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Original Research Paper

Dental Science

PHOTODYNAMIC THERAPY, ITS USES WITH AN INSIGHT ON PHOTOSENSETIZERS USED IN DENTISTRY

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ABSTRACT Developing science and technology have led to the invention of various newer modalities in the field of dentistry. One such modality of non-invasive treatment is Photodynamic Therapy which is used of multiple purposes, as a diagnostic tool for oral lesions, for the management of lesions in the oral cavity caused by the herpes simplex virus (or HSV), to achieve and maintain sterility inside the root canal, for plaque removal, treatment of oral candidiasis, as a tool in the treatment of peri-implantitis and peri-implant mucositis etc. An important part of Photodynamic therapy is Photosensitizer, there are various generations of photosensitizers and various newer advancements with incorporation of nanotechnology and gene therapy , which had been elaborated .

KEYWORDS : Photodynamic therapy, Photosensitizers, generations, newer advances

INTRODUCTION

Over the past few decades there has been a shift of research and technological innovations more towards non-invasive modalities of treatment and one such modality gaining reputation is photodynamic therapy (PDT).

HISTORICAL BACKGROUND

The ancient Egyptians understood that the sun had healing powers in treatment of skin conditions like vitiligo, psoriasis and skin cancer [1,2]. The same was used as heliotherapy extensively as treatment modality for tuberculosis. Later the Era of phototherapy started in 1890s, when a scientist Niels Finsen from Denmark worked with light sources in all ranges from small active rays to UV radiation in treatment of lupus vulgaris and smallpox [3,4] and has received Nobel Prize in 1903 [5].

In 1913, Fredrich Meyer-Betz tested with an intravenous injection of 200 mg hematoporphyrin (derived from protoporphyrin IX, with 2 vinyl groups hydrated) on himself [7,8] and noted the development of extreme pain and swelling, which was confined to the areas exposed to light; this area remained photosensitive for several months after the incident. He concluded that hematoporphyrin was a Photosensetizer (PS) agent.

The basic science and clinical applications of hematoporphyrin derivatives were given by Dougherty et al. [9] who later in 1986, established the International Photodynamic Association and expanded it globally. In 1999, FDA approved PDT to treat precancerous skin lesions of the face or scalp, cancers and certain other diseases. Photofrin® is the most extensively studied and clinically used photosensitizer. With their continuous efforts biochemists synthesized particles that mimicked as improved PSs, now suggested as potentially beneficial to mediate PDT for attacking cancer, infections and many other diseases.

Applications Of PDT In Dentistry

In treatment of pre-malignant and malignant lesions of the head and neck region, including the oral cavity mainly:

1. The topical application of the photosensitizer aminolevulinic acid (ALA) is used as a diagnostic tool for oral lesions, in a procedure known as ALA-based photodynamic diagnosis.
2. PDT used for the management of lesions in the oral cavity caused by the herpes simplex virus (or HSV), for rapid healing with no acute side effects of PDT [11].
3. Use of PDT in both the prevention and treatment of alveolar osteitis and post-extraction pain [12].
4. In endodontics, to achieve and maintain sterility inside the root canal by the complete elimination of bacterial species colonizing it and causing infections [13].
5. PDT-assisted plaque removal, also famous as photodynamic antimicrobial chemotherapy (PACT) [14]. First used and pronounced by Bevilacqua et al. [15], by using toluidine blue and an LED laser light.
6. PDT is known to be an effective antibacterial technique, there is evidence to suggest its efficacy in the treatment of periodontal diseases [14,16,17]
7. PDT in combination with mechanical debridement around the infected implant surface provides a useful tool in the treatment of peri-implantitis and peri-implant mucositis [18].
8. Antimicrobial PDT in the treatment of oral candidiasis [10]
9. As an adjunct to non-surgical periodontal therapy in the management of Chronic periodontitis

The Photodynamic therapy (PDT) also termed photoradiation therapy, phototherapy, photochemotherapy, photo-activated disinfection (PAD), or light-activated disinfection (LAD), involves the combination of visible light, usually through the use of a diode laser and a photosensitizer [19]. The PDT involves three main components i.e. light source, a non-toxic photosensitizer and oxygen.

