Photodynamic Therapy Applications in Cancer, Infections and Cardiovascular Disease

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Review article

Photodynamic Therapy Applications in Cancer, Infections and Cardiovascular Diseases

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ABSTRACT

Photodynamic therapy (PDT) or light treatment is a procedure to treat certain types of diseases that uses a photosensitizer (PS) which upon light activation produces cytotoxic oxygen species destroying tumor cells. PDT is minimally-invasive and can be repeated a few times without accumulating significant toxicity in the surrounding tissues. While PDT application in cancer treatment is well established and widely recognized by the scientific community, and its use in the fight against microbial infection is gaining momentum with the rapid increase in antimicrobial multi-drug resistance, its use in the treatment of cardiovascular diseases is clearly marginal. This mini-review presents a brief historical background of PDT, photo-activatable agents utilized, mechanism of photodynamic action, studies in vitro and in vivo, clinical trials, limitations and future prospects of its application in various types of cancer, infections caused by pathogens such as COVID-19, and heart diseases.

KEYWORDS Photodynamic therapy, cancer, infections, cardiovascular diseases, light treatment, photodynamic inactivation, bacteria, virus, COVID-19, parasites.

INTRODUCTION

Photodynamic therapy (PDT) is a photochemical treatment and a relatively noninvasive method that is used to treat certain types of diseases such as cancer. It is an adjuvant treatment to overcome some obstacles of common monotherapies such as surgery, chemotherapy, and radiation therapy. PDT involves the delivery of a light-absorbing component, known as photosensitizer (PS), to tumor tissues upon systemic administration followed by visible light (600-850 nm) irradiation in the presence of endogenous oxygen [1], [2]. The range of light with sufficient penetration and energy is referred to as the phototherapeutic window. Excitation of PS in the red or near-infrared (NIR) region produces cytotoxic reactive oxygen species (ROS), such as singlet oxygen ($^1O_2$), to cause irreversible eradication of tumor cells, and induce immune inflammatory responses and damage to tumor vasculature. PDT is an FDA-approved treatment for bronchial, esophageal, gastric, cervical, skin, head, and neck cancers [3]-[5]. The effectiveness of PDT both as a therapeutic and palliative method for cancer is well documented [6].

In 2022, the three leading causes of death in the US were heart disease (699,659 deaths, 45.8%), cancer (607,790, 39.8%), and unintentional injury (218,064, 14.3%) [7]. Cancer is a global health issue and presents a substantial challenge to medicine. The US National Center for Health Statistics has reported a projection number of 1,958,310 new cancer cases and 609,820 cancer fatalities in the US for 2023 [8]. Mortality patterns indicated an accelerated decline in lung cancer, stabilized for prostate, and slowed down for breast. Morbidity and mortality of cancer are still on the rise. The therapeutic outcome of standard anti-cancer protocols remains limited. Hence, the fight against cancer continues, and the development of novel treatments or combinations is critically needed to provide options for patients.

Infections caused by microbes such as bacteria, viruses, fungi, and parasites, either as seasonal, endemic, emerging, or re-emerging pathogens, have persisted all throughout human history [9]. In 2021, COVID-19 infection was the third leading cause of death in the US and claimed 462,193 lives, but it became the fourth place in 2022 with a decrease of 47% [7]. Nosocomial infections or healthcare-associated infections (HAIs) are particularly challenging to clinical practitioners and are the most common complications of hospital care that became aggravated during the COVID-19 outbreak [10]. CDC HAI Data Archive reported that 1 of every 31 hospitalized patients in the US contracted HAI, which means that approximately 633,300 patients contract one of these infections annually [11]. Difficulty in the treatment of infections is amplified by antimicrobial multi-drug resistance, which is becoming increasingly apparent as a major health concern worldwide, restricting the capability of available drug therapeutics to cure diseases [12]. Global interactions due to ease of travel between countries and climate shifts contribute to and shape the next onslaught of pathogens. In preparation for the next wave of the pandemic, humans must create a selection of alternatives to preserve lives. Light is a powerful tool that can be utilized with ease and has proven to be efficacious in treating infections for thousands of years.

Cardiovascular diseases (CVDs) are the leading cause of global mortality and a major contributor to disability, taking an estimated 17.9 million lives each year, which comprise about 32% of all deaths. CVDs are a group of disorders of the heart and blood vessels that include coronary heart disease, cerebrovascular disease, rheumatic heart disease, and other conditions. More than four out of five CVD deaths are due to heart attacks and strokes, and one-third of these deaths occur prematurely in people under 70 years of age [13]. National Vital Statistics Reports published in 2021 indicated an increase of 3.3% in death rates caused by cardiovascular disease in the US. There is a total of 173.8 deaths per 100,000 US standard population in 2021 compared to 168.2 in 2020 (about 697,000 people) [14]. Approximately 20.1 million Americans age 20 and older have coronary artery disease (about 7.2%) [15]. This number is staggering despite advances in treatments that include new medications (ivabradine, valsartan, semaglutide, to name a few, aside from the traditional statins, blockers, etc.), surgery (angioplasty/stents, coronary artery bypass, heart valve, among others), bionic pacemakers, mechanical hearts, technological devices (Holter monitor, Zio patch, phone apps, and others), and cardiac rehabilitation (exercise, diet, and lifestyle counseling). Hence, scientists and medical professionals are constantly developing alternative ways to improve the current state-of-art practices to enhance quality of life of the patients. These include nanomedicine for enhanced drug delivery [16], and the use of light as a treatment modality in vascular diseases [17].

In this review, the application of PDT in cancer therapy approved by the US Food and Drug Administration (FDA) is presented. PDT applications for infectious and cardiovascular diseases are also included.

CANCER

Historical Background

Photodynamic therapy (PDT) is a light-based technology that is a relatively noninvasive method to treat cancer compared with other common cancer therapy modalities. Light has been used for over a thousand years in ancient Egypt, India, and China to cure skin diseases such as psoriasis, vitiligo, rickets, and cancer [18]. It was not until the 18th century that sunlight was widely used as a medical treatment. In 1903, Niels Finsen was awarded the Nobel Prize in using phototherapy by using ultraviolet light to treat tuberculosis [19]. In 1900, in Munich, Germany, Oscar Raab discovered the phenomenon underlying the scientific basis of PDT [20]. Raab, a medical student working with Professor Herman von Tappeiner, discovered by chance that the combination of acridine red and light killed Infusoria, a species of paramecium. He correlated this characteristic light-mediated cytotoxicity of acridine dyes with the optical property of fluorescence, similar to photosynthesis observed in plants after light absorption. Von Tappeiner extended the potential application of fluorescent molecules in medicine [21], leading to the discovery of the first therapeutic application of an interaction between a PS and light in which von Tappeiner, together with Jesionek (a dermatologist), used a combination of eosin and white light to treat skin cancer [22]. Von Tappeiner also demonstrated the requirement of oxygen and, together with Jodlbauer, used photodynamic action to describe this phenomenon [23].

Decades later, numerous investigators studied the property of porphyrins as tumor-localizing compounds, present as iron-chelating agents in hemoglobin, after intravenous injections [24], [25]. In 1955, Schwartz and others tried to purify the tumor-localizing fraction from an impure hematoporphyrin (HP) mixture using acetic and sulfuric acid followed by sodium acetate to produce hematoporphyrin derivative (HpD) [26]. Lipson and Baldes showed that HpD, when administered to patients undergoing bronchoscopy or esophagoscopy, could lead to the detection of invisible tumors, paving the discovery of imaging using porphyrin derivatives [27]. Diamond and others proved for the first time that HP injection into mice with brain tumors after light irradiation produced necrosis in all except in deeply-seated tumors [28].

The effect of photoactivated fluorescein as an anticancer therapy was first investigated by Thomas Dougherty [29]. In 1975, Dougherty and others at Roswell Park Cancer Institute (Buffalo, NY) reported the first successful tumor cure with HpD administration in the presence of red light in tumor mouse models [30]. In 1976, Kelly and Snell reported the first human study of PDT using HpD in patients with bladder cancer [31]. In 1978, Dougherty conducted the first large group of patients successfully treated with PDT [32]. The primary tumor types that responded positively were squamous cell carcinomas (SCC), basal cell carcinomas (BCC),

malignant melanomas, and metastatic skin lesions arising from primary breast, colon, and endometrium tumors. This successful demonstration of clinical PDT efficacy led to the commercial production of Photofrin [33], [34].

Photosensitizer Drugs for Anti-Cancer PDT

Photosensitizers are light-activatable compounds or drugs utilized for PDT in clinics [35], [36]. Approved photosensitizers for cancer treatment are ALA (δ-aminolevulinic acid) **1**, photofrin **2**, verteporfin **3**, temoporfin **4**, taloporfin **5**, and padeliporfin **6** (Figure 1).

The first generation of PS is hematoporphyrin and its derivatives isolated in 1841 by Schere from the hemoglobin of red blood cells through treatment with concentrated sulfuric acid. Hematoporphyrin was later purified in the form of photofrin. This first generation of PS has been widely used for treating a variety of cancers in clinics. However, there were some limitations and intrinsic drawbacks such as poor chemical purity, short wavelength of light, prolonged half-life, and intense accumulation in normal tissues, causing toxicity. The precise molecular structure of photofrin is unknown. It is proposed that photofrin and HpD contain a mixture of oligomeric porphyrins linked with ether and ester bonds. Fig.1 shows the structure of photofrin as the ether linkage.

