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Antimicrobial photodynamic therapy in onychomycosis management: A systematic review of clinical trials

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ABSTRACT

Objectives: Onychomycosis is a prevalent fungal nail infection often resistant to conventional antifungal therapies. Antimicrobial photodynamic therapy (aPDT) has emerged as a promising alternative, though its efficacy remains under investigation. This systematic review aimed to assess the effectiveness of aPDT in managing onychomycosis.

Methods: Conducted according to PRISMA guidelines and registered in PROSPERO (CRD42024520247), this review included clinical trials evaluating the antimicrobial efficacy of aPDT for onychomycosis. Searches were performed in PubMed, Scopus, Web of Science, Embase, Cochrane Library, ClinicalTrials.gov, and gray literature. Two reviewers independently screened, selected, and extracted data on study characteristics. Risk of bias was assessed using the Cochrane tool and Newcastle-Ottawa scale; certainty of evidence was evaluated using GRADE.

Results: Eighteen studies involving 591 participants (mean age: 54.2 years) met inclusion criteria. The most common light source was diode laser (450–700 nm), and photosensitizers included methylene blue, aminolevulinic acid, and methyl-5-aminolevulinate. aPDT significantly reduced onychomycosis severity (30–90 % OSI reduction) and achieved mycological cure rates up to 100 % when combined with fractional CO_2 laser. Clinical cure rates ranged from 20 % to 80 %, with notable improvements in nail appearance. Histological and microbiological analyses confirmed fungal reduction, and patient satisfaction was generally high. Overall, studies showed low risk of bias. The certainty of evidence was moderate for randomized controlled trials and low for non-randomized trials.

Conclusion: aPDT demonstrates promising potential in onychomycosis management, showing clinical and microbiological efficacy. However, variability in protocols and outcomes requires further standardized clinical trials to establish optimal treatment parameters.

1. Introduction

Onychomycosis is a highly prevalent nail disease globally, affecting approximately 5.5 % of the population [1,2]. This condition is characterized by a fungal infection of the nail, resulting in discoloration, and thickening of the affected nail plate [2]. Dermatophytes, notably *Trichophyton rubrum* or *Trichophyton mentagrophytes*, yeasts, and non-dermatophyte molds primarily affect the nail bed, matrix, and plate, particularly in adult toenails [2]. However, diagnosing and treating these infections pose significant challenges [3]. Moreover,

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onychomycosis can have adverse physical, emotional, and aesthetic effects, significantly impacting the patient's quality of life [4]. Similar fungal infections, often caused by zoonotic dermatophytes such as *Trichophyton mentagrophytes*, affect animals and pose comparable therapeutic challenges, highlighting the relevance of onychomycosis within a One Health framework [5–7]. The current conventional therapeutic options for onychomycosis include topical treatments, systemic (oral) therapy, and surgical intervention [2,8,9]. While oral antifungals are effective, they carry risks of hepatic toxicity, cardiac disturbances, poor patient compliance, and adverse drug interactions [10–12]. In contrast, topical antifungals are generally well-tolerated with minimal side effects, but their efficacy is limited due to poor penetration and absorption into the nail plate, leading to prolonged treatment durations and high recurrence rates [10,13,14]. Surgical procedures may not always provide substantial benefits, as they can alter the nail's appearance and impair long-term healing [9,10].

The management of onychomycosis faces challenges, particularly due to an incomplete understanding of its underlying mechanisms and the various factors that influence fungal growth and individual susceptibility [8]. These challenges contribute to the restricted effectiveness of conventional treatments and the high prevalence of the condition, emphasizing the need for more effective and safer alternative therapies [10]. One promising strategy is antimicrobial photodynamic therapy (aPDT) [15]. aPDT has been revealed as a promising procedure, showing antimicrobial properties, and is increasingly used for the treatment of infections of onychomycosis [16]. The therapy involves three key components:a photosensitizer, a light source, and molecular oxygen [16]. When the infected tissue is treated with the PS and exposed to light of a specific wavelength, it generates reactive oxygen species (ROS), heat, and activates the host immune system [17]. Recent studies have identified aPDT as an alternative treatment for various diseases [18–20], including cutaneous infections [21–23]. Thus, aPDT is an emerging and promising technique with growing evidence for its use in onychomycosis treatment. Given the global prevalence of onychomycosis, the systemic toxicity of oral treatments, and the challenges of topical therapies in penetrating the nail plate, alongside patient resistance to antifungals, a systematic review has highlighted the potential of aPDT for treating this condition [15]. However, the inclusion of various study types–such as clinical trials, case reports, and a single randomized clinical trial (RCT)–may limit the reliability of the findings. Since then, several clinical studies and RCTs have been published, providing a stronger foundation for conducting a more robust systematic review. Thus, this approach enables a more rigorous analysis and offers more solid evidence on the effectiveness of aPDT in treating onychomycosis. Therefore, this review aims to fill this gap and assess the efficacy of aPDT in managing onychomycosis.

2. Material and methods

2.1. Protocol and registry

This systematic review was conducted in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA 2020) guidelines [24] and the recommendations outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* [25], and based on previous publications [19,26]. The review protocol was registered in the *International Prospective Register of Systematic Reviews* (PROSPERO) under the registration number CRD42024520247.

2.2. Eligibility criteria

Studies were included if they met the following criteria: (a) studies involving adult participants diagnosed with onychomycosis; (b) studies evaluating the efficacy of aPDT for the treatment of onychomycosis, regardless of the type of photosensitizer, laser source, exposure duration, or power density; (c) studies reporting outcomes such as antimicrobial activity, mycological cure rates, clinical improvement, and adverse effects associated with aPDT; and (d) study designs encompassing randomized controlled trials, clinical trials, cohort studies, pilot studies, and case series with a minimum of 10 participants.

The exclusion criteria were as follows: (i) studies involving populations affected by fungal infections other than onychomycosis; (ii) studies investigating treatment modalities other than aPDT, including topical or systemic pharmacological therapies;

(iii) studies that did not report at least one of the predefined outcomes (mycological cure rate, antimicrobial activity, clinical improvement, or adverse effects); (iv) secondary research articles such as systematic reviews, meta-analyses, scoping reviews, narrative reviews, conference abstracts, and letters to the editor; and (v) duplicate publications or studies lacking full-text availability.

2.3. Search strategy

Searches were conducted across the PubMed, Scopus, Web of Science, Embase, and Cochrane Library databases. The search strategy was initially developed for PubMed and subsequently adapted for use in the remaining databases, with guidance from a specialized librarian to ensure methodological rigor (Supplementary Material – Appendix A). In addition to electronic searches, a manual screening of reference lists was performed to identify relevant studies that may not have been retrieved through database searches. To capture unpublished or ongoing studies, the ClinicalTrials.gov registry (www.clinicaltrials.gov) was also consulted. Furthermore, gray literature was explored via the System for Information on Gray Literature in Europe (SIGLE) database. No restrictions were applied to publication date or language. The electronic search was conducted independently by two reviewers (ROA and LORU) and included all articles indexed up to April 3, 2025.

2.4. Study selection and data collection

All retrieved studies were initially imported into an online reference management system (EndNote Web; Thomson Reuters Inc., Philadelphia, PA, USA), where duplicates were identified and removed. Titles and abstracts were screened based on predefined eligibility criteria. Two reviewers (ROA and LORU) independently assessed the full texts of studies deemed potentially eligible or when the abstracts lacked sufficient information for inclusion. In cases of disagreement, a third reviewer (GPN) was consulted to reach consensus. When necessary, corresponding authors were contacted for clarification on study design or to obtain missing data.

One reviewer extracted data, with independent verification by a second reviewer. Extracted variables included: author and year of publication, sample size, number of participants per group, participant demographics (age, sex), characteristics of the study population, intervention protocols, assessment methods, main outcomes, and conclusions. Specific parameters related to aPDT application were also collected, including the type of light source, photosensitizer (type and concentration), use of optical fibers, laser wavelength (nm), total energy delivered (J), energy fluence (J/ m^2), power density (mW/ m^2), and irradiation time.

The inter-reviewer agreement during the study selection process was calculated using the kappa (κ) score. Disagreements were resolved through discussion and consensus among all authors.

2.5. Quality assessment and risk of bias of individual studies

The risk of bias for each included study was assessed using tools appropriate to the specific study design. Two independent reviewers (ROA and LORU) conducted the quality assessments. Any discrepancies were resolved through discussion, and when consensus could not be reached, a third reviewer (GPN) was consulted.

For RCTs studies, the Cochrane Risk of Bias tool was employed,

evaluating key domains including random sequence generation, allocation concealment, blinding of participants and personnel, completeness of outcome data, and selective reporting. The evaluation followed the guidance outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*, version 6.5.0 [25]. Each domain was rated as "low risk" (yes), "high risk" (no), or "unclear risk" when information was insufficient or ambiguous. A study was considered to have a low overall risk of bias when all key domains for each outcome were judged as low risk. Studies with at least two domains rated as unclear were classified as having an unclear risk of bias, while those with one or more domains rated as high risk were deemed to have a high overall risk of bias.

For non-randomized studies, quality was assessed using the Newcastle–Ottawa Scale (NOS), which evaluates three main components: selection of participants, comparability of study groups, and ascertainment of the outcome. The NOS assigns a maximum of nine stars, with higher scores indicating higher methodological quality. Studies receiving five or fewer stars were considered to have a high risk of bias, while those with six or more stars were judged to have a low risk. The selection domain can contribute up to four stars, comparability up to two stars, and outcome assessment up to three stars [27].

2.6. Certainty of the evidence: grading of recommendations: assessment, development, and evaluation (GRADE)

The certainty of evidence for each outcome was independently evaluated by two reviewers (GPN and ROA) using the GRADE framework (http://www.gradeworkinggroup.org/), which is designed to assess the overall confidence in the effect estimates across studies included in a meta-analysis. This system classifies the quality of evidence into four categories: high, moderate, low, and very low, providing a transparent and structured method to support clinical recommendations [28].

