

Emerging Horizons in Cancer Therapy: Illuminating the Potential of Photodynamic Therapy (PDT) For Enhanced Treatment Strategies

**Mohd Yusuf¹, Neelam Yadav², Rizwan Ul Hasan³, Azmat Zehra⁴, Bushra Begum⁵
Soumya Verma⁶, Mohammad Asif^{7*}**

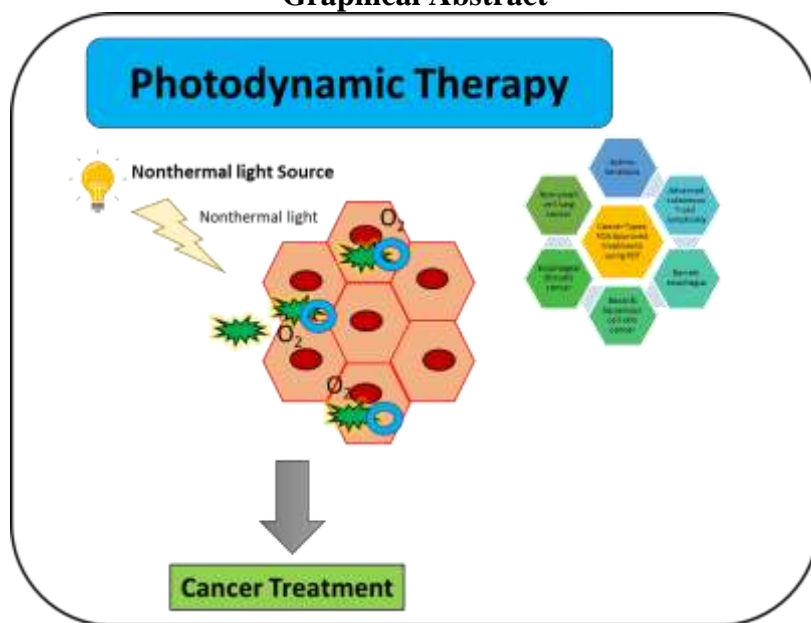
¹*Department of Natural and Applied Sciences, School of Science and Technology, Glocal University, Saharanpur, U.P. 247121 India.*

^{2,3,4,5,6,7*} Era College of Pharmacy, Era University, Lucknow, 226003, Uttar Pradesh, India.

Email: yusuf1020@gmail.com, aasif321@gmail.com

<p>Article History</p> <p>Received: 06 June 2023 Revised: 09September 2023 Accepted:01 November 2023</p>	<p>Abstract</p> <p><i>Photodynamic therapy (PDT) involves light activation, in presence of molecular oxygen, and certain dyes that are taken up by the target tissue. The therapy includes giving a photosensitizing drug to the target tissue, which accumulates and then exposing the tissue to a precise wavelength of light. The medicine is activated by the light and release reactive oxygen species that kill the target tissue. PDT is a medical treatment that treats specific illnesses by using light-sensitive medicines and particular light sources. The dyes used in the therapy are termed as photo sensitizers. The mechanism of interaction of the photo sensitizers and light along with the effects produced in the target tissue. Current status of clinical PDT is discussed along with the new photo sensitizers being used and their role in therapy. Despite the promising results of PDT, significant additional work is needed to bring this new modality of treatment into modern clinical practice. Improvements in the area of light source delivery, light dosimetry and computation of models of treatment are necessary to proper treatment delivery. The present work encompasses new insights on PDT to combat various types of cancer cells as a novel technique with its specific limitation and future aspects.</i></p>
<p>CC License CC-BY-NC-SA 4.0</p>	<p>Keywords: <i>Photodynamic therapy (PDT), Light, Dyes, Cancer, Novel techniques.</i></p>

Graphical Abstract



1. Introduction

The concept of employing photodynamic therapy (PDT) as an innovative treatment approach was first proposed in the early 1900s. A significant landmark in the development of photosensitizers occurred back in 1841 when Schere successfully extracted hematoporphyrin from dried blood by removing iron [1-2], laying a foundation for subsequent advancements. This concept eventually led to the formulation of the definition of photodynamic action, a term attributed to Hermann von Tappeiner, who emphasized the pivotal role of light. Photodynamic therapy aimed at treating infections by utilizing reactive oxygen species (ROS) to disrupt and eliminate microbes gained significance against bacteria and viruses. However, the progression of this idea was hindered by the World Wars, resulting in a delay of around six decades [4-5]. The turning point arrived in 1960 when R. L. Lipson and S. Schwartz conducted transformative studies at the Mayo Clinic, revealing that malignancies could be identified using hematoporphyrin derivatives activated and viewed through appropriate filter systems. S. Schwartz's hematoporphyrin derivative (HpD) marked a breakthrough, composed of multiple porphyrins, including monomers, dimers, and oligomers [6]. In 1978, Dougherty et al. recorded the inaugural clinical PDT case involving a patient with metastatic breast cancer in the skin. Subsequent developments led Furuse et al. to carry out phase II clinical trials involving Photofrin (porfimer sodium) for early-stage lung cancer between 1989 and 1992. Notably, 1993 saw the first health agency approval for PDT using Photofrin in Canada for bladder cancer treatment, followed by the FDA's approval for esophageal cancer treatment in 1995 [2-4,7-9]. Photofrin's application expanded to early non-small cell lung cancer treatment in 1998. The historical timeline of PDT is visually depicted in Figure 1. Notably, the initial applications of PDT included the clinical use of eosin for skin cancer treatment, exemplified by Tappeiner and Jesionek's efforts to treat skin tumors using topical eosin. Over time, photosensitizers (PSs) have undergone a three-generation classification based on their evolutionary progression. Around the turn of the century, the first preclinical uses of PDT were documented. In the early 19th century, Raab proved the dependency on light, as well as the necessity that the light be of wavelengths absorbed by the sensitising 'dye' [10]. Dougherty and colleagues reported a clinical report of PDT's therapeutic potential in a large group of cancer patients in the late 1970s [11]. Cramer et al. described the dynamic aspects of PDT including the various cell death pathways as well as antivascular and immune stimulatory activities that create a PDT response [12]. Mechanism-informed PDT procedures boost PDT's role in multimodality therapeutic methods. The simple schematic representation for PDT treatment of cancer cell is depicted in Fig. 1.

