Infection and Drug Resistance

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REVIEW

# Photodynamic Therapy for the Treatment of Fungal Infections

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**Abstract:** Cutaneous fungal infections are common in humans and are associated with significant physical and psychological distress to patients. Although conventional topical and/or oral anti-fungal medications are commonly recommended treatments, drug resistance has emerged as a significant concern in this patient population, and safer, more efficacious, and cost-effective alternatives are warranted. Recent studies have reported effectiveness of photodynamic therapy (PDT) against fungal infections without severe adverse effects. In this review, we briefly discuss the mechanisms underlying PDT, current progress, adverse effects, and limitations of this treatment in the management of superficial and deep fungal infections.

**Keywords:** photodynamic therapy, fungal infection, review

## Introduction

Cutaneous fungal infections are categorized as superficial and deep infections and are associated with significant physical and psychological distress to patients. Conventional therapy may be ineffective, particularly for deep fungal infections. Furthermore, antifungal agents may cause severe adverse effects, such as liver toxicity, drug interactions, and drug resistance.[1] Some superficial fungal infections, such as tinea pedis and cruris are recommended treatment continued for two weeks, post clinical cure for topical agents, and recalcitrant cases usually need continued systemic therapy to eliminate pathogens,[2] which is known to reduce patient compliance and remains therapeutically challenging in clinical practice.

Reportedly, photodynamic therapy (PDT) is effective against fungal infections and serves as an alternative treatment strategy. PDT was originally discovered in 1900 and was used for its anti-microbial action; however, this treatment is gradually being accepted as an anti-fungal treatment option since the 1980s.[3]

The rapid onset of action, mild adverse effects, combinations with other therapies, and applicability in patients with contraindications to other drugs or in those with unresponsiveness to oral antifungal agents serve as advantages of PDT. Little to no risk of development of resistance and its repeatability are other advantages of this treatment. Currently, PDT is widely used to treat many cutaneous fungal infections, such as onychomycosis, tinea capitis, pityriasis versicolor (PV), oral candidiasis, vulvovaginal candidiasis (VVC), chromoblastomycosis (CBM) and cutaneous sporotrichosis, among others, of which onychomycosis is the focus of most research. PDT is a potentially promising therapeutic alternative for treatment of cutaneous fungal infections.

In this review, we discuss the published mechanisms underlying PDT, in addition to representative research on PDT in superficial and deep skin mycoses, and summarize the reported efficacy and limitations of this therapy for the management of fungal infections.

## Mechanisms Underlying the Effects of Photodynamic Therapy

PDT involves the use of the following three elements: a photosensitizer (PS), a light source, and molecular oxygen.[1] The PS frequently used in clinical practice include 5-aminolevulinic acid (5-ALA), methylamino levulinate (MAL), and

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methylene blue (MB). Light sources include red, green, and blue light, and lasers, among others. The mechanism underlying PDT effects is as follows: the PS absorbs energy under the action of light, changes its energy state, and reacts with oxygen molecules to generate reactive oxygen species (ROS), which selectively injure the infected or proliferative tissue.

PS produce their effects via the following mechanisms: A Type I reaction involves an interaction between the PS and the substrate, which generates free radicals, including hydroxyl radicals, hydrogen peroxide, and a superoxide anion that reacts with oxygen molecules to generate ROS, which cause fungal apoptosis.[4] A Type II reaction involves direct transfer of energy from the PS to oxygen to form singlet oxygen ($^1O_2$), a potent ROS,[5] which initiates cell injury (Figure 1).[6]

Type III and IV reactions have also been described in the literature.[7,8] These reactions are cytotoxic to intracellular structures in the absence of oxygen. Type III PSs are usually classified as antioxidant carrier sensitizers (ACS), which result in the generation of efficient $^1O_2$ and reduce the concentration of native free radicals in target cells. A Type IV reaction involves binding of a PS to its cellular target site after the activation of light excitation. Among the aforementioned mechanisms underlying PDT effects, Type I and II are indirect reactions, whereas Type III and IV reactions lead to direct activation of the PS molecule, which produces secondary reactions independent of interactions with oxygen (Figure 1).

ROS are key participants in phototoxic reactions. Some in vitro experiments have shown the possible mechanisms contributing to the growth-inhibiting effect of PDT, including destruction of biofilm formation and fungal cell wall structure secondary to enhanced ROS production.[5,9,10] PDT produces oxidative damage to cellular structures and DNA, causes structural modifications in the plasma membrane, and inhibits enzymatic systems.[11] Studies have reported that PDT-mediated therapy directly destroys microorganisms and also promotes neutrophil and lymphocyte infiltration at the affected sites to augment its fungicidal effect.[12,13]

## Role of Photodynamic Therapy in Superficial Fungal Infections

### Onychomycosis

Onychomycosis is one of the most common superficial fungal infections encountered in clinical practice, with a relapse rate of 25%–30%.[14] It is caused by dermatophytes, yeasts, and non-dermatophyte molds (NDMs).[15] The most common etiological pathogen is *Trichophyton rubrum*, one of the dermatophytes.[16] Many topical and oral agents cannot penetrate

