ORIGINAL RESEARCH

Clinical Efficacy & Safety of Oral Polypodium Leucotomos Extract for Photoprotection: A Systematic Review

Giselle Prado MD[1], Rebeca Teplitz BA[2], Richard Winkelmann DO[3], James Del Rosso DO[4], Darrell Rigel MD, MS[5]

[1]National Society for Cutaneous Medicine, New York, NY
[2]New York Institute of Technology College of Osteopathic Medicine, Old Westbury, NY
[3]Department of Dermatology, OhioHealth Hospital
[4]JDR Dermatology Research, Las Vegas, NV
[5]Department of Dermatology, NYU School of Medicine, New York, NY

ABSTRACT

Background: Polypodium leucotomos extract (PLE) is a naturally derived compound from a fern native to South America. PLE has been shown to have antioxidant and photoprotective properties. Several different preparations of PLE are commercially available.
Objective: To review the efficacy and safety of PLE for photoprotection in humans.
Methods: A systematic review was conducted in 3 databases (Medline, Embase, and Cochrane) for studies that reported on the clinical efficacy and safety of PLE in humans. A data collection form was created for collecting study variables.
Results: Eighteen studies with sample sizes ranging from n=5 to n-61 were included. The most common formulation of PLE studied was Fernblock® (Heliocare, Ferndale Healthcare, Ferndale, MI) in 18 studies. Most studies reported beneficial photoprotective effects of PLE as evidenced by increased MED. No serious adverse effects were reported.
Conclusions: Multiple studies have shown the beneficial photoprotective effects and safety of the Fernblock® PLE formulation, but there is minimal evidence to support the safety and efficacy of other formulations. Given that the extraction methodology varies for herbal nutraceuticals and can affect its efficacy, these findings cannot be extrapolated to other formulations of PLE.

INTRODUCTION

A complete sun protection package includes sun protective clothing, sunscreen, and avoidance of the midday sun. Sun protection can also be affected by oral ingestion of certain compounds. Psoralen is one such compound that leads to photosensitization. On the other hand, polypodium leucotomos extract (PLE) has been shown to have photoprotective properties.

Polypodium leucotomos is a fern native to South America that is widely recommended by dermatologists for its antioxidant and photoprotective properties. PLE does not act as a sunscreen, but has been shown to have

some photoprotective efficacy. It works at both the molecular and cellular level to decrease UV-mediated cell apoptosis and necrosis. PLE inhibits the generation of Reactive Oxygen Species (ROS) as well as UV-induced AP1 and NF-κB. It also prevents damage to DNA and protects against endogenous antioxidant systems natural to the skin. [1]

Several different preparations of PLE are commercially available. The most popular formulation of PLE is Heliocare (Ferndale Healthcare, Ferndale, MI). However, the extraction methodology of an herbal supplement can affects its potency and effects in humans.[2] Without testing each specific formulation in humans, it can be difficult to compare different products that claim to have the same ingredients.

This study reviews the efficacy and safety of PLE for photoprotection in humans and determines the most studied formulations of PLE.

METHODS

Data Sources:
We searched three computerized bibliographical databases for articles published since inception to September 2018: Pubmed, Cochrane Library CENTRAL, and Embase. Search terms included: "polypodium leucotomos extract," "oral sunprotection," "heliocare," and "fernblock." The search was restricted to publications in English. This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Prospero registration no. CRD42018106975). We reviewed trial registers (clinicaltrials.gov). Reference lists of all included studies and of recent reviews were also assessed. Electronic publications in advance of print were also included.

Inclusion Criteria:
We included any human studies that referenced polypodium leucotomos extract.

Exclusion Criteria:
Case reports and studies done on animals or *in-vitro* were not included.

