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Photodynamic therapy: a distinct therapeutic modality

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Abstract

Photodynamic therapy (PDT) is an innovative treatment modality that utilizes a combination of a photosensitizing agent, specific wavelengths of light, and molecular oxygen to selectively target and destroy abnormal cells or tissues while sparing healthy surrounding structures. This approach has gained significant attention in the medical field due to its potential to provide effective and less invasive treatment options for various conditions. The development of PDT was driven by the need for treatments that overcome the limitations of conventional modalities such as surgery, radiation therapy, and chemotherapy. PDT offers several benefits over these approaches, including its ability to provide targeted therapy, reduced side effects, minimal damage to healthy tissues, and versatility in treating different diseases. One of the key advantages of PDT is its selectivity. By utilizing photosensitizers that accumulate in diseased or abnormal cells, PDT can precisely target the affected tissue while minimizing damage to healthy tissues. This selectivity allows for focused treatment, reducing the potential for unnecessary harm to surrounding structures. Furthermore, PDT offers faster recovery times and potentially better cosmetic outcomes compared to surgery, as it does not require extensive incisions or removal of tissues. Additionally, the localized nature of PDT minimizes systemic toxicity and long-term complications, making it a well-tolerated treatment option. PDT has demonstrated efficacy in various medical fields, including oncology, dermatology, and ophthalmology. It has been used to treat different types of cancers, including skin, lung, oesophagal, and bladder cancer, as well as manage conditions like age-related macular degeneration and certain dermatological disorders. This article reviewed the development, mechanism, and applications of PDT in the medical field.

Keywords: Photodynamic therapy, Photosensitizers, Targeted therapy, Non-invasive treatment.

1. Introduction

Photodynamic therapy (PDT) is an innovative treatment modality that has gained significant attention in the medical field. It combines the use of a photosensitizing agent, the light of specific wavelengths, and molecular oxygen to selectively destroy abnormal cells or tissues while sparing healthy surrounding structures [1]. PDT has emerged as a promising approach for the treatment of various medical conditions, including cancer [2,3], dermatological disorders [4], and ophthalmic diseases [5].

The process of PDT involves the administration of a photosensitizing agent, which is a special type of drug that accumulates in the target cells [2]. Once the photosensitizer has been absorbed, it is activated by exposure to specific wavelengths of light, typically in the visible or near-infrared range [1]. This activation generates reactive oxygen species (ROS), such as singlet oxygen, which induce cellular damage and ultimately lead to cell death [2]. The development of PDT was driven by the need for more effective and less invasive treatment options. Conventional treatment modalities such as surgery, radiation therapy, and chemotherapy have limitations in terms of selectivity, invasiveness, and side effects. PDT overcomes some of these challenges and offers several benefits [6].

One of the primary purposes of developing PDT was to achieve targeted therapy [1]. By utilizing photosensitizing agents that selectively accumulate in diseased or abnormal cells, PDT can be directed precisely to the target tissue or tumour, while minimizing damage to healthy tissues. This selectivity allows for focused treatment, reducing the potential for unnecessary harm to surrounding structures [7]. Additionally, PDT can be repeated multiple times without cumulative toxicity, making it suitable for repeated treatments or long-term management [4].

Compared to earlier treatment modalities, PDT offers several advantages. It is a minimally invasive or non-invasive procedure, depending on the specific application, resulting in reduced morbidity and improved patient

tolerance [2]. Unlike surgery, PDT does not require extensive incisions or removal of tissues, leading to faster recovery times and potentially better cosmetic outcomes [8].

PDT also exhibits a favourable side effect profile compared to conventional therapies such as chemotherapy or radiation therapy [2]. The localized nature of PDT enables the preservation of healthy tissues and organs, reducing systemic toxicity and minimizing long-term complications. This aspect is particularly significant when treating sensitive areas like the eye or skin [9].

2. History of PDT

Photodynamic therapy (PDT) has its roots in the early 20th century when researchers began exploring the effects of light on cells and tissues. The concept of PDT emerged with the discovery of photosensitizing agents, which are compounds that can be activated by light to produce cytotoxic effects in cells [10].

