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Phthalocyanine photosensitizers in antimicrobial photodynamic therapy as a multifunctional strategy for combating antimicrobial resistance

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Abstract

With antimicrobial resistance (AMR) on the rise, there is an urgent need for non-antibiotic approaches to treatment. Antimicrobial photodynamic therapy (aPDT) is being investigated as a non-antibiotic strategy for treating infections caused by multidrug-resistant (MDR) organisms. In this review we offer a thorough examination of phthalocyanines (Pcs) and metallophthalocyanines (MPcs), second-generation photosensitizers investigated mainly for bacterial and fungal photoinactivation. Antiviral aPDT is discussed separately because Pc-specific antiviral evidence remains comparatively limited. Our analysis focuses on how central-metal electronic configuration, spin–orbit coupling, and peripheral substitution influence intersystem crossing, triplet-state formation, and reactive oxygen species (ROS) generation in metallophthalocyanines. We also consider the physicochemical constraints that come with these compounds, namely their tendency to undergo aggregation-induced quenching (AIQ) in aqueous solution. To counter this and to get past the outer membrane of Gram-negative species, we evaluate synthetic changes such as cationic peripheral functionalization. The paper further explores how Pcs are being combined with pharmaceutical nanotechnology – be it liposomes, metallic nanoparticles or graphene oxide – to improve bioavailability and open the door to synergistic photothermal therapy (PTT). The promise of Pc-conjugates linked to bioactive agents like antibiotics is likewise noted. Yet for all the in vitro and preclinical data accumulated over the years, phthalocyanine-based aPDT has seen little use in the clinic. We close with an appraisal of the reasons for this shortfall, from issues of dosimetry and localized hypoxia to difficulties in penetrating biofilms, and put forward the case for engineering stimulus-responsive nanoplatforms as a way to bridge the regulatory and biological divide.

Keywords Antimicrobial photodynamic therapy (aPDT), Metallophthalocyanines (MPcs), Nanodrug delivery systems, Antimicrobial resistance

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1 Introduction

When microorganisms fail to respond as they should to antimicrobial agents, the result is antimicrobial resistance (AMR), a condition that complicates the treatment of infections and elevates the likelihood of disease transmission, serious illness or even mortality [1]. While one can trace AMR in part to the natural course of microbial evolution, its appearance and dissemination have been hastened considerably by the overuse and misuse of antimicrobials [2]. The situation is further compounded by the fact that new antibiotics are expensive and take too long to develop, leaving the pipeline of viable options for resistant bacterial infections thin [3]. It is no surprise then that there is an urgent call for non-antibiotic alternatives [4].

In this regard, photodynamic therapy (PDT) and photothermal therapy (PTT) have gained favour as non-invasive means of inactivating bacteria, even multidrug-resistant (MDR) strains [5, 6]. PDT has much to recommend over standard antibiotic regimens: it is repeatable, minimally invasive and quick, with a relatively low propensity to select stable resistance because it damages multiple cellular targets simultaneously [7]. This is even more relevant given that many of the latest antimicrobials on the market are little more than derivatives of older classes with no novel mode of action [8], which underscores the value of a different approach [9].

Antimicrobial photodynamic therapy (aPDT) is capable of inactivating both Gram-positive and Gram-negative bacteria, regardless of their susceptibility to antibiotics [9, 10]. The mechanism at work involves a photosensitizer (PS) that, after absorbing light, is elevated to an excited singlet state. From there it may engage in Type I photochemistry via electron or hydrogen transfer, or cross over to a triplet state of longer duration. In the latter case, energy is passed to molecular oxygen to form singlet oxygen (Type II) or radical species are produced through electron transfer. Either way, reactive oxygen species (ROS) are generated to inflict oxidative damage on the microbe [7, 11, 12] (Fig. 1). Where oxygen is in short supply, the Type I route will tend to predominate. Such

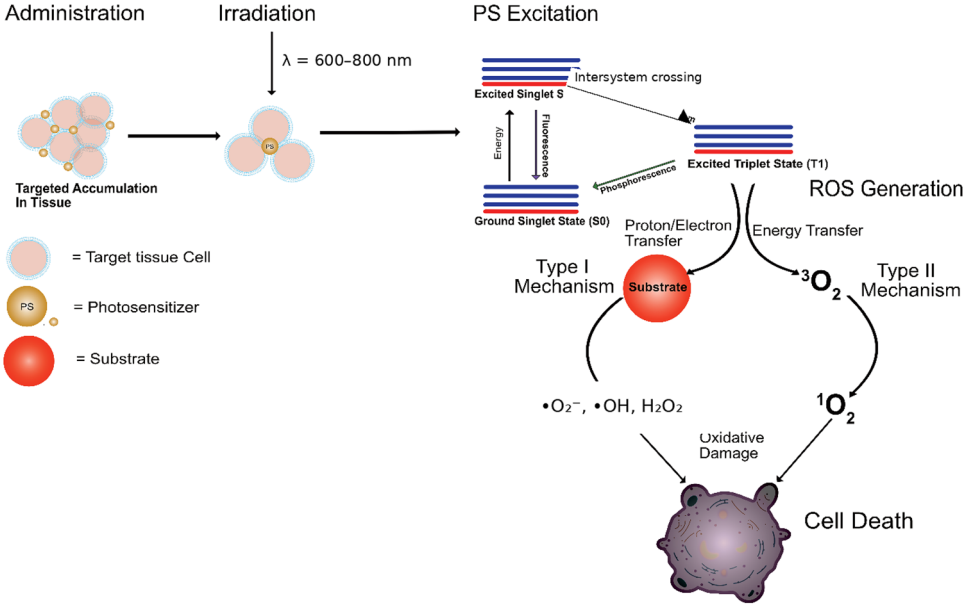


Fig. 1 Type I and Type II photochemical pathways involved in photodynamic therapy (PDT). Schematic prepared for this review incorporating graphical elements from BioDraws (https://biodraws.com), used under CC BY-SA 4.0

photodynamic effects can also stifle microbial growth in sublethal doses by the same process of oxidation.

The ROS produced in a photodynamic process set off irreversible chemical changes in the extracellular polymeric substance (EPS) matrix and cellular biomolecules alike [13]. Such reactions are capable of compromising biofilm-matrix constituents as well as microbial nucleic acids, proteins and membranes. Indeed, experiments have demonstrated that aPDT can suppress the metabolic activity of microorganisms in biofilms by raising intracellular ROS levels and undermining the EPS matrix [14].

There is an urgent need for antimicrobial approaches with mechanisms that resistant pathogens cannot readily circumvent, given that the proliferation of multidrug-resistant bacteria and fungi has left conventional antibiotic development in its wake. Antimicrobial photodynamic therapy (aPDT) is a case in point; it employs a light-activated photosensitizer to produce reactive oxygen species of short duration that assault several cellular targets at once. Phthalocyanine-based photosensitizers have come to the fore as especially viable options on account of their synthetic flexibility, tunable photophysics and absorption in the deep-red/near-infrared spectrum.

Yet the existing literature is somewhat fragmented. One might find reviews concentrating on the synthesis required to make phthalocyanines more soluble or to prevent aggregation [15], or others that map the structure–activity of antibacterial phthalocyanines but give little attention to delivery methods or the resistant organisms themselves [16]. Some cover nanocarrier conjugates, though they do not reflect the latest in nanoparticle technology or data on drug resistance [17]; a monograph from last year does deal with drug-resistant pathogens but fails to put nanotechnology-enabled delivery into a systematic context [18]. We aim to put this in perspective here. This review will build on what has been published, starting with the wider issue of antimicrobial resistance and the photophysical case for phthalocyanines over porphyrins (noting the heavy-atom effect), before turning to a thorough accounting of aPDT efficacy against the pathogens of clinical concern. It will conclude with an examination of the nanotechnology platforms necessary to overcome issues of tissue penetration and solubility, thus offering a more complete view of the translational pipeline.

2 Phthalocyanines as photosensitizers: from porphyrins to second-generation macrocycles

As the original class of photosensitizers put to clinical use, porphyrins have set the standard and are the structural model for most other tetrapyrrolic agents, phthalocyanines included. The porphyrin macrocycle is an 18-π-electron aromatic ring made up of four pyrrole subunits linked by methine (meso-) carbon bridges; it may be found as a free base or as a metal complex with an ion in the central cavity [19, 20]. In the UV-visible range, one will note an intense Soret (B) band at 400–430 nm and four Q bands of lesser intensity from 500 to 700 nm, the latter being where clinical absorption is usually drawn from [20].

Photofrin® (porfimer sodium), a hematoporphyrin derivative put forward by Dougherty et al., was the first to gain U.S. Food and Drug Administration (FDA) approval in 1995 and is activated at 630 nm. Yet this first-generation product has its limitations: a convoluted oligomeric make-up, extended cutaneous photosensitivity and a meagre singlet-oxygen quantum yield of around 0.01 in phosphate-buffered saline (PBS) [20]. To

get around such shortcomings, second-generation chlorins like Foscan® (temoporfin) were put on the market; these provide a more distinct chemical entity with better red-light absorption [21].

Then there are the phthalocyanines (Pcs). While related to porphyrins in structure, they are built differently: the meso-methine bridges are swapped out for nitrogen atoms and a benzene ring is fused to each isoindole unit. The result is a larger 16-atom inner ring with 42 π-electrons and an 18-π-electron aromatic system that is more fully conjugated [19, 22]. This has the effect of red-shifting and simplifying the spectrum. Where a porphyrin relies on a Soret band for therapeutic activation, a phthalocyanine presents a single, sharp and very strong Q band in the 650–700 nm region (or 600–800 nm depending on the metalation and substitution) for deeper light penetration at a given dose [20, 23].

With the right diamagnetic metal in the centre (Zn^{2+}, Al^{3+}, etc.), both types can produce cytotoxic reactive oxygen species in good yield through Type II photochemistry. Compared with first-generation porphyrin formulations such as Photofrin, many phthalocyanines provide stronger and spectrally narrower Q-band absorption in the red region. Their performance, however, remains strongly dependent on metalation, substitution pattern, aggregation state, and formulation. They do have a tendency to aggregate in water via π–π stacking which can stifle their activity, something that must be offset with charged or solubilizing groups on the periphery [24, 25].

