



MOLECULAR MECHANISMS AND EMERGING THERAPEUTIC STRATEGIES IN PHYTOPHOTODERMATITIS

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Abstract:

Phytophotodermatitis is an acute, non-immunological phototoxic skin reaction caused by plant-derived furocoumarins following exposure to ultraviolet A (UVA) radiation. It can produce erythema, edema, vesiculation, bullae, pain, and persistent post-inflammatory hyperpigmentation. UVA-activated furocoumarins induce DNA photoadduct formation, reactive oxygen species generation, oxidative stress, mitochondrial dysfunction, and activation of MAPK and NF- κ B signaling, resulting in keratinocyte injury and inflammation. Current management is predominantly supportive, including decontamination, photoprotection, topical corticosteroids, analgesics, wound care, and treatment of hyperpigmentation. However, molecularly targeted therapies remain limited. Emerging approaches include Nrf2-mediated cytoprotection, modulation of oxidative stress and inflammatory signaling, mitochondrial protection, DNA damage response modulation, advanced photoprotective formulations, and targeted inhibition of melanogenesis. This review examines the molecular mechanisms and current and emerging therapeutic strategies for Phytophotodermatitis, highlighting potential targets for improved prevention and pharmacological management.

Keywords: Phytophotodermatitis; Furanocoumarins; Psoralens; UVA; Phototoxicity; Oxidative Stress; DNA damage; Inflammation; Post-Inflammatory Hyperpigmentation; Photoprotection

1. INTRODUCTION

Phytophotodermatitis (PPD) is an acute, non-immunological phototoxic skin reaction resulting from the interaction between plant-derived photosensitizing compounds and ultraviolet A (UVA) radiation in the 320–400 nm range. Unlike photoallergic dermatitis, PPD does not require prior sensitization or antigen-specific immune memory and can therefore occur in any sufficiently exposed individual. The principal photosensitizers are furocoumarins (furanocoumarins or psoralens), naturally occurring secondary metabolites present in several edible, medicinal, ornamental, and wild plants, particularly members of the Apiaceae, Rutaceae, Moraceae, and Fabaceae families. Common sources include celery, parsley, parsnip, carrot, citrus fruits, bergamot, fig, and *Psoralea corylifolia*. [1]

Clinically, PPD is characterized by sharply demarcated erythema, burning or pain, edema, vesiculation, and bullae, generally developing within approximately 24 hours and reaching maximum intensity at 48–72 hours after exposure. Lesions may display linear, streak-like, drip-shaped, handprint, or geometric configurations that reflect the pattern of plant contact. The acute inflammatory phase may resolve over several weeks, but post-inflammatory hyperpigmentation frequently persists for weeks to months and may become the predominant residual manifestation. Heat, sweating, moisture, and occlusion can increase dermal penetration of photosensitizers and intensify the phototoxic response. Diagnosis is primarily clinical and relies on exposure history, lesion morphology, and photodistribution, while histopathological examination may assist in distinguishing PPD from other photodermatoses when the presentation is atypical. [2,3]

At the molecular level, furocoumarin phototoxicity is initiated by UVA-mediated excitation of these compounds. Their planar molecular structure facilitates interaction with DNA, particularly pyrimidine bases, resulting in photoadduct

formation and, for suitably structured linear furocoumarins, DNA interstrand cross-linking. In parallel, photochemical reactions can generate reactive oxygen species, leading to oxidative damage, mitochondrial dysfunction, cellular stress, and activation of inflammatory pathways. These processes ultimately contribute to keratinocyte injury, epidermal necrosis, inflammatory mediator release, and subsequent alterations in cutaneous pigmentation. The magnitude of injury varies according to furocoumarin structure, concentration, tissue distribution, dermal penetration, and UVA exposure, with 5-methoxypsoralen and 8-methoxypsoralen representing particularly important phototoxic compounds.

Accordingly, this review examines the molecular pathways underlying phytophotodermatitis and evaluates current and emerging pharmacological strategies for its prevention and treatment. Particular emphasis is placed on the transition from conventional symptomatic management toward mechanism-based pharmacological approaches targeting photochemical injury, oxidative stress, inflammation, cellular damage, and post-inflammatory pigmentation.

