IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

Recent Therapeutic Status of Photodynamic Therapy for the Treatment and Diagnosis of Cancer Current Challenges and Novel Approaches of Photodynamic Therapy

[1] Pratikeswar Panda*, [2] Rajaram Mohapatra, [3] Abhijeet Mohanty and [4] SudhansuSekhar Rout

[1]Department of Pharmaceutics, Siksha 'O' Anusandhan University, Bhubaneswar, India

[1]School of pharmaceutical science

Bhubaneswar, 751003, Odisha, India

Abstract: Photodynamic therapy (PDT) is a cancer and infectious illness therapy that uses reactive oxygen species (ROS) are produced by light and a photosensitizer to cause cellular damage. In this review, we focus on recent advancements of PDT and how they may be manipulated to improve clinical outcome in cancer patients. PDT has demonstrated a promising translation into cancer therapeutics when combined with chemotherapy, PTT and immunotherapy. Additionally, PDT is being used to treat bacterial infections in order to combat antibiotic resistance. We have now covered the new paths PDT is taking in the treatment of infectious and cancerous disorders. In summary, we think that the development of PDT for cancer may be greatly influenced by advancements in nanomaterials and thoughtful design

Keywords - Photodynamic therapy (PDT), oxygen species (ROS), translation, chemotherapy, immunotherapy, antibiotic resistance.

INTRODUCTION

Recent big clinical studies for cancer, with a few major exceptions, have unable to discover significant changes in treatment outcomes despite advances in basic research that have improved our understanding of tumor biology and inspired the production of new generations of targeted therapies [1]. Furthermore, there are unfortunately few new medications that have received clinical approval. These sobering facts show that in order to advance, attention must be placed on other current treatment methods that are still not well recognized. PDT has the ability to address several unmet medical needs at the moment [2]. Although it is still in its infancy, it has already proven to be a clinically effective treatment approach for the therapy of both malignant and benign disorders. PDT was the first drug-device combination that the US Food and Drug Administration (FDA) approved about two decades ago, although it is still not widely used in clinical settings [3]. The initial element of PDT is PHOTOSENSITIZER, a photosensitive agent that localizes to a targeted cell or tissue. The sensitizer must be exposed to light of a specific wavelength in order to be activated in the second step. Reactive oxygen species are created when the photosensitizer converts light energy into molecular oxygen. The presence of the light-absorbing photosensitizer triggers these effects. As a result, the pharmacological reactions to the photosensitizer are exclusively triggered in the specific tissue regions to which light has been exposed [4,5]. A medication (photosensitizer) is added to light energy in the second stage of photodynamic therapy (PDT), which targets cancerous and precancerous cells. A specific wavelength of light radiation, generally from a laser, activates photosensitizers. The photosensitizer is safe prior to light activation. However, the photosensitizer turns poisonous to the targeted tissue after being activated by light, that shown in **fig-1**[6].

PDT has received a lot of attention, and several logical techniques have recently been put out. Previous reviews have talked a lot about PDT's advancements, and some of them focus on certain topics like hypoxic tumors, PDT that responds to the tumor microenvironment (TME), different PS types and how to activate them, and the nanomaterials that are employed in PDT [7,8]. Additionally, a discussion of new PDT methods using ultrasound, microwaves, and X-rays. PDT's therapeutic impact is fairly restricted to cancers on the skin or in areas close to the organ because it only functions when the light reaches the target area [9-11]. photosensitizers (PSs) PS present a challenge for systemic delivery because they are typically simple to aggregate and lack targeting, which reduces the clinical PDT efficacy [12]. Additionally, the O2 content in tumors is gravely deficient due to increased cancer cell proliferation and limited blood supply, which significantly reduces PDT efficacy. Therefore, substantial research is being done to optimize workable PSs systems in order to get over the aforementioned constraints [13-15]. Today, a variety of photosensitizer drugs are available to treat a variety of ailments, such as age-related macular degeneration, acne, psoriasis, and various cancers of the lungs, skin, brain, bladder, bile duct, pancreas, esophagus, and head and neck. In addition to these conditions, PDT helps cure fungal, viral, and bacterial infections. According to studies, this light-based therapy may enhance your body's immune system respond and provides it another tool to help eliminate harmful and precancerous cells [16,17].

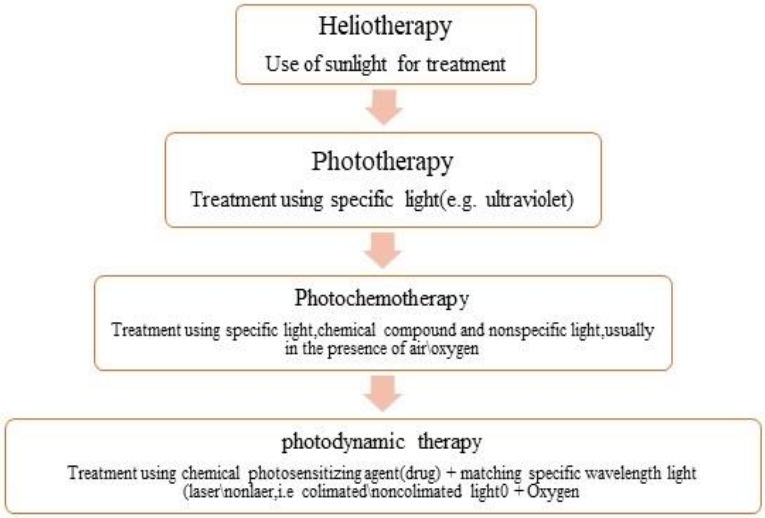

Fig 1-Evolution of photodynamic therapy

2. MECHANISM OF ACTION

PDT has the advantage that the photosensitizer can be administered in one of two ways: topically or intravenously. However, these affect how it is distributed biologically. Because biodistribution changes over time, another way to manage PDT's effects is by timing light exposure. The sensitizer moves from its ground state (singlet state) to an electrically activated state with a relatively long lifetime (triplet state) after absorbing light (photons), via an electrically excited singlet state with a brief lifetime. The triplet may react in one of two ways when engaged [18]. It can first transfer an electron from a hydrogen atom to produce radicals when reacting directly with a substrate, such as the cell membrane or a molecule. These radicals mix with oxygen to create molecules that contain oxygen. Contrarily, the triplet can transfer its energy to oxygen immediately, producing singlet oxygen, a reactive oxygen species (ROS). Anoxic tissue seldom becomes photosensitized since practically all PDT drugs relies on oxygen for its effects. In vivo studies revealed that the PDT effects of porphyrins were eliminated when tissue hypoxia was produced by clamping. The ratios of type I to type II reactions is influenced by the kind of sensitizer being employed, the reagent and oxygen levels, as well as the sensitizer's desire for adhering to the substrate. Only cells that are close to the area of ROS synthesis (regions of photosensitizer localization) are directly affected by PDT because of the strong interaction and brief half-life of the ROS. Since singlet oxygen has a half-life of 0.04 seconds in biological systems, its influence has a radius of 0.02 m. The kind of sensitizer, its intracellular and extracellular site, the overall dose administered, the overall dose of light exposure, the light intensity rate, the amount of oxygen accessible, and the interval between the drug's delivery and the light exposure are all taken into considerations that how much photodamage and cytotoxicity occurs that shown in **fig-2 and 3** [19].

