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RESEARCH ARTICLE

PHOTOTHERAPY IN HEALTH AND DENTISTRY: A LITERATURE REVIEW

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ABSTRACT

Introduction: Photodynamic Therapy (PDT) associated with a photosensitizer (PS) nontoxic and sensitive to light, has been showing efficient results in several areas of health, owing to the selective destruction of cells. **Objective:** This study was literature review was to select articles that prove the method using Photodynamic Therapy (PDT) of improving health conditions and can be applied in the most diverse areas of health. **Results:** In this literature search, it was observed that a PDT when applied to health is very effective, as it fights cancer and microbial contamination. When applied in dentistry, especially in procedures in the areas of endodontics and periodontics, a great effect is perceived as an adjunct treatment and contributes to the reduction of infections caused by resistant bacteria. In addition, it has been shown that photodynamic inactivation (PDI) is not damaged as adjacent tissue cells. **Conclusion:** It can be seen through this literature review that a PDT is an excellent microbicide, beyond to working very well in the selective destruction of cells. However, this is an adjunctive treatment that always ceases to be combined with other procedures for greater effectiveness.

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INTRODUCTION

Photodynamic therapeutic technique (PDT) is a resource widely used in several areas of health, because it is simple and easy to be applied and it is a process that involves a chemical reaction activated by light, causes selective destruction of cells(Issa and Manela-Azulay, 2010). Tennert *et al* (Tennert *et al.*, 2014) claim that the results come from the activation of a photosensitizing agent by the action of light, and all its action occurs only to the target cell. With that, we can say that PDT results in a sequence of photochemical and photobiological processes, and can bring benefits to several areas of health. In the presence of oxygen found in the cells, the activated photosensitizer (PS) can regulate with molecules in its vicinity by transferring electrons or hydrogen, leading to the production of free radicals (type I reaction) or by transferring energy to oxygen (type II reaction) leading to singlet oxygen production (Perussi, 2007). Type I reactions: formation of free radicals (• OH) through electron transfer between the PS in the excited triplet state and system components, generating superoxide anion-radical (• O2–).

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$$O_2 \rightarrow \bullet O_2^-$$
$$\bullet O_2^{-} + {}^*O_2 \rightarrow H_2O_2 + O_2$$
$$\bullet O_2^- + H_2O \rightarrow O_2 + OH^- + \bullet OH$$

Type II reactions: energy transfer 5 from the PS in the triplet state ($^3S1^*$) with singlet oxygen formation ($^1O2$).

$$^1S0 \longrightarrow {}^1S1^* \longrightarrow {}^3S1^*$$
$$^3S1^* + {}^3O2 \longrightarrow {}^1S0 + {}^1O2$$

Initially, PDT technique was tested using the LASER system, which provided excellent results; however, the high cost of maintenance and the difficulty in transport forced researchers to seek other ways to obtain the expected result (Silvia Nunez, Aguinaldo Silva Garcez, 2015). Therefore, the development of research and the advancement of technology allowed new tests with lamps with built-in filter system where the selection of light occurs in a small range of 10nm known as light-emitting diodes (LED) (Issa and Manela-Azulay, 2010). Different PS have been studied, such as halogenated xanthenes (Bengal Rose - BR), phenothiazines (Toluidine Blue - TBO and Methylene Blue - MB), acridines and chlorine conjugates (e6) (Vatansever *et al.*, 2013). All of these reagents can be applied in the healthcare field. The dyes called phenothiazines have an extensive absorption from 600 to 660nm and, consequently, an efficient therapeutic window for light penetration in the tissues (Kurwa and Barlow, 1999).

Lim *et al.* (Lim *et al.*, 2013) described that MB was effective for use in PDT, as it generates singlet oxygen and improves its phototoxic capacity. Studies suggest that the use of MB has positive effects in the treatment against cancer cells (Silvia Nunez, Aguinaldo Silva Garcez, 2015), however, there is a need for a threshold dose for the preservation of adjacent tissue cells to occur (K Orth 1, A Rück, G Beck, A Stanescu, 1995). PDT can be applied in several clinical practices: combating neoplastic diseases (Heukers *et al.*, 2019); dermatological treatments (acne) (Moy, Frost and Moy, 2020); Respiratory tract infections (Dias, Blanco and Vanderlei S. Bagnato 1, 2020); dental treatment (Oliveira *et al.*, 2015); microbiological control and surface disinfection (Silva *et al.*, 2019). In dentistry, low power lasers are tested due to their bactericidal, analgesic and hemostatic effect (Vasconcelos Catão *et al.*, 2014). Currently, there are optical fiber systems designed exclusively for the application of PDT in root canals and periodontal pockets, in addition to appropriate photosensitizers and indicated for this purpose (EDUARDO, 2015). In addition, in periodontal treatments, there is a wide range of studies in photodynamic therapy, because in addition to obtaining good results, the technique demonstrates minimal side effects (Vasconcelos Catão *et al.*, 2014).

