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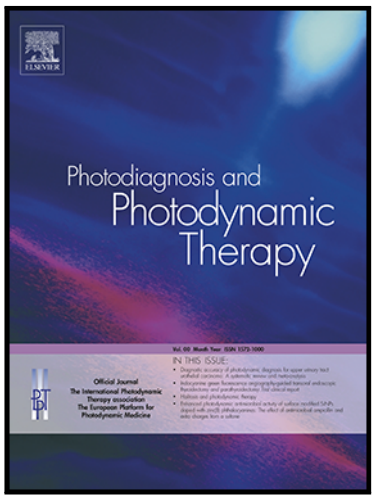


# Efficacy of anti-microbial photodynamic therapy in managing herpes simplex virus: A systematic review of clinical studies

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**Highlights**

- aPDT monotherapy showed outcomes comparable to antivirals.
- Combination therapy improved pain, viral load, and cytokines.
- Adjunctive aPDT accelerated healing and reduced recurrence.
- Evidence quality was very low due to bias and heterogeneity.

# Efficacy of anti-microbial photodynamic therapy in managing herpes simplex virus: A systematic review of clinical studies

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## ABSTRACT

*Background*: Herpes simplex virus (HSV) infections are a common clinical concern, often requiring effective antiviral treatments. Anti-microbial photodynamic therapy (aPDT) has gained attention as a potential adjunct to conventional therapies for managing HSV outbreaks. This systematic review aimed to evaluate the efficacy of aPDT in treating HSV infections.

*Methods:* Following PRISMA guidelines, PubMed/MEDLINE, Scopus, Embase, and Web of Science online databases were systematically searched for relevant studies on July 2025. Healing time was considered as the primary outcome, and secondary outcomes included lesion size, viral load, and patient-reported outcomes. Clinical studies evaluating efficacy of aPDT against other therapeutic approaches with at least 10 patients were considered eligible. Quality appraisal of the included studies was conducted using the revised Cochrane risk-of-bias tool for randomized trials (RoB2) and the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I). In addition, the certainty of evidence was assessed with a modified version of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework adapted for reviews without quantitative synthesis.

*Results:* aPDT monotherapy demonstrated clinical outcomes comparable to conventional antiviral therapy, with reductions in viral load and edema but limited superiority in clinical healing parameters. In contrast, adjunctive use of aPDT with antiviral therapy consistently improved pain, inflammatory markers, viral load, healing outcomes, and recurrence rates compared with either treatment alone.

*Conclusion:* aPDT appears to be an effective adjunctive therapy for HSV infections, but further high-quality studies are necessary to refine treatment protocols and confirm its clinical benefits.

***Keywords*:** Lasers; Laser Therapy; Photochemotherapy; Photodynamic Therapy; Herpes Simplex; Herpes Labialis; Herpes Genitalis.

## 1. Introduction

Herpes simplex virus (HSV) infections are among the most widespread viral diseases in the world, and they can cause notable discomfort and health problems for many people [1-3]. There are two main types of this virus, HSV-1 and HSV-2, and both continue to be major global health issues. According to recent statistics, about 3.7 billion people under the age of 50 are infected with HSV-1, and more than 490 million are living with HSV-2 [4, 5]. These infections often lead to recurrent herpes labialis, commonly referred to as cold sores, around the mouth (mostly associated with HSV-1), or herpes genitalis with genital ulcers (mainly related to HSV-2, but increasingly HSV-1 as well), causing both physical pain and emotional stress, particularly due to the stigma associated with these conditions [6]. Beyond the immediate clinical manifestations, HSV persists lifelong through latency in sensory ganglia with periodic reactivation, and frequent recurrences may significantly impair quality of life [1, 7, 8].

The primary treatment strategy for HSV involves antiviral agents such as acyclovir, valacyclovir, and famciclovir [9]. These medications reduce outbreak severity and transmission risk and may be used for both suppressive and episodic therapy. However, antiviral resistance has increasingly been reported, particularly in immunocompromised individuals, prompting investigation into alternative therapeutic approaches.

Photodynamic therapy (PDT) was originally developed as a targeted treatment for certain cancers, including melanoma and other solid tumors, because it can selectively destroy abnormal cells while sparing healthy tissue [10]. The therapy involves administration of a photosensitizer that accumulates in abnormal cells, followed by exposure to light of a specific wavelength, which produces reactive oxygen species (ROS). These ROS cause localized oxidative damage to cellular membranes, proteins, and nucleic acids, ultimately resulting in cell death [11].

Over the past decade, the applications of PDT have expanded beyond oncology, and antimicrobial photodynamic therapy (aPDT) has emerged as a promising approach against a broad spectrum of pathogens [12]. aPDT has demonstrated effectiveness against multidrug-resistant bacteria and fungi, and increasing evidence suggests that photodynamic inactivation can also target enveloped viruses such as HSV [13]. The mechanism involves generation of singlet oxygen and other ROS that damage viral envelopes, disrupt capsid proteins, and fragment nucleic acids, thereby reducing viral infectivity and local inflammation [12]. In addition, aPDT has gained

attention for treating mucocutaneous HSV lesions, particularly when rapid lesion progression limits the therapeutic window for antivirals [14].

More recently, research has described an additional oxygen-independent mechanism known as Type III photochemical action. In this pathway, certain light-activated compounds such as psoralens and tetracyclines bind directly to microbial DNA or ribosomes and produce lethal damage upon activation even in hypoxic or anaerobic environments. This mechanism is particularly relevant for mucosal or ischemic tissues affected by HSV, where oxygen availability may limit traditional aPDT activity [15].

Simultaneously, integration of nanotechnology into aPDT is shaping future developments. Nanoparticle-based photosensitizers may enhance tissue targeting, improve intracellular delivery, and increase ROS generation under physiologically challenging conditions. These advances may help overcome limitations of conventional antivirals, particularly in recurrent or drug-resistant HSV infections [11, 15].

