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Sun protection in a pill: the photoprotective properties of *Polypodium leucotomos* extract

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Conflicts of interest: N.G. has independently used patented products containing *Polypodium leucotomos* extracts for over 20 years in his dermatology practice in Hawaii. He has no affiliation or industry relationship with these companies. The authors have no financial support or conflict of interest to disclose.

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Abstract

Background Physical blocks (i.e. wearing appropriate clothing), exposure avoidance, and the use of sunscreens are the main methods of photoprotection currently used. However, phytochemical and natural botanical extracts such as polypodium leucotomos, a tropical fern found in Central and South America, demonstrate a strong potential as adjuncts to sunscreen protection.

Method A review of the literature was performed focusing on the photoprotective properties of PL extracts, including antioxidant, immunoregulatory, anti-inflammatory and antitumorigenic effects in the context of sunburn, photodermatoses, chronic skin damage, photoaging, and skin cancer.

Results PL supplementation acts at a molecular and cellular level to enhance endogenous antioxidant systems and inhibit generation of reactive oxygen species, thus decreasing UV-mediated oxidative DNA mutations. PL has also been shown to accelerate removal of UV-induced photoproducts, highlighting its anti-carcinogenic role. By reducing UV-induced inflammatory responses and inhibiting extracellular matrix remodeling, PL demonstrates some protective effects against photoaging and PUVA induced phototoxicity.

Conclusion The use of a systemic protective agent would provide significant advantages such as a more uniform coverage over the total body surface area, regardless of individual factors such as potency of the creams, amount applied, sweating, or bathing. Oral administration of PL extracts and its favorable safety profile could have significant implications in the prevention of skin cancer.

Introduction

The deleterious effects of ultraviolet (UV) radiation on the skin have been extensively documented. These include burns, hyperpigmentation, photoallergy, photoaging, chronic skin damage, and skin cancer.[1] Physical blocks (i.e., wearing appropriate clothing), exposure avoidance, and the use of sunscreens to absorb or reflect UV photons are the main methods of photoprotection currently used.

A novel approach consists of examining oral antioxidants compounds; many agents such as ascorbate, tocophenol, or carotenoids have shown varying efficacy.[2] However, phytochemical and natural botanical extracts such as *Polypodium leucotomos* (PL) demonstrate a strong potential as adjuncts to sunscreen protection.[3]

PL is a tropical fern, from the *Phlebodium* genus, found in Central and South America (Fig. 1). It contains polyphenolic compounds, mainly benzoate and cinnamates; 4-hydroxycinnamic acid (caffeic acid) inhibits UV-induced peroxidation and production of nitric oxide (NO), while its derivative, ferulic acid, is a UV photon acceptor.[4] PL also contains monosaccharides and acidic molecules, e.g., quinic, shikimic, glucuronic, malic, coumaric, and vanillic acids. Some of these acids are conjugated to glucuronic acid and sulfates and metabolized by CYP450-dependent monooxygenases ($t_{1/2}$ = 4–6 h). Owing to its low

Figure 1 *Phlebodium pseudoaureum* by R. Moran, 2012. Used with permission[19]

toxicity and good absorption profile, PL has been shown to be a particularly interesting photoprotective agent.[3]

Fernblock® (more recently Heliocare®) is a commercialized antioxidant PL extract that has been used in humans for over 20 years as a dietary supplement in more than 10 countries, including Spain, Italy, Austria, Singapore, and New Zealand.[5]

PL extracts have various beneficial properties, including anti-inflammatory action, DNA photoprotection, immunoregulation, and anticarcinogenic potential.[6–8]

The purpose of this review is to compile a comprehensive overview of the different biological effects of PL reported in the literature based on cellular, animal, and human studies.

Methods

PubMed, EMBASE, and ScienceDirect database searches were conducted using keywords polypodium leucotomos. Fifty-five articles in English were retrieved; 39 of 55 articles were of dermatological relevance. To focus on photoprotective properties, studies pertinent to PL use in patients with psoriasis, atopic dermatitis, vitiligo, and melasma were excluded, while articles commenting on antioxidant, immunoregulatory, anti-inflammatory, and antitumorigenic effects in the context of sunburn, photodermatoses, chronic skin damage, photoaging, and skin cancer were included (n = 18 of 55). Table 1 cross-references PL photoprotective effects along with the cellular or molecular mechanisms involved and the relevant experimental study.

