Chapter

Advances in Locally Delivered Antimicrobials for Periodontitis Treatment

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Abstract

Periodontal disease represents an inflammatory disease of the tissues supporting the maintenance and functionality of the teeth on the dental arches. The main cause of periodontitis consists in periodontal dysbiosis, which will trigger an inflammatory response, progressively leading to periodontal tissue breakdown. Scaling and root planing represent the gold standard in treating periodontal diseases but, as it was already established, these measures are unable to completely eliminate the subgingival bacterial plaque. Therefore, new adjunctive therapies have emerged, involving systemic and local delivery of various antimicrobial products. This chapter aims to provide current knowledge on the local application of different periodontal supplementary therapies. The chapter focuses on local forms of antimicrobials, such as irrigations, gels or controlled release systems but also on laser/LED-assisted periodontal pocket photodynamic antibacterial therapy (PDT), along with various photosensitizers. Moreover, we present data from current guidelines regarding the recommendations for the main locally delivered antimicrobials.

Keywords: antimicrobials, local adjunctive periodontal therapy, periodontitis, photodynamic antibacterial therapy, photosensitizer

1. Introduction

Periodontal disease is an immuno-inflammatory condition that affects periodontal tissues, caused by multifactorial etiologies [1]. The disease is the result of complex interactions between periodontopathogenic bacteria, organized in biofilm, and the host's immune response; the latter is considered to account for almost 80% of the risk [2].

In periodontal health, there is a balance between the microbial flora and the host's immune system. Disrupting this balance will trigger an immune response, activating the mechanisms of innate and adaptive immunity. Periodontal pathogens

generate a number of products that will cause the destruction of the extracellular matrix, as well as increase the permeability of the host cell membranes, leading to a subsequent tissue invasion [3]. Among the most aggressive periodontal pathogens are *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*, *Prevotella intermedia* or *Aggregatibacter actinomycetemcomitans* [4].

Following the interaction between the pathogenic flora and the immune system, the release of proinflammatory molecules takes place, molecules that will exacerbate the inflammatory status, with the subsequent appearance, over time, of periodontal attachment loss and the progressive deep invasion of pathogens and their products [5]. If proper periodontal therapy is not instituted, the disease can have unfavorable consequences, such as the occurrence of dental hypersensitivity, dental mobility, pathological dental migration and, ultimately, tooth loss. Moreover, the complications of periodontal disease can extend to systemic level, exacerbating already established conditions such as diabetes, rheumatoid arthritis or cardiovascular diseases [6]. Factors that can affect the appearance and evolution of periodontitis can be both local (poor oral hygiene, dental malposition, incorrect prosthetic or orthodontic treatments) and general; the latter include modifiable factors, such as lifestyle, certain drugs or even systemic pathologies, but also non-modifiable factors (genetic, epigenetic factors or uncontrollable diseases) [7].

The first step in periodontal treatment includes addressing the factors that led to the onset and development of periodontal disease. This particular phase of treatment includes periodontal scaling and root planing (SRP) which are, to date, the therapeutical gold standard, which cannot be replaced by other therapeutic means. SRP aims to disorganize the periodontal biofilm and create "biologically acceptable" areas and surfaces, which would allow healing and obtaining the status of "periodontal health" [8].

The major disadvantage of SRP is its inefficiency in periodontal pockets with complex anatomies, where access is difficult or even impossible; thus, adjunctive, systemic or local antibacterial therapies are sometimes required. Systemic antibiotic therapy, however, is accompanied by a number of less favorable characteristics, such as hepatic or renal toxicity, the risk of gastrointestinal complications, the appearance of resistant microorganisms or poor biodistribution in sites of interest [9]. Thus, a favorable alternative is the local administration of therapeutic, antimicrobials or anti-inflammatory agents, in various forms of administration. Pharmacological agents placed directly in the periodontal pocket can generate an adequate concentration for a sufficiently long period of time, without systemic complications and with improved patient compliance [10]. Below we will present the main local forms of antibacterial drug therapy.

2. Classification of local antibacterial therapy systems

Local forms of antibacterial drug therapy can be used either at home, by the patient or in the dental office, is considered professional methods. They can also be classified as nonsustained, sustained or controlled release systems (**Figure 1**).

Nonsustained release systems are characterized by the immediate release of the active agent, without in situ retention; these systems usually include supra- and sub-gingival irrigation solutions. In the case of sustained release devices, a high concentration of chemotherapeutic agent is obtained in the periodontal pocket for an extended period; this is the case with varnishes or gels. These forms of therapy can also be applied at home, but absolutely require a good knowledge of the application technique by the patient.