This systematic review aims to evaluate the efficacy of aPDT in managing HSV infections through assessment of clinical studies. Outcomes of interest include lesion healing time, pain reduction, inflammatory markers, recurrence rates, and overall clinical improvement. By synthesizing current evidence, the review seeks to clarify the potential role of aPDT as a treatment modality for HSV infections and provide insight into its clinical applications.

## 2. Methods

### *2.1. Protocol development and registration*

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Table S1 and S2) [16], and its protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; ID: CRD420251002913).

### *2.2. PICOST framework and focused question*

The PICOST framework was used to formulate the focused question of this review.

- **Population**: Patients (humans) of any age or gender presenting with clinical manifestations of HSV-1 or HSV-2 infection at any body site.
- **Intervention**: aPDT.

- **Comparison**: Standard medication-based antiviral therapy, other alternative treatment approaches, or spontaneous healing.
- **Outcome**: Primarily healing time, lesion size, and recurrence. Also, Secondary outcomes included patient-reported measures such as pain, serological findings, infection or inflammatory biomarkers, and HSV quantification.
- **Study design**: Clinical studies with at least 10 patients, including randomized or non-randomized controlled clinical trials and retrospective cohort studies.
- **Timeframe**: No restrictions were placed on the publication timeframe.

Based on this framework, the focused question was defined as follows: "*in clinical studies including at least 10 patients per arm with clinical manifestations of HSV infection, what is the efficacy of aPDT in terms of healing time, lesion size, serological findings, and patient-reported outcomes, and how does it compare with other treatments, including conventional antiviral therapy?*"

*2.3. Eligibility criteria*

As specified in the PICOST framework, any clinical study including at least 10 patients in each intervention arm, in which aPDT was performed in at least one group to manage HSV infection, was considered eligible. In contrast, review articles, conference abstracts, animal studies, case reports, and letters were excluded. Additionally, other photo-assisted modalities such as photobiomodulation therapy (PBMT) were not considered eligible.

*2.4. Search strategy*

The search strategy was first developed for PubMed/MEDLINE in collaboration with an experienced medical librarian specialized in systematic review research and was then adapted for the remaining databases. It combined Medical Subject Headings (MeSH) and free-text terms into the search query. Table S3 presents the search queries used within each database. In addition to the electronic search, manual searches were performed for all issues published in the 21st century through July 2025 in the following journals: *Journal of Biophotonic*, *Journal of Lasers in Medical Sciences*, *Journal of Photochemistry and Photobiology B: Biology*, *Lasers in Medical Sciences*, *Lasers in Surgery and Medicine*, *Photobiomodulation, Photomedicine, and Laser Surgery*, and *Photodiagnosis and Photodynamic Therapy*. Reference lists of all retrieved full-text articles were also screened to identify additional relevant studies. Additionally, a manual search using Google Scholar was performed to ensure comprehensive coverage. Finally, the search was

re-performed on January 10, 2026, to ensure that no new studies had been published during the conduct of this review.

*2.5. Study selection*

Two independent reviewers (P.A. and P.H.) screened titles and abstracts for relevance. Afterward, selected articles' full-texts were retrieved for full-text appraisal. Agreement between reviewers at both the title/abstract screening phase and the full-text eligibility phase was assessed using Cohen's unweighted κ. Disagreements at any stage were resolved through consultation with a third reviewer (K.A.M.K.).

*2.6. Data extraction*

Data were extracted using a pre-defined structured data collection form. The following information was collected:

- **Study characteristics:** author(s), publication year, study design, and sample size.
- **Irradiation details:** type of laser, wavelength, type and concentration of photosensitizer, irradiation mode, power density, energy density, duration of irradiation, and number of irradiation sessions per week.
- **Outcome data:** patient-reported outcomes including visual analog scale (VAS) and McGill Pain Questionnaire (MPQ) scores for pain; serological findings such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) levels; microbiological outcomes including HSV quantification; and clinical findings such as edema and recurrence rate.

Data extraction was performed independently and in parallel by two authors (P.A. and K.A.M.K.), and any inconsistencies were resolved through consultation with a third expert author (R.F.).

*2.7. Risk of bias assessment*

The risk of bias in the included studies was assessed using established Cochrane tools according to study design. Randomized controlled trials (RCTs) were evaluated using version 2 of the Cochrane Risk-of-Bias tool for randomized trials (RoB 2), which examines five domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result [17]. Non-randomized studies of intervention (NRSIs) were assessed using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I), consisting of seven domains including confounding, classification of interventions, selection into the study, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result [18]. Each RCT was assigned an

overall judgment of high, some concerns, or low risk of bias based on the collective domain-level assessments with RoB 2, and NRSIs were assigned an overall judgment of serious, moderate, or low. Two independent reviewers (P.A. and P.H.) conducted all assessments, and any inconsistencies were resolved through consultation with a third expert reviewer (R.F.). Agreement between reviewers was evaluated using Cohen's weighted κ with quadratic weights to account for the magnitude of disagreement between categories, and inconsistencies were resolved through consultation to reach consensus.

*2.8. Certainty of evidence assessment*

The certainty of the evidence was evaluated using a modified form of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework adapted for reviews without quantitative synthesis, in which results are reported narratively [19]. The evaluation examined major domains across the included studies, namely methodological limitations (risk of bias), indirectness of evidence, imprecision, inconsistency, and possible publication bias, to judge the overall confidence in the evidence.

## 3. Results

*3.1. Study selection*

Figure 1 presents the PRISMA flow diagram of the literature search process. Initially, 1,107 records were identified across the databases. After removing 385 duplicates using the citation manager software (EndNote, v 2025.2, Clarivate, Philadelphia, PA) 722 records remained for screening. Of these, 714 were excluded by two independent reviewers, with strong agreement (κ = 0.89), leaving eight articles for full-text assessment [20-27]. The full texts were retrieved and evaluated, but three were excluded because they did not meet the PICOST framework and eligibility criteria [20-22]. The two reviewers demonstrated perfect agreement during the full-text screening phase (κ = 1.00). In addition, one study was identified through a manual Google Scholar search and included [14]. Consequently, six studies were ultimately included in the systematic review [14, 20-22].

