



Photodynamic Therapies in the Treatment of Periodontal Disease



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Abstract

Objectives: Many studies in the literature address the effect of photodynamic therapy in the management of pathologies related to periodontal tissue. Due to the lack of standardized information and the absence of a consensus, this review presents the effect of photodynamic therapy (PDT) on microorganisms involved in periodontal diseases.

Materials and methods: The literature and original research articles were used to investigate the effect of Photodynamic therapy (PDT) in periodontal diseases. Online MEDLINE/PubMed database were the main source. Google scholar were used a second search date base for online resources where access was not approachable through MEDLINE. Access date were between 01/9/2007 and 30/01/2017. The research was confined to English Language literature. The literature search retrieved references on antimicrobial photodynamic therapy.

Results: In total, 38 photodynamic relevant articles were included in the review, comprising work completed on a variety of cell types and places. Although results consistently demonstrated the potential of laser irradiation to affect antimicrobial photodynamic therapy in a wavelength and dosage-dependent manner, the relevance of other key irradiation parameters, such as irradiance, to such effects remained unclear.

Conclusion: The *in vivo* and *in vitro* studies present in the literature, indicate that aPDT may potentially become successful. In addition, infectious procedure associated with conventional therapy can be successful in the management of periodontal disease.

Keywords: Photodynamic treatment; Antimicrobial photodynamic therapy (aPDT); Periodontal disease

Abbreviations: PDT: Photodynamic Therapy; TD: Treponema Denticola; CAL: Clinical Attachment Level; AP: Aggressive Periodontitis; GBI: Gingival Bleeding Index; ER: Erythrosine; MB: Methylene Blue; PPD: Probing Pocket Depth; TF: Tannerella Forsythia

Introduction

Periodontal disease is defined as an “inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms, which lead to progressive destruction of the periodontal membrane and alveolar bone, with formation of periodontal pockets and gingival recession” [1]. Periodontal disease extent from simple gum inflammation to an aggressive gum disease that results in damage to supporting structure, periodontal ligament and bone which are considered the main support to the teeth and in the worst cases teeth could be missing [2]. When gingivitis is not treated, it could be deteriorated to ‘periodontitis’ which means inflammation around the tooth [3].

Three clinical parameters are typically recorded in periodontal disease [4]

- Bleeding on probing, this reflects the presence of an inflammatory infiltrate in gingival tissues with loss of integrity of the sulcular epithelium.
- Clinical attachment level, which reflects the amount of periodontal tissue loss [4].

- Pathological deepening of the periodontal pocket more than 3mm, which describes the deepening of the gingival sulcus where the dental plaque biofilm can propagate apically along the root surface [5].

The application of photosensitive dyes into pockets and their activation by light promote killing of periodontal pathogens. Outcomes of clinical studies in subjects with chronic periodontitis show beneficial results of PDT on the reduction in gingival inflammation [6]. Photodynamic treatment is a technique combining laser energy with a photosensitizer to product singlet oxygen molecules and free radicals to break down targeted cells [7]. The process of a PDT requires the presence of a photosensitizing drug in addition to an oxygen agent in the target tissue (microorganisms). The interaction between the photosensitizer and microorganisms occurs within a few minutes, and this period (incubation or preirradiation time) is taken into consideration before laser irradiation to ensure that the dye is absorbed by the bacteria [8,9]. The clinical application of PDT in the treatment of periodontitis has been tested for nonsurgical management of aggressive forms

of the disease. In previous work, PDT and nonsurgical periodontal treatment showed similar clinical outcomes after 3 months, and both led to statistically significant reductions in tumor necrosis factor- α (TNF- α) and receptor activation of nuclear factor (RANKL) Levels 30 days following treatment [7]. Moreover, PDT can destroy the vasculature surrounding tumor cells, and activates immunological responses against them [10]. PDT is relatively non-invasive, and treatments can be repeated without induction of resistance [11].

One of the potential alternative approaches to periodontal therapy is the association of the conventional treatment with antimicrobial Photodynamic therapy (aPDT), a first report on the comparison of conventional debridement with or without the adjunctive use of antimicrobial Photodynamic therapy (aPDT) in the treatment of chronic periodontitis revealed higher improvements of clinical parameters in the aPDT group [8].

An ideal photosensitizer for PDT should have specific properties.

