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Review

The impact of antimicrobial photodynamic therapy on peri-implant disease: What mechanisms are involved in this novel treatment?

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ABSTRACT

According to the American Academy of Implant Dentistry, 3 million Americans have dental implants, and this number is growing by 500,000 each year. Proportionally, the number of biological complications is also increasing. Among them, peri-implant disease is considered the most common cause of implant loss after osseointegration. In this context, microorganisms residing on the surfaces of implants and their prosthetic components are considered to be the primary etiologic factor for peri-implantitis. Some research groups have proposed combining surgical and non-surgical therapies with systemic antibiotics. The major problem associated with the use of antibiotics to treat peri-implantitis is that microorganisms replicate very quickly. Moreover, inappropriate prescription of antibiotics is not only associated with potential resistance but also and most importantly with the development of superinfections that are difficult to eradicate. Although antimicrobial photodynamic therapy (aPDT) was discovered several years ago, aPDT has only recently emerged as a possible alternative therapy against different oral pathogens causing peri-implantitis. The mechanism of action of aPDT is based on a combination of a photosensitizer drug and light of a specific wavelength in the presence of oxygen. The reaction between light and oxygen produces toxic forms of oxygen species that can kill microbial cells. This mechanism is crucial to the efficacy of aPDT. To help us understand conflicting data, it is necessary to know all the particularities of the etiology of peri-implantitis and the aPDT compounds. We believe that this review will draw attention to new insights regarding the impact of aPDT on peri-implant disease.

Contents

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1. Introduction

According to the National Institutes of Health (NIH), infections caused by microorganismal biofilms are considered to be a public health problem, as biofilm-associated diseases might be responsible for 80% of all infections in humans (http://grants.nih.gov/grants/guide/pa-files/PA-07-288.html). A biofilm is a complex interaction between a surface and microbial cells that are protected by an extracellular matrix of polymeric substances [1,2], which confers resistance to antibiotic treatment [3]. In addition, these microbial networks are responsible for the most common oral diseases: dental caries, periodontitis, and peri-implantitis [4–6].

With the growing number of dental implant procedures, the prospective number of sites with implant-associated diseases has also increased [7]. Specifically, given the common incidence of peri-implantitis [8–10] and considering that the etiopathogenesis of peri-implantitis is not well delineated, the most effective treatment for peri-implantitis has not been conclusively established. Similarly to periodontal disease, peri-implantitis is a destructive inflammatory process that leads to pocket formation and loss of supporting bone; in peri-implantitis in particular, the disease site surrounds an osseointegrated implant. Peri-implantitis has been estimated to occur in 10.7–47.2% of dental implant patients within 10 years of post-treatment observation, and these data are considered alarming [11]. According to NHANES 2009–2010, the prevalence of periodontitis in the United States among adults aged 30 years and older was 47.2%. This percentage is even higher at 70.1% for adults older than 65 years [12]. The cost associated with the treatment and prevention of this disease reached 14.3 billion dollars in 1999 [13]. In an attempt to reduce these numbers, antibiotic therapy is often recommended for patients receiving periodontitis and peri-implantitis treatment procedures [14]. According to some authors, the advantage of antibiotic use is the short course of administration, which may contribute to patient compliance [15]. Despite the clinical relevance and the effective use of systemic antibiotics to treat numerous infectious diseases, the currently available scientific information on the use of these agents in the treatment of periodontal and peri-implant diseases is insufficient to support any official recommendations on the use of these medicines [16]. It is important to emphasize that antibiotics are antimicrobial substances that can lead to side effects of varying intensities, and their unselective use can increase selection for bacteria that are resistant to antibiotics. In 2014, a new report by the World Health Organization (WHO) revealed that antimicrobial resistance is currently a serious threat and is no longer simply a future problem. This phenomenon is occurring across many different regions of the world and can affect anyone, independent of age or country.

