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Pratikeswar Panda
Department of Pharmaceutics, Siksha 'O' Anusandhan University, Bhubaneswar, Odisha, India

Corresponding Author:
Pratikeswar Panda
Department of Pharmaceutics, Siksha 'O' Anusandhan University, Bhubaneswar, Odisha, India

Recent therapeutic status of photodynamic therapy for the treatment and diagnosis of cancer

Pratikeswar Panda

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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

1. 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 tumour 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 recognised. 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 localises 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]. 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 [5].
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 tumours, PDT that responds to the tumour microenvironment (TME), different PS types and how to activate them, and the nanomaterials that are employed in PDT [6]. 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 [7].

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 [8]. Additionally, the O_2 content in tumours 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 optimise workable PSs systems in order to get over the aforementioned constraints [9].

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, oesophagus, 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 [10].

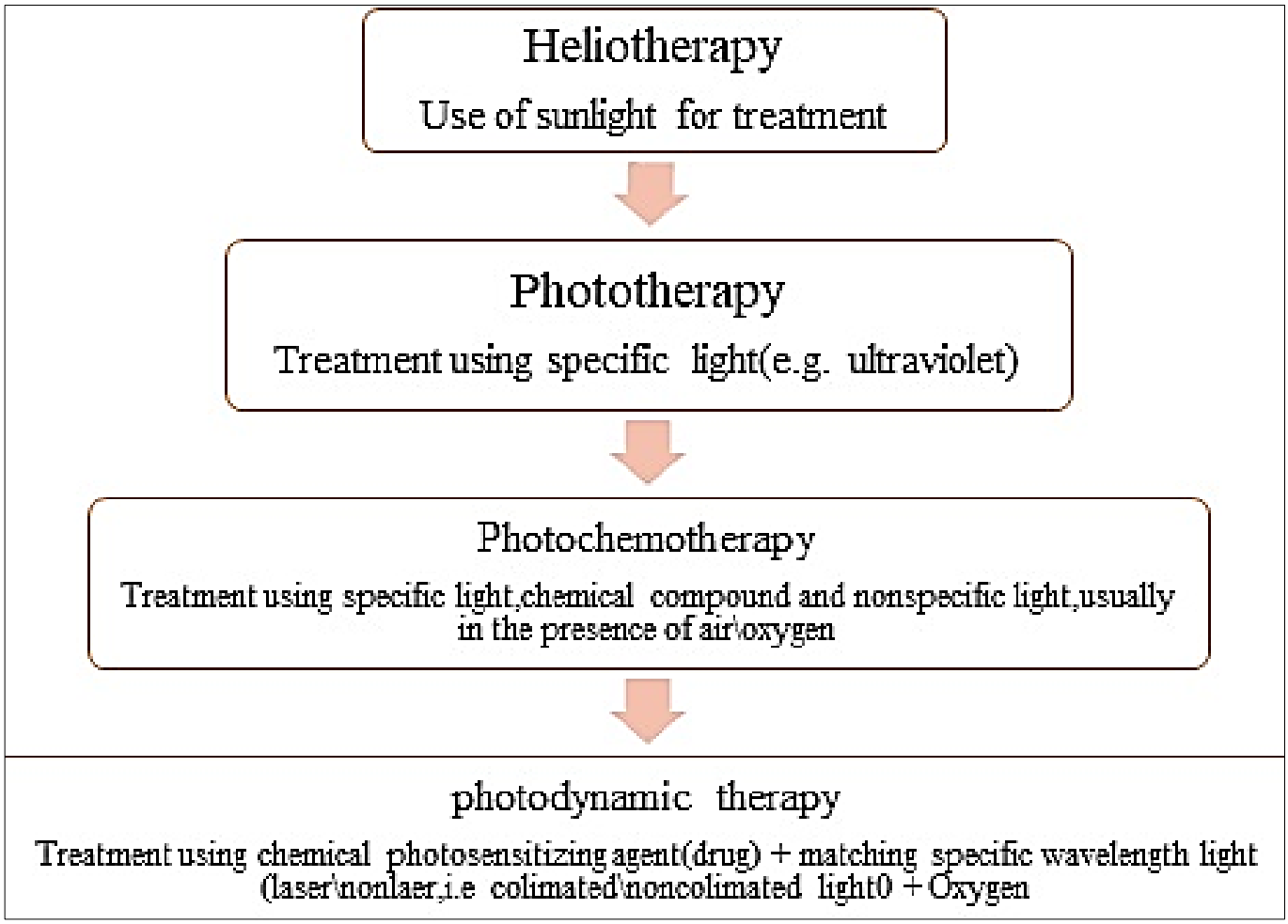

Fig 1: Evolution of photodynamic therapy

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 bio distribution 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 [11]. 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 photo damage and cytotoxicity occurs that shown in fig-2 and 3 [12].

