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PHOTODYNAMIC THERAPY-A NEW EMERGING TREND IN DENTISTRY

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ABSTRACT

Photodynamic therapy is a novel, non-invasive therapeutic approach with increased pathogen and site specificity. It is a powerful laser-initiated photochemical reaction, involving the use of photosensitizer (dye) that is activated by light of specific wavelength to form toxic oxygen species like singlet oxygen and free-radicals. These chemical species are very reactive, can damage proteins, lipids, nucleic acids and other cellular components. Various applications of photodynamic therapy are treatment and diagnosis of cancer, in bacterial, fungal, parasitic and viral infections, periimplantitis, periodontitis, endodontic infections and oral biofilms such as plaque. The biggest advantage of PDT is the absence of any genotoxicity, no mutagenic effect and no risk of developing resistance to its antimicrobial action and increased healing process which favours its long-term use and safety. Thus, PDT represents a novel therapeutic approach in the management of various medical as well as dental conditions.

INTRODUCTION

Photodynamic therapy (PDT) has emerged as a non-invasive therapeutic modality for the treatment of various infections by bacteria, fungi, and viruses in recent years [1]. Although the original technique was first employed for the treatment of cancer [2] in 1980s. The word photodynamics means the application of dynamics of photons of light on the biological molecules. It (PDT) is the light-induced non-thermal inactivation of cells, microorganisms, or molecules. This utilizes light to activate a photosensitizing agent in the presence of oxygen. The exposure of the photosensitizer to light results in the formation of toxic oxygen species, causing localized photodamage and cell death. Clinically, this reaction is cytotoxic and vasculotoxic [3].

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Photodynamic therapy is widely used in medical as well as in dental field in the treatment of various diseases like cancer, psoriasis, actinic keratosis, rheumatoid arthritis, age related macular degeneration [4], in endodontic infections, caries, oral and mucosal infections, oral thrush, periodontitis and periimplantitis [5]. Applications of PDT in dentistry are growing rapidly [6] so in this review we will discuss the role of PDT in dentistry only.

History

Light has been used as a therapeutic agent for many centuries. In ancient Greece the sun was used in heliotherapy or the exposure of the body to the sun for the restoration of health. In 1900 Oscar Raab, a German medical student, discovered that the combination of the chemical acridine and light at certain wavelengths was lethal to Paramecium caudatum, a certain infusoria species [7]. Three years later, H. von Tappeiner and A. Jesionek treated skin tumours with eosin and white light [8].

In 1904 they described their observation as "photodynamic action". Finally, Von Tappeiner coined the term photodynamic. It was John Toth, who renamed it as PDT. PDT was approved by the Food and Drug Administration in 1999 to treat precancerous skin lesions of the face or scalp [9].

Mechanism of Action

It basically involves three nontoxic ingredients: visible light; photosensitizer; and oxygen. It is based on the principle that a photosensitizer (i.e. a photoactivable substance) binds to the target cells and can be activated by light of a suitable wavelength.[Fig-1] Following activation of the photosensitizer through the application of light of a certain wavelength, singlet oxygen and other very reactive agents are produced that are extremely toxic to certain cells and bacteria. This so called triplet state which can undergo two kinds of reaction [Fig-2].

In type I reaction, it can directly react with substrate and transfer a hydrogen atom or electron to from free radicals [10] while in Type II reaction, which is more common the triplet can transfer its energy directly to oxygen to generate singlet oxygen which can oxidize many biological molecules such as proteins, nucleic acids and lipids, and lead to cytotoxicity [11]. Singlet oxygen has very short lifetime in biological systems and short radius of action (0.02 μm) too.

Photosensitizers

PDT uses several photoactive components like tricyclic dyes, tetrapyrroles and fucocoumarins [Fig-3].The ideal photosensitizer should be chemically pure and of known specific composition. It should have a strong absorption with high extinction coefficient (E) at longer wavelength (red) region preferably between 700 to 800 nm. It must have an excellent photochemical reactivity and minimal dark toxicity.It preferably retained by target tissues (tumour cells) only and rapidly excreted out from the body system [12].

