REVIEW

Antimicrobial Photodynamic Therapy for the Remote Eradication of Bacteria

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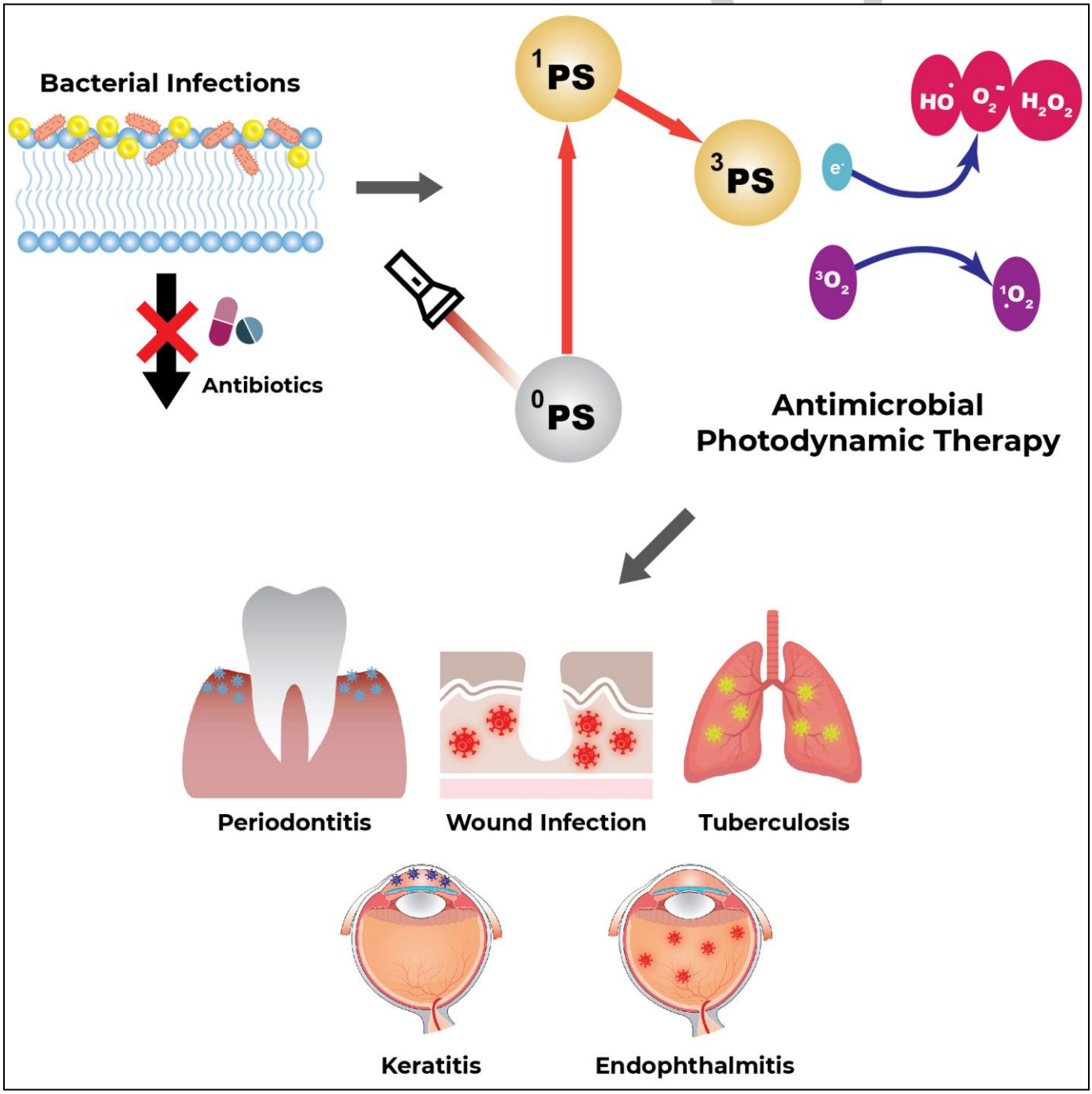

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Abstract: The emergence of multi-drug resistant bacteria strains has been an uphill battle in modern healthcare worldwide, due to the increasing difficulty of killing them. The evolving pathogenicity of bacteria has led to researchers searching for more effective antimicrobial therapeutics to successfully eliminate them without undesirable consequences to the human body. In recent years, antimicrobial photodynamic therapy (APDT), an obsolete technique for cancer treatments, has been reported to eradicate bacteria and biofilm-related infections. The principle of antimicrobial photodynamic therapy solely relies on the photosensitizers (PSs) generating reactive oxygen species, in the presence of oxygen and light, to destroy pathogens. Thus, it can target a broad spectrum of microorganisms, owing to the indirect interaction between PSs and the bacteria, resulting in the less likelihood for the development of drug resistant bacteria strains. This review will focus on the recent progress of APDT in the last five years and some future perspectives of APDT. The mechanism of APDT against bacteria and biofilms, various PSs used for APDT, and some common multidrug-resistant bacteria strains will be briefly introduced. The reported in vivo applications of APDT in the several types of bacterial infections that includes periodontitis, wound infections, keratitis, endophthalmitis and tuberculosis in the last five years will be summarized in detail.

1. Introduction

Bacteria, regardless of pathogenic or non-pathogenic strains, are ubiquitous in our environment and in our bodies, exposing us to millions of various species every day. Among the non-pathogenic strains, most of these strains live harmoniously in our gut, playing essential roles to maintain our gut system.[1] In contrary, the pathogenic bacteria strains are indeed a great threat to the public health, leading to a multitude of infections that we face today.[2] Bacterial infection, has been one of the major health concerns globally, resulting in the rise in mortality rates before the early 20th century.[3] Fortunately, the discovery of penicillin by Alexandra Fleming in 1928 has turned the tables on bacterial infections with the mass production of antibiotics in 1940s, giving an upper hand in the battle against bacterial infections.[4] However, the over-consumption and misuse of antibiotics has caused an alarming surge in the number of multidrug resistant (MDR) bacteria strains, also known as 'superbugs.' Methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecalis*, ciprofloxacin-resistant *Pseudomonas aeruginosa* and ampicillin-resistant *Escherichia coli* are just some examples of these superbugs.[5] Statistically, these MDR bacteria strains have brought about at least 700 000 deaths each year worldwide, and it is predicted that these figures could potentially escalate to 10 million by the year 2050.[6] The evolving pathogenicity of such bacteria strains would evade the host immune system easily, that leads to an increasing difficulty to eradicate them.[7] Moreover, to bypass the action of antibiotics, bacteria normally would form biofilm to shield themselves from the diverse and drastic environment for survival, which in turn enhances their resistance to antibiotics by up to 1000 times as compared to the planktonic ones.[8, 9] Being a highly structured clusters of microbial cells attached to a surface and embedded in a rich polymeric matrix, biofilms enhance bacterial resistance to immune clearance and antibiotics.[10] Hence, the formation of bacterial biofilms could further intensify the antibiotic resistant and prolong infection.[11] Therefore, there is a need to develop alternative antimicrobial therapeutics, that is non-invasive, non-toxic, and importantly, one that is less likely to induce drug resistance, to tackle the problem of MDR bacteria strains.[12] One of such antimicrobial therapeutics is the use of antimicrobial photodynamic therapy (APDT).

Photodynamic therapy (PDT) was originally discovered as an anticancer therapy to fight against malignant and non-malignant tumours. The principle of PDT employs the synergistic effect of two individually non-toxic segments, a photosensitizer and light, to oxidatively kill the cells and tissues. At the right excitation of the photosensitizer, a photochemical reaction will be initiated that produces reactive oxygen species (ROS) called singlet oxygen ($^1O_2$).[13] Subsequently, the latter can oxidatively damage the surrounding macromolecules such as nucleic acids, proteins, and lipids, leading to cell death, or pathogenic microorganisms.[7, 14] Even though, the inactivation of microorganisms via light has been around for more than 10 decades, the research on APDT have been few because of the advancement of antibiotics in the 20th century. PDT remains as one of the treatments for cancer, alongside with radiotherapy, chemotherapy, and surgery.[15] However, with the growing demand for alternative antimicrobial approaches in the fight against MDR bacteria strains, researchers have re-explored APDT due to its attractive therapeutics' characteristics such as non-invasiveness, non-toxicity, and broad antibacterial spectrum.[16] Furthermore, APDT has been reported to disrupt biofilms.[17] For example, Yang and his co-workers reported that the use of 5-aminolevulinic acid photodynamic therapy was able to eliminate both planktonic and viable biofilm-associated of *Pseudomonas aeruginosa* and damages the structural integrity of the biofilms.[18] Henceforth, APDT has advanced into an antibacterial approach for MDR bacteria.[19] Although APDT could not target systemic infections owing to the limitation of using light, but APDT is relevant for local infections. Currently, APDT is employed in animal models of localised bacterial infections such as periodontitis, wound infections, keratitis, endophthalmitis and tuberculosis which will be further discussed in section 3. If APDT can successfully take over or reduce the use of antibiotics for bacterial infections, the situation against bacterial resistance can be alleviated to a great extent. As such, APDT can be considered as one of the most promising

