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Review article

Antimicrobial photodynamic therapy for the treatment of oral infections: A systematic review

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Abstract Oral infection is a common clinical symptom. While antibiotics are widely employed as the primary treatment for oral diseases, the emergence of drug-resistant bacteria has necessitated the exploration of alternative therapeutic approaches. One such modality is antimicrobial photodynamic therapy (aPDT), which utilizes light and photosensitizers. Indeed, aPDT has been used alone or in combination with other treatment options dealing with periodontal disease for the elimination of biofilms from bacterial community to achieve bone formation and/or tissue regeneration. In this review article, in addition to factors affecting the efficacy of aPDT, various photosensitizers, the latest technology and perspectives on aPDT are discussed in detail. More importantly, the article emphasizes the novel design and clinical applications of photosensitizers, as well as the synergistic effects of chemical and biomolecules with aPDT to achieve the complete eradication of biofilms and even enhance the biological performance of tissues surrounding the treated oral area.
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Introduction

The oral cavity is home to more than 700 bacterial species,[1] which further create microbial community and plays a vital role in maintaining oral health. Dysbiosis indicates an imbalance and disruption of the normal oral microbial community, which may develop into an inflammatory response and ultimately oral tissue damage. These

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reactions contribute to the development of oral diseases such as dental caries and periodontal diseases. According to the "Global Oral Health Status Report" released by the World Health Organization (WHO) in 2022, identified dental caries, severe periodontal disease, tooth loss, and oral cancer as the most prevalent oral illnesses.[2] Untreated dental caries is the most prevalent disease worldwide, affecting approximately 200 million people. Moreover, severe periodontal disease, which is a primary cause of tooth loss, influences an estimated 500 million people globally.

Periodontal disease is a gum infection caused by bacteria, which further form a biofilm and grow on tooth surface, then causing deep pocketing and resulting in inflammation and sensitivity, and ultimately leading to bone and tooth loss. The use of dental implants to replace missing teeth has been common practice for decades and has proven to be a reliable method for restoring oral function and aesthetics[3]; nonetheless, complications do occur in patients. This may be due to implant design, changes in surface texture caused by wear or aging, smoking and/or chewing tobacco, having systemic diseases, poor oral hygiene, etc., which lead to the accumulation of bacteria biofilm attaching to implant surfaces and cause periodontal problem.[4] There are two types of peri-implant diseases: peri-implant mucositis and *peri*-implantitis.[5,6] Peri-implant mucositis is characterized by the occurrence of inflammation around the implant, which can manifest symptoms like redness, swelling, and bleeding on probing. More importantly, this condition does not involve any further loss of bone following the initial healing phase. On the other hand, *peri*-implantitis is characterized by the same signs of inflammation, as well as evidence of bone loss seen on radiographs and an increased probing depth compared to depth measurements taken after the implant placement.[7]

Biofilms are microorganisms adhered to tooth surfaces, organized and encapsulated by a self-produced polymeric extracellular matrix.[8] It has been noticed that biofilms develop resistance to antibiotics after long-term use, which may impede the efficacy of *peri*-implantitis treatment. Undoubtedly, removing bacteria is particularly important when dealing with *peri*-implantitis and dental caries. For this reason, the control and elimination of biofilms play a crucial role in the prevention and treatment of oral diseases.[9]

Presently, mechanical debridement is the predominant approach for the treatment of dental caries and periodontal diseases. This includes techniques such as scaling and root planing (SRP), use of polishing brushes, utilization of air-powered abrasive instruments, as well as manual and ultrasonic scalers.[10,11] Despite efforts to eradicate microorganisms, the intricate topography of tooth and implant surfaces makes complete elimination challenging.[12] As a result, adjunctive measures such as the use of antiseptics and antibiotics can be incorporated with mechanical debridement to optimize therapeutic outcomes. While antibiotic treatment may provide temporary reduction of subgingival microorganisms, prolonged and repeated use can lead to the development of antibiotic resistance in periodontal pathogens. For example, chlorhexidine is widely employed as an antiseptic for periodontal infections; notwithstanding, its antimicrobial properties, it can result in various several adverse effects such as taste changes, burning sensations, tooth staining, mucous irritation, and allergic responses.[13,14] To this end, there is a growing necessity to develop new therapeutic approaches such as antimicrobial photodynamic therapy (aPDT), and the respective advantages and disadvantages of different treatment methods for periodontal diseases are also shown in Table 1. The use of aPDT as an adjunctive modality in the management of dental caries and periodontal disease gains a lot of interests.[15–18]

Antimicrobial photodynamic therapy

Antimicrobial photodynamic therapy, also known as photoantimicrobial chemotherapy, refers to a method of utilizing light energy and a photosensitizer (PS) to generate reactive oxygen species (ROS) in an oxygen-containing environment. This targeted approach is capable of targeting and harm microorganisms (Fig. 1)[28]; more importantly, aPDT does not lead to bacterial resistance.[29] This is because the action of aPDT is restricted to the specific area where the photosensitizer is activated by light, which means that there is no risk of inducing bacterial resistance. It is well-known that the excited triplet state of photosensitizers undergoes two types of reactions. First one, known as type I reaction, involves the transfer of electrons and hydrogen.[30] During this reaction, free radicals quickly react with oxygen to produce highly ROS such as superoxide, hydrogen peroxide, and hydroxyl radicals. The second is a type II reaction in which the triplet-state PS reacts directly with oxygen, which in turn produces singlet oxygen.[31] With its high chemical reactivity, singlet oxygen can interact with biological substrates, causing oxidative damage and ultimately resulting in bactericidal effects by disrupting cell membranes and cell walls.[32,33] The methods of aPDT involve the use of both Type I and Type II reactions, with the degree of potency depending on the concentration of PS and the oxygen environment. However, several factors have hindered the widespread adoption of aPDT in dentistry, such as the types and dosages of PS, light source, treatment time, tissue depth, oral environment, and more (Fig. 2). To achieve an ideal treatment goal, it is crucial to select the appropriate combination of modalities.

