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Antimicrobial photodynamic therapy for the potential treatment of oral candida infection in HIV/AIDS Patients: A Scoping Review

Desiana Radithia [1 *], Zakiyyah Darojah [2] and Zanira Ghaisani Rochman [2]

[1] *Department of Oral Medicine, Faculty of Dental Medicine, Universitas Airlangga, Surabaya 60132, Indonesia.*
[2] *Department of Dental Science, Faculty of Dental Medicine, Universitas Airlangga, Surabaya 60132, Indonesia.*

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Abstract

Objectives: Evaluate the impact of antimicrobial photodynamic therapy (aPDT) using various photosensitizers on *Candida* colonies and clinical symptoms associated with oral candidiasis, a common oral manifestation in HIV/AIDS patients.

Methods: A scoping review was conducted in PubMed and ScienceDirect, following Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA). A literature search was conducted in electronic databases to identify relevant articles up to October 25, 2024.

Results After excluding articles, only three were eligible for review. Based on the findings, aPDT performed better in reducing the number of *Candida* and clinical signs in the oral mucosa of HIV/AIDS patients.

Conclusion: **A**ntimicrobial photodynamic therapy (aPDT) treatment using methylene blue (MB), with or without Potassium iodide (KI), can reduce *Candida* colonies and clinical symptoms in HIV/AIDS patients, offering a potential alternative therapy to enhance their quality of life. Further research is needed to refine antimicrobial photodynamic therapy (aPDT) parameters for treating oral candidiasis in these patients.

Keywords: Antimicrobial photodynamic therapy; Opportunistic infections; Oral candidiasis; HIV; AIDS

1. Introduction

Oral candidiasis (OC) is a common opportunistic infection of the oral mucosa, primarily caused by *Candida albicans* [1]. Although *Candida* species are part of the normal flora in the mouth, they can become pathogenic under certain conditions [2]. While *C. albicans* is the most frequent cause, other non-albicans species—such as *C. glabrata*, *C. tropicalis*, *C. krusei*, *C. dubliniensis*, and *C. parapsilosis*—can also trigger infections, leading to increased awareness of these variants over time [3].

OC affects many groups, particularly children, the elderly, and women. Risk factors include poor oral hygiene, smoking, malnutrition, excessive antifungal use, and weakened immunity. People with compromised immune systems, such as those with HIV, are especially vulnerable to OC [1, 3]. In fact, OC is often an early sign of AIDS and an indicator of disease severity. It is the most frequent opportunistic infection in HIV-positive individuals, with prevalence ranging from 0.9% to 83%. Clinical forms of OC in these patients include pseudomembranous (thrush), erythematous, atrophic, hyperplastic, and angular cheilitis [3].

* Corresponding author: Desiana Radithia

Fluconazole, an azole antifungal, is typically the first-line treatment for OC in HIV-positive patients. However, many *Candida* species found in these patients show resistance to azoles, and using them can lead to oropharyngeal candidiasis [2, 3]. As a result, the World Health Organization (WHO) recommended nystatin suspension as an alternative in 2014 [3]. Despite this, studies show nystatin is not more effective than fluconazole in treating OC among infants, children, or HIV/AIDS patients. Given the limitations of current treatments, new therapeutic strategies are needed to manage OC effectively, particularly in patients with resistant infections [1, 4].

Antimicrobial photodynamic therapy (aPDT), when combined with antifungal agents, has shown great potential in inactivating *Candida albicans* strains susceptible to fluconazole. aPDT involves applying a photosensitizer (PS) to the affected area, followed by exposure to light at a specific wavelength. This process, in the presence of oxygen, generates reactive oxygen species (ROS), which play a key role in damaging microbial cells. ROS disrupts essential cell components by triggering lipid peroxidation, enzyme inactivation, and nucleic acid oxidation. They also break down the biofilm matrix, allowing antifungal agents to penetrate deeper layers and bind to ergosterol, a key fungal membrane component. This binding forms channels in the membrane, leading to the leakage of intracellular components and eventual fungal cell death [16].