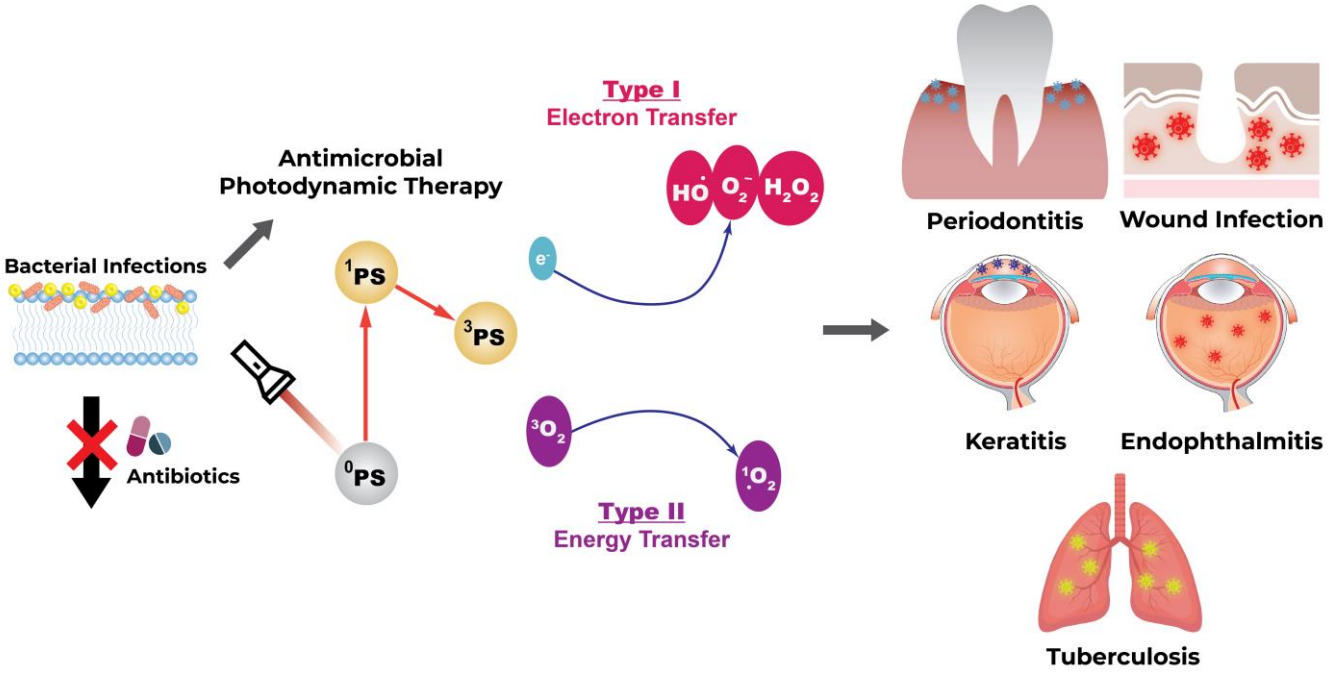

Figure 1. Schematic illustration of antimicrobial photodynamic therapy against various bacterial infections

treatments for bacterial infections, particularly for the MDR bacteria. In this review, we will first introduce the importance of APDT as an antimicrobial tool in bacterial infections. Next, we will briefly describe the mechanism of APDT against bacteria and biofilms, the various photosensitizers utilized for APDT, and several commonly targeted MDR bacteria strains. Then, we will be summarizing in detail the reported in vivo applications of APDT in the several types of bacterial infections in the last five years. This review aims to focus on the recent progress of APDT in the last five years and some future perspectives of APDT.

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2. Antimicrobial PDT in Bacterial Infections

The use of PDT as a therapeutic modality to combat infections is an emerging field against diseases of microbial origin due to the inappropriate excessive prescription of antibiotics, which have resulted in the evolution of microbial cells to increase their resistance. These microbial defense mechanisms adaptations, include the encodement of new proteins, and reinforcement of the outer wall to prevent the penetration of antibiotic drugs.[20, 21] Therefore, the urgent need for an alternative approach to combat such bacterial infections has garnered increasing interest in APDT as the mechanism of action is remarkedly different from that of most antibiotic drugs currently available in the market. In this section, we will be introducing the mechanism of APDT and its action towards bacteria and biofilms, the different photosensitizers being applied in APDT, and highlighting several commonly targeted MDR bacteria strains.

2.1. Mechanism

The principle of antimicrobial photodynamic therapy (APDT) is dependent on three individual components, namely the photosensitizer, light of appropriate wavelength, and molecular oxygen. Upon exposure of light on the photosensitizer, reactive oxygen species (ROS) will be generated, that incudes hydroxyl radicals (OH), super oxide anions (O_2^-) and hydrogen peroxide (H_2O_2), causing oxidative damage to the surrounding biomolecules, leading to cell apoptosis, or killing of pathogenic microbes. The whole system of APDT is basically mediated by two types of mechanisms: electron transfer and energy transfer. As illustrated in Figure 2, the Jablonski diagram shows the process of APDT. When the photosensitizer (PS) is excited, it absorbs the light energy of an appropriate wavelength, and it promotes from the grounds singlet state (S_0) to the electronic excited singlet state (S_1). Usually, the PS at this state will demote back to the singlet ground state (S_0) and emit fluorescence or converted to a longer-living excited triplet state (T_1) via an intersystem crossing. When the PS is at this triplet state, it can then emit phosphorescence to return to the ground state or react with oxygen through two pathways: type I that involves the electron transfer from the excited PS to produce ROS; type II involves the PS transmitting energy to molecular oxygen, resulting in the formation of singlet oxygen ($^1O_2$).[12, 22, 23] The type I reaction would happen in the bacterial cell membrane via hydrogen extraction with unsaturated phospholipid molecules. The molecules will then further interact with oxygen to form lipid peroxides, disrupting the bacterial cell membrane, causing it to be more permeable.[24] Simultaneously, type II reaction will occur whereby the PS at the triplet state can transfer energy with O_2 to form $^1O_2$. Being the most potent species of ROS, $^1O_2$ can cause oxidative stress to biological molecules such as DNA, proteins, and lipids, and thus effectively eradicating bacteria.[25]

2.2. Various photosensitizers for antimicrobial photodynamic therapy

By employing the appropriate photosensitizers with superb characteristics for APDT, it will enhance the efficacy in treating bacterial infections. Some of these characteristics include: 1) capable to absorb light in the range of 600 nm to 800 nm, so as to ensure a high penetration depth into the tissues; 2) high extinction coefficients; 3) surface charge that can be controlled; 4) very stable upon exposure to light; 5) negligible toxicity in the absence of light; 6) able to be soluble in water; 7) high affinity towards bacterial cells for localization.[26] In this sub-section, we will be briefly introducing some of the reported photosensitizers that have been utilized in the last five years for treatment of bacterial infections via antimicrobial photodynamic therapy.

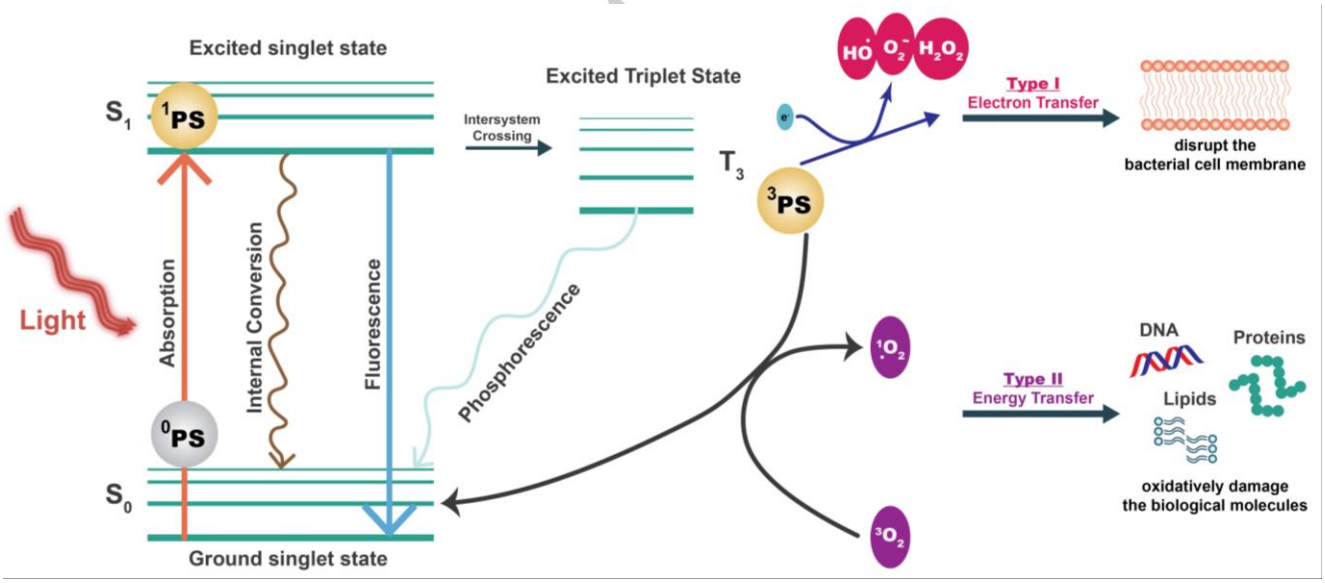


Figure 2. Jablonski diagram to illustrate the antimicrobial photodynamic therapy.