Evaluation begins by considering the study design, whether randomized controlled trials or observational studies, followed by an analysis of five domains that may decrease the quality of evidence: risk of bias, inconsistency, indirectness, imprecision, and potential for publication bias. Additionally, certain factors may increase the rating, such as evidence of a large treatment effect, adequate control for confounding variables, and a clear dose–response relationship. Each domain was rated as having "no concerns," "serious concerns," or "very serious concerns," and these judgments informed the final classification of evidence certainty. A rating of "high" indicates strong confidence that the reported effect closely reflects the true effect, whereas a "very low" rating implies substantial uncertainty, with the actual effect potentially differing markedly from the estimate [28].

3. Results

3.1. Study selection

A total of 717 records were initially retrieved through comprehensive searches across multiple databases: 116 from PubMed/MEDLINE, 245 from Scopus, 136 from Embase, 186 from Web of Science, 33 from the Cochrane Library, and one additional record identified through manual searching. After removing duplicates, 348 studies remained for title and abstract screening. Of these, 22 studies were selected for full-text review to assess eligibility. Following full-text analysis, four studies were excluded based on the predetermined criteria, resulting in the inclusion of 18 studies: 10 randomized controlled trials [16,29–37] and 8 non-randomized clinical studies [38–45] (Fig. 1). The inter-rater reliability for the selection process demonstrated excellent agreement (kappa = 0.925) across the evaluated databases.

3.2. Characteristics of the studies

Table 1 presents the general characteristics of the studies included in this systematic review. The selected studies were published between 2010 and 2025 and involved sample sizes ranging from 10 to 72 participants, totaling 591 individuals with a mean age of approximately 54.2 years. The articles originated from different countries, such as Spain [16,29,30,33,34,36,38–40], Brazil [37,42–44], Egypt [31,41], Thailand [32], Israel [35], and Greece [45]. Regarding the characteristics of onychomycosis, confirmed cases included distal and lateral subungual onychomycosis in toenails (DLSO) [29,30,32,34,37–39,41,44,45], bilateral ungual onychomycosis [35], and severe onychomycosis affecting the big toenail [33,40,42,43]. In general, clinical and mycological diagnoses were based on typical clinical signs–such as scaling, subungual debris, onycholysis, and discoloration–and laboratory tests, including PAS staining, fungal culture, and polymerase chain reaction (PCR) test.

3.3. Lasers parameters and photosensitizer

The laser parameters and photosensitizer types used are described in

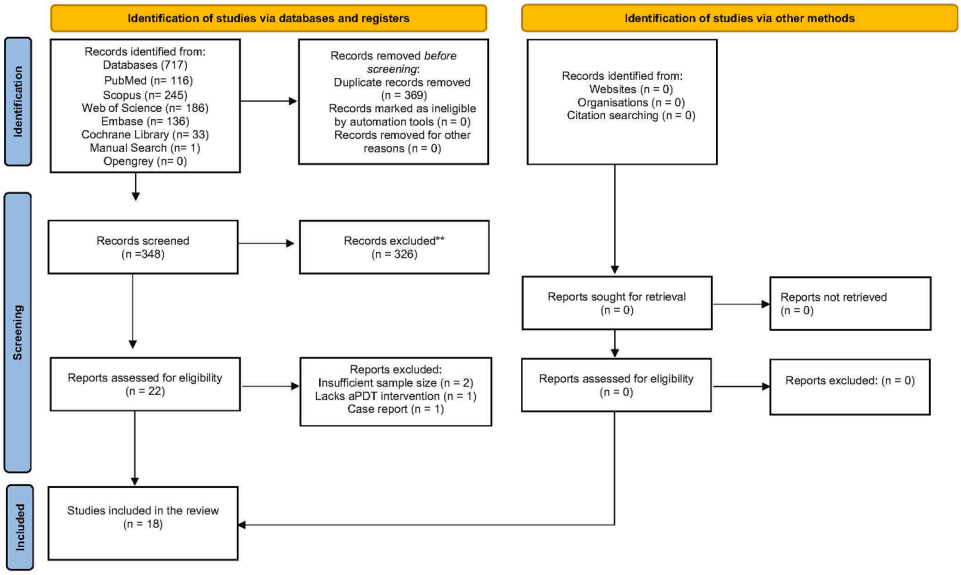

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart.

Table 1
General data of the included studies in the systematic review.

Authors, year (local)	Groups Number of subjects (n) and sex (M/F):	Mean Age (years)	Characteristics of the Participants Included	Application Protocol	Assessments	Outcomes: Results	Conclusion
Navarro-Pérez et al., 2025 (Spain)	aPDT-TB + Ciclopirox 8% 10 (M:7/ F:3)	66.10 ± 10.29	Patients over 18 years old, diagnosed via microbiological culture and PCR in a specialized diabetic foot unit, were included. Nail samples were required to be sufficiently large for both tests and were cultured in Sabouraud dextrose agar for 1 to 3 weeks in an external laboratory.	At the first visit, patients were prescribed Ciclopirox 8% and received hygiene recommendations. Follow-ups occurred every two weeks for two months, with aPDT applied during the second, third, and fourth visits. Each session involved 10 min of diode laser activation following nail preparation and application of a photosensitizer.	Onychomycosis Severity Index (OSI); type of onychomycosis; clinical cure.	*Baseline/ 3 Months/6 Months* OSI- N° events of 10 (%) Mild: 1(10)/ 3 (30)/ 8(80); Moderate: 1 (10)/ 4(40)/ 1(10); Severe: 8(80)/ 3 (30)/ 1 (10) Type of onychomycosis- N° events of 10 (%) Distal: 1(10)/ 3 (30)/ 0(0); Distal-Lateral: 4 (40)/ 3 (30)/ 0 (0); Superfcial:1(10)/ 1(10)/ 1(10); Dystrophic: 4 (40)/ 3 (30)/ 0 (0) Clinical cure- N° events of 10 (%): 0 (0)/ 0 (0)/ 9 (90)	This study demonstrated clinical improvement, mycological cure, efficacy, and safety of ciclopirox 8% combined with photodynamic therapy using toluidine blue gel. Over six months, this approach proved to be a viable treatment option for managing ONM in patients with diabetes.
García-Oreja et al., 2025 (Spain)	aPDT -TB gel with red-laser 12 (M:7; F:5)	M: 58.3 F: 41.7	Patients over 18 years with a confirmed diagnosis of onychomycosis, established by microbiological culture and/or a previously conducted PCR test.	Patients received hygiene recommendations, including daily washing with pH 5.5 soap, thorough foot drying, and footwear disinfection. Weekly visits over 9 weeks involved diode laser therapy PDT. Each session included nail debridement, disinfection, 3 minutes of 810 nm irradiation, photosensitizer application (5 min), 10 min of 635 nm laser activation, cleaning, and 3 minutes of 1064 nm final irradiation.	Clinical and mycological cure; Observation for adverse effects during treatment, like pain, subungual hematoma, or subungual wound. (b) The emergence of recurrences at 3- and 6-months post-treatment.	The clinical, mycological, and complete cure 100%: 12/12 patients and 17/ 17 nails Negative microbiological culture 100%: 12/12 Positive PCR 66.7% (8/12) patients and 64.7% (11/17) nails. No patient experienced pain 75% (9 out of 12) did not have any other adverse effects 8.3% (1/12) subungual hematoma 16.7% (2 out of 12) subungual hematoma and injury to the laser-treated nails	The combination of diode laser therapy and red-laser PDT with toluidine blue gel seems effective and safe for the treatment of mild, moderate, and severe onychomycosis.
Gómez et al., 2024 (Spain)	I. aPDT -MB 0.1%: 10 (M:7; F:3) II. aPDT -MB 2%: 10 (M:8; F:2) III. aPDT - Flavin mononucleotide 0.1%: 10 (M:6; F:4) IV: aPDT - Flavin mononucleotide 2%: 10 (M:5; F:5)	I: 61.5 II: 63 III: 59 IV: 57	Adult patients with moderate dermatophyte onychomycosis affecting the first toenail, with mycological diagnosis of It included male and female adult patients with moderate dermatophyte onychomycosis affecting the first toenail, with mycological diagnosis	The cream emulsion was prepared by incorporating deionized water, urea, MB/FMN, glycerin, vaseline, and lanolin. The emulsion was applied to the lesion and maintained in direct contact for 5 days before each weekly laser irradiation, secured by an occlusive bandage for 12 h per day. The study consisted of 10	Onychomycosis Severity Index (OSI); Nail involvement; Mycological cure rate; Complete cure rate.	OSI – *Baseline / 27 weeks / 35 weeks* I. 16.3 ± 7.79 / 10.3 ± 6.9 / 7.4 ± 6.2 / II.14.5 ± 6.5 / 5.8 ± 5.5 / 2.4 ± 2.3 III. 14.9 ± 6.9 / .5 ± 6.6 / 4.9 ± 4.7/ IV. 12.1 ± 7.4 / 9.1 ± 8.1 / .9 ± 6.6 Nail involvement *(%) – Baseline / 27 weeks / 35 weeks* I. 36.0 ± 19 / 23.0	aPDT using cream integrating 2% w/w MB or 0.1% w/w FMN together with 40% w/w urea can be a very promising novel topical treatment for toenail onychomycosis with a high efficacy, safety and tolerance.

