Laser Activated Photothermal Therapy as a Targeted Treatment in Periodontal Disease: A Comprehensive Literature Review

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KEYWORDS
Photothermal therapy; periodontitis; nanoparticles; laser therapy; tissue regeneration.

ABSTRACT
Background: This study aims to assess the efficacy and clinical implications of photothermal therapy (PTT) in the management of periodontal disease by evaluating its impact on bacterial load reduction, tissue regeneration, and overall treatment outcomes.
Materials and Methods: A literature review spanning recent advancements in PTT for periodontal disease was conducted. PubMed, Web of Science, and Scopus databases were searched for relevant studies published within the last decade (2013-2023). Inclusion criteria encompassed original research articles and clinical trials investigating PTT's mechanisms, experimental methodologies, clinical outcomes, and safety profiles. Data extraction included information on photothermal agents, laser parameters, experimental designs, and clinical implications.
Results and discussions: The selected five studies elucidated significant bacterial reduction, tissue healing, and modulation of inflammatory responses in clinical trials. Furthermore, it revealed promising outcomes, showcasing improved clinical parameters following PTT interventions, albeit with limitations in sample sizes and study durations. PTT exhibits substantial potential in managing periodontal disease by selectively targeting pathogens and modulating host responses.
Conclusion: The available literature underscores its efficacy in reducing bacterial load and promoting tissue regeneration. Future research should focus on refining protocols, optimizing parameters, and conducting robust clinical trials to establish PTT as an effective adjunct in routine periodontal care.

1. Introduction

Periodontal disease, encompassing gingivitis and periodontitis, stands as a prevalent and multifaceted oral health challenge worldwide. Characterized by the dysbiotic interaction between microbial pathogens and host inflammatory responses within the periodontal tissues, this condition poses significant hurdles in its effective management.[1] Traditional therapeutic interventions, predominantly centered on mechanical debridement, systemic antibiotics, and surgical approaches, often encounter limitations in eradicating pathogenic bacteria while facilitating comprehensive tissue repair.[2] Consequently, the quest for alternative therapies has led to exploring innovative modalities, among which photothermal therapy (PTT) emerges as a promising frontier in periodontal care. Based on light-induced thermal energy conversion principles, PTT represents a novel and targeted approach to combating periodontal pathogens while promoting tissue regeneration. The core principle of PTT involves using light-absorbing materials, such as gold nanoparticles (GNPs) or carbon-based nanomaterials, as photothermal agents.[3,4,5,6,7,8] These agents exhibit exceptional optical properties that efficiently convert absorbed light into localized heat energy, particularly in the near-infrared (NIR) spectrum. This selective energy conversion induces a controlled hyperthermic effect precisely at the site of the periodontal pathogens.[9,10] Using GNPs or carbon-based nanomaterials as photothermal agents showcases their unique ability to absorb NIR light, resulting in a localized temperature elevation in the surrounding tissue. This thermal effect, precisely directed at the site of infection, enables the targeted destruction of periodontal pathogens.[10] The resultant hyperthermia disrupts the structural integrity of the microbial cell membranes, rendering the pathogens vulnerable to elimination while potentially mitigating their ability to develop resistance. Furthermore, this localized thermal effect has been demonstrated to modulate the host's inflammatory response, thereby aiding in the reduction of tissue inflammation and promoting the initiation of reparative processes.[11]

The transformative potential of PTT in periodontal disease treatment lies in its focus on addressing the fundamental challenges encountered by conventional therapies. Unlike systemic antibiotics that often face resistance or mechanical debridement issues that may not eliminate deep-seated pathogens, PTT offers a minimally invasive, precise, and targeted approach. By selectively targeting pathogens while sparing healthy tissues, PTT holds promise in controlling infection and fostering tissue regeneration, thereby potentially limiting periodontal tissue loss.[12] (Figure 1)

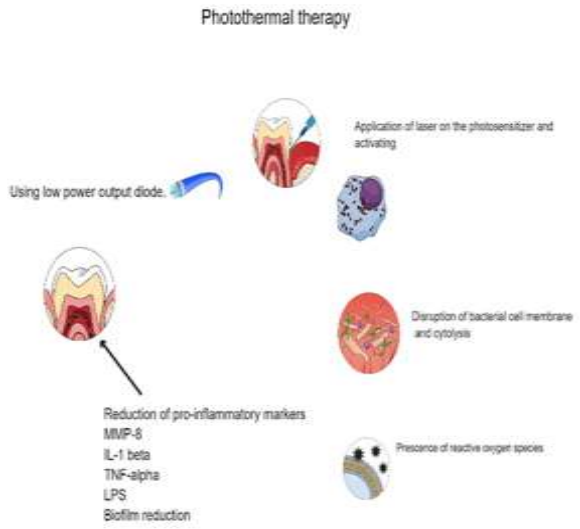

Figure 1: Mechanisms of photothermal therapy

Unlike its predecessor, photodynamic therapy, which requires a robust and functional vasculature and oxygen requirement for generation of radical oxygen species to function. PTT is predominantly oxygen independent, which makes it a wise choice in inflammatory mechanisms where due to the state of dysbiosis, acidic and hypoxic conditions prevail.[13]

Though advantages and disadvantages prevail in both systems (Table 1).