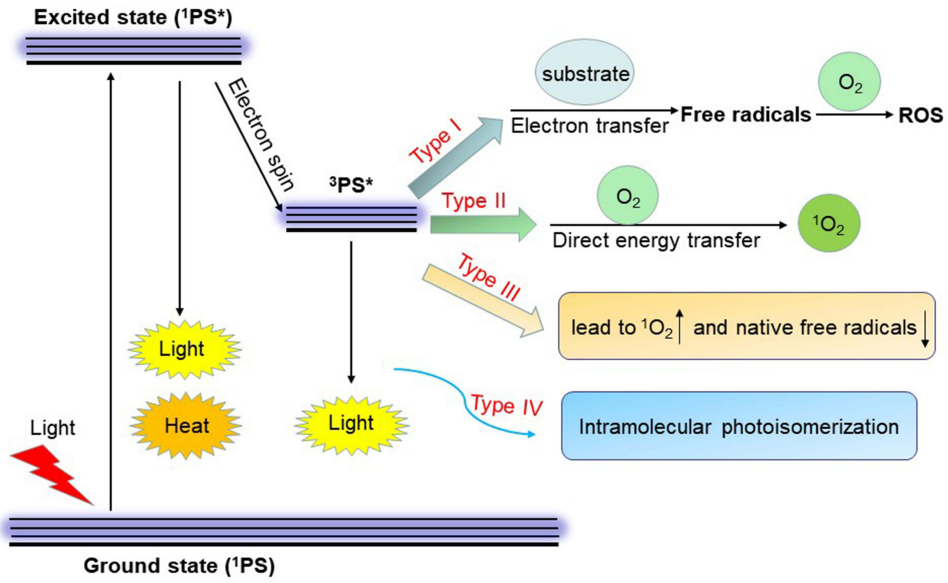


**Figure 1** Mechanisms of action of photodynamic therapy. Following light absorption, excited state $^3PS^*$ reacts with $O_2$ to produce ROS and $^1O_2$ (type I and II reactions). Type III PSs combine properties leading to the generation of $^1O_2$ and reduction of native free radicals in target cells. Type IV mechanism involves a structural change from excited state $^1PS^*$ by photoisomerization to enable molecular target binding of the activated PS* to its cellular target site. (* represents the excited state).
**Abbreviations**: PS, photosensitizer; $^1PS$, singlet photosensitizer; $^3PS$, triplet photosensitizer; ROS, reactive oxygen species; $^1O_2$, singlet oxygen; $O_2$, oxygen.

the nail plate and are not absorbed owing to the insufficient blood supply to the nail plate, which is invariably thickened in a diseased state.[14] Currently, PDT is a promising strategy to enhance nail penetration. A systemic review showed that PDT led to negative results on microscopy and/or culture studies in 67% of patients (N = 58) who received this treatment.[17] PDT combined with other physical therapies, such as lasers results in good penetration of the nail plate. A clinical trial (n=7) in which PDT with combined with carbon dioxide ($CO_2$) laser to treat recurrent onychomycosis reported a mycological cure rate of 100%.[18] Some in vitro experiments and mouse models have shown that PDT could disrupt bacterial and fungal biofilms,[19–22] such as *Pseudomonas aeruginosa, Staphylococcus aureus*, and *Candida* strains biofilms, which refers to a freely suspended microbial community that provides protection against host defenses.[17] Theoretically, the anti-biofilm action of PDT can prevent recurrent onychomycosis.

Various PSs are used for PDT; however, these may show different levels of antifungal effects. Reportedly, nail penetration of MB is better than that of ALA, and MB is therefore associated with higher complete cure rates.[1,23,24] MB usually does not require pre-treatment except in patients with nail hyperkeratosis measuring at least 2 mm, who require nail microabrasion.[25] In contrast, ALA requires pre-treatment and prolonged exposure because the ALA molecule is required to undergo enzymatic conversion into a protoporphyrin for pre-use activation.[25] Furthermore, high water solubility and absorption bands in the red spectrum are important features that determine selection of PS for the treatment of onychomycosis.[26]

New-generation PSs wrapped in nanoemulsions are shown to have good effectiveness and a high safety profile.[27] A clinical trial using aluminum-phthalocyanine chloride with nanoparticles reported photoactivation for treatment of deeper nail layers.[28] Two other studies have shown that light-induced gold nanoparticles could inhibit spore germination and achieve high complete cure rates.[29,30] Nanoemulsions may serve as an excellent delivery system for PS and enhance penetration of aqueous tunnels created by pre-treatment using urea solution.[28] Newer PS may possess intrinsically good nail penetration capacity, which may reduce incubation time, obviate the need for pre-treatment, and also be effective under low-oxygen conditions.[31]

Evidence from many in vitro studies supports the role of PDT as a potential therapeutic alternative for *Trichophyton rubrum* infection. Rose Bengal and *Citrus aurantifolia* essential oil (Citrus EO) PS activated by light are shown to reduce the growth of *T. rubrum*.[32,33] Citrus EO is activated by sunlight, and no special light source is required. Sylsens B was shown to be an effective PS to prevent *T. rubrum* microconidia germination.[26] Although these in vitro studies have shown promising results, no clinical trials have corroborated these findings. Further in vivo studies are required to verify the fungicidal effects of these agents (Table 1).