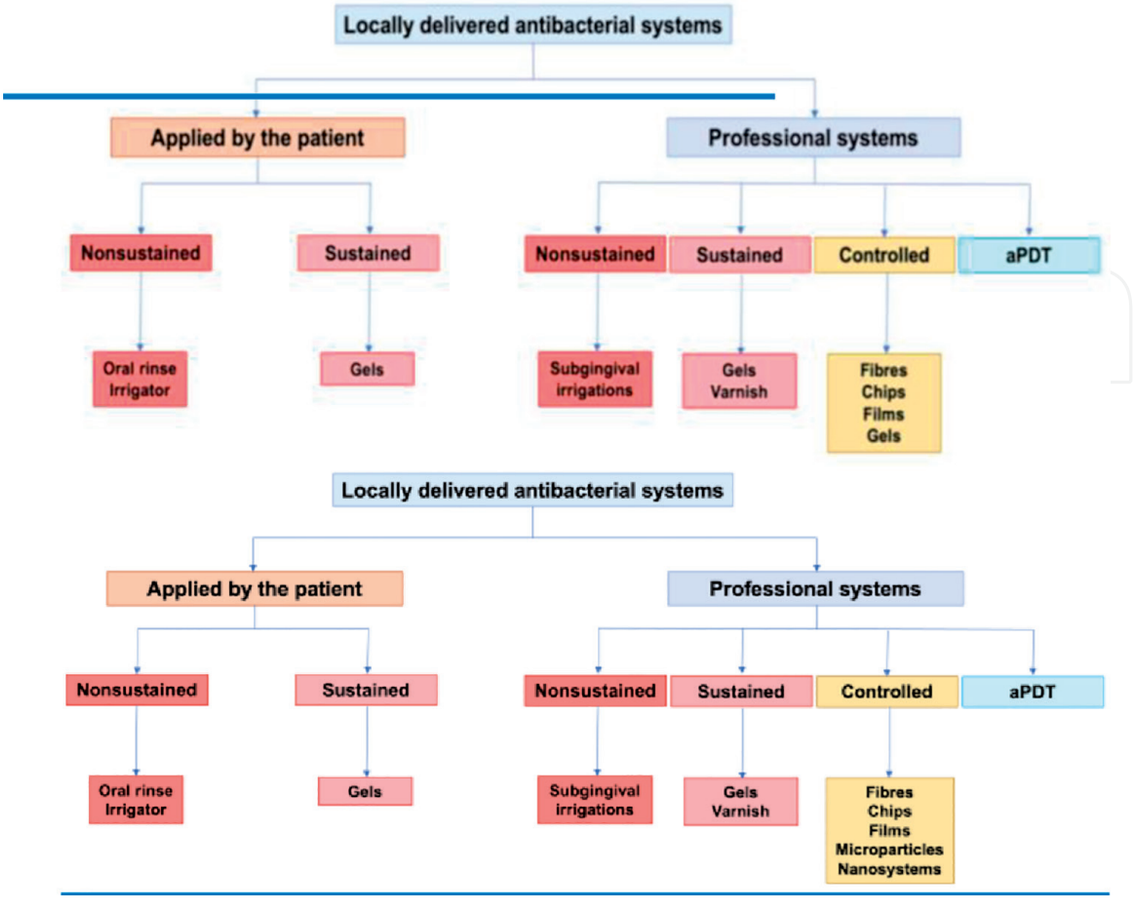

Figure 1.
Classification of locally delivered antibacterial systems.

Controlled-release systems include fibers, chips, films or certain gels that contain the active substance in the delivery medium and are placed in the periodontal pocket by a specialist in the dental office; they will slowly release adequate concentrations of the active substance over a period longer than 24 hours.

A potentially efficient method involves the photodynamic antibacterial therapy of periodontal pockets, which involves the application of light radiation (laser or LED), often together with a photosensitizing substance.

3. Irrigation solutions

Irrigation systems usually involve the use of a cannula connected to a syringe containing solutions of various active substances, such as chlorhexidine, triclosan, povidone-iodine, ozonated water or even sodium hypochlorite [11]. Bacteria and their products can be eliminated by the constant pressure of the solution on the tissue, along with drug activity [12].

The obtained data generally indicate that these irrigation solutions may lead to a number of improvements in periodontal parameters (plaque index, bleeding index on probing, depth on probing or periodontal clinical attachment loss), but these benefits appear to be in the short-term [13–16]. The main explanation for this phenomenon is given by the transient action of the active substance which is easily washed from the site by the action of saliva and crevicular fluid.

Chlorhexidine concentrations in irrigation solutions investigated in clinical trials range from 0.02% to 0.2%. The data provided, however, indicate that they do not bring an additional benefit over SRP alone [17, 18]. The use of povidone-iodine generated a minimal probing depth reduction of 0.28 mm [19]. The use of 0.5% sodium hypochlorite in subgingival irrigation did not generate unwanted side effects but also no additional periodontal benefit [20]. Da Costa et al. [21] performed a systematic review that evaluated the use of chlorhexidine mouthwash as an adjunct to SRP for chronic periodontitis. The authors observed that additional mouth rinsing with chlorhexidine resulted in slightly greater probing depth reduction than SRP alone, a negligible effect on clinical attachment level and potential for tooth staining [21].

