

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

ScienceDirect

journal homepage: [www.e-jds.com](http://www.e-jds.com)

Review article

# The impact of antimicrobial photodynamic therapy on pain and oral health-related quality of life: A literature review

Rashin Bahrami <sup>a</sup>, Maryam Pourhajibagher <sup>b\*</sup>,  
Nariman Nikparto <sup>c</sup>, Abbas Bahador <sup>d\*\*</sup>

<sup>a</sup> Department of Orthodontics, School of Dentistry, Iran University of Medical Sciences, Tehran, Iran

<sup>b</sup> Dental Research Center, Dentistry Research Institute, Tehran University of Medical Sciences, Tehran, Iran

<sup>c</sup> Nastaran Dental Clinic, Tehran, Iran

<sup>d</sup> Department of Microbiology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Received 26 June 2024; Final revision received 30 June 2024

Available online 17 July 2024

## KEYWORDS

Antimicrobial photodynamic therapy;  
Oral health-related quality of life;  
Oral infections;  
Denture stomatitis;  
Pericoronitis;  
Molar extraction

**Abstract** Antimicrobial photodynamic therapy (aPDT) is a non-invasive approach used for microbial decontamination, and it can also be beneficial as an adjunctive strategy for oral infections. The success of treatment in the long term is increasingly recognized to be influenced by patient's perception of the disease and its improvement. Recently, aPDT has been suggested as a dual approach to tissue repair, pain relief, and enhancement of oral health-related quality of life (OHRQoL). The first pathway involves the antimicrobial and anti-inflammatory effects of aPDT. It not only eliminates microorganisms but also helps regulate the immune response and reduce inflammation, leading to a faster and more effective healing process. This, in turn, provides relief from pain and associated symptoms, aiding in the management of treatment complications. The second pathway involves aPDT's ability to modulate nociception and alleviate pain. aPDT induces analgesia by releasing neurotransmitters such as  $\beta$ -endorphin, serotonin, and acetylcholinesterase. It also interacts with mitochondria through photoreceptors, initiating intracellular processes that alleviate pain. Furthermore, the therapy inhibits nerve fibers, reducing nerve impulse conduction and altering the pain threshold. Considering that the impact on patients' pain and OHRQoL is an important aspect of the decision-making process, this study aimed to review patient-based outcome measures during aPDT and assess its effects on pain and OHRQoL in patients. Understanding these factors will contribute to a better

\* Corresponding author. Dental Research Center, Dentistry Research Institute, Tehran University of Medical Sciences, 16 Azar Street, Tehran, 1455845874, Iran.

\*\* Corresponding author. Department of Microbiology, School of Medicine, Tehran University of Medical Sciences, 16 Azar Street, Tehran, 1455845874, Iran.

E-mail addresses: [m-pourhajibagher@sina.tums.ac.ir](mailto:m-pourhajibagher@sina.tums.ac.ir) (M. Pourhajibagher), [abahador@sina.tums.ac.ir](mailto:abahador@sina.tums.ac.ir) (A. Bahador).

assessment of the overall benefits and effectiveness of aPDT as a treatment option for oral infections.

© 2024 Association for Dental Sciences of the Republic of China. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

Antimicrobial photodynamic therapy (aPDT) is a non-invasive medical approach with wide applications, including dentistry.<sup>1</sup> In dentistry, aPDT is utilized for microbial decontamination and can serve as an adjunctive strategy for oral infections.<sup>2</sup> The effectiveness of aPDT in eliminating microbes is achieved through an oxidative reaction that occurs upon specific illumination. This process requires the presence of three components: a nontoxic dye known as the photosensitizer (PS), visible light of a resonant wavelength, and molecular oxygen.<sup>3</sup> Essentially, aPDT utilizes light energy and a PS to generate reactive oxygen species (ROS) in an environment containing oxygen.<sup>4</sup> The PS absorbs light, transitioning to its triplet state, and subsequently undergoes two reaction mechanisms to return to its ground state: the type I mechanism, where charge transfer occurs to a substrate or ROS such as hydrogen peroxide and oxygen radicals, and the type II mechanism, where energy is directly transferred to molecular oxygen, generating highly reactive singlet oxygen.<sup>5,6</sup>

While existing review studies have primarily focused on the biological and microbiological effects of aPDT,<sup>2,7–9</sup> it is crucial to evaluate the patient-centered outcomes of this therapy for treatment success. Assessing the impact of treatment on the patient's quality of life can be achieved through the concept of oral health-related quality of life (OHRQoL). This evaluation aims to determine the treatment's ability to improve the aspects of daily life that matter most to patients. OHRQoL plays an integral role in overall health and well-being, and the World Health Organization (WHO) recognizes its significance within the Global Oral Health Program.<sup>10</sup> Oral infections and dental procedures can significantly impact OHRQoL, highlighting the need to consider this aspect when evaluating treatment options. Previous studies have highlighted the association between dental/oral pain and OHRQoL, as pain can cause suffering, eating and sleeping disorders, school absenteeism, and social, psychological, and economic consequences, negatively affecting OHRQoL.<sup>11–13</sup>

Recent studies have shown that aPDT can effectively manage pain and improve OHRQoL through two pathways.<sup>14–17</sup> The first pathway involves the antimicrobial and anti-inflammatory effects of aPDT. By activating a PS with a specific light wavelength, ROS are generated, targeting and eliminating microorganisms. This elimination of microbes suppresses the immune system, leading to reduced inflammation. Consequently, the healing process of damaged tissues is accelerated, aiding in the control of treatment-related complications.<sup>18</sup> The effectiveness of this pathway can vary depending on the type of PS used. For instance, emodin (Emo), a natural PS, exhibits anti-

inflammatory properties similar to a local non-steroidal anti-inflammatory drug (NSAID), particularly as a cyclooxygenase 2 (COX-2) inhibitor.<sup>19</sup> The second pathway involves aPDT's ability to modulate nociception and alleviate pain. Laser light is absorbed by mitochondrial photoreceptors, initiating an energy transduction process that induces electrochemical changes within cells. This process triggers a series of intracellular events that result in analgesia by reducing the conduction velocity of nerve impulses, specifically those transmitted by delta A and type C nerve fibers.<sup>20,21</sup>

Considering that incorporating information about quality of life into clinical decision-making is crucial when choosing a treatment, this study aimed to review patient-based outcome measures during aPDT and assess its effects on pain and OHRQoL in patients. By understanding these factors, a more comprehensive evaluation of the overall benefits and effectiveness of aPDT as a treatment option for oral infections can be achieved.

