



Can Artificial Intelligence Enhance the Antimicrobial Effectiveness of Photodynamic Therapy? What We Know and What We Do Not Know?

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Abstract

Introduction: This review examines the question, “Can artificial intelligence enhance the antimicrobial effectiveness of photodynamic therapy (PDT)?” We discuss current knowledge and uncertainties surrounding this topic, address the limitations of existing approaches—such as the complexities of predicting reactive oxygen species generation and the necessity for large datasets for AI training—and propose future strategies that integrate AI with PDT.

Methods: In the present literature review, the authors used keywords such as Antimicrobial photodynamic therapy, Photosensitizers, and Artificial intelligence, and conducted a literature search via Google Scholar and PubMed from January 2000 to November 2024.

Results: The reviewed literature indicates that AI has been used to enhance antimicrobial therapy by identifying optimal photosensitizers, predicting treatment outcomes, and enabling real-time monitoring. In antimicrobial PDT (aPDT), AI facilitates personalized therapy by selecting appropriate agents and light parameters based on microbial profiles, although clinical implementation remains limited.

Conclusion: While the combination of AI and PDT is theoretically possible, it has not yet been implemented. Consequently, this article may serve as a foundation for future research on personalizing laser-based treatments through AI.

Keywords: Antimicrobial photodynamic therapy; Photosensitizers; Artificial intelligence; Microbial infections; Internet of things.



Introduction

Photodynamic therapy (PDT) is based on a non-thermal photochemical reaction that requires three essential components: light-sensitive compounds known as photosensitizers (PSs), oxygen, and visible light. While PDT is primarily utilized for cancer treatment, it also shows promise in combating microbial infections. Given the rising challenge of antimicrobial resistance, there is a critical need to develop new antimicrobial therapies. The term “antimicrobial PDT” or “aPDT” highlights the antimicrobial capabilities of this technique. In aPDT, PSs are applied topically at the infected site, followed by exposure to visible light, which induces photobiological inactivation of microorganisms.^{1,2} This method can selectively target and destroy various microbial cells, including bacteria, fungi, and viruses, thereby facilitating the elimination of infections.³

In recent years, artificial intelligence (AI) has increasingly been utilized across various fields, including microbiology, structural modeling of biomolecules, genomic research, drug discovery and development, and medical data analysis. AI is currently assisting in clinical

decision-making and disease monitoring, with promising applications in genomic information analysis and handling large digital datasets. By harnessing advanced algorithms, machine learning (ML), and deep learning (DL) techniques, AI can enhance disease diagnosis, predict outbreaks, and personalize medical treatments for individual patients.^{4–9} These advancements have led us to consider that AI-based aPDT could enhance the efficiency of traditional aPDT by personalizing its parameters. Our research has found that no studies have yet explored the practicality and feasibility of combining AI with aPDT. We believe that integrating these methods could offer benefits that maximize antimicrobial effects while minimizing potential side effects.

One primary advantage of AI-based aPDT that we predict lies in its ability to generate accurate predictions and optimize treatment plans.¹⁰ Conventional aPDT approaches often rely on generalized parameters and assumptions, which may not account for the unique characteristics of individual patients or microbial strains.¹¹ AI algorithms, on the other hand, can process vast amounts of clinical and experimental data, leading to personalized

treatment recommendations that better align with the specific needs of patients.¹² Moreover, AI algorithms can also enhance the efficiency of aPDT by expediting the identification of optimal PSs for specific antimicrobial applications. Through AI-powered computational models, an extensive range of PSs can be computationally evaluated, reducing the time-consuming and costly trial-and-error process associated with discovering effective PSs through conventional methods.¹³ AI-driven analysis can identify novel compounds with superior antimicrobial properties,¹⁴ leading to the development of more potent and targeted aPDT approaches. Additionally, by integrating AI with imaging techniques, such as fluorescence microscopy and spectroscopy, the progress of aPDT and its impact on microbial cells can be continuously assessed. AI algorithms can analyze the acquired data in real-time, providing clinicians with immediate feedback on the treatment's efficacy and enabling adjustments, if necessary, during the ongoing session.¹⁵

This review examines the question, "Can artificial intelligence enhance the antimicrobial effectiveness of PDT? What do we know, and what do we not know?" We discuss current knowledge and uncertainties surrounding this topic, address the limitations of existing approaches—such as the complexities of predicting ROS generation and the necessity for large datasets for AI training—and propose future strategies that integrate AI with PDT.