Furthermore, with a better knowledge of its mechanics, PDT can be used to therapeutic requirements outside of cancer.

Photodynamic treatment (PDT) primarily depends on the creation of singlet oxygen through the excitation of a photosensitizer in order to eliminate target tumour cells. PDT can be used to treat a variety of cancers. In fact, the first preclinical uses date back to the 1900s. In 1978, Dougherty reported the use of PDT to treat skin cancers. Several other studies conducted around 1980 proved the efficacy of PDT. As a result, the approach has piqued the interest of many academics since then. In 1995, the FDA approved hematoporphyrin derivative as a clinical use of PDT [2]. Over the previous century, we have seen significant advancement in this subject. PDT is nowadays, have been used to treat skin cancer, age-related macular degeneration, and some forms of lung and esophageal cancer [6]. The procedure is minimally invasive and may be done as an outpatient procedure with little adverse effects. However, it is crucial to remember that PDT is not appropriate for all people and circumstances, and the choice of treatment will be determined by the patient. Photodynamic therapy (PDT) is a minimally invasive medical treatment that consists of administering a photosensitizing medication followed by exposure to a specified wavelength of light. Because the medicine and light operate in tandem to eliminate the diseased tissue, it is an effective therapy option for some forms of cancer and skin disorders. One of the primary benefits of PDT is its focused nature, which lessens the danger of injury to adjacent healthy tissue while also lowering the likelihood of adverse effects [7,8]. PDT has also been demonstrated to be extremely successful in the treatment of some illnesses, with high cure rates and low recurrence rates [9]. PDT recovery time is also generally brief, with many patients able to resume normal activities within a few days of the procedure. To circumvent the constraints, many photosensitizers have been designed/synthesised. We present a basic review of the mechanisms of action of PDT in cancer, including the effects on the immune system and vasculature, as well as pathways associated to tumour cell killing. In this work, PDT is discussed to combat cancer cells as a novel and emerging techniques with their specific limitations and future aspects.

Mechanism and Functional Hypothesis

Heliotherapy encompasses the deliberate use of sunlight or alternative sources of radiation, spanning UV, visible, or infrared spectra, with the explicit intent of harnessing their therapeutic potential. This practice, traceable back to antiquity, finds its systematic acknowledgment in the works of Herodotus within ancient Greece. Remarkably, Herodotus described the strategic utilization of sunlight for medicinal purposes, a tradition that has persisted through history. During the 18th and 19th centuries, the therapeutic prowess of sunlight came to the forefront as it was employed to address an array of ailments including tuberculosis, rickets, scurvy, rheumatism, paralysis, edema, and muscle weakness. It is worth noting that this era marked a significant turning point for the understanding and application of heliotherapy. However, it wasn't until the 20th century that heliotherapy solidified its place within modern medicine. Notably, Danish physician Niels Ryberg Finsen emerged as a pivotal figure during this era. Finsen's groundbreaking work involved treating chickenpox using red light exposure, an approach that demonstrated remarkable efficacy by preventing the inflammation of pustules. His work not only spotlighted the potential of light in therapeutic contexts but also laid the foundation for the incorporation of light-based treatments into mainstream medical practices. Moreover, heliotherapy's historical trajectory has transitioned from ancient anecdotes to systematic applications in the modern medical landscape. The diligent observations of past scholars and the innovative insights of pioneers like Niels Ryberg Finsen have collectively propelled heliotherapy into a position of relevance, facilitating its integration as a valuable therapeutic modality.

Photodynamic therapy (PDT) is a two-step process that involves the administration of a photosensitizing drug followed by exposure to a specific wavelength of light. The existing limits of PDT use in cancer will be discussed, as addressing difficulties linked with photosensitizer design/synthesis, as well as light application and tissue oxygenation, may pave the way for more successful PDT techniques. Furthermore, novel promising approaches to improve outcome in PDT, such as selectivity, bioengineering, subcellular/organelle targeting, and so on, will be discussed in depth, because the potential of pioneering and exceptional approaches aimed at overcoming limitations and revealing the full potential of PDT in terms of clinical translation is undeniably exciting.

A greater grasp of innovative concepts in the area (for example, improved, two-stage, and fractional PDT) will almost certainly be highly valuable for pursuing and enhancing successful PDT tactics. The mechanisms of action are based on the production of singlet oxygen ($^1\text{O}_2$), preferably with high yield, by the excitation of a specific photosensitizer (PS), which transfers its excited energy to molecular oxygen in tumour tissues via a triplet state manifold [13]. Tumor cell necrosis and/or apoptosis are triggered by cytotoxic singlet oxygen and other secondary molecules such as reactive oxygen species (ROS). The next section will outline the detailed mechanisms of action of PDT.

Administration of Photosensitizing Drug

The patient is given an intravenous injection of a photosensitizing drug, which is absorbed by the target tissue. The drug is activated by specific wavelengths of light, causing it to produce reactive oxygen species. The FDA has approved photodynamic therapy to treat various types of cancers (Fig. 2a & 2b).