Light source

PDT requires a source of light to activate the photosensitizer by exposure to low power visible light at a specific wavelength.[Fig-4] Most photosensitizers are activated by red light between 630 to 700 nm, corresponding to a light penetration depth of 0.5 to 1.5 cm [13,14].

Applications of Photodynamic Therapy In Dentistry

Clinically, the photodynamic reaction is cytotoxic and vasculotoxic. Depending on the type of agent, photosensitizers may be injected intravenously, ingested orally, or applied topically. PDT is widely used in the management of dental caries,oral and mucosal infection, endodontic infection, periimplantitis and periodontitis.

Dental caries

Dental caries results from an ecological imbalance in the physiological equilibrium between tooth minerals and oral microbial biofilms, mainly supragingival plaque [15]. Photodynamic therapy could be used as dental caries preventive by targeting dental fermentative plaque microorganisms and as a minimally invasive technique to eliminate bacteria within carious lesions.[16] Recently, the combined application of photodynamic therapy and case in phosphopeptide-amorphous calcium phosphate, a compound with established remineralization capabilities, proved to be a successful treatment approach in removing the cariogenic bacteria and arresting root surface caries[Fig-5] in vivo [17].

Photodynamic antimicrobial chemotherapy (PACT) in Oral & Mucosal infections

It has been known since the beginning of the last century that micro-organisms can be killed by the combination of dyes and light, but the interest in antimicrobial PDT was hampered by the introduction of antibiotics. PACT has the potential to be such an alternative, especially for the treatment of localized infections of the skin and the oral cavity. Micro-organisms that are killed by PACT include bacteria, fungi, viruses, and protozoa. The development of resistance to PACT appears to be unlikely, since in microbial cells singlet oxygen and free radicals interact with several cell structures and different metabolic pathways.

PACT is equally effective against antibiotic-resistant as well as antibiotic-susceptible bacteria and repeated photosensitization has not induced the selection of resistant strains [18] Antioxidant enzymes, such as superoxide dismutase and catalase, protect against some oxygen radicals, but not against singlet oxygen [Fig-6].

In Endodontic Infections

The current endodontic treatment procedures to eliminate infection include mechanical removal of the infected contents of the canal system, irrigation with an antibacterial/tissue-dissolving agent (usually sodium hypochlorite), inter-appointment dressing of the canal with calcium hydroxide (which has modest antibacterial activity) and obturation of the root canal space. The complexity, however, of the root canal system with its isthmuses, ramifications, as well as the presence of dentinal tubules, make complete debridement and removal of bacteria with instrumentation, irrigation and the standard medicaments almost impossible. Photodynamic therapy has been employed in recent years to target microorganisms in root canals in vitro [19] and in vivo[20]. These studies suggested the potential of photodynamic therapy as an adjunctive technique to eliminate residual root canal bacteria after standard endodontic chemo-mechanical debridement [Fig-7]. Methylene blue has been

used as the photosensitizer for targeting endodontic microorganisms in several studies [21].

In Periodontal Diseases

PDT can be considered as an adjunctive to conventional mechanical therapy. The technical simplicity and effective bacterial eradication are the two reasons why photodynamic therapy is extensively studied in periodontics. Antimicrobial PDT not only kills the bacteria, but may also lead to the detoxification of endotoxins such as lipopolysaccharides. These lipopolysaccharides treated by PDT do not stimulate the production of pro-inflammatory cytokines by mononuclear cells.[Fig-8] Thus, PDT inactivates endotoxins by decreasing their biological activity [22]. It has been demonstrated that bacteria associated with periodontal disease can be killed through photosensitization with toluidine blue O by irradiating with helium - neon soft laser [23]. In an animal study on periodontitis, it was found that PDT was useful in reducing the redness, bleeding on probing, and Porphyromonas gingivalis levels [24].

Peri-Implantitis

Plaque-induced peri-implantitis is an inflammatory condition that affects soft and hard tissues surrounding an osseointegrated dental implant and may lead to its failure [25]. The incidence of periimplantitis in patients with chronic periodontitis is up to five times greater than in patients who are free of this disease [26] The management of peri-implantitis includes the mechanical removal of biofilm from the implants, the local application of antiseptics and antibiotics to kill bacteria in the surrounding periimplant tissues, and regenerative surgery help to re-establish the bone–implant interface [27] Photodynamic therapy, in combination with guided bone regeneration(GTR), produced bone defect fill and reosseintegration and greater bone gain than mechanical biofilm removal from the implants and guided bone regeneration in ligature-induced peri-implantitis in dogs.