The groundwork for the development of PDT was laid in the 19th century by the observations of several scientists. In 1841, Friedrich Meyer-Betz noted that some dyes became toxic when exposed to light. Later, in 1900, Oscar Raab discovered that acridine dyes could induce tissue damage when illuminated with certain wavelengths of light. These early findings provided the initial clues for the potential use of light-activated compounds in therapeutic applications [10,11].

The modern era of PDT began in the 1960s when the first clinically significant photosensitizing agent, hematoporphyrin derivative (HPD), was synthesized [5]. HPD was derived from hematoporphyrin, a substance found in red blood cells, and it showed promising results in experimental cancer treatment. Subsequent research focused on improving the photosensitizing agents and refining the treatment protocols [12].

One of the major breakthroughs in PDT came with the development of Photofrin®, a purified form of HPD, in the 1980s [13]. Photofrin® was approved by the U.S. Food and Drug Administration (FDA) in 1995 for the treatment of certain types of cancer, including oesophageal and non-small cell lung cancer. This marked a significant milestone in the clinical application of PDT [5].

Over the years, researchers have continued to explore and develop new photosensitizing agents with improved properties, such as higher selectivity and better tissue penetration. Advances in light sources, such as lasers and light-emitting diodes (LEDs), have allowed for better control and precise delivery of light to the target tissues [4].

The understanding of PDT mechanisms and their potential applications has also expanded. Researchers have elucidated the intricate processes involved in the generation of reactive oxygen species (ROS) and their effects on cells and tissues. This knowledge has facilitated the development of targeted PDT approaches and the exploration of PDT in various medical fields, including oncology, ophthalmology, and dermatology [14].

3. Reasons for the developing PDT

Before the development of photodynamic therapy (PDT), several treatment modalities were commonly used for various medical conditions. These modalities included surgery, radiation therapy, and chemotherapy. Each modality had its advantages and disadvantages, and they are listed in Table 1.

Photodynamic therapy (PDT) has been developed for several reasons, driven by the need for effective and less invasive treatment options for various medical conditions. The reasons for developing PDT include its potential to offer targeted therapy, reduced side effects, minimal damage to healthy tissues, and versatility in treating different diseases [6, 9, 18, 19].

A key rationale for the advancement of photodynamic therapy (PDT) lies in its capacity to deliver precise and targeted therapeutic intervention [1]. Through the utilization of distinct photosensitizing agents that exhibit preferential accumulation in diseased or aberrant cells, PDT can be specifically directed towards the intended tissue or tumour site. This inherent selectivity enables focused treatment, thereby minimizing the potential harm inflicted upon surrounding healthy tissues and promoting their preservation.

The reduced side effects associated with PDT compared to conventional treatments are another important reason for its development [20]. PDT primarily targets the localized area of treatment, minimizing systemic toxicity and side effects commonly associated with chemotherapy or radiation therapy. This makes PDT a potentially well-tolerated treatment option for patients [20,21].

Furthermore, PDT has the advantage of causing minimal damage to healthy tissues [20]. The selectivity of photosensitizers and the ability to control the delivery of light enable the destruction of abnormal cells while preserving the integrity of nearby healthy tissues. This aspect is particularly crucial in treating sensitive areas such as the eye or skin [20, 22, 23].

The versatility of PDT in treating different diseases is another reason for its development [24]. PDT has shown efficacy in various medical fields, including oncology, dermatology, and ophthalmology. Its potential applications range from treating different types of cancers [25], including skin, lung, oesophageal, and bladder cancer, to managing conditions like macular degeneration and certain dermatological disorders [26].

4. Mechanism of PDT

The detailed mechanism of photodynamic therapy (PDT) is as follows,

Administration of Photosensitizer: A photosensitizing agent, typically a light-sensitive drug, is administered to the patient either orally, intravenously, or topically [27]. The photosensitizer may accumulate in target cells or tissues due to their specific properties or through active targeting strategies.

Table 1. Different treatment options before the development of PDT.