An interesting approach is the use of desiccants in the irrigation of periodontal pockets. These are generally aqueous solutions of a mixture of hydroxybenzenesulfonic and hydroxymethoxybenzenesulfonic and sulfuric acid, which have a hygroscopic surface and a denaturing action [22]. These solutions have the ability to dehydrate the bacterial biofilm matrix. Irrigation with Hybenx®, a mixture of sulfonated phenols, additional to SRP, generated, after evaluation by DNA pyrosequencing, the elimination of 13 periodontopathogenic bacterial species [23]. In another study by Isola et al., SRP adjuvant therapy with Hybenx® resulted in more significant reductions in probing depth, clinical attachment loss and bleeding on probing, as well as red complex pathogens (*Porphyromonas gingivalis, Treponema denticola* and *Tannerella forsythia*) when compared to SRP alone [24].

Recently, we also investigated the effect of probiotic irrigation solutions (*Lactobacillus reuteri* DSM 17938); results at 3 months indicated significant improvements in periodontal attachment and bleeding on probing [25].

Therefore, the data in the literature on irrigation solutions are quite heterogeneous and, to date, there is no information to support the long-term effectiveness of these methods. Due to these limitations of subgingival irrigation solutions, their use is not a reliable method of professional control of bacterial plaque.

4. Varnishes

Varnishes used in periodontal treatments are generally based on chlorhexidine. Commercially available preparations include: Cervitec® Plus (Ivoclar/Vivadent AG, Schaan, Liechtenstein), with 1% chlorhexidine and 1% thymol in a polyvinyl butyral viscous base; EC40® (Biodent BV, Nijmegen, The Netherlands), solution of 35% chlorhexidine diacetate in 37% alcohol base stabilized with 27% sandarac; BioC® (Biodent BV, Nijmegen, The Netherlands), the supersaturated concentration of 20% chlorhexidine diacetate [26].

All these products have shown improvements in periodontal destruction rates but also reductions in bacterial load [27–30].

5. Gels

Gels are perhaps one of the most commonly used sustained release systems due to their ease of application, with the aid of cannula syringes and wide availability. Periodontal gels can be found in ready-made, available as commercial products (Chlo-Site®, Elyzol®, Atridox®, Periocline) or as pharmacy/laboratory products.

The active substances include chlorhexidine, triclosan or antibiotics, such as tetracycline, doxycycline, metronidazole or azithromycin, but also phytotherapeutic products such as curcumin or propolis. These substances are found in various polymer-based formulas, including xanthan, carbopol or chitosan.

Chlo-Site® is a gel containing 1.5% chlorhexidine in a xanthan matrix; it dissolves in 10–30 days after application, with an in situ therapeutic concentration maintained for 15 days, on average [12]. This prolonged release is possible because the matrix is mucoadhesive, which prevents it from being washed by saliva or GCF. In a systematic review, Tan et al. observed a 0.56 mm reduction in probing depth and a 0.53 mm periodontal attachment gain following the application of this gel [26]. Overall, the data support an additional beneficial effect of chlorhexidine gel application over SRP alone [31, 32].

Atridox® is a bi-component system, a 10% doxycycline hydrochloride thixotropic gel; it solidifies on contact with GCF. Studies have shown that doxycycline levels can remain above 1000 μg/mL for 18 hours in GCF, after which they begin to gradually decrease [33]. The doxycycline-based gel is effective as adjunctive therapy to SRP in terms of both clinical [34, 35] and microbiological parameters [36].

Minocycline 2% is found in biodegradable preparations with hydroxyethyl cellulose matrix, aminoalkyl methacrylate, triacetin and glycerin, such as Dentomycin® and Periocline®. In a study by van Steenberghe et al., the concentration of minocycline in GCF reached 1300 μg/mL at 1 hour but decreased to 90 μg/mL after 7 hours [37]. A minocycline and poly lactic-co-glycolic acid/N-methyl-pyrrolidone gel was developed, with favorable periodontal clinical results [38].

Metronidazole gel (Elyzol®) is a compound that becomes viscous on contact with GCF, which contains 40% metronidazole benzoate in an oil-based mixture (glyceryl monooleate and sesame oil), which is slowly broken down by GCF enzymes in 25% metronidazole [26, 39]. Data from the literature also support the efficacy of this preparation in combination with SRP, without the occurrence of systemic side effects [39–41].

