REVIEW ARTICLE

CONTENTS

Current landscape of photosensitizers in photodynamic therapy: challenges and future perspectives – a literature review

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ABSTRACT

Aim: To provide an updated overview of photodynamic therapy (PDT), emphasizing the evolution of photosensitizers, their mechanisms of action, and current challenges and innovations aimed at improving therapeutic outcomes.

Materials and Methods: A structured literature review was conducted using PubMed, Scopus, and Embase databases to identify studies published between 2000 and 2025. Search terms included photodynamic therapy, photosensitizers, nanoparticles, reactive oxygen species, and drug delivery systems. Experimental studies, clinical trials, and review articles focused on photosensitizer development and applications were analyzed.

Photosensitizers have advanced through three generations. First-generation agents such as Photofrin demonstrated clinical success but were hindered by shallow tissue penetration and prolonged photosensitivity. Second-generation compounds achieved stronger absorption within the therapeutic window (650-800 nm) and higher singlet oxygen yields but encountered solubility and delivery limitations. Third-generation systems integrate targeting ligands or nanocarriers, improving selectivity, bioavailability, and pharmacokinetics. Despite these advances, PDT remains limited by insufficient light penetration, tumor hypoxia, and non-specific toxicity, and is therefore used only in select clinical settings. Recent approaches, such as multifunctional theranostic photosensitizers, gene-encoded PSs, and combination therapies with immunotherapy or chemotherapy, aim to overcome these barriers.

Conclusions: Continued innovation in photosensitizer chemistry, nanotechnology-based delivery, and combination strategies promises to enhance PDT's selectivity, depth, and clinical effectiveness across oncology, dermatology, and infectious disease treatment.

KEY WORDS: photodynamic therapy, nanoparticles, reactive oxygen species, drug delivery systems, photosensitizing agents

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INTRODUCTION

Photodynamic therapy (PDT) is an advanced therapeutic approach that combines three essential components: a photosensitizer (PS), light of a specific wavelength, and molecular oxygen present in tissue [1-2]. The process begins with administration of the photosensitizer, which selectively accumulates in target tissues such as tumors or infected areas. Upon illumination with light of an appropriate wavelength, often in the red spectrum to ensure tissue penetration-the photosensitizer absorbs photons and is excited from its ground singlet state to an unstable excited singlet state [3-5]. This excited state quickly undergoes intersystem crossing to a more stable, longer-lived triplet state, which can then transfer energy directly to molecular oxygen to generate reactive oxygen species (ROS), particularly highly cytotoxic singlet oxygen [6-7]. These reactive molecules induce oxidative damage leading to cell membrane disruption, mitochondrial damage, and DNA damage, which ultimately trigger programmed cell death (apoptosis) or necrosis of the targeted cells. Besides direct cytotoxicity, PDT also disrupts tumor vasculature, causing ischemia, and stimulates an immune response that can further assist in destroying abnormal tissues. This multimechanistic action underpins PDT's clinical relevance across a range of applications including oncology, dermatology, and infectious diseases [7-10].

The role of photosensitizers in PDT is central; they must have selective accumulation in diseased tissues, low dark toxicity, and high phototoxicity upon light activation. Different generations of photosensitizers have been developed over the years to improve therapeutic outcomes. First-generation photosensitizers, such as porfimer sodium, showed efficacy but suffered from limited tissue penetration, prolonged photosensitivity, and less specific targeting. Second-generation PSs were designed to have improved absorption properties and shorter skin photosensitivity duration [11-12]. Third-generation photosensitizers enhance targeting further by conjugation with biomolecules (e.g., antibodies or peptides) or encapsulation in nanoparticles to achieve higher selectivity, deeper tissue penetration, and better pharmacokinetics, reducing off-target effects. Understanding these advancements in photosensitizer technology is crucial for clinicians and researchers to optimize PDT protocols.