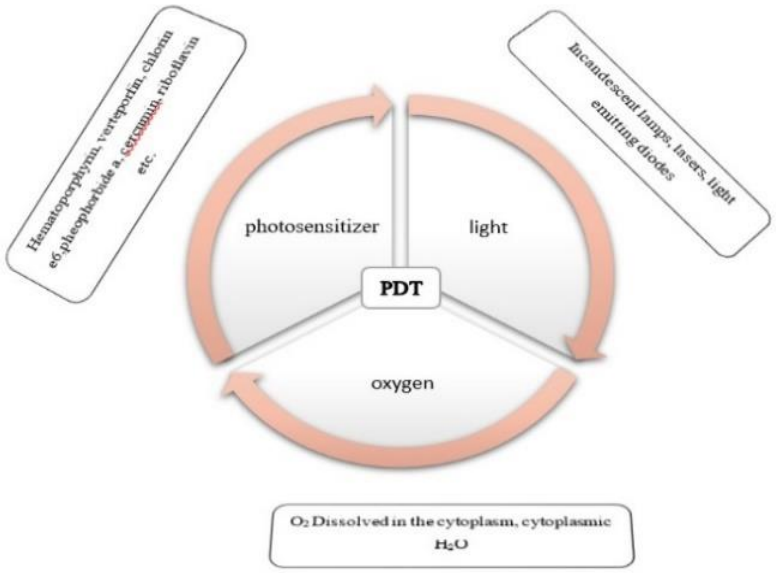

Fig 2- main component of photochemical reaction during photodynamic therapy

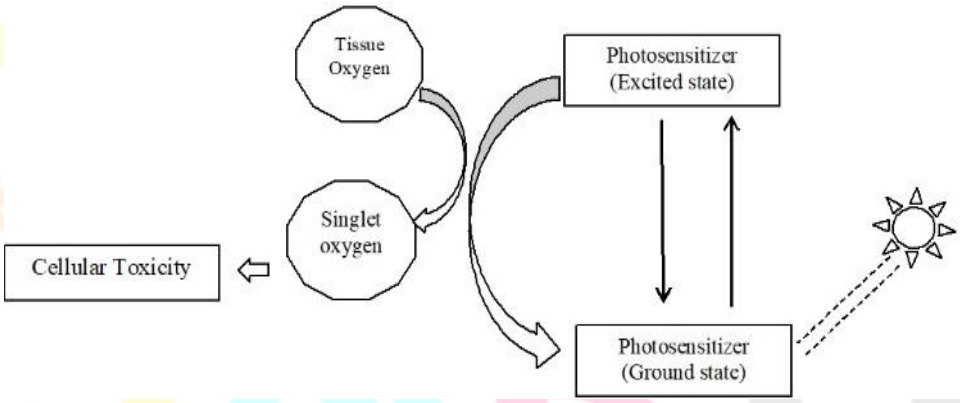

Fig 3-mechanism of action photodynamic therapy

2.1. Delivery photodynamic therapy

Photodynamic therapy is a two-step procedure. A photosensitizer will be administered to you at first. The therapy may be consumed, applied topically, or given intravenously depending upon where the tumor is located inside the body. Within 24 to 72 hours, the majority of the drug will have primarily departed normal cells, but it will still be present in malignant or precancerous cells. The light will then be directed straight at the tumor.

Depending on where the tumor is, different lighting techniques are used. The light is directly directed at the cancer in skin tumors. To check for tumors in your throat, lungs, and airways, your doctor will insert an endoscope into your neck. An endoscope, a tiny, lit tube, can help a doctor see inside the body. The doctor positions the endoscope and then passes a fibre optic wire through it to transmit light to the treatment areas. It should be shown in **fig-4**. Extracorporeal photopheresis (ECP), a form of PDT, is used to cure abnormal white blood cells that may cause skin problems in people with cutaneous T-cell lymphoma. ECP entails taking your blood cells out of your body, photo sensitively treating them, exposing them to light, and reintroducing them into your body through a vein. Photodynamic therapy is typically administered as an outpatient, which implies that patients don't spend the night in the hospital after your treatment and instead go home. One can utilize photodynamic therapy alone or in conjunction with other cancer therapies [49-52].

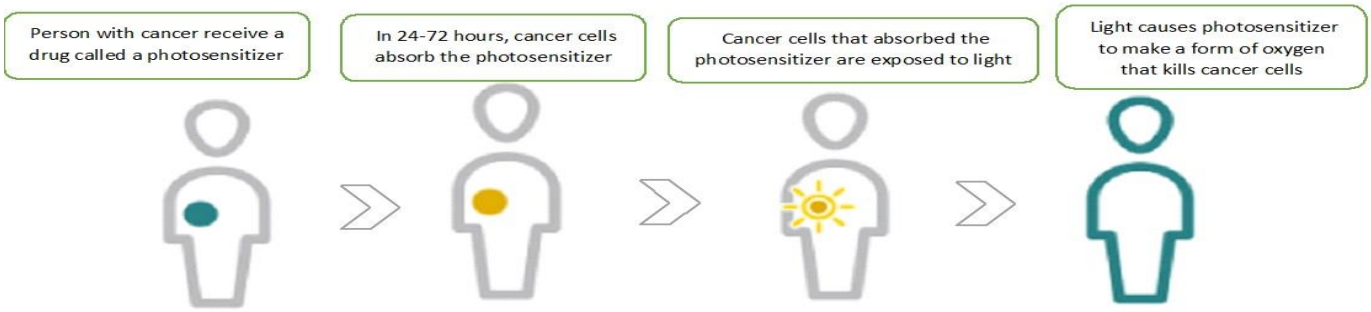

Fig 4- Delivery Photodynamic therapy

3. EFFECTS OF PDT ON TUMORS

There are now three main routes by which PDT induces tumor removal. In the first case, cancer cells can be immediately killed by ROS produced by PDT. PDT also affects the blood vessels around the tumor, which causes an infarction of the tumor. Not the least of which is that PDT can trigger an immune reaction against tumor cells. These three mechanisms might interact with one another. It is yet unclear how significant each one is in relation to the total tumor response. But it is evident that for long-term tumor care, a combination of all of these elements is necessary, there have some different PDT based mediated that effect on tumor describe in table-1[20,21].

3.1. Direct tumor-cell killing

It has been shown that direct photodamage brought on by in vivo PDT treatment of tumors can reduce the number of clonogenic tumor cells [22]. One hypothesis is that the photosensitizer is distributed unevenly throughout the tumor. Furthermore, Mladen Korbelik and associates demonstrated in 1995 that tumor cells are cut off from the vascular supply, which reduces the quantity of photosensitizer accumulated and causes tumor-cell death [23].

The quantity of oxygen in the tissue that PDT is aiming for is another factor that might restrict direct tumor-cell death. An oxygen deficit may result from the photochemical oxygen consumption that occurs during the photodynamic action as well as the immediate effects of PDT on the tissue microvasculature. During the following exposure of photo-sensitized tissue, there have been reports of a large and abrupt fall in tissue oxygen tension [24,25]. Depending on where the photosensitizer was when the light was turned on, the oxygen tension may briefly increase. Although it has been demonstrated that the long-term tumor response is affected by the development of hypoxia and microvascular damage following PDT, the response may be constrained by the oxygen decreases that take place during PDT. There are two ways to deal with this problem. In the first, the light fluence rate is lowered to reduce oxygen consumption rates, and in the second, the PDT light delivery is fractionated to allow the tissue to re-oxygenate [26–28]. The fluence rate modifies the signal to a different extent depending on where the photosensitizer is located [29].

3.2. Vascular damage

The amount of nutrients transported by the blood arteries also impact on how healthy tumor cells are. Growth components supplied by the tumor or host cell are therefore necessary for the formation and maintenance of blood vessels. Thus, a possible cancer treatment strategy involves focusing on the tumor vasculature [30,31]. A negative effect of photodynamic therapy (PDT), which uses a variety of photosensitizers to treat solid tumors, is vascular damage and blood flow stagnation. Hypoxia brought on by microvascular stasis is a powerful tool for cytotoxicity and tumor regression [32].

PR aggregatory eicosanoids, such as thromboxane, which cause vessel constriction and amplified platelet aggregation and thrombus development. An alternate pathway to platelet activation and the production of PR aggregatory chemicals during PDT may be explained by direct damage to platelets. Polymorphonuclear leukocytes attach to sites of endothelium damage and may help to activate platelets further [33,34]. Leukotrienes, which encourage vascular leakage and elevations in tissue interstitial pressure, are among the extra vasoactive substances that adherent leukocytes may also produce. The interaction of arterial constriction, platelet aggregation (and thrombus development), and higher interstitial pressure results in a halt in blood flow and consequent tissue hypoxia. In animal models, tumor shrinking requires sustained levels of tissue hypoxia for a number of photosensitizers utilized in PDT [35].

3.3. Immune response

Photoimmunotherapy is an oncological treatment for several tumors that combines immunotherapy with photodynamic tumor therapy. Immunotherapy and photodynamic therapy work in concert to boost the immune system's response and treat metastatic cancer [36-38].