2. ETIOLOGY OF PHYTOPHOTODERMATITIS

PPD results from cutaneous exposure to plant-derived photosensitizing compounds followed by exposure to ultraviolet A (UVA; 320–400 nm) radiation. The principal phototoxic constituents are furocoumarins (psoralens), which absorb UVA and undergo photochemical activation, initiating cellular and tissue injury. The occurrence and severity of PPD depend on the concentration and composition of furocoumarins, the plant tissue involved, duration and intensity of contact, dermal penetration, and subsequent UVA exposure. Clinically relevant phototoxic plants are distributed among several botanical families, particularly Apiaceae, Rutaceae, Moraceae, and Fabaceae. [4,5]

Apiaceae (Umbelliferae) is one of the most important botanical families associated with PPD. Members contain linear furocoumarins such as 8-methoxypsoralen (8-MOP), 5-methoxypsoralen (5-MOP), imperatorin, phellopterin, and isopimpinellin. *Ammi majus* is a significant source of xanthotoxin and other psoralen derivatives and illustrates the dual pharmacological and phototoxic properties of furocoumarin-containing plants. Common food and vegetable plants, including celery (*Apium graveolens*), parsnip (*Pastinaca sativa*), and parsley, can also cause phototoxic reactions, particularly during harvesting, processing, or prolonged handling. Mechanical disruption facilitates release of photosensitizers, while moisture and sweating may enhance dermal penetration. Wild and invasive species, including wild parsnip, *Heracleum* spp., *Daucus carota*, *Anthriscus sylvestris*, *Notobubon galbanum*, and *Angelica* spp., represent additional sources. Giant hogweed (*Heracleum mantegazzianum*) is particularly important because its sap can cause extensive erythema, vesiculation, bullae, and persistent pigmentation following sunlight exposure.

The Rutaceae (citrus family) constitutes another major source of furocoumarin-mediated phototoxicity. Lime and other Citrus species contain psoralens and methoxypsoralens in their peel, juice, and essential oils. Fresh lime juice is a well-recognized cause of PPD, often producing streaked, splash-like, or irregular lesions corresponding to the pattern of contamination. Bergamot (*Citrus bergamia*) is particularly relevant because its essential oil may contain high concentrations of bergapten (5-MOP) and has therefore been associated with phototoxicity in cosmetic and fragrance applications. Other relevant Rutaceae include *Citrus maxima*, *Dictamnus albus*, and *Ruta graveolens*. Thus, the family encompasses dietary, medicinal, ornamental, and cosmetic sources of phototoxic exposure.

The Moraceae (mulberry family) includes several potentially phototoxic species, particularly *Ficus*. *Ficus carica* (common fig) contains furocoumarins in its leaves and sap and may cause marked phototoxic dermatitis following handling and subsequent sunlight exposure. Gardening, harvesting, and traditional medicinal use can facilitate exposure. Other potentially phototoxic species include *Ficus pumila* and *Brosimum gaudichaudii*. Fig-associated phototoxicity is of particular interest because some *Ficus* species have traditionally been used for pigmentation disorders, although uncontrolled exposure may result in epidermal injury and persistent post-inflammatory hyperpigmentation.

The Fabaceae (Leguminosae) represents another reservoir of psoralen-type compounds. *Psoralea corylifolia* (syn. *Cullen corylifolium*), commonly known as babchi or bakuchi, contains furanocoumarins and related bioactive constituents and has traditionally been used for pigmentary disorders such as vitiligo. However, concentrated herbal preparations may deliver substantial amounts of photosensitizing constituents, increasing the risk of phototoxic reactions following UVA exposure.

Importantly, the presence of furocoumarins alone does not determine phototoxicity. Risk is influenced by their quantity, chemical composition, photoreactivity, and the characteristics of exposure. Linear furocoumarins such as 5-MOP and 8-MOP possess two photoreactive sites and can efficiently generate DNA photoadducts and interstrand

cross-links after UVA activation. Plant tissue and preparation are also important because furocoumarins may accumulate in leaves, sap, peel, seeds, fruits, and essential oils. Cutting, crushing, juicing, or processing can increase skin contamination, while heat, sweating, moisture, and occlusion may enhance penetration.

MOLECULAR PATHWAYS AND PATHOPHYSIOLOGY OF PHYTOPHOTODERMATITIS

Phytophotodermatitis is a non-immunologically mediated phototoxic disorder resulting from the interaction between plant-derived photosensitizing compounds, predominantly furocoumarins, and ultraviolet A (UVA) radiation. Unlike allergic contact dermatitis, PPD does not require prior sensitization and can occur in any individual when sufficient quantities of a photosensitizing phytochemical and appropriate ultraviolet radiation are present. The pathophysiology is therefore fundamentally determined by a sequence of photochemical and cellular events rather than an antigen-specific immune response. At the molecular level, PPD can be conceptualized as a cascade initiated by photoactivation of furocoumarins and subsequently amplified through DNA damage, reactive oxygen species (ROS) generation, mitochondrial dysfunction, stress-activated kinase signaling, inflammatory mediator release, keratinocyte death, and dysregulated melanogenesis. The severity and persistence of the cutaneous response depend on the concentration and structural characteristics of the furocoumarin, extent of epidermal penetration, UVA exposure, and capacity of the skin to counteract oxidative and genotoxic stress. [6-8]

