ACCSCIENCE PUBLISHING

INNOSC Theranostics and Pharmacological Sciences

REVIEW ARTICLE

Current view on photodynamic therapy in medicine

David Aebisher[1]*, Julia Tomaszewska[2], Emilia Tomaka[2], and Dorota Bartusik-Aebisher[2]

[1]Department of Photomedicine and Physical Chemistry, Medical College of The Rzeszów University, Rzeszów, Subcarpathian, Poland

[2]Department of Biochemistry and General Chemistry, Medical College of The Rzeszów University, Rzeszów, Subcarpathian, Poland

Abstract

Light has been used for medical purposes for centuries, but the first steps toward photodynamic therapy (PDT) were taken in the early 20th century. PDT is an innovative therapeutic approach that involves three key components: A photosensitizer (PS), molecular oxygen, and visible light. The destruction of diseased tissues and cells in PDT occurs through the activation of a PS by near-infrared or visible radiation. This activation, in the presence of molecular oxygen, generates singlet oxygen and other reactive oxygen species. PDT has been successfully applied to treat various types of cancer, particularly superficial ones. This review outlines the principles of PDT and discusses its application in cancer treatment, specifically in the context of pancreatic and esophageal cancer. While PDT is effective, it can also have adverse effects on the human body, such as changes to cell and organelle membranes. PDT is a modern, non-invasive treatment modality utilized for both non-malignant conditions and also various types of tumors in diverse locations. Enhancing the efficacy of PDT and reducing its side effects may be possible by combining PSs with nanomaterials, which would also allow for targeted therapy to specific receptors. PDT is continuously being developed to improve its effectiveness, and ongoing studies aim to minimize unwanted side effects and identify contraindications for its use.

Keywords: Photodynamic therapy; Photosensitizers; Pancreas; Esophagus

***Corresponding author:**
David Aebisher
(daebisher@ur.edu.pl)

Citation: Aebisher D, Tomaszewska J, Tomaka E, Bartusik-Aebisher D. Current view on photodynamic therapy in medicine. *INNOSC Theranostics and Pharmacological Sciences*. 2025;8(2):16-30.
doi: 10.36922/itps.4559

Received: August 17, 2024

Revised: December 8, 2024

Accepted: December 16, 2024

Published online: January 6, 2025

Copyright: © 2025 Author(s). This is an Open-Access article distributed under the terms of the Creative Commons Attribution License, permitting distribution, and reproduction in any medium, provided the original work is properly cited.

Publisher's Note: AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations

1. Introduction

Light has been used in medical therapy since ancient times. The Egyptians, Chinese, and Indians employed light to treat a variety of diseases, including vitiligo, rickets, psoriasis, skin cancer, and even psychosis. One of the earliest known uses of sunlight for medicinal purposes was heliotherapy, which the Greeks introduced around 3000 years ago. Herodotus, a renowned physician of the second century BC, is often considered the father of heliotherapy. The Greeks favored a form of treatment in which the entire body was exposed to sunlight. At the beginning of the 20th century, the first literature reported on the "photodynamic effect" was presented by a medical student Oscar Raab and his professor Herman von Tappeiner. They showed that exposure of certain dyes to sunlight could lead to cell death, as these dyes sensitized microorganisms to light.

In 1948, Figge and Weiland conducted extensive research on the possibility of using various porphyrin derivatives in photodynamic therapy (PDT) and diagnostics.[1] They demonstrated the use of hematoporphyrin (HDP) as a tool for cancer detection. However, at that time, this approach still carried the risk of toxic side effects. They also assessed the effectiveness of other compounds, such as coproporphyrin, protoporphyrin, and zinc HDP. In 1955, scientist Schwartz investigated the nature of HDP and found that it was a mixture of many different porphyrins, each with distinct properties. PDT gained further development when it was discovered that HDP derivatives increased the fluorescence of tumors in patients. This breakthrough was made by a team of doctors from the Mayo Clinic. In a review by Kessel D published in 2019, the historical details of the 1972 first usage of fluorescent in biology were described.[1] This study demonstrated the ability to eliminate glioma cells in tumors in both animal models and established cell cultures.[1,2]

Soon after, this mechanism was extended to the treatment of cancers of the lungs, esophagus, reproductive organs, brain, and head and neck. By the end of 1996, it was estimated that tens of thousands of patients with various types and stages of cancer had been treated with PDT. In Poland, the use of PDT began in 1986. Despite advances in cancer treatment over the past decades, cancer remains a major medical challenge, claiming millions of lives and negatively affecting the quality of life of survivors. The primary treatments for cancer remain chemotherapy and radiotherapy, both of which have serious side effects. Patients undergoing these treatments often report severe pain. Consequently, finding alternative treatment regimens that provide improvement in health status, with the possibility of complete recovery and minimal to no side effects, is a priority for clinicians and researchers.[3]

This review explores various important aspects of PDT, including its mechanism of action, and provides an overview of its historical development. We also highlight the promising results of photosensitizer (PS) use, combination therapies, and the prospects these innovations bring. The current directions of PDT are presented in Figure 1.

2. Mechanism of action of PDT

PDT relies on the concomitant presence of molecular oxygen, a PS, and near-infrared or visible light. Each of these ingredients is non-toxic on its own and does not damage tissues or cells. Ideally, the PS is absorbed and accumulates within the target cells. Since the PS is harmless when not exposed to light, any potential toxicity in PDT can be minimized by selectively illuminating only specific areas. A PS absorbs light energy and transfers it to nearby molecules that do not absorb light. This energy or electron transfer results in the production of highly reactive molecules, enabling PDT to function through three primary mechanisms: Direct destruction of target cells, damage to blood vessels that lead to ischemia and tumor cell death, and activation of the immune response. PSs enhance the activation of immune cells, such as neutrophils, macrophages, and lymphocytes, which, in turn, increase the secretion of interleukin (IL)-6, IL-10, and tumor necrosis factor (TNF), contributing to tumor cell death. Cell death in PDT occurs through two mechanisms: necrosis and apoptosis. Necrosis refers to the local death of tissues, which triggers acute inflammation at the site of injury. The byproducts of necrotic tissue breakdown are toxic to the body. On the other hand, apoptosis is programmed cell death, controlled enzymatically, and does not induce inflammation. PS is a molecule with electrons arranged in specific molecular orbitals. In its ground state, PS contains electron pairs with opposite spins in low-energy orbitals. When exposed to light of a specific wavelength, PS absorbs energy, causing an electron to be excited into a higher-energy orbital without changing its spin. This change creates a short-lived singlet state. The PS may return to its ground state by releasing heat or light. Alternatively, it may transition to a triplet state through intersystem crossing (ISC), where the electron spin is reversed. The longer PS remains in the triplet state, the greater the likelihood that it will encounter other molecules, leading to the formation of chemically reactive compounds. There are two primary processes that occur

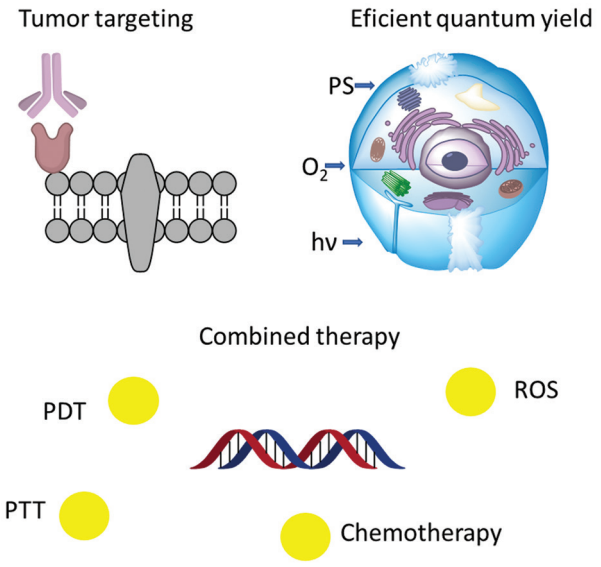


Figure 1. Current directions of photodynamic therapy
Abbreviations: PS: Photosensitizer; PDT: Photodynamic therapy; PTT: Photothermal therapy; ROS: Reactive oxygen species; h: Planck's constant; v: The frequency of light, O_2: Oxygen molecules.