Another fascinating finding was achieved by Barbara Henderson and colleagues, who demonstrated the development of tumor-specific immunity by employing a tumor-cell lysate collected after PDT using Photofrin to immunize mice against the development of new cancers. Lysates produced from tumors treated to UV or ionizing radiation have been proven to be less successful at inducing an immune response than this immunization method. These PDT vaccines appear to trigger an IL-12-induced cytotoxic T-cell response. PDT may be useful as a systemic immune treatment, according to studies using PDT and tumor-cell lysates. To find out if patients using PDT can get comparable results, more research is necessary [39,40].

Table 1- PDT-mediated effect on tumour

Effect of PDT	Reaction	Result
Direct tumour cell killing	• Cellular signalling • Changes in calcium and lipid metabolism cytotoxicity	• Organelle Damage • Apoptosis • Necrosis
Vascular Damage	• Prostaglandin synthesis • Thrombosis • Platelet activation	• Microvascular shutdown • Vessel leakage • Tumor Hypoxia • Tumour starvation
Host immune response	• Inflammation • Heat stock proteins • Cytokine secretion • Complement activation	• Cytotoxic T-cell • Antibody mediated cytotoxicity • Long term memory immunity • Destruction of metastases

4. CHALLENGES

4.1. Tumor targeting efficiency

Most conventional organic PSs' clinical application has been severely constrained by the poor tumor targeting efficacy associated with most of them. On the one hand, it is believed that the aberrant physiological traits of tumors are what lead to the higher amount of various PSs in tumor tissue than the surrounding healthy tissues. However, fundamental PS properties like structure, physical properties, and surface modification can have a big impact on how well they can target tumors [53,54]. In this regard, enhancing the PSs' tumor targeting effectiveness may be difficult and challenging. PDT surface alteration to overcome this problem, drugs with targeted delivery and moiety could be used to deliver photosensitizing drugs specifically to the tumors. Excellent opportunities for surface functionalization will be presented by the use of nanomaterials in PDT, which can improve the effectiveness of tumor targeting. Some clinically approved examples of photosensitizers that describe in **table-2** [55].

4.2. Deep Tissue PDT

Normally, visible light is required for photoexcitation during the PDT using conventional, older-generation PSs. Due to the significant visible light absorption of the majority of tissue chromophores, visible light penetration depth is only about 3mm. As a result, the photodynamic outcome is considerably hindered by the increasing tissue depth and weakening light intensity [56]. The alternative option is to employ a light source that isn't constrained by tissue thickness, like an X-ray or internal light.

Due to internal lighting's inadequate energy transmission to the PS, detrimental X-ray impacts on normal tissue, and weak ROS formation efficiency, it is evident that more research is needed in these fields. Deep tissue PDT is currently challenging to apply effectively in general [57,58].

4.3. Tumor Hypoxia

Evidently, the amount of oxygen in the immediate environment has a significant impact on the photodynamic effect. As a result, PDT's anticancer effects are greatly diminished in hypoxic tumors, where oxygen is predominantly utilized by rapidly expanding tumor cells [59,60].

Additionally, PDT is an oxygen-intensive technique that would exacerbate tumor hypoxia and reduce PDT effectiveness. Nanoplatforms made of PS and nanomaterials, like the MnO2 nanosheets mentioned above, that can catalyze the breakdown of H2O2 to produce O2, were created to address tumor hypoxia. Additionally, some methods, such light fractionation for controlled "on" and "off" periods of light exposure, can aid in the reperfusion of O2. These techniques, however, are ineffective when tumor hypoxia is brought on by the tumor cells' fast cellular expansion [61,62].

As an alternative, PSs that are oxygen independent, including as TiO2 and g-C3N4, PSs that can induce the O2-independent type I response, and combination therapies with O2-independent techniques (such chemotherapy and PTT), can all be utilized to treat tumor hypoxia [63,64].

4.4. More Efficient and More Reliable Nanomaterial-Based Photosensitizers

PS plays a crucial part in PDT. Therefore, the physical, chemical, and pharmacokinetic properties of PDT play a significant role in the treatment's outcomes [65,66]. Great tumor targeting ability PSs are still in high demand, as are PSs with high ROS production efficiency, good stability, and strong biocompatibility under physiological settings [67]. However, it should be understood that the nanomaterials still have flaws, which restrict their actual therapeutic application. For instance, the lengthy, multi-step processing required for UCNPs (Upconverting nanoparticles), nanosheets, and many other (heavy) metal-based nanomaterials' toxicity. As a result, continuing and intensive work is still required to maximize the potential of nanomaterials in PDT by creating more effective and reliable nanomaterials [68-72].

Table 2- Clinically approved photosensitizers

PHOTOSENSITIZER	CANCER TYPES
Photofrin (HPD)	lung, oesophagus, bladder, bile duct, ovarian, brain
ALA	skin, oesophagus, bladder, brain
ALA esters	skin, bladder
Foscan (mTHPC)	head and neck, brain, lung, skin, bile duct
Verteporfin	ophthalmic, skin, pancreatic
Purlytin (SnEt2)	skin, breast
Taloporfin, LS11, MACE, Npe6	liver, colon, brain
Fotolon (PVP-Ce6), Radachlorin, Photodithazine	nasopharyngeal, sarcoma, brain
Silicon phthalocyanine (PC4)	cutaneous T cell lymphoma
Padoporfin (TOOKAD)	prostate
Motexafin lutetium (LuTex)	breast
HPPH	head and neck, oesophagus, lung [100-104]

5. RECENT ADVANCEMENTS

The use of PDT in firmly established cancers is now possible because to advancements in nanotechnology. Better PS carriers, a larger PS absorption peak, and improved performance in a hypoxic TME can all be attributed to new innovative NPs [73]. And also, PDT may benefit greatly from photosensitizer delivery systems with nanostructures. Due to the huge surface-to-volume ratio, the initial one is concerned with the large number of dyes that can be transported to the specific site, whilst the second one is concerned with preventing the dyes' premature release before they reach the target, boosting their exact avoiding their negative effects and accumulating in the target tissue. Since the loaded dyes are somehow connected to the second, have limited circulatory resistance and become amphiphilic when combined with nanostructures, which also encourages tumor accumulation [74]. The favored accumulation of nanoscale materials in tumor tissues as a result of the increased permeability and retention (EPR) effect is another benefit. Finally, a variety of groups can be functionalized onto their surface to alter their surface chemistry, cell absorption, pharmacokinetics, and biodistribution to suit a particular use [75]. Now-a-days some of drug that induces photosensitivity that shown in the **table 3**.

Table 3- List of Drugs that Induces Photosensitivity

Drug classifications	Drugs
Antifungal agent	Griseofulvin, itraconazole, flucytosine
Antibacterial agen	Nalidixic acid, ofloxacin, enoxacin, ciprofloxacin, pefloxacin, lomefloxacin, fleroxacin, , tetracycline, tosufloxacin doxycycline
Antihistamine	Diphenhydramine, mequitazine
Antiinflammatory	Ketoprofen, suprofen, tiaprofenic acid piroxicam, actarit, ampiroxicam, diclofenac, naproxen
Antipodagric	Benzbromarone
Antidiabetic	Tolbutamide, glibenclamide, chlorpropamide carbutamide, glymidine sodium
Prostatomegaly therapeutic agent	Tamsulosin
Lipid-lowering drug	Simvastatin
Antitumor agent	5-FU, dacarbazine, tegafur, flutamide
Photochemistry therapeutic agent	8-Methoxypsoralen, hematoporphyrin derivative ,trioxypsoralen
Antirheumatic	Sodium aurothiomalate, methotrexate
Vitamin	Etretinate, Vit. B_{12}, pyridoxine

Nanoparticles, simultaneously biodegradable and inert can be used to improve photodynamic therapy. Singlet oxygen can be created as a result of exposure to light since the photosensitizers are contained inside biodegradable nanoparticles (typically polymers and lipid-based structures) and released in a controlled manner [76,77]. However, when using non-biodegradable nanoparticles, the PS are often adhesions on their base (either externally or internally, in the case of porous structures), and they are not always completely released to form singlet oxygen [78,79].