Side Effects of PDT

Side effects of PDT observed during dental treatment are:-
Burning pain, stinging or itching which are restricted to the illuminated area during the light exposure. They rarely continue for few hours
Erythema and mild edema of the treated area
A light overdose causes blistering, ulceration or excessive necrosis
A cutaneous photosensitivity with systemic PDT for 4 to 6 weeks, even upto 6 months
Residual hyperpigmentation and hypopigmentation, but they resolve soon
Allergic reactions like urticaria to the photosensitizers are seen.
Systemic PDT with the use of various sensitizers can cause nausea, vomiting and liver function abnormalities

The major side-effect after the use of intravenous photosensitizers used in photodynamic therapy is photosensitivity. Systemic administration of the sensitizer results in a period of residual skin photosensitivity, due to accumulation of the photosensitizer in the skin. This photosensitizer can be activated by daylight, causing first- or second-degree burns.

Limitations In PDT

The clinical simplicity of drug, light, and oxygen-based reaction has stimulated the current expansion of PDT. A sensitizer is delivered into a patient; the tumor bed is properly illuminated, resulting in apoptosis and tumor necrosis with vascular cessation. Yet even the best currently available systemic photosensitizers accumulate to a certain degree in other organs, particularly in the skin, causing prolonged photosensitivity after exposure to light.

New Frontiers in Oral Antimicrobial Photodynamic Therapy

The role of photodynamic therapy as a local treatment of oral infection, either in combination with traditional methods of oral care, or alone, arises as a simple, nontoxic and inexpensive modality with little risk of microbial resistance. Lack of reliable clinical evidence, however, has not allowed the effectiveness of photodynamic therapy to be confirmed. Studies have been performed using different treatment conditions and parameters with insufficient clinical and microbiological findings. The reduced susceptibility of complex oral biofilms to antimicrobial photodynamic therapy may require the development of novel delivery and targeting approaches.

Recently, the advantages of targeted therapy become more apparent, and the use of light alone, antibody–photosensitizer and bacteriophage–photosensitizer conjugates or non-antibody based targeting moieties, such as nanoparticles are gaining increasing attention.

- Phototherapy
- Antibody-targeted antibacterial approaches using photodynamic therapy
- Nanoparticale- based antimicrobial photodynamic therapy

PERSPECTIVES AND FUTURE DIRECTIONS

In general, however, PDT remains on the periphery of the treatment options for head and neck cancer, various dental diseases and is considered as a competitive rather than a complementary therapy. Thus far, the lack of accurate dosimetry and appropriate illumination devices, coupled with poorly defined treatment parameters, has diminished the success of PDT. The development of new, more tumor-specific photosensitizers and light delivery systems, and well-designed, randomized, and standardized controlled trials should improve the efficacy of PDT and accelerate the FDA's approval of its use for the treatment of various medical as well as dental conditions.

Figure 1.Showing Photodynamic reaction

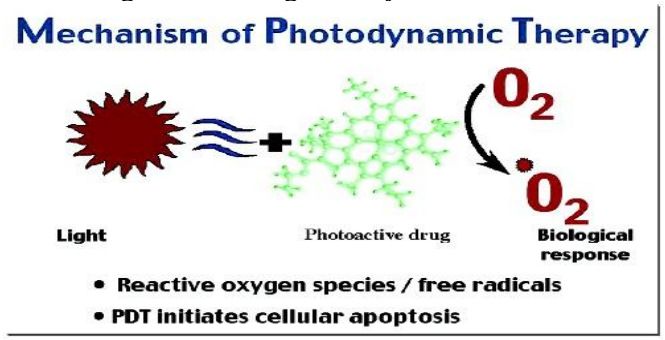


Figure 2. Showing "Triplet state"