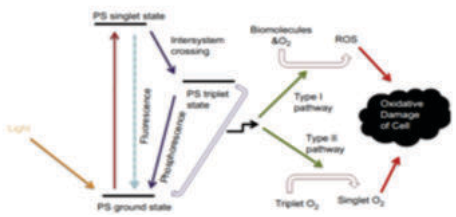

Figure 1: Mechanism of Action of PDT

Sources: www.googleimages .com/ PDT

Photosensitive Dyes

Photosensitizer an element proficient of light absorption of specific wavelength and with an ability to convert it into useful energy. When used unaccompanied, the two components (i.e. photosensitizer and light) are detrimental. However, when combined they will lead to the creation of lethal cytotoxic substances (ROS) which can selectively damage bacteria or human cells (Sharman et al. 1999). Hence, PDT has been projected as a means of reducing bacterial load or even to eliminate periodontal pathogens [20].

Ideal Properties Of Ps Agent

Should be only wholesome compound to permit preparation under good manufacturing practice (GMP) situations having good quality control and low production costs, and have better stability enabling storage.

Should have a strong absorption peak in the red to near-infrared spectral region (between 650 and 800 nm) because absorption of single photons with wavelengths longer than 800 nm does not provide enough energy to excite oxygen to its singlet state.

Possess long lifetime at the triplet state
PSs should possess a substantial triplet quantum yield leading to good production of ROS upon irradiation.

It should have appropriate photostability, no dark toxicity and relatively rapid clearance from normal tissues, thereby minimizing the side effects of photo toxicity

The interval between drug administration and irradiation (drug–light interval, DLI) to be as long as possible (up to 4 days), so that the PS was given sufficient time to clear from normal tissues, while remaining concentrated in tumours.

Have appropriate energy at the triplet state to provide sufficient energy at the transfer to ground state

Some of the most effective PS compounds have been found preferentially to low-density lipoprotein (LDL) among various serum proteins, and it has been proposed that overexpressed LDL receptors that are sometimes found on tumour cells could be important in tumour localization [21].

The ideal PS structure is very different between anti-cancer drugs and antimicrobial drugs. Anti-cancer PSs tend to be lipophilic with little or no overall charge (either positive or negative). Antimicrobial PSs, on the other hand, should have pronounced cationic charges, and in many cases the more charges the better especially for targeting Gram-negative bacteria. Anticancer PSs are usually expected to have long wavelength (far red/near-infrared) absorption bands for good tissue penetration of the exciting light, whereas for antimicrobial PSs, this property is much less important as infections that will be treated by PDT tend to be rather superficial in nature

Generations Of PSS

First Generation

First generation PSs have been available since the 1960s. They include cyclic tetrapyrroles, comprising substituted derivatives of porphyrin, chlorin and bacteriochlorin, which are structural derivatives of hematoporphyrin with an activation wavelength of 620-650nm [22,23].

Drawbacks Of These PSS Are

- high aggregation tendency
- lack of specificity
- low solubility in physiological liquids
- cutaneous phototoxicity.

Hence by current standards for use in PDT most of the first generation PSs are unsuitable, but they provided a source for the synthesis of new PSs. Hematoporphyrin is commercially known as Photofrin®, is most widely studied and clinically used photosensitizer to date. It was initially permitted for treatment of lung, bladder, esophageal and early stage cervical cancers in the 1950s, later as used a PS agent [25,26]. Moreover, hypericin, eosin, methylene blue and rose bengal previously employed as PS agents; currently have different indications [27].

Porphyrins possess unique advantages in PDT due to their strong 1O2 generation efficiency and excellent fluorescence property. One of porphyrins derivative, Photofrin is recorded as the first-generation PS for PDT. Unfortunately, Photofrin suffers from poor water solubility and low extinction coefficient in the NIR region.

Second Generation

Second generation PSs developed in the late 1980s, as an attempt to improve the efficacy of first generation agents with better pharmacokinetic properties and a lower toxicity [28, 29]. In addition, these PSs have a near infrared absorption and a high 1O2 yield compared with the first generation compounds [30].

