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Antimicrobial Photodynamic Therapy

Alaa Hussein Almola[a], Amina G.O. Al-Ani[b], Sura M.Y. Al-Taee[c]*

[a,b,c]*Department of Biology, College of Sciences, University of Mosul, Mosul-IRAQ*

[a]*Email: alasbio58@uomosul.edu.iq*

[b]*Email: amesbio115@uomosul.edu.iq*

[c]*Email: suramahmoud@uomosul.edu.iq*

Abstract

Photodynamic therapy PDT has appeared in recent years as a non –surgical method for the treatment of cancer and many inflammatory conditions resulting from infection with bacteria, fungi, or viruses and in this side known as Antimicrobial Photodynamic Therapy .This treatment is an oxygen-depending photochemical reaction and occurs as are a result of activating photosensitive compound which leads to the production of cytotoxic oxygen types mostly O_2 (singlet oxygen). PDT system composed of three ingredients: light source, photosensitizers and oxygen. PDT can be used in periodontal pocket treatment in order to avoid the use of antibiotics and their side effect as well as reduce the emergence of resistant strains. The application of PDT are in continuous progress and the future of PDT is bright and promising more development especially in the treatment of cancer and many inflammatory disease such as wound and periodontal infection. So, this review aims to explain the mechanism of action and their role in the treatment of the inflammatory injuries.

Keywords: Photodynamic therapy; Mechanisms; Photosensitizing; Photodynamic reaction**.**

1. Introduction

Photodynamic therapy (PDT) was designed as an alternative to conventional cancer treatments. In contrast to traditional therapies (surgery, chemotherapy, and radiotherapy) , PDT has a low risk of negative effects and can be used multiple times . It causes necrosis or apoptosis in cells , It can also be used to kill improperly growing live tissue [1].

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* Corresponding author.

Some disorders, like bacterial, fungal, and viral infections, can be treated using PDT, also known as antimicrobial photodynamic treatment, because they all have not controlled proliferation and the presence of unwanted “microbial cells” in common [2 ,3]. The application of PDT was known firstly in ancient civilizations, Egypt and India. Then, the idea faded and returned at the beginning of the twentieth century in western civilization by the Danish scientist Niels Finsen, when he recorded the first successful use of PDT for Lupus Vulgaris treatment by using arc lamp. In 1903, "photodynamic action" was coined to describe the response between a visible light source and dyes that are linked to oxygen [1,2]. PDT was first used for treatment of human malignancies by coating the skin with photosensitizers day and making illumination with a lamp. Later, a laser was utilized to activate the dye using a highly intense a wavelength-appropriate light source and the PS was injected in a consistent manner [1].

2. The Mechanism Action of PDT

Antimicrobial activity of PDT is built on photosensitizers (PS) that is most nontoxic, visible light in adequate wavelength and oxygen which is promoted the phototoxic effect . The produced reactive oxygen species (ROS) can harm biomolecules and induce cellular structure oxidation, leading to microorganism death , Each of these components (PS, light, and oxygen) is safe in and of itself, but when combined, they form fatal cytotoxic ROS that preferentially kill cells [4]. The mechanism of PDT action can begin with excitation of PS to reach triplet state which is represent the excited long –lived state. This triplet state transfer energy to oxygen .Finally ,the result of transfer energy to molecular oxygen is synthesize singlet oxygen or may be interact with other molecules to produce hydroxyl radical and other radicals these reactions can cause various damage of microbial component or may effect on the metabolic pathways of microbial cells (Figure1) [5,6]. PDT is nontoxic and does not cause any accumulation of toxicity in body .therefore ,it can be used repeatedly and for several times [7].