Beneficial results were also obtained after applying 0.5% azithromycin [42], 0.4% moxifloxacin [43] or 3% satranidazole gels [44].

Another therapeutic option is given by deeply eutectic antimicrobial gels, such as choline and geranate gel (CAGE). Nakajima et al. demonstrated in a CAGE in vitro and in vivo study deep tissue penetration and antimicrobial activity against *P. gingivalis* [45].

Phytotherapeutic products, such as propolis [46] or turmeric [47], have also been addressed in the development of gels with subgingival application. Dave et al. observed significant reductions in plaque index, bleeding on probing, probing depth and periodontal clinical attachment loss after turmeric gel [48]. The 21-day application of turmeric gel versus chlorhexidine gel also showed significant reductions in plaque and gingival index, similar for both substances [49]; it should be noted, however, that turmeric gel was more easily tolerated by patients than chlorhexidine gel, the latter causing a bitter taste and pigmentation. The application of turmeric gel has also generated significant reductions in periodontal pathogens [50, 51].

6. Microparticle systems

Microparticles (microspheres) are solid, spherical polymeric structures with a diameter of 1–1000 μm, uniformly dispersed in a polymer matrix [2]. They contain

active substances, generally antibiotics such as tetracycline, minocycline, doxycycline, metronidazole or clindamycin [11]. Microspheres can be made of resorbable and non-resorbable materials. The material of choice in their manufacturing remains, however, poly lactic-co-glycolic acid, due to its stability and the possibility of adjusting the released dose [2].

Arestin® (OraPharma, Inc., Warminster, PA, USA), a minocycline-based product, was approved by the FDA in 2001; it is presented as a single-dose cartridge, with 4 mg of bioresorbable microspheres of poly lactic-co-glycolic acid, with a diameter of 20–60 μm [26]. This powdered product hydrolyzes on contact with the crevicular fluid and provides a minocycline concentration of 340 μg/mL for 14 days [52]. Numerous studies support the clinical and microbiological efficacy of this product in patients with periodontitis, with and without systemic risk conditions [53–55].

Doxycycline-based products were also studied, with very favorable results. It has also been shown that a high concentration of doxycycline in the periodontal pocket was maintained for 20 days [56]. Ali et al. demonstrated, by developing a double emulsion system of microspheres of poly lactic-co-glycolic acid and doxycycline, a significant reduction of *P. gingivalis* and *Fusobacterium nucleatum* pathogens [57]. Clinically significant improvements and reductions in *P. gingivalis* have also been observed with the combination of doxycycline with metronidazole, encapsulated in solid lipid microparticles [58]. Wang et al. investigated the incorporation of bioactive agents into polylactic-co-glycolic acid microspheres dispersed in a thermo-reversible polyisocyanopeptide hydrogel; doxycycline and lipoxin were charged separately in acid-terminated and ester-coated polylactic-co-glycolic acid [59]. According to the authors, this system showed adequate injectability as well as long-term structural stability; in addition, no inflammatory response has been reported in vivo [59].

Very good results were also observed after the use of microspheres with tetracycline [12] or clindamycin [60].

7. Nanosystems

Nanosystems include products in the form of nanoparticles, nanofibers, mycelium or liposomes. These are systems that are still in the research phase, and no commercial products are available so far. Nanoparticles include nanospheres and nanocapsules in the solid state, amorphous or crystalline, with a diameter of about 10–200 nm [11].

The major advantage of these systems, in addition to their biocompatibility, is the ability of the product to reach less accessible sites, precisely because of the very small size of the particles, and can penetrate even the attachment epithelium [61]. Moreover, the high ratio between surface area and volume characteristic of these systems favors the loading with the active substance, reducing the frequency of application [2].

Although the concept of nanoparticles is not new in dentistry, the focus on loading them with antimicrobial substances has received relatively recent attention. PEG-PLA nanoparticles with minocycline have been shown to have prolonged-release properties, in effective concentrations and with improvements in periodontal parameters [61]. Another study evaluated the biocompatibility and antibacterial capacity of chitosan nanoparticles with doxycycline [62]; the authors showed that 50 nm particles showed approximately 75% capture efficiency and 28% loading capacity, good cellular compatibility, as well as antibacterial and anti-inflammatory activity [62].

Liposomes are microscopic vesicles based on lipids, unilamellar or multilamellar. Liposomes are produced from cholesterol, long-chain fatty acids, non-toxic surfactants, sphingolipids, glycolipids and membrane proteins [11]. The advantages of these products include biocompatibility, good distribution, stability, biodegradation capacity, as well as protection of the active substance against environmental factors [63]. Liu & Yang demonstrated, in a murine model of periodontitis, the efficiency of liposomes with minocycline 2% on both periodontal parameters and TNF-α [64]. The main disadvantage is the high production cost, along with the complexity of their realization and the still high degree of instability. However, liposome-based systems can be a promising direction in adjunctive periodontal therapy.