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Table 1 (*continued*)

Authors, year (local)	Groups Number of subjects (n) and sex (M/F):	Mean Age (years)	Characteristics of the Participants Included	Application Protocol	Assessments	Outcomes: Results	Conclusion
			of DLSO by fungal culture and histological examination of nail clipping using PAS staining.	weeks of treatment, involving weekly laser applications, resulting in a total of 10 sessions. Each session was conducted with a 7-day interval between applications.		± 14.9 / 17 ± 13.9 II. 15.0 ± 7.8 / 9.5 ± 8.3 / 5.2 ± 5.1 III. 26.1 ± 23.2 / 20.2 ± 9.2 / 16.3 ± 16.2 IV. 32 ± 26.4 / 23.2 ± 16.8 / 21.8 ± 17.7 Mycological cure N° events of 10 (%) *27 weeks / 35 weeks* I. 0 (60) / 7 (70) / II. 3 10 (30) / 7 (70) / III. 5 10 (50) / 7 (70) / IV. 4 (10 40) / 6 (60) Complete cure N° events of 10 (%) *27 weeks / 35 weeks* I. 0 (0) / 3 10 (30) / II. 2 (20) / 5 (50) / III. 1 (10) / 7 (70) / IV. 2 (20) / 3 (30)	
Alberdi et al., 2023 (Spain)	I. 40% urea combined with aPDT mediated Methylene blue: 10 (M:6; F:4) II. Fr Er:YAG laser combined with aPDT mediated Methylene blue:10 (M:6; F:4)	I. 62.0 ± 14.4 II. 53.6 ± 14	Patients with moderate first-toe toenail onychomycosis, with mycological diagnosis of distal and lateral subungual onychomycosis (DLSO) by histological examination of nail clipping using PAS staining and fungal culture.	I. 40% urea ointment was employed to soften the plates of the affected nails and vaseline was applied in periungual skin. Once the urea and vaseline were applied, the nail was covered by an occlusive dressing for 12 h at night. After any of the pretreatment used, a PDT mediated by MB (MB/PDT) was carried out in 9 sessions, with one session every 2 weeks. II. Fractional ablative treatment was carried out using the Pixel® 2940 nm Module. During laser application, the handpiece was kept static, and that is why the laser beams always reached the same points creating holes on the nail plate surface. Nine pulses per area treated were applied scanning the entire affected surface.	Onychomycosis Severity Index (OSI); Degree of improvement; Nail involvement; Histological analysis (PAS).	OSI - *Baseline / 28 weeks / 40 weeks* I. 12.2 ± 5.3 / 2.7 ± 1.8 / 3.7 ± 3.6 II. 15.9 ± 6.1/ 7.1 ± 6.2 / 8.5 ± 5.6 Degree of improvement N° events of 10 (%) *28 Weeks / 40 weeks* No: I. 0 10 (0) / 0 (0); II. 3 10 (30) / 3 (30) Mild: I. 1 10 (10) / 0 (0); II. 1 event of 10 (10) / 4 (40) Moderate: I. 5 (50) / 2 10 (20); II. 1 (10) / 10 (0) Outstanding: I. 4 (40) / 6 (60); II. 5 (50) / 3 (30) Nail Involvement *(%) – Baseline / 28 week / 40 week* I. 38.0 ± 20.8 / 11.5±8.5 / 4.5 ± 4.0 II. 31.5 ± 21.5 / 10.5 ± 8.6 / 13.5 ± 8.8 Histological Analysis N° events of 10 (%) *28 Weeks / 40 weeks* PAS stain (+): I. 8 (80) / 3 (30) / II. 7 (70) / 6 (60) PAS stain (-): I. 2 20) / 7 (70) / II. 3 (30) / 4 (40)	Although both pretreatments favor the action of aPDT for the treatment of onychomycosis, the use of urea at 40% is more efective in the medium term.

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Table 1 (*continued*)

Authors, year (local)	Groups Number of subjects (n) and sex (M/F):	Mean Age (years)	Characteristics of the Participants Included	Application Protocol	Assessments	Outcomes: Results	Conclusion
						Patients' satisfaction N° events of 10 (%) *Dissatisfed/Fairly satisfied/Very satisfied /Extremely satisfed:* I. 1 (10)/6 (60)/3 (3)/ 0 (0) / II. 0(0) /3(30) /5(50) /2 (10)	
Sobhy et al., 2022 (Egypt)	I. aPDT-MB 17 (M:1; F:16) II. aPDT-MB + Fractional CO_2 laser: 17 (M:2; F:15) III. Fractional CO_2 laser: 17 (M:3; F:14)	I: 38.9 ± 9 II: 39 ± 13 III: 43 ± 11.7	Patients with positive fungal cultures, patients refusing to take oral antifungal agents or with contraindication to oral antifungal agents and patients who did not respond to previous oral antifungal agents given for at least 6 months.	All patients were instructed to apply topical urea 20% 12 h before the session to soften the nails. Group I patients were treated using 6 bimonthly sessions of aPDT- MB 2% and IPL Group II patients were treated using 6 bimonthly 2 passes of fractional CO_2 laser followed by aPDT Fractional CO_2 laser was applied over the affected nails Group III patients were treated using 6 bimonthly sessions of fractional CO_2 laser.	Clinical improvement was assessed by a blinded independent observer by calculating the proximal nail plate diameter (PND); Mycological evaluation; Mycological examination, Mycological examination, standardized digital clinical and dermoscopic photographs.	Mycological evaluation - N° events of 17 (%) *Candida / Trichophyton violaceum / Trichophyton mentagrophytes / Trichophyton rubrum*: I: 11 (64.7) / 2 (11.8) /3 (17.6) /1 (5.9) II: 12 (70.6) / 2 (11.8) / 0 (0) / 2 (11.8)/ III: 12 (70.6) / 5 (29.4) / 1 (5.9) /0 (0) Clinical assessment of improvement: *Proximal nail diameter (%) - Baseline / 6 months* I: 12.94 ± 15.32 / 59.71 ± 17.36 II:19.71 ± 17.54 / 78.71 ± 21.86 III: 23.24 ± 21.21 / 65 ± 22.36 Patient satisfaction I: 5.53 ± 1.42; II: 9.47 ± 0.62; III: 7.0 ± 1.41	The fractional CO_2 laser and photodynamic monotherapy, and their combination achieve high success rates, good patient satisfaction and safety profile. Fractional CO_2-assisted aPDT is associated with the highest improvement over either fractional CO_2 or aPDT alone.
Navarro-Bielsa et al., 2022 (Spain)	I. aPDT - MAL II. aPDT + Topical Terbinafine III. aPDT + systemic Terbinafine 20 (M:11/ F:9)	59.4 ± 17.1	All patients had a microbiological diagnosis and some of them had been previously treated with oral and/or topical antifungals without success.	The treatment protocol involved 3-h sessions of methyl aminolevulinate photodynamic therapy (MAL-PDT) under occlusion, followed by irradiation for 7–9 min. Six sessions were conducted at intervals of 1 or 2 weeks. To optimize photosensitizer penetration, nail plates were softened with a 40% urea ointment applied 7 days prior to each PDT session. In Groups II and III, PDT was combined with systemic terbinafine (250 mg/day) and with topical terbinafine application, respectively.	Cure Rates; Microbiological cure.	Clinical resolution (%) I: 6 events of 7 (85) / II: 3 of 3 (100) / III: 7 of 8 (87) Clinical and microbiological resolution (%) I: 5 of 7 (71) / II: 3 of 3 (100) / III: 5 of 8 (62.5) Persistence (%) I:1 of 7 (14); II: 0 of 3 (0); III: 2 of 10 (20) Microbiological evaluation *Trichophyton rubrum/ A. terreus/ T. mentagrophytes/ A. sydowii/ A. fumigatus/ F. oxysporum*	aPDT is a therapeutic alternative for onychomycosis and can be administered either in monotherapy or combined with antifungals, allowing for a reduction in the duration and possible adverse effects of antifungal treatment and achieving higher cure rates than those obtained with either treatment alone.

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Table 1 (*continued*)

Authors, year (local)	Groups Number of subjects (n) and sex (M/F):	Mean Age (years)	Characteristics of the Participants Included	Application Protocol	Assessments	Outcomes: Results	Conclusion
						N° events of 20 (%): 11(55)/ 3(15)/ 2 (10)/ 2 (10)/ 1 (5)/ 1 (5) After aPDT I- Events (%): 0 (0)/ 1 (14) / 1 (14)/2 (28)/ 1 (14)/ 1 (14) II- Events (%): 2 (66)/ 0 (0)/ 1 (33)/ 0 (0)/ 0 (0%)/0(0%) III- Events (%): 5 (50)/ 1 (1)/ 0 (0)/ 0 (0)/ 0 (0)/ 0 (0)	
Abdallah et al., 2022 (Egypt)	I. aPDT-MB II. $FrCO_2$ -aPDT-MB 21 (M:4/ F:17)	32.5 ± 9.89	Patients with similar fungal infections on at least two toenails, one on each foot, were enrolled. Diagnosis confirmed through clinical evaluation, mycological analysis, and fungal isolation. Participants had no prior physical or laser treatments and had not used systemic or topical antifungals for at least six months before the study.	Both used 2% methylene blue (MB) as a photosensitizer, activated by IPL PDT. The left toenail underwent FrCO2 laser pre-treatment, while the right was softened with 40% urea ointment before each session. Treatments were conducted biweekly over six sessions following infection confirmation.	Direct microscopy, fungal cultures, clinical evaluation.	Mycological cure rate/ Perfect nail improvement/ *Partial improvement - N° events of 21 (%):* Week 24 *(3 months post-treatment):* I: 11(57.1)/ 4 (19)/ 6 (33.3) II: 16 (76.2)/ 6 (33.3)/ 10 (52.4) Mycological cure rate N° events of 21 (%) *Week 36:* I: 19 (83); II: 21 (100)	Both treatments effectively reduced the severity of onychomycosis with a high degree of safety and tolerability.
Bowornsathitchai et al., 2021 (Thailand)	I. aPDT-MB: 15 (M:3; F:7) II. 5% amorolfine nail lacquer: 12 (M:3; F:5)	I. 67.2 ± 15 II. 56 ± 9.8	Adult patients, aged between 18 and 90 years, with distal and lateral subungual toenail onychomycosis (DLSO) diagnosed clinically and mycologically. Patients with a limitation of systemic antifungal use or refused to take systemic antifungal medication, the diagnosis was made when at least one clinical and one laboratory criteria were met. Toenails with discoloration patches or streaks, onycholysis, subungual hyperkeratosis and debris, and nail plate thickening.	Participants both in I and II groups were instructed to use 40% urea cream with occlusion for five consecutive nights prior to attending each appointment at a clinic every two weeks. In group I: the treatments were given every two weeks for a total of six sessions, with the last session on week 10. In II participants were instructed to filing nails before each weekly application of the lacquer was particularly emphasized to ensure the best penetration. AMO treatment was continued for 22 weeks up until the last assessment.	Onychomycosis severity index (OSI); mycological and clinical cure rate and patient's satisfaction.	I / II Mycological cure rate (%) 11 events of 15 (73.3%) / 8 events of 12 (66.67%) Clinical cure rate (%) 4 events of 15 (26.7%) / 2 events of 12 (16.7%) Clinical and mycological cure (%) 4 events of 15 (26.7%) / 2 events of 12(16.7%) Patients' satisfaction *Dissatisfied / satisfied / Satisfied / Extremely Satisfied: Events of 15(%)* I. 1 (6.67) / 2 (13.33) /8 (53.33) / 4 (26.67) *Events of 12* II. 2 (16.67) / 3 (25) / 5 (41.67) /2 (16.67) OSI *Baseline / 6 weeks / 10 weeks / 14 weeks / 22 weeks* I: 14 / -2 / -3 / -4 / -3 II: 6 / 0 / 0 / 0 / 0	aPDT-MB appears to be a promising and safe alternative treatment for non-dermatophyte onychomycosis especially in patients with contraindications for systemic antifungal drugs and tend to have greater improvement when compared with topical amorolfine.

