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Abstract

Porphyrins are organic compounds that continue to attract much theoretical interest, and have been called the “pigments of life”. They have a wide role in photodynamic and sonodynamic therapy, along with uses in magnetic resonance, fluorescence and photoacoustic imaging. There is a vast range of porphyrins that have been isolated or designed, but few of them have real clinical applications. Due to the hydrophobic properties of porphyrins, and their tendency to aggregate by stacking of the planar molecules they are difficult to work with in aqueous media. Therefore encapsulating them in nanoparticles (NPs) or attachment to various delivery vehicles have been used to improve delivery characteristics. Porphyrins can be used in a composite designed material with properties that allow specific targeting, immune tolerance, extended tissue lifetime and improved hydrophilicity. Drug delivery, healing and repairing of damaged organs, and cancer theranostics are some of the medical uses of porphyrin-based nanocomposites covered in this review.

Keywords

Porphyrin, Nanoparticle, Nanocomposite, Drug delivery, Theranostics

1. Introduction

In the past, intravenous injection of pharmaceuticals containing insoluble suspensions was considered impossible due to the danger of embolisms. Nowadays, improvements in nanoparticle (NP) suspensions including nano-drugs has increased the therapeutic index. Nano-drugs with improved activity, reduced toxicity and the ability to target the diseased tissues have emerged [[1], [2], [3]]. However, many nanoparticles are still solid macromolecular constructions, which are too disperse, not

necessarily polymers, and generally less than 200 nm in diameter [1,[4], [5], [6]]. Since the late seventies, the use of nanoparticles as drug targeting vehicles has faced the problem of the lack of the biodegradability of polymers [7]. Development of nano-vehicles depends on polymers with good biocompatibility and biodegradability properties, which has been helped by the introduction of albumin [8], polyalkyl cyanoacrylate [9], polylactate and glycolate [10], lipids in solid form [11], and chitosan [12] NPs. Overall these nanovehicles were proposed for the treatment of different diseases of the liver or reticuloendothelial system (as well as cancer or infectious disease) because of the ability to concentrate in these tissues. The biodistribution of NPs is goverened by the natural opsonization process that appears after intravenous injection, and the next level was specific targeting to tissues and organs [13,14].

It is worth mentioning that the targeting of NPs via specific antibodies that recognize cancer cells was utilized in the early eighties [15]. Recent bioconjugation methods, like the Huisgen 1,3-dipolar cycloaddition reaction (named “click chemistry”), are suitable for NP construction [16]. Targeted delivery is considered the most likely option to improve the treatment of many diseases. Targeted delivery gives us three valuable advantages that traditional systemic delivery lacks: (1) the therapeutics will act at the intended action site, limiting off-target effects, including the damaging side-effects of chemotherapy; (2) the lower dose needed with targeted delivery can better focus the therapeutic agent to the target site, and reduce systemic side effects; (3) targeted delivery can transport the therapeutics to places that are not easily accessible by traditional drugs. The first attempt at improving delivery were carriers attached to antibodies. Two FDA-approved examples were Brentuximab vedotin (Adcetris) and Trastuzumab emtansine (Kadcyla)], while some others are still in clinical testing [17]. However, some limitations of this approach cause problems, such as structural heterogeneity, inconsistent preparation, and restricted solubility [17,18]. Drugs that contain antibodies are generally useful only in some cases. Additionally, other NP delivery vehicles (such as liposomes, polymer based NPs, metal based NPs, and protein based NPs), have the potential to carry out more effective and more reliable delivery due to encapsulating therapeutic cargos within the particle with a higher cargo to carrier ratio [3,16].

Porphyrins belong to a class of heterocyclic macrocycles. These organic compounds are constructed from four conjugated pyrrole rings arranged in a circle. The pyrrole α-carbon atoms are connected with methylene bridges [19]. Porphyrins have a total of 26 π-electrons, of which 18 π-electrons are in a planar, continuous macrocycle [20]. The basic chemical structure of porphyrin and its main family members are summarized in Fig. 1.

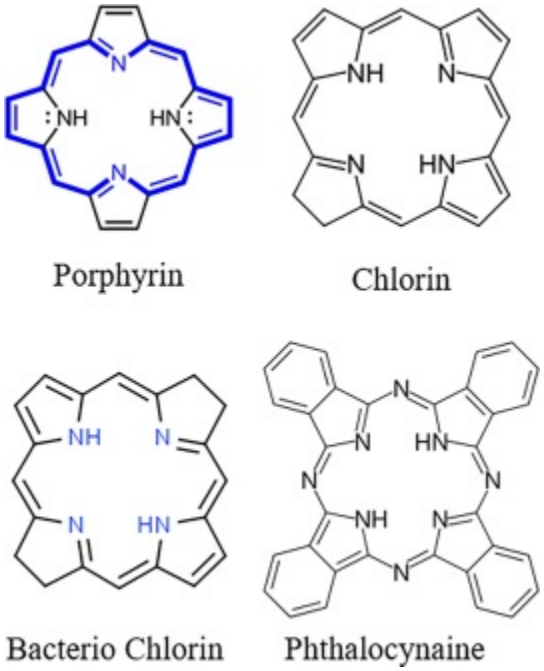

Fig. 1. Basic chemical structure of porphyrins and the main family members.

The understanding of porphyrin structures has advanced appreciably in recent years, and many publications have described detailed structures for porphyrin and metalloporphyrin molecules and their different roles in biomedical applications. Generally, porphyrins are a class of tetrapyrrole macrocycles with a 1-D or 2-D or sometimes 3-D skeleton. By replacing the α, β and other carbon atoms of porphyrins, by nitrogen atoms and the other alternatives, their properties can change dramatically, and also their biomedical applications. In addition, aspects of the chemistry of porphyrins are related to their acting as ligands in coordination complexes, depending on their structural properties which are controlled by bond angles and bond distances, as well as the nature of the metal and also the presence of functional groups. Generally, by using members of the first row of transition metals in the structure of porphyrins, toxicity is decreased to the minimum, however some second and third row transition metals such as Pt, Pd and Ru also have low cellular toxicity. By using amine-based ligands or linkers as the substituents, the biomedical applications of these compounds in photodynamic therapy, drug delivery and gene delivery are widened. However, carboxy-based linkers are also efficient for drug delivery, due to their potential bonding affinity with several drugs via hydrogen bonds [[21], [22], [23], [24]]. In this review article, a logical perspective about the relationship between the structural chemistry of porphyrins and their biomedical applications is presented.

Recently, porphyrin-based nanomaterials have received much attention due to various photophysical and photochemical properties of porphyrins [25,26]. The porphyrins can be extended to form other molecules using a central metalation process, which further tunes the photophysical properties of the porphyrins. Although the porphyrin family is famous for their light-mediated generation of highly reactive oxygen species, especially singlet oxygen, most porphyrin-based chemicals also have good fluorescence properties and photoacoustic properties, which make them potential candidates for simultaneous imaging/therapy applications called “theranostics” [[27], [28], [29]]. In this review, we

summarize the latest advances in preparation and delivery of porphyrin nanosystems and their biomedical applications.

2. Cancer theranostics using porphyrin-based nanomaterials

2.1. Cancer theranostics

Investigators have been interested in porphyrins and the related compounds for their powerful photosensitizing properties, their ability to selectively accumulate inside tumors and other abnormal tissues and cells, and their ability to remain inside tissues for long periods. These properties have enabled them to be used in biomedical applications from imaging for diagnosis (like fluorescence and magnetic resonance imaging (MRI)) to therapeutic uses (e.g. photodynamic, sonodynamic, boron neutron capture [30], and radiation therapy (RT)). Among them, PDT (photodynamic therapy), SDT (sonodynamic therapy) and BNCT (boron neutron capture therapy) are binary cancer therapies that require the simultaneous localization of the compound to the targeted tissue and the local (spatially confined) application of physical energy such as light (in PDT), ultrasound (in SDT) or a low-energy neutron beam (in BCNT). Therefore, porphyrins and their derivatives can be used in therapies that have potential for local control of tumors with fewer side effects than surgery or other cancer therapies (like radiotherapy, and chemotherapy). Also, since porphyrins are effective as metal chelators, they can transport metallic radioisotopes for use in cancer radiotherapy. Moreover, most porphyrins are hydrophobic and prefer an aggregated form, which may affect the therapeutic outcome resulting in a reduction in singlet O_2 generation and lower fluorescence quantum yields; therefore, many porphyrin nanocarriers have been investigated as photosensitizers for PDT applications [30]. Photofrin is one of the porphyrin derivatives used as a photosensitizing agent in cancer therapy. Another porphyrin derivative is Visudyne (benzoporphyrin derivative mono acid ring A), which has been approved as a pharmacological agent in ophthalmology by the Food and Drug Administration of United States (FDA). However, porphyrins and related derivatives still have the limitation of low aqueous solubility, making them hydrophobic and prone to aggregate. This aggregation is the main reason for the decrease in therapeutic efficacy, because generally only the monomeric species are photochemically active. However, porphyrins prefer to accommodate in tumors because of the unusual properties of cancer neovasculature. The highly permeable endothelium of tumor capillaries and the deficiency of lymphatic drainage in tumors allows selective accumulation in tumors over time after intravenous injection. However the selectivity of porphyrins for tumors is variable, and porphyrin cytotoxicity has to be considered that could affect healthy cells. Recently, with the advances made in nanotechnology for biomedical applications, a variety of NPs (i.e. inorganic and hybrid nanoparticles, liposomes, and polymeric micelles) have been applied to incorporate porphyrins, which generally improves their behavior in aqueous media. These nanocarriers should have suitable biocompatibility, biodegradability and should allow simple preparation and modification for the desired goals [30]. Porphyrins loaded inside NPs could solve some of the difficulties that have been mentioned above, and provide improved diagnostic and therapeutic properties. The use of porphyrins as multimodality imaging agents can impact the modern drive towards personalized medicine, monitoring and predicting the success of therapy, and yielding a better comprehension of disease states [30].

