Polypodium leucotomos as an Adjunct Treatment of Pigmentary Disorders

[a]MARK NESTOR, MD, PhD; [b]VIVIAN BUCAY, MD; [c]VALERIE CALLENDER, MD; [d]JOEL L. COHEN, MD; [e]NEIL SADICK, MD; [f]HEIDI WALDORF, MD

[a]Director, Center for Clinical and Cosmetic Research, Center for Cosmetic Enhancement, Aventura, Florida; Voluntary Associate Professor, Department of Dermatology and Cutaneous Surgery, University of Miami, Miller School of Medicine, Miami, Florida; [b]Bucay Center for Dermatology and Aesthetics, San Antonio, Texas; Voluntary Clinical Assistant Professor, University of Texas Heath Science Center, Department of Physician Assistant Studies, San Antonio, Texas; [c]Associate Professor of Dermatology, Howard University College of Medicine, Washington, D.C., Callender Dermatology and Cosmetic Center, Glenn Dale, Maryland; [d]Director, AboutSkin Dermatology and DermSurgery, Englewood, Colorado; Associate Clinical Professor, Department of Dermatology, University of Colorado, Denver, Colorado; [e]Sadick Dermatology, New York, New York; Clinical Professor of Dermatology, Weill Cornell Medical College, New York, New York; [f]Director of Laser and Cosmetic Dermatology, Associate Clinical Professor of Dermatology, Mount Sinai School of Medicine, New York, New York

ABSTRACT

Introduction: Extracts of the tropical fern *Polypodium leucotomos* 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 *Polypodium leucotomos* may provide protection against the detrimental photoaging effects of sunlight and can also help reduce the frequency and severity of polymorphous light eruption. *Polypodium leucotomos* has also been shown to be beneficial for the prevention and potential treatment of several aesthetically relevant conditions. **Objective:** The purpose of this review is to investigate the beneficial role of *Polypodium leucotomos* as an adjunct treatment for vitiligo, melasma, and postinflammatory hyperpigmentation. **Results:** Based on a review of relevant literature including the results of a randomized, placebo-controlled study, the oral administration of *Polypodium leucotomos* significantly improved the severity of melasma in women after 12 weeks. Three randomized, double-blind, placebo-controlled studies have demonstrated significant improvements in vitiligo when oral *Polypodium leucotomos* therapy was combined with psoralens plus ultraviolet A and narrowband ultraviolet B. No controlled studies have assessed the efficacy of *Polypodium leucotomos* for the treatment of postinflammatory hyperpigmentation; however, its known antioxidant and anti-inflammatory properties and demonstrated effectiveness for melasma support its use for treating this condition. No adverse events have been associated with the use of *Polypodium leucotomos*. **Conclusion:** In addition to preventing many harmful effects associated with sunlight exposure, orally administered *Polypodium leucotomos* also appears to provide adjunctive benefits in treating vitiligo, melasma, and may have the potential to help with postinflammatory hyperpigmentation. (*J Clin Aesthet Dermatol.* 2014;7(3):13–17.)

Polypodium leucotomos is a tropical fern that is native to Central and South America. Clinical and nonclinical research performed over the past 30 years has demonstrated that extracts of *P. leucotomos* possess beneficial properties attributed to the presence of numerous compounds with antioxidant and photoprotective properties including p-coumaric, ferulic, caffeic, vanillic, 3,4-dihydroxybenzoic, 4-hydroxybenzoic, 4-hydroxycinnamic, 4-hydroxycinnamoyl-quinic, and chlorogenic acids.[1,2]

When taken orally, *P. leucotomos* provides some degree of protection against the harmful effects of ultraviolet radiation,[3,4] thereby helping to minimize the photoaging effects of sunlight, including hyperpigmentation and textural changes.[5] *P. leucotomos* may owe its ability to help

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ADDRESS CORRESPONDENCE TO: Mark S. Nestor, MD, PhD; E-mail: nestormd@admcorp.com

in preventing the photoaging process specifically by maintaining the structural integrity of the extracellular matrix that typically is affected by UV damage through increased matrix metalloproteinase expression and inhibition of collagen synthesis.[6,7]

P. leucotomos appears to be particularly beneficial for photosensitive individuals. Several recent open-label studies have demonstrated the ability of *P. leucotomos* to reduce the frequency and severity of polymorphous light eruption.[8–10] Long-term treatment with an extract of *P. leucotomos* has been shown to reduce inflammation and relieve itching in children and adolescents with atopic dermatitis.[11] In addition to its photoprotective and anti-inflammatory effects, *P. leucotomos* has also been shown to be beneficial for the treatment of several clinically important pigmentary conditions.

