

# *Polypodium leucotomos*: A Potential New Photoprotective Agent

Neal Bhatia

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**Abstract** As the understanding of the immune system pathways, cytokine balances, and cellular interactions continues to expand, so must the potential applications of therapies that can impact the process of diseases instead of just controlling their symptoms. In the case of *Polypodium leucotomos* extract, which is derived from a tropical fern of the *Polypodiaceae* family, the future potential of applications in dermatology and beyond will be better understood as its incorporation into daily routines gives rise to the development of new regimens. Clinicians may position this agent as an option for daily maintenance, accept its use in combinations, or use it as a template for further development of oral supplementation that may evolve into a true immunomodulator. The antioxidant activity of *P. leucotomos* extract is primarily driven by caffeic acid and ferulic acid, resulting in the control of cutaneous responses to ultraviolet-induced erythema, in the interception of inflammatory mechanisms, and the promotion of other cytotoxic responses. Histologically, the impact of *P. leucotomos* extract induces an effect on the overall reduction of angiogenesis, photocarcinogenesis, and solar elastosis, while on the cellular level there are improvements in cell membrane integrity and elastin expression. Future applications for *P. leucotomos* extract could include the potential for photoprotective effects, and subsequent research efforts should focus on determining the optimal dosage regimen, duration of action, and utility of combinations with sunscreens, among other outcomes. Recently published data have also demonstrated how the antioxidant effects of oral *P. leucotomos* extract can delay tumor development in mice models, suggesting there

might be a protective role that could be described with further clinical research. In addition, it is important to recognize the distinction between photoprotection and chemoprevention, in that there has yet to be any in vivo or controlled clinical trial data in human subjects that show a role for *P. leucotomos* extract in the prevention of carcinogenesis.

## Key Points

The antioxidant activity of *Polypodium leucotomos* extract is primarily driven by caffeic acid and ferulic acid, resulting in control of ultraviolet-induced erythema, inflammatory mechanisms, and promotion of other cellular responses.

The impacts of *P. leucotomos* extract include an overall reduction of angiogenesis, photocarcinogenesis, and solar elastosis. On the cellular level there are improvements in cell membrane integrity and elastin expression.

Future research into the applications for *P. leucotomos* extract should focus on the potential magnitude of the inherent photoprotective effects, the optimal dosage regimen, duration of action, and utility of combinations with sunscreens.

## 1 Introduction

When did dermatology become so reliant on botany? Who would have predicted that in recent years new therapies for dermatology would have their derivations from plants? For

N. Bhatia (✉)  
Director of Clinical Dermatology, Therapeutics Clinical  
Research, San Diego, CA, USA  
e-mail: bhatiaharbor@gmail.com



**Fig. 1** *Polypodium leucotomos*. The benefits of an aquatic fern originating in Central America have been used for centuries by Native Americans as an anti-inflammatory agent, which today has application, with its natural protective mechanisms against the impact of ultraviolet light [3]. Photograph: Copyright Ferndale Laboratories, MI, USA; used with permission

example, ingenol mebutate gel comes from the Australian plant *Euphorbia peplus* [1], sincatechins ointment is a derivative of the Chinese tea leaves derived from *Camellia sinensis* [2], and these therapies and aloe vera, among many others, have been available to dermatologists for several years for various applications.

Over time, the role of *Polypodium leucotomos* extract (PLE), derived from a South American tropical fern of the *Polypodiaceae* family (Fig. 1), has evolved as an agent for controlling ultraviolet (UV)-induced erythema, inflammatory mechanisms based on antioxidant properties, and promotion of other cellular responses. Current therapeutic regimens are only as efficacious as the understanding and application of their mechanisms of action and their potential utilities allow [3].

## 2 Antioxidant Effects of *Polypodium leucotomos*

The antioxidant activity of *P. leucotomos* can be linked primarily to the impact of phenolic compounds, the most potent of which are caffeic acid and ferulic acid, which scavenge reactive oxygen species and have anti-inflammatory effects [4]. They counteract the impact of UV immunosuppression in vitro to restore the activity of dendritic cells and lymphocytes [4].

