Mechanisms of photodynamic therapy

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2.1 Introduction

Photosensitive substances and light have been used in medicine for many years. However, photodynamic therapy (PDT) began in the 1960s after Lipson and Baldes reported that neoplastic tissues containing the photon emitter of a porphyrin mixture could be fluoresce under ultraviolet light radiation [1]. PDT is a therapeutic technique that comprises the application and activation of a photosensitizer (PS) by light with an appropriate wavelength. PDT produces singlet cytotoxic oxygen by combining light-absorbing drugs called photosensitive agents and molecular oxygen [2].

In the last 100 years, PDT has become a safe and effective skin treatment option for acne, sebaceous hyperplasia, and verrucae [3–6]. PDT is based on the local or systemic application of photosensitive compounds—PSs that accumulate intensely in pathological tissues. PDT uses light-activated drugs to treat diseases ranging from cancer to molecular degeneration related to age and antibiotic-resistant infections [7]. It is recognized as an attractive alternative model for treating various malignant and nonmalignant skin diseases [8]. It has become a powerful candidate for oxidative stress-mediated noninvasive techniques for rapid diagnosis. For the treatment of various cancerous and noncancerous diseases, PDT appeared as a superior therapeutic and lesser invasive approach [9]. This treatment involves the application of photosensitive devices to the affected area, and then light with specific wavelengths of light. PDT is based on systemic or exogenous administration of PS or PS-prodrug. Its uptake by target tissues and subsequent light activation aimed at causing selective damage and destruction of the diseased tissues [3]. Clinical indications of PDT can be largely divided into cancer and noncancerous indications [10].

PDT is well tolerated by patients due to its selective effect. The photodynamic protocol is painless and its application simplicity allows the use of patients. PDT is

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an efficient, simple, and multifunctional method based on the combination of photosensitive drugs and light (usually laser diodes or lasers). These factors are relatively harmless individually, but when used together in the presence of oxygen molecules, free radicals are produced that trigger a series of biological events [11].

A number of light applicators have also been developed to facilitate clinical protocols. Hopper and colleagues described PDT's potential as a better selective site on the target site, low systemic toxicity, invasiveness, and functional and cosmetic effects are lower than conventional therapies, with higher functional and cosmetic effects [12].

2.2 Mechanisms of photodynamic therapy

The principle of PDT is based on multiple steps of process. The molecular mechanism of PDT is based on three nontoxic components, and the mutual interaction between the mutually linked tissues produces the desired effect within the pathological tissues. PDT is based on three components as shown in Fig. 2.1: [14].

- The first component is the presence of PS.
- Light with the appropriate wavelength adapted to the absorption spectrum of a given photosensitize.
- Presence of dissolved oxygen (O_2) in the tissues [15].

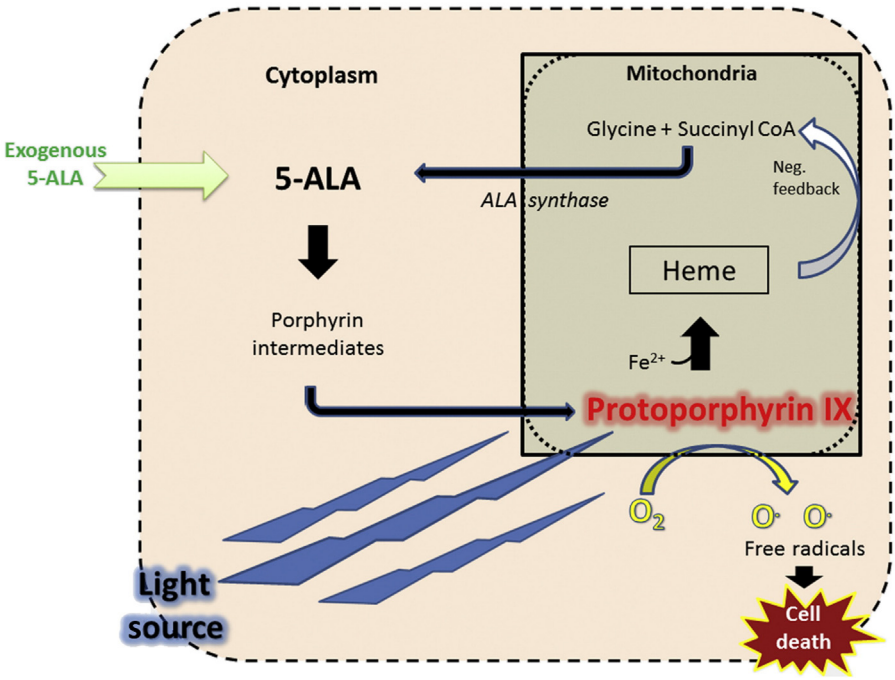

Figure 2.1 Mechanism of photodynamic therapy [13].

