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Potential of photodynamic therapy in the management of infectious oral diseases

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Abstract

Photodynamic therapy (PDT) can take place in the presence of three elements: Light with an appropriate wavelength; a photosensitizer; and the presence of oxygen. This type of treatment is very effective overall against bacterial, viral and mycotic cells. In the last 10 years many papers have been published on PDT with different types of photosensitizers (e.g., methylene blue, toluidine blue, indocyanine green, curcumin-based photosensitizers), different wavelengths (e.g., 460 nm, 630 nm, 660 nm, 810 nm) and various parameters (e.g., power of the light, time of illumination, number of sessions). In the scientific literature all types of PDT seem very effective, even if it is difficult to find a standard protocol for each oral pathology. PDT could be an interesting way to treat some dangerous oral infections refractory to common pharmacological therapies, such as candidiasis from multidrug-resistant *Candida spp.*

Key Words: Photodynamic therapy; oral infections; Photodynamic therapy vs candidiasis; Blue light; 460 nm; *Streptococcus mutans*

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Core Tip: In recent years there are more and more multidrug resistant infections at the oral level, and this has led researchers to find alternative solutions to conventional pharmacology that have no impact on systemic health. Among these, there is photodynamic therapy, which has demonstrated efficacy both *in vitro* and *in vivo*, for treating bacterial, viral (reducing recrudescence) and fungal infections, particularly multidrug-resistant *Candida spp.*

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INTRODUCTION

There are over 780 results in PubMed when searching the keyword “Photodynamic Therapy for Oral Infection,” with an exponential growth of the works published in the last 10 years. All this denotes the strong scientific interest of this instrument in the field of infectious pathologies of the oral cavity.

Photodynamic therapy (PDT) can take place in the presence of three elements: Light with an appropriate wavelength; a photosensitizer; and the presence of oxygen. When a photosensitizer is activated by light, it will either lose energy or form an oxygen triplet[1]. This second type of PDT is linked to the amount of oxygen, while the first type of PDT can work in anaerobic conditions[2]. The interaction that the photosensitizer has with oxygen can determine the formation of hydrogen peroxide, hydroxyl radicals, superoxide radical oxygen, and singlet oxygen. These products determine the killing of microorganisms due to damage to the cell membrane and their metabolic activity[1].

The maximum absorption of light by the photosensitizer occurs at a wavelength between 600 nm and 800 nm. In fact, a higher wavelength would not have enough energy to stimulate oxygen to produce radicals[1]. The penetration of the wavelength comprised between 700-1100 nm is wider than that comprised between 400-700 nm[2].

Among the infections that afflict the oral cavity, endodontic infections are caused by microorganisms that colonize the inside of the tooth and can give rise to infections in the periapical bone tissue. One of the most important microorganisms in this infectious process is *Enterococcus faecalis* (*E. faecalis*), which is also the most studied *in vitro* and *ex vivo* model. The difficulty of eradicating this microorganism responsible for endodontic re-infections and refractory infections has prompted researchers to make use of PDT in eradicating this microorganism. Researchers have found that the photosensitizer curcumin activated by LED (450 nm, 67 mW/cm², and 20.1 J/cm²) has shown very interesting results in reducing the colony forming units of *E. faecalis*[1]. Other authors have tested Ce6 methyl ester (Zn(II)e6Me), a chlorophyll-derived photosensitizer activated by red light (627 nm, 75 mW, 3150 J/cm²) for 90 s, with success against *E. faecalis*. Furthermore, an *in vitro* study found that a PDT using 500 g/mL of *Chlorella* plus 660 nm diode laser at an energy density of 23.43 J/cm² was effective against *E. faecalis* biofilms[1].

The most frequent infectious disease at the gingival level is periodontitis. It is an infectious process mediated by various microorganisms, including *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* that leads to inflammation and destruction of bone and gingival tissue with loss of stability of the dental elements. *Curcuma longa* activated by blue LED lights (450-470 nm, output power density 1.2 W/cm²) and Ce6 have shown the most effectiveness among the natural photosensitizers[1]. PDT carried out with *Curcuma longa* and diode light at 460 nm has also shown efficacy in drug-induced gingival hypertrophy[3].

