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Review

Randomized and Controlled Clinical Studies on Antibacterial Photodynamic Therapy: An Overview

Fernanda Alves [1], Mirian D. Stringasci [1], Michelle B. Requena [1], Kate C. Blanco [1,2], Lucas D. Dias [1], Thaila Q. Corrêa [1] and Vanderlei S. Bagnato [1,2,*]

[1] São Carlos Institute of Physics, University of São Paulo, São Carlos 13566-590, SP, Brazil; alvesf@usp.br (F.A.); mirianstringasci@ifsc.usp.br (M.D.S.); requenamichelle@usp.br (M.B.R.); kateblanco@ifsc.usp.br (K.C.B.); lucas.dias1@usp.br (L.D.D.); thaila@ifsc.usp.br (T.Q.C.)
[2] Department of Biomedical Engineering, Texas A&M University, College Station, TX 77843, USA
* Correspondence: vander@ifsc.usp.br; Tel.: +55-16-3373-9810

Abstract: The emergence of drug-resistant bacteria is considered a critical public health problem. The need to establish alternative approaches to countering resistant microorganisms is unquestionable in overcoming this problem. Among emerging alternatives, antimicrobial photodynamic therapy (aPDT) has become promising to control infectious diseases. aPDT is based on the activation of a photosensitizer (PS) by a particular wavelength of light followed by generation of the reactive oxygen. These interactions result in the production of reactive oxygen species, which are lethal to bacteria. Several types of research have shown that aPDT has been successfully studied in in vitro, in vivo, and randomized clinical trials (RCT). Considering the lack of reviews of RCTs studies with aPDT applied in bacteria in the literature, we performed a systematic review of aPDT randomized clinical trials for the treatment of bacteria-related diseases. According to the literature published from 2008 to 2022, the RCT study of aPDT was mostly performed for periodontal disease, followed by halitosis, dental infection, peri-implantitis, oral decontamination, and skin ulcers. A variety of PSs, light sources, and protocols were efficiently used, and the treatment did not cause any side effects for the individuals.

Keywords: antimicrobial photodynamic therapy; bacteria; randomized clinical trial

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1. Introduction

Currently, one of the most important clinical challenges in the world is the increasing resistance of bacteria to antibiotics. According to recent reports about drug-resistant infections, the actual scenario shows a risk is being posed to the ability to treat common infections with any single kind of antibiotic, with antimicrobial resistance being one of the top 10 global public health threats facing humanity [1,2]. Humans have exposed microorganisms, specifically pathogenic microbial populations, to antimicrobial agents, such as antibiotics and antiseptics, to control infectious diseases. The overuse of these substances makes disease-causing microorganisms develop various resistance mechanisms to drugs commonly used to treat them, which is a severe worldwide threat to managing infectious diseases [3]. To overcome the resistance problem, the search for alternative approaches is necessary. Antimicrobial photodynamic therapy (aPDT) has become a promising and potential treatment, since it is nontoxic, noninvasive, and has presented effective results against microorganisms, while not causing them to quickly develop resistance [4].

The mechanisms of aPDT are based on the interaction of the photosensitizer (PS) molecule with light in a compatible wavelength in the presence of molecular oxygen (Figure 1). When the PS molecule in its singlet ground state (S_0) absorbs a photon (hν), it transitions to the singlet excited state (S_n). From S_n, the PS can release energy through fluorescence emission (f) or through internal conversion, releasing heat, then returning to the ground state, S_0. The PS molecule may, from S_n, still undergo an intersystem crossing (ISC) to a triplet excited state (T_1) with a longer lifetime. From T_1, the PS may return to

S_0 after emitting phosphorescence (P) or after participating in reactions that lead to the generation of reactive oxygen species (ROS): type I reactions and type II reactions. In a type I reaction, when the PS is in the T_1, it can transfer a proton or an electron to the substrate to form a radical anion or radical cation; these radicals may react with oxygen to produce ROS. In a type 2 reaction, the PS in the T_1 can directly transfer energy to molecular oxygen (a triplet in the ground state), producing excited-state singlet oxygen ($^1O_2$). Both type 1 and 2 reactions occur simultaneously, but depending on the chemical structure of the PS, one of the reactions will be preferential. The efficiency of the aPDT is often related to the $^1O_2$ quantum yield of the PS [5–8]. The photoproducts species are responsible for inducing the death of the target cell. Then, aPDT represents a multi-target damaging process, since the reactive oxygen species generated can interact and damage all structures that are close to them. For this reason, the effectiveness of the aPDT is also related to the PS localization and uptake, where the oxidative process will occur [9,10]. Moreover, the ability of the ROS to damage a nonspecific site means that aPDT is unlikely to induce resistance in the microorganisms, and this characteristic is an advantage of aPDT over antibiotics. Antibiotics, regardless of the class, bind to and act on a specific target, to that the bacteria is more likely to develop resistance to them.

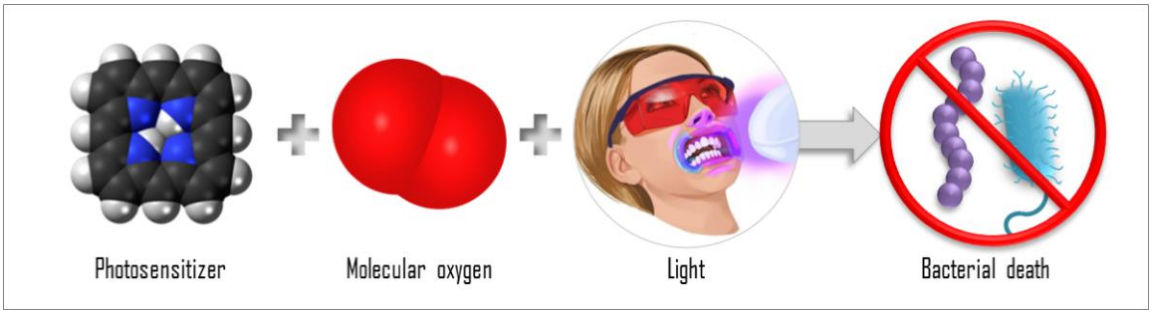

Figure 1. Scheme of the antimicrobial photodynamic therapy (aPDT) components: interaction of PS, molecular oxygen, and light, causing bacterial death.

Photodynamic action has been applied to non-melanoma skin lesions with well-established protocols and is strongly recommended by the American and European academies of dermatology [11–13]. Moreover, many other areas have promisingly benefited from this technique with marked improvement in human-health-concerning infections; however, these do not have defined, validated, effective, and secure protocols.

For example, some aPDT applications, such as the control of disease vectors, are also a great gain that photodynamics can offer. Through the use of appropriate PSs, it is possible to place breeding sites for vectors of the main diseases, such as dengue, etc., in suitable forms that allow the larvae to absorb the substance. With this and with the help of sunlight, the elimination of these larvae can reach 90%, without any aggression to the environment [14,15]. Decontamination of blood banks is also a source of infection for humans [16] and photodynamic with riboflavin and UVA light allows a considerable decrease in the viral and bacterial load of blood bags, thus decreasing the chances of contamination of receptors [17].