## Tinea Pedis

Tinea pedis is a common fungal skin infection; topical antifungal medications remain the mainstay of treatment, and oral antifungal drugs are considered in cases of infection that remain refractory to local therapy.[34] Tinea pedis is a chronic and contagious condition with reservoir effect; therefore, long-term treatment (over >4 weeks) is recommended in recalcitrant cases.[2] PDT was attempted for the management of tinea pedis to overcome the limitations of long-term drug therapy. However, this approach was not more effective than conventional therapies. Two clinical studies investigated ALA-PDT for the treatment of interdigital tinea pedis, the most common type of mycotic infection of the feet.[35,36] In the two studies, complete cure rates were obtained at 30% and 22% at follow-up. ALA-PDT treatment of interdigital tinea pedis showed lower response rates than conventional topical allylamines (naftifine and terbinafine) therapy with mycological cure rates of 62%–100% and clinical cure rates of 66%–86%.[37] It may be attributable to the fact that PDT treatment administered to irregular surfaces may result in light-blind areas, which may serve as a source of re-infection (Table 1).

## Tinea Cruris

Tinea cruris is a fungal infection of the groin, buttocks, and perineal and perianal skin. Reportedly, cure rates range from 80% to 90% following accurate diagnosis and optimal therapy.[38] However, an alarming trend of recalcitrant tinea cruris is being observed, with reduced treatment compliance in patients.[39] PDT has been attempted to overcome this concern; however, long-term outcomes were not favorable.

**Table 1** Overview of the Treatment Regimen, Outcome, and Side Effects for PDT Treatment of Fungal Infections Articles Cited in This Review

| References | Study Type | Case Number | Fungal Species | PS | Light Source | Light Wavelength (nm) | Light Dose ($J/cm^2$) | Treating Sessions (Interval Time) | Combination Treatment | Outcome | Follow Up | Adverse Effects |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Onychomycosis** | | | | | | | | | | | | |
| de Oliveira GB et al[18] | Clinical trial | 7 | *T. rubrum* (n=6); Epidermophyton floccosum (n=1) | 16% MAL | LED | NA | NA | 2 sessions (60-day intervals) | Fractional $CO_2$ laser 10.600 nm | 1-year follow-up: MC 100%; CIC 79% (15/19) (nail four quadrants count) 43% (entire nail plate) No relapse. | 30 days; 1 year | NA |
| Morgado LF et al[28] | Clinical trial | 20 included (16 finished) | NA | AlClPc (entrapped in nanoemulsions) | LED (red light) | 660 | 30.9 | 4.45±1.76 sessions (15-days interval) | No | MC 40% CIC 60% | 1 month | Pain (VAS 2.76±1.87) |
| Tawfik AA et al[29] | In vivo experience (rabbit) | 80 | *T. mentagrophytes* | 3 groups: MB; Gold nanoparticles; MB + gold nanoparticles | LED (red and green light) | Red (650); Green (530) | 80; 100 | 4 sessions (48-hours intervals) | No | CC: MB 40%; Gold nanoparticles 96%; MB + gold nanoparticles 34% | 48 hours after the 4th session | NA |
| Cronin L et al[32] | In vitro study | Spore suspension ($A_{300}$=0.6) | *T. rubrum* | Rose Bengal | Laser (green) | 532 | 68; 133; 228 | NA | No | Percentage growth inhibition 15–51% | NA | NA |
| Fekrazad R et al[33] | In vitro study | Suspensions ($10^6$ cells/mL) | *C.albicans; T. rubrum* | Citrus EO; Indocyanine green | Infrared (IR) laser; Natural and tungsten lights | 810±10 (IR laser) | 55 (IR laser) | NA | No | Cell reduction rates: Citrus EO + natural and tungsten light: 99.99% (*C.albicans* and *T.rubrum*); Indocyanine green + IR laser: 91.67% (*C.albicans*) 74.5% (*T.rubrum*); Fluconazole + IR laser: 38.5% (*T.rubrum*) | NA | NA |

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| Smijs TG et al[26] | In vitro study | Suspension and spore solution | *T. rubrum* | Sylsens B; DP mme | Red light | 600 | 108 | NA | No | Inhibition rates: Suspension cultures: Sylsens B (10μM-50μM): 100% DP mme (30μM): 95%; Microconidia: Sylsens B (1–5μM): 100% DP mme (4–5μM): 80–90% | 2 days; 7 days; 3 months | NA |
| **Tinea pedis (interdigital type)** | | | | | | | | | | | | |
| Sotiriou E et al[35] | Clinical trial | 10 | *T. rubrum* (n=4); *T. mentagrophytes* (n=6) | 20% 5-ALA | Red light | 570–670 | 50 | 1 or 3 sessions (2-week intervals) | No | CC after 3 treatments: 60% (6/10) CC at the end of follow-up: 30% (3/10) | 2 months | Burning sensation during irradiation, erythema up to 1 week after therapy. |
| Calzavara-Pinton PG et al[36] | Clinical trial | 9 | *T. mentagrophytes* (n=4); *T. rubrum* (n=2); *C. albicans* (n=3) | 20% 5-ALA | Broadband red light | 575–700 | 75 | 1 or 4 sessions (1-week interval) | No | CC after 1 or 4 treatments: 67% (6/9) CC at the end of follow-up: 22% (2/9) | 4 weeks | Localized erythema and edema during and soon after exposure; pain; desquamation after 3–5 days. |
| **Tinea cruris** | | | | | | | | | | | | |
| Sotiriou E et al[40] | Clinical trial | 10 | *T. rubrum* | 20% 5-aminolevulinic acid (ALA) | Red light | 570–670 | 50 | 1–2 sessions (2-week intervals) | No | MC after 1–2 treatments: 80% (8/10) MC at the end of follow-up: 40% (4/10) | 8 weeks | Mild burning and stinging during the exposure; erythema and edema up to 3–4 days after therapy. |
| **Tinea Capitis** | | | | | | | | | | | | |
| Lu J et al[42] | Case report | 1 | NA | 20% 5- ALA | LED | 630 | 80 | 3 sessions (1-week interval) | Itraconazole 100 mg/day | CC 1/1 No recurrence. | 3 months | Burning sensation during irradiation; temporary edema, erythema, itch, and stinging up to 1 week after therapy. |