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Table 1 (*continued*)

Authors, year (local)	Groups Number of subjects (n) and sex (M/F):	Mean Age (years)	Characteristics of the Participants Included	Application Protocol	Assessments	Outcomes: Results	Conclusion
Alberdi et al., 2020a (Spain)	I. aPDT-MB + TN: 10 (M:5; F:5) II. aPDT-MAL + TN: 10 (M:7; F:3)	I. 67.5 II. 66.4	Patients confirmed diagnosis of onychomycosis by mycological analysis; Severe onychomycosis in the big toe; Age equal to or over 18 years old; Normal results on liver function tests; Absence of contraindications for the treatments used MB or MAL; Absence of serious medical conditions, liver or kidney failure; Not being pregnant or breastfeeding; Have not used antifungals in the last 6 months, or medications that could interact with terbinafine.	All patients received 250 mg/day of oral terbinafine for 12 weeks, in addition to preparing their nails with 40% urea before each treatment session to increase the penetration of the photosensitizer. Group I received PDT with methylene blue, while Group II received PDT with methyl aminolevulinate. Both groups were irradiated with an LED lamp for 10 min. Nine sessions of PDT were carried out over 16 weeks at two-week intervals.	Clinical assessment using the Onychomycosis Severity Index (OSI); Digital photographs before and during treatment; Assessment of mycological culture; Histological analysis (PAS diastase staining).	Evolution of OSI scores *Baseline / After 52 weeks* I. 24.2 ± 4.6 / 0.7 ± 0.6 II. 18.5 ± 10.1 / 2.1 ± 2.0 Degree of clinical improvement *16 weeks / 40 weeks / 52 weeks* I. 49.6 ± 19.5 / 88.2 ± 13.2 / 67.0 ± 34.5 II. 60.8 ± 37.6 / 67.0 ± 34.5 / 89.2 ± 25.8 Nail involvement *Baseline / After 52 weeks* I. 64.8 ± 24.3 / 1.7 ± 1.6 II. 63.6 ± 41.6 / 6.0 ± 5.5 Histological analysis- N° events of 10 (%) *Baseline / After 52 weeks* *PAS staining (+)* I. 10 (100) / 0 (0) II. 10 (100) / 10 (100) PAS staining (-)-N° events of 10 (%) I. 0 (0) / 10 (100) II. 1 (10) / 0 (90)	Both modalities resulted in significant and similar improvements in clinical cure and treatment of nails affected with severe onychomycosis, without major adverse complications. In conclusion, aPDT is an effective method to accelerate the healing process mediated by terbinafine as it has a synergistic effect.
Alberdi et al., 2020b (Spain)	I. aPDT-MB: 10 (M:6; F:4) II. aPDT-MAL: 10 (M:9; F:1)	I. 63.6 II. 64.7	Patients with mild to moderate signs of distal and lateral subungual onychomycosis in the first toe; Infection confirmed by PAS (periodic acid-Schiff) staining and microbiological culture to identify only dermatophytes as causative agents; Onychomycosis Severity Index (OSI) approximately 13; Approximately 35% nail involvement.	Both groups received protection of the skin around the nail with petroleum jelly to prevent injury. Affected nails were pretreated with 40% urea for two weeks. Then, patients in G1 received application of 2% methylene blue on the nail and adjacent area, leaving the product in contact for 3 min. And in G2, methyl aminolevulinate was used, applied to the nail under occlusion and protected from light for 3 h. Then, irradiation with an LED lamp occurred for 10 min in both groups, repeating the protocol nine times at two-week intervals.	Clinical assessment; Onychomycosis Severity Index (OSI); Mycological analyses; Fungal cultures; Biopsy.	Evolution of OSI scores *Baseline / 40 weeks* I. 12.1 ± 5.4 / 3.6 ± 3.2; II. 14.8 ± 6.0 / 5.4 ± 4.4 Degree of clinical improvement- N° events of 10 (%) Nail invovement - *Baseline / 40 weeks* I. 37.5 ± 20.4 / 14.0 ± 3.6; II. 33.0 ± 18.4 / 14.5 ± 12 Cure rate in 40 weeks N° events of 10 (%) *Mycological Clinical / Full heal / Treatment success / Clinical improvement* I: 7 (70) / 7 (70) / 0 (0) / 0 (0) II: 6 (60) / 4 (40) / 1 (10) / 1 (10) Histological analysis N° events of 10 (%) *Baseline / 40 weeks* PAS staining (+) I. 10 (100) / 3 (30) II. 10 (100) / 4	aPDT mediated by MB or MAL is a safe and effective method, with satisfactory results in the treatment of mild to moderate nail onychomycosis.

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Table 1 (*continued*)

Authors, year (local)	Groups Number of subjects (n) and sex (M/F):	Mean Age (years)	Characteristics of the Participants Included	Application Protocol	Assessments	Outcomes: Results	Conclusion
						events of 10 (40) *PAS staining (-):* I. 0 events of 10 (0) / 7 events of 10 (70) II. 0 events of 10 (0) / 6 events out of 10 (60)	
Alberdi et al., 2019 (Spain)	I. aPDT-MB: 20 (M:4; F:16) II. IPL: 20 (M:9; F:11)	I: 64.4 II: 64.1	Previous treatment with oral and/or topical antifungals without success, presence of comorbidity and/or polypharmacy that could generate risk when combined with systemic antifungals, negative for antifungal treatment.	The nails were prepared with prior cutting by a podiatrist and softening with 40% urea, followed by the application of 2% methylene blue for 3 min on their surface, removal of residues and cleaning with 70% alcohol, and the application low-power diode laser for 5 min in G1, and the application of ultrasonic gel followed by irradiation with an intense pulsed light system in G2, repeating both every 1-2 weeks for up to eight sessions.	Microbiological analysis of fungal growth; clinical analysis (color, thickness and adherence of the nail to the nail bed); and OSI (Onychomycosis severity index)	Evolution of OSI scores *Baseline / 16 weeks / 28 weeks* I. 13.1 ± 8.6 / 6.2 ± 6.4 / 4.1 ± 4.7 II. 17.3 ± 7.9 / 4.1 ± 2.1 / 2.7 ± 2.0 Evolution of the mycological response (%) *PAS (+) Culture (+)* *After:8 sessions -12 weeks post-treatment:* I: 25% with PAS (+) Culture (-) II: 20% with PAS (+) Culture (-) Complete cure of patients- N° events of 20 (%) *After 8 sessions / After 12 weeks post-treatment* I: 10 (50) / 14 (70) II: 12 (60) / 16 (80)	Both photodynamic therapies mediated by methylene blue and intense pulsed light therapy proved to be effective, safe and well tolerated in the treatment of onychomycosis. Both approaches resulted in significant improvements in both the clinical and mycological appearance of the affected nails, with a notable reduction in Onychomycosis Severity Index scores over the treatment period.
Koren et al., 2018 (Israel)	I. aPDT-ALA: 30 II. Amorolfine nail lacquer: 26	49	Patients with typical clinical finding and positive mycological culture of bilateral toenail onychomycosis.	G1: Patients had 20%-ALA applied to the toenails and kept under occlusion using an opaque shield for 3 h. At the end of the incubation period, red light. All patients received 6 treatment sessions at 3-week intervals. G2: Patients' toenails were painted with 5% amorolfine nail lacquer, and the patients were instructed to re-apply the nail lacquer once a week.	Microbiologic test, fungal cultures, Satisfaction rate.	Percentages of positive mycological cultures- N° events of 30 (%) *3 months / 9 months* I. 15 (50) / 25.2 (84) II. 13 (50) / 22.1 (83) Patient Satisfaction I. 3.27 ± 0.52 / -2.97 ±0.52 II. 3.27 ± 0.24 / 2.88 ±0.34	The treatment with aPDT-ALA offers a safe and effective alternative for managing onychomycosis, delivering promising outcomes comparable to conventional therapies.
Morgado et al., 2017 (Brazil)	aPDT - Aluminium-Phthalocyanine Chloride- NE-AlClPC): 20 (M:8; F:12)	53.3 ± 14.7	Patients > 18 years of age, and laboratory diagnosis of onychomycosis.	Four PDT sessions were repeated every fifteen days. Prior to the first session, patients were instructed to use a 40% urea topical solution for one week to enhance the permeation of the photodynamic sensitizer. The PS, a nanoemulgel containing 65 μM AlClPc, was applied to the dorsal side of the infected nail and left for 15 min to allow	Clinical cure; mycological cure.	Clinical cure - N events of 20 (%) 12 (60) Mycological cure- N events of 20 8 (40)	The aPDT-NE-AlClPC presents a promising alternative for onychomycosis treatment. Although conventional oral and topical therapies show variable efficacy, this protocol stands out for its safety and effectiveness, making it a valuable option in clinical practice.