In terms of design, both are highly amenable to tuning. Whether it is the meso- and β-positions of a porphyrin or the α (non- peripheral) and β (peripheral) ring positions and axial sites of a phthalocyanine, one can modulate the photophysics, charge and solubility to suit the application. Both will host a variety of metal ions to influence triplet-state yield by way of the heavy-atom effect. That said, phthalocyanines are seeing increased favour in antimicrobial work involving nanoparticles and biomolecule conjugates because the peripheral positions and easy axial substitution on metals like Si or P afford a finer hand on pharmacokinetics and aggregation [16, 22, 26, 27]. Figure 2 lays out the main structural concepts.

Metallophthalocyanines are governed in their excited-state photophysics by the central metal ion. One finds that closed-shell diamagnetic centers, for instance Zn^{2+}, Al^{3+}, Si^{4+} or Ga^{3+}, will tend to facilitate efficient triplet-state/ROS formation and more enduring excited states [28, 29]. The opposite is true of paramagnetic or open-shell types like

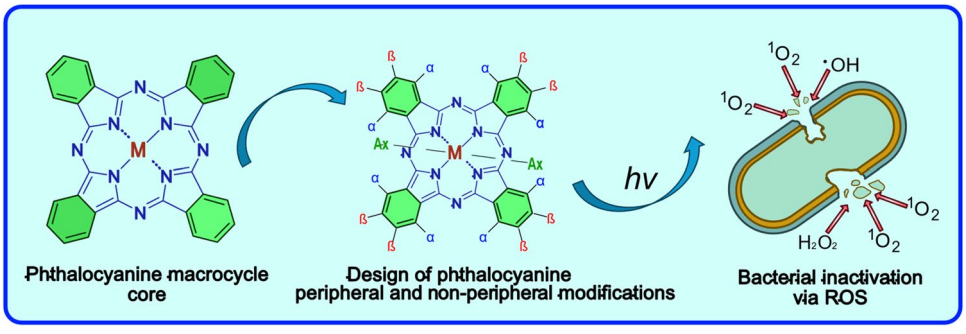


Fig. 2 Structural and photophysical design features of metallophthalocyanines in antimicrobial photodynamic therapy (aPDT). Schematic prepared for this review. Legend: M = central ion; Ax = axial ligand; α = non-peripheral substitution position; β = peripheral substitution position

Cu^{2+}, Ni^{2+}, Fe^{2+} and Co^{2+}; these can drive rapid internal conversion and non-radiative deactivation with a consequent loss of photodynamic efficiency [19, 28].

Upon light absorption by a photosensitizer an electron is raised to an excited singlet state. While intersystem crossing (ISC) to a triplet of longer life is spin-forbidden in theory, it is bolstered by greater spin–orbit coupling. This is the heavy-atom effect: atoms of high atomic number, be they part of the molecule or external to it, serve to enhance such processes [30]. Central metals or peripheral atoms like bromine and iodine of high atomic number can thus put more population into the triplet state. Halogenated porphyrins offer a case in point, where bromination and iodination have been shown to markedly lift the quantum yields of both singlet-oxygen and triplets [31]. For phthalocyanines this is a handy way to modulate ISC and ROS production, provided one takes into account the metal's electronic configuration and any competing non-radiative decay.

There is also the matter of solubility and aggregation, which are the province of the axial and peripheral substituents rather than the metal alone. With Si^{4+} and Al^{3+} one has the option of axial ligation; the right ligand can serve as a steric spacer to keep the species monomeric and photoactive in water and curtail π–π stacking [19]. To target Gram-negative bacteria, cationic moieties such as pyridinium or quaternary ammonium can be employed to draw the photosensitizer to the outer membrane via electrostatic forces [32]. Aggregation-induced quenching is held in check using bulky groups on the periphery, say tert-butyl or phenoxy [28]. Complementary reactivity is available from anthraquinone (AQ) units: while the ZnPc portion may be disposed of to Type II ROS, an AQ design opens Type I radical routes that can be of value when oxygen is in short supply [29, 33]. Table 1 summarizes the key structural design variables governing phthalocyanine photodynamic performance, along with their respective functional advantages and limitations.

3 Microorganisms (bacteria, fungi, viruses) versus aPDT

For antimicrobial photodynamic therapy (aPDT) to be at its most effective, photosensitizers (PSs) need to make their way into or form a close association with the target bacterial cells; mere presence at the cell surface is not enough. This can be a problem with Gram-negative bacteria where the intricate cell-envelope tends to repel neutral or negatively charged PSs and curtail photoinactivation [34]. Gram-positive bacteria are

Table 1 Principal structural design variables influencing the photophysical and antimicrobial performance of phthalocyanines

Component	Design choice	Primary effect	Limitations / drawbacks (references)
Metal ion	Diamagnetic: Zn(II), Al(III), Si(IV), Ga(III)	Promotes ISC; increases $^1O_2$ generation.	Paramagnetic Cu(II), Ni(II), Fe(II), Co(II) can quench excited states. [28, 29]
Peripheral charge	Cationic groups: ammonium, pyridinium	Improves binding to Gram-negative surfaces.	Excessive positive charge may increase mammalian-cell toxicity. [32, 34]
Substitution site	Bulky peripheral / non-peripheral groups	Suppresses π–π stacking and aggregation.	Non-polar bulky groups may increase lipophilicity and complicate formulation. [19, 28]
Hybridization	Anthraquinone (AQ)	Supports complementary Type I/II ROS generation.	AQ may reduce photostability or synthetic tractability. [29, 33]

different in that they have a single cytoplasmic membrane encased in a thick, porous wall of peptidoglycan and teichoic or lipoteichoic acids (Fig. 3).

The eukaryotic nature of fungi means they have much in common with mammalian hosts, which makes the development of selective antifungal agents no easy task. While *Malassezia*, *Candida* and dermatophytes are behind most superficial skin, hair and nail infections, *Candida* and *Aspergillus* species present a more serious clinical threat as causes of invasive pulmonary and bloodstream infections, with high mortality rates in immunocompromised individuals [35, 36].

Standard therapies such as azoles, polyenes, allylamines, ciclopirox and amorolfine work by interfering with ergosterol synthesis or membrane function [36, 37]. Yet efficacy can be variable and they often demand long-term use. There are also concerns over hepatotoxicity, dermatologic side effects, drug–drug interactions and the steady rise of resistance [38, 39]. In the case of *C. albicans*, one can see resistance to amphotericin B and fluconazole [40], and treatment failure is compounded by biofilm formation, yeast-to-hyphae shifts and other adaptive mechanisms [41].

Here aPDT presents an alternative, especially where conventional drugs are hampered by toxicity or resistance. A range of photosensitizers from porphyrins to phthalocyanines have been put to the test for antifungal photoinactivation. The light-triggered oxidative damage aPDT inflicts on several cellular targets is a mechanism quite unlike that of standard antifungals, making it a useful complement [38, 42]. *C. albicans*, being a key mucosal pathogen and cause of invasive candidiasis, serves as the model organism of choice in many aPDT studies with rose bengal, methylene blue or curcumin [35, 36, 43, 44]. *Trichophyton rubrum*, a common source of onychomycosis, has also been a subject of investigation. Since the dense structure of an infected nail can keep topical agents at bay and lead to poor patient compliance, a light-based approach with a photosensitizer has been considered a way around the problem [45, 46].

The modality has even been used to eradicate *Fusarium* species like *F. oxysporum* and *F. solani*, as well as *Colletotrichum* phytopathogens [34, 47].

In the antiviral space, aPDT could be preferable to current drugs which are under constant pressure from the flexible genetics and rapid mutation of viruses [48]. By way of photodynamic oxidation, aPDT will destroy essential structural elements be they lipid envelopes, capsid proteins, nucleic acids or internal enzymes [49]. Clinical results have borne this out for HSV-1 and HSV-2 in recurrent genital or labial cases [48, 50–52].

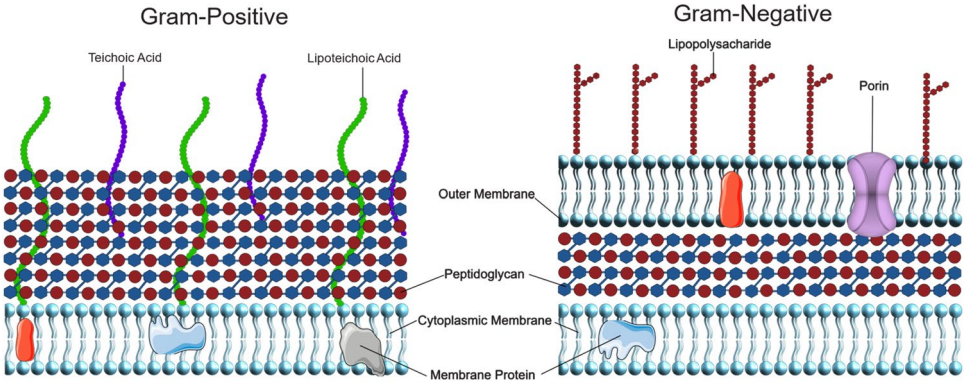


Fig. 3 Schematic representation of Gram-positive and Gram-negative bacterial cell-envelope structures. Schematic prepared for this review, incorporating graphical elements from BioDraws (https://biodraws.com), used under CC BY-SA 4.0

Other reports detail inactivation of norovirus, HIV, SARS-CoV-2 and bacteriophage T4 [50, 53, 54]. Such work is largely proof of concept using modified porphyrins, curcumin or methylene blue and should not be taken as evidence for the antiviral power of phthalocyanines, an area in need of more validation.

More recently, nanoparticle systems have been trialled against SARS-CoV-2 [55–57]. There are also new ways of thinking about the application of aPDT, such as embedding photosensitizers in fabric for self-sanitizing materials that respond to sunlight or artificial light [46]. To get better synergy, researchers have looked at enhanced pairings; methylene blue with radachlorin, for instance, has shown potent activity against the coronavirus [58].

