Photodynamic therapy: A paradigm shift in overcoming drug-resistant tuberculosis (Review)

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Abstract. Tuberculosis (TB) poses a notable threat to global public health. Conventional antibiotic treatments are hampered by long treatment courses, notable toxicity and rising levels of drug resistance. By contrast, photodynamic therapy (PDT) offers a promising alternative to antibiotics. This approach employs photosensitizers (PSs), light and oxygen to generate reactive oxygen species, which induce oxidative stress to eliminate *Mycobacterium tuberculosis*. The present review explores the mechanisms, benefits and primary challenges of PDT in the context of TB treatment. The present review also discusses advanced strategies that address hurdles, such as the robust mycobacterial cell wall, hypoxic environments and biofilm formation. These strategies include rational PS design, innovative nanodelivery systems and synergistic combination therapies. The present review also explores pathways for future clinical translation, highlighting the potential of PDT as a viable supplement or alternative to traditional TB chemotherapy through interdisciplinary innovation.

Contents

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Abbreviations: PDT, photodynamic therapy; TB, tuberculosis; MTB, Mycobacterium tuberculosis; ROS, reactive oxygen species; ALA, 5-aminolevulinic acid; AIE, aggregation-induced emission

Key words: PDT, TB, drug resistance, MTB, nanomedicine, biofilm, targeted delivery

1. Introduction

Tuberculosis (TB) remains one of the leading causes of death from infectious diseases worldwide. For 2023, the World Health Organization reported ~10.8 million new cases of TB worldwide, alongside 400,000 new cases of drug-resistant TB; TB infection was responsible for almost double the number of mortalities compared with the number of mortalities attributed to HIV/acquired immune deficiency syndrome in 2023 (1). Although TB is both preventable and curable, its treatment remains challenging because it requires a complex multi-drug regimen. Poor adherence to this regimen is a notable concern in TB treatment and is associated with doubled mortality rates (2). Irregular medication intake is strongly associated with treatment failure, relapse and the emergence of drug resistance in TB (3). Additionally, patients with TB frequently experience adverse drug reactions, including hepatotoxicity, nephrotoxicity and gastrointestinal issues (4). TB treatment is more complex in vulnerable populations, such as children, pregnant individuals and patients with HIV co-infection. These populations encounter treatment complications such as complex dosage adjustments and increased risks of adverse reactions. In children, doses must be weight- and age-adjusted due to differing drug metabolism; in pregnant individuals, physiological changes alter drug distribution, requiring dose modifications; and in HIV co-infected patients, drug-drug interactions between TB and antiretroviral agents necessitate careful regimen adjustments. These factors collectively complicate TB treatment in these groups (5-8).

A global systematic review and meta-analysis reported separately pooled prevalence estimates for different drug-resistance phenotypes in TB: 11.6% for multidrug-resistant TB (MDR-TB), 15.7% for isoniazid-resistant TB, 9.4% for rifampicin-resistant TB and 2.5% for extensively

drug-resistant TB (XDR-TB). These estimates were pooled independently and are not nested proportions (9). The treatment of drug-resistant TB involves complex regimens, extends over 18-24 months and incurs high financial costs. As a result, the cure rates for drug-resistant TB are markedly lower than those for drug-susceptible TB. Mortality rates are ~2 to 3% for drug-susceptible TB, compared with around 40% for MDR-TB and up to 60% for XDR-TB (10). Drug-resistant TB imposes a notable economic burden on patients, families and society, presenting a notable obstacle to TB control and prevention efforts (11).

Therefore, there is a requirement for innovative therapeutic strategies that are either non-invasive or minimally invasive and do not rely on antibiotics. Photodynamic therapy (PDT) has gained attention as a promising non-invasive therapeutic technique for managing and treating TB (12-15). This approach involves the use of a photosensitizer (PS) that is activated by light at a specific wavelength to produce reactive oxygen species (ROS), which are damaging to bacteria; this mechanism effectively eradicates pathogens while exhibiting a low risk of promoting drug resistance (16). Consequently, PDT exhibits potential for the treatment of TB, especially in the context of its drug-resistant variants.

