



Review article

Photodynamic cancer therapy using liposomes as an advanced vesicular photosensitizer delivery system

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ABSTRACT

The multidisciplinary field of photodynamic therapy (PDT) is a combination of photochemistry and photophysics sciences, which has shown tremendous potential for cancer therapy application. PDT employs a photosensitizing agent (PS) and light to form cytotoxic reactive oxygen species and subsequently oxidize light-exposed tissue. Despite numerous advantages of PDT and enormous progress in this field, common PSs are still far from ideal treatment because of their poor permeability, non-specific phototoxicity, side effects, hydrophobicity, weak bioavailability, and tendency to self-aggregation. To circumvent these limitations, PS can be encapsulated in liposomes, an advanced drug delivery system that has demonstrated the ability to enhance drug permeability into biological membranes and loading both hydrophobic and lipophilic agents. Moreover, liposomes can also be coated by targeting agents to improve delivery efficiency. The present review aims to summarize the principles of PDT, various PS generations, PS-loaded nanoparticles, liposomes, and their impact on PDT, then discuss recent photodynamic cancer therapy strategies using liposomes as PS-loaded vectors, and highlight future possibilities and perspectives.

1. Introduction

Cancer is currently one of the leading causes of death worldwide, with almost 10 million deceases reported in 2018 [1]. Up to now, some traditional cancer treatments, including radiotherapy, chemotherapy, and hyperthermia, or a combination of them, have been employed. Still, their disadvantages, particularly poor tumor selectivity and high side effects, make them far from the ideal treatment [2,3]. Photodynamic therapy (PDT) as another strategy for cancer treatment has been given attention due to creating noninvasive cancer therapy and its relatively selective and local treatment [4]. Although its considerable benefits, conventional PDT is suffering from several disadvantages. Some common photosensitizers (PSs) have shown unwanted side effects and poor bioavailability due to their hydrophobicity and self-aggregation tendency [5,6].

On the other hand, in recent decades, liposomes, which are advanced vesicular drug delivery systems (DDS) containing a core of aqueous solution surrounded with a self-assembled bilayer of phospholipids, has

shown a great potential for prolonging the blood circulation time and increasing drug permeability into biological membranes [7,8]. Numerous advantages of liposomes, such as the potency of loading both hydrophobic and hydrophilic agents and the ability to be functionalized, make them competent for various kinds of applications like targeted cancer therapy, treatment of skin disorder, vaccine, and gene therapy [9–11].

One of the most recent and successful applications of liposomes is loading common photodynamic agents to improve their solubility, specificity, bioavailability, and aggregation tendency [12,13]. Therefore, liposomal photosensitizers as third-generation formulations have shown great potential to increase the efficiency of photodynamic cancer therapy [14]. The goal of this review is to illustrate the principle concept of PDT, liposome and their main features, providing a detailed update of liposomes applications in PDT strategies for the treatment of several cancer types, highlighting the impact of liposomes in comparison with using common formulations without liposomal encapsulation and evaluation other possibilities of PS-loaded liposomes.

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2. PDT in cancer therapy

PDT has been shown to be a successful approach to treat early lung cancer, Barrett's esophagus cancer, bladder cancer, head and neck malignancies. Moreover, it has been considered the best treatment for skin cancer [15–17]. PDT approach employs a photosensitizing chemical substance, called a photosensitizing agent or PS, that is actively or passively accumulated within a tumor site and activated once exposed to light at an appropriate wavelength to eradicate malignant cells. After exposure, the PS transits from its low-energy ground state to a short-lived singlet-excited state, and an intersystem crossing causes the generation of triplet-excited PS with lower energy level and longer life. The activated PS transfers the absorbed energy from their triplet-excited states to molecular oxygen and generates cytotoxic reactive oxygen species (ROS) such as hydrogen peroxides, superoxide anion, and hydroxyl radicals (type I). The excited PS energy can also cause the formation of a singlet-excited state of oxygen (singlet oxygen, $^1O_2$). The type II photochemical process is when the singlet oxygen, which is able to oxidize the targeted tumor (Fig. 1) [18,19]. The reactive species generated by both PDT types can react with biomolecules which leads to (i) trigger cell death by necrosis, apoptosis and autophagy, singularly or simultaneously, (ii) cause vascular injury and thereby tumor ischemia, and (iii) indirectly cause cancer cells death by activation of the host immune system against tumor antigens [18–22].