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**Table 1** (Continued).

| References | Study Type | Case Number | Fungal Species | PS | Light Source | Light Wavelength (nm) | Light Dose ($J/cm^2$) | Treating Sessions (Interval Time) | Combination Treatment | Outcome | Follow Up | Adverse Effects |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Pityriasis versicolor (PV)** | | | | | | | | | | | | |
| Alberdi E et al[43] | Pilot trial | 5 | *Malassezia spp.* | 2% MB | Red LED lamp | 630±5 | 37 | 6 sessions (2-week intervals) | No | CC: 5/5<br>No relapse. | 4 weeks; 22 weeks | Hypopigmentation, no other side effects or pain. |
| **Oral candidiasis** | | | | | | | | | | | | |
| Freire F et al[47] | In vitro study; in vivo study in a murine model | $10^7$ CFU/mL of suspension (OD570); 15 BALB/c mice | *C. albicans* | Methylene blue (MB); new methylene blue (NMB) | Red diode laser | 660 | 10; 20; 40; 60 J | 5 days of daily treatment | Potassium iodide (KI) | Log reduction of CFU/mL:<br>MB+KI (40 J): 2.31 log<br>NMB (60 J): 1.77 log<br>Reduction of mice bioluminescent photon flux ($log_{10}$) :<br>MB+KI (40J): 2 log<br>NMB (60 J): 1 log | NA | NA |
| Campos L et al[48] | Case report | 1 | *Candida* spp. | 0.01% MB | Laser | 660 | 178 | 1 session | No | CIC: 1/1 | 72 hours | NA |
| Chibebe JJ et al[49] | In vivo experiment in *Galleria mellonella* model | 16/group | *C. albicans* Can14 (wild-type); Can37 (fluconazole-resistant) | MB (1 mM) | Red light | 660±15 | 0.9 | 1 time | Fluconazole (14 mg/kg) | Can14:<br>MB-PDT prolonged suivival.<br>Can37:<br>MB-PDT reduced fungal burden by 0.2 log;<br>MB-PDT +fluconazole prolonged suivival. | 100 hours - 150 hours | NA |
| **Esophageal candidiasis (EC)** | | | | | | | | | | | | |
| Qiu H et al[51] | Clinical study | 2 | *Candida* spp. | Photocarcinorin (PSD-007) | Semiconductor laser | 630 | 135; 270 | 1–3 sessions (1-month and 6-month intervals) | No | Case 1: CC 2/2 EC lesions<br>Case 2: CC 1/1 EC lesions<br>No recurrence in two cases. | 14 months; 24 months | Substernal pain within 5–7 days after PDT. (both cases)<br>A low-grade fever lasted for 5 days post PDT. (case 1) |

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| **Vulvovaginal candidiasis (VVC)** | | | | | | | | | | | | |
| de Santi M et al[55] | In vivo study in a murine model | 37 | *C. albicans* | MB (100 μM); PpNetNI (10 μM) | Laser (MB); LED (PpNetNI) | 660 nm (laser); 630 nm (LED) | 6048 (laser); 85 (LED) | 1 time | No | Reduction of fungal CFUs: 1 order of magnitude (both PSs) | 7 days | No |
| Machado-de-Sena RM et al[56] | In vivo study in a murine model | 77 | *C. albicans* | MB (1 mM) | Red laser | 660 | 18 J; 36 J | 1 or 2 sessions (24-hour intervals) | No | Reduction of fungal CFUs: 1session: 1.62 log (after 24 h) 1.16 log (after 96 h); 2 sessions: 1.66 log (after 24 h) | 24 hours; 96 hours | NA |
| **Chromoblastomycosis (CBM)** | | | | | | | | | | | | |
| Hu Y et al[58] | Case report; in vitro study | 1 case; $0.5–2.5\times10^3$ conidia/mL (in vitro) | *F. monophora* | 20% 5-ALA | LED | 635 | 10 J | Case: 2 sessions (each including 9 times, 1-week interval) | Case: Terbinafine (250 mg/day) In vitro study: No combination. | Case: Mycological cure and clinical greatly improvement. In vitro study: Reduce fungal CFUs by 2–4 log. | Case: 1 year; In vitro study: 7 days | Hypopigmentation |
| Lyon JP et al[59] | In vitro study | Suspension of $1–5\times10^6$ CFU/mL | *F. pedrosoi; Cladophialophora carrionii* | MB (16 μg/mL; 32 μg/mL; 64 μg/mL) | LED | NA | 200 mW/$cm^2$ | 1 time | No | Reduction of fungal CFUs: 4 log approximately (32 μg/mL achieved better result) | 7–10 days | NA |
| Huang X et al[60] | In vivo study in *Galleria mellonella* model | No specific description | *F. monophora* | 5- ALA | Laser (red light) | NA | NA | 1 session | No | Extend median survival by 2.5 days. Increase hemocyte density by $1.34\times10^3$ cells/μL 4h after PDT. | 10 days | No |

