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PUBLISHED PAPER'S TITLE : PHOTODYNAMIC THERAPY : A NEW AVENUE IN PERIODONTAL THERAPY

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Research Paper

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PHOTODYNAMIC THERAPY : A NEW AVENUE IN PERIODONTAL THERAPY

Dr. Tushar Pathak

Declaration

The Declaration of the author for publication of Research Paper in Asian Journal of Modern and Ayurvedic Medical Science (ISSN 2279-0772) I *Tushar Pathak* the author of the research paper entitled *PHOTODYNAMIC THERAPY : A NEW AVENUE IN PERIODONTAL THERAPY* declare that , I take the responsibility of the content and material of my paper as I myself have written it and also have read the manuscript of my paper carefully. Also, I hereby give my consent to publish our paper in ajmams , This research paper is my original work and no part of it or it's similar version is published or has been sent for publication anywhere else.I authorise the Editorial Board of the Journal to modify and edit the manuscript. I also give my consent to the publisher of ajmams to own the copyright of my research paper.

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ABSTRACT *:* The use of light for the treatment of infections heralds a new therapeutic era against a variety of pathogens including those associated with oral infections,wound infections,viral and fungal infections, and even the "superbug" infections.By preserving the use of antibiotics for only those cases where they are truly needed,we diminish the potential for antibiotic resistance.Clearly,this is of great benefit to the patients we treat.

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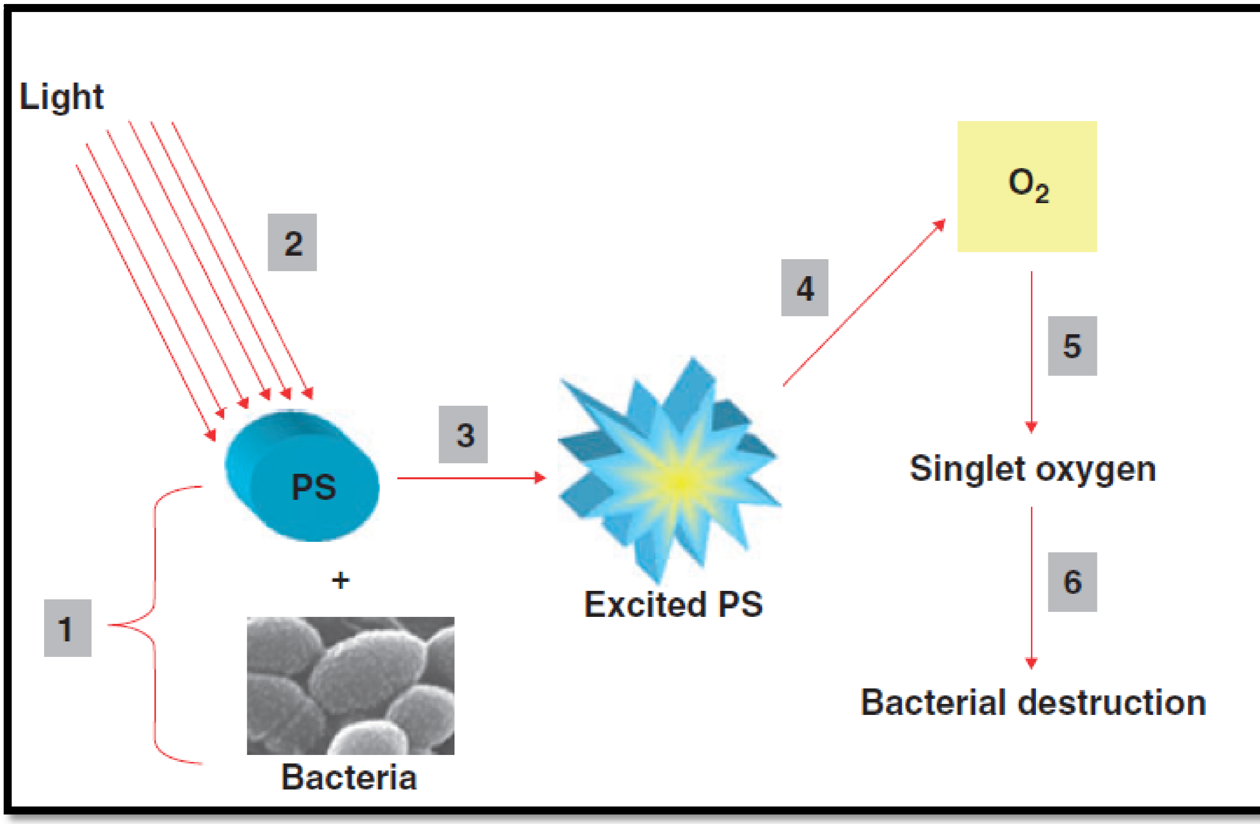
INTRODUCTION

