Nanoparticles Enhanced Photodynamic Therapy in Treatment of Periodontitis

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***Abstract*—Periodontitis is a chronic inflammatory disease characterized by progressive destruction of the supporting structures of teeth. Conventional therapy, including scaling and root planing (SRP), may not completely eliminate pathogens in deep periodontal pockets. Photodynamic therapy (PDT) has emerged as a minimally invasive adjunctive approach that uses a photosensitizer activated by specific light wavelengths to generate reactive oxygen species, leading to targeted microbial destruction. However, limitations such as poor photosensitizer retention and limited light penetration reduce its long-term efficacy. Incorporating nanoparticles enhances PDT by improving drug delivery, biofilm penetration, ROS generation, and tissue targeting. Preclinical studies demonstrate improved antimicrobial, anti-inflammatory, and regenerative outcomes. In our study we are discussing about the applications of nanoparticle-enhanced PDT in periodontal therapy .**

***Index Terms*—Nanoparticles, Photodynamic therapy, Photosensitizer, Drug delivery , Reactive oxygen species, Adjunctive periodontal treatment.**

I. INTRODUCTION

DEFINITION

Periodontitis is a chronic inflammatory disease affecting the supporting structures of the teeth, including the gingiva and alveolar bone. Periodontal therapy is the treatment of inflammatory periodontal diseases aimed at eliminating the etiological factors, arresting the progression of disease and restoring the periodontal tissues to health and function. In complex sites, complete elimination of these factors is not possible. In such cases photodynamic therapy is used. Nanoparticles are recently introduced technology in the photodynamic therapy. This article focuses on nanoparticles enhanced photodynamic therapy in treatment of periodontitis.

PHOTODYNAMIC THERAPY:

A treatment modality that uses a photosensitizing agent activated by light of a specific wavelength in the presence of oxygen to produce reactive oxygen species that selectively destroy target cells, including periodontal pathogens.

PRINCIPLE OF PHOTODYNAMIC THERAPY IN PERIODONTITIS

1. Core Components of PDT

Photodynamic therapy in the treatment of periodontitis relies on three essential elements: A photosensitizer (PS) a non-toxic agent that selectively binds to target pathogens.

Light of a specific wavelength (typically in the red or near-infrared range) to activate the PS. Oxygen, which is required for the generation of reactive oxygen species (ROS).

Together, these components ensure that ROS are produced only at the site where the PS has accumulated and light is applied, minimizing damage to surrounding healthy tissues.

2. Selective PS Binding and Activation

The photosensitizer preferentially attaches to microbial cells within periodontal biofilms.

When exposed to light-commonly in the red spectrum for deeper tissue penetration-the PS is excited from its ground state to a singlet state, and then through intersystem crossing, transitions into a longer-lived triplet state[1].

3. Mechanism of ROS Generation

Two distinct photochemical pathways are involved:

Type I pathway: The triplet-state PS transfers electrons or hydrogen atoms to surrounding substrates, forming reactive radicals such as superoxide (02-) and hydroxyl (OH-).

Type II pathway: The PS transfers energy to ground-state oxygen (3O2), generating singlet oxygen (1O2), a potent oxidizing species[2].

4. Antimicrobial Action and Biofilm Disruption

The ROS produced attack and oxidize key cellular components including bacterial membranes, proteins, polysaccharides, and nucleic acids. This leads to the destruction of microbial cells and the breakdown of biofilm structures[3].

The ability of red and NIR light to penetrate tissues allows PDT to be effective even within deep periodontal pockets.

5. Targeted Action and Clinical Safety

Since the PS is only activated in areas where light is applied, tissue damage is confined to infected periodontal sites.

This localized activation makes PDT a safe, minimally invasive antimicrobial therapy suitable for precise periodontal treatment.

II. APPLICATIONS OF PHOTODYNAMIC THERAPY

1. Adjunct to Non-Surgical Periodontal Therapy

Photodynamic therapy is commonly used as an adjunct to scaling and root planing (SRP). This combination has been shown to enhance treatment outcomes by:

Significantly reducing probing pocket depth (PPD) and bleeding on probing (BOP) compared to SRP alone, particularly evident at 3- to 6-month follow-ups.

Providing modest but statistically significant improvements in clinical attachment level (CAL).

A comprehensive systematic review involving 14 randomized clinical trials reported that SRP combined with adjunctive PDT (aPDT) led to improved PPD outcomes at 3 months. Notably, better results were observed in studies utilizing indocyanine green (ICG) as the photosensitizer[4].