when the PS is in the triplet state. In the first process, the PS removes an electron from a reducing molecule in its vicinity. Molecules that donate electrons include, for example, tyrosine in proteins, guanine in nucleic acids, or tryptophan. This electron transfer creates a pair of radical anions and radical cations. In an oxygen-rich environment, the PS radical anion transfers its electron to molecular oxygen, generating a superoxide anion, which effectively restores the PS to its original state. The superoxide anion can act as a reducing agent or as a monovalent oxidant. Although it does not directly interact with lipids, nucleic acids, or carbohydrates, the superoxide can oxidize small molecules such as leucoflavins, sugar tautomers, sulfates, tetrahydroflavins, and catecholamines. Superoxide radical reaction with other biologically relevant radicals may lead to the formation of potentially toxic, cell-damaging products. In biological systems, the most common phenol is the amino acid tyrosine. When the superoxide reacts with nitric oxide, a strong oxidant, peroxynitrite, is produced, which can react with carbon dioxide and bicarbonates to form nitrosoperoxycarbonate. The carbonate radical anion is a single-electron oxidizer that can remove electrons from tyrosine and tryptophan. In addition, superoxide can oxidize protein clusters, such as enzymes involved in the Krebs cycle and dehydratases. Disruption of these clusters, particularly the iron-sulfur [4Fe-4S] clusters, can have harmful effects. First, it impairs aerobic energy production and biosynthetic pathways by inactivating Krebs cycle enzymes. Second, it generates hydroxyl radicals, that is, strong oxidants, through the Fenton reaction, where released iron from the [4Fe-4S] clusters acts as a catalyst for hydrogen peroxide. The iron ions, in their reduced form, bind to anionic molecules, such as nucleic acids, proteins, lipids, and other cellular components. The stable hydrogen peroxide can diffuse through membranes and react with iron bound to biomolecules, generating highly reactive hydroxyl radicals. The radicals can damage cells at the site where they are formed. In the second process, the energy of the PS is transferred to molecular oxygen, which, in its ground state, is a triplet. The transfer of energy excites one of the two unpaired electrons into a high-energy orbital, causing a spin flip, which converts oxygen into a singlet. Singlet oxygen ($^1O_2$) is considered the main destructive agent in PDT. While biological systems have enzymatic defenses against superoxide, there are no developed antioxidant enzymes to remove $^1O_2$, likely due to its short lifespan.[4]

3. Mechanisms of cancer cell destruction in PDT

PDT targets cancer cells, specifically their microcirculation, as well as the functioning of the host's immune system. To achieve the desired therapeutic effect, certain conditions must be met, influencing each of these aspects. PDT reduces the number of clonogenic cancer cells through direct photodamage; however, this event does not lead to the complete eradication of pathological cells. This limitation arises from serveral factors, one of which is the heterogeneous distribution of the PS within the tumor. Another key factor is the availability of oxygen in the tissue being treated. Limited oxygen availability can restrict the direct killing of cancer cells (Figure 2). These constraints give rise to two primary mechanisms: photochemical oxygen consumption and the direct impact of PDT on tissue microcirculation. The amount of oxygen available during PDT depends on the photobleaching of the PS. As the PS is reduced, the rate of oxygen consumption during therapy also decreases. Fractionating the delivered light is crucial, as it allows the tissue to reoxygenate during breaks in illumination. Furthermore, PDT-induced microcirculation damage, particularly when higher doses of PSs such as Photofrin are used, disrupts oxygen delivery to tissues. Vascular mechanisms of PDT vary significantly with different PSs. For instance, PDT with Photofrin leads to vasoconstriction, leakage of macromolecules from vessels, leukocyte adhesion, and clot formation, all of which are associated with platelet activation and the release of thromboxane. PDT can also induce vasoconstriction by inhibiting the production or release of nitric oxide by the endothelium. Damage to the normal vascular system surrounding the tumor can significantly hinder the effectiveness of PDT. Studies have shown that cancer cannot be effectively treated when the tissue surrounding the tumor is damaged during PDT. Recent research suggests that treatment with a high fluence rate inhibits tumor cure. However, no differences in tumor perfusion or oxygenation were observed between treatments with low or high fluency. These findings indicate that the protection provided by the normal vascular system around the tumor is a crucial factor in the long-term control of cancerous tissue during PDT (Table 1). To optimize the efficacy of PDT, it is important to regularly monitor parameters such as the concentration of the PS in the tissues, the rate of photobleaching, blood oxygen levels, and blood flow.[3]

4. Literature search method

Articles for this review were retrieved from online databases (PubMed/MEDLINE) using the following search terms: "photodynamic therapy," "PDT," and "photosensitizers."

5. Results

The total number of articles identified was 92 and the number included in the current review is 45. In this paper, only studies in English are selected. The first cited here

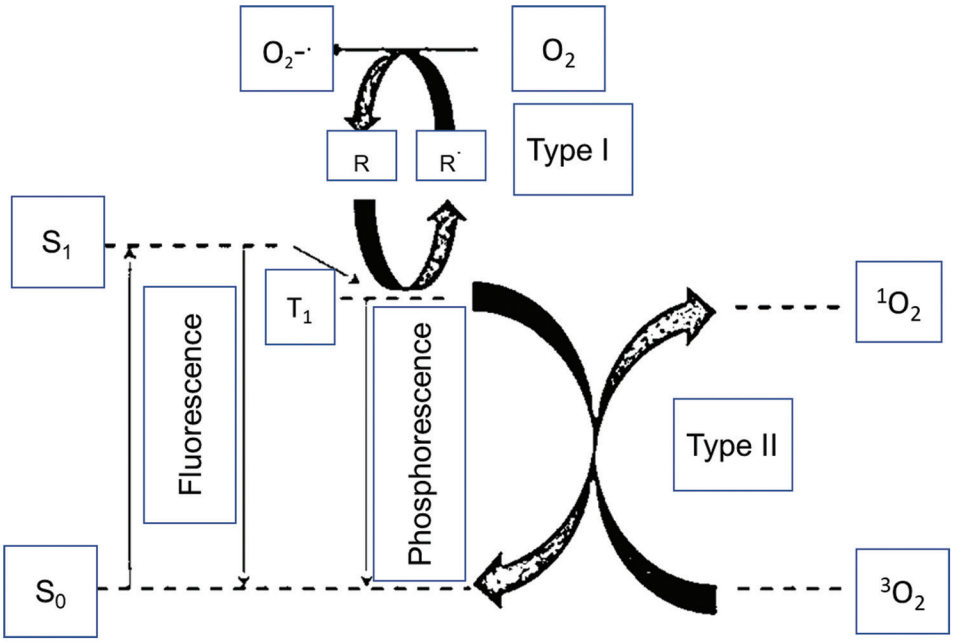


Figure 2. The mechanistic presentation of photodynamic therapy
Abbreviations: $^1O_2$: Singlet oxygen; $^3O_2$: Triplet oxygen; O_2: Oxygen; O_2^-: Superoxide anion; R: Radical; R·: Free radical.

Table 1. Efficacy of photodynamic therapy in the treatment of various cancers

Type of cancer	Photodynamic therapy (%)
Skin	85 – 95
Head and neck	70 – 90
Lung	50 – 70
Esophageal	70 – 80
Bladder	70 – 85
Pancreatic	60 – 75
Prostate	60 – 80

clinical study involved 15 patients with unresectable, high-stage tumors.[5] All patients were allergic to verteporfin at a dose of 0.4 mg/kg, whereas 13 received treatment using single fiber lasers and two with multiple fibers, each 690 nm in length, placed transdermally. The light dose was gradually increased until constant necrosis was achieved, and all procedures were monitored using a computed tomography (CT) scan. Necrotic changes of 12 nm in size were observed in all patients, though the volumes varied. No side effects were reported in patients who underwent chemotherapy. This study concluded that PDT with verteporfin for the treatment of malignant pancreatic cancer (PCa) is safe, and the compound is flexible in terms of administration.

The next study aimed to evaluate PDT in PCa through a similar phase 1 trial.[6] It involved 16 patients with adenomas located near the head of the pancreas that were not amenable to surgery. Patients were administered an oral dose of 0.15 mg/kg mesotetrahydroxyphenyl chlorite, followed by light delivery to the tumor through percutaneous fiber insertion under CT guidance 3 days later. Three patients subsequently received chemotherapy. Significant tumor necrosis was observed in all patients, as evidenced by imaging studies. Fourteen of the 16 were discharged after 10 days. Several adverse events, including gastrointestinal bleeding and duodenal obstruction, were recorded, which may have been related to the treatment. The median survival after PDT was 9.5 months, with seven out of 16 patients surviving for 1 year. This study highlighted that, while pancreatic tumor necrosis was achieved as expected, caution should be exercised, particularly in cases of tumors infiltrating the duodenal wall.