New porphyrin derivatives and their immobilization on iron oxide NPs were found to provide promising nanotools for PDT. Specifically, a zinc porphyrin derivative, ZnPR-COOH, was synthesized, characterized and immobilized onto prior synthesized iron oxide NPs via oleylamine. Characterization of this novel nanosystem (ZnPR-IONP) was achieved using different methods, such as UV–Vis spectrophotometry, fluorescence, X-ray photoelectron spectroscopy (XPS) and transmission electron microscopy (TEM). To explore the potential of the photosensitizer for PDT they quantified the singlet oxygen yield of ZnPR-IONP and the free ligand ZnPR-COOH, using 9, 10-anthracenedipropionic acid (ADPA) [31]. The results showed an increased singlet oxygen quantum yield after the porphyrin was attached to IONP (ZnPR-IONP). Furthermore, another porphyrin derivative called PR-TRIS3OH, combining various polar groups (TRIS), for improved water solubility was synthesized and immobilized in nanosystems. The singlet oxygen yield was measured, and was similar to ZnPR-COOH/ZnPR-IONP, and more than two-fold higher in the form of PRTRIS-IONP nanoparticles. The impressive singlet oxygen yield of PRTRIS-IONP along with its water solubility, suggests that these new nanotools could be used in PDT.

Although iron oxide based nanosystems that can be used PDT have been known for a decade, the production of new water-soluble porphyrin-based ligands has allowed iron oxide nanoparticles (IONPs) to be investigated for new medical uses. A zinc porphyrin derivative containing a phenoxy and three phenyl groups, with a carboxylic acid group at the meso location, was produced (ZnPR-COOH) and attached to the IONP surface to enhance the water-solubility of the NPs (ZnPR-IONPs). The hydrophilic porphyrin derivative possessed three TRIS groups (PRTRIS3OH). The ligand with high water solubility was immobilized on the IONPs surface to produce water stable NPs. The photosensitizer drugs and the NP conjugate were characterized, and the good singlet oxygen yield suggested they could be a candidate for PDT of cancer [32].

Gemcitabine hydrochloride is a chemotherapeutic drug with FDA-approval, used in the treatment of various cancers. Gemcitabine suffers from several problems. Firstly, it has a short *in vivo* half-life (about 8–17 min), secondly, it is rapidly excreted by the kidneys, and thirdly, its poor membrane permeability, all taken together suggest a nano-delivery method would be advantageous. Penon and coworkers [33] prepared periodic mesoporous organosilica NPs (PMOs) for light-activated for delivery of gemcitabine for cancer treatment. They used porphyrins as photosensitizers which were incorporated inside the PMO pores. Additionally, the ability of gemcitabine to be loaded into the mesoporous structure was investigated. They used both one-photon, and two-photon activation depending on the photosensitizer structure and its aggregation state. Ethylene-based PMOs were covalently attached to a tetrasilylated porphyrin (PS1) and the resulting J-aggregates in the mesostructure were suitable for two-photon PDT. The researchers found that the monosilylated porphyrin (PS2) did not form J-aggregates, although it could mediate one photon PDT. Synergistic cancer cell killing was observed by two-photon excited PDT plus gemcitabine delivery.

The commercially available tetra-amino porphyrin (PSa) was monosilylated by isocyanatopropyltriethoxysilane [33] and together with the tetrasilylated compound [34] formed from aminophenylporphyrin (PSb) provided EPMO (ethylene-based periodic mesoporous organosilica) NPs by a sol-gel process using bis-(triethoxysilyl)ethane and cetyltrimethylammonium bromide (CTAB). Co-condensation of bis-(triethoxysilyl)ethane gave the silylated photosensitizers PS1 or PS2. These two

compounds produced PS1-EPMOs and PS2-EPMOs, respectively (Fig. 2). PDT was mediated by two-photon irradiation (800 nm) and combined with gemcitabine delivered via PS1-EPMOs NPs killed 62% of the cells, showing potential efficacy for cancer treatment [35] (Fig. 3).

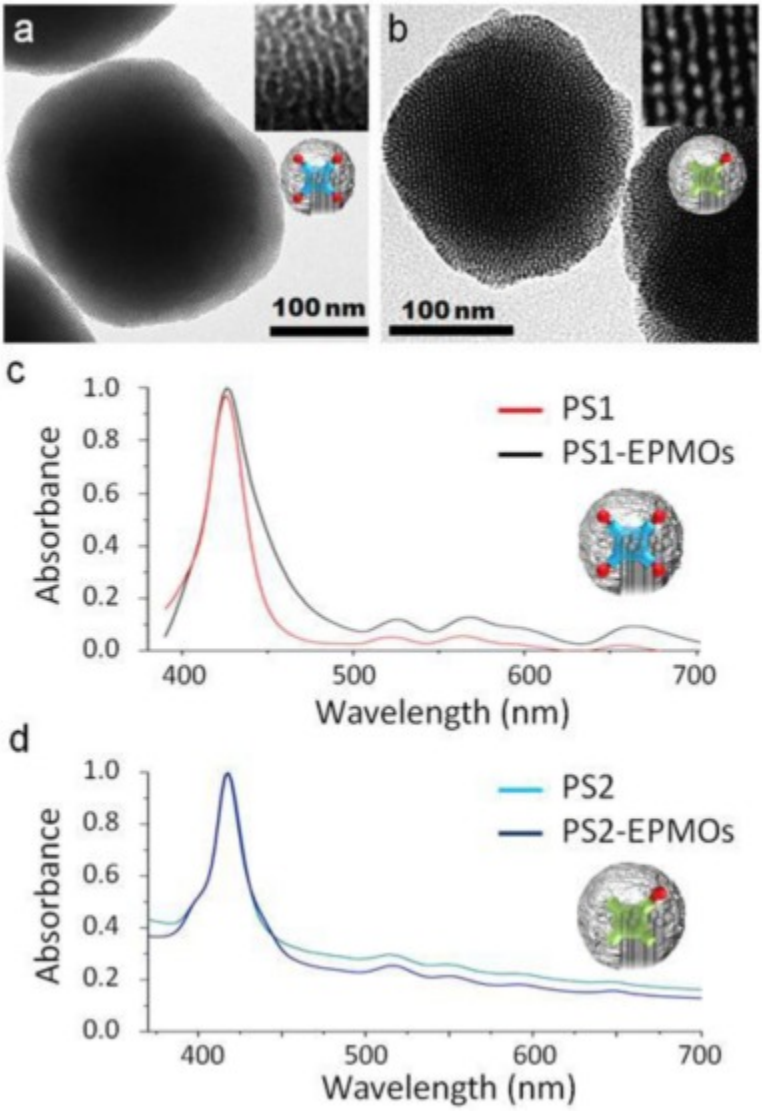

Fig. 2. PS1-EPMO and PS2-EPMO nanoparticles and their HRTEM micrographs, respectively (a and b). Images exhibit usual mesoporosities. Photosensitizer precursors and their visible UV-spectrum via their NPs in EtOH (c and d) [35].