*3.2. Study and patient characteristics*

All of the included studies were published between 2021 and 2025. The pool of studies comprised four RCTs [14, 23, 24, 26], one controlled clinical trial (CCT) [25], and one retrospective cohort study [27]. Of the six studies, five evaluated the efficacy of aPDT on perioral or oral lesions associated with HSV-1 [14, 23-26], while only one assessed genital herpetic lesions related to

HSV-2 [27]. Two studies mainly investigated short-term outcomes with a maximum follow-up of 7 days [25, 26], whereas two others and the remaining two had maximum follow-up durations of six months [23, 24] and one year [14, 27], respectively. Control groups in all included studies received conventional medication-centered antiviral therapy. In five studies, all involving patients with HSV-1–related oral or perioral lesions, topical acyclovir was administered [14, 23-26]. However, in the single study including patients with HSV-2–related genital herpetic lesions, oral famciclovir was used in the control group [27]. aPDT was the sole therapeutic intervention in test experimental group in two studies [14, 25], while all other studies used aPDT as an adjunctive to standard antiviral medication [23, 24, 26, 27].

In total, 249 patients were included in this review, of whom 94 and 155 were allocated to the control (standard antiviral medication–centered) and test (aPDT) groups, respectively. None of the included patients had serious or uncontrolled systemic conditions, except for six patients receiving aPDT in Mello et al.'s trial who were oncologic patients [25]. Age and gender of participants were not reported in two [25, 26] and one study [26], respectively. In the remaining studies, a total of 88 female patients (45 in control and 53 in test) and 93 male patients (34 in control and 59 in test) were enrolled. Detailed summaries of the studies and patients' characteristics are presented in Table 1.

*3.3. Radiation parameters*

Except for the study by Chen et al. [27], which included patients with HSV-2–related genital herpes and used a 633 nm light-emitting diode (LED) as the light source, all other studies employed diode lasers with wavelengths ranging from 633 to 660 nm [14, 23-26]. Only two studies reported the emission mode, and in both cases, it was continuous wave [14, 25]. Beam area was also not reported in two studies [26, 27]; however, among the remaining four, it was consistently within the range of 2.5 to 3 $mm^2$ [14, 23-25]. All five studies that used LASERs for treatment of oral and perioral lesions employed methylene blue photosensitizer [14, 23-26]. Four of these studies used a concentration of 0.005% [14, 23, 24, 26], while one study used double this concentration (0.01%) [25]. Pre-irradiation period varied with methylene blue from one [14] to five minutes [25, 26]; However, pre-irradiation application period with 5-aminolevulinic acid (ALA) used on genital lesions was considerably longer, at 3 hours [27]. Total delivered energy slightly varied within studies from 3 [14] to 4.8 J [26]; however, energy density varied significantly from 4 $J/cm^2$ [25]

to 300 J/cm$^2$ [23, 24]. Table 2 presents an overview of the radiation parameters and protocols across the included studies.

When the included protocols were ranked by per-session photodynamic dose, treatment intensity increased from the lowest-fluence methylene blue protocol [25], through the intermediate-fluence protocols [14, 26], to the highest-fluence protocols [23, 24]; the highest dye concentration thus coincided with the lowest delivered light dose, whereas the standard-concentration protocols delivered the highest fluences. The single 5-ALA protocol [27] could not be ranked against the methylene blue protocols owing to its distinct pharmacokinetics. This ordering represents a qualitative approximation only, as power density, beam area, and number of sessions were inconsistently reported.

### *3.4. Results of the individual studies*

#### *3.4.1. Clinical outcomes*

Half of the included studies explicitly reported no side effects or adverse events with either adjunctive aPDT [26] or aPDT alone [14, 25, 26]; however, the remaining three studies did not clearly report them [23, 24, 27]. Regarding lesion size and lesion characteristics, Ramalho et al. observed that combined aPDT and topical acyclovir resulted in a significantly smaller lesion size than topical acyclovir alone on day one ($p < 0.0131$); however, no difference was detected between groups from days two to seven [26]. Similarly, Mello et al. reported no difference in lesion size on days one, two, three, or seven [25]. In addition, La Selva et al. found no difference between aPDT and topical acyclovir in lesion temperature at 3 days ($p = 0.217$) [14]. Mello et al. also reported that lesion stage was significantly better in irradiated immunocompetent patients compared with irradiated immunocompromised patients on days two and three ($p < 0.05$) [25] (Table 3).

Edema was lower in both aPDT and aPDT combined with topical acyclovir compared with topical acyclovir alone on day one in Ramalho et al. ($p = 0.0182$) [26]. Similarly, Mello et al. reported significantly lower edema in both immunocompetent and immunocompromised patients receiving aPDT compared with topical acyclovir alone on day two ($p < 0.05$) [25].

Regarding healing outcomes, La Selva et al. found no difference between aPDT and topical acyclovir in remission time ($p= 0.718$) [14], and Ramalho et al. also detected no difference between groups in healing time on any day. In contrast, Chen et al. reported faster healing with aPDT compared with oral antiviral therapy in genital herpes [27].

With regard to recurrence and long-term outcomes, La Selva et al. found no difference in recurrence rate at 1 year ($p = 0.317$) [14], whereas Chen et al. reported lower recurrence rate and higher restricted mean survival time with aPDT compared with oral antiviral therapy [27].

