Porphyrins in Photodynamic Therapy: A Review

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Abstract: Porphyrins have emerged as versatile and highly effective photosensitizers in the field of photodynamic therapy (PDT). This promising therapeutic approach relies on the light-induced generation of reactive oxygen species (ROS) by photosensitizing agents. This comprehensive review explores the multifaceted role of porphyrins across various PDT applications, encompassing anticancer PDT, immuno-PDT, antimicrobial PDT, and antiviral PDT. Porphyrins exhibit the potential to serve as organic supramolecular platforms for developing various photosensitizers (PSs) tailored for specific PDT modalities. The exceptional capacity of porphyrins to specifically accumulate in target cancer cells or microorganisms, their proficiency in generating ROS upon exposure to light, and their capability to amass within cell mitochondria to facilitate apoptosis establish porphyrins as invaluable assets in a wide array of therapeutic applications. Ongoing research endeavours and clinical investigations continually unveil the vast potential of porphyrin-based PDT in combatting a wide range of diseases, spanning from cancer and infections to viral ailments. Furthermore, porphyrins hold promise in addressing drug-resistant cancers and antimicrobial resistance through non-invasive PDT, offering efficient alternatives to commercially available PDT drugs. In the context of advanced cancer management, porphyrin-based PDT offers the prospect of combinatorial therapy, enabling a sequence of immunogenic post-PDT actions that can effectively overcome anticancer resistance and tackle metastatic cancers. The future of PDT appears promising, with porphyrin scaffolds expected to play pivotal roles in advancing this field.

INTRODUCTION: Heliotherapy or phototherapy as a therapeutic model traces its origin back to ancient Indian, Chinese, Greek, and Egyptian civilisations.[1-2] The earliest example of the treatment of vitiligo in India through the use of photochemotherapy involved the ingestion of leaves of *Psoralea corylifolia* by the patients followed by exposure to solar radiation, the therapeutic effect being mediated by furocoumarins present in the leaves. Physicians across other ancient civilisations also realised the healing effect of solar radiation in the treatment of skin diseases like psoriasis, vitiligo, rickets, cancer, and psychosis.[3] Heliotherapy was used as

a tool by Hippocrates, an ancient Greek physician, in developing treatment regimens for a variety of skin diseases.[4] In 18th and 19th century France, exposure to sunlight was part of a standard treatment protocol for diseases like tuberculosis rickets, scurvy, rheumatism, and muscle weakness, among others.[3] The 1903 Nobel prize awardee Niels Finsen applied red light to treat smallpox pustules successfully; he used UV–radiation to treat cutaneous tuberculosis. He also has been credited to have developed the use of carbon arc therapy for the treatment of cutaneous tuberculosis. However, Oscar Raab, under the supervision of Professor Herman von Tappeiner, discovered that paramecium exposed to acridine was susceptible to light exposure [5] and thus laid the foundation stone for modern scientific explorations of photodynamic therapy. The observed effect, greater than that of acridine or light alone, was labelled as "Photodynamische" or "Photodynamic effect" by Tappeiner. Tappeiner and Jesionek were able to treat skin tumours using a combination of eosin and white light.[6] Ledoux-Lebards first demonstrated that molecular oxygen was an essential requirement in such processes,[7] followed by Walter Straub and Tappeiner (together with Jodlbauer), independently.[8] One of the most significant findings in developing PDT was the discovery of Hp by Scherer.[4] He achieved its isolation from dried blood through the addition of H_2SO_4. Subsequently, Thudichun (1867) described the spectral properties of the mixture of compounds.[4] The name hematoporphyrin (Hp) was coined by Hoppe-Seyler.[4] The effect of light on microorganisms, erythrocytes, animals and humans in the presence of Hp was studied between 1908 and 1913. Experiments on white mice by Hausman led him to realise that the phototoxic effect was dependent on the PS and light. Consequently, he hypothesised that the peripheral tissue damage was linked to the observed phototoxic effect.[4, 9] A German doctor, Friedrich Meyer Betz (1912), intravenously injected himself with 200 mg of Hp and experienced oedema and hyperpigmentation for months.[4, 10-11] Policard (1925) through his experiments on experimental rat sarcomas and porphyrins observed the characteristic brick red fluorescence post excitation with white light.[4, 11] Progress in PDT thereafter remained dormant for several decades partly due to the synthetic challenges to obtain alternatives of Hp. Porphyrins and their derivatives have gained widespread usage as photosensitizers (PSs) in cancer treatment due to their favourable characteristics, including long-lived triplet excited states, a visible absorption spectrum, and efficient phototoxicity against cancer cells.[12] Their clinical application dates back to the 1940s when they were employed in disease diagnosis and demonstrated an affinity for accumulating in tumour tissues.[13-18] A mention must be made here of Auler and Banzer (1942), who reported the localisation of porphyrins in tumours in tumour-bearing rats and the lymph nodes.[13] Research studies by Figge *et al.*[14-16] and Rasmussen-Taxdal *et al.*[17] accurately

determined tumours in patients and tumour-bearing animals by exploiting the fluorescence properties of natural porphyrins. The same was achieved by Winkelman (1961) using hematoporphyrin derivatives (HpD) and synthetic porphyrins.[19-20] However, Kelly and Snell were credited with the first human study on the selective accumulation of tetraphenylporphinesulfonate in cancerous bladder cells and the subsequent elimination of tumorous tissue through illumination with light.[21] Further, Dougherty *et al*. successfully treated a variety of cutaneous lesions using HpD as PSs and a light source.[22] Since then, the development of better synthetic methods for obtaining porphyrins and other tetrapyrrolic PSs and their multifunctional derivatives and research into the applications of PDT to cancer, anti-microbial and antiviral therapeutics have garnered much-needed attention.[23-25]

1.1.1 Cancer Photodynamic Therapy:

PDT in the modern essence involves the synergistic action of three essential components, viz. an appropriate light source, a photosensitiser (PS) and molecular dioxygen to bring about tumour ablation and destruction of unwanted cells.[2, 23, 26-29] The primary process in PDT begins with the administration of PS to a patient's body. The PS is selectively up-taken by the rapidly dividing malignant cells, following which a radiation source of a specific wavelength irradiates the affected tumorous area. The absorption wavelength of the PS must be complementary to the wavelength of light used.[30] This radiation exposure activates the PS, which converts physiological dioxygen to ROS through either an energy transfer or an electron transfer process, as described in more detail in **section 1.2**. The ROS produced, in turn, brings about cell death through a combination of the apoptotic and necrotic pathways.[27, 31-34] PDT can induce an acute inflammation that can activate an immune response against the tumour cells and also lead to the destruction of tumour vasculature, disrupting oxygen and nutrient supply, thereby creating a hypoxic environment which ultimately leads to cell death.[27, 35] The link between induction of immune response (*in vitro* and *in vivo*) and cell-death mode has been investigated by many a research groups with contradictory outcomes. While some reports indicated an apparent efficacy of apoptotic cells at inciting an immune response,[27, 32-33] others suggested that necrotic tumours cells performed better at eliciting an immune response.[27, 31, 34] Necrosis afflicted cells release their cytoplasmic content into extracellular space through the damaged plasma membrane invoking an inflammatory response that attracts leukocytes into the tumour environment thereby boosting anti-tumour immune response.[27, 35] In apoptotic cells, however, these contents are caged within the intact plasma membranes and subsequently phagocytosed by macrophages.[27, 35] PDT thus affects tumour cells through three main pathways, viz. i) ROS

production that kills cancer cells, ii) production of acute inflammation triggering an immune response against the tumour and iii) destruction of tumour vasculature, creating an environment that is inconducive to cellular growth and development.[27, 35] The effect of PDT is a result of all three therapeutic pathways combined together.[27, 35] Central to an effective PDT treatment regime are PSs, a majority of which use the porphyrin macrocycle as a template. This is because of the ease of tunability of the photochemical and thus photobiological aspects of the macrocycle through structural modifications, high biocompatibility, and selective cellular uptake.[36-37] An ideal PSs should preferentially accumulate in the tumours, have a high quantum yield of $^1O_2$ generation, have low dark cytotoxicity, high phototoxicity, be amphiphilic and preferentially absorb in the therapeutic window (600-900 nm) region.[35, 38-43]

1.1.2 Anti-microbial Photodynamic Therapy:

The applications of porphyrins as anti-cancer Photodynamic Therapy (cPDT) agents have been extensively researched upon.[35, 37, 44-46] Several research groups have devised porphyrin-based photosensitisers (PSs)[36-37, 47-48] and multifunctional nanoparticles (NPs)[37, 49-52] that have shown promising results in treating specific cancer cells *in vitro* as well as *in vivo*. Parallel to the development of cPDT, in the last decade, another potential application of porphyrins has gained ground in the form of antimicrobial photodynamic therapy (aPDT).[53-57] The principle is like cPDT, the difference being that the target species here are microbes. Microbial strains tend to develop resistance to prolonged and recurrent usage of antibiotics.[53] This has become a serious global public health problem, leading to the failure of many a treatment for infectious diseases. aPDT can address this issue of drug resistance since this technique utilizes light energy for the destruction of microbial cells.[58] The key element responsible for a successful aPDT effect is the PS. Like in cPDT, the chief factors that are considered when deciding upon an ideal PS include sufficiently strong absorption in the visible region, photostability, high quantum yield of $^1O_2$ generation, ease of synthesis and biocompatibility. Porphyrin and its analogues score on all counts; they have unique tunable physiochemical properties that make them ideal for use as PSs. Moreover, the microbicidal effects of these PSs are manifested through the generation of ROS that affects multiple targets on pathogens, thereby eliminating the possibility of antibiotic resistance.[59] The tetrapyrrolic macrocycles can be derivatised by modifying their *meso* or β-pyrrolic positions or through the insertion of para or diamagnetic metal ions in their central core, which alters their properties and increases their efficiency as PSs.[37, 60]

1.1.3 Anti-viral Photodynamic Therapy:

Akin to the therapeutic developments of cPDT and aPDT, the applications of PDT against viruses have gained much ground.[61-63] Porphyrin derivatives have been reported to show excellent dark toxicities against viruses like HIV, HSV-1 and 2, equine herpesvirus type 1, and Zika virus among others.[64-74] This naturally spurred research into viruses' photodynamic inactivation (PDI).[59, 75] The first report of a PDT-based inactivation of enveloped viruses was published in 1990.[75] The authors studied photoinactivation of HSV-1 and HIV-1 using sapphyrin and dihematoporphyrin (DHE). The results indicated a 50% HIV-1 eradication with sapphyrin at a test concentration of 4 μM, at 16 μM concentration, the compound affected a complete photo-annihilation of HIV-1. The inhibitory effects were like DHE. None of the compounds was toxic against the uninfected test H9 leucocyte cells in the absence of light. However, significant dark toxicity was also observed in HIV-1-infected H9 cells. Since then, several research groups have explored PDI of viruses using a diverse range of compounds like curcumins, perylenequinones, hypocrellins and related compounds, metal oxides and inorganic materials, FDs, porphyrin and porphyrinoids, psoralens, riboflavin and others.[61-62] Most of the reports cite some degree of increased antiviral activity on irradiation and rely heavily on the hypothesis of light-induced damage to vital biomolecules.[62] In some cases, ROS produced as a result of photosensitisation most likely brings about the viricidal effect, yet other reports indicate oxygen-independent anti-viral activities. The situation is complicated by a class of compounds showing light and dark toxicity effects. However, the mechanism of PDI of viruses still requires firm experimental verification.