## Concept of pain relief impact of antimicrobial photodynamic therapy

Oral infections such as denture stomatitis and herpes labialis, as well as dental procedures like molar extraction and free gingival graft (FGG) surgery, can result in pain and impact various aspects of an individual's life. These complications can affect speech, function (such as eating and swallowing), nutritional status, and appearance, ultimately leading to a reduction in social interactions and family life.<sup>22</sup> Consequently, the overall OHRQoL can be significantly impacted.<sup>23</sup> The use of anti-inflammatory analgesics, antibiotics, antifungals, and corticosteroids has been employed to minimize complications associated with oral infections and dental procedures. However, these conventional topical or systemic medications have several disadvantages, including bacterial resistance, toxic reactions, high cost, patient cooperation issues, and gastric problems. Moreover, conventional treatments may not always yield optimal results, and some cases may not respond well to conventional approaches.<sup>24–26</sup> Therefore, it is important to explore alternative and adjunctive treatment options that can minimize complications related to oral infections and dental procedures, without the disadvantages of conventional treatments. Alternative approaches aim to provide safe, effective, user-friendly, and cost-effective treatment methods.<sup>27</sup>

One promising alternative treatment option is aPDT. It involves the use of a photosensitizer, light (such as lasers or light-emitting diode [LED]) with a specific wavelength, and oxygen.<sup>1</sup> When these components interact, singlet oxygen

and free radicals are formed, leading to the elimination of microorganisms.<sup>2</sup> aPDT is a simple, affordable, non-invasive, and widely utilized treatment method in dentistry to reduce microbial load (please see Fig. 1); it offers the advantage of having no side effects<sup>27–30</sup> Additionally, aPDT offers a dual approach to tissue repair and pain relief: *anti-inflammatory* and *analgesic* effects.<sup>14–16</sup>

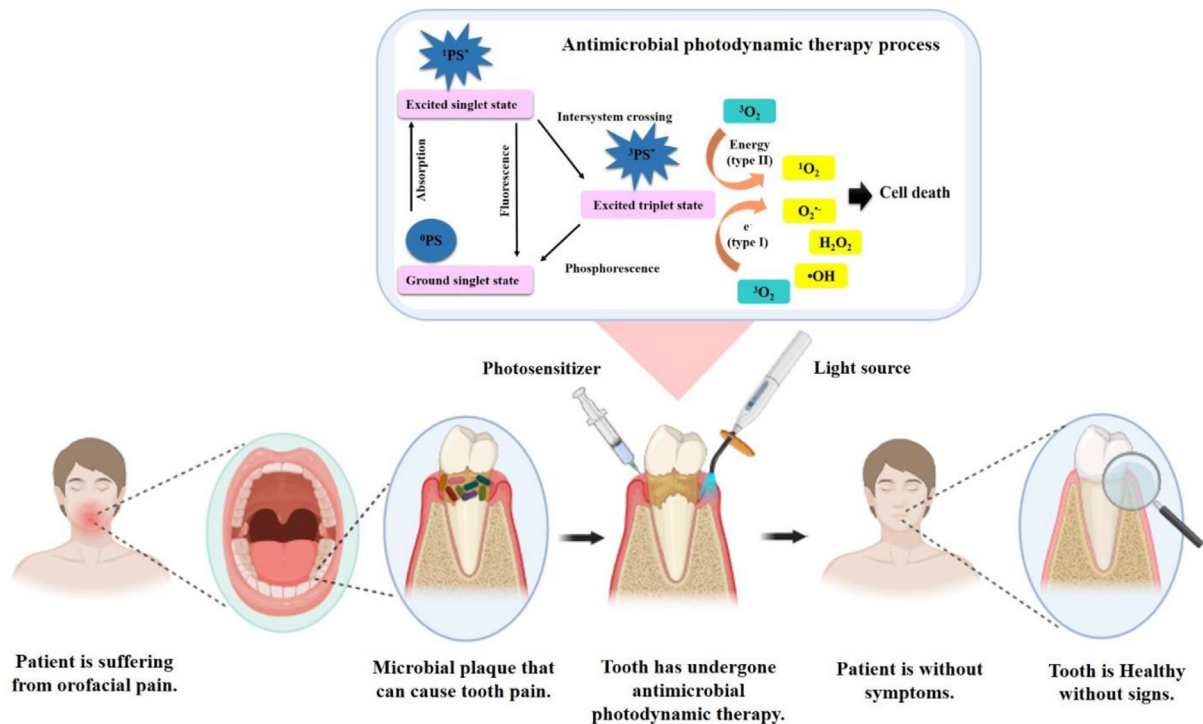
### Anti-inflammatory effect

The combined antimicrobial and anti-inflammatory effects of aPDT make it an effective strategy for wound healing and pain management. By utilizing the process of "microorganism biological cleaning," aPDT accelerates the healing process in contaminated areas, leading to faster recovery times and reduced symptoms and complications for patients.<sup>31,32</sup> The main mechanism behind aPDT involves the generation of ROS, which possess cytotoxic properties and can oxidize various cellular components of bacteria, fungi, and viruses. These ROS target crucial structures such as lipid membranes, mitochondria, and DNA within microorganisms, inducing a lethal photochemical reaction that causes irreversible damage and ultimately leads to the death of these microorganisms.<sup>27,31,33</sup> In addition to its potent antimicrobial properties, aPDT also contributes to the reduction of inflammation. Microorganisms can stimulate the immune system, triggering an inflammatory response.<sup>34</sup> By effectively eliminating these microbes, aPDT helps suppress the immune response and diminishes inflammation. This has a wide range of effects on inflammatory cells and pain-related substances.<sup>20</sup> aPDT improves cellular respiration and biostimulates various types of cells

and acts involved in the healing process, including proliferation and migration of fibroblasts, as well as tissue remodeling.<sup>20</sup> Additionally, it decreases the presence of inflammatory cells such as leukocytes and neutrophils, as well as mediators like interleukin (IL)-1, further reducing the overall inflammatory response.<sup>20</sup>