Outcome measures:
Outcomes related to change in sun protection efficacy included: minimal erythemal dose, minimal melanogenic dose, melanin index, melasma area and severity index (MASI), melasma quality of life scale (MELASQOL), investigators global assessment of erythema, colorimetry, and erythema index. Changes in skin quality were measured as transepidermal water loss, skin sebum content, wrinkle depth, and hydration. Changes in histopathology were quantified by number of sunburn cells, cyclobutane pyrimidine dimers, proliferating cells, matrix metalloproteinase 1 levels, Langerhans cells, and mast cells.

Data extraction and synthesis:
One reviewer (G.P.) extracted data, another reviewer (R.T.) checked the extracted data for accuracy, and the reviewers met to discuss any disagreements. We created and piloted a data collection form for recording study design, sample sizes, primary outcomes, adverse events, and length of follow-up. Disagreements were resolved by discussion.

RESULTS

The search yielded 288 unique articles whose titles and abstracts were screened by 2 reviewers. Full text papers were

retrieved for 38 articles. Eighteen studies were found to meet inclusion criteria (8 randomized controlled trials, 8 pre-post test studies, and 2 patient surveys).

The studies tended to have relatively small sample sizes (n=5 to n=61). (Table 1) The most common formulation of PLE studied was Fernblock® (Ferndale Healthcare, Ferndale, MI) (17/18). Most studies reported beneficial photoprotective effects of PLE as evidenced by increased minimal erythemal dose (MED). MED was measured in 8 studies and results showed a uniform increase in MED. [4,6,7,11,14,16,17,19]

Biopsies also showed the histologic effects of using PLE. Patients taking PLE orally had lower numbers of sunburn cells, cyclobutane pyrimidine dimers, mast cells, and proliferating cells. [3,14,15]

PLE can also be used as an adjunctive treatment in polymorphous light eruption. Three studies found a benefit to PLE use in this population.[16,20,21] Although the level of evidence was lower for this indication (2 surveys and 1 pre-post exposure study), patients uniformly reported a decrease in symptoms. After irradiation, less patients developed polymorphous light eruption symptoms if they were taking PLE.

No serious adverse events were reported. The most common adverse event was mild gastrointestinal discomfort.

Table 1: Summary of studies investigating the photoprotective effects of PLE.

Author & Year	Study Design	Comparators	No. Pts Tx w/ Oral PLE	No. Pts Comparator	Tx. Duration	Endpoints	Results
Gonzalez 1997[6]	Open label RCT	Oral PLE* 1080mg vs. Topical PLE 10%	12	9	1 day	IPD, MED, MMD, MPD IHC	Oral PLE increased IPD, MED (2.82x), MPD (2.75x) IHC: Photoprotection of Langherhans cells by oral and topical PLE.
Vila 2010[7]	Single blind, RCT	Oral PLE* 240mg x 2 doses vs. No Tx	5	5	1 day	Common deletion marker, MED	No difference in common deletion values.
Martin 2012[8]	Double blind, RCT	Oral PLE 240mg BID vs. Placebo	21**		12 weeks	MELASQoL, MASI, physician and patient assessment	PLE improved MASI and MELASQoL. Physician and patient assessment showed more improvement with PLE.
Ahmed 2013[9]	Double blind, RCT	Oral PLE* 240mg TID +sunscreen vs. Placebo +sunscreen	16	17	12 weeks	Melanin index change, MASI, MELASQoL	Melanin index improved 28.8% with PLE and 13.8% with placebo group. MASI improved in both groups. MELASQol no change in either group.
Cestone 2014[10]	Single blind, RCT	Oral PLE* 240mg BID + sunscreen vs. Placebo +sunscreen	20	10	12 weeks	Melanin index, TEWL, wrinkle depth, skin moisturization, gloss value, elasticity, firmness	Decreased TEWL, melanin index, and wrinkle depth with PLE. Increased skin moisture, gloss value, elasticity, and firmness with PLE. No adverse events.
Nestor 2015[11]	Double blind, RCT	Oral PLE* 240mg BID vs. Placebo	20	20	60 days	MED, UV induced erythema intensity response, sunburn, adverse events	Increased MED and decreased UV induced erythema intensity with PLE. Less likely to have an episode of sunburn with PLE. No adverse events.

