ISSN 2744-1636
Bioengineering Studies
Review Article
Vol. 5, No. 2, 2024, pp.12-19
https://doi.org/10.37868/bes.v5i2.id311

Introduction to Drugs for Photodynamic Therapy of Malignant Tumors

Boris Kovalenko[1*]
[1] Department of Natural Sciences, International University of Sarajevo

*Corresponding author: bkovalenko@ius.edu.ba

Received May 3, 2024
Revised Apr. 3, 2024
Accepted Jun.16, 2024
Online Oct. 20, 2024

Abstract

Photodynamic therapy (PDT) offers a safer alternative to surgery, chemotherapy, and radiotherapy for cancer treatment. Photosensitizers (PS) accumulate selectively in tumor cells and, upon specific-wavelength light activation, generate singlet oxygen that oxidizes DNA, inducing apoptosis and activating the STING pathway for antitumor M1 macrophage polarization. Originating from Oskar Raab's 1900 discovery with eosin, PDT advanced in the 1970s via hematoporphyrin derivatives, despite issues like skin photosensitivity. Improved second-generation PS, such as chlorin e6 and pheophorbide a from chlorophyll, provide better absorbance at 664 nm for deeper tumors and efficacy against colorectal cancer, melanoma, and glioblastoma. Phthalocyanines and curcumin conjugates show further promise. Polymer delivery systems like PVP enhance bioavailability, prevent aggregation, boost light absorption, and target tumors selectively, reducing side effects. This review synthesizes PDT's mechanisms, evolution, and delivery innovations, underscoring its potential in oncology.

Keywords: Photodynamic therapy, Photosensitizers, Polymer drug carriers

1. Introduction

Cancer is treated in different ways depending on the type and severity. The most radical method of cancer treatment is surgical removal of the tumor, which is not always possible or necessary. Other therapies are used instead of or together with surgery, the main ones being chemotherapy and radiotherapy. Recently, however, scientists have become interested in an alternative treatment option – photodynamic therapy (PDT).

PDT is a promising area of cancer treatment in which specific drugs (photosensitizers, PS) are injected into the body intravenously, orally, or locally (depending on the type of cancer). These substances are then accumulated in the tissues affected by the tumor. To activate the PS, these tissues are illuminated with light of a certain wavelength (depends on the type of PS). The main advantage of modern PDT is its higher safety for patients compared to chemotherapy and ionizing radiation therapy because modern PS accumulate mainly in cancer cells and remain inactive until illumination.

2. Mechanism of Action of Photosensitizers

Generally, PS transfers the absorbed light energy to oxygen molecules, which switch from the ground energy state to the excited state (from triplet oxygen to singlet oxygen). The oxygen molecules activated in this way oxidize the DNA of the cancer cell. Oxidative DNA damage leads to apoptosis [1].

In addition, DNA fragments produced via oxidative DNA damage can activate the STING (Stimulator of Interferon Genes) protein, Figure 1. That results in the activation of downstream nuclear factor kappa-B (NF-κB), which promotes the expression of inducible nitric acid synthase (iNOS), guanylate binding protein 5 (GBP5), major histocompatibility complex-II (MHC-II), CD80, and CD86. All of these molecules are biomarkers of the M1 macrophage, polarizing macrophages into the antitumor M1 phenotype. Autophagy becomes an immune response to cancer [2].