AIM

The aim of this review is to provide a comprehensive overview of the photodynamic mechanism, emphasizing the critical role and evolution of photosensitizers, the underlying biochemical reactions leading to cytotoxicity, and their clinical applications. It also discusses the advantages and limitations of current photosensitizer generations and outlines future trends and innovations to enhance the specificity and efficacy of PDT, thereby broadening its therapeutic scope in oncology and beyond.

MATERIALS AND METHODS

A structured literature search was conducted using the PubMed, Scopus, and Embase databases to identify peer-reviewed studies published between January 2000 and April 2025. The search strategy included combinations of keywords and MeSH terms such as "photodynamic therapy", "photosensitizing agents", "photosensitizers", "nanoparticles", "drug delivery systems", "reactive oxygen species", "porphyrins", "chlorins", "phthalocyanines", and "bacteriochlorins". Inclusion criteria comprised experimental studies, clinical trials, systematic reviews, and narrative reviews focusing on the development, mechanisms, and clinical applications of photosensitizers in PDT. Articles without English full-text availability or those unrelated to therapeutic PDT applications were excluded. Reference lists of relevant papers were screened manually to identify additional sources. A total of 39 publications meeting the inclusion criteria were selected and analyzed. Data synthesis followed a narrative review methodology, emphasizing the evolution of photosensitizer generations, classification by chemical structure, advances in nanocarrier-based delivery systems, and future research directions aimed at improving PDT efficacy and clinical translation.

REVIEW AND DISCUSSION

MECHANISM OF PDT AND ROLE OF PHOTOSENSITIZERS

The basic photochemical mechanism of PDT involves two primary pathways of ROS generation known as Type I and Type II photoreactions (Figure 1). Upon light activation, the PS transitions to an excited triplet state and can interact with nearby molecules via these two pathways. In the Type I mechanism, the excited PS undergoes electron or hydrogen atom transfer reactions with substrate molecules, leading to the formation of radical species and radical ions such as superoxide anion ($O_2^{\bullet -}$), hydroxyl radicals (HO^-), and hydrogen peroxide (H_2O_2) [13-14]. These reactive radicals cause oxidative damage leading to cell death. In contrast, the Type II mechanism involves direct energy transfer from the excited triplet PS to ground-state molecular oxygen ($^3O_2$), producing highly cytotoxic singlet oxygen ($^1O_2$). Singlet oxygen is considered the main cytotoxic agent in PDT as it rapidly reacts with cellular components like lipids, proteins, and nucleic acids within a very short diffusion distance, inducing cell damage and death. Both pathways can occur simultaneously, but PDT efficacy often relies primarily on the Type II pathway, especially under normoxic conditions [15]. However, Type I pathways can dominate in hypoxic environments, relevant in many tumor tissues, supporting PDT efficacy despite limited oxygen availability.

Key characteristics of an ideal photosensitizer for effective PDT include selective accumulation within target tissues to minimize damage to healthy cells and high quantum yield of singlet oxygen generation to maximize therapeutic effect. Photostability is essential to withstand repeated light exposure without degradation, ensuring consistent ROS formation. Low dark toxicity ensures that the PS is non-toxic in the absence of light, enhancing safety. Additionally, an ideal photosensitizer should absorb light strongly within the therapeutic window of absorption of light at red or near infrared wavelengths 650-800 nm, where tissue penetration of light is optimal, allowing treatment of deeper lesions. These properties collectively enable targeted, efficient, and safe photodynamic treatment. Understanding these mechanistic and molecular