Additionally, many infectious diseases are caused by contamination in food [18]. In the case of raw foods (meats, grains, vegetables, and fruits), the number of contaminants that remain in the food when it reaches the consumer's hands are large. The action of aPDT has been shown to be adequate for the preservation and elimination of infectious factors in food. Finally, water-borne diseases are also a global burden that is estimated to cause several million deaths and innumerable cases of sickness every year. The application of photodynamic processes has been exploited to address the decontamination of waters, where sunlight-mediated aPDT can eliminate pathogens present in municipal and other water supplies [19]. These examples are some cases on the subject, which demonstrate that photodynamic inhibition can go far beyond human health.

The antimicrobial potential of PDT has also been widely and successfully applied for the management of bacterial infectious diseases, such as for the oral decontamination of orthodontic patients [20,21]; for the inactivation of *Streptococcus mutans* biofilm [22,23] and *Staphylococcus aureus* biofilm in in vitro and in vivo studies [24]; in the treatment of pharyngotonsillitis [25,26]; against bacteria that cause pulmonary diseases [27–29]; in the decontamination of blood [16,30,31]; and in cooperative and competitive aPDT effects [32]. Some studies have focused on the development of new compounds for the enhancement of aPDT [33]. In this context, researchers have synthesized nanoparticle and dye diffusion in bacterial biofilms for aPDT applications [34], such as the use of superhydrophobic sensitizer techniques in the treatment of periodontitis [35].

The natural evolution of these in vitro and in vivo aPDT findings is to translate them to clinical trials aiming to define and validate effective and secure protocols. There are several types of clinical studies, such as randomized controlled trials (RCT), cohort studies, case–control studies, case series, case reports, and opinion reports. Considering the hierarchy of evidence parameters among them, RCT can be considered the gold standard of clinical trials, providing the most reliable evidence of the effectiveness of interventions. RCTs are designed to have the participants randomly assigned to one of two or more clinical interventions which minimize the risk of confounding factors influencing the results [36].

Considering the lack in the literature of reviews reuniting RCTs studies with aPDT applied in bacteria, we performed a systematic review aiming at aPDT randomized clinical trials to treat bacteria-related diseases.

2. Materials and Methods

The present systematic review searched aPDT randomized clinical trials for the treatment of bacteria-related diseases. The studies were collected from The Web of Science database, using the keywords "Photodynamic", "bacteria", and "randomized controlled", from 2008 to 2022.

3. Results and Discussion

Figure 2 summarizes the percentage of each aPDT application in the studies evaluated. Periodontal disease was the most common application explored in the studies (65%), followed by halitosis (14%), dental infection (10%), peri-implantitis (6%), oral decontamination (2%), and skin ulcers (2%), respectively. Tables 1–6 show the studies' details organized by diseases found in the present search.

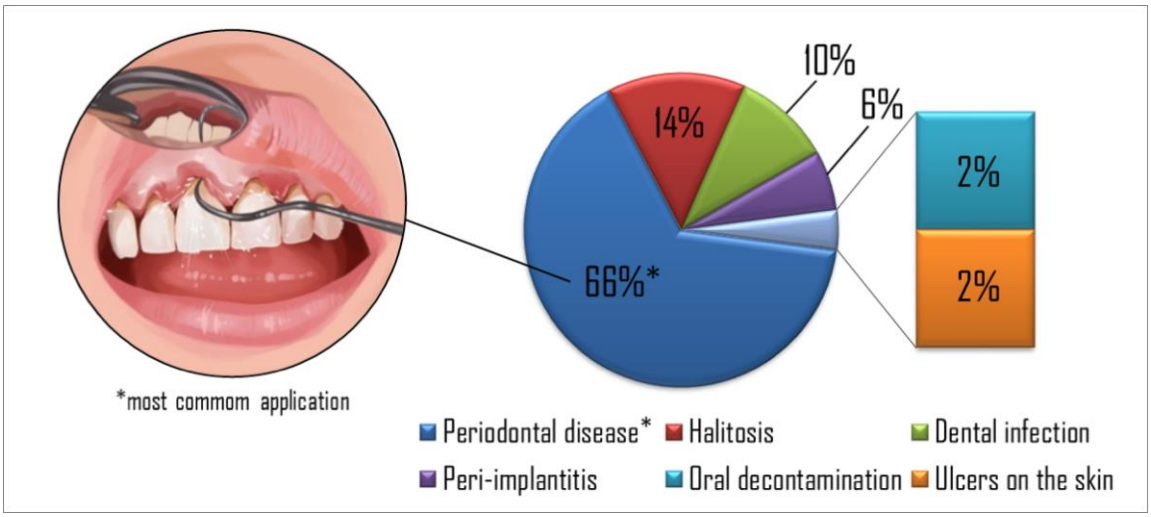

Figure 2. The percentage of targets in the papers reviewed showed periodontal disease as the most common application found in the studies, followed by halitosis, dental infection, peri-implantitis, oral decontamination, and skin ulcers, respectively.

Table 1. Randomized clinical trials that evaluated aPDT for the treatment of periodontal disease. SRP—scaling and root planning.

Ref.	Year of Publication	Country	Number of Patients	Treatment Site	Goal	Clinical Condition	Protocols	Light Parameters	PS, Concentration, and DLI	Follow-Up	Main Results
[37]	2008	Netherlands	24	Periodontal pocket and gingiva	Evaluate the clinical and microbiological adjunctive uses of aPDT for nonsurgical periodontal treatment in chronic periodontitis	Chronic periodontitis	Control Group (n = 12): SRP using hand instruments and sonic instrumentation; aPDT Group (n = 12)	670 nm, 75 mW, for 1 min	HELBO Blue Photosensitizer, (HELBO Photodynamic Systems, Austria) for 3 min	3 and 6 months after treatment	A single aPDT session added to SRP failed to improve probing depth reduction and clinical attachment level gain, but it resulted in a greater reduction in bleeding scores compared with SRP alone
[38]	2009	Germany	24	Periodontal pocket	Evaluate the clinical and microbiological effects of the adjunctive use of aPDT in nonsurgical periodontal treatment	Patients receiving supportive periodontal therapy	Randomly treated with either subgingival SRP followed by a single episode of aPDT (test) or subgingival SRP alone (control)	670 nm, power density of 75 mW/cm^2	Phenothiazine chloride (HELBO Blue Photosensitizer®, HELBO Photodynamic Systems)	6 months	The additional application of a single episode of PDT to SRP failed to result in an additional improvement in terms of PPD reduction and CAL gain, but it resulted in a significantly higher reduction in bleeding scores than following SRP alone
[39]	2009	China	10	Periodontal pocket	Possible added benefits of repeated adjunctive aPDT to conventional treatment of residual pockets in patients enrolled in periodontal maintenance	Patients with residual pockets	Treatment randomly assigned 5 times in 2 weeks (Days 0, 1, 2, 7, 14) with aPDT (test) or nonactivated laser (control) following debridement	670 nm, irradiance of 75 mW/cm^2	Phenothiazine chloride (HELBO Blue Photosensitizer, HELBO® Photodynamic Systems GmbH) for 3 min	12 months	Repeated (5 times) aPDT adjunctive to debridement yielded improved clinical outcomes in residual pockets in maintenance patients