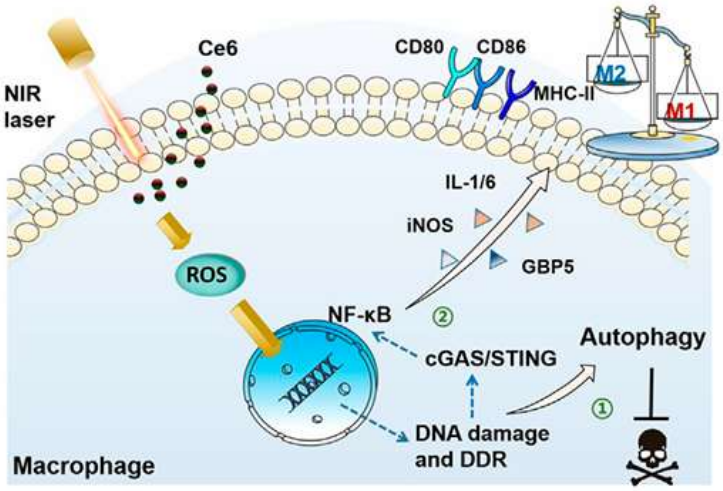

Figure 1. Activation of STING pathway [2]

3. Photosensitizing Drugs: History and Modernity

The concept of PDT has been known to scientists for a relatively long time. In 1900, German medical student Oskar Raab discovered that fluorescent dyes, such as eosin, Figure 2, cause the death of certain microorganisms (e.g., paramecia) in the presence of light, while in the dark they remain harmless [3]. Soon after this discovery, it was realized that such an effect was only observed in the presence of oxygen, and the first attempts were made to use the new phenomenon, called 'photodynamic action', for the therapy of superficial skin cancer [4]. However, due to the two world wars that followed, these experiments were interrupted, and the development of PDT did not continue until the 1970s.

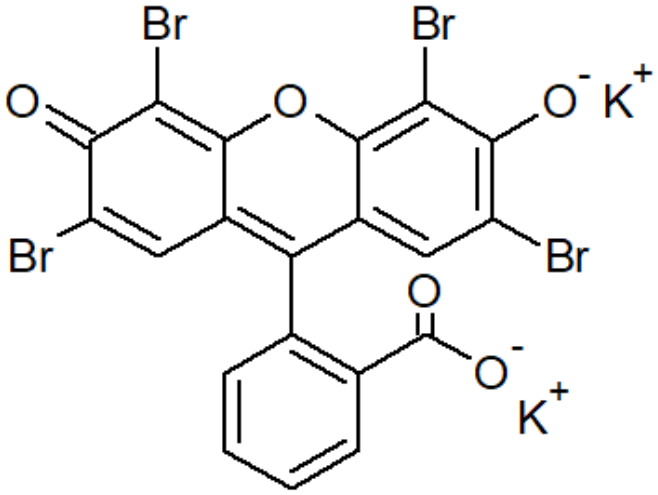

Figure 2. Chemical structure of eosin K

In 1972, American researchers Ivan Diamond et al. published a paper in which they described the destruction of glioma cells transplanted into rats by the action of hematoporphyrin, Figure 3, irradiated with light [5]. In the absence of light, hematoporphyrin showed no antitumor activity.