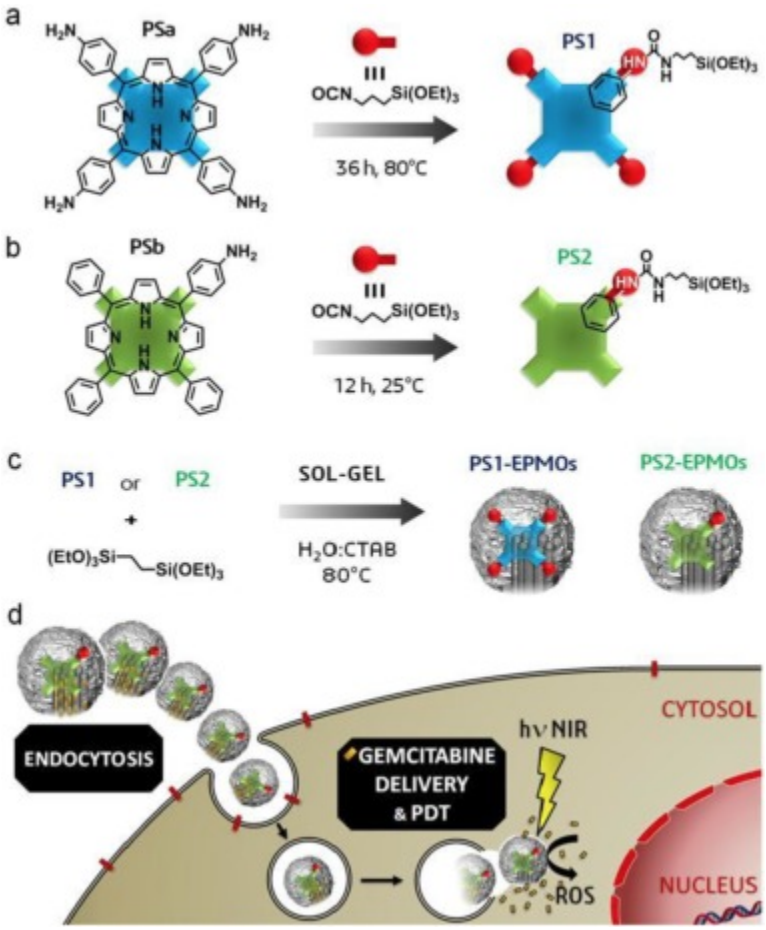

Fig. 3. PS1, PS2 and their photosensitizer precursors Silylation (a and b). ethanephotosensitizer via PMO nanoparticles production by Sol-gel (c). Functions of PMO nanoparticles for drug delivery and photodynamic therapy (synergistic manner) (d) [35].

Despite the availability of many different kinds of nanoscale materials, only a small number can be finely tuned for biomedical applications. It was shown that Zr(IV) incorporated in a porphyrinic MOF (metal–organic framework) formed NPs that could be used for targeted PDT. Using a bottom-up method, the MOF nanoparticle size can be precisely determined by tuning the functional motifs that are used to construct the MOF components The type of porphyrinic linker employed in the metal-organic framework NPs affect the properties irrespective of their size. Moreover, the size-dependent theranostic potential of these MOF clusters was studied in cancer cell models [36].

A porphyrinic Zr-MOF, called PCN-224 was suggested to be a strong candidate because of its good chemical stability and possession of nanoporous channels, permitting effective diffusion of photogenerated singlet oxygen [[37], [38], [39]]. The cubic phase of PCN-224 crystals would permit isotropic growth of crystals, enabling clearer size determination without interference from other variables (e.g., aspect ratio, and thickness) that would apply in a rod or a plate-shaped morphology (Fig. 4).

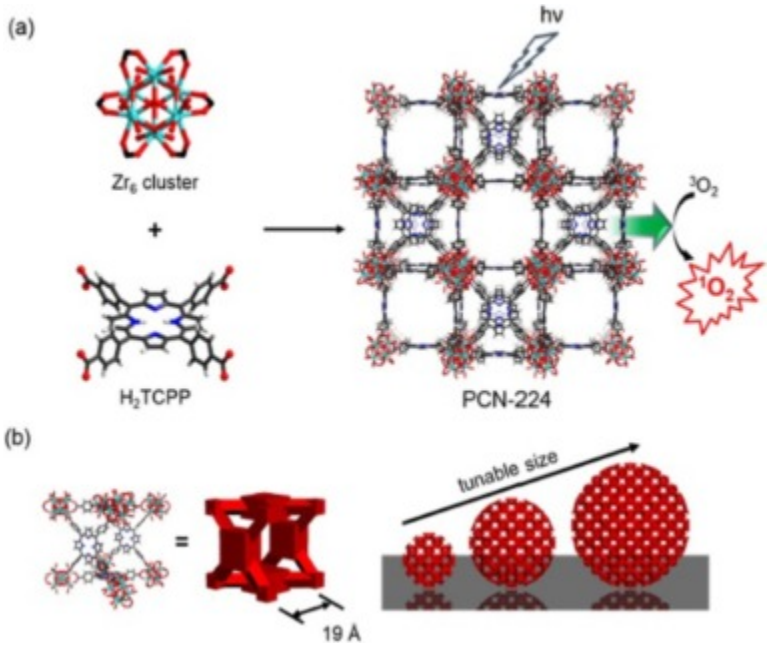

Fig. 4. PCN-224 construction Image. (a) a cluster of Zr6 with the open formula of (Zr6O4 (OH) 4(H2O) 6(OH) 6(COO) 6), tetratopic linker with the open formula of (tetrakis (4-carboxyphenyl) porphyrin with the open formula of (H2TCPP)), and image of PCN-224 as the 3D nanoporous framework. (b) A PCN-224 cubic unit and a schematic image of spherical PCN-224 NPs in cubic units structure form, potential to make various sizes [36].

Penon et al. produced a porphyrin-based gold NP conjugate that was water soluble including an antibody that recognizes the erbB2 receptor that is overexpressed on the surface of specific cancer cells. They used a monophasic technique to produce NPs that could photo-generate a high quantity of singlet oxygen, and the anti-erbB2 antibody bound to erbB2 receptors that were expressed on SK-BR-3 human breast cancer cells. The water-soluble, antibody-porphyrin NP conjugates were suggested to be useful for targeted PDT [40].

2.1.1. X-PDT (X-ray-activated photodynamic therapy)

Popovich et al. [41] reported that a LuAG:Pr3+@SiO2-PpIX nanocomposite could mediate X-ray activated PDT. It was prepared using a three-stage procedure: (a) the $Lu_3Al_5O_{12}:Pr^{3+}$ (LuAG:Pr3+) core was by prepared by photo-induced precipitation, (b) the amorphous silica covering was applied by a sol-gel method; and (c) protoporphyrin IX (PpIX) was chemically conjugated to the surface. The three-layered nanocomposite allowed X-ray activation of the Pr3+ to emit red luminescence; alternatively the energy transfer non-radiatively excited PPIX to produce singlet oxygen. The fluorescent probe 3'-(p-aminophenyl) fluorescein was activated by reaction with singlet oxygen and confirmed the X-ray activated PDT.

3. Different porphyrin-based nanoparticles

Nanoparticles can be engulfed by macrophages leading to accumulation inside the liver and the spleen after intravenous administration leading to their rapid removal from the bloodstream. Covering the NPs by poly (ethylene glycol) (PEG) extends the circulation time in the blood, leading to increased the accumulation inside tumors. One study prepared a theranostic nanoconstruct via the coating of Au nanoshells with poly (lactic acid) to form NPs that could be loaded with doxorubicin. They

subsequently attached a Mn-porphyrin to the Au shell using PEG linkers. The final construct showed good colloidal stability and an extended blood circulation time because of the introduction of PEG. Linking the Mn-porphyrin to the NP gave a high value of relaxivity (r_1 value of 22.18 mM^{-1} s^{-1} of Mn^{3+}), desirable for magnetic resonance imaging of cancer. Irradiation with a near-infrared laser allowed photothermal tumor destruction. The synergistic combination with doxorubicin chemotherapy suggested this nanoconstruct could function as an anti-cancer theranostic agent [14,42].

A report from Jimenez et al. described a zinc porphyrin compound containing eight triethoxysilyl groups attached by covalent bonds to mesoporous organosilica nanoparticles via the CuAAC-click reaction. They have showed that this compound could mediate doxorubicin delivery and the imaging of breast cancer cells by a two-photon imaging technique [43].

3.1. Liposomal porphyrins for cancer theranostics

Liposomes are spherical vesicles with an aqueous core surrounded a lipid bilayer. The use of liposomes to load and transport porphyrin molecules is of interest due to their ability to increase the solubility of PDT agents, and easy post-modification of the surface to enhance the accumulation and release in the cancer cells [44]. It has been proven that the formation of liposomes could decrease the dark cytotoxicity but enhance the PDT efficiency of the porphyrin, due to their ability to dissolve the hydrophobic PDT drugs inside the lipid bilayer [45,46]. Liposomes were first demonstrated in 1960, and are one of the few nanoparticle systems that have been successfully employed in clinical studies [[47], [48], [49], [50]], showing their potential to be used for delivery of PDT drugs, especially porphyrins [51,52].