8. Fibers

Fibers represent carrier systems made of different materials, impregnated with the active substance. They are placed circumferentially in the periodontal pocket and may or may not be sealed with acrylic cements to keep them in place.

Actisite® is perhaps the best-known fibers system; it consists of non-resorbable fibers impregnated with 25% g/g tetracycline, equivalent to 12.7 mg tetracycline hydrochloride. Actisite® maintains a constant concentration in gingival crevicular fluid (GCF) for a period of 10 days, equivalent to 8 μg/mL in systemic intake [65].

Although it has demonstrated clinical benefits [66], Actisite® is no longer used due to its non-biodegradable nature. Moreover, it seems that the application of fibers in periodontal pockets has been associated with a high degree of discomfort for the patient and with inflammatory signs after their removal [2].

Periodontal Plus AB® has emerged as a resorbable variant of tetracycline-impregnated collagen fibers. They are applied in the periodontal pocket and have a resorption period of about 7 days. This system has proven to be effective in terms of probing depth and periodontal clinical attachment loss [67]. Abraham et al. comparatively investigated in an interventional study the effects of additional administration in the periodontal pockets of chlorhexidine gel (Chlo-Site®), metronidazole gel (Metrogyl®) and tetracycline fibers (Periodontal Plus AB®); the authors showed favorable effects on plaque index and gingival index at 30 days for all three methods, but the effects were more significant for tetracycline fibers [68].

9. Semi-solid systems

Semi-solid systems include films, chips or strips that are inserted into the periodontal pocket; the controlled release of the drug is achieved either by its diffusion or by dissolving the carrier system [11]. These devices adapt to the shape and size of the periodontal pocket, are relatively easy to insert and the discomfort felt by patients is minimal [2].

Non-resorbable acrylic systems, with tetracycline or metronidazole as an active substance, were initially investigated [69]; although effective in antibacterial activity, these systems have been shown difficult to manipulate and remove from the periodontal pocket, being also associated with a local inflammatory response [70].

Periochip® is a chip of hydrolyzed gelatin crosslinked with glutaraldehyde, measuring 4.0 × 5.0 × 0.35 μm, containing 2.5 mg of chlorhexidine gluconate [26]. Periochip® releases chlorhexidine in a biphasic manner; in the first 24 hours, about 40% of the drug is released and the rest of the drug is released linearly for 7–10 days [71].

Another similar device is PerioColTM-CG®, which contains approximately 2.5 mg of CHX gluconate in a biodegradable matrix of type 1 collagen derived from freshwater fish [72].

In general, data on the use of these chlorhexidine chips support their effectiveness in reducing periodontal parameters, in association with SRP versus SRP alone, at assessments of 3, 9 and even 12 months postoperatively [73–75].

A number of biodegradable polymers, such as poly-hydroxybutyric acid and poly lactic-co-glycolic acid, atelocollagen, gelatin or chitosan/poly lactic-co-glycolic acid, in the form of tetracycline-impregnated films were investigated with significant reductions of probing depths and inflammation, quantified by bleeding on probing [2]. Moreover, the 25% tetracycline-impregnated polylactic-co-glycolic acid film demonstrated continuous release of the pharmacological agent for 10 days after placement [76].

10. Photodynamic antibacterial therapy

Photodynamic antibacterial therapy (aPDT) is based on the chemical effects of light. The main components involved in photodynamic antibacterial therapy consist of the light energy source, the photosensitizer and molecular oxygen. Their association will generate a flow of reactions with therapeutic effects [77].

Laser radiation can generate a number of bactericidal effects through photothermal effects, even in the absence of a photosensitizing substance. Nd:YAG lasers have selective absorption in pigments, are effective in destroying bacterial species such as *P. gingivalis* [78]. Moreover, laser radiation can decrease the release of bacterial products, such as endotoxins [79]. Thus, photodynamic therapy involves decreasing bacterial activity, inflammatory status, promoting decontamination and healing of affected periodontal sites.

The use of aPDT in adjunctive periodontal therapy can be amplified by applying a photosensitizing substance in the periodontal pocket and irradiating it with a light source (laser or LED) of a wavelength appropriate to the used substance [47, 80]; cytotoxic reactive oxygen species are generated after exposure to light, with effects involving protein, cell membrane and bacterial organ damage [81] (**Figure 2**).

A photosensitizer or photoactivatable agent, such as methylene blue, is applied in the periodontal pocket. Exposure of tissue to light at the appropriate wavelength in the presence of molecular oxygen generates the formation of reactive oxygen species (ROS); ROS causes non-thermal cytotoxic effects by damaging microorganisms' proteins, cell membranes and organelles [47, 82].