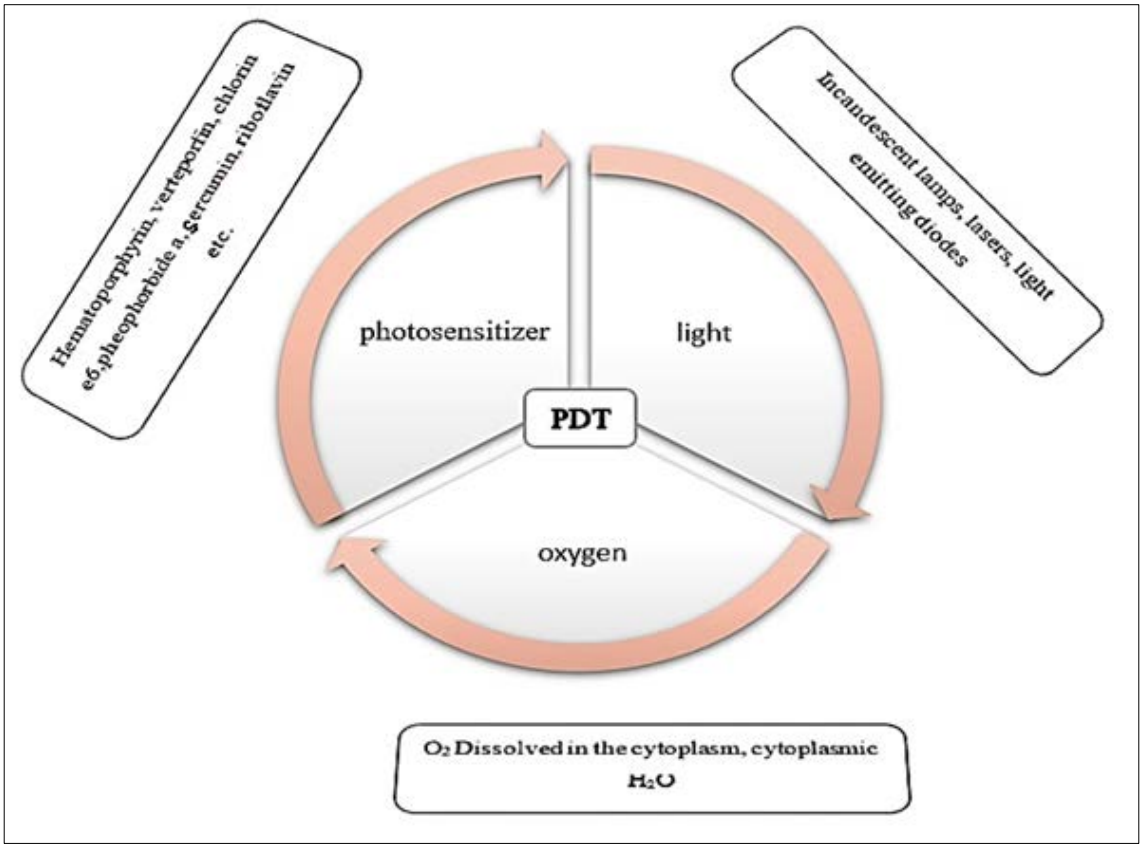

Fig 2: Main component of photochemical reaction during photodynamic therapy

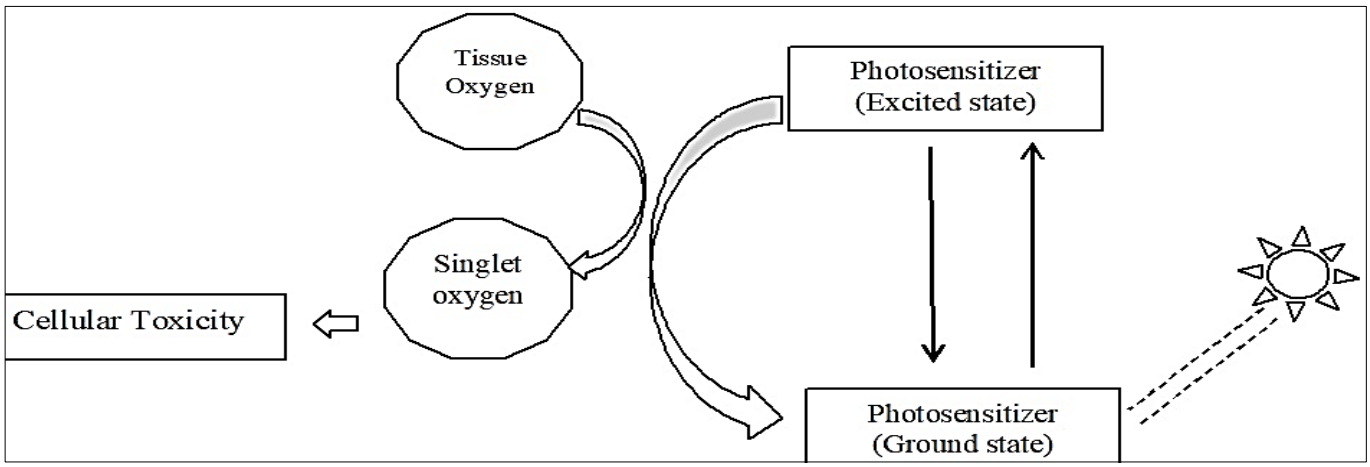

Fig 3: Mechanism of action photodynamic therapy

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 tumour 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 tumour [13].