δ-Aminolevulinic acid (ALA) and its methyl ester (methyl aminolevulinate, MAL) are the most widely used PS for dermatologic PDT, and are approved for actinic keratosis, squamous cell carcinoma (Bowen disease) and basal cell carcinoma. ALA is considered a prodrug in which an abundant amount of protoporphyrin IX (PPIX) upon external administration is produced. PPIX is a potent photosensitizer and is exploited for PDT use [37]. Berlin and others first showed in 1956 excessive protoporphyrin accumulation and high photosensitivity after exogenous administration of ALA in humans [38]. Years later, in 1990, Kennedy and Pottier reported the earliest clinical trial with ALA-PDT for superficial basal cell carcinomas [39].

Mechanism of photodynamic action

The therapeutic efficacy of PDT depends on three components: (a) a light-activatable photosensitizer (PS) with optimum tumor localization, (b) light irradiation with appropriate wavelength to achieve tumor destruction, and (c) endogenous molecular oxygen (O_2). The typical process commences with either topical or systemic injection of the PS for tumor accumulation. Maximum PS uptake in the tumor after injection is critical for optimal PDT efficiency. After sufficient elapsed time, the PS reaches a maximum concentration within the vasculature and in the tumor. Once the maximum PS concentration at the tumor is achieved, with respect to the healthy tissue, light is applied at a specific wavelength at which the PS has maximum absorption. Upon absorption of a photon with suitable energy, the PS in the ground state (S_o) undergoes excitation to the higher energy excited state (S_1), which can return to its original ground state emitting fluorescence or is converted into its triplet state (^{3}PS*) by intersystem crossing. This triplet T1 state has a relatively long lifetime that can initiate 2 competitive reactions (Fig.2), giving rise to two oxidative mechanisms Type I and Type II [40].

Type I reaction involves electron or proton transfer to an oxygen molecule and neighboring molecules producing anionic or cationic radicals, respectively, and further colliding with another oxygen molecule to form chemically reactive oxygen species (ROS). Type I reaction leads to superoxide ion via one-electron transfer to O_2 molecule. The superoxide anions are not directly detrimental to the cells but can participate in a reaction that produces hydrogen peroxide (H_2O_2). When superoxide anions react with H_2O_2 via Fenton reaction, reactive hydroxyl radicals can be formed that can abstract hydrogens from biomolecules or add to double bonds contained in unsaturated lipids. Cellular membranes can also readily absorb hydrogen peroxide, which can react with superoxide molecules ionizing any species with low activation energy. PDT-initiated membrane damage is a critical course of action causing necrosis and destruction of blood vessels.

Type II reaction involves the transfer of energy from the PS excited triplet T1 state to the ground state oxygen $^3O_2$ molecule converting it into excited singlet oxygen $^1O_2$, a highly-reactive chargeless ROS that can diffuse to the cytoplasm, and attack cellular organelles and biological membranes. Almost all PSs have a high quantum yield in this Type II reaction. It is reported that PSs produce one singlet of oxygen for every two photons absorbed. Singlet oxygen seems to be the primary cytotoxic agent in PDT-mediated biological damage. Approximately 10^{18}-10^{19} singlet oxygen per mL is needed to cause tissue necrosis as estimated in some studies [41]. The lifetime of singlet oxygen is about 40 ns and diffuses to about 20 nm, which is less than the diameter of most animal cells. Theoretically, this relatively short distance of diffusion of singlet oxygen renders PDT very specific and controllable. Localization of the PS influences the site of action and efficacy of PDT at the subcellular level.

Type III mechanism has been suggested to occur in highly hypoxic environments. Type III is a triplet-doublet process, or modified Type I, which takes place between the PS in the triplet state [PS^3] and the free radicals present in the system. This third photosensitive mechanism acts without ROS intermediates. In this type-III mechanism, the activated photosensitizer itself can have a specific targeting property for macromolecules in the cells. After direct combination with a Type III-PS, the targeted biomolecule can be destroyed directly and efficiently by the PS in its excited state. This mechanism can avoid oxygen concentration in PDT, improve treatment efficacy, and resolve the problems of deep-seated tumor phototherapy. A study was conducted to test that Type III is the mechanism followed in hypoxic conditions [42]. An elegant fluorescent PS designed to specifically recognize RNA without the disturbance from DNA was tested in hu-

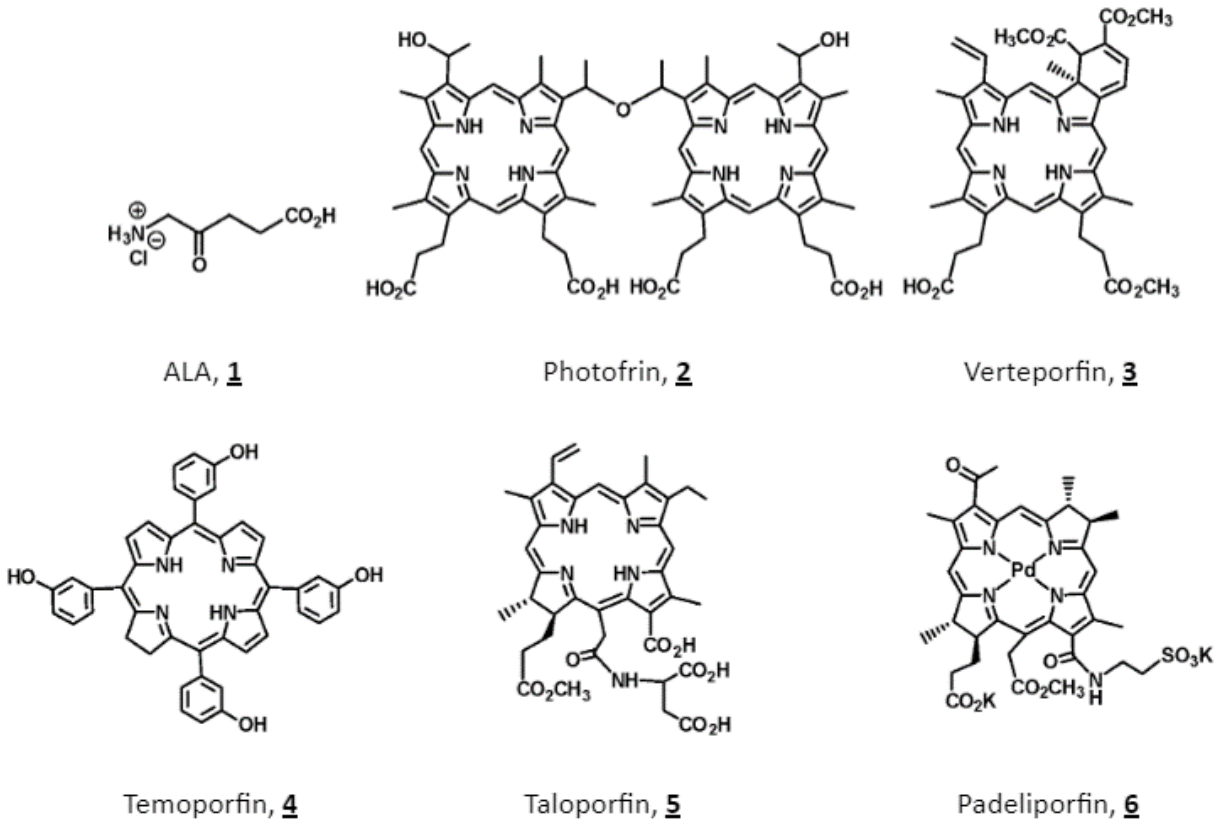

FIGURE 1. Molecular structures of current photosensitizers approved for PDT. ALA **1**, Photofrin **2**, Verteporfin **3** (Visufdyne), Temoporfin **4** (Foscan), Taloporfin **5** (LS 11), and Padeliporfin **6** (Tookad soluble).

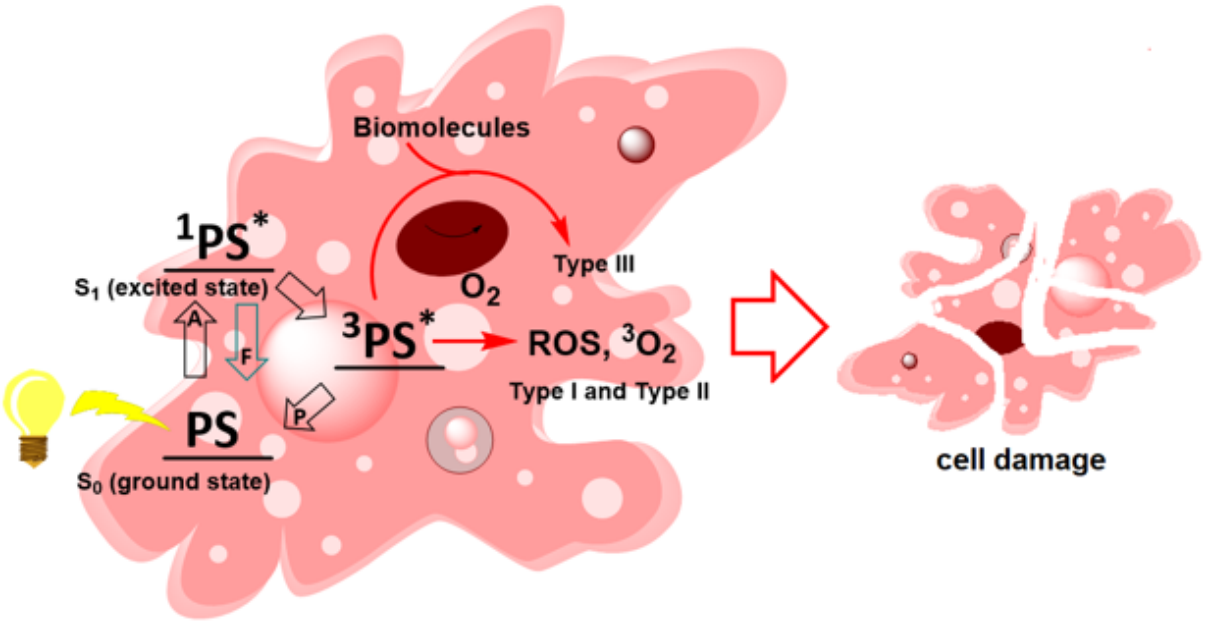

FIGURE 2. Reaction mechanisms Type I and II generating reactive oxygen species (ROS) and cytotoxic singlet oxygen ($^3O_2$) during PDT, causing cancer cell destruction. Type III mechanism occurs in a highly hypoxic environment in which the activated PS interacts directly with biomolecules. Types I/II/III cause cell damage. Photosensitizer (PS), absorption (A), fluorescence (F), phosphorescence (P).

