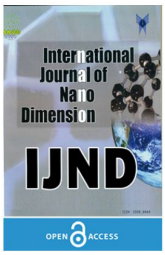

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Revolutionizing cancer treatment through nanoengineered photosensitizer formulations for advanced photodynamic therapy

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REVIEW PAPER

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Abstract:

Photodynamic therapy (PDT) is an approved minimum-invasive therapeutic approach authorized for the clinical treatment of various types of cancer and antibiotic-resistant microbial disorders. During PDT, a photosensitizing compound known as a photosensitizer (PS) deliberately accumulates in tissues. The PS is activated when exposed to a specific wavelength of visible light, generating reactive oxygen species and causing tumor regression and cell death. PDT has the advantage of being low in systemic toxicity and selective in destroying tumors accessible to light, making it an attractive alternative to other conventional cancer treatments without affecting healthy cells. Despite the challenges of poor aqueous solubility and lack of selectivity associated with PS, PDT has shown promise by employing nanoformulations, enabling selective distribution and concentration in highly localized tumor regions. Centered on the utilization of nanoparticles and nanocarriers in PDT to mitigate treatment drawbacks, the study unveils the effectiveness of nanoformulated photosensitizing agents in tumor destruction. This reveals refined PDT strategies for overcoming limitations and propelling advancements in theranostic applications.

Keywords: Drug delivery; Nanoformulation; Nanomedicine; PDT; Theranostics; Therapy

1. Introduction

Cancer occurs when the growth and spread of the body's cells are unregulated, and they escape the standard restraints that restrain normal growth. Human cells typically grow and multiply as needed, called cell division, and are used to create new cells. When the cell becomes old or damaged, the body replaces it with new cells [1]. When the orderly process is disrupted, abnormal or damaged cells multiply and grow uncontrollably. These abnormal cells can form lumps of tissue that we know as tumors [2]. Some tumors are cancerous, and some are benign (non-cancerous). The spread of cancerous tumors causes them to infect nearby tissues and spread along the other areas of the body to form new cancerous tumors. This process is called metastasis [3]. The term cancerous tumor may also refer to a malignant tumor. Cancers often form solid tumors, but they are not usually formed by cancers of the blood, such as leukemia. Benign tumors don't spread to neighboring tissues or invade them. Cancerous tumors sometimes grow back after being removed, but benign tumors don't. Sometimes benign tumors can be quite large, but some can present with serious symptoms or even lead to death, such as benign brain tumors [4–7].

Cancer development may take years before clinical signs appear. Cancer has many types, each with a different cause, symptom, and treatment. There are several types of cancer, among them lung cancer, colon cancer, breast cancer, skin cancer, and prostate cancer [8–11]. Treatment varies based on the types and stages of cancer while minding the overall health and preferences of the patient. On the other hand,

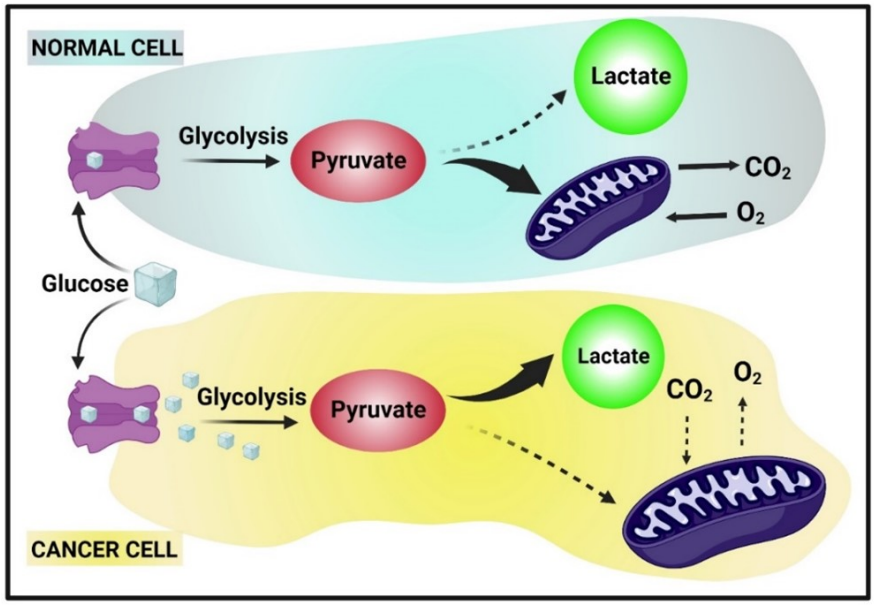

Figure 1. Mechanism of cancer development.

some cancers spread more quickly and are more aggressive [12–15]. Some of the fastest-spreading cancers are pancreatic liver melanoma, esophageal cancer, and brain tumors; some slow-spreading cancers are prostate, thyroid, cervical, breast, and ovarian cancer. Cancers seem to be sporadic (not inherited) most of the time; however, there have been cases of hereditary cancers. It has been shown that breast cancer risk is elevated when an inherited mutation is found in the genes BRCA1 (breast cancer 1) or BRCA2 (breast cancer 2) [16–18]. Lynch syndrome is also associated with hereditary nonpolyposis colorectal cancer (HNPCC), which occurs in the uterus, gastritis, and ovaries. A hereditary mutation in the retinoblastoma gene causes retinoblastoma in young children [19].

Annual figures for new cancer cases and deaths in the United States are calculated by the American Cancer Society using incidence data from central cancer registries and mortality data from the National Center for Health Statistics [20]. The organization anticipates that the United States will witness 609,820 cancer-related deaths and 1,958,310 newly diagnosed cancer cases in the year 2023 [21]. Prostate cancer incidence rose by 3% yearly between 2014 and 2019, amounting to almost 99,000 new cases. Other than that, the male incidence trends were more favorable than the female ones. For instance, between 2015 and 2019, the rate of decrease in lung cancer in women was half that of men (1.1% vs. 2.6% yearly). The rates of cancer in the breast, uterine corpus, liver, and melanoma all have been increasing day by day [22]. Given the recognized constraints of conventional therapies, this review seeks to outline the mechanism of cancer along with progression and implications of photodynamic inactivation in cancer treatment.

2. Hallmarks /mechanism of cancer

To promote the growth, survival and maintenance for the long term, cancer cells rewire their metabolism. Normal cells release energy through the citric acid cycle and oxidative phosphorylation in the mitochondria. Unlike normal cells, cancer cells predominantly release high energy through another process named aerobic glycolysis. This process is a less efficient process in which the glucose uptake, glycolysis, and fermentation of lactic acid occur at high levels. This process takes place in the cytosol, even if the presence of oxygen is high. This mechanism was named the 'Warburg effect' after the observation by Otto Heinrich Warburg Figure. 1 [23]. A correlation between molecules and organelles in the development and occurrence of cancer is categorized as a cancer hallmark.

2.1 Evading growth suppressors

For disease cells to avoid certain cycles, it is necessary to avoid major areas of strength that adversely influence cell division [24]. Many cancer suppressors that can limit the growth and multiplication of cells in different ways have been identified by their characteristic inactivation in animal or human diseases. Gain-or-loss-of-capability assays in mice have confirmed many of these characteristics as true growth silencers [25]. The two prototype growth suppressors encode the retinoblastoma-related (RB) and TP53 proteins. These proteins can function as fundamental control centers inside two basic, corresponding cell administrative circuits that determine whether cells choose to initiate or develop apoptotic and senescent programs [26].

2.2 Avoiding immune destruction

Studies on the relationship between illness and the resistant framework have demonstrated that every known natural and adaptable safe effector component supports the growth executives and the identifiable proof [27]. When NK cells come into contact with particular ligands on growth cells, they can identify the few underlying altered cells. As a result, some altered cells are destroyed, while the remaining cells

are retained and processed by dendritic and macrophage cells [28, 29]. After that, these macrophages and dendritic cells are stimulated to release T- and B-cells to artificial substances made from cancer cells and to deliver different inflammatory cytokines. More cytokines are produced when T-and B-cells activate, which helps to age and develop immune system microorganisms and antibodies that are specifically targeted for growths, as well as to stimulate natural resistance. Any additional cancer cells are eliminated when the adaptable immune system is functioning at its peak, and more importantly, an immune memory targeted for a particular growth is formed [30–32].

Adaptive agents, including $CD4^+$ helpers to equalize the immune system against microorganisms, $CD8^+$ cytotoxic lymphocytes, and antibodies, precisely target synthetic growth antigens expressed by cancer cells while sparing healthy cells. Typical cell proteins known as growth antigens undergo miscommunication due to genetic abnormalities, variations in expression, or alterations in posttranslational modifications [27]. In cases where growth structures have a robust viral origin, as seen in hepatocellular carcinoma induced by hepatitis B or cervical disease caused by the human papillomavirus, viral proteins can serve both as growth antigens and as targets for the immune system's anti-tumor response [33–36].

The immunosurveillance hypothesis is back, but it has been updated to take into account newly discovered data due to the safe responses against growths in disease patients and animal models. Rather than characterizing immunosurveillance as the mechanism by which disease is identified and eliminated and a malignant growth outcome as the result of this mechanism breaking down, it is now believed that the mechanism can have approximately three distinct associated outcomes in various individuals and tumor types: elimination, equilibrium, and disposal [37–39]. When a highly immunocompetent person cultivates a highly immunogenic cancer, the intrinsic immune system will be optimally stimulated, releasing highly immunostimulatory cytokines, inducing severe inflammation, triggering a group of T-and B cells, and stopping the growth quickly. However, there might not be a complete evacuation due to a less immunogenic growth or possibly immunocompetent individual, which might allow some disease cells to survive and continue to be monitored by the protective framework. Long-term progressive development of the growth would be linked to recurrent safe framework implementation and cancer cell eradication, followed by additional patterns of cancer regrowth and impervious interaction [40, 41]. The equilibrium state may persist indefinitely, emulating elimination, or it may be perturbed by alterations in cancer that enable it to evade immune monitoring or by modifications in the resistant system that impair growth monitoring. Either eventual change results in growth escape [30, 42].

2.3 Enabling replicative immortality

The capacity for unrelenting proliferation is one of the characteristics of cancerous cell populations. This characteristic enables successive aberrations to be acquired by clonal lineages, which can promote increasingly autonomous growth, invasiveness, and resistance to treatment. Innate cellular mechanisms have been developed to control replicative potential and prevent the spread of cancer [43]. These processes have the potential to produce a persistent cytostatic state if they are triggered by the lack of typical terminal differentiation cues. This condition, known as "senescence," can be brought on by exogenous variables like oxidative environments or DNA-damaging agents, as well as internal cellular processes like telomere dysfunction and oncogene expression [44].

2.4 Tumor-promoting inflammation

An environment of inflammation fosters a cellular microenvironment that is conducive to the growth of genomic aberrations and the start of carcinogenesis [45, 46]. Although acute inflammation is generally thought of as a self-limiting process and a crucial immune system component with therapeutic significance, insufficient resolution of inflammatory responses frequently contributes to several chronic illnesses, including cancer [47, 48]. Several epidemiological and clinical researches demonstrate that persistent, untreated inflammation both encourages and exacerbates cancer. A multitude of cancer types are linked to persistent inflammation, suggesting a robust correlation between inflammation and the development of cancer [48–50].