The Rise of AI in aPDT

The aPDT is a cutting-edge therapeutic approach that harnesses the power of light and photosensitizing agents to combat microbial infections.¹⁻³ This innovative technique offers a promising alternative to traditional antimicrobial treatments, such as antibiotics, with the advantage of reduced antibiotic resistance development. However, there are few examples, mainly related to the formation of mutants that can neutralize reactive oxygen species. AI can predict random mutations using AI technologies based on multimodal integration (MMI) to advance precision oncology.¹⁶

The process of predicting gene mutation status based on AI technologies, known as MMI, typically involves four main steps:

- *Multimodal data curation:* Multimodal data preparation involves selecting tumor patients whose molecular characteristics have been clearly identified using methods such as ARMS-PCR, next-generation sequencing (NGS), or immunohistochemistry. Imaging data, including radiological scans, are extracted from PACS, while histopathological whole-slide images are obtained through digital scanning.
- *Feature extraction and selection:* Hand-crafted approaches and DI methods extract multimodal features from the data.
- *Model building and validation:* Prediction models are

constructed using ML or non-linear methods, and model performance is validated using metrics such as the area under the receiver operating characteristic curve, accuracy, specificity, and sensitivity, often evaluated with 95% confidence intervals.

Genotypic prediction and in-depth exploration output:

The final step involves predicting the mutation status in probabilistic or binary (positive, negative) form, which can be used to estimate patient prognosis and treatment response and to explore gene synergistic mechanism correlations. The difference between hand-crafted approaches and DL methods lies in the former requiring manual annotation and being more interpretable. At the same time, the latter autonomously analyzes features and trains neural networks for various tasks. Jamal et al¹⁷ used AI and ML to predict resistant and susceptible point mutations in *Mycobacterium tuberculosis* with an accuracy ranging between 66.66%-100%. A novel approach leveraging the AlphaFold framework has demonstrated high accuracy in identifying protein mutations that are potentially linked to disease. Typically, mutation prediction poses a significant challenge due to the fact that numerous known and unknown variables are involved and mutations are often treated as stochastic events. Nevertheless, artificial intelligence offers the capability to establish a cause-to-mutation association model, where the contributing factors are used as inputs, and the resulting mutation—whether defined by its location or altered amino acid—is modeled as the output.¹⁸

The fundamental principle behind aPDT involves a precise interplay of light, PS, and molecular oxygen, which collectively targets and eliminates a wide range of microorganisms, including bacteria, viruses, and fungi.¹⁹ Taken together, several factors have been identified as important in improving the effectiveness of the treatment. Some of these factors include:

PSs properties: The intrinsic capacity of some PSs to preferentially accumulate in cancer cells can contribute to the selectivity of aPDT.²⁰ Increasing the hydrophilic properties of PSs has been shown to improve selectivity and efficacy.²¹

Membrane binding: Photodynamic efficacy is directly proportional to the membrane binding of PSs, indicating that favorable membrane interactions are a key factor for achieving high selectivity and efficacy.²²

Light delivery: The absorbance spectrum is crucial for effective aPDT, as it determines the efficiency of light absorption by the PS. Optimizing the light delivery process can help improve the selectivity and efficacy of the treatment.²⁰

Type of photo-induced cell death: The impact of the type of photo-induced cell death on the clinical outcome of aPDT has been recognized. aPDT with low light fluency rates, which predominantly cause apoptotic cell death, minimizes side effects, improves tumor control, and

reduces treatment-related morbidity.²³

Multimodal clinical data: Developing models that can predict the outcome of aPDT using multimodal clinical data can help improve the selection of appropriate cases for treatment and enhance the overall efficacy of the therapy. Despite the lack of established treatment guidelines for certain conditions, such as chronic central serous chorioretinopathy,²⁴ aPDT is considered safe and effective. However, the unpredictable outcomes and the invasive nature of the treatment make it essential to continue researching and developing strategies to improve the selectivity and efficacy of aPDT.