*3.4.2. Patient-reported outcomes*

Except for the study by Chen et al., which investigated genital herpes [27], all remaining five studies reported patient-reported outcomes, most frequently pain. Both studies solely administrating monotherapy with aPDT, La Selva et al. and Mello et al., reported that VAS pain scores did not vary between aPDT and topical acyclovir therapy at three days ($p = 0.195$ and $p > 0.05$) [14, 25]. Additionally, in Mello et al.'s study no difference was observed between topical acyclovir and aPDT and immunocompetent and immunocompromised patients at one, two, three, and seven days regarding VAS pain scores ($p > 0.05$) [25]. Furthermore, no significant difference was observed in pain score following aPDT and control treatment with topical acyclovir in Vellappally et al.'s or Ramalho et al.'s studies [24, 26]. It was also shown by Ajmal that monotherapy with aPDT resulted in MPQ pain scores higher than monotherapy with topical acyclovir or combination therapy at 2 weeks, 4 weeks, and 6 months ($p > 0.05$) [23] (Table 3).

Similar to the results observed with aPDT monotherapy, Ramalho et al. found that pain scores did not differ significantly among topical acyclovir, aPDT, or aPDT combined with topical acyclovir at 1, 2, 3, 4, 5, 6, and 7 days [26]. In contrast, Vellappally et al. reported that combination therapy resulted in lower pain scores, according to both McGill Pain Questionnaire (MPQ) and VAS, at 4 weeks, 3 months, and 6 months ($p < 0.05$) [24]. These findings were partially confirmed in Ajmal's study as well, where VAS pain scores following combination therapy were lower than with aPDT or topical acyclovir alone at 2 weeks, 4 weeks, and 6 months ($p < 0.05$) [23].

*3.4.3. Microbiological and serological outcomes*

Three of the included studies reported microbiological or serological outcomes (Figure 2). Le Selva et al. found that aPDT resulted in lower levels of HSV-1 in saliva ($p = 0.043$) and lesions ($p = 0.036$), as measured by real-time polymerase chain reaction (qPCR), at 3 days [14]. Similarly, Vellappally et al. and Ajmal reported that topical acyclovir therapy combined with aPDT led to lower HSV-1 levels compared with monotherapy using either aPDT or topical acyclovir at 2 weeks, 4 weeks, 3 months, and 6 months ($p < 0.05$) [23, 24].

Similar to the trend observed with HSV-1, Vellappally et al. reported that topical acyclovir therapy combined with aPDT led to lower levels of both interleukin 6 (IL-6) and tumor necrosis

factor alpha (TNF-α) compared with monotherapy using either aPDT or topical acyclovir at 2 weeks, 4 weeks, 3 months, and 6 months ($p < 0.05$) [24]. However, Ajmal found that, in terms of reducing IL-6 levels, combination therapy outperformed monotherapy with either aPDT or topical acyclovir at 4 weeks, while aPDT alone or combined with topical acyclovir showed better outcomes at 3 and 6 months ($p < 0.05$). Additionally, TNF-α levels were lower with combination therapy only at 2 and 4 weeks ($p < 0.05$) [23] (Table 3).

*3.5. Risk of bias assessment*

As presented in Figure 3, three of the included RCTs were judged to have a high overall risk of bias [23, 24, 26], while only one had a low overall risk of bias [14]. The most concerning domains were bias arising from the randomization process, with high risk of bias in two studies [23, 24], and selection bias in the results, with some concerns in three studies [23, 24, 26]. Ramalho et al.'s study showed some concerns in all domains and therefore was assigned a high overall risk of bias [26].

With regard to the included NSRIs, one study had a moderate and the other a serious overall risk of bias. Chen et al.'s study was assigned a moderate overall risk of bias due to moderate risk within the domain of bias arising from measurement of the outcome [27]. Mello et al.'s study had a serious risk of bias in the same domain, in addition to moderate risk of bias arising from deviation from intended interventions and confounding [25].

*3.6.Certainty of evidence*

As shown in Table 4, the quality of evidence was rated as very low, mainly due to methodological limitations, particularly the high risk of bias in two-thirds of the studies, with only one study showing a low overall risk of bias, and the inclusion of retrospective and non-randomized study designs. The certainty was further reduced by imprecision related to the small number of publications and by inconsistency arising from heterogeneity in intervention and population characteristics.

## 4. Discussion

HSV infections remain a persistent challenge in clinical practice, as they are characterized by recurrent mucocutaneous lesions that can cause considerable discomfort and social stigma [7, 28, 29]. Although antiviral agents such as acyclovir continue to represent the cornerstone of treatment, their limitations, including variable efficacy, the potential for drug resistance, and systemic side effects, underscore the need for alternative or adjunctive therapeutic approaches [30]. In

immunocompetent individuals, HSV lesions typically heal spontaneously within 7–14 days; however, recurrence rates remain high, and some patients experience delayed healing or incomplete resolution [31]. aPDT has emerged as a promising non-invasive alternative that leverages light-activated photosensitizers to target viral particles and promote tissue repair [32, 33]. This study aimed to assess the effectiveness of aPDT in a larger group of immunocompetent individuals, focusing not only on lesion healing but also on recurrence rates and patient-reported outcomes, including pain and overall satisfaction. By addressing these multifaceted aspects, the study seeks to provide a more comprehensive understanding of aPDT's potential role in HSV management.

This systematic review synthesizes evidence from six clinical studies [14, 20-22] evaluating the efficacy of aPDT in managing HSV infections, with attention to lesion healing time, pain reduction, inflammatory markers, recurrence rates, and overall clinical improvement. The findings indicate that aPDT as a standalone treatment generally provides outcomes comparable to conventional antiviral therapy, particularly outperforming conventional antiviral therapy in reducing viral load and controlling inflammation, whereas its combination with antiviral therapy is particularly beneficial for pain reduction, lesion healing, and lowering recurrence rates in HSV infections. These results align with the growing body of literature supporting aPDT's role in managing drug-resistant infections and other conditions, including cancers, through targeted production of reactive oxygen species (ROS) [10, 11, 34].