Tedesco et al. [53] synthesized liposome-based zinc phthalocyanine incorporating a nitrosyl ruthenium complex and using liposomes based on dipalmitoylphosphatidylcholine (DPPC) and cholesterol. Their results showed a dramatic enhancement of the PDT effect against B16/F10 melanoma cells. The high efficiency of this system was explained by the interaction between the excited zinc phthalocyanine and the nitrosyl ruthenium complex, leading to release of NO radicals due to an electron transfer process which was enabled by the formation of the liposomes. Hiraka et al. [54] prepared pH-sensitive liposomes using a combination of anionic and cationic lipids plus Fe-porphyrin. The resulted liposomes showed remarkable PDT efficiency against MKN28 cells. Managa et al. [55] investigated the photophysical properties of liposomes based on F127 polymer, Zn-porphyrin, combined with graphene quantum dots (GQDs). The results indicated a synergistic effect of the GQDs and the porphyrin on singlet oxygen generation, as well as the high stability of the nanoconstruct due to π-π stacking. The formation of the liposomes led to enhanced cell uptake [56], and finally pH-responsive drug release due to changes in environmental pH [57].

The applications of porphyrin-based liposomes are not limited to PDT. One group of researchers prepared a theranostic construct composed of porphyrin dyad nanoparticles (TPD NPs) to allow magnetic resonance imaging (MRI) as well as PDT for cancer treatment. The liposomal NPs contained two different porphyrins, a non-metal porphyrin lipid, and a conjugated Mn–porphyrin. The metal-free porphyrin acted as a photosensitizer for PDT, while the Mn–porphyrin acted as a contrast agent for MRI. The theranostic porphyrin dyad nanoparticles (~60 nm) could accumulate inside tumors and were taken up by the tumor cells. 24 h after intravenous injection, MRI images of the tumor area were much

brighter than the surrounding healthy tissue, allowing laser irradiation of the tumor location for PDT [58].

3.2. Cerasomal porphyrins and cancer photodynamic theranostics

Researchers are studying ways of improving the physical and chemical stability of liposomes [59], to overcome problems of short shelf-life and the rapid clearance from the blood circulation. Liposomes with a PEG coating have longer blood circulation times [60], but may have problems with skin toxicity [61,62] and in addition anti-PEG IgM formation may lead to accelerated blood clearance (ABC). Moreover, the larger overall size and hydrophilic nature of PEGylated liposomes can decrease the interaction with cells and prevent the porphyrin uptake into cancer cells [63].

Cerasomes are a new type of hybrid nanoparticle that can be thought of as partially silica-coated liposomes. Cerasome-forming lipids (CFLs) are composed of three basic components: hydrophobic alkyl chains, hydrophilic lipid molecules with triethoxysilane headgroups, and a connector unit. The siloxane coating provides cerasomes with greater mechanical and thermal stability compared to normal liposomes, and the bi-layer construction makes them less dense and more flexible than silica NPs [64]. Cerasomes can be stored in a water-based solution for months at 4 °C without any change in size [45]. Cerasomes exhibit better biocompatibility than silica NPs due to the liposomal architecture and have been used as drug delivery systems [65,66]. Liang et al. [67] reported the preparation of porphyrin containing cerasomes by a sol-gel self-assembly process based on porphyrin-organoalkoxysilylated lipids. The resulted cerasomes showed good tumor accumulation, better stability, and enhanced biodistribution. Moreover, the porphyrin molecules still were able to produce singlet oxygen after irradiation with 400–700 nm light.

3.3. Porphysomes for cancer theranostics

Mineral-based nanoparticles have the potential for nano-oncology, but their possible toxicity is a source of concern. Multifunctional porphysomes that are derived from porphyrins and phospholipids have been introduced as photothermal, photodynamic and photoacoustic imaging agents [[68], [69], [70]] (Fig. 5).

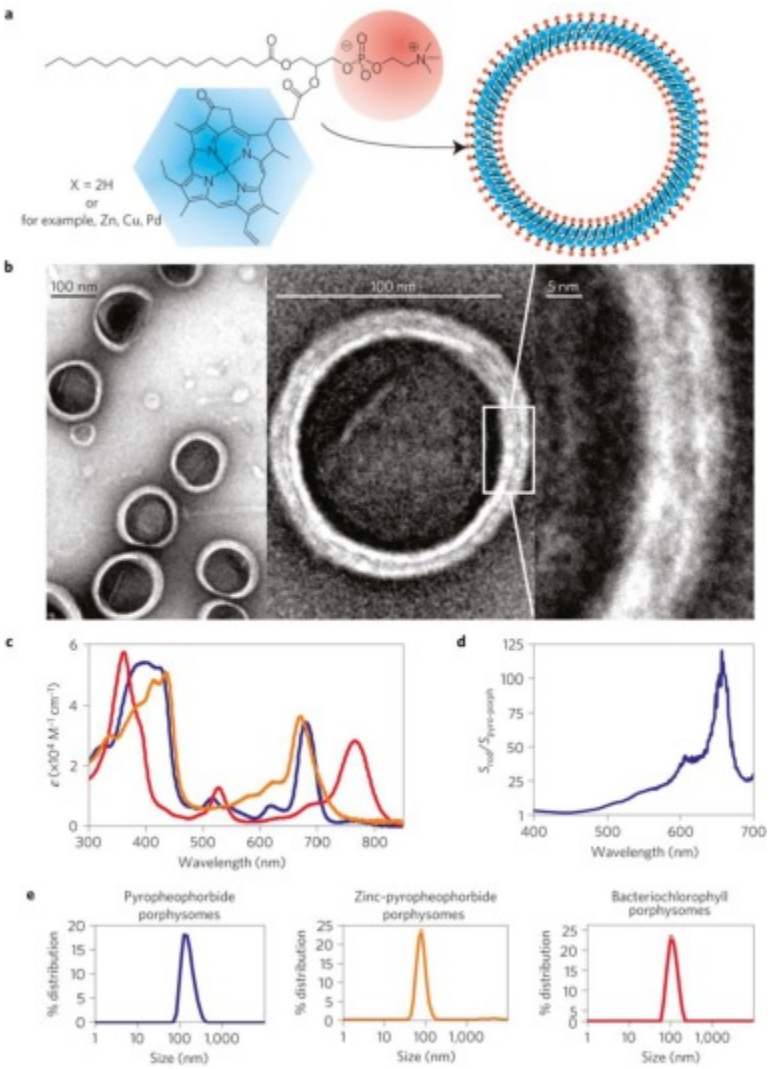

Fig. 5. (a) A typical scheme for porphysome, containing porphyrin and long-chain lipid. The phospholipid headgroup (red) and porphyrin (blue) are highlighted in the subunit (left) and assembled nanovesicle (right). (b), Electron micrographs of negatively stained porphysomes (5% PEG–lipid, 95% pyropheophorbide–lipid). (c), Absorbance of the porphyrin–lipid subunits added in porphysomes formed from pyropheophorbide (blue), zinc-pyropheophorbide (orange) and bacteriochlorophyll (red) in PBS. (d), Resonance light scattering spectra ratio between gold nanorods and pyropheophorbide porphysomes. Nanorod and porphysome concentration was adjusted to have equal optical density at 680 nm. (e), Dynamic light scattering size profiles of indicated porphysomes recorded in PBS [71].

Porphysomes are another kind of nanocarrier that are produced by self-assembly of porphyrin-lipid conjugates into bi-layered vesicles. They show fluorescence self-quenching but also specialized photophysical properties like photoacoustic and photothermal. The sensitive imaging of the lymphatic system by photoacoustic tomography was made possible by the use porphysomes. When the porphysomes are biodegraded in the tissue, the fluorescence self-quneching is released, generating intense near-infrared fluorescence for low-background. fluorescence imaging. Porphysomes have minimal acute toxicity in mice, up to intravenous doses of 1000 mg kg^{-1}. Tumor xenograft-bearing mice accumulate porphysomes, allowing photothermal tumor destruction by laser irradiation. Porphysomes have a multifunctional capability for biophotonic imaging and therapy [70]. They can be used for

fluorescence and spectroscopic tracking, and for photothermal and photodynamic tumor destruction [[72], [73], [74]]. Porphyrin-containing NPs have a role as agents in techniques like photoacoustic tomography (also named optoacoustic tomography) [75,76], optical frequency domain imaging [77] and multifunctional approaches [78]. Another method is quantum dots which function as fluorescent probes with absorption coefficients of 10^5-10^6 $M^{-1}cm^{-1}$ [79]. Gold NPs have even higher extinction coefficients (10^9-10^{11} $M^{-1}cm^{-1}$) [80].

