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Photodynamic Therapy for the Diagnosis and Treatment of Cancer

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Abstract: Cancer is the second leading cause of death worldwide. The International Agency for Research on Cancer global report of 2020 estimated 19.3 million new cancer cases and almost 10.0 million cancer deaths. The global cancer burden is expected to be 28.4 million cases in 2040, a 47% rise from 2020. Photodynamic therapy (PDT) relies on the presence of oxygen, light at a specific wavelength, and photosensitizers. Among these components, photosensitizers are the primary focus of intensive research for optimization. So far, PDT has been used to treat brain, head, neck, pancreas, breast, prostate, skin, colorectal, oral, lung, bronchial, and liver cancers. The combination of PDT with standard cancer treatment options is proving more effective against most resistant cancers. Photodynamic diagnosis is superior to white light cystoscopy in detecting tumors. Based on the recent literature review, it is clear that the effective use of PDT for cancer treatment will require the modulation of other metabolic pathways to combat drug resistance and improve treatment outcomes. These modulations can include cell cycle inhibition, inhibition of DNA repair mechanisms, inhibition of cell adhesion, and many other molecular mechanisms that can enhance the pharmacokinetics and pharmacodynamics activities of PS and reduce tumor resistance to treatment. This review looks at the principles of PDT, its application to cancer diagnosis and treatment, and its limitations. PDT has enormous potential for cancer diagnosis and treatment in developing countries because of its low cost and wide range of applications. Analysis of recent research on PDT shows that PDT has massive potential for cancer treatment and should not always be used as the last resort after all other cancer treatment options have failed.

Keywords: Photosensitizers, Photodynamic Therapy, Reactive Oxygen Radicals, Photodynamic Diagnosis, Cancer

1. Introduction

Cancer is the second leading cause of death worldwide [1]. The International Agency for Research on Cancer worldwide report of 2020 estimated 19.3 million new cancer cases (18.1 million excluding nonmelanoma skin cancer) and almost 10.0 million cancer deaths 9.9 million excluding nonmelanoma skin cancer [2]. Presently female breast cancer has surpassed lung cancer [2]. Furthermore, the global cancer burden is expected to be 28.4 million cases in 2040, a 47% rise from 2020 [2]. Cancer cases are on the rise both in developed and developing countries. Accessing reliable and affordable cancer diagnosis and treatment in developing countries is difficult. Research conducted by Hernandez *et al*. in 2018 concluded that the annual price of mAb therapies is about $100,000 higher in oncology and hematology than in other disease states [3]. At the early stage of cancer development, surgery can prevent the cancerous tissue from developing further than at a late-stage diagnosis when cancer cells have started uncontrolled spread to distant organs (metastasis). Surgery at the early stage of cancer development depends on the type of cancer, the patient's age, the severity of the disease, and many other

comorbidities. Typical cancer treatment includes chemotherapy, immunotherapy, cryotherapy, surgery, bone marrow transplant, radiotherapy, and hormonotherapy [4-6]. These treatment options have adverse effects on the patient.

On the other hand, photodynamic therapy (PDT) for cancer diagnosis and treatment is much cheaper and highly efficient with few adverse side effects. PDT targets and kills cancer cells using a visible light source at a specific wavelength [7]. Unlike radiotherapy, where the external beam produces ionization radiation, PDT utilizes non-ionizing electromagnetic irradiation. It is worth noting that PDT has other clinical applications, such as disinfection and treatment of multidrug resistance viral and bacterial infections [8, 9].

The critical components for the successful application of PDT are oxygen, light, and photosensitizer. Among these components, photosensitizers are the most critical components under intensive research for optimization [10]. Photosensitizers are substances that are converted to active intermediates when exposed to light. So far, PDT has been used to treat brain, head, neck, pancreas, intraperitoneal cavity, breast, prostate, skin, lung, and liver cancers [11, 12]. In circumstances where all other cancer treatments have failed, or the disease is inoperable, PDT or in combination with other cancer treatments, can be the best option for treatment of certain types of cancer. Despite its massive potential for cancer treatment, PDT is highly underutilized. This review looks at the principles of PDT, its application to cancer diagnosis and treatment, and its limitations. PDT has enormous potential for cancer diagnosis and treatment in developing countries because of its low cost and wide range of applications.

1.1. History of PDT

Light's use for treating physical and mental illnesses dates back to the beginning of civilization. During ancient civilization, it was known as heliotherapy [7]. Indeed, ancient civilizations such as Egypt, China, Greece, India, and Rome utilized phototherapy to treat vitiligo, psoriasis, rickets, skin cancer, and psychosis [7]. At the beginning of the 20th century, advances in science allowed Arnold Rikli, Oscar Raab, Niels Finsen, and Herman von Tappeiner to rediscover photodynamic therapy [13]. They used photodynamic therapy to treat skin cancer, although with varied results. PDT was resuscitated in the 1960s after applying the hematoporphyrin derivative (HDT) in the treatment of bladder cancer [14]. One decade later, PDT was used in a mice model to treat breast cancer and later in patients with skin, prostate, breast, and colon tumors [15]. The increased success of HDT in cancer treatment led to its approval in Canada to treat bladder cancer in the early 1990s [16]. The drug was marketed as porfimer sodium (Photofrin®), a semi-purified version of HDT.

Although porfimer sodium presented some side effects, among them severe and prolonged skin photosensitivity, it was approved by the Food and Drug Administration in the USA for treatment of oesophageal and bronchial cancers and Barrett's esophagus [17, 18]. Many other countries around the world further approved it. From then on, many more compounds have been approved for treating various cancer, bacterial, fungal, and viral diseases. It is clear from Figure 1 that the PDT has been around for a very long time, and it is here to stay.