2.1. Effective parameters on PDT

PDT methodology and efficacy depend on PS type, exposed light, oxygen concentration surrounding the target, and amount of PS uptake in target cells (Fig. 2) [23,24]. Generally, various properties of PS types depend on their physicochemical features, such as hydrophobicity, charged groups, charge-to-mass ratio, and type and number of rings, which can affect the PDT efficiency [25]. One of the most effective physicochemical parameters of PSs is singlet oxygen quantum yield ($^1O_2$ QY), i.e., the amount of singlet oxygen generation per photon absorbed by the PS, which shows the activity of its formulations [26,27]. The half-maximal inhibitory concentration (IC_{50}) value is another important parameter that stands for the certain concentration giving 50% cell proliferation inhibition in comparison with the control, and it is defined for each PS. The effective parameters influencing PS IC_{50} value are PS type, exposed light, incubation time, and treated cells [28,29]. Another PS feature that plays a vital role in the cell death type mechanism is to have specific subcellular localization in different organelles, such as

mitochondria, lysosomes, endoplasmic reticulum, plasma membrane [30]. On the other hand, the condition of exposed light is able to affect the amount of PS phototoxicity via their various wavelength, energy density, and exposure time [31,32]. To minimize the PDT side effects, the exposed light should be strongly absorbed by the PS and poorly by the tissues. The biological tissues optical window is wavelengths between 650 and 800 nm, which show low absorption of light [18,19].

2.2. Photosensitizer classification

According to their evolution, PSs have been classified as first-, second- and third-generation (Fig. 3). The earliest PSs in the clinical application were developed in the 1970s and early 1980s, also known as first-generation PSs, which mainly were hematoporphyrin derivative (HpD) or porfimer sodium (Photofrin®), including porphyrin monomers, dimers, and oligomers. Due to several disadvantages of first-generation PSs, such as low tumor selectivity, poor light absorption in the spectrum portion with optimal light penetration in tissue and prolonged skin photosensitivity, second-generation of PSs, such as hypericin, chlorin e6 (Ce6), Al(III) phthalocyanine chloride tetrasulfonic acid (AlPcS4), and zinc phthalocyanine (ZnPc), have been developed since the late 1980s. They include various derivatives of porphyrins, phthalocyanines, naphthalocyanines, chlorins, and bacteriochlorins, and the specific wavelength exposed for their activation is between 650 and 800 nm [24,25]. Compared to HpD, the second-generation PSs presented higher quantum yields of singlet oxygen, more tumor selectivity, and tissue accumulation time and fewer side effects, more specificity of phototoxicity, and higher uptake efficiency [33–35]. While they have been used to treat solid tumors without any toxicity in the absence of light, their selective affinity had to be ameliorated to increase PDT efficiency and safety [36,37]. To improve suboptimal optical/photochemical properties and unfavorable pharmacokinetics of these PSs and maximize tumor selectivity, third-generation PSs have been developed [38,39].

Currently, there are two ways for third-generation PS fabrication: (a) modification of second-generation PSs with peptides and antibodies conjugation to obtain specific targeted PSs or (b) utilizing NPs to encapsulate or conjugate PSs to increase their affinity and uptake in the targeted tissue and eliminate phototoxic side effects [22,40]. Up to now, third-generation PSs have been widely studied using various types of nanoparticles for PDT, as among others gold-NPs [41–43], silica-NPs [44–46], PLGA (Poly(D,L-lactide-co-glycolide))-NPs [47–49], TiO_2 (Titanium dioxide)-NPs [50–52], micelles [53–55] and liposomes [56–58].

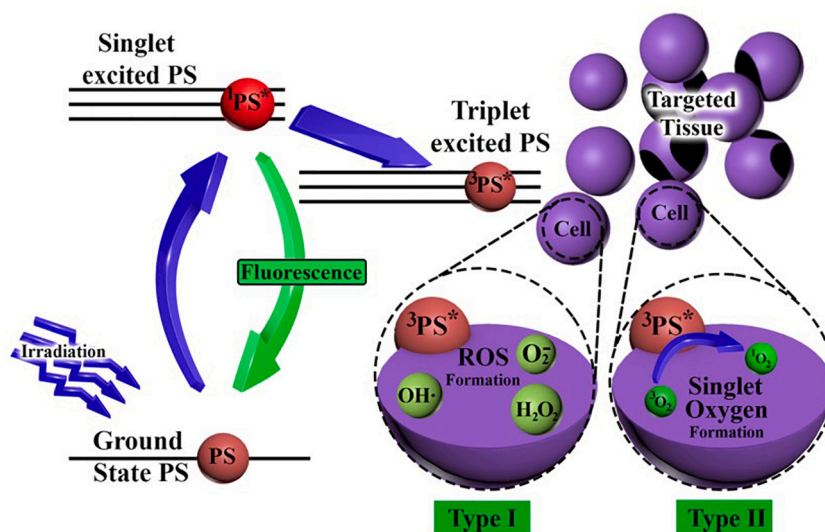


Fig. 1. Schematically type I and type II PDT mechanism of the singlet ROS and oxygen generation after light irradiation in the targeted tissue.

