



Application of Calahuala (*Phlebodium* spp) fern complex for the formulation of diverse medicinal and cosmetic products

Armando Cáceres^{1*}, Sully M. Cruz²

¹Farmaya Laboratories 4a calle A 3-00 zona 3, Guatemala

²School of Pharmacy, University of San Carlos, Ciudad Universitaria zona 12, Edificio T-10, Guatemala

Correspondence to

Armando Cáceres
Email:
acaceres@farmaya.net

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Abstract

Extracts of the tropical fern *Phlebodium* complex of Polypodiaceae family, appear to possess beneficial properties for the skin, attributed to the presence of numerous compounds within the extract that have antioxidant and photoprotective properties. Orally administered *Phlebodium* complex may provide protection against the detrimental photoaging effects of sunlight, can help reduce the frequency and severity of polymorphous light eruption, and is beneficial for the prevention and potential treatment of several aesthetically relevant conditions. The purpose of this review is to describe beneficial role of *Phlebodium* complex as an adjunct treatment for vitiligo, melasma, and post-inflammatory hyperpigmentation. Various extracts applied topically or taken orally have shown several beneficial antioxidant, photo-protectant, anti-mutagenic, and immunoregulatory effects. Modern studies have evaluated the efficacy of *Phlebodium* extracts as a photoprotective agent and for use in several photo-aggravated dermatologic disorders such as polymorphous light eruption, photodermatoses, vitiligo, melasma, psoriasis, atopic dermatitis, and more recently, in minimizing infections in high-performance athletes. It is these multiple mechanisms of action, in combination with a favorable side effect profile, which make *Phlebodium* complex a promising adjunctive treatment for several dermatologic disorders. Aerial part has proved to exert antioxidant, photo-protective and immunomodulatory activities; extract of fronds is a natural mixture of phytochemicals endowed with powerful antioxidant properties as flavonoids compared to rhizome. *Phlebodium* fern extract of fronds and rhizome blocked the deleterious effect of UV irradiation *in vitro* and *in vivo* as a natural photoprotectant and potential adjuvant to phototherapy of various skin diseases.

Keywords: Antioxidant, Photoprotective, Immunomodulatory, Rhizome, Fronds.



Introduction

Pteridophytes include ferns and fern allies that have a long history on earth represented by more than 10 000 species distributed in varied climatic regions. Traditional uses have been transmitted from generation to generation to cure common diseases as well as a food source, ornamentation, and control of pests.¹⁻⁴ In Central America, ferns are collected or cultivated for floral trade, as medicine or other commercial uses.⁵

Based on the modern molecular analysis and trends in classification, four fern families have been proposed. They are- Asplenaceae, Cyatheaceae, Polypodiaceae and Schizaeaceae, which are gaining wider acceptance and use.⁶ Polypodiaceae is a large, diverse monophyletic family of epiphytic ferns, which includes eight sub-families, 17 to 60 genera depending on the source, and more than 1200

species distributed worldwide.^{7,8}

Calahuala is a complex of ferns which includes members of *Polypodium* and *Phlebodium* genera.⁹ It has been traditionally used for treating several diseases in the regions of natural distribution,^{10,11} particularly skin diseases (e.g., psoriasis and atopic dermatitis).¹³ Dry rhizomes are commonly found in local markets and health food stores in Honduras and Guatemala, and are used for cosmetic and phytotherapeutic purposes.¹² Recently, several phytocosmetic products based on it have been introduced in European markets. This review focuses on the use, validation and phytochemistry of Calahuala complex.

The genus *Phlebodium*

Calahuala (Kallawala) is a complex of traditionally used



ferns in Mesoamerica for the treatment of diverse chronic diseases. At least two species are recognized as being used from this complex, *Phlebodium decumanum* (Willd.) J. Sm. (syn. *Polypodium aureum* L., *P. decumanum* Willd., *P. leucotomos* Poir. *P. multiseriale* Moore & Houlst.), and *Phlebodium pseudoaureum* (Cav.) Lellinger (syn. *Polypodium aerolatum* Humb. et Bonpl. ex Willd., *P. pseudoaureum* Cav., *Goniophlebodium aerolatum* (Humb. et Bonpl. ex Willd.) C. Presl.). The two nervules in the areola distinguish genus *Phlebodium* from all other member of Polypodiaceae. Both species are diploid, but due to hybridization have developed triploid and tetraploid *P. aureum*, (L.) J. Sm. which are commonly used in Mesoamerica indistinctly.⁷

