Polypodium leucotomos: A Review of the Literature Summarizing Clinical Safety Profile

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INTRODUCTION

Polypodium leucotomos is a fern native to Central and South America used by Native Americans to treat inflammatory disorders (1). Oral and topical *P. leucotomos* extracts (PLE) have several beneficial properties. The 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 appears to prevent photoaging by maintaining extracellular matrix integrity (6,7) and preventing damage to DNA repair enzymes (5,8,9). Anti-mutagenic effects of PLE are attributed to its ability to block UV radiation-induced COX-2 expression (10-2) and promote activation of the tumour suppressor p53 (8). Finally, PLE has immunoregulatory effects in response to UV radiation demonstrated by inhibited infiltration of neutrophils and mast cells and reduced loss of antigen-presenting Langerhans cells (4). Recent studies have evaluated the efficacy of PLE orally and topically for use in several inflammatory diseases, UV-induced conditions, melasma, and photoprotection. A specific extract of *Polypodium leucotomos* (PLE) is available commercially (Heliocare®, IFC) and has been evaluated in a variety of basic science and clinical studies.

Despite decades of anecdotal evidence supporting the excellent safety profile of PLE, no publication has reviewed the adverse event outcomes reported in clinical studies. The purpose of this literature review is to summarize the safety profile of PLE in humans and animals.

METHODS

A PubMed search for clinical trials relating to PLE or the synonym anapsos and a review of data on Ames and murine testing were conducted. Studies that were not randomized or placebo-controlled were included if performed on a large number of patients. Considerable effort was made to find older, foreign articles although not all were found. The primary safety endpoint of the review was any mention of an adverse event.

RESULTS

Ames testing for carcinogenicity with PLE were negative (13). Acute toxicity studies performed with 1 g/kg of PLE in mice were negative after 10 days (13). Medium-term toxicity studies with 200 mg/kg of PLE daily for 28 days were negative (13). Long-term toxicity studies with 200 mg/kg of PLE daily for 90 days were negative (13).

ACKNOWLEDGEMENT

This review was funded in part by a grant from Ferndale Healthcare, Inc.

Clinical Studies	Condition, (*N*)[a]	Adverse Events
Padilla HC, Laínez H, Pacheco JA. *Int J Dermatol*. 1974;13:276-82.	Psoriasis (*N*=36)	None
Del Pino G, De Sambricio GF, Colomo GC. *Med Cutan Ibero Lat Am*. 1982;10:203-8.	Psoriasis (*N*=22)[b]	GI intolerance (*N*=1)
Alvarez BP. *Med Cutan Ibero La Am*. 1983;11:65-72.	Psoriasis (*N*=495)[b]	Severe pruritus (*N*=1), GI disturbances (*N*=1)
Jimenez D, Doblare E, Naranjo R, et al. *Allergol Immunopathol*. 1987;15:185-9.	Atopic dermatitis (*N*=46)	None
González S, Pathak MA, Cuevas J, et al. *Photodermatol Photoimmunol Photomed*. 1997;13:50-60.	Photoprotection (*N*=21)[b]	None
Alvarez XA, Pichel V, Perez P. *Methods Find Exp Clin Pharmacol*. 2000;22:585-94.	Senile dementia (*N*=30)	Pruritus (*N*=2), arrhythmia, dizziness, cognitive impairment (for each, *N*=1)
Middelkamp-Hup MA, Pathak MA, Parrado C, *et al. J Am Acad Dermatol*. 2004;50:41-9.	Photoprotection (*N*=10)[b]	None
Middelkamp-Hup MA, Pathak MA, Parrado C, *et al. J Am Acad Dermatol*. 2004;51:910-8.	Photoprotection (*N*=9)[b]	None
Reyes E, Jaén P, de las Heras E, *et al. J Dermatol Sci*. 2006;41:213-6.	Immunological effects with PUVA (*N*=10)	None
Middelkamp-Hup MA, Bos JD, Rius-Diaz F, *et al. J Eur Acad Dermatol Venereol*. 2007;21:942-50.	Vitiligo (*N*=25)	GI discomfort (*N*=4)
Caccialanza M, Percivalle S, Piccinno R, *et al. Photodermatol Photoimmunol Photomed*. 2007;23:46-7.	Photoprotection (*N*=28)[b]	None
Villa A, Viera MH, Amini S. *J Am Acad Dermatol*. 2010;62:511-3.	UVA-induced biomarkers (*N*=5)	None
Caccialanza M, Recalcati S, Piccinno R. *G Ital Dermatol Venereol*. 2011;146:85-7.	Photoprotection (*N*=57)[b]	None
Ramírez-Bosca A, Zapater P, Betlloch I. *Actas Dermosifiliogr*. 2012;103:599-607.	Atopic dermatitis (*N*=40)[b]	None
Tanew A, Radakovic S, Gonzalez S. *J Am Acad Dermatol*. 2012;66:58-62.	Polymorphic light eruption (*N*=35)[b]	None
Solivellas BM, Martín TC. *Infect Drug Resist*. 2012;5:149-53.	Infections in athletes (*N*=50)	None
Aguilera P, Carrera C, Puig-Butille JA, *et al. J Eur Acad Dermatol Venereol*. 2013;27:1095-100.	Photoprotection in high risk MM patients (*N*=61)[b]	None
Ahmed AM, Lopez I, Perese F. *JAMA Dermatol*. 2013;149:981-3.	Melasma (*N*=16)	None
Nestor MS, Berman B. Presented: Practical Dermatology and Dermatopathology Symposium, Vail, CO. August 16, 2014.	Photoprotection (*N*=20)	Mild episodic fatigue, bloating, headaches (*N*=4)

[a]does not include placebo-treated subjects; [b]uncontrolled study

CONCLUSIONS

A total of 19 human and six laboratory studies were included in this review spanning over 40 years of research from 1972 to 2014. PLE was administered topically and systemically in doses ranging from 120 to 1080 mg. This review demonstrated PLE is well tolerated at all doses. Adverse effects were not reported from any murine study. In humans, adverse effects included mild to moderate gastrointestinal complaints and pruritus in very few patients (16/1016; 2%) which resolved upon drug cessation and without sequelae. Serious adverse events have not been reported. Additional long-term studies are needed to determine the true lifetime morbidity risk associated with PLE; however, current evidence suggests it can be safely used long-term.

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