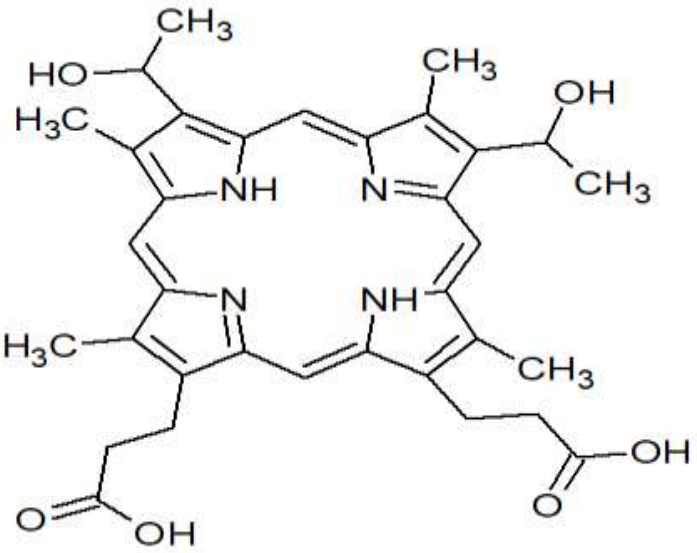

Figure 3. Hematoporphyrin chemical structure

American scientist Thomas Dougherty and his colleagues continued work in this direction and showed that PDT with hematoporphyrin derivative irradiated with light with a wavelength of more than 600 nm, can be used not only for superficial cancer [6]. The same authors showed that the energy required to achieve PDT with hematoporphyrin derivative as a PS of the same efficacy as ionizing radiation therapy is 100 times higher than for ionizing radiation therapy [7]. In addition to low energy efficiency, hematoporphyrin derivative (first-generation PS) has other disadvantages. For instance, a side effect of this drug is increased photosensitivity of patients' skin, which can last for weeks or even months [8]. Moreover, the main target of the hematoporphyrin derivative is the tumor vasculature, which both increases hypoxia, leading to resistance to radiotherapy and further PDT, and increases the risk of cancer recurrence [9], [10].

The second-generation photosensitizer, chlorin e6, Figure 4, which can be obtained from chlorophyll a in a relatively simple two-step synthesis [11], has several advantages over the hematoporphyrin derivative. Its molar absorbance in the visible region of the spectrum is higher, Figure 5, which indicates greater photodynamic activity, the absorbance maximum of chlorin e6 corresponds to a wavelength of 664 nm (for the hematoporphyrin derivative it is 630 nm), so the greater penetrating ability of such light allows us to talk about the possibility of using chlorin e6 for therapy of cancer of deeper localization [12].

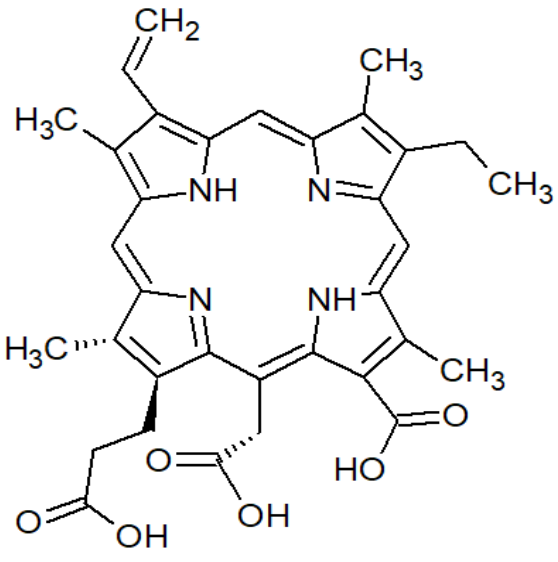

Figure 4. Chlorin e6 chemical structure

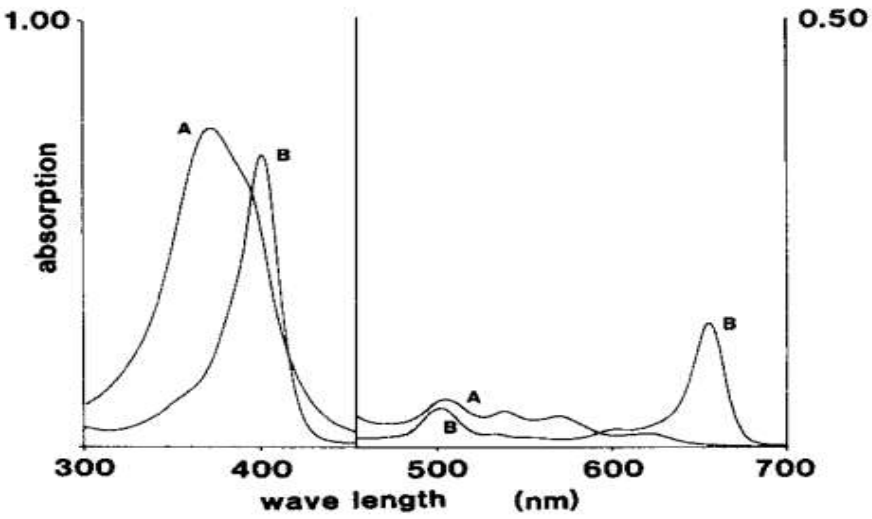

Figure 5. UV/vis spectra of hematoporphyrin derivative, A, and mono-L-aspartyl chlorin e6, B