As far as photosensitizers are concerned, different photosensitizers have different degrees of selectivity and efficiency toward specific cells. Some photosensitizers are more effective at targeting certain bacteria than others.[34] For example, Methylene blue (MB) may be more effective treating Gram-positive bacteria due to its more pronounced dye induction compared to Gram-negative bacteria.[35,36] The amount of photosensitizer used and the method of administration may influence the therapeutic efficacy. Using too little photosensitizer may not produce sufficient effect, while using too much may grow the risk of side effects and damage to healthy tissue.[37] In fact, different photosensitizers have their optimal wavelengths of light for activation, so the correct matching of wavelength and photosensitizer is very important. Rationally, the duration of treatment affects overall effectiveness; shorter treatment time may not be effective enough; yet, longer

Table 1 Treatment methods of oral infections and their advantages and disadvantage.[19–27].

Method	Process	Advantages	Disadvantages
Mechanical debridement	Scaling and root planing	● Decrease periodontal inflammation. ● Improve hygiene and bad breath.	✓ Discomfort. ✓ Hypersensitivity. ✓ May not completely eliminate bacteria. ✓ Depends on practitioner's skill.
Chemical therapy	Antiseptics and antibiotics	● Rather good short-term result. ● Eliminate or suppress pathogenic bacteria. ● Enhance healing and tissue regeneration.	✓ Bacterial resistance. ✓ Staining, taste alteration, or allergic reactions. ✓ Alter oral microbiota. ✓ Not effective against biofilms or deep pockets.
Laser irradiation	Er:YAG laser, Nd:YAG laser, diode laser, etc.	● Rather good antimicrobial result. ● Less anxiety for patients compared to traditional methods. ● Enhance healing and tissue regeneration. ● Reduce recovery and healing times. ● Target diseased areas precisely and accurately.	✓ Equipment is more expensive. ✓ May cause thermal damage to tissues or implants. ✓ May not improve clinical outcomes compared to standard treatments. ✓ It may be costly and require special training.
aPDT	Light and photosensitizers	● Non-invasive and painless procedure. ● Do not develop bacterial resistance. ● Reduce inflammation and bleeding. ● Selectively target pathogenic bacteria without affecting healthy tissues.	✓ Higher cost compared to traditional treatment. ✓ Sensitivity to light for several days or weeks after the treatment.

Abbreviations: Er:YAG, erbium-doped yttrium aluminum garnet; Nd:YAG, neodymium-doped yttrium aluminum garnet; aPDT, antimicrobial photodynamic therapy.

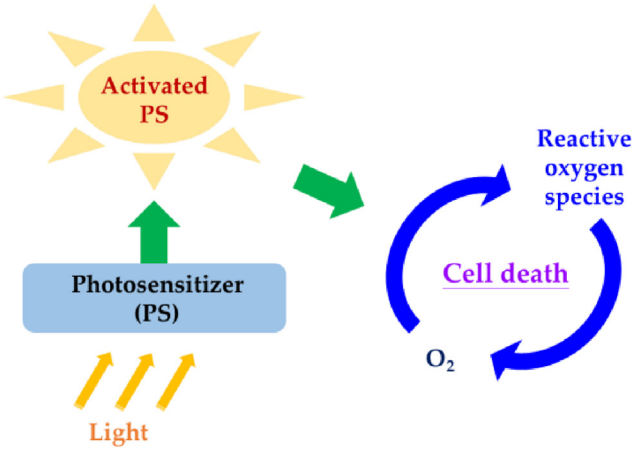

Fig. 1 Mechanism of antimicrobial photodynamic therapy.

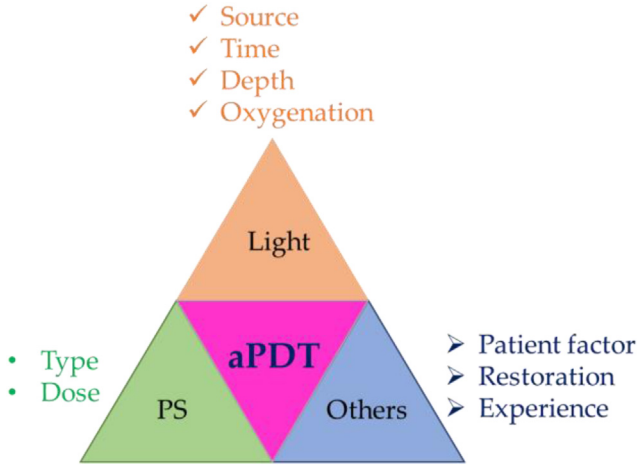

Fig. 2 Factors influencing the treatment efficacy of aPDT.

treatment times may elevate the risk of side effects or damage to healthy cells.[38]

On the other hand, patients with compromised immune systems or other underlying health conditions may not respond well to photodynamic therapy.[39] Furthermore, improper dental hygiene can lead to the production of bacteria and debris that reflect light and interfere with the treatment, making light more difficult to reach the targeted area.[40] Overall, photosensitizers used in aPDT have the potential to damage healthy tissue, causing side effects such as irritation, vomiting, and nausea. Therefore, it is crucial to use the minimum concentration required for an appropriate light source to eliminate bacteria.