This combination mainly leads to the formation of high-cytotoxic single-oxide oxygen (type 2 photooxidation, dominant mechanism) and also to generate reactive oxygen species (ROS) (photooxidation type 1), which cause the death of tumor cells [16]. Cytotoxic species are represented by ROS, which are generated by electrons or energy transfers from the original photoexcitation PS. The main reactivity is associated with single oxygen ($^1O_2$), which can effectively attack various subcellular components such as aromatic and sulfur-containing amino acid side chains, guanosine nucleotides, unsaturated lipids, and steroids [17]. PS is transferred from its original state to an excited single state at a particular wavelength of light. In the presence of oxygen, excited PS can react with the substrates to form radical ions. Excited triple-state reactions occur in two types (Types I and II) and produce active radicals that cause cell damage and tissue necrosis or apoptosis. To criticize available clinical PSs, some kind of ideal must be used for comparison. Type I pathways occur when excited molecules react with the substrate and produce cytotoxic species of atoms or atoms. The excited triple-state PS reacts with the molecular oxygen that produces the single oxygen by energy transfer (Type II) [18].

2.2.1 Photosensitizers

For medical chemists, the essential elements of all these procedures are PSs, the area of the photodynamic action, which absorb the appropriate wavelength of light and produce the desired biological response [19]. Apart from light and oxygen, one of the three key elements of PDT is the presence of photosensitivity agents. These are mostly dye defined as substances that absorb light at a specific wavelength and cause photochemical or photophysical reactions [20].

However, the ideal photosensor would vary from physicians to purists [3,21,22]:

- It must maintain the purity of its chemical components and its well-known composition.
- It must be cytotoxic in the light and the lowest toxicity in the darkness.
- It must be stable at ambient temperature.
- It must be retained preferably by the target tissue location.
- It must have greater selectiveness for neoplastic tissues.
- There must be a short period of time between administration and maximum accumulation in the tumor tissue.
- Activation at wavelengths with an optimal penetration of the tissue and a rapid removal of the body.
- The minimum absorption range is between 400 and 600 nm. This prevents the possibility of excessive photosensitivity due to sunlight.
- It should be cheap, easy to synthesize, and easily available.
- Photosensitive effects only occur when a particular wavelength is present.

PSs are classified according to three basic structures, such as porphyrin, chlorinated, cyanide, and other dyes, as shown in Fig. 2.2. Photosensitive chemicals currently use different molecular structures in the PDT, and photosensitive chemicals can be divided into three generations.

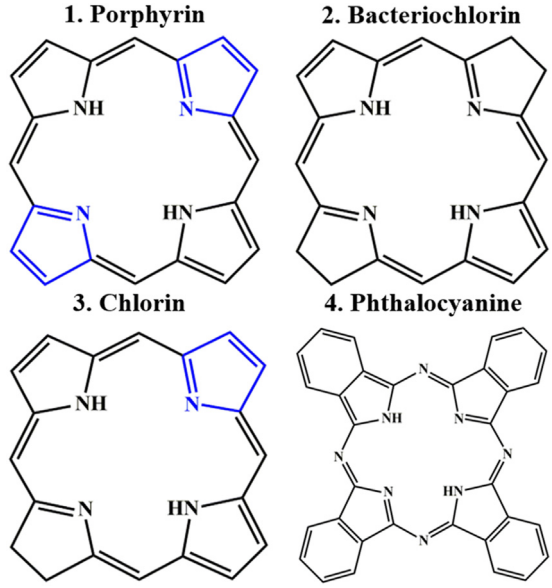

Figure 2.2 Basic structure of PSs. [18]. *PSs*, Photosensitizers.