### Analgesic effect

aPDT is a therapeutic approach that combines the use of low-level lasers with PSs.<sup>35</sup> The analgesic mechanism of the laser beam in aPDT involves various neurotransmitter substances.<sup>36</sup> One of the key substances affected by the laser is  $\beta$ -endorphin, which is an endogenous compound known for its pain-relieving properties. The laser beam stimulates the release of  $\beta$ -endorphin, leading to analgesia.<sup>14</sup> Furthermore, the laser beam also influences the levels of serotonin and acetylcholinesterase, both of which play important roles in pain modulation. By altering the concentrations of these substances, the laser beam can further contribute to the analgesic effects.<sup>36</sup> Another aspect of the analgesic mechanism in aPDT is the modulation of nociception, which refers to the perception of pain. The low-level laser directly interacts with the mitochondria through specialized photoreceptors.<sup>20,21</sup> These photoreceptors absorb the laser light and initiate a process called energy transduction, leading to electrochemical changes within the mitochondria. These changes trigger a cascade of intracellular events that ultimately result in analgesia.<sup>20,21</sup> Additionally, laser therapy in aPDT has been observed to decrease the conduction velocity of nerve impulses. This reduction in nerve impulse conduction is



**Figure 1** Mechanism of antimicrobial photodynamic therapy. PS: photosensitizer,  $^0\text{PS}$ : Ground singlet state,  $^1\text{PS}^*$ : Excited singlet state,  $^3\text{PS}^*$ : Excited triplet state.

**Table 1** Summary of the general characteristics of clinical studies of antimicrobial photodynamic therapy's impact on pain and oral health-related quality of life.

Oral infection/ dental procedure	Patients		Antimicrobial photodynamic therapy							Variables		Outcome	Refs
	Gender (male/ female)	Age (mean ± SD)	Photosensitizer				Light source		Pain	OHRQoL			
			Type (gel/ solution)	Concentration	Application	Time	Type	Irradiation parameters			Sessions		
Denture stomatitis	27/13	54.20 ± 15.39	Methylene blue (solution)	450 µg/mL	Spray	10 min	GaA1As diode laser	Wavelength: 660 nm Energy density: 28 J/ cm <sup>2</sup> Output: 100 mW Continuous Exposure time: N/A	16 sessions (2 times a week; interval: 72 h; for 8 weeks)	-	OHIP-EDENT	The OHRQoL was significantly enhanced following methylene blue- mediated aPDT in the denture stomatitis patients.	37
Free gingival graft	18/35	43.01 ± 10.5	Emodin (gel)	10 × 10 <sup>-4</sup> g/L	Applied on donor site	5 min	LED	Wavelength: 450 ± 10 nm Output intensity: 1000 ± 1400 mW/cm <sup>2</sup> Energy density: 60–80 J/cm <sup>2</sup> Exposure time: 1 min	2 sessions (the day of surgery and 48 h later).	VAS NSAID intake	-	Emodin- mediated aPDT reduced postoperative (free gingival graft) pain especially during first week after surgery.	16
Molar extraction	15/25	41.25 ± 13.97	Methylene blue (solution)	0.01%	Applied in the fresh socket	5 min	InGaAIP	Wavelength: 660 ± 10 nm Power: 100 mW Output energy: 9 J Fluency: 300 J / cm <sup>2</sup> Irradiance: 3.33 W / cm <sup>2</sup> Exposure time: 90 sec	Single session	-	OHIP-14	Methylene blue- mediated aPDT combined with the low-level laser therapy (GaA1As laser; wavelength: 808 ± 10 nm, output: 100 mW, output energy: 4 J, fluence: 133 J/cm <sup>2</sup> , irradiance) 3.33 W / cm <sup>2</sup> , 40 s) improved OHRQoL post third molar extraction.	38
Periodontitis (Stage III, Parkinson's disease patients)	18/7 (SRP group) 21/4 (aPDT group)	73.3 (SRP group) 71.6 (aPDT group)	Chloro- aluminum phthalocyanine (gel)	0.003%	Injected inside the periodontal pocket	N/A	Diode laser	Wavelength: 630 nm Energy: 4 J Power: 150 mW power density: 300 J/cm <sup>2</sup> Exposure time: 1 min	Single session (1 time after traditional SRP)	-	OHIP-14	Chloro-aluminum phthalocyanine mediated aPDT following SRP significantly improved OHRQoL compared to SRP alone.	39
Denture stomatitis (Type 2 diabetes mellitus)	5/15 (miconazole group) 7/13 (aPDT group) 8/12 (miconazole+ aPDT group) 7/13 (chlorhexidine group)	58.5 (miconazole group) 61.3 (aPDT group) 60.2 (miconazole+ aPDT group) 57.8 (chlorhexidine group)	Methylene blue (solution)	0.005%	Applied on palate, tongue and the denture	5 min	Diode laser	Wavelength: 660 nm Power: 100 mW Energy density: 3527 mW/cm <sup>2</sup> Radiance: 9 J Exposure time: N/A	Single session	-	OHIP-14	The combination of topical miconazole 2% and methylene blue- mediated aPDT had synergistic impact on improvement in OHRQoL.	40
Dental caries (Selective removal of decayed tissue)	6/14 (distilled water group) 9/17	55.9 (distilled water group) 6.15	Methylene blue (solution)	0.01%	Adding and filling the entire cavity	5 min	InGaAIP	Wavelength: 660 ± 10 nm Power: 100 mW Output energy: 9 J Fluency: 300 J / cm <sup>2</sup> Irradiance: 3.33 W / cm <sup>2</sup> Exposure time: 90 sec	Single session	-	ECOHIS	The application of methylene blue- mediated aPDT as novel antimicrobial technique during dental caries treatment especially in on pediatric dental, did not have negative	41

(continued on next page)

Table 1 (continued)