Rose bengal with a light source for illumination (375 nm, 3 mW/cm²) could be very useful for reducing the bacterial load of *Streptococcus mutans*, the most important etiological agent of dental cavities. Ozonated water used as a photosensitizer and activated by 460 nm LED lights has also demonstrated efficacy against *Streptococcus mutans*[4].

The most frequent oral viral infectious diseases are associated with herpes simplex type 1. Clinically, this is a condition that involves the formation of vesicles filled with infectious liquid that when they explode give rise to erosion and the formation of crusts if they affect the vermilion border of the lips. In this context, the gold standard treatment is represented by topical or systemic antivirals, particularly in extensive systemic cases. However, the reduction of effectiveness of traditional pharmacological treatments has prompted several researchers to find different solutions to mitigate these infections, including PDT[5]. For example, the most common photosensitizer for the treatment of *Herpes simplex* infection is methylene blue at concentrations between 0.1% and 1%, activated by lights with a wavelength of 660 nm. In another *in vitro* study, indocyanine green also showed good results when activated by wavelengths of 810 nm[6,7].

Human papillomavirus (HPV) plays a prominent role in causing viral infections in the mouth. According to the World Health Organization reports, it is estimated that in developed countries a growing prevalence of HPV-related cancer is reported each year, particularly for males. There are over 200 subtypes of HPV, but some of these can trigger malignant tissue transformations, including HPV 16. Surgical excision and histological evaluation represent the treatment of choice. Sometimes these lesions can reach considerable dimensions, are located in sites that are difficult to reach and can be recurring. These reasons have led clinicians to try PDT on the oral cavity in a patient with a large squamous papilloma in the soft palate. In this case, a formulation containing 5-aminolevulinic acid is injected at the perilesional level and activated with wavelengths of 630 nm at a power of 100 J/cm² and at 300 mW/cm² of power density for 6 min. After two sessions, the lesion healed[8].

PDT has also been proposed in the treatment of oral lesions from coronavirus disease 2019. In fact, *in vitro* studies have shown that methylene blue was able to inhibit the severe acute respiratory syndrome coronavirus 2 spike protein and its angiotensin converting enzyme-2 receptor. It was also used to treat the typical crusted lip lesions associated with coronavirus disease 19 at very low concentrations[9].