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Table 1 (*continued*)

Authors, year (local)	Groups Number of subjects (n) and sex (M/F):	Mean Age (years)	Characteristics of the Participants Included	Application Protocol	Assessments	Outcomes: Results	Conclusion
				sufficient permeation. After removal of the nanoemulgel, the nail was exposed to red LED irradiation.			
Gilaberte et al., 2017 (Spain)	I. aPDT-MAL: 22 (M:15; F:7) II. Placebo (pPDT): 18 (M:9; F:9)	I: 56.5 II: 59.7	Patients with any type of Onychomycosis that met one of the following criteria: prior treatment with oral and/or topical antifungals unsuccessfully, presence of comorbidity and/or polypharmacy which can generate risk if combined with systemic antifungals therapy; or refusal to undergo antifungal treatment.	Three weekly treatment sessions with MAL-PDT or PDT with placebo, that is, irradiation only. And on both nail plates were softened with 40% urea ointment before PDT sessions, in addition to being sanitized in the pre-treatment with 70% alcohol, and after lighting the area treated was protected from light for 24 h.	Assessment of clinical cure after 36 weeks of follow-up using the Onychomycosis Severity Index; cultures microbiological; impact on quality of life.	I / II Complete clinical cure (%) 4 events of 22 (18.18) / 1 of 18 (5.56) Reduction in disease severity in OSI > 75% 9 events of 22 (40.91) / 3 of 18 (16.67) Microbiological Cure 7 events of 22 (31.8) / 2 of 18 (11.1) Improved quality of life (points) *Before and after:* 39.27- 43.36 (12.96) / 34.72- 39.22 (10.45)	The study shows statistical similarity between 40% urea + aPDT-MAL and 40% urea + pPDT in treating onychomycosis. However, specific findings suggest this approach may be a viable alternative for managing onychomycosis.
Tardivo et al., 2015 (Brazil)	aPDT-MB + TB 2%: 62	-	Patients with diagnosed of onychomycosis.	The protocol initially involved superficial scraping of the affected nail to remove any debris or surface material, followed by the application of a photosensitizing solution. After allowing a 5-minute incubation period for optimal photosensitizer absorption, the nail was irradiated with superficial light for 3 minutes. The number of sessions varied between 1 and 22, with treatments occurring once a month. The frequency and total number of sessions were adjusted based on the severity of the onychomycosis and the rate of nail growth.	Microbiological and clinical analysis.	Elimination of fungal infection- N events of 62 (%) *Complete* 28 (45) *Partial* 25 (40) *No change* 9 (15)	This study demonstrated encouraging results, with a significant favorable response rate of patients treated. Furthermore, the absence of adverse side effects such as pain, burning or discomfort during treatment is a positive point.
Figueiredo Souza et al., 2014 (Brazil)	I. aPDT-MB: 40 II. Fluconazole: 40	I: 57 II: 49.8	Patients with onychomycosis of the distal and lateral subungual nail diagnosed clinically and mycologically; Patients confirmed by direct microscopic examination of subungual material; Patients with positive mycology or culture.	For 24 weeks, G1 (MBLED/PDT) received a placebo capsule per week and a PDT session with 2% methylene blue aqueous solution every 15 days, as did G2, who received 300 mg of oral fluconazole per week and PDT sessions with placebo (hematoxylin diluted 1:10) with an interval of 15 days between sessions.	Clinical and mycological cure.	Clinical and mycological cure- N events of 20 (%) *With abrasion / without abrasion* *Baseline* I. 0 (0)/ 0 (0) II. 0 (0)/ 0 (0) *12 months:* I. 12 (66.7)/ 20 (90.1) II. 10 (45.6)/ 10 (45.6)	aPDT-MBLED is a safe, effective, and well-tolerated treatment for onychomycosis, with high patient adherence. The statistically significant difference in efficacy underscores its superiority over conventional treatments like fluconazole.
Souza et al., 2014 (Brazil)	I. aPDT-MB in SDSO: 11 (M: 7; F: 4) II. aPDT-MB in	I. 54.2 II. 48.8	Clinical signs of onychomycosis including discoloration, nail	Patients were treated with fortnightly sessions of 2% methylene blue	Mycological evaluation; Clinical assessment (physical signs, changes in	I/II Clinical response - N events of 11 (%) *Mild clinical*	The results of this study confirm that aPDT-MBLED is safe and effective, with a

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Table 1 (*continued*)

Authors, year (local)	Groups Number of subjects (n) and sex (M/F):	Mean Age (years)	Characteristics of the Participants Included	Application Protocol	Assessments	Outcomes: Results	Conclusion
	MDSO: 11 (M: 5; F: 6)		plate dystrophy, subungual debris, or onycholysis; Patients with positive mycology, culture or microscopy.	aqueous solution on the lesion, irradiated with a light-emitting diode device at night for six months. and hyperkeratotic lesions or dermatophytomas were treated with a rotary abrasive device with a 3 mm diamond tip.	color, texture and integrity of the nail).	*response* 12 weeks: 5 (45)/: 0 (0) 24 and 48 weeks: 0 (0)/ 0 (0) *Moderate clinical response:* 12 weeks: 3 (27.3)/ 0 (0) 24 and 48 weeks: 0 (0)/ 7 (63.6) *response marked:* 12 weeks: 3 (27.3)/ 0 (0) 24 weeks: 5 (45.5)/ 0 (0) 48 weeks: 4 (36.4)/ 7 (63.6) *Complete clinical response:* 12 weeks: 0 (0)/ 4 (36.4) 24 weeks: 6 (54.5) / (0) 48 weeks: 7 (63.6) / 11 (100)	favorable outcome in the treatment of SODS caused by *T. rubrum.* Finally, MB facilitates the diagnosis of the presence of fungal biofilm on the nail plate and nail bed.
Sotirou et al., 2010 (Greece)	aPDT- ALA 30 (M: 20; F:10)	59.6	Patients with clinical features of distal and lateral subungual toenail onychomycosis; Positive direct microscopic examination for fungal elements; Identification of *T. rubrum* in cultures of Sabouraud dextrose agar; Concomitant conditions that did not allow systemic treatment with anti-fungal agents.	For 10 consecutive nights, the nail plate was treated with 20% urea ointment under occlusion. Subsequently, patients underwent three treatment sessions, with two-week intervals between them. In each session, 20% 5-aminolevulinic acid was applied under an occlusive dressing to the entire nail bed area, followed by red light treatment.	Clinical cure Mycological evaluation.	Clinical Assessment - N events of 30 (%) *Clinical cure:* 12 months: 13 (43); 18 months: 17 (57) *No clinical cure:* 12 months: 11 (37); 18 months: 29 (63) Mycological examination (%)- N events of 30 *Negative:* 12 months: 13 (43); 18 months: 17 (57) *Positive:* 12 months: 11 (37); 18 months: 29 (63)	aPDT offers an effective, safe alternative for treating onychomycosis in patients unsuitable for systemic antifungals. It acts locally, avoids systemic side effects, and permits repeated treatments without cumulative or mutagenic risks.

aPDT: Photodynamic therapy; ALA: 5-aminolevulinic acid; FMN: flavin mononucleotide; IPL: Intense Pulsed Light; MAL: Methyl-5-aminolevulinate; MB: Methylene blue; MBLED: Methylene blue light emitting diode; MDSO: Mild to moderate distal and lateral subungual onychomycosis; OSI: Onychomycosis severity index; PCR: Polymerase chain reaction; PDT: Photodynamic therapy; pPDT: Placebo photodynamic therapy; SDSO: Severe Distal-Lateral Subungual Onychomycosis; TN: Terbinafine; TB: Toluidine blue; VAS: Visual Analogue Scale.

Table 2. The diode laser was the most commonly used, reported in 89 % (n = 16) of the studies used the diode laser [16,29,33,34,36–40,42–45] while 11 % (n = 2) employed the Intense Pulsed Light (IPL) [31,41]. The wavelengths used ranged from 450 to 700 nm, with energy fluence from 12 to 120 J/cm^2. Laser application duration ranged between 300 and 798 s, and power density varied from 20.6 to 150 mW/cm^2. Output power ranged from 200 to 3100 mW, with a total applied energy of up to 75 J. The diameter of the optical fiber used ranged from 16 μm to 4000 μm. Regarding the photosensitizing agents used in aPDT, methylene blue (MB) was the most frequently employed [16,29–34,37,41,43,44], followed by methyl-5-aminolevulinate (MAL) [33,34,36,40], toluidine blue (TB) [38,39], 5-aminolevulinic acid (ALA) [35,45], aluminum-phthalocyanine chloride (AlClPc) [42], and flavin mononucleotide (FMN) [29].

3.4. General outcomes related to aPDT for onychomycosis management

3.4.1. Onychomycosis severity index (OSI)

Nine studies evaluated treatment outcomes using the Onychomycosis Severity Index (OSI), reporting progressive clinical improvement throughout the treatment period [16,29,30,32–34,36,38,41]. Among these, six studies demonstrated a significant reduction in disease severity, with an average OSI decrease of approximately 70 % [16,29,30,34,38,41]. One study reported an even greater reduction of 90 % [33]. In contrast, two studies showed more modest improvements, with OSI reductions of 30 % [32] and 40 % [36]. Notably, all studies except for Navarro-Pérez et al. (2025) [38] used 40 % urea cream as a pre-treatment adjunct prior to laser or light-based therapy, highlighting its potential role in enhancing treatment efficacy.

Table 2
Laser and photosensitizer parameters of the eligible studies.