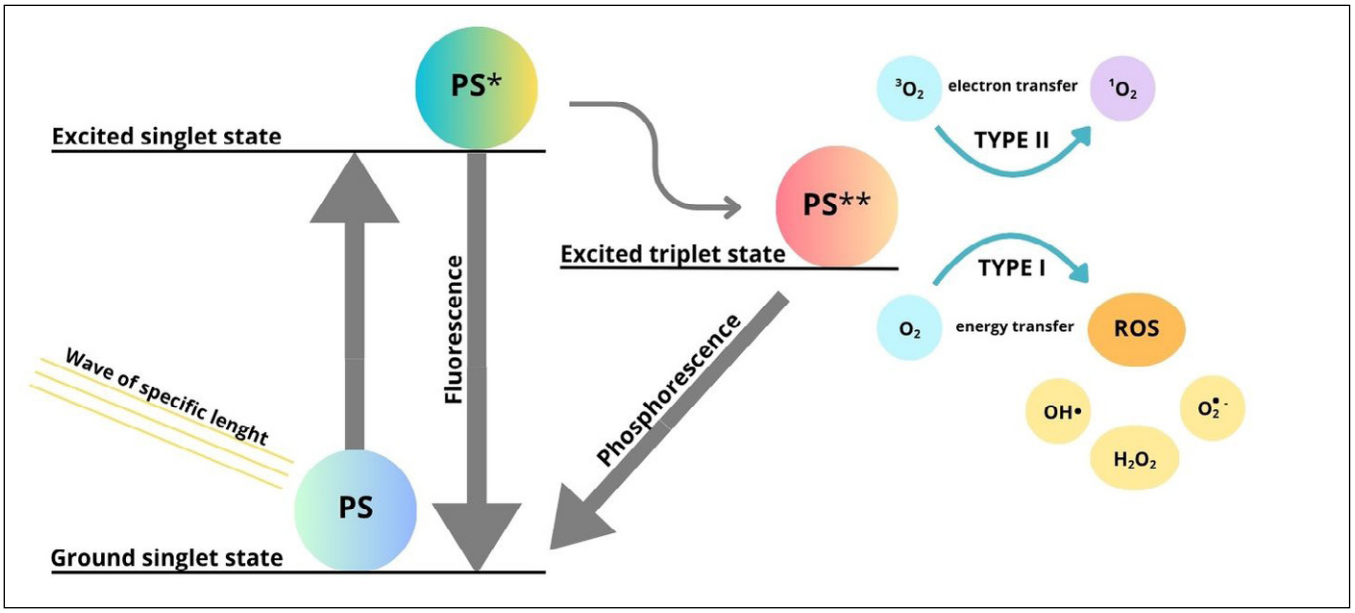

Fig. 1. Photodynamic reaction. PS – photosensitizer
Source: Authors' own work

Table 1. Examples of photosensitizers based on generations.

Photosensitizer generation	Examples
1st generation	• Hematoporphyrin (Hp); • Hematoporphyrin derivative Photofrin® (HpD).
2nd generation	• Phorphyrins: benzoporphyrin derivatives, texapyrin, 5-aminolevulinic acid (5-ALA); • Chlorins: talaporfin sodium, temoporfin - Foscan®; • Phthalocyanines; • Thiopurine derivatives; • Bacteriochlorin analogues.
3rd generation	1st or 2nd generation photosensitizer: • combined with molecules targeting specific cancer cell receptors; • combined with LDL lipoproteins; • conjugated with monoclonal antibodies directed against specific antigen or tumour surface markers (e.g. growth factor receptors, transferrin).

Source: Authors' own work

considerations guides the design and application of photosensitizers to improve PDT outcomes in clinical settings [16-20].

CLASSIFICATION OF PHOTOSENSITIZERS

BASED ON GENERATIONS

PSs used in PDT are classified into three main generations based on their chemical properties, clinical history, and advancements in targeted delivery technologies (Table 1). The 1st generation photosensitizers were naturally occurring porphyrins, such as hematoporphyrin (Hp) and its derivative Photofrin® (HpD), a water-soluble mixture of porphyrin dimers and oligomers, also known as sodium porfimer. HpD and its commercial product Photofrin® was first introduced for clinical use on a commercial scale in the 1970s by Dougherty et al., and remains one of commonly used PS [7, 21]. They offer the advantage of well-documented safety profiles and established clinical protocols; however, their use is limited by prolonged skin photosensitivity resulting from high skin accumulation and the long half-life of the photosensitizer, as well as by suboptimal tissue penetration due to absorption at shorter light wavelengths (~630 nm) and non-specific accumulation in both healthy and diseased tissues [20, 22-24]. These limitations often lead to side effects and restrict treatment depth. Consequently, as early as the 1980s, studies on the next generation of photosensitizers were initiated.