Verteporfin, talaporfin, temoporfin are few examples: these include core or structurally modified or substituted porphyrins, bacteriochlorins, chlorins, phthalocyanines or other macrocyclic compounds [31]. The most commonly used and well-known are 5-aminolevulinic acid (ALA) and a structurally modified version of hematoporphyrin [28, 29].

ALA is 5-aminolevulinic acid so-called intrinsic photosensitizer, that is converted in situ to protoporphyrin IX. The introduction of exogenous ALA in vivo inhibits the first step of porphyrin synthesis, resulting in the accumulation of protoporphyrin IX in the tissue [28,29]. Topical ALA and its ester derivatives have been approved by the FDA and used to treat many diseases, like pre-cancer conditions, basal and squamous cell carcinoma of the skin, Bowen's disease, and actinic (solar) keratoses and gastrointestinal cancers [32].
Phthalocyanines (Pcs) are the second-generation PSs containing intensely blue-green-colored aromatic macrocyclic compound. Pcs exhibit strong absorption band at the red region, and the presence of metal atom, such as Zn, Al, and Si, yields a long T1 lifetime and a high 1 O2 generation quantum yield. [29] However, the drawback of Pcs includes strong aggregation in aqueous solution and slow in vivo clearance should be solved before their application in clinical PDT

Third Generation

Third generation PSs are the most recently developed compounds of medicinal use; the derivatives of the second generation PS compounds possess various advantages in their use [28]. These are second generation PS compounds that are usually conjugated with some biological molecules or they have built in "photo-quenching" properties, i.e., these photosensitive materials only become activated at their specific target site (e.g., protein, receptor) [32].

Possible carrier molecules for the former group includes monoclonal antibodies, non-antibody-based protein carriers, monosaccharides, polymers, polymeric nanoparticles (NPs) or liposomes; while cellular markers for the latter group include tumor surface markers (e.g., epidermal growth factor receptor), receptors (e.g., low-density lipoprotein (LDL)

receptors, transferrin receptors, folic acid receptors, integrin receptors) and transporters (e.g., glucose transporters) [28,32]. The conjugation of fullerenes with polyethylene glycol (PEG) increases their tumor localization and increases their solubility in water-based solvents and in vivo biological conditions [33].

Type and generation of photosensitizers

Generation	Photosensitizers
First	Porphyrins
	• Photofrin
	• Hematoporphyrin
	• Hematoporphyrin derivatives (HPDs)
	-Porfimer sodium
Second	Porphyrins
Non-porphyrins	• Metalloporphyrins
• Psoralen	• Porphycenes
• Anthracyclines	• Pheophorbides
• Chalcogenopyrylium	• Purpurin
• ADPMs	Tinethyletiopurpurin (SnET2)
• Cyanines	• Chlorins
• Phenothiazium dyes	Mono-L-aspartyl chlorin e6
Methylene blue	• Phthalocyanines
Toluidine blue	Aluminum disulfonated phthalocyanine
• Xanthenes	Naphthalocyanine
Erythrosine	• 5-Aminolevulinic acid (ALA)
• Monoterpene	• Benzoporphyrin derivative (BPD)
Azulene	• Texaphyrin
	• Meta-Tetra (hydroxyphenyl) porphyrins (mTHPP)
	• Talaporfin sodium (LS11) mTHPC
Third	2nd generation plus biologic conjugates (e.g., antibody conjugate, liposome conjugate)

Figure 1: Generations of Photosensitizers
Sources: www.googleimages .com/ types and generations of Photosensitizers

Other PSs that are organic and presently being studied for medical use are:
Indocyanine dyes, such as indocyanine green (ICG), IR-825, and IR-780, show considerable application in fluorescence imaging and PDT due to their NIR absorption and excellent biocompatibility. it can selectively accumulate in mitochondria, which is favourable to overcome the hypoxia factor and enhance the PDT efficiency.

BODIPYs (boron-dipyrromethene) have many ideal PS features, i.e., high extinction coefficient, environment insensitivity, high photostability, excellent biocompatibility, and high 1O2 generation quantum yield.

