitized and nonsensitized patients	Open treatment trial	Oral and topical PLE were photoprotective. PLE significantly increased the UV dose required for immediate pigment darkening, the minimal erythema dose, and the minimal phototoxic dose.
Melasma	Ahmed A, et al (2013)	40	240 mg TID (720 mg total daily) x 12 weeks	Randomized, double blinded, placebo controlled	PLE was not significantly better than placebo as an adjunct to sunscreen for melasma treatment.
	Goh CL, et al (2018)	40	480 mg daily x 12 weeks	Randomized, double blinded, placebo controlled	PLE was an effective coadjutant treatment for melasma in combination with topical 4% hydroquinone and SPF 50.
Actinic Keratosis	Auriemma M, et al (2015)	34	960 mg QD x 1 month then 480 mg QD x 5 months after 2 PDT sessions (2 weeks apart)	RCT	PLE improved PDT clearance and decreased AK recurrence rates at month 6 in bald males with >2 scalp AKs.
	Miola AC, et al (2022)	50	500 mg oral PLE BID vs Placebo + either colchicine, ingenol mebutate, or sunscreen	RCT	Colchicine was effective and tolerable in treating AKs and cutaneous field cancerization. There was no difference when PLE was added.
	Pellacani G, et al (2023)	131	Topical PLE+SPF100 vs oral PLE 240 mg QD+SPF100 vs self-administered sunscreen	Open label RCT	Topical and oral PLE groups demonstrated decreased AKs and field cancerization parameters. Oral PLE+SPF100 showed the greatest improvements, suggesting a potential photoprotective advantage.

TABLE 1. (CONTINUED)

Clinical Studies Summary					
Skin Condition	**Study**	**Subjects**	**Dose**	**Type**	**Outcome**
Photo-dermatoses	Caccialanza M, et al (2007)	28 (26 PMLE; 2 solar urticaria	480 mg daily x 15 days before UV exposure	Open treatment trial	PLE significantly reduced skin reactions and subjective symptoms in patients with treatment nonresponsive PMLE. Two patients with solar urticaria did not improve.
	Caccialanza M, et al (2011)	57 (53 PMLE; 4 solar urticaria)	480 mg daily x 15 days before UV exposure	Open treatment trial	PLE significantly reduced skin reactions and subjective symptoms in patients with treatment nonresponsive PMLE. Three of four patients with solar urticaria did not improve.
	Tanew A, et al (2012)	35	Weight dosing: <55 kg=720 mg QD; 56-70 kg=960 mg QD; >70 kg=1200 mg QD	Open, uncontrolled (no placebo)	After PLE, 30%and 28% of patients did not react after UVA or UVB exposure. The mean number of UVA and UVB irradiations required to elicit PMLE significantly increased (UVA: *P*=0.005, UVB: *P*=0.047)
Vitiligo	Middelkamp-Hup MA, et al (2007)	50	250 mg TID+NB-UVB twice weekly x 25-26 weeks	Randomized, double-blinded, placebo-controlled	PLE group trended towards increased re-pigmentation compared to placebo across all anatomical locations. PLE repigmentation was nearly statistically significant in the "head and neck" (*P*=0.06)
	Reyes E, et al (2006)	19	PUVA+ oral PLE 720 mg daily vs PUVA+placebo for 12 weeks	Randomized, double-blinded, placebo-controlled	PLE+PUVA significantly increased skin repigmentation, normalized T-cell activation, and , decreased peripheral blood mononuclear cells proliferation compared to PUVA+placebo.
	Pacifico A, et al (2006)	44	480 mg oral BID+NB-UVB vs NB-UVA+placebo	Randomized, prospective, controlled study	PLE+NB-UVA significantly increased repigmentation compared to placebo. PLE+NB-UVA may also enhance the speed and extent of repigmentation.
Atopic Dermatitis	Ramirez-Bosca A, et al (2012)	105	Daily PLE (240 mg, 360 mg, or 480 mg by age) vs placebo	Randomized, double-blind, placebo-controlled	PLE may control pruritus more effectively than antihistamines and decrease their consumption. There was no difference in topical corticosteroid usage between groups.