Table 1: Comparison between PDT and PTT

Parameters	**PDT**	**PTT**
Irradiation method	Combination of Interstitial or topical	Combination of Interstitial or topical
Oxygen requirement	Required	Not required-can work in hypoxic condition
Primary mode of action	Radical oxygen species generation	Hyperthermia
Triggering agent	Photosensitizers-porfimer sodium, chlorins, phthalocyanines, bacteriochlorins, toluidine blue	Photoabsorbsers-gold nanoshells, indocyanine green
Treatment sensitivity	Require monitoring photosensitizer uptake	Monitoring tissue damage required-Optical resonance and diffuse optical tomography
Economics	Inexpensive low power laser; Cost of photosensitizer high	Expensive and high-power output lasers; cost of photo absorber less
Fluence	Low	High
Treatment duration	Multiple visits and long duration	Lesser visits and short duration

The feasibility and judicious use of both the systems in dental and periodontal conditions depend mainly on the operator experience, tissue characteristics and prognosis of the condition. In highly acidic conditions, where

dysbiosis is prevalent and chances of hypoxia is predominantly anticipated, it would be better to use PTT rather than PDT.[14] The primary mode of action in PTT is to coagulate by causing hyperthermia. In PDT the action is to release ROS (reactive oxygen species).[15]The triggering agent in both PDT and PTT requires photosensitizer and photo absorber respectively with both systems having upgraded the initiating agent in the recent years. The incorporation of nanotechnology has provided excellent results in surgical oncology and in areas where endogenous thermolysis is required.[16] Though the fluency is low in PDT and high in PTT, the laser apparatus, along with feasibility and cost of the initiating agents require proper treatment planning and curtail within the expectations of the operator.[17] Treatment modality and duration is generally multiple for PDT and lesser for PTT.[18,19] The current review aims to delve into the evolving landscape of PTT in periodontal disease management. It seeks to elucidate the underlying mechanisms, experimental methodologies, preclinical and clinical outcomes, existing challenges, and prospects of PTT as an innovative therapeutic modality in periodontal care.

2. Material and methods

The current review encompasses relevant studies exploring the role of photothermal therapy (PTT) in periodontal disease. A systematic approach was employed to collect pertinent literature, select studies, and evaluate their relevance to construct a comprehensive understanding of the topic. An extensive search strategy was carried out across prominent scientific databases, including PubMed/MEDLINE, Web of Science, Scopus, and Cochrane. The search was done incorporating Medical Subject Headings (MeSH) terms such as "photothermal therapy," "periodontal disease," "nanoparticles," "carbon nanotubes," and "laser therapy." The search covered articles published within the last ten years (2013-2023), focusing on recent advancements in PTT for periodontal disease. The inclusion criteria encompassed original research articles and clinical trials written in English. Articles were given priority based on their relevance to photothermal therapy as a therapeutic approach for periodontal disease. The selection prioritized studies elucidating PTT mechanisms, experimental methodologies, preclinical and clinical outcomes, safety assessments, and future perspectives. Studies presenting data on photothermal agents and laser systems, used in vivo models, and comparative analyses were given particular importance (Figure 2). The retrieved five articles were screened based on headings and abstracts to ascertain their relevance to the review's scope. Full-text screening was conducted for articles meeting the inclusion criteria, and data extraction was performed. Information regarding photothermal agents used, laser parameters, experimental methodologies, outcomes, safety assessments, and limitations was extracted for analysis.

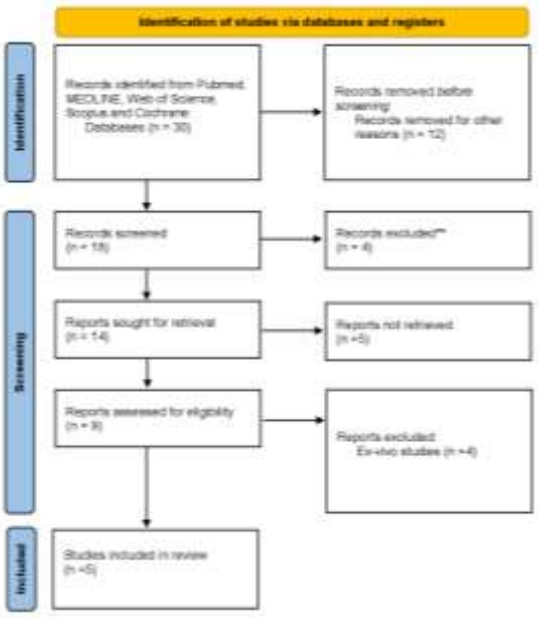

Figure 2: Flowchart indicating selection process of articles retrieved from digital databases