Role of AI in the Identification of New PSs or Antimicrobial Agents

AI can optimize the dosage and timing of aPDT by performing virtual screening of vast chemical libraries to predict the potential of compounds to act as PSs or antimicrobial agents. ML models, such as DL or molecular docking, can analyze chemical structures and predict their binding affinity to microbial targets.²³ AI can aid in the design of novel PS molecules by using generative models, like generative adversarial networks or recurrent neural networks, to generate new chemical structures with desired properties.²⁵ AI can analyze existing structure-activity relationship data to identify patterns and relationships between molecular structures and antimicrobial efficacy, guiding the modification of existing compounds to enhance their performance.^{26,27} AI-driven robotics and automation can facilitate high-throughput screening of potential PSs and antimicrobial agents, rapidly testing numerous compounds for their activity against specific pathogens. AI can mine large datasets of chemical and biological information to discover potential PSs or agents, using natural language processing techniques to extract relevant information from scientific literature, patents, and databases.²⁸ ML models can be trained on known PS or antimicrobial agent data to predict the efficacy of new compounds, considering various chemical properties, structural features, and biological interactions.²⁸ AI can optimize compounds for multiple objectives simultaneously, such as antimicrobial activity, biocompatibility, and photostability, ensuring that the resulting agents are well-suited for aPDT. AI algorithms can continually improve their predictions as more experimental data become available, leading to more accurate identification of effective PSs or agents over time. AI can explore the synergistic effects of combining PSs with other treatment modalities, such as antibiotics or immunotherapies, to enhance antimicrobial activity.²⁹ AI can assess the safety and potential toxicity of newly identified compounds, ensuring that they are suitable for clinical use. By harnessing AI for these purposes, researchers and pharmaceutical companies can accelerate the discovery and development of PSs and antimicrobial

agents that are more effective in aPDT, ultimately improving the outcomes of aPDT for various infections.³⁰

AI systems can enable precise delivery of PSs to microbial cells. Modified PSs can be tailored to bind specifically to bacteria or biofilms, increasing the accuracy of aPDT and reducing harm to healthy cells. AI can design devices for precise light delivery in aPDT, ensuring that PSs are activated only where intended, optimizing treatment while minimizing unintended damage.¹³ Integrating nanoscale sensors into aPDT systems allows continuous monitoring of treatment progress, enabling adjustments based on real-time feedback to enhance efficacy.³¹

AI can also be utilized for the controlled release of drugs,³² allowing gradual dispersion of PSs at the infection site, ensuring a sustained antimicrobial effect. In the context of treating local infections, some PSs, such as curcumin, have intrinsic antimicrobial properties, and their continuous release at the site of infection may be accompanied by an antimicrobial effect. Of course, it should be mentioned that such PSs in the concentrations used for aPDT usually have a limited antimicrobial effect. AI's capacity to integrate aPDT with other antimicrobial approaches can synergistically enhance overall treatment effectiveness. AI-driven aPDT can contribute to mitigating antimicrobial resistance by employing diverse mechanisms and targeting specific microbial structures or pathways. Additionally, AI coupled with imaging techniques can visualize PS distribution, monitor ROS production, and assess treatment effectiveness in real-time. The incorporation of AI into aPDT holds promise for precision, efficiency, and adaptability, ultimately improving its effectiveness in combating microbial infections while minimizing potential side effects.³³ A summary of how AI can contribute to this field is presented in [Figure 1](#).

Monitoring aPDT Using AI

Recent progress in PSs, illumination sources, and light delivery techniques has contributed to reduced treatment durations and minimized tissue phototoxicity in aPDT, thereby facilitating its broader adoption in clinical practice. Despite these advancements, further refinement is required to standardize treatment parameters—particularly PS and light dosages—and to develop reliable quantitative tools for planning aPDT dosimetry and tracking therapeutic responses. Accurate measurements of factors such as PS concentration, tissue optical properties, blood perfusion, and oxygenation are essential for conducting effective dosimetry, monitoring treatment response, and evaluating clinical outcomes.^{34,35} Continuous monitoring is important in aPDT to optimize treatment delivery parameters, improve aPDT effect, decrease collateral healthy tissue damage, and improve cosmetic outcomes. There are two classes of aPDT dosimetry: explicit and implicit. Explicit dosimetry is a dynamic and difficult