Various photosensitizing agents have been investigated in periodontal therapy, including phenothiazine derivatives (methylene blue, toluidine blue), xanthens (erythrosine, eosin-Y, Bengal roses), riboflavin derivatives, indocyanine green, fullerene derivatives, bordipiromethane [47, 83].

Numerous studies have investigated the efficacy of aPDT with methylene blue and toluidine blue, the latter demonstrating higher efficacy. Diode laser and toluidine blue aPDT effects on *Porphyromonas gingivalis* were evaluated [84]; treatment with toluidine blue and 2.2 J/cm^2 light dose reduced *P. gingivalis* by 2.43 log. In another study, black-pigmented bacteria *P. gingivalis* and *P. intermedia* reacted strongly to the 690 nm wavelength toluidine and laser treatment protocol, reducing bacterial growth by up to 2 logs [85].

A research group led by Azizi investigated the efficacy of aPDT with toluidine blue and phenothiazine chloride in the disinfection of zirconium implants contaminated

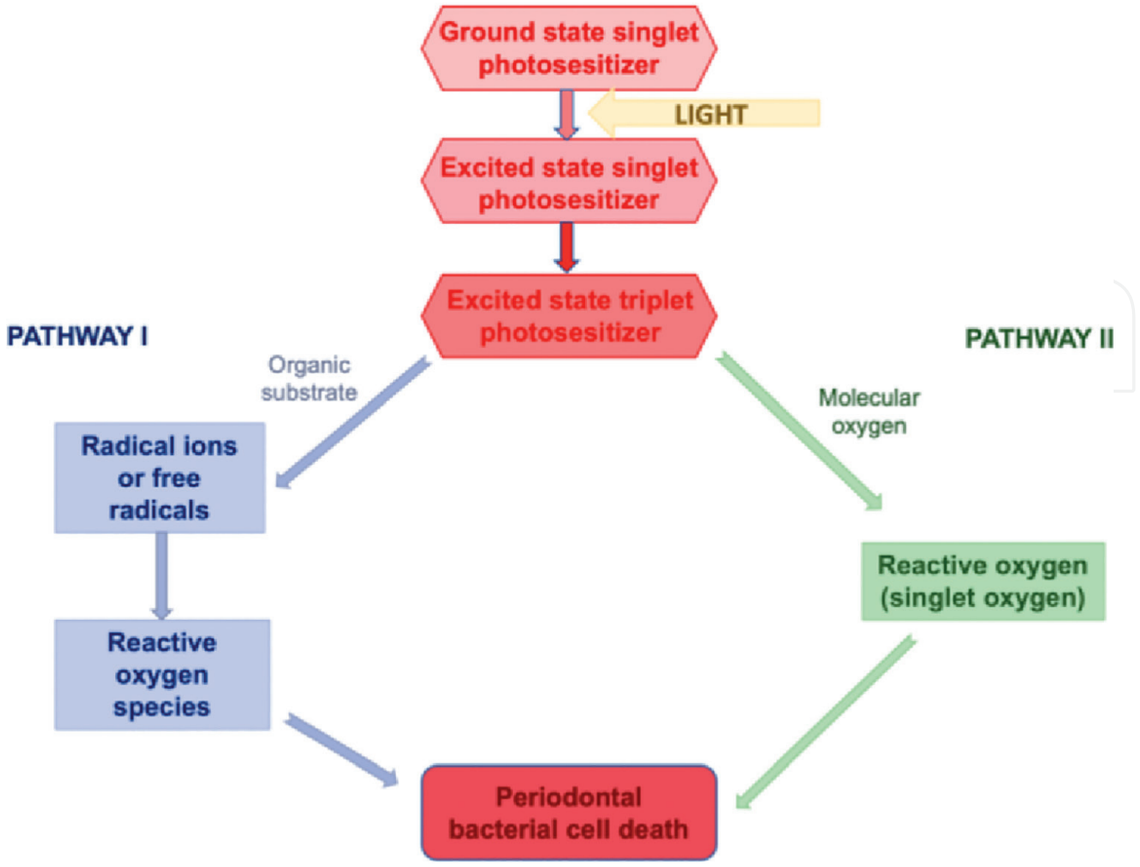

Figure 2.
Mechanism of action in aPDT.

with *P. gingivalis*, *P. intermedia* and *A. actinomycetemcomitans* [86]. Only toluidine blue showed a significant reduction in the number of bacteria; bacterial reductions after aPDT with both photosensitizers were greater than the chlorhexidine positive control.

A strong therapeutic effect has been observed for the association of riboflavin in aPDT against the pathogens *P. gingivalis*, *Fillifactor alocis*, *P. micra*, *Campylobacter rectus*, *Fusobacterium nucleatum*, *Eikenella corrodens* and *P. intermedia* [87].