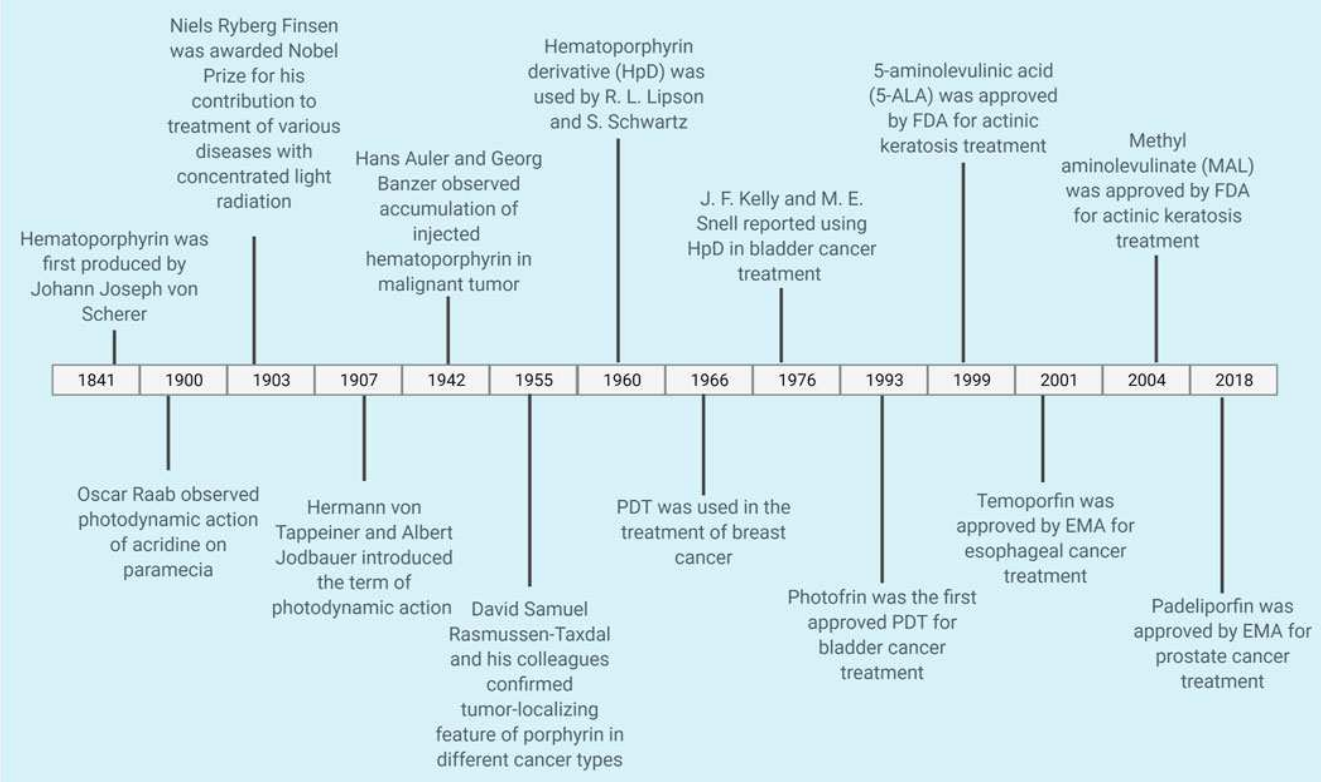

Figure 1. *Trends in advances of Photodynamic Therapy from 1841 onwards. Courtesy of Gunaydin et al., 2021 [7].*

As stated earlier, one of the essential parameters in PDT is photosensitizers (PSs). PSs are categorized into the first generation, second generation, and third generation. The first-generation PSs comprised mainly of naturally occurring porphyrins and their derivatives (Figure 3). The first-generation PSs presented several molecular and cellular challenges, such as low absorption bands at red wavelengths, high hydrophobicity, cytotoxicity, and phototoxicity [19, 20]. The second-generation PSs were designed to overcome some of these challenges. Some examples of the second-generation PSs include benzoporphyrin, 5-aminolevulinic acid, protoporphyrin IX, phthalocyanine, and chlorin, as illustrated in Figure 3.

The third-generation PSs are made by modifying existing drugs to improve their pharmacokinetic properties [21]. These modifications include antibody conjugation (Figure 2) and encapsulated agents into carriers (e.g., liposomes, micelles, nanoparticles, polymer, magnetic gold, quantum dot, or dendrimer). In general, the key characteristics that must be considered when designing PDT PSs are long and variable absorption wavelengths, high quantum yield, low toxicity, improved pharmacokinetics, hydrophobicity/amphiphilicity, purity, and stability.

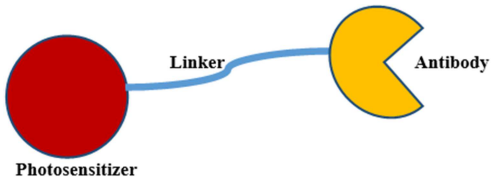

Figure 2. *Bioconjugation and encapsulation of a typical third-generation photosensitizer. A photosensitizer is linked to an antibody to improve selectivity and specificity toward cancer cells.*