According to estimates, chronic inflammation and infection are the etiological links for approximately 25% of all cancers [51]. Several studies have shown that inflammatory bowel diseases like Crohn's disease and ulcerative colitis greatly increase the risk of colorectal cancer [52]. A positive correlation exists between the severity and duration of inflammatory diseases and the risk of respiratory system cancer. Additionally, correlations between inflammatory disorders like chronic pancreatitis as well as esophageal cancer and Barrett's metaplasia and esophagitis have been discovered [53, 54]. Recent research has demonstrated that persistent, including the most severe form of breast cancer, inflammatory breast cancer, and untreated inflammation contributes significantly to the development of the disease. Ovarian epithelium inflammation is linked to ovarian cancer [55–57].

Additional hallmarks of cancer encompass initiating invasion and metastasis, inducing or accessing vasculature, promoting genome instability and mutation, evading cell death, disrupting cellular metabolism, maintaining proliferative signaling, and recent findings revealing an extensive array of cellular mechanisms as cancer hallmarks [58].

3. Various Types of Treatment for Cancer

There are multiple treatments available in the market to treat cancer Figure. 2.

3.1 Chemotherapy

Approximately fifteen years ago, research on the biological action of mustard compounds led to the development of chemotherapy for cancer [59]. A frequent challenge in cancer treatment is choosing the chemotherapeutic agent that provides the most effective results while maintaining the safest side effect profile. Even though there are estab-

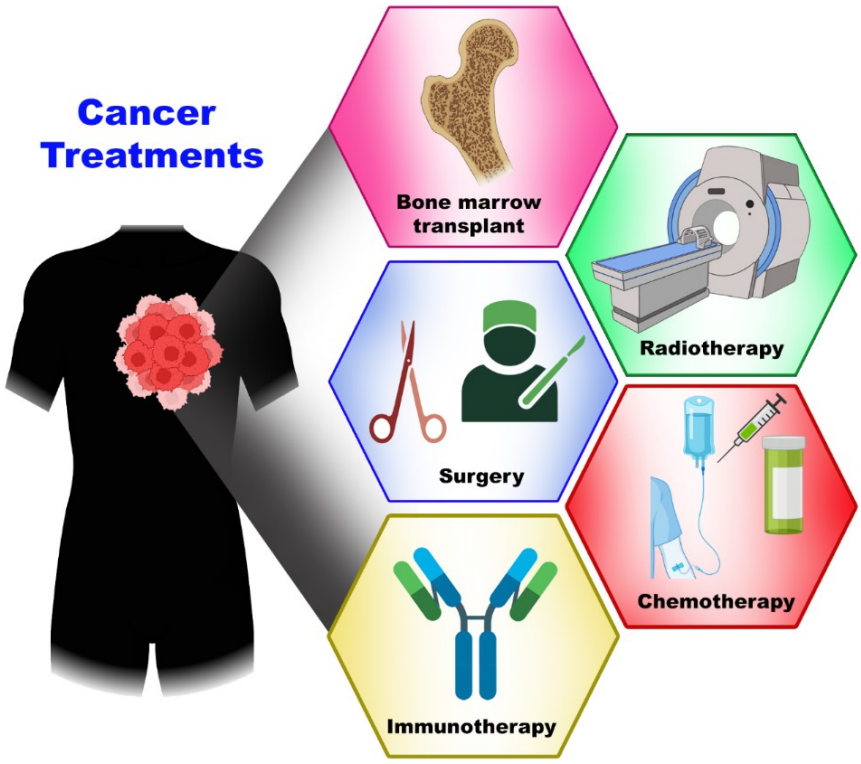

Figure 2. Commercially available treatments for cancer.

lished protocols for chemotherapy, modifications to these protocols have been made after comprehensive clinical trials. These changes have shown a notable increase in the effectiveness and tolerability of specific medications. Anticancer drug tolerance, pharmacokinetics, and pharmacodynamics are all very individual. One factor that contributes to these variations is an individual's genetic composition [60]. In contemporary healthcare, patients diagnosed with localized disease, for whom local therapeutic interventions like surgery or radiation therapy alone are inadequate, can undergo chemotherapy in three primary clinical scenarios: (1) as the primary induction treatment for advanced disease or cancers lacking alternative effective treatment approaches; (2) as neoadjuvant treatment; and (3) as adjuvant treatment following local therapeutic methods such as surgery, radiation therapy, or both [61].

When a patient presents with advanced cancer and has no other available treatment options, chemotherapy is given as the first line of treatment. This approach has been the predominant strategy for managing patients with advanced metastatic disease, focusing on enhancing the overall quality of life, slowing tumor progression, and alleviating symptoms associated with the tumor [62]. Research across various tumors has shown that chemotherapy enhances survival with advanced disease, supporting the notion that medication initiation should be prompt. However, it's noteworthy that only a few patients initially presenting with the disease can derive benefits from cancer chemotherapy. Curable cancers in adults comprise choriocarcinoma, acute myelogenous leukemia, Wilms tumor, Burkitt's lymphoma, and acute lymphoblastic leukemia. In children, curable cancers include acute lymphoblastic leukemia, Wilms tumor, and embryonal rhabdomyosarcoma [63].

Neoadjuvant chemotherapy is the term used to describe the use of chemotherapy with locally advanced cancer for which there are less-than-perfect alternative local therapies, such as surgery. Neoadjuvant therapy is currently most frequently used to treat osteogenic sarcoma, locally advanced laryngeal cancer, anal cancer, rectal cancer, bladder cancer, gastroesophageal cancer, breast cancer, and non-small cell lung cancer (NSCLC). The neoadjuvant approach is designed to reduce the size of the tumor, aiming to facilitate and enhance the effectiveness of surgical resection [64].

3.2 Immunotherapy

Immunotherapy was formerly categorized as either "active," involving methods like vaccines designed to activate the patient's immune system, or "passive," which entails the introduction of preexisting immune effectors such as antibodies, cytokines, activated T cells, NK cells, or lymphokine-activated killer cells. The passive approach assumes a direct action on the tumor, operating independently of the patient's immune system [65]. Nevertheless, it is now apparent that both passive and active immunotherapies hinge on the patient's immune system for sustained tumor control or complete tumor eradication [66].

Monoclonal antibodies with anticancer properties constitute a well-established category of immunotherapeutic agents designed to directly target specific antigens expressed by cancer cells. More than a dozen of these antibodies have received approval from the FDA as standard treatments for diverse cancers, including rituximab for B-cell lym-

phoma and trastuzumab for breast cancer [67]. Despite a comprehensive understanding of the direct antitumor mechanisms underlying these antibodies, cure rates continue to be notably low. The observed temporary remissions during therapy indicate the effectiveness of their direct antitumor action. However, the substantial limitation arises from the administration of these antibodies at a relatively advanced stage of the disease, when the patient's immune system is already significantly compromised, thereby severely restricting their potential impact. Under more favorable conditions, antibody treatment has the potential to directly induce cytotoxic or cytostatic effects on tumor cells [68].

Additionally, it can lead to the loading of antibody-bound tumor antigens onto antigen-presenting cells (APCs) within the tumor microenvironment. This process facilitates the propagation of the immune response at the tumor site, ensuring sustained tumor elimination even after the monoclonal antibody infusion has ceased. The subsequent cross-presentation to antitumor T- and B-cells may trigger the generation of additional antibodies against these antigens. The effector T-cell response not only establishes memory but also transitions from a monoclonal antibody response targeting a single epitope to a polyclonal response against multiple epitopes. This multifaceted approach helps prevent antigen-negative tumor escape, contributing to a more robust and enduring immune defence against cancerous cells [69].

Initially, conventional forms of immunotherapy directly targeting cancer will persist in tandem with treatments focused on the immune system within the tumor microenvironment. These include cytokines, antibodies regulating T-cell activity, and inhibitors of regulatory T-cell (Treg) or myeloid-derived suppressor cell (MDSC) activity. An example of such an immunomodulatory medication is ipilimumab, a recently approved antibody that fosters cytotoxic T-cell activity by amplifying T-cell activation and proliferation [70]. Alternatively, another approach involves employing immunotherapies, encompassing both established and novel methods, for the prevention of cancer in individuals deemed at high risk [71]. Investigations into the tumor microenvironment are furnishing insights into the immunosurveillance of tumors, spanning from early premalignant lesions to more advanced dysplastic lesions and, ultimately, cancer. Each stage exhibits distinct compositions of tumor-derived and immune system-derived components, influencing the impact of immunotherapy in varying ways. It should be simpler to modulate these premalignant microenvironments in order to eradicate aberrant cells because they are less established, and immunosuppression is less ingrained [72].

3.3 Radiation Therapy

In radiotherapy, ionizing radiation destroys or kills cancer cells by damaging their genetic material, preventing them from growing and dividing. Cancer cells cannot be killed right away by radiation therapy; they must undergo days or weeks of treatment before their DNA is damaged enough for them to die. Once radiation therapy ends, cancer cells continue to die for weeks or months; despite the fact that radiation damages both normal cells along with cancerous cells, mostly normal cells are capable of recovering and functioning properly. Because of this, it is usually given in fractions, which makes it easier to recover at the time intervals [73]. To facilitate surgery, radiotherapy can be applied preoperatively to shrink the tumor or provided postoperatively as adjuvant therapy to reduce local complications. Radiation therapy is applicable for the treatment of nearly all solid tumors, as well as certain leukemia and lymphomas. Despite its widespread utility, there are drawbacks, including both early and late side effects. Early side effects manifest in the initial stages of cancer treatment. In most cases, these side effects are short-term, mild, and easily treatable. It usually takes a few weeks for them to go away after treatment ends. In the beginning, the most prevalent side effects include fatigue, alterations in the skin such as itching, tenderness, swelling, or soreness, as well as nausea and vomiting. Hair loss and mouth problems are usually early side effects when radiation treatment is given to the area being treated. Some late side effects take months or even years to manifest [74]. It can occur in any normal tissue where the body has been exposed to radiation. It's crucial to highlight that the likelihood of experiencing late side effects depends on the specific area treated and the dosage of radiation administered. It is possible to avoid serious long-term side effects by planning treatment carefully. Additionally, radiotherapy is ineffective for solid tumors with hypoxic regions because hypoxic cells are resistant to ionizing radiation [75].

3.4 Stem cell therapy for cancer

For more than thirty years, stem cells have been utilized in chemotherapy and radiation treatments for cancer as well as in the restoration of blood and immune systems that have been weakened by cancerous cells. In addition to being used in immuno-reconstitution, stem cells have been shown to aid in tissue regeneration and act as delivery systems for cancer therapies. The concept of "cancer stem cells" has recently emerged, leading scientific communities to explore new avenues for cancer research and potential future treatment modalities [76]. Engineered neural stem cells, or NSCs, are a potentially effective new therapeutic approach for treating cancer. NSCs can now access invasive as well as primary tumor foci thanks to their tumor-homing capabilities, which open up new delivery options. In preclinical models, it has been observed that NSCs engineered with a wide variety of cytotoxic agents significantly reduce tumor volumes and significantly extend survival [77]. Extracellular matrix isolated from different cancer cell types also influences stem cell growth. This concept, conversely, can aid in finding the role of stem cells in cancer therapy [78].