Depending on where the tumour is, different lighting techniques are used. The light is directly directed at the cancer in skin tumours. To check for tumours 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 & fig-5 [14].

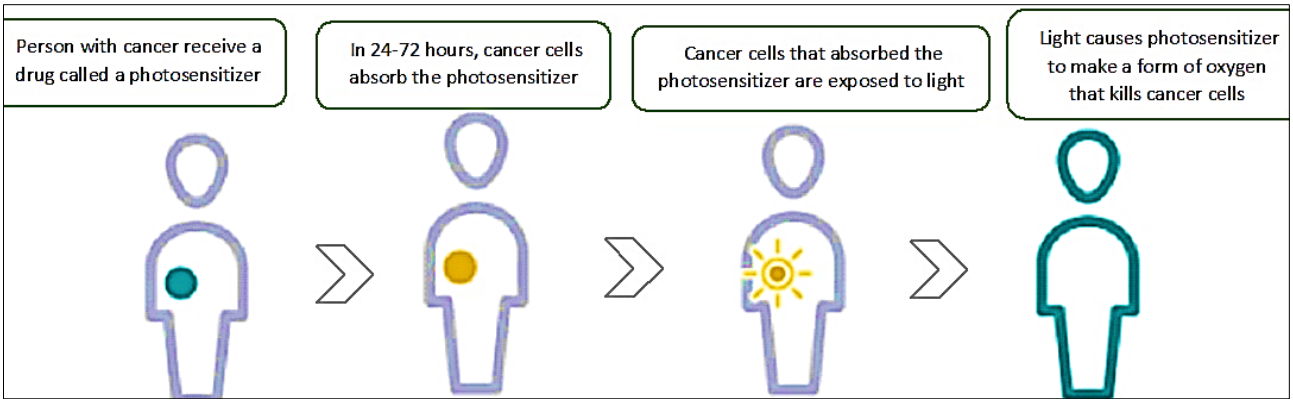

Fig 4: Delivery Photodynamic therapy

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 [15].