Although dental implants are a successful treatment modality [17], peri-implantitis is the most common cause of late failure and can occur years after osseointegration [18]. To address this issue, increased attention has been paid to non-surgical alternatives for treatment of localized infections [19]. Recently, antimicrobial photodynamic therapy (aPDT) has been considered as an adjunct treatment approach to the bacterial decontamination of teeth and implants affected by periodontal and peri-implant disease. aPDT involves exposure to a combination of a photosensitizer [20] and an appropriate wavelength of laser light, resulting in the destruction of different oral pathogens in planktonic and biofilm forms [21,22]. *In vitro* and *in vivo* studies confirmed that a major periodontopathogenic bacterium, *Porphyromonas gingivalis*, is susceptible to aPDT [22–24]. Despite promising results, several factors should be considered in order to obtain good treatment outcomes in patients, such as the type of PS, total exposure time, wavelength, intensity of laser irradiation, and the combination of another treatment with aPDT. Thus, we address the impact of aPDT on peri-implant disease and discuss all of the factors related to this novel therapy.

1.1. Bacterial adherence to implant surfaces – a key factor in peri-implantitis

Peri-implantitis is a complex and interesting disease in which alterations in bone and connective tissue homeostasis involve intricate interactions between bacteria and the inflammatory immune response of the host [25]. Bacteria are considered to play a principal role in initiating the host inflammatory process [14]. Increased understanding of the various factors contributing to peri-implantitis has revealed that the clinical phenotype is not simply the translation of microbial challenge into a standard host response. Strong evidence has suggested that smoking, diabetes, and susceptibility to periodontitis are powerful determinants of peri-implantitis development as well as disease severity [26,27]. To create a strategy for treating peri-implantitis, it is crucial to understand all the factors involved in the development of the disease and its mechanisms of action.

Regarding the bacteria that are responsible for initiating host inflammatory processes and bone loss, two points should be considered: the bacterial species involved and the host immune response to the bacteria. Molecular analysis of oral microorganisms has identified approximately 700 species of bacteria inside the mouth of any individual [28]. Due to high diversity, it is therefore necessary that oral bacteria adhere to solid surfaces for the development of oral disease. This specificity occurs via mechanisms of adherence, i.e., several cell surface structures (especially those proteinaceous and carbohydrate molecules) of different bacterial species can identify receptors in the salivary pellicle, and these structures coat enamel and/or dental implant materials and their prosthetic components. Importantly, the chemical composition of different materials can have a significant impact on biofilm formation [29–31], initiating gene expression and determining the bacterial profile of the species adhering to the biofilm. Recently, an *in vitro* study evaluated the effect of several implant materials in comparison to enamel on bacterial adhesion. A preference of *Streptococcus mutans* and *P. gingivalis* for the chemical composition of enamel surfaces was suggested [32], as it was not possible to detect bacteria on titanium or zirconia materials. In general, streptococci and actinomyces initially dominate the bacterial composition of the tooth surface and can recognize receptors in the salivary pellicle [33–35]. In the case of dental implant surfaces, while some findings have reported similarities in the microbiota composition between the surfaces of both healthy and infected implants and teeth [36–39], other findings have indicated that peri-implantitis may be more complex and diverse than periodontitis [38,40]. Overall, black-pigmented *Prevotella* species, *Aggregatibacter actinomycetemcomitans,* and *P. gingivalis* are found in higher quantities in peri-implantitis lesions than in healthy control tissue and at comparable levels in periodontitis samples; however, enterobacteria and staphylococci have been identified around implants [41]. Another important factor that regulates bacterial coloniza-

tion profiles and should be considered before planning treatment is the type of edentulism: either full or partial. Some findings demonstrated that 1 month after total dental extraction in individuals with periodontal disease, *A. actinomycetemcomitans* and *P. gingivalis* were undetectable in the oral cavity [42]. Similarly, *Streptococcus sanguinis, S. mutans,* and lactobacilli were visibly reduced in edentulous adults with or without standard removable dentures compared with dentate patients [43]. Therefore, the environment can be considered as the main factor that influences the microbial colonization profile.