A key finding across the included studies is the greater efficacy of combination therapy (aPDT with antiviral treatment) compared with either treatment alone. Ajmal et al. and Vellappally et al. reported that combining aPDT with antiviral therapy produced larger reductions in HSV-1 levels, pain scores, and pro-inflammatory cytokines (IL-6 and TNF-α) over extended follow-up periods [23, 24]. Chen et al. similarly observed faster healing and lower recurrence rates with aPDT plus antiviral medication compared with antiviral therapy alone in patients with recurrent genital herpes [27]. Overall, these outcomes suggest a synergistic effect, in which aPDT enhances the clinical response achieved by antiviral therapy rather than replacing it.

The advantage of combination therapy can be explained by the complementary mechanisms of action. Acyclovir, a nucleoside analog, is selectively activated in infected cells by viral thymidine kinase and inhibits viral DNA polymerase, suppressing replication within the host cell [35]. In contrast, antimicrobial photodynamic therapy acts locally by generating ROS that

damage viral envelopes, capsid proteins, and nucleic acids, leading to direct viral inactivation [36]. aPDT also modulates inflammation by reducing cytokines such as IL-6 and TNF-α, which may contribute to symptom relief and tissue repair [15, 36, 37]. Because aPDT primarily acts at the lesion site, systemic adverse effects are limited. Together, intracellular viral suppression and local viral destruction likely account for the improved outcomes observed when therapies are combined.

Across studies, aPDT monotherapy generally showed clinical results comparable to conventional antiviral therapy. Pain scores, healing time, and recurrence rates were typically similar between treatments, while some reductions in viral load and inflammatory markers were observed with aPDT alone. These findings suggest that aPDT may serve as an alternative local treatment when antivirals are contraindicated or poorly tolerated, although it did not consistently demonstrate superior clinical healing outcomes on its own.

The studies also indicate that aPDT can be used in diverse patient populations, including immunocompetent individuals, oncologic patients, and pediatric cases. Improvements in edema and lesion characteristics were observed across these groups, although the magnitude of benefit varied and appeared more pronounced when aPDT was combined with antiviral therapy. This supports the view that the therapy's primary value lies in adjunctive use rather than universal replacement of antivirals.

However, variability in long-term efficacy was observed. Some studies showed early improvements in edema or lesion size during the acute phase without sustained superiority over antiviral therapy. Differences in photosensitizers, light wavelengths (approximately 633–660 nm), and energy densities likely contributed to this heterogeneity. Standardization of treatment parameters and evaluation of repeated treatment sessions may improve consistency and durability of outcomes. Practical considerations remain important. Unlike topical antiviral therapy, aPDT requires specialized equipment and trained personnel, which may limit accessibility. Emerging portable light sources and simplified protocols may improve feasibility in outpatient or home settings. Advances in nanoparticle-based photosensitizers may further enhance tissue targeting and ROS generation, potentially improving treatment precision.

Despite its promise, several limitations in the current evidence base must be acknowledged. First, the small sample sizes (ranging from 24 to 59 participants per study, totaling 249 patients) limit the generalizability of the findings and reduce statistical power to detect consistent long-term effects. Larger, multicenter RCTs are therefore needed to confirm the efficacy of aPDT across

broader and more diverse populations. Second, considerable heterogeneity exists in aPDT protocols, including differences in photosensitizer type and concentration, light source, wavelength (approximately 633–660 nm), energy density, and number of treatment sessions. Outcome measures also varied substantially across studies, encompassing different clinical parameters, inflammatory markers, viral load assessments, and follow-up durations. Because of this variability and heterogeneity in both interventions and reported outcomes, a quantitative meta-analysis was not feasible. Third, risk-of-bias assessments conducted using RoB 2 for RCTs and ROBINS-I for non-randomized studies identified methodological concerns, particularly in non-randomized designs where confounding and selection bias were noted. These limitations highlight the need for well-designed, adequately powered, and standardized RCTs to strengthen the overall evidence base.

The clinical implications of this review should be interpreted in light of the pattern of findings. aPDT monotherapy generally demonstrated outcomes comparable to conventional antiviral therapy for short-term clinical parameters such as pain, lesion size, and healing time, while showing additional biological effects, including reductions in viral load and inflammatory markers. In contrast, the combination of aPDT with antiviral therapy consistently produced broader and more sustained benefits, particularly in reducing pain, decreasing viral load and pro-inflammatory cytokines, accelerating lesion healing, and lowering recurrence rates. These findings position aPDT primarily as a promising adjunctive therapy rather than a universal replacement for antivirals, especially in patients with recurrent or difficult-to-manage HSV infections. Its non-invasive nature and localized mechanism of action further enhance its appeal as a patient-friendly option with minimal systemic side effects. Nevertheless, practical challenges, including the requirement for specialized equipment such as diode lasers or LED devices and trained personnel, may limit accessibility in resource-constrained settings. Cost-effectiveness analyses and real-world implementation studies are therefore necessary to evaluate the feasibility of integrating aPDT into routine clinical practice.

The therapeutic effect of aPDT may also vary by anatomical site of infection, although the present evidence permits only limited inference. Five of the six included studies evaluated oral or perioral HSV-1 lesions [14, 23-26], whereas only one assessed genital HSV-2 lesions [27], leaving the review heavily weighted toward oral disease. Across the oral studies, aPDT was generally comparable to topical acyclovir, with adjunctive benefit for pain, viral load, and inflammatory

markers but no consistent superiority in healing time [14, 23-26], whereas the single genital study reported faster healing and lower recurrence with aPDT than with oral antiviral therapy [27]. This apparent site-related difference must be interpreted cautiously, however, because site was confounded with several other variables: the genital study used a different photosensitizer (5-aminolevulinic acid rather than methylene blue), a different light source (LED rather than diode laser), a different comparator (oral famciclovir rather than topical acyclovir), and a non-randomized retrospective design [27]. With only one non-oral study available, the independent contribution of infection site cannot be isolated.