2. Distinctive strengths of PDT vs. conventional antibiotics

Antimicrobial PDT represents a paradigm shift from the conventional molecular targeting approach; this method directly targets pathogens through physicochemical mechanisms, conferring notable advantages against drug-resistant *Mycobacterium tuberculosis* (MTB), biofilm formation and intracellular parasitism (17-20).

Core advantages include: i) Multifaceted mechanisms: PDT generates ROS that cause non-specific oxidative damage to membranes, proteins and nucleic acids (21). This multitarget strategy, which is independent of bacterial metabolic activity, is also effective against dormant and persistent cells that might otherwise evade treatment. ii) A low risk of resistance: The physicochemical nature of PDT-mediated antimicrobial effects means that it is inherently difficult for bacteria to develop resistance to PDT through conventional genetic mutations, as there is no single molecular target for them to effectively modify (14,15). iii) Precision targeting: The ability to confine the therapeutic effect of PDT to illuminated areas offers notable targeting precision. This effectively reduces off-target treatment effects, enhancing treatment safety for host tissues and the resident microbiota (16). iv) Synergistic immunomodulation: PDT stimulates beneficial local immune responses, reprogramming the microenvironment by activating macrophages and modulating inflammation, and thus, enhancing intracellular pathogen clearance (22).

For localized drug-resistant TB lesions, topical application methods, such as bronchoscopic drug delivery, focus the bactericidal effects of treatments directly on the diseased site. This approach minimizes the risk of drug dissemination and systemic toxicity, thus expanding the therapeutic window (23). Furthermore, non-oral administration of therapeutics improves patient compliance with treatment plans and allows for targeted delivery of therapeutic agents to pathological tissues, which reduces their required dosage and frequency (24,25). This also protects therapeutic agents from gastrointestinal degradation and bypasses hepatic first-pass metabolism, thus enhancing their bioavailability.

3. Fundamental principles and key components of PDT

Photodynamic effects depend on three required components: A PS, light of a specific wavelength and oxygen. The process begins when the PS absorbs photons, elevating it from the ground state to a transient singlet excited state. The PS then undergoes intersystem crossing to reach a more stable triplet excited state. From this stable triplet state, the excited PS can follow two main reaction pathways: i) A type II reaction, which transfers energy to molecular oxygen to produce singlet oxygen ($^1O_2$); or ii) a type I reaction, which involves electron transfer to biological substrates, resulting in the production of ROS, such as the superoxide anion (O_2-) and the hydroxyl radical (•OH) (26,27). Typically, type I and II reactions occur simultaneously, with the predominant reaction pathway determined by the specific PS used, substrate concentration and local oxygen levels. Notably, the efficiency of the type II pathway largely relies on oxygen availability, which represents an important limiting factor in the hypoxic microenvironment of TB lesions (28,29).

4. PS design strategies

There are several key characteristics that PSs should exhibit for use in PDT: i) High target specificity for accumulation in pathological tissues, such as infectious foci or tumors; ii) strong absorption within the near-infrared optical therapeutic window for superior tissue penetration; iii) a high $^1O_2$ quantum yield; iv) minimal dark toxicity; v) notable biocompatibility and a favorable metabolic clearance profile; and vi) a well-defined chemical structure (30-32). The optimal PS design is application-specific; strategies for combating microbial pathogens differ from those targeting cancerous cells due to the different underlying biological contexts. As summarized in Table I, these contextual differences translate into distinct design priorities for anticancer and antimicrobial photosensitizers. Specifically, anticancer PSs emphasize tumor-selective accumulation, receptor- or microenvironment-mediated targeting, NIR-responsive optical properties, structurally optimized phototheranostic platforms and nanocarrier-assisted delivery for deep-tissue treatment (33-38). By contrast, antimicrobial PSs prioritize broad-spectrum pathogen inactivation, cationic membrane-targeting strategies, visible-light applicability in localized infections, strong ROS output, anti-biofilm performance and representative antimicrobial PS platforms such as cationic porphyrins, cationic ZnPc, cationic BODIPY and composite systems (35,39-50).

The design strategies for anticancer and antimicrobial PSs reflect a fundamental functional dichotomy. Anticancer PSs target tumors precisely and modulate the tumor microenvironment, while antimicrobial PSs are designed for broad-spectrum lethality and physically disrupt microbial membranes (36,51). Despite the differences in targeting mechanisms between anticancer and antimicrobial photosensitizers, they share a

Table I. Comparison of design strategies and characteristics between anticancer and antimicrobial photosensitizers.