Treatment Modality	Pros	Cons
Surgery [15]: Surgery involves the physical removal of tumours or diseased tissues. It has been a cornerstone of cancer treatment and remains a primary treatment option for many solid tumours.	• Direct removal of tumours or affected tissues. • Immediate reduction in tumour burden. • Can be curative for localized tumours.	• Invasive procedure with associated risks, such as infection, bleeding, and anesthesia complications. • May cause scarring or disfigurement. • Difficult to remove tumours in certain anatomical locations or when tumours are widespread.
Radiation Therapy [16]: Radiation therapy uses high-energy radiation to kill cancer cells and shrink tumours. It can be delivered externally (external beam radiation) or internally (brachytherapy).	• Non-invasive treatment option. • Can be used for localized or widespread tumours. • May preserve organ function when surgery is not feasible.	• Potential damage to healthy tissues in the radiation field, leading to side effects. • Cumulative toxicity over time. • Multiple treatment sessions required.
Chemotherapy [17]: Chemotherapy involves the use of drugs to kill or inhibit the growth of cancer cells. It is usually administered systemically through the bloodstream and can target cancer cells throughout the body.	• Can reach cancer cells that have spread beyond the primary site. • Can be used as an adjuvant therapy to surgery or radiation. • Some chemotherapeutic agents have curative potential for certain types of cancers.	• Non-specific and can also affect healthy cells, leading to side effects. • Potential for drug resistance. • Limited effectiveness in certain types of cancers.

A large number of photosensitizing drugs have been experimented with in vitro and in vivo during the last 20 years. The most used photosensitizers and precursors in photodynamic therapy are presented in Table 2 [28,29].

The physicochemical properties of a photosensitizer play a crucial role in its effectiveness. An ideal photosensitizer should possess desirable features such as chemical purity, specific localization in neoplastic tissue, quick accumulation in hyperproliferating tissue after administration, rapid clearance from normal tissues, activation at wavelengths with optimal tissue penetration, high quantum yields for singlet oxygen generation, and no dark toxicity [29].

The key requirement for optimal response to photosensitization is an adequate amount of drug localized in the target tissue. While initially taken up by both normal and hyperproliferating cells, photosensitizers tend to be retained longer in hyperproliferating cells [13]. The exact mechanisms behind this selective prolonged retention are not fully understood, but factors such as increased blood vessel permeability and poor lymphatic drainage in neoplastic tissues may contribute to the drug's retention in neoplastic lesions.

Hematoporphyrin derivative (HPD) was the first photosensitizer extensively investigated for clinical photodynamic therapy (PDT). Another photosensitizer, Photofrin (PII), exhibits multiple absorption peaks that can be advantageous for diagnostic purposes. However, PII has a relatively weak absorption at the wavelength of 630 to 635 nm, limiting its tissue penetration. Additionally, the prolonged accumulation of porphyrin-based photosensitizing drugs in the skin and their slow clearance result in persistent photosensitivity, necessitating avoidance of light for 4 to 6 weeks after the treatment [30]. The outline mechanism of PDT is given in Figure 1.

Accumulation in Target Cells: The photosensitizer preferentially accumulates in the target cells or tissues, which could be cancer cells, abnormal blood vessels, or diseased tissues [20]. This selective uptake may occur due to factors such as increased vascularity or receptor expression on the target cells.

Activation by Light: After sufficient time for the photosensitizer to distribute and localize, the target area is exposed to specific wavelengths of light [27]. The light can be delivered externally using lasers or light-emitting diodes (LEDs) or internally using fiber optics for localized treatment.

Energy Transfer: Upon light exposure, the photosensitizer absorbs the light energy and undergoes a process called energy transfer [9]. This energy transfer may involve the excitation of electrons within the photosensitizer molecule.

Generation of Reactive Oxygen Species (ROS): The excited photosensitizer molecule interacts with molecular oxygen present in the surrounding environment, resulting in the production of reactive oxygen species (ROS), mainly singlet oxygen ($^1O_2$) [20]. ROS are highly reactive molecules that can induce cellular damage.

Induction of Cellular Damage: The generated ROS, particularly singlet oxygen, causes oxidative stress and inflicts damage on cellular components, including lipids, proteins, and DNA [31]. This damage disrupts cellular functions and can ultimately lead to cell death.