When exposed to specific light, photoantimicrobial photosensitizers (PSs) generate reactive oxygen species (ROS) in the immediate vicinity of microorganisms, damaging a range of biological materials within them. The multi-site nature of this action on microbial targets gives aPDT a relatively low propensity to select stable resistance; nevertheless, sublethal exposure may induce transient stress adaptation or phenotypic tolerance [59–61]. A review of the photodynamic conditions and their biological impact in Pc-based aPDT and closely related azaporphyrinoid systems is set out in Table 2 for clinically important drug-resistant pathogens. The data makes clear how cell-envelope architecture creates a marked difference in susceptibility. Gram-positive strains are highly vulnerable; for instance, the tetracationic Zn(II)-phthalocyanine RLP068/Cl has a minimum bactericidal concentration (MBC) of 0.05 μM and will bring about a ≥ 5-log reduction in *Staphylococcus aureus* resistant to methicillin, oxacillin, erythromycin or linezolid. Against VanA/VanB vancomycin-resistant *Enterococcus faecium* the reported MBC is 0.1 μM. Gram-negative bacteria are another matter. Their outer membrane, rich in lipopolysaccharide, affords protection and demands much higher dosing for similar results. To obtain a ≥ 5-log kill of carbapenem-resistant *Klebsiella pneumoniae* with RLP068/Cl, concentrations of 10–40 μM are needed, some 100 to 400 times the amount used on Gram-positive bacteria. In the case of extended-spectrum β-lactamase-producing *Escherichia coli*, anionic tetrasulfonylphenoxy-chloroindium(III) phthalocyanine was unable to inactivate the organism even at 100 J/cm² and 100 μM, owing to charge repulsion at the outer membrane and AcrAB-TolC efflux [62]. Such a disparity in dosing is precisely why cationic functionalization and the use of nanotechnology for delivery (see Sect. 4) have become engineering imperatives if Pc-based aPDT is to be effective against Gram-negative resistant pathogens.

4 Nanotechnology

With the help of recent developments in nanotechnology, there are now workable strategies to overcome some of the more intractable problems associated with photosensitizers. These include issues such as aggregation, a lack of aqueous solubility, and difficulties in targeting or delivering agents to tissue and biofilms. Such methods hold particular promise for Pcs in the context of aPDT [70, 71]. In a typical nanotechnology-driven aPDT formulation, one will find photosensitizers encapsulated, adsorbed or covalently bound to a variety of carriers: liposomes, polymeric nanoparticles and micelles, nanoemulsions, dendrimers, carbon nanomaterials or metallic/metal-oxide nanoparticles [17]. The range of platforms available offers a means to control Pc dispersion and

Table 2 Representative phthalocyanine and closely related azaporphyrinoid photosensitizer studies against clinically prioritized drug-resistant bacterial and fungal pathogens, with treatment conditions and reported minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC), and efficacy values

#	Pathogen (resistance type)	Photosensitizer used	Treatment conditions	Efficacy / MIC / MBC reported	Reference
1	MRSA (methicillin-resistant *Staphylococcus aureus*), clinical isolate panel	Monosubstituted tricationic Zn(II) phthalocyanine (ZnPcE)	In vitro aPDI; MBC across MRSA panel; in vivo mouse skin-infection model	MBC 0.019–0.156 μM against the MRSA panel	[63]
2	MRSA / oxacillin-, erythromycin-, linezolid-, daptomycin-resistant *S. aureus* (cfr/poxtA)	RLP068/Cl - tetracationic Zn(II) phthalocyanine chloride	630 nm LED, 120 mW/cm^2, 4 min, 30 J/cm^2; PS 0.05–2 μM	MBC 0.05 μM; ≥5-log reduction in all tested MRSA strains	[64]
3	Vancomycin-resistant *Enterococcus faecium* (VanA/VanB) and *E. faecalis* (linezolid/oxacillin-resistant, optrA+)	RLP068/Cl	630 nm LED, 30 J/cm^2 (120 mW/cm^2, 4 min); PS 0.1–10 μM	MBC 0.1 μM for VanA/VanB *E. faecium* and optrA + *E. faecalis*; ≥5-log reduction	[64]
4	Carbapenem-resistant *Klebsiella pneumoniae* (blaNDM, blaKPC, blaVIM-1, blaOXA-48-like; one mcr-1.2+)	RLP068/Cl	630 nm LED, 30 J/cm^2; PS 5–40 μM	MBC 5–20 μM for ≥ 3-log; 10–40 μM for ≥ 5-log reduction	[64]
5	Carbapenemase-producing (KPC) *Klebsiella pneumoniae*	Zn(II) tetramethyltetrapyridinoporphyrazinium methylsulfate (ZnTM2,3PyPz)	White light; 3 μM PS; 30 min irradiation (10 min for reference *E. coli* ATCC 25922)	Complete/near-complete photoinactivation at 3 μM	[65]
6	Extended-spectrum β-lactamase-producing (ESBL$^+$) *Escherichia coli*	Chloroindium(III) phthalocyanine (tetrasulfonylphenoxy-InPc)	660 nm LED, 14 mW/cm^2, 50–100 J/cm^2; PS 10 and 100 μM	Inactive; no significant CFU reduction up to 100 μM (outer-membrane barrier and efflux resistance)	[62]
7	Multidrug-resistant *Escherichia coli* (abrasion-wound infection model)	Cationic Zn(II) phthalocyanine nanoemulsion (ZnPc-NE, ~ 210 nm, + 73.1 mV)	Topical aPDT in vivo rat wound model; ~23.7% ZnPc skin deposition	Significant photodynamic inactivation of MDR *E. coli* in infected wounds	[66]
8	Multidrug-resistant *Pseudomonas aeruginosa* (respiratory/chronic-wound isolates, some metallo-β-lactamase-producing)	Water-soluble cationic phthalocyanine	Photocytotoxicity assay, planktonic and biofilm forms	No significant difference in photoinactivation between resistant/susceptible or planktonic/biofilm forms ($p > 0.05$)	[67]

Table 2 (continued)

#	Pathogen (resistance type)	Photosensitizer used	Treatment conditions	Efficacy / MIC / MBC reported	Reference
9	Multidrug-resistant *Pseudomonas aeruginosa* (burn-wound infection)	Zn phthalocyanine nanoemulsion (NE/ZnPc)	40 µg/mL PS, 2 h dark incubation, 13 J/cm^2 laser; in vitro and in vivo burn model	Significant reduction in bacterial burden vs. untreated infected controls	[68]
10	Fluconazole-resistant *Candida albicans*	Chloroindium(III) phthalocyanine (InPc)	660 nm LED, 14 mW/cm^2, 50–100 J/cm^2; PS 10–100 µM	Substantial photoinactivation at 100 µM / 100 J/cm^2	[62]
11	Fluconazole- and flucytosine-resistant *Candida tropicalis* (ATCC 13803)	Fe(III) phthalocyanine-tetrasulfonic acid in chitosan–tripolyphosphate nanoparticles (FNP), sequential with flucytosine	Sequential aPDT (FNP + light) then flucytosine; planktonic and biofilm/pseudohyphal cultures	Enhanced antifungal killing vs. either treatment alone	[69]
12	*Candida auris* (MDR reference strains) and azole-resistant *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*	RLP068/Cl	630 nm LED, 30 J/cm^2; 1-h dark preincubation; PS 0.1–5 µM	≥ 3-log fungicidal endpoint at low micromolar concentrations, including *C. auris*	[64]

Note: ZnTM2,3PyPz is a zinc porphyrazinium derivative included as a closely related azaporphyrinoid comparator. aPDI, antimicrobial photodynamic inactivation; aPDT, antimicrobial photodynamic therapy; ATCC, American Type Culture Collection; CFU, colony-forming units; ESBL, extended-spectrum β-lactamase; FNP, iron(III) phthalocyanine–chitosan–tripolyphosphate nanoparticles; KPC, Klebsiella pneumoniae carbapenemase; LED, light-emitting diode; MBC, minimum bactericidal concentration; MDR, multidrug-resistant; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant Staphylococcus aureus; PS, photosensitizer

delivery, to target microbes, and to orchestrate combined photodynamic and photothermal effects all at once.

The objective is to design nanoparticle formulations that do not compromise the photophysical integrity of the Pc payload but instead sidestep the constraints of conventional delivery. A good formulation must be stable, have acceptable elimination kinetics and be amenable to scalable manufacturing [72]. It should also exhibit high ROS-generating efficiency with minimal dark toxicity and strong red or near-infrared (NIR) absorption, whether from the photosensitizer or an optically active component of the nanocomposite. Where a highly lipophilic Pc might fail to disperse in an aqueous environment, or a hydrophilic version shows little affinity for cellular uptake, these nanotechnology-enabled systems can provide the necessary balance. It is important to distinguish the source of red/NIR absorption, as it is not an inherent quality of every nanoparticle but is dependent on the physical mechanisms at play in the material class. Plasmonic metal nanostructures, for instance, make use of localized surface plasmon resonance (LSPR) to absorb in the red-to-NIR spectrum; gold and silver particles of a certain size and shape can serve as light-harvesting antennae for a phthalocyanine or as photothermal transducers in a PDT/PTT platform [73, 74]. Then there are upconversion nanoparticles (UCNPs), like lanthanide-doped NaYF4:Yb, Tm/Er, which take in NIR light at 980

nm via multiphoton absorption and re-emit it at a shorter wavelength to excite a co-loaded Pc in tissue beyond the reach of direct red light [75]. Carbon-based materials such as graphene oxide or nanodiamonds draw on their delocalized π-electron systems for broad optical absorption into the NIR, a trait use in photothermal conversion and in modulating Pc aggregation through π–π stacking [76, 77]. This is distinct from the 650–700 nm band of the phthalocyanine itself, which is a function of its 18π-aromatic macrocyclic system. Correctly ascribing this absorption to the appropriate nanomaterial is key to understanding how a carrier complements the intrinsic properties of the Pc. Research on everything from silica and polymeric systems to micelles and nanotubes has shown that the architecture, charge and size of the carrier can have a profound effect on Pc behaviour and intracellular interactions [78–102], effectively resolving the shortcomings of older Pc formulations [103]. As nanotechnology becomes the linchpin for turning Pc photochemistry into viable antimicrobial products, the following subsections outline five design approaches to improve solubility, delivery and anti-biofilm activity, before offering some clarification on the mechanics of NIR absorption in these various classes.