2. Single vs. Multiple PDT Sessions

While several clinical protocols employ a single session of PDT following SRP, others have investigated multiple applications, revealing that:

Repeated PDT sessions lead to more pronounced reductions in PPD and BoP.

They also contribute to improved microbiological profiles and better regulation of inflammatory cytokines, such as decreased IL-17 and increased IL-10, particularly in patients with aggressive periodontitis[5].

3. Effectiveness in Different Periodontitis Types

In aggressive (grade C) periodontitis, adjunctive PDT demonstrated significant improvement in deep periodontal pocket depth and CAL at both 3- and 6-month intervals.

For chronic periodontitis, PDT showed short-term benefits in reducing PPD and BoP, although CAL improvements were less consistent across studies[6].

4. Immuno-Modulatory and Microbial Effects Clinical research has shown that PDT contributes to:

Significant reductions in pro-inflammatory cytokines.

Decreased levels of major periodontal pathogens, including species from the “red complex” group.

In patients with type 2 diabetes and periodontitis, adjunctive PDT also improved BoP and reduced microbial markers, although it did not significantly affect glycemic control (HbA1c levels).

5. Clinical Advantages and Safety

PDT is a minimally invasive procedure that typically does not require anesthesia. Treatment is quick, often taking less than one minute per site.

It exhibits broad-spectrum antimicrobial activity, including efficacy against antibiotic- resistant organisms.

Importantly, no major side effects have been reported across numerous clinical trials, reinforcing its safety

In patients with type 2 diabetes and periodontitis, adjunctive PDT also improved BoP and reduced microbial markers, although it did not significantly affect glycemic control (HbA1c levels)[7].

III. LIMITATIONS

1. Residual Systemic Photosensitivity

Systemic administration of photosensitizers (PSS) can cause them to accumulate in the skin and mucosa, leading to prolonged sensitivity to light. Patients may experience burns when exposed to sunlight or strong indoor lighting after treatment[8].

2. Photosensitizer Washout and Low Retention

In periodontal pockets, bleeding and exudates can flush out the PSs. Additionally, proteins in the tissue may outcompete bacteria for PS binding, reducing their concentration at the target site and weakening PDT's effectiveness[9].

3. Mismatch Between Light and Photosensitizer

If the light source doesn't match the absorption spectrum of the PS, it may not activate properly. This mismatch can reduce microbial killing or cause unwanted heat effects[10].

4. Limited Light Penetration in Deep Pockets

Inflammation, bleeding, and the opaque nature of deep periodontal pockets interfere with light delivery. This reduces reactive oxygen species (ROS) production and limits bacterial elimination in deeper tissues[11].

5. Short-Term Benefits and Variable Outcomes

Studies show that combining PDT with scaling and root planing (SRP) results in only slight, temporary improvements (e.g., ~0.25-0.34 mm reduction in probing depth), with little to no long-term benefit after six months. Some clinical trials report no lasting advantage in treating chronic or aggressive periodontitis.

6. Dependence on Oxygen Availability

PDT relies on oxygen to produce ROS. In low-oxygen (hypoxic) environments typical of inflamed or deep periodontal pockets, its effectiveness is significantly reduced[12].

INCORPORATING NANOPARTICLES IN PHOTODYNAMIC THERAPY MECHANISM OF ACTION

1. Photosensitizer Delivery via Nanocarriers

Incorporating photosensitizers (e.g., chlorine6 [Ce6], indocyanine green [ICG]) into nanocarriers improves their solubility, stability, and targeted delivery to periodontal tissues and bacterial biofilms.

Up conversion nanoparticles (UCNPs), such as NaYF4 doped with Er3+ or Mn2+, enable the conversion of near-infrared (NIR) light (808-980 nm) into visible or ultraviolet light, thereby activating the photosensitizer directly at the infection site[13].

2. Light Activation and Enhanced ROS Production

Upon NIR light exposure, photosensitizer-loaded nanoparticles reach an excited triplet state and initiate two main pathways:

Type I mechanism: Involves electron or hydrogen transfer, producing reactive radicals like superoxide (02-) and hydroxyl (OH-).

Type II mechanism: Involves energy transfer to molecular oxygen, generating singlet oxygen (102).

Gold nanoparticles (AuNPs) further enhance photosensitizer activation via surface plasmon resonance, resulting in amplified reactive oxygen species (ROS) generation[14].