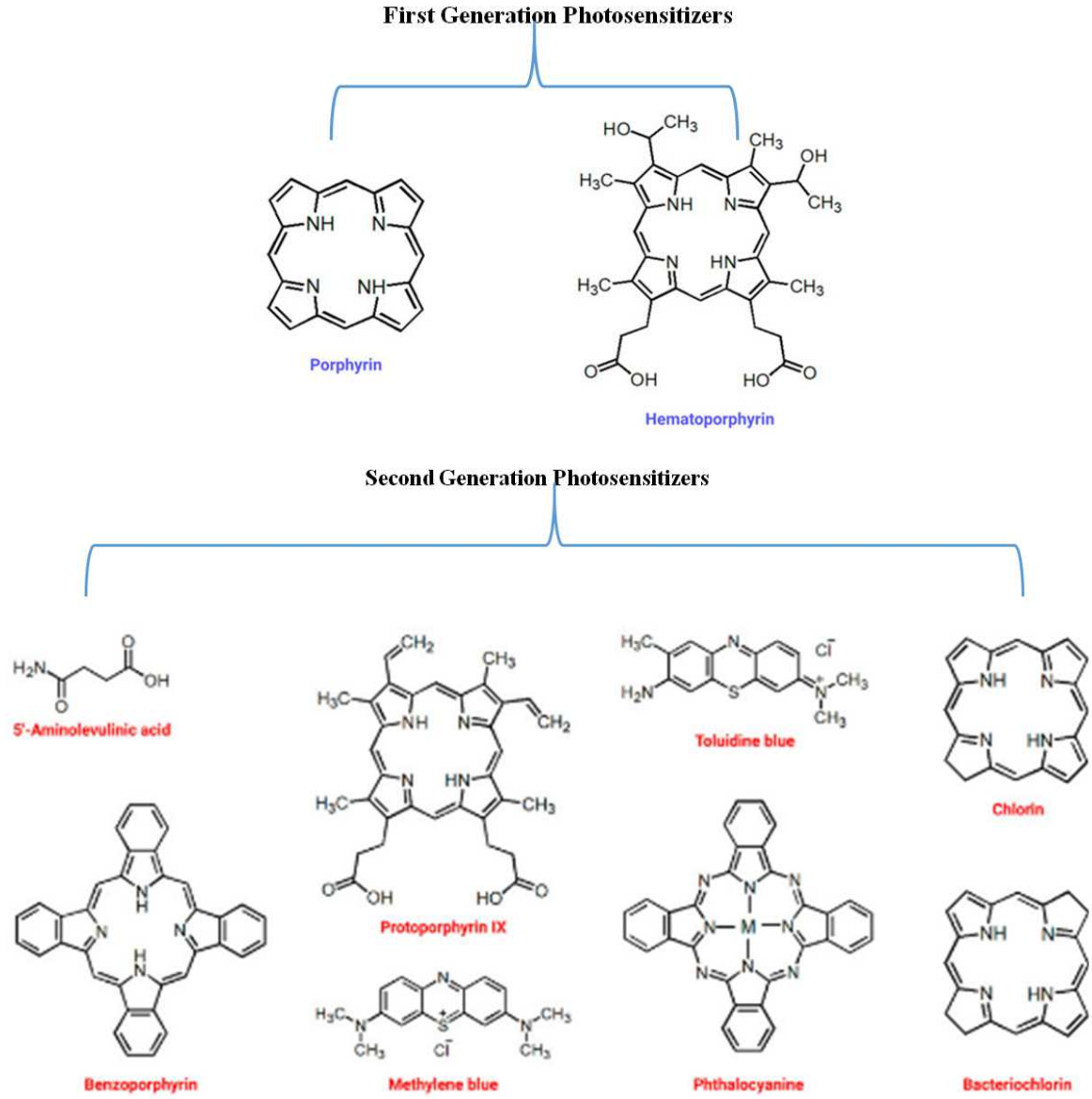

Figure 3. *First- and second-generation photosensitizers. The first generation is mainly comprised of naturally occurring porphyrins and their derivatives. Most second-generation photosensitizers are based on porphyrin and chlorin structures, such as benzoporphyrins, phthalocyanines, and protoporphyrin IX.*

1.2. Aim of This Review

This review aims to critically analyze the recent advances in photodynamic therapy (PTD), focusing on its application to cancer treatment in an African medical setting. Cancer diagnosis and treatment are costly. Unfortunately, most cancer illnesses are also incurable. With proper clinical trials on the effectiveness of PDT and its adverse effects, PDT can genuinely be the way forward for treating cancer and many other diseases that are increasingly resisting drugs and overcoming the host's natural immunity. Photodynamic therapy will undoubtedly play a significant role in cancer diagnosis and treatment in the near future.

2. Strategies for Photodynamic Therapy

Light, photosensitizer, and oxygen are the three most essential components required for treating cancer with photodynamic therapy. Figure 4 illustrates the mechanisms of PDT. In general, the patient with cancer is injected with PS at a specific dosage, usually intravenously. She/he is then exposed to light at a specific wavelength. The presence of oxygen in the tumor leads to the formation of reactive oxygen species (ROS) due to the interaction between light and PS.