3.5 Surgery

Over the years, cancer surgery has undergone significant advancements, becoming a pivotal component in the comprehensive approach to cancer treatment. Technological progress has played a crucial role, with the integration of robotic-assisted surgery standing out as a transformative development. This progress has revolutionized the precision and efficiency of cancer procedures, empowering surgeons to execute intricate operations with heightened dexterity

and improved visualization. Consequently, outcomes have seen enhancement, and recovery times have been notably reduced [79]. Laser-assisted surgery, another noteworthy advancement, has gained prominence in the treatment of specific cancer types. This technique allows for the precise removal of tissue while minimizing damage to surrounding healthy cells. The result is a more targeted approach to tumor removal, contributing to increased effectiveness in cancer treatment. The integration of cutting-edge imaging technologies, such as MRI, CT scans, and intraoperative ultrasound, has markedly enhanced the precision of cancer surgeries. Real-time visualization of tumors enables surgeons to carry out more precise tumor removal, thereby minimizing the risk of leaving residual cancer cells [80]. Minimally invasive approaches, such as laparoscopic surgery, have become standard practice in numerous cancer procedures. Smaller incisions not only reduce postoperative pain but also lead to shorter hospital stays and expedited recovery. These techniques are particularly preferred for various cancers, such as colorectal and gynecological cancers. Endoscopic procedures have provided an additional dimension to cancer surgery by allowing surgeons to access tumors through natural body openings or small incisions [81]. This procedure eliminates the need for extensive surgical incisions, proving particularly advantageous in the treatment of gastrointestinal and respiratory tract cancers. The collective impact of these advancements has transformed the landscape of cancer care, offering patients more effective and less invasive treatment options. The synergy of technological innovations, minimally invasive techniques, and personalized medicine has propelled the field forward, instilling hope for improved outcomes and a promising future in the ongoing battle against cancer [9, 82].

3.6 Gene therapy

Traditional treatments like surgery, chemotherapy, and radiation therapy have advanced considerably, yet their effectiveness is frequently hampered by adverse side effects and the emergence of drug resistance [83]. In recent times, gene therapy has emerged as a promising and groundbreaking approach to address cancer at its origins by targeting the underlying genetic abnormalities propelling malignancy [84]. Gene therapy entails modifying or replacing genetic material within a patient's cells to treat or prevent disease. Specifically in the realm of cancer, the goal of gene therapy is to correct or eradicate the genetic mutations driving the uncontrolled cell growth observed in tumors [85]. Some cancers result from mutations or deletions in critical tumor suppressor genes. Gene therapy can involve the delivery of functional copies of these genes into cancer cells, restoring their ability to regulate cell growth and division. Oncogenes are genes that, when mutated or overexpressed, promote cancer development. Gene therapy can target these oncogenes, either by silencing their expression or by introducing genetic material that inhibits their function, thereby curbing cancer progression. The identification and elimination of cancerous cells are pivotal functions performed by immune cells. Gene therapy can be employed to enhance the immune system's capacity to recognize and eradicate cancer cells, thereby reinforcing the body's innate defense against the disease. Apoptosis, a process of programmed cell death, serves as a mechanism to hinder the survival of abnormal cells. Gene therapy can induce apoptosis in cancer cells, triggering their self-destruction and inhibiting further tumor growth. One of the challenges in gene therapy is efficiently delivering therapeutic genes to target cells [86]. Several delivery systems have been developed, including viral vectors (such as adenoviruses and lentiviruses) and non-viral methods (such as electroporation and liposomes). Each method has its advantages and limitations, and ongoing research aims to optimize delivery systems for improved safety and efficacy. Gene therapy for cancer has shown promising results in clinical trials. Significant achievements include the authorization of CAR-T cell therapy for specific forms of leukaemia and lymphoma. Chimeric Antigen Receptor (CAR) T-cell therapy modifies a patient's immune cells to express receptors targeting particular cancer cells, leading to robust and focused anti-cancer activity. Moreover, oncolytic viruses, genetically engineered to replicate within and eliminate cancer cells selectively, have exhibited effectiveness in clinical trials. These advances underscore the potential of gene therapy as a transformative tool in the oncologist's arsenal. Gene therapy represents a revolutionary approach to cancer treatment, holding the potential to transform the landscape of oncology [87].

4. Limitations in Cancer Treatment

Even with the increased efficacy and prolonged survival provided by contemporary treatments, physicians and patients alike remain deeply concerned about the enduring and lasting effects of chemotherapy in the treatment of cancer. Current chemotherapy treatments have some drawbacks. One of the major limitations of chemotherapy is its non-specific targeting. Chemotherapy drugs can affect not only cancer cells but also normal, healthy cells, leading to a range of side effects. This lack of selectivity can result in damage to vital organs and tissues, causing issues such as nausea, hair loss, and compromised immune function. Cancer cells can develop resistance to chemotherapy over time [88]. This resistance may be inherent in some cancers or acquired during the course of treatment. As a result, initially responsive tumors may become less susceptible to the effects of chemotherapy, leading to treatment failure and disease recurrence. Chemotherapy is often less effective in advanced stages of cancer. As the disease progresses, cancer cells may become more aggressive and resistant to treatment. In these instances, chemotherapy may be employed to alleviate symptoms and enhance the quality of life, but it may not offer a cure. Chemotherapy has the potential to harm rapidly dividing healthy cells, including those in the bone marrow, gastrointestinal tract, and hair follicles, resulting in side effects such as anemia, gastrointestinal problems, and hair loss. Balancing the need to destroy cancer cells with the preservation of normal tissue function is a significant challenge in chemotherapy. Chemotherapy drugs circulate throughout the body, affecting not only the primary tumor site but also distant sites where micrometastases may be present. While this is necessary to address systemic disease,

it can also result in collateral damage to healthy tissues and organs. Certain types of cancers are less responsive to chemotherapy [89]. For example, some brain tumors, pancreatic cancers, and certain sarcomas may be less susceptible to traditional chemotherapy agents. In these cases, alternative or complementary treatment approaches may be explored. Chemotherapy can suppress the immune system, making patients more susceptible to infections. This therapy can pose additional challenges, especially in patients who are already immunocompromised. Some chemotherapy drugs may increase the risk of developing secondary cancers later in life. The long-term effects of chemotherapy on the DNA of normal cells are still an area of active research. There is a pressing demand for innovative strategies to enhance tolerance and mitigate the side effects of chemotherapy in cancer patients [90].

Radiation therapy breaks DNA, which leads to cell death. Compared to normal cells, cancer cells are more severely impacted by this. However, as the number of patients undergoing chemotherapy rises, medical professionals encounter patients experiencing radiotherapy side effects. Long-term side effects can be avoided by identifying and treating acute side effects as soon as possible [91]. Radiation can harm neighboring healthy cells in addition to killing or slowing the growth of cancer cells. Adverse effects may result from harm to healthy cells. Weariness is a common side effect of radiation therapy. Feeling weary and exhausted is called fatigue. It may develop gradually or all at once. Individuals experience weariness in different ways, so you might experience it more or less than someone else receiving the same dosage of radiation therapy to the same area of your body [92].

While gene therapy holds significant potential for cancer treatment, it encounters various limitations and challenges that require attention and resolution. There are some limitations in gene therapy in treating cancer. One of the major obstacles in gene therapy for cancer is efficiently delivering therapeutic genes to target cells. The delivery system needs to navigate through diverse physiological obstacles, including the immune system and the intricate tumor microenvironment. Gene therapy can trigger immune responses, leading to the destruction of the introduced therapeutic genes or the vector carrying them. This immune response can limit the effectiveness and duration of the treatment. Securing exclusive expression of therapeutic genes solely in cancer cells poses a challenge [93]. Unintended expression in normal tissues has the potential for off-target effects, potentially resulting in toxicity or other undesired reactions. Gene expression may not be sustained over an extended period, necessitating repeated administrations. This limitation poses challenges related to patient compliance, potential immune reactions, and the risk of developing resistance to the treatment. Tumors are often heterogeneous, meaning they consist of diverse cell populations with distinct genetic and molecular profiles. Designing a gene therapy that effectively targets all the different cancer cell types within a tumor is a significant challenge. Developing and implementing gene therapy can be expensive. The high costs associated with research, development, and clinical trials may limit accessibility, particularly in resource-constrained healthcare systems and developing countries. Pinpointing patients who are most likely to derive benefits from gene therapy poses a significant challenge. The lack of reliable predictive biomarkers makes patient selection difficult, potentially leading to suboptimal treatment outcomes. Some cancers may develop resistance to gene therapy over time. The resistance observed can be attributed to the dynamic nature of tumors and the cancer cell's capacity to evolve and adapt in response to therapeutic interventions.

The concept that tumor growth may accelerate in the immediate postoperative phase finds support in numerous clinical and experimental findings. Metastasis is a prevalent cause of morbidity and mortality in cancer patients. The paradoxical idea that surgery, intended as a curative measure to eliminate and diminish tumor mass, can potentially expedite the formation of metastases is substantiated by both experimental and clinical evidence [94].

5. Alternative treatment- Photodynamic therapy

In recent years, countless people have continued to lose their battle with the disease, suffer from the side effects of existing treatments, and see the quality of their lives deteriorate dramatically despite efforts to find a cure and treatment. It is difficult to find a single cure for cancer because of its diversity and complexity. Photodynamic therapy (PDT) may be a strong contender for efficiently targeting malignant cells without affecting healthy cells around them [95]. PDT has gained traction for its effectiveness by targeting light at the target place. It is a non-invasive emerging technique. While still in its early stages, this treatment modality has proven successful and has received clinical approval for addressing both malignant and non-malignant conditions. It has been a long time. PDT got approval from the FDA for the first drug-device combination, but it has yet to be clinically utilized fully.

PDT requires three essential elements: a light-reactive molecule called photosensitizer (PS), light in a proper wavelength, and oxygen in biological cells. One at a time, all of these are non-toxic, but together, in the presence of oxygen and light, they initiate a photochemical reaction; the excited PS generates a highly reactive compound known as singlet oxygen ($^1O_2$) [96]. This process oxidizes cellular macromolecules and causes significant cytotoxicity in cancer cells. Highly effective in addressing lung, skin, and head and neck cancer, this treatment involves a PS that does not directly react with biomolecules. Instead, light energy is transferred to molecular oxygen, generating reactive oxygen species (ROS). A PS should not exhibit any cytotoxicity properties in the absence of light; this property is defined as dark toxicity. The generation of cytotoxic species is restricted where the three compounds are co-localized [97].