VITILIGO

Vitiligo is an acquired, chronic loss of skin pigmentation. Generalized vitiligo is characterized by white and often symmetrical patches, which usually increase in size with time, corresponding to a substantial loss of functioning epidermal melanocytes.[12] Segmental vitiligo is characterized by white patches with a unilateral distribution that sometimes corresponds with a dermatome. Other distribution patterns can be encountered that cross several dermatomes, or correspond to large areas delineated by Blaschko's lines.[12]

Although vitiligo affects persons of all races and genders,[13] it is especially troublesome for dark-skinned individuals, especially when it affects the face and other exposed areas. The pathophysiology of vitiligo remains unclear and may involve genetic and autoimmune factors,[14] neural injury, or cytotoxic effects.[13] Vitiligo is psychologically more damaging than hyperpigmentation disorders. In addition to diminished quality of life,[15] it may result in depression, anxiety, decreased self-esteem, and even suicidal ideation.[16]

Therapies for vitiligo. The goal of treating vitiligo is to make it less noticeable either by restoring lost pigment or eliminating remaining pigment. A standard of therapy for vitiligo for many years has been phototherapy involving the use of various psoralens and exposure to ultraviolet A light (PUVA). The treated skin becomes pink after UVA exposure and then eventually fades to a more normal skin tone. For areas of vitiligo affecting less than 20 percent of the body surface area, psoralens are applied topically. If the affected area is greater than 20 percent, psoralens are administered orally. PUVA can achieve up to 100-percent repigmentation in some patients, but requires several treatment sessions per week for many months.[17] Severe sunburn, blistering, and abnormally dark repigmentation are major potential side effects of topical PUVA therapy. Narrowband UVB therapy has also become available and does not require the use of psoralens. One study demonstrated up to 75-percent repigmentation using narrowband UVB alone, but it also required multiple weekly sessions for one year or more.[18] The mechanism is unknown and results are variable.

At the present time, studies appear to suggest the 308nm excimer laser may be the treatment of choice for localized vitiligo.[19] Treatment sessions are performed 2 to 3 times weekly using doses of 100mJ/cm^2 to as high as 2,000 to 3,000mJ/cm^2 depending on the area of the body being treated. The goal is to achieve mild erythema in the affected area without causing thermal injury. The onset of repigmentation occurred after a mean of 13 treatments in lesions located on the face, trunk, arms, and legs and after a mean of 22 treatments in lesions located on the elbow, wrist, and dorsum of the hand, knee, and foot. Response rates were variable, but among patients responding to treatment, there was no relapse after 1 to 2 years. Children seem to respond better than adults and darker skin responds better than lighter skin. Adverse events are uncommon.

The efficacy of the excimer laser may be improved when used in combination with topical therapies. Topical treatments for vitiligo include corticosteroids (betamethasone valerate, fluticasone and clobetasol propionate), agents in the calcineurin inhibitor class of immunosuppressants (tacrolimus, pimecrolimus), and vitamin D_3 analogues (calcipotriol).

In one comparative study, topical tacrolimus and clobetasol achieved repigmentation in 41.3 and 49.3 percent of patients, respectively.[20] In another comparative study, median repigmentation among patients treated with tacrolimus and fluticasone was only 15 and five percent, respectively, after six months.[21] Corticosteroids have also been used in combination with retinoids[22] and calcipotriol[23] with improved results. Adverse events associated with the use of topical corticosteroids include skin atrophy and telangiectasias.[20]

Beneficial effects of *Polypodium leucotomos*. As indicated above, psoralens + UVA (PUVA) has frequently been used for the treatment of vitiligo. A randomized, double-blind, placebo-controlled pilot study assessed the combined efficacy of PUVA plus *P. leucotomos* versus PUVA plus placebo on T-lymphocytes from patients with generalized vitiligo (N=19) and healthy controls (N=19).[24] The percentage of patients with >50 percent skin re-pigmentation was significantly higher among patients treated with PUVA/*P. leucotomos* than PUVA/placebo-treated patients ($p<0.01$). The overall re-pigmentation response was inversely correlated with the decrease in CD3+CD25+ T-cells.

Narrowband UVB (NB-UVB) has also been used for treating vitiligo and a subsequent randomized, double-blind, placebo-controlled study compared the efficacy of NB-UVB together with *P. leucotomos* for improving re-pigmentation versus NB-UVB and placebo.[25] Adult patients with patients with vitiligo (N=50) were randomized to receive oral *P. leucotomos* 250mg or placebo three times daily combined with NB-UVB twice weekly for 25 to 26 weeks.