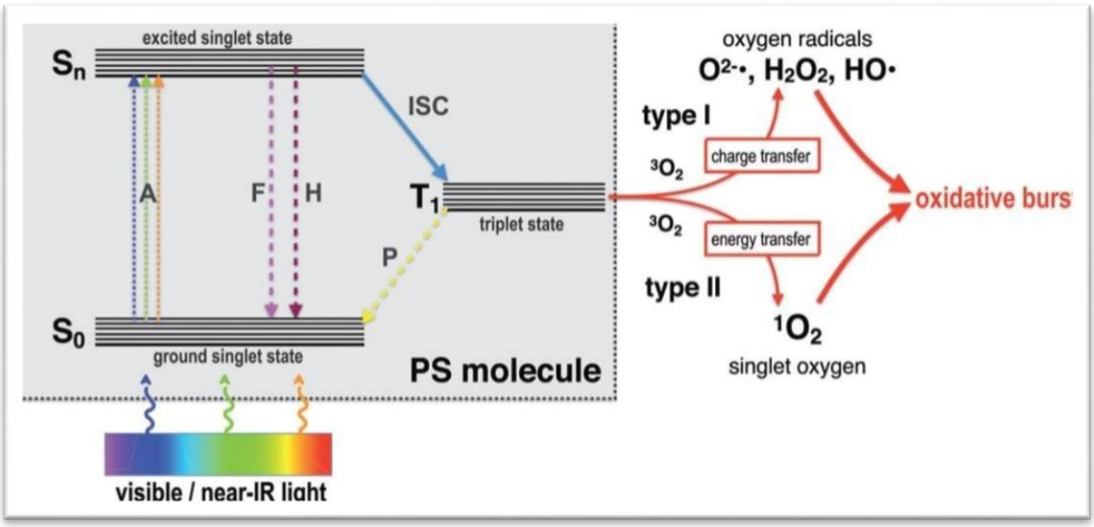

Figure 1: Processes of PDT [5].

3. Light Source

The convergence of researchers in various fields of science, whether physics, engineering, biochemistry, pharmacy and other medical fields is absolutely necessary for the development of any therapeutic technology. The first uses of the light source go to the traditional bulb, but these traditional lighting don't give good results due to the multicolor and strong heat [8,9]. In the photosensitizer excitation process, different wavelengths of light are usually used, and the range of light that activated photosensitizer between 630-700 nm .Three light systems can be used for this reason. This systems include: Diode laser systems, non - coherent light "non - laser" sources, this system used for larger areas and the final system is light source such as "light emitting" diodes (LED) [10]. The most common one in the terms of use is the laser and light emitting diode. In the medical field, the use of lasers as source of light has greatly increased due to the great progress in laser application techniques and the improvement of optical fiber technology [11,12]. Usually, the laser used helium and neon as mixture form gas. but recently, the laser uses a gallium arsenide of semiconductor diode as crystal . LED emits light wave in various lengths in the presence of a certain power, the advantage of LED is the low cost of it and can be applied various LEDs in various ways to obtain especial arrangement ,also can be used it for large areas [9].

4. Photosensitizer's

According to the discovery of the photodynamic technique during the twentieth century, researchers have worked on developing acceptable PS. The end of the nineteenth century (1860s) in Germany, Many dyes were synthetized in the weaving industry[13]. Several approaches, including as Methylene Blue, Toluidine Blue, and SAPYR, have been employed in the last 20 years to improve PS by using modified structure of PS or produce new groups of PS [4].

5. The Key Target Structures of PDT

PDT has the advantage of being non-selective, focusing on a variety of molecular targets such as several proteins as well as lipids , and molecules of nucleic acids [14]. PDT-mediated bacterial death is usually due to the damage occur in the DNA and cytoplasmic membranes which are represent the most important components in the bacterial cell [15]. The efficiency of PDT against different microorganisms is determined by the PS type, concentration, and type of microorganism or class such as bacteria or fungus or may be virus , they may specify the zone of activity, which is determined by the physicochemical parameters of the microbe-PS interaction. The relative solubility of PS in water and lipids, ionization constant light absorption characteristics, and singlet oxygen production are all important factors in the PS reaction [16]. There are great variety in the interaction , as well as other properties related to structure , permeability and capacity of binding with molecules of different types of cell walls of different bacteria [17]. Because the outer section of cell wall of positively Gram bacteria that is composed of thick peptidoglycan and teichoic acid .It is substantially more porous, allowing PS to touch the cytoplasm membrane, PDT is more effective in inactivating them [16]. Gram-negative bacteria, on the other hand, have a significantly more complicated morphology. In addition to peptidoglycan, the outside section of their cells' wall contains lipopolysaccharide with negative charge , many

proteins, and lipoproteins. This organization of structure produce a barrier that prevents PS from being incorporated [2].Therefore , the effect of PDT will differ greatly in its effect on the type of bacteria , whether they are gram-negative or gram –positive, so this issue must be taken into account when using PDT dinically. The microorganisms can be reduced activity of PDT when it found in biofilm, this is because to the difference in the structure of microorganisms cell membrane within biofilm and the effect of other molecules that may be found in biofilm , such as the matrix of extracellular polysaccharide and factors of quorum sense , that obstruct PS-microorganism interaction [17]. PDT has been shown to be effective against bacteria that cause periodontitis like "Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Capnocytophaga gingivalis, Fusobaterium nucleatum, Prevotella intermedia, and Streptococcus sanguis in periodontics". PDT has been explained as an effective against Actinomyces israelli, F.nucleatun, and P.gingivalis in endodontics [5 , 14]. Bacteria are more likely to acquire resistance to treatments that target a single target structure, such as antibiotics or most antiseptics, which follow "key-lock principle", Pathogens can easily resolve the antimicrobial challenge in this case by introducing punctual mutations, expressing proteins involved in the extrusion of toxic substrates, or change the regulation of enzymes in relation with defense. As previously mentioned, PDT is a strategy focuses on several goals with non-selective action . As a result, it has been determined that bacteria developing resistance to PDT is extremely unlikely [18,19].This is because PDT affects several targets specifically against bacteria without affecting body tissues.