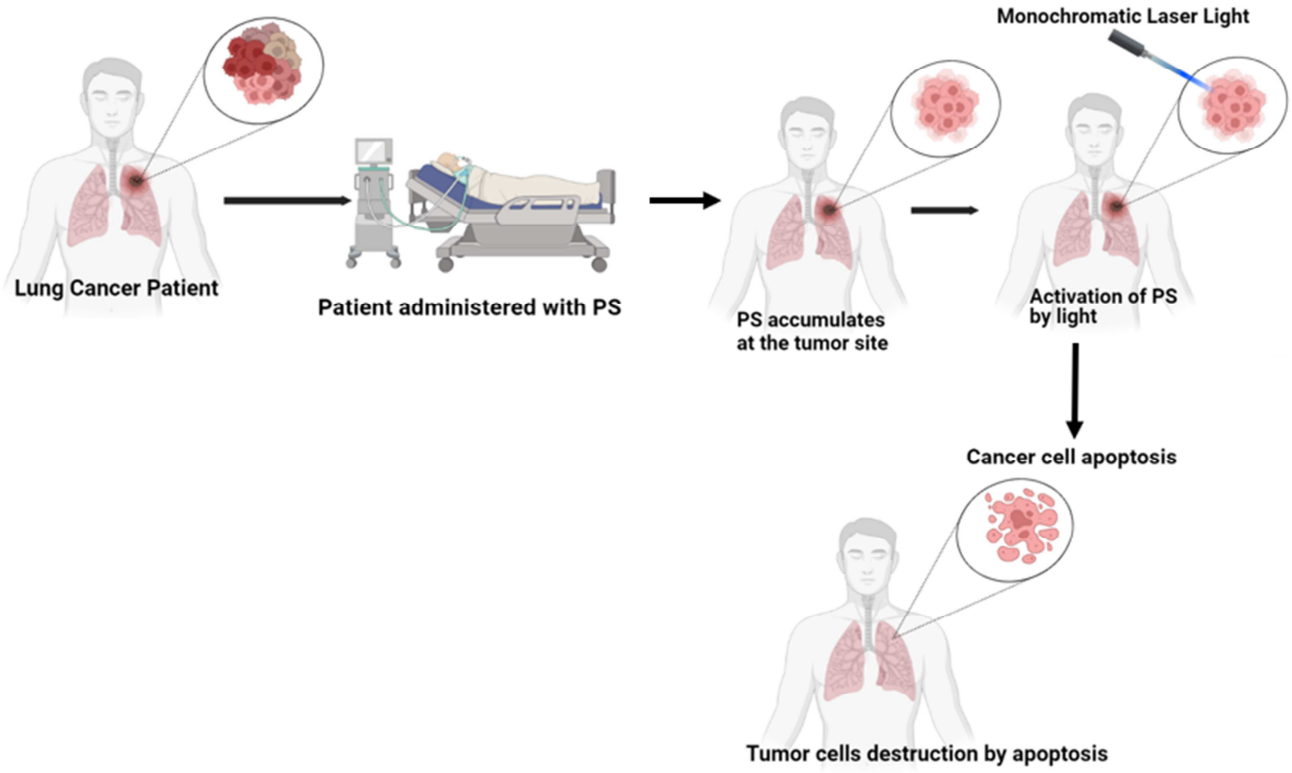

Figure 4. *Photodynamic therapy for the treatment of cancer. The patient is first administered with the photosensitizer (PS), which later accumulates in the tumor. The photosensitizer is then activated with light, which produces reactive oxygen species (ROS). ROS can damage the cell and its components, leading to the cancer cell's death through necrosis, apoptosis, necroptosis, or autophagy.*

PSs are always in the inactivated state before they are exposed to the light. Once activated, they lead to the formation of ROS. As reported by Ming *et al*. 2021, the formation of ROS requires plenty of oxygen in the tumor microenvironment [22]. The ROS have effector functions, i.e., cancer cell killing capabilities. The therapeutical application of PDT for cancer treatment involves two stages; formation of ROS when light interacts with PS and destruction of cancer by ROS. Unfortunately, most of the tumor microenvironment is hypoxia and obstructed by the ROS defense systems [22]. Excellent systems have now been developed to reduce tumor tissue hypoxia [22]. The most significant drawbacks to using PDT in cancer treatment are finding a suitable PS with appropriate specificity and selectivity, better water solubility, less toxicity to healthy cells, and skin photosensitivity. More research is currently underway to overcome these limitations, and some promising results have been reported [23-25]. The primary focus has been on developing novel strategies to increase specificity and selectivity, which can, in turn, increase efficiency.

2.1. PDT Light Sources and Dosimetry Parameters

Successful PDT requires delivery of an appropriate light dose to the entire cancerous tissue. One area to be considered when designing the light source for PDT is its ability to penetrate the cancerous tissue at desired photoactivation wavelengths. In most cases, the delivery of appropriate light

doses is determined by the extent of photoirradiation and the corresponding PDT effect. The American Association of Physicists in Medicine (AAPM) Report No. 88 states that the application of PDT for cancer treatment must ensure that the product of photoirradiation fluence rate and photoirradiation exposure time should exceed the threshold required to induce cell killing [26].

For a successful PDT, higher tissue penetration of light is observed in the deep red to near infra-red regions [27]. Thus, for *in vivo* application of PDT, preference is given to PSs that can be activated at wavelengths greater than 650 nm because of their deep tissue penetration capabilities. Two light sources are used for PDT; laser light and non-laser light (Table 1). Laser light sources are a bit expensive compared to non-laser light. Laser light sources include Argon and Argon-pumped Dye Lasers, Metal Vapor-pumped Dye Lasers, Solid State Lasers, Optical Parametric Oscillators, and Diode Lasers. The non-laser light sources include Tungsten Filament Quartz Halogen Lamps, Xenon Arc Lamps, Metal Halide Lamps, Phosphor-coated Sodium Lamps, and Fluorescent Lamps. Other light sources may include Light Emitting Diodes (LED) and Femtosecond Solid State Lasers. Laser light is preferred among the two sources of light due to its high power and wide wavelength range. Furthermore, laser light can easily be coupled to optical fibers for endoscopic use. [28]

Table 1. *Light Sources for Photdynamic Therapy for Cancer Treatment.*

Light Sources for Photodynamic Therapy			
Sunlight*	**Lamp**	**LED (a light-emitting diode)**	**Laser**
			
Freely available during daylight	Low cost	Low cost	Expensive
Simple	Simple	Small	Monochromatic
Broad spectrum	Broad spectrum	Low power	High power
Example include the Sun	Examples include Tungsten Filament Quartz Halogen Lamps, Xenon Arc Lamps, Metal Halide Lamps, Phosphor-coated Sodium Lamps, and Fluorescent Lamps	Examples include LED bulbs, LED panels lights, LED tube lights	Examples include Argon and Argon-pumped Dye Lasers, Metal Vapor-pumped Dye Lasers, Solid State Lasers, Optical Parametric Oscillators, Femtosecond Solid State Lasers, and Diode Lasers

*[29]

Different laser light sources have demonstrated their advantages and disadvantages. The argon laser light is one of the most widely used laser lights. Although argon laser light requires a high level of adjustment, it can easily be altered to different wavelengths to match the photoactivation wavelength of the PS in use.