Oral infection/ dental procedure	Patients		Antimicrobial photodynamic therapy						Variables		Outcome	Refs		
	Gender (male/ female)	Age (mean $\pm$ SD)	Photosensitizer			Light source			Pain	OHRQoL				
			Type (gel/ solution)	Concentration	Application	Time	Type	Irradiation parameters					Sessions	
Oral mucositis (Oncologic patients)	10/0 (nystatin group) 8/2 (photobiomodulation group) 8/2 (aPDT group)	60.1 $\pm$ 10.6 (nystatin group) 57.3 $\pm$ 7.2 (photobiomodulation group) 60.5 $\pm$ 6.8 (aPDT group)	Curcumin (solution)	7.5 m	Sprayed (10 mL) inside the oral cavity	10 min	LED	Wavelength: 450 nm Output intensity: 67 mW/cm <sup>2</sup> Fluency: 20.1 J/cm <sup>2</sup> Exposure time: 10 min	4 sessions (1 time VAS a week; for 4 weeks)	-	-	effect on OHRQoL. Curcumin-mediated aPDT reduced pain score and had more effectiveness in early clinical improvement compared photobiomodulation (Laser DMC Therapy EC; wavelength: 660 nm, power: 100 mW, irradiation time: 3 s per point) and nystatin treatments. Post endodontic treatment pain in teeth with periapical lesion and pulp necrosis was significantly reduced following methylene blue- mediated aPDT. Methylene blue- mediated aPDT by reduction in H <sub>2</sub> S gas concentration and enhancing the OHRQoL improvement.	42	
Endodontic treatment (Pulp necrosis and periapical lesion)	11/19 (control group) 13/17 (aPDT group)	34.23 $\pm$ 10.98 (control group) 35.03 $\pm$ 11.27 (aPDT group)	Methylene blue (solution)	0.005%	Applied inside the root canal (activation by the helical technique)	3 min	GaAlAs diode laser	Wavelength: 660 nm Power: 100 mW Energy density: 320 J/cm <sup>2</sup> Total energy: 9 J Exposure time: 90 sec	Single session	VAS	-	-	Post endodontic treatment pain in teeth with periapical lesion and pulp necrosis was significantly reduced following methylene blue- mediated aPDT. Methylene blue- mediated aPDT by reduction in H <sub>2</sub> S gas concentration and enhancing the OHRQoL improvement.	43
Halitosis (Patients with removal dentures; H <sub>2</sub> S levels >112 ppb)	12/8 (full mouth disinfection and tongue scrapping group) 10/10 (aPDT group)	66.42 $\pm$ 1.45 (full mouth disinfection and tongue scrapping group) 67.91 $\pm$ 2.37 (aPDT group)	Methylene blue (solution)	0.005%	Applied on the tongue (middle and dorsal surface) and denture	5 min	Diode laser	Wavelength: 660 nm Radiant power: 100 mW Energy density: 3527 mW/cm <sup>2</sup> Radiance: 9 J Exposure time: N/A	Single session	-	OHIP-14	-	Methylene blue- mediated aPDT by reduction in H <sub>2</sub> S gas concentration and enhancing the OHRQoL improvement.	44
Acute severe pericoronitis	14/16 (conventional protocol group) 19/10 (aPDT group)	17.4 $\pm$ 3.5 (conventional protocol group) 19.6 $\pm$ 5.1 (aPDT group)	Methylene blue (solution)	0.0005%	Applied under the pericoronal flap	2 min	Diode laser	Wavelength: 660 nm Energy fluency: 25 J/ cm <sup>2</sup> Power output: 150 mW Power density: 1.1 W/cm <sup>2</sup> Exposure time: 1 min	Single session	MPQ VAS	-	-	Methylene blue- mediated aPDT effectively decreased TNF- $\alpha$ and microbial load. However, it exhibited similar impact on pain score as conventional debridement when applied under the pericoronal flap. Methylene blue- mediated aPDT combined with the low-level laser therapy (gallium aluminum arsenide laser; wavelength: 808 $\pm$ 10 nm, output power: 100 mW,	45
Molar extraction	7/3 (control group) 5/ 5 (aPDT group) 7/3 (low level laser therapy group) 6/4 (aPDT + low level laser therapy group)	38.60 $\pm$ 17.02 (control group) 32.30 $\pm$ 8.86 (aPDT group) 50.10 $\pm$ 12.51 (low level laser therapy group) 44.00 $\pm$ 11.39 (aPDT + low level laser therapy group)	Methylene blue (solution)	0.01%	Applied in the fresh socket	5 min	InGaAIP	Wavelength: 660 $\pm$ 10 nm Output power: 100 mW Output energy: 9 J Fluency: 300 J / cm <sup>2</sup> Irradiance: 3.33 W / cm <sup>2</sup> Exposure time: 90 sec	Single session	VAS	-	-	Methylene blue- mediated aPDT combined with the low-level laser therapy (gallium aluminum arsenide laser; wavelength: 808 $\pm$ 10 nm, output power: 100 mW,	46

Generalized gingivitis	5/10 (aPDT group) 6/9 (dental scaling group)	16.1 ± 1.4 (aPDT group) 15.9 ± 1.3 (dental scaling group)	Methylene blue (solution)	0.0005%	Injected into periodontal pockets	No less than 2 min	Diode laser	Wavelength: 670 nm Power: 150 mW Fluence: 22 J/cm <sup>2</sup> Density: 1.1 W/cm <sup>2</sup> Exposure time: 1 min	Single session	MPQ VAS	-	output energy: 4 J, fluence: 133 J/cm <sup>2</sup> , 40 seconds, and irradiance: 3.33 W/cm <sup>2</sup> ) showed the lowest postoperative pain. There was no significant difference in pain score reduction between dental scaling with or without aPDT. The pain reduction observed with methylene blue-mediated aPDT may be attributed to its antimicrobial effect (reducing pathogenic load) and anti-inflammatory effect (significantly reducing TNF- $\alpha$ levels). <sup>47</sup>
Endodontic treatment (Pulp necrosis)	12/18 (control group) 10/20 (aPDT group)	46.97 ± 13.23 (control group) 46.73 ± 16.30 (aPDT group)	Methylene blue (solution)	1.56 $\mu$ M/mL	Applied inside the root canal	3 min	Laser Duo (MM Optics)	Wavelength: 660 nm Power: 100 mW Fluence: 600 J/cm <sup>2</sup> Exposure time: 3 min	Single session	VAS	-	The use of methylene blue-mediated aPDT as adjunctive antimicrobial technique during endodontic treatment showed a notable impact compared to the group solely irrigated with 2.5% sodium hypochlorite, effectively reducing postoperative pain at both the 24-hour and 72-hour marks after a one-time treatment for single-rooted teeth with necrotic pulps. <sup>48</sup>
Chronic periodontitis	15/29 (SRP group) 22/22 (aPDT group)	38.4 ± 9.6 (SRP group) 40.8 ± 8.3 (aPDT group)	Methylene blue (solution)	10 mg/mL	Applied topically (2 mL) into the pocket	1 min	Diode laser	Wavelength: 655 nm Intensity: 60 W/cm <sup>2</sup> Exposure time: 1 min	Single session	VRS	-	Methylene blue-mediated aPDT enhanced patient satisfaction by decreasing symptoms such as gingival bleeding, halitosis, pain, and discomfort while eating after the treatment. <sup>49</sup>

