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Protoporphyrin IX Associated with Visible Light for the Treatment of *Trichophyton rubrum* Causing Onychomycosis - An Updated Review

Matheus Alexandre da Silva Taliari[1], Andressa Costa Fontes[1], Fellipe Genasculi Araujo[2], Luis Lênin Vicente Pereira[1,3], Luciana Estevam Simonato[1,4], José Martins Pinto Neto[1,4], André Wilian Lozano[1,4], Nilton Cesar Pezati Boer[1], Wagner Rafael da Silva[1], Rafael Guerra de Aquino[1,2], Farid Jamil Silva de Arruda[2], Fábio Zanusso Prates[5], Noedi Leoni de Freitas[1,6], Jean Donizete Silveira Taliari[1,2,4], Rogério Rodrigo Ramos[1,2*]

[1]Universidade Brasil (UB), Fernandópolis, Brazil
[2]Centro Universitário de Santa Fé do Sul (UNIFUNEC), Santa Fé do Sul, Brazil
[3]Centro Universitário de Jales (UNIJALES), Jales, Brazil
[4]Fundação Educacional de Fernandópolis (FEF), Fernandópolis, Brazil
[5]Santa Casa de Votuporanga, Votuporanga, Brazil
[6]União das Faculdades dos Grandes Lagos (UNILAGO), São José do Rio Preto, Brazil

Corresponding author:
Rogério Rodrigo Ramos, Projected Road F1 s/n, Santa Rita Farm, Medical School, Universidade Brasil, Box: 15613-899, Fernandópolis, Brazil.
E-mail: rogerio.enfer@gmail.com

Abstract

Systemic medications used during the treatment of onychomycosis caused by Trichophyton rubrum may have relapse, making them costly and insignificant for the patient. Photodynamic therapy (PDT) is an advantageous therapeutic option for disease control, mainly due to the absence of risk of microbial resistance. The action of PDT is combined by three elements: photosensitizer (PS), visible light (VL) and molecular oxygen, leading to the formation of reactive oxygen species (ROS) or singlet oxygen formation ($^1O_2$), both ROS (type I mechanism) as $^1O_2$ (type II mechanism) induce damage and death to microbial cells. This research was proposed as a study through a non-systematic review, to investigate the action of PS "Protoporphyrin IX" (Pp IX) associated with visible light on T. rubrum, contemplating clinical and relevant data regarding the treatment of onychomycosis by PDT. PubMed survey was conducted from June 2021 to April 2022. The research strategy included clinical trials, randomized trials, systematic reviews, meta-analyses and reviews in English. Pp IX has affinity for T. rubrum, which is justified by the incorporation of Pp IX into the cell membrane, which led to inhibition by LV irradiation. Thus, the photodynamic process of Pp IX may lead to cell death by type I and II mechanisms. The data found are promising, however, new studies in vitro and in vivo are suggested, since few studies have been found related to the theme.

Keywords: *Trichophyton rubrum*; Onychomycosis; Phototherapy; Protoporphyrin IX; Low-level light therapy; Oxigen-reactive species; Singlet oxygen; Drug Induced Liver Injury; Roussel Uclaf Causality Assessment Method

1. Introduction

Onychomycosis, known as nail had, is an infection caused by dermatophytes, non-dermatophyte fungi (NDF) or yeasts. In particular, this disease is mainly affected by dermatophytes (90%), with *Trichophyton rubrum* as the main causative agent (71%). It usually presents with a white or yellowish-brown discoloration of the nail, oiclysis and/or thickening of the nail plate[1-4]. Due to these aspects, onychomycosis brings an aesthetic problem to the patient, consequently, ends up distancing itself from society and with low self-esteem affecting quality of life.