4.1 Lipid-based nanocarriers: liposomes and lipid nanoparticles

The hydrophobic nature of phthalocyanines makes them susceptible to π–π stacking in aqueous media, a process that quenches the triplet state and lowers singlet-oxygen yield [104]. Placing them inside a liposomal bilayer is an effective way to counter this; the physical separation of monomeric Pc units prevents self-quenching and brings back the photophysical activity [104]. With cationic liposomal formulations one can also introduce a targeting element. The net-positive surface facilitates electrostatic docking to the anionic bacterial envelope and the biofilm's exopolysaccharide matrix, which aids penetration and uptake in a manner not seen with unencapsulated Pc [105]. This was borne out in trials with *Staphylococcus aureus* biofilms using liposome-encapsulated zinc phthalocyanine (zeta potential + 18 to + 19 mV, 117–144 nm). Here the liposomal variant proved more effective at eradicating mature biofilms than the free photosensitizer, owing to better retention in the matrix. That said, for inhibiting early biofilm formation the free Pc is still the better option, indicating that lipid encapsulation is a compromise between diffusion speed and the ability to hold within the matrix for eradication [105]. The same logic applies to nanoemulsion carriers. A cationic Zn(II)-phthalocyanine nanoemulsion (isopropyl myristate/egg phosphatidylcholine/cetyltrimethylammonium bromide [CTAB]) of around 210 nm and + 73 mV has been shown to all but eliminate resistant strains and promote in vivo wound healing beyond what the laser or carrier could do on their own [66]. In short, these lipid-based systems serve to shield the macrocycle from water for solubility, ensure delivery through membrane fusion or electrostatic means and deliver superior anti-biofilm results by virtue of longer retention in the matrix.

4.2 Polymeric nanoparticles, micelles, and hydrogels

The self-assembly of amphiphilic polymers into micelles or nanoparticles around Pc cores is a means of solubilizing the photosensitizer via a hydrophilic corona and keeping its aggregation in check; after all, both excessive aggregation and inadequate dispersion will compromise ROS output [106]. The case of amphiphilic AABB-functionalized Zn(II)-phthalocyanine nanoparticles is instructive: their thermodynamically least stable

form proved to be the most bactericidal. By disassembling at the bacterial surface to release photoactive monomers directly at the bacterial target site, these assemblies demonstrate that one can improve pathogen delivery with the right degree of stability rather than the highest possible [106]. Other systems have shown similar efficacy. Indium(III)-phthalocyanines encapsulated in biodegradable polyhydroxybutyrate (PHB) nanoparticles are capable of a 2.57-log reduction in methicillin-susceptible as well as resistant *S. aureus* through photoinactivation, though the position of the substituent influences how well they are loaded [107]. Then there are the hyperbranched polyphthalocyanine micelles of about 70 nm which, by virtue of their dual PTT and PDT action, have been effective in vivo against implant-related infection, eradicating 95–97% of MRSA and its biofilm [108]. For topical applications, hydrogels offer a different approach to holding the Pc at the wound site for a prolonged, light-activated release [109, 110]. Brief NIR irradiation of a succinoglycan–riclin–zinc-phthalocyanine hydrogel, for instance, yielded 26–27 mm inhibition zones versus *E. coli*/*S. aureus* and halved biofilm formation [110]. In another example, a chitosan hydrogel was used to present a covalent zinc phthalocyanine–colistin conjugate. This allowed the chitosan to provide aqueous dispersibility while the combination of polymer-driven membrane permeabilization and ROS generation from the light made for a more potent treatment than either part on its own [111].

4.3 Targeted conjugates for antimicrobial photodynamic therapy

The untargeted form of Pc-based aPDT is limited by its reliance on the photosensitizer being in close quarters with the pathogen and a tendency to produce ROS off-target. One way to remedy this is to graft some form of recognition element, be it a peptide or an aptamer, an antibody fragment or small-molecule ligand, onto the Pc or its carrier so that the photosensitizer is concentrated at the microbial surface prior to any irradiation. An illustration of this can be found in the work where the cell-binding domain of a *Staphylococcus aureus* phage endolysin was conjugated to a photoactivatable silicon phthalocyanine; the endolysin's inherent affinity for the cell wall allowed for the targeted inactivation of staphylococci, both intracellular and within biofilms [112]. With smaller recognition units, one can get comparable results from antibiotic-ligand conjugation. The amphiphilic zinc(II)-phthalocyanine–ciprofloxacin conjugates discussed in Sect. 5 are a case in point: they have yielded log-reduction values as high as 9.2 in *E. coli* and 7.23 in *S. pneumoniae* (biofilm models included) without giving up their dark antibacterial properties. In the same vein, Polymyxin B has been put to use in functionalizing Pc for chemo-photodynamic wound therapy on the strength of its natural draw to Gram-negative lipopolysaccharide [113]. While targeting via antibody or aptamer is more of an established practice in oncologic aPDT, as with the peptide-directed phthalocyanine–gold nanoparticles used on epidermal growth factor receptor (EGFR)-overexpressing cells [114], the design principles are readily applicable to antimicrobial applications and present a clear avenue for translation.

4.4 Metallic and plasmonic nanoparticles (Au, Ag)

In addition to solubilization, the introduction of gold and silver nanoparticles provides a physical mechanism of action. Take Au nanoparticles for instance: when conjugated with Pc they not only prevent the photosensitizer from aggregating but can also serve as plasmonic antennae. Provided the size and shape are right, their localized surface plasmon

resonance (LSPR) will either intensify local fields or turn light into heat to affect a combined PTT/PDT response [73].

The versatility of this approach is seen in mesoporous silica-coated gold nanorods bearing tetrazolyl-substituted silicon phthalocyanine. These have been used as an NIR-activated nano-switch to take on antibiotic-resistant *E. coli* in a synergistic fashion [74]. More generally, the chemistry of Pc–gold hybrids have been made into a design platform for a range of biological uses through gold-nanoparticle–phthalonitrile conjugates [115], which goes beyond the antimicrobial cases just cited. Silver is not as frequently employed as a direct carrier for Pc. It is more typical to find it co-formulated with Pc-modified chitosan in order to widen the antibacterial spectrum by way of ROS generation from the Pc and the release of silver ions [116]. As plasmonic/inorganic nanoparticles are discussed further below, this subsection stays brief and defers to the following subsection for the mechanism-specific discussion of red/NIR absorption.

4.5 Multi-functional and combination nanoplatforms

To mitigate the risks of resistance and the reliance on light or oxygen, recent studies have coupled Pc-mediated photodynamic action with a second modality of a different mechanism. For instance, a "one-for-two" zinc(II)-phthalocyanine nanoparticle that self-assembles to offer both Type I photodynamic and photothermal activity was able to suppress MRSA growth almost entirely at 50 nM with a short 655 nm irradiation, putting it ahead of methylene blue and tetraphenylporphyrin tetrasulfonic acid [117]. In other approaches, PEGylated graphene oxide functionalized with Pc creates a triple-mode platform by way of carbon-mediated photothermal conversion alongside the Pc's photodynamic properties [76]; orthogonally conjugated silicon-phthalocyanine–porphyrin oligomers do the same in a single scaffold for the PDT/PTT eradication of multidrug-resistant infections [118]. Where tissue is opaque or too deep for light to reach, sonodynamic pairing is an option. Under ultrasound alone, phthalocyanine–artesunate conjugates have been shown to produce as much as ten times the ROS of protoporphyrin IX, the standard sonosensitizer [119]. Then there are upconversion nanoparticles loaded with Pc which take deep-penetrating NIR light and turn it into visible light of the appropriate wavelength for the Pc; when paired with chitosan they can handle wound healing and antibacterial duties at once [75]. The common thread is that an autonomous secondary method of killing makes up for aPDT's shortcomings in deep-wound or biofilm settings where oxygen tension and light penetration are issues (Table 3).

Nanotechnology delivery is what makes this possible across the board, operating through five means to further aPDT: first, by keeping the photosensitizer from aggregating and improving its solubility to boost ROS; second, better surface properties aid cellular uptake so the photosensitizer is right where the bacterium is; third, some localized photothermal heat will make the bacterial membrane more permeable and vulnerable to ROS; fourth, physical disruption of biofilms allows ROS to get to bacteria that would otherwise be shielded; and fifth, plasmonic nanoparticles (Au, Ag) can amplify local electromagnetic fields for greater ROS output. In this way nanocarriers are not just vehicles but active agents in the process, a dual role that serves to improve overall efficacy [34]. Figure 4 provides a summary of these mechanisms.

From a translational perspective, hydrogels and nanoemulsions are most naturally suited to topical or wound-site delivery, whereas liposomes and polymeric systems offer

Table 3 Cross-platform comparison of representative phthalocyanine nanocarriers for antimicrobial photodynamic therapy

Platform	Representative quantitative evidence	Translational strength and limitation	Refs.
Liposomes / nanoemulsions	Liposomes: 117–144 nm; +18 to + 19 mV Improved mature-biofilm eradication Nanoemulsion: ~210 nm; +73 mV Resistant-strain inactivation and wound healing	Strength: aggregation control, retention, and topical delivery Limitation: formulation stability, sterilization, and scale-up	[66, 105, 106]
Polymeric nanoparticles / micelles	PHB nanoparticles: 2.57-log reduction in *S. aureus* Hyperbranched micelles (~ 70 nm): 95–97% eradication of MRSA and its biofilm	Strength: Pc solubilization, controlled assembly, and combined PDT/PTT Limitation: polymer reproducibility, degradation, and release control	[108, 109]
Hydrogels	Pc hydrogel: 26–27 mm inhibition zones against *E. coli* and *S. aureus* Biofilm formation reduced by ~ 50%	Strength: prolonged local retention and practical wound-site application Limitation: primarily suited to accessible or superficial infections	[110–112]
Gold / silver systems	Au nanorods: synergistic PTT/PDT against resistant *E. coli* Pc–chitosan–Ag: broader antibacterial action	Strength: local-field enhancement, heat, or complementary Ag-ion activity Limitation: inorganic persistence and added safety characterization	[73, 74, 117]
Upconversion nanoparticles	Lanthanide-doped system excited at 980 nm NIR-triggered antibacterial and antifungal photodynamic activity	Strength: converts deeper-penetrating NIR light to Pc-exciting wavelengths Limitation: conversion efficiency, material complexity, and long-term disposition	[75]