(continued on next page)

Table 1 (continued)

Patients		Antimicrobial photodynamic therapy						Variables		Outcome	Refs		
		Photosensitizer		Light source		Pain		OHRQoL					
Oral infection/ dental procedure	Gender (male/ female)	Age (mean ± SD)	Type (gel/ solution)	Concentration	Application	Time	Type	Irradiation parameters	Sessions	Pain	OHRQoL	Outcome	Refs
Molar extraction	58/92	Under 18 (8%) 19 to 24 (42%) 25 to 30 (25%) Over 30 (25%)	Toluidine chloride (solution)	155 µg/mL	Applied in the fresh socket	1 min	Diode laser	Wavelength: 660 nm Power: 50 mW Exposure time: 1 min	Single session	Dichotomous scale (yes or no)	Postoperative problems (no problems, mild problems, medium problems, and intensive problems)	The combination of toluidine chloride-mediated aPDT and low-level laser therapy (Diode laser; wavelength: 660 nm, intensity: 90 mW, 3 min) greatly improved postoperative issues such as swelling, halitosis, and analgesic use following third molar surgery.	50

Abbreviations: aPDT, antimicrobial photodynamic therapy; ECOHIS, Early childhood oral health impact scale; GaAlAs, Gallium–aluminum–arsenide; g/L, Grams per liter; InGaAlP, Indium gallium aluminum phosphide; J/cm<sup>2</sup>, Joules per square centimeter; J, Joule; SD, Standard deviation; Min, Minute; mW/cm<sup>2</sup>, Milliwatt per square centimeter; µg/mL, Microgram per milliliter; µM/mL, Micromole per milliliter; mg/mL, Milligram per milliliter; mW, Milliwatt; MPQ, McGill pain questionnaire; Nm, Nanometer; N/A, Not applicable; OHIP, Oral health impact profile; OHRQoL, Oral health-related quality of life; Refs, References; LED, Light-emitting diode; NSAID, Non-steroidal anti-inflammatory drugs; SRP, Scaling and root planning; Sec, Second; TNF- $\alpha$ , Tumor necrosis factor-alpha; VRS, Verbal rating scale; VAS, Visual analog scale; W/cm<sup>2</sup>, Watt per square centimeter.

achieved by inhibiting the activity of delta A and type C nerve fibers. Slowing down the transmission of pain signals through these nerve fibers effectively alters the pain threshold, making individuals more tolerant of pain.<sup>14,20,21</sup>

### Pain and oral health-related quality of life

Table 1 presents an overview of the application of aPDT in dentistry. It highlights the effectiveness of aPDT as an adjunctive treatment and antimicrobial method for addressing oral infections and managing complications following dental procedures. The clinical studies included in the table are categorized into two groups. The first group of studies focused on the use of aPDT for managing various oral infections, such as denture stomatitis,<sup>37,40</sup> gingivitis,<sup>47</sup> periodontitis,<sup>39,49</sup> pericoronitis,<sup>45</sup> mucositis,<sup>42</sup> and halitosis.<sup>44</sup> The second group of studies examined the application of aPDT during specific dental procedures, including third molar extraction,<sup>38,46,50</sup> FGG,<sup>16</sup> dental caries,<sup>41</sup> and endodontic treatment.<sup>43,48</sup> Overall, the findings of these studies indicated that aPDT did not cause side effects such as pain or negatively impact the patient’s quality of life. Reviewed studies also investigated the effects of aPDT on pain and the quality of life of patients with oral and dental problems. These studies aimed to determine whether aPDT could effectively control pain and improve OHRQoL better than conventional treatments.

Pain, especially when experienced in the orofacial region, can have a significant impact on various aspects of an individual’s life. For understanding the effect of oral conditions and evaluating the effectiveness of dental treatments requires considering pain as one of the most crucial patient-reported outcomes.<sup>51</sup> To assess the levels of pain, researchers have employed questionnaires, with the Visual Analog Scale and McGill Pain Questionnaire being the prominent tools used.<sup>16,42,43,45–48</sup> Reviewed studies showed the significant benefits of aPDT in alleviating pain after dental treatments such as third molar extraction, FGG surgery, post-endodontic therapy in teeth with periapical lesion and pulp necrosis, and pain associated with oral infections such as gingivitis, periodontitis, pericoronitis, and mucositis. Additionally, aPDT has demonstrated its effectiveness in reducing intraoral microorganisms, exhibiting minimal toxicity, preventing the development of microbial resistance, and preserving the natural balance of the oral microbiota.<sup>16,42,43,45–50</sup>

This effectiveness of aPDT is influenced by the properties of the PS used and the characteristics of the applied light source. One PS of interest is Emo, which exhibits anti-inflammatory properties like NSAIDs, specifically as COX-2 inhibitors. Furthermore, a study by Yaghobee et al. demonstrated that Emo-mediated aPDT (LED, 450 nm, 1000 ± 1400 mW/cm<sup>2</sup>, 60–80 J/cm<sup>2</sup>, 60 s) led to accelerated wound healing and reduced postoperative pain in the context of a free gingival graft procedure.<sup>16</sup> Emo, when activated at 450 nm, up-regulates urokinase plasminogen activator (uPA) and inhibits plasminogen activator inhibitor (PAI-1), thereby enhancing fibrinolysis and promoting fibroblast migration to the wound area.<sup>52</sup> Another PS extensively studied in previous research is methylene blue (MB). MB is the most used PSs in previous studies,<sup>43,45–49,53</sup>