The biggest hurdle in elucidating the threshold for PDT light dosage is determining the appropriate photoirradiation fluence rate and photoirradiation exposure time that can induce the killing of cancer cells. The issue here is that in most cases, the drug and light distribution are not always uniform in the entire tumor volume [30]. Several dosimetric techniques (PDT parameter versus treatment effect) are under investigation, such as image-assisted evaluation of PDT-induced biological effect [31, 32], measurement of fluorescence photobleaching of the photosensitizers, and measurement of total light energy absorbed by the drug per unit tissue volume [33, 34], and measurement of singlet oxygen luminescence [32, 35]. Recently chemoluminescent probe-incorporated nanoparticles have been used to monitor ROS levels after photoirradiation [36, 37]. Thus, for efficient application of PDT for cancer treatment, the PS delivery mechanisms, light sources, and dosimetry must be appropriately optimized for clinical application.

2.2. Photosensitizers and Photocytotoxicity Mechanisms

As stated earlier, one of the essential components of PDT is photosensitizers. The success of PDT is critically dependent on the intrinsic chemical and physical properties of PS to absorb light at a specific wavelength and then trigger a photochemical or photophysical chain reaction that leads to the production of ROS. PDT is a form of non-ionizing radiation therapy. The photosensitizer interacts with light to produce singlet oxygen. The singlet oxygen is converted to triplet state oxygen through changes in its spin state by a process known as intersystem crossing (Figure 5). In the triplet, state oxygen interacts with molecules in its vicinity to produce ROS. ROS such as superoxide and hydroxyl radicles are produced when the excited PS accepts a hydrogen atom. The low-energy molecular orbitals of PSs have a couple of electrons with opposite spins [38].

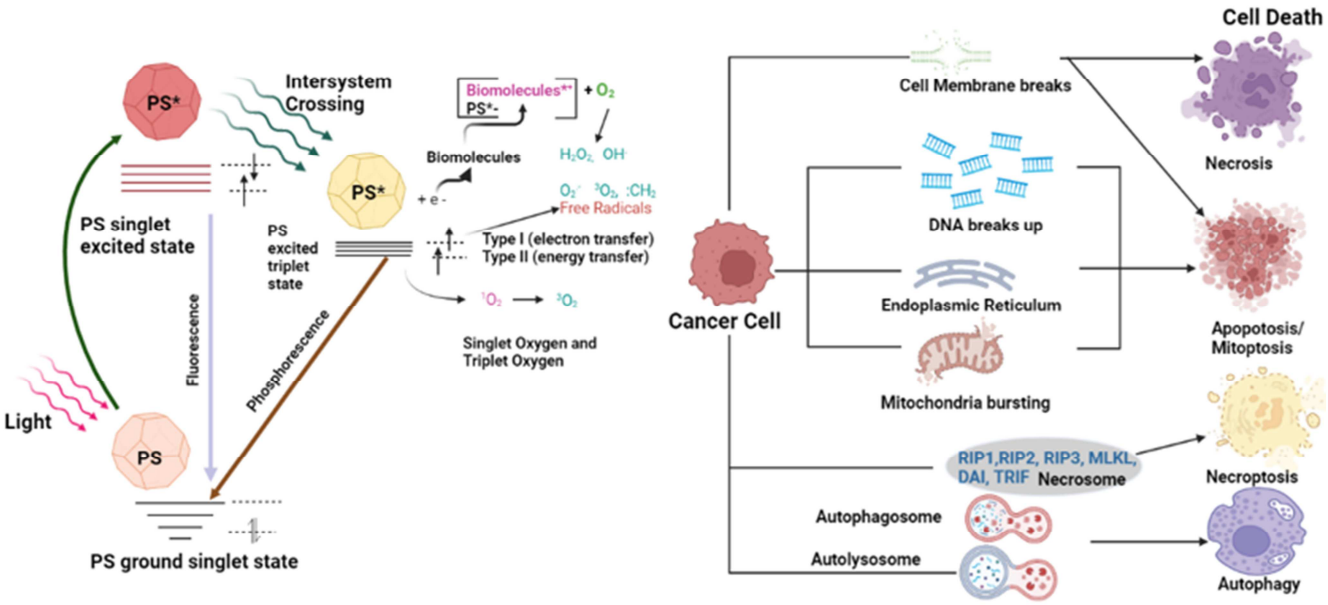

Figure 5. *Photodynamic therapy mechanism. The photosensitization process starts with a photon absorption that converts the photosensitizer (PS) ground singlet state to a more energetic state known as a singlet excited state PS*. The intersystem crossing covers the PS* to a triplet excited state (PS*-). PS*reacts with nearby biomolecules via Type I electron transfer and Type II energy transfer, generating reactive oxygen species (ROS). ROS can damage the cell and its components, leading to the cancer cell's death through necrosis, apoptosis, necroptosis, or autophagy. RIP (receptor-interacting protein kinase), MLKL (mixed lineage kinase domain-like protein), DAI (DNA-dependent activator of interferon regulatory factors), TRIF (TIR domain-containing adapter-inducing interferon-β, where TIR stands for Toll-like receptor).*

Many characteristics make a particular substance an ideal candidate as PS for PDT. Some of these characteristics are; the ability to selectively target or accumulate in the cancer tissue, solubility and stability *in vivo* and *invitro*, ability to generate ROS when exposed to light at a long wavelength (600-800 nm), and ability to be excreted or biodegradable in the patient body and cheap to produce.