Anti-Tumour Effects: The cellular damage induced by PDT triggers a series of biological responses, including inflammation, immune activation, and vascular disruption [20]. These responses contribute to the overall anti-tumour effects of PDT and can help in the destruction of cancer cells and tumour regression.

It's important to note that the exact mechanisms and processes may vary depending on the specific photosensitizer used, the light parameters, and the target tissue. Researchers continue to explore and refine the understanding of the PDT mechanism to optimize treatment outcomes.

Table 2. Photosensitizers and their precursors used in experimental and clinical photodynamic therapy applications.

S.No.	Photosensitizers and their precursors
1.	**Chlorines** Monoaspartyl chlorine e6, diaspartyl chlorine e6 Chlorine e_6 sodium, bacteriochlorin a Benzoporphyrin derivative monoacid ring A
2.	**Porphyrins** Hematoporphyrin derivative Dihematoporphyrin ether/ester Porfimer sodium Tetrasodium-meso-tetraphenylporphyrin-sulphonate Metallotetra-azaporphyrin
3.	**Porphyrin precursors** δ-Aminolevulinic acid (ALA) δ -Aminolevulinic acid (ALA)-methyl-, propyl-, hexyl-esters
4.	**Pheophorbides** Pheophorbide a, bacteriopheophorbide
5.	**Phthaallocyanines** Chloroaluminum tetra-sulfonated phthalocyanine Zinc(II)phthalocyanine Silicone naphthalocyanine Aluminum sulfonated phthalocyanine
6.	**Porphycenes** 9-Acetoxy-2,7,12,17-tetra-N-propylporphycene 2-Hydroxyethyl-7,12,17-tris(methoxyethyl)porphycene 23-carboxy-24-methoxycarbonylbenzo(2, 3)-7,12, 17-tri(methoxyethyl)-porphycene
7.	**Photofrin (porfimer sodium)** It was one of the first photosensitizers approved for clinical use and is still utilized in PDT for certain indications. PHOTOFRIN® (2 mg/kg) is slowly administered as an IV injection over 3 to 5 minutes. **ALA (5-aminolevulinic acid)** is a precursor molecule that is converted into a photosensitizer called protoporphyrin IX (PpIX) in cells. It is used in PDT for various dermatological conditions, including actinic keratosis and certain types of skin cancer.
8.	**Foscan (temoporfin)** Foscan is a second-generation photosensitizer that has been used in PDT for head and neck cancers. It does not require the use of a precursor molecule like some other photosensitizers. Unlike porphyrin-based photosensitizers such as Photofrin, Foscan is a chlorine-based photosensitizer that is already in its active form and does not rely on the activation of a precursor.
9.	**Verteporfin** This photosensitizer is approved for the treatment of age-related macular degeneration (AMD) using PDT. Verteporfin also does not require the use of a precursor molecule for activation. Verteporfin is administered directly into the bloodstream and accumulates in the abnormal blood vessels of the retina. When activated by specific light wavelengths, it generates reactive oxygen species, causing damage to the targeted vessels.
10.	**Others** Fluoresceins (fluorescein sodium, tetrabromofluorescein- eosin) Anthracenes (anthraquinone, acridine orange, yellow) Hypericin Furocoumarin (5-methooxypsoralen, 8-methoxypsoralen) Chlorophyll derivatives Purpurins (metallopurpurin, tin etiopurpurin Sn ET2) Phenothiazines Methylene blue, violet green Azure C, thionine, Nile blue A Hypocrellin Rose Bengal Rhodamine 123 Lutetium texaphyrin