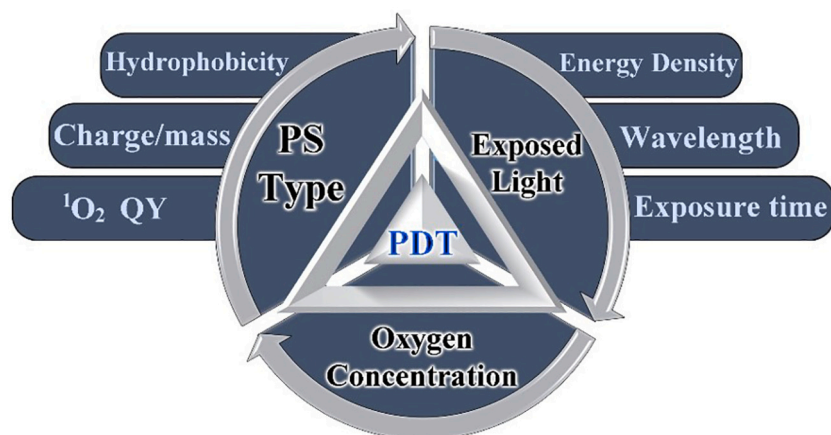


Fig. 2. PS type, exposed light, and oxygen concentration as three vital parameters in PDT.

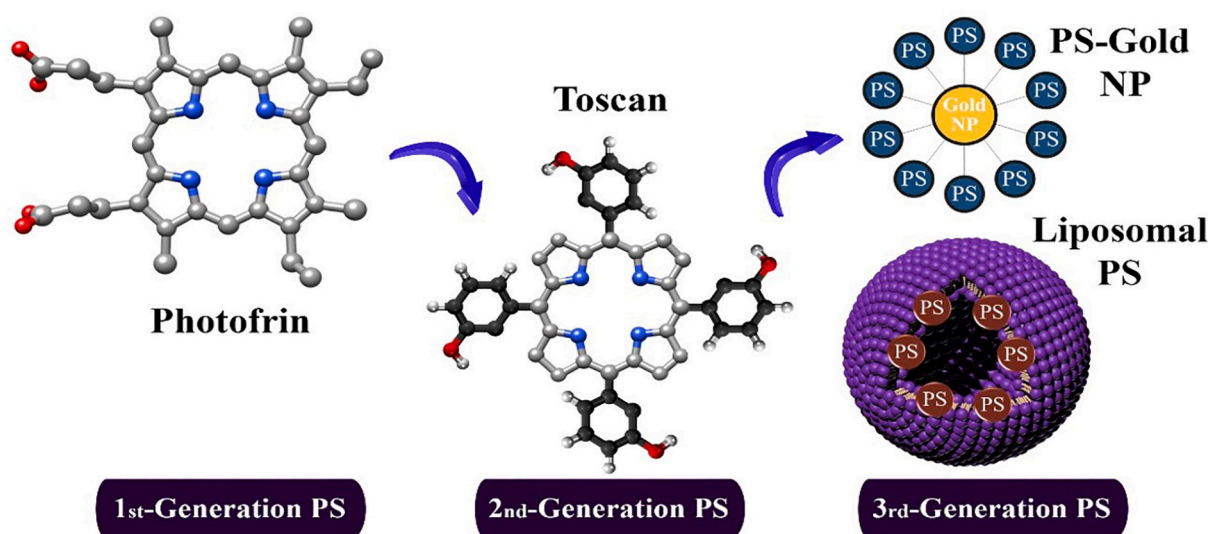


Fig. 3. Schematic structure of typical examples of three different generations of PSs.

The most ideal DDS used for PDT application is a biodegradable carrier, biocompatible with minimum immunogenicity, able to have a selective PS delivery with no uptake by non-target cells, and able to deliver the PS in its monomeric form, reducing aggregation chance [12,13]. Liposomes as lipid-based vesicles with a bilayer membrane made by biocompatible phospholipids have been successfully and widely utilized to encapsulate pharmaceutical agents for various applications, in particular cancer therapy [59]. They can load PS with high entrapment efficiency, change its solubility, improve its bioavailability, and prevent the reduction of singlet oxygen quantum yields due to reduced PS tendency to aggregation. Therefore, liposomal PSs can potentially be employed as novel third-generation formulations [60–62].