Furocoumarins are structurally related coumarin derivatives characterized by a fused furan ring and include psoralen, 5-methoxypsoralen, 8-methoxypsoralen, bergapten, xanthotoxin, isopimpinellin, imperatorin, angelicin, and related compounds. Their concentrations vary considerably among plant species, cultivars, tissues, developmental stages, and environmental conditions. Plant tissues such as peels, sap, leaves, and oil-rich structures may contain relatively high concentrations, while mechanical injury, microbial exposure, and other forms of environmental stress can modify their biosynthesis. Consequently, the phototoxic potential of a plant is determined not simply by the presence of furocoumarins but by their molecular composition, concentration, dermal availability, and photochemical reactivity.

The initiating event in PPD is absorption of UVA photons by furocoumarins. UVA radiation within approximately 320–400 nm is particularly important because it efficiently activates these compounds within the skin. Absorption of a photon promotes the furocoumarin from its ground state to an electronically excited state, followed by intersystem crossing to a longer-lived triplet state. The excited molecule can subsequently undergo two principal photochemical pathways. In the first, an oxygen-independent mechanism, the activated furocoumarin directly interacts with cellular macromolecules, particularly nucleic acids. In the second, an oxygen-dependent mechanism, the excited molecule transfers energy or electrons to molecular oxygen, generating highly reactive oxygen species. These two mechanisms occur in parallel and provide the molecular foundation for the extensive cellular injury characteristic of PPD.

DNA represents one of the principal intracellular targets of photoactivated furocoumarins. Psoralen-type compounds can intercalate between DNA base pairs, positioning the photosensitizer in close proximity to pyrimidine residues. Following UVA activation, the furocoumarin can form covalent photoadducts with pyrimidine bases, particularly thymine. Linear furocoumarins containing two reactive sites may subsequently absorb another photon and form interstrand DNA cross-links. These lesions are particularly cytotoxic because they physically prevent separation of the DNA strands required for replication and transcription. Accumulation of DNA photoadducts therefore activates cellular DNA-damage surveillance systems and disrupts normal cell-cycle progression. Depending on the magnitude of injury, cells may undergo checkpoint-mediated arrest, DNA repair, senescence, apoptosis, or necrotic death. The extent of DNA damage is strongly influenced by the molecular structure of the furocoumarin, with linear compounds generally displaying greater capacity for DNA cross-link formation and phototoxic injury than angular derivatives. The DNA-damage response constitutes an important molecular bridge between the initial photochemical event and subsequent cellular dysfunction. DNA lesions activate multiple surveillance and repair pathways designed to preserve genomic integrity. Poly(ADP-ribose) polymerase-1 is involved in the recognition and response to DNA strand damage; however, excessive activation can consume substantial amounts of NAD⁺ and contribute to depletion of cellular ATP. This metabolic stress may impair DNA repair, compromise mitochondrial function, and ultimately contribute to cellular death. Persistent or extensive DNA damage can additionally activate p53-dependent signaling, resulting in cell-cycle arrest and pro-apoptotic gene expression. Interstrand cross-links are particularly difficult to resolve and may require coordinated DNA repair mechanisms. Consequently, repeated exposure to psoralen-containing substances together with UVA has mechanistic relevance to photomutagenesis and photocarcinogenic risk.

The second major molecular axis of PPD is oxidative stress. Photoactivated furocoumarins can participate in energy-transfer and electron-transfer reactions that generate singlet oxygen, superoxide, and other ROS. These reactive