Table 1. *Cont.*

Ref.	Year of Publication	Country	Number of Patients	Treatment Site	Goal	Clinical Condition	Protocols	Light Parameters	PS, Concentration, and DLI	Follow-Up	Main Results
[40]	2009	Austria	58	Periodontal sites	To evaluate aPDT for its bactericidal potential and clinical effect in the treatment of periodontitis	Periodontitis	Group 1 (control group) was managed with an EMS Piezon Master 600 ultrasonic system (EMS Electro Medical Systems, Nyon, Switzerland); Group 2 (laser group) was managed by aPDT in addition to ultrasonic treatment	680 nm, 75 mW	Methylene blue at 0.005% for 3 min	3 months after treatment	The application of a single cycle of aPDT was not effective as an adjunct to ultrasonic periodontal treatment
[41]	2010	Germany	60	Periodontal pocket	Evaluate whether aPDT can reduce probing depth in persistent periodontal pockets, change the microbial composition, and decrease the total load of subgingival bacteria more than conventional mechanical debridement	Chronic periodontitis	Control Group (n = 29) treated with conventional ultrasonic debridement; aPDT Group (n = 25) treated with PS and light	635 nm, 100 mW, for 1 min	Tolonium chloride (Asclepion-Meditec, UK) at 5% concentration for 30 s	3 months after treatment	Both therapies resulted in the same clinical effect; however, aPDT is less harmful to the teeth and microbial counts were reduced by about 30%–40%, but returned to baseline values after 3 months, irrespective of treatment

Table 1. *Cont.*

Ref.	Year of Publication	Country	Number of Patients	Treatment Site	Goal	Clinical Condition	Protocols	Light Parameters	PS, Concentration, and DLI	Follow-Up	Main Results
[42]	2012	Brazil	33	Periodontal sites	Evaluate the long-term clinical and microbiological effects of aPDT associated with nonsurgical periodontal treatment	Chronic periodontitis	(1) SRP group; (2) SRP and irrigation with toluidine blue O (TBO group); and (3) SRP, irrigation with TBO, and low level laser irradiation (aPDT group)	660 nm, power 30 mW, spot size 0.07 cm^2, energy 4.5 J	Toluidine blue O phenothiazine dye (100 μg/mL; Sigma Chemical Co., St Louis, MO), for 1 min	180 days	aPDT as an adjunct to periodontal treatment produced statistically significant reductions in some of the key periodontal pathogens but produced no statistically significant benefit in terms of clinical outcome
[43]	2013	Brazil	22	Periodontal sites	To evaluate an aPDT protocol as an adjunct to ultrasonic debridement in patients with severe chronic periodontitis	Chronic periodontitis	(1) Patients were submitted to full-mouth ultrasonic debridement with an ultrasonic scaler; (2) aPDT protocol was carried out (one side of the mouth) with 0.005% methylene blue; (3) after 2 min, the light (660 nm) was applied	660 nm, 100 mW, light dose = 320 J/cm^2	0.005% methylene blue	3 months	aPDT and ultrasonic debridement showed good clinical improvements; however, aPDT did not provide any additional benefit when used with ultrasonic debridement

Table 1. *Cont.*

Ref.	Year of Publication	Country	Number of Patients	Treatment Site	Goal	Clinical Condition	Protocols	Light Parameters	PS, Concentration, and DLI	Follow-Up	Main Results
[44]	2014	Italy	30	Periodontal sites	To study the potential adjunctive effect of microbiological/clinical photodynamic protocol using an LED lamp (red spectrum) and to compare it to SRP	Chronic periodontitis	(1) Patients were treated with SRP; (2) treatment sites were allocated by a toss; (3) toluidine blue was applied and the location was illuminated by using an LED lamp (red spectrum—628 nm)	628 nm, 2000 mW/cm^2, light dose = 20 J/cm^2	Toluidine blue-Fotosan Agent®-(0.1 mg/mL) in 1% xanthan gel	-	A single protocol using an LED light system (red spectrum) and toluidine blue enhance short-term clinical and microbiological outcomes of the mechanical procedure
[45]	2014	Brazil	30	Periodontal sites	To evaluate the aPDT combined with nonsurgical periodontal and doxycycline on clinical and metabolic effects in patients that show type 2 diabetes mellitus	Chronic periodontitis	All subjects of both groups (SRP and SRP + aPDT) were treated with SRP in combination with doxycycline (100 mg/day, for 2 weeks); (1) in the SRP + aPDT group, a diode laser (660 nm) for 1 min and phenothiazine chloride as PS were applied	660 nm, 28 mW/cm^2, light dose = 16.72 J/cm^2	Phenothiazine chloride (10 mg/mL)	3 months	aPDT (single use) did not show any clinical improvement as an adjunct to SRP but significantly reduced the glycated hemoglobin levels (HbA1c)

Table 1. *Cont.*

Ref.	Year of Publication	Country	Number of Patients	Treatment Site	Goal	Clinical Condition	Protocols	Light Parameters	PS, Concentration, and DLI	Follow-Up	Main Results
[46]	2014	Korea	41	Periodontal sites	To elucidate clinical and antimicrobial effects of daily phototherapy (PT) as an adjunct to SRP in patients with chronic periodontitis	Chronic periodontitis	All participants underwent full-mouth SRP with periodontal curettes and an ultrasonic device: (1) SRP + PT group assigned electric toothbrushes with embedded LEDs (single frequency, 635 nm wavelength, 13 mW/cm^2); (2) SRP group assigned electric toothbrushes without LEDs; irradiation time was 3 min per session	Single frequency, 635 nm, 13 mW/cm^2, 3 min	-	4 weeks	The clinical parameters were improved in both groups; probing pocket depth (PPD) was significantly decreased in the SRP + PT group at the follow-up; furthermore, PPD and clinical attachment levels showed greater changes in the SRP + PT group than in the SRP group; no significant antimicrobial intergroup differences were noted
[47]	2014	India	88	Periodontal pocket and gingiva	Evaluate whether adjunctive use of aPDT to SRP has any short-term effectiveness in chronic periodontitis	Chronic periodontitis	Group 1(n = 44) assigned SRP by hand scalers, universal curettes, and ultrasonic scaler; Group 2 (n = 44) assigned SRP according to Group 1 + aPDT	655 nm, 60 mW/cm^2, for 60 s	Methylene blue (Sigma-Aldrich, St. Louis, MO, USA) at 10 mg/mL concentration for 3 min	1, 3, and 6 months after treatment	A single application of this aPDT protocol was found to be effective in reducing gingival inflammation and probing pocket depth, evaluated over 6 months