5.1 Mechanism of PDT

The mechanism of PDT involves three non-toxic components: the photosensitizer, light with a significant wavelength, and oxygen present in cells. PDT follows two types of mechanism reactions: type I and Type II. Both are nearly

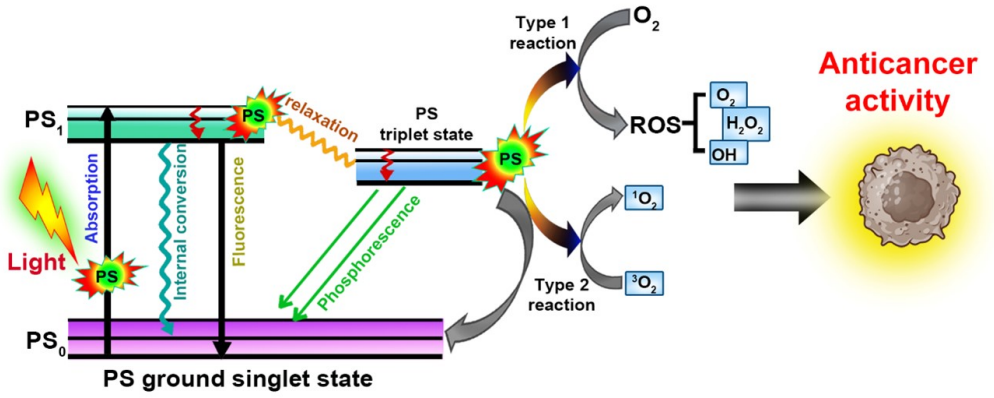

Figure 3. Mechanism of photodynamic therapy.

similar but depend on the oxygen molecules inside the cells. There is a similarity in both mechanisms. Following PS's entry into the cell, it is exposed to light at a wavelength that matches its absorption spectrum, which causes a reaction that produces ROS [98]. It quickly converts energy from the singlet state S0 to the excited energy state S1 by photon absorption. When the PS is excited, it can either undergo intersystem crossing to the triplet state by spin conversion of electrons in the higher energy orbital, or it can revert to the ground state and emit fluorescence Figure. 3. The triplet state can be influenced for tens of microseconds by molecules of oxygen or other substrates [99]. In the PS-excited triplet state, ROS are generated by two alternate pathways: (i) A type I reaction occurs when the PS in the excited triplet state pairs up with various receptor molecules, generating free radicals that then react with molecule oxygen to generate ROS. In addition to ROS, this process generates HO• (hydroxyl radical), O_2-• (superoxide radical), and HO• (hydroxyl radical), depending on the target molecules like lipids, nucleic acids, and proteins. (ii) Type II reactions directly transfer energy from an excited PS to $^1O_2$. The compounds generated in type I and type II reactions define the therapeutic advantages of photodynamic activity. Type I and type II responses can happen simultaneously in a photodynamic response. Type of PS, molecular oxygen content, and amount of substrate in tissues are some of the parameters that affect the ratio of type I to type II reactions [100]. Since the majority of investigations have shown that the type II response occurs, $^1O_2$ is thought to be a major factor in the phototoxicity associated with PDT. The type II reaction, being a simpler system and thermodynamically preferred for red-absorbing PS, generally occurs more frequently than the type I reaction. PS triplets emit only when their energy exceeds the excitation energy of $1O_2$, which is 94.5 kJ/mol. Consequently, $1O_2$ is considered the primary mediator of PDT phototoxicity. Photon absorption rapidly transforms singlet energy S0 into excited energy S1 through photon absorption. When the PS is in the excited state, it can either undergo intersystem crossing to the triplet state by spin conversion of electrons in the higher energy orbital, or it can revert to the ground state and emit fluorescence. One of the crucial characteristics of a PS is the development of its quantum yield (ϕ) and the lifetime (τ) of its triplet state [101]. The PDT response can be enhanced when both mechanisms occur simultaneously for certain PS. The relative extent of type I and type II mechanisms can be determined based on the PDT protocol, PS characteristics, and local oxygen concentration. Tumour microenvironments are often described as hypoxic because of insufficient blood flow near the center. In addition to consuming oxygen, the PDT can drastically reduce the local oxygen concentration, favoring type I reactions.

PDT induces the production of ROS, leading to oxidative reactions that impact various biomolecules, such as DNA, lipids, and proteins, integral to different cellular structures. Some amino acid residues in proteins, such as tyrosine, tryptophan, methionine, histidine, and cysteine, are highly reactive and susceptible to ROS [102]. Since tyrosine residues play a role in intracellular signal transmission pathways, they are susceptible to oxidation. Lipid hydroperoxides may develop from unsaturated lipids within intracellular membranous organelles, such as the endoplasmic reticulum. As a result, the membrane becomes permeabilized, the cell cycle is arrested, or the membrane ruptures. Additionally, ROS can cause DNA nucleotides, especially guanine, to oxidize. As a result, the DNA strand could be ruptured or DNA-protein cross-linked, which can cause cell death [8].

5.2 Clinical applications of photodynamic therapy in cancer

The ultimate goal here is to selectively destroy a target tissue. Various therapeutic areas have applied this concept, including oncology, where light can be used to access solid tumors that have not metastatically spread. PDT has shown promise in treating non-melanoma skin malignancies such as squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), as well as non-melanoma precancerous lesions such as actinic keratosis (AK). Furthermore, PDT can be used off-label to treat acne [103]. The ease with which PDT may be applied topically and light-induced target tissue delivery achieved in contrast to other treatment approaches such as surgery and cryotherapy is the reason for its effectiveness. PDT also offers cosmetic advantages over cryotherapy or surgery. A further advantage of PDT is that it can treat multiple lesions at once when applied to the cutaneous system. The utilization of PDT with topically applied PS for the

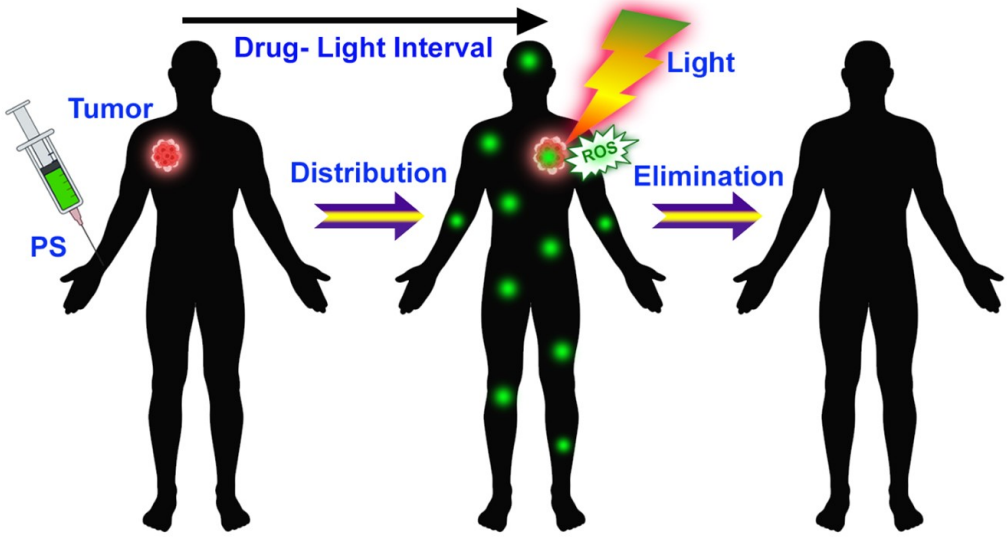

Figure 4. Schematic diagram of the clinical application of PDT.

treatment of actinic keratosis, basal cell carcinomas, and squamous cell carcinomas is currently prevalent. Simultaneously, PDT with systemically administered PS finds widespread use in treating conditions such as head and neck cancer, esophageal cancer, and endobronchial cancer [104]. A two-step protocol is required to apply the PDT protocol: first, PS needs to be delivered to the target tissue, and then a suitable wavelength of light must be used to irradiate it. Photochemical reactions occur when PS is combined with light to produce ROS. ROS causes oxidative cellular damage, which ultimately leads to the destruction of the target tissue. Upon administration, the PS should be allowed to reach and preferably accumulate in target tissues for a period of time after administration [105]. Treatment of PDT involves topical or intravenous PS, which accumulates at the tumor site during the period of light where exposed. According to the pharmacokinetics and biodistribution properties of PS, the length of time between drug administration and light release is called the drug-light interval (DLI) Figure. 4. A specific wavelength of light is applied to the target tissue once PS concentration reaches its peak, corresponding to the absorption band of PS but with a longer wavelength. As a result of this exposure to light, a large amount of ROS is formed, which causes oxidative damage to biomolecules and cell structures, ultimately leading to cancer cell death. A significant challenge in optimizing clinical protocols for PDT lies in precisely combining the three PDT components and their variables, as this greatly influences the efficacy of the therapy. Several factors influence the therapeutic effect of PS, including the type, dose, location, wavelength, and fluence rate, as well as other tumor factors, such as local oxygen supply [106].

5.3 Advantages of the PDT in cancer

In achieving selective PDT, two crucial factors must be considered: Light is delivered exclusively to the target tissue by certain PS due to its inherent ability to accumulate in tumor tissue. PS is more likely to selectively accumulate in tumors when applied topically, as they are directly applied to the lesions. During intravenous administration (IV), PS must stay in the bloodstream for a sufficient amount of time to collect within the tumor [107]. PS molecules can passively collect in tumor tissue by passing through the tumor vasculature in many solid tumors with fenestrated vasculature and decreased lymphatic outflow. This process is referred to as EPR. Because both singlet oxygen and hydroxyl radicals have half-lives of less than one microsecond, PDT has even more selectivity. PDT stops oxidative reactions from spreading into nearby healthy tissues by restricting the destruction range to less than 20 nm from the site of formation. PDT offers a significant advantage over traditional therapeutic methods due to its high selectivity, enabling the destruction of tumors while preserving the surrounding healthy tissue. In instances of recurrence or the presence of multiple lesions, PDT treatments can be repeated with reduced side effects, thanks to their high selectivity and absence of specific mechanisms of resistance [108]. PDT can be used in combination with radiation treatment, chemotherapy, or surgery because of its low adverse effects and non-interfering nature. It has also been found that PDT and conventional anticancer drugs can work synergistically in many cases. Another remarkable advantage of PDT treatments is the absence of significant sequelae. Treatment should not cause thermal effects, although patients often report painful burning sensations in dermatological treatments. Connective tissue is not destroyed, so tissues retain their functional and anatomical integrity. For example, dermatological treatments provide an excellent cosmetic effect, unlike surgical procedures, which often leave scars [109].