2.1.1 First-generation photosensitizers

Photosensors were first introduced commercially in the 1970s by Dr. Thomas Doherty and his colleagues. They tested a water-soluble mixture of the "hematopolypirin derivative" (HpD) of hematoporphyrin, protoporphyrin, and deuteroporphyrin and their derivatives, monomers, dimers, and oligomers and their esters [3]. The first PS approved by the FDA was Photofrin (Axcan Pharma, Mont-Saint-Hilaire, Canada). It is involved in the treatment of various types of cancers, such as lung, esophagus, esophageal, and nonsmall lung, brain, etc. [23]. First-generation PDT sensitizers, such as Photofrins, exhibited prolonged patient photosensitivity, poor clearance, and lacked long-wavelength absorption, important factors contributing to the limitation of these PSs in PDT. Furthermore, after PDT, due to the long half-life of PS and high accumulation of PDT, hypersensitivity to light in the skin persists for several weeks due to high accumulation in the skin [24,25]. To overcome these limitations, the development of new PS generations has become imperative.

2.1.2 Second-generation photosensitizers

First-generation PS is not very specific to cancer cells and tends to accumulate in normal tissues. The first-generation PS is not rapidly clear of the human body and has no sensitivity. The disadvantages associated with the first generation of PSs have led to a wide range of investigations to improve the efficacy of PS molecules [26]. The second generation of PS is more effective and technically advanced than

the first generation of PS. The second-generation PS improved purity, long-wavelength absorption, photosensitivity, and tissue selection. The second generation of PS is fulfilled with several serious disadvantages with the use of the first generation of PS [18,27]. Second-generation PSs are usually single substances, not necessarily porphyrins, and improve selectiveness and activity. The synthesis of improved (second-generation) PSs has moved to modified tetrapyrrole (porphyrin) compounds, such as benzoporphyrin (Visudynes), chlorin (Temoporfins), and porphycene (ATMPn). They have a stronger long-wavelength absorption [28]. In contrast to the first-generation PS, these porphyrinoid compounds allow greater tumor specificity and penetration into deep tissues. Because the absorption spectrum is between 650 and 800 nm. In addition, it eliminates faster from the body, reducing side effects and patient's time in the dark room (less than 2 weeks). The main disadvantage of the second-generation PS is that it has less solubility in water. This is a significant limitation factor in intravenous administration, which forces the search for new ways of giving drugs [29].

2.1.3 Third-generation photosensitizers

Second-generation PSs have several critical problems, such as lack of water solubility, body penetration rate, and photolysis. The second-generation PS showed no sufficient tumor selection. The problem of the widespread clinical application of PDT in cancer is also a difficulty in the preparation of pharmaceutical products. This would allow parenteral administration of PSs [28]. Most PSs used in photodynamic cancer therapy are porphyrins, chlorins, bacteriochlorins, or phthalocyanines from which other compounds are developed to maintain their functionality and improve delivery to the targeted sites. The development of most of the third-generation PSs is based on the synthesis of substances with higher affinity to the tumor tissue, which reduces damage to surrounding, healthy tissues. Therefore PS may have undergone several chemical changes before reaching an improved delivery, improved efficiency at targeted tumor sites, and reduced toxicity at nontumor sites [30–33]. The third-generation photosensitive agents have an additional target mechanism, for example, through covalent attachment to monoclonal antibodies [34]. PDT has revealed a variety of agents, some of which are effective for high-level oxygen release and the treatment of cancer cells, while the treatment of healthy cells is less effective [35]. These PSs usually consist of a second-generation PS or a photoactive drug that is combined with or encapsulated in biodegradable/biocompatible nanoparticles. Consequently, PS stability and hydrophilicity are improved, and pharmaceuticalkinetics, pharmaceuticaldynamics, and biodistribution in vivo are improved. Furthermore, it minimizes unwanted side effects. These solutions allow the selectivity to be improved and the accumulation of PSs to be greater in the affected areas, thus allow the possibility of reducing the dose of the drug while maintaining satisfactory therapeutic effects [18,36]. Chemical structure of clinically approved or under-clinical developing photosensitizing agents is given in Fig. 2.3.