Abbreviations: PLE: Polypodium leucotomos extract, UVR: Ultraviolet radiation, UVB: Ultraviolet B radiation, UVA: Ultraviolet A radiation, NB-UVA: Narrow-band ultraviolet light A, RTC: Randomized clinical trial, QD: Once daily, BID: Twice daily, TID: Three times daily, PDT: Photodynamic therapy, AK: Actinic Keratosis, SPF: Sun protection factor, PMLE: Polymorphous light eruption

DISCUSSION

Photoaging/Skin Cancer

PLE protects against phototoxicity, making it beneficial in preventing photoagaing and skin cancer. Middelkamp-Hup et al evaluated PLE in reducing psoralen-UVA (PUVA)-induced phototoxicity clinically and histologically.[5] Ten participants were exposed to PUVA or PUVA+oral PLE 7.5 mg/kg. PLE subjects exhibited consistently reduced signs of phototoxic damage. In a comparable study, PLE-treated skin displayed reduced erythema, sunburn cell formation, DNA damage, epidermal hyperproliferation, and dermal mast cell infiltration.[6] This suggests that PLE is an effective chemo-photoprotective agent against UV-radiation and PUVA-induced phototoxicity.

Nestor et al conducted a double-blinded RTC with 40 patients comparing oral PLE-240 mg (60 days BID) vs placebo.[2] The placebo group showed a greater likelihood of >1 sunburn episode (*P*=0.04). PLE subjects demonstrated greater likelihood of increased minimal erythema dose (*P*=0.01) and decreased UV-induced erythema intensity (*P*<0.01).

Kohli et al used a split-back design to examine PLE's protective effects against UV-irradiation-induced skin damage grossly and histologically.[7] Twenty-two patients were irradiated with UVA and UVB on their left back on day 1. On days 3 and 4, patients consumed PLE-240 mg 2 hours and 1 hour before UV treatment on their right back. Skin erythema and pigmentation were assessed via Investigator's Global Assessment (IGA) 24 hours after each session, along with colorimetry and biopsies for immunohistochemistry analysis. The average IGA score was 19% lower in the PLE group (*P*<0.05). On colorimetry, the relative erythema intensity was 8% lower in the PLE group (*P*<0.05). Histological assessment of biomarkers associated with UV damage found that all deleterious effects were significantly reduced (*P*<0.05), with a 32% improvement in pyrimidine dimers and decreased UVA-induced phototoxicity.

Villa et al assessed PLE on the mitochondrial DNA 'common-deletion' (CD), a marker of chronic UVA radiation.[8] Ten participants received UVA at minimal erythema dose (MED) with pretreatment of oral PLE-240 mg 8 and 2 hours prior. Though

not statistically significant, PLE showed a clear trend toward preventing increased CD levels 24 hours after UVA irradiation and with increasing UVA doses.

Aguilera et al explored PLE's photoprotection in high-risk skin cancer patients.[9] Sixty-one melanoma-prone patients received PLE-720 mg one day and PLE-360 mg 3 hours before UVB exposure. Subjects served as their own controls. Results showed a significant increase in mean MED across all groups, indicating reduced UV-radiation sensitivity. In subgroup analysis, darker eye color and lower baseline MED predicted a better response to PLE.

Mohammad et al investigated PLE's protection against visible light.[10] Twenty-two participants were given oral PLE-480 mg for 28 days and exposed to visible light. Statistically significant reductions in persistent pigment darkening, delayed tanning, and inflammation were noted. A nonsignificant decrease in pigmentation was observed (P=0.07).

Emanuele et al compared daily oral PLE vs a PLE/pomegranate combination for 3 months on 40 participants.[11] Both groups demonstrated improvements in photoaging-related biophysical parameters. PLE/pomegranate showed superior reductions in erythema index, melanin index, and sebum content. Gonzalez et al explored the photoprotective properties of oral and topical PLE.[12] Twenty-one patients were divided into psoralen-sensitized and nonsensitized groups and given either oral PLE-1080 mg or topical-PLE. Both preparations protected skin from acute sunburn reaction and PUVA-induced phototoxicity. These studies underscore PLE's systemic photoprotective properties, offering benefits against photoaging and skin cancer development.

Actinic Keratosis

The first RTC investigating PLE and precancerous actinic keratosis (AK) found that supplementation after photodynamic light therapy (PDT) improved PDT clearance and decreased AK recurrence 6 months post-treatment.[13] Thirty-four bald men with 2+ scalp AKs underwent 2 PDT sessions one week apart, followed by either oral PLE daily (960 mg for 1 month, then 480 mg for 5 months) or nothing. All patients demonstrated reductions in AK numbers, which was statistically significant for both PLE and control groups at month 2, but only PLE at month 6. The PLE cohort also had superior clearance rates compared to controls (P=0.04). PLE may act synergistically with PDT for AK treatment via increased clearance rate and recurrence prevention.