One of the first studies published by a research team led by Dr. Middelkamp-Hup [5] in 2004 investigated the role of oral PLE and its effect on the photobiological reactions of psoralen and ultraviolet A (PUVA) therapy as well as the resultant impact on cellular populations. The study, performed on healthy volunteers, demonstrated that after two doses of oral PLE 7.5 mg/kg given 12 h apart, there

was a reduction in the population of sunburn cells, improvements in the population of Langerhans cells, and increased vasodilation in the specimens, all of which were related to the antioxidant-induced inhibition. The anti-inflammatory and cellular changes demonstrated in the immunohistochemical in vitro assays appear to be linked to the impact of UV-induced immunosuppression, attempting to preserve activity of dendritic cells and lymphocytes [5]. As a result of the activity of PLE, localized immune competence suggests that restoration of tumor surveillance would reduce potential carcinogenesis in photodamaged skin. In addition, the infiltration of mast cells induced by UV light was demonstrated to be countered by the activity of PLE, which indicated promotion of cellular immunity given the proposed role of mast cells in tumor growth and angiogenesis [5, 6]. In the big picture, there is an overall reduction of angiogenesis, photocarcinogenesis, and solar elastosis. However, on the cellular level there are improvements in cell membrane integrity and elastin expression [5]. In addition, there is a reduction in lipid peroxidation along with an increase in expression of matrix metalloproteinase (MMP)-1 in fibroblasts and keratinocytes. Finally, there is activation of tumor suppressor p53 gene and inhibition of the molecular marker cyclooxygenase (COX)-2 [5].

Recently published data suggested the antioxidant effects of oral PLE led to significantly delayed tumor development ( $p = 0.023$ ) in mice models, which could lead to further investigation into the agent's photoprotective nature [7]. The research team at the School of Medicine of Reus in Spain that conducted the study examined hairless mice irradiated with UV. They followed several important markers to assess the role of oxidative stress to determine whether daily oral administration of PLE could delay or prevent tumor formation by increasing antioxidant defenses and epidermal p53 expression. Taking into account that immunosuppressive effects of UV radiation can have both cutaneous and systemic consequences, there were assessments of Langerhans cell activity, p53 expression, and Ki-67 expression to follow changes in epidermal proliferation [7]. There were several notable observations from the study. After 42 weeks of exposure to UVA/UVB lamps, 57 % of irradiated mice in the group taking oral PLE (300 mg/kg mixed in water) developed squamous cell carcinoma (SCC) compared with 87.5 % of the untreated mice. Actinic keratoses were observed in 85 % of untreated mice compared with 28 % of the mice treated with oral PLE. The PLE-treated group also demonstrated increased relative expression of p53+ cells, suggesting potential improvements to mechanisms promoting DNA repair and apoptosis. More importantly, there were increased numbers of p53+ cells in the areas free of tumor in PLE-treated mice compared with the non-treated group. Given the

delayed development of cancers, this finding supports the researchers' hypothesis that PLE may have a role in promotion of apoptosis and other effects linked to p53-mediated tumor suppression. Finally, in PLE-treated mice, erythrocytic glutathione disulfide decreased and plasma total antioxidant capacity increased. These effects have been considered to contribute to slowing tumorigenesis, and proposed photoprotective effects, linked to the antioxidant properties of PLE. On the basis of the objective reduction in tumor development and the laboratory findings, it was the hypothesis of the authors that the photoprotective effect of oral PLE may benefit patients with cumulative UV exposure [7].

### 3 Impact of *P. leucotomos* on DNA Repair and Mutagenesis

Pivotal studies have been performed to assess the effects of *P. leucotomos* on the genome level; one in particular examined UV-induced COX-2 expression in hairless mice [8]. In proposed pathways of mutagenesis, COX-2 is upregulated with cumulative UV light exposure, resulting in production of prostaglandin E, which induces epidermal hyperplasia with loss of differentiation [9]. This proliferation of potentially atypical keratinocytes is believed to correlate clinically with the signs of photodamage, and possible evolution to actinic keratosis and SCC [8, 9].