man breast MC7 cancer cells and results showed the half-maximal inhibitory concentration (IC_{50}) of the PS as ∼15 nM in normoxic and ∼25 nM in hypoxic conditions. It was concluded that after light irradiation, the excitation energy could be transmitted directly to RNA molecules to kill cells or induce tumor cells to undergo apoptosis, and oxygen was not required in this process. Hence, the PS had an excellent photo-killing effect on tumor cells in normoxic and hypoxic conditions.

The mechanism of selective PS retention and localization into tumors includes a high proliferative rate of neoplastic cells, poor lymphatic drainage, increased vascular permeability, binding to low-density lipoproteins, an increased amount of collagen binding to PSs due to abnormal structure of tumor stroma, and infiltration of macrophages in the tumor trapping the PSs [43]. The efficacy of these mechanisms depends on the type of PS, cell type, overall light dose, and tumor oxygenation status, among others.

PDT at the cellular level

Subcellular accumulation of the PS is an important factor that determines the site of action for PDT-induced photodamage. In general, the PS will localize in the plasma membrane, lysosomes, mitochondria, Golgi apparatus, or endoplasmic reticulum.

Three major mechanisms for tumor cell destruction induced by photodynamic action are apoptosis, autophagy and/or necrosis.

Apoptosis is a programmed highly-regulated cell death process. PSs that localize in the mitochondria, typically cationic or positively charged and amphiphilic species, are observed to induce the apoptotic pathway. PDT damage to the mitochondria triggers membrane permeabilization that results in leakage of cytochrome c into the cytosol activating caspase-mediated apoptosis [44]. Its morphological characteristics can be identified under light microscopy, and include cell shrinkage, chromatin condensation, nuclear fragmentation, blebbing of the cytoplasmic membrane, and, finally, the formation of apoptotic bodies [45], [46].

Autophagy, or self-eating, is a conserved cellular degradation process eliminating molecules and subcellular elements, including nucleic acids, proteins, lipids and organelles. These damaged organelles are engulfed by a double membrane structure, referred to as autophagosome, which fuses with lysosomes to degrade its contents [47], [48]. Both types of cell death (apoptosis and autophagy) do not generate an inflammatory response since the cytoplasmic membrane is conserved until the cellular debris is eliminated by neighboring or by specialized organelles. Autophagy has been observed as a cell death mechanism in response to PDT as a cytoprotective mechanism of cells. The autophagic pathway appears to be the primary mechanism when apoptosis is impaired and with higher PDT doses. Mitochondrial- and ER-targeted PS trigger a pro-survival autophagic response, while lysosomal-targeted PS can inhibit autophagy [49]. Anionic PSs are taken up by endocytosis and tend to localize in the lysosomes [50].

Necrotic cell death is characterized morphologically by generalized swelling of cell membranes, often accompanied by some condensation of nuclear chromatin, rupture of the plasma membrane, and an irregular DNA degradation pattern. Cell death pathway caused by necrosis is considered an accidental unprogrammed event that occurs under total ATP depletion, resulting from external stimuli such as extreme physico–chemical stress, heat, osmotic shock, mechanical stress, freezing, thawing, and high concentrations of hydrogen peroxide [51]. Cytoplasmic membranes and membranous organelles dilate, and this increased swelling causes the breakdown of the plasma membrane, which releases the cytoplasmic contents into the extracellular space. The release of the intracellular contents including proteins and nucleic acids leads to massive cellular damage affecting neighboring cells, which triggers inflammatory and autoimmune reactions [52]. Necrosis is much more inflammatory than apoptosis or autophagy. Necrosis is observed rather than apoptosis with higher PDT usage depending on the PS and light dosage. When the site of PS localization is the plasma membrane, necrosis is the preferred pathway. Photofrin-activated PDT can lead to instant ROS formation when the plasma membranes are the main targets by altering incubation protocol, rendering necrosis-like phenotype, while cytoplasmic activation induces apoptosis [53].

Apoptosis is induced with mild PDT and PS mitochondrial localization and photodamage. Necrosis dominates with high PDT doses or PS plasma membrane localization. Autophagy is favored with low PDT-induced injury to organelles and can be overwhelmed upon lysosomal impairment. PDT at the cellular level is indeed complex, but understanding the response at the subcellular level is critical in elucidating the exact molecular structural effects of PSs.

PDT for various types of cancer in the clinics

The potential of PDT in clinics has been recognized by numerous investigators. There has been an exponential increase in the number of publications involving new materials and applications for PDT in medicine for the last 20 years. PDT has potential as a palliative stand-alone or combination therapy due to its lack of systemic effects and its ability for organ-function sparing action.

PDT has been applied for the treatment of lung [54], esophagus [55], [56], skin [57], [58], head and neck [59], bladder [60], pancreas [61], prostate [62], breast [63], [64], brain [65], [66], gastric [67], and bile duct [68] cancers, and for macular degeneration [69]. Scientists and clinicians have already demonstrated the potential beneficial effects of PDT on various types of cancers compared to standard therapy.

Limitations of PDT in the clinics

Photosensitivity which can last for months is the major side effect of PDT. It is usually mild to moderate in severity and does not require treatment. Reported side effects include

burning and itchy sensations during illumination. In rare cases where the side effect is so severe, patients discontinue the treatment [70]. Systemic immune response manifested as localized swelling at the injection site is frequently seen following PDT treatment. Inflammation in the short term serves a protective purpose. Changes in tumor vasculature are an early indicator of PDT-mediated inflammation [71].

PDT is restricted in treating large tumor masses and has a treatment depth limit. Since visible light only penetrates 5–10 mm into tissues, only superficial lesions can benefit from PDT. New fiber optics and microendoscopic technologies have been developed for more precise placement of fibers inside the tumor site using interstitial, endoscopic, intraoperative, or laparoscopic light distribution devices [**?**].

No consensus has been established and agreed upon universally in the clinics on the PS and light dosage. The highest response rates can be achieved using standardized protocols. Optimal PS and light doses, as well as the drug–light time interval, may differ on a case-to-case basis. Hence, improving dosimetry has been an ongoing goal for clinical PDT.

Possible solutions to address PDT limitations have been proposed such as novel nanosystems for efficient oxygen delivery, changing light excitation sources, and combination treatments [72].

INFECTIOUS DISEASES

Photodynamic antimicrobial chemotherapy (PACT) combines a photosensitizer or a chromophore, and light to treat microbial infections. As with PDT, a phototherapeutic window at 600-850 nm, which is the range of light with sufficient penetration and appropriate energy, is utilized during the treatment to produce highly reactive oxygen species such as hydroxyl radicals (Type I) or singlet oxygen species (Type II), or direct interaction of activated PS with biomolecules (Type III). An infected area is exposed to light treatment together with a photoactivable drug. PACT destroys pathogens through the production of reactive oxygen species (ROS) causing selective destruction of microorganisms while sparing mammalian cells. Significant advantages of PACT include low cost, photoinactivation of bacteria [73], [74], viruses, fungi [75], [76], and parasites at both dormant or vegetative states, effective phototoxicity against wild–type and antibiotic-resistant microbial strains, low mutagenic potential, high selectivity in the eradication of pathogens as compared with host cells, and low probability of drug resistance due to its multiple targeted killing effects. Most of the multi-drug resistant microbes arise from infection caused by the ESKAPE *(Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species)* pathogens and have become the leading cause of nosocomial infections worldwide [77].

Photodynamic inactivation (PDI) of microorganisms has attracted considerable attention due to its unique mode of action, in which pathogens are less likely to generate multidrug resistance due to the fact that PDI can be applied in a minimally invasive manner and repeated several times modulating side effects if any [78], [79].

Photosensitizer Drugs for Anti-Microbial PDT

Antimicrobial resistance (AMR) has emerged as a global health concern and is estimated to be one of the most common causes of death worldwide by 2050 [80], [81]. Antimicrobial photodynamic therapy (aPDT) proposes an alternative treatment for localized infections in response to the looming crisis caused by AMR. Thus, several strategies have been developed involving target-specific antimicrobial PDT agents, which include the conjugation of known PS building-blocks to target-specific antimicrobials, or combining them with nanoparticles [82].

