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Application of Porphyrin nanomaterials in Photodynamic therapy

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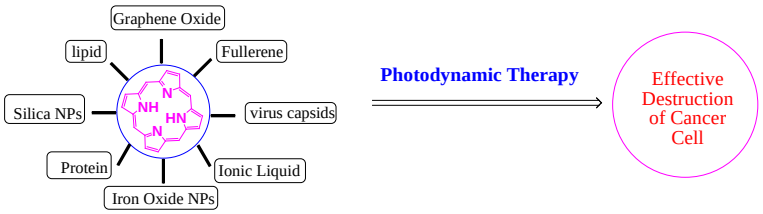
ABSTRACT



Cancer is one of the most deadly diseases and many methods have been developed for cancer therapy. Photodynamic therapy (PDT) is an advanced modality for the treatment of malignant tumors as it is widely used for clinical cancer treatments. The principal of PDT is based on the selective internalization of a drug (photosensitizer) which upon irradiation with light generates reactive oxygen species that kill cancer cells. Various porphyrin nanomaterials and their precursors have promising applications in the fields of drug delivery and PDT in oncology due to their unique optical and photothermal properties. The recent developments of nanoporphyrins for their application in cancer diagnosis and cancer treatment through photodynamic therapy have been reviewed.

Keywords: porphyrins; nanomaterials; photodynamic therapy; cancer; photothermal therapy

INTRODUCTION

Cancer is one of the hard-hitting diseases that cause immense terror in human beings. Cancer is also called as malignancy or malignant tumor. Cancer is an uncontrollable growth of cells that results in lumps or masses of tissue called tumors. A malignant tumor forms when cancerous cell manages to divide, grow and move throughout the body either by destroying healthy tissues of blood and lymph systems (invasion) or by making new blood vessels to feed itself (angiogenesis). Cancerous cells damage the body by interfering with digestive, nervous, and circulatory systems and they can release hormones that can alter body functions.

There are more than 120 different types of cancer that affects humans. Cancer treatment depends on the type of cancer, the stage of the cancer, age, health and physical condition. Recently, advances in various cancer therapies have been made in order to better fight cancer diseases.[1] Photodynamic therapy (PDT) belongs to one of the most promising fields of medicine and has been applied worldwide for cancer treatment.[2] The PDT has several advantages over conventional therapies due to its minimally invasive nature, selectivity, the ability to treat patients with repeated doses without initiating resistance or exceeding total dose limitations (as associated with radiotherapy), fast healing process resulting in little or no scarring, the ability to treat patients in an outpatient setting and the lack of associated side effects.[3] Porphyrins represent an important class of photosensitizer that are frequently used in PDT.

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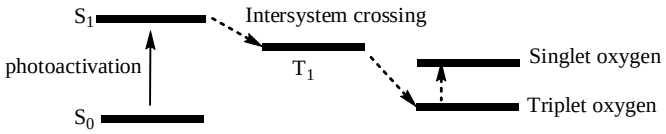
Nanotechnology has revolutionized PDT procedure by application of nanomaterial based agents. The application of nanomaterial-based agents may change the pharmacokinetic properties of the drug and may exhibit promising PDT efficacy.[4] The use of nanomaterials ensures high loading and delivery capability in targeted PDT treatment.[5] Moreover, the size of nanoparticles can be easily tuned for selective and easy accumulation in tumor cells through the enhanced permeability and retention effect (EPR). Nanomaterials such as TiO_2, ZnO and fullerenes are well known to generate singlet oxygen species. A wide range of materials comprised of metal-based (gold, silver and silica) to polymer-based (chitosan, dextran and poly ethylene glycol) can be used for the development of various nanoparticles to give a breakthrough in PDT process.[6,7] Although promising, inorganic nanoparticles have not yet achieved broad clinical application because of concerns about their long-term safety and surface-dependent drug-loading property. Various porphyrin based nanomaterials have been extensively explored in selective drug delivery and PDT in cancer treatment due to their unique optical, photothermal and pharmakinetic properties that ensures high PDT efficacy.