Periodontitis is one of the major causes of tooth loss in adults and is considered primarily an anaerobic bacterial infection caused by the so called red complex species.[1] Enzymes,endotoxins, and other cytotoxic factors from these bacteria lead to tissue destruction and initiate chronic inflammation.[2] Debridement in the form of scaling and root planing (SRP) is the most effective method to treat this disease, sometimes with supplemental surgical therapy; however, systemic antimicrobial therapy can be beneficial by reducing tooth loss and surgical needs.[3] However, therapy that relies solely on decontamination might not be sufficient to treat the disease, irrespective of its proven abilities to kill these pathogens.[4] Additionally, concerns regarding systemic antibiotic use include side effects such as pseudomembranous enterocolitis, superinfection, other gastrointestinal disorders,[5] and emergence of antibiotic resistance.[6] Locally delivered antibiotics are an acceptable alternative for efficacy and are less likely to cause systemic side effects. However, disadvantages include inconvenience (because of a required change in oral hygiene habits), cost (repeated treatments),[7] and usability in relatively small areas in the oral cavity that are not convenient for management of a generalized disease. Other approaches to the local delivery of antimicrobial agents were investigated, including the use of photodynamic therapy (PDT).[8] Since the 1890s, scientists used the staining properties of dyes to develop the idea of selective toxicity. This created the foundation for our modern use of chemotherapy. The application of light and dyes to destroy microbial species in vitro has been reported for many years.[9,10] Well established photosensitizers such as methylene blue were reported to be antibacterial, antiviral and antiprotozoal since the Second World War.[11,12]