The possibility that light delivery may be insufficient at certain sites is mechanistically reasonable, as the efficacy of aPDT depends on delivering adequate light fluence to the photosensitizer within the lesion, an outcome influenced by anatomical accessibility, lesion geometry, tissue optical properties, and the depth at which the photosensitizer localizes [15]. Accessible, relatively flat perioral lesions permit uniform direct-contact laser application, whereas curved, moist, or less accessible mucosal sites such as the genitalia may receive less uniform illumination, and the use of a surface-localizing dye (methylene blue) versus an intracellularly accumulating prodrug (5-aminolevulinic acid/protoporphyrin IX) further modulates the effectively treated depth. In the present review, however, no direct evidence of underdosing was observed at any site; notably, the genital study achieved its favorable outcomes despite a lower-irradiance LED, suggesting that adequate therapeutic effect can be obtained at non-oral sites when the photosensitizer and protocol are appropriately matched. Site-stratified studies employing standardized, anatomy-specific dosimetry are therefore needed to determine whether therapeutic efficacy and optimal light parameters genuinely differ across HSV infection sites.

A further consideration relevant to clinical translation concerns whether aPDT can be repeated and whether HSV might develop resistance to it over time. Because aPDT is non-invasive, acts locally at the lesion site, and is associated with minimal systemic toxicity, it can be administered repeatedly, both as multiple sessions within a single course and as separate courses across successive recurrences. This property is particularly relevant for HSV, which persists lifelong through latency in sensory ganglia and reactivates periodically; a modality that can be safely reapplied at each recurrence without cumulative toxicity therefore offers a practical advantage. Consistent with this, none of the included studies reported treatment-limiting adverse effects attributable to aPDT, with half explicitly documenting an absence of side effects [14, 25,

26]. With respect to resistance, the mechanism of aPDT differs fundamentally from that of nucleoside-analogue antivirals. Acyclovir and related agents act on a single, specific molecular target, including viral thymidine kinase and DNA polymerase, such that point mutations in the corresponding genes can confer resistance, a phenomenon increasingly reported, particularly among immunocompromised patients [35]. In contrast, aPDT exerts its effect through the non-specific generation of ROS, and through the oxygen-independent Type III photochemical pathway, which simultaneously damage multiple structural targets, including the viral envelope, capsid proteins, and nucleic acids [15, 36]. Because this multi-target oxidative action does not rely on a single site that could be altered by mutation, the emergence of resistance is considered highly unlikely, and repeated cycles of antimicrobial photodynamic inactivation have not been shown to select for resistant microbial populations [38-40]. This absence of inducible resistance is among the principal advantages attributed to aPDT and may render it especially valuable in recurrent or antiviral-resistant HSV infections. Nevertheless, the available evidence on resistance derives largely from bacterial and fungal models, and longitudinal clinical data specifically assessing whether HSV develops reduced susceptibility to aPDT after repeated exposure are currently lacking, representing an important direction for future research.

Future research should address the identified gaps by establishing standardized aPDT protocols, including optimal photosensitizer concentrations, light parameters, energy densities, and treatment frequencies to maximize therapeutic consistency. Long-term studies with extended follow-up are essential to clarify the durability of recurrence prevention and the impact on patient quality of life, particularly among individuals with frequent reactivations. Further investigation in special populations, such as pregnant women or individuals with severe immunosuppression, may expand its clinical applicability. Additionally, comparative trials evaluating aPDT, both alone and in combination, against emerging antiviral agents or immunotherapeutic strategies would help define its precise role within the evolving landscape of HSV management.

## 5. Conclusion

In conclusion, this systematic review highlights the potential of aPDT as a therapeutic option for HSV infections, particularly in recurrent cases and situations where conventional antiviral therapy may be limited. Overall, aPDT monotherapy demonstrated clinical outcomes comparable to standard antiviral treatment, while its combination with antiviral agents such as acyclovir

consistently yielded greater benefits, including improved pain control, faster lesion healing, and reductions in viral load and inflammatory markers. Despite these encouraging findings, substantial heterogeneity in treatment protocols, outcome measures, and study quality limits the strength of the current evidence. Accordingly, well-designed RCTs with larger sample sizes, standardized aPDT parameters, and extended follow-up periods are required to more clearly define the optimal clinical role and long-term benefits of aPDT in HSV management. Future research should also further elucidate the biological mechanisms underlying aPDT's effects to support its broader and more effective clinical application.

**Data Availability**

All data supporting the findings of this study and used to conduct it are reported and presented in this article.

**AI Statement**

During manuscript preparation, artificial intelligence (AI) was used solely for proofreading an entirely human-generated text; no other AI tools were employed in the writing process.

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**Conflicts of Interest**

None.

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**Ethical Approval**

This study was exempt from institutional review board approval and ethical review, as it relied solely on publicly available data and information.

**Author contributions (CRediT)**

**P.A.**: Conceptualization, Investigation, Methodology, Visualization, Writing-original draft, Writing-review and editing. **K.A.M.K.**: Conceptualization, Investigation, Methodology, Writing-original draft, Writing-review and editing. **P.H.**: Conceptualization, Methodology, Visualization, Writing-original draft, Writing-review and editing. **R.F.**: Conceptualization, Methodology, Project Administration, Supervision, Writing-original draft, Writing-review and editing.

**Supplementary material**

The Supplementary material for this study can be found online at: [Link to DOI].