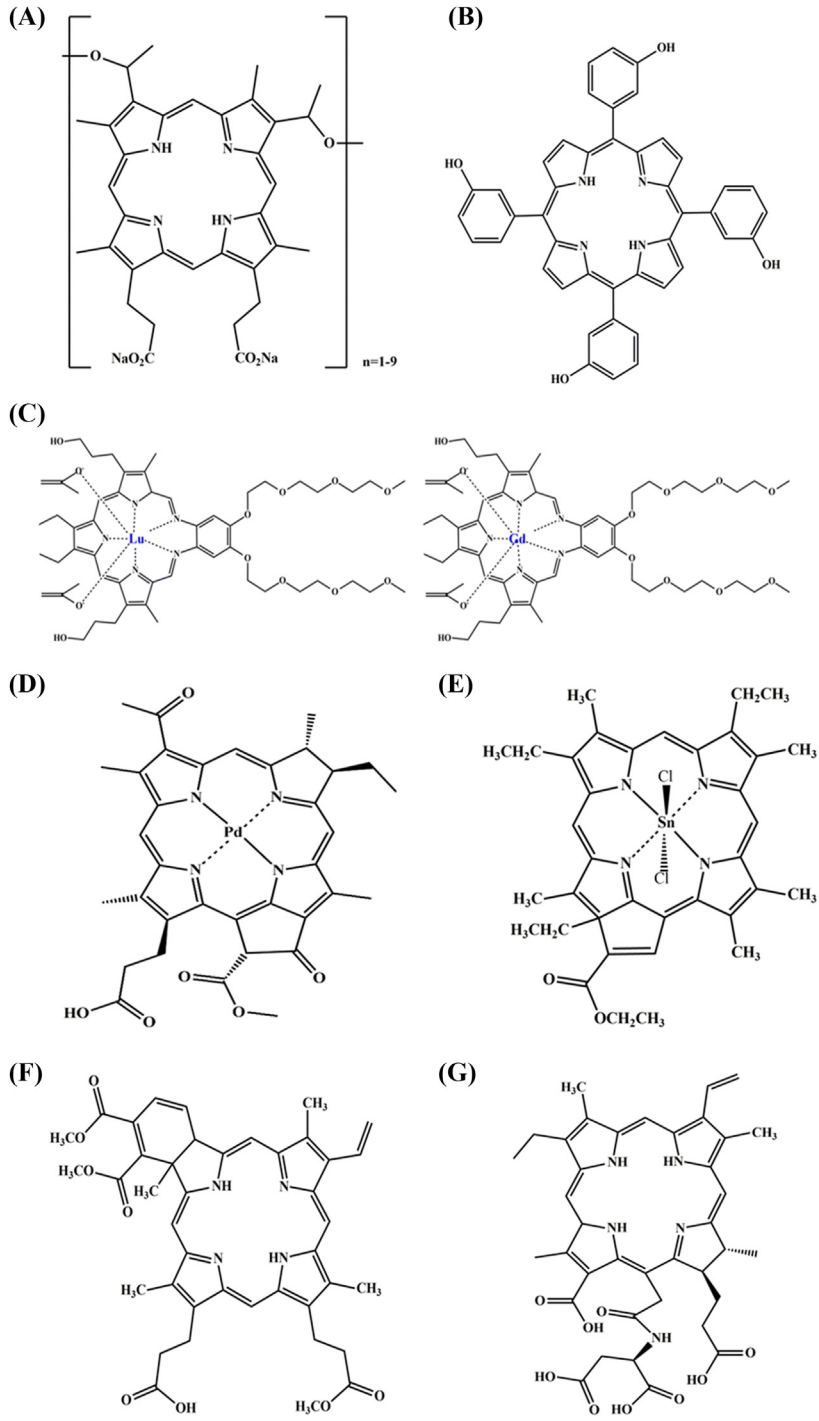

Figure 2.3 Chemical structure of clinically approved or under-clinical developing photosensitizing agents. (A) Porfimer sodium (Photofrin), (B) Temoporfin (Foscan), (C) Motexafin lutetium and Motexafin gadolinium, (D) Palladium bacteriopheophorbide, (E) Purlytin, (F) Verteporfin (Visudyne), and (G) Talaporfin (Laserphyrin) [18].