intermediates attack membrane lipids, proteins, nucleic acids, and intracellular organelles. Oxidation of membrane polyunsaturated fatty acids produces lipid peroxides and reactive secondary aldehydes that alter membrane structure, permeability, and receptor function. Oxidative modification of proteins may impair antioxidant enzymes, DNA-repair proteins, mitochondrial respiratory complexes, and signaling molecules. ROS-mediated nucleic acid damage further increases the burden produced by direct furocoumarin–DNA photoadducts. Thus, direct photochemical damage and oxidative injury are not independent processes but mutually reinforcing mechanisms that substantially amplify cellular stress. The skin possesses an extensive antioxidant network to restrict this oxidative injury. Superoxide dismutase, catalase, glutathione peroxidases, reduced glutathione, and thioredoxin-dependent systems collectively maintain redox homeostasis. A critical regulatory mechanism is the Keap1–Nrf2–antioxidant response element pathway. Under basal conditions, Nrf2 is continuously regulated through its interaction with Keap1. Increased oxidative stress modifies this regulatory system, allowing Nrf2 to accumulate and translocate into the nucleus, where it promotes transcription of genes involved in antioxidant defense, glutathione synthesis, xenobiotic detoxification, and cellular protection. Activation of this pathway represents an endogenous attempt to restore redox balance. However, when ROS generation exceeds the antioxidant capacity of keratinocytes, persistent oxidative stress develops and promotes lipid peroxidation, mitochondrial injury, inflammatory signaling, and cell death. The Nrf2 pathway therefore represents both a protective mechanism and a potential pharmacological target in phototoxic skin injury.

Mitochondrial dysfunction provides another critical link between oxidative stress and keratinocyte death. ROS can oxidize mitochondrial proteins, membrane lipids, and respiratory-chain components, resulting in disruption of mitochondrial membrane potential and increased mitochondrial ROS production. Progressive mitochondrial injury may promote permeability transition and release of pro-apoptotic mediators, subsequently activating the caspase cascade. At the same time, mitochondrial dysfunction reduces ATP production and thereby compromises energy-dependent DNA repair, antioxidant defense, membrane integrity, and cellular recovery. Severe mitochondrial injury may therefore transform an initially reversible oxidative insult into irreversible cellular damage. The interaction between mitochondrial ROS production, DNA injury, and cellular energy failure is particularly important because these pathways can form a self-amplifying cycle in which oxidative damage promotes mitochondrial dysfunction, while damaged mitochondria generate additional ROS.

Photochemical and oxidative injury subsequently activate intracellular stress-signaling pathways. Mitogen-activated protein kinase signaling, particularly the ERK, JNK, and p38 pathways, represents an important molecular response to cellular stress. These kinases regulate proliferation, differentiation, inflammatory gene expression, apoptosis, and adaptation to oxidative injury. JNK and p38 activation are particularly relevant to stress-induced cellular responses, whereas ERK signaling may influence cellular survival and repair depending on the magnitude and duration of activation. Reactive oxygen species can function as signaling molecules by modifying redox-sensitive proteins upstream of these pathways. Consequently, ROS generated during furocoumarin phototoxicity are not merely destructive intermediates but also act as molecular signals that translate photochemical injury into changes in gene expression and cell fate.

Nuclear factor- κ B constitutes another central regulatory pathway linking cellular damage with inflammation. Oxidative stress, DNA injury, and cellular stress signals can activate NF- κ B, resulting in nuclear translocation and transcription of genes encoding inflammatory cytokines, chemokines, adhesion molecules, and other mediators. Damaged keratinocytes consequently become active participants in the inflammatory response. They release interleukin-1 family cytokines, interleukin-6, tumor necrosis factor, chemokines, and other signaling molecules that recruit and activate inflammatory cells. Cyclooxygenase-2 induction and increased prostaglandin production further enhance vascular dilation and permeability. Histamine, bradykinin, and nitric oxide contribute to vasodilation, edema, sensory nerve activation, and inflammatory amplification.

The inflammatory response subsequently reinforces oxidative injury. Recruitment of neutrophils and macrophages to damaged skin results in additional production of ROS, proteolytic enzymes, cytokines, and lipid mediators. These mediators increase tissue injury and stimulate additional inflammatory signaling in neighboring keratinocytes. A positive feedback loop is therefore established between ROS production, NF- κ B activation, cytokine release, leukocyte recruitment, and further oxidative stress. This molecular interaction explains why the tissue response can continue to evolve after the initiating plant exposure has ceased. The resulting cellular and vascular changes manifest clinically as erythema, edema, burning, tenderness, vesiculation, blistering, and, in severe cases, epidermal necrosis and desquamation.

The clinical morphology of PPD is also directly related to its molecular pathophysiology. The reaction occurs only in areas where the photosensitizer and UVA exposure overlap. Consequently, lesions may display linear, streak-like, drip-shaped, hand-shaped, or geometric patterns corresponding to the original plant contact. Moisture, sweating, heat, and occlusion can enhance dermal penetration of the photosensitizer and increase the effective tissue concentration. Because UVA is relatively penetrating and can pass through ordinary window glass, exposure may occur under environmental conditions in which individuals do not perceive substantial ultraviolet exposure. The delay between exposure and development of clinically apparent inflammation reflects the time required for accumulation of photochemical damage, cellular signaling, inflammatory mediator production, and tissue injury.