Table 1. *Cont.*

Ref.	Year of Publication	Country	Number of Patients	Treatment Site	Goal	Clinical Condition	Protocols	Light Parameters	PS, Concentration, and DLI	Follow-Up	Main Results
[48]	2015	Brazil	34	Periodontal pocket	Evaluate the clinical and microbiological effects of aPDT in the treatment of residual pockets of patients with chronic periodontitis subjected to supportive therapy	Chronic periodontitis	Control group (n = 16) assigned saline solution; aPDT group (n = 18) assigned PS + light	660 nm, 90 J/cm^2, 40 mW, for 90 s	Methylene blue (Chimiolux®, Hypofarma, Brazil) at 0.01% concentration for 5 min	7 days, 3, 6, and 12 months after treatment	aPDT protocol used failed to demonstrate additional clinical and bacteriological benefits in residual pockets treatment
[49]	2015	Brazil	20	Periodontal sites	To study the efficiency of multiple sessions of aPDT in combination with SRP *versus* SRP in patients that show AgP	Aggressive periodontitis	(1) Patients received full-mouth supragingival scaling; (2) SRP was carried out; (3) phenothiazine chloride was added; (4) a diode soft-laser light (670 nm) was applied subgingivally	670 nm, 0.25 W/cm^2, light dose = 2.49 J/cm^2	Phenothiazine chloride (10 mg/mL)	-	The application of aPDT (4 sessions) as an adjunctive protocol to SRP, promotes additional microbiologic, clinical, and immunologic benefits

Table 1. *Cont.*

Ref.	Year of Publication	Country	Number of Patients	Treatment Site	Goal	Clinical Condition	Protocols	Light Parameters	PS, Concentration, and DLI	Follow-Up	Main Results
[50]	2015	Iran	20	Periodontal sites	To evaluate the impact of adjunctive laser therapy (LT) and aPDT on patients with chronic periodontitis.	Chronic periodontitis	All patients received SRP; (1) only SRP; (2) SRP with laser therapy—810 nm; (3) SRP + aPDT mediated by Emundo® mixture	Step 1—transgingival irradiation by bleaching handpiece (0.5 W, 10 s); Step 2—irradiation by a 300 µm bare fiber in a circular pattern (0.5 W, 15 s); (c) Step 3—Granulation tissue removal using a 300 µm bare fiber (0.5 W, 25 s)	Emundo® mixture	3 months	All groups showed improvements in terms of clinical attachment level (CAL) gain, periodontal pocket depth (PPD) reduction, papilla bleeding index, and microbial count compared with baseline; the results showed more significant improvement in the 6-week evaluation in terms of CAL in groups 2 and 3 than in group 1; group 2 also revealed a greater reduction in PPD than the other treatment modalities

Table 1. *Cont.*

Ref.	Year of Publication	Country	Number of Patients	Treatment Site	Goal	Clinical Condition	Protocols	Light Parameters	PS, Concentration, and DLI	Follow-Up	Main Results
[51]	2015	India	60	Periodontal sites	To evaluate the effects of indocyanine green as an adjunct to nonsurgical periodontal therapy in terms of reduction in the percentage of viable bacteria and host tissue injury	Periodontitis	SRP group (only SRP); laser group—SRP and application of diode laser at 810 nm for 5 s;test group—indocyanine green (SRP) and application of diode laser beam at 810 nm in a continuous wave mode with 0.7 W output for 5 s along with 0.5 mL of 5 mg/mL ICG solution	810 nm with 0.7 W output for 5 s	0.5 mL indocyanine green, 5 mg/mL injected through a blunt end cannula till the pocket was overfilled	6-month period after treatment	Laser-activated ICG dye may enhance the potential benefits of SRP and can be used as an adjunct to nonsurgical periodontal therapy

Table 1. *Cont.*

Ref.	Year of Publication	Country	Number of Patients	Treatment Site	Goal	Clinical Condition	Protocols	Light Parameters	PS, Concentration, and DLI	Follow-Up	Main Results
[52]	2015	Italy	26	Periodontal pocket	Report the 4-year follow-up results of multiple aPDT cycles (PAPD) associated with SRP compared to sham treatment associated with SRP alone	Chronic periodontitis	Control group (n = 138 teeth)—sham + SRP; aPDT group (n = 138 teeth)—PAPD + SRP	aPDT: 635 nm, 100 mW Noncontact—gingival pocket external 11.6 W/cm^2, 3.8 J/cm^2 each passage Photoablative 810 nm, 1 W Contact—gingival pocket internal + external: 353.4 W/cm^2, 66.7 J/cm^2 Contact—gingival pocket internal: 35.3 W/cm^2, 6.7 J/cm^2 each passage	Methylene blue at 0.3% concentration for 5 min	4 years (every 3 months during the 1st year and then every 6 months until the end)	PAPD + SRP provided a significant and durable improvement compared with sham + SRP alone

Table 1. *Cont.*

Ref.	Year of Publication	Country	Number of Patients	Treatment Site	Goal	Clinical Condition	Protocols	Light Parameters	PS, Concentration, and DLI	Follow-Up	Main Results
[53]	2016	Malaysia	20	Periodontal sites	To evaluate the efficacy of aPDT in reducing *Aggregatibacter actinomycetemcomitans* (Aa) in periodontitis patients	Periodontitis	Conventional nonsurgical periodontal therapy (NSPT) was performed; in addition, the test side received adjunct aPDT	A red LED lamp with a frequency of 628 Hz; gingiva and pocket were irradiated for 10 s	Methylene blue, 1 min of DLI	7 days, 1 and 3 months	There was a clinical improvement in 1 and 3 months compared with baseline, while the bleeding on probing was reduced only in the aPDT group in month 3; however, no difference in the quantification of Aa was detected between the groups
[54]	2016	Brazil	20	Periodontal pockets	Investigate the local effect of adjunct aPDT to ultrasonic periodontal debridement (UPD) and compare it to UD only	Moderate to severe generalized chronic periodontitis in type 2 diabetic patients	Control group (n = 20)—UPDT; test group (n = 20)—UPD + aPDT	660 nm, 60 mW with irradiance of 2.15 W/cm^2, total energy of 3.6 J and fluency of 129 J/cm^2	0.005% methylene blue—Chimiolux DMC for 60 s	180 days	After 180 days, there were statistically in the UPD group and the UPD + aPDT group; however, the intergroup analysis did not reveal statistically significant differences in any of the evaluated clinical parameters

Table 1. *Cont.*

Ref.	Year of Publication	Country	Number of Patients	Treatment Site	Goal	Clinical Condition	Protocols	Light Parameters	PS, Concentration, and DLI	Follow-Up	Main Results
[55]	2016	Iran	18	Periodontal pocket	Compare the microbiologic effectiveness of the aPDT as an adjunctive treatment modality for nonsurgical treatment in chronic periodontitis	Moderate–severe chronic periodontitis, presence of at least 2 teeth with a pocket depth of 4–10 mm in each quadrant, gingival bleeding, and presence of at least 5 natural teeth in each quadrant	Four quadrants were randomly treated by SRP, diode laser (810 nm wavelength, 1.5 W, and 320 µm fiber, contact, and sweeping technique), SRP + aPDT (with diode laser 808 nm, 0.5 W), and laser + SRP (with diode laser 808 nm, 1 W) in each patient	808 nm, 0.2 W power	-	3 months	aPDT was more effective as an adjunctive treatment to SRP than SRP alone; however, no distinct differences were found between both treatment modalities regarding the reduction in certain pathogen bacteria
[56]	2016	Brazil	13	Periodontal pocket	Evaluate the efficacy of aPDT as an adjuvant to conventional periodontal treatment in down syndrome patients	Down syndrome patients who presented at least one tooth in each quadrant of the mouth with probing pocket depth equal to or greater than 5 mm were included	Conventional treatment with SRP + a sham procedure and the experimental treatment SRP + aPDT	660 nm, 120 J/cm^2 divided into 4 points of 30 J/cm^2 per tooth (1.2 J per point); the application time was 30 s/point with a spot size of 0.04 cm^2	Methylene blue 0.01% (Chimiolux®, DMC, São Carlos, SP, Brazil), for 4 min	1 month	Both types of periodontal treatment, with and without aPDT, were similarly effective and were associated with good clinical response