DPP (dipalmitolyphosphatidylcholine) has been widely used in organic solar cells, organic field effect transistor, fluorescence sensing, and bio imaging due to its excellent photostability and high fluorescence quantum yield. However, the low O2 generation quantum yield and non-targeting property of DPP prevent its application in PDT.

Curcumin is a photoactive, polyphenolic compound derived from the turmeric root. Curcumin shows excellent phototoxicity to cancer cells and cytoprotectivity to normal cells. However, the poor water solubility and a rapid clearance from the living body prevent this natural PS from in vivo applications. Many trials to overcome these disadvantages and improve the bioavailability of curcumin, such as formation NPs or micelle nanostructures, and assembling with liposomal carriers are in pipeline. Curcumin is activated by blue light [34]. Most applications of curcumin are as an antimicrobial PS aiding in eradication of oral pathogens [35].

Furocoumarins are natural and synthetic compounds with structure consisting of a furan ring fused with coumarin. Furocoumarins have been already used in treating skin diseases and cutaneous T-cell lymphoma due to their ROS generation capability under UV light irradiation. The generated ROS would further impair cellular functions through lipid peroxidation, guanine and strand break oxidation in nucleic acids, proteins oxidation, and enzyme inactivation. However, furocoumarins suffer from poor solubility and selectivity, and several long-term side effects, such as skin phototoxicity. Although surfaced modification with water-soluble groups and tumor-targetable probes can overcome these drawbacks, the UV light excitation feature is limited in PDT of deep cancer. [36]

Riboflavin (vitamin B2) has been explored as an antimicrobial PS. It has been tested for antimicrobial [37] and blood product sterilization [38] applications, and also as a photoactivated crosslinker for corneal stiffening [39]. Riboflavin has two peaks in the UVA (360 nm) and blue (440 nm) regions. Maisch et al. [40] have synthesized a cationic version of riboflavin designed as an antimicrobial PS.

Newer Advances In Dyes

Most effective PSs tend to be insoluble, hydrophobic molecules with a high propensity to aggregate means that encapsulation in nano-drug carriers may make a big difference to their performance [41]. Moreover many other nanostructures such as plasmonic gold nanoparticles, mesoporous silica nanoparticles, carbon nanotubes, graphene and upconversion nanoparticles have found uses in PDT [42]. There is another group of nanostructures where the actual nanoparticle itself acts as the PS absorbing light and producing ROS, as in the case of fullerenes [43], titanium dioxide [41] and some types of quantum dots [44].

Nanoparticle PS Delivery

A variety of nanoparticles are used to solubilize, encapsulate and deliver PSs to both tumours and microbial cells [45]. Liposomes, micelles, nano emulsions can all be constructed out of lipids or amphiphilic polymers that self-assemble into delivery vehicles for PSs [46]. These Nano vehicles have many advantages, the most important of which are providing a big increase in photochemical efficiency, and the ability to localize in tumours after IV injection due to the EPR effect [47]

Titanium Dioxide

It has long been known that titanium dioxide (TiO2) or titania acts as a large band gap semiconductor. When excited with UVA light, an electron is excited from the valence band into the conductance band leaving behind a positively charged hole. The electron can produce superoxide from oxygen, whereas the hole can produce hydroxyl radicals from water. These ROS have been used in the process of photocatalysis which is used to kill micro-organisms and degrade organic pollutants [48]. In recent times TiO2 nanoparticles have been used as PDT agents often as composites or hybrids [49,50].

Quantum Dots

Although many researchers have prepared conjugates between quantum dots and various different PSs to carry out PDT [51– 53], a recent study showed that graphene quantum dots could mediate PDT on their own without any added PS [52].

Future Trends

In present technological era nucleic acid-based therapeutics as a form of gene therapy, KillerRed has been used as an optogenetic tool to allow the light-mediated inactivation of specific groups of neurons in Caeorhabditis elegans in transgenic zebrafish, in Xenopus laevis embryos [53] and in the mouse retina [54]. Another such genetically encoded PS is the flavoprotein 'miniSOG' [55].

Furthermore, theranostic agents could also be designed to incorporate a method to monitor the effectiveness of treatment, possibly in real-time, and in the days following treatment. Porphysomes (self-assembled nanostructures from lipid-conjugated porphyrins) are an interesting example of a

theranostic PDT agent [56].