Advancements in technology have transformed dentistry, improving treatment outcomes while minimizing patient discomfort. One such emerging technology is aPDT, which has gained attention for its ability to provide a safer, more effective alternative to conventional antifungal therapies. Research suggests that aPDT could revolutionize the treatment of oral candidiasis by accelerating healing, reducing pain, and minimizing adverse side effects [16].

As understanding of aPDT improves, it is likely to play an increasingly important role in clinical practice. Compared to traditional antifungal treatments, which can have significant side effects, aPDT offers a promising therapeutic option by stimulating biological activity and targeting pathogens more precisely. Given the limitations of conventional antifungal therapies, further exploration of aPDT is essential. This review aims to investigate the mechanisms by which aPDT enhances fungal eradication and improves treatment outcomes. A deeper understanding of these processes can help refine clinical practices, reduce reliance on antifungal drugs, and improve patient care. As research progresses, aPDT may become a cornerstone of oral candidiasis treatment, offering more effective and patient-friendly solutions [16].

2. Material and methods

This study is a scoping review, which is a literature review compiled through a comprehensive search of studies relevant to the specific topic to be discussed and assessment and synthesis of data carried out using predetermined methods so that it can be used as a basis for conducting evidence-based practice. This scoping review adheres to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) method that aims to report systematic reviews [5].

2.1. Eligibility criteria

The data used in this study are articles published in the international journal related to certain topics. The inclusion and exclusion criteria were designed using the PICO (Population, Intervention, Comparison, Outcome) framework. The PICO framework is defined as follows:

1. Population (P): The study population consisted of patients diagnosed with HIV/AIDS and oral cavity co-infected with oral candidiasis. Inclusion criteria were patients clinically confirmed positive for *Candida spp*. and signed an informed consent. Exclusion criteria patients who were pregnant or breastfeeding, who were wearing removable partial denture or complete denture, and who had a history of allergies were excluded from this study.
2. Intervention (I): The interventions given to this group were aPDT with various types of light sources and photosensitizers.
3. Comparison (C): The comparison in this review included other therapies, namely photosensitizer concentration. The therapy was applied with the same laser but with different concentrations of methylene blue (MB) as the photosensitizer agent. However, conventional therapy included antifungal drugs.
4. Outcome (O): The primary outcome is a reduction in the number of *Candida* colony growths or reduced inflammation in the oral mucosa of patients.

2.2. Search strategy

Electronic searches were conducted for literature published in the electronic databases: PubMed and ScienceDirect. The boolean operator used the keyword ((((Photodynamic) OR (Antimicrobial Photodynamic)) OR (aPDT)) AND (Oral

Candidiasis)) AND (HIV), resulting in 399 articles. Literature searches were conducted in the following electronic databases from their start of day 1 January 1989 to 25 October 2024.

The search and selection process, which includes identification, inclusion, and exclusion is illustrated in **Figure 1.** In the identification stage, the initial exclusion criteria included removing articles after screening for duplication. Records were initially screened and excluded based on the relevance of titles to the inclusion criteria. In the next stage, reports were assessed for relevant details within their abstracts. Following this, records with irrelevant abstracts were excluded, and the remaining records were further evaluated against the eligibility criteria.

2.3. Data strategy and analysis

The titles and abstracts were independently reviewed by two reviewers (ZD/ZGR) to obtain the full text of relevant articles. The data was then extracted, having been previously prepared in Excel sheets by ZD. All data were double-checked by ZD and ZGR followed by consultation with DR. The data extraction form includes the author, year, title, study design, characteristics of population, characteristics of intervention, characteristics of comparisons, and outcome measures.