The main advantage of using PDT in health is its simplicity in handling. With this, it can be applied in several clinical environments, hospital, private offices to promote health and act as an adjunct in countless health treatments and microbial control of cross infections. Therefore, the PDT can open a promising field for clinical implementation in precision medicine. In the literature, numerous studies are presented with several positive results for health.

PDT and its relationship with cancer: The main data from selected literature works Shows that phototherapy (PT) when applied to health is saved in an alternative treatment for some types of cancer (Wilson and Patterson, 2008; Maria and Ramalho, 2011; Rahnama *et al.*, 2015; Heukers *et al.*, 2019). Conventional treatments, such as chemotherapy and radiotherapy, are aggressive and cause numerous adverse effects, such as oral changes and swallowing dysfunction, triggering various types of structural and physiological changes (Santos *et al.*, 2019). Thus, PDT could be an alternative, since, after the photosensitizing agent is applied, the drug is absorbed by the cancer cells and only the region to be treated is irradiated, as stated by Gananathan *et al.* (Gananathan, Chakraborty and Karunasagar, 2020). Still according to the same authors, the PS can be coupled with specific biomarkers for individual cancer patients, which in turn can lead to efficient precision drugs. The treatment saves the risk of radiation or the emergence of resistance.

Ribeiro (Ribeiro, 2016) demonstrated through the analysis of 20 cancer patients submitted to head and neck X-rays to complementary treatment with low-level laser therapy (LLT) and photodynamic therapy (PDT). Concomitantly, the presence and control of infection and the clinical control of osteoradionecrosis (ORN) were evaluated. And the results obtained were excellent with the use of PDT (Figure 1a), because showing a degree of clinical improvement in 100% of the sample. Thus, the author affirms that LT and PDT, associated with conventional treatments can present good results, and should be recommended for use as an adjunctive treatment in the clinical control of ORN. Santos *et al*. (Santos *et al.*, 2017) applied the PDT methodology using methylene blue (MB-PDT) in the treatment of breast cancer, in conjunction with chemotherapy and surgery to cure cancer. Their results were positive, which allowed the authors to state that PDT is an excellent adjunctive therapy for surgery of breast tumors and, possibly, other types of tumors. The mechanism of PDT associated with MB, also provided an alternative in treatments against cancer cells through application in *Hela cells*, derived from cells obtained from a patient's cervical cancer, demonstrating that this type of dye has immense potential to be used in therapy in alternative treatments against cancer cells besides proving a greater efficiency in the absorption of photosensitizer by the analyzed cells (Lv *et al.*, 2017)

PDT in healing and dermatology: PDT is also being studied for dermatological and healing treatments, as shown (Vasconcelos Catão *et al.*, 2014), these authors evaluated the effects of red laser, infrared, photodynamic therapy, and green light-emitting diode (LED) on the healing process of skin burns through clinical and histopathologic analysis in rats. As a result, they determined that all treatments involving light favored the healing process of third-degree burns in rats. Associated with hyaluronic acid, it can be used in cases of facial rejuvenation. Huang *et al*. (Huang *et al.*, 2020) showed a series of cases was evaluated, in which the safety and efficacy of a 5-aminolevulinic acid gel ALA with hyaluronic acid (ALA-HA) and diode-emitting light (LED-RL) for facial rejuvenation. Figure 1b shows results with incredible improvements in fine lines and depigmentation.

