

## PHOTODYNAMIC THERAPY IN THE COMPLEX TREATMENT OF THE PATIENT WITH PERIODONTAL IMPAIRMENT. REVIEW.

Raluca-Cristina Mocanu<sup>1</sup>, Marius Maris<sup>2\*</sup>, Irina-Georgeta Sufaru<sup>3\*</sup>, Ionut Luchian<sup>3</sup>, Diana-Maria Anton<sup>1</sup>, Georgeta-Maria Laza<sup>1</sup>, George-Alexandru Maftel<sup>1</sup>, Mihaela Maris<sup>4</sup>, Maria-Alexandra Martu<sup>3</sup>.

<sup>1</sup>Phd Student "Grigore T. Popa" University of Medicine and Pharmacy, Iași, Romania

<sup>2</sup>"Titu Maiorescu" University, Faculty of Dental Medicine, Bucharest, Romania.

<sup>3</sup>UMPh « Grigore T Popa » Iasi, Faculty of Medical Dentistry, Depart. of Periodontology

<sup>4</sup>DMD, PhD, Private Practice, Bucuresti, Romania

\*Corresponding authors: Maris Marius: [marius@drmaris.ro](mailto:marius@drmaris.ro)

Sufaru Irina-Georgeta: [irina\\_ursaescu@yahoo.com](mailto:irina_ursaescu@yahoo.com)

#All authors had equal contributions with the first author.

### Abstract

The antimicrobial potential of photodynamic therapy has been known since the beginning of the last century. Photodynamic therapy products cause damage to various components of microbial cells or can irreversibly alter metabolic activity. This leads to microbial elimination. This mechanism of action is based on the energy absorbed by intracellular photosensitization which is transferred to the oxygen molecule to damage the oxidative reaction pathways in the plasma membrane and the genetic material of microbial cells. This effect is limited to microbial cells with no toxic effects on host cells. Based on the advantages and characteristics of antimicrobial photodynamic therapy, it has been proposed that periodontal and peri-implant diseases be potential targets of this new type of chemotherapy.

**Keywords:** *photodynamic therapy, adjunctive periodontal treatment, antibacterial*

### Introduction

The first use of light for therapeutic purposes dates back to around 1400 BC, when sunlight was used as a source to treat skin diseases [1]. In 1801, ultraviolet (UV) rays were discovered, and scientists began to understand the therapeutic effect of sunlight. Later, during the 19th century, interest in heliotherapy increased in the scientific community and various scientists began to use sunlight to treat various diseases such as rickets, peritoneal tuberculosis, lupus vulgaris, etc. Towards the end of the 19th century, Lahmann built and used the first artificial light sources in Germany. Its construction was made of a carbon arc lamp in combination with a parabolic mirror. He successfully treated a patient with lupus vulgaris and recorded an improvement in another patient who had the same condition [2].

In the early twentieth century, Niels Finsen received the Nobel Prize for his therapeutic results in treating lupus vulgaris with concentrated doses of UV radiation from a carbon arc lamp. This has been considered the beginning of modern phototherapy [1].

In the mid-20th century, scientists and physicians began using artificial light sources to treat neonatal jaundice, psoriasis, and many different skin conditions [3]. Today this technology is known as phototherapy. Phototherapy can be used with or without a photosensitizer. When used in conjunction with a photosensitizer, phototherapy is known as photochemotherapy [2].

Photodynamic therapy (PDT) is a type of photochemotherapy that involves three components: light, a photosensitizer and oxygen. The therapeutic possibilities of photodynamic therapy were first

introduced in the 19th century, but it was not until the 1990s that the first photosensitizers were approved for clinical use. Currently, photodynamic therapy is mainly used in the treatment of cancer [4]; however, there are numerous studies that have shown that photodynamic therapy also has an antimicrobial effect [5-7].