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 utilise photodynamic therapy alone or in conjunction with other cancer therapies [16, 17].

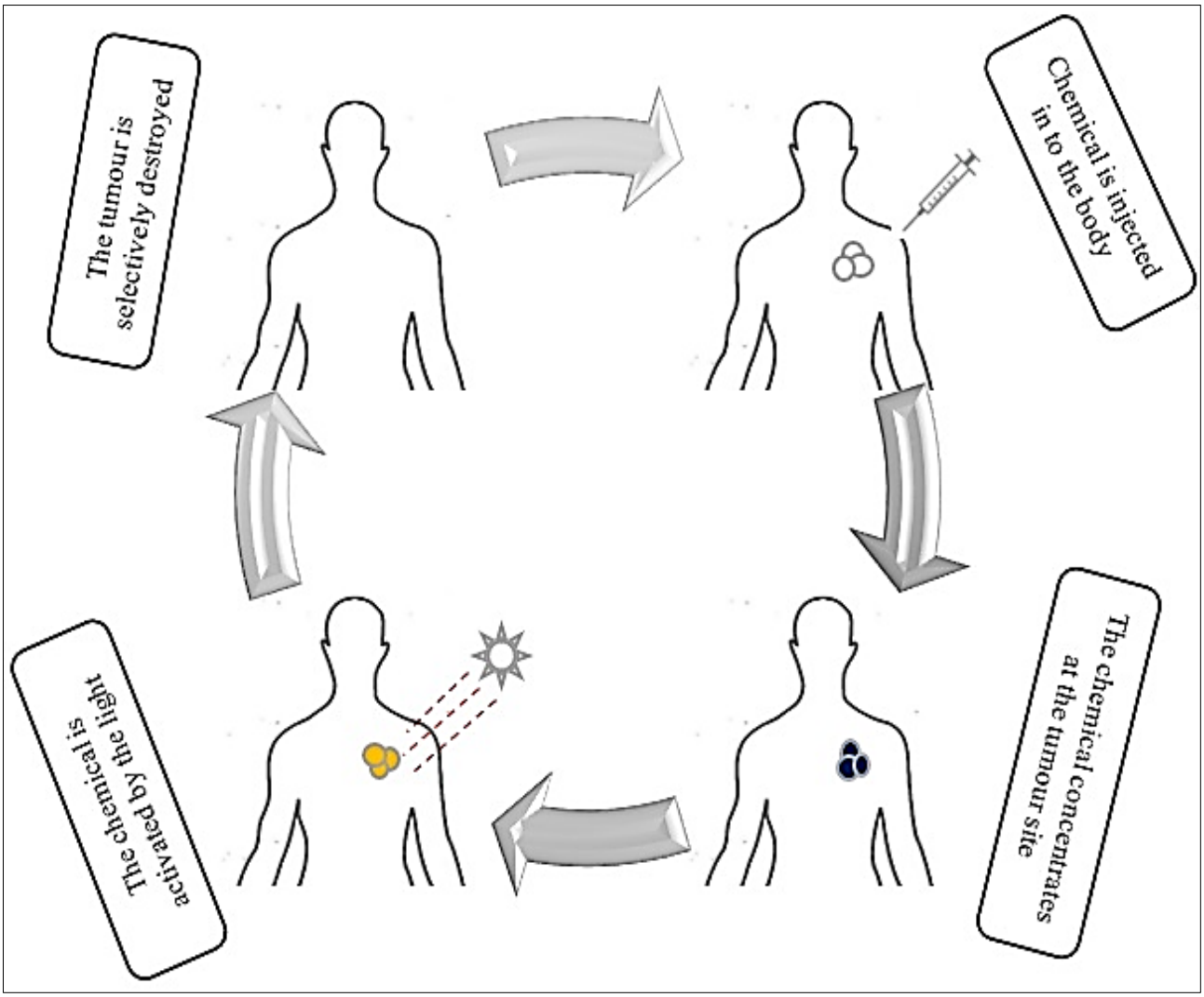

Fig 5: Action of photodynamic therapy in body

3. Effects of PDT on tumors

There are now three main routes by which PDT induces tumour removal. In the first case, cancer cells can be immediately killed by ROS produced by PDT. PDT also affects the blood vessels around the tumour, which causes an infarction of the tumour. Not the least of which is that PDT can trigger an immune reaction against tumour cells. These three mechanisms might interact with one another. It is yet unclear how significant each one is in relation to the total tumour response. But it is evident that for long-term

tumour care, a combination of all of these elements is necessary, there have some different PDT based mediated that effect on tumour describe in table-1 [18, 19].

3.1 Direct tumour-cell killing

It has been shown that direct photodamage brought on by *in vivo* PDT treatment of tumours can reduce the number of clonogenic tumour cells [20-22]. One hypothesis is that the photosensitizer is distributed unevenly throughout the tumour. Furthermore, Mladen Korbelik and associates demonstrated in 1995 that tumour cells are cut off from the vascular supply, which reduces the quantity of photosensitizer accumulated and causes tumour-cell death [23].

The quantity of oxygen in the tissue that PDT is aiming for is another factor that might restrict direct tumour-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]. 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 tumour 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. The fluence rate modifies the signal to a different extent depending on where the photosensitizer is located [25].

3.2 Vascular damage

The amount of nutrients transported by the blood arteries also impact on how healthy tumour cells are. Growth components supplied by the tumour or host cell are therefore necessary for the formation and maintenance of blood vessels. Thus, a possible cancer treatment strategy involves focusing on the tumour vasculature. A negative effect of photodynamic therapy (PDT), which uses a variety of photosensitizers to treat solid tumours, is vascular damage and blood flow stagnation. Hypoxia brought on by microvascular stasis is a powerful tool for cytotoxicity and tumour regression [26].