Photosensitizer

A variety of photosensitizers have been utilized, including compounds commonly used in dental practices such as methylene blue, toluidine blue, indocyanine green, curcumin, erythrosine, curcumin, chlorella, rose bengal and urucum, etc.[41,42] As shown in Fig. 3, an ideal photosensitizer should possess specific characteristics that make it effective and safe to use. For instance, photosensitizers should have high absorption in the visible range and penetrate deep enough into tissues to effectively generate singlet oxygen. Additionally, a photosensitizer should possess the properties of high photostability and low toxicity to remain active after exposure to light without harming surrounding healthy cells and tissues. In a study by the Xing group,[43] the photosensitizer protoporphyrin IX was conjugated with lipopolysaccharide neutralizing peptide sequences for efficient real-time fluorescent imaging of living bacterial strains and effective photoinactivation of drug-resistant Gram-negative bacterial strains. The specific strategy can selectively target bacterial strains over mammalian cells with less damage to mammalian cells. Moreover, administering the photosensitizer to the treatment site should be as simple and straightforward as possible. The absorption of each photosensitizer falls into different light zones. In fact, there are two commonly used shades, listed in Tables 2 and 3. Red light can penetrate deeper into tissues, while blue light is a common light source used in dentistry for resin curing, making it easy to achievable. Details were described later.

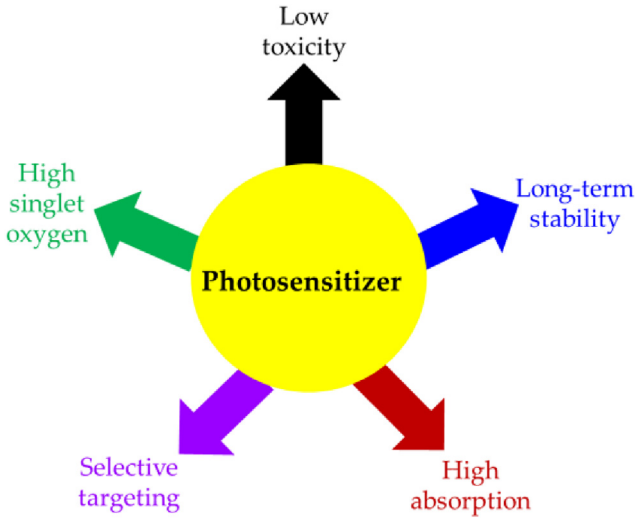

Fig. 3 Properties of an ideal photosensitizer.

Toluidine blue

Toluidine blue (TB) is a beneficial cationic photosensitizer approved by the Food and Drug Administration (FDA) for clinical use. TB has low excitation energy and high cell membrane permeability, while being relatively inexpensive. Furthermore, the small molecular size, hydrophilicity, and ability to form dimers make TB ideal for binding to microbial cell membranes. The absorption of TB solutions varies with concentration, allowing excitation in various modality using light sources from 600 to 660 nm.[58] Several studies have shown that TB is effective in the treatment of oral diseases.[59–61] For example, Vahabi et al. applied 0.1% TB to a bacterial suspension of *Streptococcus mutans* (*S. mutans*), which was then exposed to a 633 nm diode laser.[62] The findings of the study demonstrated that the combination of TB and diode laser can significantly reduce the number of viable bacteria. In another study, Habashneh et al. used TB combined with a 635 nm diode laser to treat periodontal pockets in patients with periodontitis.[63] This treatment was successful in significantly improving clinical attachment levels.

Methylene blue

Methylene blue (MB) is one of the commonly used dyes in the phenothiazine family. The range in which MB absorbs light falls within the red-light region, specifically between 600 nm and 660 nm. In addition, MB is FDA-approved for high-dose oral and intravenous administration in humans without any deleterious effects.[64] Also, MB exhibits a strong ability to absorb light with wavelengths over 620 nm, which allows better penetration into tissues. In addition to low toxicity, MB is effective in killing cariogenic bacteria.[65] Recently, MB has gained popularity in the field of dentistry as a photosensitizer. Oliveira et al. studied the effectiveness of MB-mediated aPDT on microorganisms such as *Enterococcus faecalis* (*E. faecalis*) and *Staphylococcus aureus* (*S. aureus*), resulting in a notable decrease in the number of viable bacteria.[66] This finding suggests that this modality holds potential as an effective treatment for periodontitis. Ribeiro da Silva et al. also found that photoantimicrobial chemotherapy using MB was effectively in reducing the pain and duration of oral mucositis in young patients.[67]

Indocyanine green

Indocyanine green (ICG) is a fluorescent dye with low toxicity in tissues and high absorption in the near-infrared range.[68] In recent years, ICG-mediated photodynamic therapy has been effective in the treatment of a variety of oral diseases, including periodontitis and tooth hypersensitivity. ICG-aPDT has the major advantage of selectively targeting cells and producing high levels of singlet oxygen

Table 2 Photosensitizers irradiated by red light during aPDT.