2.3. Applications of photodynamic cancer therapy

PDT has numerous advantages over other traditional cancer therapies, including low systemic toxicity and the potential to kill tumor cells selectively because the PS is only activated in the presence of light. PDT mostly has a superficial impact and can be used to treat surface illnesses, including; (i) premalignant conditions (i.e., mucous dysplasia and actinic keratosis); (ii) *in situ* carcinoma; (iii) superficial malignancies (i.e., malignant pleural mesothelioma or intraperitoneal disseminated carcinomatosis); and (iv) sensitive areas (i.e., head and neck) [63,64]. On the other hand, since PDT is triggered locally and has minimal tissue

penetration, it can be combined with radio- or chemotherapy in clinical applications. For instance, in conjunction with surgery to irradiate the tumor bed and improve the chances of long-term local disease management [63–66].

HpD is known as the first clinically used PS for photodynamic cancer therapy in the late 1970s, and up to now, the clinical use of several PSs has now been approved, such as 5-aminolevulinic acid (5-ALA) and temoporfin (meso-tetra-hydroxyphenyl-chlorin, mTHPC) [67,68]. According to the USA National Institute of Health clinical trials website, 284 clinical trials for PDT are currently undergoing (Table 1).

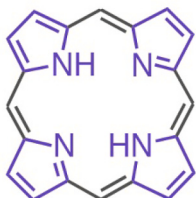
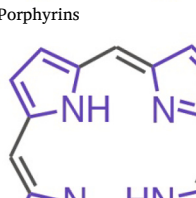
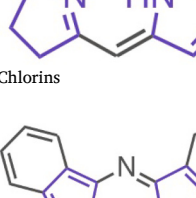
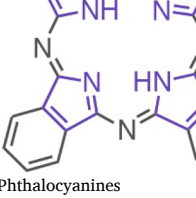
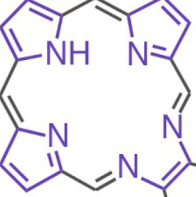
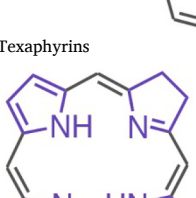
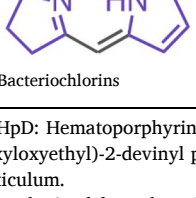
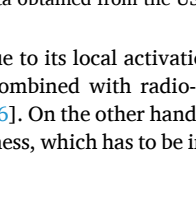
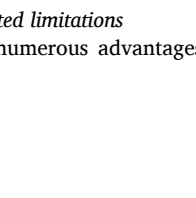
2.4. PDT limitations

2.4.1. Protocol-related limitations

Several issues have limited the development of PDT protocols, such as the lack of standard procedures, inaccessibility to deep-rooted tumors, and photosensitivity for prolonged durations following treatment. More studies will give the data needed to optimize treatment methods and develop worldwide agreements on standardization. In addition, one of the most challenging clinical issues is that PDT can only be employed for treating topical lesions because the penetration depth of lights in the visible spectral regions varies from a few millimeters to up to one centimeter through tissues and the wavelength of irradiation in PDT protocols is usually less than 700 nm [13,18]. Therefore, as previously

Table 1

Classification of clinically approved and under clinical trials PSs for cancer therapy [13,35,64,69–76].*

PS generation	Classification	PS	Localization	Wavelength (nm)	Approved	Trials	Ongoing cancer clinical trials
1st		HpD, Porphimer sodium, Photofrin	Golgi apparatus, Plasma membrane	630	Worldwide	USA, UK	Esophageal, lung, bile duct, bladder, brain, and ovarian cancers
2d		5-ALA, Levulan	Mitochondria, cytosolic membrane	635	Worldwide	USA, UK	Actinic keratosis, skin, bladder, brain, and esophageal cancers
		MAL, Metvix	Mitochondria, cytosolic membrane	570–670	Europe	Finland, Germany	Actinic keratosis, non-melanoma skin cancer and skin aging
	Porphyrins	Verteporfin, BDP	Mitochondria	690	Worldwide	UK	Ophthalmic, pancreatic and skin cancers
		Temoporfin, mTHPC, Foscan	Cytoplasm	652	Europe	USA	Skin, lung cancer, head and neck, brain, and bile duct cancer
		Ce6 derivatives	Lysosomes, endosomes	660	–	Belarus, Russia	Nasopharyngeal, sarcoma, and brain cancers
		Rostaporfin, Purlytin, tin-ethyl-etiopurpurin	Lysosomes, endosomes	660	–	USA	Breast cancer and Kaposi's sarcoma
		Talaporfin, LS11, Laserphyrin	Lysosomes, endosomes	660	–	USA	Liver, colon, and brain cancers
	Chlorins	HPPH, Photochlor	Lysosomes, Mitochondria	665	–	USA	Lung, head and neck, and esophagus cancers, BCC
		Pc4	Golgi apparatus, mitochondria, ER	675	–	USA	Cutaneous T-cell lymphoma, non-melanomatous skin cancer, Bowen's disease
	Phthalocyanines	Lutex, lutetium texaphyrin	Lysosomes	734	–	USA	Breast, prostate, and cervical cancers, glioblastoma, age-related macular degeneration, and arterial disease
		Padoporfin, Tookad	Mitochondria	762	–	USA	Prostate cancer
	Texaphyrins						
	Bacteriochlorins						