Nanospheres, polymersomes, liposomes, lipoproteins, and micelles are all organic NP which have been used as drug delivery systems with good biocompatibility [[81], [82], [83], [84], [85]]. While organic NPs cannot generally be used as optical agents, because they lack near-infrared spectral absorption peaks, when they are combined with porphyrins they often produce self-assembled nanoparticles with high absorption of light. However these structures are often not suitable as biophotonic probes because of they lack stability, solubility or biological compatibility [86]. Porphysomes, are self-assembled organic NPs that also possess liposome-like properties such as the potential to be loaded with drugs, near-infrared light absorption, fluorescence quenching, and good biocompatibility.
Lysophosphatidyl choline could be conjugated to pyropheophorbide by an acylation reaction, leading to the production of a supramolecular porphysomes assembly. Two absorption peaks, (400 nm and 680 nm) are seen in pyropheophorbide porphysomes. Another porphyrin structure which is similar to bacteriochlorophyll, formed porphysomes with an absorption peak about 760 nm. Shifting the absorption bands (440 nm and 670 nm) is a result of inserting metal ions into the porphyrin-lipid conjugate, and demonstrated that porphysomes could form metal-chelating bilayer vesicles. In vivo toxicity studies of porphysomes in mice, showed that after two weeks there were no changes in hepatic function, endogenous porphyrin metabolism, or the number of white blood cells. They also reported there were no changes in heart, liver, spleen, lung and kidney tissues, removed at necroscopy and stained with H&E (hematoxylin and eosin). The properties of porphysomes like, tunable absorption coefficients and their ability to function as photothermal and photoacoustic sensitizers make them promising for multimodal imaging and theranostic applications [[87], [88], [89], [90]].

Researchers demonstrated that porphysomes could be utilized for targeted PDT by conjugating folic acid which is recognized by the folate receptor that is over-expressed in many cancer cell lines [91,92]. Microbubbles containing porphysomes exhibited multipurpose photoacoustic and ultrasonic properties, due to their porphyrin-lipid structure containing a gas bubble which could be used in ultrasound imaging. Researchers have transformed these microbubbles into nanoparticles with varying (from 5 nm to 500 nm) Instead of drugs releasing. Their small sizes enable better penetration into tissue but has a negative effect on their acoustic reflectivity. The delivery of drugs can be followed by image guidance based on ultrasound imaging, and measuring the drug concentration in the tissue by fluorescence imaging [93]. In another study, Carter et al. [94] modified the porphyrin molecule with a long chain lipid based on results obtained from molecular dynamics simulation. The results showed 10 mol % porphyrin–phospholipid was sufficient to allow light-trigged membrane permeabilization. Xu et al. [95] developed a reduced glutathione (GSH)-responsive porphyrin derivative that could form porphysomes with high DOX loading capacity. The porphysome structure is destroyed upon penetration into the cell due to the presence of high amounts of GSH. Hence, the DOX drug will be released, and the fluorescence of the porphyrin will be recovered. Nathan et al. [96] have also shown

that the modification of porphyrins using a l-glutamide lipid chain led to the formation of porphysomes with better PDT efficiency compared to the usual liposomal formulations.

3.4. Coated membrane NCs for targeted delivery

Nanocarriers (NCs) can be used for targeted delivery of cancer therapy, when they are coated with a preparation derived from cell membranes (CCMCNCs). Bose et al. reported the preparation of CCMCNCs, and their direct delivery of therapeutics to cancerous tissue. CCMCNCs are coated with a variety of molecules such as proteins with different functions, such as recognizing tumor cells, enhanced adhesiveness, and extended blood circulation times. This allows improved targeting, increased intra tumoral permeability, and better binding of the NCs to specific tumors [43]. Cells provide the building blocks of CMCNCs as a hybrid nano-platform containing both synthetic and natural components [97]. The core has the potential to be loaded with therapeutics, such as genes, drugs, or a combination of both drugs and genes, as well as imaging agents. Proteolipid structures originating from cell membranes sources make up the external structure [[98], [99], [100]]. Different combinations of glycan Q4 structures, proteins and lipids compose these proteolipid structures [101]. In addition, targeting ligands such as lymphocyte surface receptors (like CD44), immunoglobulin superfamily members, integrins, cadherins, and selectins can all be incorporated encouraging cell-matrix and cell-cell interactions [102,103].

The well-studied cadherins are protein molecules that participate in cell-cell adhesion, regulation of genes by bata-catenin pathways, migration of cells, and cell signaling by the EMT (epithelial-to mesenchymal transition) [104]. Unlike the cadherins, integrins have roles both in ECM (cell-extracellular membrane) and cell-cell interactions, and have tissue-specific and cell-specific functions. Integrins, such as integrin alpha-1 (ITa1), integrin alpha-2 (ITa2), integrin alpha-5 (ITa5), integrin beta-1 (ITb1), integrin beta-3 (ITb3), integrin beta-4 (ITb4), and integrin beta-5 (ITb5), are widely expressed on the plasma membrane of different cancer cells [105]. Coating these proteins upon the surface of the nanocarrier may improve tumor targeting, extend blood circulation time, and reduce toxicity [106]. Nano-theranostics, such as semiconducting QDs (like CdSe), metal-organic frameworks, metallic nanoparticles (e.g., Au), magnetic nanoparticles (e.g., Fe_3O_4), are often used in cancer diagnosis and treatment [4,6,107,108].

Porphyrins can play a role in CCMCNCs as nano-theranostics and nano-therapeutics. Li et al. created a new biomimetic nano-platform named TPZ@PCN@Mem. It contained the bioreductive drug, tirapazamine (TPZ) loaded into the porphyrinic metal-organic framework PCN-224 to produce the CCMCNC for tumor-targeted combination therapy. The TPZ@PCN@Mem nano-theranostic structure avoided recognition by the immune system, and accumulated inside tumor tissues [109]. TPZ@PCN@Mem produced a massive quantity of ROS (reactive oxygen species) upon laser irradiation that could destroy cells or tumors. However PDT of hypoxic tumors, can be limited by photochemical depletion of available oxygen. Tumors that have high metabolism and become hypoxic, adapt by triggering the Warburg effect [110]. Delivery of the bioreductive drug TPZ allows production of a cytotoxic agent only when oxygen concentrations are very low [111].

Ying et al. used a “cascade bioreactor” nanoconstruct by incorporated the enzymes glucose oxidase (GOx) and catalase inside the CCMC porphyrin-based Zr-MOF PCN-224. When the lipid vesicles were engulfed by the cells, the GOx depleted the glucose stores thus starving the cellular

metabolism, while at the same time the catalase produced oxygen from the hydrogen peroxide formed in the GOx reaction, thus increasing the oxygen available for singlet oxygen production upon PDT by laser irradiation [112].

3.5. Virus-like particles (VLPs)

Viral capsids function as non-infectious protein-based nanoparticles – known as VLPs (virus-like particles) [113]. Although the first oncolytic viral therapy was approved by U.S. FDA, but no recent virus-derived remedies for delivery of genes have been approved. VLPs have many advantages including low cost, natural construction, and the potential to carry large amounts of cargo large compared to other types of NPs. In addition, numerous copies of protein receptors helps VLPs to be recognized by bacteria and mammalian cells. Also, their encapsulated viral genomes could be useful as a therapeutic cargo [114,115]. Because VLPs are natural, they provide easy surface functionalization via different surface chemistry approaches that have been well discussed in the literature [116].

Researchers have suggested that reactive amino acids could be applied to couple the cargo and ligands either on the inside or the surface of the capsids or VLPs. These VLPs may have lower toxicity than metal nanoparticles, greater stability compared with liposomes, and are more uniform compared to polymeric nanoparticles. The delivery efficiency of the vehicles depends on surface functionalization, and the surface can be decorated with different biomolecules. Also, specific cellular targeting decreases immune responses, and may potentially encourage extravasation. Many methods require covalent attachment to either natural or non-natural reactive amino acids (Fig. 6), however, phage-display technology can allow expression of peptides or proteins by genetic programming of the primary sequence of amino acids [117,118].