Even though hematoporphyrin derivative is currently actively used in clinical PDT, chlorin e6 and its derivatives are increasingly attracting the attention of researchers showing activity against colorectal cancer cell lines SW480, HCT116, LoVo, and DLD1 [13], [14], melanomas A375, B16F10 [11], [15]. They have already been introduced into clinical practice in Japan [16], Russia, and Belarus [17].

Another chlorophyll derivative, pheophorbide a, Figure 6, can also be considered as a promising PS with proven activity, e.g., against glioblastoma [18]. The synthesis of pheophorbide a from chlorophyll a is also relatively easy and involves two steps [19].

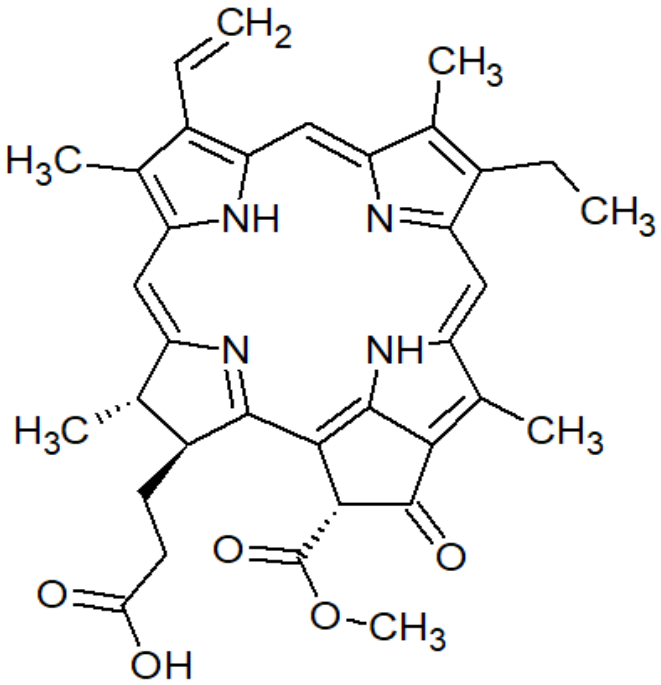

Figure 6. Pheophorbide, a chemical structure

Based on some results, it can be said that chelates of phthalocyanines with metal ions can also be considered as promising PSs. For example, the anti-cancer activity of disulfonated zinc phthalocyanine, in PDT at different partial pressures of oxygen was investigated in vitro , as seen in Figure 6 [20].

A significant advantage of phthalocyanines is that they are a long-known class of organic compounds for which synthesis methods are well understood [21]. However, they have previously been used as dyes [22].

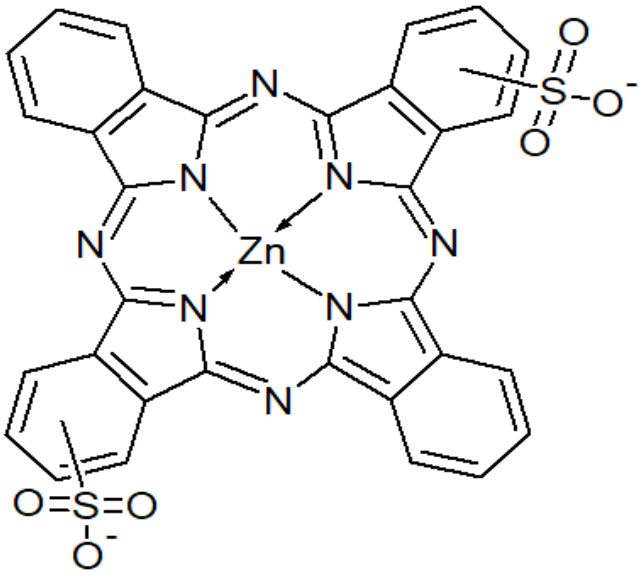

Figure 7. Disulfonated zinc phthalocyanine chemical structure

A number of promising chemotherapeutic agents of natural origin, such as curcumin and its derivatives, can also be considered as PSs, as seen in Figures 8 and 9 [23]. Moreover, conjugates of curcumin with the more typical PS chlorin e6, which have enhanced photodynamic activity, have been obtained [24].