Design criterion	Properties of anticancer photosensitizers	Properties of antimicrobial photosensitizers
Primary target	Selective tumor destruction; inhibition of angiogenesis and metastasis (33).	Rapid, broad-spectrum inactivation of bacteria, fungi and viruses (39,40).
Targeting mechanism	Receptor-mediated targeting (e.g., folate receptor, RGD peptide); enhanced permeability and retention effect (33,34).	Cationic modifications exploiting negative bacterial membrane charge (41,42)
Optical window	650-900 nm (NIR-I) or 1,000-1,350 nm (NIR-II) for deep tissue penetration (35).	400-700 nm (visible light) for superficial and localized treatments (35).
ROS profile	ROS generation under hypoxia; balanced type I/II reactions (36).	High singlet oxygen or free radical yield for rapid bacterial disruption (43).
Structural features	Porphyrins, phthalocyanines, BODIPY, AIEgens and metal complexes (37).	Cationic porphyrins, quaternary ammonium BODIPY and silver/polymer composites (42).
Delivery system	Nanocarriers, such as liposomes, MOFs and polymers, with targeting ligands (37).	Surface immobilization on bacterial surfaces, topical applications, and inhalable nanocarriers for targeted delivery (44).
Microenvironment	Complex tumor microenvironment (36).	Infectious microenvironments, comprising biofilms, hypoxic conditions and neutral pH (45).
Performance priority	Deep-tissue penetration, hypoxic activity and circulation stability (38).	Rapid ROS generation, high-affinity binding to targets and anti-biofilm capability (46).
Representative agents	Photofrin®, verteporfin, ZnPc, I-BODIPY and AIEgens (36).	TMPyP, cationic ZnPc (ZnPc+), cationic BODIPY and Ag@PS composites (47-50).

ROS, reactive oxygen species; AIEgens, aggregation-induced emission luminogens; NIR, near-infrared; MOFs, metal-organic frameworks; RGD, arginylglycylaspartic acid; ZnPc, zinc phthalocyanine; TMPyP, meso-tetra(N-methyl-4-pyridyl)porphine.

common photochemical core, which generates ROS upon light activation. This mechanism exerts cytotoxic effects, whether targeting cancer cells or microbial pathogens. Additionally, both types of PS can enhance selective delivery through nanocarrier platforms, improving delivery efficiency and minimizing damage to surrounding healthy tissues, whether in tumor tissues or infection sites. These shared design features drive the development of multimodal therapies, which, despite targeting different pathological states, can integrate synergistic mechanisms to achieve more effective cancer and antimicrobial treatments.

5. Antimicrobial mechanisms of PDT and MTB tolerance

PDT-generated ROS induce broad-spectrum oxidative stress, non-specifically targeting important bacterial biomolecules, such as membrane lipids, metabolic enzymes and nucleic acids. These ROS are responsible for: i) Oxidizing unsaturated fatty acids in microbial membranes, initiating lipid peroxidation chains that compromise membrane integrity, increase permeability and cause content leakage (52); ii) causing oxidative amino acid damage and peptide bond cleavage, disrupting protein structure and function, which in turn leads to protein aggregation and degradation (53); and iii) inducing DNA strand breaks and base modifications, triggering genetic mutations and compromising genomic integrity (53). In addition to inducing direct oxidative damage, ROS inhibit key metabolic pathways, such as long-chain fatty acid degradation, arresting microbial growth (54).

Mycobacteria exhibit tolerance to ROS through several complex defense mechanisms, including: i) A notably dense hydrophobic mycolic acid cell wall that restricts exogenous molecule penetration (55); ii) biofilm formation, which is bolstered by the aforementioned lipid-rich cell wall (56); iii) potent antioxidant enzymes, such as catalase-peroxidase and superoxide dismutase, which neutralize ROS (57); and iv) expression of the melH gene, which encodes an epoxide hydrolase that mitigates ROS-induced stress by modifying cell wall lipids, thus fortifying the cell wall and promoting the persistent survival of bacteria (58). To improve the efficacy of PDT, PSs must overcome the protective cell wall barrier and modulate the pathogenic microenvironment.