It was the goal of the investigators of this study to examine if the potential photoprotective effects of PLE could be determined from the assay [8]. The study design involved feeding PLE 300 mg/kg or vehicle for 10 days to hairless Xpc<sup>+/-</sup> mice, which were then UV irradiated one time. In addition to measuring the reduction of the overexpression of COX-2, the investigators assayed for p53 expression and for reduction of cyclobutane pyrimidine photoproducts to survey for defects in DNA repair as a result of UVB exposure, in the environment of UV-induced oxidative DNA damage [8]. Finally, the researchers evaluated the role of PLE in the removal of cells that expressed 8-hydroxy-2'-deoxyguanosine, a known biomarker for oxidative stress and carcinogenesis [10]. The role of 8-hydroxy-2'-deoxyguanosine is linked to the effect of endogenous oxidative damage to DNA and as a factor of initiation and promotion of carcinogenesis [10]. In the mice treated with PLE, there were 79 % fewer 8-hydroxy-2'-deoxyguanosine-positive cells 24 h after feeding compared with in the non-treated group ( $p < 0.03$ ), in conjunction with a 5-fold reduction in UV-induced COX-2 levels ( $p < 0.05$ ), and significant reduction of UV-induced mutations detected 2 weeks after UV exposure. The conclusions were that PLE reduces UV-induced COX-2 levels by promotion of p53 expression, correlating with a reduction

in prostaglandin-mediated inflammation that is linked to photoaging. These photoprotective and subsequent anti-inflammatory effects have yet to be demonstrated in patients [9].

"UV signatures" is a term used to describe the development of specific changes to the DNA helix, most notably the formation of pyrimidine dimers, which result in defects in cross-linking of nucleotide bases as well as mutations leading to single-strand breaks [11]. Mutations associated with UV light are identified by abnormal cross-links involving thymidine or cytosine—more commonly with thymidine [11]. Damage to DNA induced by UV is also wavelength specific in that UVA is linked to oxidative damage to guanine residues and a common deletion mutation of mitochondrial DNA (mtDNA), while UVB creates direct damage to DNA via formation of cyclobutane pyrimidine dimers (CPDs) and pyrimidine-pyrimidine (6-4) photoproducts. The visual changes to the skin resulting from these events include erythema and epidermal hyperplasia; by comparison, visible light induces immediate erythema followed by delayed pigment darkening with synthesis of new melanin [5, 9, 11].

### 4 Oral *P. leucotomos* Extract Decreases Ultraviolet-Induced Damage of Human Skin

An important study was designed to determine if PLE exhibits photoprotective effects. The study was conducted and published by Middelkamp-Hup et al. [12] and examined the role of oral PLE on skin injured by UV light. The study involved nine healthy subjects of various ages and with Fitzpatrick skin types II–III, who were exposed to PUVA with or without two doses of oral PLE. Subjects were excluded if there was any history of skin cancer, photosensitivity, or previous dermatoses on the skin of the back, as well as any UV exposure over the past 8 weeks. The minimal erythema dose (MED) was determined after multiple sites were exposed to increasing UV radiation (UVR) doses, primarily up to two or three times the MED in the study population. In order to determine the histological components of the effects of therapy, biopsies were taken from the skin of the photoexposed backs of the subjects, both treated and untreated with oral PLE extract [12]. Assessments and biopsies were all completed 24 h post-exposure, and the study outcomes were measured at 24 h for the PLE-treated group and the control group.

The study was designed such that multiple photoprotection parameters were investigated in the subjects with exposure to varying doses of artificial UVR, without and with two doses of PLE, each dose measuring 7.5 mg/kg. The patients were irradiated with UVB + UVA: 1,000-W xenon arc lamp/2-mm filter/surface mirror; the heat from

the infrared radiation was dissipated by a fan. At that point, the UVR intensity was measured with a radiometer after 30 min of warming up [12].

Clinical assessments revealed that the patients treated with PLE developed less erythema up to 24 h ( $p < 0.01$ ). Histological evaluations of the biopsies performed in the PLE-treated group were summarized as demonstrating less maturation disarray and keratinocyte microvesiculation/vacuolization as well as significantly fewer sunburn cells/mm epidermis ( $p = 0.03$ ). Most significant were the immunohistochemistry analyses of the specimens of the PLE-treated skin, which revealed the following [12]:

1. Significant reduction in CPDs ( $p < 0.001$ )
2. Significant reduction in epidermal proliferation (Ki-67 positivity) ( $p < 0.001$ )
3. Significantly fewer tryptase-positive mast cells in papillary dermis at 24 and 72 h ( $p < 0.05$ )
4. Greater preservation of Langerhans cells quantity [ $p =$  not significant (NS)] and morphology at 24 and 72 h
5. Decrease in the surface area occupied by microvessels at 24 and 72 h ( $p =$  NS).