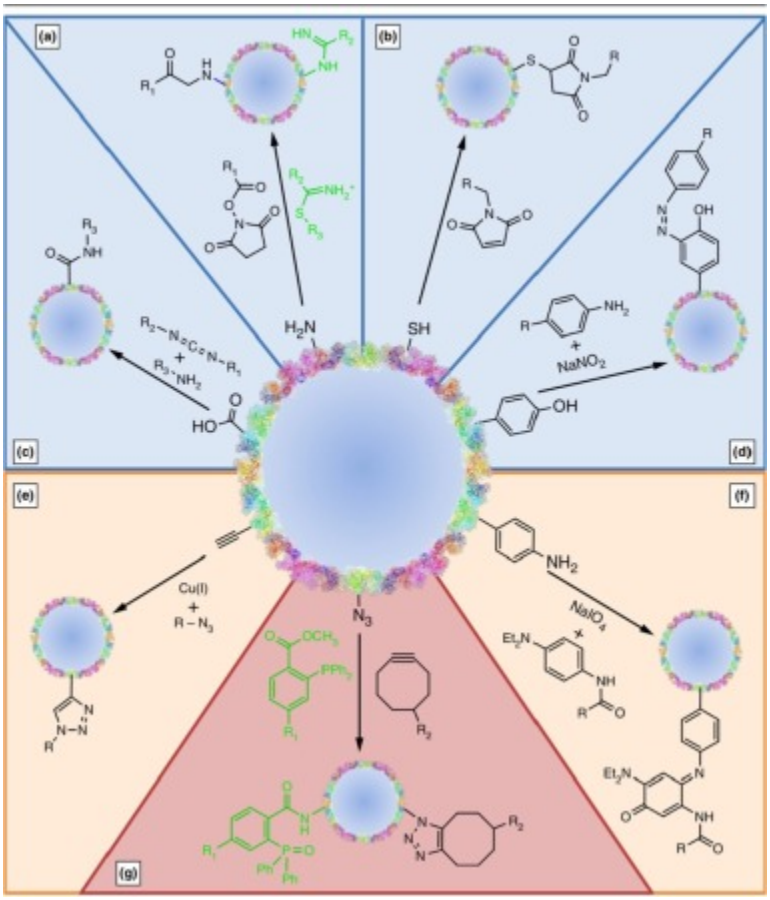

Fig. 6. A different approach for surface modification of VLPs; (a) Primary amines (lysines, N-termini): NHS-ester conjugation (left, black) is most common. Thioimidate conjugation (green, right) has recently been described and is based on the reaction of imidoesters. (b) Thiols (cysteines): maleimides are mainly employed for covalent bonding. Thiols can also form disulfide bonds under mild oxidative conditions. (c) Carboxylic acids (glutamic acid, aspartic acid): carbodiimide activates the acid to react with primary amines. (d) Phenol (tyrosine): oxidation of the ligand moiety to diazonium permits for ortho-attachment to the phenol group. (e) Alkynes (uAA): alkynes react with azides in the presence of Cu(I). (f) P-aminophenylalalnine (uAA): the reaction is similar to that displayed with tyrosine (d), but remains completely orthogonal. (g) Azides (uAA): azides can undergo the Staudinger ligation (left, green), Cu(I)-catalyzed click chemistry (e) or Copper-free click chemistry (black, right). The Staudinger ligand has fallen out of favor because of kinetic limitations and has not recently been utilized for VNP functionalization. The reaction of the cyclooctyne or other copper-free click chemistry reagent has yet to be ascertained employing VNPs and is displayed only to conceptualize how click chemistry can become copper-free [116].

One type of cargo that can be loaded into VLPs is small molecules, and porphyrins fall into this category [16,119]. This approach involves both covalent and non-covalent methods. Non-covalent approaches do not require chemistry, while covalent approaches have the benefit of efficient encapsulation and stability of the loaded cargo. VLPs derived from plant-based viruses are considered to be safer than those from animal-based viruses. A CCMV preparation was loaded with polystyrene sulfonate by non-covalent electrostatic interaction with coat proteins [120,121]. Fluorescent probes and antibiotics have been non-covalently connected to CPMV using small molecules that bind to the RNA genome by electrostatic interactions [122]. However, there are difficulties in loading and preserving these small cargoes [123,124]. Non-covalent loading of photosensitizers into VLPs has been used to develop

multifunctional nanoconstructs. For example, Masarapu et al. [125] used the Physalis mottle virus (PhMV) coat protein, which was expressed in *Escherichia coli* to develop VLPs. Then, doxorubicin, rhodamine B or Zn-EpPor molecules were loaded as a chemotherapeutic drug, fluorescent compound, or photosensitizer to make multifunctional VLPs. The covalent approach is of interest due to the stronger binding between the photosensitizer molecules and the ligands in the VLP. For example, Rhee et al. [126] first synthesized an azide-tailed metalloporphyrin derivative and used click-chemistry to attach it to the ligands of bacteriophage Qβ VLP as a functionalized glycan to be used for specific PDT of cells bearing the CD22 receptor.

3.6. Stem cells and extracellular vesicles

Mesenchymal stem cells (MSCs) could be used as nanocariers of drug molecules due to: 1) ability to be isolated from the bone marrow or other tissue of patients [127,128]; 2) ability to be further functionalized chemically or genetically to enhance their selectivity [129]; 3) good biocompatibility and avoidance of immune rejection by the body [130]; and 4) high tumor affinity with long retention time in tumors in-vivo [131,132]. Porphyrin-lodad MSCs have also been applied for delivery of porphyrins as photosensitizers into cancer cells for photodynamic therapy. Cao et al. [133] loaded hydrophobic purpurin-18 (PP-18) molecules into silica nanoparticles (SNPs), and the PP-18-SNPs were later loaded into MSCs. The designed PP-18-SNPs-MSCs were used for *in-vitro* PDT of breast cancer cells and for *in-vivo* PDT of breast tumors in rats. In another study, porphyrin molecules were first loaded into fluorescent dye-labeled poly-methyl methacrylate (PMMA) nanoparticles, and then loaded into MSCs. The obtained nanocarriers were used for successful simultaneous fluorescence imaging and *in-vitro* PDT of osteosarcoma [134].

Extracellular vehicle (EVs) are cell-derived membrane vesicles that can penetrate cells via an endogenous mechanism. EVs are capable of functionally transferring biological information, and since this discovery, the potential use of EVs as carriers for drug delivery has attracted scientific interest. EVs may have several benefits over other drug delivery carriers, such as their ability to overcome natural barriers, inherent cell targeting properties, and stability in the circulation. However, because of the lack of methods for scalable isolation of EVs and their efficient loading with drugs, the applications of EVs as drug delivery systems has been limited. Furthermore, their inherent cell targeting features could be improved via EV engineering in order to accomplish better targeted drug delivery [135,136]. Vader et al. [137] reported the possibility of loading EVs with large proteins, but it is yet to be ascertained how their immunogenicity is affected by the sonication or separation processes, or by saponin treatment. Fuhrmann et al. carried out a comparison of strategies for loading hydrophilic and hydrophobic porphyrins into EVs, and compared these to free drug or porphyrin-loaded liposomes in terms of cellular uptake. Treating cancer cells with porphyrin loaded EVs followed by irradiation showed reductions cell viability. Nevertheless, finding the most suitable approach for clinical use is yet to be determined [138,139].

3.7. Porphyrin polymeric nanoparticles

Polymerization of porphyrins is another approach to enhance their therapeutic effects and overcome some common drawbacks of porphyrins (*i.e.*, their low absorption coefficients, poor water-solubility, and leaching from delivery carriers). The polymerization of porphyrins (i.e., introducing porphyrins into the polymer backbone) could modulate the HOMO-LUMO energy bandgap and, consequently change

the balance between radiative decay rate, non-radiative-decay rate and intersystem crossing rate in the excited porphyrin molecules [140,141]. Therefore, porphyrin-based conjugated polymers could serve as theranostic materials with light-harvesting properties and enhanced efficiency in either photodynamic therapy (PDT) or photothermal therapy (PTT) as well as NIR fluorescence emission.

For example, Wu and Xu reported that a >9-fold enhancement of emission after one-photon excitation (at 380 nm) and 30-fold enhancement after two-photon excitation (at 800 nm) were observed for an anionic hematoporphyrin (HP) electrostatically conjugated to a cationic conjugated polymer (PFB) due to the occurrence of FRET from PFB to HP [142]. In another study, Xing et al. [143] reported that a block-co-polymer containing cationic conjugated polythiophene and porphyrin could carry out simultaneous fluorescence imaging and in-vitro PDT of pulmonary adenocarcinoma cells (A549) and renal cell carcinoma (A498). Cheng et al. [144] synthesized polymer-dots containing a co-polymer of polyfluorene derivative (PFBT) and tetraphenylporphyrin (TPP). These polymer-dots showed bright fluorescence with a good singlet oxygen quantum yield for image-guided PDT of xenograft tumors in Balb/c nude mice. As mentioned above, non-radiative decay rates could also be modulated through polymerization of the porphyrins. In order to further increase the non-radiative rate, a donor-acceptor pair contained in a structured porphyrin-conjugated polymer was reported by Guo et al. [145] for efficient PTT *in vitro* and *in vivo*. The D–A structure introduced intramolecular charge transfer along the backbone, resulting in broadened absorption peaks, red-shifted Q band, and increased extinction coefficient (4.23×10^4 $mol^{-1}cm^{-1}$ at 800 nm) as compared to the porphyrin photothermal agent alone.