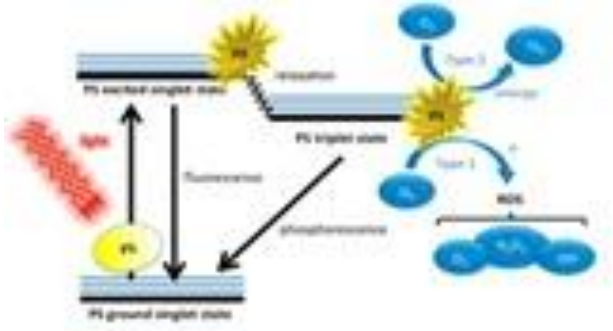


Figure 3. Different Photosensitisers used in PDT

Photosensitizer	
Platform	**Example**
Dyes	
- tricyclic dyes with different *meso*-atoms	Acridine Orange Methylene Blue Rose Bengal
- phthalocyanines	Toluidine Blue O
	sulphonated metallo-phthalocyanines (Photosense®)
Porphyrins	porphyrin derivative (HPD) (Photofrin®) 5-aminolevulinic acid (ALA) as prodrug benzoporphyrin derivative (BPD) lutetium texaphyrin
Chlorins	mono-L-aspartyl chlorin e_6 (NPe6) temoporfin (Foscan®) tinethyletiopurpurin (SnET2) talaporfin sodium (LS11)
Furocoumarins	psoralen