The use of combinational techniques with other therapy modalities also aided in the development of very effective PDT in the interim that shown in **fig-5**. Combinational techniques with PDT that include chemotherapy, PTT, immunotherapy, radiotherapy, and gene therapy may improve PDT outcomes at low therapeutic doses while minimizing adverse effects on healthy tissues. Additionally, the use of combinational techniques may help monotherapy overcome difficult issues such resistance development and tumor spread [105,106]. Here, the types of PDT associated with chemotherapy, PTT coupled with immunotherapy, and rationally created PNMs are given.

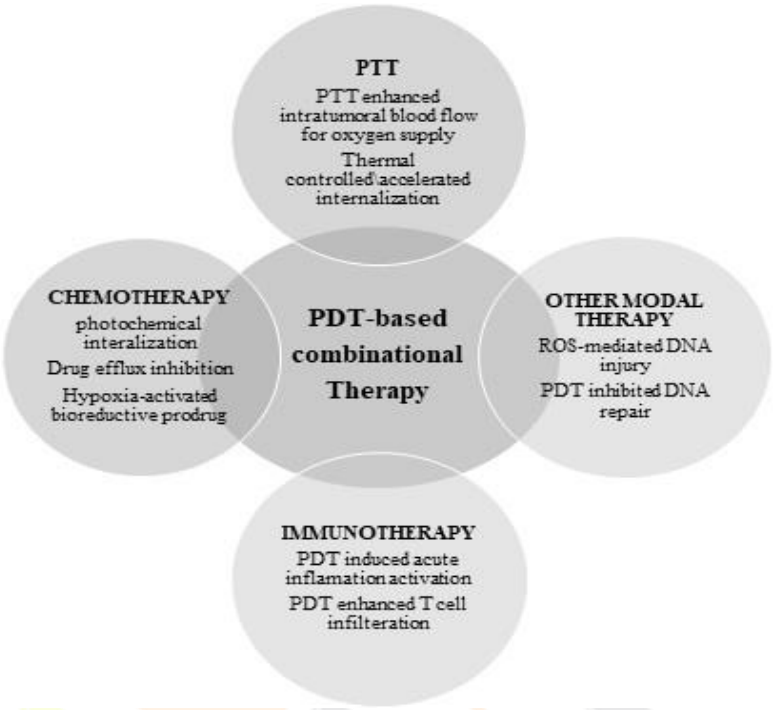

Fig 5- different type of PDT-based combinational Therapy

5.1. Recent advances in X-PDT

Radiosensitizers or scintillating materials are used in X-ray driven PDT. Due to the sheer ability of their inner shell electrons to accomplish this, high-Z elements are particularly efficient at absorbing X-ray photons and turning them into released electrons and visible range photons. The most widely used scintillators are nanoparticles of high-Z elements doped with rare earth elements because of their advantageous characteristics for high-energy physics and radiology. A material's ability to scintillate may be affected by factors such nanometric size, flaws, coatings, and media contact. Materials such as vitroceramics, films, coordination compounds, MOFs, and organic-inorganic nanocomposites can be made from the materials [80].

One of the main problems is the required radiation dosage for the patients during X-PDT. The required dose of radiation for the patient to can be decreased by some scintillators, which have the option of creating sustained luminescence rather than fluorescence when exposed to radiation. Fluorescence typically lasts for a few microseconds, whereas persistent luminescence can last anywhere between minutes and hours after the initial excitation. As a result, the radiation dose needed for excitation can be greatly reduced. Evidence suggests that continuous luminescence lowers the oxygen consumption rate during photodynamic therapy (PDT) and may prevent the unfavorable hypoxia that decreases photodynamic therapy effectiveness [81,82].

5.2. Recent advances in CR-PDT

Cherenkov radiation-driven PDT relies on the fact that the majority of radiopharmaceuticals deposit in tumours in a selective way, allowing for more targeted photodynamic elimination. But low fluence rates—which are normally insufficient to permit a high photodynamic efficiency—are used to produce Cherenkov radiation [80].

However, CR-PDT has one significant advantage over X-PDT: it makes it possible to target multiple metastases more successfully than with external X-rays. Additionally, despite the fact that the photons obtained by radionuclides are significantly fewer than those produced by external radiation (and possibly inadequate to exert significant phototoxicity), it is probable that the harm caused directly by the radioactive elements works in concert with CR-PDT to successfully ablate tumors [83].

Even though there have been many encouraging results, much more research must be done before X-PDT and CR-PDT are accepted as standard clinic treatments. Understanding the causes of cell death caused by radiation and PDT is essential, as is the definition and optimization of the materials used as scintillators [84].

6. STRATEGIES REGARDING PDT

PDT's ability to treat cancers effectively is constrained by the oxygen supply to the tumors, which is often diminished by poor microcirculation, particularly in the tumor center. Because PDT uses oxygen, it causes the local hypoxia and prevents the procedure from working to its full capacity. In order to increase the tumor ablation, some methods to boost the oxygen availability to the malignancies during PDT have been proposed [85].

Cheng et al suggested Oxygen-enriched perfluorocarbon nanodroplets with an average size of 200 nm have been loaded with photosensitizers that are triggered at 780 nm in order to increase reactive oxygen levels and prevent tumour growth in photodynamic treatment. The use of nanodroplets increases the PDT able to both in vivo and in vitro and also prolongs the half-life of singlet oxygen. With intravenous injection, the tumors were significantly ablated, but with intratumor delivery, they were completely destroyed [86].Kim et al. demonstrated that mesoporous silica nanoparticles may be connected to manganese ferrite nanoparticles, which are typical Fenton catalysts, and loaded by chlorin e6 to successfully generate O2 via the Fenton reaction inside cancer tissues due to the excess H2O2 derived from the tumor metabolism. This mixture may function as a therapeutic, diagnostic and a contrasting agent for magnetic resonance imaging while enabling a continuous PDT process by providing the tissue with the required amount of oxygen via the Fenton reaction [87]. Jia et al. noted that cerium oxide nanoparticles offer a good substitute by transforming hydrogen peroxide into molecular water and oxygen even in the absence of light irradiation. Therefore they, a creative technique to boost the efficiency of PDT by providing oxygen to the hypoxic tissues. The NaGdF4: Yb,Tm@NaGdF4 up conversion nanoparticles were used by the researchers in a mesoporous core-shell structure. They can convert NIR light into UV light, which activates cerium oxide to produce ROS. The hollow interior of the nanoparticles makes them particularly effective for PDT tumor ablation, and they can also be used as a pharmaceutical carrier for a combined therapy [88]. Red blood cells (RBCs) can function as both a photosensitizer and an oxygen carrier, which increases PDT's efficiency in hypoxic environments. For instance, On the surface of RBCs, Wang et al. combined a hypoxic probe and the photosensitizer Rose Bengal. When the hypoxic probe is activated by low oxygen levels, it goes through an orthogonal near-infrared up conversion that causes the oxygenated hemoglobin to release oxygen when 980 nm light is delivered. As a result, the photodynamic process is maintained for longer and produces more tumor ablation [89].He and his colleagues gave a presentation entitled "Hybrid Nanomedicine Developed using Metal-Organic Framework Nanoparticles with Photosensitizer Terminations for Photodynamic Therapy and Hypoxia-Activated Cascade Chemotherapy. As a result, scientists used porous nanocarriers called nanoscale metal-organic frameworks (NMOFs) to transport photosensitizers and chemotherapeutics that are activated by hypoxia. Results from both in vitro and in vivo studies show that the nanoparticles release on demand and cause a significant amount of tumor ablation, making this an effective anticancer technique [90]. By combining the mobility of gold nanoparticles with a hydrophobic photosensitizer (zinc phthalocyanine derivative), Stuchinskaya et al. prevented the hydrophobic photosensitizer from aggregating before it was required. They then decorated the nanoparticles containing tumor-specific antibodies (anti-HER2 for breast cancer) using covalent connections made with the coating layer of polyethylene glycol. Singlet oxygen generation in cancer cells was highly efficient using a specific technique [91].

