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## Antimicrobial photodynamic therapy: Periodontal point of view

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### Abstract:

The dental plaque-induced periodontal disease presents the characteristic signs of inflammation and loss of supporting periodontal tissue. Biofilm removal, antibiotics along disinfectants are considered conventional methods of periodontal therapy. However, it has some limitations. Antimicrobial photodynamic therapy (PDT) seems to be a unique and interesting therapeutic approach toward periodontal therapy. There is a great need to develop an evidence-based approach to the use of PDT for the treatment of periodontitis and periimplantitis. However, the low wavelength lasers exhibiting deep tissue penetration basically do not interact with the periodontal tissues within the pocket. Therefore, PDT as a low-level therapy with short irradiation time does not produce any thermal change within the gingival tissue and root surface or destruction of the intact attachment apparatus at the base of pockets. PDT may be an effective way to treat the bacteria linked to periodontal diseases and could provide a better option than antibiotics or other mechanical methods for treating periodontal diseases and may prove to be a promising alternative to conventional periodontal therapy in near future.

**Keywords:** Antimicrobial photodynamic therapy, inflammation, periodontal therapy, periodontitis.

**Manuscript:**

**Introduction:**

The dental plaque-induced periodontal disease presents the characteristic signs of inflammation and loss of supporting periodontal tissue. Biofilm removal, antibiotics along disinfectants are considered conventional methods of periodontal therapy.<sup>[1]</sup> Scaling and root planing removes deposits, calculus and, necrotic cementum consisting of bacteria and endotoxins.<sup>[2],[3]</sup> however it has some limitations.<sup>[4],[5]</sup> Photodynamic therapy (PDT) is considered as best therapy to treat infections by bacteria, viruses, and fungi in recent years.<sup>[6]</sup>

It uses low power lasers along with appropriate wavelength to kill microorganisms treated with photosensitizer drug.<sup>[7]</sup> This therapy is defined as an oxygen-dependent photochemical reaction that occurs upon light-mediated activation of a photosensitizing compound leading to the generation of cytotoxic reactive oxygen species; predominantly singlet oxygen.<sup>[8]</sup>

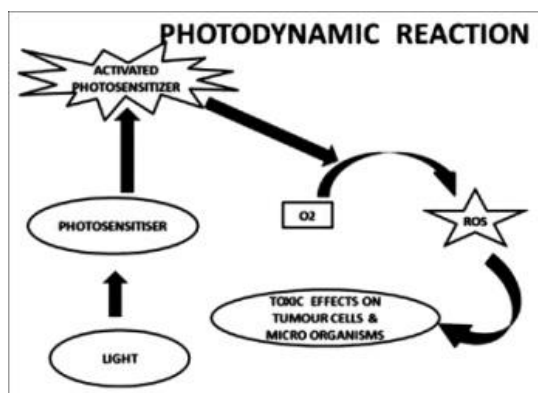
PDT has been consistently used to treat bacterial infections. They are also used in the treatment of oral cancer, bacterial, and fungal infections, and in the photodynamic diagnosis of the malignant transformation of oral lesions.<sup>[9]</sup> This review is aimed to discuss the role of PDT in periodontal therapy.

### Historical Perspective of Photodynamic Therapy

- Use of a plant extract for the restoration of skin pigmentation: 1400 BC.<sup>[10]</sup>
- Phototoxic effects of psoralens: 1250 AD.<sup>[10]</sup>
- Use of contemporary PDT: Niels Finsen.<sup>[11]</sup>
- Concept of cell death induced by the interaction of light and chemicals: Raab.<sup>[12]</sup>
- The term “Photodynamic action”: Von Tappeiner.<sup>[13]</sup>
- Clinical use of PDT: Dougherty *et al.*<sup>[14]</sup>
- Effect of cyanide photosensitizer on Gram-negative and Gram-positive species: Wilson.<sup>[15]</sup>

## Principles of photodynamic therapy

The principle of PDT is that the photosensitizer binds to the target cell and it gets activated by light having a suitable wavelength. During this activation, free radicals get formed which are toxic to the cell (Figure 1).<sup>[16]</sup>



**Figure 1: Principles of photodynamic therapy**

By light irradiation, the dye (photosensitizer) is excited to its triplet state, the energy of which is transferred to molecular oxygen. The product formed is the highly reactive singlet oxygen capable of reacting with biological systems and destroying them. Only the first excited state with the energy of 94 kJ/mol (22 kcal/mol) above the ground state is important and the second excited state does not react.<sup>[17]</sup>

## Mechanism of action

The three components of PDT are oxygen, photosensitizer, and light.