The contagion of the disease occurs by direct contact of the fungus with the nail through the distal subungueal area and/or the lateral nail plate (LNP), this means that the diseased nail can contaminate other healthy nails. This can be explained by the fact that the nail unit does not have effective cellular immunity, and is therefore susceptible to fungal infection[5]. In addition, fungal production of enzymes with proteolytic, keratinolytic and lipolytic activities helps to degrade keratin in the nail plate and this facilitates fungal invasion of the nail, increasing the risk of infection[6,7]. For Peres *et al*.[8], infections caused especially by dermatophyte *T. rubrum*, is related to the failure of the host's immune response or the ability of the pathogen to escape the defense system and thus remain in the superficial layers of the skin. It should also be added that the components of the fungal cell wall, such as galactomannas scans, may have immunosuppressive effects, and membrane transport proteins, important virulence factors that guarantee the success of colonization in favorable environments[9,10].

The growth mechanism of dermatophytes is related to keratinized tissue and nail pH. Fungi grow very well in a medium containing rigid keratin and are able to use this tissue as the only source of carbon and nitrogen. At alkaline pH, two subtilisins (Sub3 and Sub4) and metalloproteases of the family of fungalisins (family M36) are the main endoproteases secreted by dermatophytes, together with exopeptidases. The latter enzyme catalyzes the cleavage of the terminal peptide bond by releasing two aminopeptidase leucines from the M28 family (Lap1 and Lap2) and two dipeptidil peptidases from the S9 family (DppIV and DppV). In a medium with acid pH, dermatophytes secrete an aspitic protease of the peptin family (Pep1) as an endoprotease and tryptophytis of the sedolysine family, X-prolil peptidases and carboxypeptidases of the Family S10 as exoproteases[11,12,13]. These considerations point out that dermatophyte enzymes have the ability to hydrolyse keratin and survive in protein medium and are still resistant to acid and alkaline pH.

Conventional treatment of nail had involves topical or oral therapy. Topical treatment is more compatible with the patient, being devoid of adverse effects, as long as the infections are mild, but suffers a setback, which is inadequate penetration into the nail[14]. This factor can be explained by the formation of fungal biofilms, allowing fungi to avoid therapies and contribute to antifungal resistance[15]. In the case of persistent infection, oral treatment is used, although quite effective, they are hepatotoxic and cause drug interactions. It is noteworthy that these antifungal therapies often result in failure and commonly used antifungals have limited cellular targets. Resistant strains also appear, concomitantly with high-cost

treatments for long periods, with probable side effects, in addition to the recurrence of the disease after discontinuation of therapy[8,14,16].

The difficulties in the treatment of fungal infections by conventional methods have led to the search for a safer, more effective, easy-to-perform and more cost-effective treatment. While some medications only produce side effects or only fungistatic effects, photodynamic therapy (PDT) consists of the destruction of visible light (VL) living tissue in the presence of a photosensitizer (PS) and molecular oxygen (O_2) by response of reactive oxygen species (ROS) and singlet oxygen ($^1O_2$)[17,18]. Due to the adverse effects and setbacks observed in the need for a safe therapeutic option for nail had, the study aims to investigate the action of exogenous Protoporphyrin IX (Pp IX) associated with visible light on *T. rubrum*, contemplating clinical data and providing readers with an update on current approaches for the treatment of onychomycosis by PDT.

2. Insensibility of Conventional Treatment of Onychomycosis Associated with *T. rubrum*

The standard treatment for nail had, consists of the use of local (topical) and systemic (oral) drugs or a combination of both for 4 to 6 months. Due to the long period of drug treatment, the patient ends up generating lack of interest in therapy and, thus, the patient's adherence to treatment becomes ineffective and usually promotes side effects such as liver and kidney failure[19].