Indocyanine green has also been evaluated as a potential photosensitizer. It consists of two aromatic parts connected by a polyunsaturated chain; it is a dye commonly used in medicine, especially in imagistic investigations [88]. It penetrates rapidly into tissues and has low toxicity, being approved by the FDA for clinical use and recognized as non-toxic [89].

The absorption range for indocyanine green is between 600 nm and 900 nm and emits fluorescence between 750 nm and 950 nm [90]. Indocyanine green aPDT does not require the presence of oxygen to activate and release free radicals and singlet oxygen [91]; indocyanine green therapy is also called photothermal therapy. Thus, indocyanine green may be more effective than other photosensitizers in the periodontal pocket, an environment characterized by hypoxia. A recent meta-analysis [92] observed statistically significant improvements in aPDT results with indocyanine green at 3 months and 6 months after therapy, compared with single SRP; probing depth demonstrated an average additional reduction of 1.17 mm and 1.06 mm at 3 and 6 months, respectively; for clinical attachment loss, an average additional gain of 0.70 mm and 1.03 mm was observed at 3 and 6 months, respectively [92]. We have recently investigated the effects of 5 mg/mL indocyanine green irradiation by 810 nm

diode laser, supplementary to SRP in patients with periodontitis and type II DM, compared to SRP alone. We observed that SRP + aPDT generated more significant reductions in bleeding on probing, probing depth and clinical attachment loss but not for plaque index and HbA1c than SRP alone [93].

Attention has also been paid to the potential of curcumin as a photosensitizing agent. Curcumin absorbs light from the edge of UV and visible radiation, over a range of 300–500 nm, with maximum absorption of about 420 nm [83].

The antibacterial activity of various concentrations of photoactivated turmeric with LED light at a wavelength of 420–480 nm for 1 minute was investigated against *A. actinomycetemcomitans* in an in vitro study [94]. Bacteria with exponential growth were combined with a solution of turmeric concentration ranging from 25 to 0.098 μg/mL; 0.12% chlorhexidine solution was used as a positive control. The results demonstrated a dose-dependent antibacterial activity of the turmeric solution [92]. In the absence of blue light irradiation, the turmeric concentration of 25 μg/mL resulted in a logarithmic reduction of *A. actinomycetemcomitans* of 6.03 ± 0.39 log10; the turmeric concentration of 0.78 μg/mL under irradiation completely eradicated *A. actinomycetemcomitans*, an effect also obtained after co-culture with chlorhexidine 0.12%. At the same time, maximum signal intensity of hydroxyl radical production was observed following the association of turmeric with LED irradiation [47].

Sreedhar et al. observed in a clinical and microbiological study in patients with periodontitis that the additional use of curcumin gel generated an antibacterial effect on *P. gingivalis*, *P. intermedia* and *A. actinomycetemcomitans*, but PDT amplified the benefits of curcumin, further enhanced by repeated PDT sessions [95].

An interesting nano-carrier was designed by Shlar and colleagues who used a curcumin derivative as a photosensitizer; curcumin-loaded cyclodextrin was coated with 5–20 layers of poly-L-lysine, poly-L-glutamic acid and carboxymethyl-β-cyclodextrin (CM-cyclodextrin). CM-cyclodextrin was covalently crosslinked or left unchanged. The authors noted that crosslinking provided greater stability and less release of curcumin [96].

Data in the literature indicate that the bactericidal effects of turmeric as a photosensitizing agent may depend on the type of carrier or solvent used, which may alter the wavelength where the efficiency is maximum [97]. In addition, turmeric has a high rate of photodegradation, which translates into the need to use it almost immediately after preparation [98].

A complex systematic review, conducted by Salvi et al. [99], aimed to investigate the effects of aPDT on SRP in patients with untreated periodontitis after a follow-up of 6 months. The authors observed a high heterogeneity and variability regarding the protocols and the results, with patient-reported benefits still unclear [99].

11. Locally delivered antimicrobials in the current therapeutic guidelines

Based on the current classification system of periodontal conditions [100], and solid findings from randomized controlled trials (RCTs), new guidelines have emerged, providing recommendations for periodontitis treatment stages I-III [101] and IV [102]. According to the proposed guidelines, locally administered sustained-release antimicrobials, such as chlorhexidine (Periochip®) or antibiotics (Atridox®, Arestin®), may be considered as an adjunct to subgingival instrumentation, due to proven efficiency and relatively low risk of side effects [101]. This recommendation is based on a systematic review performed by Herrera et al. [103], which included

50 different studies on locally delivered antimicrobials (gels, chips and fibers); the authors concluded that their use exerted statistically significant benefits in terms of probing depth reduction and short-term clinical attachment gain [103].