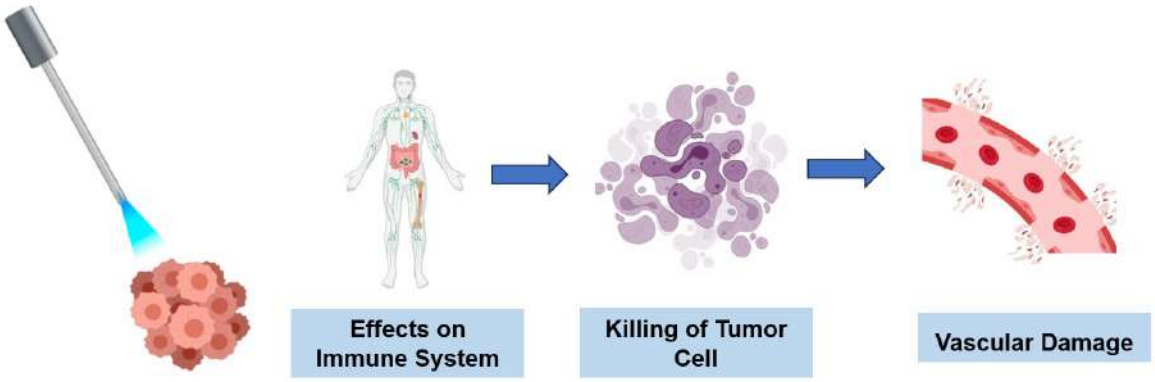

Figure 1. Outline of mechanism of PDT on Tumours.

In photodynamic therapy (PDT), the effectiveness of the treatment depends on the absorption rate and the time of reaction of the photosensitizing drug. The absorption rate refers to how well the drug is taken up by the target tissues or cells, which can be done through topical, oral, or intravenous administration. Once inside the body, the drug selectively accumulates in the desired cells, such as cancer cells or abnormal blood vessels.

The time of reaction is the duration between drug administration and light activation. After the drug is absorbed, it needs to be activated by specific wavelength light. This activation initiates chemical reactions that generate reactive oxygen species (ROS), causing cell damage. The duration of the reaction is critical for achieving the desired therapeutic effects.

Factors influencing absorption rate and time of reaction include drug properties, dosage, the light source used, and characteristics of the target tissue. Optimization of these factors is crucial for ensuring effective treatment by enhancing drug uptake and efficient activation.

5. Applications of PDT in medicine

5.1 Cancer treatment

Photodynamic therapy (PDT) has shown promise as a treatment modality for various types of cancers, including skin cancer, lung cancer, esophageal cancer, head and neck cancer, and bladder cancer.

5.1.1 Skin Cancer

PDT can be used for non-melanoma skin cancers such as basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) [32, 33]. It involves the application of a photosensitizing agent topically or injected systemically and selectively accumulates in cancer cells. The photosensitizer is activated by light of a specific wavelength, leading to the production of reactive oxygen species that cause cell death and destruction of the tumour [32, 33].

Studies have reported high cure rates and good cosmetic outcomes with PDT in the treatment of superficial and thin BCCs and AKs. PDT offers several advantages in skin cancer treatment, including its non-invasive nature, selectivity for abnormal cells, and minimal scarring compared to surgical interventions. It is particularly suitable for treating multiple lesions, field cancerization, and areas that are difficult to access surgically [33-35].

However, the effectiveness of PDT can vary depending on the specific characteristics of the skin cancer, such as size, depth, location, and subtype. PDT may not be suitable for treating advanced or deeply invasive skin cancers, and in such cases, other treatment modalities like surgery, radiation therapy, or chemotherapy may be recommended [11,33,34].

5.1.2 Lung Cancer

PDT can be used as a local treatment option for early-stage lung cancer or palliative treatment for advanced lung cancer. It involves the administration of the photosensitizer systemically and targeting tumour cells in the lungs. Light of a specific wavelength is delivered via bronchoscopy, activating the photosensitizer and leading to tumour destruction [36, 37].

In early-stage lung cancer, PDT has demonstrated good outcomes, with high response rates and favourable overall survival rates. Several studies have reported effective tumour control and local disease management with PDT, comparable to surgery in select cases. PDT has been used as a curative treatment for early-stage non-small cell lung cancer (NSCLC) in patients who are not candidates for surgery or refuse surgery. Chhatre *et al.* [38] assessed the survival outcomes of patients with advanced non-small cell lung cancer (NSCLC) treated with photodynamic therapy (PDT) in comparison to chemotherapy and radiation therapy. The study analyzed data from a large cohort of patients and evaluated their overall survival rates and progression-free survival rates. The findings of the study suggested that PDT, when used as a treatment modality for stage III or stage IV NSCLC, demonstrated promising survival outcomes. The results showed comparable or even improved survival rates when compared to conventional treatments such as chemotherapy and radiation therapy. This indicates the potential efficacy of PDT as an alternative or adjunctive treatment option for advanced NSCLC. The research provides important insights into the use of PDT in lung cancer treatment and highlights its potential as a

therapeutic approach. However, it is essential to note that further research and clinical trials are required to validate these findings and determine the optimal integration of PDT into the management of advanced NSCLC.