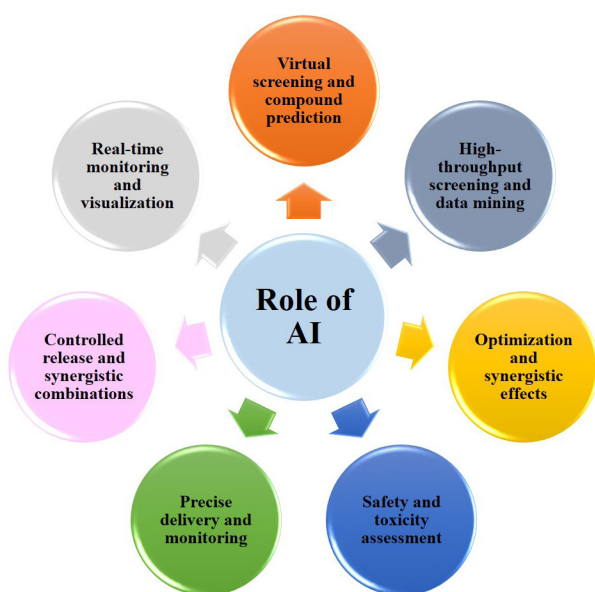


Figure 1. Role of Artificial Intelligence in the Identification of New Photosensitizers or Antimicrobial Agents in the Antimicrobial Photodynamic Therapy Process

problem due to the complicated interaction between light, PS, and microenvironment of the involved tissue. Implicit dosimetry, on the other hand, uses photobleaching of the PS or singlet oxygen luminescence monitoring.³⁶

Generation of Treatment Data and Microbial Reactions

Treatment data included several variables investigating the first course of treatment after diagnosis by using the following variables:

- Tissue debridement (including surgical debridement, autolytic debridement, enzymatic debridement, and mechanical debridement);
- Systemic antibiotic therapy;
- Local antibiotic therapy;
- Local antiseptic application;
- Wound dressings;
- Antimicrobial wound dressings;
- Medicated dressings (including growth factors).

All variables were recorded with yes, no, or unknown.

Data are submitted to an Excel sheet, checked for consistency and harmonized using Data Quality Check Software (QCS), and analyzed with Stata and SAS statistical software.³⁷

Recently, it has been revealed that DNA aptamers hold promise for preferentially targeting and destroying microbes while sparing mammalian cells, offering potential applications in the development of novel antimicrobial therapies. DNA aptamers are short, single-stranded DNA molecules that can bind to specific target molecules with high affinity and specificity. Furthermore, the structural flexibility and small size of aptamers enable precise recognition of cellular elements, which can be leveraged for preferential targeting of microbial cells over

mammalian cells. Research has demonstrated the potential of DNA aptamers in targeting pathogenic microorganisms. Recently, Pourhajibagher et al³⁸ demonstrated that aPDT using DNA-aptamer-nanographene oxide as a targeted bio-theragnostic system is a promising method for detecting and eliminating *Porphyromonas gingivalis*, a main bacterium involved in periodontitis, in real time and in situ. While the targeted aPDT using a PS-DNA aptamer complex for the preferential destruction of microbes is an area of ongoing research, the potential of aptamers in targeting specific pathogens, such as bacteria and protozoa, has been recognized.³⁹

Gradual Delivery of Photosensitizers to an Infection Site

In recent years, notable advancements have been made in engineering innovative biomaterials—including nanoparticles, microparticles, hydrogels, and microneedles—that enable precise, targeted drug delivery to specific tissues. It has become increasingly clear that employing sustained-release systems to preserve therapeutic drug levels over prolonged durations can significantly improve treatment efficacy, persistence, and overall therapeutic outcomes.

Among the essential roles of polymer-based drug delivery platforms is the controlled, prolonged release of PSs. A range of biodegradable polymers, such as poly (glycolic acid) (PGA), polylactic acid (PLA), poly-β-benzyl-L-aspartate (PBLA), and poly (lactic-co-glycolic acid) (PLGA), have been formulated. These materials gradually degrade via hydrolysis of their ester linkages, allowing for the continuous release of encapsulated PSs over time. A recent in vitro and in vivo investigation by Pourhajibagher et al⁴⁰ demonstrated the potential of a curcumin-nisin-loaded poly(L-lactic acid) nanoparticle system for antimicrobial photo-sonodynamic therapy in managing burn wound infections. Their UV-absorbance findings showed that approximately 20–40% of the total CurNis content was released in a rapid initial burst during the first hour, followed by a sustained release of nearly 80% over a 14-day period.