Abbreviations: HpD: Hematoporphyrin derivative; 5-ALA: 5-aminolevulinic acid; BDP: benzoporphyrin derivative; MAL: Methyl aminolevulinate; Ce6: Chlorin e6; HPPH: 2-(1-Hexyloxyethyl)-2-devinyl pyropheophorbide-a; mTHPC: *meso*-tetrahydroxyphenylchlorine; BCC: basal cell carcinoma; Pc4: Silicon phthalocyanine; ER: endoplasmic reticulum.

* Updated data obtained from the USA National Institute of Health clinical trials website.

mentioned, due to its local activation and minimum tissue penetration, PDT can be combined with radio- or chemotherapy or together with surgery [63–66]. On the other hand, there is considerable concern about PDT effectiveness, which has to be improved to avoid related side-effects [13,18].

2.4.2. PS-related limitations

Although numerous advantages of photodynamic cancer therapy,

this strategy applies PSs have several considerable drawbacks. The major inconvenience of most common PSs is their hydrophobicity, and although hydrophobic compounds tend to leak out of the circulatory system in tumors, they often have the tendency to self-aggregation in an aqueous biologic medium which causes poor solubility, weak bioavailability, off-target activation and could also affect their photosensitivity and photophysical properties due to their inadequate pharmacokinetics [22,25,77–79]. In turn, high doses of PSs must be administered to obtain

a clinically relevant level [5,6]. One of the successful strategies to remedy these drawbacks is employing DDS and nanoparticles (NPs), which can encapsulate or be conjugated with PSs to transport them to target tissue more effectively, changing the overall lipophilicity of PS molecules and increasing their bioavailability and stability [80,81].

3. Nanoparticle applications in PDT

Over the last few decades, there has been extreme interest in various applications of NPs in different kinds of scientific fields. The application of nanotechnology on medicine challenges, which is known by nanomedicine, for different types of cancer, such as hepatoma [82–85], breast cancer [86–89], skin melanoma [90–93], osteosarcoma [94–97] and leukemia [98,99] has shown great potential in cancer therapy using DDS over the past decades [100,101]. Most recently, diverse organic and inorganic NPs (Fig. 4a,b) have been attracted the researchers' attention for various kinds of photodynamic applications, such as PSs incorporation, being downconverting PSs and energy transducers. Fig. 4c is two statistical graphs showing the increasing attraction in NPs for various applications and the progressing of NPs in PDT usages. However, the focus here is on the PSs delivery systems application of several types of organic NPs, including nanovesicles, nanospheres, nanocapsules and micelles (Fig. 4a), and inorganic NPs, such as gold NPs (AuNPs), carbonic NPs, mesoporous silica NPs (MSN) and quantum dots (QDs) (Fig. 4b). For PS-loaded organic NPs, PSs can be usually released by following a combination of deterioration and diffusion process, and their release profile is dependent on three main parameters, including (i) PS loading type, which can be encapsulated, surface-bonded, and matrix-adsorbed; (ii) PS diffusion through the matrix (for nanospheres) and the carrier wall (for nanocapsules); and (iii) NPs' degradation rate [102–104].

Depending on the type and preparation protocol of the NPs, they have several advantages; (i) the ability to apply the surface modification to have targeted therapy or increase the biodistribution [105–107]; (ii) taking advantage of the enhanced permeability and retention (EPR) effect, which allows PS-loaded NPs to diffuse and remain in tumor tissue [108,109]; (iii) increasing the PSs uptake in tumor site due to having a sizeable surface-area-to-volume ratio (SA/V) [110–112]; (iv) decreasing the side effects for PSs tending to damage all cell types by preventing non-specific accumulation in normal tissues [113–115] and (v) the ability to design multifunctional approaches such as chemo/photodynamic therapy and optical imaging/PDT [116–119]. Table 2 summarizes the data from some of the most used representative NPs for the PDT

application.