The calcium phosphate-encapsulated core-shell produced nanoparticles (UCNPs-Ce6@SiO2@Calcium Phosphate-Doxorubicin) were created by Liu et al. They are biocompatible, biodegradable, pH-sensitive (enabling the chemotherapeutic to be released in the tissue), and they transmit therapeutic activity by PDT under 808 nm radiation indicating the prevalence of Chlor. Finally, it can be used as a diagnostic imaging technique because rare metals exist [92]. Another tactic is that the development of nanoparticles that can be broken down by enzymes like hyaluronidase and matrix metalloproteinases that are abundantly expressed in tumors. Hyaluronic acid nanoparticles are combined with chlorin E6 in the nanomaterial developed by Li et al., which breaks down the components of hyaluronidase to reveal the photosensitizer. This makes them able to serve as theragnostic materials, which can be used as both therapeutic and diagnostic agents [93].

Another illustration provided by Zhang et al. is MMP2-responsive chimeric peptide nanoparticles combined with protoporphyrin-IX, which MMP-2 is active when it turn from a sphere into big fibers, and this sphere-to-fiber transition promotes tumor persistence of the nanoparticles [94]. Protoporphyrin-IX is joined to a peptide nanoparticle known as PpIX-Ahx-K8(DMA)-PLGVR-PEG8, which according to Dai et al., is sensitive to pH and enzyme. To prevent nonspecific uptake, this nanoparticle takes on a circular morphology while in movement. They undergo a charge reverse and PLGVR sequence cleavage by MMP-2 when in tumour environments. Due to the low pH, the DMA group splits concurrently. This justification led to an even greater rise in the selective absorption by tumor tissues

[95].Jeong et al. examined human serum albumin nanoparticles coated with chlorin e6 in an effort to create a much biocompatible technology for improved PDT efficiency. The nanoparticles, which had a diameter of about 88 nm, were shown to be non-cytotoxic in the dark but to produce a sizable amount of singlet oxygen when exposed to the right wavelength of light. Surprisingly, when administered intravenously to mice, they significantly increased the specificity of tumor delivery relative to free photosensitizers and improved imaging properties due to chlorin e6 fluorescence [96]. The research by Xu et al. on mesoporous cerium oxide-coated photothermal conversion nanomaterials for tumor-responsive chemo-photodynamic treatment and bioimaging. The author noted that dendritic cells were drawn to damaged cells and that this led to an efficient accumulation in tumors in vivo after intravenous injection. The treatment may also affect tumors in other areas due to the potent cancer vaccine effect that the immune response elicited [97]. Dong et al. created hollow, porous CaCO3-PDA-PEG nanoparticles that contained chlorin e6. They discovered that these nanoparticles selectively released the photosensitizer as they broke down in acidic conditions, such as tumors. In contrast to other formulations and free photosensitizer, In the acidic medium, singlet oxygen generation was accelerated, and the photosensitizer was more efficiently absorbed when it was administered inside the nanoparticles. It is important to emphasize that chlorin e6 is supplied in a liposomal formulation, unlike the CaCO3-PDA-PEG formulation, which does not induce a significant weight loss in the mice, perhaps due to an intrinsic toxicity [98]. Zhu et al. developed ROS and consumed glucose inside cancer cells using GOx-loaded MSNs containing PS-embedded lipid membrane shells under 730 nm radiation, leading to a synergistic PDT and ST treatment [99].

7. FUTURE DIRECTIONS

PDT will undoubtedly continue to be used in the future, either alone or in combination with other therapies including chemotherapy, radiation, surgery. Other ways to enhance PDT include the creation of fresh photosensitizers and the optimization of PDT procedures like light fractionation or medication administration [41]. Well-designed clinical studies using readily available photosensitizers and other phototherapeutic agents will also increase the chance of using PDT in the treatment of cancer and other disorders [42,43].

To improve the tumour selectivity of those substances, researchers are looking into the possibility of conjugating photosensitizers to cancer-associated antibodies [44,45]. Both malignancy and angiogenesis-related ocular illnesses have been treated successfully in preclinical animals using this strategy. However, there are certain problems with using large molecules (monoclonal antibodies) in PDT. Among them are potential toxicity, difficult transportation, and complex synthesis [46–48].

8. CONCLUSION

PDT is still regarded as a novel and effective antitumor tactic. Its entire potential hasn't been realized, and its spectrum of applications—whether used independently or in conjunction with other recognized or unproven treatment modalities—is undoubtedly still untapped. PDT has a number of advantages over surgery, chemotherapy, and radiotherapy, including a lower long-term morbidity rate and the fact that it does not restrict patients' access to future therapies for recurrent or residual disease. Mutations that provide resistance to radiotherapy or chemotherapy do not impair the effectiveness of treatment for tumors since there are no inherent mechanisms for 1O2 removal and a different mechanism of cytotoxicity. Additionally, PDT can be repeated without losing its effectiveness. PDT can also be applied repeatedly without losing its effectiveness. These are major limiting elements for radiation and chemotherapy. Lastly, many traditional. Immunosuppression could result from anticancer therapies. A therapeutic approach with excellent local anticancer activity and the potential to increase the immune response for efficient metastasis destruction may develop from PDT-induced immunogenic cell death coupled with creation of a strong local inflammatory response. Specialists in physics, medicine, biology and chemistry are inspired by PDT's interdisciplinary distinctiveness, and their limitless creativity is the only thing stopping its further development and creative uses.

I. ACKNOWLEDGMENT

The authors are very much grateful to Prof. Monaj Ranjan Nayak, president, Siksha o Anusandhan for his inspiration and facilities.

REFERENCES

[1] Bergh J. Quo vadis with targeted drugs inthe 21st century?J Clin Oncol. 2009;27:2-5.

[2] Fojo T, Grady C. How much is life worth:cetuximab, non-small cell lung cancer,and the $440 billion question.J Natl Can-cer Inst. 2009;101:1044-1048.

[3] Hampton T. Targeted cancer therapies lag-ging: better trial design could boost suc-cess rate.JAMA. 2006;296:1951-1952

[4] Epstein, J. H. Phototoxicity and photoallergy. Semin. Cutan. Med. Surg. 18, 274–284 (1999).

[5] Epstein, J. H. Phototherapy and photochemotherapy. N. Engl. J. Med. 322, 1149–1151 (1990).

[6] Agostinis P, Berg K, Cengel KA, Foster TH, Girotti AW, Gollnick SO, Hahn SM, Hamblin MR, Juzeniene A, Kessel D, Korbelik M. Photodynamic therapy of cancer: an update. CA: a cancer journal for clinicians. 2011 Jul;61(4):250-81.

[7] Li X, Lovell JF, Yoon J, Chen X. Clinical development and potential of photothermal and photodynamic therapies for cancer. Nat Rev Clin Oncol. 2020;17:657–674.

[8] Lo PC, Morgade MS, Pandey RK, Ng DK, Torres T, Dumoulin F. The unique features and promises of phthalocyanines as advanced photosensitisers for photodynamic therapy of cancer. Chem Soc Rev. 2020;49:1041–1056

[9] Shafirstein G, Bellnier D, Oakley E, Hamilton S, Potasek M, Beeson K. et al. Interstitial photodynamic therapy-a focused review. Cancers. 2017;9:12.

[10] Liu J, Shi J, Nie W, Wang S, Liu G, Cai K. Recent progress in the development of multifunctional nanoplatform for precise tumor phototherapy. Adv Healthc Mater. 2020. 2001207.

[11] Lucky SS, Soo KC, Zhang Y. Nanoparticles in photodynamic therapy. Chem Rev. 2015;115:1990–2042.

[12] Yang M, Yang T, Mao C. Enhancement of photodynamic cancer therapy by physical and chemical factors. Angew Chem Int Ed. 2019;58:14066–14080.

[13] Fan W, Huang P, Chen X. Overcoming the Achilles' heel of photodynamic therapy. Chem Soc Rev. 2016;45:6488–6519.

[14] Li X, Zhang Q, Ahmad Z, Huang J, Ren Z, Weng W. et al. Near-infrared luminescent CaTiO3:Nd3+ nanofibers with tunable and trackable drug release kinetics. J Mater Chem B. 2015;3:7449–7456.