Prediction of the pharmacokinetics of Photosensitizers Using AI

AI in different ways, including DL and ML algorithms, is increasingly being used to predict the ADMET (absorption, distribution, metabolism, excretion, and toxicity) processes of drugs such as PSs. By integrating multi-omics data, including genomics, transcriptomics, proteomics, and metabolomics, with pharmacokinetic and toxicological models, AI enables more accurate and holistic predictions regarding a drug's metabolism, organ-specific distribution, and potential toxicity. This synergy enhances our understanding of the molecular foundations governing ADMET behavior and contributes to the creation of more reliable predictive systems.^{41–43}

Additionally, the integration of organ-on-a-chip (OoC) platforms with AI has shown considerable potential in assessing drug responses at the organ level. AI further supports the development, optimization, and operational control of OoC devices, as well as the analysis and interpretation of complex datasets, thereby broadening the practical applications of this emerging technology.⁴⁴

While AI holds promise in the discovery, evaluation, and development of drugs and personalized medicine, it is important to note that there are still challenges and limitations in fully realizing its impact in this field.⁴⁵

Prediction of the Safety and Toxicity of Photosensitizers Using AI

AI and ML are playing an increasingly prominent role in advancing safety and toxicology research. These methods are being utilized across various stages of drug development and safety assessment—including preclinical testing, post-marketing monitoring, and investigations into cellular toxic responses such as DNA damage and oxidative stress.⁴⁶ Deep learning architectures, particularly convolutional neural networks, have shown effectiveness in forecasting toxic effects by analyzing cellular images following drug exposure, successfully capturing diverse toxicity signatures across different compounds, staining techniques, and cell types.⁴⁷ Additionally, AI-based strategies have facilitated the rapid construction of physiologically based pharmacokinetic (PBPK) models for numerous substances, supported the development of predictive *in silico* toxicity models, and enabled comprehensive analysis of heterogeneous datasets to uncover mechanisms of toxicity efficiently.⁴⁵ AI has also demonstrated high predictive accuracy (89% balanced classification) in determining *in vitro* pulmonary toxicity through high-throughput image analysis.⁴² This review outlines the progress and ongoing challenges of merging AI/ML with conventional toxicology tools such as PBPK modeling, quantitative structure-activity relationship modeling, adverse outcome pathway, toxicogenomics, and high-content image screening, and concludes with insights into future directions. These innovations mark a significant step forward in transforming toxicology from traditional animal testing frameworks toward modern, *in vitro*-driven risk assessment models.⁴⁶

The determinants entered into the equation for safety and cell toxicity detection using AI include various features and characteristics of the compounds being studied. These determinants can be derived from different sources such as chemical descriptors, molecular structures, and high-throughput imaging data. For instance, in the context of toxicity prediction, advanced AI-based approaches look for similarities among compounds or project the toxicity of the compound based on input features.⁴⁴ These features can include physicochemical properties, bioactivity, and toxicity-related characteristics. In the case of predicting *in*

vitro pulmonary toxicity using high-throughput imaging and AI, the determinants entered into the equation would involve features extracted from the imaging data to accurately classify a number of chemicals.⁴⁶

Discussion

The incorporation of AI into microbiology science has already shown promising results in various areas such as treatment planning and diagnostic assistance.⁴⁸⁻⁵¹ Combining AI and aPDT has the potential to offer several benefits, including eliminating microorganisms independently of their antimicrobial resistance pattern, predicting which microorganisms are likely to develop resistance to aPDT, optimizing the dosage and timing of aPDT, designing new PSs that are more selective in targeting bacteria, simulating the interaction between PSs and bacteria, combining aPDT with antibiotics and antifungal drugs to treat skin and mucosal infections, and identifying new PSs that are more effective in killing bacteria. By leveraging the power of AI, researchers can improve the efficacy of aPDT and develop more personalized treatment strategies that are tailored to the specific needs of each patient.

The efficiency of aPDT strongly depends on PS concentration and its physico-chemical properties, as well as the amount and time of ROS produced after the light delivery.⁵² AI can analyze these factors and optimize the dosage and timing of aPDT via chemical perturbation of the biofilm, PS optimization, variable time of exposure and light doses, peptide approaches, timing and dosage investigations, optimization of light dose, and incubation time to improve its efficacy and reduce side effects. Additionally, AI can predict which microorganisms are likely to develop resistance to aPDT, allowing for the development of more effective treatment strategies.^{51,53} By simulating the interaction between PSs and bacteria, AI can provide insights into the mechanisms of aPDT and guide the development of new treatment strategies.