1.2. Biofilm complexity and bacterial invasion

The persistence of dental plaque changes the dental ecosystem, and new bacterial composition appears to affect the environment, thus resulting in clinical disease. The cell-to-cell interactions involved in coaggregation are responsible for dynamic biofilm construction, which is categorized as either cooperative or competitive [44]. It has been known that bacteria of the genus *Fusobacterium* exhibit partnerships with initial, early, and late colonizers and thus serve as a bridge in the succession of genera in naturally developing dental plaque [45,46]. The ability of *F. nucleatum* to adhere to biofilm at different stages can be explained by its two distinct types of adherence, classified based on their inhibition by either D-galactose or L-arginine. While the adherence of *F. nucleatum* to Gram-negative bacteria is galactose sensitive, its adherence to Gram-positive bacteria is mediated by arginine-inhibitable adhesins [47]. Below the gum line, the environment changes and becomes anaerobic. In this context, subgingival anaerobic bacteria dominate the environment, which has a higher overall species diversity than that of supragingival biofilms [28]. Among the anaerobic bacteria considered to be periodontopathogens, *P. gingivalis* is known to misdirect the host defense and increase tissue-destructive inflammation [48], thus influencing disease initiation and progression. Scientific evidence has shown that *P. gingivalis* is commonly found in patients with periodontitis [49,50] and is associated with peri-implantitis [51,52]. Additionally, interaction with early microbial colonizers, such as *Streptococcus* species, can also promote the migration of *P. gingivalis* in subgingival biofilms [53].

In addition to their interactions with other bacteria, some pathogenic species adhere to oral epithelial cells and induce interleukin production [54]. A small number of microorganisms are able to bind to and invade different types of host cells, thereby eliciting proinflammatory responses and periodontal destruction [54,55]. *P. gingivalis*, for example, is capable of producing a number of virulence factors such as fimbriae, lipopolysaccharide (LPS), capsules, and proteases, which can bind to and activate human epithelial cells, thus resulting in cytokine release [56,57]. Another bacterial species involved in the stimulation of the innate immune response is *F. nucleatum*. Recently, a novel type of adhesion was identified as being involved in bacterial attachment to host epithelial cells; this type of adhesion is unique to the oral microbiota and may play an important role in *Fusobacterium* colonization in the host [58]. It has been postulated that these bacteria not only induce peptide production against periodontopathogens but also influence the immune response through the induction of cytokines and chemokines [59]. The invasion of epithelial cells [60] was also demonstrated by the Gram-negative anaerobic bacteria *Treponema denticola,* characterized as the “red complex” by Socransky et al. [61]. *T. denticola* possesses several virulence factors responsible for adherence, tissue penetration, cytotoxicity, and immunomodulation and is involved in inhibiting the complement system [62].

Gingival epithelial cells are the first human cells with which bacteria of the biofilm interact. Once bacterial proteins binds to their receptors, gingival epithelial cells produce a wide array of responses, thus increasing the abundance of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukins (ILs), which indirectly attempt to eliminate the infection [63]. Different cytokine response profiles are induced by distinct bacterial species; pathogenic species, for example, can provoke an inflammatory response, while those considered to be commensal produce an insignificant inflammatory response. In an *in vitro* study, primary human gingival epithelial cells (HGECs) were incubated with several species of dental plaque bacteria to determine the levels of specific interleukins. The results showed that the cells stimulated with live *P. gingivalis* produced high levels of IL-1b but that the same cells stimulated with live *A. actinomycetemcomitans* produced high levels of IL-8. In contrast to pathogenic bacteria, the commensal *Streptococcus gordonii* induced low levels of pro-inflammatory cytokines [63].

Peri-implant tissue surrounding the implants provides a barrier resisting frictional forces and protecting the soft tissue against microorganisms. Thus, the penetration and injury of the epithelial layer are important steps in the pathogenesis of peri-implantitis.

1.3. Stages of peri-implant disease

When individuals lose their teeth due to periodontal disease, the pathogenic microorganism remains inside the mouth. Within almost 30 min of transmucosal implant placement, bacteria initiate colonization on the implant surfaces [64]. The progression of the adherent biofilm on the dental implant seems to be the driving force in the commencement and development of peri-implant disease. When signs of inflammation without loss of connective tissue are identified following initial bone remodeling around the implant during healing, it is believed that peri-implant mucositis has been established. For this stage of the disease, mechanical therapy (with or without adjunctive use of antiseptic rinses) is commonly the initial treatment of choice [65,66]. However, during disease progression, inflammatory mediators produced by the soft tissue activate osteoclastogenesis and the subsequent loss of the marginal, supporting bone around the functioning implant [25]. At this stage, peri-implantitis becomes established. The presence of increased levels of pathogens in peri-implantitis is a serious treatment issue, as discussed below. Treatment difficulties at this point are directly related to the complexity of the biofilm, the probing depth, and the inflammatory immune response of the host.