PHOTODYNAMIC THERAPY (PDT)

Photodynamic therapy (PDT) is a type of photochemotherapy that destroys target cancerous cells in the presence of oxygen when light irradiates a photosensitizer, generating large quantities of reactive oxygen species.[8] During PDT, a sensitizer can be administered intravenously, intraperitoneally, or topically and it selectively localizes in a tumor due to physiological differences of tumor cells from healthy cells such as elevated levels of low-density lipoprotein (LDL) receptors, high fraction of tumor-associated macrophages, lower intracellular pH, and large amounts of collagen, leaky microvasculature and poor/or lymphatic drainage by tumors.[9] Localization of photosensitizer in cancer cell depends on its nature and properties as well. Hydrophobic sensitizers attach with LDL and hydrophilic compounds bind to albumin and globulins.[10] Cationic sensitizers accumulate in mitochondria; anionic species collect in lysosomes, perinuclear region and/or vesicles of the cell.[11] Following localization, fluorescence from the sensitizer can be used to diagnose and detect the tumor.

The target cancerous cells are irradiated with light at a wavelength according to the absorption band of the photosensitizer.[12] Upon light exposure at appropriate wavelength, photosensitizer undergoes transformation from ground state (S_0) to first excited state (S_1) and then intersystem crossing to triplet excited state (T_1). Further, the reaction with molecular oxygen can take place by two different processes. In Type I process, ion radicals formed by interaction of an excited photosensitizer with an adjacent sensitizer molecule via hydrogen abstraction or electron transfer, react with ground state triplet oxygen to produce superoxide anion, hydrogen peroxide and hydroxyl radical. In type II process, energy transfers directly from T_1 to triplet oxygen to generate singlet oxygen (Scheme 1). Direct energy transfer requires that photosensitizer should be in same triplet state multiplicity as ground state oxygen. The lifetime of singlet oxygen is very short (0.2 μs) inside cells due to its high reactivity. Therefore, PDT procedure is localized at the point of singlet oxygen generation. The singlet oxygen is cytotoxic and causes destruction of cancer cell via erythema, edema, apoptosis or necrosis.[13] It is believed that the Type-II mechanism dominates for most reported porphyrin molecules during PDT.



Scheme 1: Generation of singlet oxygen by type II sensitization process

The first generation photosensitizer includes hematoporphyrin (Hp) which has been isolated from haemoglobin and has many drawbacks such as toxicity and prolonged accumulation in tissues. The second-generation photosensitizer drugs with less toxicity and short accumulation in tissues have also been developed. However, their hydrophobic nature and poor tumor selectivity limits their application in PDT. In the third- generation photosensitizer drugs, their accumulation in healthy tissues is reduced by employing targeted delivery using carrier molecules. Activatable PDT is a relatively new PDT approach to achieve high degree of selectivity.[14] Activatable photosensitizers are photodynamic inactive in healthy tissue environment on laser irradiation as there is no singlet oxygen generation. In tumor cells, they are tuned to be photodynamic active by methods, such as enzymatic,[15] nucleic acid,[16] and environmental (such as pH and hydrophobicity) activation mechanisms.[17] Therefore, high level of PDT efficacy is achieved by selective approach of activatable photosensitizers.

PHOTO THERMAL THERAPY (PTT)

Photothermal therapy (PTT) represents a doable approach for the treatment of diseases by utilizing laser. Similar to PDT, in PTT procedure a light-absorbing agent called thermal enhancer is administrated followed by irradiation with local laser to achieve highly selective treatment.[18] PTT agents absorb light and dissipate the vibrational energy as heat. The targeted tissues within a thermal ablation get destroyed by necrosis.[19] To achieve selective heating at the target tissue, a biocompatible photothermal agent with large absorption coefficient in the near infra red regions is required primarily. In PTT process, the percentage increase in the temperature mainly depends on the wavelength and coefficient of near infra red absorption as well as on the power of the excitation light.[20] Different kind of photothermal agents have been used for the conversion of near-infrared light energy to heat, within tumors.[21] Recently, nanoporphyrin structures have also been used as promising photothermal agents.

PORPHYRIN NANOMATERIALS IN PHOTODYNAMIC THERAPY

Porphyrins are well known agents to treat cancer via photodynamic therapy. Photodynamic therapy was developed in the early 1900s[22] but it was used for the first time in cancer treatment when the food and drug administration (FDA) approved a hematoporphyrin derivative known as Photofrin® (porfimer sodium) as photosensitizer in 1990 (Figure.1). Other common hematoporphyrin derivatives which can be used as photosensitizers in PDT include Photogem® and Photosan-3®. They are known as first generation photosensitizers. Owing to their adverse properties such as skin phototoxicity and low absorption in the visible spectrum, second generation phosensitizers have been targeted which include *meta* isomer of 5,10,15,20-tetra(hydroxyphenyl)porphyrin (*m*-THPP), and 5,10,15,20-tetrakis(4-sulfanatophenyl)-21H,23H-porphyrin ($TPPS_4$) (Figure 2). Nanotechnology has revolutionized PDT procedure by the application of porphyrin based nanomaterials.