Author/Year	Light source	PS/ concentration	Wavelength (nm)	Energy fluence (J/cm^2)	Power density (mW/cm^2)	Irradiation time (s)
Navarro-Pérez et al., 2025	Diode laser	TB 2%	635	37	18-50	600
García-Oreja et al., 2025	Diode laser	TB 2%	810-1064	125	NR	600
Gómez et al., 2024	Diode laser	MB and FMN: 0.1% and 2%	660 FVN: 450	37	MB: 61.6 FVN: 20.6	MB: 600 FVN: 1800
Alberdi et al., 2023	Diode laser	MB 2%	635	37	70	600
Sobhy et al., 2022	IPL	MB 2%	560 - 700	12	NR	180
Navarro-Bielsa et al., 2022	Diode laser	MAL 16%	630	37	30	420-540
Abdallah et al., 2022	$FrCO_2$-assisted IPL	MB 2%	640	18	NR	420
Bowornsathitchai et al., 2021	Diode laser	MB 1%	630-640	120	150	798
Alberdi et al., 2020a	Diode laser	MB 2% MAL 16%	635	37	62	600
Alberdi et al., 2020b	Diode laser	MB 2% MAL 16%	635	37	62	600
Alberdi et al., 2019	Diode laser	MB 2%	670	10	200	300
Koren et al., 2018	Diode laser	ALA 20%	630	75	70-100	NR
Morgado et al., 2017	Diode laser	AlClPc 65 μM	660	30.9	51.5	600
Gilaberte et al., 2017	Diode laser	MAL 16%	635	37	70	420-600
Tardivo et al., 2015	Diode laser	MB and TB 2%	600 -750	18	100	180
Figueiredo Souza et al., 2014	Diode laser	MB 2%	630	18	100	180
Souza et al., 2014	Diode laser	MB 2%	630	18	100	180
Sotiriou et al., 2010	Diode laser	ALA 20%	570 -670	40	40	300-600

ALA: 5-aminolevulinic acid; AlClPc: Aluminium-Phthalocyanine Chloride; FMN: Flavin Mononucleotide; IPL: Intense pulsed light; MAL: Methyl aminolevulinate; MB: Methylene blue; NR: No reported; TB: Toluidine blue.

3.4.2. Microbiological and histological outcomes

Histological evaluation of nail samples was conducted using Periodic Acid-Schiff (PAS) staining to detect fungal elements [16,29,30,33]. Studies demonstrated a significant reduction in PAS-positive staining over time following aPDT. When MB was used as the photosensitizer, a 70–75 % reduction was observed [16,29,39,34]. When aPDT with MB was combined with terbinafine, the mycological response reached 90 % [33]. Furthermore, the combination of MAL-based aPDT and antifungal therapy resulted in complete elimination of PAS-positive staining [33]. Several studies evaluated fungal culture outcomes over time, consistently demonstrating a significant mycological response following aPDT treatment [30–32,34–37,39,42,45]. Most studies reported average mycological cure rates between 70 and 80 % [32,34,35,37,40,41]. One study documented a moderate cure rate of approximately 60 % [45], while two others reported lower rates near 45 % [42,43]. In contrast, significantly lower outcomes were seen in one study, with a 25 % cure rate [31]. In addition, one study showed a 100 % mycological cure rate at the end of treatment [39].

For the photosensitizing agents, conventional aPDT protocols mediated by MB generally demonstrated mycological cure rates ranging from approximately 70 % to 85 % [32,34,37,41]. When combined with fractional CO_2 laser ($FrCO_2$), the mycological cure rate reached 100 % [41]. aPDT mediated by MAL showed mycological response rates varying from 40 % [36,42] to 70 % [40]. Additionally, when MAL-aPDT was combined with terbinafine, the mycological effectiveness increased to 100 % [40]. For ALA-aPDT interventions, studies reported mycological activity rates ranging from 50 % to 60 % [35,45].

3.4.3. Clinical improvement and cure rates

Clinical evaluation revealed that a significant proportion of patients with onychomycosis showed moderate to exceptional improvement following aPDT treatment [30,33,34,38,41]. Several studies reported high clinical cure rates following aPDT treatment, with values ranging from approximately 90 % to 100 % [38,39] and around 80 % in others [37,40]. Cure rates of approximately 70 % were documented in a broader group of studies [16,29,33,34,44,45], while moderate outcomes around 60 % were observed in a few cases [30,42,45]. One study reported more modest cure rates near 50 % [41], and some documented lower rates, ranging from 20 % to 35 %, notably in patients who had previously failed to respond to antifungal therapy [31,32,36].

Conventional aPDT protocols employing MB have shown clinical cure rates ranging from approximately 70 % to 80 % in cases of toenail onychomycosis of all severities–mild, moderate, or severe [16,33,34,44], as well as in distal and lateral subungual onychomycosis cases [37]. Other studies have reported lower cure rates of 50–60 % in patients with moderate dermatophyte onychomycosis affecting the first toenail, confirmed as DLSO by mycological diagnosis [29,30,41]. Cure rates as low as 30–35 % have been reported, particularly in patients who had not responded to previous oral antifungal treatments [31,32]. For aPDT mediated by MAL, a clinical cure rate of 60 % was reported in patients with mild to moderate DLSO [34], increasing to 90–100 % when combined with terbinafine [33,40]. However, a much lower cure rate of 20 % was observed in patients with a history of unsuccessful oral and/or topical antifungal treatments [36]. In studies involving TB-aPDT, clinical cure rates reached 90–100 %, even among patients treated at specialized diabetic foot units [38,39]. When using ALA mediated aPDT, a cure rate of 60 % was reported in patients with distal and lateral subungual toenail onychomycosis [45].

3.4.4. Patient satisfaction pain assessment and quality of life

Patient satisfaction was assessed in four studies [30–32,35]. High levels of satisfaction–including ratings of "Very Satisfied" and "Extremely Satisfied"–were reported across all groups, indicating a generally positive patient experience, with slight advantages observed in the aPDT-treated groups. Pain assessment using the Visual Analogue Scale (VAS) showed a reduction in pain, with comparable average pain scores between the group treated with antimicrobial photodynamic therapy (5.3 ± 3.2) and the group treated with antimicrobial ointment alone (4 ± 2.6) [35]. Additionally, one study reported a 12.96 % improvement in patients' quality of life, which was significantly higher compared to the placebo group (pPDT) [36].

3.5. Antimicrobial photodynamic therapy approaches

3.5.1. Effect of aPDT to pharmacological drug

Three included studies evaluated the efficacy of antimicrobial photodynamic therapy as an adjunctive approach to conventional pharmacological treatment for onychomycosis [33,38,40]. All studies reported high rates of clinical success, regardless of the type of photosensitizing agent used: 2 % TB [38], 2 % MB [33], or 16 % MAL [33,40].

Notably, the combination of aPDT with 16 % MAL and topical terbinafine demonstrated higher cure rates compared to aPDT alone or its combination with systemic terbinafine therapy [40]. When comparing the efficacy of methylene blue-mediated antimicrobial photodynamic therapy (2 % MB-aPDT) to that of conventional antifungal treatment with fluconazole, significantly higher clinical and mycological cure rates were observed with aPDT [37].

3.5.2. Effect of aPDT and lasertherapy

The effects of antimicrobial photodynamic therapy and/or laser therapy in the treatment of onychomycosis were investigated in three studies [30,31,41]. All studies employed 2 % MB as the photosensitizing agent and reported high clinical cure rates and favorable mycological responses. When comparing the efficacy of methylene blue-mediated aPDT to intense pulsed light laser therapy, both modalities demonstrated therapeutic effectiveness; however, aPDT showed superior performance regarding improvements in OSI scores and mycological outcomes [16]. Moreover, when aPDT was combined with fractional CO_2 laser therapy, the studies observed enhanced therapeutic efficacy compared to aPDT alone, suggesting a synergistic effect between the two approaches [31,41].

3.5.3. Effect of aPDT and amorolfine nail lacquer

Two studies evaluated the efficacy of antimicrobial photodynamic therapy mediated by different photosensitizing agents in comparison to the use of 5 % amorolfine-based antifungal nail lacquer for the treatment of onychomycosis [32,35]. In one study, aPDT mediated by 1 % MB demonstrated greater efficacy in treating onychomycosis caused by non-dermatophyte fungi, especially in cases of moderate severity and over a short treatment duration, when compared to amorolfine lacquer [32]. Conversely, the study conducted by Koren et al. 2018 [35], which tested 20 % aminolevulinic acid (ALA-aPDT) in patients with severe onychomycosis, found no significant differences between the treatment groups in terms of mycological cure rates, pain intensity, or patient satisfaction.

3.5.4. Different protocols of aPDT photosensitizing agents

Three studies compared different photosensitizers used in aPDT for the treatment of onychomycosis [29,33,34]. The comparison between 2 % MB and 16 % MAL demonstrated high efficacy for both agents, with no statistically significant differences, regardless of whether they were combined with terbinafine treatment [33,34]. Similarly, the comparison between MB and FMN at concentrations of 0.1 % and 2 % revealed that both 2 % MB and 0.1 % FMN achieved the highest mycological and complete cure rates, again without significant differences between them [29]. In addition, when evaluating combinations of photosensitizing agents, one study investigated the use of aPDT with a blend of 2 % MB and 2 % TB for the treatment of fungal nail bed infection, reporting 45 % complete clearance and 40 % partial clearance [43].

3.5.5. Other interventions with aPDT use

One study compared 40 % urea and fractional Er:YAG laser as pretreatments for MB-aPDT in moderate toenail onychomycosis [30]. Both methods improved clinical and mycological outcomes by week 28, but only the urea group-maintained progress at week 40. Urea showed higher cure rates (70 % vs. 40 %) and was more effective in the medium term. No side effects were observed [30]. Another study evaluated the safety and effectiveness of photodynamic therapy using Aluminium-Phthalocyanine Chloride in nanoemulsions for treating onychomycosis [42]. As the first clinical trial using nanomedicine-based aPDT for this condition, it showed 60% clinical cure, no adverse effects, and 40 % mycological cure among healed lesions. The local, noninvasive approach avoids systemic side effects and may be safely repeated without inducing fungal resistance [42].

3.6. Risk of bias in included studies

The risk of bias analyses, presented in Fig. 2 (for RCTs) and Table 3 (for non-randomized clinical studies), evaluate the methodological quality of the included clinical studies. Among the randomized controlled trials, seven studies were classified as having a low risk of bias [16,29–31,33,35,36], while three studies were considered to have a high risk of bias [32,34,37]. A critical concern identified was selection bias, with three studies lacking clear information regarding allocation concealment [34,35,37]. Additionally, blinding of outcome assessors was either not described or insufficiently reported in five studies [16,29,30,34,37], and one study explicitly stated that outcome assessments were not blinded [32]. Despite these limitations, the remaining domains assessed generally indicated a low risk of bias (Fig. 2). The clinical studies were assessed for quality using the Newcastle-Ottawa Scale, and all included studies were classified as having a low risk of bias, with scores ranging from 6 to 9 stars on the NOS criteria (Table 3). However, minor methodological limitations were identified across studies. These included issues related to sample selection [38,39,42,43,45], limited comparability due to lack of adjustment for additional confounding factors [38,39,42–45], and insufficient follow-up duration, such as evaluation performed only 30 days after intervention [43].