with associated light sources typically ranging from 630 to 700 nm in wavelength.<sup>8</sup> The light penetration depth of most PSs (such as toluidine chloride, MB, and chloro-aluminum phthalocyanine) falls within the range of 0.5 cm (at 630 nm) to 1.5 cm (at 700 nm).<sup>39,50,54</sup> Moreover, the laser beam used in aPDT exhibits anti-inflammatory effects by reducing the concentration of prostaglandin (PGE<sub>2</sub>), altering the path of arachidonic acid, and mitigating the effects of tumor necrosis factors (TNF- $\alpha$ ) in acute inflammatory states.<sup>55</sup> It is important to note that TNF- $\alpha$  is known to contribute to the deterioration of soft connective tissue and alveolar bone.<sup>55</sup> Additionally, laser stimulation promotes natural biological processes that accelerate the healing process, such as increased production of adenosine triphosphate (ATP), which is crucial for cellular energy and regeneration.<sup>56,57</sup> Laser therapy also helps restore the optimal redox state of cells, as damaged or inflamed tissues often exhibit a low redox state. Laser energy stimulates these cells, leading to improved healing.<sup>56,57</sup> In brief, aPDT reduces the microbial load and decreases the levels of inflammatory cytokines such as TNF- $\alpha$ . It also promotes angiogenesis and increases ATP production, leading to enhanced cell proliferation and accelerating the natural healing processes. By accelerating healing, aPDT reduces patient discomfort and pain. In addition, the analgesic mechanism of aPDT inhibits the inflammation arachidonic acid pathway. Also, the laser beam in aPDT involves the modulation of various neurotransmitters like  $\beta$ -endorphin, serotonin, and acetylcholinesterase. This modulation affects nociception and reduces the conduction velocity of nerve impulses.

Pain is a main aspect of OHRQoL, which aims to assess the impact of oral health conditions on an individual.<sup>58</sup> To effectively address the physical, social, and psychological consequences of oral infections and dental procedures, it is beneficial for dentists to utilize a validated questionnaire that comprehensively evaluates the quality of life.<sup>51,59</sup> Such assessments can assist dentists in selecting the most appropriate techniques to minimize the occurrence of postoperative complications. The Oral Health Impact Profile (OHIP) is a widely recognized and reliable multidimensional questionnaire that can be employed to evaluate the consequences of oral health conditions.<sup>60</sup> By utilizing the OHIP questionnaire, dentists can identify patients who are at risk and develop interventions that consider both clinical and subjective outcomes. This approach provides a holistic understanding of the impact of oral health conditions on patients' quality of life.<sup>61,62</sup> Several studies evaluated the effects of aPDT on OHRQoL.<sup>37–41,44,50</sup> Out of the seven studies identified, five studies utilized the OHIP questionnaire,<sup>37–40,44</sup> while one study used the Early Childhood Oral Health Impact Scale (ECOHIS).<sup>41</sup> Additionally, one study specifically inquired about postoperative problems.<sup>50</sup> These studies investigated the application of aPDT as either an adjunctive treatment for managing oral diseases like denture stomatitis,<sup>37,40</sup> periodontitis,<sup>39</sup> and halitosis,<sup>44</sup> or as a novel antimicrobial technique during dental procedures such as dental caries treatment and tooth extraction.<sup>38,41,50</sup> Overall, the findings from these studies demonstrated that aPDT, whether used alone or in combination with other treatments such as low-level laser therapy or standard treatment, had a positive impact on

patients' OHRQoL.<sup>37–41,44,50</sup> Notably, the combination of aPDT with other treatment modalities showed a synergistic effect, further enhancing the improvement in patients' OHRQoL.<sup>40,50</sup>

In conclusion, aPDT has demonstrated effectiveness in providing pain relief and improving OHRQoL among patients with oral infections or undergoing dental procedures. The simplicity of the technique, combined with its efficiency, makes it a valuable addition to dental settings without consuming excessive time or incurring high costs. Based on the findings of the present literature review, aPDT is highly recommended as an adjunctive strategy that can be considered to enhance the overall treatment outcomes for patients. By incorporating aPDT into the existing treatment protocols, dental professionals can potentially achieve better pain management, expedite the healing process, and improve patients' satisfaction with their oral health care. By combining the use of antimicrobial agents and light activation, aPDT offers an innovative and effective means of combating oral infections, reducing pain, and enhancing the overall oral health experience for patients. However, further research and clinical studies are warranted to explore the long-term effects and optimal application protocols of aPDT.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgments

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

## References

1. Prazmo EJ, Kwaśny M, Łapiński M, Mielczarek A. Photodynamic therapy as a promising method used in the treatment of oral diseases. *Adv Clin Exp Med* 2016;25:799–807.
2. Jao Y, Ding SJ, Chen CC. Antimicrobial photodynamic therapy for the treatment of oral infections: a systematic review. *J Dent Sci* 2023;18:1453–66.
3. Sharman WM, Allen CM, Van Lier JE. Photodynamic therapeutics: basic principles and clinical applications. *Drug Discov Today* 1999;4:507–17.
4. Youf R, Müller M, Balasini A, et al. Antimicrobial photodynamic therapy: latest developments with a focus on combinatory strategies. *Pharmaceutics* 2021;13:1995.
5. Huang L, Xuan Y, Koide Y, Zhiyentayev T, Tanaka M, Hamblin MR. Type i and type ii mechanisms of antimicrobial photodynamic therapy: an in vitro study on gram-negative and gram-positive bacteria. *Laser Surg Med* 2012;44:490–9.
6. Correia JH, Rodrigues JA, Pimenta S, Dong T, Yang Z. Photodynamic therapy review: principles, photosensitizers, applications, and future directions. *Pharmaceutics* 2021;13:1332.
7. Pourhajibagher M, Bahrami R, Bahador A. Application of photosensitive dental materials as a novel antimicrobial option in dentistry: a literature review. *J Dent Sci* 2024;19:762–72.
8. Gursoy H, Ozcakir-Tomruk C, Tanalp J, Yilmaz S. Photodynamic therapy in dentistry: a literature review. *Clin Oral Invest* 2013;17:1113–25.