Considering the role of AI in enhancing the effectiveness of aPDT, there is a growing need for smart appliances that can leverage the integration of AI and aPDT for the targeted treatment of microbial infections (Figure 2). To address this, we have proposed a schematic design that enables the combination of AI and aPDT in practice. The design incorporates internet of things (IoT) technology to create these smart appliances. Recent studies have explored the use of IoT technology to integrate AI with conventional appliances, resulting in the development of smart appliances.^{54,55}

In our proposed design, IoT sensors will be embedded in the appliance to monitor treatment parameters in real time, such as the type and concentration of PSs, light parameters, and oxygen levels.⁵⁵ These sensors will transmit the collected data to a cloud-based platform for analysis.^{54,55} Then, AI algorithms will be employed

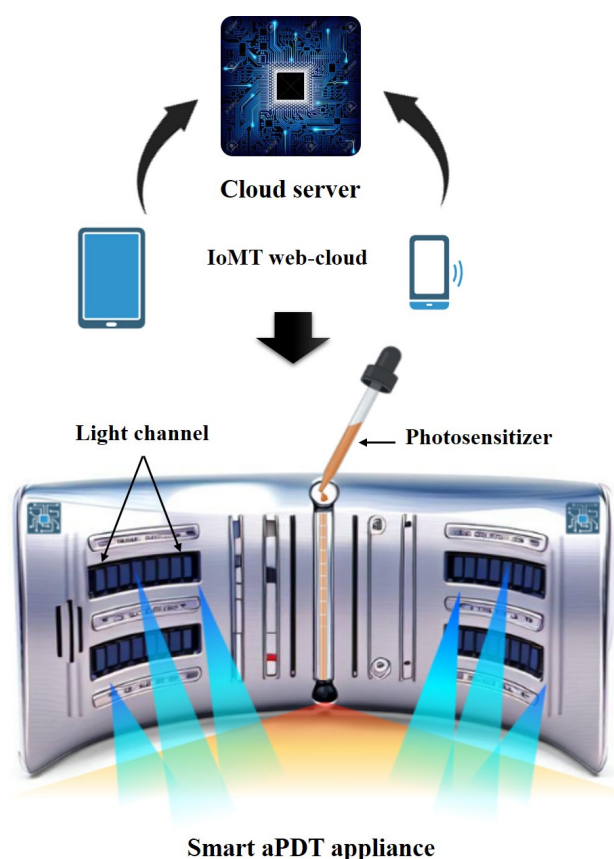


Figure 2. Smart Model of the Antimicrobial Photodynamic Therapy Appliance Based on Innovative Internet of Medical Things Technology and Nano-electronics. Abbreviations: aPDT, antimicrobial photodynamic therapy; IoT, internet of things

to analyze the sensor data.^{54,55} AI can adjust treatment parameters and predict the efficacy of aPDT based on microbial responses, thereby enhancing treatment precision. Additionally, a customizable LED light source will be incorporated into the design, capable of emitting light at the appropriate wavelength to activate the PSs. This light source can be remotely controlled through a smartphone app or the IoT platform.⁵⁵

To facilitate the aPDT process, a user-friendly mobile app or web portal is developed, allowing healthcare professionals to remotely monitor and control the treatment. Patients can also utilize the app for self-administered treatments under medical guidance.^{54,55} In the workflow, healthcare professionals can assess the patient's condition and determine the suitable PS and treatment parameters.⁵⁵ The AI algorithm will generate a personalized treatment plan based on patient data and microbial analysis, optimizing the aPDT process.⁵⁵

Conclusion

The review of the articles indicates that combining AI with PDT is feasible. With the emerging focus on personalized treatment, AI's capabilities—particularly in genetics, biomolecules, and microbiology—offer the potential to predict optimal parameters for aPDT treatments and

provide real-time monitoring. This personalized approach includes selecting the appropriate photosensitizing agent, including considerations of type, concentration, and application duration, and choosing the radiation source, including considerations of type and parameters such as time, wavelength, and session frequency. Personalizing aPDT based on AI can improve treatment outcomes and reduce resistance risks. However, despite advancements in various scientific fields, a noticeable gap exists in effectively combining AI with aPDT. Therefore, there is a pressing need for future research to bridge this gap and realize the potential of this integration using foundational data.

Authors' Contribution

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Writing—review & editing: Maryam Pourhajibagher, Rashin Bahrami, Abbas Bahador.

Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical Approval

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