PS	Recommended or used concentration	Light source	Power (mW)	Energy density (J/cm^2)	Results	Ref
TB	0.1 mg/mL	630 nm LED	—	—	Through clinical practice, aPDT has been proven to be a safe treatment for *peri*-implantitis and a treatment that reduces peri-implant pocket inflammation and infection in a short period of time.	44
	100 μg/mL	660 nm InGaAlP laser	30	50	Effectively reduced cultures of periodontal biofilm and *S. aureus* in vitro.	3
MB	200 μg/mL	660 nm diode laser	80	2.4, 4.8	The combination of 200 μg/mL MB photosensitizer with laser light at pH 10, with 60 s of irradiation time, resulted in the most effective killing.	37
	0.005%	660 nm LED	400	95	The immediate reduction of halitosis from the tongue coating was observed, but the effect was not sustained during the follow-up evaluations.	45
	100 μg/mL	660 nm diode laser	150	—	Addition of aPDT to SRP can be considered as a safe and effective technique for reducing pocket depth in patients with chronic periodontitis.	46
	200 μg/mL	660 nm laser	100	—	At the 6-month follow-up, the application of aPDT as a supplementary therapy to tissue regeneration in cases of *peri*-implantitis led to significant decontamination, evident bone regeneration, and restoration of periodontal health.	47
ICG	1000 μg/mL	808 nm diode laser	250	24	The modality reduced microleakage at the gingival margin prior to the application of composite resin restorations.	48
	5 mg/mL	808 nm laser	100	10	The *Candida* colonies were significantly reduced.	49
FTC	Planktonic culture: 0.3 mg/mL *S. mutans* biofilms: 0.6 mg/mL	660 nm GaAlAs laser	50	39.5	It effectively killed *S. mutans* adhered to the enamel surface, indicating its potential as a disinfectant for dental tissues by breaking down the bacterial aggregates.	50
	6.89 mg/mL	660 nm LED	42.8	30	The heterogeneous biofilms of dental caries were effectively eradiated.	51

Abbreviations: aPDT, antimicrobial photodynamic therapy; PS, photosensitizer; TB, toluidine blue, LED, light-emitting diode. InGaAlP, indium gallium aluminum phosphide; MB, methylene blue; SRP, scaling and root planing; ICG, indocyanine green; FTC, fotoenticine; GaAlAs, gallium aluminum arsenide.

Table 3 Photosensitizers irradiated by blue light during aPDT.

PS	Recommended or used concentration	Light source	Power (mW)	Energy density (J/cm^2)	Results	Refs
CUR	80 μM	455 nm LED	22 mW/cm^2	18	CUR-mediated aPDT appeared to be a safe treatment in clinical practice without causing any aesthetic or mechanical changes to the enamel surface.	52
RB	10 μg/mL	450—470 nm LED	—	—	The modality had antimicrobial effects on Gram-positive *S. mutans*, *S. sobrinus*, *S. sanguinis*, and *L. salivarius*, in both planktonic and biofilm states.	53
	160 μg/mL	450—470 nm LED	109	12	A promising alternative for treating periodontal pathogens, particularly in eradicating *A. actinomycetemcomitans*.	54
Erythrosine	25 μM	500—600 nm halogen-based composite curing light	663.72 mW/cm^2	39.82	The therapy can effectively reduce the amount of dental plaque microbes and may be useful for preventing and treating dental plaque in both daily life.	55
	22 μM	LED: 440—480 nm/diode laser: 830 nm	LED: 570 mW/cm^2 diode laser: 400 mW/cm^2	—	The blue light source used for photopolymerizing dental composite material can also be used in conjunction with the plaque disclosing agent erythrosine to significantly reduce the main Gram-negative periodontal pathogens.	56
	100 μM	440—500 nm LED	1000	0—63.8	The photosensitizer can be stable at different pH levels, absorb blue to violet light, maintain cell viability, and be effective against *C. albicans*.	41
Urucum	20% in spray form	395—480 nm LED	480	6.37	Halitosis decreased immediately, but the reduction was not maintained after 7 days.	57

Abbreviations: aPDT, antimicrobial photodynamic therapy; PS, photosensitizer; CUR, curcumin; LED, light-emitting diode; RB, rose bengal.

species, allowing more precise therapy with fewer adverse effects. Bashir et al. reported ICG-mediated aPDT as an adjunct to non-surgical periodontal therapy (NSPT) in managing chronic periodontitis with good therapeutic outcomes that probing depth decreased on average by 1.17 mm and 1.06 mm at 3 and 6 months, respectively.[69] Although ICG is a popular photosensitizer in aPDT, it has its limitations. One of them is its limited duration of effectiveness. Furthermore, the use of ICG has been associated with side effects such as nausea, vomiting, and allergic reactions.[70,71]

Rose bengal

Rose bengal (RB) is a well-known anionic dye, a member of the xanthene family, notable for its high absorption in the blue and green light spectrum, especially in the 500—800 nm range,[72] and is commonly used as a diagnostic tools for dental and ophthalmic examinations.[73] RB not only has good antimicrobial properties, but is also inexpensive, biodegradable, nontoxic, and has free amino groups, which are attractive for chemical bonds.[74] Furthermore, it has a high rate of singlet

oxygen generation, which makes it an effective choice for aPDT.[75] Hirose et al. found that when using concentration of more than >10 μg/mL, RB solution exhibited antimicrobial effects on oral Gram-positive *S. mutans* (a frequent cause of dental cavities) in both planktonic and biofilm states.[53] More importantly, the RB-mediated aPDT resulted in a significant decrease in cariogenic bacteria found in dental plaques. Wang et al. explored the combination of RB and medium-power blue light for the treatment of periodontal pathogens, especially *Aggregatibacter actinomycetemcomitans* (*A. actinomycetemcomitans*) and showed that this treatment reduced inflammation and promoted the healing of periodontal pockets.[54] In short, RB-mediated aPDT may be a promising therapeutic tool for periodontal diseases.