Species are described as epiphyte fern, brilliant stalk, fronds separated, bright green, 30-120 cm long.^{7,9-11} Native to Central and South America they are found on tree trunks and disintegrated stones, in humid shadowy forests. *P. decumanum* has been reported from sea level to 800 masl, and *P. pseudoaureum* from 1200-2200 masl.^{7,9-11} Both species have been described in most countries of the American continent, but are being used as medicine only in Mesoamerica, where there is a managed or cultivated production for the international markets for fronds and rhizomes.^{5,12} There is a complex of traditionally used ferns in Mesoamerica for the treatment of diverse chronic diseases. Aqueous extracts of the rhizome and fronds are used orally or topically to treat respiratory, urinary and cardiac diseases, gastric ulcer, broken bones, rheumatism, tumors, and skin diseases (psoriasis, dermatitis, vitiligo, and sunburn).⁹⁻¹³

Antineoplastic, antioxidant and immunomodulatory activity

First validation studies involving *in vitro* and *in vivo* methods and clinical trials were reported in 1967 which suggested that the saponin calagualine has anti-tumor activity demonstrated by *in vitro* and *in vivo* models. This also proved beneficial in advance cases of human neoplasia without secondary effects.¹⁴ In patients with high risk of melanoma, the oral administration of the extract led to a significant reduction of sensitivity to UVR.¹⁵

Further research about anti-neoplastic activity is related to antioxidant and immunomodulatory activity. Saponins isolated from the rhizome reduced the incorporation of nucleoproteins in a mechanism opposite to cytostatics.¹⁶ Studies on hairless mice demonstrated decreased UV-induced Cox-2 expression, inflammation, and mutagenesis¹⁷; inhibition of epidermal cell proliferation, enhancement of p53 expression and plasma antioxidant capacity¹⁸; and delay in skin tumor development.¹⁹ Other studies have demonstrated important antioxidant activity.^{20,21} The aqueous extract orally administered to mice demonstrated an immuno-modulatory activity, by prolonging cutaneous UVB radiation-induced immuno-

suppression,²² inhibiting spleen cell proliferation by Con A, lowering hypothalamic IL-1 β ,²³ prolonging cutaneous transplant survival and inhibiting polyclonal proliferation of mononuclear cells induced by lymphocyte T mitogen.²⁴ The water soluble fraction also demonstrated anti-inflammatory activity *in vitro* by decreasing tumor necrosis factor (TNF) production and increasing IL-1Ra and sTNFR2, which neutralize IL-1 and TNF activity.²⁵

Dermatologic and cosmetic application

Although some *in vitro* and *in vivo* procedures have demonstrated bioactivity by fronds and rhizomes in the 1970s, the clinical evidence is available only on dermatologic effect of calahuala extracts. Initial clinical validation studies were conducted since 1974 in the management of psoriasis.²⁶ In healthy volunteers, it lowered the lymphoblastic response to mitogens, the immunoglobulin levels and the relation of OKT8+ cells²⁷; these results might explain the improvement in psoriatic patients.²⁸ In a double-blind trial the extract improved the development of psoriasis in comparison with standard treatment.²⁹ Oral administration also protected from dermic damage by UV light in volunteers^{30,31} and photoinduced skin cancer.³³

The oral and topical application of a product containing a hydrophilic extract induced re-pigmentation by UVB in patients with vitiligo,^{33,34} prevented polymorphic eruption to light,³⁵ diminished the levels of antihistamine used in the handling of atopic dermatitis,³⁶ and protect in idiopathic photodermatoses.³⁷ In a pilot study in healthy volunteers, the topical application reduced the lymphocyte infiltration and dermic aging after UV application, suggesting protection against UV damage³⁸ or prevention of mitochondrial DNA damage.³⁹