2.2.1. Porphyrin

Porphyrin consists of a ring with four interlinked pyrrole subunits to form large π-conjugated planar dyes.[27, 28] The strong π–π* transition of a Soret peak at around 400 nm and four Q bands in the visible region is a distinctive absorption spectrum resulting from the 18 π-electron aromatic macrocycles of porphyrin.[29] Porphyrins are perceived to be a good choice of PS in APDT because of its inherent properties such as the ease of synthesizing it, the versatility of its chemical structure, the relatively high triplet state quantum yield, and the high molar absorptivity.[30] In the recent years, many researchers have reported countless porphyrin-based APDT such as protoporphyrin IX[31-33], chlorin e6[34, 35] and 5-aminolevulinic acid (a pro drug for porphyrin)[18, 36] As an example, Gourlot and his co-workers have developed a novel molecule that comprises of a π-extended porphyrin photosensitizer connected to an antimicrobial peptide via an amide linkage. Upon the excitation at 720 nm, the molecule has displayed distinctive antibacterial activity towards both *Escherichia coli* and *Staphylococcus aureus* at a low micromolar level of 1 µM.[37]

2.2.2. Phthalocyanines

Phthalocyanines are another class of heterocyclic macrocycle aromatic compounds. Unlike porphyrins, which are made of methine bridge-interconnected pyrroles, the chemical structures of phthalocyanines consist of one secondary amine bridge that interconnects the iso-indole subunits.[38, 39] Being a second-generation PS, phthalocyanines does display a strong absorption peak at the near-infrared region. It also exhibits properties such as high stability, ease of synthesis, high versatility in altering its chemical structure alteration, low intrinsic toxicity and capable to generate high amounts of ROS when irradiated, in the presence of a suitable central metal atom such as zinc, aluminum or silicon.[40] However, phthalocyanines have some disadvantages such as the slow in vivo elimination and strong aggregation ability on aqueous solution.[29] To overcome these flaws, subsequent modifications were made to the structure of phthalocyanine, such as the addition of Zn(II) which is one of the most commonly studied phthalocyanine-based photosensitizer for APDT.[41] For instance, Li and his co-workers reported a new nanodot based on a single phthalocyanine molecule (PcA) that could self-assemble in aqueous solution and remain stable for a week in the absence of light. The self-assembly of PcA forms NanoPcA that can effectively produce ROS upon the irradiation of light via the type I mechanism. Indeed, NanoPcA demonstrated outstanding antibacterial effects against *E. coli* and MRSA.[42]

2.2.3. Phenothiazinium

Phenothiazinium and its derivatives have been widely used in antimicrobial applications over the last century.[43] Owing to its high binding affinity towards both Gram-positive and Gram-negative bacteria, phenothiazinium-based photosensitizers were frequently used in the research of APDT. [44-46] Examples of phenothiazinium compounds include Rose Bengal[47, 48], toluidine blue O[49, 50] and methylene blue.[51-53] Methylene Blue (MB) is one of the two most popular phenothiazinium dyes in this category that has been commonly used in antimicrobial research.[54] MB and its derivatives can absorb long wavelengths at the near infrared region (> 650 nm), which allows for good penetration in human tissues, making them useful in clinical applications.[55] Various methylene blue based compounds with different functional groups have been reported to enhance the antimicrobial activities due to the increase of cationic groups functionalized on MB to increase the binding affinity and uptake of the PS with bacteria.[30] Feng and his co-workers developed a methylene blue loaded hemostatic material by combining the properties of both keratin and alginate, to have better mechanical strength and wound dressing properties of keratin by mixing alginate into the composite scaffolds. The composite scaffolds were interconnected with Ca^{2+}. In vitro studies show that both *S. aureus* and *E. coli* were inactivated upon light irradiation in which MB generated ROS to oxidatively damaged *S. aureus* and *E. coli*. Furthermore, to prevent further infection, the drug-loaded scaffold could produce high burst release by absorbing the wound exudate to speed up the wound healing process.[56]

2.2.4. Small-molecule Dyes

Malachite green (MG)[57, 58],4-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPYs)[59, 60] and indocyanine green (ICG)[61, 62] are some examples of small molecule organic dyes based photosensitizing agents. Usually, BODIPYs [63] and cyanine dyes [64] used as photosensitizers lately owing to biocompatibility are and their intrinsic ability to absorb light at the near-infrared (NIR) region which allows for deeper tissue penetration. As such, they are normally used for non-invasive *in vivo* imaging.[65] IR-780 iodide is an example of a type of ICG that has been reported to produce ROS under 808 nm excitation for photodynamic inactivation.[66] IR-780 iodide is a lipophilic cation heptamethine dye, that has a central chlorine atom conjugated to the rigid cyclohexenyl ring situated in between the heptamethine chain.[67] Recently, Xu and his co-workers have synthesized a modified photosensitizer by attaching a cephalosporin immediate onto IR-780 dye (CySG-2). Relying on the enzymatic recognition of the β-lactamase TEM-1 in MRSA, CySG-2 was able to specifically target methicillin-resistant *Staphylococcus aureus* (MRSA) and achieved antimicrobial photodynamic therapy in MRSA-infected mouse models upon an 808 nm light excitation. As such, CySG-2 could concurrently identify MRSA and eliminate them via APDT.

2.2.5. Aggregation-induced emission luminogens (AIEgens)

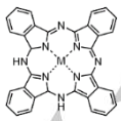
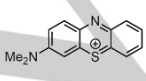
Aggregation-induced emission luminogens (AIEgens) photosensitizers (PSs) are emerging as a potential class of photosensitizers.[68] Conventional PSs such as porphyrins are usually made of planar structures and extended conjugated π systems that show aggregation-caused quenching effect (ACQ) at high concentrations as they are more inclined to aggregate under physiological conditions, which greatly compromises their photosensitization abilities.[69, 70] On the contrary, AIEgens is unique such that the molecules itself possesses mild or no emission in solution, but the aggregated AIE emits strongly with respect to aggregation, due to their restricted intramolecular motions.[71, 72] The characteristics of AIEgens such as the strong emission efficiency upon aggregation, outstanding photostability, potential for localized detection and large Stokes shift made it very appealing for bioimaging research.[73] More significantly, some

reported AIEgens have displayed a peculiar aggregation-induced enhancement of ROS production, making them very promising in PDT applications.[74] Furthermore, there has been AIEgens reported to identify bacteria or eliminate bacteria.[75-77] As an example, Wang and his co-workers developed a cationic aggregation-induced emission type of photosensitizer, MTTTPy, that can produce ROS via the type I mechanism. The chemical structure of MTTTPy allows it to accurately detect Gram-positive bacteria through electrostatic adsorption and void permeability. Furthermore, the PS could eradicate the targeted bacteria with a 95% killing efficiency at a relatively low concentration of 0.5 μM by producing oxygen-independent ROS upon exposure to white light, indicating that it can be used in treating bacterial infections under hypoxic microenvironment. *In vivo* studies also showed that MTTTPy could perform its antibacterial activities in *S.aureus* infected mice.[78]

2.2.6. Naturally occurring photosensitizers

Natural photosensitizers are used directly in APDT without further synthesis to make synthetic photosensitizers. As such, novel APDT strategies can be designed at a lower cost.[79] These PS are often extracted from edible plants, and do not need chemicals for developing synthetic photosensitizers.[5] Hypericin[80-82], curcumin[83, 84], and riboflavin[85, 86] are some of the more common natural photosensitizers that has been reported in the application APDT. Hypericin is one of the natural compounds that have been widely studied as a photosensitizer. It is a natural anthraquinone derivative that can be extracted from Hypericum perforatum. The characteristics of hypericin includes the following: 1) High singlet oxygen quantum yield; 2) low dark toxicity and 3) the ability to deactivate gram-positive bacteria strains[87, 88] Hypericin will also be loaded onto carriers such as liposomes to improve its bioavailability due to its high lipophilic structure for biomedical applications.[82] Dayyih et al. developed a thermos-responsive liposomes system to release hypericin cyclodextrin upon irradiation of NIR light at 785 nm. A NIR-dye 1,1-dioctadecyl-3,3,3,3 tetramethylindotricarbocyanine iodide (DiR) and the water soluble hypericin β-cyclodextrin inclusion complex (Hyp-βCD) were encapsulated in the liposomes to from a DiR and Hyp-βCD loaded thermosensitive liposomes (DHβCD-TSL). This DiR liposomes could be triggered by NIR light to release Hyp-βCD for synergistic photothermal and photodynamic therapy to kill Gram-positive *Staphylococcus saprophyticus*.[80]

Table 1. Summary of some reported photosensitizers for APDT in the last five years.

Structure	Class	Examples	Gram Negative	Gram Positive	Ref
		5-aminolevulinic acid (ALA)	*P. aeruginosa*		[18]
				MRSA	[36]
		Protoporphyrin IX (PpIX)		*S. aureus* MRSA	[31]
				S. aureus	[33]
				S. aureus *S. epidermidis*	[32]
		π-extended porphyrin	*E. coli*	*S. aureus*	[37]
	Porphyrin	Hematoporphyrin monomethyl ether		*S. aureus*	[89]
		Chlorin e6	*E. coli*	*S. aureus*	[34]
			P. gingivalis *F. Nucleatum*		[35]
Tetracyclic		Porphyrin-based MOF	*E. coli*	*S. aureus* MRSA	[90]
		Self-assembled ZnTPyP@NO nanoparticles	*E. coli*	*S. aureus*	[91]
		5,10,15,20-tetrakis-(4-N-methylpyridyl)-porphyrin	*E. coli* *S. typhimurium* *P. aeruginosa*	*S. aureus* *B. subtilis*	[92]
		Chloro-aluminum phthalocyanine		*S. mutans*	[93]
	Phthalocyanine			*S. mutans*	[94]
		Oligolysin-conjugated polycationic ZnPcs		MRSA	[95]
		Silicon phthalocyanine dihydroxide	*E. coli*	*S. aureus*	[96]
		Nanostructured phthalocyanine assembly (NanoPcA)	*E. coli*	MRSA	[42]
		Silicon(IV) phthalocyanines	*E. coli*	*S. aureus*	[97]
		Methylene Blue	*E. coli*		[51]
	Phenothiazinium		*P. aeruginosa*		[52]
Tricyclic			*E. coli*	*S. aureus*	[56]
			MDR *E. coli*	*MRSA*	[98]

