

# Research Progress of Photodynamic Therapy as Adjunctive Treatment for Chronic Periodontitis

Zhiwei Li

Department of Stomatology, Taihe Hospital, Hubei University of Medicine, Shiyan, China  
1378819731@qq.com

**Abstract:** Chronic periodontitis (CP) is a highly prevalent oral inflammatory disease initiated by dysbiotic dental plaque biofilms. It causes progressive destruction of periodontal supporting tissues and poses a significant risk of tooth loss in adults worldwide. Conventional therapeutic strategies, such as scaling and root planing (SRP) and antibiotic therapy, are limited by issues like incomplete eradication of deep subgingival pathogens and the emergence of antimicrobial resistance. Photodynamic therapy (PDT), a minimally - invasive treatment modality that relies on photochemical reactions to generate reactive oxygen species (ROS) for bactericidal activity, has attracted substantial attention in periodontal treatment due to its broad - spectrum antibacterial effects, minimal invasiveness, and low risk of inducing drug resistance. In recent years, combining PDT with conventional periodontal treatments has emerged as a promising approach to improve therapeutic efficacy, becoming a focus of clinical and basic research. This review comprehensively summarizes the fundamental mechanisms of PDT, highlighting the synergistic interactions among photosensitizers (PS), light sources, and molecular oxygen. It systematically reviews the clinical progress of PDT - based combination therapies, including PDT combined with SRP, antibiotics, and surgical interventions, in the management of chronic periodontitis. Moreover, the key factors influencing PDT efficacy, such as PS characteristics, laser parameters, and patient - related factors, are thoroughly examined. Finally, the current challenges and future research directions of PDT combination therapy are discussed, aiming to provide a comprehensive theoretical basis for its clinical application and further development in periodontology.

**Keywords:** Photodynamic therapy; Periodontitis; Combination therapy; Therapeutic mechanism; Clinical efficacy

## 1. Introduction

Chronic periodontitis is a chronic inflammatory disorder characterized by the breakdown of periodontal ligaments, alveolar bone resorption, and gingival recession, primarily driven by the dysbiosis of oral microbiota (e.g., *Porphyromonas gingivalis*, *Tannerella forsythia*, *Aggregatibacter actinomycetemcomitans*) and dysregulated host immune responses<sup>[1]</sup>. As one of the leading causes of tooth loss in adults worldwide, it affects approximately 40–50% of the adult population, imposing a substantial burden on oral health and quality of life<sup>[2]</sup>.

Traditional clinical management of chronic periodontitis mainly relies on mechanical debridement, with SRP being the gold standard for removing dental plaque and calculus<sup>[3]</sup>. For severe infections, systemic or local antibiotics are often used as adjunctive treatments<sup>[4]</sup>. However, the complex anatomical structure of periodontal pockets makes it difficult to completely eliminate deep subgingival pathogens through mechanical methods alone<sup>[5]</sup>. Moreover, long-term and inappropriate use of antibiotics not only induces bacterial drug resistance but also disrupts the balance of the oral microecology, thereby compromising the long-term therapeutic effect<sup>[6]</sup>. These limitations have prompted researchers to explore novel adjunctive therapeutic strategies.

PDT was introduced into periodontal therapy in the 1990s<sup>[7]</sup>. It utilizes the interaction between PS, specific wavelengths of light, and molecular oxygen to generate ROS (e.g., singlet oxygen, hydroxyl radicals), which can induce bacterial apoptosis and modulate inflammatory responses<sup>[8]</sup>. Compared with traditional treatments, PDT exhibits distinct advantages such as minimal invasiveness, broad-spectrum antibacterial activity, lack of drug resistance, and preservation of normal oral tissues<sup>[9]</sup>. In recent years, a growing body of evidence has demonstrated that combining PDT with conventional treatments can effectively overcome the limitations of monotherapy, significantly improving the therapeutic effect of chronic periodontitis<sup>[10]</sup>. This review integrates the latest research findings from both domestic and

international studies to systematically elaborate on the mechanisms, clinical applications, influencing factors, challenges, and future directions of PDT combination therapy for chronic periodontitis, aiming to provide valuable references for clinical practice and further research.