The summary of these results was that there was a photoprotective effect from PLE that reduced the consequences of photodamage and the underlying histological changes [12].

As a result of this study, several conclusions were made by the investigators to support the observation that oral PLE reduces UV-induced erythema and pigmentation as well as PUVA phototoxicity scores. Although to date there has not been clinical research evaluating the dosage strategy for oral PLE, the study proposed the rationale that administration of two 240-mg capsules of oral PLE extract for a 64-kg person of 7.5 mg/kg body weight shows consistency of UV-induced erythema to resolve with time. In addition, the investigators concluded that oral PLE extract can reduce erythema induced by acute UVR exposure as well as mitigate keratinocyte damage induced by UVR exposure, via assessment of the objective cellular changes, maturation disarray, and reduction of sunburn cells [12]. In addition, they observed a reduction of DNA damage induced by acute UVR exposure demonstrated by the reduction of thymidine dimers, and possibly a reduction in microvessel density induced by UVR exposure. However, there were several remaining questions after the study [12], including:

1. What is the magnitude of photoprotective effects that correlate with clinically relevant short- and long-term outcomes?
2. What is the optimal dosage regimen (duration of action)?

3. What would be the results if PLE were used in combinations with sunscreens?

### 5 *P. leucotomos* Use in Idiopathic Dermatoses

Many potential applications for *P. leucotomos* have been studied and evaluated, most of them based on the effects of photoexposure and the impact on the disease. A group led by Caccialanza et al. [14] studied patients with idiopathic photodermatoses, including 53 with polymorphous light eruption and four with solar urticaria. In each of these cases, PLE 7.5 mg/kg was started 15 days before solar exposure and continued throughout the exposure period at an average dose of 480 mg/day. In the study populations, 29.8 % normalized and 43.8 % demonstrated some levels of improvement. However, despite the observation that there were no adverse events reported, only one of the four patients with solar urticaria demonstrated any improvement [14]. The principles of treating solar urticaria with oral PLE extract that require further evaluation include assessment of the time of onset of solar exposure in correlation with the eruption, as well as determination of the dosage effective for counteracting the urticarial response, as confirmed by measuring objective erythema and edema (wheal and flare response). These parameters would also need to be compared with antihistamines or anticholinergic blockade, but may have shortcomings given the lack of demonstrated therapeutic or immunological effect of oral PLE extract on mast cells [3, 12–14].

Another study, published by Tanew et al. [15], examined how oral PLE affected 35 patients with long-standing polymorphous light eruption, with 18 of the patients receiving mixed UVB while the remainder were exposed to UVA alone. The patients were given variable weight-based doses ( $\leq 55$  kg = 720 mg/day; 56–70 kg = 960 mg/day;  $> 70$  kg = 1,200 mg/day) after photoprovocation, which was on dosage day 7, with a second photoprovocation after 2 weeks. In 30 photoexposed patients, 2 weeks of treatment with oral PLE significantly increased the threshold for polymorphous light eruption induction, and 30 % (9/30) of UVA-sensitive patients were not provoked (polymorphous light eruption prevented). The remaining patients ( $n = 21$ ) required an increased number of UVA exposures to induce polymorphous light eruption lesions (1.95 vs. 2.62 [ $p = 0.005$ ]) [15].

### 6 *P. leucotomos* Use in Vitiligo

Vitiligo is a condition that has also been shown to be influenced by PLE. The rationales for this potential utility

given the proposed effects of PLE include application of the antioxidant effects, decrease in production of interleukin (IL)-2, interferon- $\gamma$  and tumor necrosis factor- $\alpha$ , and enhanced production of IL-10, through inhibition of cell-mediated immune responses. However, the question posed by investigators was whether the addition of oral PLE to PUVA or narrow band (NB)-UVB phototherapy would enhance the extent of repigmentation [16, 17].