Curcumin

Curcumin (CUR) is a natural phenolic compound with a small molecular weight found on Earth.[76] Derived from the Curcuma longa plant, CUR exhibits various beneficial properties such as anti-inflammatory, antimicrobial, antitumor effects, and facilitation of wound healing.[77,78] When administered to the treatment area and exposed to light of approximately 405 nm wavelength, CUR has the ability to decrease inflammation and eliminate pathogens in the periodontal tissue and its surrounding area. CUR-mediated aPDT is effective in reducing the severity of periodontal disease and improving the overall oral conditions.[79–81] Sreedhar et al. assessed the potential of CUR gel with aPDT for the treatment of chronic periodontal disease.[82] Fifteen patients who had not previously received treatment were randomly assigned to different groups in a split-mouth design. Compared with SRP alone, the group using SRP plus CUR-mediated blue light light-emitting diode (LED) with a wavelength of 470 nm for 5 min showed a statistically significant reduction in plaque index, bleeding index, probing depth, and clinical attachment level on the first, seventh, and 21st day. They suggest that CUR gel has the potential to be used as a photosensitizer, and, together with SRP, can help to better remove periodontal pathogens. Also, in terms of killing bacteria, CUR is more effective in killing Gram-positive bacteria than Gram-negative bacteria in its photodynamic process.[83]

Fotoenticine

Fotoenticine (FTC) is a new photosensitizer derived from chlorin e–6, which has an absorption band between 660 and 680 nm.[50,84] Recently, the FTC has had impressive results in fighting against bacteria. Garcia and colleagues focused on utilizing FTC in photodynamic therapy for the treatment of dental caries.[51] They highlighted the advantages of utilizing FTC-mediated aPDT, including notable reductions in total microorganisms, such as streptococci, lactobacilli and yeasts. Furthermore, this modality successfully disrupted biofilm structures and reduced lactic acid levels.

Chlorella

Chlorella is a type of green microalga that contains high amounts of proteins, minerals, and vitamins and is often suggested as a dietary supplement.[85] Chlorella absorbs light in the red and near-infrared regions of the spectrum, which satisfies sufficient depth to the treatment site during aPDT. Chlorella can safely and effectively treat different oral diseases because of its antimicrobial and anti-inflammatory properties and is not harmful to the surrounding tissue. Hwang et al. pointed out that photodynamic therapy combined with 405 nm light source and chlorella natural powder extracts can effectively reduce the number of viable cells in *S. mutans* biofilm,[76] which can prevent dental caries. However, this approach needs further testing in well-designed clinical trials.

Erythrosine

Erythrosine is a type of xanthene that absorbs light in the visible range, making it useful for photodynamic therapy.[41] Specifically, it absorbs light at wavelengths between 500 nm and 550 nm,[86] which overlaps with the range used by dental curing units, blue, and green light.[87] Erythrosine is shown to be a more effective photosensitizer than MB in terms of the killing of *S. mutans*.[86] Gonçalves et al. found that the pH of erythrosine remained stable and that erythrosine-mediated aPDT resulted in a six-fold reduction in the number of *Candida albicans* (*C. albicans*) 2 min after application.[41]

Urucum

The seeds of a Brazilian plant called Urucum (or Annatto) are natural colorants. Urucum is a non-toxic compound that is not only inexpensive, but also possesses antioxidant and antibacterial activities that relieve inflammation and promote healing in the treated area,[88] which make it safer to use in medical applications. Oliveira et al. conducted a study to explore the characteristics of fruits from B. orellana in different colors like yellow, green, and red and the results were exciting as all the extracts from these fruits showed strong antibacterial effects, particularly against a type of bacteria called Gram-positive *S. aureus*.[89] Furthermore, it has been shown to have many potential advantages as a photosensitizer for dental aPDT.

Light source

The effectiveness of antimicrobial photodynamic therapy is closely linked to the light sources chosen, as the type and intensity of light have a significant impact on the therapeutic outcome. Nowadays, laser systems and LEDs are frequently employed as light sources in dental aPDT for several reasons.[90] Lasers are highly directional, highly monochromatic, highly coherent, and high-intensity, making them suitable light sources. However, high cost and bulky size may limit their use in certain clinical settings. Another commonly used light source is the LED, which has

the advantages of lower cost and ease of use, but lower intensity impacts its effectiveness in aPDT.

Overall, the choice of light source for dental aPDT should be based on the specific clinical indications and the resource availability. It should be noted that different types of photosensitizers have their own wavelength absorption bands. For example, shorter wavelengths ($\lambda < 600$ nm) have less tissue penetration and may and may require higher dosages, which increases chance of skin burns or photosensitivity. Relatively speaking, longer wavelength ($\lambda > 800$ nm) is safer because the transferred energy is lower and can penetrate deeper into the skin depth. Nonetheless, further research is needed to fully understand the optimal light sources and parameters for different applications.