In another study, the feasibility and safety of endoscopic PDT in the treatment of unresectable ampullary cancer were evaluated.[7] Sixteen patients received an intravenous dose of 4 mg/kg of a HDP derivative, followed by red light (630 nm wavelength) administered during duodenoscopy two days later. A constant light energy density of either 50 J or 200 J/cm^2 was used, with three or four exposures during each session. Treatment was repeated up to 5 times at intervals of 3 – 6 months. Skin hypersensitivity was the only complication observed, affecting three patients. Tumor size was assessed every 4 – 8 weeks, and biopsy specimens were taken if the tumor was not visible macroscopically.

In patients with small tumors, a reduction in tumor mass and even remission were observed for several months. However, patients with widespread duodenal involvement showed only a modest response.

Another study focused on patients with colorectal cancer metastases to the liver, a group with a poor prognosis due to the scarcity of patients eligible for curative liver resection.[8] In this phase 1 trial, PDT was used to treat 31 liver metastases in 24 patients with unresectable colorectal cancer metastases. PS 5, 10, 15, 20-tetrakis(m-hydroxyphenyl)bacteriochlorin (mTHPBC) was administered intravenously at doses of 0.6 mg/kg or 0.3 mg/kg. Tumors were illuminated for 300 – 600 s using optical fibers inserted subcutaneously after 120 h, or after 48 h in some subjects. The scattered light dose was 740 nm. Results indicated tumor necrosis in all patients 1 month after PDT. A small proportion of patients reported mild pain, and the majority experienced transient subclinical hepatotoxicity. No serious clinical complications were noted, except for pancreatic damage in one patient and skin damage in another. Harmless side effects included transient phlebitis and mild skin phototoxicity from excessive light during treatment. The study concluded that PDT with mTHPBC is a safe and effective treatment for unresectable colorectal cancer liver metastases.

Meanwhile, one study showed that treatment with PDT for locally advanced pancreatic cancer (LAPC) may be limited due to the unfavorable prognosis associated with the disease.[9] The investigators hypothesized that PDT for LAPC is safe, technically feasible, and can lead to increased tumor necrosis. In this phase 1 study, patients with untreated LAPC were administered intravenous porfimer sodium, followed by endoscopic ultrasound-guided PDT (EUS-PDT) 2 days later. EUS-PDT was performed by puncturing the tumor with a 19-gauge needle, and a 1.0 cm diameter light diffuser emitting 630 nm light was introduced. CT scans were conducted 18 days after PDT to assess pancreatic necrotic changes. Seven days following the CT scan, intravenous Nab-paclitaxel and gemcitabine were administered weekly in a 3-week cycle until disease progression or unacceptable cytotoxicity occurred. In terms of primary outcomes, 12 patients with tumors located in the head, neck, trunk, or tail of the pancreas underwent EUS-PDT. In half of these patients, an increase in tumor volume and a higher percentage of tumor necrosis was observed in comparison to the initial imaging tests. After a follow-up period of 10.5 months, the median time to progression was 2.6 months, and the median overall survival was 11.5 months. During the treatment course, eight serious adverse events were reported, although none of them were directly attributed to the therapy. The study concluded that EUS-PDT for LAPC is safe and results in measurable tumor necrosis. A phase 2 trial is planned to further investigate these findings.

5.1. The use of PDT in the treatment of pancreatic cancer

Pancreatic cancer is a condition associated with a high mortality rate. The primary treatment options are surgery or chemotherapy; however, an increasing number of cases are diagnosed at advanced stages, making surgery infeasible. In addition, chemotherapy does not bring the desired results due to the resistance exhibited by PCa cells. Given its high efficacy against cells resistant to radiotherapy and chemotherapy, PDT has emerged as a viable alternative for patients who are not candidates for surgery. Clinical practice has confirmed the effectiveness of this minimally invasive treatment method. However, PDT faces several limitations when used in clinical settings, including challenges related to insufficient delivery of PSs, dependence on tumor oxygenation, and the ability of malignant tumors to evade treatment. To address these challenges, researchers are increasingly focusing on the development of PS nanoparticles (NPs) and various nanocarrier systems to enhance the cellular uptake and distribution of PSs within the body. Encapsulation of PSs in NPs significantly increases their accumulation in PCa tumors, owing to improved solubility and stability in the bloodstream. Various strategies have been explored to develop multidrug codelivery NPs, which facilitate synergistic PDT-based therapies, thereby enhancing the effectiveness and prolonging the therapeutic response.[10]

While pancreatic surgery is technically challenging, PDT offers a minimally invasive alternative. Despite its lower invasiveness and promising potential for treating PCa, PDT is not without its adverse effects, such as gastrointestinal hemorrhage and duodenal obstruction. These side effects are partly due to the limited selectivity of current PSs, which results from their non-selective distribution. This non-specific distribution creates a risk of photodamage to adjacent organs and prevents adequate accumulation of PS at tumor sites. Furthermore, during follow-up after PDT, some cases have shown liver metastasis and tumor regrowth at the edges of the treated area.[10] It is believed that these phenomena may be attributed to insufficient oxygenation within the tumor. In addition, PDT alone is insufficient to fully combat cancer. As a result, specially modified NPs loaded with PSs are being used to enhance PS solubility, improve oxygen consumption, and facilitate more effective delivery. These NPs are often functionalized with special ligands that enable targeted delivery of PSs to cancerous pancreatic cells, thereby significantly improving the efficacy of PDT for PCa. As mentioned earlier, PDT

is more effective when combined with other therapies, such as photothermal therapy, which generates additional oxidative stress. The effectiveness of PDT in alleviating tumor burden in patients with unresectable localized PCa has been demonstrated in several clinical trials, with relatively few complications. Despite promising pre-clinical data showing enhanced efficacy of NP-based PSs compared to conventional PSs, their clinical application in the treatment of PCa remains challenging. This limitation is due to the ongoing refinement of these compounds' functionalities and the lack of research on clinically relevant models. PDT was the first approved as an endoscopic procedure for esophageal cancer in both the United States and Japan. Initially, it was used as a palliative local treatment for patients with obstructed esophageal cancer. PDT is also indicated as eradication therapy for dysplastic Barrett's esophagus, a precursor to esophageal adenocarcinoma, and is supported by level 1 evidence. In Japan, PDT has been approved as a curative treatment for superficial esophageal cancer lesions that are difficult to manage with endoscopic resection. In addition, PDT using second-generation PSs has been approved for treating early local recurrence following radiotherapy, a condition that is challenging to treat using other methods. PDT has also been evaluated in other gastrointestinal cancers, including gastric cancer, cholangiocarcinoma, and PCa.[11]

5.2. Treatment of esophageal cancer using PDT

Esophageal cancer is associated with a very poor prognosis, with a 5-year survival rate of only 12.5%. The standard treatment for this cancer has traditionally been the resection of part of the esophagus; however, due to the high morbidity associated with surgery, less invasive methods such as endoscopic mucosal resection (EMR), coagulation, and PDT are increasingly used. In PDT, the light source required for this method is provided by diffusers, which are cylindrical and highly flexible. These diffusers are positioned near the tumor site using an endoscope. To protect healthy esophageal tissue, a balloon is inflated next to the diffuser. Initial studies focused on using PDT as a palliative treatment for obstructive tumors, although it has also proven effective for treating superficial lesions. The type of PS used is a key factor determining the treatment's effectiveness. When sodium porfimer was used, the complete response rate was 87%, and similar results were achieved with mTHPBC.[12] Despite the high efficacy of PDT in treating esophageal cancer, the method is not without undesirable side effects. The most frequently recorded symptoms included transient skin photosensitivity, fistula stenosis, and perforation, particularly when red light was used. However, when green light was employed, these side effects were not observed, and the effectiveness of the therapy remained unchanged.

PDT is especially useful in the treatment of Barrett's esophagus, a condition in which the epithelial cells in the lower esophagus are affected, often as a result of chronic reflux of gastric contents into the esophagus. This condition causes damage to the esophageal epithelial cells, leading them to resemble those of the stomach, a process known as metaplasia. While most cases of Barrett's esophagus do not progress to cancer, individuals with this condition have an increased risk of developing esophageal cancer. Treatment typically involves controlling acid reflux symptoms and monitoring the esophagus for signs of malignant changes. However, when cancerous transformations occur in Barrett's esophagus, PDT is considered. PDT can be used to eliminate cancerous or altered cells, but treatment must be tailored to the individual case by a physician specialized in this type of therapy. The suitability of PDT for treating Barrett's esophagus depends on various factors, including the severity of the changes and the patient's overall health.