A poster published by Pacifico et al. [16] reported 57 patients with generalized vitiligo who were treated twice weekly for up to 6 months, randomized to 29 subjects treated with PLE 480 mg once daily in conjunction with NB-UVB and 28 subjects treated with NB-UVB alone. There was a blinded evaluation of repigmentation at baseline and at the end of the study, and the investigators reported a response rate of the combined therapy group that was significantly higher than the NB-UVB only group (40 vs. 22 %,  $p < 0.0005$ ). In responders, repigmentation was observed within the first month as compared with a mean of 3 months in the group of phototherapy only patients [16].

A pilot study also involving the combination of PLE and NB-UVB conducted by Middelkamp-Hup et al. [17] was performed in patients with vitiligo and involved treatment with NB-UVB twice weekly as well as PLE 250 mg ( $n = 25$ ) or placebo ( $n = 24$ ) three times per day for 25–26 weeks. Their observations were consistent, with higher repigmentation of the head and neck region in the PLE-treated group (44 %) compared with the placebo group (27 %) ( $p = 0.06$ ) [17].

A smaller study conducted by Reyes et al. [18] examined the role of *P. leucotomos* as an adjuvant to PUVA therapy in generalized vitiligo. This randomized, double-blind clinical trial investigated 19 patients who were given either placebo ( $n = 9$ ) or PLE 720 mg/day ( $n = 10$ ) and compared PUVA alone to PUVA plus oral PLE for the treatment of generalized vitiligo over 12 weeks. Their results were also consistent, with a significantly higher rate of moderate to excellent repigmentation (>50 %) in the PUVA plus PLE group (5/10) compared with in the PUVA alone group (0/9) [18].

## 7 *P. leucotomos* Use in Melasma

Interest in aesthetic uses of oral PLE as well as the elucidation of the impact on photoprotection has led to investigations into the use of PLE in hyperpigmentation. A randomized, double-blind, placebo-controlled study evaluating the effectiveness and tolerability of oral *P. leucotomos* in patients with melasma was performed in 21 women aged 18–50 years with epidermal melasma [19]. The participants were randomized into groups that were

treated either with oral PLE or placebo twice daily as well as solar protection with SPF 45 sunscreen for a total of 12 weeks, and photographs were taken at weeks 4, 8, and 12. They evaluated several important indices, including the Melasma Quality of Life Scale (MELASQOL), blinded investigator's Melasma Area and Severity Index (MASI), photographic assessment, and subject's self-assessment [19].

At 12 weeks, the group treated with PLE was reported to have significantly improved MASI scores (5.7 vs. 3.3;  $p < 0.05$ ) while the placebo group did not (4.7 vs. 5.7;  $p > 0.05$ ). In addition, photographic assessments revealed mild improvement in 43 % of treated subjects versus 17 % of placebo recipients, and marked improvement in 14 % of treated subjects compared with 0 % of placebo recipients. Finally, a summary of patient self-assessments reported 50 % of PLE-treated patients experienced mild improvement and 13 % reported marked improvement, while in the placebo group, 17 % reported mild improvement and none reported marked improvements [19].

A separate study published was a randomized, double-blinded trial examining the role of oral PLE as an adjunct to sunscreen in the treatment of melasma, which was significant for the fact that it involved subjects with darker skin types [20]. Moreover, it proposed the concept of oral PLE in a systemic role for photoprotection as an important component for hyperpigmentation. In the trial, 40 Hispanic women with moderate to severe facial melasma, defined by a "melanin index" of >30, were treated with oral PLE 240 mg three times daily or a placebo as well as a sunscreen SPF 55 for 12 weeks. Of note, the measurement of the melanin index was the difference between the affected skin and the normal skin using narrowband reflectance spectrophotometry. The primary objective was to measure the change in melanin index at weeks 6 and 12, while secondary objectives included evaluation of the MASI and MELASQOL. The results showed that there was improvement seen in both groups at weeks 6 and 12, but no significant intergroup difference was seen, indicating that the addition of oral PLE had no significant impact [20].

## 8 Effects of *P. leucotomos* on Photoaging and Skin Cancer

PLE has been proven useful as a pre-treatment to prevent UVA-induced skin photodamage by preventing UVA-dependent mitochondrial damage [13, 21]. The results of a pilot study conducted by Villa et al. [21] suggest that pre-treatment with PLE 240 mg orally prior to UVA exposure may prevent the increase of "common deletion", which is a 4,977-base-pair-long mtDNA. This deletion is thought to be induced by cumulative UVA exposure, which therefore

links it with photoaging and is primarily localized, found in UVA-damaged skin [22].