Overall, evidence from *in vivo* studies points to a questionable theory of microbial similarity between teeth and implants [37,67,68]. This information has guided the treatment of peri-implantitis to be similar to that of periodontitis. Efforts to control peri-implantitis have been made with different methods of open or closed debridement, systemic or local delivery of antibiotics, aPDT, and combinations of these therapies.

1.4. Treatment options

Although peri-implantitis is modulated and mediated by the host, supportive peri-implant therapy is a critical procedure for preventing the incidence and/or for treating the disease [69–71]. One of the main challenges in the treatment of peri-implantitis is the disinfection process of dental implant surfaces to reduce inflammation and stimulate re-osseointegration. Although periodontitis and peri-implantitis share similar etiological factors, in peri-implantitis, the irregular structure of the dental implant can promote plaque accumulation when exposed to the oral cavity [72] and can interfere with the quantity and quality of the biofilm that adheres to the implants. Conventional treatment for periodontal disease involves debridement of the root surfaces with mechanical instruments. Considering that decontamination of the implant surface is much more problematic than decontamination of natural root surfaces, mechanical therapy alone could be insufficient

for biofilm elimination in peri-implantitis [73]. Furthermore, titanium curettes could severely damage the implant surface, thus increasing its roughness and bacterial adherence. Consequently, plastic curettes were introduced in an attempt to reduce the damage caused by metal instruments, but plastic curettes cannot reach the macro- or micro-pores of these dental implant substrates. The ineffectiveness of these instruments results in large residual plaque areas after treatment [74]. Another treatment option is the use of an air-abrasive device. This procedure is effective for the removal of biofilm from implant surfaces [75], but one disadvantage is the risk of emphysema after treatment [76]. Thus, to further facilitate bacterial reduction, additional approaches have been used, such as the use of systemically or locally administered antibiotics that act directly on active subgingival species in the dental plaque or in adjacent epithelial tissues lining the peri-implant pocket. It is believed that local or systemic antibiotics eliminate periodontopathogenic bacteria to a greater extent than conventional therapy. This phenomenon is explained by several findings that the short-term clinical benefits achieved with conventional methods (scaling and root planing) are frequently not sustained in the long term, especially in more progressive cases [77] and in cases associated with risk factors such as smoking [78] and diabetes [79]. However, it is imperative to highlight that antibiotics are biologically active substances that can lead to side effects of differing severity. Additionally, the WHO has questioned the current practice of indiscriminate antibiotic use, which is progressively leading to antibiotic resistance, the persistence of infections, and treatment failure (http://www.who.int/mediacentre/facsheets/fs194/en/). In an attempt to diminish the inflammatory process and reduce the potential for pathogen resistance, alternative treatment methods have been introduced. One of the most promising methods for treating peri-implant mucositis and peri-implantitis is aPDT.

1.5. aPDT – definition, application, and mechanism of action

The use of light with a sensitizing agent was first described in the medical literature more than 100 years ago [80]. Interestingly, the discovery occurred incidentally after a medical student observed that paramecia, unicellular protozoa, were killed only when a dye was exposed to strong daylight. Since then, various studies have investigated the efficacy and efficiency of this approach, mainly as a cancer therapy. The applicability of this therapy is a consequence of its mechanism of action. aPDT involves the activation of a drug using light, and at the trigger time, exposure of the drug to excitation light leads to cell death via apoptosis or necrosis. The mechanism of action, although not completely understood, involves the production of reactive oxygen species (ROS), which can damage the target cell. Regarding its effects on microorganisms, the literature has shown that aPDT is more effective in inactivating Gram-positive bacteria than Gram-negative bacteria due to the chemical structure of the cell walls [81]. The driving force of aPDT is photosensitization. For this therapy to work, the PS molecule must penetrate the cell walls of the microorganisms until it reaches its final destination and binds to the plasma membrane of the microbial cell. However, besides a pronounced antimicrobial efficacy, PS should not be toxic toward mammalian cells. Since PS play a pivotal role in aPDT therapy this substance should be effective in the selectivity for microbial cells over host mammalian cells [82]. In this context, the cytotoxicity to normal tissue is minimized due to high selective affinity of the PS to the diseased tissue and microbial cells. Increasing the selective PS accumulation into the target cells can be explained by the strong interaction between PS with low-density lipoprotein (LDL) overexpressed on cancer cells [83]. In fact, the factors involved in the PS chemical structures that maximize the tumor selectivity over normal tissue and microbial cells are not still completely understood [84]. However, studies have been performed to investigate if a desired therapeutic dosage might effectively abrogate microbes without damaging the adjacent cells. The results found in the literature have demonstrated low toxicity against mammalian cells when PS is applied to a specific area [85,86].