6. Frontiers in PDT for TB treatment

Innovative PDT strategies: Exogenous delivery and endogenous activation of PSs

Targeted design of exogenous PSs. In PDT-mediated treatment of TB, it is important to design PSs that can target the unique profile of the mycolic acid-rich cell wall of MTB. A prime example of this is the PS carbol fuchsin, which leverages its intrinsic affinity for mycolic acids to achieve specific localization to MTB and generate bactericidal ROS upon illumination (40). Consistent with this concept, a recent report further highlighted a targeted PDT strategy for drug-resistant pulmonary tuberculosis based on interactions between cyclohexadiene-aminophenyl moieties and mycolic acids, underscoring the feasibility of exploiting the mycolic

acid-rich cell wall for selective photosensitizer localization (59). To further improve PS selectivity and reduce toxicity to surrounding tissues, strategies such as computer-aided derivative design or nanocarrier encapsulation for inhaled PS delivery are being explored (60,61).

Cationic porphyrins electrostatically adhere to negatively charged bacterial membranes, disrupting their integrity. Amphiphilic cationic porphyrins that self-assemble into nanoparticles can be used to address challenges such as poor solubility, aggregation and insufficient targeting of therapeutic agents. This design encapsulates the photoactive porphyrin core internally while exposing cationic groups on the surface of the nanoparticle, thus preventing aggregation-caused quenching (ACQ), maintaining high $^1O_2$ yield, and enhancing the targeting and binding efficiency of PSs for potent broad-spectrum bactericidal activity (62-64).

Endogenous PS activation. An alternative approach for improving the efficiency of PSs in PDT involves the use of exogenous 5-aminolevulinic acid (ALA) to trigger the intracellular production of endogenous porphyrins. Once ALA is absorbed by host cells within the tuberculous lesion, it is metabolized through the heme biosynthesis pathway to generate protoporphyrin IX (PpIX), a powerful PS (65). Research has demonstrated that model mycobacteria can efficiently absorb exogenous ALA and transform it into photoactive porphyrins. This discovery provides an important pharmacodynamic basis for developing PDT strategies against intracellular pathogens, such as MTB (66).

Although PpIX is an endogenous photosensitizer, its clinical utility is limited by poor water solubility and aggregation. researchers have developed a number of chemical modification strategies to overcome the limitations of PpIX, notably its poor water solubility and ACQ. These strategies include conjugating PpIX with chitosan oligosaccharides (67), synthesizing water-soluble protoporphyrin-based polymers (68) and grafting PpIX onto bacterial cellulose (69). These exogenous modifications markedly enhance the aqueous dispersibility and colloidal stability of PpIX-based PSs, thereby improving their practical utility. By combining exogenous administration of the precursor molecule ALA with endogenous PS activation, these strategies demonstrate a viable path to improving the stability and practical applicability of endogenous photosensitizers. This approach enhances the potential for *in situ* accumulation of photosensitizers within tubercle bacilli and infected host cells, enabling precise and targeted bactericidal action. Such strategies improve the stability and utility of endogenous PSs, making accurate targeting of bacterial pathogens possible within the infected cells.

Strategies to overcome hypoxia and biofilm resistance. Biofilms are a primary cause of chronic infections and antibiotic resistance, affecting a wide range of bacterial infections, including TB and other chronic conditions (70). Their extracellular polymeric substance (EPS) matrix within biofilms acts as a physical barrier against therapeutic agents, limiting the effectiveness of antibiotics and other treatments. Additionally, the hypoxic microenvironment frequently found within biofilms can notably impair the efficacy of PDT, as the type II pathway of PDT heavily relies on oxygen availability for singlet oxygen production (70). Innovative strategies to overcome oxygen dependence in PDT include: i) Type I PSs: These favor type I reactions to generate fewer oxygen-dependent free radicals (such as •OH). The dianionic small molecule C3TH, a zwitterionic molecule that self-assembles into nanoclusters for Type I PDT, produces •OH via self-ionization under hypoxia (71). Similarly, selenium-doped methylene blue represents an almost oxygen-independent PS (72). ii) Oxygen self-supplying platforms: These systems aim to sustain ROS production by continuously providing oxygen to PSs at the target site. This is achieved by either leveraging the high oxygen-carrying capacity of perfluorocarbons (73) or by employing biomimetic oxygen-generating systems based on *Chlorella vulgaris* (74). iii) Singlet oxygen batteries: This promising molecular system, which functions similarly to an energy storage device, pre-loads and then slowly releases $^1O_2$. Operating without external light or oxygen, this system uses targeting peptides to guide the slow release of pre-stored $^1O_2$ at the infection site, enabling sustained antibacterial activity within deep tissues (75).