6. Fields in Which PDT Could Be Used in Therapeutic Practice

In a research, it was used types of tonsillitis infection, bacterial as well as viral infection treated with amoxicillin systematically without first establishing the cause. The use of photo antimicrobial treatment followed by a set time, such as with a fiber-optic system, can result in adequate antimicrobial activity against tonsillitis .Use of PDT and then used of irradiation for a specific period of time, such as with a fiber-optic unit, of disease may result in adequate antimicrobial activity without exposure to systemic antibiotics disrupting microbiota of intestinal or bacteria being exposed to sub-inhibitory concentrations., which could lead to resistance [4]. Only three PS, "phenothiazinium ,dyes Methylene Blue and Toluidine Blue", as well as the heptacyanine,dye and Indocyanine,Green, have received clinical approval for use in humans in conjunction with light. PDT is most likely to be beneficial for localized infections in easily accessible areas of the body where "light transmission" is not a problem. The "ear, nose, mouth cavity, gastrointestinal tract, urogenital tract, and lungs" are all reachable for local application of PS and subsequent irradiation using endoscopes and fiber-optic equipment [4].At the present time, it can be said that the use of PDT is specific for topical treatment rather than systematic treatment , which may need more numerous studies in this direction.

7. The Main Fields for Clinical Application of PDT:

7.1. Oral Infections

There may be numerous conditions in dentistry, when using PDT could be beneficial such as limiting antibiotic use or enhancing treatment outcomes". [21]. Antibiotics that are taken systemically are a typical treatment strategy in periodontology for the case of severe periodontitis to assure preferable treatment outcomes. [22],

Alternative techniques such as PDT have recently sparked increased interest [21]. Some clinical trials have looked at the effectiveness of PDT as a juncture to the “mechanical treatment” for chronic, or aggressive periodontitis. [23 , 24]. Most of these clinical trials suggest that supplemental PDT improves clinical short-term healing” outcomes in terms of reduced bleeding on probing and“lower probing pocket depths”when compared to mechanical therapy alone [25 , 26].Overall, clinical data on PDT in periodontics is relatively limited and the results are rather debatable [26]. In contrast, a comprehensive study has revealed that using PDT in conjunction with mechanical debridement results in considerable benefits in patients with peri-implantitis, [27]. In endodontics, PDT could be a useful addition for disinfecting highly infected root canals or in the case of "singlevisit endodontics" [28]. According to [29], supplementary PDT reduces bacterial burden in root canals by a significant amount. In histological research in dogs, it was found that sequential treatment by using PDT promotes healing and reduces inflammation of periapical osseous lesions [30 , 31]. The use of PDT with conventional “endodontic therapy” led to better “radiographic healing” of primary endodontic infections after six months of endodontic treatment, according to a recent randomized clinical trial [32]. Clinical studies and case reports have shown that PDT is regarded effective as standard antifungal treatment for :fungal infections such oral candidiasis and denture stomatitis [33 , 34 , 35]. In addition ,there is a tendency to suggest the adoption of PDT as a complementary treatment for deep lesions when the carious is partially removed [24].

7.2. Infections of the Skin and Chronic Wounds

In dermatology, PDT could be an effective treatment option for a variety of skin infections, including bacterial and fungal but notably for chronic wounds [36 , 37] . Positive effects of PDT on host tissues, such as growth factors to stimulate the immune response, may lead to wound healing faster, and this is one of the benefits of the treatment of chronic wounds or ulcers using PDT [36] . [38] used the phenothiazinium derivative PPA904 as a PS in the first PDT-in-chronic-wounds randomized, placebo-controlled clinical trial chronic leg ulcers and diabetic foot ulcers", they found considerable and broadspectrum bacterial cell death as well as a compared the effects of PDT mediated by"o-aminolevulinic acid" for the treatment of chronic skin ulcers of the lower extremities infected with pseudomonas aeruginosa with red light therapy alone, promising trend toward quicker wound healing. Similarly , [39] compared the effects of PDT mediated by “o-aminolevulinic acid” for the treatment of chronic skin ulcers of the lower extremities infected with “pseudomonas aeruginosa” with red light therapy alone, they discovered that the PDT group had considerably improved healing outcomes in terms of mean ulcer area reduction. According to a randomized clinical trial, the amputation rate in the PDT-treated group using the dyes phenothiazinium methylene blue and Toluidine blue”was only 2.9% of the amputation rate in the control group. The use of PDT as a diabetic foot therapy has also been recommended. It has been proven that PDT reduces the possibility of the need the surgery [40] . Figure(2,3)