Molecular structures of common PSs used for aPDT are listed in Fig. 3 and can be classified as neutral, cationic or anionic compounds. Other PSs include phthalocyanines [83], bacteriochlorins [84], BODIPYs [85], and phenothiazines (toluidine blue, aside from MB) [86].

Improvements in the design of PSs involve the use of nanoparticles (NPs). Nanocarrier systems are shown to be effective in PS targeting and delivery into cells and improve their therapeutic efficacy by enhancing their internalization into microbial cells. Most PSs suffer from low bioavailability and poor biodistribution, which can be solved by nanoparticles to physically trap and package PSs and precisely delivered them to the target region within the bacterial cells. Nanoparticles can also reduce the efflux of PSs modulating multi-drug resistance. Additionally, PS-nanoparticle conjugate prevents the PS from forming therapeutically ineffective dimeric or trimeric aggregates. Compared to applications of NPs in cancer therapy, NP application in aPDT is still limited. However, several reviews are available that involve engineered nanocarriers [87], [88], nanozymes [89], and nanomaterials for bacterial biofilms and infections [90].

Mechanism of antimicrobial photodynamic action

Photosensitization in any biological system either in cancer cells or microbes undergoes the same mechanisms and pathways. An activated PS generating cytotoxic radicals can cause an imbalance in cellular homeostasis and damage to microbial membranes (bacterial, fungal, etc.) through the oxidation of important key biomolecules, which include proteins, lipids, and nucleic acids. The damage is triggered by Type I/II mechanisms (Fig. 2) in which cytotoxic species are generated. The free radicals formed cause functional impairment, cellular membrane damage, and morphological changes. A few researchers suggested that a different mechanism occurs in parallel with Types I/II, known as Type III which takes place between the excited PS in the triplet state [^{3}PS] and the free radicals present in the system [91]. Very little information is known about this third type. Nevertheless, Types I and II are the most common mechanisms for PDT-induced microbial cell death.

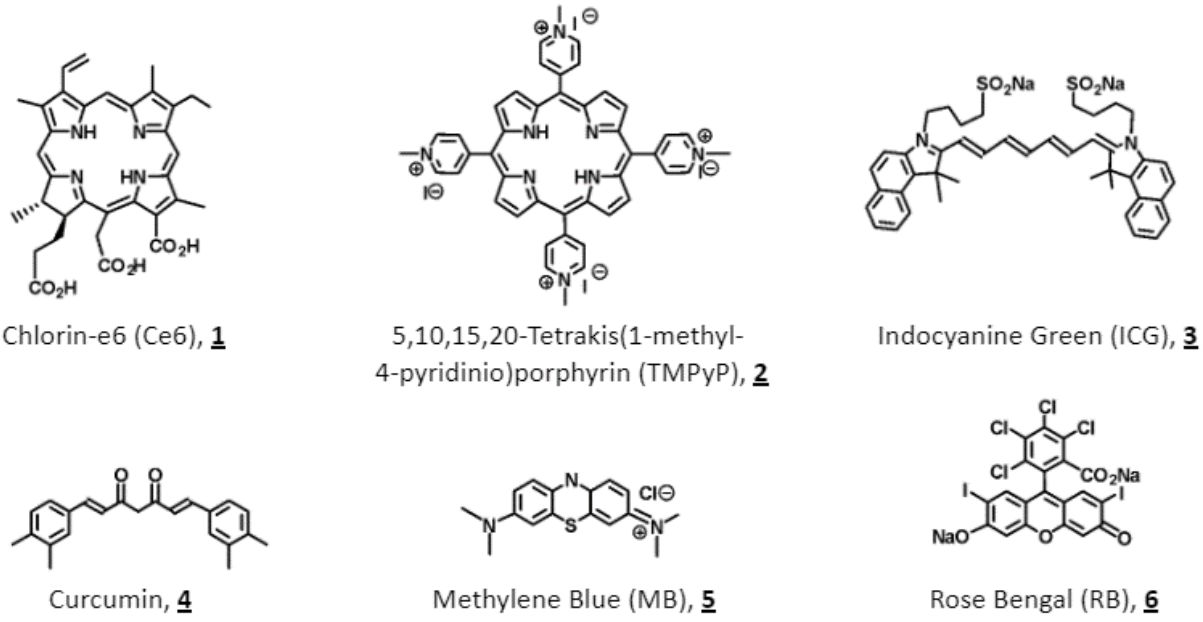

FIGURE 3. Molecular structures of common photosensitizers used for antimicrobial PDT. Neutral PSs: Chlorin-e6 **1**, Curcumin **4**; Cationic PSs: TMPyP **2**, Methylene Blue **5**; and, Anionic PSs: Indocyanine Green **3**, and Rose Bengal **6**.

Antibacterial PDT

Internalization or binding of PSs into the cytoplasmic membrane of a microbial cell is required for aPDT. Differences in susceptibility of Gram-positive bacteria (stained purple) and Gram-negative bacteria (stained pink/red) towards PDT are mainly due to the variation in the structural anatomy and physiology of their cell membranes. Gram-positive bacteria having lower antibiotic resistance contain rigid cell walls and thick multi-layers of peptidoglycans, while Gram-negative bacteria having higher antibiotic resistance contain flexible and thin monolayers of peptidoglycans [92], [93].

1. Gram-positive vs gram-negative bacteria

PDT has been studied as a promising approach to eradicating oral pathogenic disease-causing bacteria. Microbial biofilms are involved in approximately 80% of all bacterial and fungal infections in humans [94]. Pathogens that involve biofilm formation are typically resistant to commonly used antibiotics. Biofilms contain many bacteria and fungi. These biofilms can occur in different functional organs of the body and are associated with middle-ear infection, gingivitis, urinary tract infection, periodontitis, and others. Bacterial communities also produce biofilms, especially in medical implants, including vascular grafts, heart valves, intrauterine devices, pacemakers, prosthetic joints, catheters, sutures, and contact lenses.

A study conducted using a porphyrin nanoemulsion in a murine-infected wound model indicated a high PS-bacteria cell interaction was achieved with 0.5 nM and 30 J/cm^2 and 100 µM and 60 J/cm^2 that were able to kill *S. pneumoniae* in a suspension and *S. aureus* biofilm, respectively [95]. The use of NP has been demonstrated to be effective in PDI. Tin chlorin e6–nanogold conjugate was a hundred times more effective at killing *S. aureus* than free tin chlorin e6. The conjugate also displayed antibacterial activity against methicillin-resistant *S. aureus* and *Streptococcus pyogenes* [96].

To test PDT as a viable protocol to biofilm disruption on hard dental tissue, methylene blue (MB) and a 660 nm diode laser were used on the viability and architecture of Gram-positive and Gram-negative bacterial biofilms. Ten human teeth were inoculated with bioluminescent *Enterococcus faecalis* (Gram+) or *Pseudomonas aeruginosa* (Gram-). Bacterial biofilm was treated with MB, followed by a delivery of 660 nm diode laser light into the root canal biofilm via a 300 μm fiber for 240 sec (total energy of 9.6 J). Results indicated a significantly higher reduction of the Gram+ *E. faecalis* biofilm (89%) than the reduction obtained with the Gram- *P. aeruginosa*. Gram-positive bacteria are more easily killed by PDT than Gram-negative species, due to the differences in membrane structure between the two classes [97].

Another study comparing the response of these two classes of bacteria, the gram-positive organism *S. aureus* appeared to be significantly more sensitive to 5-ALA-mediated PDI than the gram-negative *E. coli* strains. The bacterial suspension was illuminated with white light from a 400-W halogen lamp for 40 min, corresponding to a light dose of 120 J.cm^{-2} [98].

Karrer and others have shown that 5-ALA-mediated PDI also induced significant inhibition of the growth of *S. aureus* but not *S. epidermidis* [99]. In contrast, Nitzan and others observed that 5-ALA-mediated PDI was effective against both *S. aureus* and *S. epidermidis* but not against gram-negative strains, including *E. coli* and *P. aeruginosa* [100]. Szocs and others also reported successful photoinactivation of *E. coli* and *P. aeruginosa* with 5-ALA [101]. These conflicting results seem to show that when a prodrug is used such as 5-ALA, PDI conducted under suboptimal conditions can lead to contradictory findings.

Additionally, PDT can eliminate wound infections that are induced by *S. aureus*, coagulase-negative staphylococci, *Enterococcus faecalis, P. aeruginosa, Enterobacter cloacae, Peptococcus magnus*, and anaerobic bacteria [102].

2. Clinical Trial

A randomized interventional clinical trial [NCT05401201] in its recruitment stage entitled Dual-Light Antibacterial Photodynamic Therapy as an Adjunctive Treatment to Corticosteroid Treatment in OLP (RELIEF-OLP) is ongoing at the University of Helsinki (Tampere University Hospital) [103]. This study is designed to investigate the effectiveness of plaque control intervention by home-use dual-light aPDT Lumoral device as an adjuvant or alternative treatment to triamcinolone acetonide (TCA) mouth rinse or other topical corticosteroid treatment on the symptoms and clinical appearance of symptomatic gingival involvement of oral lichen planus (OLP). OLP is a relatively common chronic immune-mediated disease that usually occurs on the oral mucosa surfaces. Utilizing aPDT mechanism of action, Lumoral is a medical device developed to provide a potent, targeted antibacterial action on dental plaque in a home environment. The device is used by swishing a mouth rinse, which has a strong adherence to dental plaque. The plaque-adhered photoactive mouth rinse can be activated by the Lumoral light applicator. Preliminary results have shown a promising anti-inflammatory response in addition to plaque reduction. A total of 60 subjects with histologically confirmed diagnosis of OLP with gingival involvement are now enrolled to the study. The ultimate goal of the clinical trial is to provide aPDT as standard oral hygiene self-care for the general public.