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. 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, tumour shrinking requires sustained levels of tissue hypoxia for a number of photosensitizers utilised in PDT [27].

3.3 Immune response

Photoimmunotherapy is an oncological treatment for several tumours that combines immunotherapy with photodynamic tumour therapy. Immunotherapy and photodynamic therapy work in concert to boost the immune system's response and treat metastatic cancer. Another fascinating finding was achieved by Barbara Henderson and colleagues, who demonstrated the development of tumour-specific immunity by employing a tumour-cell lysate collected after PDT using Photofrin to immunise mice against the development of new cancers. Lysates produced from tumours treated to UV or ionising radiation have been proven to be less successful at inducing an immune response than this immunisation 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 tumour-cell lysates. To find out if patients using PDT can get comparable results, more research is necessary [28].

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 ▪ Vesel 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 Tumour targeting efficiency

Most conventional organic PSs' clinical application has been severely constrained by the poor tumour targeting efficacy associated with most of them. On the one hand, it is believed that the aberrant physiological traits of tumours are what lead to the higher number of various PSs in tumour 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 tumours. In this regard, enhancing the PSs' tumour 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 tumours. Excellent opportunities for surface functionalization will be presented by the use of nanomaterials in PDT, which can improve the effectiveness

of tumour targeting. Some clinically approved examples of photosensitizers that describe in table-2 [29].

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. 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 [30].

4.3 Tumour 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 tumours, where oxygen is predominantly utilised by rapidly expanding tumour cells [31].