Usually, the patient seeks professional help when there are problems associated with onychomycosis, which include discomfort, difficulty wearing and wearing shoes, walking and aesthetic embarrassment in the nail segments in lower and upper fingers[20]. Infected nails can serve as a reservoir of fungi with potential spread to the feet, hands and groin and can spread to other family members if left untreated. It is important to emphasize that onychomycosis can result in disruption of skin integrity, providing a gateway to microorganisms that lead to the development of foot ulcers (diabetic foot), osteomyelitis, cellulitis and gangrene in diabetic patients[21]. In addition, the presence of sensitizing fungal/dermatophytic antigens in the nail lamina may predispose to other clinical conditions in individuals with onychomycosis. This includes asthma/sensitization of the respiratory tract and skin diseases such as atopic dermatitis, urticaria and erythema nodosum[22].

2.1. Local and Oral Therapy

For mild infections, local options are highlighted, amorolfine glazes 5% and cyclopirox 8%. Amorolfina is applied once a week, while cyclopirox is applied once a day[23]. Amorolfina has fungistatic and fungicide properties against dermatophytes, NDF and yeasts[24], but this drug is recommended for nail without matrix involvement and mild cases of distal and lateral subungual onycomycosis (DLSO) affecting up to two nails[25]. Cyclopyrus is a derivative of hydroxypyridon with broad-spectrum antifungal activity against *T. rubrum*, inhibiting metal-dependent enzymatic processes, including nutrient absorption, cell energy production, and intracellular peroxide degradation[26]. However, this last drug has a lower cure rate, with side effects such as periunual erythema and nail fold[22,27]. Therefore, the use of topical antifungals has low penetration in the nail unit, recurrences and reinfections are common[28].

Failure of topical treatment is indicated oral therapy with terbinafine (Lamisil), itraconazole (Sporanox, Sporaz, Orungal) and fluconazole (Diflucan, Celozol). Terbinafine, an antifungal agent of the alilamine group, inhibits fungal epoxidase esqualene, leading to the accumulation of squalene, responsible for its fungicide effect[29]. This drug is metabolized by cytochrome P450 enzymes (CYP450) and its concentration is decreased by rifampicin and increased by cimetidine[30] and warfarin can be potentiated and may present hemorrhagic events[31,32]. Therefore, drug interaction is limited and should be careful with the therapeutic combination, as it may affect the pharmacokinetic profile of other drugs.

This drug can be administered at 250 mg/day for 12 weeks or dosage of 500 mg/day for four weeks with pulse therapy and four weeks without pulse therapy[33]. During treatment, common adverse reactions may appear (Table 1). Severe adverse reactions are rare, but agranulocytosis, hepatitis, acute generalized exanthematic pustulosis and lupus erytheamsus[34] may arise.

Fluconazole is used at the dosage of 150-300 mg/week for more than six months, but is less effective[35]. It is essential to state that this drug has not been approved by the U.S. Food and Drug Administration (FDA) for nail, although it is approved in Europe for the treatment of onychomycosis[36,37], for representing a third-line therapy[38]. This drug has a long half-life, is predominantly excreted in urine and remains detectable on the nails for up to 6 months after discontinuation of therapy[39]. A high dose of 450 mg/week is observed for onychomycosis, believed to be due to its pharmacokinetic properties and advantage of improving treatment and reducing treatment costs[22].

The common adverse effects of fluconazole (Table 1) lead to discontinuation of fluconazole therapy 150 mg weekly or higher weekly doses, such as 300-450 mg[40]. Severe reactions to fluconazole are very rare, but occur during therapy such as polyneuropathy, thrombotic thrombocytopenic purpura, lower gastrointestinal tract bleeding, acute confusional state, and acute renal failure[41]. This same drug presents drug interactions, such as the use of rifampicin and cimetidine, which may present possible reductions in fluconazole levels and warfarin also presents hemorrhagic events[31,32].

Itraconazole is a triazole antifungal with a broad spectrum of activity against dermatophytes, yeasts and NDF, administered at a dosage of 400 mg/day for one week/month, with treatment duration of three months for the nails. This medicine is highly lipophilic and bioavailability increases after a meal. Seven days after the start of therapy, itraconazole is incorporated into the nail and detectable in the matrix and nail bed, and persists for up to 6 to 9 months after treatment[30,35]. This medicine is linked to the cytochrome P450 system (CYP3A4) and is responsible for the potential toxicity of itraconazole and drug interactions. In addition to these factors, adverse reactions are manifested (Table 1). After 4 weeks of continuous therapy, hepatitis tends to occur and severe liver dysfunction can be triggered, requiring liver transplantation[42].