Table 1. *Cont.*

Ref.	Year of Publication	Country	Number of Patients	Treatment Site	Goal	Clinical Condition	Protocols	Light Parameters	PS, Concentration, and DLI	Follow-Up	Main Results
[57]	2017	Italy	31	Periodontal sites	To further evaluate the effects of SRP + diode laser for the treatment of generalized aggressive periodontitis.	Generalized aggressive periodontitis	SRP + diode laser or SRP alone	810 nm laser, set at 1 W in pulsating mode at 50 Hz, toff = 100 msec, ton = 100 msec, and an energy density of 24.84 J/cm^2, with a 300 µm fiber optic delivery system	-	1 year	Both treatments demonstrated an improvement in periodontal parameters at 1 year; however, SRP + diode laser produced a significant improvement in probing depth and in clinical attachment level; however, microbial and inflammatory mediator changes were not significantly reduced compared to SRP alone
[58]	2018	Italy	36	Periodontal sites	To investigate and compare a desiccant agent as an adjunct to SRP versus SRP alone for the treatment of chronic periodontitis	Chronic periodontitis	-	-	-	-	No aPDT or light therapy was performed

Table 1. *Cont.*

Ref.	Year of Publication	Country	Number of Patients	Treatment Site	Goal	Clinical Condition	Protocols	Light Parameters	PS, Concentration, and DLI	Follow-Up	Main Results
[59]	2019	Brazil	16	Periodontal sites	To evaluate the clinical effects and the subgingival microbiota after multiple sessions of aPDT associated with surgical treatment of severe chronic periodontitis (SCP)	Chronic periodontitis	All participants underwent 4 sessions of full-mouth SRP: test group (TG)—multiple sessions of aPDT and surgical periodontal treatment (ST); control group (CG)—ST only, in a split-mouth design	Laser diode, 660 nm, 60 mW/cm^2, 0.6 J/cm^2, 60 s per site	10 mg/mL of phenothiazine chloride for 5 min	Baseline (preintervention), 60 days (30 days after the end of nonsurgical therapy), and at 150 days (90 days after surgery)	A reduction in probing depth was observed at 150 days for the TG, when compared with the CG; clinical attachment level gain was higher in the TG at 60 and 150 days; changes in the subgingival microbiota were similar between the groups, but the TG revealed a larger number of bacteria associated with periodontal disease at the end of the experiment

Table 1. *Cont.*

Ref.	Year of Publication	Country	Number of Patients	Treatment Site	Goal	Clinical Condition	Protocols	Light Parameters	PS, Concentration, and DLI	Follow-Up	Main Results
[60]	2019	Turkey	24	Periodontal sites	To evaluate the microbiological and clinical effects of aPDT as an adjunctive tool to the nonsurgical periodontal protocol in patients that show aggressive periodontitis (AgP)	Generalized aggressive periodontitis	(1) SRP was applied to 12 subjects with ultrasonic; (2) toluidine blue was applied at the bottom of the periodontal pocket; (3) an LED source (625–635 nm) was inserted parallel to the root surface and the illumination was performed	625–635 nm, 2000 mW/cm^2, light dose = 20 J/cm^2	Toluidine blue O (0.1 mg/mL)	-	The use of the aPDT (two sessions) as an adjunct to SRP did not show superior to SRP regarding microbiological and clinical results
[61]	2019	Finland	20	Periodontal sites	To evaluate clinically and microbiologically the outcomes following one single session of subgingival mechanical debridement	Periodontitis	40 patients were randomly assigned 2 treatments: 1. SRP using ultrasonic and hand instruments followed by one single session of SRP followed by 1 x immediate application of aPDT and 2 x subsequent applications of aPDT without SRP (test); 2. SRP alone (control)	635 nm, 117.64 J/mm	Toluidine blue 0.1% for 1 min	6 months after treatment	Enhanced the clinical and microbiological outcomes compared with SRP alone

Table 1. *Cont.*

Ref.	Year of Publication	Country	Number of Patients	Treatment Site	Goal	Clinical Condition	Protocols	Light Parameters	PS, Concentration, and DLI	Follow-Up	Main Results
[62]	2020	Finland	30	Periodontal sites	To evaluate clinical periodontal and microbiological parameters after the treatment with adjunctive antimicrobial aPDT among HIV-seropositive and -seronegative patients with necrotizing ulcerative periodontitis	Necrotizing ulcerative periodontitis	Group I—provision of treatment through aPDT on the dorsum of tongue; group II—provision of treatment with the help of tongue scrappers (TS); group III—provision of treatment with the help of TS and adjunctive aPDT	670 nm, 22 J/cm^2	Methylene blue (Helbo Blue photosensitizer) with 0.005%.	3 and 6 months after treatment	aPDT was effective in improving clinical periodontal parameters and bacterial levels
[63]	2020	Brazil	-	Periodontal sites	To evaluate the impact of photodynamic therapy (aPDT) as an adjuvant treatment in patients with gingivitis and fixed orthodontic appliances	Gingivitis and fixed orthodontic appliances	-	-	-	21 days	Not performed

Table 1. *Cont.*

Ref.	Year of Publication	Country	Number of Patients	Treatment Site	Goal	Clinical Condition	Protocols	Light Parameters	PS, Concentration, and DLI	Follow-Up	Main Results
[64]	2020	Saudi Arabia	22	Periodontal sites	To evaluate the effectiveness of aPDT as an adjunct to ultrasonic scaling (in the reduction in gingival inflammatory parameters and periodontal pathogens	Gingivitis lesions	US group—patients receiving ultrasonic scaling (US) with usual oral hygiene in-instructions; aPDT group—in which patients received adjunctive aPDT with US	670 nm, 22 J/cm^2	Methylene blue (0.0005%) photo-sensitizer (HELBO Blue) for 3 min	6 months or 12 months	aPDT was effective in significantly reducing periodontal pathogens in established gingivitis lesions
[65]	2021	India	20	Periodontal sites	To determine the clinical and microbiological efficacy of aPDT using Indocyanine green (ICG) as a novel PS for the treatment of chronic periodontitis	Chronic periodontitis	All patients received full-mouth supragingival scaling; (1) SRP + aPDT mediated by ICG; (2) only SRP	Soft-tissue diode laser unit (300 mW, 810 nm); each site was irradiated for 30 s	ICG tablet was suspended in distilled water at a concentration of 1 mg/mL, with a DLI of 2 min	3 months	Sites additionally treated with ICG-mediated aPDT presented a statistically significant reduction in PD and CAL when compared with sites treated with only SRP after 3 months of treatment; adjunctive aPDT can be advocated as a treatment option for chronic periodontitis