Additionally, PDT is an oxygen-intensive technique that would exacerbate tumour hypoxia and reduce PDT effectiveness. Nanoplatforms made of PS and nanomaterials, like the MnO_2 nanosheets mentioned above, that can catalyse the breakdown of H_2O_2 to produce O_2, were created to address tumour hypoxia. Additionally, some methods, such light fractionation for controlled "on" and "off" periods of light exposure, can aid in the reperfusion of O_2. These techniques, however, are ineffective when tumour hypoxia is brought on by the tumour cells' fast cellular expansion. As an alternative, PSs that are oxygen independent, including as TiO_2 and g-C_3N_4, PSs that can induce the O_2-independent type I response, and combination therapies with O_2-independent techniques (such chemotherapy and PTT), can all be utilised to treat tumour hypoxia [32].

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. Great tumour targeting ability PSs are still in high demand, as are PSs with high ROS production efficiency, good stability, and strong biocompatibility under physiological settings. 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 maximise the potential of nanomaterials in PDT by creating more effective and reliable nanomaterials [33].

Table 2: Clinically approved photosensitizers

Photosensitizer	cancer types
Photofrin (HPD)	Lung, esophagus, bladder, bile duct, ovarian, brain
ALA	Skin, esophagus,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, esophagus, 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. 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 tumour accumulation [34]. The favoured accumulation of nanoscale materials in tumour 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. Now-a-days some of drug that induces photosensitivity that shown in the table 3 [35].

Table 3: List of Drugs that Induces Photosensitivity

Drug classifications	Drugs
Antifungal agent	Griseofulvin, itraconazole, flucytosine
Antibacterial agen	Nalidixic acid, ofloxacin, enoxacin, ciprofloxacin, parfloxacin, lomefloxacin, sfleroxacin, 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. 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 [36].

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-6. Combinational techniques with PDT that include chemotherapy, PTT, immunotherapy, radiotherapy, and gene therapy may improve PDT outcomes at low therapeutic doses while minimising adverse effects on healthy tissues. Additionally, the use of combinational techniques may help monotherapy overcome difficult issues such resistance development and tumour spread. Here, the types of PDT associated with chemotherapy, PTT coupled with immunotherapy, and rationally created PNMs are given [37].

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 [38]. One of the main problems is the required radiation dosage for the patients during X-PDT.