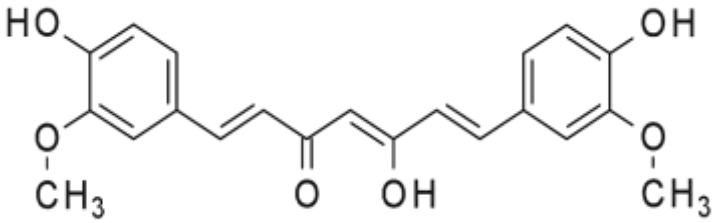

Figure 8. Chemical structure of curcumin (enolic form)

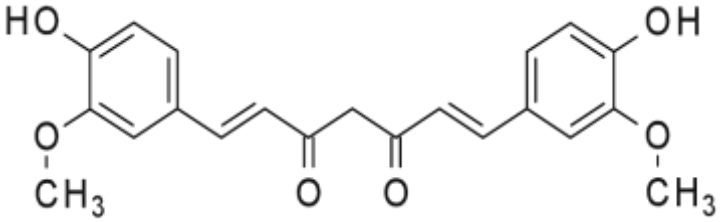

Figure 9. Chemical structure of curcumin (keto form)

4. Drug Delivery Systems for Photosensitizers

Polymers are often used as drug delivery systems for PS. The main aim of their usage is to increase the bioavailability and efficacy of PS towards cancer cells and to reduce side effects, such as photosensitivity of the skin after tumor treatment, caused by the binding of the drug to healthy tissue due to its high affinity to cell membranes [25]. One of the most suitable polymers for this purpose is PVP, a safe water-soluble polymer widely used in medicine, as presented in Figure 10.

PVP forms stable complexes with chlorin e6, which facilitate the binding of chlorin e6 to very low-density lipoproteins (VLDL) and thus selectively target the drug to cancer cells [26].

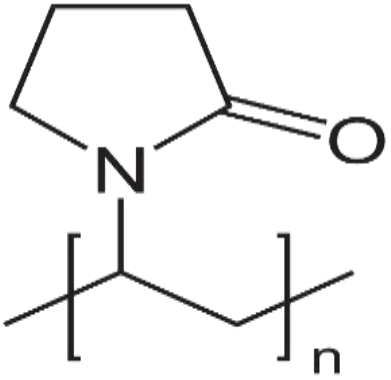

Figure 10. PVP chemical structure

Moreover, PVP enhances the efficacy of photodynamic therapy [27] by increasing the absorbance of red light by chlorin e6, presented in Figure 11. This is because PVP prevents aggregation of chlorin e6 molecules, which reduces its ability to absorb light [28].