1.2 Photodynamic Therapy: Process

Photodynamic therapy (PDT) employs a combination of light, molecular oxygen and a PS to selectively terminate cancerous cells and tissues.[35] A typical PDT treatment involves the injection of a PS into a patient’s body. Preferential accumulation of the drug takes place in abnormal rapidly dividing cells. It is followed by irradiation of the affected area with radiation of a suitable wavelength. The chain of events commences with the absorption of light by the PS, followed by several radiative and non-radiative processes that help generate ROS, ultimately instrumental in inducing cell death and tissue damage. The various processes involved in PDT have been outlined in **Figure 1.5.1**.

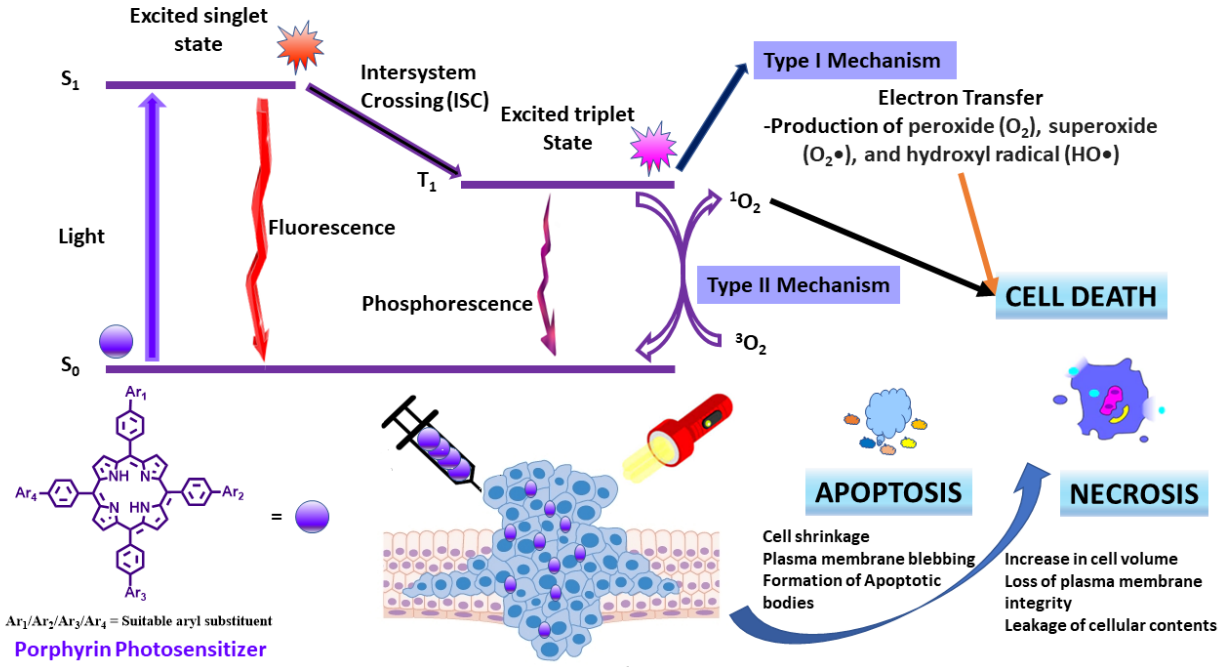


Figure 1.2.1: Processes involved in photodynamic therapy.

The primary event, applicable to cPDT, aPDT or PDI of viruses, is the excitation of the PS to a singlet excited state (S_1) on irradiation with a suitable wavelength. The lifetime of the S_1 state is of the order of nanoseconds, making the species too short-lived to affect any significant molecular damage. The S_1 state decays either by a radiative singlet to singlet process (fluorescence) or via a non-radiative inter-system crossing (ISC) from S_1 to excited triplet state (T_1). The T_1 state has a comparatively longer lifetime, typically in the micro–millisecond range, and as such the T_1 excited sensitiser has greater potential to participate in the photodynamic process. The "photodynamic effect" is modulated by energy or electron transfer from the photosensitiser to the organic substrate or molecular oxygen. Quenching proceeds either by a Type I mechanism involving electron transfer leading to the generation of ROS like peroxide (O_2), superoxide (O_2•) and hydroxyl radical (HO•) or a Type II mechanism involving energy transfer to triplet state molecular oxygen ($^3O_2$) that results in the formation of reactive $^1O_2$.[35, 76] The photoproducts are cytotoxic, and they initiate biochemical events that eventually result in the destruction of target species (tumour cells, microbes or viruses) through the multimodal mechanism.[35] PDT induces cell death through apoptosis and/or necrosis.[27, 35] PDT also causes shut down of tumour microvasculature, creating hypoxia conditions that are not conducive to tumour cells' growth. At the same time, PDT results in acute inflammation, which triggers an immune response.[27, 35] PDT-induced immune response may either be immunosuppressive or

immunostimulatory, depending upon the treatment regimen.[35] Usually, topical administration of PS, high fluence rate and a large area of illumination is associated with immunosuppression.[35, 77] In contrast, immunostimulatory effects can be seen in non-topical PDT treatment regimes.[35]

Apoptosis, a mode of programmed cell death, is characterised by cessation of cellular growth and division ultimately resulting in controlled cell death with no spillage of cytoplasmic content in an extracellular environment.[27, 35, 78] It is an energy-dependent and genetically regulated process.[35, 78] Distinguishing feature of apoptosis include enzyme-dependent biochemical processes, cell shrinkage, membrane wrinkling, and the formation of apoptotic bodies, the plasma membrane remains intact during the process.[35] Necrosis, on the other hand, involves uncontrolled cell death, rupture of the plasma membrane and spillage of cytosolic content into the extracellular environment. Tissue damage and loss of homeostasis result in acute inflammation commenced by the releasing of inflammation promoters like cytokines, growth factors and protiens.[27, 35] These in turn, draw the host's immune cells like neutrophils, mast cells, macrophages, and dendritic cells, into the damaged tissue in order to restore homeostasis. Macrophages phagocytise the damaged tumour cells. Macrophages also present antigens to CD4 helper T lymphocytes, which subsequently activate CD8 cytotoxic T lymphocytes, which can identify and neutralize any tumour cell and remain in circulation for long periods, thereby ensuring long term anti-tumour immunity.[27, 35, 77]

Not all drugs qualify as suitable photosensitiser to be used in PDT; PSs should meet specific criteria: The PS should be (1) chemically stable, (2) amphiphilic, (3) capable of generation of $^1O_2$ in high quantum yield (Φ_Δ), (4) non-cytotoxic in the dark, (5) having high affinity for tumour cells, and (6) capable of rapid accumulation in cancerous tissues. Besides, rapid clearance from patients and a high molar absorption coefficient (ε) in the biological window[35, 38-43] (600–900 nm) region are an added advantage. Absorptions at longer wavelengths (>650 nm) ensure deeper tissue penetration.[35-36, 40, 79-81]

PDT has expanded in the last two decades to include two new treatment modalities: aPDT, and PDI of viruses.[25-26, 61, 75, 82-83] Like in cPDT; the photodynamic effect depends on ROS generation through a type-I or type-II mechanism, which destroys target entities. The target structure could be bacterial cell membranes, lipid bilayers or protein envelopes of viruses, protein capsids and nucleic acids.[61] Factors affecting photodynamic inactivation include net charge, and structural features of the PSs, the wavelength of irradiation, effective uptake of PSs

and availability of molecular oxygen.[84] One of the most significant advantages of aPDT and PDI of viruses is the non-dependence of treatment protocol on any specific receptor interaction.[61] The consequence is the inability of the treated bacteria (or viruses) to develop resistance against the mechanism of action.[61, 85]