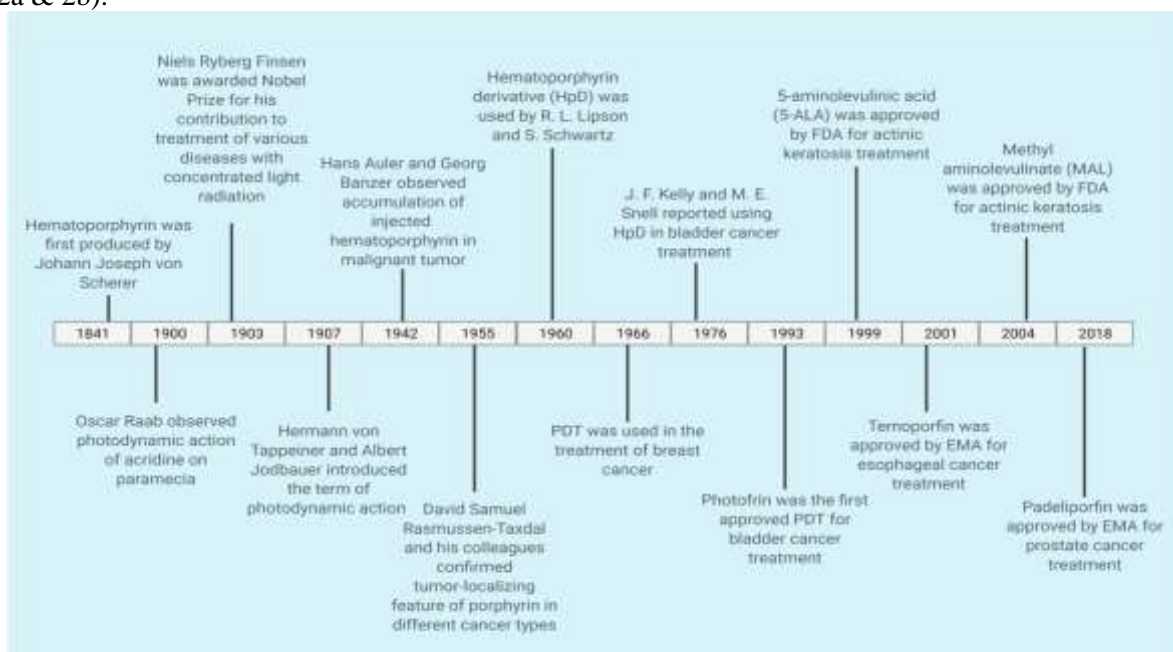


Fig. 1. Schematic representation of PDT treatment timeline: Shows selected applications of PDT for cancer (Adapted from ref [8] under CCBY Attribution, 2021).

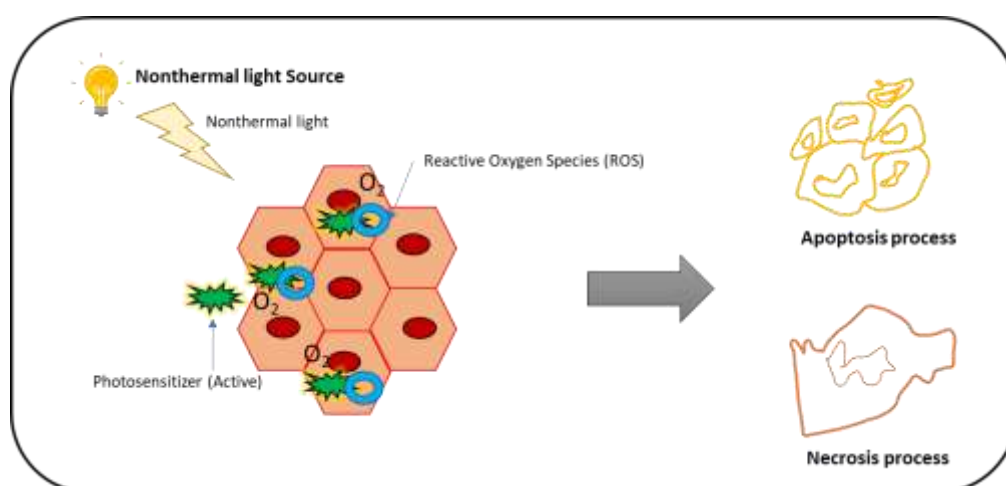


Fig. 2a. Schematic representation of PDT treatment of Cancer cells via Apoptosis and Necrosis.

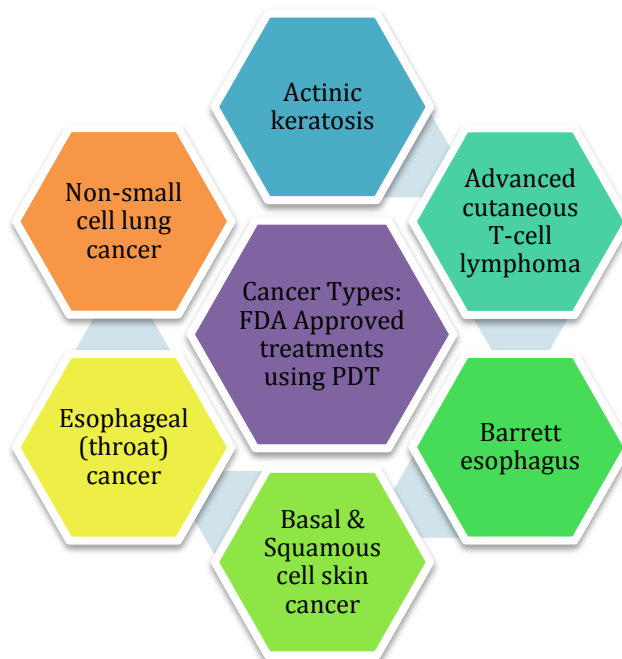
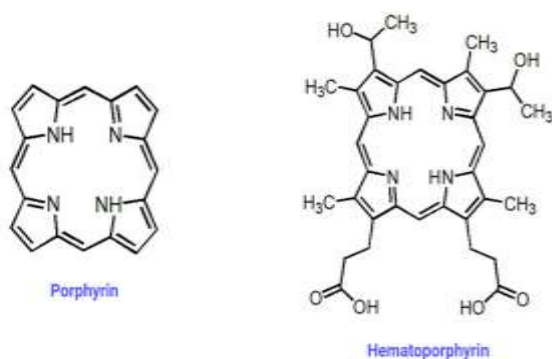


Fig. 2b. Schematic representation of FDA approved photodynamic therapy to treat various cancer types.