The first commercially approved photosensitizers for cancer treatment were produced in the 1970s by Dougherty *et al.* [39]. They tested the therapeutical properties of hematoporphyrin derivatives, protoporphyrin, and deuteroporphyrin. Since then, thousands of PSs have been developed, some of which have been approved for cancer treatment, while the majority are at various stages of clinical trials (Table 2). Hematoporphyrin and its derivatives are considered to be the first-generation PSs. Further purification of hematoporphyrin led to the production of photofrin. Photofrin® (Porfimer sodium; Axcan Pharma, Inc.) is approved worldwide for treating various cancers; lung, bladder, cervical, etc. The first-generation PSs had many intrinsic drawbacks, some of them are; poor selectivity and specificity, cellular damage of the normal cells due to their accumulation in normal tissues, prolonged half-life after administration, patients were advised to avoid sunlight or any other light exposure, poor chemical purity and short wavelength of light [40].

Nevertheless, first-generation PSs are still used for the treatment of cancer. In order to overcome some of the challenges associated with the first-generation PSs, the porphyrin structure was modified to improve purity, tissue selection, shorter half-life after administration, absorption wavelength increased to above 650 nm, and photosensitivity [39]. Structurally, most second-generation PSs are porphyrinoid compounds with porphyrin or porphyrin-based macrocyclic structures (Figure 3) [41]. The third-generation PSs are derived from the second-generation PSs or modifications of current drugs [21]. The third-generation PSs have increased specificity to minimize off-target effects. The specificity (improved accumulation of the PS in the target site) and poor water solubility are generally improved through antibody conjugation encapsulation and utilizing molecular carriers such as nanoparticles [21].

The reactive oxygen species induce the destruction of the intracellular organelles and cell membrane [7]. PTD-induced cancer cell death involves one or more cellular pathways that lead to the induction of apoptosis, autophagy, necrosis, or mitoptosis (Figure 5) [37]. One of the significant targets of PDT is the mitochondria. Recent reports on the induction of apoptosis point to the release of cytochrome c due to the mitochondrial disintegration in ROS presence [7]. The photosensitizers also directly impact caspases, BCL2 protein family members, and other apoptosis-inducing factors [7]. ROS in the plasma membrane and nuclei of a cancer cell induces necrosis. Autophagy is another common mechanism present in PDT-induced cancer cells. All cell organelles such as mitochondria, endoplasmic reticulum, and peroxisomes damaged by ROS are removed by autophagy [42]. Elucidating and enhancing the cellular processes involved in cell death is key to applying PDT to cancer treatment.

Table 2. *Completed and recruiting PDT treatment and diagnostic studies as presented on ClinicalTrials. gov.*

Status	Study Title	Cancer Type	Interventions	Phase	Photoactivation	Clinical Trials. gov Identifier
Completed	A Phase I/IIa, Open Label, Single Site Light Dose Escalation Trial of Single Dose Verteporfin Photodynamic Therapy (PDT) in Primary Breast Cancer	Breast Cancer	Drug: Verteporfin	Phase I/IIa	680 nm	NCT02872064
Completed	Low-cost Enabling Technology for Image-guided Photodynamic Therapy (PDT) of Oral Cancer Cancer. (UH3-India)	Oral Cancer	Aminolevulinic acid (ALA) and Photodynamic Therapy (PDT)	Phase 1 Phase 2	405	NCT03638622
Completed	A Study of Blue Light Flexible Cystoscopy With Cysview in the Detection of Bladder Cancer in the Surveillance Setting.	Bladder Cancer	Drug: Hexaminolevulinate hydrochloride Device: KARL STORZ D-Light C PDD Flexible Videoscope System	Phase 3	White and Blue Light Cystoscopy	NCT02560584
Completed	Photodynamic Therapy in Treating Patients With Skin Cancer	Skin Cancer	Drug: aminolevulinic acid	Phase 2	633 nm	NCT00002975
Completed	Feasibility Study of Using Navigational Bronchoscopy to Perform PDT-Photofrin® in Unresectable Peripheral Lung Cancer	Lung Cancer	Drug: Porfimer sodium Device: Fiber optic	Phase 1	A light dose of 200 J/cm of diffuser length	NCT02916745
Completed	Phase 3 Trial of Litx™ Plus Chemotherapy vs. Chemotherapy Only Treating Colorectal Cancer Patients With Recurrent Liver Metastases	Colorectal Cancer Patients With Recurrent Liver Metastases	Drug: Talaporfin sodiumProcedure: Percutaneous placement of device in liver metastasesDevice: Interstitial light emitting diodes	Phase 3	200 J/cm per Light Source at 20 mW/cm light energy	NCT00440310

Status	Study Title	Cancer Type	Interventions	Phase	Photoactivation	ClinicalTrials. gov Identifier
Completed	Photodynamic Therapy With Porfimer Sodium in Treating Patients With Precancerous Lesions, Cancer, or Other Disease of the Aerodigestive Tract	Head and Neck Cancer	Drug: Porfimer Sodium Procedure: Photodynamic Therapy	Phase 2	a computed energy dose of 75 to 150 joules, depending on the depth of penetration desired.	NCT00453336
Completed	Daylight-mediated Photodynamic Therapy of Actinic Keratoses: Comparing 0.2%HAL With 16%MAL	Actinic Keratoses	Drug: Hexylaminolaevulinate cream	Phase 1 Phase 2	Daylight-mediated Photodynamic Therapy of Actinic Keratoses	NCT02149342
Completed	Endoscopic Therapy of Early Cancer in Barretts Esophagus	Early Stage Esophageal Adenocarcinoma Barrett Esophagus	Endoscopic Mucosal Resection	Phase 2	630 nm	NCT00217087
Completed	Treatment of Oral Premalignant Lesions With 5-ALA PDT	Leukoplakia Erythroplakia	Device: PDL-585, ScleroPLUS laser Drug: 5-Aminolevulinic Acid (Levulan KerastickTM) Procedure: Fluorescence Diagnosis Imaging	Phase 1 Phase 2	585 nm	NCT00571974
Recruiting	Diagnostic Performance of Fluorescein as an Intraoperative Brain Tumor Biomarker	Brain Tumor	Drug: Fluorescein + 5-Aminolevulinic Acid	Phase 2	405 nm	NCT02691923
Recruiting	Ultrasound-Guided Verteporfin Photodynamic Therapy for the Treatment of Unresectable Solid Pancreatic Tumors or Advanced Pancreatic Cancer, VERTPAC-02 Study	Advanced Pancreatic Carcinoma Locally Advanced Pancreatic Carcinoma Metastatic Pancreatic Carcinoma Pancreatic Neoplasm	Procedure: Endoscopic Ultrasound Drug: Verteporfin	Phase 2	50 J/cm	NCT03033225