A distinctive late consequence of PPD is persistent post-inflammatory hyperpigmentation. This phase represents a transition from acute photochemical and inflammatory injury to altered epidermal and dermal pigment biology. Damage to basal keratinocytes and the epidermal–dermal interface can result in pigment incontinence, allowing melanin to enter the superficial dermis where it is subsequently engulfed by melanophages. At the same time, inflammatory signaling can stimulate melanocyte activity and increase melanosome production and transfer to keratinocytes. Cytokines, prostaglandins, endothelins, and other paracrine mediators released during inflammation can modify melanocyte function and melanogenic enzyme activity. Oxidative stress may further influence melanocyte signaling and melanogenesis. Consequently, the pigmentation observed after resolution of acute inflammation is not simply residual staining but reflects persistent changes in melanocyte–keratinocyte communication, melanin distribution, and dermal pigment clearance.

The molecular basis of hyperpigmentation also explains its prolonged clinical course. Melanin deposited within the dermis is removed relatively slowly because melanophages and dermal clearance mechanisms require considerable time to eliminate pigment. Increased melanocyte activity may simultaneously maintain epidermal pigmentation after the acute inflammatory response has subsided. Additional UVA or visible-light exposure during this recovery period can further stimulate pigment production. Thus, the pigmentary phase of PPD may persist considerably longer than the initial inflammatory phase and can become the most clinically significant residual manifestation.

3. CURRENT PHARMACOLOGICAL STRATEGIES

The pharmacological management of phytophotodermatitis is primarily directed toward preventing further phototoxic injury, controlling acute inflammation, relieving symptoms, maintaining epidermal barrier integrity, and managing persistent pigmentary sequelae. Because the initiating photochemical reaction occurs rapidly following UVA-mediated activation of furocoumarins, early removal of the photosensitizer and prevention of additional UVA exposure remain the most important interventions. Thorough washing of the affected skin with soap and water should be undertaken as soon as possible after contact with furocoumarin-containing plants or plant-derived products. Subsequent protection from sunlight, preferably through physical barriers and avoidance of direct UVA exposure, reduces the possibility of continued photochemical activation. Broad-spectrum UVA photoprotection may provide additional benefit, although the evidence specifically supporting sunscreen use in PPD remains largely extrapolated from photobiological and PUVA studies. [9-11]

Once phototoxic injury has developed, treatment is predominantly supportive and directed toward the inflammatory and symptomatic consequences of cellular injury. Topical corticosteroids remain the principal pharmacological option for clinically significant erythema, edema, and pruritus. Their therapeutic action is relevant to several pathways implicated in PPD, including suppression of NF- κ B- and activator protein-1-mediated inflammatory transcription, reduction of proinflammatory cytokine production, inhibition of cyclooxygenase-2 expression, and modulation of phospholipase A₂-dependent mediator generation. By suppressing these pathways, corticosteroids can reduce the inflammatory amplification that follows the primary photochemical insult. However, they cannot reverse DNA photoadduct formation, oxidative damage, or keratinocyte death that has already occurred. Their greatest potential therefore lies in limiting secondary inflammatory tissue injury when treatment is initiated during the active inflammatory phase.

In extensive or severe disease, systemic corticosteroids may occasionally be considered, particularly when inflammation is widespread or associated with substantial edema and discomfort. Nevertheless, routine systemic corticosteroid administration is not justified for uncomplicated PPD because the disorder is generally self-limiting and specific clinical evidence remains limited. Treatment should therefore be individualized according to the extent of phototoxic injury, severity of inflammation, blistering, and involvement of functionally important anatomical sites.

Analgesics and non-steroidal anti-inflammatory drugs may be used to control pain and inflammatory discomfort. Their pharmacological relevance derives primarily from inhibition of cyclooxygenase-dependent prostaglandin synthesis, thereby potentially reducing prostaglandin-mediated vasodilation, erythema, and pain. Antihistamines may provide symptomatic benefit when pruritus is prominent, although their role is supportive rather than disease modifying because PPD is not fundamentally an IgE-mediated hypersensitivity reaction. Sedating antihistamines may additionally improve sleep when nocturnal pruritus is troublesome.

When vesicles, bullae, erosions, or extensive epidermal injury occur, treatment should follow principles used for superficial burn-like injuries. Preservation of the epidermal barrier, appropriate wound dressings, infection prevention, and maintenance of hydration are important components of management. Large tense bullae may require carefully controlled drainage, whereas intact smaller blisters can provide a natural biological barrier. Topical antimicrobial therapy may be considered when there is clinical evidence of secondary infection. Severe generalized PPD resulting from extensive plant exposure may require hospitalization and management comparable to significant superficial phototoxic or burn injury.