After administration, a photosensitizer goes into the excited state. This excited state either comes back to the ground state or forms an energetic triplet state.<sup>[18]</sup> The triplet state photosensitizer reacts with biomolecules in two different pathways - type I and II.<sup>[19]</sup>

**Type I:** By electron/hydrogen transfer directly from the photosensitizer, producing ions, or by electron/hydrogen removal from a substrate molecule to form free radicals. These radicals react rapidly with oxygen, resulting in the production of highly reactive oxygen species

**Type II:** In type II reaction, the triplet state photosensitizer reacts with oxygen to produce an electronically excited and highly reactive state of oxygen, known as singlet oxygen ( $^1\text{O}_2$ ) which can interact with a large number of biological substrates inducing oxidative damage on the cell membrane and cell wall. Type II reaction is accepted as the major pathway in microbial cell damage.<sup>[20]</sup>

## Light source

PDT requires a source of light to activate the photosensitizer. red light between 630 and 700 nm activates Most of the photosensitizers, corresponding to a light penetration depth from 0.5 to 1.5 cm.<sup>[21]</sup> This limits the depth of necrosis. The total light dose, depth of destruction, and dose rates vary with each tissue treated and photosensitizer used.<sup>[22]</sup> Currently, the light source applied in PDT are those of gallium-aluminum-arsenide diode lasers (630–690, 830, or 906 nm), helium-neon lasers (633 nm), and argon laser (488–514 nm), the wavelength of which range from visible light to the blue of argon lasers, or from the red of helium-neon laser to the infrared area of diode lasers.<sup>[23]</sup> Recently, a nonlaser light source such as light-emitting diodes (LEDs), has been used as new light activators in PDT.<sup>[24]</sup>

## Photosensitizers

Most of the sensitizers used for medical purposes belong to the following basic structure:

1. Tricyclic dyes with different meso-atoms. E.g.: Acridine orange, proflavine, riboflavin, methylene blue, fluorescein, and erythrosine
  2. Tetrapyrroles. E.g.: Porphyrins and derivatives, chlorophyll, phylloerythrin, and phthalocyanines
  3. Furocoumarins. E.g.: Psoralen and its methoxyderivatives, xanthotoxin, and bergaptene.<sup>[25]</sup>
- First-generation sensitizers: Photofrin and hematoporphyrin derivatives.
  - Second-generation photosensitizers: 5-aminolevulinic acid (ALA), benzoporphyrin derivative, texaphyrin, and temoporfin (mTHPC).<sup>[26]</sup>

Toluidine blue O and methylene blue are generally used in antimicrobial PDT. They possess similar chemical and physicochemical characteristics. Toluidine blue O solution is blue-violet in color. It stains granules within mast cells and proteoglycans/glycosaminoglycans within connective tissues. Methylene blue is a redox indicator that is blue in an oxidizing environment and becomes colorless upon reduction. Combination of Methylene blue with light has been reported to kill the influenza virus, *Helicobacter pylori*, and *Candida albicans*.<sup>[27]</sup> Methylene blue and toluidine blue O are very effective photosensitizers for the inactivation of both Gram-positive and Gram-negative periodontopathic bacteria. Tetracyclines are also effective photosensitizers producing singlet oxygen.<sup>[28]</sup>

## Application of photodynamic therapy

The technical simplicity and effective killing are the main reasons why PDT is extensively used in periodontics. Antimicrobial PDT also leads to the detoxification of endotoxins such as lipopolysaccharide.<sup>[29]</sup>

Scaling and root planning is to be carried out before PDT. While doing the PDT, the photosensitizer is first infused in the periodontal pocket and allowed to pigment for 2 min. Then the fiber is inserted 1 mm short of the pocket and lased by moving in a sinusoidal manner from side to side toward the coronal third.

## Advantages of photodynamic therapy

- Minimally invasive technique
- Least collateral damage to normal cells
- Enhances results and superior healing
- The Exceedingly efficient broad spectrum of action
- Efficacy independent of the antibiotic resistance pattern of the given microbial strain
- The therapy also causes no adverse effects
- Lesser chance of recurrence of malignancy
- Economical to use.<sup>[30]</sup>

## Limitations of photodynamic therapy

There is a period of residual skin photosensitivity due to the accumulation of photosensitizers under the skin. Therefore, first or second-degree burns can be caused by photosensitizers when they get activated by daylight. Hence, until the drug is eliminated from the body, direct sunlight must be avoided for several hours.<sup>[30]</sup> Most of the dyes adhere strongly to the soft tissue surface of the pocket, even for a shorter period, which may affect periodontal tissue attachment during wound healing.<sup>[2]</sup>

## Future directions:

Irrespective of the advances in laser technology, synthetic chemistry, nanotechnology and photobiology, PDT, more than a quarter of a century after its first clinical approval, is still not accepted as 'standard' therapy even in areas of medicine where real improvement in outcome using standard therapy has not been achieved. In order to overcome the current challenges and rise to the height of its potential, PDT needs commitment and funds.<sup>[31]</sup>

## Conclusion:

Chemical antimicrobial agents are widely used in prophylactic and therapeutic regimens for dental plaque related diseases, which are among the most common human infections. As these agents are difficult to maintain at therapeutic concentrations in the oral cavity and can be rendered ineffective by resistance development in target organisms, there is a need for an alternative antimicrobial approach. A novel approach, photodynamic therapy (PDT), could be a solution to these problems. Lethal photosensitization of many bacteria, both Gram-positive and Gram-negative was found in many studies. The advantage of this new approach includes rapid bacterial elimination, minimal chance of resistance development, and safety of adjacent host tissue and normal microflora. Thus, the available knowledge of photodynamic therapy should encourage a more clinically oriented application of this technique.

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