### Photochemistry of photodynamic therapy

Photodynamic therapy (PDT) is a treatment in which a photosensitive dye (photosensitizer) is activated by light, leading to selective toxicity for the desired treatment [8]. As a result of activating the light, the sensitizer is transformed from the basic state to the first stimulated state. In this state, the photosensitizer must have sufficient stability to be able to pass to the

stimulated triple state (T1), which is an even more stable state. Subsequently, two different reaction processes can take place, both involving molecular oxygen. In the first type (type I), reactive oxygen species (ROS) are formed as a result of the interaction of ground oxygen with the resulting radical that is created from hydrogen abstraction or electron transfer between a stimulated sensitizer and an adjacent molecular sensitizer. In the second type (type II), singlet oxygen species are formed as a result of direct energy transfer from T1 to basic state oxygen ( $^3O_2$ ). This can only happen if the sensitizer and the basic oxygen are in the same multiplicity of the triplet state. Both types of processes are shown schematically in Figure 1.

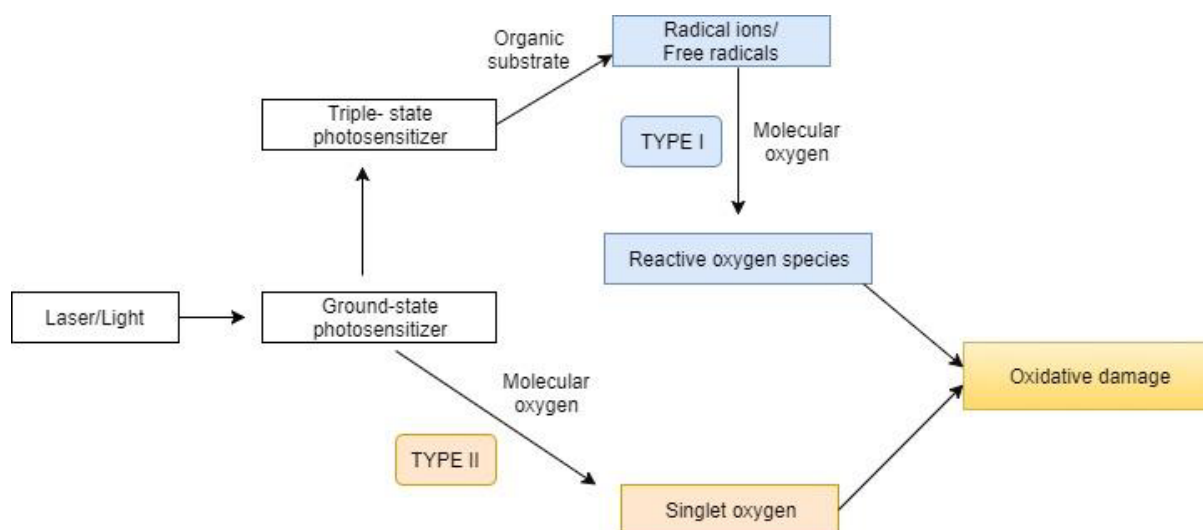


Figure 1. Photochemical mechanisms in photodynamic therapy (type I and type II) [2]

The type I reaction occurs mainly in environments of anoxia or hypoxia. In anoxic environments, the stimulated photosensitizer reacts directly with organic substrates, producing an oxidized substrate and a reduced photosensitizer. In hypoxia environments, the reduced photosensitizer reacts with oxygen and superoxide anions are produced which, as a result, can form highly reactive hydroxyl radicals [9]. Type II reactions depend on the oxygen concentration. They are commonly

associated with the formation of simple oxygen, however, there are other compounds that have a basic triplet state similar to oxygen that may be involved in this type of reaction (nitric oxide and vitamin A). Type II reactions are dominant during PDT treatments, however, type I reactions may become dominant under hypoxic conditions or in the presence of a highly concentrated photosensitizer [2].

*Oxygen in photodynamic therapy*

Oxygen is one of the three components of photodynamic therapy. In its basic state, oxygen has two unpaired electrons that are positioned on the outermost orbitals. Depending on the presence or absence of the magnetic field, these electrons can have three different configurations: both rotations aligned upwards, both rotations aligned downwards or in opposite directions. Due to these three possible configurations, the basic state of oxygen is also called the triplet state [9].