Antiviral PDT and application for COVID-19

Photodynamic inactivation (PDI) is a promising antiviral treatment that involves the same binary components in PDT: photosensitizer, light and oxygen [104], [105]. Cytotoxic reactive oxygen species (ROS) formed cause irreversible destruction of pathogens such as bacteria and viruses [106]-[108]. Photodynamic technique for viral inactivation was reported as early as the 1930s or even earlier during the 1918 Spanish flu epidemic [109], [110]. Only recently that PDI has attracted attention due to the development of new PSs with the advent of laser technology as light source [111]-[113]. Antiviral photodynamic therapy (aPDT) is a branch under the large umbrella of PDT [114], [115]. Clinical use of viral PDI or photodisinfection has been limited to refinement of blood, treatment of human papillomavirus (HPV), some Herpes simplex virus (HSV1 and 2) infection-induced mucous membrane and skin diseases, such as Herpes labialis (oral) [116], and viral complications associated with human immunodeficiency virus (HIV) [117]-[119].

The emergence of COVID-19 (coronavirus disease 2019) stunned humanity due to its contagiousness and fatal effects. Vaccines are now used to control its spread. More than two years after the initial onset of the pandemic, COVID-19 remains a serious global concern, with successive waves of increasingly more resistant and more transmissible variants. In its quest for survival, even the tiniest living organism has the ability to evolve, in particular, viral resistance to treatment as microbes develop into stronger and more resilient variants. Hence, there is still a need for effective anti-viral therapy which is not strain-specific and can therefore remain effective despite the rapid emergence of variants of concern, and in preparation for the next lethal viral infection.

A fundamental aspect of COVID-19 disease is the tissue and organ damage caused by a hyper-inflammatory response referred to as the cytokine storm. Oral and inhaled steroids have been widely used to alleviate this issue but using broad immunosuppressive agents in the context of severe infection may have potential drawbacks. Thus, PDT offers a safe, fast, cost-effective, and a simple method to inactivate microorganisms [120]-[122]. Additionally, there have been no reports of resistance, unlike other antibiotics and antiviral drugs.

In an in vitro study of SARS-CoV-2 (isolated in Russia) infected Vero E6 cells, PDT with methylene blue (MB) and Radachlorin, using a continuous laser with 662 nm wavelength at doses of 16 J/cm^2 and 40 J/cm^2 of laser irradiation, showed high antiviral activity against SARS-CoV-2 [123]. In another in vitro study to investigate the effects of the PS tetrahydroporphyrintetratosylate (THPTS) on the infectivity of SARS-CoV-2, a viral suspension of SARS-CoV-2 was pre-incubated with the THPTS in various concentrations (0.1 - 1 μM) for 4 min before near-infrared light (760 nm) exposure for 10 min. An infection procedure with these pretreated viral suspensions in ACE2-expressing Vero E6 cell cultures was performed [124]. The novel coronavirus and related coronaviruses interact directly via their spike S proteins with angiotensin-converting enzyme-2 (ACE2), a host cell metallocarboxypeptidase that initiates spike protein-mediated viral entry [125], [126]. Findings indicated a concentration-dependent reduction of viral cytopathic effects at 0.3 and 1 μM THPTS.

Another in vitro study was conducted on genetically-encoded monomeric and multimeric nanobodies containing PS (SOPP3) engineered to a diverse list of antibodies targeting the wild-type (WT) spike protein isolated from a 2003 SARS patient. As confirmed by the pseudovirus neutralization assay, this targeted photodynamic approach significantly increased the efficacy of these antibodies, not only against the WT but also the Delta and Omicron strains. Measurement of infrared phosphorescence at 1270 nm confirmed the presence of singlet oxygen ($^1O_2$) generated in the photodynamic pro-

cess [127].

To prove further the virucidal effect of PDT, a *Hypericum* extract (HE) in combination with white light exhibited inhibitory activity against the human coronavirus HCoV-229E on hepatocarcinoma Huh-7 cells. The bioactive metabolites of the *Hypericum* extracts (HE) derived from the aerial parts of *Hypericum perforatum L.*, also known as St. John's wort, have been reported to be composed of the light-dependent components naphthodianthones (hypericin and pseudohypericin), the light-independent phloroglucinols (hyperforin and adhyperforin), and flavonoids. Hypericin shows several absorption peaks in the visible spectrum with maximum absorbance at 550 and 588 nm (in ethanol) and fluorescence emission at approximately 600 nm (in ethanol). Given its potent in vitro virucidal characteristics, HE in combination with white light is proposed as a promising candidate to fight against COVID-19 [128].

1. Clinical Studies

Orofacial lesions [129] related to COVID-19 have been described in the literature even though the most common symptoms include fever, cough, sore throat, fatigue, and dyspnea. A very small study conducted in Brazil demonstrated the combination of aPDT and PBMT on 3 ICU patients (55-58 yo) with COVID-19 diagnosis. Results showed that after 0.01% methylene blue (MB) treatment followed by 660 nm light irradiation (100 mW power), tissue healing and edema reduction were observed suggesting that oral healthcare in hospitalized patients is essential in the management of COVID-19 to reduce morbidity and mortality [130]-[132].

A clinical study conducted on 300 patients within a one-month period (March 22, 2020 – April 25, 2020) reported the successful use of PDT in the disinfection of oral and nasal cavities in patients with early-stage COVID-19 during this most recent pandemic [133], [134]. In a randomized study [135], pharyngeal virus shedding was observed to be very high during the first week of symptoms (peak at 7.11×10^8 RNA copies per throat swab, until day 4). Infectious virus was readily isolated from throat- and lung-derived samples, but not from stool samples in spite of high virus RNA concentration and neither blood nor urine samples yielded the virus. Based on these previous findings, it was hypothesized that at the onset of symptoms (fever, cough, headaches) a significant amount of COVID-19 viruses are bound to the ACE2 receptors located in the mucosa of the throat, oral, and nasal cavity. The photosensitizer used was methylene blue (MB) [136] as a solution of 5% methylthionium-chloride in glucose solution applied by flushing and gargling the oral cavity and throat, and spraying the nasal cavity. This 1-min flushing was followed by 5-min irradiation (72 J/cm^2) of the infected areas, repeated 5 times with a total light dose of 360 J/cm^2. PCR test immediately after the 5-treatment cycle indicated a reduction in viral load in the oral, nasal, and throat cavities. Significant reduction of severe course disease (2.6% vs 19%) and attenuation of the disease (97% vs 81%) in the active treatment group of patients was observed. The difference in mortality rate compared to the placebo is almost double (0.7% vs 3.3%). Further studies are needed to validate the findings and test the therapeutic efficacy in patients at various stages of COVID-19.

A single-center randomized placebo-controlled single-blind clinical trial [NCT05184205] was conducted in Spain within a three-month period (December 2021-February 2022) on 75 patients (38 placebo and 37 PDT) using methylene blue (MB)-based PDT in SARS-CoV-2 positive individuals infected with the Omicron variant [137]. The procedure also used nasal PDT which was initiated by swabbing MB inside the anterior nares, including nostrils and nasal passages, of patients. A 4-minute illumination cycle inside the nostrils of patients was applied three times using new MB solution after each cycle. Findings indicated that intranasal PDT reduced infectivity at day 3 post-treatment when compared to placebo. No serious adverse effects were reported during treatment. PDT treatment was well tolerated, and nasal PDT decelerates the decline of SARS-CoV-2 specific T-cell immune responses in vaccinated individuals infected with the Omicron variant.

Photobiomodulation therapy (PBMT) or low-level laser therapy (LLLT) is a photon-based therapy that uses light to mediate a variety of metabolic, analgesic, anti-inflammatory, and immunomodulatory effects [138]-[140]. PBM devices typically deliver 10mW - 500mW (0.01 -> 0.01 Watts) with a power density ranging from 0.005 W/cm^2 to 5 W/cm^2. PBMT technique combines different wavelengths of light including blue, ultraviolet, and violet with several PSs, such as curcumin, chlorophyll derivatives, vitamin B2, indocyanine, and MB. PBMT was utilized with patients with severe COVID-19 to improve the ventilator conditions of the patients reducing hospital stay, and decreasing the burden on the health care system. Patients were subjected to 4 treatments daily and observed a significant improvement in breathing immediately after each treatment. Paroxysmal coughing fits were resolved and patients became ambulatory with physical therapy [141]. A combination of aPDT and PBMT was demonstrated to be effective in the management of COVID-19-related orofacial lesions [142]-[144].

Antifungal PDT

The alarming increase in the incidence of fungal infections presents an enormous challenge to healthcare professionals affecting both immunocompromised and immunocompetent individuals. Mycoses are rarely life-threatening, but oftentimes recurrent and chronic. Subcutaneous and superficial fungal infections affect the skin, keratinous tissues and mucous membranes [145]. Dermatophytosis (tinea or ringworm) is a fungal infection of the skin and nails, referred to as onychomycosis, which is commonly encountered in clinical practice and caused by the etiological pathogen *Trichophyton rubrum* [146]. Clinically used antifungal drugs include ergosterol inhibitors (azoles, nystatin), β-glucan inhibitors (echinocandins), thymidylate synthase inhibitors (flucytosine), mitotic inhibitors (griseofulvin), and aminoacyl-tRNA inhibitors (tavaborole), to name a few [147].