The membrane affinity of a PS is directed by its amphiphilic properties, and this is dependent on the chemical organization of hydrophobic and hydrophilic regions in its structure [87,88]. However, the type of membrane barriers of the bacterial cell, for example, can limit the simple dissemination of a PS into the bacterial cytosol. The composition of Gram-positive bacteria differs in several key ways from their Gram-negative counterparts. Overall, the outer membrane surrounding Gram-positive bacteria becomes the cell wall of this bacterial class, and their outer membrane is more permeable to hydrophobic small molecules. This structure plays a key role in protecting Gram-negative bacteria from the environment by eliminating toxic molecules and offering an additional stabilizing layer around the cell. However, a thick layer of peptidoglycans around Gram-positive microorganisms could limit the diffusion of the PS into the bacteria. Threading through these layers of peptidoglycans are teichoic acids, which are long anionic polymers whose negative charge can attract cationic molecules [89]. The outer membrane is composed of glycolipids, principally LPS, a well-known molecule responsible for much of the toxicity of Gram-negative organisms. LPS induces the production of different mediators associated with septicemia [90]. The human innate immune system is sensitized to LPS, which is an unquestionable indicator of infection. Therefore, aPDT-mediated killing of Gram-positive bacteria is definitely much easier to accomplish than that of Gram-negative bacteria. Thus, it is more challenging to obtain a highly potent PS for mediating aPDT against Gram-negative bacteria, as their cell wall prevents the uptake of anionic and neutral PSs. This theory is corroborated by previous results presented in the scientific literature.

In this review, we discuss aPDT as an alternative method for eradicating bacteria from peri-implant pockets; however, we should be cautious considering that antimicrobial/antibacterial treatment results have revealed a CFU reduction rate of greater than 3 $\log_{10}$, as stated by the American Society of Microbiology (ASM) in 2010 [91]. The bactericidal effect of aPDT using methylene blue (MB) was studied in planktonic cultures of *A. actinomycetemcomitans*, *F. nucleatum*, *P. gingivalis*, *P. intermedia*, and *S. sanguinis*. Consistent with the theory described above, the data showed that Gram-negative species were more resistant to aPDT-mediated killing than Gram-positive species. *S. sanguinis* was the most susceptible strain [92]. MB belongs to the phenothiazinium family of positively charged sanguinis dyes, and the cationic molecules present in this PS may interact with anionic regions from *S. sanguinis* cell walls. The results of this study also demonstrated that the bactericidal effect of aPDT is wavelength-dependent, dose-dependent, and bacterial species-dependent. Another example for phenothiazinium dye, which has been tested for inactivation of planktonic cells and biofilm, is toluidine blue (TB). An interesting and promising observation achieved by means of *in vitro* studies [93,94] prompted the continued use of the PS in current reports. Recently, the effectiveness of TB on multispecies biofilm grown on bovine enamel slabs was evaluated within the oral cavity. For the adhesion of early anaerobic colonizers, the results showed significant CFU reduction from a native *in situ* biofilm. The effect was sustained during the subsequent biofilm formation, and the number of cultivable microorganisms within mature oral biofilms declined by 2.21 $\log_{10}$. However, more important than the reduced number of bacteria is the disruption of the regular oral microflora when this therapy is used [95]. Remarkably, the data also revealed that when aPDT therapy with TB is applied, *F. nucleatum* could not be detected on the biofilm surface [95]. Since this bacterium plays

an important role acting as a bridge between early and late colonizers in the periodontal pocket, its reduction might lead to decreased periodontopathogens survival [96]. Similar to MB, TB was initially used by the dye industry due to its affinity for nucleic acids, and therefore binding to the nuclear material of specific tissues with high DNA and RNA content [97]. Those properties also conferred to it some negative aspects in the clinical use mainly related to its capacity to stain the tooth enamel. However, it has been reported that residual staining in the teeth and gingiva after TB therapy is not visible after aPDT application, and therefore, no esthetic problems will occur for the patients [98].