Emanuele 2017[12]	RCT	Oral PLE* 480mg Vs. PLE/Pomegrante mix 480 mg	20	20	3 months	Sebum, hydration, TEWL, melanin index, erythema index, elasticity	Improved hydration, elasticity, TEWL, and erythema both groups. Melanin index and skin sebum content reduced by only by mix. No adverse events
Goh 2018[13]	Double blind, RCT	Oral PLE* 240mg BID + HQ & sunscreen vs Placebo + HQ & sunscreen	33		12 weeks	mMASI, melanin index, erythema index, MELASQoL	Lower mMASI with PLE. No difference in melanin, erythema index, or MELASQoL. No adverse events.
Middelkamp-Hup 2003[14]	Open label, Pre and post exposure	Oral PLE* 7.5mg/kg vs. No Tx	Not reported		Not reported	Erythema, edema, biopsies, MED	Decreased erythema with PLE. Biopsy showed decreased sunburn cells, CPDs, vasodilation, mass cell infiltration, and epidermal proliferation with PLE.
Middelkamp-Hup 2004[3]	Open label, Pre and post exposure	Oral PLE* 7.5mg/kg x 2 doses	9	N/A	72 hours	Erythema, biopsies	Decreased erythema with PLE. Biopsy showed decreased sunburn cells, CPDs, proliferating cells, and mast cells with PL.
Middelkamp-Hup 2004[15]	Open label, Pre and post exposure	Oral PLE* 7.5mg/kg x 2 doses	10	N/A	1 day	MPD, erythema and edema intensity, biopsies	Decreased erythema and edema intensity with PLE after 48-72 hours Biopsy showed decreased . sunburn cells, mast cells, amd vasodilation. No differences in proliferating cells.

Tanew 2012[16]	Open label, Pre and post exposure	Oral PLE* 720mg to 1200mg daily in patients with polymorphous light eruption	30	N/A	1 month	MED, No. of exposures to induce symptoms, No. of patients with induced symptoms	30% reduction in number of patients with induced symptoms after UVA. 28% reduction in number of patients with induced symptoms after UVB. Mean number of UVA or UVB exposures to elicit symptoms increased with PLE. Increased MED with PLE. No adverse events reported
Aguilera 2012[4]	Open label, Pre and post exposure	Oral PLE* 1080mg	61	N/A	1 day	MED, melanoma gene mutation testing	Increased MED with PLE in 65% of patients. No difference in MED between patients with melanoma gene variants.
Calzavara-pinton 2015[17]	Pre and post exposure testing	Oral PLE* 240mg BID	10	N/A	2 weeks	MED, MMD	Increased MED with PLE. No change in MMD.
Truchuelo 2016[18]	Pre and post exposure testing	Oral PLE* 960mg daily	7	N/A	3 weeks	Biopsy, MMP1 levels	Without PLE, MMP1 levels increased in 71% of patients. With PLE, MMP1 levels increased in 14% of patients. Structure of epidermis unchanged by irradiation.
Kohli 2017[19]	Open label, Pre and post exposure	Oral PLE* 240mg x 2 doses	22	N/A	1 day	Erythema, MED, colorimetry, biopsies	Decrease in UVB -induced changes with PLE detected by clinical assessments, colorimetry. Increased MED in 32% of patients with PLE. Colorimetry showed decrease in UVB -induced changes in 77% of patients.