Management of post-inflammatory hyperpigmentation represents an important component of long-term pharmacological care. Because pigmentary alteration results from persistent melanocyte activation, increased melanin production, melanosome transfer, and pigment incontinence following epidermal injury, treatment should generally begin only after acute inflammation has resolved. Strict photoprotection is fundamental because continued UVA and visible-light exposure can stimulate melanogenesis and prolong pigmentation. Topical depigmenting agents may subsequently be considered. Hydroquinone inhibits tyrosinase and remains an established melanogenesis inhibitor, whereas azelaic acid can inhibit tyrosinase and influence abnormal melanocyte proliferation. Topical retinoids may promote epidermal turnover and redistribution of melanin. Other approaches, including kojic acid and vitamin C derivatives, may be considered as adjunctive strategies, although evidence specifically addressing PPD-associated pigmentation remains limited. The use of chemical peels requires particular caution in individuals with darker skin phototypes because additional irritation may exacerbate post-inflammatory pigmentation.

4. EMERGING PHARMACOLOGICAL STRATEGIES

The increasing understanding of the molecular pathophysiology of PPD provides a basis for developing mechanism-directed therapeutic strategies. Unlike conventional treatment, which primarily suppresses inflammation after tissue injury has occurred, emerging approaches aim to interfere with specific stages of the phototoxic cascade, including ROS generation, impaired antioxidant defense, DNA-damage signaling, mitochondrial dysfunction, inflammatory amplification, and melanogenesis. Most of these approaches remain investigational and are supported by evidence derived from experimental photobiology, UV-induced skin injury, PUVA research, pigmentation disorders, or related inflammatory skin diseases rather than definitive PPD-specific clinical trials. [12-14]

Nrf2-Directed Cytoprotection: The Keap1–Nrf2–antioxidant response element pathway represents one of the most attractive molecular targets because oxidative stress is a major component of furocoumarin-induced phototoxicity. Pharmacological activation of Nrf2 could enhance transcription of genes involved in glutathione synthesis, ROS detoxification, redox homeostasis, and cellular protection. Agents capable of inducing Nrf2-dependent cytoprotective responses, including selected electrophilic compounds and phytochemical-derived Nrf2 activators, may therefore provide a strategy for strengthening epidermal resistance to photochemical injury. The timing of Nrf2 activation is particularly important. Because transcriptional induction of antioxidant enzymes requires time, Nrf2-directed interventions may have greater value as preventive or early post-exposure strategies rather than treatments for established severe lesions. Topical delivery may provide an advantage by concentrating the intervention within the epidermis while minimizing systemic exposure. However, the safety, optimal concentration, dermal pharmacokinetics, and possibility of unintended effects associated with prolonged Nrf2 activation require systematic investigation.

NAD⁺ Preservation and DNA-Damage Modulation: The association between extensive DNA damage, PARP-1 activation, NAD⁺ depletion, and cellular energy failure provides a rationale for pharmacological approaches directed toward preservation of cellular bioenergetics. Nicotinamide, a precursor of NAD⁺ and a modulator of PARP activity, represents a particularly interesting candidate. By supporting intracellular NAD⁺ availability, nicotinamide could theoretically preserve ATP-dependent cellular processes and facilitate recovery following DNA damage. Its additional ability to reduce melanosome transfer provides a potential mechanistic link between cytoprotection during acute injury and attenuation of subsequent hyperpigmentation. However, evidence supporting this strategy in PPD remains indirect. Controlled phototoxicity models using standardized furocoumarin and UVA exposure would therefore be

necessary to determine whether preservation of NAD⁺ metabolism translates into clinically meaningful reduction of epidermal injury.

Modulation of ROS, MAPK, and NF-κB Signaling: Direct modulation of oxidative and inflammatory signaling represents another potential therapeutic avenue. Since ROS activate stress-responsive MAPK pathways and NF-κB, selective inhibition of excessive p38 MAPK, JNK, or NF-κB signaling could theoretically reduce cytokine production and inflammatory amplification. Similarly, modulation of cyclooxygenase-2 and prostaglandin signaling could attenuate vasodilation, edema, pain, and downstream melanogenic signaling. The major challenge is achieving selective suppression of pathological signaling without interfering with physiological immune defense and tissue repair. Consequently, highly penetrant systemic inhibitors would be inappropriate for a predominantly localized and self-limiting disorder. Topical formulations with restricted tissue exposure may provide a more rational strategy. Existing anti-inflammatory agents should therefore be evaluated initially in standardized experimental models before more selective pathway inhibitors are considered.