## 2. Fundamental Mechanisms of Photodynamic Therapy

PDT is a photochemical process that relies on the synergistic effect of three core components: PS, a specific wavelength of light, and molecular oxygen [11]. These three components work together to exert cytotoxic effects on pathogenic cells while sparing normal tissues, forming the basis of PDT's application in the treatment of chronic periodontitis [12].

### 2.1 Core Components of PDT

#### 2.1.1 Photosensitizers (PS)

PS is a key component of PDT that generates bioactive molecules upon light irradiation [13]. An ideal PS should possess properties such as matching absorption spectrum with the light source, good biocompatibility, strong tissue permeability, and specific targeting ability [14]. Traditional PS, such as hematoporphyrin derivative (HpD), have strong antiproliferative effects but are limited by inherent drawbacks including toxicity and potential allergic reactions [15]. In recent years, the development of novel PS has significantly advanced the field of PDT. These include 8-methoxysoralen, phthalocyanine compounds, indocyanine green (ICG), gold nanoparticles, and carbon nanotubes [16]. Among them, phthalocyanine compounds exhibit enhanced photosensitivity, reduced toxicity, and improved tissue penetration [17]. ICG can effectively eliminate *Candida albicans* after activation [18], while curcumin, a natural plant-derived PS, integrates antibacterial, anti-inflammatory, and antioxidant properties [19]. Additionally, methylene blue (MB) is widely used in periodontal PDT due to its high affinity for gram-negative periodontal pathogens [20].

#### 2.1.2 Light Sources

Light sources activate PS through low-power visible light, with red light (630–700 nm) being the most commonly used due to its ability to penetrate 0.5–1.5 cm into periodontal tissues. Low-power diode lasers are preferred in clinical settings for their high specificity, while light-emitting diodes (LEDs) offer advantages such as longer irradiation time, lower cost, and easier operation. In contrast, gas discharge lamps (e.g., halogen lamps) require spectral filtering and carry a risk of thermal damage to the dental pulp, limiting their clinical application [21]. The key parameters of light sources include wavelength, energy density, and irradiation time. Studies have confirmed that the optimal activation wavelength is 660 nm for MB and 450 nm for curcumin. An energy density of 80 J/cm<sup>2</sup> has been shown to achieve the best antibacterial effect, while energy densities exceeding 100 J/cm<sup>2</sup> may cause tissue damage. The typical irradiation time ranges from 3 to 5 minutes, which can be adjusted according to the depth of the periodontal pocket.

#### 2.1.3 Molecular Oxygen

Molecular oxygen is an essential prerequisite for ROS generation in PDT [22]. Upon light activation, PS transitions from the ground state to an excited state and transfers energy to molecular oxygen, producing singlet oxygen ( $^1\text{O}_2$ ) and other oxidizing ROS. Adequate oxygen levels in the periodontal environment can enhance the efficacy of PDT, while excessive oxygen may have the opposite effect [23]. However, in chronic periodontitis, inflammation and tissue destruction often lead to hypoxia in the periodontal pocket, which significantly limits the generation of ROS and thereby impairs PDT efficacy. Therefore, optimizing the oxygen supply in the periodontal pocket is a critical factor for improving the therapeutic effect of PDT.

## 2.2 Mechanisms of Action in Chronic Periodontitis

### 2.2.1 ROS-Mediated Bactericidal Effect

The ROS generated during PDT, including singlet oxygen, hydroxyl radicals, and superoxide anions, can directly damage bacterial cell membranes, proteins, and DNA, ultimately leading to bacterial death. This mechanism is particularly effective against key periodontal pathogens such as *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, and *Tannerella forsythia*. Moreover, PDT can disrupt the extracellular matrix of dental plaque biofilms, facilitating the elimination of residual

pathogens that are difficult to remove by SRP alone. Additionally, ROS can degrade antibiotic-resistant genes in bacteria, reversing bacterial resistance and enhancing the susceptibility of pathogens to antibiotics, which has been confirmed by both in vitro and clinical studies.