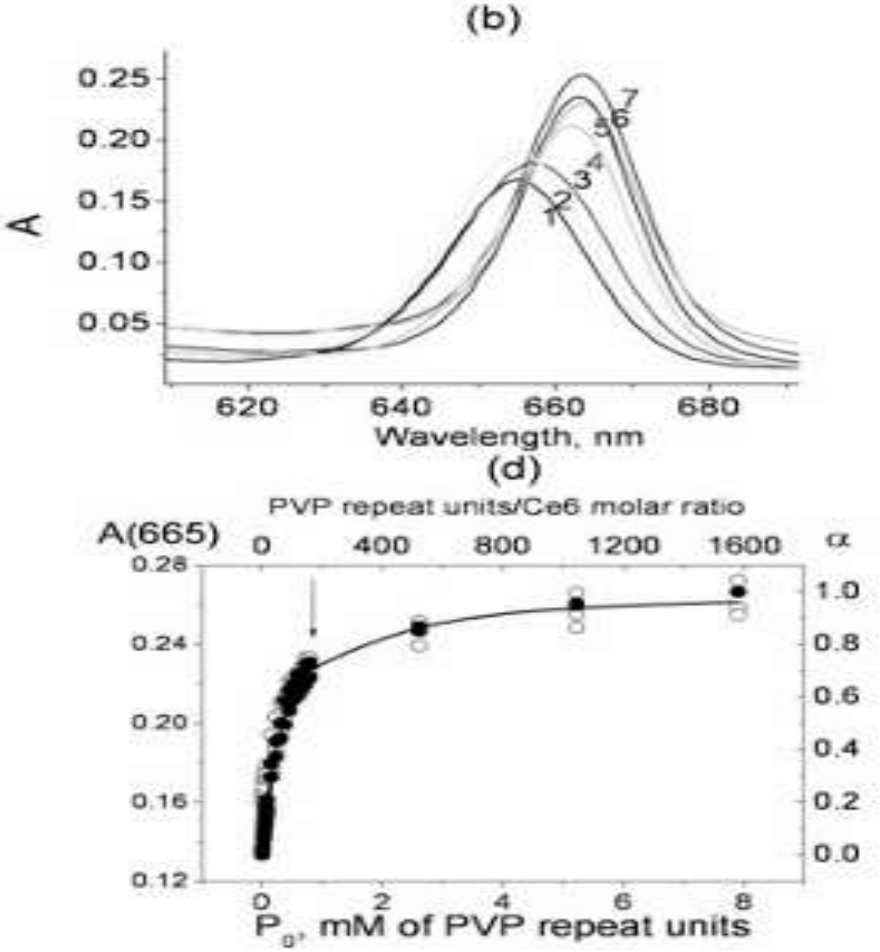

Figure 11. b – Absorbance spectra of 5 mM chlorin e6 (1) and complexes of chlorin e6 with PVP in the visible region (2 – 0.09 mM PVP, 3 – 0.9 mM PVP, 4 – 9 mM PVP, 5 – 90 mM PVP, 6 – 450 mM PVP, 7 – 900 mM PVP). d – Dependence of absorbance at a wavelength of 665 nm on PVP concentration [27]

Cross-linked polymer hydrogels, such as poly(N-isopropylacrylamide) hydrogel as a carrier for protoporphyrin IX, pheophorbide a, and protoporphyrin IX, can be used as promising delivery systems for PSs dimethyl ester, which showed good bioavailability and photodynamic activity [29].

5. Conclusion

In this review article, basic concepts concerning photodynamic therapy of malignant tumors are formulated, mechanisms of action of photosensitizers – initiation of cancer cell apoptosis and activation of immune system are described based on literature sources, the history of discovery of photosensitizing effect is briefly considered, advantages and disadvantages of photosensitizers used in clinical practice are characterized, and some promising photosensitizers are listed. In addition, initial information on polymers as delivery systems that increase the bioavailability of photosensitizing agents and their activity is given.

Declaration of competing interest

The authors declare that they have no known financial or non-financial competing interests in any material discussed in this paper.

Funding information

No funding was received from any financial organization to conduct this research.