Asymmetric Janus nanoparticles (JNPs) provide a multifaceted strategy for combating drug-resistant biofilms: One hemisphere of the JNP acts as a photothermal agent, while the other hemisphere loads lysozyme for responsive release. The surface maltose moieties on the JNPs enable specific targeting of biofilm sugar components, such as those found in bacterial biofilm matrices. This targeting allows lysozyme to be released in response to biofilm-specific components, facilitating the breakdown of the EPS from within the biofilm core, thus dismantling its protective barrier (76).

Aggregation-induced emission (AIE) PSs show notable promise in PDT due to their enhanced light emission and high ROS generation in aggregated states, effectively bypassing the ACQ that PSs typically exhibit (77). The efficacy of AIE PSs is further improved through molecular modifications such as cationization and alkyl chain adjustments, which enhance targeting efficiency and the binding of PSs to bacterial membranes (78). Additionally, a novel strategy has been described and involves the use of phages to initially degrade the EPS matrix, allowing precise bacterial localization of PSs and facilitating direct photodynamic eradication (79). Collectively, these strategies provide promising solutions for the treatment of drug-resistant TB infections.

Precise delivery and targeting strategies. The tuberculous granuloma, a characteristic structure of TB, serves a dual role in development of the disease. While this structure can restrict bacterial dissemination, it also establishes a localized immunosuppressive microenvironment that hinders the ability of the host to eradicate MTB (80). A study in llamas naturally infected with MTB have revealed abundant acid-fast bacilli within advanced pulmonary and lymph node granulomas, indicating a failure of local immune control and suggesting a high risk of MTB transmission due to notable bacterial loads (81). Furthermore, the frequently hypoxic conditions within TB lesions exacerbate persistent MTB infection by compromising oxygen-dependent host antimicrobial mechanisms (82).

Intelligent delivery systems engineered to overcome barriers include: i) Enzyme-responsive systems: These utilize smart carriers designed to be sensitive to enzymes that are specifically abundant in TB lesions, enabling the precise

release of therapeutic agents to target tissues and promoting the synergistic effects of anti-TB drugs and PSs at the disease site (83,84). ii) Biomimetic targeting platforms: By employing bacterial membrane-coating technology, these platforms enhance the uptake of nanocarriers by host immune cells, particularly macrophages, resulting in precise delivery of therapeutic agents to granulomas and intracellular infection sites (85,86). iii) Multifunctional composite structures: Examples include photothermal therapy (PTT)-PDT composites, which generate heat via photothermal activity, increases bacterial membrane permeability, and facilitating the entry of more PSs and oxygen into bacteria. This strategy not only enhances the efficacy of PDT but also sensitizes bacteria to thermal damage (87,88).

These strategies represent a shift from the passive diffusion of therapeutic agents into their targets to active pathogenic targeting, as well as from single-modality treatments to intelligently controlled, where the therapeutic strategies are optimally designed to ensure synergistic effects by taking into account the specific characteristics of the target environment, such as immune responses, microenvironment conditions and pathogen-specific features. This shift lays a foundation for clinical translation.

7. Synergistic and multimodal PDT strategies

PDT is evolving from single-modality treatments to multimodal synergistic strategies in order to enhance its therapeutic efficacy and overcome the physiological barriers associated with TB.

Photothermal and photodynamic synergy. The primary mechanism behind the synergy of PTT and PDT involves the light-activated production of heat to enhance the permeability of bacterial cell membranes, as aforementioned. This increased membrane permeability permits the entry of more PSs and oxygen into bacterial cells. As a result, notable amounts of ROS are produced within bacterial cells, leading to considerable amounts of oxidative damage to important biomacromolecules. Concurrently, the compromised membrane integrity induced by photothermal activity results in the leakage of bacterial proteins into the extracellular space, ultimately causing bacterial cell death (89).