Status	Study Title	Cancer Type	Interventions	Phase	Photoactivation	ClinicalTrials. gov Identifier
Recruiting	Photodynamic Therapy for Benign Dermal Neurofibromas- Phase II	neurofibromatosis type 1	Drug: aminolevulinic acid Drug: Levulan Kerastick	Phase 2	630 nm	NCT02728388

Status	Study Title	Cancer Type	Interventions	Phase	Photoactivation	ClinicalTrials.gov Identifier
Recruiting	Porfimer Sodium Interstitial Photodynamic Therapy With or Without Standard of Care Chemotherapy in Treating Patients With Locally Advanced or Recurrent Head and Neck Cancer	Recurrent Head and Neck Carcinoma Locally Advanced Head and Neck Carcinoma	Biological: Nivolumab Drug: Porfimer Sodium Procedure: Interstitial Illumination Photodynamic Therapy Biological: Pembrolizumab Drug: Cisplatin Drug: Carboplatin Biological: Cetuximab Other: Quality of Life Assessment Drug: Fluorouracil	Phase 2	Variable depending on the drug	NCT03727061
Recruiting	Photodynamic Therapy for Cholangiocarcinoma	Cholangiocarcinoma Non-resectable	Drug: Hematoporphyrin	Not Applicable	Photoactivation was performed at 630 nm with a light dose of 180 J/cm^2, fluence of 0.250 W/cm^2, and irradiation time of 750 seconds.	NCT04860154
Recruiting	Verteporfin for the Treatment of Recurrent High Grade EGFR-Mutated Glioblastoma	Glioblastoma Recurrent Glioblastoma	Drug: Verteporfin	Phase 1 Phase 2	689 nm	NCT04590664

2.3. Tumor-Targeted Photodynamic Therapy

Tumor-selective targeting is crucial in PDT so that normal cells are not damaged. There are two main ways of tumor-targeting in PDT, and these are passive and active targeting. Passive targeting takes advantage of the morphological and physiological differences between normal and tumorous tissues. Tumor cells tend to have uncontrolled proliferation and overexpression of specific proteins [43, 44]. One of the prominent characteristics of a cancer cell is the irregular shape and size of its leaky and tortuous vessels compared to normal cells [45]. The PS tend to quickly accumulate in tumor cells due to the heterogeneous nature of their vessels, large nuclear pores, and over-expressed components of the extracellular matrix such as collagen, elastin, and hyaluronan [46]. Specifically, over-expressed collagen interacts with porphyrin derivatives PSs [47].

The membrane receptors and enzymes over-expressed explicitly in cancer cells are generally excellent targets for PSs. Targeting of these proteins constitutes the active tumor-targeting PDT. The process is much more similar to the drug-receptor interactions. The conjugation of an antibody with the PS, for example, that directly targets a receptor on cancer cells can lead to the direct destruction of that cancer cell. An excellent example of this is the conjugation of the antibody, trastuzumab, to a PS for breast cancer treatment [48]. Trastuzumab is a humanized anti-HER2 antibody that has been approved for breast cancer treatment [49]. HER2 receptors are more over-expressed in breast cancer cells than in normal cells [50]. Active tumor-targeting can also be achieved by conjugating ligands of specific membrane protein receptors and enzymes with PS. For example, over-expressed mannose receptors can be targeted by conjugated mannose PSs [51]. A similar procedure is also applicable to epidermal growth factor receptor (EGFR) [52] and cannabinoid CB2 receptor [53], which are prevalent in cancer cells. Similar modifications can also be made to ligands of intracellular enzymes to act as potential PSs by increasing the bioresponsive elements. Thus, PDT needs to take advantage of the vast protein ligands out there as part of the cancer treatment to increase selectivity and specificity.

3. Photodynamic Diagnosis

Photodynamic diagnosis (PDD) uses fluorescent PS agents in cancer diagnosis [54]. Early cancer detection improves treatment outcomes, and a technique that combines both detection and treatment is very advantageous because it can cut treatment costs tremendously. Photodynamic diagnosis, which has many advantages over the standard white light cystoscopy, is recommended by the European Association of Urology (EAU) as a diagnostic procedure in cases of suspected carcinoma *in situ* [55]. Most cancer symptoms tend to be unspecific, and most small flat lesions can easily be missed by standard white light cystoscopy. Thus, PSs can be used for both cancer diagnosis and treatment. The fluorescent PS agents are designed to target a specific tumor selectively. PDD is regarded as an Image-Guided Surgery or fluorescent-guided resection [56]. Because the principle behind PDD is very similar to PDT, PDD can easily be turned into PDT by increasing photoirradiation or light intensity. The identification of tumors during PDD is possible through the excitation of light at a specific wavelength, and as long as the PS interacts with the tumor cell components, the emitted light can provide the position of tumorous tissues. It is further proposed that PS-specific fluorescence microscopy can be used to differentiate between cancer and normal tissue [57]. Research work done by Suchorska *et al*. showed more complete resections of the contrast-enhancing tumor and improved clinical outcomes in patients with recurrent glioblastoma [58]. PDD has repeatedly demonstrated better detection of bladder tumor-positive patients than other

cancer detection techniques [59, 60]. Future development in this area should look at the application of near-infrared fluorescence imagining (photoimmunotherapy) due to its tissue auto-fluorescence and high tissue penetration depth [61, 62].