Oral administration of the extract to bald patients improved photodynamic therapy clearance and decreased actinic keratoses recurrence,⁴⁰ and increased anti-inflammatory and melanogenic responses of the skin of healthy subject to different modalities of sun exposure;⁴¹ indicating that photo-protection properties of *P. leucotomos* extract can be achieved in a pill.⁴²

Oral or topically administered *P. leucotomos* extract was effective on skin protection, demonstrated by inhibition of ROS, increase of antioxidant capacity, photoaging relief, inhibition of apoptosis, and prevention of DNA damage and necrosis by UV. Also it modulate cell proliferation, reduces inflammation, and prevents immuno-suppression, leading to inhibition of carcinogenesis. These activities are confirmed by clinical trials in photoaging, vitiligo, polymorphous eruption, melasma,⁴² atopic dermatitis, and lupus erythematosus.⁴³⁻⁴⁵

Other pharmacologic and toxicologic studies

The decoction showed a moderate diuretic activity in rats,⁴⁵ and excellent anti-diarrheal activity.⁴⁶ A purified extract

(Anapsos™) demonstrated several *in vitro* and *in vivo* properties, suggesting that it is a neuroimmunotrophic compound with potential utility for the treatment of Alzheimer's disease, neurodegenerative diseases, and age-related disorders.⁴⁷ Its clinical administration has shown improved cognitive performance, cerebral blood perfusion and brain bioelectrical activity in patients with senile dementia.⁴⁸

It has also been demonstrated that the administration of *P. leucotomos* extract as a supplement to sedentary university students modulated the immune response both during physical performance induced by training⁴⁹; ameliorated oxidative stress and inflammatory signaling induced by strenuous exercise in adult humans⁵⁰; and prevented and reduced the risk of infectious diseases in high performance athletes.⁵¹

The toxicity and genotoxicity was evaluated in accordance with international standards of a commercial aqueous preparation of the fronds, showing no evidence of toxicity or genotoxicity in single and two repeated-dose oral tests.⁵² In a clinical trial with 40 patients and 40 controls, the administration of the extract (240 mg twice daily for 60 days) was a safe and effective means of reducing the damaging effect of UVR.⁵³ A review on PubMed literature for 40 years (1972-2014) including 19 human and six laboratory studies demonstrated no adverse effects, side effects or toxicity, suggesting an effective and safe use in clinical practice.^{54,55}

Chemical constituents of genus *Phlebodium*

Rhizome and fronds contain sugars (glucose, rhamnoglucose, arabinose, galactose, ribose), flavonoids (kaempferol, quercetin-2-O-glycosides, rutin, juglanin),⁵⁶ phenolic compounds (chlorogenic and caffeic acids mainly in fronds, benzoate and cinnamates),⁵⁷ essential oil, mucilage, saponins (calagualine), alkaloids, steroids (ecdysterone, ecdysone, polypodoaurein),^{10,58} coumarins (melilotoside), acidic molecules (quinic, shikimic, glucuronic, malic, coumaric, and vanillic acids),^{20,58} fatty acids (arachidonic, eicosapentaenoic, elaidic, linoleic, ricinoleic and oleic acids, sulphoquinovosyl diacyl glycerol), tannins, and adenosine.^{10,59,60}

The presence of adenosine and some cetosteroid saponins might be responsible for the immuno-modulatory activity demonstrated experimentally and clinically.⁶⁰ The flavonoid constituents are responsible for elastase release in human neutrophils.⁶¹ Mineral content has not been fully studied, but moderate concentration of aluminum (357 ± 10 mg/kg of dry matter).⁶² (*R*)-mandelonitrile lyase and jacalin-related lectin has been isolated from species of the genus *Phlebodium*.^{63,64} Polyphenolic compounds inhibit UV induced peroxidation and production of nitric oxide (NO), while its derivatives, ferulic acid, is a UV photon acceptor.

Conclusion

Application of *Phlebodium* complex extract has demonstrated to be effective and safe in the prevention and management of several skin diseases, *in vitro*, *in vivo* and clinical trials. It is recommended the administration of this vegetable drug in handling vitiligo, psoriasis and as a photoprotector in sunburn.

Conflict of Interests

None.

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