First Generation PSs



Second Generation PSs

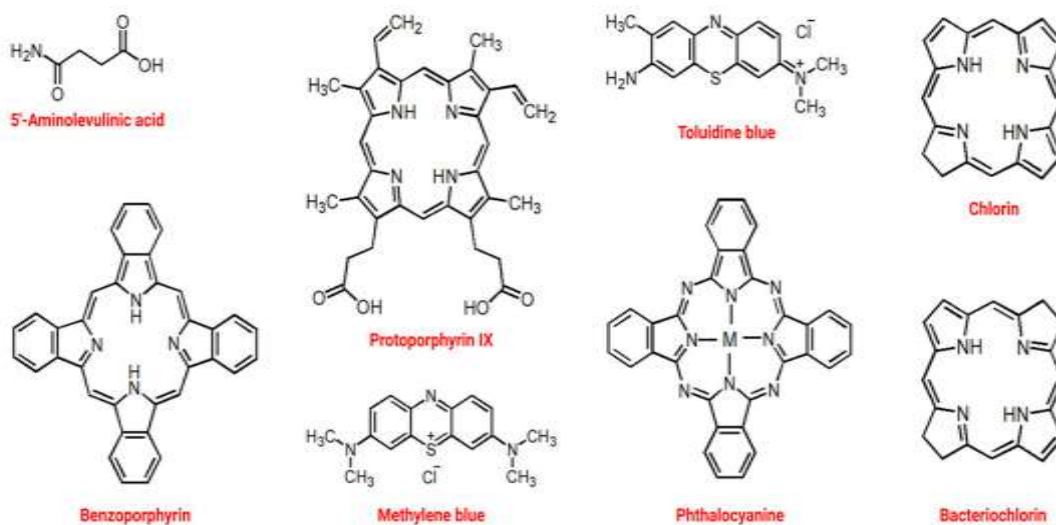


Fig. 3. Schematic representation various examples of first and second Generation photosensitizers (Adapted from ref [8] under CCBY Attribution, 2021).

The administration of the photosensitizing drug is a crucial step in the photodynamic therapy (PDT) process. The drug is usually given intravenously through a vein, although in some cases, it may be applied topically to the skin. The dose and timing of the drug administration are carefully controlled to ensure maximum effectiveness and minimize the risk of damage to surrounding healthy tissue. The patient may need to fast or follow other specific instructions before the treatment to optimize the uptake of the drug by the target tissue. Once the photosensitizing drug is administered, it is absorbed by the target tissue and accumulates over a period of time, usually several hours to a few days, depending on the specific drug and treatment regimen. The specific timing of light exposure is then carefully controlled to ensure maximum effectiveness of the therapy and minimize the risk of damage to surrounding healthy tissue. It's important to note that not all patients are suitable for PDT, and the choice of treatment will depend on the specific circumstances and the patient's individual needs and preferences. The treating healthcare provider will be able to advise the patient on the most appropriate course of treatment [14-16].

Exposure to Light

After a period of time to allow the drug to accumulate in the target tissue, the patient is exposed to a specific wavelength of light, typically delivered via a light-emitting device, such as a laser or light-emitting diode (LED). The light activates the drug, causing it to produce reactive oxygen species that destroy the target tissue.

The specific wavelength of light used in PDT and the timing of light exposure are carefully controlled to ensure maximum effectiveness and minimize the risk of damage to surrounding healthy tissue. The exact mechanism by which the reactive oxygen species produced by the activated drug destroy the target tissue is not fully understood, but it is thought to involve a combination of oxidative damage and cellular apoptosis (programmed cell death). Exposure to a specific wavelength of light is a crucial step in the photodynamic therapy (PDT) process. After a period of time to allow the photosensitizing drug to accumulate in the target tissue, the patient is exposed to light of a specific wavelength, usually delivered via a light-emitting device, such as a laser or light-emitting diode (LED).

The specific wavelength of light used in PDT and the timing of light exposure are carefully controlled to ensure maximum effectiveness and minimize the risk of damage to surrounding healthy tissue. The light activates the photosensitizing drug, causing it to produce reactive oxygen species that destroy the target tissue. The length of light exposure depends on various factors, such as the type and dose of photosensitizing drug used, the size and location of the target tissue, and the specific type of light-emitting device used. In general, the light exposure time can range from several minutes to several hours. The exposure to light is performed with the patient lying down or sitting comfortably, and they may be given eye protection to protect their eyes from the light. In some cases, they may also be given a local anaesthetic to minimize any discomfort during the treatment. It's important to note that PDT is a complex and precise procedure, and it is usually performed by trained healthcare professionals in a clinical setting. The treating healthcare provider will be able to advise the patient on the specific details of their treatment [17-20].

Photodynamic therapy (PDT) works by using a photosensitizing drug and a specific wavelength of light to produce reactive oxygen species that destroy target tissue. The exact mechanism by which this occurs is not fully understood, but several functional hypotheses have been proposed to explain the effects of PDT.

Oxidative Damage

The reactive oxygen species produced by the activated drug are highly reactive and can cause oxidative damage to cellular components such as lipids, proteins, and DNA, leading to cellular dysfunction and death.