As a result of this reality, monitoring of liver functions is recommended in patients who have been on continuous therapy for more than four weeks, associated with hepatotoxic drugs and pre-existing diseases. In case of congestive heart failure, itraconazole is contraindicated because of the increased risk of negative inotropic effects[43].

Itraconazole has significant drug interactions, so it should not be taken with benzodiazepines such as midazolam (Versed®) and triazolam (Halcion®), due to overaire sedation[31,32].

Compared to another drug, itraconazole is a stronger inhibitor of cytochrome P450 enzymes than fluconazole[44], however, both have more side effects and potential drug interactions than terbinafine[7,45,46].

Table 1. Adverse effects of systemic drugs during onychomycosis therapy.

Drugs	Drug whose metabolism is affected	Reactions	
		Common/Mild	Severe/Rare
Terbinafine	Cimetidine, rifampicin and warfarin	Rash, itching, hives, gastrointestinal symptoms, taste and liver enzyme changes.	Agranulocytosis, hepatitis, acute generalized exanthematous pustulosis, and lupus erythematosus
Fluconazole	Rifampicin, cimetidine and warfarin	Headache, rash, gastrointestinal complaints, insomnia, paraesthesia and dysesthesia	PNP, lower gastrointestinal bleeding, PTT, ARF and ACE
Itraconazole	Midazolam and triazolam	Headache and gastrointestinal symptoms	Hepatitis and severe liver dysfunction

Legend: polyneuropathy (PNP); thrombotic thrombocytopenic purpura (PTT); acute renal failure (ARF); acute confusional state (ACE).

2.2. Cognitive Considerations in Relation to Therapy

In severe cases of onychomycosis, such as LNP involvement, dermatophytomas or dystrophic onychomycosis, surgical or chemical intervention of the nail lamina associated with topical or systemic treatment with itraconazole and terbinafine[47] is indicated.

Treatment of onychomycosis requires several months of therapy, since nail growth is very slow, especially in the elderly. The choice of medication depends on the type and severity of onychomycosis and the comorbidities of the patient. In most cases, patients have DLSO due to dermatophytes involving the distal part of one or two large nails[48].

However, the use of systemic drugs is limited by hepatotoxicity and drug interactions, representing a safety concern, especially in people over 60 years of age. A 20% failure rate of oral antifungals and a high recurrence rate of 10-53 stand out. Factors that also contribute to the failure of therapy are patient susceptibility, resistant fungal growth pattern, presence of latent fungal spores on the nail, low bioavailability of the drug and lack of penetration of the drug into the nail[22,49-51].

The insensitivity of nail infection to antifungal therapy often leads to the need for an alternative therapy to fight *T. rubrum*, so researchers, as well as dermatologists, seek a beneficial treatment for nail had, a fruitful therapy with toxic levels only for the microbial agent, minimal side effects and low cost for the patient so that he does not give up therapy during the course of treatment, because of this, PDT is a therapy capable of consolidating the therapeutic option for the control of the fungal agent.

3. Drug-Induced Liver Injury in Nail Infection

The liver is a site where several medications are metabolized, a classic example are antifungals. One type of antifungal that deserves to be highlighted is terbinafine. This medicine is used to combat fungi causing onychomycosis, but liver injury may occur during treatment, damage known as drug-induced liver injury (DILI)[52,53]. DILI is defined as liver damage induced by a commercial or herbal medicine that leads to liver dysfunction[54].

This factor denotes that oral antifungals are associated with an incidence of DILI, about 4% for terbinafine, 1% for fluconazole and 2 to 4% for itraconazole[55]; however, these drugs can be fatal, especially in the elderly and long-term treatments[56].