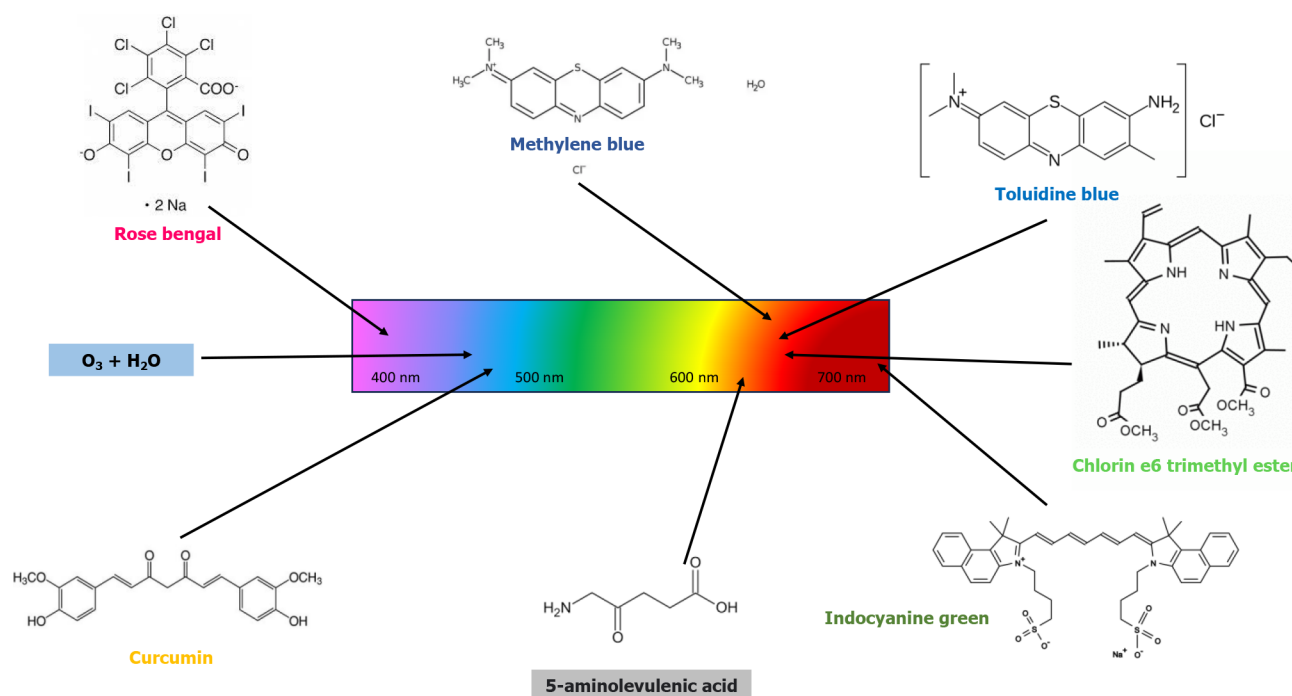


Figure 1 Schematic representation of the main photosensitizers used in oral medicine with the respective wavelength of excitation pointed in the visible light spectrum.

PDT FOR ORAL CANDIDIASIS

Oral candidiasis, as previously mentioned, is an infection that increasingly shows resistance to the main commercial antifungals, such as azoles. PDT was proposed 15 years ago as an alternative, especially in relapsing cases of oral candidiasis. Among the most tested photosensitizers, methylene blue, which is associated with laser and non-red laser lights, has demonstrated excellent antifungal properties at different concentrations[10-13]. Toluidine blue has also been widely proposed in different concentrations for the treatment of *Candida* infections in the oral cavity. A recent review on the subject has highlighted that most of these are *in vitro* studies, where the parameters used are very different between the various studies, even if almost all report the efficacy of PDT. In addition to the more common *Candida albicans*, it has also been tested against different species of *Candida* in some studies, such as *Candida glabrata*, *Candida krusei*, *Candida parapsilosis* and *Candida tropicalis*. Toluidine blue has been shown to be effective against all types of *Candida spp.* mentioned [14]. Most of the *in vitro* studies evaluated both the activity of PDT in its planktonic form and in the biofilm of the fungus. The prevailing method was that of microplates[14].

A recent compound, indocyanine green, activated by a light with a wavelength of 808 nm has also been proposed as a photosensitizer. In fact, by comparing this approach with a traditional treatment based on nystatin, a significant infection reduction was observed, which was similar to the healthy group control patient[15]. The same result was reported in another study on refractory subprosthetic candidiasis in which PDT showed better results than the group treated only pharmacologically[16]. Furthermore, in another study, PDT with indocyanine green was shown to be more effective *in vitro* than PDT performed with methylene blue[17].

Other photosensitizers tested *in vitro* against *Candida* were erythrosine and rose bengal, activated by green diode lights around 532 nm[18,19]. Erythrosine was also effective against *Candida dubliniensis*, demonstrating good efficacy in the planktonic form but less activity on the biofilm[20]. Among the natural photosensitizers reported are 5-aminolevulinic acid[21] and derivatives from *Curcuma longa*, which was first carried out in 2013[22]. In a study using LED light at 460 nm, 5-aminolevulinic acid showed *in vitro* antifungal activity higher than that of methylene blue, which was activated by red light at 660 nm[23]. A photosensitizer based on *Curcuma longa*/3% hydrogen peroxide, activated by polarized light (wavelength from 380 to 3400 nm), showed greater antifungal activity than activation with LED light at 460 nm (the wavelength most widely used in PDT to activate curcumin)[24]. Furthermore, PDT has also shown efficacy in other oral pathologies, perhaps by virtue of its antimicrobial action against microorganisms that colonize the damaged mucosal surfaces[25] or which may be at the basis of the pathogenic process[26]. The main photosensitizers used in PDT vs oral infections, with relative wavelength of activation, are summarized in Figure 1.

CONCLUSION

The increasing resistance to antibiotics, antifungals and antivirals, the side effects of the drugs themselves on some categories of patients and the possibility of resolving some infections in a single session have led researchers to propose

the use of PDT as a treatment tool for refractory infections of the oral cavity. The wide variability of the parameters used, including the wavelength, the type of photosensitizer, the pre-illumination and irradiation times, makes it difficult to have standard protocols for the treatment of each oral pathology. Further studies will be needed to find the most suitable protocols for each type of oral infection.

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FOOTNOTES

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