Programmed Cell Death (Apoptosis)

PDT may also induce programmed cell death (apoptosis) in target cells by disrupting normal cellular processes and triggering the activation of apoptotic pathways. This process results in the orderly and controlled breakdown of cells, reducing the risk of spreading cancer cells to other parts of the body.

Immune System Activation

In some cases, PDT may also stimulate the immune system to attack and destroy cancer cells. This may involve the activation of immune cells, such as natural killer cells and T cells, or the recruitment of immune cells to the site of the cancer.

Therefore, the mechanism by which PDT works is complex and may involve a combination of these and other factors. Further research is needed to fully understand the underlying mechanisms and optimize the use of PDT as a medical treatment.

Photochemical Reactions of Photosensitisers: Activation of Drug and Production of Reactive Oxygen Species

Photodynamic therapy (PDT) works by activating a photosensitizing drug within the affected tissue and producing reactive oxygen species (ROS). The photosensitizing drug is absorbed by the affected tissue, where it accumulates over time. When the drug is exposed to a specific wavelength of light, it becomes activated and produces ROS, which can damage and destroy the affected tissue. Reactive oxygen species are highly reactive molecules that can cause oxidative stress within the affected tissue. This oxidative stress can lead to the destruction of cells and cellular components, including cellular membranes and DNA. As a result, the affected tissue is effectively destroyed, leading to a reduction in the size of the affected area. The exact mechanism of how the ROS cause tissue damage is still not fully understood, but it is thought that they interact with cellular components, such as lipids and proteins, leading to their destruction. Additionally, the ROS can cause the release of other chemical species that can further damage the tissue, including free radicals and reactive nitrogen species [21-24].

Type-I and Type-II reactions are possible for excited triplet-state photosensitisers (Fig. 3). The excited singlet or triplet photosensitiser ($^1\text{Psen}^*$, S^1 ; $^3\text{Psen}^*$, T^1) can be involved in Type-I processes, however due to the limited lifespan of the excited singlet state, the photosensitiser can only respond if it is closely linked with a substrate. Both interactions occur with rapidly oxidisable or reducible substrates. The excited triplet photosensitiser ($^3\text{Psen}^*$, T^1) interacts directly with molecular oxygen ($^3\text{O}_2$) in type II processes.

Type-I Processes

Type I processes are classified as Type I(i) and Type I(ii). The transfer of an electron (oxidation) from a substrate molecule to the excited state photosensitiser (Psen^*) results in the formation of a photosensitiser radical anion ($\text{Psen}^{\cdot-}$) and a substrate radical cation ($\text{Subs}^{\cdot+}$). The vast majority of radicals generated by Type-I(i) responses, react instantly with molecular oxygen (O_2), resulting in a mixture of oxygen intermediates. For example, the photosensitiser radical anion can react instantly with molecular oxygen ($^3\text{O}_2$) to produce a superoxide radical anion ($\text{O}_2^{\cdot-}$), which can then produce the highly reactive hydroxyl radical (OH^{\cdot}), initiating a cascade of cytotoxic free radicals; this process is common in fatty acid and other lipid oxidative damage.

In other words, the Type-I process (ii) entails the reduction of a hydrogen atom to the excited state photosensitiser (Psen^*). This produces free radicals that may quickly react with molecular oxygen to form a complex combination of reactive oxygen intermediates, including reactive peroxides.

Type-II Processes

The excited triplet state photosensitiser ($^3\text{Psen}^*$) interacts directly with ground state molecular oxygen ($^3\text{O}_2$) in a spin permitted transition—the excited state photosensitiser and ground state molecular oxygen are of the same spin state (T).

When excited photosensitisers hit with molecular oxygen, triplet-triplet annihilation occurs ($^3\text{Psen}^*$, $^1\text{Psen}$ and $^3\text{O}_2$, $^1\text{O}_2$). This inverts the spin of one oxygen molecule's ($^3\text{O}_2$) outermost antibonding electrons, producing two types of singlet oxygen (1:1) while depopulating the photosensitiser's excited triplet state ($T^1 S^0$). The higher-energy singlet oxygen state (157kJ mol^{-1}) has a brief lifetime (0.33 milliseconds (in MeOH solvent), undetectable in $\text{H}_2\text{O}/\text{D}_2\text{O}$) and quickly relaxes to the lower-energy excited state (94kJ mol^{-1}). As a result, this lower-energy form of singlet oxygen ($1g$) is implicated in cell damage and death. The highly reactive singlet oxygen species ($^1\text{O}_2$) formed

by the Type-II mechanism act near the site of production and within a radius of roughly 20 nm, with a typical lifespan in biological systems of around 40 nanoseconds time duration.

Key Benefits and Advantages

Heliotherapy involves utilizing sunlight or other sources of UV, visible, or infrared radiation for therapeutic intentions. This practice, documented by Herodotus in ancient Greece, was systematically recognized for its medicinal application and was employed as an efficacious treatment approach for diverse illnesses. During the 18th and 19th centuries, sunlight therapy found utility in addressing conditions such as tuberculosis, rickets, scurvy, rheumatism, paralysis, edema, and muscle weakness. However, its integration into modern medical practice transpired primarily during the 20th century. In its early years, Danish physician Niels Ryberg Finsen garnered attention by treating chickenpox through red light exposure, effectively mitigating inflammation of pustules. In the following years, Niels Ryberg Finsen was awarded with the 1903 Nobel Prize in Physiology or Medicine for “his contribution to the treatment of diseases, especially lupus vulgaris, with concentrated light radiation”.

Photodynamic therapy (PDT) is a medical treatment that offers several advantages over other forms of cancer treatment and therapy for certain conditions. Some of the key advantages of PDT include:

Versatility

PDT can be used in combination with other forms of therapy, such as surgery or chemotherapy, to enhance the effectiveness of treatment and improve outcomes.