Antifungal PDI is an alternative approach to antifungal medications. Several in vitro and in vivo effects against fungal infections have been reported. Typical photosensitizers used for antifungal infection include methylene blue, porphyrins, chlorins, ALA, phenothiazines, curcumins, and others, similar to PSs used in infectious diseases.

An in vitro study using curcumin nanoparticle at 10 mg/mL with 10 J/cm^2 of blue light (417 nm), completely eradicated *T. rubrum* (a dermatophytic fungus) via induction of ROS and RNS (reactive nitrogen species), which was associated with fungal death by apoptosis. Nanoparticle delivery of curcumin enhanced apoptosis by an increase in NO production [148]. Others reported that *T. rubrum* cells are inhibited after treatment with deuteroporphyrin monomethylester and 5,10,15-tris(4-methylpyridinium)-20-phenyl-[21H,23H]-porphine trichloride in concentrations of 3 μg/mL or higher using white light (1080 kJ/cm^2) [149]. Another in vitro study found that methylene blue (MB) with a concentration of 0.05 mg/mL and utilizing 684 nm light dose of 28 J/cm^2 reduced the viability of *Candida albicans* by 50%. The results were associated with the permeabilization of the microbial cells by MB, which damaged the plasma membrane [150]. *C. albicans* is an opportunistic pathogenic yeast commonly found in the gastrointestinal tract (gut) and the mouth in 40-60% of healthy human adults.

In vivo PDI efficacy in animal models against several fungal pathogens has been demonstrated. A C57BL/6 mouse model was cutaneously infected with *T. rubrum* and treated with toluidine blue (TBO) as PS in 0.2% gel formulation combined with 630 nm dose of 42 J/cm^2 aPDI for 7 days for a 24-h period. aPDT was compared to treatment with the antifungal cyclopiroxolamine (CPX, 0.65 mg/mice) administered topically every 48 h for 7 days. aPDT was observed to be 64% more efficient than CPX alone as a monotherapy in reducing the fungal burden, and both treatments reduced fungal damage in the skin [151]. A mouse model of skin abrasion infected with C. albicans was developed by inoculating wounds measuring 1.2 cm by 1.2 cm with 10(6) or 10(7) CFU (colony forming unit). aPDT was evaluated using NMB and red light (635 nm or 660 nm at 78 J/cm^2 at 30 min or 120 J/cm^2 at 24 h for treatment post-infection). This study reported that PDT in vivo initiated either at 30 min or at 24 h post-infection significantly reduced *C. albicans* burden in the infected mouse skin abrasion wounds [152].

1. Clinical Studies

Clinical studies in humans for the treatment of fungal infection using aPDT have been reported.

Onychomycosis, the most common superficial fungal infection of the fingernails or toenails, is characterized by discoloration, thickening, and separation from the nail bed. Common in older adults 50 years or older and with a relapse rate of 25%–30%, it is caused by dermatophytes, yeasts, and non-dermatophyte molds [153]. Topical and oral agents cannot penetrate the nail plate and are not absorbed due to insufficient blood supply to the nail plate, invariably thickened in a diseased state. Two patients with fingernail onychomycosis (caused by the *Fusarium oxysporum* or **Aspergillus terreus**) unresponsive to conventional antifungals were treated with aPDT. The nail plate was first softened with 40% urea ointment under occlusion for 12 h. Then, aPDT was performed using methyl aminolevulinate (MAL) 16% cream and illumination with 635-nm LED (dose of 37 J/cm^2). aPDT treatment improved the nail appearance and cultures were thereafter negative. Two additional treatments were administered and both patients remained disease-free after follow up evaluations [154]. In another clinical trial of 30 patients with onychomycosis, patients that received aPDT therapy combining ALA and red light (570–670 nm, dose of 40 J/cm^2) had a 43% cure rate at 12 months after treatment and 37% remained disease-free at 18 months [155].

An international randomized double-blind interventional clinical trial [NCT05110001] entitled Rose Bengal Electromagnetic Activation with Green light for Infection Reduction (REAGIR) is ongoing at the Aravind Eye Hospitals in India in collaboration with Stanford University and University of California, San Francisco [156]. The purpose of this study is to determine differences in 6-month visual acuity between medical antimicrobial treatments alone versus antimicrobial treatment plus cross-linking with rose Bengal (RB-PDT). Patients eligible for inclusion will have culture-positive fungal or acanthamoeba keratitis or smear and culture-negative corneal ulcers and moderate to severe vision loss, defined as Snellen visual acuity of 20/40 or worse. Study participants received Rose Bengal-PDT to the de-epithelialized cornea and compared with sham control receiving chlorhexidine, moxifloxacin or natamycin. This will be followed by irradiation with a 6 mW/cm^2 custom-made green LED source for 15 minutes (5.4J/cm^2). The scientific community awaits the results of this clinical study.

Antifungal PDT has demonstrated its potential as an adjuvant and potentially synergistic treatment procedure to conventional fungicides. PDT showed comparable effectiveness in treating oral fungal infections and in the treatment of superficial mycoses. A systematic review was conducted to evaluate the evidence for the effectiveness of PDT in treating oral fungal infections, as an alternative to conventional antifungal medications. PDT showed statistically non-significant increased clinical efficacy in three studies (n = 108 participants) as compared with conventional antifungal therapy. The small number of studies, small sample size, and variability of methods and outcome measures across studies highlight the need for more standardized studies with longer follow-up periods to enable the recommendation of PDT as an option for treatment against antifungal infection [157]. Increasing resistance and few licensed treatment alternatives, larger randomized controlled trials, and optimization of treatment protocol are warranted to evaluate the potential of aPDT as an alternative to conventional antifungal therapy either alone or in combination with other methods, especially in cases that remain refractory to standard local therapy [158], [159].

Antiparasitic PDT

Drug resistance is also rapidly spreading in parasites, becoming part of a never-ending list of drug-resistant pathogens leading to antimicrobial resistance that continues to endanger the ability of the conventional standard protocol to treat common infections [160]. Pathogens evolve over time to survive and no longer respond to medications, increasing the risk of severe illness and fatality.

1. Leishmaniasis

Leishmaniasis is a parasitic disease found in the tropics, subtropics, and southern Europe, and classified as a neglected tropical disease caused by the infection of *Leishmania* parasites spread by the bite of phlebotomine sand flies [161]. Commonly present in underdeveloped countries, cutaneous leishmaniasis (CL) is placed by WHO as one of the ten most important infectious diseases worldwide, being present in more than 85 countries. Medication used for CL treatment includes the administration of pentavalent antimonials such as Pentosan® and Glucantime®, or Amphotericin B in more severe cases [162]. However, these drugs are known for their wide range of adverse side effects such as nausea, vomiting, hepatic alterations, and cardiac disorders, among others, combined with an increasing rate of drug resistance [163].

Photodynamic therapy (PDT) is an alternative to the conventional treatment for CL, being non-invasive and presents few application restrictions for the patients. As with the previous application of PDT against infection, inactivation of infected cells with a parasite is through the photochemical process that results from the interaction between a PS and light at an appropriate wavelength to produce ROS. Natural and synthetic PSs such as curcumin, hypericin, 5-aminolevulinic acid, phthalocyanines, phenothiazines, porphyrins, chlorins and nanoparticles have been applied. Recent advances on using PDT for treating *Leishmania* species have been reviewed [164].

In an in vitro study conducted to evaluate the response of macrophages infected with *L. braziliensis* and *L. major* to curcumin treatment with PDT indicated that curcumin concentration of 7.8-15.6 µg/mL presented photodynamic inactivation using LED (λ = 450 ± 5 nm), with a light dose of 10 J/cm^2 [165]. Cell destruction and internalization of curcumin in both macrophages and intracellular parasites were observed using microscopy techniques. An increase in mitochondrial membrane polarity and a decrease in the number of parasites recovered was observed in the PDT groups. This study showed that PDT with curcumin has the potential to inactivate infected macrophages.

Another study was performed to evaluate the in vitro phototoxic, morphological, and apoptotic effect of various PS-(methylene blue, toluidine blue, chloro-aluminum phthalocyanine, and pheophorbide-a) mediated PDT on the viability of *L. tropica* promastigotes. Experimental results revealed that parasite viability was significantly different in groups treated with MB, TBO, and Pheo-a, with or without irradiation. Chloro-aluminum phthalocyanine (PC) treatment did not lead to any alterations in cell viability in *L. tropica* promastigotes with or without irradiation. DAPI staining indicated that apoptotic bodies and nuclear fragmentation were observed in MB-, chloro-Al PC-, and Pheo a-mediated PDT groups [166].

A similar study using amphiphilic chlorin derivatives was used with one PS CHL-OH-A (a chlorophyll derivative) exhibiting the highest antiparasitic activity at 24 h (0.33 μmol L^{-1}) and 48 h (0.14 μmol L^{-1}) after irradiation at 660 nm (6.0 J.cm^{-2}). The PSs tested induced parasitic cell death, mainly by an apoptotic-like process upon light exposure. These amphiphilic chlorins exerted leishmanicidal activity suggesting their use for aPDT in the treatment of cutaneous leishmaniasis [167].