1.3 Photosensitisers:

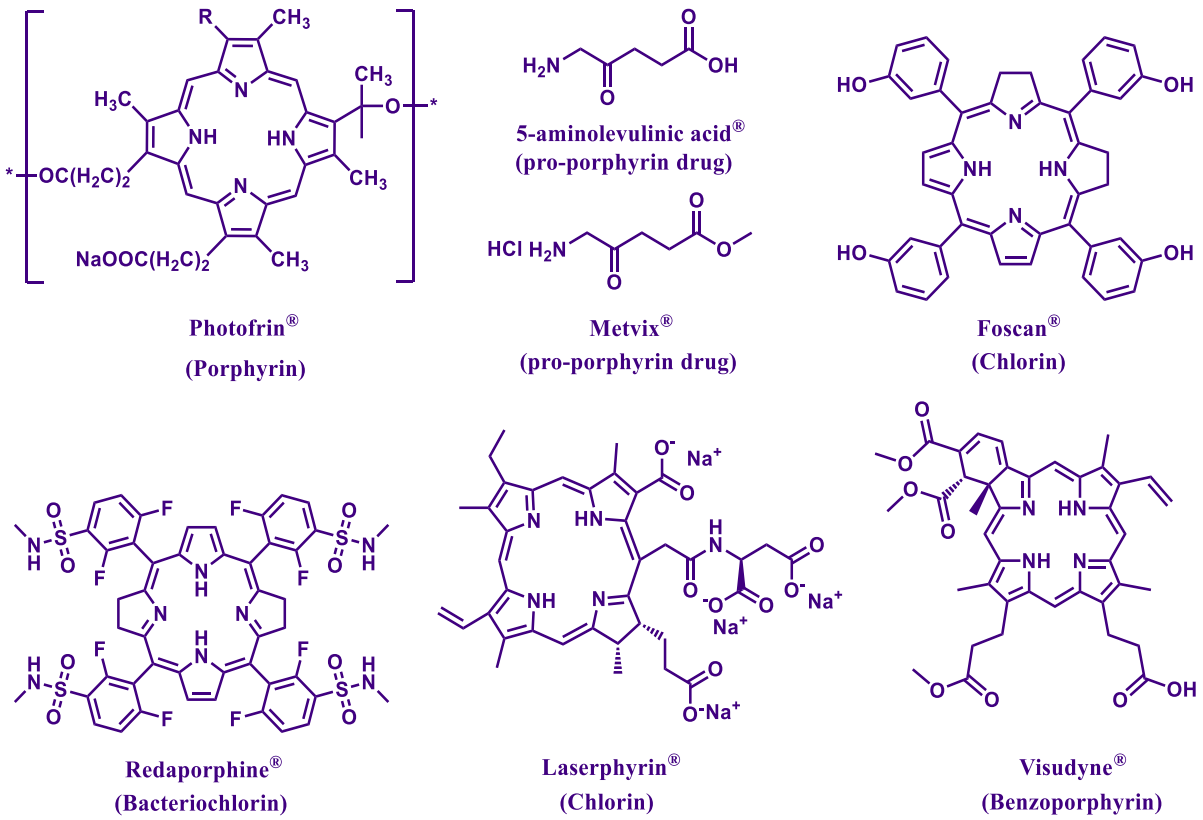


Figure 1.3.1: Some PSs approved for clinical use.

PSs are specific molecules that mediate energy or electron transfer processes. In terms of PDT, PSs absorb suitable radiation and generate ROS or radicals by specific pathways (**Fig 1.5.1**); the ROS or radicals generated are primarily responsible for initiating cell damage. Over the years, a wide range of molecules have been employed as PSs, however, the tetrapyrrolic macrocycles have been the most studied and most applied.[35-36, 79-81] This is due to specific properties like selective uptake in cancerous tissue, absorption in the therapeutic window region,[35, 38-43] and low dark toxicity. The porphyrins constitute the first-generation PSs; these had adsorption in the lower wavelength side of the biological window. The second-generation PSs include porphyrin derivatives and synthetics made from the 1980s onwards. These had absorptions at a comparatively longer wavelength in the biological window region. The third-

generation PSs, on the other hand, are multifunctional entities with improved tumour targeting capability, generally achieved by conjugation of a PS molecule with antibody conjugates or through nanoencapsulation, or moieties capable of performing therapeutic, diagnostic as well as targeting functions.[35, 86-98]

Ideal PSs are molecules that can be activated by specific wavelengths of light, typically in the visible or near-infrared range, to produce reactive oxygen species (ROS) that can destroy target cells or tissues. The characteristics of an ideal PS can vary depending on the specific application, but generally, it should possess the following attributes:

1. High absorption in the therapeutic window: Ideal PSs for cancer photodynamic therapy (PDT) should possess a high absorption capacity in the therapeutic window range of 600-800 nm. This allows for deeper tissue penetration and minimizes damage to surrounding healthy cells.
2. Efficient generation of reactive oxygen species (ROS): PSs should have excellent efficiency in generating reactive oxygen species upon light activation. ROS, such as singlet oxygen, are responsible for inducing cytotoxic effects and damaging cancer cells.
3. Selective accumulation in cancer cells: The PSs should possess properties that enable preferential accumulation in cancer cells rather than normal cells. This can be achieved through active targeting mechanisms, such as conjugation with tumour-specific antibodies or peptides, or passive targeting based on the enhanced permeability and retention (EPR) effect.
4. Rapid clearance from normal tissues: After PDT treatment, the PSs should be rapidly cleared from normal tissues to minimize potential side effects and phototoxicity to healthy cells.
5. Low dark toxicity: PSs should exhibit minimal toxicity in the absence of light activation to avoid unnecessary damage to healthy tissues. This ensures that the PSs remain inert until activated by light.
6. Stability and biocompatibility: Ideal PSs should be stable, both chemically and photochemically, under physiological conditions. They should also be biocompatible to minimize immune responses and adverse reactions.
7. Easy synthesis and modification: PSs should have a straightforward synthesis route, allowing for cost-effective production. Moreover, they should be amenable to

modification, facilitating the incorporation of targeting ligands or other functional moieties to enhance their specificity and efficacy.

8. Photostability: PSs should exhibit high photostability, meaning they can withstand repeated cycles of light activation without undergoing photodegradation or loss of their photodynamic properties.
9. Non-toxic degradation products: Upon light activation and ROS generation, the PSs should ideally degrade into non-toxic by-products that can be easily eliminated from the body.
10. Compatibility with various light sources: PSs should be compatible with a range of light sources, including lasers and light-emitting diodes (LEDs), to allow for flexibility in clinical settings.

Porphyrin and its structural analogues like chlorins and bacteriochlorins are among the most widely used PSs in PDT.[35, 37, 49, 53, 61, 63] Over the years, a wide range of synthetic formulations of porphyrins have been synthesised, isolated, and evaluated for their biological activities. The common strategy for derivatisation included substitution reactions at the four *meso*- and eight β-pyrrolic positions or addition across the β-pyrrolic C=C bond, independent of the porphyrin electron delocalisation pathway.[37] Moreover, the inner pyrrolic core of porphyrins is well suited for complexation with metal atoms resulting in the formation of metalloporphyrins. The synthetic modifications of the porphyrin macrocycles illustrate properties that are well-suited for the requirements of PDT. Tunable absorption (high molar extinction coefficient) and emission properties, coupled with a high knack for efficient electron–, energy– or hydrogen–transfer, superior $^1O_2$ generation capacity under photoirradiation, selective uptake by tumour cells and biocompatibility make these macrocycles very attractive targets for biomedical use.[37, 53] Many porphyrin-based PSs have been approved for clinical use,[37] and the synthesis and applications of many more have been extensively reviewed in the literature.[23, 53, 61-62, 79, 99-103] Rendering porphyrins amphiphilic through the incorporation of ionic as well as lipophilic groups at *meso*- position enhances their PDT efficacy,[26, 104-106] so does functionalisation of porphyrins with plasmonic NPs (NPs),[86, 89, 107-110] magnetic NPs,[96-98, 111-114] *meso*porous silica NPs,[115-120] block copolymers,[37, 121-125] supramolecular polymers[37, 126-131] and carbon-based NPs like C_{60}, C_{70}, graphene oxide etc.[132-143] Strategies like nano-encapsulation[37, 106, 144-145] has been developed to address localisation of otherwise hydrophobic PSs in tumour sites. The quantum of progress achieved in porphyrin-based PDT is huge and commensurate with the progress in synthetic aspects made in the last couple of decades. Detailed reviews have highlighted various

aspects of scientific developments. In the work presented in the current thesis, we have focused on the derivatisation of porphyrins through cycloaddition reactions and hydrophilisation of the derivatives to explore their potential as agents for PDT.

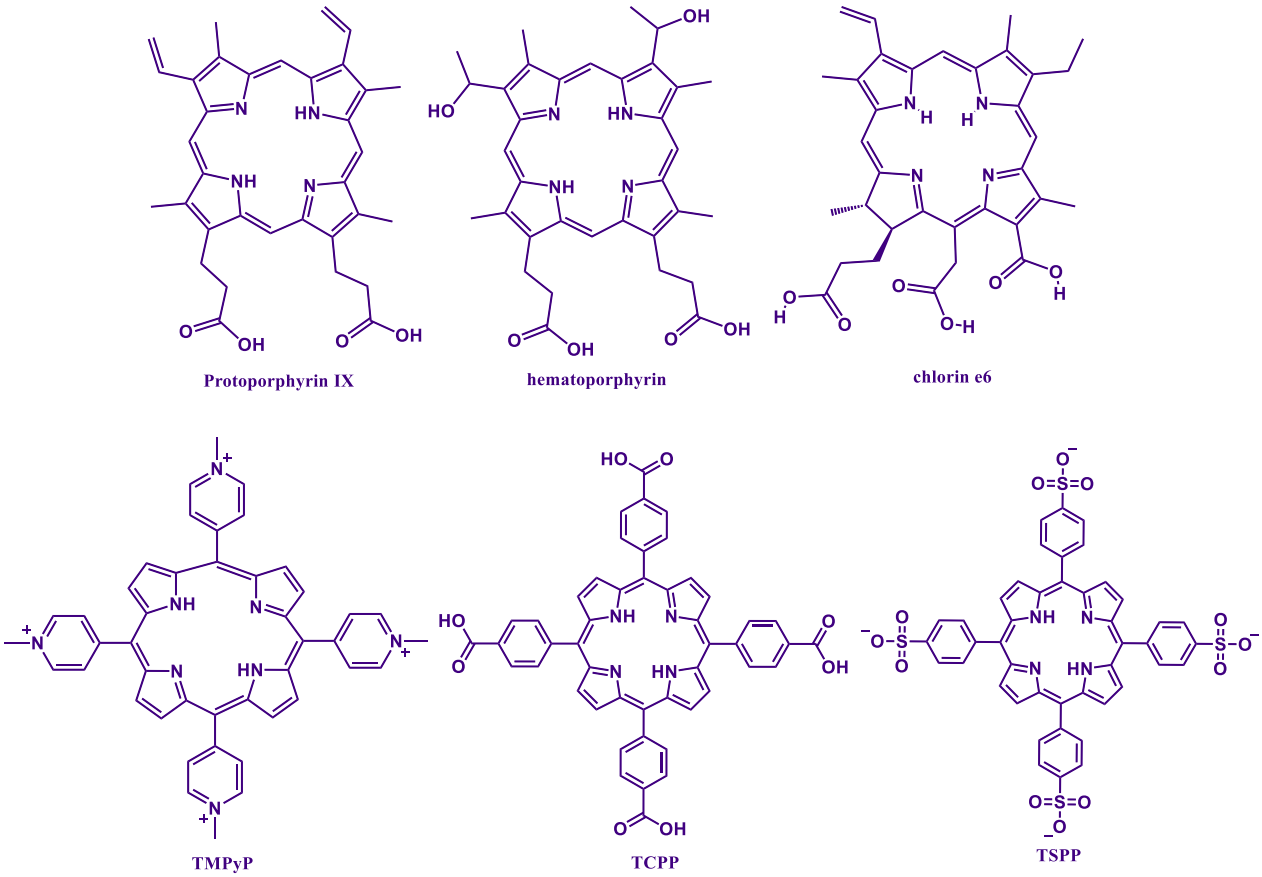


Figure 1.3.2: Porphyrins employed as PSs in PDT.