In Oral and maxillofacial diseases, the two commonly used PSs are of blue and green groups. The PSs under Phenothiazium dyes are Methylene blue and Toluidine blue showing optimum results when activated with a laser of wavelength 640-680 nm. The other group consisting of Indocyanine green and Malachite green with sensitivity to activation with a laser of wavelength 800-830nm.

CONCLUSION

Many significant advances have been made in PS design during the last 20 years, and second, third and even fourth-generation PSs have been described. The requirements for an optimal photosensitizer are the following:

- commercial availability in its pure chemical form
- cost-effectiveness
- ease of administration
- long wavelength absorbing-capacity
- low dark toxicity but strong photo cytotoxicity
- good selectivity towards target cells and rapid elimination

Although there is currently no PS which adheres to all the above-mentioned criteria, this list provides a general guideline for the development of novel agents. Currently, there are only a few PSs that have received official approval for clinical use around the world, thus it is imperative to carry out more research in this field to find additional compounds for treatment.

The development of novel PSs should address issues with mutagenicity selectivity and the more precise targeting of PSs, dependable activation by an appropriate wavelength of light (both of which were the main objectives during the development of third generation PSs) and options for pain-free outpatient therapy. The possible development of photosensitizers with longer activation wavelengths will also allow for deeper tissue penetration.

REFERENCES

[1] Abdel-kader, M.H. Chapter 1 The Journey of PDT Throughout History: PDT from Pharos to Present. In Photodynamic Medicine: From Bench to Clinic; Royal Society of Chemistry: London, UK, 2016; pp. 1–21. [Google Scholar]

[2] Kessel, D. Photodynamic Therapy: A Brief History. J. Clin. Med. 2019, 8, 1581. [Google Scholar] [CrossRef][Green Version]

[3] Møller, K.I.; Kongshoj, B.; Philipsen, P.A.; Thomsen, V.O.; Wulf, H.C. How Finsen's light cured lupus vulgaris. Photodermatol. Photoimmunol. Photomed. 2005, 21, 118–124. [Google Scholar] [CrossRef]

[4] Grzybowski, A.; Pietrzak, K. From patient to discoverer--Niels Ryberg Finsen (1860–1904)—The founder of phototherapy in dermatology. Clin. Dermatol. 2012, 30, 451–455. [Google Scholar] [CrossRef] [PubMed]

[5] Gøtzsche, P. Niels Finsen's treatment for lupus vulgaris. J. R. Soc. Med. 2011, 104, 41–42. [Google Scholar] [CrossRef][Green Version]

[6] Sharma, S.K.; Mroz, P.; Dai, T.; Huang, Y.-Y.; Denis, T.G.S.; Hamblin, M.R. Photodynamic Therapy for Cancer and for Infections: What Is the Difference? Israel J. Chem. 2012, 52, 691–705. [Google Scholar] [CrossRef] [PubMed][Green Version]

[7] Szeimies, R.-M.; Dräger, J.; Abels, C.; Landthaler, M. Chapter 1 History of photodynamic therapy in dermatology. In Comprehensive Series in Photosciences; Calzavara-Pinton, P., Szeimies, R.-M., Ortel, B., Eds.; Photodynamic Therapy and Fluorescence Diagnosis in Dermatology; Elsevier: Amsterdam, The Netherlands, 2001; Volume 2, pp. 3–15. [Google Scholar]

[8] Sternberg, E.D.; Dolphin, D.; Brückner, C. Porphyrin-based photosensitizers for use in photodynamic therapy. Tetrahedron 1998, 54, 4151–4202. [Google Scholar] [CrossRef]

[9] Dougherty, T.J.; Gomer, C.J.; Henderson, B.W.; Jori, G.; Kessel, D.; Korbelik, M.; Moan, J.; Peng, Q. Photodynamic therapy. J. Natl. Cancer Inst. 1998, 90, 889–905. [Google Scholar] [CrossRef][Green Version]

[10] Akpan, A.; Morgan, R. Oral candidiasis. Postgrad. Med. J. 2002, 78, 455–459. [Google Scholar] [CrossRef]