### 2.2.2 Immune Regulatory Effect

PDT not only exerts a direct bactericidal effect but also modulates the host immune response to enhance pathogen clearance and tissue repair. It can activate macrophages and T lymphocytes, promoting their phagocytic activity and pathogen recognition ability. Furthermore, PDT can regulate the secretion of cytokines in periodontal tissues, upregulating the expression of pro-inflammatory cytokines (e.g., TNF- $\alpha$ , IL-1) to enhance the immune response against pathogens, while inhibiting the release of immunosuppressive factors (e.g., TGF- $\beta$ , IL-10) to restore the balance of the immune-inflammatory response in periodontal tissues. This dual regulatory effect on the immune system contributes to reducing periodontal inflammation and promoting tissue regeneration.

## 3. Clinical Applications of PDT Combination Therapy for Periodontitis

### 3.1 PDT Combined with Scaling and Root Planing (SRP)

SRP is the cornerstone of non-surgical treatment for chronic periodontitis, but it is often ineffective in eliminating pathogens in deep periodontal pockets, furcation areas, and other anatomical [24]. Combining PDT with SRP has been shown to significantly enhance therapeutic outcomes. In vitro and clinical studies have demonstrated that the combination of SRP and PDT can more effectively reduce the levels of key periodontal pathogens such as *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* in periodontal pockets compared to SRP alone. Clinically, this combination therapy results in a significant reduction in probing pocket depth (PPD) and clinical attachment loss (CAL) at 3 and 6 months post-treatment, while also improving indicators such as bleeding on probing (BOP) [25].

The synergistic mechanism of SRP combined with PDT is multifaceted. On one hand, SRP mechanically removes the majority of dental plaque and calculus, reducing the bacterial load and providing a favorable environment for PDT. On the other hand, PDT can eliminate residual biofilms and pathogens that are not completely removed by SRP by disrupting the extracellular matrix of biofilms [26]. Additionally, PDT can downregulate the expression of inflammatory factors such as MMP-9 and ICAM-1 in periodontal tissues, reducing gingival inflammation and swelling, and promoting the repair and regeneration of periodontal supporting tissues [27].

### 3.2 PDT Combined with Antibiotic Therapy

Antibiotic therapy is commonly used as an adjunctive treatment for moderate-to-severe chronic periodontitis, but the emergence of bacterial drug resistance has become a major challenge limiting its long-term efficacy. The combination of PDT and antibiotics exhibits a significant synergistic antibacterial effect, effectively overcoming this limitation. The synergistic mechanism mainly includes two aspects: first, PDT increases the permeability of bacterial cell membranes, facilitating the entry of antibiotics into bacterial cells and enhancing their intracellular concentration; second, the ROS generated by PDT can directly degrade antibiotic-resistant genes in bacteria, reversing bacterial resistance and improving the sensitivity of pathogens to antibiotics.

Clinical studies have confirmed the efficacy of this combination therapy. Hu et al. found that the combination of minocycline and PDT significantly reduced the number of drug-resistant *Porphyromonas gingivalis* in periodontal pockets compared to minocycline monotherapy. A meta-analysis by Li et al. further demonstrated that antibiotic-PDT combination therapy significantly improved CAL and reduced BOP in patients with moderate-to-severe chronic periodontitis, with a higher therapeutic response rate than antibiotic monotherapy. Additionally, de Almeida et al. [28] reported that acidic methylene blue-mediated PDT combined with antibiotics achieved enhanced therapeutic outcomes in the treatment of experimental periodontitis.

### 3.3 PDT Combined with Surgical Treatment

For patients with advanced chronic periodontitis who require surgical intervention (e.g., flap surgery), PDT serves as a valuable adjunctive therapy to improve surgical outcomes. During periodontal flap

surgery, intraoperative irradiation of the surgical field with PDT can effectively reduce the bacterial load in the gingival crevicular fluid, lowering the risk of postoperative infection [29]. Postoperatively, PDT can promote wound healing by reducing inflammation and enhancing tissue regeneration. Song et al. reported that the combination of PDT and flap surgery accelerated the regeneration of periodontal ligaments and alveolar bone, with a higher rate of new attachment formation at 6 months post-operation compared to flap surgery alone. Aoki et al. [30] also noted that laser-assisted PDT can improve periodontal and peri-implant wound healing.