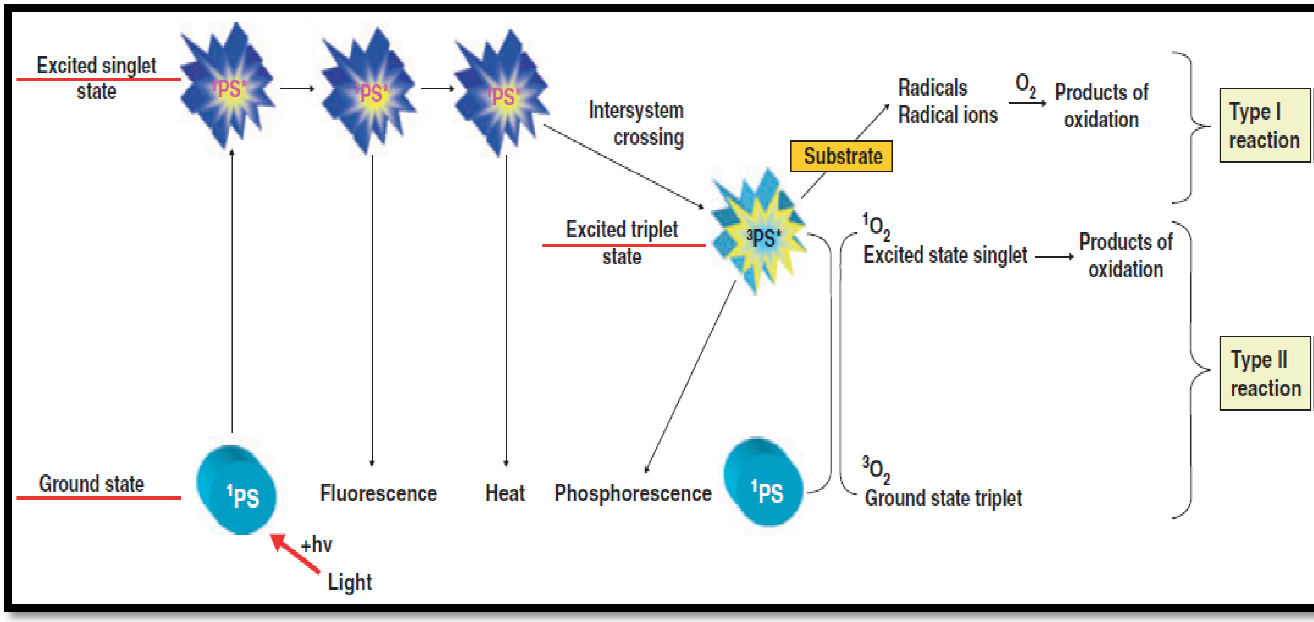
Recent years have seen extensive investigations into the antimicrobial activity of light activated agents (photosensitizers) that selectively bind to periodontal bacteria. Wilson first proposed the use of photosensitization as a tool for the treatment of periodontal diseases and methylene blue was selected due to its century-long history of safe use in humans.Activated photosensitizing agents cause the production of highly reactive oxygen that is, in turn,responsible for killing the bacteria inhabiting bacterial pockets and proximate mucosa . Virulence factors associated with gram negative bacteria are also inactivated. The use of photosensitization for killing periodantal pathogens may provide important therapeutic benefits, including no antibiotic resistance, the ability to treat the full depth of periodontal pockets, the ability to inactivate bacterial virulence factors, as well as a high level of safety and ease of use. Indeed, a number of recently published studies support this therapeutic concept. Photo disinfection treatment is a straightforward, two step clinical procedure. The first step is the irrigation of the affected periodontal site with the photosensitizing solution that selectively binds to bacteria. The second step consists of illuminating the site with the light –diffusing tip from a non-thermal diode laser of the appropriate wavelength (670nm) for 60 seconds.

HOW IT WORKS?



Mechanism of photodynamic therapy action. A photosensitizer is taken up by microorganisms(1) and following exposure to light of the appropriate wavelength (2) becomes activated to an excited state (3). Then, the photosensitizer transfers energy from light to molecular oxygen (4) to generate singlet oxygen and free radicals (5) that are cytotoxic to cells (6).

The basic phenomenon requires that the photosensitizer within affected areas of the periodontium (i.e., within periodontal pockets) be light activated or excited from its so-called ground or singlet state (which is a single peak if analyzed spectrophotometrically) into either a doublet or triplet state. This leads to the transfer of energy (electrons) that precipitates the formation of singlet oxygen species, which are cytotoxic, thereby mediating bacterial kill[11,12] Typically, the light must be of a specific wavelength as described by others, but even broad-spectrum light can activate photosensitizers such as toluidine blue. Because high-power lasers may induce trauma to surrounding tissues through thermal injury, lowpower light with a photosensitizer is an attractive alternative therapy.



TYPE I AND TYPE II REACTIONS IN PHOTODYNAMIC THERAPY

(Courtesy : Nikolaos S. Soukos & J. Max Goodson; Periodontology 2000, Vol. 55, 2011).

STEPS IN PHOTODYNAMIC THERAPY :

- Stained
- Sensitized
- Destroyed following exposure with light of a suitable wavelength and enegy density.

STEP 1 : Staining the microorganisms

Diffusion-detertmining step with migration and attachment of the dye molecules.

-on the wall of the microorganisms

-process parameters : Viscosity, pH-value, temperature, charge, time, structure of the plaque etc.

STEP 2 : Exposure and activation of photosensitizer

-Energy-controlled step

-determined by phtsical-optical properties

-with excitation of the sensitizer molecules

-from singlet state to triplet state.

-process parameterts: optical, electronic/ chemical states , pH- value, time etc.