Several review articles have given a comprehensive account of PSs developed over the last two decades for use in PDT along with their mode of function.[26, 35, 44, 61-62, 80, 146] The development has been porphyrin centric, with various PSs based on porphyrin and its derivatives approved for clinical use or clinical trials.[35] The list includes porphyrins, chlorins, bacteriochlorins, texaphyrins and pro-protoporphyrin drugs like 5-aminolevulinic acid (ALA) (**Figure 1.6.1**).[35] Apart from these, a host of other cationic, anionic and neutral PSs have been evaluated for their efficacy as PSs for PDT. A brief description of developments in this regard is included below:

1.3.1 Cationic porphyrin PSs:

Cationic porphyrin (CP) PSs mainly comprise *meso*-tetra-aryl substituted porphyrins or molecules having variable *meso*-substitution patterns bearing a net positive charge (**Figure 1.6.1.1-1.6.1.5**).[26, 66-67, 147-151] The simplest of the cationic PSs is 5,10,15,20-tetra-(4-

methylpyridinium) porphyrin (**TMPyP**) with four *meso*-(4-methylpyridinium) substituents. Several synthetic methods have been reported in the literature to synthesise **TMPyP**, with the compound most commonly reported as an iodide, chloride or tosylate salt.[152-154] **TMPyP** is among the most widely studied PSs.[155-161] The compound reportedly has DNA intercalation properties and promotes apoptosis in a PDT treatment regime.[62, 155, 160, 162] However, the high affinity of **TMPyP** for all kinds of nucleic acid is disadvantageous for it to be an ideal PS for cPDT, as is its lack of selectivity.[26] As such, several approaches have been explored to enhance its therapeutic outcome in PDT, including PS formulations containing combinations of **TMPyP** and other hydrophilic PSs,[151, 159] conjugations of **TMPyP** with graphene oxide,[158, 163] Au,[164-165] Ag,[166-167] iron oxide NPs,[168-169] nanoencapsulation[170] and metalation with biologically active metals.[156, 171-174]

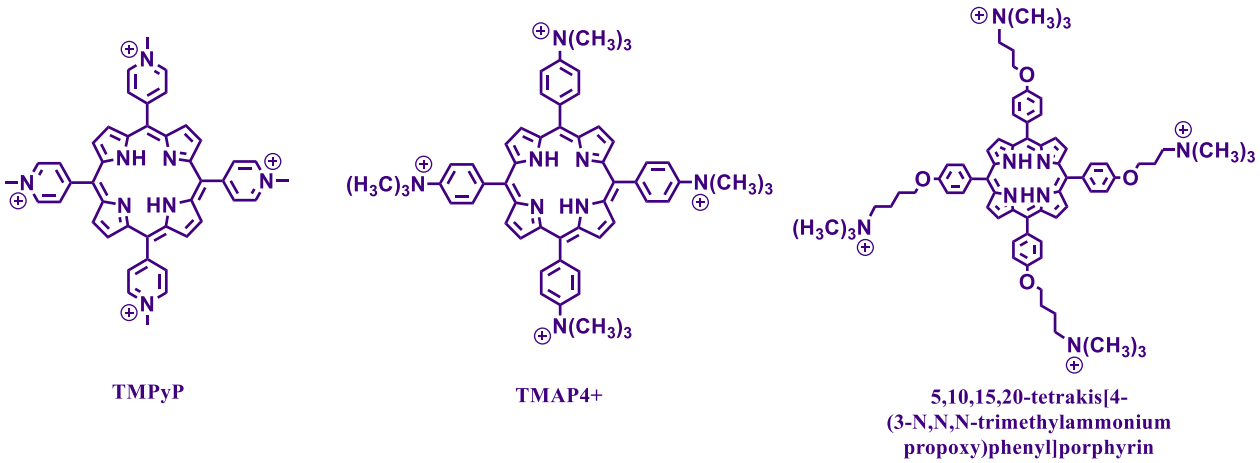


Figure 1.3.1.1: Tetra-cationic porphyrins used as PSs in PDT.

TMPyP has a net charge of four units which imparts to its necessary hydrophilicity for photobiological applications. However, numerous publications have suggested that PSs bear a combination of high cationic charges and that added lipophilicity usually translates to better therapeutic efficacy.[26, 67, 175] Other tetra cationic PSs used for *in vitro* trials and/or DNA binding studies include 5,10,15,20-tetra(4-N,N,N-trimethylammoniumphenyl) porphyrin (**TMAP^{4+}**),[176-180] 5,10,15,20-tetrakis[4-(3-N,N,N-trimethylammoniumpropoxy)phenyl] porphyrin.[176] CPs bearing a blend of cationic- and neutral *meso*-substituents (**Figure 1.6.1.2** and **1.6.1.3** and several others[149, 174-175, 181]) have shown promising PDT-based activity against cancer cells, microbes and viruses *in vitro*.[26, 61, 66-67, 147-148]

Amphiphilic porphyrins bearing *meso*-(4-nitrophenyl) substituents in combination with *meso*-(4-methylpyridinium) were reported by our research group (**Figure 1.6.1.3**) as dual inhibitors

of HIV and cancer (A549 lung cancer cells), the latter under PDT conditions.[67] The best inhibitory effects, in either case, were shown by the Zn complex **compound 8** (HIV entry inhibition >99%, 4 μM, IC_{50} = 1.1 μM) with three *meso*-(4-nitrophenyl) and one *meso*-(4-methylpyridinium) substituent indicating that the presence of the nitrophenyl groups added amphiphilic characteristic to the compound. This, along with the mono-cationic *meso*-(4-methylpyridinium) moiety, helped in the effective cellular uptake of the PSs, enhancing the therapeutic outcome. Interestingly, while the anti-cancer activities of the compounds were manifested under photo-illumination, the inhibitory effects against HIV were observed in the dark.

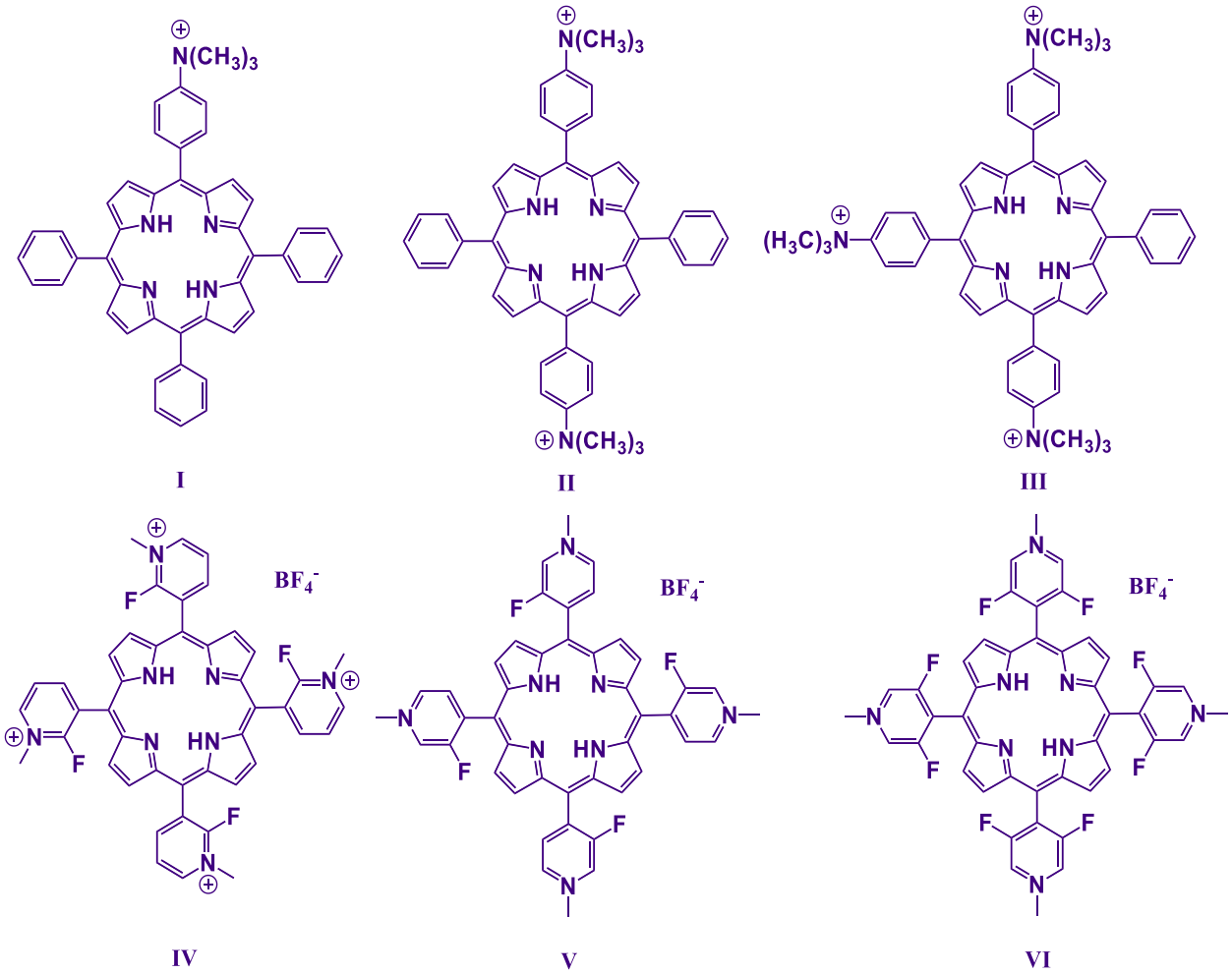
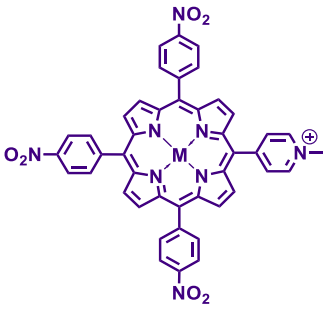
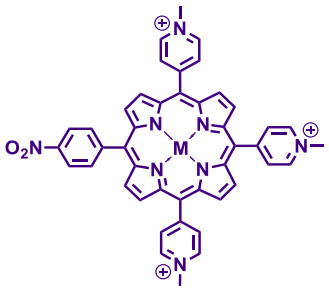