3.7. Level of evidence by Grade approach

In this review, randomized clinical trials were rated as having “moderate” certainty, primarily due to downgrading in the inconsistency domain, which reflected methodological heterogeneity across studies. In contrast, non-randomized studies were rated as having “low” certainty, due to downgrades in both the inconsistency and imprecision domains, the latter associated with the relatively small number of patients evaluated (n = 197). Details on the evaluation of each GRADE domain are provided in Table 4.

4. Discussion

aPDT has emerged as a promising approach for the treatment of dermatological fungal infections such as onychomycosis, whose management is often hindered by the limitations of conventional therapies [46,47]. To adress these challenges, this systematic review evaluated 18 eligible clinical trials, demonstrating the efficacy of aPDT as a safe and effective alternative for onychomycosis management. The findings demonstrated that aPDT, whether used as a standalone or adjunctive treatment, achieves high clinical success rates across different stages of infection, showing effective action against resistant dermatophyte biofilms.

The analysis of the clinical findings showed that the application of aPDT resulted in significant improvements in the clinical parameters of onychomycosis, contributing to the progressive resolution of the infection - clinical cure [16,29,32–34,36,41,44], and in reducing the area affected by onychomycosis [29–31,33,34]. These results corroborate the promising potential of aPDT as a therapeutic strategy, especially in contexts where surgical interventions and the prolonged use of systemic antifungals present significant challenges [48]. From a clinical point of view, onychomycosis represents a complex and challenging condition, characterized by intrinsic factors that hinder therapeutic success [2]. These factors include the deep localization of the fungus in the nail plate, which acts as a physical barrier against the effective penetration of topical antifungals, often resulting in subtherapeutic concentrations at the site of infection [49]. In addition, systemic antifungal treatments are associated with a number of limitations, including drug interactions, adverse effects, contraindications and the need for prolonged therapies, factors that often compromise patient adherence to the therapeutic protocol [50,51]. Another critical aspect that adds to the complexity of treatment is the presence of fungal biofilms, highly resistant structures that not only make it difficult to completely eradicate the infection, but

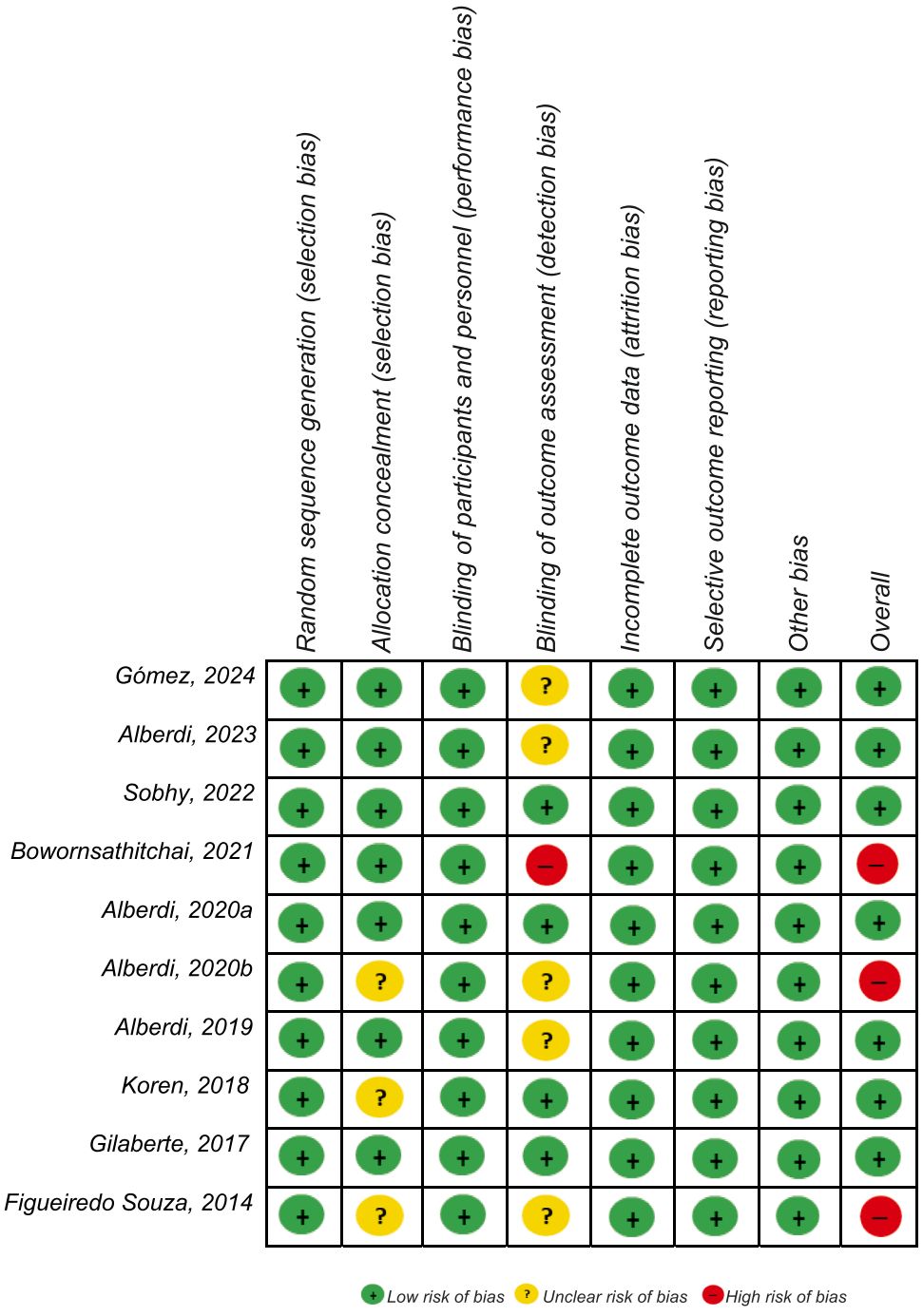

Fig. 2. Overview of Risk of Bias Evaluation Utilizing the Cochrane tool.

also contribute significantly to recurrence and therapeutic failures [10]. In this context, aPDT presents itself as an innovative approach by combining its antimicrobial action with a favorable safety profile, without the systemic side effects commonly associated with conventional antifungals [49]. In addition, aPDT's ability to directly target fungal structures, even in hard-to-reach places, could represent a considerable advance in overcoming the limitations imposed by traditional treatments [2,48].

The efficacy of aPDT in eliminating microorganisms is attributed to the mechanism by which light emitted from laser or light-emitting diode (LED) devices activates photosensitizing molecules. In the presence of oxygen, this activation leads to the generation of ROS and singlet oxygen, which trigger phototoxic and oxidative reactions, resulting in pathogen destruction and structural disruption of biofilms [46,52]. Additionally, the elevated temperature induces toxic levels of adenosine triphosphate and oxygen, leads to the disruption of the fungal mitochondrial membrane potential and ultimately inhibits fungal growth until it ceases entirely [53]. From a microbiological perspective, aPDT has demonstrated significant efficacy in reducing classical onychomycosis pathogens, especially *Trichophyton rubrum*, a dermatophyte well-known for its high resistance to conventional antifungal agents [54]. Most studies have evaluated the ability of aPDT to eliminate fungal cultures, with a focus on this dermatophyte [16,30–36,40,44], reporting significant mycological reductions, with some protocols achieving rates above 70 % elimination of the fungal load [16,30,33,34,44]. One of the most advantageous aspects of aPDT in the management of onychomycosis is

Table 3
Risk of bias in the selected non-randomized clinical trials.

Studies	Selection				Comparability		Outcome			Total
	Exposed Cohort	Non exposed cohort	Ascertainment of exposure	Outcome of interest not present at start	Main Factor	Additional Factor	Assessment of outcome	Follow-up long enough	Adequacy of follow-up	
Navarro-Pérez et al., 2025	☆	0	☆	☆	☆	0	☆	☆	☆	7
García-Oreja et al., 2025	☆	0	☆	☆	☆	0	☆	☆	☆	7
Navarro-Bielsa et al., 2022	☆	☆	☆	☆	☆	☆	☆	☆	☆	9
Abdallah et al., 2022	☆	☆	☆	☆	☆	☆	☆	☆	☆	9
Morgado et al., 2017	☆	0	☆	☆	☆	0	☆	☆	☆	7
Tardivo et al., 2015	☆	0	☆	☆	☆	0	☆	0	☆	6
Souza et al., 2014	☆	☆	☆	☆	☆	0	☆	☆	☆	8
Sotirou et al., 2010	☆	0	☆	☆	☆	0	☆	☆	☆	7

Table 4
Evidence profile: Antimicrobial photodynamic therapy in the treatment of onychomycosis.

Quality assessment								
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty	Explanations
10	randomized trials	not serious	serious[a]	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect.	⨁⨁⨁◯ MODERATE	[a]Studies presented high methodological differences.
8	clinical trials	not serious	serious[a]	not serious	serious[b]	all plausible residual confounding would reduce the demonstrated effect.	⨁⨁◯◯ LOW	[a]Studies presented high methodological differences. [b]Total number of people evaluated was 197.

its ability to promote efficient disinfection without inducing antimicrobial resistance mechanisms [55]. Unlike conventional antifungal therapies, in which resistance can be attributed to specific mutations or adaptations, aPDT uses reactive oxygen species, such as singlet oxygen and free radicals, as mentioned above, which attack multiple cellular targets, including lipids, proteins and nucleic acids. This broad action makes it difficult for the treated microorganisms to survive and adapt [31,56].