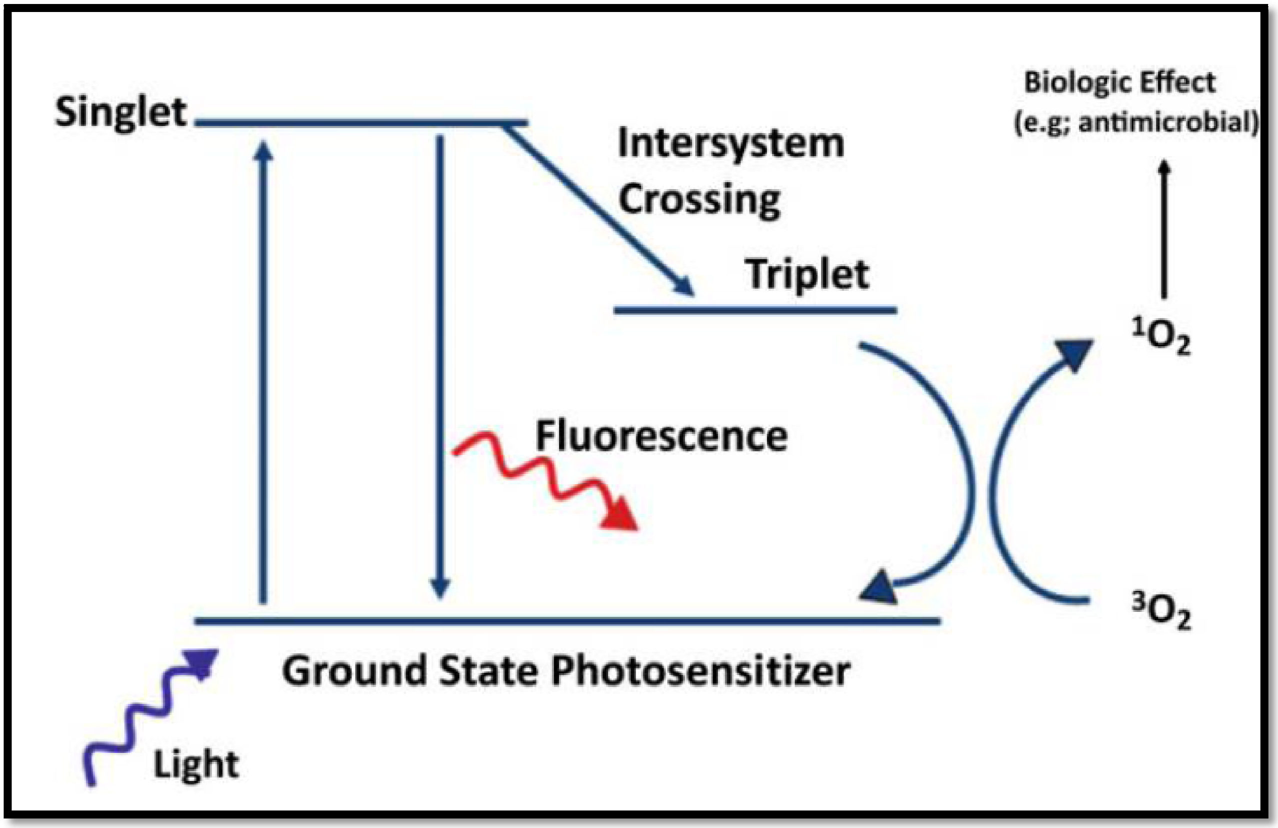
STEP 3 : Oxygen radical formation and

-destruction of the microorganisms

-Formation of singlet-oxygen radicals and

-oxidative destruction of membrane lipids and enzymes

-process parameters,chemical states, pH-values, time etc.



Principals of Photodynamic Therapy By Dr. Brian Wilson, Princess Margaret Hospital, Toronto.

THE KEY REACTION :

-Through the energy suplied via the laser light the photosensitizer is stimulated and converted into the triplet state.