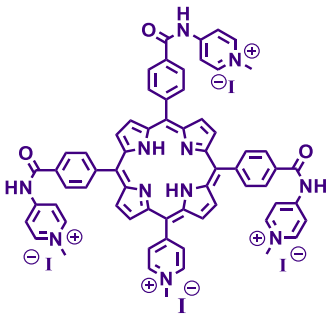
Figure 1.3.1.2: Cationic porphyrins used as PSs in PDT studies.[182]



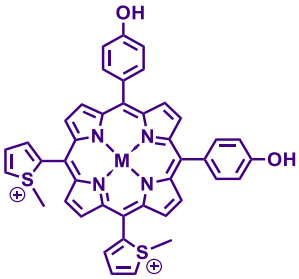
Compound 8: M=Zn, IC_{50} = 1.1 μM
Compound 6: M=2H, IC_{50} = 1.7 μM
(A549 lung Cancer Cell Line)
HIV entry inhibition: Compound 8 >99%



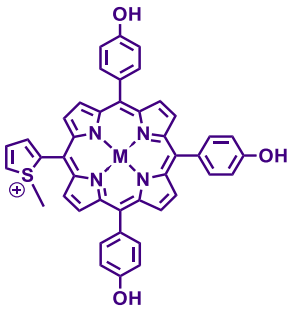
Compound 7: M=Zn, IC_{50} = 1.56 μM
Compound 5: M=2H, IC_{50} = 2.01 μM
(A549 lung Cancer Cell Line)



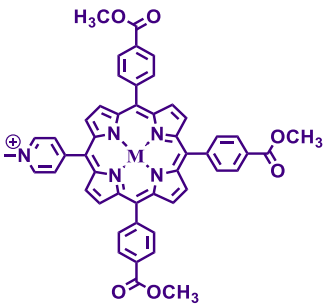
Compound B.3: IC_{50} = 0.66 μM,
A549 lung Cancer Cell



$T_2(OH)_2MZn$: M=Zn, IC_{50}=7.05 μM
$T_2(OH)_2MZn$: M=2H, IC_{50}=12.93 μM
HIV entry inhibition: $T_2(OH)_2MZn$ >75%
HIV entry inhibition: $T_2(OH)_2M$ >50%



$T(OH)_3MZn$: M=Zn, IC_{50}=13.77 μM
$T(OH)_3MZn$: M=$_2$H, IC_{50}=14.54 μM
HIV entry inhibition: $T(OH)_3MZn$ >50%
HIV entry inhibition: $T(OH)_3M$ >50%



$MPyEt_3Zn$: M=Zn, IC_{50}=11.53 μM
$MPyEt_3$: M=$_2$H, IC_{50}= 8.81 μM

Figure 1.3.1.3: Cationic porphyrins used as PSs in PDT and/or anti-HIV studies.[66-67, 147-148, 183]

Our research group was also the first in the world to report di- and mono-cationic *meso*-(2-methylthiophenium) substituted porphyrins (**Figure 1.6.1.3**). The compounds **$T_2(OH)_2MZn$**, **$T_2(OH)_2M$** and **$T(OH)_3MZn$**, **$T(OH)_3M$** bearing *meso*-(4-hydroxyphenyl) in addition to the thiophenium moieties proved to be effective against A549 lung cancer cells under PDT conditions and in the dark against HIV, *S. Aureus* and *E. Coli*. The results we obtained have opened the possibility of creating a library of new cationic compounds that could be an alternative in biomedical uses compared to the well-popular nitronium counterparts.[147] In either of the reports,[66-67, 147] a precise amplification of inhibitory effects is apparent upon Zn complexation. Apart from these, we were also able to demonstrate that the placement of positively charged *meso*-substituents independent of the porphyrin aromatic ring current enhances the PDT activity of such PSs. The **compound B.3** (**Figure 1.6.1.3**) with a pyridinium group strategically placed in direct conjugation with a porphyrin ring and three distal pyridinium groups placed independent of the porphyrin electron delocalisation cycle had better

photosensitising abilities than TMPyP ($IC_{50}^{B,3} = 0.66\ \mu M, IC_{50}^{TMPyP} = 1.49\ \mu M$, A549 lung cancer cell line).[183]

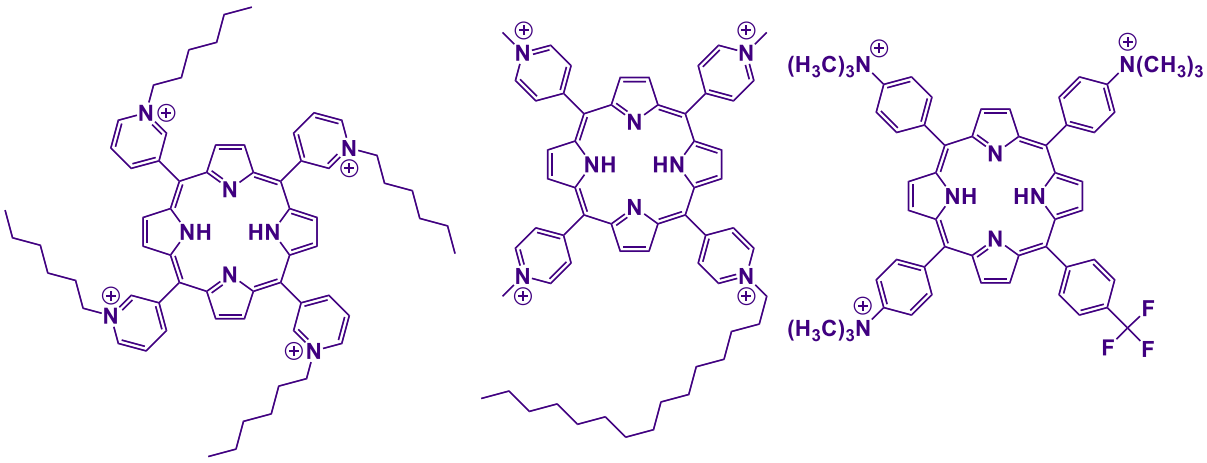


Figure 1.3.1.4: Cationic amphiphilic porphyrins: ZnTnHex-3-PyP; TMPyP4-C14; TFAP(3+).

Other than applications as PSs for cPDT, CPs have also shown noteworthy photodynamic anti-microbicidal and virucidal effects.[26, 61, 174, 179, 184] CPs are effective against both Gram (+ve) and Gram (–ve) bacteria and a host of viruses.[26, 84] The mechanism of action involves the excitation of PSs by absorption of light and subsequent quenching through either an oxygen-independent electron transfer (a type-I mechanism) or an oxygen-dependent energy transfer (type-II mechanism) process resulting in the generation of cytotoxic ROS and $^1O_2$, respectively. These interact with the pathogens (e.g. bacteria, fungus, yeasts, viruses etc.), resulting in oxidative stress that ultimately brings about a "killing effect".[26, 185] Susceptible species include *S. aureus*, methicillin-resistant *S. aureus* (MRSA), *Streptococcus mutans*, *E. faecalis*, *E. faecium*, *E. Coli*, *Pseudomonas aeruginosa*, *Helicobacter pylori*, *Candida albicans*, HIV, HSV, T4 and T7 bacteriophages and others.[26, 84, 186-187] Non-development of antibiotic resistance is one of the most significant advantages of aPDT,[26, 61, 84] While disadvantages include limited systemic applications, lack of solubility, target selection, aggregation of PSs leading to self-quenching and low ROS generation, and economic viability.[84]

As such, the search for new and better PSs for applications in cPDT, aPDT and PDI of viruses continues through structural modifications and/or nano-conjugation, assuring targeted delivery and specificity in target interaction. The functionalisation of PSs with bioactive molecules is also an attractive field that requires thorough investigation.