9. Rajesh S, Koshi E, Philip K, Mohan A. Antimicrobial photodynamic therapy: an overview. *J Indian Soc Periodontol* 2011;15:323–7.
10. Sischo L, Broder HL. Oral health-related quality of life: what, why, how, and future implications. *J Dent Res* 2011;90:1264–70.
11. Barasuol JC, Santos PS, Moccellini BS, et al. Association between dental pain and oral health-related quality of life in children and adolescents: a systematic review and meta-analysis. *Community Dent Oral Epidemiol* 2020;48:257–63.
12. Moura-Leite FR, Ramos-Jorge J, Ramos-Jorge ML, Paiva SM, Vale MP, Pordeus IA. Impact of dental pain on daily living of five-year-old Brazilian preschool children: prevalence and associated factors. *Eur Arch Paediatr Dent* 2011;12:293–7.
13. Clementino MA, Gomes MC, De TC, et al. Perceived impact of dental pain on the quality of life of preschool children and their families. *PLoS One* 2015;10:e0130602.
14. Silveira PCL, Silva LA, Freitas TP, Latini A, Pinho RA. Effects of low-power laser irradiation (lpli) at different wavelengths and doses on oxidative stress and fibrogenesis parameters in an animal model of wound healing. *Laser Med Sci* 2011;26:125–31.
15. Artés-Ribas M, Arnabat-Dominguez J, Puigdollers A. Analgesic effect of a low-level laser therapy (830 nm) in early orthodontic treatment. *Laser Med Sci* 2013;28:335–41.
16. Yaghoobee S, Pourhajibagher M, Bahrami R, Isaabadi M. Nanomodulin mediated photodynamic therapy for wound healing of donor site after free gingival graft: a parallel clinical trial. *Photodiagnosis Photodyn Ther* 2024;45:103958.
17. Ang JM, Riaz I Bin, Kamal MU, Paragh G, Zeitouni NC. Photodynamic therapy and pain: a systematic review. *Photodiagnosis Photodyn Ther* 2017;19:308–44.
18. Souza MA, Bonacina LV, Trento A, et al. Influence of the apical limit of instrumentation and photodynamic therapy on the postoperative pain of lower molars with asymptomatic apical periodontitis. *Photodiagnosis Photodyn Ther* 2021;36:102489.
19. Park MY, Kwon HJ, Sung MK. Evaluation of aloin and aloe-emodin as anti-inflammatory agents in aloe by using murine macrophages. *Biosci Biotechnol Biochem* 2009;73:828–32.
20. Karu T. Mitochondrial mechanisms of photobiomodulation in context of new data about multiple roles of atp. *Photomed Laser Surg* 2010;28:159–60.
21. Metin R, Tatli U, Evlice B. Effects of low-level laser therapy on soft and hard tissue healing after endodontic surgery. *Laser Med Sci* 2018;33:1699–706.
22. Duong HY, Rocuzzo A, Stähli A, Salvi GE, Lang NP, Sculean A. Oral health-related quality of life of patients rehabilitated with fixed and removable implant-supported dental prostheses. *Periodontol* 2000 2022;88:201–37.
23. Riva F, Seoane M, Reichenheim ME, Tsakos G, Celeste RK. Adult oral health-related quality of life instruments: a systematic review. *Community Dent Oral Epidemiol* 2022;50:333–8.
24. Vila-Nova TEL, Leão R de S, Santiago Junior JF, Pellizzer EP, Vasconcelos BC do E, Moraes SLD. Photodynamic therapy in the treatment of denture stomatitis: a systematic review and meta-analysis. *J Prosthet Dent* 2023;130:825–32.
25. Ouanounou A, Ng K, Chaban P. Adverse drug reactions in dentistry. *Int Dent J* 2020;70:79–84.
26. Mohan M. Pharmacological agents in dentistry: a review. *Br J Pharmaceut Res* 2011;1:66–87.
27. Carrera ET, Dias HB, Corbi SCT, et al. The application of antimicrobial photodynamic therapy (apdt) in dentistry: a critical review. *Laser Phys* 2016;26:123001.
28. da Silva CC, Chaves Júnior SP, Pereira GLD, et al. Antimicrobial photodynamic therapy associated with conventional endodontic treatment: a clinical and molecular microbiological study. *Photochem Photobiol* 2018;94:351–6.
29. Bahrami R, Pourhajibagher M, Gharibpour F. Antimicrobial photodynamic therapy for the management of gingivitis and white spot lesions in fixed orthodontic patients: a systematic review. *Int Orthod* 2024;22:100821.
30. Bahrami R, Nikparto N, Gharibpour F, Pourhajibagher M, Bahador A. Antimicrobial photodynamic therapy for managing the peri-implant mucositis and peri-implantitis: a systematic review of randomized clinical trials. *Photodiagnosis Photodyn Ther* 2024;45:103990.
31. Dougherty TJ. An update on photodynamic therapy applications. *J Clin Laser Med Surg* 2002;20:3–7.
32. Bevilacqua IM, Nicolau RA, Khouri S, et al. The impact of photodynamic therapy on the viability of streptococcus mutans in a planktonic culture. *Photomed Laser Surg* 2007;25:513–8.
33. Stájer A, Kajári S, Gajdács M, Musah-Eroje A, Baráth Z. Utility of photodynamic therapy in dentistry: current concepts. *Dent J* 2020;8:43.
34. Turajane K, Ji G, Chinenov Y, et al. RNA-seq analysis of peri-implant tissue shows differences in immune, notch, wnt, and angiogenesis pathways in aged versus young mice. *JBMR Plus* 2021;5:e10535.
35. Tonin MH, Brites FC, Mariano JR, Freitas KMS, Ortiz MAL, Salmeron S. Low-level laser and antimicrobial photodynamic therapy reduce peri-implantitis-related microorganisms grown in vitro. *Eur J Dermatol* 2022;16:161–6.
36. Chow RT, David MA, Armati PJ. 830 nm laser irradiation induces varicosity formation, reduces mitochondrial membrane potential and blocks fast axonal flow in small and medium diameter rat dorsal root ganglion neurons: implications for the analgesic effects of 830 nm laser. *J Peripher Nerv Syst* 2007;12:28–39.
37. Alhamdan MM, Basunbul GI. Oral health-related quality of life among complete denture stomatitis patients treated with methylene-blue-mediated photodynamic therapy. *Appl Sci* 2024;14:926.
38. Souza MRJ, Meyfarth S, Fraga RS, et al. Do antimicrobial photodynamic therapy and low-level laser therapy influence oral health-related quality of life after molar extraction? *J Oral Maxillofac Surg* 2023;81:1033–41.
39. Al-Kheraif AA, Javed R, Al-Momani MM, Wasi A, Mohamed BA, Khan AA. Effectiveness of photodynamic therapy on clinical and biomarker related periodontal parameters and oral health related quality of life (ohrqol) in Parkinson's disease patients with stage iii periodontitis. *Photodiagnosis Photodyn Ther* 2023;43:103690.
40. Al-Aali KA, Alqahtani AS, AlZaid AA, Almujel SH, Alsalam M, Alanazi KK. Efficacy of adjunct photodynamic therapy on Candida growth and oral health quality of life in denture stomatitis patients with type 2 diabetes mellitus wearing implant-retained overdentures: a randomized clinical study. *Photodiagnosis Photodyn Ther* 2023;42:103630.
41. dos Reis Pio LR, Faria LV, Pinheiro LHM, et al. Effect of treatment with selective caries removal associated to antimicrobial photodynamic therapy on children's oral health-related quality of life: a non-randomized clinical study. *J Clin Pediatr Dent* 2022;46:287–92.
42. de Cássia Dias Viana Andrade R, Azevedo Reis T, Rosa LP, de Oliveira Santos GP, da CristinaSilva F. Comparative randomized trial study about the efficacy of photobiomodulation and curcumin antimicrobial photodynamic therapy as a coadjuvant treatment of oral mucositis in oncologic patients: antimicrobial, analgesic, and degree alteration effect. *Support Care Cancer* 2022;30:7365–71.
43. Alves-Silva EG, Arruda-Vasconcelos R, Louzada LM, et al. The effect of photodynamic therapy on postoperative pain in teeth with primary endodontic infection. *Photodiagnosis Photodyn Ther* 2022;37:102700.