Mitochondrial-Targeted Pharmacological Protection: Mitochondria represent an emerging target because they occupy a central position between oxidative stress, cellular energy failure, and apoptosis. Furocoumarin-induced ROS may disrupt mitochondrial membrane potential and increase mitochondrial ROS production, creating a self-amplifying cycle of oxidative injury. Mitochondrial-targeted antioxidants, agents that stabilize mitochondrial membranes, and inhibitors of excessive mitochondrial permeability transition could potentially interrupt this cycle. Such interventions may be particularly valuable during the early phase of phototoxic injury, before mitochondrial dysfunction progresses to irreversible apoptosis or necrosis. The development of topical mitochondrial-targeted formulations could potentially provide localized cytoprotection while reducing systemic exposure, although this remains an experimental concept requiring substantial pharmacological validation.

Targeting Melanogenesis and Pigment Persistence: Persistent hyperpigmentation represents one of the most clinically important long-term consequences of PPD and therefore provides an additional target for emerging pharmacological strategies. The molecular targets include tyrosinase activity, melanocyte signaling, melanosome synthesis, melanosome transfer, and inflammatory paracrine communication between keratinocytes and melanocytes. Agents such as tranexamic acid, thiamidol, and niacinamide provide mechanistically distinct approaches. Tranexamic acid can interfere with inflammatory and plasmin-dependent pathways involved in melanogenic signaling, whereas thiamidol directly inhibits human tyrosinase. Niacinamide can reduce melanosome transfer from melanocytes to keratinocytes. Combining these mechanisms with rigorous UVA and visible-light photoprotection may provide greater control of persistent pigmentation than targeting melanogenesis alone. Nevertheless, these approaches should be initiated only after resolution of active inflammation to avoid treatment-induced irritation and further pigmentary alteration.

Advanced Barrier and Photoprotective Technologies: Prevention remains an important target for pharmacological innovation. Barrier-supportive formulations containing ceramides and other epidermal lipids could theoretically reduce penetration of furocoumarins into viable epidermal layers. Another potential strategy is the development of topical formulations capable of binding, complexing, or efficiently removing lipophilic furocoumarins from the skin surface. Cyclodextrin-based systems, adsorbent barriers, and specialized cleansing formulations may provide opportunities for reducing the effective photosensitizer concentration before UVA exposure. Advanced photoprotective formulations could additionally be optimized specifically for the UVA wavelengths responsible for furocoumarin activation. Nanocarrier-based delivery systems may improve localization of antioxidants, anti-inflammatory agents, or photoprotective compounds within the epidermis. However, nanotechnology should not automatically be considered synonymous with improved safety, as particle size, surface chemistry, penetration, and interaction with compromised skin may themselves influence toxicity.

Rational Combination Therapy: The multifactorial nature of PPD suggests that combination therapy may ultimately be more effective than single-target intervention. A rational topical formulation could combine an anti-inflammatory component with an antioxidant or Nrf2-directed cytoprotective agent, barrier-supportive components, and high-level UVA protection. Such a strategy would theoretically act at several stages of the pathological cascade: limiting inflammatory amplification, reducing secondary oxidative injury, strengthening epidermal defense, and preventing continued photochemical activation. The development of such formulations should follow a mechanism-based sequence, beginning with validated experimental models and progressing toward controlled clinical studies.

Combination approaches may be particularly valuable because direct reversal of furocoumarin-induced DNA photoadducts is unlikely to be pharmacologically achievable once these lesions have formed.

Pharmacogenomics, Biomarkers, and Precision Pharmacology: Interindividual differences in PPD severity and duration of pigmentation indicate that host factors may influence therapeutic response. Variation in antioxidant capacity, DNA-repair efficiency, inflammatory signaling, melanogenic activity, and constitutive pigmentation may contribute to differences in clinical phenotype. Pharmacogenomic studies could therefore identify individuals who are particularly susceptible to severe phototoxic injury or persistent hyperpigmentation. Biomarker development represents a complementary strategy. Oxidative DNA products, lipid peroxidation markers, inflammatory cytokines, antioxidant-response proteins, and markers of epidermal injury could potentially be used to quantify disease activity and pharmacodynamic response. Standardized measurements of erythema, pigmentation, and tissue injury would facilitate evaluation of emerging therapies and enable more meaningful comparisons between experimental studies.