In the healing process, photodynamic therapy can also promote positive effects on tissue regeneration of wounds, as shown by studies by Oyama *et al.* (Oyama *et al.*, 2020). According to the authors, the PDT acts in the wound regeneration process, in the microbiological control and stimulating the proliferation of fibroblasts, which, in turn, produces collagen and elastin. Another action of therapy using light and a photosensitizer is to decrease the bacterial load (Silva *et al.*, 2019). Brown (Brown, 2012) demonstrated *in vivo* use of PDT in vacations, the study conducted a clinical trial of patients with leg ulcers, and after the application of photodynamic therapy, bacterial counts were significantly lower compared to before therapy ($p<0.001$) (Brown, 2012). In addition, the study showed promising results obtained in a patient after 2 months (Figure 2a), which showed improvement in healing and there were no serious adverse events related to treatment or pain.

PDT and the fight against parasites: The internalization of methylene blue and the application of the PDT acted on the viability and morphology of *Leishmania major* and the promastigote of *Leishmania braziliensis* in culture medium, as demonstrated by Pinto *et al.* (Pinto *et al.*, 2017). The treatment decreased viability by more than 70% in the tested parasitic concentrations, in addition to triggering significant morphological changes in promastigotes (Pinto *et al.*, 2017). This allows us to state that methylene blue associated with red led light has potential as clinical applications in parasite treatments. In the study by Fonseca *et al.* (Fonseca *et al.*, 2019), the effectiveness of PDT in vivo and its high trichomonic activity was assessed using transmission electron microscopy (Figure 2b). Thus, it is possible to observe the advanced effects of PDT, such as intense cell damage, with structural disorganization and intense vacuolization, discontinuity of the membrane, extensive cytoplasmic extraction and large sets of debris (Fonseca *et al.*, 2019). As a result, the authors stated that photodynamic therapy, associated with low cost and ease of application, signals its great therapeutic potential not only when conventional treatment fails, but also routinely in women with trichomoniasis.

PDT in dentistry: PDT in association with the correct PS is applied in dentistry and shows positive effects as an adjunct to traditional procedures. As in the case of combating caries (Plotino, Grande and Mercade, 2019), periodontal treatments (Wilson and Patterson, 2008) and combating infections and inflammations of the oral mucosa (Wainwright, 2003). In the search for techniques to remove decayed tissue with biosafety and more comfort to the patient, photodynamic therapy acting as an antimicrobial (aPDT) has been proposed as an adjunctive treatment of dental caries (Mota *et al.*, 2016; Méndez *et al.*, 2018). aPDT could eradicate a wide spectrum of microorganisms without inducing resistance to the drug, in addition to allowing repeatability, low toxicity and because it is a minimally invasive treatment.

PDT associated with antimicrobial therapies can and should be applied in a very practical way in dentistry (Foggiato and Silva, 2019). As discussed by professionals and researchers a lot, caries is the most common chronic disease in childhood and leads to tooth loss throughout life, being caused by bacterial colonization of the enamel surface, mainly by *Streptococcus mutans* (Lima *et al.*, 2018). Leal *et al.*(Leal *et al.*, 2017) investigated the action of PDT in the control of *Streptococcus mutans in vitro*. According to the authors, significant bacterial inactivation was demonstrated after 1 and 2 min of irradiation in bacterial suspension, which shows the efficiency of PDT in combating this microorganism. In combating specific deteriorated dentin bacteria, aPDT also has a significant effect. The author Azevedo (Azevedo, 2010) obtained positive results in microbial control, indicating that there was a decrease in the bacterial potential of the cultivated samples, in both concentrations. Clinical studies conducted by Mota *et al*. (Mota *et al.*, 2016) presented that the use of PDT in a 6-year-old patient with a deep caries lesion was, after three months, demonstrated through the final radiograph that the lesions did not progress and detected a furcation region that remained intact (Figure 3).