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## Tables

### Table 1

A summary of the design, participants, and characteristics of the included studies.

| Author (s), year | Study design | N# of patients | Type of HSV (location) | Follow-up | Treatment Modalities (N) | Age (mean ± SD) [range] | Gender | Clinical outcomes | Patient-reported outcomes | Serological or microbiological findings | Complications |
|---|---|---|---|---|---|---|---|---|---|---|---|
| La Selva et al., 2025 [14] | RCT | 24 | HSV-1 (lips) | 3 days, 7 days, and 1 year | Control: Topical acyclovir QD for 7 days (12)<br>Test: single session aPDT (12) | 37 ± 11 [18-59]<br>35 ± 13 [15-60] | F: 11, M: 1<br>F: 9, M: 3 | No difference in remission time ($p$ = 0.718), recurrence rates in 1 year ($p$ = 0.317), or temperature at 3 days ($p$ = 0.217) was observed | No difference in pain levels according to a 100 score VAS on day 3 ($p$ = 0.195) or OHIP-14 scores in 1 year ($p$ = 0.634) were observed. | More HSV-1 viral load was detected in control group on day 3 according to qPCR in both saliva ($p$ = 0.043) and lesion ($p$ = 0.036) at 3 days. | None. |
| Chen et al., 2024 [27] | Retrospective cohort | 41 | HSV-2 (genitalia) | 1 year | Control: Oral antiviral therapy (33)<br>Test: aPDT + Famciclovir 0.25g TID (8) | Median: 46 [34-56]<br>Median: 47 [42-54] | F: 20, M: 13<br>F: 5, M: 3 | Healing time was faster with aPDT (5.4 vs. 7.2 days). Also, recurrence rate was lower (37.5% vs. 71.3%). Additionally, the restricted mean survival time was significantly higher with aPDT (9.94 vs. 4.14 days) | NA | NA | NA |
| Mello et al., 2022 [25] | CCT | 36 | HSV-1 (intraoral or perioral) | 1, 2, 3, and 7 days | Control: Immunocompetent patients receiving 50mg/g acyclovir cream five times a day (4)<br>Test 1: Immunocompetent patients receiving aPDT (26)<br>Test 2: oncologic patients receiving aPDT (6) | NA<br>NA<br>NA | F: 3, M: 1<br>F: 21, M: 5<br>F: 1, M: 5 | At 48 hours, both Test groups demonstrated less edema than control ($p$ < 0.05); however, no difference in lesions size was detected between groups at any time. Test 1 group had significantly better lesions stage at 48 hours and 72 hours compared to Test 2. | There was no significant difference in VAS pain scores (0–10 scale) between the groups at 24, 48, and 72 hours, as well as one week ($p$ > 0.05). | NA | NA |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Vellappally et al., 2022 [24] | RCT | 45 | HSV-1 (gingivostomatitis) | Immediate post-op, 2 weeks, 4 weeks, 3months, and 6 months | Control: Topical antiviral therapy with acyclovir (14)<br>Test 1: aPDT (15)<br>Test 2: Topical antiviral therapy with acyclovir + aPDT (16) | 18 ± 0.2<br>17.9 ± 0.2<br>18.6 ± 0.6 | F: 6, M: 9<br>F: 3, M: 12<br>F: 4, M: 12 | NA | Pain scores, both according to MPQ and 10-point VAS were lower in Test 2 compared to Test 1 and Control at 4 weeks, 3 months, and 6 months ($p < 0.05$) | Test 2 resulted in lower HSV-1, IL-6, and TNF-α quantification than that of Test 1 and Control at 2 weeks, 4 weeks, 3 months, and 6 months ($p < 0.05$). | NA |
| Muhammad Ajmal, 2021 [23] | RCT | 44 | HSV-1 (lips) | Immediate post-op, 2 weeks, 4 weeks, 3months, and 6 months | Control: Topical antiviral therapy with acyclovir (15)<br>Test 1: aPDT (14)<br>Test 2: Topical antiviral therapy with acyclovir + aPDT (15) | 17.8 ± 0.7<br>16.7 ± 0.9<br>17.0 ± 0.5 | F: 5, M: 10<br>F: 4, M: 10<br>F: 6, M: 9 | NA | According to MPQ, Test 1 had higher pain scores than other groups at 2 and 4 weeks. However, according to 10-point VAS, Test 2 resulted in lower pain compared to both other groups at 2 and 4 weeks. | Test 2 resulted in lower HSV-1 quantification than that of Test 1 and Control at 2 weeks, 4 weeks, 3 months, and 6 months ($p < 0.05$). Also, IL-6 levels were lower than the other two groups at 4 weeks in Test 2. However, both Test 1 and 2 had lower levels of IL-6 at 3 and 6 months. TNF-α levels were lower in Test 2 only at 2 weeks and 4 weeks. | NA |
| Ramalho et al., 2021 [26] | RCT | 59 | HSV-1 (lips) | 1, 2, 3, 4, 5, 6, and 7 days | Control: Topical antiviral therapy with acyclovir 5% five times a day (16)<br>Test 1: aPDT (25)<br>Test 2: Topical antiviral therapy with acyclovir 5% five times a day + aPDT (18) | NA<br>NA<br>NA | NA<br>NA<br>NA | The only observed difference in lesion size was on day 1, when Test 2 had significantly lower values than Control ($p < 0.0131$). Also, no difference was detected between groups regarding healing time on any days. Edema was lower in Test 1 and 2 compared to control on day 1 ($p = 0.0182$) | Pain scores did not vary significantly between groups on any days. However, tingling was lower in Test 1 compared to Control on day 1 ($p = 0.0048$) | NA | NA |

**Abbreviations**: **aPDT**: Antimicrobial photodynamic therapy; **CCT**: Controlled Clinical Trial; **F**: Female; **g**: gram; **HSV**: Herpes Simplex Virus; **IL-6**: Interleukin 6; **M**: Male; **MPQ**: McGill Pain Questionnaire; **N**: Number; **NA**: Not Available; **OHIP-14**: Oral Health Impact Profile-14; **QID**: Four times a day; **qPCR**: quantitative Polymerase Chain Reaction; **RCT**: Randomized Controlled Trial; **SD**: Standard Deviation; **TID**: Three times a day; **TNF-α**: Tumor Necrosis Factor Alpha; **VAS**: Visual Analogue Scale.

