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Potential of photodynamic therapy in the management of infectious oral disease

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Abstract
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INTRODUCTION

By typing the keyword "Photodynamic Therapy for Oral Infection" on the PubMed search engine, there are over 780 results, 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 can take place in the presence of three elements: light with an appropriate wavelength, a photosensitizer, the presence of oxygen. When a photosensitizer is activated by light, it can undergo two phenomena: losing energy or forming an oxygen triplet [1]. This second type of Photodynamic therapy is linked to the amount of oxygen, while the first type PDT can work in an anaerobic condition [2]. The interaction that the photosensitizer has with oxygen can determine the formation of hydrogen peroxide (H_2O_2); hydroxyl radicals ($^{\cdot}OH$); superoxide radical oxygen (O_2); singlet oxygen ($^1O2$). All 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 and 800 nm, in fact a higher wavelength would not have enough energy to stimulate oxygen to produce radical
[1]. The penetration of the wavelength comprised between 700-1100 nm is wider than that comprised between 400 and700 nm [2].

Among the infections that afflict the oral cavity, we have endodontic infections, supported by microorganisms that colonize the inside of the tooth and which can also give rise to infections in the periapical bone tissue. One of the most important microorganisms in this infectious process is Enterococcus faecalis, which is also the most studied *in vitro* and *ex vivo* model. The difficulty to eradicate 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/cm^2, and 20.1 J/cm^2), has shown very interesting results in reducing the CFU 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/cm^2) 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/cm^2 is 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 *P. gingivalis*, A. *actinomycetemcomitans* and which leads to inflammation and destruction of bone and gingival tissue, with loss of stability of the dental elements. Among the natural photosensitizers that have shown the most effectiveness, we have *Curcuma Longa* activated by blue LED lights (450–470 nm, output power density 1.2 W/cm^2) and Ce6[1]. Photodynamic therapy 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/cm

[2]) could be very useful to reduce the bacterial load of *S. 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 *S. mutans* [4].

Among the most frequent oral viral infectious diseases is associated to 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 in particularly extensive systemic cases. However, inside viral infections, the reduction of effectiveness to traditional pharmacological treatments has prompted several researchers to find different solutions to mitigate these infections, including PDT [5]; For example, the most commonly used photosensitizer for the treatment of *Herpes simplex* infection is Methylene Blue, at concentrations ranging 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) [6,7].By considering the viral infections in the mouth, a prominent role is due to human papillomavirus (HPV). Following the World Health Organization reports, it is estimated that in developed countries, a growing prevalence HPV-related cancer is reported each year, in particular for the masculine gender. By considering the viral infections in the mouth a prominent role is due to *Human papillomavirus* (HPV), following the World health organization reports, it is estimated, in developed countries, that a considering HPV-related cancer are reported each year in which in masculine gender, WHO-HPV report.

There are over 200 subtypes of HPV, but some of these are capable of triggering malignant tissue transformations, including HPV 16. Surgical excision and histological evaluation of the removed piece represent the treatment of choice. Sometimes these lesions can reach considerable dimensions, of several centimeters; sometimes they are placed in sites that are difficult to reach and can be strongly recurring. These reasons have led some clinicians to try photodynamic therapy also on the oral cavity in a patient with a large squamous papilloma in the soft palate. In this case, a formulation

containing 5-aminolevulenic acid is used with photosensitizer; it is injected at the perilesional level and activated with wavelengths of 630 nm at a power of 100 J/cm^2 and at 300 mW/cm^2 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 COVID 19. In fact, *in vitro* studies have shown that Methylene Blue was able to inhibit the SARS-CoV-2 spike protein and its ACE2 receptor, and it was also used to treat the typical crusted lip lesions associated with COVID-19 at very low concentrations [9].

Photodynamic Therapy for Oral Candidosis

Oral candidiasis, as previously mentioned, is an infection that increasingly shows resistance to the main commercial antifungals, such as azoles. Photodynamic therapy 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 photodynamic therapy. In addition to the more common *C. albicans*, it has also been tested against different species of Candida in some studies, such as *C. glabrata, C. krusei, C. parapsilosis, and C. tropicalis*. Toluidine blue has been shown to be effective against all types of *Candida spp.* mentioned [14]. Most of the *in vitro* studies were studies in which both the activity of PDT in its planktonic form and in the biofilm of the fungus were evaluated. 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 is the same as in the healthy group control patient [15]. The same result was reported in another study on refractory subprosthetic

candidiasis. In this case, PDT showed better results than the group treated only pharmacologically [16]. Furthermore, in another study, it was observed that it proved to be more effective *in vitro* than PDT performed with Methylene Blue [17].Other photosensitizers tested *in vitro* against Candida are erythrosine and Rose Bengal, activated by green diode lights around 532 nm [18,19]. Erythrosine was also effective against *C. dubliniensis*, demonstrating good efficacy in the planktonic form but less activity on the biofilm [20]. Among the natural photosensitizers reported are 5-aminolevulenic acid (5aa) [21] and derivatives from Curcuma longa. The first work carried out using this photosensitizer dates back to 2013 [22]. In a study using LED light at 460 nm, 5aa 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% H2O2, activated by polarized light (wavelength from 380 to 3400 nm), showed greater antifungal activity than activation with LED light at 460 nm, the wavelength so far most widely used in photodynamic therapy 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].

CONCLUSION

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

Link footnotes

WHO-HPV report: https://www.who.int/news-room/fact-sheets/detail/human-papilloma-virus-and-cancer.

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