Oral rinses with chlorhexidine also might be recommended, for a limited period of time and in specific cases [101], due to its known side effects, and only after optimizing the mechanical plaque control.

With respect to aPDT, the guidelines do not recommend its standard use in periodontitis patients. This decision is based on the high heterogeneity which characterizes the RCTs, with various photosensitizers, laser types, different wavelengths, dosage and number of sessions. Moreover, it is stated that, even if there were no reported adverse effects of aPDT, the high cost of this particular procedure is not justified in standard practice [101].

Drug delivery system	Active drug	Mechanism of delivery	Advantages	Disadvantages
Subgingival irrigation	Chlorhexidine Triclosan Antibiotics	Application in the periodontal pocket with the aid of a syringe	Good disease site reaching Adequate concentration in situ Cost saving Easy application	Poor maintenance of drug concentration in time Relatively uncontrolled and inconsistent drug delivery Requires multiple applications Microorganisms' resistance can occur
Gels	Chlorhexidine Tetracycline Metronidazole Doxycycline Minocycline	Application in the periodontal pocket with the aid of a syringe/canula	Patient acceptability Easy application	Poor retention at the site Difficulties in obtaining an accurate dosage
Microparticle systems	Minocycline Ofloxacin	Microspheres in the unit-dose cartridge	Good maintenance of drug concentration in time Can reach even narrow pockets	Resistant microorganisms can emerge
Fibers	Tetracycline HCl Chlorhexidine	Inserted in the periodontal pocket and isolated with the aid of cement	Good maintenance of drug concentration in time	Require a second session for their removal Emergence of resistant microorganisms Signs of local irritation can occur
Films	Chlorhexidine Tetracycline Metronidazole	Flexible polymer inserted in the periodontal pocket	Thin and flexible Easy insertion Less discomfort Prolonged effect High site-specificity	Difficult to apply in narrow, less accessible pockets

Table 1.
Summary of currently available locally delivered antimicrobials.

The indications and the contraindications for the locally delivered antimicrobials are generally the same for all the mentioned systems. They include as follows:

Indications

- Always, as adjunctive to scaling and root planing
- Deep and localized periodontal pockets in patients with periodontitis Grade A or B
- Patients with periodontitis who do not respond to conventional treatment
- Patients with periimplantitis
- Furcation lesions Grade I or II
- Contraindications
- As a replacement for scaling and root planing
- As a replacement for surgical periodontal therapy
- As a replacement for systemic antimicrobial therapy/prophylaxis
- Not a substitute for self-performed plaque control by patients
- Generalized periodontal pockets
- Patients with allergies/contraindications to the specific active drug
- Patients with a history/risk of infective endocarditis, to avoid the risk of bacteriemia

The main advantages and disadvantages of locally delivered antimicrobials are presented in **Table 1**. Additionally, general advantages can be mentioned: drug dosage is lower than for the antibiotics with systemic administration; certain agents cannot be taken through a systemic route (such as chlorhexidine); more adequate local concentration for the active drug.

As general disadvantage, certain techniques might be time-consuming; moreover, due to site-specificity, other bacterial niches from the oral cavity are not reached, including tonsils, buccal mucosa or tongue.

12. Conclusions and future directions

Continuous discoveries in the understanding of the mechanisms which cause periodontal disease, as well as those which accelerate tissue destruction, have led to the development of new methods of treatment. It is clear at this time that non-surgical periodontal debridement by scaling and root planing is often insufficient for the resolution of periodontal disease. Thus, local adjunctive therapy is increasingly used in current practice. Local drug treatment against bacterial plaque, in combination with SRP, involves a wide variety of products already commercially available or under research.

There is currently insufficient data to establish a "gold standard" in local antimicrobial therapy. Current guidelines recommend the usage of oral rinses with chlorhexidine and locally administered sustained-release antimicrobials in the standard treatment of periodontitis patients but in specific cases.

The main concern in the design of these products is to ensure an optimal concentration of the drug in situ and to maintain the long-term potential beneficial effects, without local or systemic complications. Numerous carriers have been investigated over time. In addition to the slow-release products already available, a promising prospect is offered by nanoparticle-based antibacterial therapy or aPDT therapy.

Moreover, the current research directions are focused on the development of multi-component products, with the incorporation of agents to produce not only the disinfection of periodontal pockets but also a resolution of inflammation at the molecular level.

Of course, SRP remains a *sine qua non* condition in periodontal therapy for the disorganization of bacterial biofilm, but current trends suggest a much more complex therapeutic intervention, individualized per patient, with complex and complete addressing of the factors which maintain and aggravate the periodontal disease. In our opinion, the identification of a universally effective adjunctive therapy product is a utopia precisely because of the variability of periodontal disease etiopathogenesis. We believe that it is crucial not only to know the available products but also to identify the most effective compound and technique for the patient in the dental chair.

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