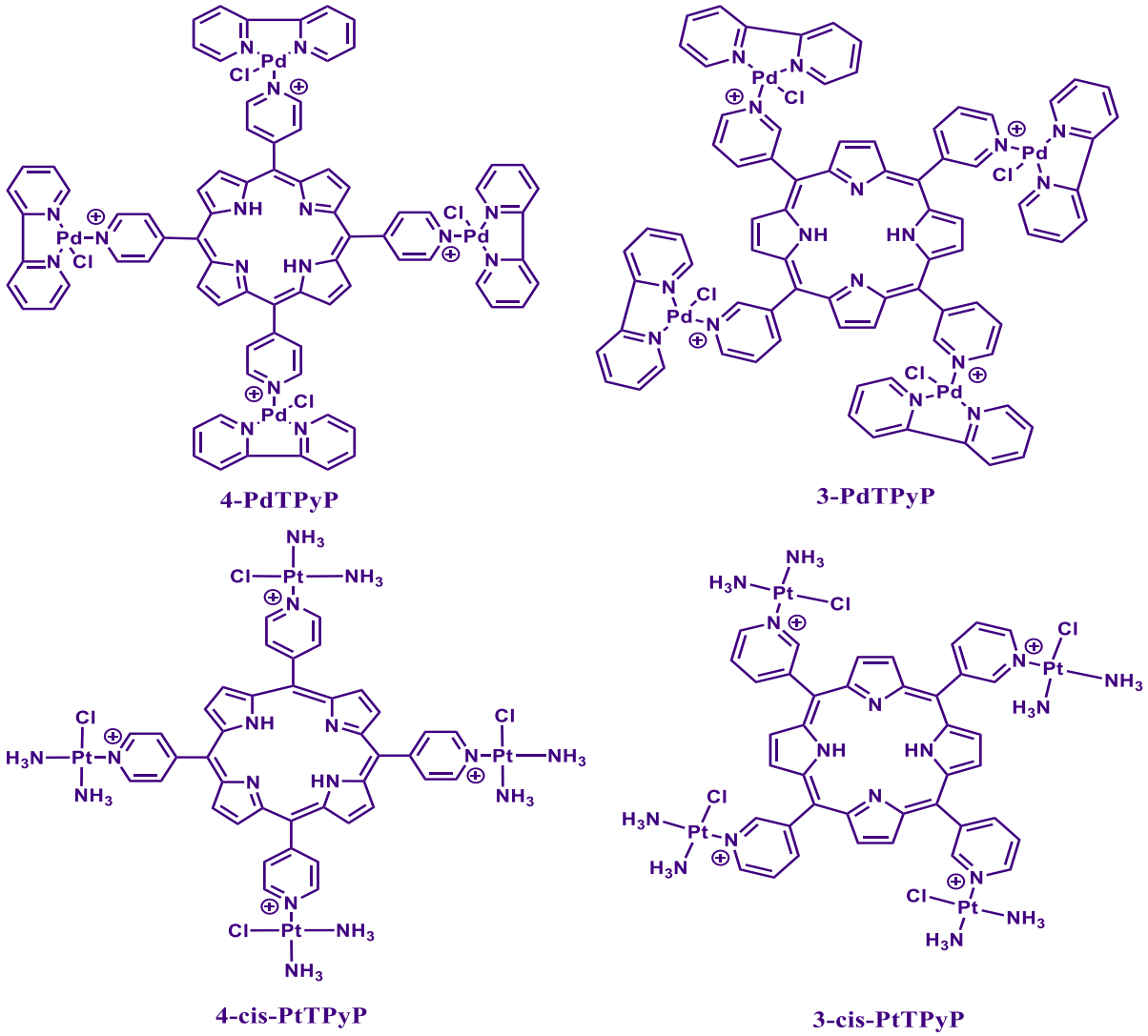


Figure 1.6.1.5: Cationic porphyrins used as PSs in aPDT.[186-187]

1.3.2 Anionic porphyrin PSs:

Anionic porphyrin (AP) PSs have been extensively used for biomedical applications owing to their far-reaching biochemical functions.[108, 187-193] APs play crucial roles in natural systems,[194] examples include Fe-metal complexes like hemin, hematin and protoporphyrin-IX (**PPIX**) (**Figure 1.6.2.1**).[195-196] **PPIX** is the biosynthetic precursor of hemes and chlorophylls and performs various biological functions.[196-197] Coordination of PPIX with iron (II) results in the formation of heme, a constituent of homeoproteins including haemoglobin and cytochrome P450 enzymes which are important agents for oxygen transport, cellular oxidations and reductions, electron transport, and drug metabolism.[197-200] While Fe (III) coordinated hemin (a chloride of heme) is the prosthetic group for a large number of proteins. It serves as a co-factor for enzymes in living cells,[201] hematin (a hydroxide of heme), also coordinated to Fe (III), is

known to inhibit porphyrin synthesis and boost the production of globins.[202] PPIX, because of its bio-compatibility, has been extensively used as a PS in cPDT. The usual mode of administration is either endogenous through administration of ALA which is biosynthesised into **PPIX** in mammalian cells[203-204] or exogenous, wherein the compound **PPIX** itself is administered directly.[205] **PPIX**-based PDT treatments have been successfully used to treat cutaneous cancerous lesions.[206] Other reports indicate the efficacy of the drug and its derivatives in mitigating human oesophageal carcinoma cells, lung cancer cells (in C57BL mice) and cervical cancer.[205, 207-208] The fluorescence properties of the compound have been explored as a tool for detecting of cancer cells.[209-211] Apart from that, with the advent of nanotechnology, several **PPIX**-nanoparticle conjugates have been developed as effective PSs for PDT in the last two decades.[207, 212-215]

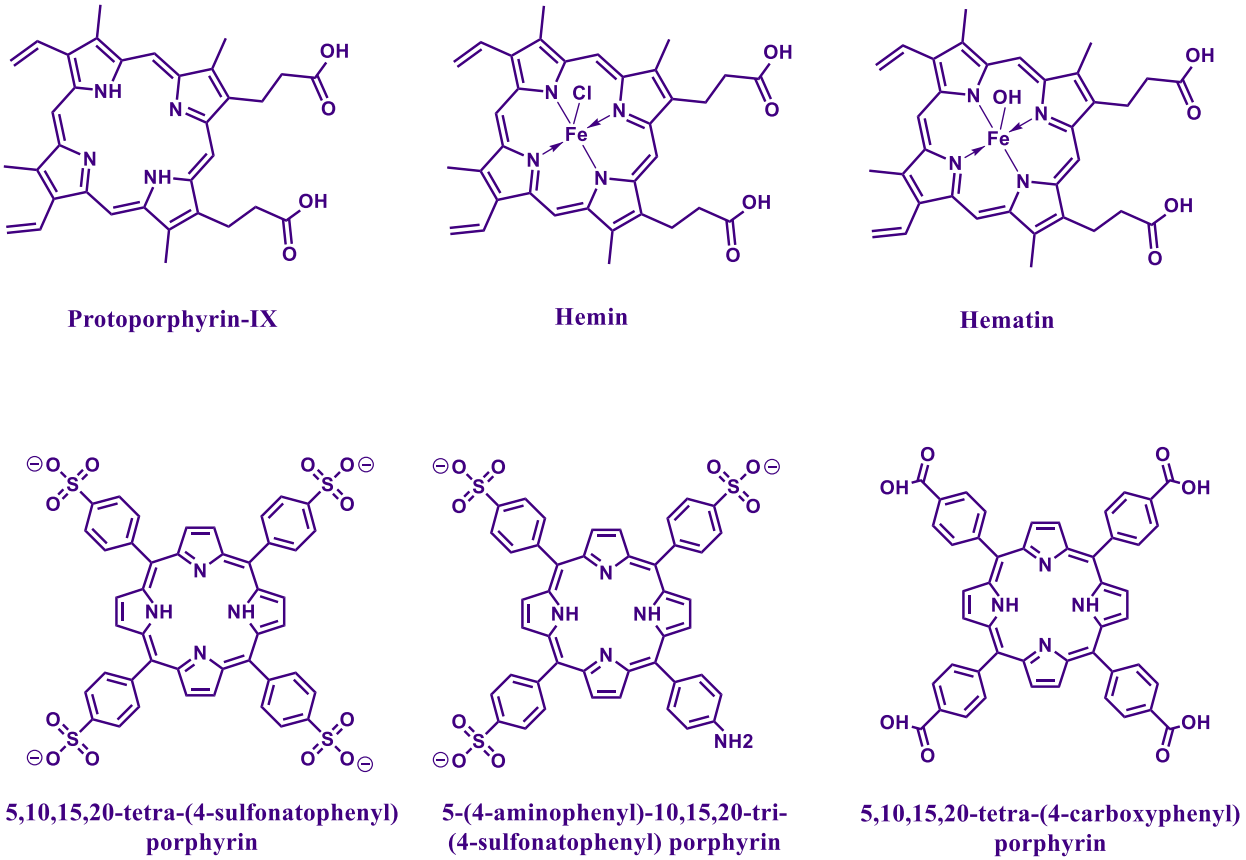


Figure 1.3.2.1: Some natural and synthetic anionic porphyrins.

Other anionic PSs derived from natural sources include the hematoporphyrin derivative (HpD) and its derivatives. HpD has been effectively used for PDT-based treatment of brain, laryngeal, lung, skin, gastric, and oesophageal carcinomas. Photofrin®, a first-generation PS, is a proprietary combination of monomers, dimers, and oligomers of HpD. Often referred to as the

"gold standard" for non-cutaneous derived cancers, Photofrin® is among the most approved for clinical PDT.[36, 146, 216] Though HpD and Photofrin® were successful PDT agents, certain limitations like their complex structure, absorption at lower wavelengths limited their use to cutaneous tissues mostly. This led to the development of chemically pure second-generation PSs with light absorption at longer wavelengths facilitating the treatment of deep-seated tumours.

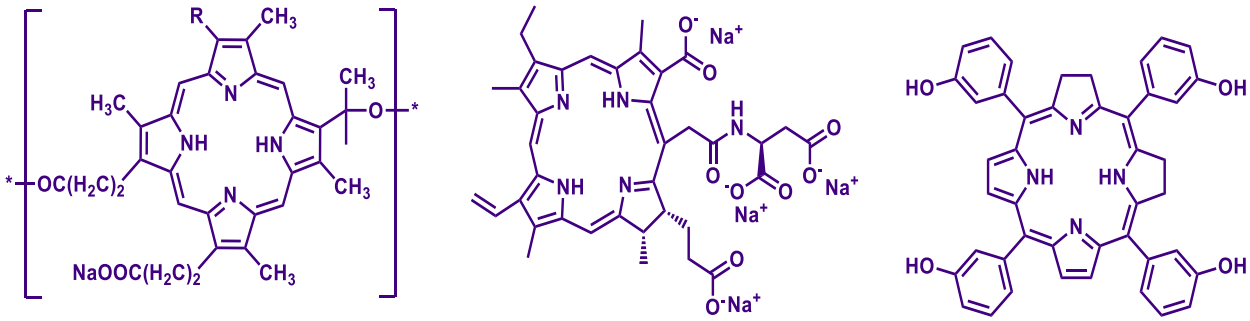


Figure 1.3.2.2: Some anionic porphyrins clinically approved for cPDT.