4. Microporous organic polymers

In recent decades, microporous organic polymers (MOPs) with high surface area have been investigated in some industrial processes, such as gas absorption, catalysis, electronics, and recently for controlled drug release [146,147]. Covalent organic frameworks (COFs) and metal-organic frameworks (MOFs) are crystalline hybrid MOPs. In COFs the organic ligands are covalently bonded to each other [148,149], while in MOFs polydentate organic linkers are coordinated to transition metal cations [[150], [151], [152]]. Both COFs and MOFs have been extensively used as nanocarriers for different biomedical applications [153,154]. In particular, porphyrins-loaded COFs and MOFs are discussed in the following section.

4.1. Covalent-organic frameworks (COFs)

COFs have been used to deliver porphyrin molecules into cancer cells and tumors, and have shown enhanced therapeutic efficiency compared to free porphyrins. For example, Tao et al. [155] synthesized fluorinated COFs by crosslinking the photosensitizer meso-5, 10, 15, 20-tetra (4-hydroxylphenyl) porphyrin (THPP) with poly (ethylene glycol) (PEG) and perfluoro-sebacic acid (PFSEA) via a one-pot esterification. The developed porphyrin-loaded COFs were used for simultaneous oxygenation and PDT of solid tumors. Another porphyrin-COF nanocomposite was synthesized using 5,10,15,20-tetrakis (4-aminophenyl)porphine (Tph) and 2,5-dihydroxy-1,4-benzenedicarboxaldehyde (Dha). The obtained porphyrin-loaded COF nanoparticles possessed high photothermal conversion efficiency (21.7%) with a good singlet oxygen quantum yield, and were used for simultaneous PTT (at 808 nm) and PDT (at 650 nm) of HeLa cancer cells [156]. Recently, 3-D porphyrin-based COFs were synthesized by Lin et al. [157]. They found that the microporous

material possessed a high surface area and could generate singlet oxygen, while metalation of the porphyrin rings caused a decrease in its photosensitization ability.

Covalent triazine frameworks (CTFs) are members COFs with triazine unit, with exceptional porosity, good chemical stability, and can be fabricated with both crystalline and amorphous constructions [158]. Luo et al. investigated two porphyrin-based porous covalent bonded triazine frameworks (PCTFs). The porphyrin was attached using the Friedel–Crafts reaction. The CTFs possessed a large Brunauer–Emmett–Teller surface area (up to 1089 $m^2 g^{-1}$ area) and absorbed CO_2 up to 139.9 mg g^{-1} at 273 K/1.0 bar. They also had selective absorption of CO_2/CH_4 up to 6.1 mg g^{-1} at 273 K/1.0 bar. The researchers described new attempts to produce porphyrin-based covalent bond triazine frames (PCTFs) using a single-step Friedel–Crafts reaction with $(NCCl)_3$ and a tetra-reactive 5, 10, 15, 20-tetraphenylporphyrin (TPP). $(NCCl)_3$ was used as an electron-deficient monomer for the polymerization, and the porphyrin nucleus provided a coordination site for metal ions [146]. PCTF drugs have a large surface area and the capacity for CO_2 absorption, good drug loading, and tailorable drug release (Fig. 7). The reaction needs only moderate conditions without poisonous or costly catalysts, to reduce the expense for construction of novel MOPs. The chemical composition of PCTFs was proved by spectral characterization (FTIR and ^{13}C NMR). For FTIR spectra, the bands appeared at 1620 and 1400 cm^{-1} assigned to the quadrant and stretching of the semicircular triazine ring, in line with pervious reports [146]. There was a peak near 800 cm^{-1} for the ring of para-substituted benzene. In PCTF the Mn-porphyrin showed a peak at 1040 cm^2 for the N–Mn in-plane bending. These porous PCTFs have the potential to be used as drug carriers in biomedical applications [159].

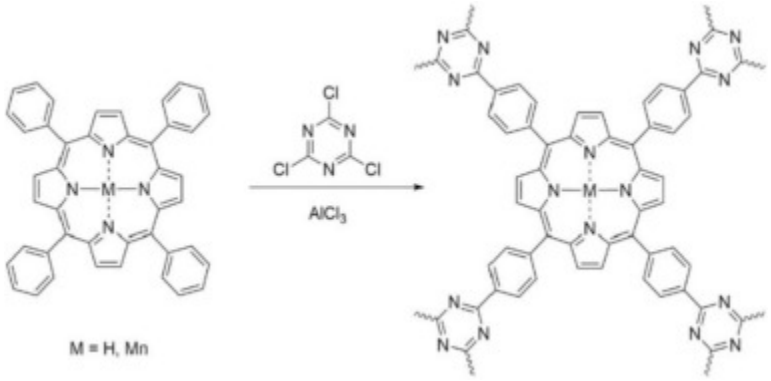

Fig. 7. Schematic demonstration of the PCTF and PCTF-Mn producing [146].

Recently, a porphyrin nanocage-embedded polymer was synthesized as single molecule nanoparticles (34.6 ± 1.8 nm by dynamic light scattering) and used for fluorescence imaging (red emission with a quantum yeild of 6.9% in water) of U87MG cells, and was also labeled by radioactive ^{64}Cu for positron emission tomography (PET) imaging. They were able to monitor the delivery, pharmacokinetic behavior, biodistribution, and excretion of the nanoparticles in animal models in real time [160].

4.2. Metal-organic frameworks (MOFs)

Metal–metalloporphyrin frameworks (MMPFs) are a new class of nanomaterials that have received much attention due to their versatile functionality. The MMPFs compose a coordination that can be custom-designed metalloporphyrin ligands. The porphyrin core enables the synthesis of different types

of metalloporphyrin cores via a metalation process. The MMPFs could be synthesized via different approaches. The direct synthesis approach includes crystal engineering [161,162], pillared-layer strategy [163,164], nanoscopic metal–organic polyhedrons (MOP) [[165], [166], [167]], and indirect synthesis based on the post-modification of the MOFs based on porphyrin-based ligands [168,169].

Numerous studies have been done on metallic-organic frameworks as carriers of drugs, especially porphyrin-based compounds, for biomedical applications
[[170], [171], [172], [173], [174], [175], [176], [177], [178]]. For example, Zheng et al. [179] reported the synthesis of a metal-organic framework@porous organic polymer (MOF@POPs) using a post-modification approach which is illustrated in Fig. 8. The synthesized MOF@POP with a size of 165 nm showed better PDT effects compared to the porphyrin-loaded POPs alone. The PDT application of MOF-based porphyrins is not limited to colloidal system. Zhou et al. [180] developed a thin polymer using a MOF-templating approach which contained porphyrin molecules and showed PDT effects against *E. coli*.

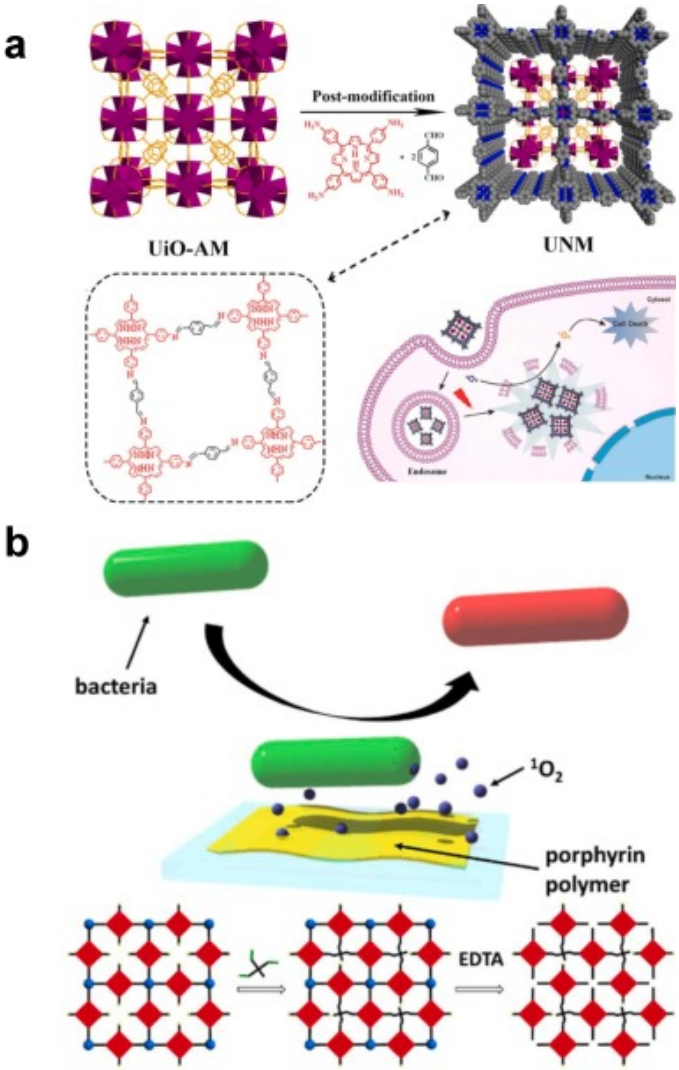

Fig. 8. (a) the MOF@POPs based on UiO-AM and polyaniline as MOF and porous organic polymer, respectively [179] and (b) Developing water-soluble MOF-templated porphyrin polymer thin film with high PDT effect against bacteria [180].