The application of PDT to localize and treat early-stage solid tumors can be highly effective, often requiring just one treatment. PDT is usually used in advanced situations, frequently involving small tumors, because light has a limited capacity to permeate into tissues. Patients with such cancers can benefit from PDT because it delays cancer progression and improves their quality of life. It was necessary to develop new strategies to deliver light to internal or bulky

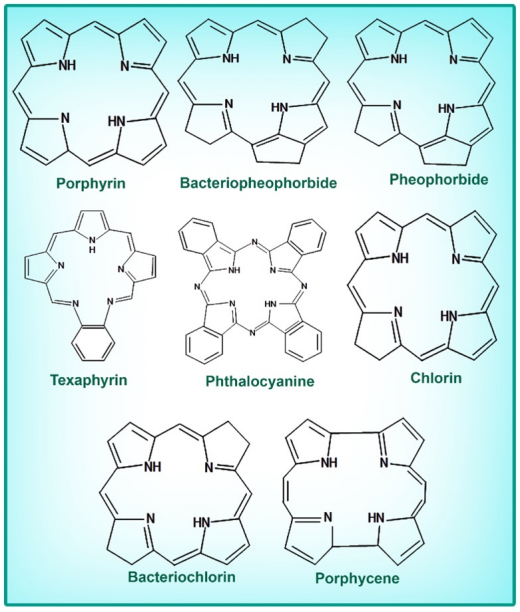

Figure 5. Structure of porphyrin-based PS.

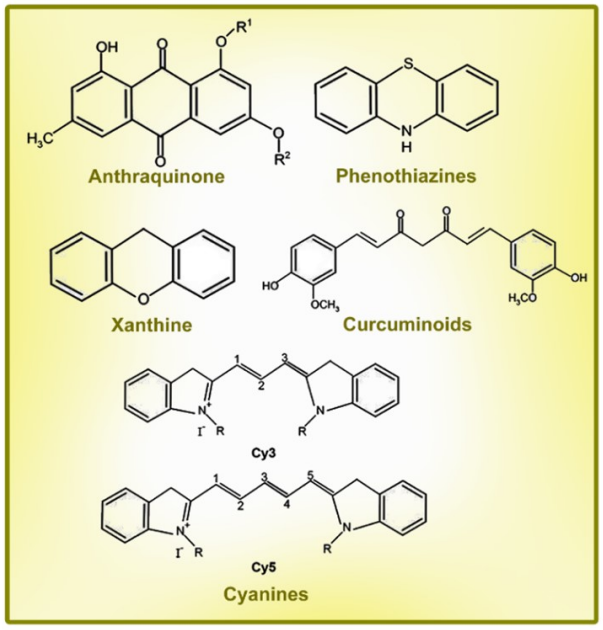

Figure 6. Structure of non-porphyrin-based photosensitizers.

tumors to overcome the low penetration of light in such tissues. A laser-coupled optical fiber has been successfully used to irradiate internal tumors facing body cavities through endoscopy. Interstitial irradiation can be used in larger tumors to ensure that all tumor cells receive sufficient light to achieve homogeneous light distribution and ensure that all tumor cells receive sufficient light. This can be achieved by introducing several optic fibers inside the tumor mass [110].

5.4 Commercially available PS

Creating an optimal PS that fulfills all requirements is a challenging task. Despite the difficulty, numerous PSs have gained approval for clinical use, although they may not meet all the criteria of an ideal PS. The majority of these approved PSs fall within the categories of first and second generations. Additionally, some PSs are currently undergoing approval for clinical trials.

5.4.1 The first generation of photosensitizers

First-generation PSs which are based on porphyrins, demonstrate efficacy against various cancers, such as those affecting the brain, larynx, lungs, esophagus, stomach, and skin [104]. Among these, derivatives of hematoporphyrin (HpD) represent prominent examples within the first-generation PS category. The initial photosensitizer clinically approved for PDT was a hematoporphyrin derivative resulting from the purification of Hp. There are several types of mixtures of porphyrins in HpD, including dimers, monomers, and oligomers. Indeed, porfimer sodium, a derivative of hematoporphyrin derivative (HpD), has been prominently featured in early clinical trials as a PS [111]. Porfimer sodium boasts various advantages, such as its efficacy in effectively destroying tumor cells, minimal dark toxicity, and the ability to formulate the PS as a water-soluble preparation. Despite advancements, porfimer sodium continues to find application in the treatment of various cancer types, underscoring its enduring relevance in clinical settings [112].

The constrained light absorption capacity of these PS in the red region of the electromagnetic spectrum significantly reduces the depth to which light can penetrate, thereby compromising the efficacy of the treatment. The lower extinction coefficients of PSs require the administration of a higher quantity of the drug to achieve the desired phototherapeutic response. However, this elevated dosage often results in PS aggregation. Metal ions are commonly introduced to counteract aggregation and improve PS stability. The position and type of substitution can alter the lipophilicity of the PS [113].

Spanning 48 to 72 hours during the drug-light interval is crucial to shield the patient from light exposure. Another challenge associated with PS is the prolonged accumulation and retention of these substances in the skin and normal tissues, resulting in severe photosensitivity post-PDT. Effectively managing these issues involves avoiding high-energy light and sunlight exposure or using protective eyewear and clothing post-PDT. The initial generation of PSs faced challenges such as high biodistribution, low bioavailability, and prolonged photosensitivity in the early stages of clinical trials [114].

5.4.2 Second generation PS

Second-generation PSs exhibit notable enhancements in spectral and photochemical characteristics attributable to their structure and composition advancements. These improvements manifest in a prolonged wavelength absorption, particularly in the red and near-infrared (NIR) spectrum ranging from 650 to 800 nm, thereby facilitating enhanced penetration into deep-seated tissues. Moreover, compared to their first-generation counterparts, second-generation PSs demonstrate substantial enhancements in photosensitivity, stability, and tissue selectivity. Only a few of these drugs have been approved for clinical use in cancer treatment

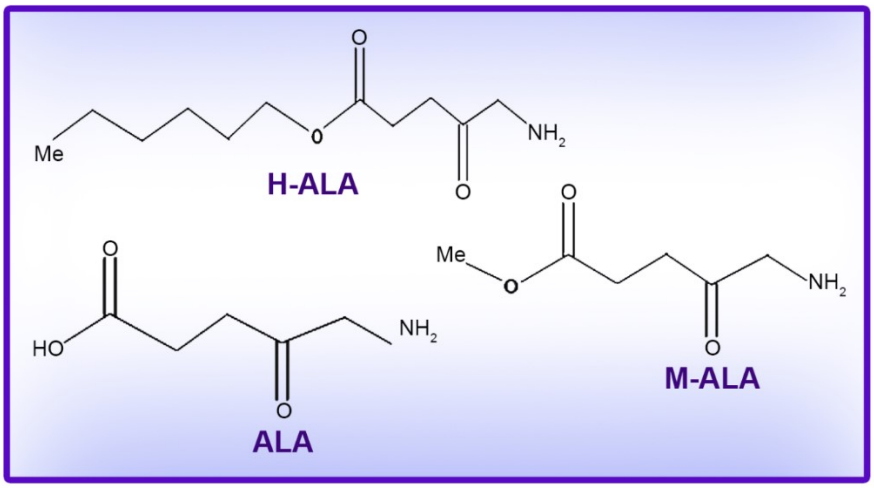

Figure 7. Structure of ALA-based PS.

[115].

The primary objective in developing second-generation PSs was to address the limitations encountered by their first-generation counterparts. These advanced PSs can be categorized into two main groups: Porphyrinoid compounds and non-porphyrinoid compounds [116]. Porphyrinoid compounds encompass macrocyclic structures like benzoporpyrins, bacteriochlorins, bacteriopheophorbides, purpuins, protoporphyrin, chlorins, pheophorbides, texaphyrins, and phthalocyanines Figure. 5.

On the other hand, there are numerous compounds that are not porphyrinoid, including curcuminoids, phenothiazines, cyanines, anthraquinones, and xanthenes Figure. 6. 5-Aminolevulinic acid (ALA), a frequently employed second-generation photosensitizer, serves as a precursor to porphyrin. Extensively researched over the years, ALA has shown significant promise in the realms of PDT and photodiagnosis for the treatment of cancer [117]. The second-generation PS demonstrates an enhanced ability to induce cell death, characterized by elevated quantum yields and a higher concentration within tumor tissue compared to Hp [118]. These PS also exhibit a shorter accumulation time, enabling same-day treatment following drug administration. This facilitates the implementation of PDT in an outpatient setting, increasing its acceptability and convenience for patients. In addition to their swift treatment duration, second-generation photosensitizers demonstrate a reduced duration of cutaneous photosensitivity. Physical and chemical factors, including the nature of charged groups, lipophilicity, the quantity and type of rings, and core substituents, primarily influence the characteristics of these photosensitizers. Some second-generation photosensitizers, such as mono-L-aspartyl chlorin e6 (MACE), AIPcS4, and aminolevulinic acid (ALA), exhibit a relatively hydrophilic nature, particularly those comprised of porphyrin ring structures like chlorin e6, bacteriochlorophyll a, and SnET2. In contrast, certain unsubstituted phthalocyanine compounds demonstrate higher hydrophobicity. While ALA is not a direct photosensitizer, its cell uptake leads to its metabolism into protoporphyrin IX [119].

ALA, a derivative of photofrin, belongs to the second generation of porphyrins. Certain members of this second-generation protoporphyrin are designed to target emerging vasculature specifically. Third-generation porphyrins are formed when second-generation photoporphyrins are linked with biological motifs such as antibodies or other synthetic materials like liposomes. Figure. 7 displays ALA and several currently employed derivatives. In the context of PDT on human glioma spheroids, ALA and its esters demonstrated efficacy. Specifically, benzyl-ALA (b-ALA) and hexyl-ALA (h-ALA) exhibited comparable cell-killing potential to the parent ALA, albeit necessitating concentrations 10–20 times lower to achieve a similar response. These ALA derivatives showcased their photosensitizing effects upon metabolizing into protoporphyrin IX. The heightened cell-killing efficiency observed with these ALA esters was attributed to their improved ability to penetrate cell membranes, enabling activity at lower doses [120].