2nd generation photosensitizers include structurally well-defined compounds such as porphyrins (e.g., benzoporphyrin derivatives, texaphyrin, and 5-ami-

nolevulinic acid); chlorins (e.g., talaporfin sodium and temoporfin); phthalocyanines; thiopurine derivatives; and bacteriochlorin analogues [7, 21]. These agents have enhanced photophysical properties, including stronger absorption peaks in the near-infrared region (around 650-800 nm), which allows deeper tissue penetration due to reduced light scattering and absorption by endogenous chromophores [24]. Additionally, they exhibit higher singlet oxygen quantum yields, which improve therapeutic efficacy, and demonstrate fewer side effects due to greater selectivity for cancerous tissues and faster elimination from the body [20]. 5-aminolevulinic acid (5-ALA) is currently one of the most commonly used photosensitizers. It is a prodrug that is endogenously converted into protoporphyrin IX (PpIX), which becomes activated upon stimulation with light at a wavelength of 630-650 nm [21, 25]. PpIX accumulates mainly in mucous membranes, enabling selective destruction of epithelial cells while sparing deeper tissues. Owing to its oral or topical administration and rapid clearance from healthy tissues, 5-ALA minimizes photosensitivity and is widely used in clinical practice [23, 26]. However, many second-generation PSs are hydrophobic, complicating their solubility and systemic delivery, which presents challenges for clinical translation and forces the search for new methods of drug delivery [20, 27].

3rd generation photosensitizers are characterized by enhanced selectivity for cancer cells while minimizing accumulation in healthy tissues, thereby reducing collateral damage. They are build upon prior generations by incorporating targeting moieties such as antibodies, peptides, or ligands that enable selective binding to specific cellular markers expressed preferentially on tumor or pathogenic cells. This generation also utilizes advanced drug delivery systems including nanocarriers like liposomes, micelles, dendrimers, and nanoparticle conjugates to enhance PS solubility, stability, and selective accumulation within diseased tissues. These strategies markedly enhance tumor selectivity, minimize off-target effects, and reduce systemic toxicity [15-24]. Examples include photosensitizer conjugates with monoclonal antibodies targeting specific antigens or tumor surface markers, complexes with molecules that recognize cancer cell receptors, low-density lipoproteins (LDL), or nanoparticle-based delivery systems, all representing the forefront of precision photodynamic therapy (PDT) technologies. This classification highlights the evolution of photosensitizer development aimed at overcoming the limitations of earlier generations by improving selectivity, tissue penetration, and overall therapeutic index in clinical applications [21, 27, 28].

BASED ON CHEMICAL STRUCTURE

Porphyrins and their derivatives are a fundamental class of photosensitizers in PDT, characterized by a tetrapyrrolic macrocycle structure capable of efficient light absorption and reactive ROS generation [20, 24, 29]. Clinically, porphyrins like Photofrin and hematoporphyrin derivatives (HpD) have been extensively used for treating various cancers, including those of the lung, esophagus, skin, and brain. Their mechanism involves selective uptake by tumor cells and vascular tissues, followed by light activation inducing oxidative damage leading to tumor cell death. Case studies have shown effectiveness in improving prognosis in cerebral gliomas and various carcinomas, although challenges such as prolonged skin photosensitivity and limited light penetration necessitate advancements in PS development [22-24].

Chlorins, such as talaporfin sodium, represent a second-generation photosensitizer subclass with enhanced absorption properties in the near-infrared region, around 660-700 nm, which allows for deeper tissue penetration compared to porphyrins. Talaporfin has been used effectively in clinical settings, particularly for lung cancer and brain tumors, due to its favorable photophysical and pharmacokinetic profile [23, 24].