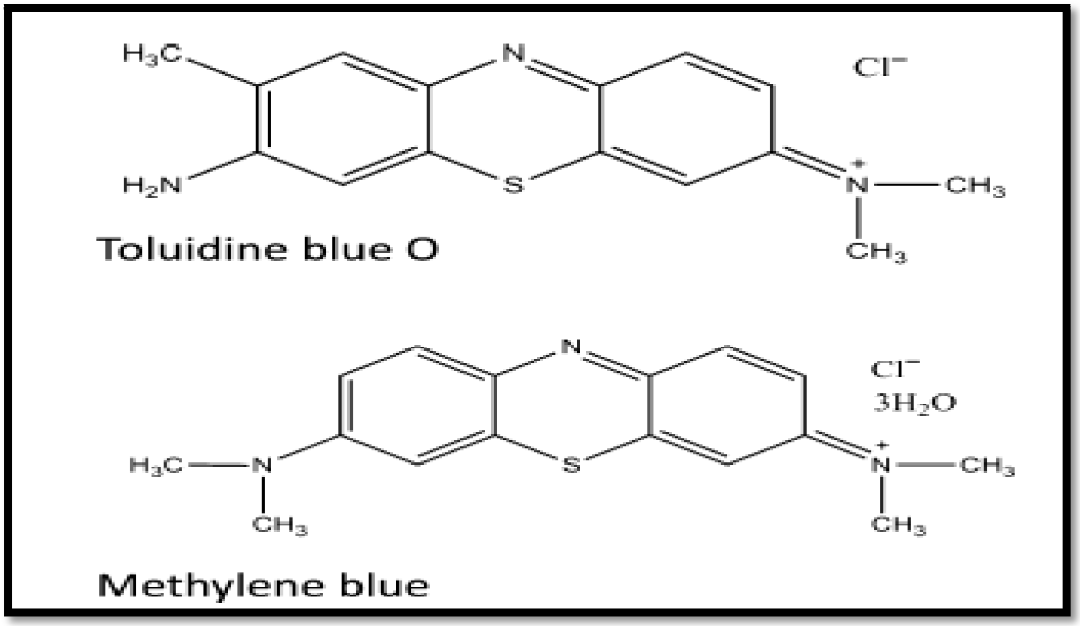
-The photosensitizer (the appropriate one) can transfer its energy to molecular oxygen , leading to the formation of singlet- oxygen (1 O_2 oxygen radicals).

The rate constant of the reaction between the activated photosensitizer and oxyzen is 3x 10^9 M^{-1} $sec^{-1.}$

THE PHOTOSENSITIZERS :

A dye in solution, that can be activated by light repeatedly.

Carbon rings function as "molecular prisms, they collect and store light.



Chemical structures of the phenothiazine photosensitizers toluidine blue O, C15H16N3SCl (also known as tolonium chloride) and methylene blue C16H18ClN3S (also known as methylthionine chloride).

Approved photosensitizers for use in photodynamic therapy :

1. Hematoporphyrin derivative (Porfimer sodium) Photofrin
2. Benzoporphyrin derivative monoacid Ring A (Verteporfin) Visudyne
3. 5-Aminolevulinic acid (ALA) Levulan
4. Methylaminolevulinate (MAL) Metvix
5. Meta-tetra hydroxyphenyl chlorine (Temoporfin) Foscan

GENERAL REQUIREMENTS OF A PHOTOSENSITIZER FOR FIGHTING BACTERIA:

-Photoactive with suitable laser
-non toxic
-Simple, drop-free, safe application
-moistening
-with controlled viscosity
-can also be used on open wounds
-no side effects
-stable over time

Licensed for use under the MPG or AMG (Medical Preaparations Act)

BIOLOGICAL TARGET MOLECULES ACHIEVED THROUGH THE RADICAL REACTIONS:

-Whilst carbohydrate bonds are rarely damaged by oxygen radicals, in the case of lipids, there is great damage.Since lipids are a major component of membranes (e.g. cell members), very sensitive disturbances to the membrane properties can be caused.

-Particularly susceptible to damage by oxygen radicals are unsaturated fatty acids in the membranes.

(Quoted from : Identification of photolabile outer membrane proteins of Porphyromonas gingivalis, Bhatti M,Nair SP, MacRobert AJ, Henders, In : Curr Microbiol, vol 43/2 (2001) pp.96-99)

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. Evolving therapeutic strategies for biofilm-related infections include the use of substances designed to target the biofilm matrix, nongrowing bacteria (persister cells) within biofilms and / or quorum sensing.[13] The use of bacteriophages[14] and naturally occurring or synthetic antimicrobial peptides may offer the possibility of bacterial targeting without the emergence of resistance. Recently, the advantages of targeted therapy become more apparent, and the use of light alone, antibody–photosensitizer and bacteriophage–photosensitizer conjugates or nonantibodybased targeting moieties, such as nanoparticles, are gaining increasing attention.