An interventional clinical trial [NCT02355899] entitled Evaluation of the Suitability of PD P 506 A in the PDT of Distal Subungual Onychomycosis (DSO) of the Great Toenail was completed at the Klinik für Dermatologie, Klinikum Lippe, Germany [168]. PD P 506 A is a dermal patch of 4 cm^2 in size loaded with 2 mg 5-ALA (as 5-ALA HCl) per cm^2, and administered to each great toenail for 4 hours, followed by illumination with red light of defined wavelength. Study participants were 18-75 yo. Large toe nails were evaluated with negative laboratory test results for onychomycosis (KOH test, periodic acid-Schiff or PAS stain, and mycology culture) according to different treatment phases and severity of adverse events graded as mild, moderate, severe, life-threatening, and fatal. The final results are yet to be published from this study.

2. Malaria

Malaria is an infectious life-threatening disease caused by parasites of the genus *Plasmodium*, and it is spread to humans by the bite of the female anopheles mosquito. *Plasmodium* species capable of inducing human disease are the *falciparum, vivax, malariae, ovale*, and *knowlesi*. The first is the most widespread and virulent, responsible for 80% of infections and about 90% of deaths, especially in Africa [169]. Due to antimalarial drug resistance, malaria remains a leading cause of death of children in Africa. The recommended treatment is an artemisinin-based combination therapy (ACT) and other antimalarial drugs such as chloroquine, quinine, exifone, and rufigallol. Through heme-drug interaction (by π-π interactions), these drugs inhibit the β-hematin or hemozoin formation responsible for autocatalyzed heme degradation caused by the parasite in the infected red blood cells. Porphyrins are reported to inhibit heme crystallization in the acidic food vacuole of the malaria parasite [170]. As current antimalarial drugs, porphyrins are able to inhibit the β-hematin formation or heme aggregation by strong π-π stacking interactions. Thus, porphyrin-based PSs are utilized to fight malaria. Declines in cases and deaths caused by malaria are due to the development of new strategies such as the use of aPDT for the control of the infection vector or to induce inactivation of *Plasmodium falciparum* and targeting the hemozoin inhibition, with the aim of preventing and treating malaria. A porphyrin derivative was found to

be active in vitro against *Plasmodium falciparum* at 20 nM and a slight delay of mice survival was observed on the *Plasmodium berghei* Swiss mice model at 50 μmol/kg/day. It was concluded that pharmacomodulations should be further developed to better understand porphyrin behavior in the parasites compared to host cells [171], [172].

The use of δ-aminolevulinic acid-protoporphyrin IX (ALA-PpIX) was exploited and demonstrated to be an effective modality to cause destruction of both resistant and susceptible strains of parasites, including at a high load mimicking severe drug-resistant malaria. These current findings set the concept of an ALA-PpIX-based PDT platform, "the REAP (Rapid Elimination of Active *Plasmodium*) strategy". This approach provides another tool for the defense against multi-drug resistant malaria and other intracellular blood pathogens, dependent on heme-synthesis biochemical pathway [173].

Limitations of aPDT in the clinics

The emergence and spread of drug-resistant pathogens that have acquired new resistance continue to imperil our ability to treat common infections and remain to be a therapeutic challenge for clinicians. PDT offers a viable option in the treatment of pathogens that have acquired resistance to conventional medications. Although it offers many benefits over standard treatment methods, ROS-mediated microbial killing is often faced with accessibility, poor selectivity, and off-target damage. PDT tends to damage normal cells and results in side effects in the treatment area. Usually, the most adverse effects of PDT, including local erythema, edema, pain, swelling, redness, burning, scarring, stinging sensations, and itching, which occur within the first PDT session, are mild and tolerable. Slight blistering and minimal exudation may occur in a few patients. Hyper- or hypopigmentation or scars may persist over a long period of time, particularly in patients with deep fungal infections using ALA-PDT. However, most adverse effects are temporary and usually disappear within 2 weeks after PDT [174].

Nanoparticles as PSs have been designed for enhanced drug delivery and therapeutic effects that can better meet the complex biofilm microenvironment against drug-resistant microbes. The use of nanomaterials may lead to accumulation in the environment and this could result in unforeseen dangers. Some metallic NPs such as iron, silver, platinum, palladium, gold, and metal oxide are found to cause damage to the cell membrane, DNA, and proteins. These particles tend to enter the bloodstream and reach vital organs of the human body resulting in toxicity [175].

Additionally, despite the upward trend in the popularity of PDT in adults, pediatric application of PDT is not common. Due to certain limitations, substandard optimum treatment regimens and potential side effects, PDT in the pediatric population is still in the initial phases of evaluation in clinical trials. The selection and use of non-toxic PSs, concentration of the PS, and light dosage limit its use in children. Photosensitizers administered intravenously can be very uncomfortable in young patients [176].

Despite a plethora of literature evidence describing the photodynamic inactivation of bacteria, viruses, fungi, and parasites, PDT is far from being considered as a standard therapy for infectious diseases. This could be attributed to the lack of antimicrobial photosensitizers with optimum physicochemical properties and the inability to deliver them into infected tissues. However, interest in its use as an alternative to standard treatment for infections will continue.

CARDIOVASCULAR DISEASES

Light therapy or PDT in the clinics has focused primarily on the treatment of cancer as discussed in the first section of this mini-review. Advances in laser technology, endovascular delivery systems, and macrocyclic synthetic chemistry have extended PDT, not only in infectious diseases as mentioned in the previous section but also in atherosclerotic applications. The potential of selective destruction of targeted tissues exhibited by PDT contributed to its emergence as an alternative treatment in CVDs, in which interventional tools or catheter-based approaches can be relatively nonselective and carry a significant risk of damage to the normal arterial wall.

Photoangioplasty is PDT of vascular de novo atherosclerotic, and potentially restenotic lesions [177]. Restenosis is the recurrence of stenosis, which is a reduction of the lumen diameter narrowing the blood vessels after percutaneous coronary intervention (either with or without stent implantation), causing restricted blood flow. This is a common adverse effect of endovascular procedures, such as angioplasty, vascular, and cardiac surgeries, used to treat vascular damage resulting from atherosclerosis and related narrowing or re-narrowing (restenosis) of the blood vessels [178]. Vascular smooth muscle cell (VSMC) proliferation with migration into the intima is a major contributor to restenosis after angioplasty or stent deployment. No systemic pharmacological agent has yet been shown to resolve this problem. Current techniques that alter cell proliferation involve the elution of a cytotoxic drug from the stent wall or by brachytherapy using the catheter-based system for radiation delivery or radioactive stents [179]. PDT provides an alternative strategy to regulate VSMC proliferation.

Photosensitizers for PDT in Cardiovascular Disease

High lipid content of vascular plaque and drug lipophilicity in atherosclerosis promote selective accumulation of hydrophobic photosensitizing agents. Uptake of hydrophilic and lipophilic agents is observed to be comparable indicating that impaired endothelial permeability and passive diffusion into the arterial wall from the vasa vasorum and from the lumen augment active transport mechanisms [180].

Hematoporphyrin derivative (HpD), being the first PS to be utilized in malignant neoplasms, was also the first of a number of photosensitizers with selective accumulation within atherosclerotic plaque [181], [182]. HpD was found to accumulate in atheromatous lesions of the aorta

in rabbits and monkeys. Photofrin, a more purified form of HpD, also exhibited localization and cell destruction in a 4:1 ratio in the smooth muscles of atherosclerotic plaques compared to nonatherosclerotic arteries [183]. Other photosensitizers activated at 660-690 nm and required liposomal or intralipid formulation for atherosclerosis have been described including phthalocyanines, chlorins, purpurins, and benzoporphyrin derivatives [184]. These photoactive drugs have been shown to accumulate in greater concentration in atherosclerotic plaque than in normal arterial walls and are considered safe with brief skin phototoxicity as the only significant side effect. Despite this obvious selective damage of the plaque and sparing of the underlying media, the lack of efficacy limiting its widespread use might be attributable to inadequate penetration of the 630-nm light through the endoluminal blood. The propensity of treated patients to display prolonged cutaneous phototoxicity further hampered clinical application.

Efforts to improve the photodynamic efficacy of PS for CVD application using nanoparticles are underway. Nanoparticles (NPs) are tiny particles with size ranging from 1 to 100 nm. NPs can be classified into different classes depending on their properties, sizes, or shapes. These different groups include fullerenes, metal, polymeric, or ceramic NPs. Due to their nanoscale size and high surface area, NPs possess unique physical, chemical, and optical properties making them suitable candidates for a wide variety of applications in medicine, imaging, catalysis, energy, and environmental-related research [185].

The synthesis of a multimodal theranostic nanoagent based upon magnetofluorescent NPs for the treatment of inflammatory atherosclerosis has been described. The nanotherapeutic agent, composed of dextran-coated iron oxide conjugated to modified light-activated chlorin moieties, were shown to be readily taken up by murine macrophages in vitro and is highly phototoxic with an LD_{50} of 430 pM. Localization of the nanoagent within macrophage-rich atherosclerotic lesions can be imaged by fluorescence microscopy. Irradiation of the atheroma with 650 nm light caused the eradication of the inflammatory macrophages, which may induce lesion stabilization. These nano agents were shown to display limited skin photosensitivity, were highly efficacious, and may potentially provide an integrated imaging and therapeutic nanoplatforms for atherosclerosis [186], [187].