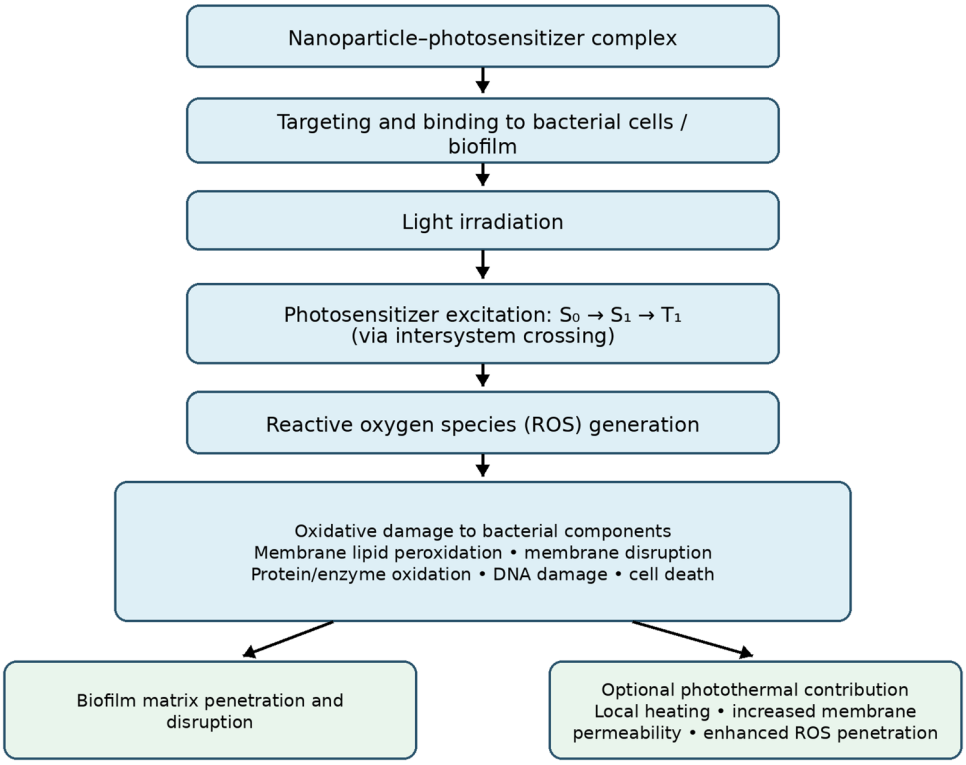


Fig. 4 Flowchart summarizing the complementary mechanisms of nanotechnology-enabled antimicrobial photodynamic therapy (aPDT). Original schematic created by the authors of this review

broader formulation flexibility but require tighter control of stability, release, and manufacturing reproducibility. Metallic and upconversion systems add optical functionality but also increase characterization, safety, and long-term-disposition requirements. These are relative development burdens rather than formal cost-effectiveness estimates [72, 103, 120].

4.6 Clinical trial evidence and the translational gap

Clinical evidence for Pc-based aPDT remains limited. The evidence below is therefore separated conceptually into Pc-specific human studies and contextual aPDT studies using other photosensitizer classes. RLP068/Cl (Vulnofast® gel) is the most clinically developed Pc-class antimicrobial agent discussed here and has undergone randomized Phase IIa evaluation in infected diabetic foot ulcers. No Pc-based agent covered in this review has entered a large Phase III trial stratified by antimicrobial resistance for systemic or deep-tissue infection. Published trial reports and recent reviews instead indicate that much of the broader aPDT clinical pipeline uses phenothiazinium dyes such as methylene blue [121–126]. This was borne out in the D.A.N.T.E. study, a Phase IIa randomized, double-blind, placebo-controlled trial (n = 62). Here, three strengths of RLP068/Cl were given as an adjunct to amoxicillin–clavulanate in diabetic patients. The compound yielded a dose-dependent and statistically significant drop in pathogenic and total bacterial load right after one PDT session – at 0.50% the reduction was up to – 3.00 ± 1.82 log colony-forming units per milliliter (CFU/mL) compared with – 1.00 ± 1.02 for placebo – but the trial design did not show an overall wound-healing advantage as the effect waned over time [121]. Yet a later uncontrolled, retrospective multicenter review of 64 patients who underwent repeated RLP068/Cl-PDT sessions demonstrated sustained clinical efficacy; bacterial load was down significantly and stayed so for some two weeks, and ulcer area shrank during follow-up even in cases involving exposed bone or Gram-negative infections [122]. Clinical experience has been reviewed in other contexts as well. One account of aPDT benchmarks cited an earlier Phase IIa trial with a phenothiazinium photosensitizer where post-treatment bacterial load was lower (p < 0.001) and complete healing at three months was 50 per cent versus 12 per cent for placebo. The same authors reported on the use of RLP068/Cl-PDT as an adjunct, noting quick eradication of bacteria and granulation with no local pain or safety concerns [123]. In vitro work has also been done to underpin the continued use of RLP068/Cl, demonstrating it is highly bactericidal against resistant *Candida* and both Gram-positive and Gram-negative species, though the latter and the yeast demand 5–20 μM of photosensitizer while Gram-positive bacteria can be handled with roughly 100 times less [64]. Recent surveys of the field indicate that phenothiazinium dyes remain more prevalent in clinical aPDT research than second-generation phthalocyanines. One example is a Phase III nasal-photodisinfection study for surgical-site-infection prevention (ClinicalTrials.gov identifier NCT05090657; planned n = 4,514), which uses methylene blue [124, 125]. By contrast, a proof-of-concept study using aluminum phthalocyanine chloride nanoemulsions for onychomycosis is among the few human trials to evaluate a Pc-class photosensitizer for a drug-resistance-relevant indication [126].

5 Covalent conjugation of phthalocyanines with antibiotics and other bioactive molecules

The phthalocyanine background set out above serves as a point of departure for this section, which is concerned with the covalent conjugation of Pcs to synthetic antibiotics, antimicrobial peptides and the like to improve their selectivity and therapeutic versatility [127]. There is continued interest in Pcs as second-generation PSs given the considerable promise they hold [128]. One needs only look at their industrial history since 1907 to see how much use has been made of them on account of their photophysical robustness. As porphyrin-like macrocycles, they have optical properties that are easily fine-tuned by way of metal incorporation or substituent changes; they also exhibit strong absorption in the far-red (around 670 nm) for better tissue penetration, all of which recommends them for PDT [129]. Indeed, several Pc derivatives are now clinically approved in ophthalmology and oncology [129]. Zinc(II) phthalocyanine (ZnPc) in its unsubstituted form is perhaps the best known of the Pc-based PSs for its efficacy in PDT [129], yet its poor solubility in water is an impediment to clinical use. To get around this and boost bioavailability, one must resort to chemical modification or put it into specialized formulations like liposomes [17]. The scope of PDT has been widened well beyond oncology by ZnPc conjugates with everything from antiparasitics and antidepressants to anti-inflammatories and antibiotics. In some cases, targeting moieties including folic acid, biotin, carbohydrates and epidermal growth factor (EGF) or Arg-Gly-Asp (RGD) peptides have been employed to take advantage of overexpressed tumor receptors for greater cellular uptake [127]. While such targeting was first put to work in oncologic therapy, the underlying chemistries and logic are readily applicable to the design of antimicrobial photosensitizers. We discuss these here as an example of the range of Pc-bioconjugation methods that have been validated and can be used in future engineering efforts.

5.1 Synthetic approaches for covalent conjugation

A number of approaches have been put forward for the attachment of biologically active moieties to a phthalocyanine core. One can link materials to the Pc macrocycle once it is in its finished form, or do so with the nitrile precursor before the cyclotetramerization step is undertaken. Such groups are joined to the Pc core by way of an alkyl or aromatic spacer, or simply by a direct bond [127]. The structural modifications made to the material will have a bearing on the photochemical properties of the final conjugate.

To see how well these compounds perform in terms of solubility and as a means of targeted delivery, they have been evaluated in their free state and within micellar polyvinylpyrrolidone (PVP) structures. In work by Da Silva et al., the PVP encapsulates were put to the test for their capacity to generate reactive singlet oxygen with 1,3-Diphenylisobenzofuran (DPBF). The results showed a photodegradation efficiency of between 59 and 91% in phosphate buffer and 92 to 100% in N, N-dimethylformamide (DMF). While the optical signatures of the Pcs in the PVP encapsulates remained intact, the exact wavelengths at which maximum absorbance occurs could not be defined [130].

5.2 Antibiotic and antimicrobial drug conjugates

Ciprofloxacin (CIP) has also proven to be a viable antibiotic for incorporation into Pc-based drug delivery systems. Two amphiphilic, asymmetric Zn(II)-based Pc-CIP conjugates developed by Magadla et al. were specifically engineered for use as dual-action

photodynamic antimicrobial chemotherapeutic agents. Each Pc-Zn precursor had benzo[d]thiazole-derived phosphonium or thiol groups attached to it to enhance amphiphilicity and to encourage bacterial internalization. The CIP was attached to each precursor via N-acylation of the piperazine ring of CIP using a spacer molecule based on phenoxyethylcarboxy activated with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and 4-dimethylaminopyridine (DMAP) [131]. The spectral data indicated that both conjugates were suitable for PDT purposes, displaying strong Q-bands at wavelengths of 684 nm and 687 nm; moderate fluorescence quantum yields in dimethyl sulfoxide (DMSO); and high singlet oxygen quantum yields. Electrochemical impedance spectroscopy and square wave voltammetry confirmed that both conjugates penetrated biofilms composed of *Escherichia coli* and *Streptococcus pneumoniae*. Time-of-flight secondary ion mass spectrometry and Raman spectroscopy provided evidence that both conjugates induced intracellular reactive oxygen species-mediated destruction. Both conjugates exhibited significant light-driven killing of bacteria with reported dark toxicity, yielding log-reduction values of 9.2 and 7.23 against *E. coli* and *S. pneumoniae*, respectively. Thus, these conjugates demonstrate considerable promise for the treatment of infections caused by biofilm-forming pathogens [131]. The standard antibiotic used for treating tuberculosis (TB) is isoniazid (INH) which disrupts the biosynthesis of mycolic acids, critical components of the cell walls of *Mycobacterium tuberculosis* [132]. Nkanga et al. prepared a targetable delivery system for INH by attaching hydrophilic INH to a hydrophobic tetrasubstituted Zn-phthalocyanine bearing four peripheral phenoxybenzaldehyde moieties [133]. An acid-catalyzed hydrazone bond was employed to link the INH to the ZnPc forming a ZnPc-INH complex capable of releasing INH upon changes in pH [133].