**Table 2**

A summary of the radiation parameters and protocols in the included studies.

| Author(s), year | Emit type | Wavelength (nm) | Emission Mode (repetition rate, pulse duration) | Beam area ($mm^2$) | Photosensitizer (concentration) [pre-irradiation period] | Application and angulation | Radiation time [per point] (total) | Power (W) | Power density (intensity) ($W/cm^2$) | Energy (J) | Energy density (fluence) ($J/cm^2$) | Number and frequency of sessions |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| La Selva et al., 2025 [14] | Diode LASER (InGaAlP) | 660 | Continuous | 3 | Methylene blue (0.005%) [1 minute] | Direct contact and perpendicular | NA | 0.1 | 33.3 | 3 | 120 | 1 |
| Chen et al., 2024 [27] | LED | 633 | NA | NA | 5-Aminolevulinic Acid (20%) [3 hours] | NA | (20 minutes) | NA | 0.084 | NA | 100 | Once a week |
| Mello et al., 2022 [25] | Diode LASER | 660 | Continuous | 2.8 | Methylene blue (0.01%) [5 minutes] | NA | [40 seconds] | 0.1 | NA | NA | 4 | 3 to 7 |
| Vellappally et al., 2022 [24] | Diode LASER | 640 | NA | 2.5 | Methylene blue (0.005%) [NA] | Direct contact and perpendicular | [30 to 40 seconds] | 0.15 | NA | 4 | 300 | NA |
| Muhammad Ajmal, 2021 [23] | Diode LASER | 660 | NA | 2.8 | Methylene blue (0.005%) [NA] | Direct contact and perpendicular | (30 seconds) | 0.15 | NA | 4.5 | 300 | NA |
| Ramalho et al., 2021 [26] | Diode LASER | 660 | NA | NA | Methylene blue (0.005%) [5 minutes] | NA | [120 seconds] | 0.04 | NA | 4.8 | 120 | NA |

**Abbreviations**: **cm**: centimeter; **InGaAlP**: Indium Gallium Aluminum Phosphide; **J**: Joule; **LED**: Light-Emitting Diode; **mm**: millimeter; **NA**: Not Available; **nm**: nanometer; **W**: Watt

**Table 3**

A summary of short-term and long-term outcomes of treatment in the included studies.

| Study | Treatment arms | Short-term outcomes (≤ 4 weeks) | Long-term outcomes (3–12 months) |
|---|---|---|---|
| **La Selva et al., 2025** [14] | Topical acyclovir vs. single session aPDT | No significant difference in lesion resolution time, pain on day 3, and lesion temperature on day 3. Lower salivary and lesion HSV-1 load on day 3 in the aPDT group. | No difference in recurrence rate or OHIP-14 quality-of-life scores, both at 1 year. |
| **Chen et al., 2024** [27] | Oral antiviral therapy vs. aPDT + oral famciclovir | Lesion healing was faster with aPDT. | Recurrence rate was lower and restricted mean survival time was higher with aPDT, both at 1 year. |
| **Mello et al., 2022** [25] | Immunocompetent patients receiving topical antiviral vs. Immunocompetent patients receiving aPDT vs. oncologic patients receiving aPDT | No significant difference in pain or lesion size between groups. aPDT arms were superior to control for edema. Lesion stage was better in immunocompetent patients receiving aPDT than oncologic patients receiving aPDT. | None. |
| **Vellappally et al., 2022** [24] | Topical acyclovir vs. aPDT vs. topical acyclovir + aPDT | Lower pain, HSV-1, IL-6, and TNF-α with combination therapy compared to aPDT or topical acyclovir alone. | Lower pain, HSV-1, IL-6, and TNF-α with combination therapy compared to aPDT or topical acyclovir alone. |
| **Muhammad Ajmal, 2021** [23] | Topical acyclovir vs. aPDT vs. topical acyclovir + aPDT | Lower and higher pain with combination therapy and aPDT alone, respectively. Lower HSV-1, IL-6, and TNF-α with combination therapy compared to aPDT or topical acyclovir alone. | Lower HSV-1 with combination therapy compared to aPDT or topical acyclovir alone. Lower IL-6 with aPDT either alone or in combination with acyclovir compared to topical acyclovir alone. |
| **Ramalho et al., 2021** [26] | Topical acyclovir vs. aPDT vs. topical acyclovir + aPDT | On day 1, combination therapy and aPDT alone were superior to topical acyclovir alone for edema. On day 1, lesion size was lower with combination therapy compared to the control. Also, on day 1, tingling was lower with aPDT than control. | None. |

**Table 4**

Quality of evidence according to the GRADE framework modified for studies without meta-analysis.

| *Study design* | *Certainty assessment* | | | | | *Effect* | *Number of participants (studies)* | *Certainty in the evidence* |
|---|---|---|---|---|---|---|---|---|
| | *Methodological limitations of the studies* | *Indirectness* | *Imprecision* | *Inconsistency* | *Likelihood of publication bas* | | | |
| Randomized and non-randomized trials | Serious | Not serious | Very serious | Serious | Not serious | Some studies showed better results with combination therapy (aPDT + topical acyclovir) compared to monotherapy with acyclovir | 249 (6) | ⨁◯◯◯ Very low |

**Figure legends**

**Figure 1.** PRISMA flowchart of the review.

**Figure 2.** Risk of bias assessment among (A) randomized and (B) non-randomized studies.

**Figure 3.** An overview of the reported serological and microbiological outcomes. (A) Salivary biomarker, including IL-6 and TNF-α; (B) HSV-1 quantification. (*: combination therapy better than either aPDT or antiviral therapy alone; †: both aPDT alone and in combination with antiviral therapy were superior than antiviral therapy alone)