The advantages of PDT in the carious process include the elimination of bacteria in a very short time without causing any damage to the surrounding tissues. And, with that, it allows access to areas with complex anatomy and low risk of bacteremia in immunocompromised patients and high reproducibility (Bargrizan *et al.*, 2019). Rosa *et al.* (Rosa *et al.*, 2017) analyzed the effect of laser or LED phototherapy on the acceleration of bone formation in the median palatal suture after rapid maxillary expansion in guinea pigs by Raman spectroscopy. In their studies they were conclusive that LED irradiation associated with rapid maxillary expansion has improved bone repair. PDT used as low level laser therapy (LLL) has several applications in the dental field. For example, its application in the treatment of temporomandibular jaw dysfunction (TMD) (Cavalcanti *et al.*, 2016). The authors compared the physical therapy and medication protocol (PDT) with LLL therapy in the treatment of pain associated with TMD in 60 patients divided into 3 groups with three types of treatment (laser, anti-inflammatory drugs, muscle relaxants; hot bags; placebo). The results showed that LLL and PDP are effective ways to control pain associated with TMD. PDT has been promising for conventional endodontic treatment, as it is capable of eradicating microorganisms present in endodontic infections (Oliveira *et al.*, 2018). Figure 4 shows a radiograph, in which the patient with asymptomatic apical periodontitis underwent surgical endodontic treatment associated with PDT. After six months, the patient was asymptomatic and the radiographic examination showed healthy periradicular tissues. Recently, PDT has been suggested as a promising effective complement to standard antimicrobial cleaning and intracanal modeling for the treatment of periapical lesions (Plotino, Grande and Mercade, 2019).

In association with periodontitis, studies of Akram *et al.* (Akram *et al.*, 2016) evaluated the bactericidal efficacy of dynamic photodynamic antimicrobial therapy (aPDT) against periodontal pathogens. In their results, the authors observed that the application of aPDT was effective in reducing the count of periodontal microbes. Results equivalent to the work of Palareti *et al.* (Palareti *et al.*, 2016), conducted controlled and randomized clinical trials of the effects of antimicrobial photodynamic therapy (aPDT) on surgical periodontal treatment (ST); as a result, a significantly greater decrease in the depth of the deep periodontal pockets was obtained. In addition, the treatment reduced periodontal pathogens of the red complex, which includes *Porphyromonas gingivalis*, *Treponema denticola* and *Tannerella forsythia* (formerly Bacteroides forsythus), are recognized as the most important pathogens in adult periodontal disease (Suzuki, Yoneda and Hirofuji, 2013). This study with aPDT brought significant results to the periodontal clinical parameters.

Oral cancer, another point of action of dental surgeons, photodynamic therapy has been extensively studied in the treatment of carcinomas (Jin *et al.*, 2019; Olek *et al.*, 2019; Wang *et al.*, 2020). Oral pre-malignant lesions are conditions with a high potential for malignancy, these cells can be treated with photodynamic therapy (PDT) as a non-invasive method for oral pre-cancerous lesions (Maloth *et al.*, 2016). Figure 5 demonstrates a study carried out to evaluate the effectiveness of photodynamic therapy, having two groups: control, which was treated with conventional therapy; and treaty, which passed through the PDT. The result obtained was a reduction of at least 20% in the size of the lesion (Maloth *et al.*, 2016); according to the authors, with minimal side effects.

New PDT applications: Currently, several studies are being done to develop products that apply PDT in health. Silva *et al.* (Silva *et al.*, 2019) develop and test a Photodynamic inactivity device from a box containing light emitting diode (LED) (Figure 6). PDT has an effective antimicrobial action, there are studies for its use in sterilization processes, and it is currently also applied in the decontamination of diverse surfaces, as demonstrated by studies of Foggiato *et al.* (Foggiato, Silva and Castro, 2018) and Silva *et al.* (Silva *et al.*, 2019). Studies show the potential of photodynamic therapy in successful decontamination, because the Photodynamic Inactivity Device was used to disinfect contaminated acrylic plates and titanium disc plates; Silva *et al.* promoted a significant reduction (in the number of microorganisms when compared to positive control ($p<0.001$).