Translational Perspective: Despite the expanding understanding of PPD molecular mechanisms, translation into pharmacological therapies remains limited by the self-limiting nature of the disease, delayed clinical presentation, absence of standardized severity scales, and scarcity of controlled PPD-specific clinical trials. Future studies should prioritize standardized experimental phototoxicity models using defined furocoumarins and calibrated UVA exposure. Three-dimensional reconstructed skin models containing keratinocytes and melanocytes, human skin explants, and appropriate animal models can facilitate mechanistic screening before clinical translation.

5. CONCLUSION

Phytophotodermatitis is a chemically and photobiologically complex, preventable disorder in which furocoumarins interact with UVA radiation to induce interconnected DNA damage, oxidative stress, mitochondrial dysfunction, inflammation, and altered melanogenesis. A stage-specific, mechanism-based pharmacological framework integrating exposure control, photoprotection, redox modulation, anti-inflammatory strategies, barrier protection, and targeted approaches to pigmentation could advance PPD management from predominantly supportive care toward evidence-based preventive and therapeutic interventions.

References

1. Moreau, J. F., English, J. C., 3rd, & Gehris, R. P. (2014). Phytophotodermatitis. *Journal of pediatric and adolescent gynecology*, 27(2), 93–94. <https://doi.org/10.1016/j.jpbg.2013.11.001>
2. Harshman, J., Quan, Y., & Hsiang, D. (2017). Phytophotodermatitis: Rash with many faces. *Canadian family physician Medecin de famille canadien*, 63(12), 938–940.
3. Sasseville D. (2009). Clinical patterns of phyto dermatitis. *Dermatologic clinics*, 27(3), 299–vi. <https://doi.org/10.1016/j.det.2009.05.010>
4. Kavli, G., & Volden, G. (1984). Phytophotodermatitis. *Photo-dermatology*, 1(2), 65–75.
5. Ellis, C. R., & Elston, D. M. (2021). Psoralen-Induced Phytophotodermatitis. *Dermatitis : contact, atopic, occupational, drug*, 32(3), 140–143. <https://doi.org/10.1097/DER.0000000000000691>
6. Bowers A. G. (1999). Phytophotodermatitis. *American journal of contact dermatitis : official journal of the American Contact Dermatitis Society*, 10(2), 89–93. [https://doi.org/10.1016/s1046-199x\(99\)90006-4](https://doi.org/10.1016/s1046-199x(99)90006-4)
7. Bonamonte, D., Foti, C., Lionetti, N., Rigano, L., & Angelini, G. (2010). Photoallergic contact dermatitis to 8-methoxypsoralen in *Ficus carica*. *Contact dermatitis*, 62(6), 343–348. <https://doi.org/10.1111/j.1600-0536.2010.01713.x>
8. Hatcher, V. R., & Miller, C. K. (2024). Phytophotodermatitis. *The New England journal of medicine*, 391(21), 2035. <https://doi.org/10.1056/NEJMicm2410140>
9. Machado, M., Vidal, R. L., Cardoso, P., & Coelho, S. (2015). Phytophotodermatitis: a diagnosis to consider. *BMJ case reports*, 2015, bcr2015213388. <https://doi.org/10.1136/bcr-2015-213388>
10. Mansilla-Polo, M., Martín-Torregrosa, D., Abril-Pérez, C., & Botella-Estrada, R. (2023). Phytophotodermatitis as a clinical problem and as a therapeutic option: Case report and review of the literature. *Photodiagnosis and photodynamic therapy*, 41, 103304. <https://doi.org/10.1016/j.pdpdt.2023.103304>
11. Maniam, G., Light, K. M., & Wilson, J. (2021). Margarita Burn: Recognition and Treatment of Phytophotodermatitis. *Journal of the American Board of Family Medicine : JABFM*, 34(2), 398–401. <https://doi.org/10.3122/jabfm.2021.02.200382>

12. Grosu Dumitrescu, C., Jîjie, A. R., Manea, H. C., Moacă, E. A., Iftode, A., Minda, D., Chioibaş, R., Dehelean, C. A., & Vlad, C. S. (2024). New Insights Concerning Phytophotodermatitis Induced by Phototoxic Plants. *Life (Basel, Switzerland)*, 14(8), 1019. <https://doi.org/10.3390/life14081019>
13. Agha, I. A., Montaquila, S., & Alobaidi, H. (2024). Unique Acute Phytophotodermatitis Reaction and a Visual Diagnostic Guide. *Cureus*, 16(4), e59199. <https://doi.org/10.7759/cureus.59199>
14. Lacroix, G., Samaran, Q., & Herlin, C. (2026). Phytophotodermatitis: An under-recognized diagnostic pitfall in chemical burns. *Annales de chirurgie plastique et esthetique*, 71(5), 467–471. <https://doi.org/10.1016/j.anplas.2026.01.006>