A key factor in the effective delivery of MOF-based porphyrin nanocomposites is surface modification, which leads to the targeted delivery of the nanocomposites. MOF UiO-66 is a zirconium terephthalate which can be loaded with cargo, forming ~200 nm coated nanoparticles synthesized by functionalized linkers, and covalently surface modified using mild reactions to attach chains of poly (ethylene glycol) (PEG). At pH 7.4 the PEG chains provide enhanced stability to phosphates and overcome the ‘‘burst release’’ phenomenon, while at pH 5.5, stimuli-responsive drug release is achieved. Furthermore, the cellular uptake is governed by the NP surface chemistry, so that PEGylated UiO-66 escapes lysosomal degradation [181].

Moreover, MOF nanoparticles with attached polymer chains such as polyaniline-modified UiO-66 could be used in anticancer photothermal therapy [182]. Zr porphyrin-based MOFs formed 90 nm diameter NPs that were taken up by HeLa cells [36]. The versatility of the click assembly protocol could help a variety of MOFs to show selective cell targeting [183].

A discrete organoplatinum (II) metallocage was recently reported by Yu et al. [184]. They used the chemotherapeutic drug cis-$(PEt_3)2$ Pt $(OTf)_2$ as a building block to construct this metallocage to be loaded with porphyrin molecules. This new design prevented the aggregation of the porphyrins (*i.e.*, due to π-π stacking) and improved the singlet oxygen quantum yeild. The metallocage-loaded NPs showd tri-modal functionality, and could be used for simultaneous fluorescence imaging (red emission), chemotherapy and PDT.

5. Porphyrin-based nanomaterials combined with other therapeutic methods

5.1. Chemotherapy

Bioluminescence and fluorescence imaging can be used to monitor drug release using advanced theranostic techniques. Fluorescence imaging reporters over a wide spectral range can be incorporated into the nanoplatforms. A bi-functional fluorescence and anti-tumor drug delivery system was produced by encapsulating doxorubicin (DOX) inside the hydrogel formed from porphyrins with a four-arm copolymer of PEG-PCL as a drug carrier. The imaging ability was improved because the drug and the fluorescence signals were separated via the hydrogel. The inhibition of tumor growth could be followed through bioluminescence imaging [185,186]. Other researchers have prepared fluorescent copolymers to overcome the shortage of fluorescent porphyrin-compounds [187]. In vivo fluorescence imaging with the four-arm PEG-PCL copolymer (POR-PEG-PCL) demonstrated that the porphyrin-hydrogel could be used as an implant as a systemically administered nanogel-probe [187]. The POR-PEG-PCL hydrogel functioned as a drug carrier for Dox anti-tumor drug delivery which is a dual fluorescent therapeutic nanosystem. Other fluorescent drug delivery systems have been monitored using rhodamine to monitor the biodistribution after intratumoral injection [188]. Tumors that have been stably transfected with the luciferase enzyme were grown in the liver of tumor of nude mice were used for dual bioluminescence and multispectral fluorescence imaging to follow the tumor response in real-time [189]. Hydrogels are increasingly being used for drug delivery or as tissue engineering platforms [190,191].

Bera et al. reported a novel nanocarrier based on the tetrasodium salt of meso-tetrakis (4-sulfonatophenyl)porphyrin (TPPS) attached to gold nanoparticles (TPPS-AuNPs). The nanocarrier was loaded with the antitumor drug doxorubicin (DOX) and was selectively internalized by tumor cells

compared to normal cells. The attachment of TPPS onto the gold nanosurface provided excellent stability and biocompatibility. Porphyrin interacted with the gold nanosurface forming a strong association complex. DOX-loaded nanocomposite (DOX@TPPS-AuNPs) demonstrated enhanced cellular uptake with significantly reduced drug efflux in MDR brain cancer cells, with increased retention time. It caused 9 times greater apoptosis via triggered release at acidic pH. DOX was loaded on the porphyrin-modified gold NPs with high encapsulation efficacy (~90%) but was capable of releasing ~81% of DOX at low-pH. DOX-loaded TPPS-AuNPs exhibited higher inhibition of cellular metastasis, invasion, and angiogenesis [192].

5.2. Radiotherapy

Radiotherapy (RT) is an efficient method to treat many types of cancer. However, debilitating side effects are often observed due to high X-ray doses (50–75 Gy). To overcome this limitation, developing new therapeutic nanomaterials with dual-functional capability could be a new strategy [[193], [194], [195], [196]]. Recently, radiotherapy agents based on porphyrin co-loaded nanomaterials have received attention due to the possibility of simultaneous radiotherapy and radiodynamic therapy of different cancers. For example, a nanoscale MOF was developed using either Hf12 or Hf6 secondary building units (SBUs) and Ir (2,2′-bipyridine)[2-(2,4-difluorophenyl)-5 (trifluoromethyl)pyridine]$_2^+$ based ligands. This nanoscale MOF showed efficient production of hydroxyl radicals as well as singlet oxygen and superoxide anions under X-irradiation and carried out radiotherapy and radiodynamic therapy [197]. The same group developed another nanoscale MOF based on Hf-DBB-Ru [DBB-Ru = bis (2,2′-bipyridine)(5,5′-di (4-benzoato)-2,2′-bipyridine) ruthenium (II) chloride], whiche could target the mitochondria of MC38 cells. The designed nanomaterial showed both radiotherapy and radiodynamic therapy effects due to efficient generation of hydroxyl radicals (*i.e.*, by Hf6 SBUs) and singlet oxygen (*i.e.*, by DBB-Ru photosensitizers) [198]. A similar concept was also applied to prepare an indoleamine 2,3-dioxygenase inhibitor-loaded nanoscale MOF to enhance checkpoint blockade immunotherapy. It has been proposed that nanoscale MOFs could be utilized for delivery of different therapeutic agents, such as porphyrin and radiotherapy agents than could effectively kill cancer cells via a combination of different modalities. These structures could be further modified with other therapeutic agents for developing newer generations of therapeutic nanomaterials.

6. Porphyrin-based nanomaterials combined with magnetic resonance imaging

Porphyrin molecules and magnetic-resonance agents could be loaded into the nanocarrier and provide a dual-functional theranostic nanomaterial. As an example, Mn(III)- meso-tetrakis (4-sulphonatophenyl) porphyrin (Mn(III)-TPPS) was loaded on hydrophiobic polymethyl methacrylate nanoparticles with further surface modification with anionic molecules for simultaneous sonodynamic therapy and MRI imaging of rat breast tumor. The ROS generation initiated by irradiation of shock waves and MRI enabled to monitor the tumor size and treatment progress [199].

7. Conclusions and future work

Porphyrins display good photochemical properties, especially singlet oxygen generation, which makes them a suitable candidate for PDT. However, porphyrins suffer from low water-solubility. Hence, efficient delivery of porphyrins requires a proper nanoscale formulation. Therefore, different types of

nanoparticles have been proposed to transport the hydrophobic porphyrin molecules in biological media. Moreover, other nanocarriers such as metal-organic frameworks and extracellular vesicles are of increasing interest.

Furthermore, porphyrins undergo an aggregation-caused quenching (ACQ) effect which quenches their photophysical properties such as fluorescence and singlet oxygen generation, when the local concentrations reaches a certain level and they become aggregated. To address this issue, porphyrin-based aggregation-induced emission (AIE) dyes have been developed and investigated [189,200,201]. These AIE dyes are not emissive in their individual solubilized molecular state, but their fluorescence is turned on in an aggregated state. This property makes them suitable for high loading into different nanocarriers. Hence, it is expected that by a combination of porphyrins and AIE-active moieties, a new generation of porphyrins with a variety of properties suitable for bioapplications such as fluorescence imaging, photoacoustic imaging (PA), magnetic resonance imaging (MRI), photodynamic therapy (PDT), photothermal therapy (PTT), and recently radiotherapy (RT) and radiodynamic therapy (RDT) could be produced.

The multifunctional nature of porphyrins and their derivatives is expected to play a vital role in future clinical therapy. The deep exploitation of novel porphyrins and their derivatives has recently gained increasing scientific interest. Developing new porphyrins with different properties is of importance for many bioapplications.

Data availability statement

Not applicable.

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Declaration of competing interest

The other authors declare no conflicts of interest.

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