One study examined the effects of Photofrin in 77 patients with unresectable, obstructive esophageal cancer.[12] Patients were initially administered Photofrin at a dose of 1.5 – 2.0 mg/kg, followed by endoscopic treatment with 630 nm light 48 h later. The most common complications following PDT were minor, including esophageal stenosis, esophagitis, pleural effusion, and sunburn. Twenty-nine patients required more than one cycle of PDT, and an additional seven patients required the implantation of an expandable metal stent due to recurrent dysphagia. The study concluded that PDT is a safe and effective treatment for alleviating obstruction and bleeding in esophageal cancer.

In the subsequent study, patients with advanced esophageal cancer were randomized to receive either PDT using sodium porfimer and an argon laser dye, or laser therapy using a neodymium-doped yttrium aluminum garnet (Nd: YAG) laser.[13] A total of 236 patients were randomized, and 218 were treated at 24 sites. Dysphagia improved equally in both groups, with nine complete tumor responses occurring after PDT and two after Nd: YAG therapy. Better outcomes were observed in patients whose tumors were located in the upper and lower thirds of the esophagus, as well as in patients with longer tumors or those who had previously undergone treatment. Compared to the Nd: YAG, PDT patients experienced more mild-to-moderate complications, including sunburn. In addition, treatment discontinuation occurred in only 3% of patients after PDT, compared to 19% after Nd: YAG, primarily due to side effects. PDT with sodium porfimer demonstrated overall equivalent efficacy in alleviating dysphagia in esophageal cancer compared to Nd: YAG laser thermal ablation, with an objective tumor response

rate that was equal to or better than Nd: YAG. The main limitation of PDT is temporary photosensitivity, but PDT is easier to perform and involves fewer invasive procedures than Nd: YAG laser therapy, which was a key conclusion of the study.

In another study on esophageal cancer, patients were orally administered 60 mg/kg of 5-aminolevulinic acid (ALA). Twenty-four hours after administration, gastroscopy was performed. Initially, tumor localization was done using white light, after which the light source was switched to red light with an intensity of 100 J/cm^2 for 600 s. Gastroscopy was repeated 48 h later and again seven days after the first procedure. The degree of dysphagia was recorded both before treatment and 14 days after treatment. The study included patients with advanced, unresectable tumors – two of whom had squamous cell carcinoma of the middle esophagus and three had terminal esophageal adenocarcinoma – mild, self-limited reactions were observed in all patients. Treatment had no significant effect on liver and kidney function, hemoglobin concentration, or leukocyte count, which helped ensure the accuracy of the test results. Most patients showed improvement in dysphagia. The final conclusion of the study was that PDT, using ALA as a PS and non-laser therapy, may provide an effective approach for treating dysphagia in such patients.[14]

Given the promising results of new PSs, such as ALA, in reducing skin phototoxicity during PDT, Maier *et al.*[15] conducted a study to evaluate the effectiveness of poly hematoporphyrin (Photosan) as a PS in PDT for advanced esophageal cancer. This study aimed to compare the effectiveness of ALA with Photosan in the treatment of advanced esophageal cancer, with a focus on skin phototoxicity and dysphagia reduction. Following diagnosis, 22 patients received therapy using ALA, whereas 27 patients received Photosan. PDT was delivered using a dye laser with a wavelength of 630 nm, and hyperbaric oxygen therapy was used as an adjunct. Both groups demonstrated therapeutic effects, including visible narrowing of the tumor's diameter and length, with slightly greater effectiveness noted for the Photosan treatment. Neither group experienced severe treatment-related complications, and no cases of sunburn were reported. No mortality occurred during the treatment period. The study concluded that Photosan is more effective than ALA in PDT for esophageal cancer.

Another study involved 64 patients with various types of cancer, including five with esophageal cancer.[16] The PS was administered intravenously, and light with a wavelength of 630 nm was delivered through quartz fibers. After treatment, complete remission was achieved in 48 of the 58 treated patients, including those with esophageal cancer. The only significant side effect was skin hypersensitivity. The study showed that PDT is effective in treating superficial tumors.

The greatest risk factor for esophageal cancer is Barrett's esophagus. Kelly *et al.*'s[17] conducted a study to compare argon plasma coagulation and PDT for the ablation of Barrett's esophagus. A total of 65 patients were included, with 34 assigned to argon plasma coagulation and 34 to PDT using ALA. Multiple sessions were conducted over 24 months. After completion of treatment, a macroscopic reduction in the area of Barrett's esophagus was observed in all patients. In the argon plasma coagulation group, better results were noted in terms of esophageal obstruction (97%) and a lower incidence of occult glands (24%) compared to PDT (50%). Both methods were effective in the ablation of Barrett's esophagus.

In a separate study,[18] patients with esophageal cancer were monitored for 5 years and underwent PDT using the same PSs as in the previous study. A biopsy of the primary segment of Barrett's esophagus was taken according to the Seattle protocol, followed by endoscopy. Patients who did not respond to PDT or had recurrent neoplasia underwent additional EMR therapy. Initially, better results were observed in patients treated with ALA, and most patients responded well. Compared to Photofrin, ALA showed greater effectiveness and caused fewer relapses. However, after longer follow-up, there was no significant difference in the long-term complete reversal of intestinal metaplasia and dysplasia. Four patients in each group developed invasive esophageal adenocarcinoma. The likelihood of long-term remission was significantly increased in patients who initially responded to ALA-PDT therapy. As a result, radiofrequency ablation combined with EMR has become the preferred minimally invasive ablative therapy due to its lower therapeutic efficacy compared to PDT.

In Ackroyd *et al.*'s study,[19] 36 patients with dysplastic Barrett's esophagus, who received omeprazole for acid suppression, were assigned to receive oral ALA at a dose of 30 mg/kg or a placebo. Four hours later, laser endoscopy was performed. Follow-up endoscopic examinations were performed at 1, 6, 12, and 24 months. In the ALA group, 16 of 18 patients showed a reduction in the affected area. In the placebo group, a 10% reduction in surface area was observed in two patients, whereas no changes were noted in 16 patients. None of the patients treated with PDT showed columnar epithelial dysplasia in the treated area, whereas 12 patients in the placebo group still exhibited dysplasia. No serious side effects, either short- or long-term, were observed. The therapeutic effects lasted up to 24 months.

The question of whether PDT has long-term effectiveness in patients with high-grade dysplasia in Barrett's esophagus

was addressed by Gray and Fullarton.[20] In their research, 21 patients received Photofrin intravenously 48 h before endoscopy, during which laser light with a wavelength of 630 nm was administered. Biopsies and endoscopies were performed every 6 – 12 weeks. Gray and Fullarton found that 16 patients remained free of high-grade dysplasia for a median of 62 months. Three patients developed an adenoma between the 40th and 50th month. PDT was effective in 84% of cases, making it a viable treatment for patients unable to undergo surgery.

Another question regarding whether Barrett's esophagus can be completely removed was addressed by Hage *et al.*[21] In their study, patients were assigned to three groups, where the first group received ALA-PDT intravenously in one dose, followed by light administration after 4 h. The second group received the same compound in two doses, with light applied after the same interval. The third group was treated with argon plasma coagulation in two sessions. The best result was achieved in the third group, where complete elimination was observed in 100% of patients after 6 weeks. In the first and second groups, complete elimination was observed in 86% and 93% of patients, respectively. In summary, argon plasma coagulation alone or ALA-PDT combined with coagulase can lead to the complete regression of Barrett's epithelium.

5.3. Immunological effects of PDT

The use of PDT also has adverse effects on the human body. PDT-induced changes in cell membranes, as well as in organelle membranes when using most PSs, may lead to side effects. These changes can affect signaling pathways, including increased expression of early immune response stress genes and proteins. Another potential effect is inflammatory cell damage. In such cases, membrane lipids are damaged through the degradation of phospholipids, leading to the release of fragments of arachidonic acid and lipids, which act as mediators of inflammation. While inflammatory signaling after PDT can have detrimental effects, it also has beneficial outcomes, such as the initiation and support of leukocyte recruitment from the blood. A notable consequence is the swift accumulation of neutrophils, which can remain in tumor blood vessels and significantly contribute to endothelial damage. As a result, the disintegration of these neutrophils results in the release of harmful oxygen radicals, myeloperoxidase, and lysosomal enzymes, which break down proteins and damage cancer tissue.