2.2.2 Light with the appropriate wavelength

Because light is an essential component of PDT, the clinical effectiveness depends heavily on its precision in delivery to target tissues and its doses. This is translated into light flow, light flow rate, light exposure time, and light transmission mode. In order to achieve PDT successfully in vivo, sufficient light must be provided to all diseased tissues. The clinical effectiveness of PDT depends on the dose, exposure time, and light distribution method. This involves understanding the relative effects of light flow through different tissues and absorption and diffusion [37,38]. All important factors in PDT light supply play an important role in supporting successful treatments that give good therapeutic effects [39]. PDT is performed with different light sources, including lasers, light-emitting diode light, and laser diodes. In PDT it is important to be able to predict the spatial distribution of light within the target tissue. The wavelength of light is either dispersed or absorbed when entering the tissue, and the scope of both processes depends on the type and wavelength of light used. PDT uses several sources of light, including ultraviolet (330−400 nm), red (600−700 nm), and near-infrared (700−1000) [40]. Most PDT studies reported that PS is administered by intravenous or oral injections, and that, after hours or days, the tumor is exposed to specific wavelength nonthermal light [39,41]. PS is activated and kills cancerous cells. Light penetration was reported to be 3 mm underneath of the skin in clinical study.

2.2.3 Presence of dissolved oxygen (O_2) in the tissues

The third important component of the PDT mechanism is molecular oxygen. Oxygen is important for ROS production during PDT. For effective PDT, the oxygen concentration in the target tissue environment is a significant importance. Oxygen concentration in the tissues truly affects the effectiveness of the PDT treatment. In fact, oxygen concentration can vary significantly between different tumors and even between different regions of the same tumor, depending on the density of the vasculature. After PDT, vascular damage could allow the ablation of tumor cells by anoxia caused by obstruction of blood vessels. However, during PDT, vascular damage caused by PDT can cause tumor hypoxia due to local oxygen consumption that could cause neovascularization and prevent the efficient treatment of PDT, which leads to a recurrence of the tumor. It is therefore necessary to provide oxygen during PDT to maintain tumor oxygenation to improve tumor response on the basis of increased ROS amount [42,43]. The basic methods for increasing oxygen availability in tumors are two: indirect oxygen introduction and direct oxygen introduction. An indirect way to increase the concentration of oxygen in tumor cells is to decompose hydrogen peroxide in oxygen using catalase enzymes. The direct supply of oxygen to tumors is achieved using oxygen carriers such as perfluorocarbons and hemoglobin, which are usually used to overcome the hypoxia of tumors in PDT procedures [44].

2.3 Applications of photodynamic therapies in different diseases

PDT is based on selective destruction of pathological tissues by accumulation of PSs. Compared to other oncology treatment methods, PDT distinguishes itself from a selectivity of equal therapeutic results. Over the past few decades, many studies have been carried out related to PDT for various types of cancer treatment. There were few studies on the human immune system, and few studies were conducted on the human immune system. PDT can also be recommended for premalignant cancer [45,46].

2.3.1 Malignant diseases

At present, most mechanical research on PDT is still focused on anticancer applications. But as the localization properties of PSs to the tumors are discovered, the development of PDT as a modality of treatment for metastatic forms of cancer becomes possible. Aiming to address the invasive nature of previous anticancer therapeutic strategies (e.g., radiotherapy, chemotherapy, and surgery), PDT was developed as a promising alternative [47–54]. The main advantage of PDT is that it selects tumor tissue and minimizes damage to nonmalignant cells [55–59]. PDT is a minimally invasive treatment that is clinically used to treat several cancers such as skin, esophagus, neck, lung, and biliary cancers. PDT can induce the death of cancer cells through three combined mechanisms: direct cell damage due to the induction of ROS production, indirect damage due to the closure of tumor blood vessels, stimulating the patient's immune system by increasing the antibody production of cancer cells in T cells [60–62]. Breast cancer is the most common type of female carcinoma and is the most important cause of women's cancer mortality worldwide. The first option for breast cancer treatment is combined chemotherapy drugs, radiation therapy, and surgical interventions. Nevertheless, the drug does not yet penetrate the tumor tissue at an adequate level and there are observed systemic side effects [63,64]. Overcoming these disadvantages, PDT is considered to be a promising, safe, and minimally invasive procedure. Furthermore, if a known and limited portion of a tumor appears on MRI scans, it is much easier to repeat PDT treatment than conventional therapy [65]. To this, recently, Xu et al. reported multistimuli-responsive theranostic nanoplatform integrating functions for improving diagnosis and therapeutic efficacy against HER2-overexpressed breast cancer. The researchers have shown that the double target strategy mediated by HER2 and CD44 receptors significantly increased the cell absorption of GNR-HA$^{-ALA/Cy7.5}$-HER2 [66].