In advanced or recurrent lung cancer, PDT is often used as a palliative treatment to alleviate symptoms such as airway obstruction, bleeding, or tumour-related complications. PDT can provide relief and improve quality of life by targeting and destroying tumour tissue, reducing tumour burden, and improving airway patency [39].

5.1.3 Oesophageal Cancer

PDT can be used as an adjuvant treatment for oesophagal cancer. The treatment involves the administration of the photosensitizer intravenously, preferentially accumulating in cancer cells. Light is delivered to the oesophagus via an endoscope, activating the photosensitizer and destroying the tumour cells [40,41].

Several studies have reported positive results with PDT in oesophagal cancer treatment. For example, a study published in the Journal of Clinical Oncology found that PDT achieved a complete response in 77% of patients with early stage oesophagal cancer, with a median survival of 3.9 years. Another study published in Gastroenterology showed a complete response rate of 61% in patients with superficial oesophagal squamous cell carcinoma treated with PDT.

5.2 In Dermatology

PDT is used to treat various dermatological conditions, including acne, actinic keratosis, psoriasis, basal cell carcinoma, and other superficial skin cancers [42,43].

5.2.1 Acne [44,45]

Photodynamic therapy (PDT) has shown promise in the treatment of acne, particularly in cases where other treatment options have failed. The procedure involves the application of a topical photosensitizing agent, such as aminolevulinic acid (ALA), to the affected area, followed by a waiting period to allow the photosensitizer to be absorbed by the sebaceous glands. Once absorbed, the photosensitizer is activated by exposure to light, typically blue or red light. This activation triggers a series of reactions that lead to the destruction of bacteria associated with acne and a reduction in sebaceous gland activity. By targeting the underlying causes of acne, PDT offers a potential solution for patients who have not achieved satisfactory results with conventional treatments.

5.2.2 Actinic Keratosis (AK) [46,47]

PDT, or photodynamic therapy, is a highly effective treatment option for actinic keratosis, a precancerous condition resulting from sun damage. The treatment process begins with the application of a topical photosensitizing agent, such as methyl aminolevulinate (MAL), directly to the affected area. After application, a waiting period is required to allow sufficient absorption of the photosensitizer by the abnormal cells. Once absorbed, the photosensitizer is activated by exposure to specific wavelengths of light, commonly red light. The activation of the photosensitizer initiates a cascade of reactions that effectively destroy the abnormal cells, leading to the resolution of actinic keratosis lesions. Through this targeted approach, PDT offers a successful and non-invasive treatment option for individuals with actinic keratosis, helping to prevent its progression into more serious skin conditions such as skin cancer.

5.2.3 Psoriasis [48]

PDT can serve as an effective adjunctive treatment for psoriasis, particularly for localized plaques. The treatment process begins with the application of a photosensitizing agent, such as aminolevulinic acid (ALA), directly to the psoriatic plaques. Following application, a waiting period is necessary to allow the photosensitizer to be taken up by the hyperactive skin cells. Once absorbed, the photosensitizer is activated through exposure to specific wavelengths of light, commonly red light. The activation of the photosensitizer plays a crucial role in reducing the excessive proliferation of skin cells and inflammation associated with psoriasis. By targeting the underlying mechanisms of the condition, PDT offers a promising approach to alleviate the symptoms and improve the overall management of psoriasis, particularly in localized plaques.

5.3 In Ophthalmology

PDT is used for treating various eye conditions, such as age-related macular degeneration (AMD) and certain types of ocular tumours [49].

5.3.1 Treating age-related macular degeneration using PDT [50-53]

Photodynamic therapy (PDT) is a treatment option for age-related macular degeneration (AMD), particularly for the neovascular or "wet" form of the disease. The following are the different stages involved in the treatment.