In evaluating the effectiveness of PDT in controlling inflammation, a study involving 28 patients with severe chronic periodontitis is particularly relevant. Patients were randomly assigned to either the PDT treatment group or a control group. Using the Luminex test, the expression of important cytokines – such as IL-1α, IL-1β, IL-8, vascular endothelial growth factor (VEGF), interferon-γ, TNF-α – was quantitatively assessed. Significant differences in cytokine levels were observed between the groups for IL-1α, IL-1β, IL-8, and VEGF, whereas the remaining cytokines showed no statistical differences. This study suggests that PDT may enhance the benefits of periodontal treatment by modulating immune responses.[22]

Increasing research indicates that PDT may also be effective in treating non-cancer conditions, such as genital warts and condyloma. A study was conducted to confirm the high cure rates and low recurrence rates in the treatment of condyloma with ALA-PDT. At various time intervals after treatment, the recruitment and significance of immune cells at the lesion sites were examined using immunohistochemical analysis. The study involved 15 patients who had several cycles of PDT. The infiltration of clusters of differentiation (CD) 3, CD4, CD8, CD1a, and CD68 cells was assessed using immunocytochemical staining, and biopsy samples were collected at baseline and at various times during the study. The best results were achieved in the treatment of anal condyloma. As treatment progressed, there was an increase in the infiltration of CD4+ T lymphocytes and Langerhans cells in the skin. Patients who responded to treatment also exhibited an increase in CD8+ lymphocytes. These results suggest that rapid activation of the immune response (CD4+ lymphocytes, Langerhans cells) may be responsible for healing to confirm previous clinical data.[23]

Wu *et al.*'s[24] assessed the effectiveness of PDT in reducing inflammatory infiltrates in periodontal disease, with a particular focus on how it affects the organization of the collagen network. Two drug delivery systems (DDS) were tested: Liposomes and nanoemulsions. The study involved 16 patients with advanced periodontal disease who were candidates for tooth extraction. The patients were divided into two groups, with one group receiving liposomes and the other receiving nanoemulsions. Seven days before therapy began, each patient had one tooth undergo PDT, whereas another tooth served as a control. After PDT, the density of the collagen fibers increased in the treated tooth compared to the control. PDT affected the immune system in both groups, but the responses differed. In the liposome group, the number of macrophages decreased, while in the nanoemulsion group, the number of Langerhans cells decreased. These results demonstrate that PDT has an impact on the immune system when used as a therapy for gingivitis and chronic periodontitis.

Another study aimed to investigate the effect of PDT as a therapy for multiple plantar warts.[5] The study involved

61 patients with the condition, who were randomly assigned to appropriate treatment groups. One group received PDT, whereas the other, the control group, was treated with cryotherapy. Several parameters were evaluated during the treatment: the assessment of skin lesions, pain levels, relapse rates, and side effects. Both groups showed improvement in skin lesions, but the PDT group demonstrated a slightly higher improvement (13.39 ± 3.88% before treatment to 1.48 ± 2.50% after the final treatment). After 3 months of therapy, the recurrence rate was significantly lower in the PDT group, whereas cryotherapy showed a recurrence rate of 20 – 53%. The study concluded that PDT had a more positive effect on the recurrence rate of multiple plantar warts compared to the traditional cryotherapy method.

Meanwhile, Theodoraki *et al.*[25] examined the effectiveness of PDT in treating head and neck squamous cell carcinoma (HNSCC). For an anti-tumor response to occur, PDT must trigger a local inflammatory reaction within the tumor cells. This study involved nine patients with HNSCC. Blood samples were collected before, during, and after PDT to assess the effects on the immune system. The frequency and number of T and B lymphocytes, CD4+CD39+ T regulatory cells (Tregs), and natural killer (NK) cells were evaluated using flow cytometry. The results showed an increase in the number of Tregs and NK cells in patients treated with PDT. In addition, serum concentrations of IL-6 and IL-10 were elevated, whereas the level of perforin decreased. Despite being a topical therapy, PDT produced a systemic response. The increased number of immune cells observed supports the effectiveness of PDT in HNSCC patients.

Immunosuppression may reduce the effectiveness of PDT. Niacinamide, that is, Vitamin B3, has been shown to prevent immunosuppression caused by UV radiation. However, the cause of immunosuppression during PDT is not well understood. Therefore, Thanos *et al.*[26] investigated the effect of niacinamide on immunosuppression induced by PDT. The study involved 22 healthy participants who tested positive in a Mantoux test. The second group received niacinamide orally at a dose of 500 mg, or a placebo, once daily for one week. Specific sites were then irradiated to assess immunosuppression at both irradiated and control sites. The study reported that PDT with the vehicle or placebo caused significant immunosuppression, whereas oral niacinamide therapy reduced it. Contrarily, low-frequency PDT did not induce immunosuppression in patients treated with topical niacinamide. The conclusion was that niacinamide could potentially prevent PDT-induced immunosuppression as a low-cost, effective method.

Meanwhile, de Moraes *et al.*[27] explored histomorphological changes and immunodetection following PDT using chloroaluminum phthalocyanine (AlClPc). The study involved eight participants who were scheduled for tooth extraction. Seven days before the extraction, 40 μL of AlClPc nanoemulsion was injected into their gums, followed by radiation exposure. The opposite side was used as the control. Tissue samples were collected 7 days after exposure and analyzed. The results showed edema in the treated tissues. No side effects were reported, and the therapy was well tolerated. These findings indicate that AlClPc is safe for clinical use in gingival tissue.

Evangelou *et al.*[28] investigated the effect of PDT on leukocyte migration following clinical treatment of basal cell carcinoma. The lesions were treated with methylaminolevulinate (MAL), and samples were collected before and after treatment. The study found that MAL caused rapid infiltration of neutrophils after PDT. In addition, a decrease in the number of Langerhans cells was observed just 1 h after PDT. The decrease in Langerhans cells could potentially impair the antitumor response, suggesting the need for further research in this area.

Finally, a study explored the use of PDT in the treatment of periodontitis. The clinical material used was gingival fluid. Two groups were studied: One group received scaling and root planning alone, whereas the other group received PDT with a 638-nm laser and toluidine blue. Bleeding was assessed over a 3-month period, and a mouth rinse test was performed to evaluate the level of polymorphonuclear cells. Improvements were observed in all outcomes compared to baseline, with the only significant difference noted in TNF-α. The study concluded that a single PDT exposure did not produce significant results in the treatment of periodontitis.[29]

6. Discussion of commonly used PSs in PDT

Porphyrins are a group of organic chemical compounds that contain a porphyrin ring. These compounds are activated by light in the wavelength range of 600 to 700 nm. The porphyrin ring consists of four (five-membered) rings connected by methine bridges (–CH=), forming a planar structure. The central metal ion, typically a magnesium ion, is coordinated with the ring and plays a key role in many of the biological functions of porphyrins. The most well-known porphyrin is heme, a key component of hemoglobin, which is responsible for transporting oxygen in the blood. Other porphyrins are involved in various biological processes, such as cellular respiration, electron transport in mitochondria, and metabolism. One example of a porphyrin-based PS is HDP, which is used in PDT. When exposed to light, HDP undergoes a photodynamic

reaction that leads to cellular destruction. HDP is activated by light in the wavelength range of 763 nm. Chlorophyll, another porphyrin, plays a vital role in photosynthesis in plants. It absorbs sunlight and converts it into chemical energy, which is then used to synthesize organic compounds.

Chlorophyllins are chemical compounds derived from chlorophyll. More specifically, they are chlorophyll derivatives in which the magnesium ion is replaced by another metal, most commonly copper. These compounds are known for their characteristic green color, similar to chlorophyll, and have various medical and industrial applications. The activation range for this PS is 690 nm.

Phthalocyanines are a group of organic dyes containing a phthalocyanine ring, whose structure is similar to that of chlorophyll. However, phthalocyanines contain nitrogen atoms in a place where the magnesium is found in chlorophyll. The most important and well-known member of this group is copper phthalocyanine. Phthalocyanines are activated by light in the range of 650 – 800 nm.

Bacterioporphyrins are chemical compounds that, like other porphyrins, contain the characteristic porphyrin ring. They differ from typical porphyrins such that they are found in bacteria, and their structure may vary from those present in eukaryotic organisms. The activation range for bacterioporphyrins is 600 – 700 nm.

7. Distribution of PSs to cancer cells

The mechanisms underlying the distribution of PSs used in PDT to cancer cells are not fully understood. However, it is believed that their selective permeability through cancer tissue plays a key role in this process. As the hydrophobicity of a given chemical compound increases, the affinity of the PS for cancer tissue also increases. This notion is supported by studies showing that PSs bound to liposomes exhibit greater effectiveness and selectivity in targeting cancer cells. The distribution of these sensitizers is enhanced by the inclusion of amphiphilic systems, which facilitate their delivery to the cancer cells. These systems are stable in aqueous environments, yet possess non-polar compartments that can accommodate substrates. One effective strategy involves combining PSs with low-density lipoproteins (LDLs), as various types of cancer cells secrete a significant number of membrane receptors for LDLs. In cancer cells, PSs localize in the plasma membrane, Golgi apparatus, rough endoplasmic reticulum, and mitochondrial membrane. The mode of PS transport into the cell determines the type of cellular response in the target tissue. When PSs are transported by albumin, extensive impairment of the vascular system occurs, leading to tumor ischemia and hypoxia (Table 2). Conversely, when PSs are transported by LDLs, early and significant damage to cancer cells takes place, primarily through necrotic and apoptotic processes.