Cost-effective

Compared to other forms of cancer treatment, such as surgery or chemotherapy, PDT can be a cost-effective option for many patients, especially in the long term.

Minimally invasive

PDT is a minimally invasive procedure that does not require surgery or other invasive techniques, making it a less traumatic form of treatment for many patients.

Targeted treatment

PDT is a targeted form of therapy that specifically targets the affected tissue, minimizing the risk of damage to surrounding healthy tissue and reducing the risk of side effects.

High efficacy

PDT has been shown to be highly effective in treating certain types of cancer and other conditions, with high cure rates and low recurrence rates.

Short recovery time

The recovery time after PDT is generally short, with many patients able to return to normal activities within a few days of the procedure.

It's important to note that the specific advantages of PDT will depend on the patient's individual circumstances and the specific treatment regimen used, and not all patients will be suitable for the therapy. The treating healthcare provider will be able to advise the patient on the most appropriate course of treatment.

Comparison of PDT and Other Existing Treatments

PDT is continually being found extraordinary because of its non-invasiveness novel strategic, and great sensitivity, optical approaches gaining popularity in tumour therapy [25,26]. Photodynamic therapy (PDT) can be compared with other treatments for certain conditions, such as cancer or skin conditions, in terms of its advantages and disadvantages. Some of the key differences between PDT and other forms of treatment include:

Surgery

Surgery is a highly invasive form of treatment that involves removing the affected tissue. While surgery can be highly effective for certain types of cancer, it can also be associated with significant risks and long recovery times. In contrast, PDT is a minimally invasive form of treatment that specifically targets the affected tissue, reducing the risk of damage to surrounding healthy tissue and minimizing the risk of side effects.

Chemotherapy

Chemotherapy is a systemic form of treatment that uses drugs to destroy cancer cells throughout the body. While chemotherapy can be highly effective in treating certain types of cancer, it can also cause

significant side effects and affect the patient's overall health. In contrast, PDT is a targeted form of therapy that specifically targets the affected tissue, minimizing the risk of side effects and improving the patient's overall quality of life.

Radiation therapy: Radiation therapy is a form of treatment that uses high-energy rays to destroy cancer cells. While radiation therapy can be highly effective in treating certain types of cancer, it can also cause long-term side effects, such as damage to healthy tissue and increased risk of secondary cancers. In contrast, PDT is a minimally invasive form of therapy that specifically targets the affected tissue, reducing the risk of damage to surrounding healthy tissue and minimizing the risk of side effects. It's important to note that the most appropriate form of treatment will depend on the patient's individual circumstances, such as the type and stage of the cancer or condition, and the patient's overall health. The treating healthcare provider will be able to provide the patient with more information and guidance on the most appropriate course of treatment [26].

Cutaneous squamous cell carcinoma (SCC), the second most prevalent skin cancer, has historically been addressed through surgical interventions; however, the limitations of surgery prompt consideration for critical anatomical sites emphasizing tissue preservation. Photodynamic therapy (PDT) has emerged as an extensively studied alternative, offering noninvasive or minimally invasive treatment avenues. Research underscores its safety, efficacy, and cosmetic benefits. Mechanisms behind PDT's effectiveness have been explored, yet clinical validation faces constraints due to limited sample sizes and tumor depth. Encouraging outcomes are predominant in microinvasive SCC cases, confined to the papillary dermis, yet constrained by insufficient transcutaneous permeation of photosensitizers over keratinized tumors. Overcoming this involves strategies like laser or microneedle pre-treatments and photosensitizer encapsulation in nanoparticles. This article extensively examines PDT's efficacy and safety in cutaneous SCC, delves into its mechanisms, explores adjunctive agents, and explores recent advances integrating adjuvant therapies to enhance its potential [25].

Limitations

Photodynamic therapy (PDT) is a promising medical treatment for certain types of cancer and other conditions, but like any medical procedure, it has certain limitations that should be considered, given below:

Limited applicability

PDT is only effective for certain types of cancer and other conditions, and it may not be suitable for all patients. The specific conditions that can be treated with PDT and the outcomes of the therapy depend on various factors, such as the type and stage of the cancer, the patient's overall health, and the specific treatment regimen used.

Side effects

Like any medical procedure, PDT can cause side effects, such as pain, redness, and itching at the site of the treatment, as well as more serious side effects, such as eye damage or burns. These side effects can vary depending on the specific treatment regimen and the patient's individual circumstances.

Relatively high cost

PDT can be a relatively expensive procedure, especially for patients who do not have insurance coverage for the treatment. This can be a barrier for some patients who would otherwise benefit from the therapy.

Light penetration factor

The effectiveness of PDT can be limited by the depth of the target tissue, as light may not penetrate deep enough to reach the entire target area. This may require additional treatments or alternative forms of therapy to achieve the desired results.

So, while PDT is a promising medical treatment with many potential benefits, it is important to carefully consider the limitations and risks of the therapy, as well as the specific circumstances and needs of the patient, before deciding whether it is an appropriate form of treatment. The treating healthcare provider will be able to provide the patient with more information and guidance on these and other factors.