Targeting abnormal blood vessels: In AMD, abnormal blood vessels grow beneath the macula, leaking fluid and causing damage to the retina. PDT aims to target and close these abnormal blood vessels. A photosensitizing agent, such as verteporfin, is injected into the patient's bloodstream, which selectively accumulates in the abnormal blood vessels.

Activation of photosensitizer: The photosensitizer is activated by illuminating the affected area with a specific wavelength of light, typically using a laser. The activated photosensitizer produces reactive oxygen species, leading to the destruction of the abnormal blood vessels.

Minimizing damage to surrounding tissue: PDT is designed to selectively target abnormal blood vessels while minimizing damage to the surrounding healthy tissue. The photosensitizer is localized within the targeted blood vessels, reducing the risk of collateral damage.

Reduction of leakage and inflammation: By closing off the abnormal blood vessels, PDT helps reduce the leakage of fluid and blood into the macula. This can lead to a decrease in macular oedema, inflammation, and subsequent vision loss.

It's important to note that PDT is typically used in combination with other treatments for AMD, such as anti-vascular endothelial growth factor (VEGF) injections. PDT may be recommended for certain cases of AMD based on the location, size, and type of abnormal blood vessels present.

5.3.2 PDT as a treatment modality for certain types of ocular tumours [54,55]

Targeted tumour destruction: PDT utilizes a photosensitizing agent that preferentially accumulates in tumour cells or their blood vessels. This photosensitizer is then activated by light of a specific wavelength, leading to the production of reactive oxygen species. These reactive oxygen species cause localized damage to the tumour cells, resulting in their destruction.

Selective tumour ablation: The photosensitizer is designed to selectively accumulate in tumour cells or the vasculature of the tumour, thus minimizing damage to healthy surrounding tissues. This selectivity allows for precise targeting of the tumour and reduction in potential side effects.

Minimally invasive procedure: PDT is generally considered a minimally invasive procedure as it involves the administration of a photosensitizing agent followed by light activation. The light can be delivered externally using lasers or fiber-optic devices, allowing for precise control of treatment parameters.

Preservation of vision: In some cases, PDT can be used to treat ocular tumours while preserving vision. This is particularly important for tumours located in or near critical visual structures.

5.4. In Infectious Diseases

PDT has shown potential in the treatment of various infectious diseases, including bacterial, fungal, and viral infections [56,57].

5.4.1 Bacterial infections

PDT offers an effective means of targeting and eliminating bacteria by employing several mechanisms. The mechanisms include, selectively accumulating in bacteria, generating reactive oxygen species upon light activation, and effectively eradicating bacterial cells. Additionally, PDT has the ability to disrupt bacterial biofilms, which are protective layers formed by bacterial colonies that can enhance resistance against conventional antimicrobial therapies [56,58].

5.4.2 Fungal infections

PDT can be effective against various fungal infections, including superficial infections of the skin and mucous membranes. Photosensitizers can target fungal cells and, upon light activation, produce reactive oxygen species that damage fungal structures and lead to cell death.

5.4.3 Viral infections

PDT has shown promise in inactivating enveloped viruses, such as herpes simplex virus (HSV), human immunodeficiency virus (HIV), and influenza virus. It can disrupt the viral envelope and inhibit viral replication [59,60]. The application of PDT for infectious diseases is still an active area of research, and its clinical use may vary depending on the specific infection and individual patient factors.

6. Applications of PDT in Dentistry

Photodynamic therapy (PDT) has various applications in dentistry, including treating oral infections, periodontal diseases, oral premalignant lesions, etc.,

6.1 Treatment of periodontal disease

PDT has emerged as a potential adjunctive treatment for periodontal diseases, including gingivitis and periodontitis [61,62]. The process involves the application of a photosensitizing agent, such as methylene blue or toluidine blue, directly into the periodontal pockets. Following application, the photosensitizer is activated by exposing it to a laser or LED light. This activation triggers a series of photodynamic reactions, resulting in the destruction of bacteria residing in the periodontal tissues. Simultaneously, PDT helps to mitigate inflammation in the affected periodontal tissues, contributing to the overall healing process. By utilizing this targeted approach, PDT shows promise in effectively combating bacterial infections and reducing inflammation in periodontal diseases, potentially offering a valuable addition to the treatment options available for periodontal therapy [61,62].