3. Localized Antimicrobial Activity

The ROS produced induce oxidative damage to microbial membranes, proteins, and genetic material, disrupting cellular function and leading to bacterial cell death. Nanoparticle-based delivery systems improve tissue penetration and ensure effective biofilm inactivation, even in deep periodontal pockets[15].

4. Synergistic and Protective Effects

Combining photodynamic therapy (PDT) with photothermal therapy (PTT)-using agents like ICG or AuNPs-produces both oxidative and thermal stress, enhancing antimicrobial efficacy and biofilm disruption. Additionally, certain nanoparticles (e.g., cerium oxide [CeO2], black phosphorus nanosheets [BPNSS]) possess ROS-scavenging capabilities post-treatment, minimizing collateral damage to surrounding periodontal tissues and supporting inflammation resolution[16].

ROLE OF NANOPARTICLES IN PERIODONTAL THERAPY:

Nanotechnology has gained attention for its use in biomedical fields including dentistry. Nanoparticles offer multifunctional advantages due to their unique properties and ability to deliver drugs effectively.

Types of Nanoparticles - Inorganic Nanoparticles
These can be engineered into various shapes and sizes and offer good dispersibility. Elements like gold naturally support bone regeneration, and their surface can be modified for better cellular uptake and reduced toxicity.

Silver Nanoparticles (AgNPs)
Known for broad-spectrum antimicrobial effects, AgNPs disrupt bacterial membranes, impair DNA replication, and inhibit ATP production. They also support osteogenic differentiation of periodontal ligament fibroblasts. Green synthesis methods like using plant extracts offer
eco-friendly and safer alternatives. For instance, AgNPs synthesized with Oroxylum indicum extract enhanced cell proliferation, reduced inflammation, and promoted bone differentiation. Silver nanoparticles (AgNPs) show strong antibacterial properties and combining them with drugs like ebselen can enhance safety and efficacy.

Gold Nanoparticles (AuNPs)
First used in the 1970s, AuNPs are now studied for their regenerative capabilities. Studies show that 45nm AuNPs can influence macrophages and encourage periodontal tissue regeneration. They activate autophagy-related pathways, promoting cell differentiation.
Additionally, L-cysteine-modified AuNPs were more effectively absorbed and enhanced osteogenic activity compared to D-cysteine variants. AuNPs also restored autophagy in inflamed periodontal stem cells, aiding bone regeneration[17]. Other NPs, like polydopamine-modified silica, can modulate the immune response and reduce oxidative stress. These findings suggest that nanoparticles may play a key role in future periodontal therapies.
Improving the Periodontal Environment with Nanoparticles.

NPs contribute to periodontal therapy through three main mechanisms: Antibacterial and Anti-Biofilm Activity
Silver, iron oxide, and platinum nanoparticles can directly kill bacteria or disrupt biofilms. Carbon quantum dots can penetrate biofilms effectively.
Their unique mechanisms help prevent antibiotic resistance. Microenvironment Modulation and Drug Delivery
Nanoparticles like cerium oxide and polydopamine have antioxidant properties and reduce tissue damage. Some serve as drug carriers:
Inorganic: hydroxyapatite (for tetracycline), silver (for chlorhexidine/metronidazole), silica (for silver ions)
Organic: chitosan (minocycline), PLGA (metformin)
Periodontal Regeneration
Gold nanoparticles (AuNPs) support bone cell growth by triggering autophagy. Magnesium oxide NPs improve scaffold strength and promote osteogenesis[18].

RECENT STUDIES AND CLINICAL TRIALS:
Recent Preclinical Studies

1. Indocyanine Green (ICG) & Polycationic Nanoparticles (sPDMA ICG)

In vivo rat model of periodontitis: sPDMA ICG NPs combined with laser remarkably reduced alveolar bone loss CEJ–ABC distance normalized and bone volume fraction (BV/TV) significantly improved compared to controls.
Inflammation markers (TNF-α, IL-1β) were markedly reduced, and histology showed nearly
intact gingival architecture.

2. Black Phosphorus Nanosheets (BPNSs) + ICG aPDT

Novel use of BPNSs with ICG–aPDT effectively scavenged ROS, protecting healthy periodontal tissue while combating bacteria.

3. Cerium Oxide–Chlorine 6 NPs (CeO_2 Ce6)

Hybrid CeO_2 Ce6 NPs demonstrated strong antibacterial and anti-inflammatory activity both
in vitro and in vivo, thanks to CeO_2's intrinsic antioxidant effects.