4. Combination of PDT with Other Anti-cancer Therapeutic Modalities

The combination of PDT with other anti-cancer therapeutic modalities such as chemotherapy, surgery, radiotherapy, and immunotherapy has proven to be very effective against different types of cancer [7]. Indeed, PDT has been implicated in attenuating multidrug resistance cancer [7]. Resistance to chemotherapy in cancer cells is associated with cellular pump dependence [63], increased metabolism of drugs, decreased drug entry, and defective apoptotic pathways [64, 65]. Recent research findings have demonstrated practical tumoricidal activities of PDT when combined with chemotherapy [66, 67]. The combination of PDT and chemotherapy has been effective against advanced gastric adenocarcinoma [68], ovarian [69], and breast cancer cells [70]. An enhanced additive and not synergistic effect has been observed in treating cancer when PDT is combined with radiotherapy [71]. Indeed, the combination of PDT and radiotherapy has been used to treat the non-small-cell bronchogenic tumor and bulky endobronchial tumors with an excellent success rate [72, 73]. Similar attempts have been made with surgery combined with PDT [74]. Clinical trials involving a combination of PDT and surgery have shown promising results in the treatment of Perifolliculitis capitis abscedens et suffodiens [75], multiple squamous cell carcinomas [50], and systemic lupus erythematosus [76]. Anti-tumor immunotherapy has been very effective in eliminating tumors. Recent studies have shown that PDT can augment immunotherapy in cancer treatment [7]. Indeed, PDT can stimulate immune responses against dead cell antigens and immunogenic cell death, enhancing immune memory for cancer cells targeted by the immune system [7].

5. Cancers Treatment Using Photodynamic Therapy

PDT is a non-invasive cancer treatment. It is highly utilized for treating precancerous lesions and nonmelanoma skin cancer because of its easy accessibility to light [77]. PDT can also target internal tumors by administering systemic PS and irradiating the tumors with light at a specific wavelength via optical fibers. Thus, PDT is producing promising outcomes in dermatology [78], gastroenterology [79], neurosurgery [80], pneumology [81, 82], gynecology [83], urology [84] and ophthalmology [38] tumors treatment. PDT is recommended for treatment in many cancers, including colorectal, bladder, bile duct, lung, esophageal, prostate, head and neck, brain, skin, pancreas, breast, and cervix.

6. Side Effects of PDT

Just like all other medical procedures, PDT also has some side effects. Some of these include sensitivity to light after treatment due to the PS that can last up to three months, skin infections, scales, crusts, blisters or swelling at the point where the PS was administered, skin discoloration, itching, stinging or burning sensation [85]. Other side effects are related to the type of cancer being treated; for example, PDT treatment of esophageal cancer can cause hiccups, difficulty swallowing, nausea and vomiting, dehydration, fever, narrowing or scarring of the esophagus [86].

7. Mechanisms of Resistance to PDT

The treatment of cancer with PDT depends on the type of cancer, its location, the tumor size, and the individual's general wellbeing. The light source and PS must be able to reach the affected area. PDT-resistant cell lines have only been isolated *in vitro* [87, 88]. Cross-resistance between PDT and other cancer treatment modalities has not been reported. The resistance mechanisms in PDT treatment involve the activities induced by the structure of the PS. The majority mainly involve upregulation and downregulation of protein expression levels, i.e., the increased activity of drug pumps, modulation of cellular pathways, alteration or repair of the ROS target molecules, and alteration of the PS chemical structure [88]. The reactive oxygen species produced by the photoactivation of the PS lead to the activation of antioxidant enzymes.

Furthermore, heat shock proteins act as chaperons in folding all misfolded proteins into their proper native structures, thus reversing the damage caused by the PDT [88]. Based on the recent literature review, it is clear that the effective use of PDT for cancer treatment will require modulation of other metabolic pathways to combat drug resistance and improve treatment outcomes [87]. These modulations can include cell cycle inhibition, inhibition of DNA repair mechanisms, inhibition of cell adhesion, and many other molecular mechanisms that can enhance the activities of PS and reduce cell resistance to treatment [88, 89].

8. Future Perspectives

Cancer remains one of the biggest challenges to human health across the world. For more than half a century, PDT has been successfully employed in the treatment of different types of cancer. Because of its simplicity, PDT can easily be used for cancer treatment in low-income countries, where cancer treatment remains an enormous challenge and death rates due to cancer are rising. Combining PDT with other cancer treatment modalities such as surgery, chemotherapy, immunotherapy, or radiotherapy is proving more effective against multidrug-resistant cancer [90] and is an area that needs more intensive research. It will be imperative to introduce other modalities that can suppress cellular and molecular mechanisms that increase resistance to PS-induced

activities and simultaneously enhance those activities that will improve treatment outcomes. All the components for PDT treatment need to be optimized and standardized to effectively treat cancer. Future research should focus on improving the properties of PSs to enhance efficacy and specificity for a particular cancer type. Particularly the development of esterified PSs derivatives will quickly improve penetration across the cell membrane. Further development of PS delivery technology based on tumor targeting and nanoparticles encapsulating with antibodies could lead to better diagnosis and specificity. Thus, this review recommends the introduction of PDT to the frontline treatment of cancer and encourages massive PDT trials in developing countries, where cancer cases and deaths are on the rise and treatment options are limited.

9. Conclusion

The critical components for successful treatment of cancer with PDT are the PS, light, and oxygen, and each of them needs careful optimization. PDT has massive potential in treating cancer at a reduced cost, although it is often given as the last resort after all other treatment options have failed. Although PDT has its limitations, they can easily be overcome when the treatment is approached holistically. Cancer treatment is beyond the reach of most people in low-income countries, yet cancer cases in these countries are on the rise.

Competing Interests

The authors declare no conflict of interest.

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