Second-generation PSs like zinc phthalocyanine (ZnPc), aluminum phthalocyanine tetra sulfonate (ALPcS4), and silicon phthalocyanine (HOSiPcOSi (CH3)2(CH2)3 N(CH3)2 or Pc4) fall under the phthalocyanine category. Additionally, chlorin-structured PSs such as monoaspartyl chlorin e6 (NPe6) and temoporfin are widely utilized in the treatment of colorectal cancer (CRC), showcasing significant potential efficacy [121]. The major limitation of Ce6 is hydrophobicity, leading to poor biodistribution and rapid clearance. Various nanosystems have been designed to address this limitation, improve solubility, and enhance bioavailability. These nanosystems play a crucial role in boosting the accumulation of Ce6 in tumors by selectively targeting cancer through Active and passive targeting mechanisms. While second-generation PSs have shown promise in PDT, they face limitations such as low solubility in aqueous solutions and inadequate tumor selectivity. These issues not only impact PS uptake but also influence their subcellular distribution. Third-generation PSs have been developed to augment the efficacy of PDT. These incorporate second-generation PSs conjugated to nanoparticle carriers and antibodies, leading to enhanced selectivity and specificity for cancerous

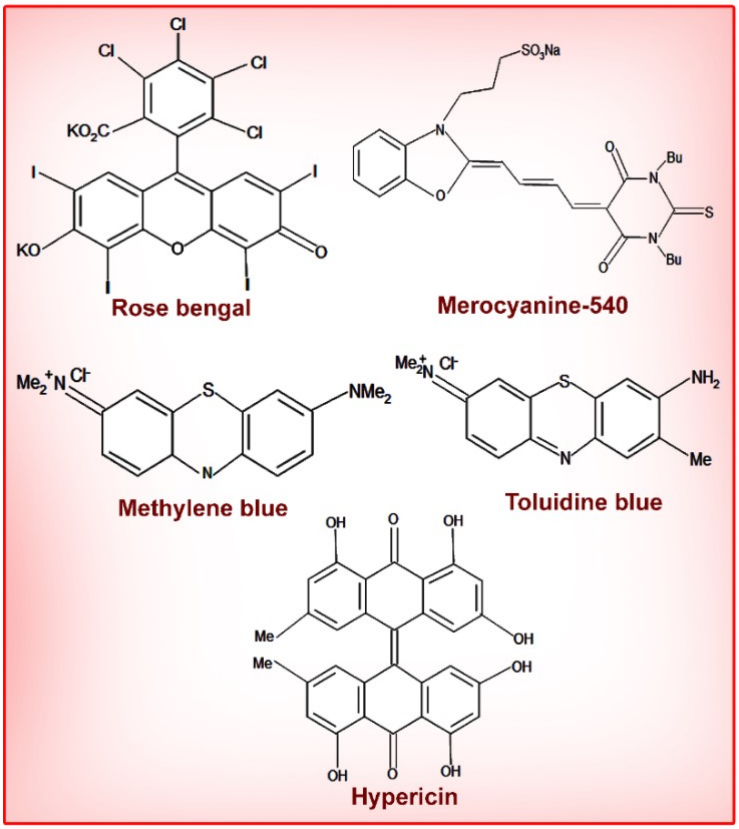

Figure 8. Structure of third-generation photosensitizers.

tissues [122].

5.4.3 Third-generation of photosensitizer

Presently, considerable attention is directed towards third-generation PSs, designed to be activated by longer-wavelength light, exhibiting reduced photosensitivity and enhanced tumor selectivity. Two distinct strategies have been pursued to attain this objective. Targeted distribution, incorporating ligands such as biotin, peptide, folate, and similar agents, is employed to enhance efficacy while minimizing adverse effects. One approach involves modifying the existing PSs by attaching various biologic conjugates to actively target the tumor site [123]. The second strategy entails linking the PS to a delivery vehicle or carrier capable of efficiently transporting it from the point of administration to the tumor site. Folate (FA) and transferrin are commonly used targeting ligands, with reports documenting the conjugation of FA to a platinum porphyrin complex using an ethylenediamine linker. Activation of carboxylic acids from both the platinum porphyrin complex and FA results in the formation of amide bonds with the linker, creating a new FA-targeted PS designed explicitly for FRα-positive cells. Confocal microscopy confirmed the endocytosis of this engineered PS within FRα-positive HeLa cells, while FRα-negative A549 cells exhibited no endocytosis. The engineered PS demonstrated a 78% cell killing rate in FRα-positive cells, in stark contrast to the 25% cell killing observed in FRα-negative cells [124, 125]. A comparable outcome was observed with π- extended diketopyrrolopyrrole-porphyrin targeted to folate receptor alpha (FRα), displaying selectivity for the FRα positive HeLa cells. In vivo investigation in mice with induced carcinoma nasopharyngeal epidermoid demonstrated promising results following treatment with pyropheophorbide conjugated with folate, incorporating a spacer of 1kDa PEG. Compared with non-targeted controls without the PEG spacer, this PS accumulated more in the tumor. As compared to non-targeted PS and non-PEGylated PS formulations, PEGylated folate-targeted PS effectively eradicated subcutaneous KB tumors induced in BALB/c nude mice with a reduced dosage. No tumor recurrences were observed even 90 days after PEGylated folate-targeted PS treatment [125]. With precision, third-generation PS aims to enhance targeted delivery and biodistribution compared to their predecessors. While the majority of these third-generation PSs have found extensive use in PDT research Figure. 8, their clinical applications remain limited due to a deficiency in invivo selectivity.

5.5 Limitations of the PDT

The major limitation of PDT is that it cannot treat metastatic disease as a local therapy. Some clinical reports have described how PDT affects patients' immune systems, which may cause lesions outside of the irradiated area. Many research groups are working on understanding the immune system response induced by PDT, one of the hottest topics in the field today. Ultimately, the goal is to promote an immune response capable of recognizing and eliminating

tumor cells outside the irradiated area, for example, metastasis. With this approach, PDT will have the capability of systemic action, complementing its local action [126].

5.5.1 Issues with Conventional PS

Some key considerations and challenges associated with this therapeutic approach are reported. PDT is a medical treatment that utilizes photosensitizing agents, light, and oxygen to selectively destroy or damage targeted cells and tissues. Some notable issues exist with photosensitizers in PDT. One significant challenge is achieving high selectivity for cancer cells. Photosensitizers should ideally accumulate more in cancer cells than normal cells to minimize damage to healthy tissues [127]. Some photosensitizers may have limited penetration depth in tissues and can be a concern when treating tumors or lesions located deep within the body. The absorption spectra of photosensitizers should match the wavelength of light used for activation. Issues may arise if the selected photosensitizer has a limited absorption range or the light penetration depth is insufficient. PDT relies on the presence of oxygen to generate ROS and induce cell damage. Hypoxic regions within tumors may be less responsive to PDT. Photosensitizers can undergo photobleaching, a process where they lose their ability to generate ROS after light exposure [128].

Photobleaching can limit the effectiveness of repeated PDT sessions. The photosensitizer should be biocompatible and non-toxic in the absence of light. Some photosensitizers may cause adverse effects, limiting their clinical application. Efficient delivery of photosensitizers to the target site is crucial. Issues related to drug delivery, including formulation and pharmacokinetics, can impact the overall success of PDT. Patients undergoing PDT may experience photosensitivity reactions, making it necessary to avoid exposure to sunlight or other bright light sources for a period after treatment. The interaction between PDT and the immune system is complex. While PDT can stimulate immune responses, the overall impact on antitumor immunity may vary [129]. Some photosensitizers may be expensive to produce, limiting their widespread availability and use, particularly in resource-limited settings. While PDT has shown promise in various medical applications, addressing these challenges associated with photosensitizers is crucial for enhancing the efficacy and expanding the clinical utility of this therapeutic approach. Ongoing research and advancements in the field aim to overcome these issues and further improve the outcomes of PD [130].

5.6 Ideal Photosensitizer for PDT

An ideal PS should be chemically pure, soluble in injectable solvents and body fluids to obtain regulatory approval, and chemically stable structures to contribute to the prolonged availability of active PS. PS should absorb light in the therapeutic window (600-800 nm) where tissue penetration is greater. This ensures that light can reach deeper tissues, allowing for the treatment of tumors or lesions located beneath the skin surface. These agents should be easy to synthesize on a large scale. PS should exhibit minimal dark toxicity to ensure the safety of the patient. Efficient energy transfer and high quantum yield for singlet oxygen production are crucial for effective PDT [131]. Singlet oxygen is a highly reactive species responsible for inducing cellular damage and apoptosis. Photosensitizers should be efficiently cleared from the body after the treatment to minimize potential side effects. PS should be easily formulatable into various delivery systems, such as nanoparticles, liposomes, or micelles, to enhance their pharmacokinetics and bioavailability.

Enhancements in the clinical domain are crucial in addressing key challenges, primarily focusing on tumor selectivity, PS design, and penetration depth. Many PSs exhibit broad photosensitivity, compelling patients to avoid outdoor activities due to associated life changes. This reluctance poses challenges in obtaining patient consent for PDT. Therefore, there is a pressing need for the development of PSs that effectively target tumors, minimizing undesirable PS biodistribution [132]. Dyes, also referred to as photosensitizers, help PDT by aiding in the targeted treatment of specific cells or tissues. These dyes absorb light at specific wavelengths, leading to the excitation of their electrons. Subsequently, this excited state transfers energy to oxygen molecules, leading to ROS generation. The selection of an appropriate dye is crucial, as different dyes exhibit varying absorption spectra, impacting the penetration depth of light and the specificity of the therapy's target [133].

6. Application of Nanomedicine in PDT

Nanomedicine has emerged as a revolutionary field, offering unprecedented opportunities to enhance the efficacy of various therapeutic modalities. Among the available treatment techniques, PDT stands out as a promising approach for treating cancer. PDT involves the use of photosensitizing agents, light, and oxygen to selectively destroy cancer cells. Despite its potential, PDT faces challenges related to limited tissue penetration, non-specific distribution of photosensitizers, and insufficient selectivity [134]. Nanomedicine offers solutions to these challenges, providing a platform for the development of targeted and efficient PDT strategies. Nanoparticles play a pivotal role in improving the delivery of photosensitizers to target sites. Various types of nanoparticles, including liposomes, polymeric nanoparticles, and inorganic nanoparticles, have been engineered to encapsulate and deliver photosensitizing agents. This encapsulation enhances the stability, solubility, and bioavailability of the photosensitizers, ensuring their efficient delivery to cancer cells. Nanoparticles can enhance the cellular uptake of photosensitizers, ensuring their efficient delivery into cancer cells. This is achieved through active or passive targeting mechanisms, enabling higher concentrations of photosensitizers within the tumor microenvironment [135]. As a result, PDT becomes more effective in inducing localized cytotoxicity. Nanoparticles can serve dual purposes by acting as diagnostic and therapeutic agents. Theranostic nanoparticles allow for real-time monitoring of treatment response, enabling clinicians to adjust therapy as needed. This integration of diagnostics and therapeutics contributes to personalized medicine, optimizing treatment strategies based on individual patient characteristics. While nanomedicine has shown remarkable promise in improving PDT, challenges re-

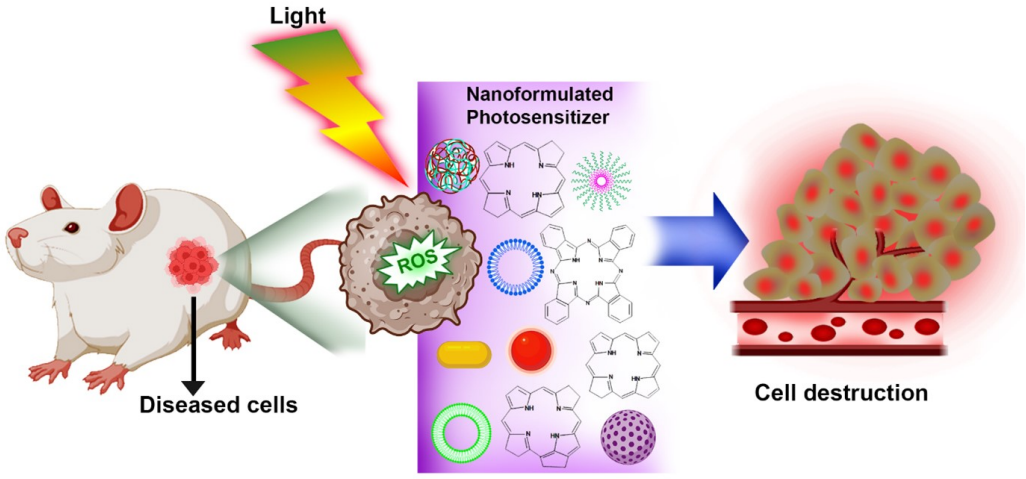

Figure 9. Nanoparticles and their potential use in photodynamic therapy.

main. Issues such as nanoparticle toxicity, immunogenicity, and large-scale production need to be addressed for clinical translation. Nanoparticles offer solutions to longstanding challenges associated with PDT, providing a platform for targeted drug delivery, enhanced photosensitizer uptake, and combination therapies Figure. 9 [136].