LED

LED light has a broad spectral range and emit incoherent light that is neither directional nor coherent. While similar to lasers, LEDs are less costly and less technically complex. LED light has also been shown to have a longer shelf life, less heat generation, and minimal tissue damage compared to other light sources.[91] On the other hand, portable and easy-to-use LED lights are a common light source in dental clinic to cure dental composites for filling cavities and restoring teeth. It goes without saying that LED technology in dentistry provides more efficient and effective treatment for patients and helps in the early detection and treatment of oral diseases. Today, the characteristics of the above-mentioned LEDs allow them to be used as an alternative light source for aPDT. Studies have indicated that aPDT involving 50 ppm MB and a red LED with a wavelength of 660 nm immediately reduces halitosis from the tongue coating.[45]

Laser

Laser is a monochromatic, coherent and directional light source. This means that it focuses over a narrow range and all photons maintain a constant phase relationship with each other. The laser produces a strong and concentrated beam of energy,[92] making it useful for disinfecting inflamed wounds and even root canals in the oral cavity. However, lasers require expensive special equipment. They can overheat and damage the surrounding tissue if not done properly. Taymouri et al. studied the effect of photodynamic therapy using a diode laser on the gingival crevicular fluid levels, inflammatory mediators, and periodontal clinical status in patients with chronic periodontitis.[93] This laser-based therapy improved clinical symptoms, effectively reducing the levels of inflammatory mediators (IL-1β and IL-17).

Applications in oral infection

Periodontitis

Periodontitis is a chronic inflammation that affects the periodontal tissue, causing the deterioration of the supportive structures. The use of MB in photodynamic therapy has been shown to be effective in reducing inflammation and improving clinical manifestations of periodontitis.[94] Derikvand et al. conducted an investigation evaluating the efficacy of aPDT utilizing a 660 nm diode laser and MB as an adjuvant method to SRP in improving clinical periodontal parameters.[46] This adjuvant therapy may have advantages in reducing probing depth, plaque index, and gingival index in periodontal treatment. Similarly, Martu et al. found that diode laser or MB-mediated aPDT was treatment options for the significant eradication of the periodontal pathogen *A. actinomycetemcomitans*.[95] Nevertheless, further large-scale modality studies comparing aPDT with other therapeutic measures are warranted, not only by assessing clinical parameter but also by specific bacterial species.

Peri-implantitis

Peri-implantitis is a pathological condition that affects the tissues surrounding a dental implant. It is characterized by inflammation of the connective tissue around the implant and progressive loss of supporting bone. Nonsurgical treatments of *peri*-implantitis include mechanical debridement and the use of antiseptics.[96] Complete elimination of bacteria from dental implants is difficult due to the complex anatomy involved; as an alternative option for treating this condition, aPDT may be considered. Nicolae et al. evaluated changes in clinical parameters including probing pocket depth, clinical attachment level, gingival index, gingival bleeding index and plaque index in patients with *peri*-implantitis after treatment with TB-mediated aPDT as an adjunct to the standard SRP.[97] Huang et al. investigated the influence of various MB concentrations of 50, 100, and 200 μg/mL at pH 4, 7, and 10 and irradiation time of 0, 30, and 60 s on bacteria survival and the amount of lipopolysaccharide (LPS) remaining on titanium implants.[37] The results of this study demonstrated that irradiation with 200 μg/mL MB at pH 10 for 60 s is a feasible method to eliminate bacteria and LPS on titanium surfaces.

Tooth decay

Dental caries is prevalent in both deciduous and permanent teeth during childhood. One way to prevent caries in these young teeth is through the use of pit and fissure sealants in dental clinics.[98] However, sealant treatment may not always provide a stable long-term outcome in preventing tooth decay.[99] This is due to a number of factors such as inadequate cleaning of the tooth surface before treatment, the intricate shape of the pit and fissure, wear and tear on the sealant material, marginal fractures and microleakage.[100] Using a combination of various types of PS and white light could be a potential solution in dealing with the microbial mixture caused by tooth decay. Soria-Lozano et al. used an in vitro method to explore the effect of white light combined with MB, RB and CUR on cariogenic microorganisms *S. mutans*, *S. sanguis* and *C. albicans*.[101] It was found that aPDT combined with the three PSs significantly reduced the growth of the three strains by 6 log10.

Halitosis

Halitosis or bad breath is a prevalent issue impacting a significant number of individuals worldwide. In the majority of cases (90%), this condition is primarily attributed to oral factors, whereas systemic factors account for the remaining 10%.[102] The unpleasant odor is primarily generated by volatile sulfur compounds (VSCs) produced by Gram-negative bacteria.[103] Therefore, the amount of VSCs produced by the metabolism of these bacteria is utilized as a measure of bad breath. Commonly used methods for treating halitosis include 0.2% chlorhexidine, essential oils, hydrogen peroxide, tongue scrapers, chewing gum, and breath spray, etc.[104–106] However, the irregular surface of the tongue can make it challenging to thoroughly clean the entire tongue.[107] In a systemic review, Woźniak et al. examined the effectiveness of lasers and aPDT in eliminating intraoral halitosis from 1994 to September 2021.[108] They found that in most studies on aPDT, MB and 660 nm laser were employed. Almost all the studies in the review indicated that aPDT was an effective treatment for bad breath. In summary, photodynamic therapy can be a valuable treatment for halitosis because it reduces the number of volatile sulfur compounds and improves breath odor. Still, additional research is necessary to fully comprehend the underlying causes of these beneficial outcomes and develop more effective treatment protocols.