The diagnosis of liver injury is a major challenge for physicians and is based on a combination of factors such as exclusion from other causes that can elevate biochemical liver tests and causality assessment methods, which can be based on expert opinion or standardized methods specific to the liver. In this sense, the Roussel Uclaf Causality Assessment Method (RUCAM) is indicated[53,57]. Currently, RUCAM is an instrument used to assist in determining specific causality of DILI, thus specifically assessing the probability of high levels of drug-induced liver-associated enzymes[52,58].

4. Photodynamic Therapy

Because it is a broad and complex field of a multidisciplinary nature (biochemistry, materials science, chemistry, engineering and medicine), PDT has been investigated for more than 100 years and, for this reason, scientific research has grown exponentially in the last two decades. PDT was introduced to act as a complementary approach to conventional therapies to reduce the recurrence of cellular damage and extend survival with minimal side effects[59-61]. Thus, it can be considered that PDT is a consolidated therapeutic modality that has its activity in the photooxidation (destruction of target cells) of biological matter, which results from the activity of ROS and $^1O_2$ (Figure 1). These species are generated in situ and cause cell death by LV (Figure 2) in the presence of PS and O_2[62].

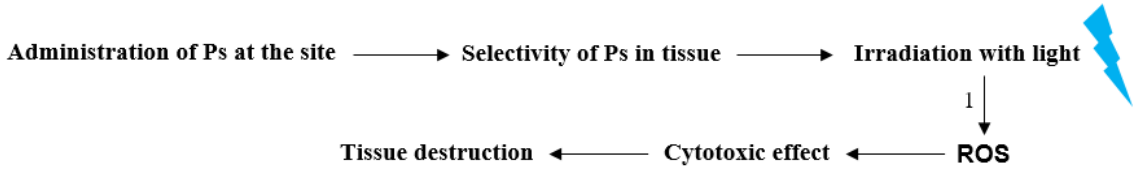

Figure 1. PDT simplified flowchart. Caption: (1) Photodynamic action; (ROS) reactive oxygen species.

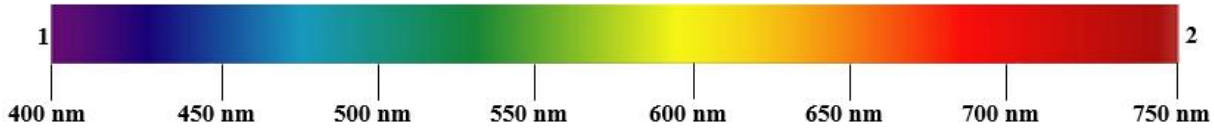

Figure 2. Visible spectrum of light (400-750 nm). **Legend:** (nm) nanometer; (1) ultraviolet spectrum below 400 nm; (2) infrared spectrum above 750 nm.

4.1. Photosensitizer "Protoporphyrin IX"

Currently, there are several PS for PDT, but few studies on basic structure and its activity, which makes the investigation of structure and activity of great interest in terms of photobiology. It is also added that the clinical future for the application of PDT will be highly dependent on efficient PS[63,64] with minimal toxicity in the dark, low mutagenic potential and highly chemically stable[65,66], which will contribute to the advancement and popularization of PDT. Regarding the previous approach, there is a need to seek PS of commercial origin and/or derived from low-cost synthesis, which provides better permeability and incorporation in both tissues and cells, with reduced photosensitive reaction capable of curing the lesion with minimal adverse reactions and restoring the normal structure and function of the tissue.

PS "Pp IX" (Figure 3) is a dye with the ability to absorb energy from one light source and transfer this energy to another molecule, presenting photodynamic activity[67,68]. The solubility of this PS appears to be one of the characteristics of relevance, since the photochemical and pharmacokinetic properties depend on it. Another relevant factor is that it occupies a special place in the porphyrin family due to its important role in various clinical-therapeutic applications, including PDT[69,70] for adhering to membranes and cellular components[71,72] and for having an intense light absorption peak around 405 nm (Soret band) and a much weaker absorption band at 635 nm[73], which allows its activation *in vivo* by red light, while blue, green or yellow light are used in superficial applications, for example on the skin[74-76], which makes Pp IX viable for both dermatological treatment and antimicrobial photodynamic inactivation.