6.2 Treatment of oral infections

PDT offers a potential treatment option for oral infections, including oral candidiasis and peri-implantitis, by utilizing a photosensitizing agent applied to the affected area. Upon exposure to laser or LED light, the photosensitizer is activated, leading to selective targeting and eradication of the microorganisms responsible for the infection. This photodynamic process effectively destroys the pathogens, offering a promising approach to managing oral infections through PDT [63,64].

6.3 Treatment of Oral Premalignant Lesions

PDT offers a potential treatment option for oral premalignant lesions, including leukoplakia and erythroplakia. The process begins with the application of a photosensitizing agent, such as 5-aminolevulinic acid (ALA), to the lesion. Following the application, the photosensitizer is activated through exposure to a laser or LED light. This activation selectively targets and destroys the abnormal cells within the lesion. By eliminating these abnormal cells, PDT promotes healing and reduces the risk of malignant transformation in oral premalignant lesions [65].

6.4 In Endodontics

Photodynamic therapy (PDT) exhibits promising potential in the realm of endodontics, specifically in the treatment of endodontic infections and the disinfection of root canals [66-68]. However, it is crucial to emphasize that despite the encouraging results, additional research and clinical trials are necessary to establish the most effective protocols, ensure safety, and determine the long-term efficacy of PDT in endodontic procedures.

7. Contra-indications of PDT

PDT is contraindicated for patients with known allergies or sensitivities to the photosensitizing agent used in PDT should not undergo the treatment. PDT is generally avoided during pregnancy due to limited safety data on the developing foetus. Patients with known photosensitivity disorders or those who are taking medications that increase sensitivity to light may not be suitable candidates for PDT. If

the target lesion is in a location that cannot be effectively reached by light exposure, PDT may not be feasible. PDT may not be appropriate for advanced or deeply invasive cancers that require more aggressive treatment modalities like surgery, radiation therapy, or chemotherapy.

7. Limitations of PDT

Photodynamic therapy (PDT) has several limitations that should be considered. The following are a few limitations of PDT [69].

Limited tissue penetration: The effective treatment depth of PDT is limited to a few millimeters below the tissue surface. Light used to activate the photosensitizer can only penetrate a certain distance, restricting its application to superficial or accessible lesions.

Light delivery challenges: PDT requires precise and targeted delivery of light to the treatment area. This can be challenging in cases where the target tissue is located deep within the body or in areas that are difficult to access, such as certain organs or structures.

Photosensitivity: Following PDT, patients may experience photosensitivity, where the treated area becomes highly sensitive to light. This necessitates the avoidance of direct sunlight or bright indoor lighting for a certain period after treatment.

Variable response: The effectiveness of PDT can vary depending on the type and location of the treated condition. Some tumours or lesions may not respond well to PDT, limiting its applicability in certain cases.

Combination therapy often required: In many instances, PDT may be used in combination with other treatment modalities, such as surgery, radiation therapy, or chemotherapy, to enhance its therapeutic outcomes. This adds complexity to the treatment process and may increase the risk of potential side effects.

Cost and availability: PDT is an expensive treatment as it is associated with photosensitizer drugs, light sources, and specialized equipment.

Therefore, future advancements in technology must focus on developing new photosensitizers with improved properties such as enhanced selectivity, higher quantum yields, and better tissue penetration; advanced light sources; molecular imaging and guiding techniques; the development of targeted and personalized PDT approaches. This includes the use of specific targeting ligands, antibody conjugates, or nanoparticles to selectively deliver photosensitizers to cancer cells or specific disease targets.

8. Conclusion

PDT is a promising therapeutic approach with a wide range of applications. Its non-invasive characteristics, targeted action, and minimal adverse effects make it highly appealing across various medical disciplines. Although PDT has proven effective, it is important to acknowledge its limitations in determining its suitability for specific conditions. However, with continuous research and technological advancements, PDT is expected to evolve and offer new possibilities in the treatment of diseases, paving the way for improved patient outcomes and quality of life.

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