8. Side effects and contraindications in PDT

PDT has relatively few contraindications. These include hypersensitivity to the ingredients of topical preparations used in the treatment of dermatological conditions and diseases associated with photosensitivity (e.g., lupus and porphyrias). Patients with porphyrias, a group of rare metabolic diseases linked to impaired porphyrin synthesis, may be at increased risk of photosensitization reactions. As such, the use of PDT may be limited in these individuals. People with advanced kidney or liver disease may have a reduced ability to eliminate photosensitizing agents, which could increase the risk of side effects. The safety of PDT during pregnancy has not been fully investigated, and as a precaution, it is generally recommended to avoid PDT in pregnant women, particularly during the first trimester. It is worth emphasizing that each case should be considered individually, with decisions regarding the use of PDT made by the attending physician, who must take into account the patient's overall health and the specifics of their condition. Regardless, side effects manifest as a modulation of the inflammatory response and local immunosuppression, which may result in pain, burning, swelling, and redness at the irradiation site. These symptoms typically resolve within a few hours after the procedure, although swelling and erythema may persist for several days. A late side effect may include hyper- or hypo-pigmentation at the treatment site, particularly in patients with darker skin types. Skin peeling is also a normal reaction to PDT. In addition, PDT may increase the expression of antigens on the surface of cancer cells, which can enhance the immune response. General reactions such as fatigue or headache have also been reported in some patients.

It is important to note that PDT has shown promising results as a treatment for Barrett's esophagus, though its use may be limited due to certain undesirable effects. With ongoing studies in modern laboratories and clinical facilities, efforts are underway to improve the efficacy of PDT while minimizing side effects. Furthermore, research is exploring the potential impact of genetic abnormalities on PDT effectiveness. By integrating the knowledge gained so far, PDT has the potential to become a breakthrough treatment in medicine.[30]

9. New perspectives in PDT

The heavy atom effect and chemical configuration play crucial roles in enabling boron-dipyrromethene (BODIPY) derivatives to generate $^1O_2$ for PDT. BODIPY and its

Table 2. The most commonly used photosensitizers in photodynamic therapy

Photosensitizer	Generic name	Wavelength (nm)	Application
Porphyrins	Photofrin, 5-aminolevulinic acid	600 – 700	Skin (superficial), head and neck, internal tumors (sometimes)
Chlorophyllins	Verteporfin	690	Eye diseases, mainly macular degeneration
Phthalocyanines	Chlorine aluminum sulfonate	650 – 800	Surface and internal
Bacterioporphyrins	Fotoditazin	600 – 700	Bacterial skin infections
Hematoporphyrin	Tookad	763	Prostate cancer

derivatives are synthesized by reacting 2,2'-dipyrromethene derivatives with boron trifluoride-diethyl ether complex ($BF_3(C_2H_5)_2O$) in the presence of triethylamine or 1,8-diazabicyclo5.4.0]undec-7-ene. Recent advancements have led to the design and synthesis of BODIPY-based platinum complexes for PDT, where the introduction of platinum atoms has been shown to improve both solubility and $^1O_2$ quantum yield.[31] BODIPY-hetero[5]helicene compounds, which combine the structures of BODIPY and hetero [5]helicene, have also been synthesized. These compounds exhibit excellent optical properties and high ISC efficiency, with ISC efficiency correlating to the torsion angles of the compounds. Studies have explored their potential as PDT agents, and one BODIPY-hetero[5] helicene compound was found to effectively kill cancer cells upon light exposure. The anticancer efficacy of this compound was verified using clonogenic and MTT assays, showing that they can effectively target and kill cancer cells from various tissue origins, including U2-OS, MCF-7, and MDA-MB-231 cell lines after photo exposure [B]. PDT using aza-BODIPY has also been shown to induce apoptosis in MCF-7 breast cancer cells by activating p53 and caspase 3. Flow cytometry analysis revealed that 28% of the cells underwent apoptosis. Gene expression analysis post-PDT exhibited downregulation of epidermal growth factor, lymphoid enhancer-binding factor 1, WNT family member 1, transcription factor 7, and transforming growth factor beta receptor II genes, alongside upregulation of caspase 3 and tumor protein P53. PDT also impairs cell connectivity and affects the cell cycle. Notably, these effects were not observed in control cells and MCF-7 cells under dark field conditions, indicating that aza-BODIPY possesses potent antitumor photodynamic activity.[32,33]

Boron-dipyrromethene compounds are widely utilized in various fields, particularly in biomedicine and technology. In biomedicine, BODIPYs are used as fluorescent probes for bioimaging and as $^1O_2$ generators in PDT. They also serve as fluorescent sensors, bioconjugate components, laser dyes, and switches. In technology, BODIPYs are applied in solar fuel generation, photovoltaic devices, antenna systems, photoredox catalysis, photooxidation of organic pollutants, and the photoinitiation of polymerization. A key challenge in the development of BODIPY compounds is improving their solubility in water and physiological media while preventing the formation of non-fluorescent aggregates. One promising approach is the incorporation of hydrophilic fragments, such as polyethylene glycol (PEG), N,N-bis(2-hydroxyethyl)amine, sugars, nucleotides, or ionic groups (carboxylic, sulfuric, and ammonium acids) into the BODIPY structure, which enhances their solubility in water and prevents aggregation. The integration of PEG into drugs improves their solubility in water, facilitates cellular uptake, and increases the overall therapeutic efficacy.[34]

The amphipathic polymer PS PEG-BODIPY was developed as a carrier for DDS with real-time tracking properties. Composed of a hydrophilic PEG segment and a hydrophobic BODIPY segment, PEG-BODIPY enables the encapsulation of anticancer drugs, such as doxorubicin (DOX), into micelle spaces. These micelles spontaneously self-assemble in aqueous environments into bilayer amphiphilic polyethylene glycol-grafted (PEGylated) BODIPY polymers. A cellular uptake study of PEGylated BODIPY and DOX@PEGylated BODIPY nanoformulations showed that MDA-MB-231 cells endocytosed these nanoformulations within 24 h.[35] The fluorescence intensity of PEGylated BODIPY significantly increased with the concentration of nanoformulations, and both types of nanoformulations were primarily localized in lysosomes.

The results of studies on the anticancer effects of PEGylated BODIPY and DOX@PEGylated BODIPY nanopreparations demonstrated high phototoxicity and low toxicity in dark conditions.[36] Upon irradiation, PEGylated BODIPYs exhibited cytotoxicity with an IC50 of approximately 25 nM, whereas DOX@PEGylated BODIPYs showed even stronger phototoxicity, with an IC50 of around 10 nM. The higher IC50 for DOX@PEGylated BODIPY can be attributed to the combination of BODIPY-mediated PDT and DOX chemotherapy.

In DOX@PEGylated BODIPY nanopreparations, BODIPY compounds generate $^1O_2$ during light irradiation, not only inducing phototoxicity in cancer cells but also

promoting the degradation of the nanopreparations. This degradation facilitates the release of DOX into the cell nucleus, thereby enabling the combined action of PDT and chemotherapy. In conclusion, these micelles can serve as nanocarriers for chemotherapeutic drugs such as DOX, thus enabling a dual treatment approach of photodynamic and chemotherapeutic anticancer treatment. The synthesized water-soluble BODIPY dyes, designated 24 and 25, modified with PEG, showed improved solubility and fluorescence quantum yield in water while minimizing the tendency to aggregate.[37]

BODIPY conjugates 24 and 25 demonstrated no toxicity to MCF-7 cells at low concentrations for 24 h. These dyes were permeable to MCF-7 cells and accumulated in the cytoplasm, as confirmed by confocal microscopy. These findings highlight the promising potential of these conjugates for use in fluorescence bioimaging.[38]

By combining the modified BODIPY with hydrophilic PEG, the amphipathic polymer PEG-BODIPY 26 was synthesized, exhibiting effective PDT capabilities with "favorable" phototoxicity against HepG2 and 4T1 cell lines. Amphiphilic macromolecules 26 can self-assemble into micelles of appropriate size, allowing for long-term circulation in the body and targeted accumulation in tumor sites. Polymer PEG-BODIPY 26 functions both as a PS and as a fluorescent probe, presenting excellent therapeutic and imaging properties *in vitro* and *in vivo*.