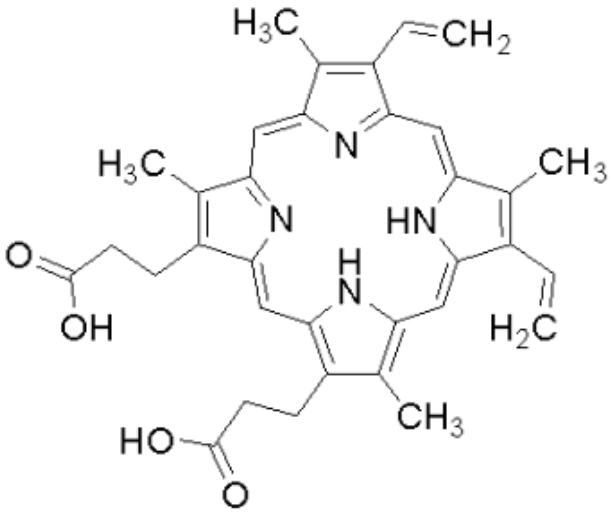

Figure 3: Molecular structure of Pp IX.

4.2. Mechanism of Action

The photodynamic process is initiated by the absorption of radiant energy. This irradiation should occur at an adequate wavelength (λ), i.e., PS should be irradiated in a spectral region where it has absorption bands. By absorbing a photon, PS reaches the excited state and, later, the chain of dynamic processes described in the modified Jablonski diagram occurs (Figure 4). In this process, different light sources can be used, such as white sunlight from solar irradiation (natural light) or preferably an artificial irradiation source that emits in the visible region (light-emitting diode (LED) or Lasers). However, the photodynamic process will be

proportional to the number of photons absorbed by the PS in the appropriate λ and consequently proportional to the intensity of emission of the source in the absorption λ of the respective PS[75,77,78].

In the photodynamic process, the PS that is in the fundamental state absorbs radiant energy by moving into the singlet excited state (^{1}PS*). After excitation, PS is driven to the excited triplet state (^{3}PS*) or can return to the fundamental state by phosphorescence without chemical alteration. In ^{3}PS* the species can generate ROS. These species can be generated by abstraction or absorption of electrons or hydrogens, leading to the formation of radicals (mechanism of action of type I). Also by deactivating ^{3}PS* by transferring energy to $^3O_2$ leading to the formation of $^1O_2$ (type II mechanism of action), both mechanisms (Figure 4) promote cell death[79-82].

PS and λ of the irradiation source are two inseparable elements in the therapeutic process of PDT, however, the selection of these elements are also related to the depth of tissue to be treated. In treatment with PDT, ultraviolet (UV) and infrared (IR) irradiation (IR) is excluded; UV for causing tissue damage and IV for reaching heat waves, being restricted to the LV region. For treatments to be performed in regions of greater depth in the tissue, it is necessary to radiate in red or near infrared, where light reaches greater penetration into the biological tissue. On the other hand, the treatments to be performed on the epidermis or dermis do not require λ greater penetration into the tissue, in this case, the use of blue and violet light is indicated for therapy, for not harming deeper tissues[83-85].