The synergy between PDT and PTT is evident in the activity of polydopamine-modified CuS@HKUST nanocomposites, a nanocomposite comprising copper sulfide nanoparticles integrated within the HKUST-1 metal-organic framework, which demonstrate improved photothermal performance and ROS generation. These properties grant the nanocomposite notable bactericidal activity against both gram-positive bacteria, such as *Staphylococcus aureus*, and gram-negative bacteria, such as *Escherichia coli*. As such, these nanocomposites achieve sterilization rates of almost 100% in PTT-PDT with low laser power density and a brief irradiation time (90).

Photodynamic-chemotherapy combination. Research has shown that rationally-designed AIE luminogen (AIEgen) probes, which are molecules that become highly fluorescent and exhibit increased ROS generation upon aggregation, can precisely target the peptidoglycan biosynthesis pathway of the MTB cell wall via metabolic labeling, contrary to conventional diagnostic dyes (which rely on physical adsorption or affinity-based staining). This targeting also permits the specific labeling and highly sensitive imaging of MTB for diagnosis, thus allowing AIEgens to exhibit notable theranostic activity. These probes generate ROS upon illumination and exhibit synergy with antibiotics to enhance bactericidal efficiency (91). In a similar approach, when addressing multidrug-resistant bacteria responsible for bovine mastitis, specific porphyrin-based PSs exhibit broad-spectrum antimicrobial activity at low concentrations. Through photodynamic activation, these PSs induce a priming effect that restores the sensitivity of drug-resistant bacteria to conventional antibiotics (92).

These findings suggest that the co-treatment of pathogenic diseases with PDT and antibiotics represents a refined strategy for targeting drug resistance: i) AIEgen probes precisely label MTB; ii) low-dose light generates trace ROS that act as molecular scalpels to disrupt bacterial drug-resistance mechanisms, including efflux pumps and high membrane integrity, disarming bacteria; and iii) conventional antibiotics subsequently eliminate the susceptible MTB population.

Integration of PDT and sonodynamic therapy (SDT). Combining PDT with SDT offers a promising alternative to current strategies for addressing deep-tissue infections. In contrast to traditional PDT, SDT leverages the capability of ultrasound to penetrate tissues non-invasively and target specific lesions, such as pulmonary granulomas and deep-seated abscesses. Upon ultrasound activation, SDT induces acoustic cavitation, producing temporary high temperatures, elevated pressure and strong shear forces in target tissues. This mechanism directly disrupts bacterial structures and increases biofilm permeability (93). This approach has exhibited potential in the treatment of TB, providing a robust framework for theranostic applications of PDT-SDT co-treatment in deep-seated lesions (94,95).

Although SDT shows notable promise as a therapeutic strategy targeting TB, it is hindered by low sonosensitizer-mediated ROS production, which reduces the effectiveness of this strategy against bacterial populations (96). To address this challenge, researchers have developed sodium molybdenum bronze nanoplatforms, which leverage the combined effects of SDT and PTT to markedly increase ROS production. This combined treatment strategy has been shown to not only enable the effective eradication of *S. aureus* but also to disrupt biofilms, thus representing an innovative approach for the treatment of deep-tissue bacterial infections (97). These findings underscore the potential of sono-photodynamic combination therapy, which consists of the combined use of ultrasound-activated SDT and light-activated PDT, in treating deep-seated TB infections.

8. Immunomodulation and host response

Phototherapy combines direct bactericidal activity with host immune modulation to treat diseases. Macrophages, as the primary immune defense, help maintain homeostasis by phagocytosing pathogens and secreting cytokines. Upon MTB invasion, macrophages mediate bacterial killing and

initiate adaptive immunity. However, this process involves a dynamic interplay between host bactericidal mechanisms and microbial immune-evasion strategies, allowing persistent MTB infection to occur when macrophages remain immunocompetent (98,99).