		P. aeruginosa	*S. aureus*	[53]
	Toluidine Blue O	*P. gingivalis*		[49]
		P. gingivalis		[50]
		F. nucleatum		
	Rose Bengal	*E. coli*	MRSA	[47]
			S. mutans	[48]
			S. sobrinus	
			S. sanguinis	
			L. salivarius	
	Indocyanine green		MRSA	[61]
			MRSA	[62]
Small-molecule Dyes	BODIPYs	*E. coli*	*S. aureus*	[59]
		MDR *P. aeruginosa*		[60]
	Malachite green	*E. coli*	*S. aureus*	[58]
		P. aeruginosa	*S. aureus*	[57]
	CTRA/DGal		*S. aureus*	[99]
	TTPy		*S. aureus*	[73]
			S. epidermidis	
	TriPE-NT	*E. coli*	*S. aureus*	[77]
		MDR *E. coli*	MDR *S. aureus*	
		K. pneumoniae	*S. epidermidis*	
Aggregation-induced Emission Luminogens (AIEgens)		MDR *K. pneumoniae*	MDR *S. epidermidis*	
	MTTTPy (Alkoxy-modified triphenylamine with a cationic pyridine, an ethyl 4-bromo-6-formylthieno[3,4-b]thiophene-2-carboxylate derivative as the bridging group)	Amp^r *E. coli*	*S. aureus*	[78]
		P. aeruginosa	*E. faecalis*	
		K. pneumoniae		
	CE-TPA		MRSA	[68]
	Resveratrol		MRSA	[100]
Naturally Occurring	Curcumin		MRSA	[84]
		P. aeruginosa		[83]
	Hypericin		*S. saprophyticus*	[88]
			S. saprophyticus	[80]

	Riboflavin	*E. coli*		[86]
Inorganic	Few sheets of black phosphorus	*E. coli*	*S. aureus*	[101]
	Terbium-doped zinc oxide	*P. aeruginosa*		[102]
	UCNPs@TiO_2	*P. gingivalis* *F. nucleatum*	*S. sanguinis*	[103]
Others	Water-soluble cationic thienoviologen derivative (nTPy-Rs)	*E. coli*	*S. aureus*	[104]

2.3. Common multi drug-resistant bacteria strains

Indeed, the rise in multi-drug resistant (MDR) bacteria strains have become a serious public health concern globally. As such, these strains could lead humanity into the "dark ages" whereby antibiotics fail to be effective in fighting bacterial infections.[105] In this sub-section, we will be providing an overview of some of the antibiotic-resistant strains, and how did the bacteria strains develop resistance their respective antibiotics.

2.3.1. Methicillin-resistant Staphylococcus aureus

Staphylococcus aureus (SA) belong to the Firmicutes family. It is a common gram-positive bacteria and known to be nonmotile.[106] Normally, when individuals are colonized by SA in their skin or nasal mucosa, they are asymptomatic.[107] Such individuals were known to contribute to the increment of SA related hospital infections such as postpartum pregnant women, pregnant women, and neonatal intensive care units (NICUs) and healthy neonates.[108] Additionally, SA is often related to bone-related infections, skin infections, sepsis, pneumonia, impetigo, and endocarditis in hospitalized patients.[109-111] Although penicillin was one of the first few antibiotics developed to counter SA infections, it was then replaced by methicillin over the years. Methicillin is a penicillinase-resistant semisynthetic penicillin which is expected to be resistant to the hydrolysis of β-lactamase and inhibits the penicillin-binding-proteins (PBPs), to achieve antimicrobial activity.[112, 113] However, the evolution of SA to MRSA has occurred due to the abusive use of methicillin antibiotics.[114] As a result, SA has grown to be methicillin-resistant to escape the therapeutic effects of all β-lactam antibiotics, leading to the formation of methicillin-resistant *Staphylococcus aureus* (MRSA).[115] The three main endogenous resistance mechanism of MRSA are as follows: 1) lower outer membrane permeability to increase drug resistance; 2) efflux systems that can effectively remove the drug itself; and 3) excessive production of β-lactamase to hydrolyze the β-lactam antibiotics or binding to the extracellular antibiotics to prevent it from approaching the target site. Moreover, MRSA acquired its antibiotic resistance through the genetic mutations that reduces drug accumulation, the acquisition of resistance genes via plasmid-mediated transduction, transformation, and insertion of drug-resistant genes to produce excessive β-lactamase, and biofilm-mediated resistance with the strong adhesion and drug resistance of biofilm to resist host immune responses and evade antibiotic killing.[116]

2.3.2. Vancomycin-resistant Enterococcus

The vancomycin-resistant *Enterococcus (VRE)* is another burdensome nosocomial Gram-positive pathogen. The *enterococci* were reported as one of the leading pathogens across a range of adult hospital infections between the years 2015 to 2017 in the United States, with the majority of human infections associated with *Enterococcus faecalis* and *Enterococcus faecium*.[117, 118] *Enterococci*-related infection ranges from wound infections, dysbiosis gastrointestinal tract infections, urinary tract infections and endocarditis.[119] To fight the *Enterococcus* bacteria, researchers developed vancomycin, a glycopeptide antibiotic.[120] Unlike methicillin that targets the penicillin binding proteins, vancomycin binds to the terminal D-Ala-D-Ala moiety of the peptidoglycan precursor. Thus, PBPs were unable to cross-link the peptidoglycan, hindering the formation of the cell wall, which leads to cell bursting due to osmotic pressure.[121] Overtime, the overuse of vancomycin has led to mutation of enterococci into vancomycin-resistant *Enterococcus* (VRE).[122] The main mechanism of VRE development is through the modification of peptidoglycan precursor from D-Ala-D-Ala to D-Ala-D-Lac[123] or D-Ala-D-Ser.[124] Due to the emergence of VRE, the therapeutic options against enterococcal infections were limited. In 2017, the VRE was recognized as a serious threat by the Centers for Disease Control and Prevention, because of the high mortality rates and exceedingly great healthcare cost incurred yearly.[125] According to the global list of antibiotic-resistant bacteria, the vancomycin-resistant *Enterococcus faecium* was identified as a high priority pathogen by the World Health Organization.[126, 127]

2.3.3. Ampicillin-resistant Escherichia coli

Escherichia coli (E. coli) is one of the more well-known bacteria from the Enterobacteriaceae family.[128] The majority of *E. coli* strains are harmless or known to be beneficial to healthy individuals by supplying vitamin K to its host in the large intestines.[129] However, the pathogenic *E. coli* strains are responsible for various extraintestinal infections, and urinary tract infections (UTI).[130-132] Even though antibiotics were used for the treatment of *E. coli*-related infections, the emergence of multidrug-resistant *E. coli* was found to contribute to the increase in mortality rates.[133] Normally, *E. coli* infections are treated using a β-lactam type of antibiotic known as ampicillin. Ampicillin is able to pass through the outer membrane of *E. coli* to reach the periplasm whereby it can halt the formation of the cell wall and impede cell division.[134] However, the defence mechanism of *E. coli* would increase its resistance towards via the increment of efflux pump to raise the efflux of ampicillin and decrease the accumulation of the drugs in the bacteria, leading to a drop in the action of ampicillin towards *E. coli*.[135]

2.3.4. Ciprofloxacin-resistant Pseudomonas aeruginosa

Pseudomonas aeruginosa (P. aeruginosa) is a Gram-negative bacterium that is considered to be an opportunistic pathogen.[136] This bacterium is a ubiquitous microorganism that is responsible for a variety of serious infections such as nosocomial infections, wound and soft tissue infections, and urinary tract infections, in patients who has compromised immune system or comorbidities.[137] To combat *P. aeruginosa* infections, ciprofloxacin, a type of fluoroquinolone antibiotic, has been used extensively due to its effectivity against *P. aeruginosa*.[138] As such, this antibiotic is still of utmost importance in treating *P. aeruginosa* infections.[139] However, there has been a surge in *P. aeruginosa* bacteria strains being resistant to ciprofloxacin. For example, a study has shown that 30% of *P. aeruginosa* isolates among CF patients in the United Kingdom were resistant in ciprofloxacin.[140] Ciprofloxacin would penetrate the mammalian tissues and cells and bind noncovalently to the topoisomerase IV, type II topoisomerase and deoxyribonucleic acid (DNA) gyrase enzymes of the bacteria, hindering the DNA replication process.[141] To evade the action of ciprofloxacin, *P. aeruginosa* would modify its target site via a mutation process of the genes encoding the DNA gyrase and topoisomerase IV and increase in the expression of

efflux pumps to reduce the intracellular accumulation of antibiotics.[142]

3. *In Vivo* Applications of APDT

Due to the variable anatomy in vivo, the experimental set up and conditions are expected to be much more complex and challenging as compared to controlled in vitro situations. However, the widespread success of in vitro APDT experimentation has allowed for more studies to venture out into pre-clinical animal models in recent years. In this section, we will be discussing the in vivo applications that has been reported in the last five years in the eradication of bacteria via antimicrobial photodynamic therapy.