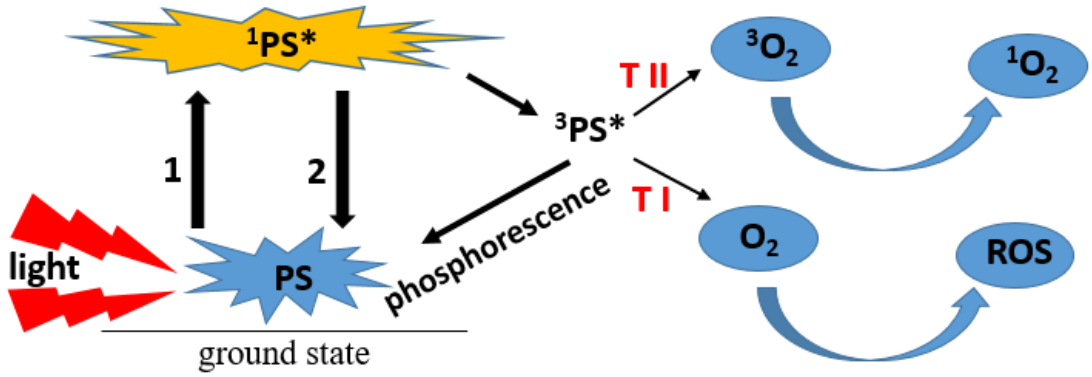

Figure 4: Simplified Jablonski diagram. Mechanism Type I and Type II of photosensitization. Caption: (PS) ground state photosensitizer; (1) absorption of radiant energy; (^{1}PS*) singlet excited state; (2) excited photosensitizer can return to ground state as fluorescence; (^{3}PS*) triplet state; (T I) Type I Mechanism; (T II) Type II Mechanism; ($^3O_2$) triplet oxygen; ($^1O_2$) singlet oxygen; (ROS) reactive oxygen species.

5. Photodynamic Action of the Photosensitizer Associated with Visible Light

Ramos *et al.*[18] demonstrated in their study the Pp IX dimethyl ester obtained by derivatization of Pp IX in an analogous procedure described by Uchoa *et al.*[86]. In the *in vitro* study by Ramos *et al.*, Pp IX homogenized with *T. rubrum* was irradiated with blue LED ≈ 400 nm. The samples were submitted to 12 cycles of 10 minutes of irradiation with LED. The authors reported that the control group had an average growth of more than 3.000 colony-forming units (CFU). On the other hand, the sample of *T. rubrum* + Pp IX with irradiation, there was an intensified reduction in the first six cycles. No significant differences were observed between the seventh and the other subsequent cycles, remaining between 0 and 1 CFU. Another

aspect, also very important, is that the authors described the incorporation of PS into *T. rubrum* by fluorescence microscopy. The internalization of Pp IX in the cell resulted in photooxidative damage when irradiated with λ of 400 nm, region in which this PS presents the band with the highest absorption intensity, the Soret band. The incorporation and internalization of PS in *T. rubrum* shows that the elimination of the fungal agent occurred by a photoinduced process, since this process is initiated by the transfer of hydrogens or electrons, radical reactions or electrophilic attack of singlet oxygen in cell membranes[18,87].

An advantage of the use of blue light (400-480 nm) is that this λ can reduce the proliferative activity of keratinocytes, modulating the immune responses of T cells and safely improving superficial infections[88,89].

Another approach to reduce the infectious process is red light with λ from 620 to 770 nm for deeper treatment of up to 6 mm, being able to stimulate mitochondrial activity and modulate the release of cytokines from macrophages[90,91].

The nanomaterial called carbon points (CDs) stands out. CDs are a new class of carbon-based fluorescent nanoparticles with physical and chemical characteristics. Researchers like Wu *et al.*[92] and Kang *et al.*[93] consider CDs an ideal candidate for drug delivery applications due to their photophysical properties, low toxicity, adjustable surface functionality and adaptive synthesis[92,93]. These particularities of CDs together with PS have gained research interest in PDT[94].

Amide crosslinking is a strategy that is based on interactions between carboxyl and primary amine groups. The factor that favors this bond is the EDC (1-ethyl-3-(3-dimethylamino) carbodiimide propyl). EDC is a zero-length reticultive that can be used in conjunction with N-hydroxyuccinimide (NHS) to efficiently produce amide bonds between two suitable molecules[95,96]. An *in vitro* study shows that Pp IX was previously covalently linked through carbodiimide chemistry, and also excitation of two photons and singlet oxygen, which evidences an important mechanism for PDT[97-101].