Future Perspectives

The future perspectives of Photodynamic therapy (PDT) are promising, as the technology continues to advance and its applications continue to expand. Some of the key areas of focus for future research and development include (Fig. 4):

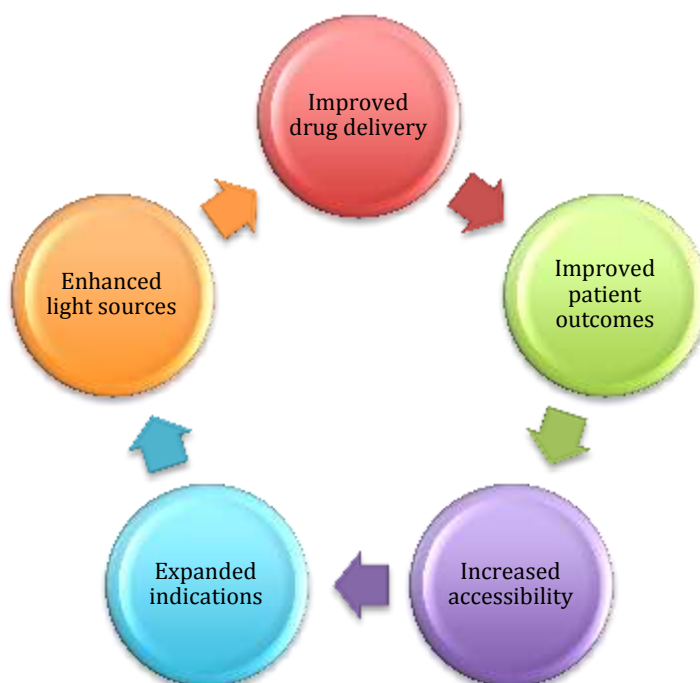


Fig. 4. PDT: Key areas of focus for future research and development.

- Researchers are working to develop new and more effective photosensitizing drugs that can be delivered more efficiently to the affected tissue. This could result in higher cure rates and reduced side effects.
- One of the key goals of future research is to improve patient outcomes and quality of life after PDT. This could involve developing new techniques to minimize side effects, improve patient comfort during the procedure, and reduce recovery times.
- While PDT is widely available in many countries, access to the treatment is still limited in some regions. In the future, it is hoped that advancements in technology will make PDT more widely accessible, especially in resource-limited settings.
- Currently, PDT is used to treat a range of conditions, including certain types of cancer and skin conditions. However, there is ongoing research to determine its efficacy in treating other conditions, such as neurological and cardiovascular diseases.
- The effectiveness of PDT is largely dependent on the specific wavelength of light used. Researchers are working to develop new light sources that can be used more effectively and safely in PDT, resulting in improved outcomes for patients.

Thus, the future perspectives of PDT are highly positive, with ongoing research and development aimed at improving its safety, efficacy, and accessibility. As the technology continues to advance, it is hoped that PDT will become a standard treatment option for a growing number of conditions, improving the quality of life for patients around the world.

2. Conclusion

Photodynamic therapy (PDT) is a potential medical treatment option for some cancers and skin diseases. Many patients choose it because of its focused nature, great effectiveness, and relatively fast recovery period. While the particular benefits of PDT may vary depending on the patient's

circumstances, it is often a less traumatic and cost-effective treatment choice when compared to alternative treatments such as surgery or chemotherapy. However, bear in mind that not all patients are candidates for PDT, and the treating healthcare practitioner should be consulted for tailored advice. More research and clinical trials are being conducted to increase the usage of PDT and improve its efficacy and safety. In comparison to alternative kinds of treatment, such as surgery or chemotherapy, PDT can be a more cost-effective choice for many patients, particularly over time. However, the particular benefits of PDT will vary depending on the patient's unique circumstances and the therapy plan followed. The patient's treating healthcare practitioner will be able to advise him or her on the best course of therapy. Nonetheless, PDT is a helpful treatment option for many individuals, enhancing their quality of life and addressing certain illnesses.

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Conflict of interest

The authors declare that they have no conflict of interest.

Consent for publication

Yes

Ethics approval and consent to participate

Not applicable

Competing interests

The authors declare that they have no competing interests

3. References

1. Agostinis, P.; Berg, K.; Cengel, K.A.; Foster, T.H.; Girotti, A.W.; Gollnick, S.O.; Hahn, S.M.; Hamblin, M.R.; Juzeniene, A.; Kessel, D.; Korbelik, M.; Moan, J.; Mroz, P.; Nowis, D.; Piette, J.; Wilson, B. C.; Golab, J., Photodynamic Therapy of Cancer: An Update. *C.A.Cancer J.Clin.***2011**, 61(4), 250–281. DOI: 10.3322/caac.20114
2. Kessel, D., Photodynamic Therapy: A Brief History. *J. Clin. Med.* **2019**, 8(10), 1581. DOI: 10.3390/jcm8101581
3. Dolmans, D. E.; Fukumura, D.; Jain, R. K., Photodynamic Therapy for Cancer. *Nat. Rev. Cancer* **2003**, 3 (5), 380–387. DOI: 10.1038/nrc1071
4. Ormond, A.B.; Freeman, H.S., Dye Sensitizers for Photodynamic Therapy. *Materials (Basel)* **2013**, 6(3), 817–840. DOI: 10.3390/ma6030817
5. Kessel, D., Photodynamic Therapy: Critical PDT Theory. *Photochem. Photobiol.* **2023**, 99 (2), 199–203. DOI:10.1111/php.13616
6. Hak, A.; Ali, M. S.; Sankaranarayanan, S. A.; Shinde, V. R.; Rengan, A. K., Chlorin e6: A Promising Photosensitizer in Photo-based Cancer Nanomedicine. *A.C.S. Appl. Bio Mater.* **2023**, 6 (2), 349–364. DOI: 10.1021/acsabm.2c00891
7. Itoo, A.M.; Paul, M.; Padaga, S.G.; Ghosh, B.; Biswas, S., Nanotherapeutic Intervention in Photodynamic Therapy for Cancer. *A.C.S.Omega***2022**, 7(50), 45882–45909. DOI: 10.1021/acsomega.2c05852
8. Gunaydin, G.; Gedik, M.E.; Ayan, S., Photodynamic Therapy for the Treatment and Diagnosis of Cancer—A Review of the Current Clinical Status. *Front. Chem.* **2021**, 9, 686303. DOI: 10.3389/fchem.2021.686303