In addition, recent studies have developed innovative surgical adjuncts based on PDT. For example, Tonon et al. developed a superhydrophobic-tipped antimicrobial PDT (aPDT) device, which was validated in a Wistar rat model and showed promising potential as a novel intraoperative tool for the treatment of periodontitis [31].

### 3.4 Additional Clinical Advantages

Beyond enhancing pathogen eradication and tissue repair, PDT combination therapy offers additional clinical benefits. PDT has inherent analgesic effects, which can reduce patient discomfort during and after treatment. Compared to traditional antibiotic therapy, PDT does not induce bacterial resistance, making it a sustainable treatment option. Furthermore, PDT is minimally invasive, causing little damage to normal oral tissues, and thus improving patient compliance [32]. These advantages make PDT combination therapy a patient-friendly and clinically valuable approach for the treatment of chronic periodontitis.

## 4. Factors Influencing the Efficacy of PDT for Periodontitis

### 4.1 Photosensitizer Characteristics

The characteristics of PS, including type, concentration, and delivery mode, are critical factors affecting PDT efficacy.

Type of PS: Different PS exhibit varying antibacterial spectra and biological activities. MB has a high affinity for gram-negative periodontal pathogens, making it suitable for targeting key periodontal pathogens such as *Porphyromonas gingivalis*. ICG has good tissue penetration and is suitable for the treatment of deep periodontal pockets. Curcumin, a natural PS, integrates antibacterial, anti-inflammatory, and antioxidant properties, offering multiple therapeutic benefits. Phthalocyanine compounds exhibit enhanced photosensitivity and reduced toxicity, making them promising candidates for clinical application [33].

Concentration of PS: The concentration of PS directly affects the generation of ROS. Excessively high PS concentrations can cause self-quenching, reducing ROS production, while low concentrations may fail to achieve the desired bactericidal effect. For example, the optimal concentration of MB for PDT against *Porphyromonas gingivalis* is 50  $\mu$ g/mL, and the optimal concentration of curcumin ranges from 10 to 20  $\mu$ M [34].

Delivery mode of PS: The delivery mode of PS affects its accumulation in periodontal tissues and pockets. Traditional delivery methods may result in low local concentrations of PS and systemic side effects. Novel delivery systems, such as liposomal or mesoporous silica nanoparticle systems, can improve the accumulation of PS in periodontal pockets, enhance its tissue penetration, and minimize systemic side effects [35].

### 4.2 Laser Parameters

Laser parameters, including wavelength, energy density, and irradiation time, directly influence the activation of PS and the generation of ROS, thereby affecting PDT efficacy.

Wavelength: The laser wavelength must match the absorption peak of the PS to maximize excitation efficiency [36]. For example, the optimal activation wavelength is 660 nm for MB and 450 nm for curcumin. Using a wavelength that does not match the PS's absorption spectrum will significantly reduce the generation of ROS and compromise PDT efficacy.

Energy density: Energy density is a key parameter affecting PDT efficacy. A meta-analysis by Chen et al. showed that an energy density of 80 J/cm<sup>2</sup> achieved the best antibacterial effect in periodontal PDT.

Energy densities exceeding 100 J/cm<sup>2</sup> may cause thermal damage to periodontal tissues, while energy densities below the optimal level may not generate sufficient ROS to achieve the desired bactericidal effect [37].

**Irradiation time:** The irradiation time should be adjusted according to the depth of the periodontal pocket and the type of PS. Typically, an irradiation time of 3–5 minutes is sufficient to activate PS and generate adequate ROS [38]. Prolonged irradiation time may increase the risk of tissue damage, while insufficient irradiation time may result in incomplete activation of PS.

#### 4.3 Patient-Related Factors

Patient-specific factors also play an important role in determining PDT efficacy.

**Diabetes:** Diabetes is a well-known risk factor for chronic periodontitis and can significantly affect PDT efficacy. Hyperglycemia reduces tissue oxygen levels and impairs ROS generation, thereby weakening the bactericidal effect of PDT [39]. Additionally, diabetes impairs immune function and tissue repair ability, further compromising treatment outcomes. Therefore, strict blood glucose control is necessary before PDT to improve therapeutic efficacy.