Experimental models

Experiments have shown that PDT inhibits the growth of VSMC growth and decreases the development of experimentally induced intimal hyperplasia. Photosensitization can accomplish complete cellular eradication within the vascular wall without inflammation. In vitro, exposure to phthalocyanine-initiated PDT eliminates detectable levels of basic fibroblast growth factor (βFGF and FGF-2) in solution and significantly reduces the smooth muscle mitogenesis induced by matrix-associated FGF-2 [188]. In vivo, PDT of rat carotid arteries produces a loss of βFGF staining compared with untreated sham-control arteries. The data suggest that PDT may inhibit intimal hyperplasia through local inhibition of cytokine release or activation. Another study of the effect of NPe6-induced PDT in a balloon-injured rabbit arterial model indicated complete depletion of smooth muscle cells after intraluminal irradiation with 10 $J.cm^{-2}$ inhibiting intimal hyperplasia, which is a major complication of arterial revascularization [189]. Other investigation using the combination of motexafin lutetium (Antrin) as the photosensitizing agent and endovascular illumination, or Antrin phototherapy, has been shown to reduce plaque in animal models [190].

Low-energy laser irradiation (LELI) can be used as a non-invasive treatment option in myocardial infarction or stroke. An experimental model of an infarcted heart treated with LELI (2.5-20 mW/cm^2) resulted in a 50-70% reduction in infarct size six weeks after coronary artery occlusion. LELI has a profound cardioprotective effect and has been found to modulate various biological processes, including an increase in mitochondrial respiration and ATP synthesis, accelerate wound healing, and promote the process of skeletal muscle regeneration after injury. This effect was partially attributed to a significant increase in the number of intact mitochondria and ATP content, and antioxidative enzyme activity in LELI-induced hearts of rats and dogs as compared with non-irradiated hearts [191], [192]. Another study conducted showed that cultured smooth muscle cells from both stenotic and restenotic lesions from human atherectomy specimens could be eradicated by incubation with porfimer sodium followed by light irradiation.

A recent in vitro study investigated the affinity of a photosensitizing agent ALA dendrimers for foam cells and the type of cell death triggered by the photodynamic treatment [193]. This study formulated an in vitro model of atheromatous plaque that involved a transformed Raw 264.7 macrophages to foam cells by exposure to oxidized LDLs and co-cultured with HMEC-1 endothelial cells. The ALA dendrimer exhibited a selective PDT response for foam cells against endothelial cells. A light dose of 1 $J.cm^{-2}$ eliminated foam cells accompanied with less than 50% elimination of HMEC-1. Apoptosis cell death is the preferred mode of cell death pathway without evidence of necrotic pathway. ALA dendrimers were proposed as pro-photosensitizers and as theranostic agents to be employed in photoangioplasty to aid in the treatment of obstructive cardiovascular diseases.

To address the issue of low-tissue penetration ability of excited light for photosensitizers and as an attempt to apply PDT for the treatment of atherosclerosis without external light, polymeric nanoparticles were designed that were cross-linked with an Fe^{3+}-catechol complex for stabilization and magnetic resonance imaging (MRI). Lipopolysaccharide and oxidized LDL-activated RAW264.7 macrophages were utilized as experimental models to monitor the progression of atherosclerosis. The synthesized iron nanoparticles accumulated effectively in plaques exhibited effective macrophage elimination in aortic arches and abdominal aortae but were inefficient in the thoracic aorta, aortic hiatus, and aorta-iliac

bifurcation. Reduced plaque size and thickness were revealed by T_1-weighted MRI images. This polymeric nanosystem is the first example of a combination of MRI and chemiexcited PDT for atherosclerosis [194].

Macrophages play critical roles in the development of atherosclerosis, from initiation to fatal thrombotic rupture. Photoactivation by targeting macrophages has emerged as a therapeutic strategy for the treatment of atherosclerosis. A novel phototheranostic agent consisting of a chlorophyll derivative and dextran sulfate internalized into activated macrophages and foam cells via scavenger receptor-mediated endocytosis in atherogenic mouse models. Optical imaging-guided photoactivation of the photosensitizer by light illumination reduced both atheroma burden and inflammation in the murine models. Atheroma is an abnormal but reversible accumulation of lipid material building up in the arterial wall. Immunofluorescence and histochemical analyses revealed that PDT produced an increase in macrophage-associated apoptosis and induced autophagy indicative of an enhanced efferocytosis in atheroma [195].

Various animal models, including rats, rabbits, swine, and monkeys, have been utilized to investigate the optimal selective photodynamic activity of the photosensitizer. In most of the cases, rabbits were maintained with cholesterol-rich diets, and a combination of atherogenic diet and mechanical balloon injury in the aorta or iliac arteries was performed to induce advanced lesions. Although most of the tested photosensitizers demonstrated preferential accumulation within the plaque, it should be noted that atherosclerotic plaques in rabbits are composed of high smooth muscle cell content and macrophage-derived foam cells with some fibrous components, and these lesions are different from the atherosclerotic plaques in human coronary artery [196]. Human coronary plaques are characterized as lipid-rich plaques containing a lipid core and fibrous plaques rich in collagen fibers but poor in macrophages. Larger animal models such as the cholesterol-fed swine model show similarity to humans with respect to the size of the coronary artery and in the progression of coronary lipid core-containing atherosclerotic lesions. The coronary artery of large pigs or aorta of small pigs was commonly employed to study the efficacy of PDT on restenosis [197]. This suggests that results from animal models should be treated with caution when translating and extrapolating the results to humans.

PDT for cardiovascular disease in the clinics

Vascular PDT application in the clinical setting is rather dismal. A pilot clinical study of adjuvant PDT in patients undergoing repeat femoral angioplasty for restenosis showed the technique to be safe and effective [198]. Seven patients (median age: 70 yo) sensitized with oral 5-ALA (60 mg/kg) received laser light through a standard transparent angioplasty balloon. The light was delivered to the sensitized arteries by replacing the angioplasty balloon guide wire with a 0.2 mm optical fiber. Follow-up evaluation was conducted with duplex scanning and intravenous digital subtraction angiography at six months. No evidence of restenosis on digital subtraction angiography and no arterial complications were noted. Long-term results for these patients have remained excellent. The mean (SD) follow-up period in the seven patients has been 26 months. Six patients remained asymptomatic, although one required repeat angioplasty. This is the first reported clinical trial of adjuvant arterial PDT to prevent restenosis following angioplasty.

A phase 1 clinical study of PDT in 47 patients using motexafin lutetium in the treatment of de novo iliofemoral atheromatous plaque, without previous percutaneous angioplasty, has been reported. In this study, there was no evidence of significant dose-limiting systemic toxicity. Adverse reactions were limited to infrequent, transient, self-terminating episodes of paresthesias and minor skin eruptions. No angiographic or ultrasonographic evidence of embolization, vascular trauma, or disease progression was reported that could be ascribed to the experimental treatment [199], [200].

An ongoing clinical trial entitled Vasodilatory Effects of Light on Peripheral Artery Disease is underway at the Medical College of Wisconsin [201]. This study aims to measure the blood flow in the gastrocnemius muscle in patients with documented peripheral artery disease before and after 5-min exposure to 670 nm light energy from a light emitting diode light source (with output up to 75 $mW.cm^{-2}$) placed over the gastrocnemius muscle. No reported results from this study have been published yet.

CONCLUSION

Photodynamic therapy (PDT) is a sophisticated cancer treatment that shows selective destruction of malignant cells. PDT has been extensively studied in vitro, in animal tumor models, and in clinics. Numerous clinical trials have proven PDT to considerably enhance the quality of life and survival in individuals with incurable malignancies. Beneficial characteristics make PDT a feasible option as a monotherapy or as complementary (before or after) to current standard therapies. There is a tremendous benefit provided by PDT in multitherapy settings for cancer treatment. Similarly, PDT offers great potential in the treatment of infectious diseases with an established ability to address bacterial, fungal, protozoan, and viral infections.

Photodynamic therapy for the treatment of atherosclerosis and restenosis after angioplasty was extensively investigated in the medical and academic fields for ten years between 1990 and 2000. Compared to PDT applications for the treatment of cancer and infections, its application in CVDs almost completely disappeared in the academic field after 2000 as shown by the lack of published studies, mainly, due to technology associated with photosensitizer and light-emitting devices in terms of performance, side effects, and costs. However, interest in PDT use in CVDs will eventually increase. PDT can be integrated into conventional percutaneous coronary intervention (PCI) procedures and can stabilize vulnerable plaques. Additionally, photosensitizer administration allows for treating multiple vessel segments

within a single intervention. PDT use can find its way to the prevention of neoatherosclerosis, which is emerging as a new coronary-stent-associated problem with the use of new second-generation drug-eluting stents to seal atherosclerotic lesions, but can result in reendothelialization, recruitment of macrophages, and proliferation of the neointima within the stented segment [202]. Eventually, extensive research and clinical studies are still needed to evaluate the efficacy of PDT in specific indications for cardiovascular diseases.

Less invasive therapies are interesting treatment options for patients with cancer, infections, and atherosclerosis. PDT as a cancer and infectious disease treatment is still underutilized, and wider acceptance of its benefits is lacking. The general public and clinicians need to be informed about PDT treatment as an option available for patients. Light treatment in CVDs is still in its infancy and more studies are needed to identify its role in the future.

CONFLICTS OF INTEREST

None of the authors have conflicts of interest to declare.

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