5.3 Cationic polymer and peptide conjugates

Chen and colleagues have put forward a zinc phthalocyanine–poly-L-lysine conjugate (ZnPc-PL) for use in photodynamic antimicrobial chemotherapy in the dental field [134]. The poly-L-lysine component of this molecule carries a positive charge which allows it to build up in bacterial cells, in particular *Porphyromonas gingivalis*, the main culprit behind periodontitis. Such an approach has proven superior to what is seen with neutral or anionic versions as well as earlier Ce6-PL conjugates; the cationic ZnPc-PL shows far better accumulation [134]. An analysis of the photophysical properties in DMSO produced a Soret band at 344 nm and a Q-band at 680 nm, figures that are in line with the kind of deep-tissue penetration one would need for a therapeutic agent [134]. Titration with 2,4,6-trinitrobenzenesulfonic acid (TNBS) by spectrophotometry revealed the mole ratio of ZnPc to polylysine to be close to 1:1 [134]. While the compound is highly selective in its phototoxicity against bacteria, there was no appreciable cytotoxicity observed in human periodontal ligament or rat bone marrow mesenchymal stem cells [134]. The efficacy of ZnPc-PL against *P. gingivalis* was confirmed in both in vitro and in vivo settings. When tested on an animal model with experimental periodontitis, the targeted photodynamic therapy cut bacterial loads by a factor of 100 compared to controls receiving only laser treatment or none at all. There was also a reduction in aspartate aminotransferase activity and gingival crevicular fluid volumes, a sign of diminished cellular injury and local inflammation [134]. Table 4 offers a summary of these and other Pc–bioactive molecule conjugates such as PVP-Pc and ZnPc-CIP. Work on antimicrobial

Table 4 Phthalocyanine–antibiotic/bioactive-molecule conjugates and their photodynamic properties

Conjugate / Study (Ref.)	Synthesis / Conjugation Strategy	Key Structural Features	Biological Activity / Findings	Photophysical Properties (Q-band / ΦΔ / ΦF)
Pc-Biomolecule Conjugates (General Strategies) [126, 129]	Covalent attachment to pre-synthesised Pc Coupling to nitrile precursor before cyclotetramerization Direct linkage or through aromatic/alkyl linker	Pc macrocycle modified directly or via precursor - Linkers used to improve flexibility & orientation	Structural modifications influence photodynamic antimicrobial action PVP micelles enhanced solubility & delivery	Photophysical profile varies by conjugation strategy; general trend of Q-band retention near 650–700 nm across constructs (see individual rows).
ZnPc–Ciprofloxacin (CIP) Conjugates (Magadla et al.) [130]	Amphiphilic asymmetric ZnPc precursors - CIP linked via N-acylation of piperazine ring Phenoxyethylcarboxy linker activated with EDC/DMAP	Benzo[d]thiazole-derived thiol or phosphonium substituents for amphiphilicity - Improved bacterial uptake	Strong uptake by *E. coli* and *S. pneumoniae* biofilms (electrochemical confirmation) Intracellular ROS damage (Raman, TOF-SIMS) - Very strong light-activated antibacterial activity: Log reduction up to 9.2 (*E. coli*), 7.23 (*S. pneumoniae*) Dark toxicity was reported.	Strong Q-bands at 684 nm and 687 nm; moderate fluorescence quantum yield (ΦF) in DMSO; high singlet-oxygen quantum yield (ΦΔ).
ZnPc–Isoniazid (INH) Conjugate (Nkanga et al.) [132]	INH linked to hydrophobic ZnPc using pH-responsive hydrazone bond Reaction catalysed with acetic acid	Parent Pc: tetra-substituted phenoxybenzaldehyde derivative Hydrazone linkage enables pH-triggered drug release	Designed for anti-TB drug delivery pH-sensitive INH release. Improved targeted delivery to *Mycobacterium*-related environments	Quantitative Q-band, ΦΔ, and ΦF data for the final ZnPc–INH conjugate were not reported in the cited study.
ZnPc-Polylysine (PL) Conjugate (ZnPc-PL) (Chen et al.) [133]	ZnPc conjugated to cationic poly-L-lysine (PL) - Approximate ZnPc: PL ratio = 1:1 (TNBS assay)	Strong cationic nature facilitates bacterial accumulation. Targeted to *P. gingivalis* for periodontal therapy	Highly selective for bacteria over mammalian cells (low toxicity in BMSC & HPDLC), Strong in vitro and in vivo photoinactivation of *P. gingivalis* - In dogs: 100-fold reduction in bacterial load - Reduced GCF volume and AST activity (less inflammation)	Soret band at 344 nm; Q-band at 680 nm in DMSO, with a Q-band maximum at 680 nm.

Note: ΦΔ, singlet-oxygen quantum yield; ΦF, fluorescence quantum yield; AST, aspartate aminotransferase; BMSC, bone marrow mesenchymal stem cell; CIP, ciprofloxacin; DMAP, 4-dimethylaminopyridine; DMSO, dimethyl sulfoxide; EDC, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; GCF, gingival crevicular fluid; HPDLC, human periodontal ligament cell; INH, isoniazid; PL, poly-L-lysine; PVP, polyvinylpyrrolidone; TNBS, 2,4,6-trinitrobenzenesulfonic acid; TOF-SIMS, time-of-flight secondary ion mass spectrometry. Where quantitative photophysical constants were not specified, they were not reported in the cited primary studies; the table presents only the available optical characterization and does not infer missing values

polymers and polypeptides in recent years has made it clear that factors like topology and the cationic/hydrophobic balance are key to reconciling host-cell compatibility with antimicrobial strength, design considerations that apply equally to the development of peptide-conjugated and polymeric systems with Pc [135–138].

6 Current challenges in phthalocyanine-based antimicrobial photodynamic therapy

While Pc-based aPDT is an important avenue for countering antimicrobial resistance, making the move from the laboratory to actual clinical practice has proven difficult. One finds that this is due to a host of interrelated constraints, both physicochemical and microbiological as well as photophysical, regulatory and economic in nature. For instance, there are the inherent properties of Pc macrocycles to consider, along with

biological impediments at the microbial level and the practicalities of light delivery and oxygen supply. Then there are the demands placed on drug-device combination products by regulators and the market [139, 140].

Therapeutic failure is a distinct possibility if one does not exercise care in optimization; the way Pc aggregation interacts with biofilm architecture, efflux pump activity and the antioxidant defences of enzymes can be problematic [24, 64]. On top of that, the absence of any standard dosimetry protocol, coupled with the rigour of regulations governing combination therapies, has opened up a gap in terms of commercialization [141]. In what follows, we put these obstacles under critical review with the aid of current mechanistic and quantitative data to underscore what they mean for the clinical standardization of Pc-based aPDT.

6.1 Physicochemical challenges: structural optimization

The large, planar, aromatic macrocycle of phthalocyanines is responsible for their favorable optical properties but also underlies important physicochemical limitations, particularly hydrophobicity and π–π stacking. Clinical optimization therefore requires a balance among photophysical efficiency, aqueous compatibility, biological selectivity, and synthetic feasibility.

6.1.1 Aggregation and quenching mechanisms

For phthalocyanine (Pc)-based photosensitizers (PSs), the chief physicochemical hurdle in their development is a propensity to aggregate under aqueous physiological conditions. In polar media like water, interstitial fluid or blood plasma, the planar macrocyclic rings are subject to robust π–π stacking that is thermodynamically preferred [24]. Such aggregation is more than a matter of solubility; it poses a significant photophysical constraint on Type II antimicrobial photodynamic therapy (aPDT). The formation of dimers and higher-order oligomers from Pc monomers, H-type aggregates in particular, facilitates electronic coupling and opens up fast non-radiative deactivation routes from the S_1 excited singlet state. This phenomenon, known as aggregation-induced quenching (AIQ), means absorbed energy is lost as heat in lieu of the efficient intersystem crossing (ISC) to the T_1 triplet state necessary to excite ground-state molecular oxygen ($^3O_2$) into singlet oxygen ($^1O_2$) [24]. The net effect is a lower singlet-oxygen quantum yield ($\Phi\Delta$) and diminished photodynamic performance. While one can counteract this with steric separation provided by bulky peripheral substituents or axial ligands, overly hydrophobic groups will impair aqueous compatibility by raising lipophilicity, thus calling for formulations like polymeric micelles or liposomes [103]. There is some indication from recent work that certain supramolecular assemblies, J-aggregates for instance, might still be photodynamically active or exhibit photothermal properties, but in vivo control over the structure and behavior of these aggregates is not yet something that can be done with any certainty [24].

6.1.2 The hydrophobicity-amphiphilicity balance

The aqueous solubility of unmodified Pcs is generally poor, making them hard to work with in a range of standard solvents. To be of any use biologically, a photosensitizer needs to be water-compatible enough for consistent formulation yet possess the lipophilicity required to engage with microbial membranes [142]. A good compromise is found

in amphiphilic Pcs which pair a hydrophobic macrocyclic core with hydrophilic moieties like cationic ammonium or sulfonate and carboxylate groups; these are well suited for cellular uptake. In this arrangement the hydrophobic part drives association with bacterial lipid bilayers and the hydrophilic side ensures better dispersibility in water and contact with polar membrane surfaces [142]. Should a Pc be too hydrophilic it will tend to stay in the aqueous phase and have little affinity for the membrane. That can be a problem for singlet oxygen ($^1O_2$) since its brief existence and limited diffusion in biological systems, on the order of 10–20 nm, means it can only affect targets right next to the photosensitizer [127]. On the other hand, an overly lipophilic Pc is prone to self-aggregation or precipitation in biological media, compromising bioavailability and dosing. While one could turn to nanocarrier delivery to get around such issues, that comes at the price of greater regulatory and manufacturing demands as well as formulation complexity [103].

