



## Polymeric Nanoparticle-Loaded Indocyanine Green for Antimicrobial Photodynamic Therapy in Periodontitis: A Mini-Review

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### Abstract

**Objective:** Non-surgical periodontal therapy (NSPT) is considered the gold standard for the treatment of periodontitis; however, its effectiveness may be limited by the inability to completely eliminate pathogenic microorganisms from deep periodontal pockets and complex root surfaces. As a result, residual bacteria may persist and contribute to disease progression. Antimicrobial photodynamic therapy (aPDT) has emerged as a promising alternative adjunctive approach. aPDT utilizes a photosensitizer activated by a specific wavelength of light in the presence of oxygen to generate reactive oxygen species that destroy microbial cells. Indocyanine green (ICG), a near-infrared photosensitizer approved for clinical use, has demonstrated both photodynamic and photothermal antimicrobial effects. Nevertheless, the efficacy of free ICG is limited by poor penetration through bacterial membranes, rapid clearance, and restricted diffusion through biofilms. To address these limitations, nanoparticle-based drug delivery systems as poly(lactic-co-glycolic acid) (PLGA) nanoparticles have been developed to improve photosensitizer stability, retention, and targeted delivery. This mini-review aims to summarize the current evidence regarding polymeric nanoparticles, particularly poly(lactic-co-glycolic acid) (PLGA), as carriers for photosensitizers in periodontal PDT.

**Keywords:** NSPT; Periodontitis; Photodynamic Therapy; PDT; Indocyanine Green; PLGA; Photosensitizer

### Abbreviations

NSPT: Non Surgical Periodontal Therapy; ICG: Indocyanine Green; PLGA: Polylactic Co Glycolic Acid Nanoparticles; PDT: Photodynamic Therapy.

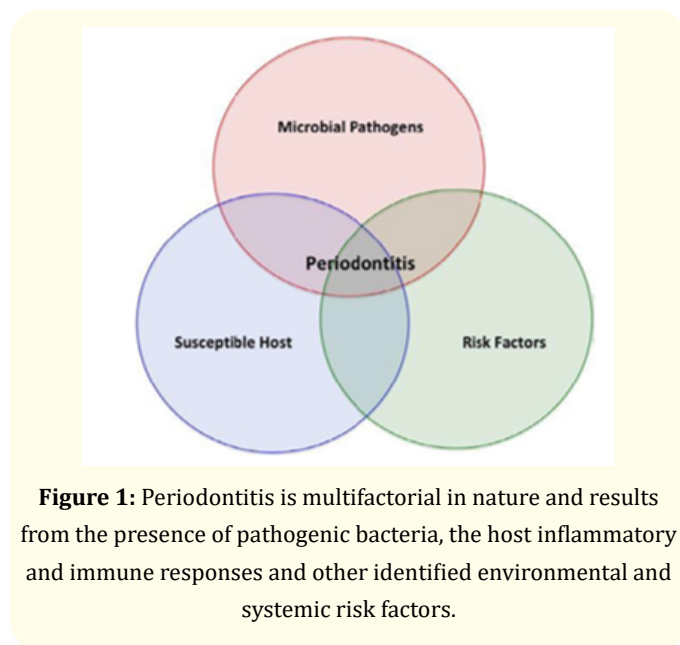
### Introduction

Periodontitis is a chronic, multifactorial inflammatory condition caused by dysbiotic dental plaque biofilms, marked by the progressive deterioration of the tissues supporting the teeth. The condition impacts the periodontal ligament and alveolar bone,

resulting in irreparable tissue damage and, if ignored, ultimately tooth loss [10].

Periodontal disorders are regarded as the most prevalent oral illnesses globally. It is believed that between 20–50% of the global population is afflicted by periodontal disease. Inhabitants of developing nations exhibit a higher susceptibility to periodontal diseases than their counterparts in industrialized nations, attributable to insufficient awareness, inadequate oral hygiene practices, a relatively costly dental treatment system, and diminished socioeconomic level (SES) [1].

The disease entails complicated dynamic interactions among particular bacterial infections, destructive host immune responses, and environment-related factors, including smoking (Figure 1) [10].



Non-surgical periodontal therapy (NSPT), particularly focused on mechanical cleaning and root debridement, is regarded as the fundamental phase of periodontal treatment. Clinical investigations indicate that this method reliably produces substantial short-term reduction in bleeding on probing (BOP), plaque indices, and total pocket depths. Thus, NSPT is firmly established in current data as the globally acknowledged gold standard for preventing the progression of periodontitis [2,3].

Apart from its clinical effectiveness, a significant obstacle of nonsurgical periodontal therapy (NSPT) is the inability to completely eliminate complex disease-associated microbial biofilms, primarily due to restricted physical access during blind mechanical instrumentation, particularly in deep periodontal pockets exceeding 5 mm, advanced furcation involvements, and complex root architecture featuring surface concavities or deep grooves [8,9].