3.1. Periodontitis

Periodontitis, also known as periodontal diseases, are inflammations in the gum and bones supporting the teeth caused by bacterial microorganisms growing on their surfaces.[143] Conventional periodontal treatment generally removes oral biofilm and plague coating the tooth and tooth root surface, minimizing subgingival bacterial recolonization[144]. However, in some cases, mechanical cleaning is still inadequate in properly eradicating recurring periodontal infections[145] as harmful pathogens continue to persist in dentine tubules, epithelial cells and connective tissue.[146] Therefore, viable treatment options for this clinical challenge remains elusive with the dire need for accompanying therapy such as the continued use of antibiotics[147] and invasive periodontal surgery.[148]

Due to detrimental issues arising from growing antibiotic resistance and the highly invasive nature of periodontal surgery, interest in antimicrobial photodynamic therapy (aPDT) resurfaced in recent years to fill the gaps as an adjunctive therapy.[149] aPDT utilizes localized and non-invasive photochemical mechanisms in eradicating pathogenic target cells by producing reactive oxygen species (ROS) that will induce oxidative stress on cellular structures, eventually leading to cell death.[150, 151]

For instance, Wu and co-workers recently developed a photo-responsive ointment by incorporating a polyethylene glycol matrix with atomic layer Fe_2O_3-modified two-dimensional porphyrinic metal-organic framework (2D MOF) nanosheets for enhanced photocatalytic activity.[152] Due to the synergistic effect between metal-linker bridging units, the porphyrin-based MOFs were reported to exhibit exceptional light-harvesting ability with improved photonic functionality. Furthermore, the thoughtfully designed 2D nanosheet structure also further endowed the system with an abundance of active sites and fast energy migration due to the increased surface area available. These highly biocompatible and biodegradable 2D MOF-based structures demonstrated a wide-spectrum of anti-microbial activity against various commonly found oral pathogens such as *Porphyromonas gingivalis, Fusobacterium nucleatum, Staphylococcus aureus* (99.87 ± 0.09%, 99.57 ± 0.21%, and 99.03 ± 0.24%) by producing a synergistic effect of ROS and released ions which displayed remarkable therapeutic effects compared to conventional clinical periodontal treatments such as the administration of minocycline and vancomycin, owing to its enhanced angiogenesis and effective antibacterial activity that was able to timely alleviate the targeted inflammation.[152]

Moreover, as most photosensitizers have chemical structures with strongly hydrophobic properties, alternatives such as hydrophilic chemical conjugations can be made to improve its absorption efficiency with periodontal pathogenic bacteria. Wang and co-workers have reported the hydrophilic modification of chlorin e6 (Ce6) with the incorporation of a cationic cell-penetrating TAT peptide (TAT-Ce6) to improve the solubility, penetration, and adsorption onto the negatively charged surfaces of pathogenic periodontal bacteria.[153] As the formulated TAT-Ce6 conjugate comprises of an innate nanoparticle-forming ability, tinidazole, a clinical antibiotic agent was further encapsulated to achieve more efficient and synergistic dual modal effect of both aPDT and antibiotic therapy. TAT-Ce6 was reported to exhibit superior adsorption and penetration ability with the tested periodontal pathogenic bacteria and monocyte macrophages compared to the free photosensitizer. Upon 635 nm red light excitation, tinidazole-loaded TAT-Ce6 displayed remarkable synergistic inhibition efficacy both *in vitro* and *in vivo*, in which inflammatory responses such as hemorrhage, local edma, loose arrangement of connective tissue, macrophage and lymphocyte infiltration and calcification were either partially or completely suppressed in the various treatment periodontitis rat models.[153]

Alternatively, upconversion nanoparticles (UCNPs) were also utilized to develop near-infrared (NIR) activated photocatalytic reagents for APDT. UCNPs are lanthanide-doped nanoparticles that can convert NIR light to visible light via a nonlinear optical process.[154] With the ability to absorb light at the NIR region, UCNPs could help to achieve deeper tissue penetration with low interference from blood and biological tissues.[155, 156] As such, Wang and co-workers developed core-shell nanostructures of upconversion nanoparticles and TiO_2 (UCNPs@TiO_2) and studied its inhibitory effects against periodontitis-related pathogens.[103] Upconversion fluorescence-induced APDT treatment upon irradiation with a 980 nm NIR laser emitted an intense UV light, further triggering TiO_2 via an energy transfer to bring about remarkable antibacterial effects and vast reduction in metabolic activities of the biofilms. Killing efficiencies against three common periodontitis-related pathogens were also studied (*S. sanguinis* < *F. nucleatum* = *P.gingivalis*) revealing promising potential in using UCNPs to combat oral diseases.[103]

In addition, anaerobe-induced periodontal diseases were also of great interest to many due to its inherent impropriety with APDT owing to the lack of oxygen in hypoxic environments. Interesting work have surfaced in recent years such as the incorporation of cyanobacteria into the therapeutic system for oxygen production. Qu and co-workers proposed the use of spontaneous oxygen-producing cyanobacteria as carriers for Ce6 and ultrasmall $Cu_{5.4}O$ nanoparticles with catalase activity (CeCycn-$Cu_{5.4}O$) for inflammation eradication in intractable periodontitis.[157] It was reported that adjustments in ratio of Ce6 and ultrasmall $Cu_{5.4}O$ nanoparticles allowed for a swift sterilization through APDT and long-term oxidized free radical elimination. The experimented animal models not only revealed the remarkable alleviation of hypoxia, but also immense improvements in self-oxygenated anaerobic bacterial inhibition and tissue repair.

Alternatively, Dong and co-workers proposed the incorporation of a modified MnO_2 nanolayer in the developed nanocomposite, in which allows for the catalytical decomposition of hydrogen peroxide produced during metabolic processing to be utilized and converted into sufficient oxygen for APDT at infected regions.[35] Amphiphilic silanes were used to encapsulate Fe_3O_4

nanoparticles, Ce6 and coumarin 6, and further irradiated with combined red and infrared light to bring about APDT due to the enhanced red-shifted absorption, conjugate structure and magnetic navigation performance. Rising oxygen content was observed in animal models, alleviating hypoxia in the periodontal pockets and remarkably improving ROS production to boost the efficacy of APDT. Intriguingly, the increment in local oxygen levels also showed selective inhibition of anaerobic pathogenic bacteria, providing new insights towards potential alternative periodontal treatment.

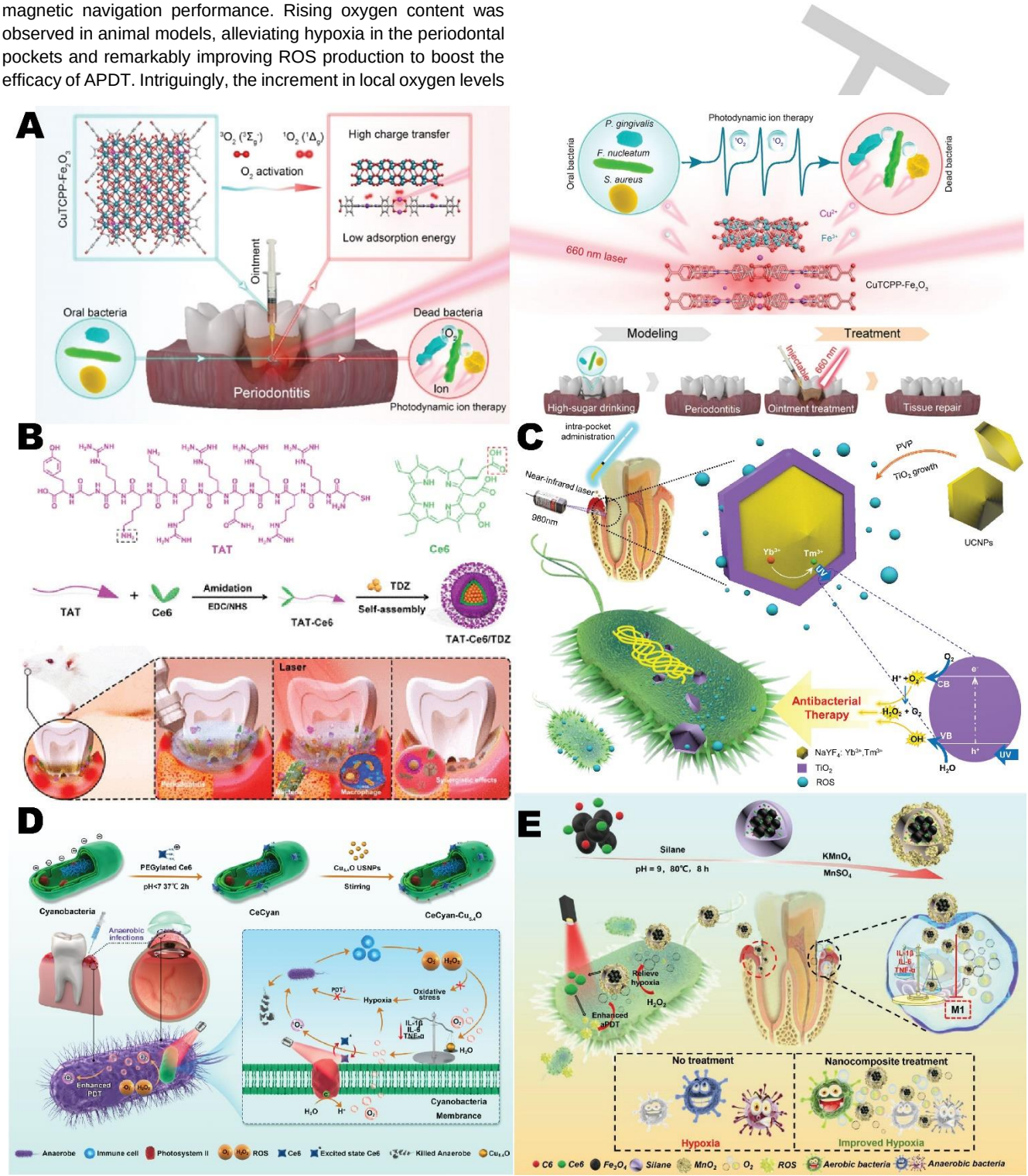


Figure 3. Schematic illustrations of various periodontitis treatment with antimicrobial photodynamic therapy. (A) A heterojunction 2D metal organic framework platform using photodynamic ion therapy. Reproduced from ref. [152] Copyright (2021), with permission from American Chemical Society; (B) A combined photodynamic and antibiotic nano-based therapy. Reproduced from ref. [153] Copyright (2021), with permission from American Chemical Society (C) A NIR-triggered antimicrobial photodynamic therapy with lanthanide-doped upconversion nanoparticle. Reproduced from ref. [103]. Copyright (2019), with permission from Elsevier; (D) An oxygen self-supplying cyanobacteria-based photodynamic therapy. Reproduced from ref. [157]. Copyright (2019), with permission from Elsevier (E) A nanozyme-based platform for self-generation of oxygen antimicrobial photodynamic therapy. Reproduced from ref. [35]. Copyright (2021), with permission from WILEY-VCH GmbH.