- i. The absorption band should be on wavelength longer than 600nm so that it is easily distinguished from biological stances, such as hemoglobin.
- ii. The molecular extinction coefficient of the absorption wave length should be large and produce sufficient singlet oxygen upon light-induced excitation.
- iii. The substance should have a high affinity for the target, distribute homogeneously, and be rapidly excreted from normal tissue [12].

Objectives

The aspect of this research topic is to conduct an extensive literature review on the topics discussing the effect of Photodynamic therapy (PDT) as an adjuvant therapy to the classic periodontal treatment.

Research query

How does the Photodynamic therapy (PDT) affect the microorganisms involved in periodontal diseases?

Materials and Methods

Available literature and original research articles were used to investigate the effect of Photodynamic therapy (PDT) in periodontal diseases. PubMed database was the main source. Google scholar was used a second search date base for online resources where access was not approachable through MEDLINE. Access date was between 01/9/2007 and 30/01/2017. The research was confined to English Language literature. The following keywords were used: "Photodynamic therapy (PDT), Antimicrobial Photodynamic therapy (aPDT), periodontal disease".

Inclusion criteria

- a) All human studies (*in vivo* and *in vitro* studies).
- b) Determine the following treatment parameters: power, power density, energy, energy density, frequency of treatment, beam and dose expressed in (J/cm²).
- c) Special condition during the treatment, for example, diabetic ulcers.

Exclusion criteria

- a) Systemic review
- b) Literature review
- c) Histological studies
- d) Animals studies

Search outcomes

As seen in Figure 1 1000 articles were reviewed and were divided based on topic. The outcome after the inclusion and exclusion criteria was 38 articles regarding to Photodynamic therapy (PDT) (Figure 2).

Results

The results of the 38 papers regarding PDT that are reviewed and summarized in Table 1.

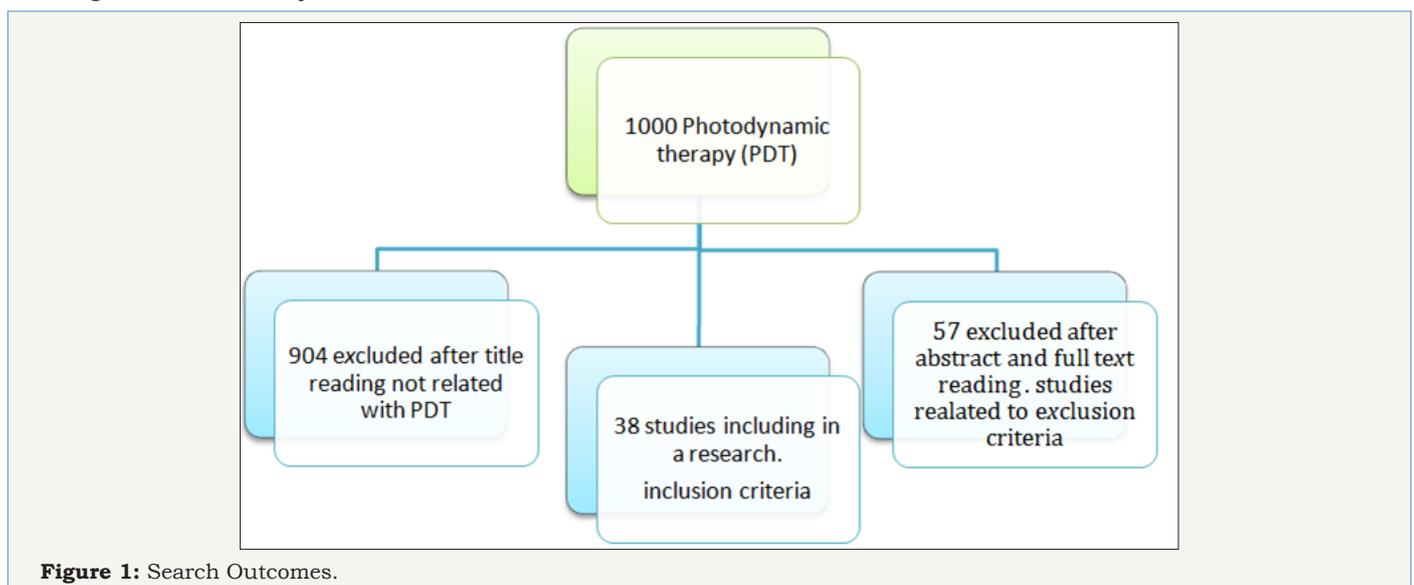


Figure 1: Search Outcomes.