Table 1. *Cont.*

Ref.	Year of Publication	Country	Number of Patients	Treatment Site	Goal	Clinical Condition	Protocols	Light Parameters	PS, Concentration, and DLI	Follow-Up	Main Results
[66]	2021	Germany	48	Periodontal sites	To evaluate the microbiological and clinical effects of aPDT procedure alone or in combination with probiotics as an adjunct to nonsurgical periodontal treatment	Chronic periodontitis	(1) Subgingival mechanical debridement was carried out; (2) toluidine blue was applied in the periodontal pockets; (3) an LED device (628 nm) (2000–4000 mW/cm^2) was applied subgingivally for 10 s at each side of the tooth	628 nm, 2000–4000 mW/cm^2, time of application = 10 s	Toluidine blue O, Fotosan Agent®, (0.1 mg/mL)	3–6 months	The combined use of subgingival mechanical debridement, aPDT, and probiotics did not lead to significant improvements in the treatment of chronic periodontitis when compared to subgingival mechanical debridement plus aPDT and subgingival mechanical debridement alone
[67]	2021	Brazil	62	Periodontal sites and gingiva	To compare the effect of aPDT and tongue scraping (standard treatment) in older people with complete dentures diagnosed with halitosis	Periodontitis	Group I—provision of treatment through aPDT on the dorsum of tongue; group II—provision of treatment with the help of tongue scrappers (TS); group III—provision of treatment with the help of TS and adjunctive aPDT	660 nm, 3183 J/cm^2	Methylene blue 0.005%, Brazil) for 5 min	3 and 6 months after treatment	The oral hygiene behavior associated with aPDT or tongue scraper was not able to reduce halitosis after a 90-day follow-up

Table 1. *Cont.*

Ref.	Year of Publication	Country	Number of Patients	Treatment Site	Goal	Clinical Condition	Protocols	Light Parameters	PS, Concentration, and DLI	Follow-Up	Main Results
[68]	2021	Saudi Arabia	51	Periodontal pocket and papilla	Evaluate the efficacy of ICG/aPDT in the treatment of chronic periodontitis in terms of clinical, microbiological, and immune-inflammatory parameters in patients with well-controlled and poorly controlled forms of type-2 diabetes mellitus (T2DM)	Chronic periodontitis	Split-mouth design—one site for control and the other for treatment (n = 17); control group—only root surface debridement (RSD); treatment group—ICG/aPDT + RSD • Controlled T2DM • Uncontrolled T2DM • Nondiabetic	810 nm, 200 mW, 4 J	Indocyanine green (Sigma Aldrich, SA, St. Louis, MO, USA) at 0.5 mg/mL concentration for 30 s in the papilla and 10 s inside the periodontal pocket depth	3 and 6 months after treatment	ICG/aPDT improved clinical and antimicrobial parameters in well-controlled and poorly controlled T2DM; glycemic status did not interfere with the reduction in periodontal parameters in either type of T2DM

Table 2. Randomized clinical trials that evaluated aPDT for the treatment of halitosis.

Ref.	Year of Publication	Country	Number of Patients	Treatment Site	Goal	Clinical Condition	Protocols	Light Parameters	PS, Concentration, and DLI	Follow-Up	Main Results
[69]	2014	Brazil	-	Tongue	To evaluate the antimicrobial effect of aPDT on halitosis in adolescents	Halitosis	-	-	-	-	Not performed

Table 2. *Cont.*

Ref.	Year of Publication	Country	Number of Patients	Treatment Site	Goal	Clinical Condition	Protocols	Light Parameters	PS, Concentration, and DLI	Follow-Up	Main Results
[70]	2016	Brazil	45	Tongue surface	Evaluate the aPDT effect for halitosis in adolescents through the analysis of volatile sulfur compounds	Halitosis stemming from lingual bacteria	Group 1 (n = 16)—aPDT; group 2 (n = 15)—tongue scraper; group 3 (n = 14)—tongue scraper and aPDT	660.52 nm, 3537 mW/cm^2 for 90 s/region; 6 regions	Methylene blue at 0.005% (165 µM) for 5 min	Immediately after treatment	A novel option (Group 2) for the treatment of halitosis with an immediate effect without involving mechanical aggression of the lingual papillae
[71]	2019	Brazil	39	Tongue	To evaluate the effectiveness of the application of aPDT in the tongue coating as a new way to control halitosis	Halitosis	(1) aPDT in 4 points of the tongue, E = 36 J, T = 90 s/point; (2) tongue scraper—10 scrapes in the tongue dorsum (Halitus); (3) tongue scraper—10 scrapes in the tongue dorsum and aPDT in 4 points, E = 36 J, T = 90 s/point	Red LED (660 nm) and tip of 2.84 cm^2 in diameter; power of 400 mW, E = 36 J, T = 90 s/point	Methylene blue 0.005% (165 µM), 2 min of DLI	7, 14, and 30 days	Not performed

Table 2. *Cont.*

Ref.	Year of Publication	Country	Number of Patients	Treatment Site	Goal	Clinical Condition	Protocols	Light Parameters	PS, Concentration, and DLI	Follow-Up	Main Results
[72]	2019	Brazil	40	Tongue	To treat oral halitosis in healthy adults with aPDT, associated with periodontal treatment	Halitosis	The participants (n = 40) with halitosis will be randomized into 2 groups: G1—treatment with aPDT (n = 20); G2—cleaning of the tongue with a tongue scraper (n = 20)	660 nm, 318 J/cm^2	Methylene blue, 0.005% for 3 min	3 months after treatment	This protocol determined the effectiveness of aPDT in the reduction in halitosis in adults
[73]	2020	Brazil	44	Six points on the back of the tongue	Evaluate the reduction in halitosis using aPDT with Bixa orellana extract and blue LED, compare it to the tongue scraping, and verify the association of both treatments	Diagnosis of sulfide (H2S) $\geq$ 112 ppb in gas chromatography	Group 1 (n = 15)—aPDT with annatto and LED; group 2 (n = 14)—tongue scraping; group 3 (n = 15)—tongue scraping and aPDT	395−480 nm for 20 s, 9.6 J per point	Bixa orellana extract in spray at a concentration of 20% *w/v* for 2 min	7 days	There was an immediate reduction in halitosis, but the reduction was not maintained after 7 days

Table 2. *Cont.*

Ref.	Year of Publication	Country	Number of Patients	Treatment Site	Goal	Clinical Condition	Protocols	Light Parameters	PS, Concentration, and DLI	Follow-Up	Main Results
[74]	2020	Saudi Arabia	45	Tongue	To evaluate the efficacy of aPDT on halitosis in adolescent patients undergoing fixed orthodontic treatment	Halitosis	Group I—provision of treatment through aPDT on the dorsum of tongue; group II—provision of treatment with the help of tongue scrappers (TS); group III—provision of treatment with the help of TS and adjunctive aPDT	660 nm, 317.43 J/cm^2 was kept 0.028 cm	Methylene blue at 0.005% for 5 min	2 weeks after treatment	aPDT along with tongue scraping showed effective immediate reduction in H2S concentration and reduction in oral pathogens
[75]	2021	Brazil	40	Tongue	Verify whether modification of oral hygiene behavior associated with aPDT or lingual scraper can reduce halitosis after a 90-day follow-up	Halitosis	Split-mouth design—one site for control and the other for treatment (n = 17); control group—only root surface debridement (RSD); treatment group—ICG/aPDT + RSD; controlled T2DM; uncontrolled T2DM; nondiabetic	660 nm, 318 J/cm^2	Methylene blue, 0.005%	90 days after treatment.	aPDT improved clinical and antimicrobial parameters in well-controlled and poorly controlled T2DM

Table 3. Randomized clinical trials that evaluated aPDT for the treatment of peri-implantitis.