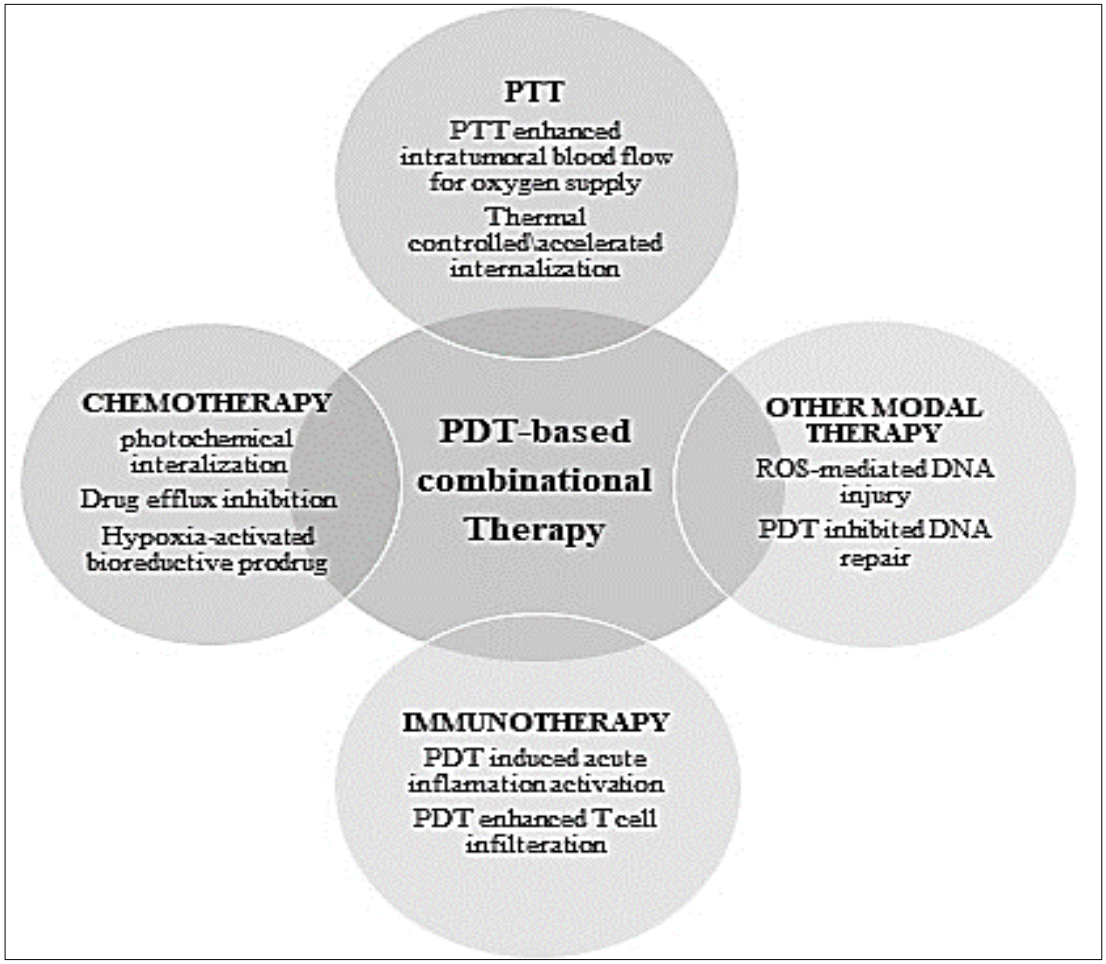

Fig 6: Different type of PDT-based combinational Therapy

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 unfavourable hypoxia that decreases photodynamic therapy effectiveness [39].

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 [40].

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 tumours [41].

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 [42].

6. Strategies Regarding PDT

PDT's ability to treat cancers effectively is constrained by the oxygen supply to the tumours, which is often diminished by poor microcirculation, particularly in the tumour centre. Because PDT uses oxygen, it causes the local hypoxia and prevents the procedure from working to its full capacity. In order to increase the tumour ablation, some methods to boost the oxygen availability to the malignancies during PDT have been proposed [43].

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 tumours were significantly ablated, but with intratumor delivery, they were completely destroyed [44].

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 O_2 via the Fenton reaction inside cancer tissues due to the excess H_2O_2 derived from the tumour 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 [45].

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 tumour ablation, and they can also be used as a pharmaceutical carrier for a combined therapy [46].

The calcium phosphate-encapsulated core-shell produced nanoparticles (UCNPs-Ce6 @ SiO_2 @ 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 [47].

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 tumours. 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 [48].

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 fibres, and this sphere-to-fibre transition promotes tumour persistence of the nanoparticles [49].

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 tumour tissues [50].

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 tumour delivery relative to free photosensitizers and improved imaging properties due to chlorin e6 fluorescence [51].

The research by Xu *et al*. on mesoporous cerium oxide-coated photothermal conversion nanomaterials for tumour-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 tumours *in vivo* after intravenous injection. The treatment may also affect tumours in other areas due to the potent cancer vaccine effect that the immune response elicited [52].

Dong *et al*. created hollow, porous $CaCO_3$-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 tumours. 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 emphasise that chlorin e6 is supplied in a liposomal formulation, unlike the $CaCO_3$-PDA-PEG formulation, which does not induce a significant weight loss in the mice, perhaps due to an intrinsic toxicity [53].

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 [54].

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 realised, and its spectrum of applications-whether used independently or in conjunction with other recognised 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 tumours since there are no inherent mechanisms for $^1O_2$ 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.

9. Conflict of interest

The author declares no conflict of interest.

10. Acknowledgements

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