Macrophages exhibit diverse functional phenotypes. M1-polarized macrophages exhibit potent antimicrobial and antitumor capabilities. Through ROS production, these immune cells participate in tissue damage, regeneration and repair processes by exerting pro-inflammatory and cytotoxic effects (100). Research has shown that PDT can drive macrophage repolarization from the M2 to M1 phenotype, amplifying the antibacterial immune response of the host. This repolarization is mediated by activation of the NF-κB and ERK/MAPK signaling pathways (101).

Multifunctional PDT nanocomposites exhibit two key advantages compared with traditional PSs: These specific nanocomposites promote the effectiveness of PDT through a self-oxygenating mechanism and simultaneously reduce the population of myeloid-derived suppressor cells (MDSCs) in diseased tissue. This dual function counteracts the MDSC-mediated suppression of T cells and other immune effectors; therefore, these nanocomposites represent a novel therapeutic strategy for treating drug-resistant infections, such as methicillin-resistant *S. aureus* (102). Notably, MTB itself actively promotes the generation and differentiation of MDSCs via secretion of immunogenic protein MPT64, creating an immunosuppressive microenvironment that facilitates immune evasion and persistent infection (103). These findings suggest that therapeutically targeting the MPT64 pathway could restore T-cell functionality in TB and enhance MTB clearance.

The immunomodulatory effects of phototherapy on macrophage polarization are bidirectional in nature. For example, low-dose ALA-mediated PDT promotes a shift in macrophage polarization from the M1 to M2 phenotype (104). A growing body of research has demonstrated that the direct bactericidal effect of combined PDT-PTT represents only the initial phase of phototherapy-induced TB clearance; the subsequent activation of coordinated host immunity, particularly the transition of macrophages from the M1-to-M2 phenotype, plays a critical role in promoting tissue repair and achieving effective eradication of MTB (86,105,106).

In the context of TB, M2 macrophages evade detection by MTB-specific CD4+ T cells, which delays adaptive immunity and creates an early survival niche that facilitates bacterial dissemination. This evasion occurs because M2-like macrophages infected with MTB are poorly recognized by memory CD4+ T cells due to their preferential secretion of IL-10, which suppresses T cell activation and proliferation. Consequently, this impaired recognition delays the adaptive immune response, allowing MTB to establish an intracellular survival niche within these macrophages. Cytokines such as IL-10 further enable M2 macrophages to function as immune decoys, diverting protective T cells from infection sites, and thus, weakening anti-TB immunity (107). These complex interactions between macrophage populations and MTB markedly influence infection outcomes and disease progression (108,109).

Chitosan-based nanoparticles, such as S-nitroglutathione- and indocyanine green-based nanoparticles, represent a promising therapeutic approach for TB by combining PDT and PTT with controlled nitric oxide (NO) release. This multifaceted mechanism effectively eradicates drug-resistant bacteria and biofilms while promoting wound healing in the host (110). NO and other reactive nitrogen species serve an important role in combating both active and dormant MTB; these molecules enhance M1 macrophage polarization and autophagy, improving the efficiency of intracellular pathogen clearance (111).

Overall, future evaluations of antimicrobial therapies must look beyond bactericidal efficacy alone, and should emphasize precise immunomodulation in balanced infection control and tissue repair.

9. Preclinical research and safety evaluation

Prior to clinical application, the safety and anti-TB efficacy of PDT requires systematic evaluation.

In vitro models. These models employ standard MTB strains such as H37Rv to assess the bactericidal efficacy of phototherapy on planktonic bacteria and biofilms. Furthermore, infected macrophage models, such as infected THP-1 or RAW264.7 cells, are utilized to evaluate intracellular bacterial elimination and host cell protection (112).

In vivo models. MTB infection models in mice, guinea pigs and rabbits have been used to simulate granuloma formation and evaluate the therapeutic efficacy of PDT. Studies have shown that phototherapy markedly reduces bacterial burden and improves histopathological outcomes in these models (86,113).

Safety considerations. Safety considerations in the context of PDT focus primarily on phototoxicity, thermal tissue damage and systemic metabolism. An ideal PS should be quickly cleared from the host body to minimize photosensitivity reactions (114-116). Furthermore, precise control of the illumination power and wavelength used in PDT of TB can prevent overheating or oxidative damage to pulmonary tissue (117). Biomimetic targeted delivery strategies, such as macrophage membrane coating, can effectively reduce systemic exposure of the host to PSs (86). Additionally, monitoring inflammatory responses and maintaining immune homeostasis in animal models is important for avoiding host immune dysregulation.