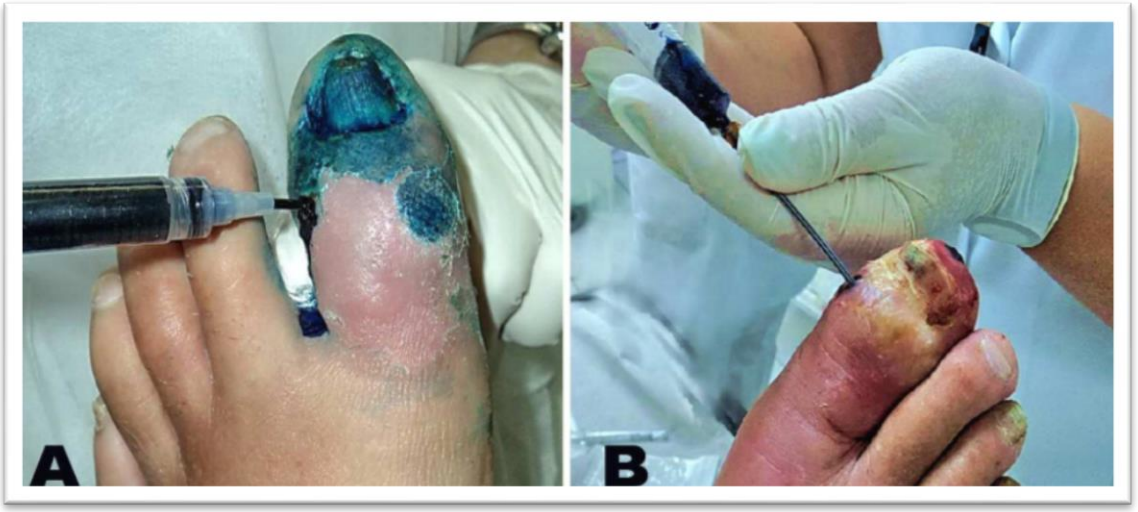

Figure 2: PDT therapy procedure. Irrigation of phenothiazinium salt into the diabetic foot hallux via an osteomyelitis fistula (A and B). [40]

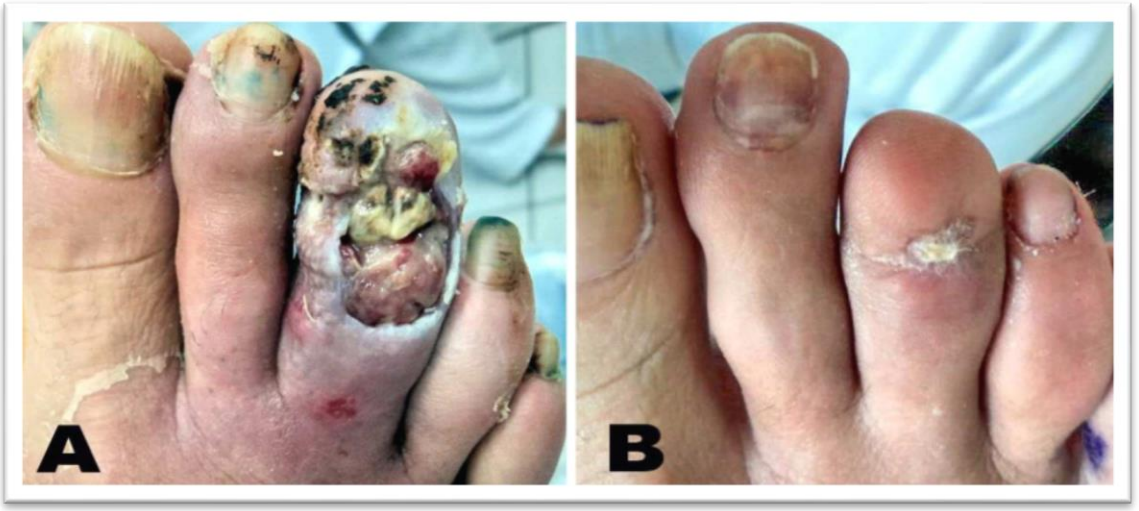

Figure 3: Typical patient progression in the PDT group. (A) Starting treatment: Wagner Grade 3 grading, middle finger ulcerated lesions with osteomyelitis above and below the finger. (B) The same finger is categorized as Wagner Grade 0 after following a four-month course of PDT therapy. [40]

8. Conclusions

Based on what has been reviewed from previous studies on this topic, it can be said that PDT technology is a very successful technology and can be developed for use in many medical fields after conducting many studies on the practical application and determining the best light sources and their appropriate wavelengths and the best of it in terms of absence of side effect on humans with the strongest effect on microorganisms as well as identifying the best photosensitizer .also many studies are need to determining of the period of time required for treatment, exposure time, frequency and stage of treatment.

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