9. Li, Y.; Hua, C.; Zhang, M., Efficacy of Non-invasive Photodynamic Therapy for Female Lower Reproductive Tract Diseases Associated with HPV Infection: A Comprehensive Meta-analysis. *LasersMed. Sci.* **2023**, 38(1), 42. DOI: 10.1007/s10103-023-03713-5
10. Raab, O., Über die WirkungFluorescirenderStoffe auf Infusorien. *Z. Biol.***1900**, 39, 524–546.
11. Dougherty, T.J.; Kaufman, J.E.; Goldfarb, A.; Weishaupt, K.R.; Boyle, D.; Mittelman, A. Photoradiation Therapy for the Treatment of Malignant Tumors. *Cancer Res.* **1978**, 38 (8), 2628–2635.
12. Cramer, G.M.; Cengel, K.A.; Busch, T.M., Forging Forward in Photodynamic Therapy. *Cancer Res.***2022**, 82(4), 534–536. DOI: 10.1158/0008-5472.CAN-21-4122
13. Maharjan, P.S.; Bhattarai, H.K., Singlet Oxygen, Photodynamic Therapy, and Mechanisms of Cancer Cell Death. *J. Oncol.***2022**, 2022, 7211485. DOI: 10.1155/2022/7211485
14. Ji, B.; Wei, M.; Yang, B. Recent Advances in Nanomedicines for PhotodynamicTherapy (PDT)-DrivenCancerImmunotherapy. *Theranostics* **2022**, 12 (1), 434–458. DOI: 10.7150/thno.67300
15. Cheung, E.C.; Vousden, K.H., The Role of ROS in TumourDevelopment and Progression. *Nat. Rev. Cancer* **2022**, 22 (5), 280–297. DOI: 10.1038/s41568-021-00435-0
16. Wan, G.; Chen, B.; Li, L.; Wang, D.; Shi, S.; Zhang, T.; Wang, Y.; Zhang, L.; Wang, Y., Nanoscaled Red Blood Cells Facilitate Breast Cancer Treatment by CombiningPhotothermal/PhotodynamicTherapy and Chemotherapy. *Biomaterials* **2018**, 155, 25–40. DOI: 10.1016/j.biomaterials.2017.11.002
17. Pham, T.C.; Nguyen, V.N.; Choi, Y.; Lee, S.; Yoon, J., Recent Strategies to Develop Innovative Photosensitizers for Enhanced Photodynamic Therapy. *Chem. Rev.* **2021**, 121(21), 13454–13619. DOI: 10.1021/acs.chemrev.1c00381
18. Han, R.; Zhao, M.; Wang, Z.; Liu, H.; Zhu, S.; Huang, L.; Wang, Y.; Wang, L.; Hong, Y.; Sha, Y.; Jiang, Y., Super-efficient In Vivo Two-Photon Photodynamic Therapy with a Gold Nanocluster as a Type I Photosensitizer. *A.C.S. Nano* **2020**, 14 (8), 9532–9544. DOI: 10.1021/acsnano.9b05169
19. Li, Y.; Zhang, R.; Wan, Q.; Hu, R.; Ma, Y.; Wang, Z.; Hou, J.; Zhang, W.; Tang, B.Z., Trojan Horse-Like Nano-AIE Aggregates Based on Homologous Targeting Strategy and Their Photodynamic Therapy in Anticancer Application. *Adv. Sci. (Weinh)* **2021**, 8 (23), e2102561. DOI: 10.1002/advs.202102561
20. Jiang, W.; Liang, M.; Lei, Q.; Li, G.; Wu, S., The Current Status of Photodynamic Therapy in Cancer Treatment. *Cancers* **2023**, 15 (3), 585. DOI: 10.3390/cancers15030585
21. Xu, Y.; Zhang, X.; Hu, G.; Wu, X.; Nie, Y.; Wu, H.; Kong, D.; Ning, X., Multistage Targeted “Photoactive Neutrophil” for Enhancing Synergistic Photo-chemotherapy. *Biomaterials* **2021**, 279, 121224. DOI: 10.1016/j.biomaterials.2021.121224
22. Wang, Y.; Xu, S.; Shi, L.; Teh, C.; Qi, G.; Liu, B., Cancer-Cell-Activated InSitu Synthesis of Mitochondria-Targeting AIE Photosensitizer for Precise Photodynamic Therapy. *Angew. Chem. Int. Ed. Engl.* **2021**, 60 (27), 14945–14953. DOI: 10.1002/anie.202017350
23. Railkar, R.; Agarwal, P.K., Photodynamic Therapy in the Treatment of Bladder Cancer: Past Challenges and Current Innovations. *Eur. Urol. Focus* **2018**, 4 (4), 509–511. DOI: 10.1016/j.euf.2018.08.005
24. Cheng, Y.J.; Hu, J.J.; Qin, S.Y.; Zhang, A.Q.; Zhang, X.Z., Recent Advances in Functional Mesoporous Silica-Based Nanoplatfoms for Combinational Photo-chemotherapy of Cancer. *Biomaterials* **2020**, 232, 119738. DOI: 10.1016/j.biomaterials.2019.119738
25. Menilli, L.; Milani, C.; Reddi, E.; Moret, F., Overview of Nanoparticle-Based Approaches for the Combination of Photodynamic Therapy (PDT) and Chemotherapy at the Preclinical Stage. *Cancers* **2022**, 14 (18), 4462. DOI: 10.3390/cancers14184462
26. Kwiatkowski, S.; Knap, B.; Przystupski, D.; Saczko, J.; Kędzierska, E.; Knap-Czop, K.; Kotlińska, J.; Michel, O.; Kotowski, K.; Kulbacka, J., Photodynamic Therapy–Mechanisms, Photosensitizers and Combinations. *Biomed. Pharmacother.* **2018**, 106, 1098–1107. DOI: 10.1016/j.biopha.2018.07.049