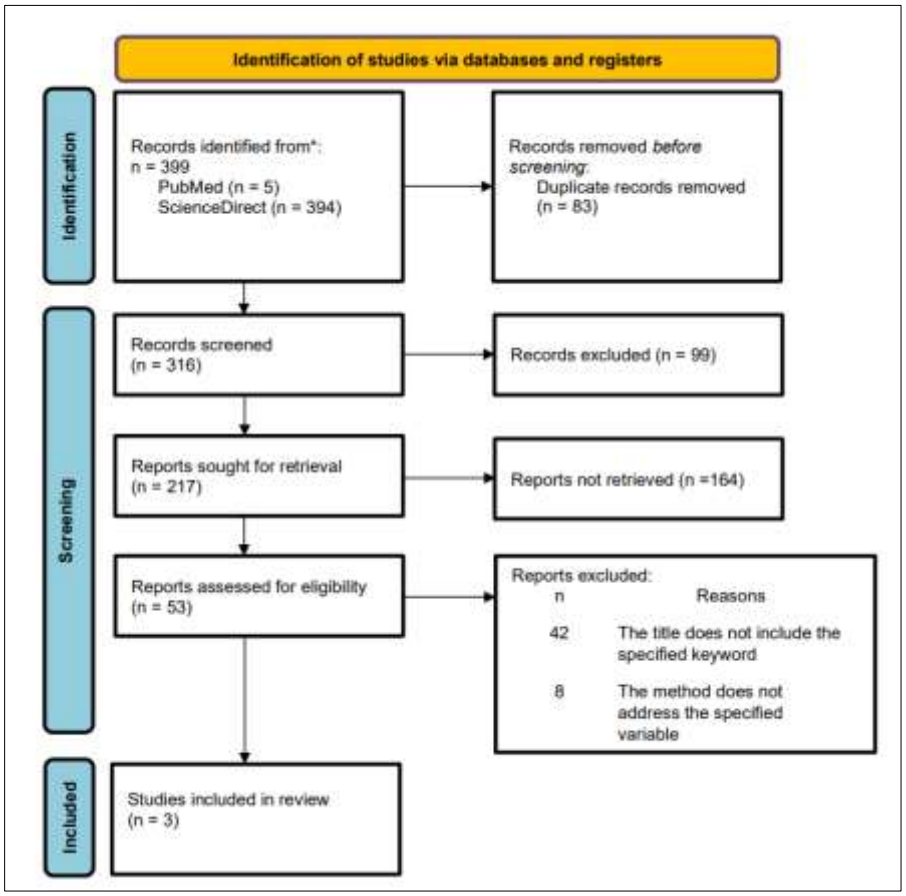

Figure 1 Flow chart search based on PRISMA

3. Results

In total, 399 articles were found from the database with specific keywords, with 83 having identical titles. After removing duplicates, 316 articles remained for further review. Screening of titles and abstracts narrowed the selection to 53 articles that met the PICO criteria. After reading the full text of the articles, 3 articles were obtained according to PICO and the inclusion criteria included in this process.

Table 1 presents the characteristics of the 3 articles that met the inclusion criteria, described by author, year of publication, title, and study design [6-8]. The population characteristics of the 3 studies, including age, gender, sample size, and group are presented in **Table 2**. In total, the 3 studies had 63 participants [6-8]. The participants had an average age range between 30 and 56.90 years. The gender distribution included 34 male participants and 8 female

participants. One study did not report the age and gender of the participants [8]. One study reported using Twin Laser [6] and two studies reported using light-emitting diode (LED) [7, 8]. All studies used methylene blue as the photosensitizer agent. Summary for the interventions is presented in **Table 3**. Based on **Table 4**, one study compared with one type of antifungal (Fluconazole) [6], one study controlled with other treatment (photosensitizer concentration) [7], and one study with both antifungal (Fluconazole, Itraconazole, Flucytosine, Amphotericin B) and other treatment (photosensitizer concentration) [8]. **Table 5** presents the outcomes including clinical evaluation, microbiological evaluation, recurrence of oral candidiasis infection, and reduction in *Candida spp.* colony growth or inflammation. One study reported using clinical evaluation [6], one used microbiological evaluation [8], and one used both clinical and microbiological evaluations [7]. Recurrence of oral candidiasis infection was reported in the control group in one study [6]. Based on the three studies, treatment in the test group with aPDT showed a reduction in oral candidiasis infection among participants [6, 8].