Results

Overview of the effects of ultraviolet radiation on the skin

Systemic UV irradiation can result in acute injuries (i.e., erythema, swelling, pain) and long-term damage (i.e., chronic inflammation, photoaging, and skin cancer) via generation of reactive oxygen species (ROS), DNA damage, inflammation, and immunosuppression.[3,9]

With chronic UV radiation exposure, endogenous antioxidant systems are unable to quench ROS, which accumulate and induce DNA mutations while promoting the production of 8-hydroxy-2′-deoxyguanosine, a marker of DNA oxidative damage linked to tumorigenesis.[8] Besides oxidative stress, cutaneous damage is also a consequence of direct photon absorption by skin chromophores.[10] UVB acts on DNA by forming cyclobutane pyrimidine dimers (CPDs) and pyrimidine–pyrimidone photoproducts that are implicated in tumorigenesis and immunosuppression.[3] Furthermore, UV photons contribute to erythema and swelling via activation of endothelial cells and cytokine production, vasodilation, increase in blood flow, and ultimately, leukocyte recruitment.[9] Paradoxically, this infiltration of immune cells is accompanied by a depletion of epidermal Langerhans cells (LCs), resulting in T-helper 1 clonal anergy.[3,8]

Another mechanism to consider is the photoisomerization and photodecomposition of *trans*-urocanic acid (t-UCA) to *cis*-urocanic acid (c-UCA), which partially affects LCs and mast cell degranulation, thereby contributing to UV-induced immunosuppression.[3]

Antioxidant properties

Studies have demonstrated that irradiation causes activation of endogenous antioxidant systems and increased glutathione (GSH) consumption to form oxidized glutathione (GSSG). PL has been shown to inhibit glutathione oxidation in blood and epidermis by allosterically modulating enzymes such as catalase.[10,11] In rats treated with PL, oxidized glutathione (GSSH) levels were decreased in both non-irradiated and irradiated groups. GSSH levels in irradiated animals were fourfold lower than in rats that

Table 1 *Polypodium leucotomos* photoprotective effects along with the cellular or molecular mechanisms involved. Note that some mechanisms are interconnected

Protective mechanism	**Cellular/**molecular level	**References**
Anti-inflammatory	Reduction of UV-induced macrophage and neutrophil infiltration	2, 5, 12
	Inhibition of UV-induced Cox-2 expression	5
	Blocks TNF-α, iNOS, AP-1, NF-κB	9
Decrease DNA mutagenesis	p53 activation	5, 11
	Removal of UV-induced photoproducts and prevents formation of cyclobutan pyrimidine dimers	2, 5, 11
	Enhances natural antioxidant system	4, 10–13
Immunoregulation	Preservation of Langerhans cells and function	2, 5, 10, 12, 13
	Blocks t-UCA photoisomerization and photodecomposition	10, 16, 17
Cell cycle and cellular integrity	Preserves cell viability and inhibits cytoskeletal disarray	1
	Inhibits matrix metalloproteinases	6

Cox, cyclooxygenase; iNOS, inducible nitric oxide synthase; t-UCA, *trans*-urocanic acid; TNF, tumor necrosis factor; UV, ultraviolet.

were not pretreated with PL, and the GSH/GSSG ratio was skewed, demonstrating that PL administered seven days before irradiation may modulate some of the systemic effects of UV radiation.[10]

The antioxidant properties of PL extracts are of particular interest in psoralen + UVA (PUVA) therapy. PUVA produces ROS and free radicals resulting in erythema, edema, and pain. This acute phototoxicity and subsequent development of hyperpigmentation is a limiting factor in the use of PUVA therapy for skin disorders. A study has demonstrated that PL-treated skin showed a statistically lower grade of erythema and edema than sites exposed to PUVA alone ($P < 0.005$), highlighting the potential of PL to quench oxidative stress.[12,13] In addition, phototoxicity induced hyperpigmentation results in tolerance to UV radiation, i.e., increasing UV doses are necessary to achieve therapeutic response, thereby increasing the risk of squamous cell carcinoma. By reducing hyperpigmentation and need for elevated doses, PL may contribute to ameliorate the safety profile of PUVA treatment.[12]

Anti-inflammatory properties

An important anti-inflammatory mechanism is the inhibition of UV-induced expression of cyclooxygenase (Cox)-2.[8] A study demonstrated that UV-induced Cox-2 levels were four- to fivefold lower in PL fed mice ($P < 0.05$).[5] These effects account for decreased leukocyte extravasation and limitation of mast cell infiltration in the irradiated area, as corroborated by reports of a 60% decrease in neutrophil infiltration ($P < 0.001$) and a 50% decrease in macrophages ($P < 0.02$).[5]

Moreover, PL has the ability to suppress the expression of pro-inflammatory markers such as tumor necrosis factor-α and inducible NO synthase as well as inhibit the transcriptional activation of AP-1 and NFκB. NO prevents apoptosis by inhibiting caspase-3 activity and/or inducing expression of anti-apoptotic factor Bcl-2, but because the exacerbated production of NO may result in additional damage, a regulatory mechanism is necessary. Various studies report an increase in NO following irradiation due to upregulation of inducible NO synthase enzyme.[9,14] This upregulation is decreased with PL pretreatment resulting in up to 60% reduction of NO production.[9]