ANTIBODY-TARGETED ANTIBACTERIAL APPROACHES USING PHOTODYNAMIC THERAPY

Antibodies conjugated with photosensitizers have been used to target Staphylococcus aureus[15,16.17] Selective killing of P. gingivalis was achieved in the presence of Streptococcus sanguinis or in human gingival fibroblasts using a murine monoclonal antibody against P. gingivalis lipopolysaccharide conjugated with toluidine blue O. In two studies, bacteriophages were used as vehicles to deliver the photosensitizer tin(IV) chlorine e6 to the surface of S. aureus strains[18,19]. This led to approximately 99.7% killing of microorganisms. The combination of pulsed laser energy and absorbing gold nanoparticles selectively attached to the bacterium for killing of microorganisms is a new technology that was introduced recently. Gold nanoparticles are promising candidates for application as photothermal sensitizers and can easily be conjugated to antibodies.

NANOPARTICLE-BASED ANTIMICROBIAL PHOTODYNAMIC THERAPY

PLGA nanoparticles loaded with various compounds (e.g. antibiotics) have been used for bacterial targeting[20]; however, the use of PLGA nanoparticles as carriers of photosensitizers has not been explored in antimicrobial photodynamic therapy until recently. In future, a more thorough evaluation of the photodynamic effects of methylene blue-loaded nanoparticles would also require knowledge of various parameters that would lead to a maximum photodynamic effect on oral microbes, such as: the amount of methylene blue encapsulated in nanoparticles; the incubation time of methylene blue-loaded nanoparticles with microorganisms; the power density (mW / cm2); and the energy fluence (J / cm2) of light. In addition, the therapeutic window where microorganisms would be killed by methylene blue-loaded nanoparticles while leaving normal cells intact, as well as the role of nanoparticle charge, should also be explored. At a later stage, a comparison between the photodynamic effects of methylene blue-loaded nanoparticles and free methylene blue would be necessary.

CURRENT PHOTODYNAMIC THERAPY STATUS

Photodynamic therapy has found its greatest success in the treatment of cancer, age-related macular degeneration,actinic keratosis and Barretts esophagus.The application of photodynamic therapy for targeting pathogenic microbes in wound infections has been explored in animal models[21]. Photodynamic therapy with topical application of ALA is used offlabel for the treatment of acne vulgaris and has been employed for clinical use as an antifungal agent. In the dental field, photodynamic therapy is approved for the palliative treatment of patients with advanced head and neck cancer in the European Union, Norway and Iceland. Recently, in Canada, the product called Periowave (http://www.periowave. com) was commercialized by Ondine Biopharma Corporation (http://www.ondinebiopharma.com) for the treatment of periodontitis. The Periowave product consists of a laser system with a custom-designed handpiece and patient treatment kits of methylene blue. A kit that includes phenothiazine chloride for clinical photodynamic therapy is now available in Austria, Germany, Switzerland and the UK (Helbo; Photodynamic Systems GmbH & Co. KG, Grieskirchen, Austria). Similar kits that include toluidine blue O are also available from other companies, including Denfotex Ltd., Dexcel Pharma Technologies Ltd., SciCan Medtech AG and Cumdente GmbH.

CONCLUSIONS

The goal of periodontal therapy is to restore a homeostatic relationship between the oral microbial community and gingival tissue. Photodynamic therapy has the potential to kill periopathogenic bacteria and inhibit destructive host responses, and this may contribute to its clinical usefulness as an adjunctive therapy.The potential applications of photodynamic therapy to treat oral conditions seems to be limitless. Applications appear not only to treat 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 enviable. Thus,it is the time to demonstrate evidence of clinical efficacy and applicability and also it is difficult to know where light will lead us in the oral cavity but the promise is clear and the opportunities are evident.

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