[11] Marotti, J.; Aranha, A.C.C.; Eduardo, C.D.P.; Ribeiro, M.S. Photodynamic Therapy Can Be Effective as a Treatment for Herpes Simplex Labialis. Photomed. Laser Surg. 2009, 27, 357–363. [Google Scholar] [CrossRef]

[12] Saini, R.; Lee, N.V.; Liu, K.Y.P.; Poh, C.F. Prospects in the Application of Photodynamic Therapy in Oral Cancer and Premalignant Lesions. Cancers 2016, 8, 83. [Google Scholar] [CrossRef] [PubMed][Green Version]

[13] Persoon, I.F.; Özok, A.R. Definitions and Epidemiology of Endodontic Infections. Curr. Oral Health Rep. 2017, 4, 278–285. [Google Scholar] [CrossRef][Green Version]

[14] Almeida, A. Photodynamic Therapy in the Inactivation of Microorganisms. Antibiotics 2020, 9, 138. [Google Scholar] [CrossRef][Green Version]

[15] Bevilacqua, I.M.; Nicolau, R.A.; Khouri, S.; Brugnera, A.; Teodoro, G.R.; Zângaro, R.A.; Pacheco, M.T.T. The impact of photodynamic therapy on the viability of Streptococcus mutans in a planktonic culture. Photomed. Laser Surg. 2007, 25, 513–518. [Google Scholar] [CrossRef]

[16] Huang, L.; Xuan, Y.; Koide, Y.; Zhiyentayev, T.; Tanaka, M.; Hamblin, M.R. Type I and Type II mechanisms of antimicrobial photodynamic therapy: An in vitro study on Gram-negative and Gram-positive bacteria. Lasers Surg. Med. 2012, 44, 490–499. [Google Scholar] [CrossRef][Green Version]

[17] Memar, M.Y.; Ghotaslou, R.; Samiei, M.; Adibkia, K. Antimicrobial use of reactive oxygen therapy: Current insights. Infect. Drug Resist. 2018, 11, 567–576. [Google Scholar] [CrossRef][Green Version]

[18] Sivaramakrishnan, G.; Sridharan, K. Photodynamic therapy for the treatment of peri-implant diseases: A network meta-analysis of randomized controlled trials. Photodiagnosis Photodyn. Ther. 2018, 21, 1–9. [Google Scholar] [CrossRef]

[19] Tapeiner HV. For knowledge of light-acting (fluorescent) substances. DMW-German Medical Weekly. 1904 Apr;30(16):579-80.

[20] Dobson J, Wilson M. Sensitization of oral bacteria in biofilms to killing by light from a low-power laser. Archives of oral biology. 1992 Nov 1;37(11):883-7.

[21] Harisa GI, Alanazi FK. Low density lipoprotein bionanoparticles: From cholesterol transport to delivery of anti-cancer drugs. Saudi Pharmaceutical Journal. 2014 Dec 1;22(6):504-15

[22] Kou, J.; Dou, D.; Yang, L. Porphyrin photosensitizers in photodynamic therapy and its applications. Oncotarget 2017, 8, 81591–81603. [Google Scholar] [CrossRef] [PubMed][Green Version]

[24] Kwiatkowski, S.; Knap, B.; Przystupski, D.; Saczko, J.; K□dzierska, E.; Knap-Czop, K.; Kotli□ska, J.; Michel, O.; Kotowski, K.; Kulbacka, J. Photodynamic therapy—Mechanisms, photosensitizers and combinations. Biomed. Pharmacother. 2018, 106, 1098–1107. [Google Scholar] [CrossRef]

[25] Lam, S. Photodynamic therapy of lung cancer. Semin. Oncol. 1994, 21, 15–19. [Google Scholar] [CrossRef][Green Version]

[26] Kessel, D. More Adventures in Photodynamic Therapy. Int. J. Mol. Sci. 2015, 16, 15188–15193. [Google Scholar] [CrossRef][Green Version]

[27] Rkein, A.M.; Ozog, D.M. Photodynamic therapy. Dermatol. Clin. 2014, 32, 415–425. [Google Scholar] [CrossRef]