Other hydrophobic compounds often used in aPDT include porphyrins, chlorins, and phthalocyanines, which are structurally comparable heterocyclic macrocycles. Porphyrins, for example, are endogenous substances and Gram-positive cell wall constituents; moreover, they act as PSs and induce a lethal autophotosensitization process that kills bacteria via an oxidative burst similar to the photodynamic inactivation of bacteria. Furthermore, the membrane affinity for PS molecules facilitates the penetration of porphyrins [99]. However, varying results were observed even when different Gram-positive bacterial species were examined. In an interesting report, researchers tested the effect of the porphyrin 5,10,15,20-tetrakis(1-methyl-4-pyridyl)-21H,23H-porphine tetra-*p*-tosylate salt (TMPyP) against *Enterococcus faecalis* monospecies biofilm and verified the inefficacy of the treatment. One explanation for this outcome is the large molecular structure of TMPyP, which may delay the penetration of this PS through the extracellular polymeric substances [97]. Additionally, electrostatic interactions between the positively charged TMPyP and negatively charged EPS could delay PS diffusion [100]. In the same report, the authors suggested that the emission of the LED light-curing unit was not ideal for excitation of TMPyP, which is another important point to consider. The wavelength of the light source excites the PS to produce free radicals and/or ROS. If the PS compound is unable to absorb laser energy, the therapy will not be efficient [92].

Limited *in vitro* data were obtained when aPDT was applied with a cationic chlorin-*e*6 derivative, commercially marketed as Photodithazine® (PDZ), on fungal biofilms from *Candida albicans* and *Candida glabrata*. The results showed a CFU reduction of approximately 1 $\log_{10}$ [21,101]. Similar to Gram-positive bacteria, fungi have a thick cell wall and no outer membrane, but fungi have a unique chemical composition. The *C. albicans* cell wall, for example, is primarily composed of glucan and chitin, very hydrophobic carbohydrates responsible for the mechanical strength of the cell wall, as well as mannoproteins [102]. Since cationic chlorin-e6 discloses similar chemical properties than *C. albicans*, the unsuccessful antimicrobial effect might not be related to PS absorption from the fungi cells. Quite divergent results were found in recent and interesting investigations [95,103–105]. A recent study showed the antimicrobial effect of aPDT associated to PDZ with 4.36 $\log_{10}$ of *C. albicans* reduction when the experiment was performed in animals [104]. Indeed, the divergences of the outcomes should be carefully analyzed. In this *in vivo* study, the PS was applied directly on the mouse tongue cells [104] and the cells permeability associated with the physiological environment might have increased the PS absorption, which is in contrast to previous study [21]. A sequence of *in situ* studies [95,103,105] have shown high effect of aPDT with chlorine e6 (Ce6) against initial and mature oral biofilm reducing significantly the numbers of viable anaerobic microorganisms. The differences in microorganisms susceptibility presented in these studies clearly underline the wavelength-dependence, since the authors combined visible-light [94] and water-filtered infrared A (wIRA) with the cationic PS [103,105] (see Section 1.6).

In another study, the investigators demonstrated that both XF-73 and TMPyP, porphyrin molecules, exposed to blue light effectively photodynamically killed *C. albicans* in suspension [106]. The positive interaction between porphyrin molecules and chitosan, a chitin derivative, can be explained by the fact that chitosan promotes greater adsorption of porphyrins on phospholipid monolayers and allows the porphyrin to stay in its monomeric form [107]. Closely related to the PS interaction, the tests performed against planktonic microorganisms could also have contributed to the experimental success of the treatment. The conflicting results found in the scientific literature prompt us to consider and further explore the possible reasons underlying this discrepancy. In the case of PS, for example, it was previously shown that TMPyP attaches to and has a high affinity for *C. albicans* cells. XF-73 compounds show a similar property. Although porphyrins and chlorin share similar chemical properties, intensity of interactions among chlorin, carbohydrates, and proteins inspires new investigation into the particularities of each microorganismal species.