[15] Liu H, Fu Y, Li Y, Ren Z, Li X, Han G. et al. A fibrous localized drug delivery platform with NIR-triggered and optically monitored drug release. Langmuir. 2016;32:9083–9090.

[16] Zhou Z, Song J, Nie L, Chen X. Reactive oxygen species generating systems meeting challenges of photodynamic cancer therapy. Chem Soc Rev. 2016;45:6597–6626.

[17] Hu T, Wang Z, Shen W, Liang R, Yan D, Wei M. Recent advances in innovative strategies for enhanced cancer photodynamic therapy. Theranostics. 2021 Jan 15;11(7):3278-3300. doi: 10.7150/thno.54227. PMID: 33537087; PMCID: PMC7847668.

[18] Gomer, C. J. & Razum, N. J. Acute skin response in albino mice following porphyrin photosensitization under oxic and anoxic conditions. Photochem. Photobiol. 40, 435–439 (1984).

[19] Moan, J. & Berg, K. The photodegradation of porphyrins in cells can be used to estimate the lifetime of singlet oxygen. Photochem. Photobiol. 53, 549–553 (1991).

[20] Dougherty, T. et al. Photodynamic therapy. JNCI Cancer Spectrum 90, 889–905 (1998).

[21] Hasan, T., Ortel, B., Moor, A. & Pogue, B. in Holland–Frei Cancer Medicine (eds Kufe, D. et al.) Ch. 40 (BC Decker, Inc., Hamilton, Ontario, 2003).

[22] Henderson, B. W. et al. Tumor destruction and kinetics of tumor cell death in two experimental mouse tumors following photodynamic therapy. Cancer Res. 45, 572–576 (1985).

[23] Korbelik, M. & Krosl, G. Cellular levels of photosensitisers in tumours: the role of proximity to the blood supply. Br. J. Cancer 70, 604–610 (1994).

[24] Tromberg, B. J. et al. In vivo tumor oxygen tension measurements for the evaluation of the efficiency of photodynamic therapy. Photochem. Photobiol. 52, 375–385 (1990).

[25] Pogue, B. W., Braun, R. D., Lanzen, J. L., Erickson, C. & Dewhirst, M. W. Analysis of the heterogeneity of pO2 dynamics during photodynamic therapy with verteporfin. Photochem. Photobiol. 74, 700–706 (2001).

[26] Pogue, B. W. et al. Photodynamic therapy with verteporfin in the radiation-induced fibrosarcoma-1 tumor causes enhanced radiation sensitivity. Cancer Res. 63, 1025–1033 (2003).

[27] Messmann, H. et al. Enhancement of photodynamic therapy with 5-aminolaevulinic acid-induced porphyrin photosensitisation in normal rat colon by threshold and light fractionation studies. Br. J. Cancer 72, 589–594 (1995).

[28] Pogue, B. W. & Hasan, T. A theoretical study of light fractionation and dose-rate effects in photodynamic therapy. Radiat. Res. 147, 551–559 (1997).

[29] Iinuma, S. et al. In vivo fluence rate and fractionation effects on tumor response and photobleaching: photodynamic therapy with two photosensitizers in an orthotopic rat tumor model. Cancer Res. 59, 6164–6170 (1999).

[30] Carmeliet, P. & Jain, R. K. Angiogenesis in cancer and other diseases: from genes to function to therapy. Nature 407, 249–257 (2000).

[31] Jain, R. K. & Carmeliet, P. F. Vessels of death or life. Sci. Am. 285, 38–45 (2001).

[32] Fingar VH. Vascular effects of photodynamic therapy. J Clin Laser Med Surg. 1996 Oct;14(5):323-8. doi: 10.1089/clm.1996.14.323. PMID: 9612199.

[33] Reed, M.W.R., Schushke, D.A., and Miller, F.N. (1991). Prostanoid antagonists inhibit the response of the microcirculation to "early" photodynamic therapy. Radiât. Res. 127, 292-296.

[34] Fingar, V.H., Wieman, T.J., and Doak, K.W. (1991). Changes in tumor interstitial pressure induced by photodynamic therapy. Photochem. Photobiol. 53(6), 763-768.

[35] Lim, H.W., Parker, D., and Marcus, A.J. (1986). Generation ofeicosanoids from mast cells exposed to protoporphyrin and irradiation. Clin. Res. 34, 763.

[36] Wang C, Xu L, Liang C, Xiang J, Peng R, Liu Z (2014). "Immunological responses triggered by photothermal therapy with carbon nanotubes in combination with anti-CTLA-4 therapy to inhibit cancer metastasis". Adv Mater. 26 (48): 8154–62. doi:10.1002/adma.201402996. PMID 25331930

[37] Lin, Z.; et al. (2015). "Photothermal ablation of bone metastasis of breast cancer using PEGylated multi-walled carbon nanotubes". Sci Rep. 5: 11709. Bibcode:2015NatSR...511709L. doi:10.1038/srep11709. PMC 4485034. PMID 26122018.

[38] Chen, Q.; et al. (2016). "Photothermal therapy with immune-adjuvant nanoparticles together with checkpoint blockade for effective cancer immunotherapy". Nat Commun. 7: 13193. Bibcode:2016NatCo...713193C. doi:10.1038/ncomms13193. PMC 5078754. PMID 27767031.

[39] Korbelik, M. & Dougherty, G. J. Photodynamic therapy-mediated immune response against subcutaneous mouse tumors. Cancer Res. 59, 1941–1946 (1999).

[40] Gollnick, S. O., Vaughan, L. & Henderson, B. W. Generation of effective antitumor vaccines using photodynamic therapy. Cancer Res. 62, 1604–1608 (2002).

[41] Ferrario, A. et al. Antiangiogenic treatment enhances photodynamic therapy responsiveness in a mouse mammary carcinoma. Cancer Res. 60, 4066–4069 (2000).

[42] de Bruijn, H. S., van der Veen, N., Robinson, D. J. & Star, W. M. Improvement of systemic 5-aminolevulinic acid-based photodynamic therapy in vivo using light fractionation with a 75-minute interval. Cancer Res. 59, 901–904 (1999).

[43] Dolmans, D. E. et al. Targeting tumor vasculature and cancer cells in orthotopic breast tumor by fractionated photosensitizer dosing photodynamic therapy. Cancer Res. 62, 4289–4294 (2002).

[44] Hamblin, M. R., Miller, J. L. & Hasan, T. Effect of charge on the interaction of site-specific photoimmunoconjugates with human ovarian cancer cells. Cancer Res. 56, 5205–5210 (1996).

[45] Birchler, M., Viti, F., Zardi, L., Spiess, B. & Neri, D. Selective targeting and photocoagulation of ocular angiogenesis mediated by a phage-derived human antibody fragment. Nature Biotechnol. 17, 984–988 (1999).

[46] Jain, R. K. Delivery of molecular and cellular medicine to solid tumors. Adv. Drug Deliv. Rev. 46, 149–168 (2001).

[47] Jain, R. K. The next frontier of molecular medicine: delivery of therapeutics. Nature Med. 4, 655–657 (1998).

[48] Friedrich, S. W. et al. Antibody-directed effector cell therapy of tumors: analysis and optimization using a physiologically based pharmacokinetic model. Neoplasia 4, 449–463 (2002).

[49] Breskey JD, Lacey SE, Vesper BJ, Paradise WA, Radosevich JA, Colvard MD. Photodynamic therapy: occupational hazards and preventative recommendations for clinical administration by healthcare providers. Photomedicine and Laser Surgery. 2013 Aug 1;31(8):398-407.

[50] Fritsch C, Goerz G, Ruzicka T. Photodynamic therapy in dermatology. Archives of Dermatology. 1998 Feb 1;134(2):207-14.

[51] Calzavara-Pinton PG, Szeimeis RM, Ortel B, Zane C. Photodynamic therapy with systemic administration of photosensitizers in dermatology. Journal of Photochemistry and Photobiology B: Biology. 1996 Nov 1;36(2):225-31.

[52] Loh CS, MacRobert AJ, Bedwell J, Regula J, Krasner N, Bown SG. Oral versus intravenous administration of 5-aminolaevulinic acid for photodynamic therapy. British journal of cancer. 1993 Jul;68(1):41-51.