							Decreased effect of UV on H&E biomarkers.
Caccialanza 2007[20]	Open label, Post exposure survey	Oral PLE* 240mg BID in patients with solar urticaria or polymorphous light eruption	25	N/A	15 days	Frequency and severity of skin manifestations	80% of patients had an improvement in symptoms. 28% had normalization of symptoms. Not effective in solar urticaria.
Caccialanza 2011[21]	Open label, Post exposure survey	Oral PLE* 240mg BID in patients with solar urticaria or polymorphous light eruption	57	N/A	Not reported	Frequency and severity of skin manifestations	74% of patients had an improvement in symptoms. No adverse events.

*Fernblock formulation.
**Distribution not reported.
BID: Twice daily.
CPD: cyclobutane pyrimidine dimer.
IHC: Immunohistochemistry.
IPD: Immediate pigment darkening.
HQ: Hydroquinone.
MASI: Melasma Area and Severity Index.
mMASI: Modified melasma area and severity index.
MED: Minimal erythemal dose.
MELASQoL: Melasma quality of life scale.
MMD: Minimal melanogenic dose.
MPD: Minimal pigment dose.
N/A: Not applicable.
No.: Number.
TEWL: Transepidermal water loss.
TID: Three times daily.
Tx: Treatment.
Vs: Versus

DISCUSSION

UV light can have harmful effects on the skin, including sunburn, immunosuppression, pigment changes, photoaging, and skin cancer.[3] Currently, the most widely used method for protection against UV damage is the use of topical sunscreens, which act as either a chemical or physical barrier against these harmful rays.[4] These topical sunscreens often fail to provide a uniform and prolonged total body surface protection. As a result of the rise of spray sunscreen use and the lack of proper application guidelines, there is a need for a systemic photoprotective agent.[5] This systematic review demonstrates the photoprotective effects of PLE. However, it is important to note that while PLE decreases photosensitization, it serves as an additional component to other sun protection measures.

Our systematic review was extensive with a precisely executed search strategy and selection process. It serves as an up to date resource for the efficacy and safety effects of PLE.

CONCLUSION

Multiple studies have shown the beneficial photoprotective effects and safety of the Fernblock® PLE formulation, but there is minimal evidence to support the safety and efficacy of other formulations. Given that the extraction methodology varies for herbal nutraceuticals and can affect its efficacy, these findings cannot be extrapolated to other formulations of PLE.

Conflict of Interest Disclosures: Dr. Prado is a fellow of the National Society for Cutaneous Medicine.

Funding: This study was supported in part through an unrestricted grant to the National Society for Cutaneous Medicine from Ferndale Healthcare.

Corresponding Author:
Giselle Prado, MD
National Society for Cutaneous Medicine,
New York, NY
Email: drgiselleprado@gmail.com

References:

1. González S, Gilaberte Y, Philips N, Juarranz Á. Fernblock, a nutriceutical with photoprotective properties and potential preventive agent for skin photoaging and photoinduced skin cancers. *Int J Mol Sci.* 2011;12(12):8466–8475.
2. Ong ES. Extraction methods and chemical standardization of botanicals and herbal preparations. J Chromatogr B Analyt Technol Biomed Life Sci. 2004;812(1-2):23-33.
3. Middelkamp-hup MA, Pathak MA, Parrado C, et al. Oral Polypodium leucotomos extract decreases ultraviolet-induced damage of human skin. J Am Acad Dermatol. 2004;51(6):910-8.
4. Aguilera P, Carrera C, Puig-butille JA, et al. Benefits of oral Polypodium Leucotomos extract in MM high-risk patients. J Eur Acad Dermatol Venereol. 2013;27(9):1095-100.
5. Teplitz, R. W., Glazer, A. M., Svoboda, R. M., Rigel, D. S. (2018). Trends in US Sunscreen Formulations: Impact of Increasing Spray Usage. J Am Acad Dermatol. 78 (1): 187-189.
6. Gonzalez S, Pathak MA, Cuevas J, et al. Topical or oral administration with an

extract of Polypodium leucotornos prevents acute sunburn and moralen-induced Phototoxic reactions as Gel1 as depletion of Langerhans cells in human skin. Photodermatol Photoimmunol Photomed 1997;13:50-40