**Smoking:** Smoking is another important factor influencing PDT efficacy. Cigarette smoke contains harmful substances that reduce the accumulation of PS in periodontal tissues and scavenge ROS, leading to a lower therapeutic response rate. Moreover, smoking impairs periodontal tissue healing and increases the risk of disease recurrence. Therefore, smoking cessation or reduction is critical for improving the outcomes of PDT combination therapy.

**Periodontal tissue status:** The severity of periodontal tissue destruction and the depth of periodontal pockets also affect PDT efficacy. Severe periodontal tissue destruction and deep pockets limit the penetration of PS and light, as well as the supply of oxygen, thereby reducing PDT efficacy. In such cases, combining PDT with surgical treatment to improve tissue accessibility is recommended [40].

### 5. Conclusions and Future Perspectives

PDT combination therapy has emerged as a promising approach for the treatment of chronic periodontitis, effectively overcoming the limitations of traditional monotherapy. By enhancing bacterial eradication, reducing inflammation, and promoting tissue repair, PDT combined with SRP, antibiotics, or surgical intervention has demonstrated significant clinical efficacy in improving key indicators such as PPD, CAL, and BOP in patients with chronic periodontitis. Additionally, PDT offers advantages such as minimal invasiveness, no induced drug resistance, and analgesic effects, making it a valuable addition to the armamentarium of periodontal therapy.

However, several critical challenges remain to be addressed before PDT combination therapy can be widely adopted as a routine clinical treatment: (1) The optimal PS and laser parameters for different subtypes and severities of chronic periodontitis have not been standardized, and there is a lack of unified clinical guidelines ; (2) The long-term efficacy and safety of PDT combination therapy require further verification through large-sample, long-term follow-up clinical trials ; (3) The molecular mechanisms underlying the synergistic effect between PDT and conventional treatments are not fully understood, and in-depth molecular biological research is needed [41]; (4) The targeting and delivery efficiency of PS need to be further improved to enhance their accumulation in periodontal pockets and reduce systemic side effects .

Future research should focus on the following directions: (1) Development of targeted and multifunctional PS: Design PS modified with periodontal pathogen-specific ligands to achieve selective accumulation in biofilms. Synthesize multifunctional PS (e.g., curcumin derivatives conjugated with bone morphogenetic protein-2) that integrate antibacterial, anti-inflammatory, and tissue-regenerative properties. Explore natural biodegradable PS (e.g., hypericin, berberine) to improve biocompatibility and reduce toxicity ; (2) Optimization of laser delivery systems: Develop miniaturized, flexible optical fiber probes adapted to the irregular anatomy of periodontal pockets, integrated with real-time feedback sensors for dynamic adjustment of laser parameters. Investigate the application of low-power continuous lasers and dual-wavelength laser combinations to enhance treatment precision and broaden the antibacterial spectrum; (3) In-depth mechanistic research: Utilize multi-omics techniques (metagenomics, transcriptomics, proteomics) to clarify the molecular mechanisms by which PDT reverses bacterial resistance and regulates the host immune-inflammatory response. Apply single-cell RNA sequencing to

identify key signaling pathways (e.g., Wnt/β-catenin, TGF-β) involved in PDT-mediated tissue regeneration ; (4) Advancement of personalized therapy: Conduct large-sample cohort studies to stratify patients based on microbiota composition, systemic disease status, and smoking habits, and develop tailored PDT combination regimens . Perform multicenter randomized controlled trials (RCTs) with ≥5-year follow-up to verify long-term efficacy and safety in special populations (e.g., pregnant women, patients with peri-implantitis) ;(5) Integration with digital dental technology: Establish artificial intelligence (AI)-driven models to automatically recommend personalized PDT parameters based on clinical and imaging data. Utilize 3D printing to fabricate custom laser guide templates for standardized treatment delivery.

With the continuous advancement of photomedicine, materials science, and digital dentistry, PDT combination therapy is expected to become a routine adjunctive treatment for chronic periodontitis, providing personalized and effective care to improve the long-term prognosis of patients with this disease.

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