[53] S.S. Lucky, K.C. Soo, Y. Zhang, Nanoparticles in Photodynamic Therapy, Chem. Rev.115 (2015) 1990–2042. https://doi.org/10.1021/cr5004198.

[54] T.J. Dougherty, C.J. Gomer, B.W. Henderson, G. Jori, D. Kessel, M. Korbelik, J. Moan, Q. Peng, Photodynamic Therapy, J. Natl. Cancer Inst. 90 (1998) 889–905. https://doi.org/10.1093/jnci/90.12.889.

[55] M. Lan, S. Zhao, W. Liu, C. Lee, W. Zhang, P. Wang, Photosensitizers for Photodynamic Therapy, Adv. Healthc. Mater. 8 (2019) 1900132. https://doi.org/10.1002/adhm.201900132.

[56] J. V Frangioni, In vivo near-infrared fluorescence imaging, Curr. Opin. Chem. Biol. 7 (2003) 626–634. https://doi.org/10.1016/J.CBPA.2003.08.007.

[57] Z. Zhou, J. Song, L. Nie, X. Chen, Reactive oxygen species generating systems meeting challenges of photodynamic cancer therapy, Chem. Soc. Rev. 45 (2016) 6597–6626. https://doi.org/10.1039/C6CS00271D.

[58] C. Wang, L. Cheng, Z. Liu, Upconversion Nanoparticles for Photodynamic Therapy and Other Cancer Therapeutics, Theranostics. 3 (2013) 317–330. https://doi.org/10.7150/thno.528

[59] B.W. Pogue, T. Hasan, A Theoretical Study of Light Fractionation and Dose-Rate Effects in Photodynamic Therapy, Radiat. Res. 147 (1997) 551–559. https://doi.org/10.2307/3579621.

[60] M. Ascencio, J.P. Estevez, M. Delemer, M.O. Farine, P. Collinet, S. Mordon, Comparison of continuous and fractionated illumination during hexaminolaevulinate-photodynamic therapy, Photodiagnosis Photodyn. Ther. 5 (2008) 210–216. https://doi.org/10.1016/J.PDPDT.2008.09.004.

[61] B.W. Henderson, T.M. Busch, L.A. Vaughan, N.P. Frawley, D. Babich, T.A. Sosa, J.D. Zollo, A.S. Dee, M.T. Cooper, D.A. Bellnier, W.R. Greco, A.R. Oseroff, Photofrin photodynamic therapy can significantly deplete or preserve oxygenation in human basal cell carcinomas during treatment, depending on fluence rate., Cancer Res. 60 (2000) 525–529. http://www.ncbi.nlm.nih.gov/pubmed/10676629.

[62] J.C. Finlay, D.L. Conover, E.L. Hull, T.H. Foster, Porphyrin Bleaching and PDT-induced Spectral Changes are Irradiance Dependent in ALA-sensitized Normal Rat Skin In Vivo, Photochem. Photobiol. 73 (2007) 54–63. Journal Pre-proof https://doi.org/10.1562/0031-8655(2001)0730054PBAPIS2.0.CO2.

[63] T.A. Middelburg, F. Van Zaane, H.S. De Bruijn, A. Van Der Ploeg-van den Heuvel, H.J.C.M. Sterenborg, H.A.M. Neumann, E.R.M. De Haas, D.J. Robinson, Fractionated Illumination at Low Fluence Rate Photodynamic Therapy in Mice, Photochem. Photobiol. 86 (2010) 1140–1146. https://doi.org/10.1111/j.1751-1097.2010.00760.x.

[64] Q. Chen, Z. Huang, H. Chen, H. Shapiro, J. Beckers, F.W. Hetzel, Improvement of Tumor Response by Manipulation of Tumor Oxygenation During Photodynamic Therapy, Photochem. Photobiol. 76 (2007) 197–203. https://doi.org/10.1562/0031-8655(2002)0760197IOTRBM2.0.CO2.

[65] R. Vankayala, Y.-K. Huang, P. Kalluru, C.-S. Chiang, K.C. Hwang, First Demonstration of Gold Nanorods-Mediated Photodynamic Therapeutic Destruction of Tumors via Near Infra-Red Light Activation, Small. 10 (2014) 1612–1622. https://doi.org/10.1002/smll.201302719.

[66] P. Vijayaraghavan, C.-H. Liu, R. Vankayala, C.-S. Chiang, K.C. Hwang, Designing Multi-Branched Gold Nanoechinus for NIR Light Activated Dual Modal Photodynamic and Photothermal Therapy in the Second Biological Window, Adv. Mater. 26 (2014) 6689–6695. https://doi.org/10.1002/adma.201400703.

[67] R. Vankayala, C.-L. Kuo, A. Sagadevan, P.-H. Chen, C.-S. Chiang, K.C. Hwang, Morphology dependent photosensitization and formation of singlet oxygen (1Δg) by gold and silver nanoparticles and its application in cancer treatment, J. Mater. Chem. B. 1 (2013) 4379. https://doi.org/10.1039/c3tb20806k

[68] T.Y. Ohulchanskyy, I. Roy, L.N. Goswami, Y. Chen, E.J. Bergey, R.K. Pandey, A.R. Oseroff, P.N. Prasad, Organically Modified Silica Nanoparticles with Covalently Incorporated Photosensitizer for Photodynamic Therapy of Cancer, Nano Lett. 7 (2007) 2835–2842. https://doi.org/10.1021/NL0714637.

[69] J. Tu, T. Wang, W. Shi, G. Wu, X. Tian, Y. Wang, D. Ge, L. Ren, Multifunctional ZnPc-loaded mesoporous silica nanoparticles for enhancement of photodynamic therapy efficacy by endolysosomal escape, Biomaterials. 33 (2012) 7903–7914. https://doi.org/10.1016/J.BIOMATERIALS.2012.07.025.

[70] S. Bharathiraja, M.S. Moorthy, P. Manivasagan, H. Seo, K.D. Lee, J. Oh, Chlorin e6 conjugated silica nanoparticles for targeted and effective photodynamic therapy, Journal Pre-proof Photodiagnosis Photodyn. Ther. 19 (2017) 212–220. https://doi.org/10.1016/j.pdpdt.2017.06.001.

[71] A. Chaix, K. Rajoua, V. Stojanovic, K. El Cheikh, E. Bouffard, A. Brocéro, M. Garcia, M. Maynadier, A. Morère, M. Gary-Bobo, F. Favier, J.-O. Durand, F. Cunin, Two-Photon Fluorescence Imaging and Therapy of Cancer Cells with Anisotropic Gold-Nanoparticle-Supported Porous Silicon Nanostructures, ChemNanoMat. 4 (2018) 343–347. https://doi.org/10.1002/cnma.201700368

[72] L. Shi, B. Hernandez, M. Selke, Singlet Oxygen Generation from Water-Soluble Quantum Dot-Organic Dye Nanocomposites, J. Am. Chem. Soc. 128 (2006) 6278– 6279. https://doi.org/10.1021/JA057959C

[73] Li WP, Yen CJ, Wu BS, Wong TW. Recent Advances in Photodynamic Therapy for Deep-Seated Tumors with the Aid of Nanomedicine. Biomedicines. 2021 Jan 12;9(1):69. doi: 10.3390/biomedicines9010069. PMID: 33445690; PMCID: PMC7828119.