Figure 4.Light source used in PDT

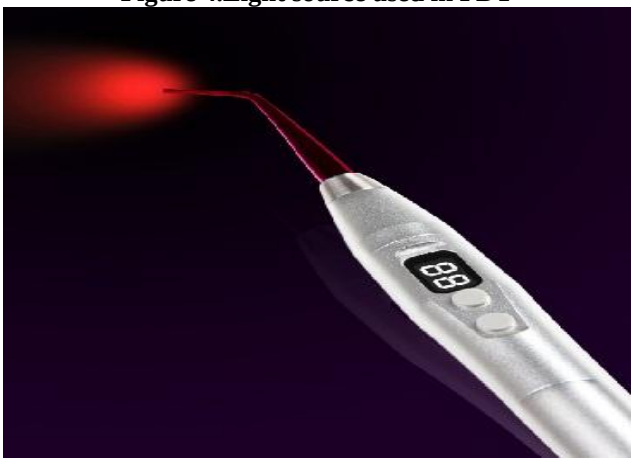


Figure 5. PDT in Oral & Mucosal infections

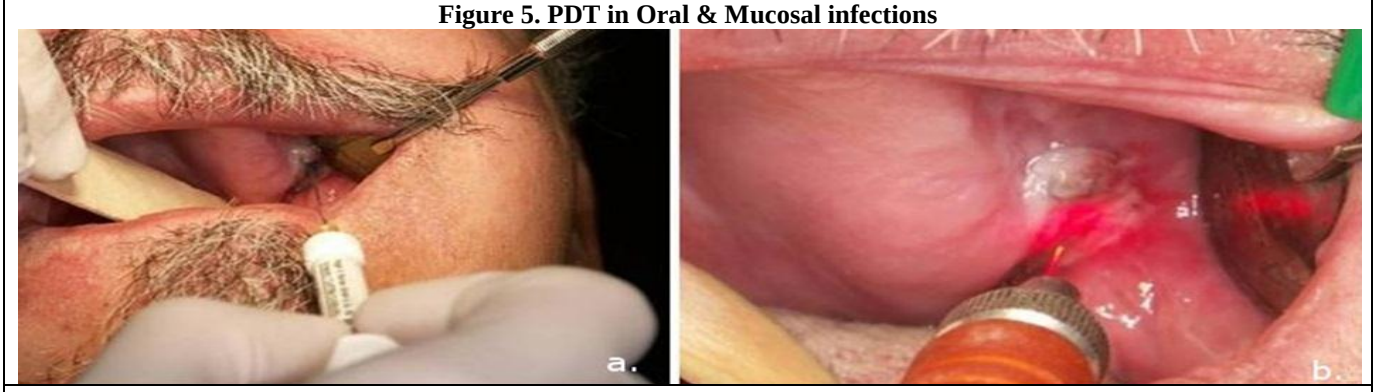


Figure 6.PDT used in Edodontic infections

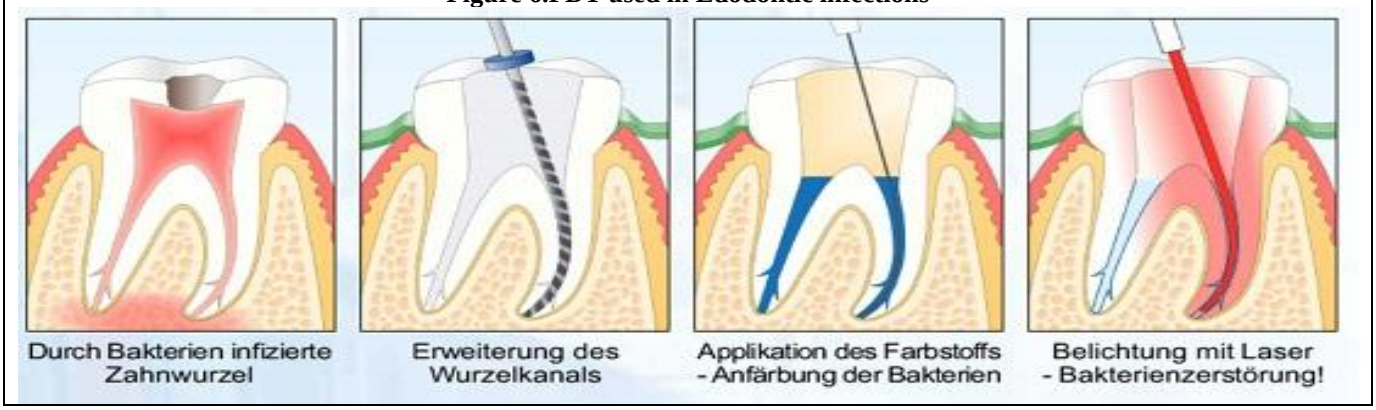


Figure 7. PDT used to treat carious lesions

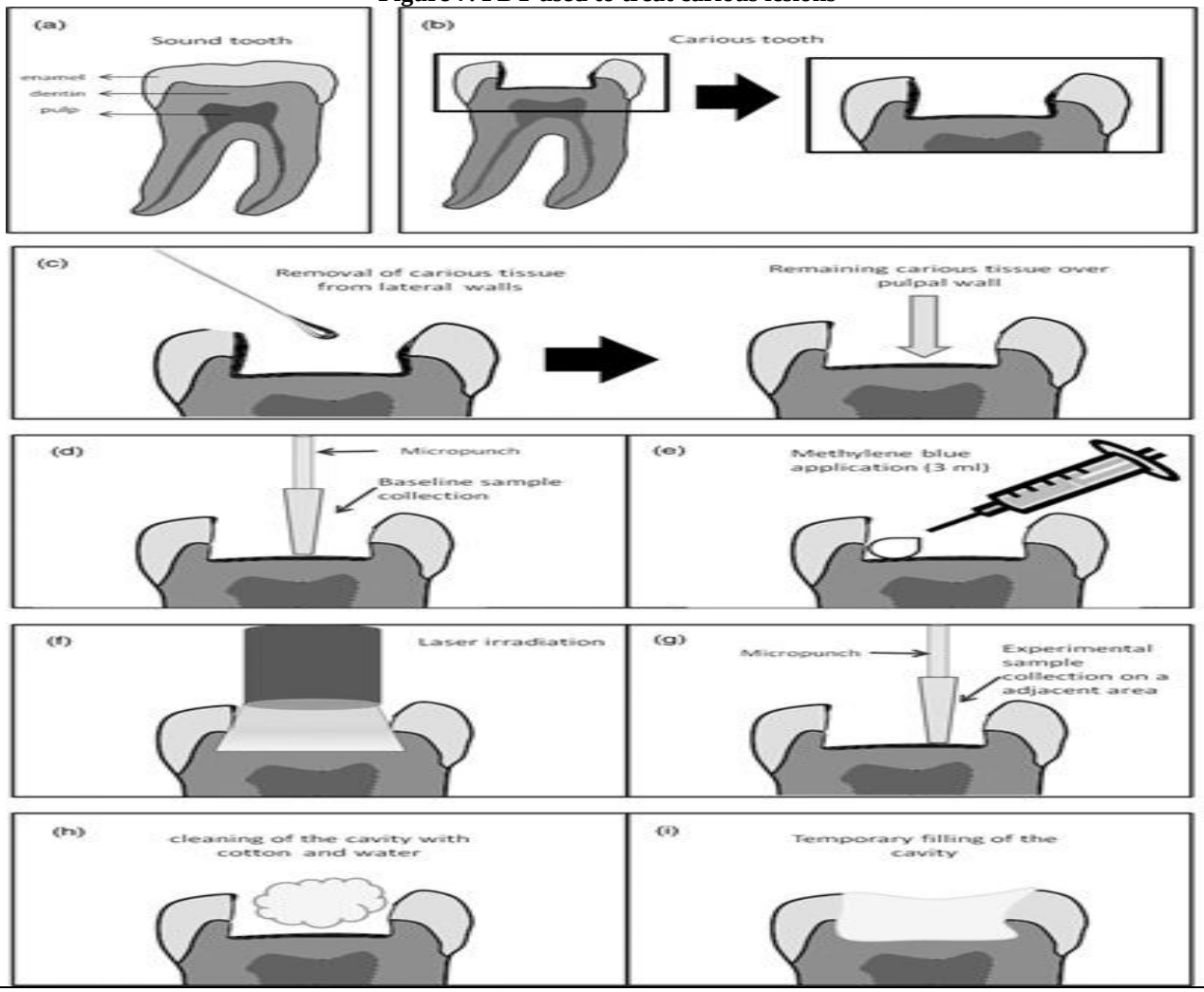
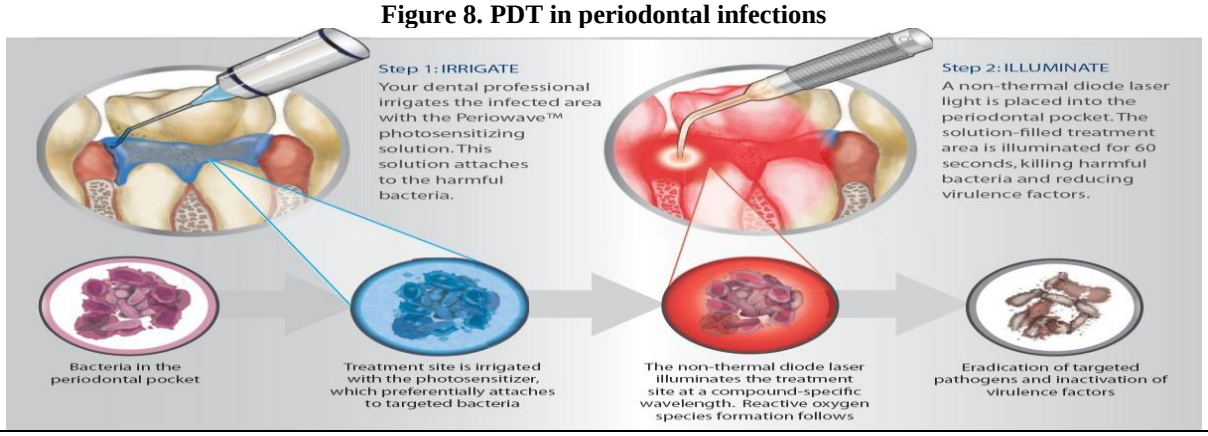


Figure 8. PDT in periodontal infections



CONCLUSION

The potential applications of photodynamic therapy to treat oral conditions seem limited only by our imagination. Applications appear not only the common oral diseases of dental caries and periodontal disease but also the conditions of oral cancer, periimplantitis, endodontic therapy, candidiasis and halitosis. Low toxicity and rapidity of effect are qualities of photodynamic therapy that are envitable. It is now the time to demonstrate clear evidence of clinical efficacy and applicability. At this time in history, it is difficult to know where light will lead us in the oral cavity but the promise is clear and the opportunities are visible.

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