Ref.	Year of Publi-cation	Country	Number of Patients	Treatment Site	Goal	Clinical Condition	Protocols	Light Parameters	PS, Concentration, and DLI	Follow-Up	Main Results
[76]	2014	Switzerland	40	Dental implants	To compare the clinical, microbiological, and host-derived effects in the nonsurgical treatment of initial peri-implantitis with either adjunctive local drug delivery or adjunctive aPDT after 12 months	Initial peri-implantitis	(1) aPDT group—the dye phenothiazine chloride was used as PS (3 min), then the pockets were irrigated with 3% hydrogen peroxide and exposed to the laser light for 10 s and aPDT was repeated 1 week later; (2) one unit dosage of minocycline hydrochloride microspheres (1 mg)	Hand-held diode laser, 660 nm, power density of 100 mW, for 10 s	Phenothiazine chloride (3 min)	3, 6, 9, and 12 months from baseline	Nonsurgical mechanical debridement with adjunctive aPDT was equally as effective in the reduction in mucosal inflammation as with adjunctive delivery of minocycline microspheres up to 12 months
[77]	2016	Serbia	52	Peri-implantitis sites	Evaluate early clinical and microbiological outcomes of peri-implantitis after surgical therapy with adjuvant aPDT	Decontami-nation of the implant surface	Control group used chlorhexidine gel (CHX) followed by saline irrigation; study group used aPDT for decontamination of the implant surface	660 nm, 100 mW for 30 s/spot	Phenothiazine chloride (HELBOR Blue Photosensitizer, bredent medical GmbH&Co. KG) was applied onto implant surface, bone, and peri-implant soft tissue, for 3 min	3 months	aPDT resulted in a significant decrease in bleeding on probing in comparison with CHX ($p < 0.001$) and showed significant decontamination of implant surfaces with complete elimination of anaerobic bacteria immediately after surgical procedure and three months later

Table 3. *Cont.*

Ref.	Year of Publication	Country	Number of Patients	Treatment Site	Goal	Clinical Condition	Protocols	Light Parameters	PS, Concentration, and DLI	Follow-Up	Main Results
[78]	2016	Iran	10	30 dental implants	Assess the clinical effects of aPDT after closed surface scaling in the treatment of peri-implant diseases	Peri-implant diseases	Control group (n = 15)—only closed-surface scaling; aPDT group (n = 15)—aPDT after closed-surface scaling	630 nm, 2000 mW/cm^2 for 120 s	Fotösan (CMS Dental, Denmark) for 3 min	1.5 and 3 months after treatment	Improvement of clinical parameters, in the treatment of peri-implant diseases

Table 4. Randomized clinical trials that evaluated aPDT for the treatment of dental infections.

Ref.	Year of Publication	Country	Number of Patients	Treatment Site	Goal	Clinical Condition	Protocols	Light Parameters	PS, Concentration, and DLI	Follow-Up	Main Results
[79]	2014	Japan	11	Premolar surfaces	Investigate the inhibitory effects of aPDT in the oral cavity of healthy volunteers	Dental plaque deposition	Control group (n = 11)—no treatment; aPDT group (n = 11)—PS + light	660 nm, 1100 mW/cm^2 for 20 s/surface of each tooth	Toluidine blue ortho (Sigma-Aldrich, USA) at 1 mg/mL concentration for 10 s	Every day until 4 days after treatment	The plaque formation on the aPDT group was inhibited after day 4 and the percentages of plaque deposition areas to total buccal and lingual tooth surfaces were significantly reduced compared with the control group

Table 4. *Cont.*

Ref.	Year of Publi-cation	Country	Number of Patients	Treatment Site	Goal	Clinical Condition	Protocols	Light Parameters	PS, Concentration, and DLI	Follow-Up	Main Results
[80]	2015	Brazil	45	90 deep carious lesions	Test whether photochemistry-based treatment (PACT) reduces bacterial viability in remaining dentin	Deep carious lesions	Control group (n = 45)—0.89% NaCl solution + light; experimental group PACT (n = 45)—PS + light	630 nm, 150 mW, 94 J/cm^2	Toluidine blue ortho (Sigma, St. Louis, MO, USA) at 100 g/mL concentration for 5 min	Immedi -ately after treat-ment	PACT led to statistically significant reductions in *mutans streptococci*, *Lactobacillus spp.* and total viable bacteria compared with the control
[81]	2017	Iran	20	Molars	Investigate the role of aPDT as a bactericidal agent in infected canals compared with calcium hydroxide therapy	Molars requiring endodontic retreatment	Group 1 (n = 10)—aPDT; group 2 (n = 10)—calcium hydroxide therapy	635 nm, 200 mW/cm^2 for 60 s	Toluidine blue (MDD, CMS Dental Denmark, Korea) at 0.1 mg/mL concentration for 5 min	Immedi -ately after treat-ment	aPDT presented better disinfectant performance than calcium hydroxide therapy
[82]	2019	Brazil	32	Teeth	To evaluate the clinical effect of aPDT on infected dentin in dental caries lesions in primary teeth	Infection	32 primary molars with deep occlusal dental caries will be selected and divided into 2 groups: G1—caries removal with a low-speed drill; G2—application of aPDT with PapacarieMBlue	660 nm, 6 J, 60 s	Methylene blue for 5 min	12 months after treat-ment	Adding methylene blue dye to the formula of PapacarieMBlue might potentiate the antimicrobial action of aPDT and work more effectively on the infected dentin combined with a conservative, minimally invasive treatment

Table 4. *Cont.*

Ref.	Year of Publication	Country	Number of Patients	Treatment Site	Goal	Clinical Condition	Protocols	Light Parameters	PS, Concentration, and DLI	Follow-Up	Main Results
[83]	2020	Brazil	30	Teeth	To evaluate the reduction in bacterial load following conventional endodontic treatment with and without antimicrobial aPDT in primary teeth	Endodontic treatment of primary teeth	Group I—patients undergoing conventional root canal therapy (n = 15); group II—patients undergoing conventional root canal therapy combined with antimicrobial aPDT (n = 15)	660 nm, J/cm^2	Methylene blue, 0.005% for 3 min	3 months after treatment	This study proved effective (aPDT) but presented the equal efficacious capability to conventional endodontic treatment alone

Table 5. Randomized clinical trials that evaluated aPDT for oral decontamination.