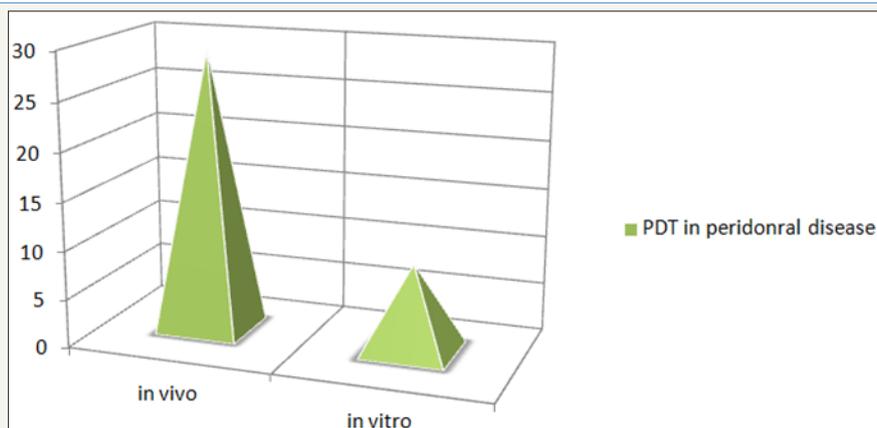


Figure 2: Demonstrate how many articles included in this review regarding to PDT.

Table 1: Laser irradiation conditions and results observed in vitro and in vivo Antimicrobial Photodynamic therapy.

Study	Reference	Laser and Wavelength (nm)	Photosensitization	Dose J/cm ²	Power Density mW/cm ²	Power	Microorganisms	Result
Qin et al. In vitro	[34]	Diode 632	Toluidine blue	3, 6, 12, and 24	53, 106, 159, 212	No info	Periodontal pathogens	The best therapeutic was observed in treatment by 1mg/ml with 12J/cm ² at 195mW/cm ² killing the pathogens
Braun A. et al. In vivo	[13]	Diode 660	Phenothiazine chloride	No info	No info	100mW	Chronic periodontitis	Positive effect on treatment outcomes
Berakdar et al. Christodoulides et al. Ge et al. Lulic et al. In vivo	[14] [15] [16] [17]	Diode 670	Methylen blue HELBOA Blue Methylen blue HELBOA Blue	No info 21	No info No info No info 75	150mW 75mW 140mW No info	<i>T. forsythensis.</i> <i>Terponema denticola.</i> <i>Fusobacterium uncleatum.</i> <i>Eikenella corrodens</i>	Reduction In bleeding scores And pocket depth
Chui C. et al. In vitro	[38]	Blue LED 425-470 Red LED 625-635	Toluidine blue Erythrosine Phloxine Rose bengal	30, 60, 90 for BL and 30,60 for RL	1.0 and 0.5	365 for BL and 185 for RL	<i>Porphyromonas gingivalis</i>	A log reduction was obtained after 30J/cm ² RL with TB and BL with RB in periodontal therapy
Braham et al. In vitro	[18]	Diode 670	Methylen blue	No info	No info	150mW	<i>Porphyromonas gingivalis</i>	Increasing bacterial killing <i>p. gingivalis</i>
Al-Zahrani et al. In vivo	[24]	Diode 670	Methylen blue	No info	No info	No info	Diabetes and periodontitis	No effect