Re-pigmentation was higher in the *P. leucotomos* group versus placebo in the head and neck area (44% vs. 27%, $p=0.06$) while less significant re-pigmentation was observed on trunk (6%), extremities (4%), and hands and feet (5%). Patients attending >80 percent of required NB-UVB sessions

showed significantly increased re-pigmentation in the head and neck area in the *P. leucotomos* group versus placebo (50% vs. 19%, $p<0.002$). Patients with Fitzpatrick skin types 2 and 3 showed more re-pigmentation in the head and neck area in the *P. leucotomos* group versus placebo (47% vs. 21%, $p=0.01$). Physician assessment of the head and neck re-pigmentation was considered clinically relevant in 72 percent of the *P. leucotomos*-treated patients versus 43 percent of the placebo group.

A second randomized study also compared the effectiveness of *P. leucotomos* when combined with NB-UVB for the treatment of generalized vitiligo.[26] Patients with generalized vitiligo (N=57) were randomized to receive combination therapy with twice-weekly NB-UVB and once-daily *P. leucotomos* 480mg (N=29) or NB-UVB phototherapy alone (N=28) for up to six months. The addition of oral *P. leucotomos* to NB-UVB resulted in 40-percent re-pigmentation versus 22 percent for NB-UVB alone. Patients treated with combination therapy showed significantly higher re-pigmentation throughout the study ($p<0.0005$). There are no published studies to date regarding the efficacy of oral *P. leucotomos* without adjunctive light therapy. There was no significant difference in the energies (joules) used in patents receiving oral *P. leucotomos* in any of the studies.[24–26]

MELASMA

Melasma is an acquired hypermelanosis that occurs on sun-exposed areas of the skin. Darkened patches are often distributed in a centrofacial pattern affecting the forehead, cheeks, upper lip, nose and chin. It is more common in women than men[27] and occurs most frequently in women who are pregnant (chloasma or "mask of pregnancy") or taking oral contraceptives or hormone replacement therapy. In one large case series (N=312), there was a higher prevalence of melasma among Hispanics and Asians.[28] The mean age at onset of melasma was 29.9 years (range, 11 to 49 years) and the female-to-male ratio was approximately 4:1. Many patients reported a family history of melasma (N=104; 33%). About 55 percent of patients reported sun exposure worsened their condition; and among female patients (N=250), precipitating factors were pregnancy (N=56; 22%) and oral contraceptives (N=46; 18%). While melasma is a relatively benign condition, it can adversely affect self-image and self-esteem and have an overall negative impact on patient quality of life.[29,30]

Therapies for melasma. Initial treatment should always include diligent sunscreen use (re-application every 2 hours with key ingredients that protect against UVA rays, such as zinc oxide, titanium dioxide, avobenzone, or ecamsule), sun protection (wide-brimmed hats), or simply avoiding sun exposure. Topical hydroquinone has been used for the treatment of melasma for many years, although controversy and questions about the safety of hydroquinone have recently emerged[31] and its use for cosmetic purposes has been banned in Europe.[32] Hydroquinone has been determined to be safe at concentrations of ≤1% in hair dyes and nail adhesives, but some advocate that it should not be used in leave-on cosmetics, although this has been a common practice in the United States for several decades.[33] One commercial product containing 0.05% tretinoin, 4.0% hydroquinone, and 0.01% fluocinolone acetonide is specifically approved for the treatment of moderate-to-severe melasma together with sun protection measures.[34] Although the safety and effectiveness of this drug combination has been demonstrated for up to 12 weeks,[35] it is only approved for short-term use (up to 8 weeks).[34]

Consequent to the hydroquinone controversy, a plethora of other topical agents has emerged to assist in the treatment of melasma including azelaic acid, arbutin, aloesin, kojic acid, saponin, soy, licorice, rucinol, mulberry, niacinamide, oregonin, yohimbine, ellagic acid, resveratrol, and dioic acid.[36,37] Nonetheless, the clinical efficacy of most of these agents remains to be demonstrated in randomized controlled trials despite promising *in vitro* and animal studies.[37]

Aside from the topical therapy, light-based procedures have been tried in the treatment of melasma as well. These studies involve the use of intense pulsed light (IPL) or laser technology (such as the Q-switched ruby laser and Q-switched alexandrite laser, Q-switched Nd:YAG laser, and erbium laser fractional photothermolysis),[36] but the quality of evidence supporting the use of lasers and other light-based modalities is not optimal or consistent.[38] Significant complications can include worsening hyperpigmentation or epidermal injury resulting in dyspigmentation.[36]