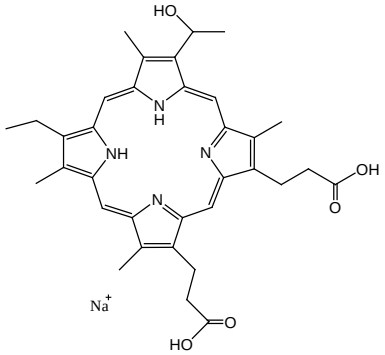


Figure 1: Structure of Photofrin®

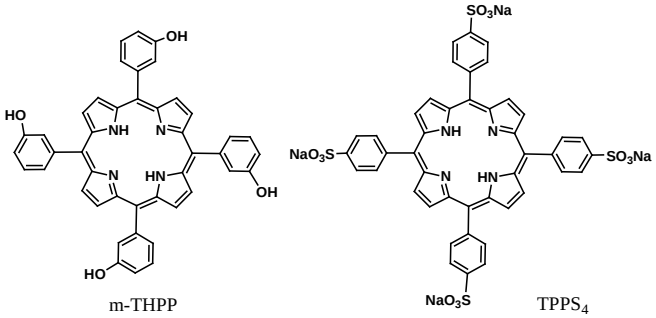


Figure 2: Molecular structures of some second generation porphyrins

2-(1-Hexyloxyethyl)-2-devinyl pyropheophorbide-alpha (HPPH, Photochlor®) (Figure 3) is a second generation photosensitizer that has been used for the treatment of lung, Barrett's esophageal, head and neck cancers.[23] HPPH is more tumor selective and safer to use as compared to photofrin® due to its lower skin photo-toxicity. A novel nanoformulation of polyethylene glycol-functionalized graphene oxide loaded with photosensitizer HPPH has been developed for photodynamic therapy of tumors. This nanoformulation shows promising photodynamic cancer cell killing efficacy *in vivo* due to the increased tumor delivery of HPPH.[24] This treatment procedure ensures long-term survival following treatment. Porphyrin functionalized graphene oxide was also used as PTT for the treatment of brain cancer.[25]

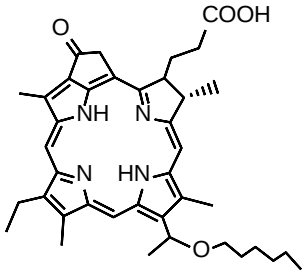


Figure 3: Structure of porphyrin (HPPH) used for the preparation of nanoformulation with polyethylene glycol-functionalized graphene oxide

Porphysomes, lipid enclosed porphyrin nanostructures, have been investigated for dual modality imaging of tumors through optical as well as photoacoustic tomography.[26] Zheng et al. has also developed porphysomes through self-assembly of porphyrin lipids. These porphysomes can absorb and convert optical energy into heat with great efficiency due to high porphyrin packing density.[27]

One of the successful strategies to improve the stability, delivery efficiency and selective accumulation of photosensitizers in target cells is to develop biocompatible nanoparticles-based activatable photosensitizers. Following this approach, polymers linked with porphyrins have also been developed for activatable PDT treatment, however, low photosensitizers packing density limits its applicability.[28] A porphyrin-based micelle formed via self-assembling amphiphilic polymer comprising polyethylene glycol and poly(D,L-lactide-co-glycolide) with porphyrin has also been developed, with high chemoselectivety.[29] Nanodevices developed by dendrimer porphyrins and dendrimer phthalocaynines have been used as effective photosentizers for PDT.[30] Virus capsids have been utilized as bio-derived nanomaterials for photodynamic therapy agents. A cancer-targeting nucleic acid aptamer decorated MS2 bacteriophage capsids loaded with cationic porphyrin photosensitizers has been developed for the treatment of human breast cancer upon photoactivation.[31] These bio-derived nanostructures are cell-specific and photogenerate reactive oxygen species causing cytotoxicity in MCF-7 cancer cells only. To overcome the problem of systemic prolonged photosensitisation syndrome in healthy tissues, porphyrin photosensitizers have also been conjugated with other biological vectors such as proteins, steroids, toxins, carbohydrates, peptides and functionalised nanoparticles.[32,33]