4. Nano-ZnO Gel + Visible Light PDT

In a controlled clinical adjunct to scaling & root planing (SRP) — bio-synthesized nano-ZnO gel with visible-light PDT showed significant periodontal improvements at 1 month (compared to SRP alone); by 3 months, benefits were sustained.

5. Magnetic Fe_3O_4 @ Silane & Ce6 NPs

Fe_3O_4-silane@Ce6/C6 NPs delivered via magnetic targeting showed 4–5 log CFU reduction in periodontal pathogens (S. sanguis, P. gingivalis, F.

nucleatum) and deep biofilm disruption.

6. Upconversion Nanoparticles (UCNPs + Ce6)
NaYF4-Mn Ce6 silane UCNPs activated by near-infrared (980 nm) overcame tissue- penetration limits, reducing periodontal biofilms by over 2 log and penetrating deeper.

7. Gold Nanoparticles for PDT/PTT
AuNP-based hydrogel (E-Au H) with NIR light achieved 87% plaque biofilm suppression and 38% enhanced bone regeneration in rat models.
Methylene blue–conjugated AuNPs also achieved >5 log reduction in MRSA biofilms compared to <1 log with MB alone.
Core-shell Au nanorods with verteporfin (AuNRs SiO_2-VP) eradicated E. coli (104 CFU/mL) under 710 nm light[19].

Clinical Trials & Meta-Analyses:
ICG-Based aPDT in Human Periodontitis
Randomized controlled trials using ICG–aPDT adjunct to non-surgical periodontal therapy (NSPT) show mixed results:
Some trials report short-term improvement in pocket depth and microbial diversity.

Future Directions Needed
Well-designed RCTs comparing nanoparticle-aPDT to SRP (both split-mouth and parallel- arm designs).
Standardization of photosensitizer dosage, light protocols, and delivery systems.
Exploration of minimally invasive, fiber-based or NIR-activated systems for deeper pocket treatments.
Longer follow-up durations and multicentre trials, especially in systemic disease populations (e.g., diabetic patients).

IV. ADVANTAGES

1. Selective and Minimally Invasive
Targeted action: The photosensitizer is absorbed primarily by. Diseased tissues, and activation by light ensures that healthy tissues remain unaffected.
Minimally invasive technique: Low-level lasers used in PDT reduce pain, accelerate healing, promote hemostasis, and typically eliminate the need for anesthesia.

2. Broad-Spectrum Antimicrobial Activity & Resistance-Free
Effective against diverse pathogens: PDT works on bacteria, viruses, fungi, and protozoa using a single photosensitizer, including strains resistant to antibiotics or within biofilms.
No resistance development: PDT generates reactive oxygen species that damage multiple parts of microbial cells, making it difficult for pathogens to develop resistance.

3. Effective in Hard-to-Reach Areas
Deep penetration: When combined with scaling and root planing (SRP), PDT enhances bacterial elimination in areas like deep pockets, furcations, and concavities where mechanical tools are less effective.
Endotoxin neutralization: PDT also helps detoxify bacterial byproducts like lipopolysaccharides, reducing inflammatory responses.

4. Supports immunity and Tissue Healing
Immunomodulatory effects: PDT helps lower inflammatory mediators and supports the function of gingival fibroblasts and collagen, aiding in tissue stability.
Enhanced healing: Low-level laser application encourages quicker tissue repair and minimizes bleeding.

5. Safe, Comfortable, and Cost-Effective
Patient-friendly: The non-invasive nature of PDT leads to higher patient compliance and fewer side effects compared to systemic antibiotics.

Cost-efficient: PDT avoids the need for expensive medications and reduces damage to surrounding tissues, making it an economical option in periodontal therapy.

V. CONCLUSION

Photodynamic therapy with nanoparticles is an emerging and promising strategy in periodontal therapy. Preclinical studies have demonstrated antimicrobial efficacy, improved biofilm penetration, targeted drug delivery and sustained release of photosensitizers, leading to better control of periodontal pathogens and inflammation. Hence it can be used in clinical practice.

CONFLICT OF INTEREST: NIL

ACKNOWLEDGEMENT: We the interns thank Dr.Maria Subash Aaron M (Reader), from Department of Periodontology and Implantology, RVS Dental College and Hospital for their constant guidance and support.

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