Polansky et al. <i>In vivo</i>	[25]	Diode 680	HELBOA Blue	No info	No info	75mW	<i>P. gingivalis</i> <i>T. forsythia</i> <i>T.denticola.</i>	<i>P. gingivalis</i> was reduced significantly, but no significant reduction of <i>T. Forsythia</i> and <i>T.denticola.</i> was found
Rühling et al. <i>In vivo</i>	[26]	Diode 635	Tolonium chloride	No info	No info	100mW	Periodontal pocket	Microbial counts were significantly reduced about 30% to 40% immediately
Sigusch et al. <i>In vivo</i>	[19]	Diode 660	Phenothiyaine chloride	No info	60	No info	<i>F. nucleatum</i>	<i>F. nucleatum</i> DNA concentration Reduced
F. D. L. Mattiello et al. <i>In vitro</i>	[20]	Diode 660	Toluidine blue	10	No info	40mW	Actinomycetemcomitans (A.a) Sterptococcus sanguinis (S.s).	Reduction in number in Dye/laser group
Lui et al. <i>In vivo</i>	[27]	Diode 940	Methylene blue	4	No info	1.0 W	Nonsurgical treatment of chronic periodontitis	Greater reduction in gingival cervical fluid at 1WK. And bleeding on probing depth at 1Mo
Giannopoulou et al. <i>In vivo</i>	[46]	Diode 660 Diode 810	Phenothiyaine chloride	3 No info	No info No info	100mW 1W	Residual pockets	There was no evidence for a specific DSL- or PDT-enhanced expression of inflammatory mediators
Filho et al. <i>In vivo</i>	[30]	Diode 660	Methylene blue	57.14	0.428	0.03W	Periodontitis in HIV patient	PDT therapy used as an adjunct to SRP could promote additional benefits in the treatment of HIV-associated periodontitis
Dilsiz et al. <i>In vivo</i>	[28]	KTP 532 Diode 808	- Methylene blue	11.7	No info	0.8W 100mW	Chronic periodontitis	Deep pockets can be improved by using adjunctive KTP laser
Campos et al. <i>In vivo</i>	[22]	Diode 660	Methylene blue	129	No info	60mW	<i>Prophyromonas gingivalis</i> <i>T. Forsythia</i>	The reduction in <i>P. gingivalis</i> and <i>T. Forsythia</i>
Voos et al. <i>In vitro</i>	[23]	Diode 532	Safranin O	5,12, and 20	No info	0.5W	<i>F. nucleatum</i> <i>P. gingivali</i>	A PDT with safranin o showed a distinct antibacterial effect on <i>F. nucleatum</i> and <i>P. gingivalis</i> in 24-hour more than treatment with 0.2% CHX

Macedo et al. <i>In vitro</i>	[31]	Diode 660	Phenothiazine chloride	2.79 per site and 16.72 per tooth	28	60mW	Periodontal disease	No effect. But was able to promote a significant reduction in glycated hemoglobin levels (HbA1c)
Queiroz et al. <i>In vitro</i>	[32]	Diode 660	Phenothiazine chloride	2.79 per site and 16.72 per teeth	28	60mW	Smokers with chronic periodontitis	No effect
Skurska et al. <i>In vitro</i>	[29]	Diode 660	HELBOA Blue	No info	No info	No info	Aggressive periodontitis (AgP)	Nonsurgical Periodontal therapy in conjunction with adjunctive systemic administration of amoxicillin and metronidazole is more effective in reducing GCF MMP-8 levels compared to the adjunctive use of PDT
Petelin et al. <i>In vitro</i>	[40]	Diode 660	Phenothiazine chloride	No info	60	No info	<i>Treponema denticola</i> (TD). <i>Aggregatibacter actinomycetemcomitans</i> (AA). <i>Tannerella forsythia</i> .	Higher reduction of bleeding on probing (BOP) at 3 and 12 months compared to US alone or SRP and reduced after 6 months <i>Treponema denticola</i> (TD), and a greater reduction of <i>Aggregatibacter actinomycetemcomitans</i> (AA), <i>Tannerella forsythia</i> (TF), and TD in medium pockets and of TD in deep pockets
Monzavi et al. <i>In vitro</i>	[41]	810 Diode	Indocyanine green ICG Emundo	6	No info	200mW	Chronic periodontitis	Reduction in periodontal pocket depth
Giannellin et al. <i>In vitro</i>	[42]	635 Diode	Methylene blue	3.8	11.6	100mW	Chronic periodontitis	Improves healing in chronic periodontitis patients
Balata et al. <i>In vitro</i>	[43]	660 Diode	Methylene blue	320	No info	100mW	Chronic periodontitis	Improvement in the treatment of severe chronic periodontitis
Fontana et al. <i>In vitro</i>	[44]	455 Blue light	Black-pigment Bacteria	12	50	No info	The eight species	Reduction in relative abundances of the eight bacteria
Birang et al. <i>In vitro</i>	[35]	Diode 810	Emundo	No info	0.5	No info	Chronic periodontitis	Benefits in the treatment of chronic periodontitis