4. Liposome application in cancer therapy

Self-assembled vesicular NPs, made up of phospholipids/surfactants, as their main components, demonstrate promising nanomedicine potential as novel biomedical nanocarriers. In the last decades, liposomes and niosomes, as the two most usual vesicle subcategories, have been widely used in cancer [128,129], gene [10,130,131], and vaccine therapies [132–134] as well as in tissue engineering [135–137]. Liposome, as advanced vesicular DDS, is able to be self-assembled using their main component, phospholipid (Fig. 5), which yields liposomes numerous unique properties like biocompatibility and biodegradability [138]. Based on vesicle structure, there are seven main categories for liposomes (Fig. 6): multilamellar large (MLV), oligolamellar (OLV), small unilamellar (SUV), medium-sized unilamellar (MUV), large unilamellar (LUV), giant unilamellar (GUV) and multivesicular vesicles (MVV) [139–142]. Amphiphilicity and biocompatibility are two main characteristics that make phospholipid tremendously suitable for drug delivery applications. In addition to the liposome, various types of DDSs made by phospholipids, such as micelles, intravenous lipid emulsions, and cochleates. In order to optimize the characterization of final vesicular DDSs, there are some additives to improve stability, entrapment efficiency, and ability of self-assembly, being cholesterol the most common one, which can be located in the bilayer by a hydrogen band between its hydroxyl group and hydrophilic head of phospholipid in liposomes [143–145].

4.1. Liposome applications

Liposomes have shown their great potential in pharmaceuticals and nanomedicine through their numerous applications, such as enhancing permeability of pharmaceutical agents through physical barriers, increasing the duration of drug circulation in the patient's cardiovascular system, and drug targeting in cancer therapy and nanomedicine usages. The main applications of liposomes are in the field of pharmaceuticals for controlled release, sustained delivery, and targeted therapy. There are also other important applications for liposomes, like diagnostic imaging by radiolabeled-liposomes [146–148] and improving transdermal delivery in modified cosmetic products [149–152]. Moreover, one of the most critical novel usages of liposomes is gene therapy. In this area, there are numerous successes achieved in the treatment of breast cancer [153,154], diabetes [155–158], and liver cirrhosis

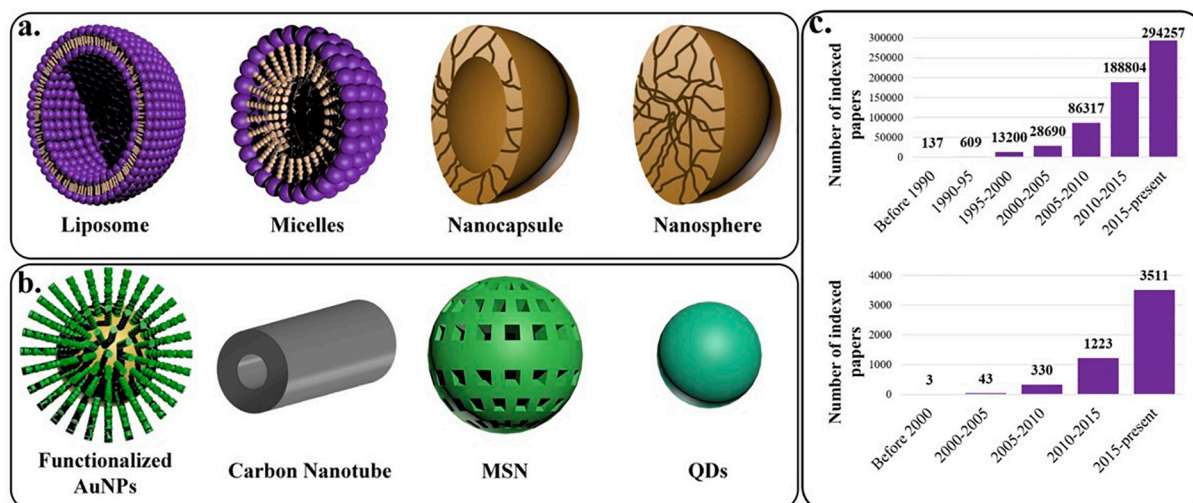


Fig. 4. 3D Schematics of the most used types of NPs for PDT, categorized in two groups; organic NPs (a) and inorganic NPs (b); and a graph representing the number of NPs Scopus-indexed papers published every five years for all kinds of applications and PDT (c).

Table 2

Representative PSs-loaded NPs used the recent studies, their advantages in comparison with traditionally used PSs and future perspectives.