[28] Kou, J.; Dou, D.; Yang, L. Porphyrin photosensitizers in photodynamic therapy and its applications. Oncotarget 2017, 8, 81591–81603. [Google Scholar] [CrossRef] [PubMed][Green Version]

[29] Kwiatkowski, S.; Knap, B.; Przystupski, D.; Saczko, J.; K□dzierska, E.; Knap-Czop, K.; Kotli□ska, J.; Michel, O.; Kotowski, K.; Kulbacka, J. Photodynamic therapy—Mechanisms, photosensitizers and combinations. Biomed. Pharmacother. 2018, 106, 1098–1107. [Google Scholar] [CrossRef]

[30] Josefsen, L.B.; Boyle, R.W. Photodynamic Therapy and the Development of Metal-Based Photosensitisers. Met. Based Drugs 2008, 2008. [Google Scholar] [CrossRef][Green Version]

[31] Allison, R.R.; Downie, G.H.; Cuenca, R.; Hu, X.-H.; Childs, C.J.; Sibata, C.H. Photosensitizers in clinical PDT. Photodiagnosis Photodyn. Ther. 2004, 1, 27–42. [Google Scholar] [CrossRef]

[32] Yang, X.; Palasuberniam, P.; Kraus, D.; Chen, B. Aminolevulinic Acid-Based Tumor Detection and Therapy: Molecular Mechanisms and Strategies for Enhancement. Int. J. Mol. Sci. 2015, 16, 25865–25880. [Google Scholar] [CrossRef][Green Version]

[33] Meisel, P.; Kocher, T. Photodynamic therapy for periodontal diseases: State of the art. J. Photochem. Photobiol. B, Biol. 2005, 79, 159–170. [Google Scholar] [CrossRef]

[34] Bernd, A. (2014) Visible light and/or UVA offer a strong amplification of the anti-tumor effect of curcumin. Phytochem. Rev. 13, 183–189 CrossRef PubMed Leite, D.P., Paolillo, F.R., Parmesano, T.N., Fontana, C.R. and Bagnato, V.S. (2014)

[35] Effects of photodynamic therapy with blue light and curcumin as mouth rinse for oral disinfection: a randomized controlled trial. Photomed. Laser Surg. 32, 627–632 CrossRef PubMed

[36] Bruni R, Barreca D, Protti M, Brighenti V, Righetti L, Anceschi L, Mercolini L, Benvenuti S, Gattuso G, Pellati F. Botanical Sources, Chemistry, Analysis, and Biological Activity of Furanocoumarins of Pharmaceutical Interest. Molecules.2019;24(11):2163.https://doi.org/10.3390/molecules24112163

[37] Makdoumi, K., Backman, A., Mortensen, J. and Crafoord, S. (2010) Evaluation of antibacterial efficacy of photo-activated riboflavin using ultraviolet light (UVA). Graefes Arch. Clin. Exp. Ophthalmol. 248, 207–212 CrossRef PubMed

[38] Ettinger, A., Miklauz, M.M., Bihm, D.J., Maldonado-Codina, G. and Goodrich, R.P. (2012) Preparation of cryoprecipitate from riboflavin and UV light-treated plasma.Transfus. Apher. Sci. 46, 153–158 CrossRef PubMed

[39] Chan, T.C., Lau, T.W., Lee, J.W., Wong, I.Y., Jhanji, V. and Wong, R.L. (2015) Corneal collagen cross-linking for infectious keratitis: an update of clinical studies. Acta Ophthalmol. CrossRef PubMed

[40] Maisch, T., Eichner, A., Spath, A., Gollmer, A., Konig, B., Regensburger, J. and Baumler, W. (2014) Fast and effective photodynamic inactivation of multiresistant bacteria by cationic riboflavin derivatives. PLoS One 9, e111792 CrossRef PubMed

[41] Brown EM, Allen LL, Pyles H, Solis J, Wileman TA, Willadsen GB. Advancements in using TiO2 bionanoconjugates for precision degradation of intracellular biological structures. J Biomed Nanotechnol. 2013;9:539–550. [PubMed] [Google Scholar]