The selected studies underwent a quality assessment to evaluate their methodological rigor, validity, and reliability. The assessment considered factors such as study design, sample size, controls, blinding, statistical analyses, and overall contribution to the field. Articles were assessed based on SANRA- (scale for assessing

narrative review articles) to provide clarity and validity in the search. The collected data were organized, categorized, and synthesized to present a coherent narrative encompassing the role of PTT in periodontal disease. The materials and methods employed in the selected studies were critically evaluated and summarized to provide insights into the latest developments, challenges, and future directions in the field of PTT for periodontal therapy.

3. Results

The exploration of available literature regarding photothermal therapy (PTT) in relation to periodontal disease reveals few studies showcasing this innovative therapeutic approach's efficacy, mechanisms, and clinical potential. Numerous In-vitro and ex-vivo studies have demonstrated the effectiveness of PTT in reducing periodontal pathogens and modulating tissue response. Research employing gold nanoparticles (GNPs) or carbon-based materials as photothermal agents elucidated their ability to target and eliminate periodontal pathogens in vitro selectively. Recent studies demonstrated significant bacterial reduction upon NIR irradiation of photothermal agents using nanoparticles, leading to improved tissue healing and reduced inflammation in in vivo models of periodontal disease.[3,4,5,6,7,8,9,10] Furthermore, comparative study using photodynamic therapy and conventional periodontal treatment with PTT provided interesting results.[20,21,22,23,24] (Table 2)

Table 2: List Of Studies Having Photothermal Therapy As Mode Of Treatment

Name	Year	Study design	Sample size	Mode	Results
Dalvi et al	2021	Clinical case report	one	Photothermal	810 diode was used. No complications and better healing after a 12-month follow-up
Dalvi et al	2019	Randomized clinical trial	20	Photothermal and photodynamic	Utilization of indocyanine green dye along with PDT and PTT resulted in better healing using a 810 nm diode
Joshi et al	2020	Split mouth clinical study	29	Antimicrobial photodynamic therapy-aPDT along with PTT*	Plaque and bleeding index yielded a non-significant result
Raut et al	2018	Randomized clinical trial	50	Photothermal therapy	Significant reduction seen in Pocket depth, clinical attachment loss & bleeding on probing
Sethi et al	2019	Randomized clinical trial	30	Photodynamic therapy	Plaque index, bleeding index, & clinical attachment level improved

4. Discussion

The available literature on photothermal therapy (PTT) for periodontal disease presents a compelling narrative regarding its potential as an innovative therapeutic approach. A preclinical study elucidated the efficacy of PTT in targeting periodontal pathogens. The investigation highlighted the selective eradication of bacteria using photothermal agents, reducing bacterial load and enhancing tissue healing in in vitro and in vivo models. The ability of PTT to precisely eliminate pathogens while sparing healthy tissues is a promising hallmark of this therapeutic modality.[25]

Literature highlights the role of PTT in promoting tissue regeneration and immunomodulation. Studies showcased the capacity of PTT to stimulate periodontal tissue repair mechanisms.[25,26] The use of nanotechnology and drug delivery systems further provided success in the outcomes. The localized hyperthermia induced by photothermal agents facilitated the modulation of host inflammatory responses, promoting tissue regeneration and potentially limiting periodontal tissue destruction.[26] Comparative analyses between PTT and conventional therapies underscored the advantages of PTT in targeted pathogen elimination. Studies comparing PTT with traditional mechanical debridement revealed PTT's superiority in selectively eradicating periodontal pathogens while minimizing damage to healthy tissues.[22,23,24,25,26]

Limited clinical trials exploring PTT in periodontal disease exhibited promising outcomes. Clinical studies demonstrated improved clinical parameters, including reduced pocket depths, enhanced clinical attachment

levels, and decreased inflammatory markers following PTT interventions.[27,28,29] These trials emphasized PTT's feasibility and initial efficacy as an adjunct to conventional periodontal therapies.[13,14]

Though some studies have provided significant results with regards to photothermal therapy. A possible hypothetical reason could be related to the possible degradation of pro-inflammatory biomarkers which results in the slowing of the progression of periodontal inflammation and a temporary arrest in the dysbiosis prevalent. One of the other possible explanations is the presence of active-matrix metalloproteinase-8 (aMMP-8),[25,26,30] a predominant pro-inflammatory marker in periodontal disease which is responsible for periodontal tissue degradation.[27,28,29,31] Treatment with antimicrobial photothermal therapy (aPTT) with Emundo® (Indocyanin green) was compared to treatment solely with SRP. (Figure 3)