Qiao et al. <i>In vitro</i>	[45]	675 Diode	Methylene blue	19.7	329	280mW	Human periodontal ligament cell and human gingival fibroblasts	Stimulated proliferation
Campanile et al. <i>In vitro</i>	[46]	670 Diode	Methylene blue	No info	No info	280mW	Periodontitis	Single or double episodes of PDT had some additional benefit over ultrasonic instrumentation alone
Bassir et al. <i>In vitro</i>	[47]	625-635 Diode	Toluidine blue	No info	2000	No info	Chronic periodontitis	Did not have additional effects on clinical parameters
Betsy et al. <i>In vitro</i>	[48]	655 Diode	Methylene blue	No info	60	No info	Chronic periodontitis	Acts as a beneficial adjunct to SRP
Boehm et al. <i>In vitro</i>	[36]	Diode 810	Indocyanine green ICG Emundo	No info	10-80	0.5W	Periodontal pockets.	Reduction of bacterial
Andersen et al. <i>In vitro</i>	[8]	670 Diode	Methylene blue	10-20	No info	150mW	Nonsurgical periodontal	Significant improvements of the investigated parameters
Seguier et al. <i>In vitro</i>	[50]	Diode 670	Phthalocyanine	121.7	0.5	No info	Chronic human periodontitis	Reduction of bacterial
Correa et al. <i>In vitro</i>	[51]	660 Diode	Methylene blue	129	No info	60mW	Unresponsive pockets	Improvement in clinical parameters in treating residual pockets
Moreira et al. <i>In vitro</i>	[52]	670 Diode	HELBO Blue	2.49	0.25	No info	Aggressive periodontitis	Promotes additional clinical, microbiologic, and immunologic benefits in the treatment of deep periodontal pockets in single-rooted teeth in patients with AgP
Freitas et al. <i>In vitro</i>	[53]	660 Diode	Methylene blue	20	100	NO info	Human dental plaque bacteria	Promising adjunct in antimicrobial periodontal treatment

Discussion

Several *in vitro* and *in vivo* human studies have demonstrated that microorganisms related to periodontal disease such as *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans* (previously *Actinobacillus actinomycetemcomitans*), *Fusobacterium nucleatum*, *Prevotella intermedia* and *Streptococcus sanguis* are significantly reduced in number by a PDT with diode laser 660nm and 670nm under different environmental conditions (*in vitro* and *in vivo* human study) [13-22]. However, it should be kept in mind that a recent study demonstrated additional clinical benefits of subgingival ultrasonic scaling are achieved by repeating (three times) PDT in [23].

Within the limitation of the study [24] no extra benefit of PDT of diode laser 670nm on clinical periodontal parameters was found in patient with diabetes. This study cannot be reliably upon because in addition to the small number of cases, it also lacks the detail that is required by the readers of the laser parameters. One clinical trial evaluating the application of one cycle of the PDT laser diode 680nm was not effective as an adjunct to ultrasonic gums, there was no further reduction in the depth of the sinus and bleeding on the probe [25]. The lack of a laser effect-in our opinion-may be attributed to exposure time about 1 minute very short. In addition, older people have a slower metabolic process than children, which negatively affects the healing process. More recently, *in vivo* studies

have shown a decrease by reduction of periodontal signs of redness, periodontal pocket, gingival cervical fluid and bleeding on probing after aPDT for the treatment of periodontitis [26-29].

Immunosuppression caused by HIV is associated with different forms of periodontal disease as well as the exacerbation of a pre-existing periodontitis. One study [30] demonstrated that clinical outcomes following the non-surgical periodontal treatment of patients with HIV-associated chronic periodontitis were improved by using the adjective PDT diode laser 660 nm procedure. Moreover, this diode laser reduced *P. Gingivalis*, *T. Forsythia*, and *A. Actinomycetemcomitans*. In 2 present clinical studies [31,32], aPDT was tested as an adjunct for the treatment of chronic periodontitis in patient with diabetes type 2 and in smoker's patient. These studies demonstrated clinical improvement after aPDT with (diode laser 660nm and 2.79J/cm²) as adjunctive therapy after SRP+aPDT was used, but they were similar to SPR group, and showed similar reductions in bleeding on probing after nonsurgical periodontal treatment in patients with diabetes. However, it is important to emphasize that poorly controlled diabetes can promote vascular alteration [31] and other metabolic alterations that can be involved in the appearance of symptoms such as gingival bleeding. Thus, it is difficult to compare diabetic patients with healthy patients and the effect of aPDT on the reduction of gingival bleeding. Furthermore, it is well accepted that smoking alters the host response, including vascular function, neutrophil/monocyte activities, adhesion molecule expression, antibody production, as well as the release of cytokine and inflammatory [33]. Therefore, the negative influence of smoking, which impairs normal host responses, might have made it difficult to verify significant differences in IL-1 β and MMP-8 concentration.