[42] Huang YY, Sharma SK, Dai T, Chung H, Yaroslavsky A, Garcia-Diaz M, Chang J, Chiang LY, Hamblin MR. Can nanotechnology potentiate photodynamic therapy? Nanotechnol Rev. 2012;1:111–146. [PMC free article] [PubMed] [Google Scholar]

[43] Mroz P, Tegos GP, Gali H, Wharton T, Sarna T, Hamblin MR. Photodynamic therapy with fullerenes. Photochem Photobiol Sci. 2007;6:1139–1149. [PMC free article] [PubMed] [Google Scholar]

[44] Ge J, Lan M, Zhou B, Liu W, Guo L, Wang H, Jia Q, Niu G, Huang X, Zhou H, et al. A graphene quantum dot photodynamic therapy agent with high singlet oxygen generation. Nat Commun. 2014;5:4596. [PMC free article] [PubMed] [Google Scholar]

[45] Master, A., Livingston, M. and Sen Gupta, A. (2013) Photodynamic nanomedicine in the treatment of solid tumors: perspectives and challenges. J. Control. Release 168,88–102 CrossRef PubMed

[46] Sadasivam, M., Avci, P., Gupta, G.K., Lakshmanan, S., Chandran, R., Huang, Y.Y., Kumar, R. and Hamblin, M.R. (2013) Self-assembled liposomal nanoparticles in photodynamic therapy. Eur. J. Nanomed. 5, 115–129 PubMed

[47] Avci, P., Erdem, S.S. and Hamblin, M.R. (2014) Photodynamic therapy: one step ahead with self-assembled nanoparticles. J. Biomed. Nanotechnol. 10, 1937–1952 CrossRef PubMed
[48] Liao, Z.X., Li, Y.C., Lu, H.M. and Sung, H.W. (2014) A genetically-encoded KillerRed protein as an intrinsically generated photosensitizer for photodynamic therapy. Biomaterials 35, 500–508 CrossRef PubMed
[49] Sette, A., Spadavecchia, J., Landoulsi, J., Casale, S., Haye, B., Crociani, O. and Arcangeli, A. (2013) Development of novel anti-Kv 11.1 antibody-conjugated PEG-TiO nanoparticles for targeting pancreatic ductal adenocarcinoma cells. J. Nanopart. Res.15, 2111 CrossRef PubMed
[50] Feng, X., Zhang, S. and Lou, X. (2013) Controlling silica coating thickness on TiO2 nanoparticles for effective photodynamic therapy. Colloids Surf. B Biointerfaces 107,220–226 CrossRef PubMed
[51] Maksimov, E.G., Gvozdev, D.A., Strakhovskaya, M.G. and Paschenko, V.Z. (2015) Hybrid structures of polycationic aluminum phthalocyanines and quantum dots. Biochemistry (Mosc.) 80, 323–331 CrossRef PubMed
[52] Shao, L., Gao, Y. and Yan, F. (2011) Semiconductor quantum dots for biomedicial applications. Sensors (Basel) 11, 11736–11751 CrossRef PubMed
[53] Zhou, L., Zhou, L., Ge, X., Zhou, J., Wei, S. and Shen, J. (2015) Multicolor imaging and the anticancer effect of a bifunctional silica nanosystem based on the complex of graphene quantum dots and hypocrellin A. Chem. Commun. (Camb.) 51, 421–424 CrossRef PubMed
[54] Lee, H., Kim, S.A., Coakley, S., Mugno, P, Hammarlund, M., Hilliard, M.A. and Lu, H. (2014) A multi-channel device for high-density target-selective stimulation and long-term monitoring of cells and subcellular features in C. elegans. Lab Chip 14, 4513–4522 CrossRef PubMed
[55] Teh, C., Chudakov, D.M., Poon, K.L., Mamedov, I.Z., Sek, J.Y., Shidlovsky, K., Lukyanov, S. and Korzh, V. (2010) Optogenetic in vivo cell manipulation in KillerRed-expressing zebrafish transgenics. BMC Dev. Biol. 10, 110 CrossRef PubMed
[56] Jewhurst, K., Levin, M. and McLaughlin, K.A. (2014) Optogenetic control of apoptosis in targeted tissues of Xenopus laevis embryos. J. Cell Death 7, 25–31 PubMed