3.2. Chronic wound infections and skin infections

Chronic wound and skin infections can be caused by the colonization of bacteria which will delay the process of wound healing.[158] Wound healing is an intricate process in response to the injury site to regain the appearance of the damaged skin.[159] The skin is the front line of immune defense and acts as a shield against the attack of foreign microbes.[160] In normal skin, pathogenic microorganisms are incapable to invade because of the human innate immunity to generate antimicrobial peptides, production of sebum and fatty acids, and low surface pH. However, when the skin is torn off, the exposed wounds become an entrance for the invasion of bacteria, and an environment for the bacteria to live on.[161] As a result, an infection occurs. Moreover, if the skin is damaged by burns, it can be exceptionally vulnerable to bacteria, because of the damaged on the cutaneous layer of the skin.[162]

Infections happens normally in cutaneous wounds and would complicate the whole recovery process of the wound, which would result in dire consequences of the patient such as morbidity, mortality, and increased cost of healthcare.[163] It has been reported in the United States that approximately a cost of 25 billion dollars or more is incurred in the treatment of wounds.[164] Although the conventional method to treat bacterial infections is the usage of antibiotics, but the surge in MDR bacteria due to the overuse of antibiotics is of great concern. Thus, there is a need for more novel and effective treatments to tackle the problem of the rise in multidrug resistant bacteria strains.[165]

APDT can be used as a mode of treatment for the various types of skin infections due to bacteria, especially for treating chronic wounds.[12] In the last five years, there has been a substantial number of reported in vivo applications on the usage of antimicrobial photodynamic therapy to eradicate MDR bacteria to promote wound healing. Unlike the conventional approach of individually irradiating a single photosensitizer to produce ROS, researchers have reported more novel approaches and molecules in APDT.

The integration of different therapeutic systems with APDT into a single modality has attracted attention because of the combination of their respective benefits which will enhance the entire APDT therapeutic effects.[15] Examples including the combination with photothermal therapy (PTT)[61, 92, 166], chemo dynamic therapy (CDT) [33, 167-169], and antibiotics[170, 171].

For instance, the combination of PDT and PTT are usually employed under different parameters due to the limitation of PDT in hypoxic environments. If a porphyrin-based PS could be active in hypoxic environment and changed to a PTT active molecule, it is possible for an intelligent antibacterial system to be developed with specificity and versatility. As such, Hu and his co-workers have developed a water-soluble cationic porphyrin, 5,10,15,20-tetrakis-(4-N-methylpyridyl)-porphyrin (TMPyP) with iodide ions, that is selective towards certain bacteria strains. TMPyP was able to achieve an adaptable response depending on the microenvironment that it is in. Under aerobic environments, TMPyP could target aerobic bacteria effectively (> 99.9%) upon the excitation of light for PDT to happen. Conversely, TMPyP could be reduced to phlorin by facultative anaerobes in hypoxic environments to achieve photothermal therapy. As such, this cationic porphyrin displayed a switchable PDT and PTT system. To increase the biocompatibility of TMPyP, $CB[7]_4$ was added to TMPyP to form a host-guest complex which maintained the cell viability over 85% at a relatively high concentration of 0.2 mM. The formation of this host-guest complex showed similar PTT and PDT effects towards E. coli and B. subtilis respectively as compared to the pure TMPyP. Furthermore, the in vivo antibacterial activity of $TMPyP/(CB[7])_4$ showed that there are almost no colonies observed after 7 days upon an excitation of 730 nm for 15 mins in a *E. coli* infected mouse model.[92]

In another instance, Xiu and his co-workers have designed a PDT-mediated chemotherapy to eliminate methicillin-resistant staphylococcus aureus biofilms. Their strategy was to develop a hypoxia-potentiating approach whereby it could kill bacteria under aerobic and anaerobic conditions. They first conjugated chlorin e6 (Ce6) onto hyaluronic acid which self assembles into nanoparticles, and then loaded the prodrug metronidazole (MNZ) to form HA-Ce6-MNZ nanoparticles (HCM NPs). The HCM NPs would release both Ce6 and MNZ when the enzyme hyaluronidase (Hyal), that is secreted by MRSA, would break down the hyaluronic acid. Upon laser exposure, Ce6 can produce singlet oxygen to kill MRSA under normoxic environment. Eventually, the oxygen levels will be reduced due to PDT which then potentiates hypoxia in biofilms and promotes the increase of nitroreductase secretion by MRSA, which can further reduce MNZ to eradicate the less active bacteria in the presence of a hypoxic environment. For in vivo investigations, the HCM NPs was used to treat subcutaneous MRSA biofilm-infected mice. The efficiency of killing the bacterial biofilm was ~99.9996% for the HCM-NPs in the presence of light, as compared to the rest of the experimental groups. Furthermore, macrophages are essential to regulate tissue healing in biofilm-infected tissues. The polarization of macrophages into anti-inflammatory phenotype is desirable which was also achieved using these HCM-NPs as well.[168]

Furthermore, other unconventional classes of photosensitizers have also emerged in APDT and being employed in treating skin and wound infections. These classes include organic dyes[61, 166, 172-174] and aggregated-induced emission luminogens[73, 175-178]. For example, Li and his co-workers developed a bacterial metabolic labeling photosensitizer that achieve a synergistic photothermal/photodynamic effect with good biocompatibility. The organic dye IR 820 and D-propargylglycine (DAA) were linked together via Azide-Alkyne cycloaddition reaction. Through a one-step incubation, IR 820-DAA will be metabolically labeled onto the surface of the bacteria by enzymatic cleavage. Upon 808 nm excitation, IR 820-DAA can produce ROS and heat to achieve antimicrobial activity. More significantly, IR 820-DAA displayed outstanding wound healing in MRSA-infected mouse, with negligible consequences at the given dose.[166]

Interestingly, there has been more intelligent approaches whereby researchers are looking at nanoparticles such as upconversion nanoparticles (UCNPs)[98, 179] and persistent-luminescence nanoparticles (PL-NPs)[180, 181] and to serve as light sources to excite the photosensitizers in a cascade manner, that has been applied in wound healing animal models.

UCNPs can be used as light sources to activate photosensitizers because of its inherent ability to convert NIR light to visible light, which allows for deeper penetration in tissues for treatment.[182, 183] Motivated by this property of UCNPs, Li and his co-workers have developed an unconventional bio-inorganic nanohybrid that carries methylene blue, and combined lysozyme (LYZ) with a UCNP-PDT system (UCMB-LYZ-HP). Instead of using light sources to excite the photosensitizers, the authors utilized the ability of UCNP to convert near-infrared light to visible light to

irradiate the photosensitizers. The positively charged MB was first encapsulated within the silica coated UCNP before the dendritic mesoporous silica (DMS) coated layer can be used to accommodate the enzyme lysozyme (LYZ). Then, a bacterial hyaluronidase (HAase)-responsive valve was added onto the surface to release the LYZ appropriately. This UCMB-LYZ-HP was reported to not only show an effective antibacterial effect on MRSA, but also successfully generated excellent therapeutic efficacy against deep-tissue (5 mm-thick) MRSA infections without any side effects in a murine model.[98]

Persistent luminescence nanoparticles (PL-NPs) are known for their long-lasting luminescence after activation owing to its ability to store excitation energy, acting like an optical battery. This peculiar self-illumination characteristic of PL-NPs could prevent tissues from being interfered with autofluorescence, and the near-infrared (NIR) afterglow would allow for deeper tissue penetration for imaging. As such, PL-NPs could serve as a self-luminous light source for the PS, and ROS could be generated continuously without external light excitation. As such, Zhang and his co-workers have reported a pH-initiated theranostic platform by combining real-time bioimaging and simultaneous APDT for bacterial infections based on PL-NPs. In this work, the authors prepared the PL-NPs by using meso silica NPs as a substrate for in-situ deposition of PL nanodots $ZnGa_2O_4:Cr^{3+}$ to form mPL NPs. Silicon phthalocyanine (Si-Pc) and cyanine 7 (Cy 7) were loaded onto the mPL-NPs via surface modifications and electrostatic attractions respectively to form mPL@Pc-Cy NPs. Cy 7 was able to quench mPL via fluorescence resonance energy transfer (FRET) effect, which in turn deactivates PDT at physiological conditions. Under acidic microenvironments, such as bacterial infections with a pH of 5.5, the charge surface of the NPs will switch to positive and release Cy 7, and the FRET effect will be suspended. As a result, the mPL NPs can irradiate the Si-Pc and its afterglow effect could maintain this excitation for a long period of time, which would enhance the APDT efficacy for bacterial eradication, and promote wound healing, and allow for real-time monitoring of the bacterial infection. In vitro studies showed that this mPL@Pc-Cy NPs was able to kill S. aureus and P. aeruginosa with antibacterial rates of over 99.5%. Similarly, in vivo studies showed that mPL@Pc-Cy NPs could inactivate S. aureus with an antibacterial rate of over 99.5%, with a wound recovery of 61.3%.[180]