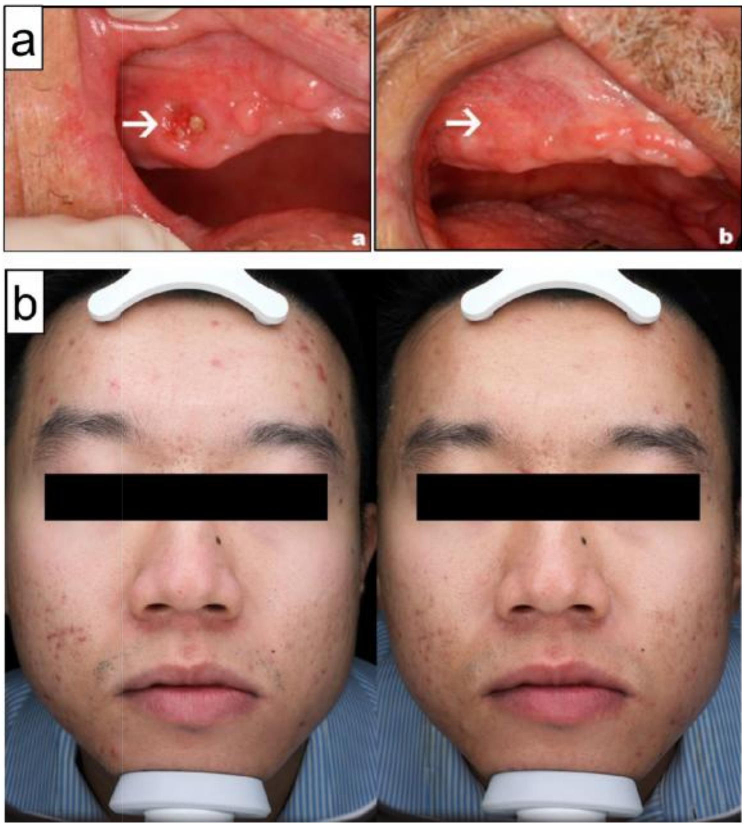

Figure 1: a) Clinical case showing ORN control with LT in a patient in the sample: (A) The patient has stage II osteoradionecrosis; (B) Control of the disease is demonstrated by repairing the bucal lining mucosa after 10 months of treatment (Ribeiro, 2016); b) (A) Standard photograph of a patient before photodynamic therapy; (B) With improvement in 4 weeks after the last treatment (Huang *et al.*, 2020)

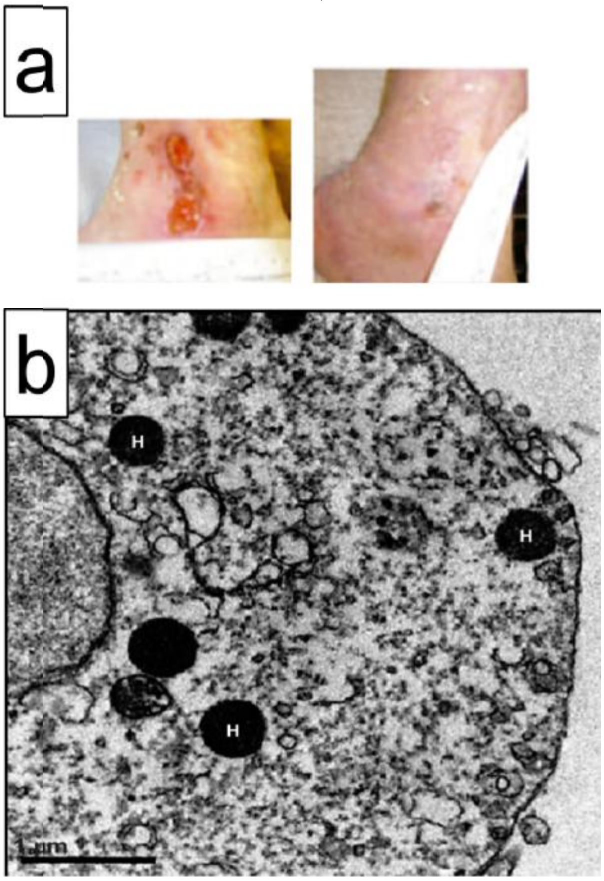

Figure 2: a) Wound healing with photodynamic therapy (PDT). In left, Pre-treatment view 2 months before PDT with PPA904. In right, Posttreatment view 2 months after PDT with PPA904 (Brown, 2012); b) The effects of PDT culminated in structural disorganization and a marked reduction in cytoplasmic electron density (Fonseca *et al.*, 2019).