Prevention of DNA photodamage

PL prevented the UV induced accumulation of CPDs in a study demonstrating significantly lower levels of CPD in PL-treated skin compared to untreated healthy volunteers ($n = 9$, $P < 0.001$). Considering that DNA repair enzymes are susceptible to oxidative stress, PL antioxidant properties may contribute to CPD reduction by improving repair enzyme function.[2] Another study conducted on mice demonstrated that 54 ± 5% CPDs remained in vehicle-fed mice versus 31 ± 5% in PL-fed mice ($P < 0.003$). 3-hydroxy-2′-deoxyguanosine-positive cells, markers of basal DNA oxidative damage, were also reduced.[5] An increase in p53 activity appears to promote clearance of CPDs and decrease oxidative stress.[11]

PL has also been reported to decrease UVA-dependent mitochondrial DNA damage, as reflected by a decrease in common deletions (mitochondrial marker of chronic UVA radiation in fibroblasts and keratinocytes).[15]

Inhibition of photoimmunosuppression and immunoregulation

t-UCA is the main by-product of histidine metabolism that absorbs UV photons, thus preventing tissue damage. However, UV absorption generates c-UCA isomer contributing to immunosuppression. A study has established that PL inhibits t-UCA photoisomerization in a dose-dependent manner and prevents the oxidative breakdown of t-UCA in the presence of ROS.[3,16,17]

PL also inhibits the depletion of antigen-presenting cells such as epidermal LC, hence safeguarding the skin's immune surveillance. When exposed to UV radiation, LCs undergo morphological changes and apoptosis. Infiltration of macrophages accompanies LC depletion and activates suppressor T cells resulting in antigenic tolerance and increased susceptibility of skin to UV-induced skin cancer.[13] Furthermore, the inhibition of adhesion molecules that allow LC migration also promotes UV-induced immunosuppression. An experimental study reported preservation of LCs in pretreated irradiated rats compared to vehicle pretreated irradiated rats. Morphological changes of LCs were also blocked by PL.[10]

Anticarcinogenic effects

PL anticarcinogenic effects are closely intertwined with its aforementioned properties (e.g., inhibition of ROS and UV-induced Cox-2, activation of tumor suppressor p53, LCs role in tumor-specific immunity).[8,12]

A particular pilot study conducted on hairless albino mice demonstrated that PL-treated mice showed a significant reduction in skinfold thickness compared to controls as well as lower degree of histological changes due to photoaging damage. An overall reduction of tumor formation was reported in PL-treated mice.[18]

In vivo animal studies support the existing histological data demonstrating gross morphologic differences between PL pretreated and control groups (i.e., less UV-induced maturation disarray, microvesiculation, and vacuolization of keratinocytes), suggesting that PL might help in the prevention of skin cancer. Nonetheless, the long-term cancer preventive effect of PL extracts in human beings has yet to be determined.[2]

Other cellular effects

UV radiation plays a prominent role in photoaging due to its effects on matrix remodeling, fibroblasts, and proliferative molecules such as transforming growth factor-β. By inhibiting the activity of matrix metalloproteinases and promoting the expression of tissue inhibitor metalloproteinase, transforming growth factor-β, elastin, and different types of collagen, PL promotes the regeneration of skin and compensates for the deleterious effects of radiation.[3,6]

Experimental studies exposing fibroblasts to UV radiation demonstrated that changes in fibroblast shape and cytoskeletal structures were induced. Cell–cell contacts were lacking, and stress fibers were disorganized. These changes were blocked by treatment with PL: stress fibers were retained, cadherin localization at intercellular cell–cell contacts was restored, and cell viability was preserved.[1,6]

Conclusion

Currently, the use of topical sunscreens is the most widely used and accepted method of protection against UV-mediated skin damage. However, the use of a systemic protective agent would provide significant advantages such as a more uniform coverage over the total body surface area, regardless of individual factors such as potency of the creams, amount applied, sweating, or bathing.[7]

A review of the literature shows that PL extracts have a variety of potentially beneficial properties by acting to protect tissue from damage and limiting the inflammatory response that ensues. PL supplementation reduces UV-induced inflammatory responses, accelerates removal of UV-induced photoproducts (CPDs), decreases UV-mediated oxidative DNA mutations, and has demonstrated some protective effects against photoaging and PUVA induced phototoxicity. Oral administration of PL could have significant implications in the prevention of skin cancer.[5]

Furthermore, pharmacological surveillance of oral PL treatments conducted in Spain and South and Central America has demonstrated no recognizable toxic effects and extracts are well absorbed and well tolerated. Nevertheless, the necessary therapeutic dose of the extracts has not clearly been investigated and cost-effective photobiologic, pharmacologic, and toxicologic studies have yet to be conducted on a larger scale in randomized controlled studies to overcome the stigma of anecdotal comments.[13]

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