References

[1] K. Yang, T. Niu, M. Luo, L. Tang, and L. Kang, "Enhanced cytotoxicity and apoptosis through inhibiting autophagy in metastatic potential colon cancer SW620 cells treated with chlorin e6 photodynamic therapy," Photodiagnosis Photodyn. Ther., vol. 24, pp. 332–341, Dec. 2018, https://doi.org/10.1016/j.pdpdt.2018.10.012.
[2] T.-T. Yu et al., "Chlorin e6-induced photodynamic effect polarizes macrophages into an M1 phenotype through oxidative DNA damage and activation of STING," Front. Pharmacol., vol. 13, Art. no. 837784, Mar. 2022, https://doi.org/10.3389/fphar.2022.837784.
[3] O. Raab, "Über die Wirkung fluoreszierender Stoffe auf Infusorien," Z. Biol., vol. 39, pp. 524–546, 1900.
[4] A. Jesionek and H. von Tappeiner, "Zur Behandlung der Hautcarcinome mit fluoreszierenden Stoffen," Münch. Med. Wochenschr., vol. 47, pp. 2042–2044, 1903.
[5] I. Diamond, A. F., McDonagh, C. B., Wilson, S. G., Granelli, S. Nielsen, and R. Jaenicke, "Photodynamic therapy of malignant tumours," Lancet, vol. 300, no. 7788, pp. 1175–1177, Dec. 1972, https://doi.org/10.1016/S0140-6736(72)92596-2.
[6] T. J. Dougherty, G. B. Grindey, R. Fiel, K. R. Weishaupt, and D. G. Boyle, "Photoradiation therapy. II. Cure of animal tumors with hematoporphyrin and light," J. Natl. Cancer Inst., vol. 55, no. 1, pp. 115–121, Jul. 1975, https://doi.org/10.1093/jnci/55.1.115.
[7] T. J. Dougherty, C. J. Gomer, and K. R. Weishaupt, "Energetics and efficiency of photoinactivation of murine tumor cells containing hematoporphyrin," Cancer Res., vol. 36, no. 7, pp. 2330–2333, Jul. 1976.
[8] P. Agostinis et al., "Photodynamic therapy of cancer: An update," CA Cancer J. Clin., vol. 61, no. 4, pp. 250–281, Jul. 2011, https://doi.org/10.3322/caac.20114.
[9] A. M. R. Fisher, A. L. Murphree, and C. J. Gomer, "Clinical and preclinical photodynamic therapy," Lasers Surg. Med., vol. 17, no. 1, pp. 2–31, Jan. 1995, https://doi.org/10.1002/lsm.1900170103.
[10] T. Reynolds, "Photodynamic therapy expands its horizons," J. Natl. Cancer Inst., vol. 89, no. 2, pp. 112–114, Jan. 1997, https://doi.org/10.1093/jnci/89.2.112.
[11] R. Shrestha et al., "Efficient synthesis of chlorin e6 and its potential photodynamic immunotherapy in mouse melanoma by the abscopal effect," Int. J. Mol. Sci., vol. 24, no. 4, Art. no. 3901, Feb. 2023, https://doi.org/10.3390/ijms24043901.
[12] S. Ahn, "Efficient preparation of highly pure chlorin e6 and its photodynamic anticancer activity in a rat tumor model," Oncol. Rep., vol. 22, no. 5, pp. 1019–1024, Sep. 2009, https://doi.org/10.3892/or_00000540.