Implementing modalities such as local or systemic antimicrobials, host-modulating drugs, lasers, or targeted biomaterials aids in minimizing the latent bacterial burden that instrumentation uncovers. These additional approaches enhance disinfection, regulate the host immune response, and improve long-term clinical healing outcomes without necessitating urgent invasive surgical procedures [8].

Antimicrobial photodynamic therapy (aPDT) is characterized as a non-invasive, targeted photochemical method employed in periodontal treatment to selectively eliminate bacteria cells in periodontal pockets while preserving surrounding healthy host tissues. The principle depends on the interplay of three essential components: a non-toxic photosensitizer (PS), a light source of a specified wavelength, and molecular oxygen [12].

Mechanistically, upon binding of the photosensitizer to target bacterial cells or subgingival biofilms, it is activated by light to an energized state; this energy is subsequently transferred to adjacent oxygen molecules, resulting in the production of cytotoxic reactive oxygen species (ROS), including singlet oxygen, which target essential bacterial cellular structures—such as cell membranes, proteins, and nucleic acids—thereby disrupting the biofilm and reducing the overall microbial load [12].

Photosensitizers (PS) employed in Antibacterial Photodynamic Therapy (aPDT) are often categorized into four principal classes according to their chemical composition and source: synthetic dyes, tetra-pyrrole derivatives, natural photosensitizers, and nanostructures [7].

Synthetic dyes utilized in antibacterial photodynamic therapy predominantly consist of phenothiazinium dyes, including Methylene Blue and Toluidine Blue, as well as xanthene dyes such as Rose Bengal and Eosin Y [7].

These dyes are extensively utilized in clinical environments and demonstrate significant efficacy against planktonic microorganisms. Nonetheless, they encounter other drawbacks; for example, anionic (negatively charged) dyes generally exhibit reduced bacterial absorption compared to their cationic equivalents. Bacteria can utilize efflux pumps to expel these dyes from the cell, thereby decreasing their concentration and enabling the bacteria's antioxidant systems to withstand inactivation. Their capacity to infiltrate biofilm colonies may also be restricted [7].

In modern periodontal treatment, ICG is progressively employed as a photosensitizer for antimicrobial photodynamic therapy (aPDT) in conjunction with traditional scaling and root debridement. This water-soluble tricarbo-cyanine dye, licensed by the FDA in 1959, demonstrates a rapid hepatic clearance rate and a strong affinity for bacterial membranes, exhibiting low toxicity [6,15,17].

It is unique by its high absorption in the near-infrared spectrum, exhibiting a peak absorption and emission profile between 800–830 nm, facilitating deep tissue penetration [5,6]. Upon activation by diode lasers, ICG demonstrates a distinctive dual-action mechanism: a photochemical effect that produces reactive oxygen species (ROS) to destroy bacterial cell structures, alongside a photothermal effect that generates localized heat to breakdown resistant biofilms [4-17].

Annunziata, *et al.* (2023) assessed the effects of multiple applications of ICG-aPDT subsequent to comprehensive ultrasonic debridement of the mouth. Although both groups exhibited considerable clinical enhancement, the supplementary ICG-aPDT treatment yielded markedly superior results in deep periodontal pockets and elevated pocket closure rates after 6 months, hence confirming its efficacy in addressing residual deep sites [4].

A recent systematic review published in 2025 assessed 16 randomized controlled studies conducted from 2015 to 2025 that investigated indocyanine green-mediated antimicrobial photodynamic therapy (ICG-aPDT) as an addition to conventional scaling and root planing (SRP) in the treatment of periodontitis. The study indicated that the majority of studies documented more substantial reductions in probing pocket depth (PPD), enhanced clinical attachment level (CAL), and notable decreases in periodontal infections and inflammatory burden when ICG-aPDT

was utilized with traditional periodontal therapy. The advantages were more obvious in moderate to deep periodontal pockets [17].

Poor local retention and a failure to sustain therapeutic concentrations at the active lesion site [14-18].

In contrast to its potential in antibacterial photodynamic therapy, the efficacy of free indocyanine green (ICG) is constrained by many physical limitations. Its anionic and very hydrophilic characteristics limit its infiltration into bacterial cells and periodontal biofilms, whereas its inadequate stability in aqueous conditions results in fast photobleaching, thermal breakdown, and self-aggregation. These constraints decrease the production of reactive oxygen species (ROS) and consequently impair the antibacterial effectiveness of ICG in periodontal applications [11-16].