The most common synthetic APs used in PDT are 5,10,15,20-tetra-(4-carboxyphenyl) porphyrin (**TCPP**) and 5,10,15,20-tetra-(4-sulfonatophenyl) porphyrin (**TSPP**) and their metal complexes.[94, 108, 217-225] In contrast to the CPs which tend to localise in mitochondria, APs tend to localise in lysosomes.[226] Among other factors, the cellular uptake of the PSs depends on the pH of the tumour tissue (pH 6.4) and normal tissue surrounding the tumour (pH 7.4).[226] APs are also known to interact with DNA and bind to G-quadruplexes with high selectivity.[194, 227-228] **TCPP**, as well as **TSPP**, have been used to prepare novel derivatives and multifunctional NPs for better tumour internalisation, higher photocytotoxicity, targeted drug delivery and multi-therapeutic treatment regime.[94, 142, 219, 221, 224-225, 229-237] Apart from applications as cPDT agents, APs have also been evaluated as agents for PDT-based microbicidal effects.[53, 192, 238-239] APs are most effective against Gram (+) bacteria, the negatively charged lipopolysaccharides in the cell wall of Gram (–) bacteria act as a deterrent to effective interaction between the porphyrins and bacterial cells.[53, 240] However, the use of membrane disorganizing agents like polymyxin B nonapeptide (PMBN) or ethylenediaminetetraacetic acid (EDTA), derivatisation with cationic polypeptides and conjugation with monoclonal antibodies or bacteriophages has been successfully employed to circumvent the limitation.[53] Additionally, several reports indicate that APs bearing carboxyphenyl or sulfonatophenyl

moieties have prominent anti-HIV activity.[68, 103, 241-243] The inhibitory effects are manifested as a result of the interaction of APs with positively charged V3 loop of HIV-1 gp120 glycoprotein thereby preventing interaction of the virus with CD4 cell receptors.[68, 103, 241-243]

1.3.3 Neutral porphyrin PSs:

Apart from CPs and APs, porphyrin PSs having no net charge have been explored as possible PDT agents under *in vitro* conditions (**Figure 1.6.3.1**).[97, 244-253] The most commonly used neutral porphyrins are 5,10,15,20-(tetraphenyl) porphyrin (**H_2TPP**), [244-250] and 5,10,15,20-tetra-(4-hydroxyphenyl) porphyrin (**THPP**).[254-260] The tetra-symmetric chlorin 5,10,15,20-(3-hydroxyphenyl) chlorin (**Foscan®**) presents one of the more successful examples. It has been approved for clinical use and was effectively employed to treat a wide variety of cutaneous lesions, pulmonary, oesophageal, gastrointestinal and head and neck tumours.[146] As with APs and CPs, neutral porphyrins conjugated to NPs exhibit enhanced photodynamic effect, greater selectivity towards cancer cell lines and higher cellular uptake.[138, 254-261]

Several publications have reported alternatives to the synthesis of the popular compounds with interesting physiochemical, spectroscopic and/or photobiological outcomes.[90, 97, 234, 252, 262-263] Sengupta *et al.*[252] reported synthetic alternatives to photobiologically inert **(NPh)TPyP**[264] which bears three *meso*-(4-pyridyl) substituents attached directly to the porphyrin ring along with a lone *meso*-(4-nitrophenyl) substituents. In contrast, the new synthons **P_3N** and **P_3NZn** had the pyridyl groups placed at a distal position through ester linkages. This rapture in π-conjugation rendered the molecules amphiphilic, and consequently, the PSs exhibited ROS-mediated anti-cancer activity against A549 lung cancer cells *in vitro* under PDT conditions. Kirar *et al.*[145] reported an A4 amphiphilic porphyrin, 5,10,15,20-tetrakis(4-pyridylamidephenyl) porphyrin, having similar rapture in π-conjugation. When doped into gelatin NPs, the compound exhibited higher hydrophilicity and biocompatibility. The PS-doped gelatin NPs induced photodamage to the breast cancer cell line (MCF-7) and human embryonic kidney cell line (HEK-293), *in vitro*, under LED excitation.

Various research groups have reported the antimicrobial activities of non-ionic porphyrins.[145, 156, 258, 265-267] The susceptible species include *S. Aureus, E. faecalis, E. Coli, P. aeruginosa* and fungal strains.[145, 156, 258, 265-270] For an effective interaction nano-conjugation (e.g. with cyclodextrins, gelatin)[145, 236] or targeted delivery using natural deep eutectic solvents (NADES) has been explored.[53, 145, 156, 258, 265-270] However, neutral porphyrins on their own are much less

effective at bringing about an effective aPDT response as compared to CPs and APs.[53] Very few reports of non-ionic porphyrins acting as antivirals could be found in the literature, photo-irradiation being required in each case for effective viricidal activity.[61, 83, 271-272]

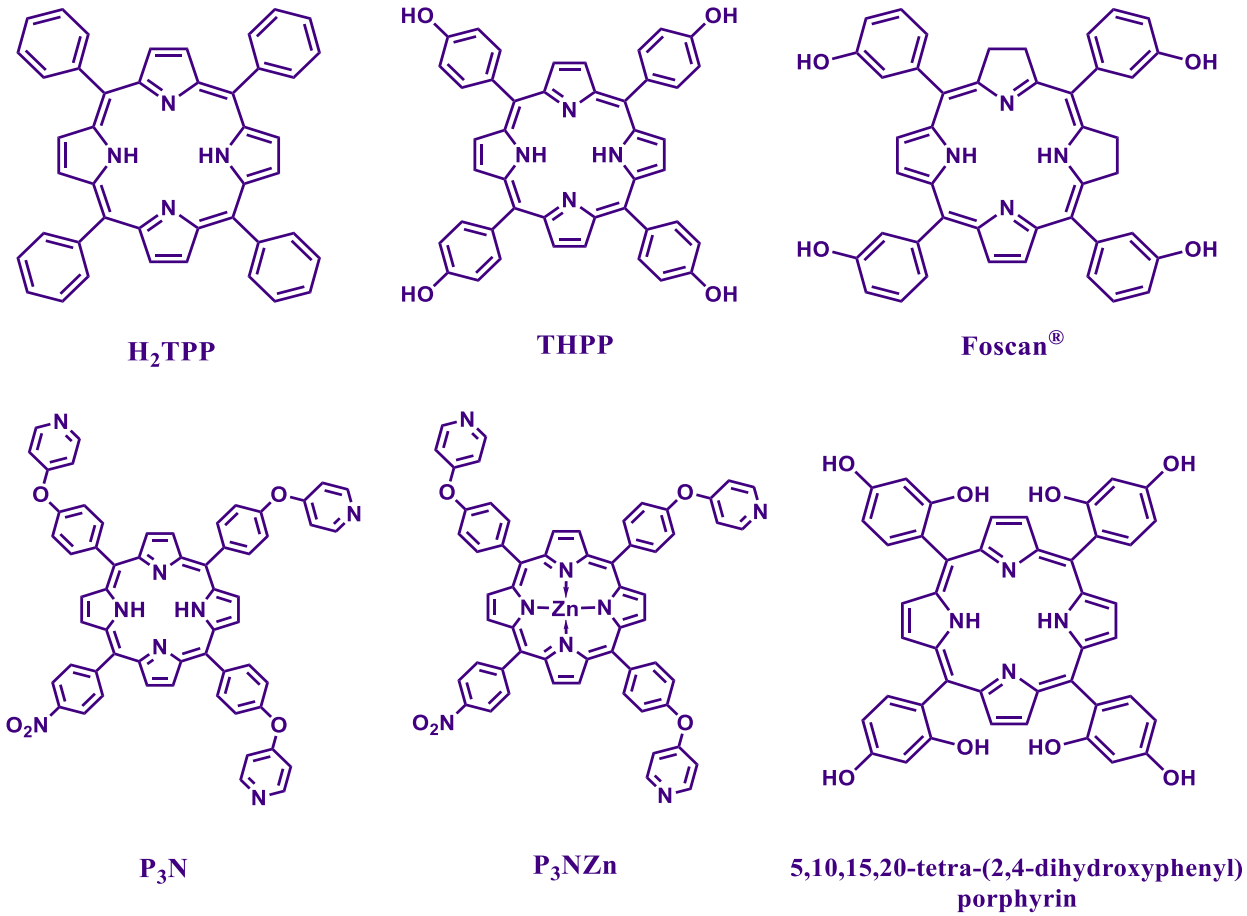


Figure 1.3.3.1: Some neutral porphyrin PSs used as PDT agents.

1.4 Zn-incorporated porphyrins as PSs for PDT applications:

Zn, an essential trace element, is a co-factor for over 300 enzymes involved in DNA, RNA replication and protein synthesis.[273-274] Zn has an immunostimulatory effect and its deficiency has the potential to affect host immunity adversely.[273, 275-277] Owing to its biological significance, Zn-incorporation has been a common strategy to obtain PSs with better photobiological outcomes.[66-67, 147, 252, 278-280] Zn insertion is usually accompanied by stabilisation of the porphyrin ring structure[280] and quenching of fluorescence.[147, 281-283] The reduction in fluorescence intensity can be attributed to the "heavy atom effect".[147, 281-283] The incorporation of Zn^{2+} in the porphyrin core most likely enhances ISC from singlet excited state to triplet excited state, thereby leading to the observed decrease in fluorescence. A higher triplet

state population ensures a longer triplet lifetime, thereby ensuring more effective interaction with molecular oxygen resulting in the production of cytotoxic $^1O_2$.[284-286]

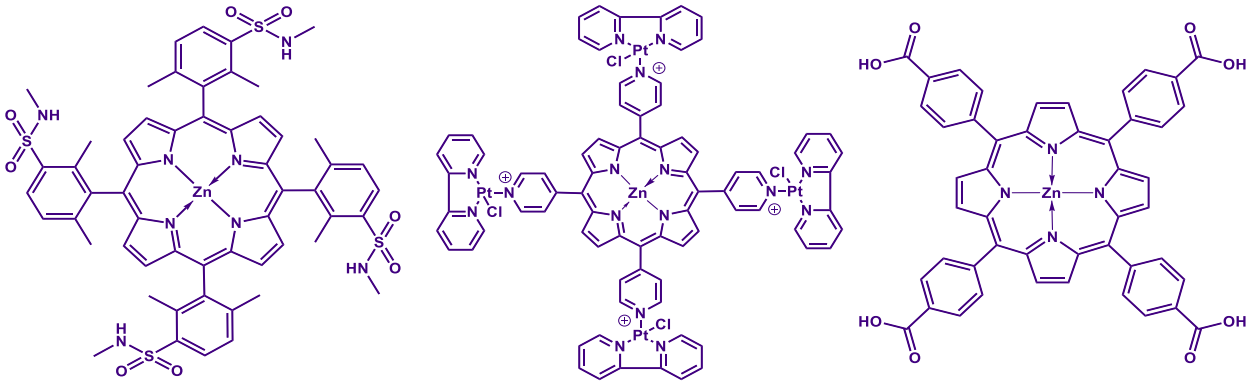


Figure 1.7.1: Zn-porphyrin PSs used as PDT agents.[278, 287]