Root canal

Root canal therapy can be assisted through the use of aPDT due to its ability to target and eliminate harmful microorganisms. Tenore et al. reported that TB when paired with a 635 nm diode laser enhanced the disinfection of *E. faecalis* in conventional endodontic surgery.[109] Another research by Sarda et al. focused on the effectiveness of various germicidal methods, including the use of diode lasers, MB-mediated aPDT and the chemical agent (sodium hypochlorite), as well as combinations of these methods.[110] When the combination therapy was used, the amount of *S. mutans* present was reduced, the combination therapies was more effectively against *S. mutans* than either therapy used alone.

Mucositis

Candidiasis is a fungal infection frequently observed in the oral cavity, particularly in individuals with compromised immune systems. Taking antifungal drug such as Nystatin may develop drug resistance, decreasing the therapeutic effect over time.[111] Tavangar et al. investigated the susceptibility of various *Candida* species to aPDT using ICG as a PS and compared ICG-mediated low-power laser therapy and Nystatin in four different *Candida* species.[49] As expected, the use of ICG in aPDT was highly effective in reducing the number of colony-forming units of all types of *Candida* tested compared to the control.

Discussion

aPDT is a treatment that relies on the interaction of light, a photosensitizer, and oxygen. The main advantages of aPDT over conventional antimicrobial therapies are its immediate onset of action, ability to eliminate resistant microorganisms, minimization of systemic adverse effects, and dual selectivity.[112] However, aPDT is often used as an adjunct to conventional therapy in clinical practice. The Luchian group conducted a randomized clinical trial in patients with conventional fixed prosthetic treatments using adjunctive aPDT and 0.2% chlorhexidine.[113] They reported that aPDT can lead to markedly more important clinical and microbiological outcomes than SRP alone or SRP plus chlorhexidine therapy, especially in the setting of periodontitis with severe tissue loss, without any side effects. Today, more and more studies are evaluating the synergistic effect of combining aPDT with other substances to create new therapeutic options, either as single therapy or for specific therapeutic uses (Table 4).

Although the use of antibiotics is still concerned due to the problem of drug resistance, the synergistic application of antibiotics and aPDT may be a feasible modality that not only reduces the dose of antibiotics but also enhances the elimination efficacy against microorganisms. Thus, Ronqui et al. noted that administering antimicrobial photodynamic therapy as the initial treatment for biofilms, followed by ciprofloxacin treatment, resulted in a significant reduction of 5.4 log in *S. aureus* biofilm and approximately 7 log in *E. coli* biofilm.[112] Di Poto et al. also reported similar findings, suggesting that pretreating *S. aureus* biofilms with aPDT and subsequently applying vancomycin at concentrations below the minimum inhibitory concentration surprisingly resulted in a complete kill of the bacteria.[119] In another study, Astuti et al. showed that 405 nm diode laser combined with 0.1% doxycycline in the Wistar rat model of Porphyromonas gingivalis-induced periodontitis, this treatment modality can produce immunomodulatory effects and promote healing role.[114] Contrary to antibiotics, probiotics, which have advantages such as reducing tissue damage and preventing bacterial resistance, have attracted attention. Probiotics are microorganisms that provide health benefits to the host after ingestion, and they have been utilized in foods, fermented products, and pharmaceutical formulations.[120] More importantly, the positive role of probiotics in managing halitosis indicates that these probiotics help remove undesirable microorganisms and facilitate the recolonization of individual microbiota. Motta et al. randomized 88 patients aged 18–25 years diagnosed with halitosis into four groups and found that aPDT with a probiotic containing *Lactobacillus salivarius* WB21 strain and xylitol was effective in eliminating halitosis.[57] The use of probiotics in oral infections still needs further exploration.

The use of non-antibiotic antibacterial materials is not only the carrier of PS, but also can improve the killing effect by using its own antibacterial ability. Chitosan, a biopolymer sourced from shrimp and crab exoskeletons, possesses several beneficial properties. In the field of dentistry, chitosan exhibited biocompatibility, biodegradability, and

Table 4 Substances used to combine with aPDT.

Substance	Results	Refs
Ciprofloxacin	Synergistic action of aPDT and ciprofloxacin led to a 5.4 log reduction in *S. aureus* biofilm and a 7 log reduction in *E. coli* biofilm.	112
Doxycycline	Combining doxycycline with aPDT not only produced immunomodulatory effects, but also promoted healing in a rat model of periodontitis.	114
Probiotic	Combining probiotics with urucum-mediated aPDT reduces halitosis.	57
Quaternary ammonium chitosan	The combination of QTS and MB improved retention, reduced biofilm accumulation, and enhanced the growth and differentiation of MG63 cells on titanium alloys.	115
Chitosan	The combination of chitosan and aPDT had a greater bactericidal effect on *S. mutans* than either treatment alone.	116
β-cyclodextrin	aPDT using MB encapsulated β-cyclodextrin activated by laser or LED effectively decreased microbial populations in multispecies biofilms composed of early colonizing microorganisms.	117
Potassium Iodide	Potassium iodide significantly enhanced the efficacy of TB-mediated aPDT in eliminating *S. mutans* and *C. albicans* due to the synergistic effect of molecular iodine and H_2O_2.	58
Dual light	Dual light therapy holds promise as a beneficial adjunctive homecare tool against *peri*-implantitis. Moreover, it offers a convenient and safe solution without any associated adverse effects.	118