[74] Lucky SS, Soo KC, Zhang Y. Nanoparticles in photodynamic therapy. Chem Rev. 2015;115(4):1990-2042

[75] de Freitas, L. F. . Nanomaterials for Enhanced Photodynamic Therapy. In: Inada, N. M. , Buzzá, H. H. , Blanco, K. C. , Dias, L. D. , editors. Photodynamic Therapy - From Basic Science to Clinical Research [Internet]. London: IntechOpen; 2020 [cited 2022 Nov 29]. Available from: https://www.intechopen.com/chapters/73761 doi: 10.5772/intechopen.94255

[76] Bechet D, Couleaud P, Frochot C, Viriot ML, Guillemin F, Barberi-Heyob M. Nanoparticles as vehicles for delivery of photodynamic therapy agents. Trends Biotechnol. 2008;26(11): 612-21

[77] Krajczewski J, Rucińska K, Townley HE, Kudelski A. Role of various nanoparticles in photodynamic therapy and detection methods of singlet oxygen. Photodiagnosis Photodyn Ther [Internet]. 2019;26(December 2018):162-78. Available from: https://doi.org/10.1016/j.pdpdt.2019.03.016

[78] Freitas LF, Hamblin MR, Anzengruber F, Perussi JR, Ribeiro AO, Martins VCA, et al. Zinc phthalocyanines attached to gold nanorods for simultaneous hyperthermic and photodynamic therapies against melanoma in vitro. J Photochem Photobiol B Biol [Internet]. 2017 Aug;173:181-6. Available from: https://linkinghub.elsevier.com/retrieve/pii/S101113441730283X

[79] Camerin M, Magaraggia M, Soncin M, Jori G, Moreno M, Chambrier I, et al. The in vivo efficacy of phthalocyanine-nanoparticle conjugates for the photodynamic therapy of amelanotic melanoma. Eur J Cancer [Internet]. 2010;46(10):1910-8. Available from: http://dx.doi.org/10.1016/j.ejca.2010.02.037

[80] Cline B, Delahunty I, Xie J. Nanoparticles to mediate X-ray-induced photodynamic therapy and Cherenkov radiation photodynamic therapy. Wiley Interdiscip Rev Nanomedicine Nanobiotechnology. 2019;11(2):1-18

[81] Lismont M, Dreesen L, Wuttke S. Metal-Organic Framework Nanoparticles in Photodynamic Therapy: Current Status and Perspectives. Adv Funct Mater. 2017;27(14):1-16

[82] Sivasubramanian M, Chuang YC, Lo LW. Evolution of nanoparticle-mediated photodynamic therapy: From superficial to deep-seated cancers. Molecules. 2019;24(3)

[83] Kamkaew A, Cheng L, Goel S, Valdovinos HF, Barnhart TE, Liu Z, et al. Cerenkov Radiation Induced Photodynamic Therapy Using Chlorin e6-Loaded Hollow Mesoporous Silica Nanoparticles. ACS Appl Mater Interfaces [Internet]. 2016 Oct 12;8(40):26630-7. Available from: https://pubs.acs.org/doi/10.1021/acsami.6b10255

[84] Glaser AK, Zhang R, Andreozzi JM, Gladstone DJ, Pogue BW. Cherenkov radiation fluence estimates in tissue for molecular imaging and therapy applications. Phys Med Biol [Internet]. 2015 Sep 7;60(17):6701-18. Available from: https://iopscience.iop.org/article/10.1088/0031-9155/60/17/6701

[85] Dai X, Du T, Han K. Engineering Nanoparticles for Optimized Photodynamic Therapy. ACS Biomater Sci Eng. 2019;5(12):6342-54

[86] Cheng Y, Cheng H, Jiang C, Qiu X, Wang K, Huan W, et al. Perfluorocarbon nanoparticles enhance reactive oxygen levels and tumour growth inhibition in photodynamic therapy. Nat Commun. 2015;6:6-13

[87] Kim J, Cho HR, Jeon H, Kim D, Song C, Lee N, et al. Continuous O2-Evolving MnFe2O4 Nanoparticle-Anchored Mesoporous Silica Nanoparticles for Efficient Photodynamic Therapy in Hypoxic Cancer. J Am Chem Soc. 2017;139(32):10992-5

[88] Jia T, Xu J, Dong S, He F, Zhong C, Yang G, et al. Mesoporous cerium oxide-coated upconversion nanoparticles for tumor-responsive chemo-photodynamic therapy and bioimaging. Chem Sci. 2019;10(37):8618-33

[89] Dai X, Du T, Han K. Engineering Nanoparticles for Optimized Photodynamic Therapy. ACS Biomater Sci Eng. 2019;5(12):6342-54

[90] He Z, Dai Y, Li X, Guo D, Liu Y, Huang X, et al. Hybrid Nanomedicine Fabricated from Photosensitizer-Terminated Metal–Organic Framework Nanoparticles for Photodynamic Therapy and Hypoxia-Activated Cascade Chemotherapy. Small. 2019;15(4):1-11

[91] Stuchinskaya T, Moreno M, Cook MJ, Edwards DR, Russell DA. Targeted photodynamic therapy of breast cancer cells using antibody-phthalocyanine-gold nanoparticle conjugates. Photochem Photobiol Sci. 2011;10(5):822-31

[92] Liu S, Li W, Dong S, Gai S, Dong Y, Yang D, et al. Degradable Calcium Phosphate-Coated Upconversion Nanoparticles for Highly Efficient Chemo-Photodynamic Therapy. ACS Appl Mater Interfaces. 2019;11(51):47659-70

[93] Li F, Du Y, Liu J, Sun H, Wang J, Li R, et al. Responsive Assembly of Upconversion Nanoparticles for pH-Activated and Near-Infrared-Triggered Photodynamic Therapy of Deep Tumors. Adv Mater. 2018;30(35):1-7

[94] Zhang Y, Vecchio D. Potentiation of antimicrobial photodynamic inactivation mediated by a cationic fullerene by added iodide: in vitro and in vivo studies. Nanomedicine. 2015;10:603-14

[95] He Z, Dai Y, Li X, Guo D, Liu Y, Huang X, et al. Hybrid Nanomedicine Fabricated from Photosensitizer-Terminated Metal–Organic Framework Nanoparticles for Photodynamic Therapy and Hypoxia-Activated Cascade Chemotherapy. Small. 2019;15(4):1-11

[96] Jeong H, Huh M, Lee SJ, Koo H, Kwon IC, Jeong SY, et al. Photosensitizer-Conjugated Human Serum Albumin Nanoparticles for Effective Photodynamic Therapy. Theranostics. 2012;1:230-9

[97] Jia T, Xu J, Dong S, He F, Zhong C, Yang G, et al. Mesoporous cerium oxide-coated upconversion nanoparticles for tumor-responsive chemo-photodynamic therapy and bioimaging. Chem Sci. 2019;10(37):8618-33

[98] Dong Z, Feng L, Hao Y, Chen M, Gao M, Chao Y, et al. Synthesis of Hollow Biomineralized CaCO3-Polydopamine Nanoparticles for Multimodal Imaging-Guided Cancer Photodynamic Therapy with Reduced Skin Photosensitivity. J Am Chem Soc. 2018;140(6):2165-78

[99] Zhu Y., Shi H., Li T., Yu J., Guo Z., Cheng J., Liu Y. A dual functional nanoreactor for synergistic starvation and photodynamic therapy. ACS Appl. Mater. Interfaces. 2020;12:18309–18318. doi: 10.1021/acsami.0c01039.

[100] De Rosa FS, Bentley MV. Photodynamic therapy of skin cancers: sensitizers, clinical studies and future directives. Pharm Res. 2000;17:1447–1455

[101] Hamblin MR, Newman EL. On the mechanism of the tumour-localising effect in photodynamic therapy. J Photochem Photobiol B. 1994;23:3–8

[102] Iyer AK, Greish K, Seki T, et al. Polymeric micelles of zinc protoporphyrin for tumor targeted delivery based on EPR effect and singlet oxygen generation. J Drug Target. 2007;15:496–506

[103] Kessel D. The role of low-density lipoprotein in the biodistribution of photosensitizing agents. J Photochem Photobiol B. 1992;14:261–262.

[104] Agostinis P, Berg K, Cengel KA, Foster TH, Girotti AW, Gollnick SO, Hahn SM, Hamblin MR, Juzeniene A, Kessel D, Korbelik M, Moan J, Mroz P, Nowis D, Piette J, Wilson BC, Golab J. Photodynamic therapy of cancer: an update. CA Cancer J Clin. 2011 Jul-Aug;61(4):250-81. doi: 10.3322/caac.20114. Epub 2011 May 26. PMID: 21617154; PMCID: PMC3209659.

[105] Tian G, Zhang X, Gu Z, Zhao Y. Recent advances in upconversion nanoparticles-based multifunctional nanocomposites for combined cancer therapy. Adv Mater 2015;27:7692-712.

[106] Chou TC. Drug combination studies and their synergy quantification using the chou-talalay method. Cancer Res 2010;70:440-6.