Ref.	Year of Publication	Country	Number of Patients	Treatment Site	Goal	Clinical Condition	Protocols	Light Parameters	PS, Concentration, and DLI	Follow-Up	Main Results
[84]	2014	Brazil	27	Oral cavity	Evaluate the effects of the aPDT with blue light and curcumin on oral disinfection for 2 h after treatment	Oral cavity decontamination	Light group (n = 9)—only light; Curcumin group (n = 9); aPDT group (n = 9)	455 nm, 300 mW/cm^2, 5 min, 200 J/cm^2	Curcumin (aPDT Pharma, Brazil) at 30 mg/L concentration for 5 min	Immedi-ately, 1 h, and 2 h after treatment	Curcumin has the potential to disaggregate oral plaque; aPDT protocol may be used for the reduction in salivary microorganisms to overall mouth disinfection before intraoral surgical procedures

Table 6. Randomized clinical trials that evaluated aPDT for the treatment of ulcers on the skin.

Ref.	Year of Publication	Country	Number of Patients	Treatment Site	Goal	Clinical Condition	Protocols	Light Parameters	PS, Concentration, and DLI	Follow-Up	Main Results
[85]	2013	Scotland	32	Legs and foot	To determine whether aPDT in bacterially colonized chronic leg ulcers and chronic diabetic foot ulcers can reduce bacterial load, and potentially lead to accelerated wound healing	Chronic leg and diabetic foot ulcers	All patients (cationic photosensitizer-PPA); G1—placebo; G2—patients with leg ulcer PPA904; G3—patients with diabetic foot ulcer PPA904	570–670 nm at a total dose of 50 J/cm^2.	[3,7-bis (N,N-dibutylamino) pheno-thiazin-5-ium bromide] for 15 min; 500 µmol/L	3 months after treat-ment	This first controlled study of aPDT in chronic wounds demonstrated a significant reduction in bacterial load

About 65% of the studies (32/49) we reviewed were related to periodontal disease and they are presented in Table 1. Periodontal disease affects the gingiva, the supporting connective tissue, and the alveolar bone, which anchor the teeth in the jaws. Gingivitis is the mildest form of periodontal disease and is caused by bacterial biofilm (dental plaque) that accumulates on teeth surface adjacent to the gingiva (gums). Periodontitis causes loss of connective tissue and bone support, being a significant cause of tooth loss in adults. In addition to pathogenic microorganisms in the biofilm, genetic and environmental factors, especially tobacco use, contribute to the cause of these diseases [86,87]. The treatment of disease is directed at slowing the progression of the disease process, with mechanical removal of the bacteria. The treatment regime depends on the severity of the disease, the presence or absence of periodontal pockets, and the extent of the loss of alveolar bone; the more advanced the destruction, the more mechanical intervention is necessary [86]. Most of the studies presented in Table 1 compare the association of aPDT with conventional methods: ultrasonic debridement and/or scaling and root planning (SRP).

Among the aPDT protocols used, phenothiazine chlorine, methylene blue, toluidine blue, and indocyanine green (ICG) were adopted as PSs with a maximum incubation period of 5 min. The regions treated with ICG were irradiated at 810 nm, while the irradiations were performed at ranges between 628 and 680 nm to use the other PSs. It is also possible to verify the irradiation protocols, with irradiance varying between 2 and 100 mW/cm^2 and fluences between 20 and 320 J/cm^2. The trials presented follow-up reviews of 21 days–12 months.

Several studies point out that there is no significant difference between the conventional procedure groups without or with the association of aPDT. In contrast, several other studies observed significant clinical differences as a reduction in bleeding scores, gingival inflammation, and some of the critical periodontal pathogens. All protocols that used ICG as PSs in association with conventional treatment observed improvement in the clinical aspect, concluding that aPDT is a promising adjunct to nonsurgical periodontal therapy [51,65,68]. A single study was performed comparing conventional ultrasonic and aPDT alone and both therapies resulted in the same clinical effect; however, aPDT was less harmful to teeth than ultrasonic therapy [41].

Moreover, aPDT has been applied to treat other infectious diseases, such as halitosis (Table 2), peri-implantitis (Table 3), dental infection (Table 4), oral decontamination (Table 5), and ulcers on the skin (Table 6). Concerning halitosis, it is an oral condition that is characterized by unpleasant odors emanating from the oral cavity caused by deep carious lesions, peri-implant disease, periodontal disease, oral infections, mucosal ulcerations, pericoronitis, and impacted food. [88] In order to develop a safe and effective protocol to treat halitosis, authors from Brazil and Saudi Arabia evaluated (2014–2021) different clinical photodynamic protocols/conditions for treating the tongue, e.g., light parameters (395–660 nm, 36–318 J/cm^2), PS type, and concentration and with different follow-up periods (7 days–3 months). These studies reported the effectiveness (reduction in oral pathogens) of aPDT against halitosis. Methylene blue has been applied as a PS to treat halitosis due to its low toxicity and high efficiency. Additionally, the authors concluded that aPDT is a useful and efficient option for treating halitosis without mechanical aggression of the lingual papillae.

Furthermore, aPDT was evaluated in treatment of peri-implantitis (Table 3). This is a pathological health condition in tissues (around dental implants), characterized by an inflammation process in the peri-implant tissue and loss of supporting bone [89]. According to our knowledge, there are three randomized controlled clinical studies concerning the application of aPDT to treat peri-implantitis. In these studies, authors reported the use of aPDT as an adjunctive option or as the primary treatment option to treat initial peri-implantitis, decontamination of the implant surface, and peri-implant diseases. Only two different PSs were applied to treat peri-implantitis, namely phenothiazine chloride and Fotosan. The authors observed a significant reduction in bleeding on probing compared

with chlorhexidine (control group) and substantial decontamination of implant surfaces. Moreover, the authors observed an effective reduction in mucosal inflammation process.

Besides periodontal disease, halitosis, and peri-implantitis, there are a set of randomized controlled clinical studies reporting the use of aPDT against dental infections (Table 4) and oral decontamination (Table 5). The authors used different parameters, PSs (toluidine blue, methylene blue, and curcumin), and control groups (e.g., antibiotics, calcium hydroxide therapy, and others) to compare the results obtained. In addition, the authors reported that aPDT can disaggregate oral plaque and reduce the pathogenic microorganisms load present in the oral cavity. In this regard, aPDT was also applied to treat ulcers (chronic diabetic foot) and the authors demonstrated a significant photoinactivation of bacteria (Table 6).

4. Conclusions

Finally, it is possible to conclude that, from 2008 to 2022, aPDT was studied mainly for dentistry applications and was demonstrated to have promising clinical results. A variety of PSs, light sources, and protocols were efficiently used, and the treatment did not cause any side effects for the individuals. However, it is important to emphasize that the lack of standardization in the studies hinders the comparison among them and hinders the translation of preclinical results to clinical studies, which can lead to the failure of the treatment. Future studies should consider performing randomized clinical trials evaluating other infectious diseases, since this treatment has demonstrated antimicrobial effectiveness in in vitro, in vivo, and clinical reports; however, there are few RCT studies that could help the feasibility of this therapy for the management of other infectious diseases. Besides that, the constant emergence of resistant bacteria to the conventional antibiotics and the improbably improbable development of resistance to aPDT, turn photodynamic therapy into a powerful alternative antimicrobial method.

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