10. Challenges and future directions

PDT shows notable promise for anti-TB treatment; however, several clinical challenges persist. The predominant issue regarding PDT in this context is the inadequate accumulation of PSs in TB lesions, especially in the deeper layers of granulomas (118). However, advancements in sophisticated targeted delivery systems are anticipated to address this problem. Additionally, effective penetration of light into deep lung tissue is limited by the natural absorption and scattering properties of biological tissues (119). This issue is exacerbated by the persistent hypoxic conditions in TB lesions, which hinder oxygen-dependent photodynamic reactions. Another notable

challenge regarding the use of PDT in TB is the lack of standardized therapeutic protocols. Key parameters in PDT such as the photodose, wavelength and treatment duration currently lack universally-accepted guidelines (120). Furthermore, the long-term biosafety and *in vivo* metabolic behavior of PS nanocarriers require thorough investigation (121). The high cost of specialized equipment further restricts widespread adoption of PDT, particularly in low-resource settings (122). Overcoming these complex challenges is important for the practical application and advancement of PDT in anti-TB treatment.

To accelerate the clinical translation of PDT, future investigations should prioritize several strategic directions: First, the design of smart stimuli-responsive materials that can respond to multiple pathophysiological cues, including acidic pH, the activity of specific enzymes and ROS variations, for use in adaptive drug delivery systems. Second, the development of oxygen-independent photodynamic strategies by developing novel PS designs, such as those targeting type I-related photochemical pathways, self-oxygenating nanoplatforms and $^1O_2$ battery materials. Third, systematic investigation of combination strategies for TB treatment, in which PDT is combined individually with chemotherapy, gas therapy, SDT, or immunomodulatory approaches, to determine synergistic therapeutic effects. Fourth, the development of multifunctional theranostic platforms based on emerging PSs with dual-functionality, particularly AIEgens, in order to develop real-time lesional imaging and treatment guidance. Fifth, fostering interdisciplinary collaboration among materials scientists, immunologists and clinicians to create a unified pathway from fundamental phototherapeutic research to clinical application.

11. Conclusions

PDT is emerging as an innovative non-antibiotic treatment strategy for TB, demonstrating potential in exerting notable impacts on disease management. By generating ROS and inducing photoactivated sensitizer-mediated localized hyperthermia, this method has been shown to effectively disrupt mycobacterial membrane integrity (123,124). PDT also serves an important role in preventing biofilm formation and treating intracellular dormant-phase MTB. The benefits of PDT include a low probability of bacteria developing therapeutic resistance, precise spatial and temporal targeting and the ability to modulate the host immune response. These features establish PDT as a promising strategy for eradicating drug-resistant and persistent MTB infections. Previous studies have highlighted the notable potential of this therapeutic strategy, especially regarding advances in rationally-designed PSs, sophisticated delivery techniques and multimodal synergistic approaches (43,118,125).

Despite its promise as a therapeutic strategy for TB, the clinical translation of PDT faces inherent challenges, such as lesion targeting, tissue penetration and treatment standardization, as aforementioned. Future progress with regards to PDT depends on sustained interdisciplinary collaboration in order to develop microenvironment-responsive materials and oxygen-insensitive, integrated theranostic platforms that address these challenges.

In conclusion, PDT represents a promising adjunctive or alternative therapy to conventional antimicrobial agents in the context of TB management. With continued innovation and focused translational work, this technology is well-positioned to contribute to TB control efforts worldwide, which is particularly relevant at present when antimicrobial resistance is of increasing importance (126,127).

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Authors' contributions

SC was responsible for conceptualization of the study and writing the original draft. YW contributed towards conceptualization and supervision of the study, as well as reviewing and editing the manuscript. GC was responsible for literature search, data extraction from published studies, and systematic analysis (investigation and formal analysis). GY was responsible for visualization for preparation of the table. JY, FS and XM contributed towards reviewing and editing the manuscript. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

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Competing interests

The authors declare that they have no competing interests.

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