Phthalocyanines exhibit strong absorption in the 670-700 nm range and are promising for deeper tissue treatment due to this property. Their chemical stability and high singlet oxygen quantum yield contribute to their effectiveness in PDT, although their hydrophobic nature often requires delivery strategies to improve solubility and targeting [20, 24, 29].

Bacteriochlorins absorb even further into the near-infrared, enabling deeper tissue penetration, which is advantageous for treating larger or more deeply situated tumors. Their structural modifications have enhanced their photostability and ROS generation capacity [24, 30].

Natural product-based photosensitizers, such as hypericin and curcumin, offer biocompatibility and exhibit photodynamic activity, with ongoing research exploring their therapeutic potential and combinational uses [3, 8, 10, 31].

Novel synthetic photosensitizers, including aza-BODIPY derivatives, are designed to combine high photostability, targeted delivery, and absorption in the therapeutic window, aiming to overcome limitations of earlier generations and expand the clinical utility of PDT through tailored chemical and photophysical properties. This diverse range of photosensitizers reflects the evolving landscape of PDT, where structural modifications and delivery technologies continue to enhance efficacy and safety profiles across various clinical applications [11, 20, 23, 24].

DELIVERY STRATEGIES FOR PHOTOSENSITIZERS

Nanoparticle-based systems have emerged as revolutionary carriers for PS in PDT, addressing challenges associated with PS solubility, stability, and selective delivery [11, 22]. Common nanocarriers include liposomes, polymeric nanoparticles, and gold nanoparticles, each offering unique advantages. Liposomes enhance PS bioavailability and reduce systemic toxicity by encapsulating hydrophobic PSs in a biocompatible lipid bilayer. Polymeric nanoparticles provide controlled release and surface functionalization possibilities, improving pharmacokinetics [20, 22, 23]. Gold nanoparticles offer excellent biocompatibility, surface plasmon resonance properties for enhanced photodynamic effects, and facile conjugation with targeting molecules. Targeted delivery is achieved by functionalizing nanoparticles with ligands or antibodies that specifically recognize tumour biomarkers or microenvironment features, enabling selective accumulation in diseased tissues while sparing healthy cells [23]. This active targeting significantly improves therapeutic efficacy and reduces side effects compared to conventional PS administration. Stimuli-responsive systems are advanced nanoparticle platforms designed to release or activate PSs in response to specific physiological triggers such as acidic pH, redox conditions, or enzyme presence in the tumour microenvironment [11, 18]. This on-demand release enhances spatial and temporal control over PDT, further minimizing off-target effects. Despite these advantages, nanoparticle systems face challenges related to pharmacokinetics and biodistribution, including potential reticuloendothelial system clearance, non-specific uptake by healthy organs, and complex in vivo behaviour that complicates dose optimization [20, 22]. Overcoming these hurdles requires careful design of nanoparticle size, surface charge, and coating to maximize circulation time and tumour accumulation. Overall, nanoparticle-based delivery systems represent a promising frontier in PDT by improving photosensitizer performance, targeting precision, and therapeutic outcomes while addressing inherent limitations of traditional photosensitizer formulations.