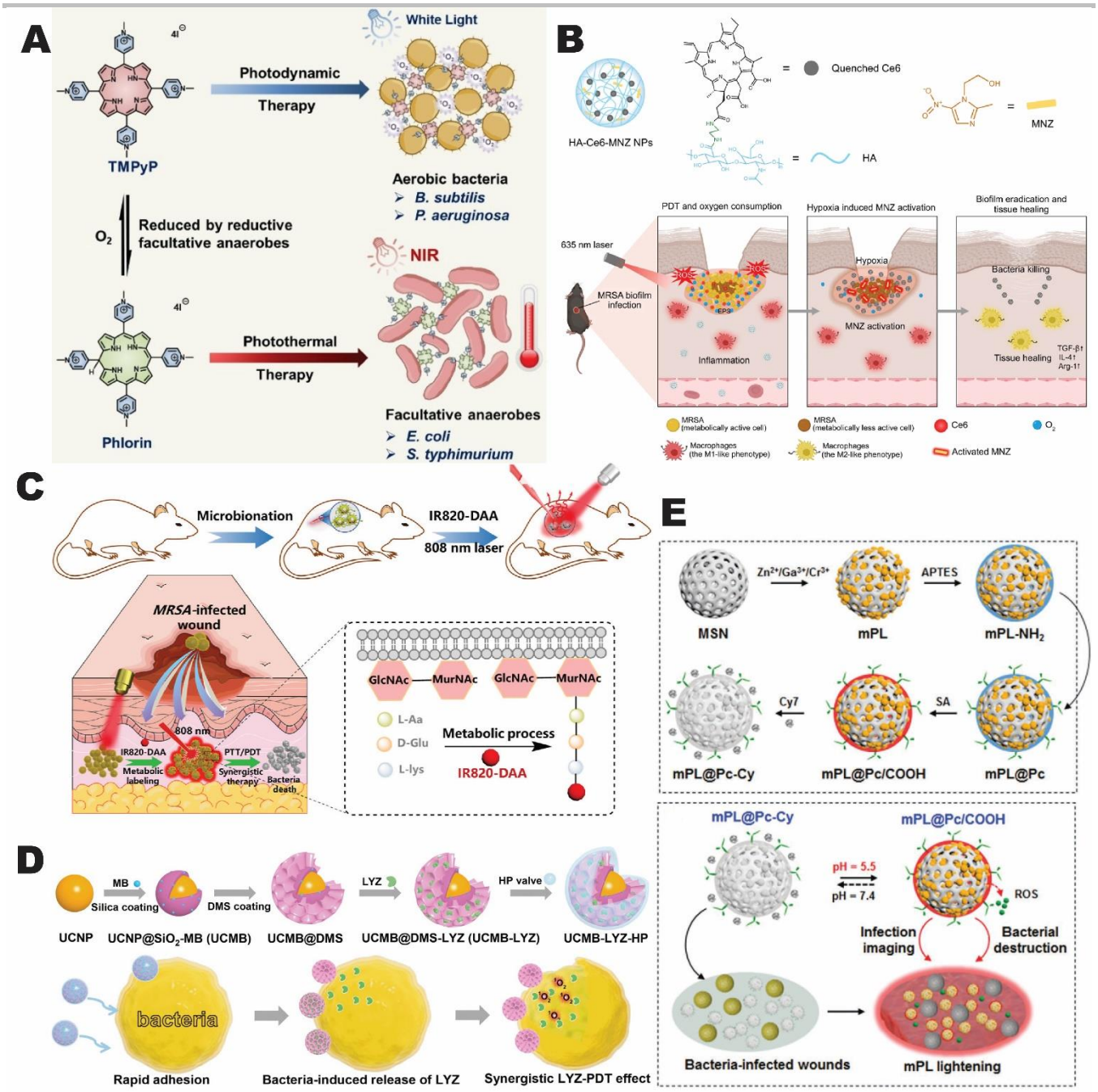


Figure 4. Schematic diagrams of different wound treatments. (A) A multifunctional therapy with photodynamic and photothermal to selectively eliminate aerobic and anaerobic interchangeably. Reproduced from ref. [92] Copyright (2022), with permission from WILEY-VCH GmbH; (B) A hypoxia-potentiating approach for a combined photodynamic and chemotherapy. Reproduced from ref. [168] Copyright (2022), with permission from Springer Nature (C) A metabolic labeling strategy for synergistic photodynamic and photothermal enhanced antibacterial effect. Reproduced from ref. [166] Copyright (2022), with permission from American Chemical Society (D) A NIR-mediated lysozyme responsive photodynamic therapy using upconversion nanoparticles. Reproduced from ref. [98] Copyright (2021), with permission from WILEY-VCH GmbH; (E) A continuous irradiation nanoplatform for simultaneous photodynamic therapy and imaging with persistent luminescence (PL) nanoparticles. Reproduced from ref. [180] Copyright (2022), with permission from WILEY-VCH GmbH.

3.3. Bacterial Keratitis

Bacterial keratitis (BK), that is caused by bacterial infection, is one of the prevalent forms of microbial keratitis with an incidence range of 50 to 60%.[184] It is an acute or chronic transient corneal lesion that happens in different areas of the cornea and can cause corneal perforation and even blindness.[185, 186] The typical causative pathogens in humans of BK are Pseudomonas aeruginosa and Staphylococcus aureus.[187] The medical treatment for BK is normally the use of a broad spectrum of antibiotics such as levofloxacin, gatifloxacin and moxifloxacin.[188] However, the continuous usage of antibiotics has led to the emergence of multi-drug resistant bacteria. Taking P. aeruginosa for example, this particular bacterium often displays many drug resistances and is related to several nosocomial infections.[189, 190] Henceforth, an alternative approach is needed to treat bacterial keratitis that is caused by multidrug resistant bacteria.

Recently, several in vivo applications based on APDT to treat bacterial keratitis have been reported. These applications have employed traditional PS such as the Rose Bengal[191] and Chlorin e6[157, 192], organic dyes like boron dipyrromethene (BODIPY)[60, 187] and aggregated-induced emission molecules[193, 194].

Interestingly, the inclusion of a persistent oxygen source in a APDT system has gained some attention. For an oxygen-dependent system, the efficiency of APDT is indeed limited in anaerobic environments. To tackle this issue, one can either increase the oxygen levels around the photosensitizers or prevent photosensitizers to undergo self-quenching.[60] Henceforth, researchers have designed APDT modalities to include a continuous oxygen source such as utilizing cyanobacteria to generate oxygen via photosynthesis[90, 157] or having an oxygen carrier like perfluorocarbon[195]. As an example, Bai and his coworkers have designed an oxygen self-supplying nanotherapeutic platform. This platform has three components: 1) perfluoropolyether as an oxygen carrier; 2) iodized boron dipyrromethene (BODIPY-I) as a photosensitizer; 3) a glycopolymer that is made up of galactose and fucose, and to specifically capture P. aeruginosa. The glycopolymer that contains perfluoropolyether was emulsified with perfluorohexane (PFH) to prevent the self-quenching of BODIPY-I (PFH/F-I). The antibacterial activity was evaluated in vitro with P. aeruginosa, and it shows that this nanotherapeutic platform have significantly decrease the number of live bacteria to 36% at a concentration of 500 μg/mL. In P. aeruginosa-infected rat cornea models, the number of bacteria colonies present was close to zero for the PFH/F-I group on the seventh day. Therefore, this self-supplying oxygen nanotherapeutic platform can provide oxygen for a longer APDT, especially in hypoxic environment.[60]

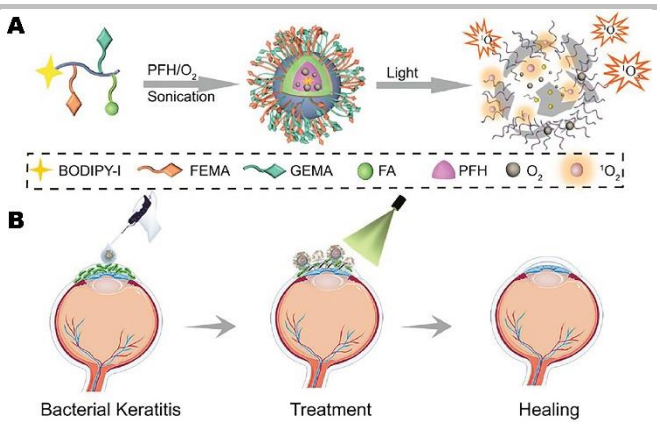


Figure 5. Schematic illustration of (A) Self-assembly of self-supplying oxygen nanotherapeutic platform (B) Nanotherapeutic-Enhanced APDT for a bacterial keratitis infected model (Cross Section of Eye) Reproduced from ref. [60] Copyright (2021), with permission from American Chemical Society.

3.4. Bacterial Endophthalmitis

Bacterial endophthalmitis is a result of fast proliferation of bacteria, which assembles into biofilms and produce exogenous toxins, causing ocular nerve and tissue damage.[196] Usually, the bacteria strains that are responsible for bacterial endophthalmitis includes pseudomonas aeruginosa, staphylococcus epidermidis, staphylococcus aureus and *E. coli*.[197] Bacteria can enter the eyes via endogenous blood circulation, exogenous eye trauma or ophthalmic surgery.[198] When bacterial endophthalmitis infection happens, the vitreous and surrounding tissue of the eye become the most susceptible to bacteria invasion. Subsequently, inflammation occurs which will rupture the ophthalmic physiological barriers, resulting in serious damage to the eye.[199] Thus, a person's vision could be impaired to a certain extent, depending on the seriousness of the infection. Moreover, if the infection is not properly controlled, the eyeball might have to be removed to curb the spread of infection.[200]

Currently, the treatment for bacterial endophthalmitis is through intravitreal injection of antibiotics. Ceftazindime and vancomycin are the antibiotics used to inactivate gram-negative and gram-positive bacteria respectively.[201, 202] However, bacteria could grow resistance towards antibiotics due to overuse or misuse of antibiotics, leading to the appearance of more multi-drug resistant bacteria stains.[176] As such, it is of utmost importance to search for more effective therapeutics to treat bacterial endophthalmitis.

In recent years, APDT has been a popular technique to treat bacterial infections owing to its characteristic of the ability to eradicate a broad spectrum of bacteria, even the multi-drug resistant strains. In the aspect of BE, researchers have employed the use of traditional PSs[200, 203] and AIEgens[204] in animal models which has shown remarkable results.