(*Continued*)



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**Table 1** (Continued).

| References | Study Type | Case Number | Fungal Species | PS | Light Source | Light Wavelength (nm) | Light Dose (J/cm$^2$) | Treating Sessions (Interval Time) | Combination Treatment | Outcome | Follow Up | Adverse Effects |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hu Y et al[9] | Case series; in vitro study | 5 cases; Suspension: 0.5–2.5×10$^3$ conidia/mL | *F. nubica* (n=1); *F. pedrosoi* (n=2); *F. monophora* (n=2) | 20% 5- ALA | LED (white light) | 635 | 36.8 mW/cm$^2$ (10 J) | Cases: 4–9 sessions (1- or 2-week intervals) | Cases: Oral itraconazole 400 mg/day; oral terbinafine 250 mg/day In vitro study: Itraconazole 1μg/mL | Cases: MC: 3/5 CC: 2/5 Clinical improvement: 3/5 No new lesions. In vitro study: Reduced approximately 2×10$^3$ CFUs of *F. monophora.* | Cases: 6 months - 2 years | Hypopigmentation (n=2) |
| Yang W et al[61] | Case report | 1 | *F. monophora* | 20% 5-ALA | LED (red light) | 630 | 90 | 3 sessions (10-day intervals) | Itraconazole 400 mg/day | CC: 1/1 No relapse. | 3 months | Pain and burning sensation during irradiation; Mild pain, swelling, and exudation whining 3–5 days after PDT. |
| Huang X et al[62] | Case report | 1 | *F. pedrosoi* | 10% ALA | Red light | 633±10 | 80–100 mW/cm$^2$ | 6 sessions (1-week interval) | No | CC: 1/1 No recurrence. | 6 months | NA |
| Lan Y et al[63] | Case report | 1 | *F. monophora* | 20% ALA | Red light | 633±10 | 96 | 4 sessions (1-week interval) | Isotretinoin 20 mg/day; Oral terbinafine 250 mg/day, itraconazole 400 mg/day; $CO_2$ laser. | MC: 1/1 Clinical improvement. | 4 months | No |
| **Sporotrichosis** | | | | | | | | | | | | |
| Gilaberte Y et al[66] | Case report and in vitro study | 1 case; Suspension optical density McFarland values 0.5. | *Sporothrix schenkii* | Case:1% MB; In vitro study: MAL (0–6 M); MB (1 μM); NMB (1.25 μM); DMMB (1.5 μM) | LED | 635 nm (case); 639.8±10 nm (in vitro study) | 37 | Case: 3 and 5 sessions (2-week intervals) | No | Case: Clinical improvement; In vitro study: Reduce fungal cells by 6 $\log_{10}$ CFUs (MB, NMB, DMMB), No change of CFU (MAL). | NA | Pain during irradiation (score 4 on a VAS) |

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| **Phaeohyphomycosis** | | | | | | | | | | | | |
| Liu H et al[68] | Case report | 1 | *Exophiala spinifera* | 20% ALA | Red light | 633 | 120 mW/$cm^2$ | 3 sessions (1-week interval) | Oral terbinafine 250 mg/day, itraconazole 200 mg/day | MC: 1/1<br>Clinical improved greatly. | 3 months | Mild burning and temporary pain during irradiation; hyperpigmentation. |
| **Majocchi's granuloma (MG)** | | | | | | | | | | | | |
| Shi L et al[12] | Case report; in vitro study; in vivo study in guinea pig model | 1 case;<br>In vitro study: suspension $1–5×10^5$ CFU/mL | *T. tonsurans* | Case: 10% ALA;<br>In vitro study: 5 mM ALA;<br>In vivo study: 10% ALA | LED | Case: 635<br>In vitro and in vivo study: 633 | Case:120;<br>In vitro study: 50, 100, 150, 175, 200;<br>In vivo study: 90. | Case: 3 sessions (3- or 4-week intervals) | No | Case:<br>CC 1/1;<br>no recurrence.<br>In vitro study: Reduced approximately $4×10^5$ CFU/mL of fungal concentrations. (175 and 200 J/$cm^2$)<br>In vivo study: Reduced the clinical lesions scoring by 6. | Case: 3 months;<br>In vitro study: 7 days;<br>In vivo study: 14 days | Case:<br>Inflammatory exudation after 1st PDT.<br>In vivo study: Erythema and exudation 24–48 hours after PDT. Scabs formed on the 8th day. |
| **Mucormycosis** | | | | | | | | | | | | |
| Liu Z et al[11] | In vitro study | 6 strains; Conidia concentration of $1–3×10^6$ CFU/mL | *R. oryzae* | MB (8, 16, and 32 μg/mL) | LED | 635±10 | 12 | 1 time | No | CFU reductions:<br>1.1 $log_{10}$ (8 μg/mL MB);<br>2.2 $log_{10}$ (16 μg/mL MB);<br>4.3 $log_{10}$ (32 μg/mL MB). | 24 hours | NA |