CLINICAL INDICATIONS AND BARRIERS TO BROADER IMPLEMENTATION

Although photodynamic therapy is widely recognized in dermatology, its clinical utility extends well beyond cutaneous applications and includes several oncological indications in which PDT has been incorporated into treatment algorithms or acknowledged in clinical recommendations. According to contemporary practice guidelines and expert panels, PDT is used in selected cases of early central lung cancer, superficial esophageal neoplasia, and high-grade gliomas, where the tumor is anatomically accessible and light delivery is feasible [20, 22, 24, 31]. In early central non-small cell lung cancer limited to the bronchial mucosa, Photofrin®-based PDT is an accepted option for patients unsuited to surgery or radiotherapy, and may be used as stand-alone therapy or palliatively to restore airway patency [22, 24]. In esophageal high-grade dysplasia and early superficial cancer, PDT provides local eradication when endoscopic resection is incomplete or contraindicated, functioning primarily as monotherapy in mucosal disease [32, 33]. In neuro-oncology, PDT serves as an adjuvant intraoperative modality: 5-ALA enables fluorescence-guided resection with subsequent photoactivation, while talaporfin sodium PDT is approved in Japan for recurrent gliomas, improving local control in selected patients [7, 23]. Across these clinical settings, PDT offers organ preservation, repeatability, and minimal systemic toxicity, making it a meaningful therapeutic tool when conventional options are limited or contraindicated.

Despite its therapeutic potential, PDT is not widely available in routine oncological practice, even in healthcare systems that could theoretically support its cost. Several barriers limit broader implementation. First, PDT requires specialized equipment, including lasers with specific emission wavelengths and dedicated light-delivery systems such as bronchoscopic or neurosurgical fibers, which increases infrastructure requirements [31, 34]. Second, expertise is center-dependent, as successful PDT relies on precise dosimetry, timing between photosensitizer administration and illumination, and operator experience. Third, the limited penetration depth of light (1–2 cm) restricts its use to tumors located near epithelial surfaces or accessible endoscopically, making many deep-seated lesions unsuitable for treatment [22, 24, 35]. Additionally, tumor hypoxia, common in advanced malignancies, reduces ROS generation and may diminish treatment efficacy, creating another physiological limitation [19, 22]. These factors explain why PDT, although promising, remains reserved for specific clinical scenarios rather than being a universally applied oncologic modality.

ADVERSE EFFECTS AND SAFETY PROFILE

Photodynamic therapy (PDT) is generally considered safe, with adverse effects dependent on the photosensitizer, anatomical site, and illumination parameters. The most frequent systemic reaction is photosensitivity, particularly after first-generation porphyrins such as Photofrin®, which may require prolonged light avoidance

due to slow drug clearance [20, 23, 24]. Newer agents, including 5-ALA, temoporfin, and talaporfin sodium, demonstrate faster elimination and a markedly lower risk of prolonged phototoxicity [21, 25, 26].

Local reactions vary by treatment site: airway PDT may cause transient edema, dyspnea, cough, or necrotic debris retention [22, 24]; esophageal PDT can induce short-lasting odynophagia, chest discomfort, or mucosal ulceration, while strictures remain uncommon with proper dosimetry [32, 33]. In neurosurgical applications, 5-ALA and talaporfin sodium may lead to localized edema or transient neurological worsening, though serious events are rare when illumination is correctly targeted [7, 23].

Pain during or shortly after illumination is common due to ROS-mediated inflammatory responses [15, 20]. Mild erythema, swelling, or superficial necrosis may also occur at the illumination site. Importantly, PDT causes minimal systemic toxicity because its effects are restricted to light-exposed tissues, distinguishing it from chemotherapy and radiotherapy [20, 23, 24, 31].

Overall, PDT has a favorable safety profile, and its adverse effects are typically predictable, self-limiting, and manageable. These considerations guide patient selection and partly explain the selective, rather than widespread, use of PDT across medical fields.