The incipience of scientific articles published on the proposed theme is in poor development not only in dermatology, but also in medical clinic and other areas of health, which is why it is essential to develop and publish exogenous Pp IX studies on *T. rubrum* with visible spectrum light treatment, to propagate current knowledge about a specific therapy of PDT for omnicomchonoosis.

Table 2 summarizes the final results of the therapy, but the PS acid 5-aminolevulinic acid (ALA). Endogenous photosensitizer, Pp IX, produced from its precursor ALA in the heme biosynthesis pathway is also important in the case of antimicrobial PDT application[102,103].

Table 2. Summary of the various forms of dermatophytosis treated with PDT.

Disease	Fungal species	PS	Final result	Reference
Interdigital mycoses	*T. mentagrophytes* *T. rubrum*	ALA (20% cream solution)	No clinical signs	Calzavara-Pinton *et al.*[104]
UR	*T. rubrum*	ALA	Growth inhibitory effect	Kamp *et al.*[105]
Onychomycosis	*T. rubrum*	ALA	Clinical and mycological healing	Piraccini *et al.*[106]
Tinea cruris	*T. rubrum*	ALA	100% healing rate	Sotiriou *et al.*[107]

Foot *Tinea*	*T. mentagrophytes* var.interdigitales *T. rubrum*	ALA cream	Absence of mycological signs after 3 treatments	Sotiriou *et al*.[108]

Legend: 5-aminolevulinic acid (ALA); unrevealed (UR).

6. Clinical and Future Perspectives

Light-on-tissue treatment is a safe, easy and effective therapeutic modality for various dermatoses, with lower cost, minimal side effects and superior efficacy compared to local or oral therapy in the treatment of patients with mycosis, atopic dermatitis, fungicides and others such as psoriasis, pityriasis, versicolor, chronic urticaria, palmoplantar pustulose and vitiligo. This therapeutic option prevents patients from suffering the side effects of local/oral therapy because it is a safe alternative without microbial resistance to the patient[109,110].

In addition, PDT has great potential in the field of tumor treatment due to its advantages, such as high treatment efficiency and strong selectivity, and brings new favorable clinical aspects, as well as a good prognosis and opportunities for future tumor therapies[111]. Another significant point is that PDT can activate the immune system through molecular patterns associated with damage (DAMPs) released or exposed to dead cells, which in turn stimulate innate and adaptive immunity, this being the first line of defense of the organism[61,112-114].

There is not much *in vitro* and *in vivo* research published on the photodynamic process of exogenous Pp IX with the combination of light devices in the visible spectrum for the inactivation of *T. rubrum*. Future issues, such as the high success rate and short-term therapy associated with Pp IX and light, should be researched to develop a safe protocol for the treatment of *T. rubrum* causing onychomycosis.

7. Conclusion

Drug treatment of onychomycosis requires several months of therapy, in addition to presenting adverse effects and recurrences. Due to these factors, PDT is a recommended therapeutic alternative for onychomycosis, because it does not present microbial resistance with minimal adverse effects at the site.

Pp IX together with visible light showed antimicrobial activity against *T. rubrum in vitro*, so it is suggested that PS may be a promising candidate in PDT for the treatment of onychomycosis. But since there is little evidence of Pp IX photosensitization on *T. rubrum*, more research with significant results is needed to justify the photodynamic process. Given this gap, research with elements of PDT (Pp IX, visible light and molecular oxygen "*T. rubrum*") are essential to develop and offer a therapy that not only satisfies the desire of the patient with onychomycosis, but also surprises him with healing and aesthetics, exceeding his expectations and improving the quality of life.

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DECLARATION OF POTENTIAL CONFLICT OF INTEREST

The authors declare no conflict of interest.

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