Aza-BODIPYs are structural analogs of organic dyes from the group of 4,4-difluoro-4-bora-3a,4a-diaza-s-indacenes (i.e., BODIPY), known for their high fluorescence quantum yield, photostability, and absorption and emission properties. These compounds exhibit absorption and emission across the visible light to near-infrared spectrum. Some aza-BODIPY derivatives also contain photosensitizing groups. Photosensitization is a process in which a PS absorbs light and transfers energy to another substance, inducing a chemical or physical reaction. These derivatives are employed in PDT for cancer treatment, using their ability to generate reactive oxygen species under light exposure. In medicine, photosensitization is most commonly associated with PDT. Tetraaryl aza-BODIPY, a derivative that serves as the basis for constructing a PS, exhibits absorption properties within the therapeutic window, ensuring effective treatment while minimizing toxicity and side effects. Due to the presence of a heavy atom, this compound can efficiently generate $^1O_2$. Another effective PS used in PDT is the biotin-conjugated aza-BODIPY derivative, obtained through Sonogashira coupling. This modification increases the compound's affinity for cancer cells, making it more effective compared to other PSs.[39]

Zinc(III)-dipicolylamine di-iodo-BODIPY is a chemical complex that has attracted significant interest due to its unique properties and potential applications in various scientific and technological fields. This compound, which consists of a zinc atom, dipicolylamine, and di-iodine BODIPY, represents an innovative combination in coordination chemistry.

These properties make zinc(III)-dipicolylamine di-iodo-BODIPY highly useful in nanotechnology, where it can be employed to construct nanomaterials with specific properties. Moreover, the compound's fluorescent capabilities open up applications in biochemistry, enabling the tracking of cells and chemicals in living organisms. In medical diagnostics, this complex can be utilized for tissue imaging, contributing to the advancement of modern diagnostic techniques. Its unique properties make it valuable across emerging fields of science, advancing progress in optical materials, nanotechnology, cell biology, and medical diagnostics. Furthermore, its ability to interact with metal ions allows for use in ion recognition and separation processes, which are applied in various branches of chemistry. Its fluorescence also enables precise tracking of biological processes at the cellular level, which is critical for analyzing disease mechanisms and molecular interactions. The compound's ability to enhance contrast can help identify pathological changes at early stages, a crucial factor for effective diagnosis and treatment. Moreover, this compound has potential applications in optical sensors, where its responsiveness to specific chemicals or ions can facilitate the detection and monitoring of various chemical processes.[40] Recent advancements in PDT utilizing nanotechnology, including the use of quantum dots as innovative PSs or energy donors, along with the combination of PDT with radiotherapy and immunotherapy, represent promising future approaches for cancer treatment.[41] The incorporation of PSs into conjugated polymer NPs has proven beneficial by improving $^1O_2$ formation through effective energy transfer. The evolution of nanotechnology has emerged as a promising avenue for enhancing the performance of existing PSs and overcoming significant challenges in cancer PDT.[42] In addition, silicon phthalocyanines are recognized as suitable PSs for PDT due to their ability to generate $^1O_2$ with a long triplet lifetime.[43]

10. Future clinical prospects of PDT

Convincing clinicians and experienced doctors to adopt PDT in clinical practice remains challenging due to the ongoing development of this treatment in cancer therapy. Treatment regimens still require optimization and standardization to ensure improved therapeutic efficacy. Moreover, unfavorable side effects have been

reported during PDT, but these were primarily due to the use of inappropriate treatment protocols. For this reason, researchers emphasize that, with the appropriate selection of PSs and continuously refined therapy techniques, undesirable effects can be minimized or avoided. In the development of PDT, a key focus should be on the potential for combining PDT with other treatment modalities, such as immunotherapy or gene therapy. Such combinations could significantly enhance the efficiency and effectiveness of PDT in cancer treatment, leading to improved clinical outcomes. Furthermore, ongoing advancements in PDT involve the development of more advanced phototherapy technologies and the refinement of personalized treatment approaches, which tailor therapy to individual patients based on their specific needs and symptoms. For PDT to be a more effective tool in cancer therapy, efforts must focus on improving its selectivity and precision, that is, further research into better methods of delivering PSs to target areas and increasing the selectivity of PDT in killing pathological cells while sparing healthy tissues. In addition, optimizing treatment protocols, including determining the ideal PS doses, light exposure durations, and overall therapy length, could significantly increase the effectiveness of PDT.

11. Conclusion

Despite its current successes, PDT continues to evolve and requires further research and innovation to fully realize its potential in treating various conditions. Both pre-clinical and clinical studies have yielded promising results regarding PDT as an effective method for treating cancers of various locations and stages. For PDT to be widely accepted by medical professionals as a legitimate treatment option, its evolving mechanism and the positive outcomes observed in past research must be acknowledged. To successfully incorporate PDT into clinical practice, physicians need comprehensive training not only in the technique itself but also in the proper use of PSs, which are critical to the therapy's effectiveness. Unfortunately, mastering PDT for cancer treatment requires an extended learning process, partly due to the risk of side effects if the light activates the PS in normal tissues, potentially causing harm. Despite these challenges, the promising results suggest that PDT could become a key therapeutic approach in the fight against cancer.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: All authors
Writing – original draft: All authors
Writing – review & editing: All authors

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

References

1. Kessel, D. Photodynamic therapy: A brief history. *J Clin Med*. 2019;8(10):1581.

   doi: 10.3390/jcm8101581

2. Chilakamarthi U, Giribabu L. Photodynamic therapy: Past, present and future. *Chem Rec.* 2017;17(8):775-802.

   doi: 10.1002/tcr.201600121

3. Nowis D, Makowski M, Stokłosa T, Legat M, Issat T, Gołab J. Direct tumor damage mechanisms of photodynamic therapy. *Acta Biochim Pol*. 2005;52(2):339-352.

4. Kwiatkowski S, Knap B, Przystupski D, *et al*. Photodynamic therapy - mechanisms, photosensitizers and combinations. *Biomed Pharmacother*. 2018;106:1098-1107.

   doi: 10.1016/j.biopha.2018.07.049

5. Luketich JD, Christie NA, Buenaventura PO, Weigel TL, Keenan RJ, Nguyen NT. Endoscopic photodynamic therapy for obstructing esophageal cancer: 77 cases over a 2-year period. *Surg Endosc*. 2000;14(7):653-657.

   doi: 10.1007/s004640000144

6. Bown SG, Rogowska AZ, Whitelaw DE, *et al*. Photodynamic therapy for cancer of the pancreas. *Gut*. 2002;50(4):549-557.

   doi: 10.1136/gut.50.4.549

7. Abulafi AM, Allardice JT, Williams NS, van Someren N, Swain CP, Ainley C. Photodynamic therapy for malignant tumours of the ampulla of Vater. *Gut*. 1995;36(6):853-856.

   doi: 10.1136/gut.36.6.853

8. van Duijnhoven FH, Rovers JP, Engelmann K, *et al*. Photodynamic therapy with 5,10,15,20-tetrakis(m-hydroxyphenyl) bacteriochlorin for colorectal liver metastases is safe and feasible: Results from a phase I study. *Ann Surg Oncol*. 2005;12(10):808-816.

doi: 10.1245/ASO.2005.09.005

9. DeWitt JM, Sandrasegaran K, O'Neil B, *et al*. Phase 1 study of EUS-guided photodynamic therapy for locally advanced pancreatic cancer. *Gastrointest Endosc*. 2019;89(2):390-398.

doi: 10.1016/j.gie.2018.09.007

10. Yano T, Wang KK. Photodynamic therapy for gastrointestinal cancer. *Photochem Photobiol*. 2020;96(3):517-523.

doi: 10.1111/php.13206

11. Huggett MT, Jermyn M, Gillams A, *et al*. Phase I/II study of verteporfin photodynamic therapy in locally advanced pancreatic cancer. *Br J Cancer*. 2014;110(7):1698-1704.

doi: 10.1038/bjc.2014.95

12. Lightdale CJ, Heier SK, Marcon NE, *et al*. Photodynamic therapy with porfimer sodium versus thermal ablation therapy with Nd: YAG laser for palliation of esophageal cancer: A multicenter randomized trial. *Gastrointest Endosc*. 1995;42(6):507-512.

doi: 10.1016/s0016-5107(95)70002-1

13. Kashtan H, Konikoff F, Haddad R, Skornick Y. Photodynamic therapy of cancer of the esophagus using systemic aminolevulinic acid and a non laser light source: A phase I/II study. *Gastrointest Endosc*. 1999;49(6):760-764.