6.1 Nanoparticle-based photosensitizers

Since 1976, nanoparticles have served as carriers for drug delivery. Initially, their application involved the delivery of nanoparticle-based vaccines characterized by sustained drug-release properties. The utilization of nanoparticle-based vaccine delivery led to an enhanced immune response [137]. Expanding on this progress, several nanoparticle-based drug delivery systems were subsequently devised to selectively deliver chemotherapeutic drugs, such as paclitaxel and doxorubicin, to tumor tissues. This strategy aims to enhance the therapeutic index of these drugs by minimizing systemic side effects. Initially, polymeric nanoparticles were utilized for encapsulating PS due to their biodegradable characteristics. Unlike anticancer agents that require release for their cytotoxic effects, PSs do not necessarily have to be liberated from the carrier as long as the carrier effectively facilitates the diffusion of molecular oxygen [138].

Nanoparticle carriers in the field of PS can be categorized into two groups according to their degradability characteristics: i) Biodegradable nanoparticles and ii) Non-biodegradable nanoparticles. Biodegradable nanoparticles synthesized from polymers, whether of natural or synthetic origin, have attracted considerable attention in various fields due to their unique properties and potential applications. Biodegradable nanoparticles undergo enzymatic or hydrolytic degradation within the biological system, facilitating their excretion and reducing nanocarrier accumulation [139]. The prevalent polymers employed in the creation of micelles and other biopolymeric nanoformulations include poly(glycolide) (PGA), polycaprolactone (PCL), and poly (D, L-lactide). Biodegradable polymers provide a significant benefit by preventing premature payload leakage, thereby ensuring the payload's stability, including therapeutic agents and PS. Moreover, the polymers' surfaces can be customized with various biomolecules to enhance targeted delivery to the tumor site. The application of biopolymers in photosensitizer delivery has demonstrated notable advancements in PDT, prompting numerous research endeavors centered on biopolymer-based approaches. The subsequent sections elucidate several examples of extensively researched biodegradable nanocarriers for PS, along with insights into their interactions and mechanisms [140].

6.2 Liposomal-formulated PDT agent

Liposomes play a crucial role as a nano-based drug delivery system due to their distinctive capacity to enclose hydrophilic drugs within the core and hydrophobic drugs within the lamellae. Numerous investigations have assessed liposomal PS formulations in comparison to non-liposomal formulations for PDT. A liposomal PDT formulation was developed by encapsulating ALA, a prodrug for the photosensitive protoporphyrin IX (PpIX), within liposomes containing dipalmitoyl-phosphatidylcholine. The enhanced uptake of liposomal ALA in human cholangiocarcinoma led to an increased intracellular production of PpIX. Consequently, this heightened intracellular generation of PpIX resulted in significantly greater photo-cytotoxic effects when compared to the use of ALA alone [141]. Liposomes have demonstrated enhanced selectivity in targeting PS or co-administered chemotherapeutic drugs, thereby reducing their potential toxic effects. Studies have indicated that the integration of PDT with liposomal carriers presents diverse opportunities to enhance the delivery and targeting of photosensitizers, particularly in combating bacterial cells. These combined or multimodal platforms hold significant promise as they have the potential to augment the efficacy of cancer PDT.

Nanoliposomes have been employed to address tumor hypoxia and enhance the effectiveness of antitumor interventions. In a specific study, indocyanine green (ICG) was paired with perfluorooctyl bromide (PFOB) and encapsulated within nanoliposomes. This innovative nanoformu-

lation exhibited superior antitumor efficacy by impeding the growth of MDA-MB-231 tumors through a dual PDT and photothermal therapy (PTT) approach. PFOB played a crucial role in providing ample oxygen to overcome tumor hypoxia, while ICG generated ROS to induce cancer cell death. Remarkably, the nanoformulation also functioned as a contrast agent for computed tomography (CT), highlighting its potential as a theranostic agent for cancer treatment [142].

PEG-modified liposomes demonstrated prolonged circulation times and specific accumulation at tumor sites through the enhanced permeation and retention effect (EPR). To overcome the limited cellular uptake of methylene blue, a zwitterionic polymer-lipid-based liposome design was implemented. Encapsulation of methylene blue within these liposomes improved its cytotoxicity compared to free methylene blue. In vitro studies demonstrated increased generation of ROS by methylene blue-liposomes due to rapid cellular uptake and higher intracellular concentrations. In vivo studies further confirmed that liposomal methylene blue formulations not only generated a significant amount of ROS but also enhanced cellular uptake through the enhanced permeation and retention (EPR) effect [143].

6.3 Polymeric nanoparticle

Creating a polymeric nanoparticle-based nanocarrier for photosensitizers represents a cutting-edge approach in the field of nanomedicine. This innovative technology has gained significant attention due to its potential to enhance the efficacy of PDT for various diseases, including cancer. The design of an effective polymeric nanocarrier involves the selection of an appropriate polymer, encapsulation method, and surface modification. Biocompatible polymers such as poly (lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), and chitosan are commonly employed due to their favorable properties [144]. The encapsulation method should ensure high drug loading and controlled release. Surface modification with targeting ligands enhances specificity, enabling the nanocarrier to selectively accumulate in the diseased tissue. The advantage of using polymeric nanocarriers is that they provide a hydrophobic environment for photosensitizers, enhancing their solubility and stability in physiological fluids. Nanocarriers protect photosensitizers from degradation and clearance, leading to prolonged circulation times and enhanced bioavailability. The surface modification enables active targeting, ensuring the preferential accumulation of the nanocarrier at the target site and reducing off-target effects. Polymeric nanocarriers can be engineered to release photosensitizers in a controlled manner, optimizing therapeutic efficacy [145]. PEG-coated PLGA nanoparticles were utilized as a nano-drug carrier for delivering the hydrophobic photosensitizer Zinc tetraphenylporphyrin (ZnTPP) to HeLa cells. The encapsulation of ZnTPP within the nanocarrier resulted in enhanced stability and improved the release of singlet oxygen into the surrounding medium. In vitro experiments conducted on HeLa cells demonstrated an augmentation in the photosensitizers' photocytotoxicity, highlighting the PEG coating's beneficial impact [146].

Interestingly, ZnTPP exhibited a distinct behavior within the nanocarrier, avoiding aggregation at the core, unlike its behavior in the toluene solution. Subsequent investigations focused on analyzing shifts in absorption and fluorescence patterns. The internalization of PLGA NPs into cells occurred through endocytosis, with the PS being delivered to lysosomes, ultimately triggering apoptosis upon irradiation. In particular, PEG-PLGA NPs demonstrated enhanced endocytosis, effectively engulfed from the extracellular space and directed to lysosomes. This process resulted in heightened mitochondrial membrane permeability, chromatin condensation, and nuclear fragmentation, ultimately leading to the formation of apoptotic bodies. Consequently, PEG-coated PLGA nanoparticles containing ZnTPP exhibit promising potential for enhancing the effectiveness of PDT in antitumor applications [147].

6.4 Albumin Nanocarrier

Cross-linked natural polymers have been investigated as nanocarriers for photosensitizers, with a specific emphasis on albumin-based formulations that demonstrate theranostic potential. In a study conducted by Wacket et al., albumin-based nanocarriers were employed for the delivery of lipophilic photosensitizers. Specifically, the photosensitizers m-tetra hydroxyphenyl-chlorin (mTHPC) and m-tetra hydroxyphenyl-porphyrin (mTHPP) were successfully loaded into albumin nanoparticles. The resulting formulation demonstrated enhanced singlet oxygen generation upon incubation with cells, highlighting the promising capabilities of albumin nanocarriers in this context [49].

6.5 Core-shell nanocarrier

In a separate investigation, an examination was conducted on a core-shell nanocarrier designed for PDT using PS. Core-shell nanocarriers for photosensitizer delivery have emerged as a promising strategy for enhancing the efficacy of PDT. The core-shell nanostructures were crafted by synergistically combining perfluorotributylamine (PFTBA) and human serum albumin (HSA) to optimize PDT outcomes. These core-shell formulations effectively addressed the quenching effects observed in PS nanoformulation through three distinct mechanisms facilitated by the albumin shell. Firstly, the potential self-quenching resulting from $\pi - \pi$ stacking was mitigated by ensuring the uniform dispersion of the PS within the nanocarrier's shell. Secondly, the incorporation of HSA contributed to the prolonged lifetime of the PS in its triplet state, thereby enhancing the generation of ROS. Thirdly, the PFTBA core played a crucial role by dissolving and preventing the interaction of ROS for an extended duration, resulting in improved cytotoxic effects. Consequently, the albumin-based nanocarriers demonstrated superior capabilities in delivering and augmenting the activity of PS in PDT, as evidenced by previous studies [138].

6.6 Dendrimer-based nanocarrier

Dendrimers are heavily branching polymers with unique 3D branching architectures and precise chemical and physical characteristics. Therapeutic pharmaceuticals can be packed into the dendrimers. However, the surface's reac-

tive functional units are probably to be synthesized using biomolecules with specific aspects. The loading capacity of dendrimers holds promise in certain respects, although the research focus is on transferring DNA, RNA, and proteins. In these situations, reactive polymers such as polyaminoines (PAM) and polyethyleneimine (PEI) are frequently used. Because of its biodegradability, water solubility, biocompatibility, biomimeticity, and storage durability, polymer NPs are an effective drug delivery material. Over the past couple of decades, dendritic scaffolds have been used in various biomedical applications, such as drug delivery, tissue engineering, vaccinations, PDT, and more [148]. The encapsulation of PS in dendrimers typically involves three common strategies: (i) entrapping PS within the core, (ii) attaching PS to functional groups in the terminal side chains, and (iii) utilizing PS as a scaffold for dendrimer synthesis. In the context of photodynamic inactivation of living cells, commercially available poly-amidoamine (PAMAM) dendrimers, particularly those with 4 generations, are frequently employed to rigorizing them within the supramolecular class of photosensitizers for PDT. Dendrimers emerge as highly promising carriers for PDT and drug delivery, primarily attributed to their minimal toxicity. In the context of cardiovascular disease, PAMAM dendrimers encapsulation of PS are employed to target and induce selective necrosis of macrophage cells participating in the growth of atheromatous plaques [149].