Nanoparticles have been employed for better and efficient delivery of hydrophobic photosensitisers.[34,35] Porphyrins conjugated to magnetic nanoparticles exhibit enhanced cellular uptake. Superparamagnetic iron oxide nanoparticles (SPIONs) are very versatile and have been used for making various nanodevices, in particular, for magnetic resonance imaging (MRI) and hyperthermia therapy.[36] Nanoconjuagtes between SPIONs and ethylene glycol derivative of porphyrin (Figure 4) (SPIONs-TPP) have been prepared by exploiting copper(I)-

mediated "click" chemistry which have been used as promising theranostic agents for photodynamic therapy.[37] SPION-TPP nanoconstructs show photocytotoxicity only upon light irradiation by promoting a photodynamic effect *in vitro* in murine amelanotic melanoma B78-H1 cells. The activity of SPION-TPP nanoconjugate is comparable to unbound porphyrin with IC_{50} values in the region of 800 nm as indicated by the singlet-oxygen generation test. However, these nanoconjugates have poor cellular uptake badly affecting the linearity of the dose-response effect. Cell delivery have been improved by conjugating these nanoconstructs with a cell-penetrating peptide (HIV TAT peptide) which shows IC_{50} value of about 500 nm and a linear dose-response effect. Internalization of these nanoparticles has been investigated through confocal microscopy by using rhodamine dye (Rhod) bound to TAT peptide sequence. These novel nanodevices (Rhod-TAT-SPION-TPP) have been effectively exploited for localisation and tracking of drugs through MRI based techniques as well as for treatment of cancer cells through photodynamic therapy.

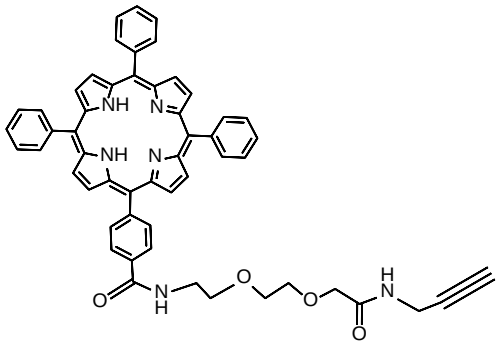


Figure 4: Structures of porphyrin (TPP) used for making nanoconjugates with superparamagnetic iron oxide nanoparticles (SPIONs)

Silica nanoparticles can be used for encapsulating photosensitizer drug for targeted drug delivery in PDT. Various porphyrin-based drugs have been loaded in silica nanoparticles such as protoporphyrin IX,[38] purpurin-18,[39] 2,7,12,18-tetramethyl-3,8-di(1-propoxyethyl)-13,17-bis-(3-hydroxypropyl)porphyrin (PHPP),[40] Pd-*meso*-tetra(4-carboxyphenyl) porphyrin,[41] hematoporphyrin[42] and porphyrin.[43] Mesopourous silica nanoparticles (MSNPs) conjugated with a near infra red fluorescent dye (ATTO 647N) are covalently linked with palladium porphyrin. The coupling of cRGDyK peptides on the surface of this complex make it versatile for the targeted delivery of drug.[44] Novel "two-in-one" magnetic-fluorescent nanocomposites have been prepared by conjugating a porphyrin to silica-coated magnetite nanoparticles through covalent bonding.[45] A carboxylic acid protoporphyrin (protoporphyrin IX) was modified by reacting with 3-aminopropyltriethoxysilane in the presence of carbodiimide to form an amide bond and then it was treated with silica coated magnetite nanoparticles to form a nanoconjugate. These nanocomposites show photodynamic and hyperthermic agents capabilities due to their magnetic and fluorescent properties. These nanodevices can be explored for in vitro- and vivo-bioimaging applications such as MRI and fluorescence microscopy.

The nanoaggregates of zinc octaethylporphyrin have been developed in presence of ionic liquid (1-hexadecy-3-methyl imidazolium bromide) (Figure 5).[46] An efficient amount of singlet oxygen generation has been investigated from porphyrin nanoaggregates by phosphorescence spectra at the near infra red (NIR) region which can a breakthrough in the development of new ionic liquid assisted porphyrin nanoaggregates as PDT agents.