Another important and intriguing class of PSs recently introduced in aPDT is curcumin [108]. This compound has been isolated from the plant *Curcuma longa,* and because this product is natural and confers antimicrobial properties, accumulating studies have investigated its therapeutic efficacy in various inflammatory diseases [109,110]. Among these studies, the antifungal effect of curcumin-mediated aPDT against oral candida infections caused by *Candida spp* has been evaluated. Previous findings have indicated this PS as an effective photosensitizing agent for the inactivation of *C. albicans* in both its planktonic and biofilm forms [85]. In addition to its antifungal properties, curcumin has been noted for its beneficial treatment outcomes for dentine carious lesions. Impressive results were obtained when mature, multispecies biofilms of *S. mutans* and *Lactobacillus acidophilus* were exposed to a curcumin solution for 5 min and were irradiated for 5 min with blue light, leading to a CFU reduction of more than 3 log10. However, a different outcome was observed when dentin carious lesions were exposed to this compound under the same concentration, time, and light conditions [111]. The depth of dentin could have reduced curcumin penetration due to their unique physicochemical properties. Dentin is a highly hydrophilic connective tissue, whereas curcumin is a hydrophobically derived polyphenol, and this difference can explain the discrepant results observed in distinct experimental designs. As curcumin is a natural product, its mechanism of action is also attractive with regard to human healthcare. It has been demonstrated that curcumin is a potent inhibitor of the generation of ROS, which are mediators of inflammation. The photodynamic effect of curcumin involves hydrogen peroxide production without the generation of singlet oxygen [112], which in turn potently enhances heme oxygenase-1 (HO-1) expression. However, it was shown that the activity of HO-1 in angiogenesis upregulates the synthesis of vascular endothelial growth factor (VEGF) under both physiological and pathological conditions [113]. Thus, the benefits of this compound depend on both its dose and the chemical environment.

1.6. A new insight into light source for aPDT success

For the clinical success of antimicrobial PDT several considerations should be pointed out. The evidences presented above showed the impact of the light source to improve the interaction between PS and cell composition from different microorganisms. Most PS is activated by specific wavelength. Despite the requirement of PS excitation, the radiation should possess good penetration properties into the tissue allowing energy transference to the cells without increasing the temperature, which would compromise the tissue health and leading to tissue injuries.

The depth of light penetration in human tissue is wavelength-dependent. Up to date, a variety of light sources have been employed for aPDT protocols, especially by means of nonlaser light generators (halogen or light-emitting diode [LED] lamps). The main issue of halogens lamps is the gas contained inside the tube that

makes the light much brighter and can induce tissue overheating [114]. On the other hand, the intensity of light emitted by LEDs on the skin is lower, since its cells maintain a good interaction with the light. However, LEDs produce relatively limited bands of green, yellow, orange or red light and this restricted emission wavelength spectrum [115] has not provided antimicrobial effects, so far. Thus, alternative strategies have been introduced in an attempt to combine the PS with the appropriate light source and improve the effect of aPDT to treat oral diseases.

Recent investigations have described a significant reduction of the total oral bacterial load during chronic wound treatments when combining visible light with water-filtered infrared-A (VIS+ wIRA) [116]. This potential effect has focused the use of the VIS + wIRA device to improve the efficacy of aPDT. The combination of both light and radiation is based on a natural process i.e., the heat radiation of the sun is filtered by water vapor in the atmosphere of the earth. Similar to sun heat radiation, the water-filtering allows to high penetration properties with a low thermal load to the skin surface (within 780–1400 nm) [117]. The mechanism of action involves the cells and cellular structures stimulation by direct radiation effect. Some reports have shown that wavelengths within wIRA influence interactions between cells and extra- cellular matrices, increasing the amount of ATP available [118,119], participating in wound repair processes and modulating the immune system and/or inducing necrosis/apoptosis of damaged cells and bacteria [120]. Thus, it seems reasonable that VIS + wIRA could increase the desired PDT outcomes, in a number of dental procedures.