6.1.3 Synthetic complexity and isomeric purity

Scalability and reproducibility are major concerns in the synthesis of third-generation phthalocyanines (Pcs), particularly when they are asymmetric or have been conjugated to a targeting moiety like an antibody, peptide or antibiotic. While Pcs are typically made by cyclotetramerizing phthalonitrile precursors, the preparation of an asymmetric A_3B-type Pc with three solubilizing groups and a single conjugation handle is another matter. That usually involves the statistical co-condensation of two distinct phthalonitriles, a process that tends to yield hard-to-separate mixtures of constitutional isomers. One is then left with the need for a good deal of high-performance liquid chromatography (HPLC) to purify the product; it is an expensive and laborious step that can erode the isolated yield and does not scale well. In the case of antimicrobial photodynamic therapy, such limitations on the synthetic and purification side drive up the cost of manufacturing and stand as a considerable impediment to bringing complex photosensitizers to market [90].

6.2 Microbiological barriers: the bacterial envelope and biofilms

The way photosensitizers interact with microorganisms is heavily dictated by biological barriers. For instance, Gram-negative bacteria and those found within mature biofilms have structural and physiological defences that curtail the binding, uptake and phototoxicity of these agents. At a basic level, the architecture of the bacterial cell envelope is what determines susceptibility to aPDT. One will find that Gram-positive bacteria are amenable to a wide array of photosensitizers on account of their porous peptidoglycan walls [140]. Gram-negative bacteria present a different challenge. An extra outer membrane serves as a formidable impediment to photosensitizer penetration in species like *Pseudomonas aeruginosa*, *Escherichia coli* and the drug-resistant *Acinetobacter baumannii*, all of which are of clinical significance. This asymmetric bilayer is a lipopolysaccharide (LPS)-rich environment where divalent cations (Mg^{2+}, Ca^{2+}) serve to stabilize the anionic groups [143]. It is possible to overcome this by cationic functionalization of Pcs with quaternary ammonium or imidazolium moieties; such modifications can displace the stabilizing cations and form a stronger electrostatic link with the LPS, thus making the outer membrane more permeable [142]. Yet there is a need for optimization of charge density. While a higher cationic charge may boost antibacterial efficacy, it risks nonspecific interactions with mammalian cells and a consequent reduction in the

therapeutic window [63]. Then there is the matter of biofilms, which are the predominant form in many chronic infections rather than free planktonic cells. These microbial communities are enmeshed in an extracellular polymeric substance (EPS) of their own making and are thought to be responsible for a good deal of chronic microbial disease [144]. The EPS matrix, with its mix of lipids, proteins, polysaccharides and extracellular DNA (eDNA), acts as a chemical sink and a physical barrier to reactive oxygen species and photosensitizers alike. Cationic photosensitizers in particular may be sequestered by the negative charges of eDNA and polysaccharides, preventing them from getting to the deeper layers of the biofilm [144, 145]. And should a photosensitizer make it through, any ROS produced at the surface stands to be neutralized by the EPS before it can get to its target. Such reaction and diffusion constraints are the main hurdle to effective aPDT of a mature biofilm.

6.3 Photophysical challenges: the hypoxia barrier and light delivery

The efficacy of aPDT with Pc-based agents is largely dictated by photophysical constraints. Conventional Type II aPDT, for instance, has a significant drawback in that it relies on molecular oxygen. Where hypoxia is present, the lack of available oxygen curtails singlet oxygen production and can have a marked effect on how well the treatment works [103]. There is also the matter of irradiation consuming oxygen at a rate that outstrips what diffusion from adjacent tissue can supply; too much irradiance will hasten this local depletion and undermine photodynamic efficiency. One might turn to fractionated or light–dark regimens to allow for reoxygenation in the intervals between exposures, yet such approaches come at the cost of longer treatment times and added complexity in a clinical setting [139]. Future studies should therefore report photosensitizer concentration, wavelength, irradiance, radiant exposure, illumination time, beam geometry, oxygenation conditions, and light–dark fractionation to support reproducibility and cross-study comparison [139, 140].

6.3.1 Type I vs. type II selectivity

There is a growing focus on Pcs that are capable of Type I electron-transfer photochemistry and the production of radical species like superoxide ($O_2^{\bullet-}$) and hydroxyl radicals ($^{\bullet}OH$), all in an effort to lessen reliance on oxygen. This stands in contrast to the majority of conventional Pcs, which are tuned for Type II photochemistry. One can shift the balance in favor of Type I routes, but structural changes are usually called for and they may have implications for solubility, aggregation or stability [103, 146]. Then there is the matter of the EPS matrix. Made up of extracellular DNA, lipids, proteins and polysaccharides for the most part, it serves as a chemical sink for ROS as well as a physical impediment to diffusion. The various components of the EPS will scavenge $^1O_2$ and other radicals, which goes some way to shielding bacterial cells from oxidative stress [147, 148]. Biofilms present another obstacle; oxygen gradients are common and the deeper strata can be hypoxic or anoxic, putting a damper on the Type II photodynamic processes that need O_2 to make $^1O_2$ [149]. All told, these constraints of reaction and diffusion do much to undermine aPDT efficacy in established biofilms, making it clear that new approaches are warranted to improve PS penetration and ROS output or to make use of the oxygen-independent Type I option.

6.3.2 Light penetration and dosing

The extent to which red light of 630–690 nm can penetrate tissue is a function of wavelength-dependent absorption and scattering. As a rule, the depth is on the order of 2–5 mm [139], making it adequate for treating superficial dermatological conditions yet inadequate when an infection is situated deeper within the tissue. Dosing for aPDT is not as straightforward as in pharmacotherapy, where one needs only consider weight (mg per kg); here the dose is a composite of drug concentration, oxygen levels, irradiance and radiant exposure. This lack of a universally recognised dosimetry standard for aPDT at present makes it difficult to put together reproducible clinical protocols or to compare results across studies [140].

6.4 Antioxidant defense upregulation

With their robust enzymatic antioxidant defences, bacteria are well equipped to counter oxidative stress and in the process can diminish the effectiveness of antimicrobial aPDT. Take superoxide dismutase (SOD) for instance: this enzyme will turn superoxide anions ($O_2^{\bullet -}$) into hydrogen peroxide (H_2O_2), after which catalase and peroxidases break the peroxide down to water and oxygen [150, 151]. Such detoxification is of particular import in Type I photodynamic action where one finds the production of radical species like superoxide and hydroxyl. By way of efficient scavenging, the enzymes limit oxidative damage and aid in the survival of the organism.

Treatment can be further confounded by sublethal aPDT exposure. When ROS generation is suboptimal, it has the effect of turning on global regulators of the oxidative stress response, such as the OxyR and SoxRS systems, which in turn upregulate genes for repair and antioxidants [152, 153]. One might call this adaptive resistance or stress priming; the resulting tolerance to later oxidative challenges is a direct consequence of that stress response. aPDT appears to have a relatively low propensity to select stable resistance because it damages multiple cellular targets simultaneously. Nevertheless, sublethal exposure may induce transient stress adaptation or phenotypic tolerance if light doses or PS concentrations are not properly calibrated [154]. It is thus essential to employ aPDT regimens with sufficient cytotoxicity so as not to inadvertently foster these bacterial survival routes.

6.5 Clinical, regulatory, and economic challenges

There are still formidable clinical, regulatory and economic hurdles to surmount even after the physicochemical and biological ones have been put to rest. From a clinical standpoint, success is a matter of delivering enough phototoxicity to microbes without compromising the host tissue in the vicinity. With cationic photosensitizers, for instance, the very properties that make them more potent against Gram-negative bacteria can also lead to unwanted interactions with mammalian cell membranes and a higher incidence of off-target cytotoxicity. Hence one has to be precise with the dosimetry of both light and photosensitizer to strike the right balance between efficacy and tissue preservation.

Regulatory considerations add another layer of complexity. In the United States, a photosensitizer–light-source system may be regulated as a combination product, depending on its constituent parts and primary mode of action. The applicable evidence requirements therefore depend on the final product configuration rather than on a single rule for all PDT systems. In the European Union, classification likewise depends on product

characteristics and intended purpose; medicinal and device constituents must satisfy the applicable medicinal-product and medical-device requirements. Consequently, the development pathway should be determined case by case rather than inferred from a single general model [120, 155].

Then there is the economics of antimicrobial development to contend with. A chronic drug provides a steady revenue stream by virtue of long-term prescriptions, but an antimicrobial is usually given for a brief course and the returns are correspondingly lower, which does little to encourage investment [141]. Some would say that if a Pc-based aPDT of high efficacy were to be approved, it could put further pressure on antibiotic sales and in so doing dampen the commercial case for funding new technologies in this space [156].

6.6 Future directions and emerging solutions

While the foregoing challenges are no small matter, they are being put to the test by research programs that are both active and well documented in the literature. The field is not one to end on a note of hardship; instead it is moving toward tangible solutions in engineering, chemistry and policy that address the four types of obstacles we have outlined. In doing so, a workable path is emerging for the clinical use of phthalocyanine-based antimicrobial photodynamic therapy.