The selection of the light source plays ios critical for the effectiveness of aPDT. In this systematic review, most of the evaluated studies employed diode lasers, except for two studies that utilized IPL [31,41]. LEDs offer advantages such as affordability, ease of use, and minimal heat generation; however, they are limited by their narrow wavelength spectrum [10]. IPL, on the other hand, stands out as a versatile polychromatic technology broadly used in dermatology due to its ability to treat various conditions by adjusting wavelength, intensity, and pulse duration, making it a viable alternative for aPDT applications [57]. However, it is important to note that aPDT, when applied alone using IPL, demonstrated only modest antifungal activity and a low cure rate in the treatment of onychomycosis [31,41]. This limited efficacy may be attributed to the thickness and compact structure of the nail plate, which hinders the penetration of both light and photosensitizer into the nail bed, where the fungal infection resides. In contrast, the combination of aPDT with fractional $FrCO_2$ laser provided significantly superior results [31,41]. $FrCO_2$ facilitates the formation of microchannels in the nail plate, enhancing permeability and allowing more effective delivery of the photosensitizer and light to the infected area. Additionally, $FrCO_2$ stimulates tissue regeneration, which may further support the resolution of the infection, particularly in cases refractory to conventional treatments [31].

Regarding the photosensitizing agents used, MB was the most commonly used, appearing in 56 % of the studies (n = 10). MB-mediated aPDT protocols consistently demonstrated favorable mycological and clinical responses, with average cure rates ranging from 70 % to 85 %. When combined with adjunctive therapies such as fractional CO_2 laser [41] or systemic antifungals like terbinafine [33,38], cure rates increased substantially, often reaching 90–100 %, suggesting a synergistic effect. Other photosensitizers, including MAL (22 %; n = 4) and ALA (11 %; n = 2) [35,45], showed more variable outcomes, with isolated aPDT protocols leading to moderate efficacy (40–70 %) but significantly improved results when combined with antifungal agents [33,40]. TB-mediated aPDT (11 %; n = 2) also showed excellent outcomes [38,39], mainly in patients with comorbidities such as diabetes [38]. Nevertheless, the clinical effectiveness of aPDT appears to be influenced not only by the type of photosensitizer but also by the severity and refractoriness of the infection. Lower response rates (20–45 %) were observed in patients with recalcitrant onychomycosis or a history of failed antifungal treatments, demonstrating the limitations imposed by fungal resistance and nail bed involvement [32,36]. These findings suggest that while aPDT, especially when mediated by MB or used in combination therapies, holds significant therapeutic potential, patient-specific factors and disease chronicity remain critical determinants of treatment success.

Furthermore, studies comparing different photosensitizing agents have shown that both MB and MAL can achieve high clinical and mycological cure rates [33,34], mainly when combined with antifungal therapies or adjunctive treatments such as fractional lasers or 40 % urea pretreatment [30,33,34]. Overall, MB-based protocols stood out for their consistent efficacy, good tolerability, and greater volume of favorable clinical evidence. MAL and TB also demonstrated promising

results, mainly when used in combination with topical antifungals [38,40]. On the other hand, agents such as ALA [35,45], AlClPc [42], and FMN [29] have shown encouraging results, but further studies are needed to confirm their comparative efficacy. A recurring feature among the studies with superior outcomes was the use of adjunctive strategies, such as topical or systemic antifungal agents [33,38,40] and nail plate preparation techniques, particularly the application of 40 % urea. These adjuvant interventions, including the use of 40 % urea and fractional Er: YAG laser [16,29,30,33,34], were shown to enhance the effectiveness of aPDT by promoting nail plate debridement and removing physical barriers to photosensitizer penetration. Notably, 40 % urea, due to its keratolytic properties, has been demonstrated to significantly improve treatment outcomes, with sustained long-term benefits [16,29,30,33,34], reinforcing its value as a preparatory strategy prior to aPDT [30].

Additionally, the use of nanoemulsions containing AlClPc [42] represents an advancement in nanomedicine applied to aPDT, offering improved photosensitizer stability, bioavailability, and selectivity. This approach provides a safe, non-invasive, and repeatable treatment option with a low risk of microbial resistance. These strategies appear to enhance both photosensitizer and light penetration into the nail matrix, thereby improving therapeutic efficacy. Protocols involving multiple treatment sessions and weekly or biweekly applications were also associated with higher and sustained cure rates [16,31,33,37,41]. When long-term follow-up was conducted, the durability of treatment outcomes was confirmed [29,30,33,34,44]. In summary, the selection of the optimal photosensitizer in aPDT for onychomycosis should be guided by infection severity, fungal species involved, prior treatment response, and the potential to combine therapies. The combination of aPDT with topical or systemic antifungals, the use of nail preparation techniques and the application of lasers can enhance the therapeutic effects, especially in refractory cases.

Beyond its clinical implications, onychomycosis has a significant impact on patients' quality of life. The infection can cause pain [58], aesthetic discomfort, and social embarrassment [59], and may also increase the risk of secondary bacterial infections [60]. In more severe cases, such as in individuals with diabetes, the condition can progress to serious complications such as lower limb amputations, thereby increasing the risk of mortality [61]. Studies included in this review indicate that aPDT contributes to improvements in quality of life indices [36] and increases patient satisfaction with treatment outcomes [30–32,35]. Although generally benign and chronic in nature, onychomycosis is characterized by high rates of recurrence and reinfection, even after prolonged treatment courses [2]. As it is not self-limiting, effective management requires comprehensive strategies that extend beyond direct therapeutic intervention. These include patient education on proper hygiene, sterilization of manicure tools, prevention of nail trauma, principally in individuals wearing inappropriate footwear or engaging in sports, management of immunosuppressive conditions, and vigilance for early signs of recurrence [62,63]. Such measures are essential to prevent treatment failure and reduce reinfection rates [10]. Furthermore, prior to selecting a therapeutic approach, healthcare professionals must carefully assess the efficacy, potential adverse effects, and cost of each option, as these factors are critical for patient adherence, clinical success, and prevention of disease progression [2,10].

The studies included in this systematic review generally presented a low risk of bias, with the exception of detection and performance bias. Although some studies did not blind outcome assessments or failed to report this information clearly, this methodological limitation should be interpreted with caution. This is primarily due to the nature of the intervention under investigation. MB, the most commonly used photosensitizer in aPDT among the included studies, causes persistent staining of the treated tissues. As a result, blinding of evaluators becomes unfeasible, compromising the possibility of masked assessments, including objective techniques such as the makes it difficult to analyze the severity index of onychomycosis [32]. Moreover, methodological heterogeneity across the studies arose from variations in infection severity and differences in treatment protocols, including distinct light sources, types and concentrations of photosensitizers, wavelengths, power densities, exposure times, and outcome assessment methods. These discrepancies precluded the performance of a meta-analysis. The level of evidence of the analyses, according to the GRADE approach, was classified as "moderate" for RCTs and "low" for non-randomized clinical studies. This classification was influenced by methodological variations between the studies, and the low number of patients evaluated in the non-randomized studies, and the consequent downgrading in the inconsistency and imprecision domains, respectively. This heterogeneity can be attributed to the lack of standardized protocols for the application of aPDT, as well as differences in the study models used. Furthermore, the scarcity of studies reporting long-term results with similar interventions and control groups limits more robust analyses and sub-analyses, even when the studies show statistically significant differences.

It is important to highlight that this review presents several limitations. Firstly, some of the included studies involved small sample sizes, which may compromise the robustness and generalizability of the findings. Additionally, most studies had relatively short follow-up periods, typically up to six months, which may have hindered the detection of higher clinical cure rates. Another critical point is that few studies assessed the recurrence of onychomycosis in either the short or long term, limiting the understanding of the sustained effectiveness of the interventions. Moreover, this review included prospective non-randomized studies, and in some cases, studies lacked a control group. While these studies provide valuable insights into the role of aPDT in the management of onychomycosis, the absence of randomization and control groups limits the ability to draw direct comparisons between different interventions and lowers the overall level of evidence.

Although the current literature on aPDT still presents significant gaps, such as limited penetration into deeper layers of the nail biofilm and the lack of standardized light parameters, the findings of this systematic review suggest that aPDT holds promise for eliminating fungal species associated with onychomycosis, as well as improving the clinical signs and symptoms of nail infection. However, several variables appear critical to optimizing therapeutic outcomes, including the type and concentration of the photosensitizer, the wavelength and intensity of the light source, the duration of exposure, and the depth of tissue light penetration. When carefully calibrated, these parameters can substantially enhance the therapeutic response, ensuring both efficacy against resistant infections and patient safety [30,47]. Therefore, future studies are warranted to standardize critical parameters of the technique. Establishing uniform protocols may enhance the antimicrobial efficacy of aPDT and contribute to more consistent and improved clinical outcomes. In addition, high-quality randomized clinical trials with representative sample sizes and long-term follow-up are essential. These studies should encompass different stages and severities of onychomycosis and aim to establish consistent therapeutic protocols and standardized methodologies, allowing for more accurate assessment of aPDT's efficacy as an adjunctive treatment. Therefore, despite the promising results observed, the consolidation of aPDT in the management of onychomycosis depends on the development of more robust clinical research that deepens the understanding of its mechanisms, optimizes therapeutic protocols, and broadens its applicability across diverse clinical contexts.

5. Conclusion

Despite the limitations of this review, the evidence indicates that aPDT is a promising and beneficial approach, demonstrating both efficacy and safety in the treatment of onychomycosis. However, due to the heterogeneity of the data analyzed, further randomized clinical trials with rigorous methodological designs and consistent long-term follow-up are recommended. Such studies are crucial to deepen the understanding of aPDT's effects, validate this review's findings, and support

robust clinical recommendations for its therapeutic use.

Data availability statement

No datasets were generated or analysed during the current study.

Ethics approval and consent to participate

Not applicable.

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Supplementary material

Appendix A. Search strategy used in the databases.

CRediT authorship contribution statement

Renata de Oliveira Alves: Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Lara Oliveira Ribeiro Urzedo:** Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Priscila Toninatto Alves de Toledo:** Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation. **Carla Ferreira-Baptista:** Visualization, Validation, Methodology, Investigation, Formal analysis. **Matheus Henrique Faccioli Ragghianti:** Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation. **Thais Cristina Pereira:** Writing – original draft, Visualization, Validation, Formal analysis. **Larissa Pereira Nunes:** Visualization, Validation, Methodology, Formal analysis, Data curation. **Rui Damazio Alvites:** Writing – review & editing, Visualization, Validation, Formal analysis. **Gabriel Pereira Nunes:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pdpdt.2025.104640.

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