Since the concept of the aPDT involves the production of ROS, responsible to damage the target cell, the rising production of ROS and singlet oxygen would improve its antimicrobial effects. In this context, the effectiveness of aPDT approach using VIS + wIRA in combination with PS has been tested on *in situ* experiments [95,103,105]. Besides a successful outcome demonstrated by CFU reduction, viability assay enabled understanding the relevant contribution of the light source in the eradication of biofilm bacteria. Interestingly, the PS was exposed onto the oral biofilms in the absence of VIS + wIRA the cells preserved their viability indicating a VIS + wIRA-dependence to destroy a vast amount of microorganisms. This new insight about the impact of the light sources on aPDT efficacy could be tested onto a pathogenic environment and be directed, in future, to treat peri-implantitis.

1.7. Could the inflammatory response activated by aPDT modulate bone resorption?

Initially, aPDT was discovered because of its antimicrobial properties. However, as researchers began to understand part of its mechanism of action, this therapy was directed towards cancer treatment. Accordingly, activation of the immune response is necessary for effective tumor control [121]. aPDT activates several cell-signaling cascades and the release of cell fragments, cytokines, and inflammatory mediators, which stimulate the recruitment of neutrophils [122]. In an interesting report, the authors investigated two distinct mechanisms of neutrophil migration induced by aPDT, and they found that the early phase reaction may be regulated by TNF-α, neutrophil chemo-attractants, or IL-6. Recently, a research group evaluated inflammatory cytokine expression after aPDT application in the treatment of oral candidiasis in a murine model [123]. Consistent with the mechanism of action of this therapy [124], the results revealed high TNF-α expression; however, the expression levels of IL-1 and IL-6 in the aPDT group were lower than and similar to those in the untreated group, respectively [123]. During the delayed phase reaction, neutrophil chemo-attractants and IL-1b are the factors regulating neutrophil migration [125]. With regard to peri-implantitis, this disease involves the destruction of alveolar bone, which leads to implant loss. During the bone resorption process, different types of cells, such as neutrophils, macrophages, dendritic cells (DCs), and T cells, participate in the immune response [126]. Furthermore, similar cytokines produced by immune cells after aPDT irradiation are released during the disease process [127]. The association among IL-1/6, TNF-α, and peri-implantitis has already been well documented [126,128]. The main question in this field is if aPDT stimulates an inflammatory response in tumor cells, could this therapy also treat peri-implantitis and exacerbate bone loss? Clearly, we must consider several issues such as the short aPDT irradiation time and the levels of cytokines produced during treatment. We believe that the present review provides new insights into the possible connections of the immune response triggered by aPDT with peri-implantitis to ensure the safety of this therapeutic approach.

2. Final considerations

2.1. Could PDT be considered as a novel modality for treating peri-implant disease?

In this review, we have summarized the most important factors related to aPDT for peri-implantitis treatment and have focused on the outcomes of previous *in vitro* and *in vivo* studies. The selected bacteria and/or fungi used in the *in vitro* experiments demonstrate the mechanism of action of PSs within microorganisms of different classes. Although the effects of aPDT on peri-implant disease have previously been investigated, the exact mechanism of action of aPDT against peri-implantitis remains largely unknown. The insufficient results found in the scientific literature with regard to using aPDT against pathogenic biofilms have not discouraged new investigations due to the advantage of this therapy in avoiding antibiotic resistance. Accordingly, we made significant effort to describe and discuss all the contradictory results found in the literature. We have demonstrated that the microorganism selected, PS properties, wavelength, and light source play critical roles in the clinical efficacy of aPDT. Focusing on peri-implant disease and considering that peri-implantitis is dominated by Gram-negative anaerobic bacteria, the PS composition ultimately determines the affinity and specificity of the PS between different species. LPS is a highly anionic and important pathogenic factor present in Gram-negative bacteria that extends beyond outer membrane proteins. Additionally, all carbon atoms that are not bound to nitrogen or oxygen atoms from the thin peptidoglycan layer confer a hydrophobic property. Thus, new studies should be directed towards the development of specific PSs. Indeed, a detailed understanding of the mechanisms of action of aPDT could position this therapy as the treatment of choice in selected cases and as an important adjunct to other therapies.

Conflicts of interest

The authors declare no conflicts of interest.

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