Table 1 Characteristic of the studies according to author, year of publication, title and study design

SN.	Author	Year	Title	Study design
1	Scwingel et al. [6]	2012	Antimicrobial Photodynamic Therapy in the Treatment of Oral Candidiasis in HIV-Infected Patients	Randomized controlled trials (RCT)
2	Du, et al. [7]	2021	Antimicrobial photodynamic therapy for oral Candida infection in adult AIDS patients: A pilot clinical trial	Randomized controlled trials (RCT)
3	Du, et al. [8]	2024	Clinical aPDT's effect on Candida albicans: Antifungal susceptibility, virulence gene expression, and correlation with leukocyte and neutrophil counts	Randomized controlled trials (RCT)

Table 2 Characteristic of population

SN.	Author	Age (Years)	Gender (n)		Sample size (No)			Group
			Male	Female	aPDT	Antifungal	Other Treatment	
1	Scwingel et al. [6]	30 ± 8	16	5	7	7	N/A	G1: aPDT G2: LLLT G3: fluconazole
2	Du, et al. [7]	51.60 ± 12.44 - 56.90 ± 9.45	18	3	21	N/A	21	G1: aPDT + KI (MB 400 µM G2: aPDT + KI (MB 600 µM)
3	Du, et al. [8]	Not reported	Not reported	Not reported	21	21	N/A	G1: aPDT + KI (MB 400 µM + antifungal G2: aPDT + KI (MB 600 µM) + antifungal

aPDT: Antimicrobial Photodynamic Therapy; **MB:** Methylene Blue; **KI:** Potassium Iodide; **N/A**: Not Applicable

Table 3 Characteristic of intervention

SN.	Author	aPDT					
		Light Source/ Number/ Wavelength (nm)	Photosensitizer Agent	Pre-irradiation Time	Light Power (mW)/ intensity (mW/cm2)	Energy Density (J/cm2)	Treatment Time/ Follow-up Time
1	Scwingel et al. [6]	Twin Laser/-/660	MB	1 minutes	30/-	7.5	1.5 minutes/7, 15, 30 days
2	Du, et al. [7]	Light-emitting diode (LED)/ -/633	MB	5 minutes	-/20.72	37.29	30 minutes/ Post-treatment (1-time/2-time)
3	Du, et al. [8]	Light-emitting diode (LED)/ -/633	MB	5 minutes	-/20.72	37.29	30 minutes/ Post-treatment sampling in 2 days (1 time/2-time)

aPDT: Antimicrobial Photodynamic Therapy; **MB:** Methylene Blue; **N/A**: Not Applicable

Table 4 Characteristic of comparisons

SN.	Author	Comparisons	
		Antifungal	Other Treatment
1	Scwingel et al. [6]	Fluconazole	N/A
2	Du, et al. [7]	N/A	Photosensitizer concentration
3	Du, et al. [8]	Fluconazole Itraconazole Flucytosine Amphotericin B	N/A

N/A: Not Applicable

Table 5 Characteristic of outcomes

SN.	Author	Clinical Evaluation	Microbiological Evaluation	Recurrence	Reduction
1	Scwingel et al. [6]	Clinical efficacy	Not reported	On day 30, 72% of patients in the control group (treatment with fluconazole) showed signs and symptoms of recurrence	In the control group treated with fluconazole, 72% of patients showed clinical improvement on day 15, while 28% showed no change in clinical presentation; however, recurrence occurred by day 30. Meanwhile, in the group treated with aPDT, all patients demonstrated better clinical outcomes and improved overall health on both day 15 and day 30

2	Du, et al. [7]	Clinical efficacy	Fungal count	Not reported	All patients in groups 1 and 2 showed clinical improvement after 2-time treatments with aPDT. Meanwhile, A linear relationship was observed between the number of aPDT treatments and Log10 (CFU/mL) (P = 0.031). Following a 1-time aPDT treatment, there was no significant decrease in Log10 (CFU/mL) (P = 0.424), but improving reduction occurred after 2-time treatments (P = 0.016). The increase in MB concentration did not significantly affect fungal reduction (P = 0.379). Overall, 2-time aPDT treatment substantially reduced *C. albicans* fungal cells, achieving reductions within the range of 0.07–4.64 Log10 (CFU/mL), with a median and interquartile range of 0.97 (0.70, 1.93) Log10 (CFU/mL). But, after 2-time aPDT treatment, did not reduce the biofilm formation ability of the surviving *C. albicans* cells.
3	Du, et al. [8]	Not reported	The results were scored as low, medium, and abundant in culture, based on turbidity levels categorized as clear, mild, and intense, respectively	Not reported	aPDT was effective in reducing the MIC of antifungals against *C. albicans* isolated from patients after the first treatment, but no further reduction was observed after the second treatment. Meanwhile, aPDT could lower the MIC of Amphotericin B and Flucytosine depending on aPDT parameters and MB concentration.