[13] J. H. Kim and I. Kim, "p62 manipulation affects chlorin e6-mediated photodynamic therapy efficacy in colorectal cancer cell lines," Oncol. Lett., vol. 19, no. 4, pp. 2871–2878, Apr. 2020, https://doi.org/10.3892/ol.2020.11522.
[14] Y. Li, Y. Yu, L. Kang, and Y. Lu, "Effects of chlorin e6-mediated photodynamic therapy on human colon cancer SW480 cells," Int. J. Clin. Exp. Med., vol. 7, no. 12, pp. 4867–4876, 2014.
[15] A. Dadadzhanova et al., "Sonodynamic effect in A375 melanoma cells with chlorin e6 induced by 20 kHz ultrasound," arXiv, 2021.
[16] H. Kataoka et al., "New photodynamic therapy with next-generation photosensitizers," Ann. Transl. Med., vol. 5, no. 8, Art. no. 183, Apr. 2017, https://doi.org/10.21037/atm.2017.03.59.
[17] M. R. Hamblin, "Photodynamic therapy for cancer: What's past is prologue," Photochem. Photobiol., vol. 96, no. 3, pp. 506–516, May 2020, https://doi.org/10.1111/php.13190.
[18] M. Cho et al., "Glioblastoma-specific anticancer activity of pheophorbide a from the edible red seaweed Grateloupia elliptica," J. Microbiol. Biotechnol., vol. 24, no. 3, pp. 346–353, Mar. 2014, https://doi.org/10.4014/jmb.1308.08090.
[19] A. J. Pallenberg, M. P. Dobhal, and R. K. Pandey, "Efficient synthesis of pyropheophorbide-a and its derivatives," Org. Process Res. Dev., vol. 8, no. 2, pp. 287–290, Mar. 2004, https://doi.org/10.1021/op034160h.
[20] M. Pola et al., "Effects of zinc porphyrin and zinc phthalocyanine derivatives in photodynamic anticancer therapy under different oxygen partial pressures in vitro," Invest. New Drugs, vol. 39, no. 1, pp. 89–97, Feb. 2021, https://doi.org/10.1007/s10637-020-00990-7.
[21] G. Zanotti, F. Palmeri, and V. Raglione, "Phthalocyanine synthesis: A state-of-the-art review of sustainable approaches through green chemistry metrics," Chem. Eur. J., vol. 30, no. 44, Art. no. e202400908, Aug. 2024, https://doi.org/10.1002/chem.202400908.
[22] M. A. Dahlen, "The phthalocyanines: A new class of synthetic pigments and dyes," Ind. Eng. Chem., vol. 31, no. 7, pp. 839–847, Jul. 1939, https://doi.org/10.1021/ie50355a012.
[23] K. T. Kazantzis et al., "Curcumin derivatives as photosensitizers in photodynamic therapy: Photophysical properties and in vitro studies with prostate cancer cells," Photochem. Photobiol. Sci., vol. 19, no. 2, pp. 193–206, Feb. 2020, https://doi.org/10.1039/C9PP00375D.
[24] S. S. Jalde et al., "Synthesis of novel chlorin e6–curcumin conjugates as photosensitizers for photodynamic therapy against pancreatic carcinoma," Eur. J. Med. Chem., vol. 147, pp. 66–76, Mar. 2018, https://doi.org/10.1016/j.ejmech.2018.01.099.
[25] Z.-R. Lu, F. Ye, and A. Vaidya, "Polymer platforms for drug delivery and biomedical imaging," J. Control. Release, vol. 122, no. 3, pp. 269–277, Oct. 2007, https://doi.org/10.1016/j.jconrel.2007.06.016.
[26] W. W. L. Chin, T. Praveen, P. W. S. Heng, and M. Olivo, "Effect of polyvinylpyrrolidone on the interaction of chlorin e6 with plasma proteins and its subcellular localization," Eur. J. Pharm. Biopharm., vol. 76, no. 2, pp. 245–252, Oct. 2010, https://doi.org/10.1016/j.ejpb.2010.06.005.
[27] T. M. Zhiyentayev et al., "Complexes of chlorin e6 with Pluronics and polyvinylpyrrolidone: Structure and photodynamic activity in cell culture," Photochem. Photobiol., vol. 90, no. 1, pp. 171–182, Jan. 2014, https://doi.org/10.1111/php.12181.
[28] S. Paul et al., "Elucidation of the monomerization effect of PVP on chlorin e6 aggregates by spectroscopic, chemometric, thermodynamic, and molecular simulation studies," J. Fluoresc., vol. 23, no. 5, pp. 1065–1076, Sep. 2013, https://doi.org/10.1007/s10895-013-1236-4.
[29] S. Belali et al., "Synthesis and characterization of temperature-sensitive and chemically cross-linked poly(N-isopropylacrylamide)/photosensitizer hydrogels for photodynamic therapy applications," Biomacromolecules, vol. 19, no. 5, pp. 1592–1601, May 2018, https://doi.org/10.1021/acs.biomac.8b00293.