Abbreviations: aPDT, antimicrobial photodynamic therapy; QTS, quaternary ammonium chitosan; MB, methylene blue; LED, light-emitting diode; TB, toluidine blue.

antimicrobial properties and can be utilized to manage periodontal diseases.[121] Moreover, Chitosan can also promote retention of photosensitizers, making it an attractive alternative to conventional materials. Lin et al. evaluated the efficacy of water-soluble quaternary ammonium chitosan (QTS) in enhancing the retention of MB on sandblasted, large grid, and acid-etched (SLA) titanium alloy surfaces infected with biofilms containing either Gram-negative *A. actinomycetemcomitans* or Gram-positive *S. mutans* bacteria.[115] They found that QTS could retain MB on the alloy surface, improve the photodynamic efficiency of the MB, and reduce the number of bacteria and residual lipopolysaccharide. More importantly, human osteoblast-like MG63 cells grown on the titanium alloy surface after aPDT treatment were equivalent to uncontaminated controls, which elicited that QTS could be a promising carrier of photosensitizers in aPDT.

Beta-cyclodextrin (β-CD) is a cyclic oligosaccharide made up of seven glucose units joined together by α-1,4-glycosidic bonds.[122] It has a hydrophobic cavity in the center that can selectively complex with hydrophobic molecules. β-CD has been explored as a potential carrier of aPDT. For example, de Paula et al. successful reduced microbial populations in multispecies biofilms composed of early colonizing microorganisms using MB photosensitizer coupled with β-CD nanoparticles and 660 nm laser or LED.[117] Notably, although β-CD has demonstrated potential as a carrier for the aPDT modality, additional investigations are necessary to fully elucidate its underlying mechanisms and to enhance the utilization of this method in clinical settings.

In addition to the use of organic antibacterial materials, the incorporation of inorganic materials into aPDT is another trend. Potassium iodide (KI) is a naturally occurring white salt that is now used as an antifungal agent in clinical medicine. Research has observed enhanced microbiocidal ability when the non-toxic KI solution combined with MB and RB photosensitizers were irradiated with light compared to photosensitizers alone.[123,124] Furthermore, KI not only prevented the staining effect caused by high concentrations of photosensitizers, but also exhibited a potentiated antimicrobial effect in dental applications. Li et al. conducted the antimicrobial efficacy, cytotoxicity, and mechanism of TB-mediated aPDT in combination with potassium iodide.[58] Their experiments revealed that KI acted to quench $^1O_2$ signals, resulting in the oxidation of excess iodide ions and the formation of iodine and H_2O_2. These findings concluded that KI had the potential to enhance TB-mediated aPDT and effectively eliminate *S. mutans* and *C. albicans* due to the synergistic effect observed.

As mentioned above, the selection of PS and the type of light source are often emphasized in aPDT research, but the use of combining different light sources is rarely reported. Remarkably, by using two light sources, the risk of complications is reduced as the treatment can be adjusted to meet the individual needs of the patient. Lähteenmäki et al. reported a reduction in visible plaque index and improved oral hygiene in seven patients aged 65—89 years at home using a commercially available Lumoral® device.[118] Moreover, aMMP-9 in peri-implant sulcus fluid, an indicator of activity in periodontal disease, was significantly reduced, further decreasing bleeding on probing. The author emphasizes the positive impact of using dual light as a valuable auxiliary homecare tool; however, further research in this area is still needed. Nikinmaa et al. combined wavelength of 810 nm aPDT and 405 nm aBL (antimicrobial blue light) with an ICG photosensitizer, and this dual light source was more effective in eliminating *S. mutans*.[125] The results of the current study provided an opportunity to formulate new theory and, at a practical level, to create tools for managing biofilms, especially in the field of preventive dentistry.

Conclusion

Photodynamic treatment has become a popular treatment option in medical and dental settings worldwide. Among the currently used periodontal treatment methods, such as mechanical debridement, surgery, antibiotics, antimicrobial photodynamic therapy has the desirable characteristics of painlessness, quick onset, and no bacterial resistance. Nowadays, antimicrobial photodynamic therapy is mainly used as an adjunct to mechanical and chemotherapy treatments. In fact, aPDT may be superior to traditional methods in some cases, and thus is feasible as a monotherapy modality. Although aPDT have been studied very successfully in vitro, translating aPDT from the bench to the bedside remains a challenge. When treating in the deep periodontal pocket, the oxygen level may be much lower than in the coronal part, blocking the progression of phototoxic effects. Perhaps in the future, new way of installing a pipe that transfers oxygen to the treatment area will yield better results. Otherwise, development of oxygen-enriched PS may be an alternative. The development of photosensitizers with antibacterial properties and high biocompatibility cannot be delayed. In vivo studies should be checked before clinical application. Moreover, thanks to developing technologies, patients can even use aPDT at home, making it more efficient and effective. Last but not least, another future trend may be the synergistic combination of chemical or biological molecules with aPDT to achieve the complete eradication of biofilms and even enhance the biological performance of tissues surrounding the treated area in the field of dentistry.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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