Pellacani et al demonstrated that oral PLE with topical sunscreen offered significant protective benefits in patients with high-risk AK recurrence.[14] This RCT randomized 131 subjects with photoaging and ≥3 AKs to [Cnt] general nonspecific photoprotection, [T] topical photoprotection (SPF-100)+PLE gel twice daily, or [TO] topical (SPF-100) + oral PLE 240 mg once daily. Outcomes, including AK area score index (AKASI), AK field assessment (AK-FAS), new lesions, and additional AK treatment (were assessed at trial initiation (t0), month 6 (t6), and month 12 (t12). In AKASI analysis, [Cnt] had a 3% increase (P=0.001) at t6, [T] had no differences, and [TO] had a 3% decrease at t6 and t12 (P=0.001). AK-FAS found significant changes in hyperkeratinization across time (t0, t6, t12): hyperkeratinization increased in [Cnt] (9.3% to 20.5% to 30%) but significantly decreased in [T] (13.6% to 10.3% to 5.9%) and [TO] (13.6% to 8.6% to 3%). At month 6, 25% of [Cnt] developed ≥1 new AK compared to 2.6% of [T] and 0% [TO] (P=0.008). At month 12, 14% of [Cnt] but 0% of [T] and [TO] developed new AKs (P<0.001). Researchers observed a significant difference in the percent of subjects necessitating additional treatment: 23% [Cnt], 10% [T], and 3% [TO] (P=0.027). Oral PLE with sunscreen may protect against AK development, decrease keratinization, lesion size, and additional treatments. Though less pronounced, [T] had significant benefits compared to [Cnt], underscoring PLE's different immunomodulatory effects when administered orally vs topically.

Miola et al compared oral PLE vs placebo and either topical colchicine, ingenol mebutate (IM), or sunscreen for AK treatment.[15] Fifty patients were randomized to oral PLE-500 mg BID or placebo for 1 month. Groups were then subdivided into 3 topical regimens: colchicine 0.5% cream BID (1 week), IM 0.05% gel once daily (2 days), or SPF-30 sunscreen. Researchers assessed total and partial AK clearance, cutaneous field cancerization (CFC) activity, forearm photoaging scale (FPS), and keratinocyte intraepithelial neoplasia (KIN) score. Both PLE and placebo had similar reductions in total (14.7% vs 16.1% P=0.26) and partial clearance (44% vs 44% P=0.26). KIN analysis showed no differences between groups.

PLE may be an effective adjuvant to PDT for AK treatment but further studies are warranted.

Photodermatoses

PLE may help prevent and treat photodermatoses, a group of immunologically mediated skin reactions provoked by UV sunlight, including polymorphic light eruption (PMLE), chronic actinic dermatitis, and solar urticaria.

Caccialanza et al investigated PLE's photoprotective properties in patients with treatment-resistant photodermatoses.[17] Twenty-six patients with PMLE, and 2 with solar-urticaria) took oral PLE-240 mg BID with typical sun exposure. Clinical response was categorized as "normalization" if no rash appeared, "clear-improvement" (50-90%), "slight-improvement" (10-50%), or "no-improvement." The majority (80%) of patients reported improvement; 31% had complete normalization and 49% had slight or clear-improvement. Neither solar urticaria patients demonstrated improvement.

Caccialanza et al performed an identical study on a larger population, yielding similar results.[18] Fifty-three patients with PMLE and 4 with solar urticaria received PLE-480 mg daily with typical sun exposure. Over 70% (P<0.05) of patients reported a clinical benefit of PLE: 29.3% had complete normalization, and 43.9% reported some degree of improvement. Only one solar urticaria patient reported improvement. No adverse effects were observed.

Tanew et al assessed whether PLE can prevent photoinduction of PMLE.[19] Thirty patients with UVA-inducible PMLE (18 UVB sensitive) were given weight-based oral PLE (≤55 kg=720 mg/day, 56-70 kg=960 mg/day, >70 kg=1200 g/day). After 2 weeks, there was a statistically significant increase in the UV-light threshold needed to induce PMLE, with 9 (30%) patients having no PMLE-induction (P=0.005). Fifteen patients continued taking PLE for the summer, of which 47% remained without PMLE and 27% experienced significant symptomatic improvement. PLE can diminish or prevent UV induction of PMLE. However, it may not be as effective for solar urticaria.

Melasma

PLE's photoprotective properties have led to its exploration as an adjunct to melasama treatment. Ahmed et al conducted an RTC to evaluate oral PLE with sunscreen for melasma.[20] Forty patients received oral PLE-240 mg or placebo TID with SPF-55 sunscreen for 12 weeks. Melasma, measured by melanin index and Melasma Area and Severity Index (MASI), improved in both groups without statistically significant differences.