The predominant agent produced by photodynamic therapy is simple oxygen. This is an extremely reactive form that occurs as a result of the pairing of electrons in the anticondential orbital, which makes the molecule unstable. The lifespan of unique oxygen is very short due to its reactivity and, as a result of this short lifetime, the energy created and the oxidative damage induced by PDT is very localized [2] (Figure 2).

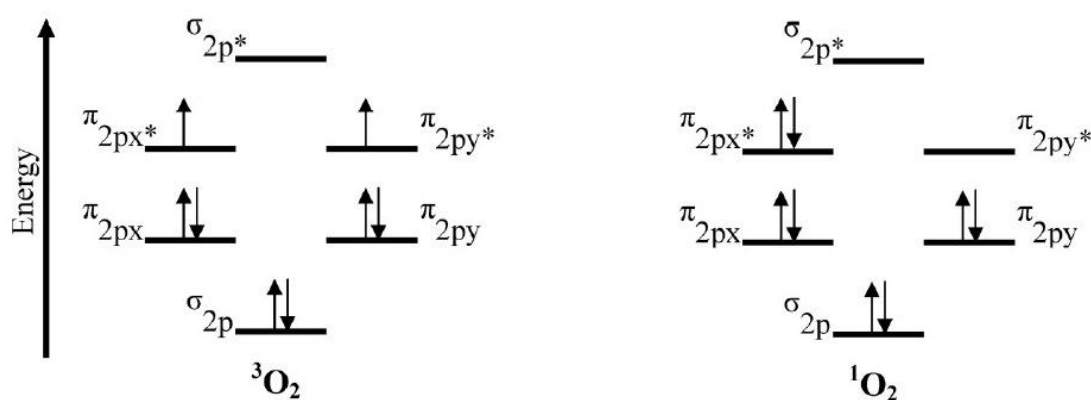


Figure 2. Oxygen states. Triplet ( $^3\text{O}_2$ ) and simple oxygen ( $^1\text{O}_2$ ) [2]

### Photosensitizers in photodynamic therapy

The first photosensitizers used for photodynamic therapy were porphyrins, chlorines and bacteriochlorines. These dyes have the strongest light absorption in the red portion of the electromagnetic spectrum. Among them there are differences in absorption spectra ranging from about 400 nm (called the Soret band) to about 800 nm, however, the most useful absorption range for PDT is between 600 nm and 800 nm. These photosensitizers are high efficiency singlet oxygen generators. The efficiency of simple oxygen production is called singlet-oxygen efficiency [2].

An optimal photosensitizer should have the following properties [10]:

1. availability in pure form

2. It should be synthesizable and easy to reproduce

3. high singlet-oxygen quantum efficiency

4. strong absorption in the spectrum (680-800 nm)

5. efficient accumulation in the tissue

6. stability and solubility in the body

7. excretion from the body after completion of treatment.

The first commercial photosensitizer was Photofrin®. It belongs to the group of photosensitizers with porphyrin. The longest absorption of the wavelength is relatively poor. At 630 nm it can be activated up to about 5 mm in tissues. At first it was approved only for the treatment of bladder cancer, but later it was approved for the treatment of many

other types of cancer (esophageal, lung, head, neck, abdominal cancer, etc.).

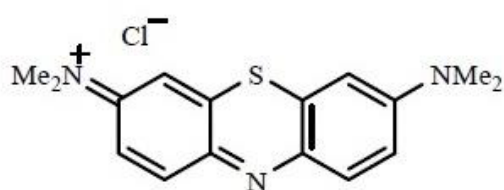
In an attempt to create a better photosensitizer, many new compounds have been synthesized. The second generation of photosensitizers includes 5-aminolevulinic acid (ALA), benzoporphyrin derivative (BPD), texafirin lutetate, temoporfin (mTHPC), tinethylethiopurpurine (SnET2), sodium talaporfin (LS11), etc. These compounds are stronger than the first generation and due to their potency can cause pain and lead to severe photosensitivity of the skin. The third generation of photosensitizers includes modified drugs that are currently available, but more studies are needed to verify the potential of these photosensitizers [10].

Although most photosensitizers belong to porphyrinoid groups, there are also several non-porphyrinic photosensitizers. These compounds include: anthraquinones, phenothiazines, xanthenes, cyanines, etc. [2].