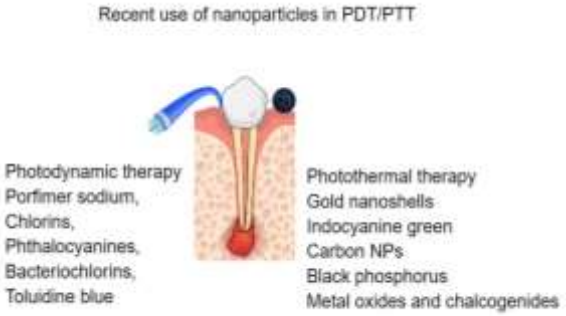

Figure 3: Photosensitizers and photoabsorbers commonly used

The effects of these treatments were then examined one month following the initial study. Treatment with aPTT and SRP yielded more pronounced positive results than treatment only with SRP.[22,23,24,32,33] Indocyaningreen works through photothermics. The SRP must be performed before aPTT because of light propagation. Blood must be reduced to promote dye absorption.[24] The MMP-8 is a zinc-dependent endopeptidase. The collagenase is secreted as inactive proenzymes and requires enzymatic cleavage of the propeptide domain for activation. This process (cysteine-switch) is very heat sensitive[27,28] However; the inhibitors of aMMP-8 (tissue inhibitor of matrix-metalloproteinase: TIMPS) are resistant to heat.[27,28,34,35] The aPTT temperature increases from 45 C to 65 C and is related to the destruction of the collagenase but not TIMPS. The MMPs are zinc-dependant endopeptidases.[30,36] They are secreted as inactive proenzymes and require enzymatic cleavage of the propeptide domain for activation. This could be the cause of the decrease of the aMMP-8.[29] Furthermore, in relation to periodontal pocket depth, significant differences were observed in reduction in pocket depth when PTT was used in conjunction with dyes such as indocyaningreen, this resulted in higher temperatures in the vicinity of 45-60 degrees resulting further in the elimination of bacteria which was inaccessible.[30] Though studies employing photodynamic therapy with dyes such as toluidine blue and methylene blue produced excellent results. A drawback that can supersede its advantages being, both these dyes can lead to an increase in MMP-8 concentration.[31,37] The immunological reactions against thermally altered bacteria or their residues in remaining pockets under the aPTT remain unknown.

5. Limitations

Despite the promising potential of photothermal therapy (PTT) in managing periodontal disease, several limitations and challenges hinder its seamless translation into routine clinical practice. A prominent limitation lies in the lack of standardized protocols for PTT in periodontal therapy. Variability in photothermal agents, laser parameters, and experimental methodologies across studies impedes the establishment of consistent and universally applicable treatment protocols.[15] The absence of standardized guidelines hinders comparative analyses and complicates the interpretation of findings, emphasizing the need for harmonized approaches in PTT research[38-40] .

Safety remains a paramount concern in the application of PTT. Determining optimal parameters, such as the concentration and size of photothermal agents, laser power, and duration of irradiation, poses a challenge. Balancing the therapeutic efficacy against the risk of potential tissue damage or unintended effects requires meticulous optimization and comprehensive safety assessments. Robust studies evaluating various parameters in diverse experimental and clinical settings are essential to delineate the fine line between therapeutic efficacy

and safety concerns. The translation of PTT from preclinical success to clinical applicability faces hurdles. Limited large-scale clinical trials with diverse patient populations and disease severities hinder the comprehensive validation of PTT's efficacy and safety in real-world clinical settings. Factors such as patient compliance, treatment standardization, and long-term outcomes necessitate meticulous evaluation to ascertain the feasibility and scalability of PTT as a routine therapeutic modality in periodontal care.

6. Conclusion

The literature highlights several avenues for future research in PTT for periodontal disease. Strategies involving advanced nanomaterials, targeted drug delivery systems, personalized treatment approaches, and comprehensive clinical trials are warranted. Furthermore, elucidating the optimal parameters and refining PTT protocols will facilitate its integration into routine periodontal care. In summary, while the literature presents promising outcomes and demonstrates the potential of PTT in managing periodontal disease, its clinical translation necessitates comprehensive evaluation, addressing safety concerns, standardization challenges, and further large-scale clinical trials to establish its efficacy, safety, and long-term outcomes.

Conflicts of Interest: The authors declare no conflicts of interest.

Author Contributions: All authors contributed to the study conception and designs Sudhir Rama Varma: Conceptualization, methodology, validation, investigation, resources, writing original draft and supervision. Lamar Wahb; & Pradeep Kumar Yadalam: Methodology, investigation, resources, writing-review and editing.

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