**Abbreviations**: PS, photosensitizer; PDT, photodynamic therapy; ALA, aminolevulinic acid; MAL, methyl aminolevulinate; MB, methylene blue; NMB, new methylene blue; DMMB, 1.9-dimethylmethylene blue; DP mme, deuteroporphyrin monomethylester; Citrus EO, citrus aurantifolia essential oil; AlClPc, aluminium-phthalocyanine chloride; PpNetNI, Protoporphyrin IX; LED, Light-Emitting Diode; $CO_2$, carbon dioxide; MC, mycological cure; ClC, clinical cure; CC, complete cure; CFU, colony forming unit; VAS, visual analogue scale; NA, not available; *T., Trichophyton; C., Candida; F., Foncecaea; R., Rhizopus.*


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In a clinical trial that included 10 patients with tinea cruris caused by *Trichophyton*, the author administered 20% 5-ALA-PDT (570–670 nm wavelengths) at a light dose of 50 J/cm$^2$ for 4 hours/ session. Direct microscopy performed after 1–2 sessions showed negative results in 8 patients (80%). However, only 4 patients (40%) showed sustained healing at 8-week follow-up.[40] Recurrence rates were as high as 50% in this study, which suggests that PDT may not be adequately effective for the eradication of fungi. The unsatisfactory therapeutic response to PDT may be attributed to high humidity and temperature in the groin, which affect the cellular uptake of ALA (Table 1).

## Tinea Capitis

Tinea capitis is one of the most common fungal infections observed in pre-pubertal children.[41] Oral antifungal medications are considered standard therapy for tinea capitis; however, the increasing prevalence of resistant strains and adverse events limit the use of conventional antifungal treatment. Lu et al[42] reported a case of relapsed suppurative tinea capitis in a child who showed mycological and clinical cure after ALA-PDT plus itraconazole treatment administered over three sessions. Treatment included topical application of 20% 5-ALA and an occlusive dressing for 3 hours, followed by irradiation using a light-emitting diode (LED) light (630 nm, 80 J/cm$^2$) for 20 min/session. The authors observed that PDT destroyed metabolically active cells in addition to resistant forms such as conidia. PDT may serve as a useful adjunct for the treatment of refractory tinea capitis (Table 1).

## Pityriasis Versicolor

Pityriasis versicolor (PV) is a chronic recurrent fungal infection of the stratum corneum. Although guidelines recommend systemic therapy for PV, this chronic condition is characterized by refractoriness to treatment. MB and MAL are common PSs used for the treatment of PV because the hydrophilicity of MB limits it to the stratum corneum, and the lipophilicity of MAL, restrains lipophilic *Malassezia*.[1,43] Alberdi et al[43] used MB-PDT (2% MB and a red LED lamp [λ= 630±5 nm, 37 J/cm$^2$]) to treat 5 women with disseminated PV on the back. MB-PDT administered over six sessions with a 2-week interval between sessions led to complete cure and good cosmetic outcomes without recurrence at the 6-month follow-up. The authors also recommended MB-PDT as a potential prophylactic treatment owing to its cost-effective and highly selective features (Table 1).

## Oral Candidiasis

Oral candidiasis is a common opportunistic fungal infection typically observed in immunocompromised patients. Infection control is extremely important in these patients to avoid serious and often fatal outcomes. *Candida albicans* is the most common pathogen that causes oral candidiasis. Compared with its planktonic form, the biofilm-forming species is more pathogenic and necessitates a higher concentration of PS and a longer incubation period.[44–46] A study performed by Freire et al, which included biofilm growth in vitro and in a mouse model showed the efficacy of new methylene blue (NMB)-mediated PDT against *C. albicans*.[47] Both the survival fraction analysis (log reduction of colony forming units (CFU/mL)) of *C. albicans* and histopathological examination showed eradication of fungi. The authors also observed that potassium iodide (KI) potentiated MB-PDT, which may be secondary to the fact that KI provides a greater number of electrons to MB to initiate a Type I photochemical reaction.

A case report and an in vivo experiment in the *Galleria mellonella* model have described that MB-PDT could rapidly heal oral lesions caused by drug-resistant *C. albicans* strains and reduce the fungal burden by 0.2 log in the animal model.[48,49] However, the role of PDT in the prevention of drug resistance remains unclear.

In addition to oral lesions, *C. albicans* causes esophageal candidiasis (EC), particularly in immunocompromised hosts such as in patients with cancer, AIDS, diabetes, or a glucocorticoid-dependent state.[50] Qiu et al[51] successfully treated EC and controlled the progression of esophageal cancer using photocarcinorin-mediated PDT. Photocarcinorin (PSD-007), a mixed porphyrin preparation, is used as a PS; however, the mechanism of photo-oxidative injury remains unknown (Table 1).