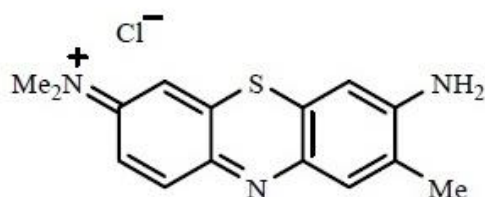
In dentistry, the most commonly used photosensitizers belong to phenothiazines. Methylene blue and

toluidine blue are the most used in the treatment of chronic periodontitis. Methylene blue is additionally used against melanoma, basal cell carcinoma and Kaposi's sarcoma [11]. The structures of methylene blue and toluidine blue are shown in Figure 3.

Methylene blue and toluidine blue belong to the phenothiazine family with similar chemical and physico-chemical characteristics. Methylene blue is a redox indicator that is blue in an oxidizing environment and on reduction becomes colourless. It was initially used as an anti-malarial drug [12]. The best absorption of methylene blue takes place at a wavelength of 666 nm. Its mechanism of action is due to its positive charge and includes the intercalation of methylene blue cations in the structure of nucleic acids. A disadvantage of methylene blue is that this chromophore is easily reduced in biological systems, which leads to reduced antimicrobial activity [13]. However, many studies report that methylene blue is effective in killing *Helicobacter pylori*, *Candida albicans*, influenza virus and periodontal bacteria [14].



**24**  
Methylene blue



**25**  
Toluidine blue

Figure 3. Chemical structure for methylene blue and toluidine blue (Ormond & Freeman, 2013)

Toluidine blue has a blue-purple colour. It is able to inactivate gram-positive and gram-negative bacteria. It interacts with lipopolysaccharides that are present in the cell membrane of Gram-negative bacteria even without easy application [15]. When exposed to a

wavelength of 630 nm, it shows maximum absorption and is effective in killing various types of microorganisms. Its mechanism of action is due to its chemical and physical properties that allow it to pass freely across the bacterial membrane and act directly on mitochondria.

Toluidine blue has been shown in various studies to be effective against periodontal bacteria in both planktonic cultures and biofilms [16].

### **Light sources**

The first light sources used for PDT were argon-pumped paint lasers, potassium titanyl phosphate (KTP) - or neodymium: lithium aluminium garnet (Nd: YAG) - pumped paint lasers and vapor paint lasers. gold or copper. All these devices are expensive and complex, which is why diode laser systems are predominantly used today. Diode lasers are easy to operate, portable and less expensive compared to previously used devices [17].

For effective PDT treatment, the light source should be able to activate the photosensitizer at a certain wavelength. Red light is most effective in use in human tissues. As a result, most of the sensitizers used are between 630 and 700 nm. This corresponds to a light penetration depth of up to 1.5 cm. This limited depth of penetration prohibits uniform illumination of larger and solid tumours [18].

Non-laser light sources, such as light emitting diodes (LEDs), have also been applied in PDT procedures. These light sources are much less expensive and are small, light and extremely flexible [19]. PDT, depending on the pathology treated, can be applied superficially, interstitially, intra-operatively and intra-cavitary.

Depending on the location and morphology of the lesion, the sources used for light delivery can be fibre optic catheters or lenses for flat field applications [20].

The light must be precise and uniform, allowing effective treatment. The fibre tip can have different shapes to allow light to diffuse in all directions. Important light source issues for PDT are accurate calibration, sensitization and easy dosimetry. Such devices would greatly

advance PDT as a routine clinical treatment [21].

### **Limitations of photodynamic therapy**

For PDT to be effective, light needs to be directed to the appropriate tissue location and depth. Providing optimal laser light and coordination between different clinicians is complex, and sometimes the availability of light sources is a major issue. There are now portable light sources that have simplified the process. PDT is an ablative procedure, and treatments do not provide material for histopathological diagnosis. Therefore, before applying PDT, a diagnosis of treatment by other methods should be made.

Another limitation of PDT is the inability of light to penetrate deep into tumours which makes it less effective for treating large tumours. Because it is a local treatment, it is also impossible to use to treat metastatic cancer [22].