The study conducted by Villa et al. [21] examined ten healthy subjects who received UVA exposure (two and three times each patient's MED-A values) combined with pre-treatment using either two doses in capsule form of 240 mg of PLE or placebo. Subjects were dosed at 8 and 12 h prior to UVA exposure during the trial. Despite the reported observation that there was no significant histological difference in UVA-exposed skin between the groups, there was a difference with regard to increase in the common deletion, with the placebo group showing a higher prevalence in cyclobutane dimer values than the PLE group. Specifically, the PLE group had less of an increase in cyclobutane dimer levels compared with the placebo group as the UVA dose was increased. This effect, however, did not reach statistical significance, which could be due to the small sample size [21].

Another potential mechanism for a protective effect of PLE in photocarcinogenesis is via activation of the tumor suppressor p53 gene and inhibition of the molecular marker COX-2, which is induced by UV exposure and involved in mutagenesis. Both effects have been demonstrated in a mouse model [8]. In another study, Aguilera et al. [23] investigated the effect of PLE in patients who were at a high risk for skin cancers; these included patients with history of melanoma, atypical mole syndrome, or family history of melanoma. The authors assessed MED-B in these patients before and after administration of 1,080 mg of oral PLE, and found a statistically significant increase in MED-B values after treatment with oral PLE, with each subject serving as his/her own control. Of note, 720 mg of oral PLE was administered in three doses (240 mg every 8 h), and then single doses of 360 mg of oral PLE were given 1 day and 3 h, respectively, prior to exposure to UVB. The authors also found that an increase in MED-B was associated with dark eyes and a lower baseline MED-B, and concluded that these two characteristics were independent factors in predicting a better response to oral PLE [23].

### 9 *P. leucotomos*: Photoprotection Versus Chemoprevention

Immunosuppression and nonmelanoma skin cancer (NMSC) risk are closely linked, and nearly 40 % of solid organ transplant recipients (SOTR) develop actinic keratosis and SCC within the first 5 years of immunosuppression. The mortality rate for skin cancers in SOTR is anywhere between 5 and 8 %, and the risks are augmented with factors such as the impact of the human papilloma virus (HPV) and cumulative UVA/B exposure [24, 25].

Among those patients under age 50 years, NMSCs took longer to occur, but by 6 years, the skin cancer risk was 200-times greater than for age-matched non-transplanted controls. It was also noted that male renal transplant patients are at particular risk of invasive SCC at sun-exposed sites, including the scalp and the external ear. Risk of malignant melanoma and Kaposi sarcoma are also increased relative to the non-transplant population [24, 25]. One study evaluated the risk for NMSC among 100 consecutive liver transplant recipients (LTR) seen by two dermatologists, finding seven NMSCs (one SCC, six basal cell carcinomas) in four patients. Among the total LTR population evaluated, 35 % were on triple-drug therapy (cyclosporin A, azathioprine and prednisolone), 48 % were on dual therapy (tacrolimus and prednisolone), and 17 % were on monotherapy (tacrolimus) [25]. Management options include changing high-risk patients from immunosuppressive therapies to regimens associated with a lower risk. Trials underway seek to ascertain the feasibility and benefit of switching patients to sirolimus-based therapy. However, there are currently no trials underway that include *P. leucotomos* as a chemoprevention agent or as an adjunct to regimens for immunosuppressed patients. In addition, the current status of oral PLE is as an over-the-counter supplement and there are no active clinical trials to investigate its use as a chemoprevention agent.

### 10 Conclusion

The demonstrated antioxidant and photoprotective properties and proposed mechanisms of action of *P. leucotomos* suggest that it may have significant potential in the management options for photodermatoses, pigmentary disorders, and, down the road, possibly even photoprotection to mitigate carcinogenesis. Patient acceptance of an oral supplementation based on antioxidants may continue to grow, but the need for an FDA-approved modality for chemoprevention is still absent from the dermatologist's treatment paradigm. More investigation into the science of antioxidants will help PLE to gain acceptance as therapy rather than supplementation, but for now dermatologists need to expand current strategies to enhance appropriate education on sun safety as well as expand the bounds of conventional treatment options for dermatoses that have yet to find a remedy.

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