## Vulvovaginal Candidiasis

Vulvovaginal candidiasis (VVC) affects approximately 75% of women of child-bearing age; *C. albicans* is the main pathogen associated with this infection.[52] The azole family of drugs is widely used against *Candida* infection; however,

these drugs block the activity of some essential enzymes and lead to adverse effects.[53] The etiological agents implicated in VVC, including *C. albicans* and *C. glabrata* may be resistant to antifungal agents, including fluconazole.[54] PDT represents a novel therapeutic adjuvant without deleterious effects.

A study performed by de Santi et al reported the use of MB- and protoporphyrin IX (PpNetNI)-mediated PDT to treat VVC in a mouse model.[55] The authors observed reductions of one order of magnitude in the CFUs of *C. albicans* after 7-day treatment without any adverse effects on the vaginal mucosa at the ultrastructural level. In addition to its fungicidal effect, PDT reduced edema and abscess formation, which provided adequate time for the host immune system to eradicate the fungi.[55]

Machado-de-Sena et al observed reduction in the fungal burden and inflammation in a murine model of VVC within 24 hours of completion of MB-PDT (Table 1).[56] However, fungal recolonization occurred 96 hours after PDT because this organism is a commensal that colonizes the healthy human mucosa. The authors speculated that MB-PDT may inhibit the formation of germ tubes, which contribute significantly the virulence of *C. albicans*. Additionally, PDT minimizes the harmful effects of toxins on the vaginal mucosa and is therefore a safe therapeutic choice.[56]

## Photodynamic Therapy for Subcutaneous or Deep Fungal Infections

### Chromoblastomycosis

Chromoblastomycosis (CBM), a chronic granulomatous subcutaneous fungal infection caused by dematiaceous fungi is associated with low cure and high relapse rates.[9] *Fonsecaea monophora, Fonsecaea pedrosoi*, and *Cladophialophora carrionii* are the most common fungal species associated with CBM. Notably, fibrosis is a major obstacle to successful oral antifungal management. Owing to diverse clinical manifestations and etiological agents, the optimal therapy for CBM remains uncertain. PDT has emerged as a promising physical approach to treating CBM, particularly in the early stages of the disease.[57]

Two in vitro experiments have shown that ALA-PDT and MB-PDT significantly decreased fungal CFUs in CBM by 2–4 and 4 orders of magnitude, respectively.[58,59] Clinical trials have reported that muriform cells pose a therapeutic challenge; following tissue invasion, fungi are transformed into muriform cells, which aid with immune system evasion and antifungal drug resistance. PDT may directly destroy muriform cells or stimulate the host immune response. An in vivo experiment in the *Galleria mellonella* model confirmed the antimicrobial effect of ALA-PDT via immunomodulation of innate immunity secondary to increased hemocyte density, cell morphological transformation, and pathogen sensitivity.[60]

Combination therapy including PDT and systemic antifungal drugs is preferred in clinical practice, because most patients present for evaluation with moderate or severe disease. There are some successful clinical practices for PDT in patients with complex CBM using ALA-PDT associated with itraconazole or terbinafine.[9,58,61] A sequential PDT protocol after failed drug therapy showed fungicidal effects similar to those observed with combination therapy.[62] In patients with CBM post PDT treatments, most lesions showed clear improvement, and mycological examination results were negative after the last therapy session, with a few pigmentary changes but no new lesions on long-term follow-up.[9]

In addition to the combination of two methods, comprehensive treatment using several methods may be beneficial. Lan et al[63] reported that PDT combined with oral antifungal agents, isotretinoin, and $CO_2$ laser showed antifungal activity against clinical CBM (Table 1). The $CO_2$ laser slightly injures the skin surface and thereby promotes penetration of the PS; such comprehensive management produces synergistic inhibitory effects.

Moreover, in vitro susceptibility tests may not accurately predict clinical response. A study has reported that several isolates of pathogenic strains from patients were sensitive to oral antifungal drugs but showed resistance in vivo.[9] The overall patient status, phenotypic changes, differential gene regulation, and biofilm formation by dermatophytes may affect treatment efficacy.[64] Therefore, clinical trials that determine the response rate of specific fungi to PDT are urgently needed.

### Sporotrichosis

Sporotrichosis, a fungal infection caused by the *Sporothrix schenckii complex*, a thermally dimorphic species, is often restricted to cutaneous, subcutaneous tissue, and lymphatic vessels.[65] Oral itraconazole is commonly used for treatment

of sporotrichosis; however, drug-induced hepatotoxicity remains a serious concern. PDT is an effective alternative for localized fungal infections without severe adverse effects.