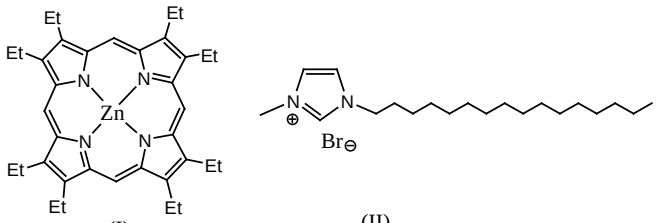


Figure 5: zinc octaethylporphyrin (I) and ionic liquid used to prepare nanoaggregates (II)

The self-organization of porphyrin bearing a naphthalene–methylpyridinium moiety and its co-assembly with cucurbit[7]uril leads to the formation of a supramolecular photosensitizer (Figure 6).[47] This noncovalent nanoassembly can effectively generate singlet oxygen and thereby helps in construction of new photosensitizers.[48] Fullerene-porphyrin nanostructures have also been developed and studied for treatment of cancer *via* PDT.[49]

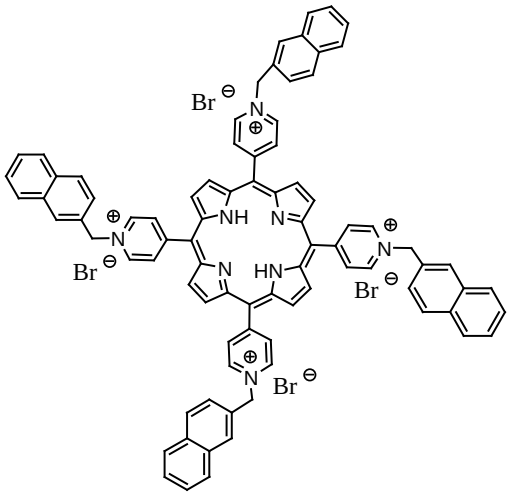


Figure 6: Structure of porphyrin used to fabricate non-covlant nanoassembly with cucurbit[7]uril

The combination of PDT and chemotherapy has gained increasing interest for cancer treatment as it permit low doses of photosensitizer and anticancer drug.[50] Cancer-targeted co-delivered systems of photosensitizers and anticancer drugs have been developed in the form of hematoporphyrin (HP)-modified doxorubicin (DOX)-loaded nanoparticles (HP-NPs) to increase the efficiency of PDT treatment of liver cancer. Hematoporphyrin is an efficient PDT agent and can act as ligand for low density lipoprotein (LDL) receptors on the

hepatoma cells. The in vitro phototoxicity in human hepatocellular carcinoma cells has enhanced in HP-NPs as compared to free HP with varying light irradiation condition. Similarly, in vivo anticancer efficacy in human hepatocellular carcinoma tumor-bearing mice has been observed to be better by HP-NPs-based PDT treatment in terms of tumor growth and immunohistology.

A novel four-armed porphyrin-cored star-shaped poly(L-lactide)-b-poly(ethylene glycol) (SPPLA-b-PEG) block copolymer has been synthesized from the ring-opening polymerization (ROP) of L-lactide initiated with porphyrin followed by coupling with hydrophilic poly(ethylene glycol).[51] Tetrahydroxyethylterminated porphyrin was specially used as an initiator. The self assembly of this amphiphilic copolymer leads to micelles formation and used as photosensitizing agents. Copolymers have also been utilized for encapsulating hydrophobic drugs such as DOX. This self-assembled copolymer exhibits efficient singlet oxygen generation and a high fluorescence quantum yield. Highly versatile 'all-in one' porphyrin-based organic nanoporphyrin was constructed by using a single organic building block, a porphyrin/ cholic acid hybrid polymer.[52] These nanoparticles could be activated to release singlet oxygen, heat and drugs simultaneously at the tumor sites for simultaneous PTT/PDT and chemotherapy upon illumination. Nanoporphyrins have been used in personalized cancer theranostics. An engineered lipoprotein mimicking nanoporphyrin structure (PLP) has been developed which allows rapid dissociation of nanostructure upon its accumulation in tumor and releases active monomeric porphyrins to produce fluorescence and photodynamic activity.[53] This is an active mechanism for imaging and customized photodynamic therapy.

CONCLUSION

There is potential to increase the efficiency and effectiveness of treatments offered against cancer. Porphyrin compounds have extended conjugation and absorb in the red region of the visible light and therefore have been extensively explored in selective drug delivery and photodynamic therapy. The coupling of porphyrinoids with nanoparticles has enlightened a new and innovative path for PDT treatment of cancer diseases. Different theranostic formulations of porphyrin nanomaterials based on silica nanoparticles, fullerene, virus capsids, protein, steroids, carbohydrates, iron oxide nanoparticles, polymers, graphene oxide and liposomes have been studied and their applications in cancer treatment have been demonstrated. Porphyrins are biocompatible and highly biodegradable hence can be used efficiently as nanocarriers and light absorbers but their relatively short absorption range limits their efficiency *in vivo*.[54] Hence, advances in modified porphyrin based nanomaterials as promising photosensitisers and photothermal agents with strong NIR absorbance is expected in the future.

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