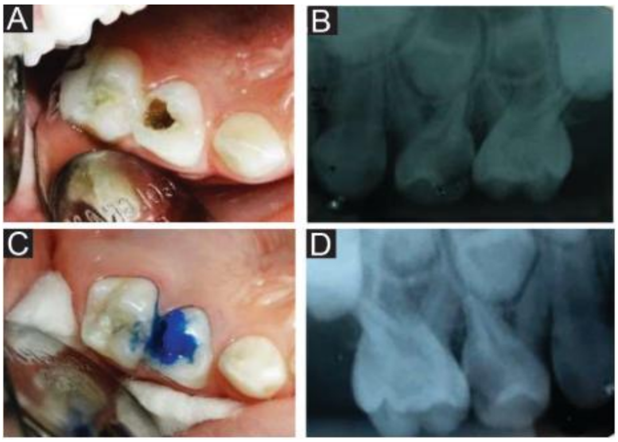

Figure 3: Case report of photodynamic therapy in the treatment of dental caries on primary teeth: A) Initial Photo of Carious Lesion. B) Initial X-Ray. C) Application of Papacárie MBlue. D) Control of the Case After 3 Months (Mota *et al.*, 2016).

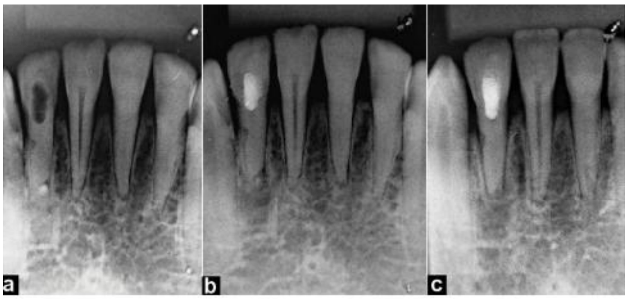

Figure 4: Follow-up Radiographic Images (a) Immediately After Surgery, (b) After 2 Months, (c) After 6 Months.

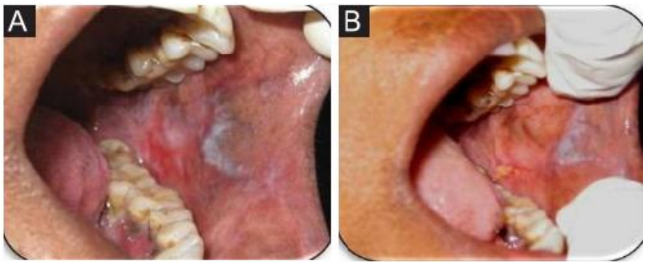

Figure 5: (A) Oral Lichen Planus (OLP) Lesion Before Therapy; (B) OLP Lesion After Therapy (Maloth *et al.*, 2016)

Figure 6: Photodynamic inactivation on the surface of the plates using ultrasonic Photodynamic Inactivation Device (Silva *et al.*, 2019).

Foggiato *et al.* (Foggiato, Silva and Castro, 2018) proposed the disinfection of orthodontic metallic instruments, resulting in a significant reduction of the microbial load trapped in orthodontic instruments ($p<0.05$). In addition, Inomata *et al.* (Inomata *et al.*, 2019) tested the use of PDT in materials based on polypropylene, aluminum and AISI SAE 304 Stainless Steel, which is often used in hospitals, resulting in significant microbial control ($p<0.05$) in the disinfection of these materials. Additionally, it is noted that PDT is a promising alternative technique for decontamination of materials that promote microbial control (Alves *et al.*, 2019), decontamination of instruments and surfaces (Foggiato, Silva and Castro, 2018; Silva *et al.*, 2019) and consequently, acting in the prevention of cross infections against microorganisms, such as viruses. Such facts recommend the use of PDT in possible clinical techniques such as supporting treatment, and in the disinfection of objects, which can be applied to control and combat the new coronavirus (Sars-Cov2), which currently caused a pandemic, killing thousands of people around the world (Yang *et al.*, 2020). At the moment, until vaccines are effective, therapeutic strategies to deal with the infection are only promising and the total elimination of outbreaks of infection, such as on surfaces, with the aim of reducing transmission in the community, has been the best option.

Conclusion

In view of the discussion presented in this paper, it was possible to observe a great effectiveness of the PDT in several areas of health, such as cancer treatment, antiparasitic, antimicrobial, against dental diseases. In addition, photodynamic therapy can generate relevant results in the healing and sterilization processes of the surface. These facts may open space for new research to develop different techniques and future clinical applications, such as the disinfection of contaminated objects. As the pandemic caused by Covid-19, PDT could be used as an adjuvant and additional benefits. Based on the context presented, understanding the functioning of photodynamic therapy allows a greater application of the technique associated with different areas of health, the development of new therapeutic targets and future studies.

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