4. Discussion

Oral candidiasis is an opportunistic infection that is diagnosed through visual examination of removable white plaque or erythema tissue in the oral cavity, and microscopic examination of oral mucosal samples with typical findings [1, 9]. Various complex organisms colonize the oral cavity. *Candida spp.*, primarily *Candida albicans*, is one of the normal commensal flora and invasive pathogens under certain conditions of the most dominant fungal species [2, 10]. Oral candidiasis is closely related to HIV infection, more than 90% of AIDS patients develop oral candidiasis during the process of HIV infection and the infection signals the progression of AIDS [9]. In patients with HIV infection, a systematic review and meta-analysis of resistant oral candidiasis found that some antifungal use led to an increase in *Candida spp.* [3]. In addition, the problem of antifungal resistance in people living with HIV/AIDS has increased, which has complicated the treatment of the infection [2, 11].

This review includes three studies that evaluated the effect of aPDT in treating oral candidiasis in people living with HIV/AIDS [6-8]. In recent years, aPDT has become a promising strategy for the treatment of diseases caused by fungi, mainly infections such as oral candidiasis [12]. Antimicrobial photodynamic therapy (aPDT) is a development of PDT for antimicrobial therapy based on the principle of photosensitizers binding to target cells, then activated by light with a specific wavelength [4, 13]. In this article, all trials reported reduced *Candida* colony counts and reduced clinical signs in people living with HIV/AIDS after aPDT treatment [6-8]. However, after 2 applications, aPDT treatment did not reduce the biofilm formation ability of surviving *C. albicans* cells [7].

aPDT uses Methylene Blue as a photosensitizer that is activated by exposure to light with a wavelength that is specifically aligned with the absorbance band of the photosensitizer [14]. The effectiveness of MB-aPDT with the addition of KI in the treatment of oral candidiasis infection in people living with HIV/AIDS has shown varied results. An MB concentration of 400 μM (equals 127.94 μg/mL) showed significant MIC reduction for Fluconazole and Flucytosine, while an MB concentration of 600 μM (equals 191.91 μg/mL) showed significant MIC reduction for Amphotericin B [8]. In another experiment, the addition of KI to the use of MB-aPDT effectively eliminated *C. albicans*, however, increasing the MB concentration from 400μM (equivalent to 127.94 μg/mL) to 600μM (equivalent to 191.91 μg/mL) did not further reduce the number of *Candida* colonies and clinical signs in people living with HIV/AIDS thus finding no prominent MB dose-related effects [7]. However, aPDT treatment without the addition of KI with an MB concentration

of 450 µg/mL MB effectively reduces the number of *Candida* colonies and clinical signs in people living with HIV/AIDS [6]. There are three possible reasons for the varying results, namely there is optical shielding, phenothiazinium dyes are prone to aggregation, the addition of KI as an effort to increase the potency [7].

Visible light from the photosensitizer will be absorbed by aPDT as the beginning of the working mechanism [15]. The suitability of aPDT treatment is required to generate reactive oxygen species (ROS). ROS generated by aPDT will result in oxidative stress resulting in damage to fungal cells through reactions with membranes and other organelles [6]. The addition of KI is confirmed to enhance the killing effect of aPDT, KI is oxidized by ROS to produce free iodine which is a stable species for antimicrobials [7].

5. Conclusion

In conclusion, aPDT treatment mediated by MB, with or without the addition of KI, can reduce the number of *Candida* colonies and clinical signs in people living with HIV/AIDS. The presence of aPDT as an alternative therapy related to HIV/AIDS may contribute to improving patients' quality of life. Better-designed and appropriate aPDT parameters for the condition of oral candidiasis infection in HIV/AIDS patients still need further exploration.

Compliance with ethical standards

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Disclosure of Conflict of interest

The authors declare no conflict of interest.

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