A double-blind, placebo-controlled study by Goh et al found more encouraging results.[21] Forty patients received oral PLE-480 mg or placebo with 4% hydroquinone and SPF-50+ sunscreen. Both groups exhibited a significant improvement in the modified-MASI (mMASI)-- 44.4% reduction in the placebo group (P≤0.01) and 54.9% for PLE (P≤0.01). PLE saw a larger comparative decrease in mMASI with statistical significance at day 56 (P≤0.05). Melasma Quality of Life (MelasQoL) scores significantly improved with PLE. Oral PLE may accelerate outcomes of hydroquinone and sunscreen for melasma, but additional studies are required.

Vitiligo

PLE may enhance skin repigmentation in vitiligo treatment when used as an adjuvant to Narrow band (UVB) light therapy.
A double-blind clinical trial by Reyes et al evaluated skin repigmentation and blood immunomodulatory effects of PLE plus PUVA light-therapy for vitiligo.[23] Nineteen patients were randomized to PUVA+PLE 720 mg daily or PUVA+placebo for 12 weeks. There was a significantly higher percentage of >50% skin repigmentation in PLE+PUVA than PUVA+placebo. Blood samples from baseline and after 12 weeks found that PLE+PUVA significantly decreased the expression of activating signals on CD8+ T-lymphocytes and the proliferative response of immune cells comparatively. This study elucidates the anti-inflammatory and immunological properties of PLE at a molecular level and correlates them to enhanced repigmentation in vitiligo.

Middlekamp et al compared repigmentation in vitiligo patients treated with NB-UVB or NB-UVB+PLE in a double-blind, placebo-controlled study.[24] All 50 patients received twice-weekly NB-UVB for 25-26 weeks, and either oral PLE 250 mg TID or placebo. Results demonstrated a strong but not statistically significant trend towards increased repigmentation with PLE compared to placebo, especially in the head/neck (P=0.06). The increased repigmentation with PLE was statistically significant among patients attending 80% of NB-UVB sessions (P<0.002). PLE patients with Fitzpatrick skin-types II and III had significantly increased repigmentation compared to placebo (P=0.01). No conclusions were drawn about Fitzpatrick types IV and V due to small sample size. There were no differences in quality of life (Skindex-29). PLE can enhance repigmentation in vitiligo patients, especially in lighter skin tones and most prominently in the head/neck.

Pacifico et al investigated PLE in vitiligo patients with medium to darker skin types and found PLE with NB-UVB significantly improved repigmentation compared to NB-UVB alone.[22] This double-blind RCT included 44 vitiligo patients with Fitzpatrick skin types III or IV. All patients underwent twice-weekly NB-UVB for 6 months with either PLE-480 mg BID or placebo. The NB-UVB+PLE group had greater repigmentation than NB-UVB alone in the head/neck (P<0.001), trunk (P=0.080), and extremities (P<0.001). At 3-month follow-up, the PLE group had maintained significantly more repigmentation than placebo, especially in the head/neck (P<0.001). The rate of NB-UVB induced erythema, pruritus, and burning was significantly lower in the PLE group (P=0.023). The addition of PLE to NB-UVB significantly enhanced repigmentation in vitiligo patients with darker skin tone, underscoring the promising potential of PLE as an adjuvant to phototherapy.

Atopic Dermatitis

Ramírez et al investigated whether PLE could reduce topical corticosteroid and antihistamine use in children with atopic dermatitis (AD).[25] One-hundred and five patients (2-17 years old) with moderate AD were randomized to oral PLE (age-dosing <6: 240 mg/day, 6-12: 360 mg/day, >12: 480 mg/day) or placebo for 6 months. Participants were given topical methylprednisolone-aceponate 0.1% for flares and desloratadine for pruritus. The percent of days subjects required topical corticosteroids did not differ between groups (11% PLE vs 12% placebo P=0.20); but PLE demonstrated a trend toward lower corticosteroid usage and number of flares comparatively. PLE, but not placebo, had significant decreases in corticosteroid usage between months 1 to 2 (P=0.012) and 4 to 5 (P=0.012). PLE patients required desloratadine on significantly fewer days than placebo (P=0.038). This trend became more significant over time, indicating a potential advantage of antihistamine intake reduction.

CONCLUSION

PLE exhibits therapeutic potential for an array of dermatological conditions with an encouraging safety profile. PLE's photoprotective properties and efficacy in mitigating phototoxicity underscore its importance in skin health. The compelling outcomes in AK and photodermatoses management reinforce PLE's therapeutic versatility. Experiments testing PLE in vitiligo, atopic dermatitis, and melasma suggest its potential role as an adjuvant therapy, but the data are mixed. Further research investigating optimal dosing and routes of administration is needed. Advancing our understanding of PLE's therapeutic effects could uncover additional applications and clinical utility.

DISCLOSURES

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