Zn porphyrin PSs (ZnPPSs) show enhanced interactions with cell membranes and exhibit higher cellular uptake with a global distribution.[280, 288] The cationic charge and amphiphilicity however play a major role in determining cellular uptake and subcellular localisation. Ezzeddine *et al*.[288] demonstrated that hydrophilic tetra-cationic ZnPPSs bearing *meso*-N-methylpyridinium substituents preferred lysosomal localisation. In contrast, the amphiphilic *meso*-N-hexylpyridinium derivatives were localised in mitochondria, endoplasmic reticulum, and plasma membrane. The effect of lipophilicity rendered through variation in the length of the alkyl chain has been reported earlier, with longer alkyl chain PSs favouring a mitochondrial uptake.[280] Zn^{2+} ions in the PS core can also interact with the phosphate group of phospholipids and show a better binding capability to both synthetic and biological membranes. Several studies have reported that ZnPPSs have shown higher ROS generation and/or $^1O_2$ generation capability than their free-base counterparts.[252] A preference for ZnPPSs for $^1O_2$ generation has been established through photophysical experiments.[278, 287] These factors make ZnPPSs an attractive drug target in cPDT, aPDT and the inactivation of viruses.[66-67, 147, 185, 252, 278-280, 288]

COMBINATORIAL PDT TO PROMOTE IMMUNO-PHOTODYNAMIC THERAPY (IPDT)

Integrating porphyrins into immunotherapy offers new prospects for immuno-photodynamic therapy (IPDT).[289-292] Recent advancements in cancer immunology have led to the emergence of cancer immunotherapy, a promising approach to combat this disease.[293-295] This innovative

therapy focuses on harnessing the body's immune system to identify, attack, and eliminate cancerous cells, offering the potential for long-term disease control.[289, 293-295]

Immunotherapeutic strategies, including immune checkpoint blockade (ICB) therapy, chimeric antigen receptor T cells (CAR-T) therapy, and cancer vaccines, have been developed to mimic the body's natural antitumor immune defences.[296-298] While these approaches have shown promise, they face challenges related to the limited immunogenicity of solid tumours and low clinical response rates, rendering them ineffective for all patients.[295, 299-303]

There is a growing interest in combinational strategies like immuno-photodynamic therapy (IPDT) to address these limitations and enhance immunogenicity for more efficient cancer immunotherapy.[304-307] IPDT has gained prominence due to its ability to induce antitumor immune responses through a mechanism known as immunogenic cell death (ICD).[304-305, 308-309] This approach aims to complement the shortcomings of individual therapies and activate the immune system effectively in cancer treatment.

During IPDT, photosensitizers are activated by specific wavelengths of light in the presence of oxygen, generating cytotoxic reactive oxygen species (ROS).[304-305, 308-309] These ROS play a crucial role in inducing apoptosis in cancer cells. However, the immunosuppressive tumour microenvironment (ITM) limits the effectiveness of PDT-induced cell death. Therefore, to enhance PDT's efficacy, there is a need to strengthen ICD with synergistic tumour therapies.[308, 310-314]

IPDT has emerged as a promising strategy, leveraging PDT to stimulate the immune response and combining it with immunotherapy.[304, 310-311, 313, 315-316] This approach aims to transform immune-OFF tumours into immune-ON ones, fostering a systemic immune response and preventing cancer recurrence.[304]

In the context of immunity, the source of tumour immunogenicity stems from the dying cancer cells, which provide the essential antigens capable of triggering tumour-specific immune responses.[317] This phenomenon underscores the significance of immunogenic cell death (ICD) as an alternative approach for activating adaptive immune responses in hosts with normal immune function.[318-321] ICD, characterized as a successful interaction between dying tumour cells and a properly functioning immune system, bridges the gap between photodynamic therapy (PDT) and immunotherapy. It rejuvenates the patient's immune system via immuno-photodynamic therapy (IPDT), offering a comprehensive approach to cancer treatment.[304]

Evidence has demonstrated that upon PDT, dying cells actively upregulate immune responses. However, the extent of immunogenicity and the subsequent molecular pathways largely depend on the induction of cell death.{Ahmed, 2020 #1221}{Galluzzi, 2017 #1222} Therefore, understanding the mechanisms of IPDT-induced ICD at the cellular level is crucial to comprehend how the immune system gets activated and, ultimately, to enhance the feasibility of IPDT.[304, 322] Apoptosis is a caspase-dependent process of programmed cell death that plays a crucial role in development, homeostasis, and immunity in multicellular organisms. Facilitating apoptosis represents one of the most active regulatory pathways to induce ICD effectively.[304, 323] Cancer cells exhibit higher sensitivity to reactive oxygen species (ROS) than normal cells, making apoptosis induced by IPDT particularly effective while avoiding overtreatment.[304, 323] Key features of IPDT-induced apoptosis include chromatin condensation, cellular fragmentation, and protease activation. Tumour cells undergoing apoptosis-initiated ICD are often linked to the localization of photosensitizers (PSs), such as the mitochondria-mediated pathway, oxidative stress-induced DNA damage, and endoplasmic reticulum (ER) stress.[324] Among these, PSs localized in the mitochondria have been widely studied for their ability to induce apoptosis. When exposed to irritant signals like ROS, the mitochondrial outer membrane becomes permeable, releasing hemeprotein cytochrome C, activating caspase proteases responsible for the apoptosis process. Another well-known signal transduction pathway is ER stress-induced apoptosis, whereby toxic stress and environmental changes affect the ER, potentially leading to cell apoptosis.[304] Key proteins involved in apoptosis, including caspase-3, caspase-7, GRP78, and CHOP, serve as critical mediators, influencing reactions such as cell migration and differentiation, ultimately provoking ICD.[325]

Necroptosis represents a form of lytic-regulated cell death characterized by cytoplasmic swelling, plasma membrane disintegration, and intracellular content leakage induced by specific stressors.[326-328] This inherently immunogenic form of cell death is accompanied by the disintegration of intact cytosolic components, triggering various inflammatory responses. Typically, necroptosis-induced ICD occurs in the presence of photosensitizers targeting the cell membrane.[329] The photoreaction facilitates the assembly of kinases RIPK1 and RIPK3 into the necrosome, causing rapid loss of membrane integrity and the release of immunogenic DAMPs (damage-associated molecular patterns). This robustly activates the innate and adaptive immune systems.[304]

Additionally, death receptors like tumour necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and toll-like receptor 4 (TLR4) are continuously activated, positively correlating with tumour cell immunogenicity. Notably, necroptosis is found to be more efficient in IPDT-induced ICD compared to apoptosis. This efficiency boost in antitumor immunity is attributed to the direct release of tumour-specific antigens without exposure to further oxidation and proteolysis by organelles.[304] This contributes to antigen uptake by tumour-associated macrophages, DCs (dendritic cells) maturation, efficient CD8+ T cell cross-priming, activation and differentiation of antigen-specific native CD8+ T cells into cytotoxic T lymphocytes, ultimately participating in antitumor immunity.[304] Thus, targeted induction of necroptosis in dying tumour cells represents a promising approach in cancer therapy, particularly for apoptosis-resistant tumours.[304, 330]

One notable porphyrin PS is Chlorine6 (Ce6), known for its rapid generation of cytotoxic reactive oxygen species (ROS) when exposed to red-light irradiation, enhancing immunogenicity.[331] This, in turn, promotes dendritic cell (DC) maturation and the infiltration of T cells into tumour sites, bolstering the effectiveness of tumour immunotherapy. Encouraged by these advantages, Peng et al. introduced a multifunctional nanomedicine termed SPM-P/C, incorporating a plasmid DNA encoding the catalase gene (pDNA-cat) and Ce6.[304, 332] SPM-P/C demonstrated the ability to stimulate robust immunity, including DC maturation and antitumor T cell infiltration through hypoxia-relieving PDT.

Zheng and colleagues harnessed the potential of Ce6 to develop an oxygen-self-sufficient nanocarrier (C@HPOC) for IPDT.[333] This innovative approach facilitated tumour-targeted co-delivery of PSs and oxygen, alleviating tumour hypoxic conditions. The increased oxygen improved PDT efficacy and enhanced the infiltration of cytotoxic T lymphocytes and natural killer (NK) cells, resulting in a potent antimetastatic and abscopal effect.

In light of the essential role played by the endoplasmic reticulum (ER) in maintaining cellular signalling, the development of ER-targeting porphyrin agents emerges as a promising strategy for effective IPDT. For instance, Deng et al. engineered an intelligent ER-targeted porphyrin encapsulated in a reduction-sensitive polymer.[334] Under near-infrared (NIR) light irradiation, these Ds-sPNPs induced ER stress, triggered immunogenic cell death (ICD), and promoted the release of DAMPs. Furthermore, the secretion of cytokines and the infiltration of CD8+ T cells at the tumour site increased, highlighting the potential of this combined PDT strategy to activate immune cells and enhance immunotherapy efficacy.

Beyond porphyrins, phthalocyanines, another class of PSs, exhibit superior photo properties that render them highly attractive for PDT. BAM-SiPc, a silicon(IV) phthalocyanine, was found to induce immunogenic necroptosis in tumour cells.[335] Additionally, Yoon's group reported on the self-assembly of morpholine-substituted silicon phthalocyanine with albumin for fluorescence imaging and IPDT.[304, 336] This approach hinged on the acid-induced abolition of the photoinduced electron transfer effect and the breakup of the nanostructure, resulting in a fluorescent turn-on. This innovation provided high signal-to-noise ratios and tumour-targeted imaging. With a superior immunogenic PDT NanoPcM effectively combating solid tumours, the combination of NanoPcM-based PDT with αPD-1-induced immunotherapy demonstrated the ability to inhibit tumour growth, reduce spontaneous lung metastasis, and trigger abscopal effects. This research opens new avenues for selecting PSs in the design of nanomaterials for promising photo theranostics in cancer imaging and IPDT.

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