Gilaberte et al[66] reported complete microbiological and clinical cures in a patient with recalcitrant cutaneous sporotrichosis, who received intralesional 1% MB-PDT combined with intermittent low-dose itraconazole. The authors also performed an in vitro photoinactivation test on the fungus isolated from the patient and observed that three phenothiazinium PSs (MB, NMB, and 1.9-dimethyl methylene blue) produced a 6 $\log_{10}$ fungicidal effect, whereas MAL did not inhibit fungal growth, even at high concentrations (6 M). This result was consistent with the clinical outcomes observed in the patient (Table 1). Reportedly, the *S. schenckii complex* produces melanoid pigments that absorb light and scavenge ROS to limit the efficacy of PDT.[67] The fungicidal efficacy of MB-PDT specifically against *S. schenckii complex* may be attributed to the method of administration, low optical interference, and high ROS production.[66]

### Phaeohyphomycosis

Phaeohyphomycosis is a fungal infection that includes a wide spectrum of infections of the epidermis and subcutaneous tissues in addition to systemic involvement. It is caused by melanized fungi, and no standard antifungal therapy is currently available for this infection. Liu et al[68] reported the use of ALA-PDT as adjuvant therapy combined with oral itraconazole and terbinafine to treat an elderly immunocompromised woman with phaeohyphomycosis caused by *Exophiala spinifera*. The authors used 20% 5-ALA red light (633 nm) at an intensity of 120 mW/cm$^2$ administered over three sessions. Mycological evaluation showed negative results with significantly improved lesions and no notable adverse effects (Table 1).

### Majocchi's Granuloma

Majocchi's granuloma (MG) is a deep suppurative granulomatous perifolliculitis primarily caused by *T. rubrum*. Shi et al[12] reported a case of refractory MG that was successfully treated after three-cycles of ALA-PDT. The lesions were treated using a plum-blossom needle before incubation with 10% ALA, followed by irradiation using red LED light (635 nm) at a power density of 100 mW/cm$^2$ for 120 J/cm$^2$. The authors simultaneously used the clinical strain isolated of the patient for in vitro and in vivo experiments in a guinea pig model. Both in vitro and in vivo experiments demonstrated that ALA-PDT directly destroys the structural framework of the fungal cells and thereby inhibits *T. tonsurans* and also recruits CD4$^+$ T lymphocytes (Table 1).

### Mucormycosis

Mucormycosis, most commonly caused by *Rhizopus oryzae* is an aggressive and invariably fatal opportunistic fungal infection that originates in the nasal tissues and spreads into the paranasal sinuses and deep organs with a rapid angioinvasive course. Mucorales are resistant to most triazoles, and surgical debridement is associated with specific limitations.[11] Liu et al[11] observed that MB-PDT inhibited the growth of *R. oryzae* and enhanced its susceptibility to azoles and amphotericin B in vitro, which explains the synergistic effects of antifungal agents combined with PDT, which was observed in the clinic to some extent (Table 1).

## Adverse Effects Associated with Photodynamic Therapy for the Management of Fungal Infections

Usually, most adverse effects of PDT, including local erythema, edema, pain, burning and stinging sensations, and itching, which occur within the first PDT session are mild and tolerable.[69,70] Slight blistering and minimal exudation may occur in a few patients. Hyper- or hypopigmentation or scars may persist over a long period of time, particularly in patients with deep fungal infections using ALA-PDT.[71] However, most adverse effects are temporary and usually disappear within 2 weeks after PDT.[72]

## Current Limitations of Photodynamic Therapy Used Against Fungal Infections

Although significant research has focused on the role of PDT against fungal infections in recent years, most studies have provided proof-of-concept evidence in case reports in contrast to clinical data obtained through large-scale randomized controlled trials to confirm the long-term efficacy and safety of PDT, to optimize PDT protocols, and definitively establish PS for optimal benefit in specific fungal infections.

Comparison between articles is difficult owing to heterogeneity across studies, which results in a lack of high-quality meta-analyses. Notably, with regard to PDT, the type and concentration of PS, incubation time, light source, wavelengths used, energy, density, duration of exposure to irradiation, frequency of treatment, and growth of microorganisms, among such variables differed across studies, and in view of the diverse treatment settings, results too tend to vary widely, which may interfere with the accuracy of results, with regard to the efficacy of PDT.

Most studies have focused on only a few fungal diseases such as onychomycosis, oral candidiasis, and CBM that are commonly observed in clinical practice or are refractory to standard therapy.[15,31,48,57,63] Further studies are needed to gain deeper insight into the exact mechanisms underlying cell death and enhanced susceptibility of fungi to antifungal medications.[9,11,60]

Few clinical studies in the literature have investigated the specific fungal response to PDT. Some studies have reported inconsistent and even contradictory results between in vitro and in vivo experiments.[9] Therefore, in vitro experiments may not accurately predict the clinical response to PDT, and systematic clinical evaluation of specific fungal susceptibility to PDT is essential.

## Conclusion

PDT may serve as a potential therapeutic alternative to address increasing drug-resistance encountered in patients with cutaneous fungal infections. PDT is effective against onychomycosis, tinea capitis, PV, oral candidiasis, and VVC in patients with superficial fungal infections. However, PDT did not offer any advantages over conazoles for the treatment of tinea pedis and tinea cruris.[73] With regard to deep fungal infections, PDT combined with antifungal drugs was shown to improve treatment efficacy in patients with CBM, sporotrichosis, phaeohyphomycosis, MG, and mucormycosis.

To summarize, PDT is safe and effective and is occasionally useful as a prophylactic and cosmetic tool. Most adverse effects of PDT are limited, temporary, and tolerable. PDT monotherapy or PDT combined with oral antifungal medications may be a promising therapeutic strategy for the management of recurrent or severe cutaneous fungal infections.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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