One study [34] has indicated that it is possible to kill bacteria in supra gingival plaque scrapings by using topically applied TB and 635nm red light from a diode laser. The effect of TB-mediated PDT in treating PP greatly depends on photosensitizer concentration, light intensity, and light energy dose. Where they found the most effective combination is that of 1mg/ml TB with 12 J/cm² light at 212mW/cm², which produced a 47-99% killing rate for different patients. Birang et al. The LLLT of the low-level diode, associated with the traditional SRP was more effective in reducing PPD than that achieved by PDT with SRP or SRP alone. This result is inconsistent with Boehm et al. [36] whose laboratory studies showed that ICG therapy with an 810nm diode laser may be useful as a dynamic optical assistant to reduce bacterial load in gingival pockets. The important point to consider when interpreting the

clinical and bacterial results obtained by PDT is the effect of the same optical sensitizers. This means ICG act as a light agent under these conditions, but also it has bactericidal effect by efficiently absorbing the laser energy within the cells and denaturing bacterial proteins.

The difference in the antimicrobial/growth-inhibiting effect between BL and RL may be a result of the difference in the wavelength property of both lights. On BL irradiation, it has been speculated that endogenous porphyrin produced by bacteria is excited, leading to a Photodynamic reaction through singlet oxygen production, resulting in an antimicrobial effect [37]. In contrast, one *in vitro* study [38] used a high-power BL, expecting a higher antimicrobial effect as well as a shorter irradiation time, which are important in clinical practice. The antimicrobial effect of high-power BL on *P. Gingivalis* [38] was detected after short time periods of irradiation of 60 and 90s. Moreover, a-PDT using a combination of BL and RB shows promise as a new technical modality for bacterial elimination in periodontal therapy.

Chlorhexidine (CHX) is a cationic agent that binds to the bacterial cell wall and leads to an increase of permeability. For a sufficient effect the CHX concentration needs to be strong enough to imbalance the osmotic pressure of the bacterial cell [39]. Voss et al. [23] showed that the gram-negative bacteria were more sensitive to treatment with CHX. In contrast, a PDT proved to be more efficient on the gram-positive species. However, the main antibacterial agent of a PDT is singlet oxygen, which is produced by the Photodynamic reaction and leads to a massive destruction, Photodynamic treatment with safranin O was significantly more efficient than subjection to 0.2% CHX, But, compared to the action of CHX and a PDT with safranin O, a PDT with safranin O were still more efficient in reducing bacterial growth. This method is more effective than treatment with 0.2% CH [40-46].

Conclusion

The *in vivo* and *in vitro* studies present in the literature, indicate that a PDT may potentially become successful. In addition, infectious procedure associated with conventional therapy can be successful in the management of periodontal disease and Photodynamic therapy has the advantage of reduced treatment time and the need for anesthesia, which destroys bacteria in a very short period of time without developing resistance to bacteria [47-53]. From the reviewed articles, we could conclude some suitable parameters for PDT as an adjunctive therapy in periodontal disease treatment. Those articles listed in Table 2 were chosen based on the positive results they demonstrated.

Table 2: Articles listed were chosen based on the positive results.

Laser and Wavelength (nm)	Photosensitization	Dose (J/cm ²)	Power Density mW/cm ²	Power	Place of Influence	Result
Diode 660	Methylene blue	57.14	0.428	0.03mW	Periodontitis in HIV patient	PDT therapy used as an adjunct to SRP could promote additional benefits in the treatment of HIV-associated periodontitis

Diode 635	Methylene blue	3.8	11.6	100mW	Chronic periodontitis	Improves healing in chronic periodontitis patients
Diode 810	Indocyanine green ICG Emundo	6	No info	200mW	Chronic periodontitis	Reduction in periodontal pocket depth

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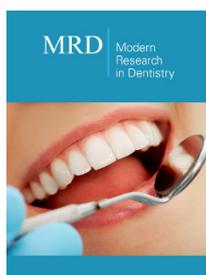
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