7. Villa A, Viera MH, Amini S, et al. Decrease of ultraviolet A light-induced "common deletion" in healthy volunteers after oral Polypodium leucotomos extract supplement in a randomized clinical trial. J Am Acad Dermatol. 2010;62(3):511-3.
8. Martin LK, Caperton C, Woolery-Lloyd H, et al. A randomized double blind placebo controlled study evaluating the effectiveness and tolerability of oral Polypodium leucotomos in patients with melasma. American Acad of Dermatol Annual Meeting. 2012; Poster# 4630.
9. Ahmed AM, Lopez I, Perese F, et al. A randomized, double-blinded, placebo-controlled trial of oral Polypodium leucotomos extract as an adjunct to sunscreen in the treatment of melasma. JAMA Dermatol. 2013;149(8):981-3.
10. Cestone E, Marzatico F, Nobile V, et al. Placebo-controlled study of the efficacy of a dietary supplement to reduce skin dark spots and to create more even complexion in Asian women. Pigment Cell Melanoma Res. 2014;27(5):995.
11. Nestor MS, Berman B, Swenson N. Safety and Efficacy of Oral Polypodium leucotomos Extract in Healthy Adult Subjects. J Clin Aesthet Dermatol. 2015;8(2):19-23.
12. Emanuele E, Bertona M, Biagi M. Comparative effects of a fixed Polypodium leucotomos/Pomegranate combination versus Polypodium leucotomos alone on skin biophysical parameters. Neuro Endocrinol Lett. 2017;38(1):38-42.
13. Goh CL, Chuah SY, Tien S, Thng G, Vitale MA, Delgado-rubin A. Double-blind, Placebo-controlled Trial to Evaluate the Effectiveness of Extract in the Treatment of Melasma in Asian Skin: A Pilot Study. J Clin Aesthet Dermatol. 2018;11(3):14-19.
14. Middelkamp-hup MA, Pathak MA, Parrado C, et al. Oral polypodium leucotomos extract protects human skin against the damaging effects of ultraviolet radiation and Puva exposure. J Eur Acad Dermatol Venereol. 2003;17:160.
15. Middelkamp-hup MA, Pathak MA, Parrado C, et al. Orally administered Polypodium leucotomos extract decreases psoralen-UVA-induced phototoxicity, pigmentation, and damage of human skin. J Am Acad Dermatol. 2004;50(1):41-9.
16. Tanew A, Radakovic S, Gonzalez S, Venturini M, Calzavara-pinton P. Oral administration of a hydrophilic extract of Polypodium leucotomos for the prevention of polymorphic light eruption. J Am Acad Dermatol. 2012;66(1):58-62.
17. Calzavara-Pinton PG, Rossi MT, Zanca A, et al. Oral Polypodium leucomotos increases the anti-inflammatory and melanogenic responses of the skin to different modalities of sun exposures: a pilot study. Photodermatol Photoimmunol Photomed. 2016;32:22-27.

18. Truchuelo M, Jiménez N, Mascaraque M, et al. Pilot study to assess the effects of a new oral photoprotector against infrared-visible radiations. J Invest Dermatol. 2016;136(5):S106.
19. Kohli I, Shafi R, Isedeh P, et al. The impact of oral Polypodium leucotomos extract on ultraviolet B response: A human clinical study. J Am Acad Dermatol. 2017;77(1):33-41.e1.
20. Caccialanza M, Percivalle S, Piccinno R, Brambilla R. Photoprotective activity of oral polypodium leucotomos extract in 25 patients with idiopathic photodermatoses. Photodermatol Photoimmunol Photomed. 2007;23(1):46-7.
21. Caccialanza M, Recalcati S, Piccinno R. Oral polypodium leucotomos extract photoprotective activity in 57 patients with idiopathic photodermatoses. G Ital Dermatol Venereol. 2011;146(2):85-7.