Category	NPs Type	Main Components	Loaded PS	Approximate Size	Treated cancer cell type	Advantages	Perspective	Ref.
Organic NPs	Micelle NPs	PEG; azobenzene; poly(aspartic acid)	Ce6	~189 nm	LCC	- Facilitating cellular uptake - Improving dose accumulation in tumor	- Multifunctional micellar nanoplateform showed the potential to be a facile and robust vehicle for a diverse range of PSs	[120]
		PNBMA-PEG	RB	~14 nm	Thyroid cancer	- Enhancing the cellular and tumoral uptake due to targeting ligands - Preventing the <i>in vivo</i> systemic toxicity	- Promising nanoplateforms for targeted neuroendocrine tumors theranostics	[121]
		POEGMA	Porphyrin	~384 nm (pH:7.4); ~543 nm (pH:5.0)	HCC	- Reducing the ACQ of the PS - Increasing the singlet oxygen generation - Reducing the aggregation of the PS - More <i>in vivo</i> PDT efficiency due to using pH-responsive micelles	- Improve various PDT applications due to provide a better microenvironment for PSs and simultaneously to reduce the ACQ	[122]
	Polymeric NPs	PCL; PEG	Ce6	~220 nm	Breast cancer	- Higher accumulation in tumor tissue compared to free Ce6 - Increased blood circulation time - Indicating efficient PS delivery to metastatic tumor tissue in lung and other sites	- More studies can be done on targeted cancer therapy for various kinds of cancer using targeting agents as two basic variables	[123]
		PLGA	ZnPcSO ₄	~385 nm	Melanoma	- Making superior therapeutic efficiency in comparison with free ZnPcSO ₄	- Increasing the phototoxicity of PS is an interesting goal for targeted PDT therapy	[124]
						- Enhancing the water solubility through the formation of stable colloids - Higher rates of cell death in cells compared with free PS	- The approach has the potential to alleviate <i>in vivo</i> PDT side effects due to having non-specific toxicity and high PDT efficiency	[125]
Inorganic NPs	Metallic NPs	Au(I)	mTHPC	~180 nm	Neuroblastoma	- Acting as a CDT/PDT combination antitumor agents - activating under TME and decreasing the undesirable damages to normal tissues	- Employing metal–organic coordination NPs for PSs loading is a novel idea, interesting for targeted therapy	[126]
		Fe(III), HA	Porphyrin	~145 nm	Breast cancer			
	Ceramic NPs	Silica	Ce6	~80 nm	Adenocarcinoma	- The ability of loading PS, neoantigen peptides, and oligodeoxynucleotide into a bMSN nanoplateform - More effective accumulation in tumor site after intravenous administration	- bMSN is a promising platform for combining PDT-immunotherapy and imaging, which have the potential to be studied for various applications as well as personalized cancer vaccination	[127]

Abbreviations: Ce6: Chlorin e6; RB: Rose Bengal; PEG: poly(ethylene glycol); PNBMA-PEG: poly(4,5-dimethoxy-2-nitrobenzyl methacrylate); LCC: lung carcinoma; POEGMA: poly(ethylene glycol) methyl ether methacrylate; ACQ: aggregation caused quenching; PCL: polycaprolactone; HCC: Hepato-cellular carcinoma; ZnPcSO₄: zinc phthalocyanine tetrasulfonated; mTHPC: *meso*-tetrahydroxyphenylchlorin; HA: hyaluronic acid; CDT: chemodynamic therapy; TME: tumor microenvironment; bMSN: biodegradable mesoporous silica nanoparticles.

[159–161].

5. Liposome application in PDT

Liposomes are renowned for their great potential in the controlled release of an expanded range of drugs and were initially used in some basic experiments, such as biological membranes' photochemistry [162,163]. Because of the various advantages and possibilities of liposomes, they were utilized to load numerous types of PSs for photodynamic cancer treatment. In liposomal PDT studies, they were used for different purposes, such as increasing selectivity, reducing side effects, decreasing immunogenicity, enhancing PS phototoxicity, and thereby providing higher PDT efficiency. Table 3 shows some commercial liposomal PS formulations which are clinically and preclinically validated for PDT. Visudyne®, a lipid/liposome-based NP containing verteporfin, is known as the first FDA-approved liposomal PS [164]. As a benzoporphyrin derivative monoacid (BPD-MA), Verteporfin has been shown great potential for an effective *in vivo* PDT. However, it is a hydrophobic

chlorin-like PS with a marked tendency to be aggregated in an aqueous solution which causes poor bioavailability. Visudyne®, as verteporfin-encapsulated liposomes, could provide a new PS formulation suitable for intravenous route of administration which can extend the circulation time. Visudyne® is the only FDA-approved drug for the PDT of age-related macular degeneration (AMD), 609 patients with age-related macular degeneration were treated in phase I and phase II clinical trials [165–167]. Foslip®, another commercial liposomal PS formulation, is meta-tetra(hydroxyphenyl)chlorin (mTHPC or temoporfin)-loaded liposome, and Fospeg® is the same formulation using pegylated-liposomes. Foslip® and Fospeg®, which could improve the PS circulation time in the bloodstream, were approved by European Medicines Agency for the PDT of advanced head and neck squamous cell carcinoma [168,169]. Ciftalan zinc (CGP55847®) is another liposomal PS, containing ZnPc (Zinc phthalocyanine) with the composition formulation of ZnPc:POPC:DOPS (1:90:10, mass ratio). This approach has been employed in patients suffering from squamous cell carcinoma of the upper aerodigestive tract [170].