CHALLENGES AND LIMITATIONS

Photodynamic therapy faces several notable challenges and limitations that impact its clinical effectiveness. A primary limitation is the restricted light penetration depth in tissues; visible and near-infrared light used to activate photosensitizers generally penetrates only a few millimetres to about 1-2 cm, depending on tissue type and wavelength [22]. This restricts PDT efficacy in treating deep-seated tumours, as deeper tissues receive insufficient light energy for effective photosensitizer activation [20, 22-24, 35]. Although longer wavelengths near the therapeutic window (650–800 nm) improve penetration, scattering and absorption by endogenous chromophores still limit treatment depth [22]. Tumour hypoxia poses another significant challenge because PDT relies on molecular oxygen to create reactive ROS that mediate cytotoxicity. Hypoxic tumour microenvironments reduce ROS generation, diminishing PDT efficacy, especially in aggressive or late-stage tumours with poor vascularization [19]. Strategies to overcome this include oxygen delivery systems and combining PDT with therapies altering tumor oxygenation [18, 22]. Off-target effects and phototoxicity result from non-specific photosensitizer accumulation in healthy tissues, leading to undesired damage upon light exposure. Patients often require strict light avoidance post-treatment to prevent skin photosensitivity and related adverse effects, impacting quality of life [20, 23]. Finally, cost and scalability issues arise with novel photosensitizers and advanced delivery systems such as nanoparticles. Manufacturing complexity, regulatory hurdles, and high production costs can limit widespread adoption and accessibility in clinical practice [20, 22-24, 29]. Addressing these challenges requires continued innovation in photosensitizer design, light delivery technologies, and combinational therapeutic approaches to enhance PDT specificity, depth, and overall therapeutic index.

FUTURE PERSPECTIVES

Future perspectives in photodynamic therapy focus on developing multifunctional photosensitizers known as theranostic agents, which combine therapeutic and diagnostic capabilities for improved treatment monitoring and personalization [11, 22, 34]. These advanced PSs can simultaneously enable imaging and targeted therapy, enhancing precision in treatment delivery [32]. Combination therapies are also a major frontier. PDT is increasingly integrated with immunotherapy to boost antitumor immune responses by inducing immunogenic cell death and modifying the tumor microenvironment to a more immune-active state [20, 34]. Clinical and preclinical studies show synergistic effects when PDT is combined with immune checkpoint inhibitors, adoptive cell therapies, or immunoadjuvants [33]. Furthermore, PDT combined with chemotherapy or photothermal therapy augments efficacy by attacking tumors through complementary mechanisms, addressing limitations like hypoxia or resistance [36]. Advances in targeted nanotechnology enable precise delivery of PSs and combination agents through stimuli-responsive, ligand-targeted, or biomimetic nanoparticles, offering spatiotemporal control over therapy [11, 18, 23]. Gene-encoded photosensitizers represent a novel approach whereby PSs are produced intracellularly, potentially allowing for highly specific and controlled PDT in targeted cells [37, 38]. Personalized PDT approaches are envisioned through integrating patient-specific tumor biology, molecular imaging, and real-time dosimetry to tailor PS selection, light dose, and combinatorial regimens for maximal efficacy with minimal side effects [11, 22]. Collectively, these developments aim to overcome current PDT limitations and broaden its therapeutic impact by combining modality synergies, enhancing targeting precision, and individualizing treatment paradigms for diverse cancers and other diseases [39].

CONCLUSIONS

In conclusion, photodynamic therapy (PDT) represents a highly versatile and evolving modality that leverages the unique properties of photosensitizers to selectively target diseased tissues through light-activated cytotoxicity mediated by reactive oxygen species. The continuous development from first- to third-generation photosensitizers has markedly enhanced selectivity, tissue penetration, and therapeutic efficacy while reducing adverse effects such as prolonged photosensitivity and off-target toxicity. Advances in nanoparticle-based delivery systems and targeting strategies further optimize PS bioavailability and tumor specificity, overcoming key pharmacokinetic challenges. Despite inherent limitations like light penetration depth and tumor hypoxia, ongoing innovations in multifunctional theranostic agents, combination therapies integrating immunotherapy or chemotherapy, and personalized dosimetry herald a new era of precise, effective PDT treatments. The potential of third-generation photosensitizers and emerging nanotechnologies is particularly promising for expanding PDT's clinical applicability across oncology and beyond, offering hope for improved patient outcomes with minimized side effects. Continued interdisciplinary research and clinical translation are essential to fully harness PDT's capabilities and address current challenges in the rapidly advancing landscape of photodynamic therapy.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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