Superficial and medium-depth chemical peels including salicylic acid, trichloroacetic acid, glycolic acid, Jessner solution, and tretinoin have also been used effectively for the treatment of melasma.[36,37] In darker-skinned individuals (such as Fitzpatrick Skin Types IV and above), however, they must be used with caution because of the risk of long-term postinflammatory hyperpigmentation.[36,39]

Beneficial effects of *Polypodium leucotomos*. A recent study demonstrated the clinical efficacy of *P. leucotomos* for the treatment of melasma. Female subjects aged 18 to 50 years with epidermal melasma (N=21) were randomized to receive oral *P. leucotomos* or placebo twice daily for 12 weeks.[40] Each subject applied SPF45 sunscreen daily. Efficacy measures included changes in the Melasma Quality of Life Scale, the Melasma Area and Severity Index, and clinical evaluation by the study investigator. Plain and UV-lamp photographs obtained at baseline and Weeks 4, 8, and 12 were evaluated by an independent, blinded investigator.

At 12 weeks, patients treated with *P. leucotomos* had significantly decreased mean Melasma Area and Severity Index scores (5.7 to 3.3; $p<0.05$), whereas the placebo group did not (4.7 to 5.7; p=NS). Photographic assessment revealed mild and marked improvement was achieved by 43 and 17 percent of *P. leucotomos*-treated patients, respectively, versus 14 and 0 percent of placebo-treated patients. Similarly, patient self-assessments revealed 50 and 13 percent of patients achieved mild and marked improvement, respectively, versus 17 and 0 percent for placebo-treated patients. Seventeen percent of placebo-

treated patients reported worsened melasma severity versus none of *P. leucotomos*-treated patients.

POSTINFLAMMATORY HYPERPIGMENTATION

Postinflammatory hyperpigmentation (PIH) is another acquired hypermelanosis that also occurs with greater frequency among darker skinned individuals. In contrast with melasma, PIH occurs in areas of the skin recently affected by injury or inflammation.[41] Common causes of PIH in dark-skinned individuals include acne vulgaris, atopic dermatitis, and impetigo.[41] One study reported 65.3 percent of African-American, 52.7 percent of Hispanic, and 47.4 percent of Asian patients develop PIH secondary to acne.[42] Similar to melasma, PIH can have a negative effect of patient quality of life.[29]

PIH is caused by overproduction of melanin when melanocytes are stimulated by injury, ultraviolet light,[42] and some medications.[43] Although the exact mechanism is unknown, the underlying mechanism appears to involve the release of mediators of inflammation, such as cytokines and chemokines, and the formation of reactive oxygen species associated with inflammation.[41]

Therapies for postinflammatory hyperpigmentation. Whenever possible, initial treatment for PIH should include the liberal use of sunscreens or avoiding sun exposure and proper management of the underlying cause or condition responsible for PIH (such as acne, eczema, and other cutaneous conditions associated with inflammation). Other treatments are similar to those of melasma described above.[32,41,44]

Potential beneficial effects of *Polypodium leucotomos*. To date, no studies have been performed that have systematically assessed the therapeutic effects of *P. leucotomos* for the treatment of PIH although there is evidence suggesting its beneficial effects. PIH appears to be caused by the release of several mediators of inflammation including prostaglandin E_2, leukotrienes-C_4 and -D_4, thromboxane-2[42] and associated reactive oxygen species.[41] Together, they are responsible for the enlargement of melanocytes and increased production of melanin.[42]

Several studies have demonstrated the anti-inflammatory properties of *P. leucotomos*. For example, *in vitro* studies have demonstrates that *P. leucotomos* is an effective scavenger of several reactive oxygen species, specifically, the superoxide anion ($^{\cdot}O_2$), hydroxyl radicals ($^{\cdot}OH$), singlet oxygen ($^1O_2$) and hydrogen peroxide (H_2O_2).[45] *P. leucotomos* has also been shown to diminish the release of cytokines in mice[46] and from human peripheral blood mononuclear cell cultures.[47] Similar to nonsteroidal anti-inflammatory drugs, the oral administration of *P. leucotomos* prevents the release of prostaglandins by inhibiting cyclooxygenase-2 in mice.[48] Based on its potential action, it is reasonable to conclude that *P. leucotomos* may have an adjunctive role in the treatment of PIH.

CONCLUSION

In addition to preventing many harmful effects associated with sunlight exposure, such as photoaging and polymorphous light eruption, orally administered *P. leucotomos* also may provide significant therapeutic benefits for vitiligo and melasma and may have the potential to help with potential post-inflammatory hyperpigmentation. To date, *P. leucotomos* has demonstrated an exceptional safety profile.

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