Photosensitivity is another problem that can take some time after applying some photosensitizers. It depends on the method of applying the photosensitizer. When administered systematically, skin photosensitivity may last for several days or weeks. Patients are instructed to avoid sun exposure, to protect their skin and eyes until the drug is completely eliminated [17].

### **Antimicrobial photodynamic therapy (aPDT)**

The antimicrobial potential of PDT has been known since the beginning of the last century. However, only with the emergence of antibiotic-resistant bacterial strains have scientists been encouraged to seek alternative treatments, especially for localized infections of the skin and oral cavity [23].

Photodynamic therapy products cause damage to various components of microbial cells or can irreversibly alter

metabolic activity. This leads to microbial elimination. This mechanism of action is based on the energy absorbed by intracellular photosensitization which is transferred to the oxygen molecule to damage the oxidative reaction pathways in the plasma membrane and the genetic material of microbial cells [24]. This effect is limited to microbial cells with no toxic effects on host cells.

The efficiency and reliability of aPDT is due to the relatively simple basic principles behind it. If all components of aPDT (light, oxygen and photosensitizer) are present in sufficient quantities during the application of this therapy, then this technique can be extremely effective and can cause damage to target cells [25].

The antimicrobial effect of photodynamic therapy has been shown to be effective in many studies and against a number of different microorganisms: *Aerergatibacter actinomycetemcomitans*, *Prevotella intermedia*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterococcus faecalis*, *Escherichia coli*, *Candida albicans*, *Pseudomonas aeruginosa*, *Porphyromonas gingivalis*, *Streptococcus sanguis* etc. It is unlikely that these microorganisms will be able to develop resistance to aPDT. This is because singlet oxygen and free radicals interact with several cellular structures and with different metabolic pathways at the cellular level [26].

### **Application of photodynamic therapy in periodontics**

The application of PDT in dentistry is growing rapidly and is used for the photodynamic diagnosis of malignant transformation of oral lesions, for the treatment of head and neck cancer, as well as for bacterial and fungal infections [27].

Periodontitis is a chronic inflammatory disease that affects the tissues around the teeth. It is induced by bacterial infection and causes major destruction of the periodontium, which can

lead to tooth decay and subsequent loss [28].

The basic treatment for periodontitis is mechanical debridement, often combined with the use of chemical decontamination or the use of local or systemic antimicrobial therapy. Mechanical debridement alone cannot eliminate all infections due to the difficulty of reaching deep bags, and as a result, a residual plaque may remain even after treatment.

Systemic delivery of antimicrobial therapy has some side effects, including antibiotic resistance, which should always be considered when treating periodontitis. Local application of antimicrobial therapy also has some disadvantages, such as the need to repeat treatments, the effect occurs only in a limited part of the periodontium and demineralization of the root surface can occur [29]. Moreover, mechanical debridement can open dentinal tubules, and the remaining periodontal bacteria are able to enter them.

The advantages of aPDT compared to other treatments are that the photosensitizer can be inserted directly into the periodontal pocket and then activated with a fibre optic tip. Another advantage is that aPDT is only effective against microbial cells, avoiding damage to host tissues. This makes it a safe procedure against periodontal microbiota [30].

Many studies have shown potential improvements after using an aPDT along with mechanical debridement [31], however there are also some studies that report different results [32]. In his meta-analysis, Atieh showed potential improvements after the use of aPDT along with detachment and root surface [33]. A reduction in probing depth and a greater gain in clinical attachment were observed in the combination of the two treatments. Similarly, in their study Sgolastra et al. reported that the combination of conventional therapeutic treatment

provides additional benefits by reducing probing depth and increasing the level of clinical attachment [34].

### Conclusions

Based on the advantages and characteristics of antimicrobial photodynamic therapy, it has been

proposed that periodontal and peri-implant diseases be potential targets of this new antimicrobial photochemotherapy. Antimicrobial photodynamic therapy is expected to solve the difficulties and problems of conventional antimicrobial therapy and can function as an adjunct to conventional mechanical treatments.

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