6.6.1 Overcoming physicochemical challenges

There is a shift in how the age-old conflict between aqueous solubility and aggregation-caused quenching is being managed; the focus is moving away from static solubilization toward a more dynamic, stimulus-responsive control of the state of aggregation. In place of the old approach of locking a Pc into a monomeric form for good, various groups have put forward "activatable" or "nano-isolation" designs where the photosensitizer is left to be quenched or disassembled while in circulation, to be activated at the site of infection by something as local as a change in pH, an enzyme or glutathione. One can see this logic in a mitochondria-targeted nanoparticle system for tumors: under normal physiological conditions the photosensitizer is rendered inactive by aggregation, but it will disassemble in the acidic microenvironment of the tumor and resume its photodynamic function [157]. The same principle is at work in a parallel strategy that puts an aggregation-gated Type I photosensitizer inside glutathione-responsive nanoparticles, effectively silencing ROS production in transit until the carrier breaks down within the cell [158]. Then there are the phthalocyanine-based probes that have been fine-tuned for their quenching and activation efficiency, such as hyaluronic-acid J-aggregation platforms which are meant to hold a switchable aggregate rather than do without one entirely [159]. When it comes to balancing amphiphilicity, the chemistry of supramolecular self-assembling amphiphiles provides a sound design template. Initially made for antimicrobial adjuvants, it can be applied to the periphery of phthalocyanines to get the right membrane partitioning with no loss of dispersibility in water [160, 161]. The synthetic side of things is also becoming more sophisticated. Green chemistry methods are coming of age; a ball-milling process for phthalocyanines, for instance, does away with up to 100 times the hazardous solvent use of conventional methods and still gives a good yield [162]. Or one might turn to continuous-flow chemistry for the kind of tight reaction control and isomeric definition that batch cyclotetramerization cannot match, a technique already proven at the

pharmaceutical level [163, 164]. Machine learning is now being brought to bear on the whole pipeline as well. Models can be run to anticipate the trade-off between toxicity and efficacy in a chemical scaffold or to guide the virtual screening of Pc substitution patterns for the best singlet-oxygen quantum yield before anything is even put in the lab [165].

6.6.2 Overcoming microbiological barriers

When it comes to the impermeable outer membrane of Gram-negative bacteria, the co-administration of an adjuvant is still the near-term answer with the most experimental backing. Agents that permeabilize the outer membrane and cationic or amphiphilic photosensitizer designs have been shown to enhance Pc binding and penetration, while a systematic review has covered methods for countering resistant phenotypes such as efflux and envelope impermeability to drive photoinactivation [166]. There is also progress on the rational side of membrane-partitioning; for instance, metal-free photosensitizers of an amphiphilic nature have been put together to intercalate stably and of their own accord into the membrane, proving that one can rely on molecular design for envelope access as much as formulation [167]. Biophysical studies are likewise shedding light on the structure-activity rules for Pc peripheral substitution by mapping the disposition of porphyrinoid photosensitizers in bacterial membranes [168].

In the case of biofilms, the new direction is combination therapy. By coupling aPDT with matrix-degrading co-therapies like DNases, dispersal enzymes and EPS-targeting glycoside hydrolases, the protective matrix is loosened so the photosensitizer can reach the bacteria within. This form of "enzymatic dispersion" is being reviewed as a separate biocatalytic option for dealing with biofilm-related infection [169, 170]. One example with direct relevance to photodynamics uses blue light and ferric ions to break down carboxylated EPS polysaccharides and at the same time deliver a broad antimicrobial effect on multidrug-resistant polymicrobial biofilms [171]. The literature is replete with reviews of aPDT in tandem with photothermal, magnetic-hyperthermia, antibiotic or cold-plasma treatments that point to an additive or even synergistic removal of the biofilm [172]. That said, some caution is in order. If done on a large scale in vivo, enzymatic dispersal of a biofilm can set free motile bacteria capable of inducing septicemia unless there is simultaneous killing of the organism. It is for this reason that a translational design which includes a bactericidal aPDT trigger alongside the dispersal is to be preferred over the latter in isolation [173].

6.6.3 Overcoming photophysical challenges

There are two complementary avenues for overcoming the hypoxia barrier. One is through oxygen-independent photochemistry, or Type I-dominant pathways. It has been shown that electron-transfer mediators like thymoquinone can convert Type II photosensitizers to Type I, thereby maintaining bactericidal ROS output even in the absence of oxygen [174]. Biotinylation has also proven effective at countering the limitations of hypoxia on a range of photosensitizer scaffolds [175], and a putative "Type III" mechanism has been put forward as yet another way to achieve hypoxia-tolerant antimicrobial photoinactivation [176].

The other approach is to ensure a local supply of oxygen. Perfluorocarbon nanoemulsions and nanodroplets, with their high O_2 solubility, have been validated with

fluorinated chlorin-type photosensitizers to bring back photodynamic efficacy under hypoxic conditions [177, 178]. An alternative is to be found in catalytic oxygen-evolving nanoplatforms; Prussian-blue-based systems that act as catalase mimetics to turn endogenous H_2O_2 into O_2 in situ offer a self-sustaining option without the need for a carrier [179]. A number of these oxygen-carrying and -generating tactics are now being assembled into a design toolkit for the poorly perfused tissue of infected sites, as covered in wider reviews of nanomedicine for PDT [180].

In terms of selectivity between Type I and Type II, rational chromophore engineering is picking up pace. Caged organic scaffolds can be fine-tuned for photodynamic reactivity by means of bio-orthogonal activation [181], while machine-learning models are used to derive singlet-oxygen photophysical behavior from the molecular structure itself, obviating the need for protracted empirical screening [182]. The field is also making headway on standardizing dosimetry for light penetration and dosing. To make cross-study comparisons possible, a power-law inactivation-kinetics model has been advanced in place of ad hoc survival-fraction reporting [183]. The lack of uniform reporting conditions is seen as the source of translational variability in aPDT, prompting calls for harmonized protocols [184]; a 2025 review of light-based wound therapy points to the same variability in photosensitizer and light dose as the main impediment to making photodynamic microbial inactivation part of routine care [185]. For an example of how to standardize antimicrobial dosimetry, one might look to the multichannel clinical systems already in use for Photofrin pleural PDT, which measure both light fluence and sensitizer concentration [186]. As for upregulating antioxidant defenses, there is interest in combination therapies as adjuvants. These involve the pharmacological suppression of microbial catalase and superoxide dismutase to render resistant cells more vulnerable to photodynamic killing [187]. Then there are mechanistically different methods, such as using metallacages to curtail endogenous nitric oxide and upset bacterial ROS homeostasis, which have resulted in the elimination of bacteria at considerably reduced doses of photosensitizer [188].

6.6.4 Overcoming clinical, regulatory, and economic challenges

Regulatory precedent exists for handling some photosensitizer–light-device systems within combination- or borderline-product frameworks, but classification depends on the final product and its intended use. Existing guidance on combination products and nanopharmaceuticals can provide a starting framework for Pc-based aPDT systems without predetermining the route for every formulation–device pairing [120, 155]. The same is true on the clinical side. Dermatologists' guidelines for the aPDT of skin infections are in flux, with regulators making it clear they view novel photosensitizer/nanotheranostic combinations as more than mere experiments by including them in practice recommendations [189]. Economically, there is a range of models to be had from the antibacterial "push" and "pull" incentive literature. While these were devised for standard antibiotics, they are readily applicable to aPDT commercialization. A thorough review covers the governmental and multilateral "push" funding meant to take the risk out of early-stage discovery, noting where such mechanisms are underused and how they can be made more efficient [190]. CARB-X is a case in point for a public-private accelerator that is already functioning in the antimicrobial arena [191]. As for "pull" incentives, whether in the form of delinked reimbursement, subscription payments, stewardship-tax funds

or transferable exclusivity vouchers, they are seen as essential to the push model for any new antimicrobial with a limited-use profile to have lasting market appeal [192–194]. Given that aPDT has a comparatively low propensity to select stable resistance, it is well suited to be given priority in such non-traditional frameworks, which tie commercial success to public health objectives instead of sales volume. Viewed in aggregate, the four areas of switchable photophysics, combination microbiology, oxygen-independent and dosimetry-standardized photophysics, and the regulatory and economic models at hand show that the obstacles previously outlined are engineering challenges to be met, not fixed roadblocks. Some have already been demonstrated in concept in recent papers. The way chemistry, policy and microbiology are aligning presents a sound plan for making phthalocyanine-based aPDT a viable option in the clinic and in the marketplace for drug-resistant pathogens.

7 Conclusions

With the steady increase in antimicrobial resistance (AMR), there is a clear imperative to look beyond conventional antibiotics. Antimicrobial photodynamic therapy (aPDT) has emerged as an attractive localized option for dealing with multidrug-resistant pathogens, and this review examines the considerable headway made in phthalocyanine (Pc)-based photosensitizers as multifunctional aPDT platforms. The appeal of Pcs and metallophthalocyanines (MPcs) lies in their ability to couple robust chemical and thermal stability with potent red/near-infrared absorption and the means to produce reactive oxygen species that can assault a variety of microbial targets. The inclusion of central metals like zinc or aluminum serves to optimize excited-state photophysics and boost singlet-oxygen output. Where Pcs have inherent drawbacks such as low solubility in water or a tendency to aggregate, these can be offset by formulating them with nanotechnology in the form of liposomes, polymeric carriers, metallic nanoparticles or graphene-based materials. Not only do such carriers aid in dispersion and delivery, they can also underpin both photothermal and photodynamic action. There are further possibilities for site-selective activation in self-assembling or stimulus-responsive systems, and covalent attachment to bioactive molecules like peptides or antibiotics can serve to refine targeting and expand therapeutic scope.

Preclinical studies demonstrate Pc-based activity against several multidrug-resistant bacterial and fungal pathogens. Although antiviral aPDT has also produced promising results, much of the available antiviral evidence involves non-Pc photosensitizers; Pc-specific antiviral efficacy therefore remains insufficiently established. Yet for all the in vitro and preclinical evidence, moving Pc-based aPDT into the clinic is not without its obstacles. One is held back by issues of manufacturing and regulatory compliance, as well as the practicalities of penetrating biofilms, illuminating deep-seated infections and dealing with local hypoxia.

Looking ahead, the prospects for Pc-based aPDT will be shaped by how far intelligent molecular and nanotechnological engineering can take us. It is necessary to put in the work to create nanoplatforms that are stable in systemic circulation but will respond to external or endogenous triggers at the infection site be it light, ultrasound or a biochemical signal. This kind of stimulus-responsive design should allow for more precise targeting with less off-target toxicity. At the same time, technical hurdles concerning oxygen levels and light penetration in deeper tissues must be surmounted, perhaps through new

device designs or photochemical mechanisms that do not rely on it. To see these strategies move from the lab to clinical practice in any meaningful way, sustainable economic models and smoother regulatory routes must also be put in place. Only by confronting these scientific and economic realities can Pc-based PSs become a truly viable part of the worldwide response to AMR.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

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