The cell death subroutine is strongly related to the success of the treatment as shown in Fig. 2.4. At the cell level, it has been shown that PDT induces several subroutines of cell death, which can be arbitrary or not. Accidental cell death is a form of death that cannot be controlled by the physical dismantling of plasma membranes caused by extreme physical, chemical, or mechanical signs.

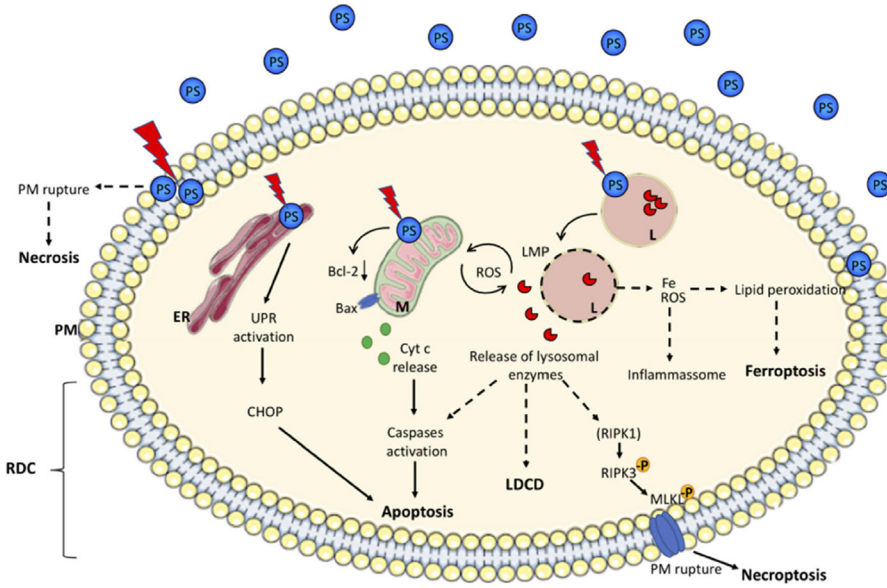

Figure 2.4 Overview of cell death subroutines that can be elicited by photodynamic therapy [67].

The main advantages of PDT use for these types of cancer are the less invasive nature compared to surgery and the broader indication than endoscopic resection. Furthermore, it can be used as a complementary treatment after the failure of a local chemotherapy radiotherapy.

2.3.2 Nonmalignant diseases

Although PDT is known for cancer treatment, it is not limited to the destruction of tumor cells. In the early 20th century, photodynamic effects on bacteria were demonstrated. Given the current challenges of antibiotic resistance and the increase in new infections, it is not surprising that PDT has attracted attention for the fight against bacteria, fungi, viruses, and protozoans [68]. The importance of antibiotic resistance is increasing in dermatology practice. An alternative approach may be to use PDT. One of the advantages of the wide spectrum of antimicrobiaI PDT is the development of direct killing resistance induced by photodynamics, which would be unlikely [69]. Dental infections represent one of the greatest expanding fields of clinical antibacterial PDT. Studies have shown that pathogens are predominant in subgenial periodontal plaques (e.g., *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Staphylococcus* spp.) have been successfully destroyed through photodynamic treatment, both in aqueous suspension and as a biofilm [70–73].

2.4 Conclusion

Overall, PDT has been used in greater numbers over the past few decades in a wide variety of practical applications. PDT is a minimally invasive clinical protocol that combines a nontoxic photonizer (PS), suitable visible light, and molecular oxygen to treat cancerous and noncancerous. The ideal PSs are chemically pure, miscible, and stable in body fluids. Despite many advanced research and preclinical studies, the translation status of PDT is unsatisfactory. The development of better and more efficient components that are free of the shortcomings of the first and second generations of PSs is one of the main strategies to improve PDT. Despite many advanced research and preclinical studies, the translation status of the DDT remains unsatisfactory. In any cases, the key source of PDT should be optimized by adjustment of parameters such as input dose, intratumoural drug levels, light source, and tissue oxygen condition. Various new PDT approaches have been studied and developed in recent decades for use against tumors. Preclinical and clinical applications of PDT and photodynamic diagnosis (PDD) have given promising results. Topical and systemic administration of PSs has been used in clinical settings.

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