doi: 10.1016/s0016-5107(99)70297-x

14. Kato H, Horai T, Furuse K, *et al*. Photodynamic therapy for cancers: A clinical trial of porfimer sodium in Japan. *Jpn J Cancer Res*. 1993;84(11):1209-1214.

doi: 10.1111/j.1349-7006.1993.tb02823.x

15. Maier A, Tomaselli F, Matzi V, Rehak P, Pinter H, Smolle-Jüttner FM. Does new photosensitizer improve photodynamic therapy in advanced esophageal carcinoma? *Lasers Surg Med*. 2001;29(4):323-327.

doi: 10.1002/lsm.1124

16. Da Cruz Andrade PV, Euzebio Alves VT, de Carvalho VF, *et al*. Photodynamic therapy decrease immune-inflammatory mediators levels during periodontal maintenance. *Lasers Med Sci*. 2017;32(1):9-17.

doi: 10.1007/s10103-016-2076-7

17. Kelty CJ, Ackroyd R, Brown NJ, Stephenson TJ, Stoddard CJ, Reed MW. Endoscopic ablation of Barrett's oesophagus: A randomized-controlled trial of photodynamic therapy vs. argon plasma coagulation. *Aliment Pharmacol*. 2004;20(11-12):1289-1296.

doi: 10.1111/j.1365-2036.2004.02277.x

18. Kohoutova D, Haidry R, Banks M, *et al*. Long-term outcomes of the randomized controlled trial comparing 5-aminolaevulinic acid and Photofrin photodynamic therapy for Barrett's oesophagus related neoplasia. *Scand J Gastroenterol*. 2018;53(5):527-532.

doi: 10.1080/00365521.2017.1403646

19. Ackroyd R, Brown NJ, Davis MF, *et al*. Photodynamic therapy for dysplastic Barrett's oesophagus: A prospective, double blind, randomised, placebo controlled trial. *Gut*. 2000;47(5):612-617.

doi: 10.1136/gut.47.5.612

20. Gray J, Fullarton GM. Long term efficacy of Photodynamic Therapy (PDT) as an ablative therapy of high grade dysplasia in Barrett's oesophagus. *Photodiagnosis Photodyn Ther*. 2013;10(4):561-565.

doi: 10.1016/j.pdpdt.2013.06.002

21. Hage M, Siersema PD, van Dekken H, *et al*. 5-aminolevulinic acid photodynamic therapy versus argon plasma coagulation for ablation of Barrett's oesophagus: A randomised trial. *Gut*. 2004;53(6):785-790.

doi: 10.1136/gut.2003.028860

22. Kim EJ, Mangold AR, DeSimone JA, *et al*. Efficacy and safety of topical hypericin photodynamic therapy for early-stage cutaneous T-cell lymphoma (mycosis fungoides): The FLASH phase 3 randomized clinical trial. *JAMA Dermatol*. 2022;158(9):1031-1039.

doi: 10.1001/jamadermatol.2022.2749

23. Séguier S, Souza SL, Sverzut AC, *et al*. Impact of photodynamic therapy on inflammatory cells during human chronic periodontitis. *J Photochem Photobiol B*. 2010;101(3):348-354.

doi: 10.1016/j.jphotobiol.2010.08.007

24. Wu C, Qiu X, He C, Ci C. Effect of 5-aminolevulinic acid photodynamic therapy with transfer factor capsules in the treatment of multiple plantar warts. *Biomed Res Int*. 2022;2022:1220889.

doi: 10.1155/2022/1220889

25. Theodoraki MN, Lorenz K, Lotfi R, *et al*. Influence of photodynamic therapy on peripheral immune cell populations and cytokine concentrations in head and neck cancer. *Photodiagnosis Photodyn Ther*. 2017;19:194-201.

doi: 10.1016/j.pdpdt.2017.05.015

26. Thanos SM, Halliday GM, Damian DL. Nicotinamide reduces photodynamic therapy-induced immunosuppression in humans. *Br J Dermatol*. 2012;167(3):631-636.

doi: 10.1111/j.1365-2133.2012.11109.x

27. De Moraes M, de Vasconcelos RC, Longo JP, *et al*. Effects of photodynamic therapy mediated by nanoemulsion containing chloro-aluminum phthalocyanine: A histologic and immunohistochemical study in human gingiva. *Photodiagnosis Photodyn Ther*. 2015;12(4):592-597.

doi: 10.1016/j.pdpdt.2015.10.009

28. Evangelou G, Farrar MD, Cotterell L, *et al*. Topical

photodynamic therapy significantly reduces epidermal Langerhans cells during clinical treatment of basal cell carcinoma. *Br J Dermatol*. 2012;166(5):1112-1115.

doi: 10.1111/j.1365-2133.2012.10823.x

29. Pourabbas R, Kashefimehr A, Rahmanpour N, Babaloo Z, Kishen A, Tenenbaum HC. Effects of photodynamic therapy on clinical and gingival crevicular fluid inflammatory biomarkers in chronic periodontitis: A split-mouth randomized clinical trial. *J Periodontol*. 2014;85(9):1222-1229.

doi: 10.1902/jop.2014.130464

30. Wang KK, Lutzke L, Borkenhagen L, *et al*. Photodynamic therapy for Barrett's esophagus: Does light still have a role? *Endoscopy*. 2008;40(12):1021-1025.

doi: 10.1055/s-0028-1103405

31. Qi F, Yuan H, Chen Y, *et al*. BODIPY-based monofunctional Pt (II) complexes for specific photocytotoxicity against cancer cells. *J Inorg Biochem*. 2021;218:111394.

doi: 10.1016/j.jinorgbio.2021.111394

32. Koli M, Gupta S, Chakraborty S, *et al*. Design and Synthesis of BODIPY-Hetero[5]helicenes as Heavy-atom-free triplet photosensitizers for photodynamic therapy of cancer. *Chemistry*. 2023;29(57):e202301605.

doi: 10.1002/chem.202301605

33. Elgun T, Yurttas AG, Cinar K, Ozcelik S, Gul A. Effect of aza-BODIPY-photodynamic therapy on the expression of carcinoma-associated genes and cell death mode. *Photodiagnosis Photodyn Ther*. 2023;44:103849.

doi: 10.1016/j.pdpdt.2023.103849

34. Zhang J, Wang N, Ji X, Tao Y, Wang J, Zhao W. BODIPY-based fluorescent probes for biothiols. *Chemistry*. 2020;26(19):4172-4192.

doi: 10.1002/chem.201904470

35. Antina E, Bumagina N, Marfin Y, *et al*. BODIPY conjugates as functional compounds for medical diagnostics and treatment. *Molecules*. 2022;27(4):1396.

doi: 10.3390/molecules27041396

36. Barattucci A, Gangemi CM, Santoro A, Campagna S, Puntoriero F, Bonaccorsi P. Bodipy-carbohydrate systems: Synthesis and bio-applications. *Org Biomol Chem*. 2022;20(14):2742-2763.

doi: 10.1039/d1ob02459k

37. Das S, Dey S, Patra S, *et al*. BODIPY-based molecules for biomedical applications. *Biomolecules*. 2023;13(12):1723.

doi: 10.3390/biom13121723

38. Ma C, Zhang T, Xie Z. Leveraging BODIPY nanomaterials for enhanced tumor photothermal therapy. *J Mater Chem B*. 2021;9(36):7318-7327.

doi: 10.1039/d1tb00855b

39. Chang HJ, Bondar MV, Munera N, *et al*. Femtosecond spectroscopy and nonlinear optical properties of aza-BODIPY derivatives in solution. *Chemistry*. 2022;28(17):e202104072.

doi: 10.1002/chem.202104072

40. Prieto-Montero R, Prieto-Castañeda A, Sola-Llano R, *et al*. Exploring BODIPY derivatives as singlet oxygen photosensitizers for PDT. *Photochem Photobiol*. 2020;96(3):458-477.

doi: 10.1111/php.13232

41. Alvarez N, Sevilla A. Current advances in photodynamic therapy (PDT) and the future potential of PDT-combinatorial cancer therapies. *Int J Mol Sci*. 2024;25(2):1023.

doi: 10.3390/ijms25021023

42. Singh N, Sen Gupta R, Bose S. A comprehensive review on singlet oxygen generation in nanomaterials and conjugated polymers for photodynamic therapy in the treatment of cancer. *Nanoscale*. 2024;16(7):3243-326842.

doi: 10.1039/d3nr05801h

43. Köse GG, Erdoğmuş A. Dual effect of light and ultrasound for efficient singlet oxygen generation with novel diaxial silicon phthalocyanine sensitizer. *Photochem Photobiol*. 2024;100(1):52-66.

doi: 10.1111/php.13834