As described in section 2.2.5, AIEgens are indeed a promising class of photosensitizer owing to its innate property of the restricted intramolecular motions, that allows them to emit very strongly and produce ROS in the aggregated state as compared to the monomer state. Inspired by this property, Li and his coworkers synthesized a cationic aggregation-induced emission luminogen using triphenylamine thiophen pyridinium (TTPy) to treat bacterial endophthalmitis via APDT. When TTPy is excited, large amounts of ROS was produced to eliminate *S. aureus*

successfully without undesirable cytotoxicity at relatively low concentration. TTPy also displayed outstanding antibacterial effects for in vivo treatments of *S. aureus* infected rat models. In addition, the high killing efficacy of TTPy led to an early innate immune response, that eventually limited further inflammation in BE rat models. As such, this would hinder the spread of infection and protect the retina from further damage.[204]

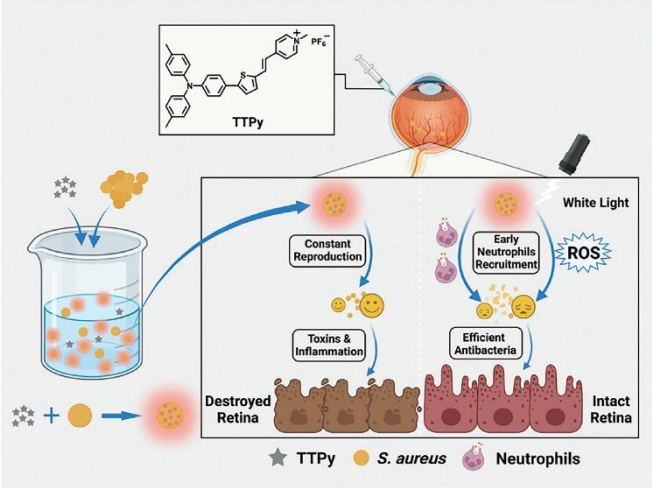


Figure 6. Schematic illustration of TTPy for rapid discrimination and excellent photodynamic antibacterial. Under white light irradiation, efficient ROS generation and early immune response induced by TTPy protected the retina from toxins and inflammation-related damage. Reproduced from ref. [204] Copyright (2022), with permission from WILEY-VCH GmbH.

3.5. Tuberculosis

Tuberculosis (TB) is a disease caused by *Mycobacterium tuberculosis* (M.tb) infection, has brought about a great burden on the global healthcare with alarming infection and death rates.[205] In 2021, the World Health Organization (WHO) has reported 10.6 million of TB infected cases and an estimated of 1.4 million of deaths. Without treatment, the rate of death from TB can reach to about 50%.[206] TB can be spread when an infected individual exhales bacteria into the atmosphere (i.e. coughing).[207] Subsequently, the alveolar macrophages in the lungs become infected and gather more macrophages and other immune cells from the surrounding blood vessels to create these dynamic clustered structures called granulomas, which are a pathological marker of TB.[208-210] Although, these granulomas were formed as a protective mechanism to "wall off" the invasion of mycobacteria, but recent studies have reported that granulomas are incapable to eliminate the bacteria inside,[207] and instead promote the expansion and dissemination of the bacteria.[211] Moreover, the emergence of multidrug-resistant TB has further increased the global healthcare burden with 450 000 new cases of rifampicin-resistant TB reported in 2021.[206] Therefore, alternative therapeutics are urgently needed to treat TB, and one of them is the use of antimicrobial photodynamic therapy. Recently, there has been several in vivo reported examples that utilized AIEgens as photosensitizers to treat TB.[212, 213]

Notably, Li and his coworkers have developed a novel TB granuloma imaging-guided photodynamic therapy for treating TB based on aggregation-induced emission (AIE) fluorophores and up conversion nanoparticles.[212] AIE photosensitizers are known for their enhanced emissions and the ability to generate ROS in their aggregated state. As such, the authors utilized an AIE photosensitizer that absorbs light at the NIR region (TTD) and DSPE-mPEG2000 to form TTD nanoparticles for the imaging of granulomas in mouse and zebrafish animal models. In vivo imaging results in the zebrafish embryo and mouse tail have shown successful accumulation of the TTD NPs at the granulomas. Furthermore, to further increase the tissue penetration for PDT, Li and his coworkers loaded an anti-TB drug (rifampin, RFP) and self-assembled asymmetric PS pyrolipid onto the core and shell of up conversion nanoparticles for a combined anti-TB treatment. Upon NIR excitation, the UCNPs convert NIR light to visible light to activate the pyrolipid photosensitizer to produce ROS and eradicate mycobacteria. Consequently, RFP is carried to the target site via the UCNPs, leading to a cascade chemotherapy to combat the remaining bacteria. In vivo analysis of an infected zebrafish model showed that the treated group had an increased rate of survival of zebrafish as compared to the untreated group, even though the granulomas were not eliminated.[212]

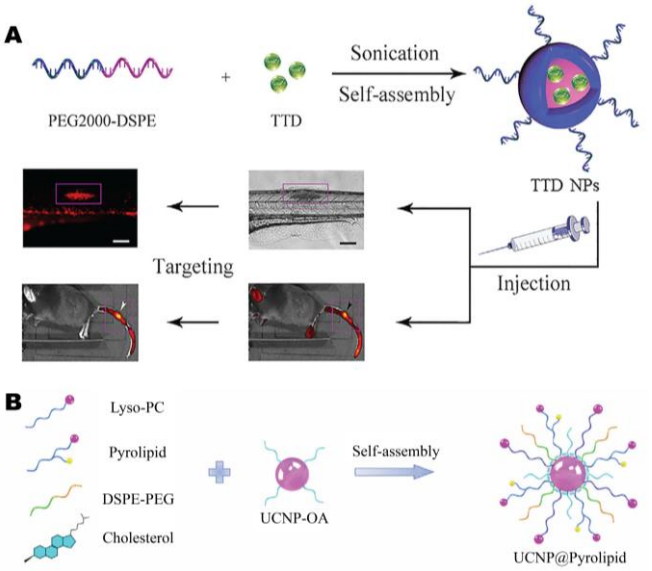


Figure 7. (A) Schematic illustration of the formation of TTD NPs for the in vivo granuloma imaging of zebrafish and mouse. (B) Schematic illustration of the self-assembly of UCNP@pyrolipid. Reproduced from ref. [212] Copyright (2020), with permission from WILEY-VCH GmbH.

4. Conclusion and Future Perspectives

In conclusion, antimicrobial photodynamic therapy is a promising therapeutic approach to eliminate bacteria, especially so for the multi-drug bacteria strains, as APDT can inactivate a broad spectrum of bacteria with low invasiveness and remote controllability. The conventional method of APDT utilizes traditional photosensitizers, ultraviolet light, and an external oxygen source. However, traditional photosensitizers have limited solubility and form aggregates in solution. In addition, ultraviolet light has a low penetration depth and high cytotoxicity. To tackle these limitations, new generations of photosensitizers have been reported with better water solubility, enhanced emission upon aggregation and the ability to absorb NIR light for deeper tissue

penetration. There have been more synergistic modalities of APDT being developed for the enhancement of antibacterial effect.

Being a light-dependent therapy, we must consider the importance of the light source itself in APDT as the photosensitizer is reliant on the interaction of light to produce reactive oxygen species. For APDT to happen, the wavelength of the light should lie in the absorption spectrum of the photosensitizer, the light has to reach the photosensitizer with minimal tissue scattering, sufficient penetration depth, and adequate light irradiation. The amount of light that could reach the photosensitizer would also determine the concentration of light being absorbed by the photosensitizer, which is affected by factors like power, illumination time and the mode of delivery of light (i.e. Optic Fibers). In addition, the biosafety of the light sources has to be accounted for, so as to prevent any cytotoxicity to tissues. An example would be the use of UV-light which is inappropriate as longer exposure to UV light is harmful to the human body. Other external factors such as cost, and equipment size should also be considered too. Hence, the choice of light source does play a crucial role for an effective APDT.

APDT does require both the presence of light and oxygen along with its photosensitizer to generate ROS for bacterial eradication. As such, interesting platforms have been reported recently, like the natural phenomenon of oxygen generation by cyanobacteria, and the afterglow effect of persistent luminance nanoparticles, have been included in APDT for the continuous and persistent supply of oxygen and light respectively.

Furthermore, there has been novel nanoplatforms reported for PDT in cancer in which the design of the PDT system can potentially be modified for antibacterial applications.[214-217]

With the current improvements to the APDT system, and the pre-clinical studies on animal models of the various bacterial infections mentioned in this review, APDT is potentially a promising treatment option for a variety of infectious diseases, especially so for drug-resistant infections. APDT may be used as an alternative treatment to traditional antibiotics, or an adjunct to conventional treatments to reduce the risk of bacterial infection. Optimistically, APDT could be used in clinical settings for treatment of bacterial infections in the future for both localized and systemic infections.

Acknowledgements

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Keywords: antibiotics • bacteria • multidrug resistance • photodynamic therapy • photosensitizers

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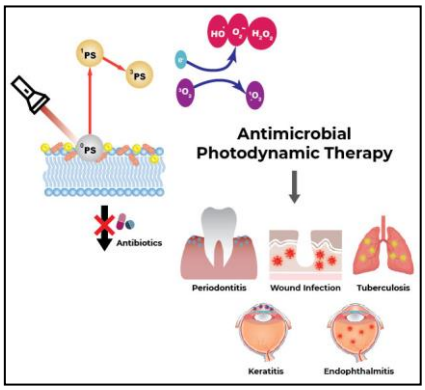

Multi-drug resistant bacterial infections are indeed a great threat to the global healthcare. In this review, we would explore the significance of antimicrobial photodynamic therapy in eradicating these bacteria strains and present in summary the reported in vivo applications of APDT in the various bacterial infections in the last five years.