44. Labban N, Assery MK, Al-Kattan R, Al-Shibani N, Alfouzan AF, Al Taweel SM. Antimicrobial capacity of photodynamic therapy on oral health-related quality of life and halitosis among elderly patients wearing removal dentures. *Photodiagnosis Photodyn Ther* 2020;32:102059.
45. Elsadek MF, Ahmed BM, Eskandrani RM. Level of pain intensity, cytokine profiling and microbial load after photodynamic therapy in acute severe pericoronitis. *Photodiagnosis Photodyn Ther* 2020;31:101830.
46. Fraga RS, Antunes LAA, Fialho WLS, et al. Do antimicrobial photodynamic therapy and low-level laser therapy minimize postoperative pain and edema after molar extraction? *J Oral Maxillofac Surg* 2020;78: 2155-e1.
47. Baeshen HA, Alshahrani A, Kamran MA, Alnazeh AA, Alhaizaey A, Alshahrani I. Effectiveness of antimicrobial photodynamic therapy in restoring clinical, microbial, proinflammatory cytokines and pain scores in adolescent patients having generalized gingivitis and undergoing fixed orthodontic treatment. *Photodiagnosis Photodyn Ther* 2020; 32:101998.
48. Coelho MS, Vilas-Boas L, Tawil PZ. The effects of photodynamic therapy on postoperative pain in teeth with necrotic pulps. *Photodiagnosis Photodyn Ther* 2019;27:396–401.
49. Betsy J, Prasanth CS, Baiju KV, Prasanthila J, Subhash N. Patients' perceptions of antimicrobial photodynamic therapy in the management of chronic periodontitis. *Photodiagnosis Photodyn Ther* 2016;14:84–90.
50. Batinjan G, Zore IF, Rupiç I, Juriç IB, Zore Z, Pandurić DG. Assessing health-related quality of life with antimicrobial photodynamic therapy (apdt) and low level laser therapy (lllt) after third molar removal. *J Laser Med Sci* 2013;4:120.
51. Oghli I, List T, Su N, Häggman-Henrikson B. The impact of orofacial pain conditions on oral health-related quality of life: a systematic review. *J Oral Rehabil* 2020;47:1052–64.
52. Radha KS, Madhyastha HK, Nakajima Y, Omura S, Maruyama M. Emodin upregulates urokinase plasminogen activator, plasminogen activator inhibitor-1 and promotes wound healing in human fibroblasts. *Vasc Pharmacol* 2008;48:184–90.
53. La Selva A, Negreiros RM, Bezerra DT, et al. Treatment of herpes labialis by photodynamic therapy. *Medicine (Baltim)* 2020;99:e19500.
54. Bashkatov AN, Genina EA, Kochubey VI, Tuchin VV. Optical properties of human skin, subcutaneous and mucous tissues in the wavelength range from 400 to 2000 nm. *J Phys D Appl Phys* 2005;38:2543.
55. Aimbire F, Albertini R, Pacheco MTT, et al. Low-level laser therapy induces dose-dependent reduction of TNF $\alpha$  levels in acute inflammation. *Photomed Laser Surg* 2006;24:33–7.
56. Amat A, Rigau J, Nicolau R, et al. Effect of red and near-infrared laser light on adenosine triphosphate (atp) in the luciferine-luciferase reaction. *J Photochem Photobiol Chem* 2004;168:59–65.
57. Hamblin MR, Huang YY, Sharma SK, Carroll J. Biphasic dose response in low level light therapy - an update. *Dose Response* 2011;9:602–18.
58. John MT, Feuerstahler L, Waller N, et al. Confirmatory factor analysis of the oral health impact profile. *J Oral Rehabil* 2014; 41:644–52.
59. John MT, Reissmann DR, Feuerstahler L, et al. Exploratory factor analysis of the oral health impact profile. *J Oral Rehabil* 2014;41:635–43.
60. De Oliveira BH, Nadanovsky P. Psychometric properties of the brazilian version of the oral health impact profile - short form. *Community Dent Oral Epidemiol* 2005;33:307–14.
61. Vinita Mary A, Mahendra J, John J, Moses J, Rajesh Ebenezer AV, Kesavan R. Assessing quality of life using the oral health impact profile (ohip-14) in subjects with and without orthodontic treatment need in Chennai, Tamil nadu, India. *J Clin Diagn Res* 2017;11:ZC78.
62. Brennan DS, Spencer AJ. Dimensions of oral health related quality of life measured by eq-5d+ and ohip-14. *Health Qual Life Outcome* 2004;2:1–9.