The complicated clinical structure of deep, narrow, and irregular periodontal pockets is exacerbated by a brief circulatory half-life and rapid clearance due to the ongoing hydrodynamic flushing of gingival crevicular fluid, resulting in inadequate local retention and an inability to maintain therapeutic concentrations at the active lesion site [14-18].

To overcome the intrinsic limitations of ICG, many carrier systems have been explored to enhance the stability, retention, bioavailability, and antibacterial activity of indocyanine green (ICG) in photodynamic periodontal therapy. Chitosan nanoparticles are the most often studied carriers in periodontal therapy due to their enhancement of ICG stability, biofilm penetration, and antimicrobial efficiency, along with their supplementary antibacterial capabilities. Additional interesting delivery technologies comprise liposomes, poly(lactic-co-glycolic acid) (PLGA) nanoparticles, albumin-based nanoparticles, mesoporous silica nanoparticles, and hydrogel formulations, all of which improve photostability, extend retention time, and provide controlled release of ICG [13].

Polymeric nanoparticles (PNPs) include chitosan, polycaprolactone (PCL), polylactic acid (PLA), and poly(lactic-co-glycolic acid) (PLGA) provide numerous therapeutic benefits, rendering them very efficient drug delivery methods. Encapsulating therapeutic molecules into a protective polymeric matrix enhances medication stability and preserves highly sensitive chemicals from premature breakdown. They enhance the bioavailability of weakly

water-soluble pharmaceuticals by enhancing their solubility and promoting their clinical utilization. The tailored architecture of PNP facilitates regulated and sustained drug release, preserving therapeutic concentrations over extended durations while minimizing dose frequency and systemic adverse effects. Moreover, their relatively small size and adjustable surface characteristics provide effective tissue infiltration, enhanced cellular absorption, and targeted distribution relative to pathological locations, consequently improving total therapeutic efficiency [19].

Poly(lactic-co-glycolic acid) (PLGA) is the predominant copolymer in modern nanomedicine. PLGA is highly valued for its formal FDA approval and excellent safety record; its lactic-acid-to-glycolic-acid ratio can be modified to accurately regulate hydrophilicity, degradation rates, and drug release profiles [19].

Ultimately, PLGA undergoes hydrolysis *in vivo* into benign, non-toxic metabolic byproducts (lactic acid and glycolic acid) that the body efficiently eliminates through conventional metabolic routes, hence minimizing the possibility of local accumulation of lactic acid or requirement for surgical removal [19].

## Materials and Methods

This mini-review was conducted through a literature search of published articles addressing antimicrobial photodynamic therapy (aPDT) in periodontitis, with particular emphasis on indocyanine green (ICG) and polymeric nanoparticle-based delivery systems. Relevant studies were identified from electronic databases including PubMed, Scopus, Google Scholar, and Web of Science. Articles published in English between 2016 and 2026 were considered. Keywords used in the search strategy included "periodontitis," "antimicrobial photodynamic therapy," "indocyanine green," "ICG," "polymeric nanoparticles," "PLGA nanoparticles," and "drug delivery systems." Original research articles, randomized clinical trials, systematic reviews, and narrative reviews relevant to the topic were included. Studies unrelated to periodontal applications or not focusing on ICG-mediated photodynamic therapy were excluded.

## Results and Discussion

The reviewed literature demonstrated that antimicrobial photodynamic therapy (aPDT) is a promising adjunctive approach to conventional non-surgical periodontal therapy. Indocyanine

green (ICG) has attracted considerable attention due to its excellent biocompatibility, near-infrared absorption, and dual photodynamic and photothermal antimicrobial effects. Clinical studies have reported improvements in probing pocket depth reduction, clinical attachment gain, and periodontal pathogen reduction when ICG-aPDT is combined with scaling and root planning.

Despite these advantages, free ICG presents several limitations, including poor stability in aqueous environments, rapid clearance from periodontal pockets, limited penetration into bacterial biofilms, and reduced retention at the target site. These shortcomings may compromise its antimicrobial effectiveness.

Recent advances in nanotechnology have enabled the development of nanoparticle-based delivery systems to overcome these limitations. Polymeric nanoparticles, particularly poly(lactic-co-glycolic acid) (PLGA), enhance the stability, bioavailability, and controlled release of ICG while improving its retention within periodontal tissues. PLGA nanoparticles also provide protection against premature degradation and facilitate sustained therapeutic activity.

Overall, the current evidence suggests that PLGA-based nanoparticle delivery systems may significantly improve the efficacy of ICG-mediated photodynamic therapy in periodontitis management. Nevertheless, further well-designed clinical trials are required to establish standardized treatment protocols and evaluate long-term clinical outcomes.

## Conclusion

PLGA-based nanoparticle systems represent a promising strategy for optimizing PDT outcomes and may contribute to more effective management of periodontitis in the future.

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