6.7 Silica Nanoparticles

Mesoporous silica nanoparticles (MSNs) and organically modified silica serve as predominant nanocarriers for photosensitizers in PDT. The customizable surfaces of these nanoparticles allow for tailoring their shape and pore size based on specific applications. Wang et al. integrated dipyrromethene boron difluoride (BODIPY) dye into a silica matrix to enhance the dye's efficiency in generating ROS. The incorporation of the silica matrix prevented the premature release of dye molecules. Furthermore, the resultant nanoparticles demonstrated increased dye uptake by tumor cells, resulting in an enhanced phototoxic effect [150]. To undertake the surface modification of silica nanoparticles, incorporating moieties designed to specifically target tumor cells. They developed a tailored silica nanoparticle carrier by introducing folic acid onto the surface and encapsulating the photosensitizer chlorin e6 (Ce6) within the conjugate. The resulting nanoparticles demonstrated both biocompatibility and remarkable stability. Notably, elevated levels of the surface-modified Ce6 nanoparticles were observed to accumulate in MDA-MB-231 cells expressing folate receptors, surpassing the accumulation of free Ce6 molecules. Moreover, upon laser irradiation at 670 nm, these nanoparticles efficiently generated ROS, leading to the induction of apoptosis in cancer cells [151].

Secured mesoporous silica nanoparticles (MSNs) were created to control the early dye release from mesopores. Cyclodextrin was used by Bayir et al. as a gating mechanism for PS Ce6-containing MSNs. Research conducted in vitro on medication release has shown that cargo release is initiated by laser irradiation via linker molecule breakage. Subsequent generations of photosensitizers, such as verteporfin, were also linked to MSNs, serving as a promising approach for melanoma treatment. This conjugation exhibited enhanced cellular internalization and cytotoxic effects in SK-MEL-28 melanoma cell lines [152].

6.8 Gold nanoparticle

Gold nanoparticles (AuNPs) are extensively explored for drug delivery carriers due to their excellent properties, biocompatibility, and chemical stability. They come in various forms, such as nanospheres, nanorods, and nanoshells. The EPR effect enables the selective accumulation of AuNPs in tumors, making them ideal for delivering hydrophobic drugs. Coating AuNPs with biocompatible materials like PEG enhances their hydrophilicity, prolonging circulation time in the bloodstream and preventing quick clearance by the reticuloendothelial system (RES). To actively target tumor sites, AuNPs can be functionalized with specific groups or targeting moieties [153].

Gold nanoparticles (AuNPs) exhibit distinctive optical properties, including surface plasmon resonance (SPR), enabling them to serve as agents for PTT and generate heat. As a result, AuNPs are frequently utilized in the development of combined PTT and PDT agents. In a study investigating the antitumor activity of a conjugate involving C11Pc (a phthalocyanine derivative) and AuNPs in mice with amelanotic melanoma, the conjugation demonstrated superior cancer targeting and cell-killing capabilities compared to free C11Pc. Despite a significant PDT response, the PS accumulated in the liver for a week, prompting the researchers to emphasize the need for improved biocompatibility for faster elimination from the system [154].

The researchers PEGylated the conjugate of AuNP-C11Pc to address this concern to enhance its biocompatibility. Moreover, they conjugated surface monoclonal antibodies, particularly anti-HER2, to target breast cancer cells. Garcia Calavia et al. developed a dual therapy agent for PTT and PDT by coating mesoporous silica over gold nanorods in another approach. The photosensitizer methylene blue (MB) was added to the silica matrix, and the plasmonic characteristics of gold nanorods improved the PDT effect. This resulted in a 31% decrease in cell viability when exposed to light at 780 nm [170].

6.9 Magnetic nanoparticle

Researchers have shown significant interest in developing theranostic nanoparticles due to their ability to serve multiple functions as a single agent. The precise localization and accumulation of PS in the target tissue are critical to the efficacy of PDT. Among the several imaging modalities, MRI stands out as a potential choice since it offers better spatial and temporal resolution and is non-invasive and radiation-free. A comprehensive assessment of PS cellular absorption in the tumor is made possible by conjugating PS to a nanocarrier coated with an MRI agent [171].

Wu et al. combined MnO2-loaded black phosphorus (MnO_2-BPN) to create a nano theranostic agent [172]. The medicine is precisely transported to the tumor site by this nanostructure, which simultaneously induces the effects of PDT and PTT. The hypoxia amelioration effect of MnO_2

Table 1. Nanoformulated PS used in treating cancer

S. No	Nanoparticles	Photosensitizers	Type of Cancer	Ref
1	Conjugated nanogel-peptide (Ac-QFFLFFQGG-COOH)	Temoporfin	Breast adenocarcinoma	[155]
2	Hydrazone-containing ALA to gold nanoparticles	Levulan	Human lung adenocarcinoma	[156]
3	Au-SiO_2	Zinc phthalocyanine	Brain	[157]
4	Solid lipid nanoparticles	Aluminum chloride phthalocyanine	Melanoma	[158]
5	Polymeric micelles based on pluronics P123 and F127	Photofrin	Breast and Ovarian cancer	[159]
6	Poly-E-caprolactone nanoparticles	Zinc phthalocyanine	Human Lung adenocarcinoma	[160]
7	Nano silver loaded polymeric nanoparticles	Hypocrellin B	Human lung carcinoma and anti-angiogenic effect	[161]
8	Methoxypolyethleneglycol-thiol-SPIONs-gold-meso-tetrakis (4-hydroxyphenyl)	Porphyrin	Breast cancer	[162]
9	Amine functionalized polyacrylamide (AFPAA)	2-[1-hexy-loxyethyl]-2-devnyl pyropheophorbide-a (HPPH)	Colon-26 carcinoma	[163]
10	Fe_3O_4/SiO_2	Curcumin	Breast cancer	[164]
11	Pd nanosheets	Ce6-polyethylenimine	Cervical Cancer	[165]
12	NaYF4:Yb,Er@silica nanoparticles	Zinc phthalocyanine	Breast cancer	[166]
13	Mesoporous silica layer	MC540 and Zinc phthalocyanine	Skin cancer c	[167]
14	NaYF4:Yb,Er@Mesoporous silica layer	Hypericin	Hela and 293T embryonic kidney cells	[168]
15	Hydrophobic interactions PMAO-PEGs	Pyropheophorbide-a	Breast cancer	[169]

Nano sheets was responsible for the notable 3.8-fold increase in PDT effectiveness of BPNs. The nanostructure showed a 37% improvement in PTT when compared to BPNs. Furthermore, the nanocarrier included the anticancer medication DOX. SPION, MnO_2, and $MnFe_2O_4$ are examples of nano theranostic agents that were used to effectively limit tumor growth by enabling the visualization of photosensitizer accumulation in the tumor using T1-weighted MRI. In a similar vein, several studies have been carried out to provide a synergistic therapeutic effect with the combination of PDT and PTT drugs guided by MRI.

6.10 Carbon nanomaterials

In addition to utilizing nanomaterials for the delivery of PS certain nanomaterials possess intrinsic photodynamic properties due to their optical characteristics. Discovered in 1985, fullerenes, such as C60 and C70, consist of 60 or 70 carbon atoms, respectively. An advantageous feature of fullerenes is their ability to evade capture by macrophages owing to their smaller cage diameter (7-10 $\AA$). When exposed to ultraviolet irradiation, fullerenes can generate ROS, making them as effective as PS. They have robust photostability and may react simultaneously in Type I and Type II [173]. However, a drawback of fullerene use lies in its non-soluble nature. Modifications have been made to address this limitation, incorporating PEG, micelles, liposomes, and chitosan into fullerene structures. Fullerenes can be employed as multifunctional agents by encapsulating them with imaging agents. A multifunctional nano-fullerene was created by Shi et al. that may be used as an MRI contrast agent in addition to inducing PDT and PTT effects. Iron oxide nanoparticles were introduced into C60 fullerene, and its surface was altered using PEG to enhance its biological stability. Folic acid was additionally affixed to the PEG to specifically deliver the nanocarrier to tumor locations. The low toxicity, selective accumulation at the tumor site, and efficient tumor ablation of the nano-fullerene, which functions as a strong PS and PTT agent, were shown in both in vitro and in vivo experiments conducted on MCF-7 cells and tumor-bearing mice models. These findings underscore the potential of fullerenes as multifunctional nanoplatforms in the field of cancer theranostics [174].

6.11 Titanium Dioxide nanoparticle

Titanium dioxide (TiO2) nanoparticles are considered potential PDT agents due to their physiological inertness and ability to generate a distinctive photocatalytic effect. The excited state of TiO2's valence band electrons produces electron-hole pairs when it is subjected to UV radiation. ROS are produced when these pairs interact with oxygen and water molecules. Nevertheless, in vitro experiments conducted on various cancer cell lines, including MCF-7, U87, T24, and U937, revealed phototoxic effects created by UV light on TiO2 nanoparticles. Despite their promis-

ing attributes, their tendency to aggregate in physiological environments has hindered the application of TiO2 nanoparticles in vivo studies. Additionally, the limited penetration depth of UV light poses a constraint on the practical use of TiO2 nanoparticles in PDT [175].

6.12 Zinc oxide nanoparticle

Zinc oxide nanoparticles (ZnO) are preferred over TiO_2 for their enhanced photocatalytic effects, making them extensively utilized in the formulation of paints and cosmetics. The phototoxic impact of ZnO nanoparticles is size-dependent. In a study conducted, different sizes of ZnO were synthesized by Lie et al., and their lethal effects were compared, especially when combined with the anticancer drug daunorubicin (DNR) [176]. The synergistic application of ZnO and DNR demonstrated increased efficacy in killing hepatocellular carcinoma cells. ZnO nanoparticles can also serve as effective drug carriers for combination therapy. In research conducted by Hariharan et al., ZnO nanospheres loaded with DOX and modified with PEG on the surface exhibited enhanced cell-killing effects when subjected to UV irradiation [177]. Recent research conducted on the nanoformulation of PS for the treatment of cancers is given in Table 1.

7. Conclusion

PDT is a potentially effective therapeutic agent for the treatment of cancer. Numerous encouraging outcomes have been observed with the use of nanoparticles in PDT. Cancer treatment using photodynamic therapy is revolutionized by nanoformulated photosensitizers. Several limitations associated with traditional photosensitizers have been addressed by integrating nanotechnology into PDT, enhancing therapeutic efficacy and minimizing side effects. Nanoformulations provide enhanced drug delivery, extended circulation times, and precise localization in cancer cells, thereby optimizing the overall therapeutic outcome. Nanoformulated photosensitizers for cancer treatment are promising and multifaceted. One avenue of exploration involves refining the design of nanocarriers to enhance their biocompatibility and reduce potential immunogenicity and toxicity. Additionally, further research is needed to explore the long-term safety profiles of nanoformulated photosensitizers, ensuring their compatibility with the intricate biological systems of the human body. Furthermore, the exploration of novel photosensitizer materials with enhanced photochemical properties and reduced dark toxicity is a key avenue for future research. Advances in nanoscience and materials engineering will likely yield photosensitizers with improved singlet oxygen generation, higher photostability, and targeted delivery. This ongoing refinement will contribute to expanding the applicability of PDT to various cancer types, potentially extending its reach to currently challenging malignancies.

Ethical Approval
This manuscript does not report on or involve the use of any animal or human data or tissue. So the ethical approval is not applicable.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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