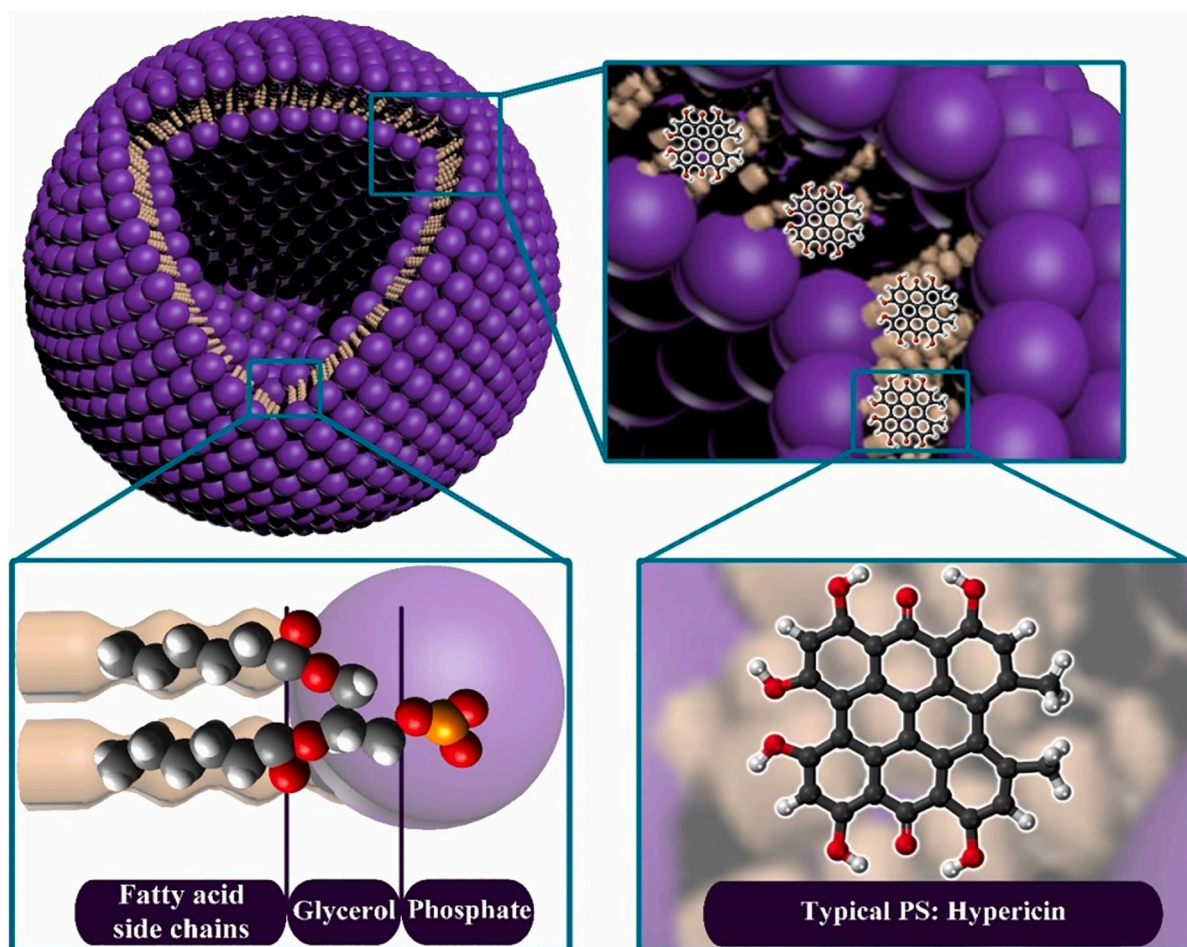


Fig. 5. 3D schematic of liposome structure, phospholipid as its main component and the structure of hypericin as a typical PS loaded in the liposome's bilayer.

Recently, numerous studies have reported the successful liposomal formulations for various PS encapsulation (such as hypericin, Zinc phthalocyanine, Chlorin e6, and Al(III) phthalocyanine chloride tetra-sulfonic acid (Fig. 7)) for the treatment of several cancer types. Table 4 is demonstrating the finding of recent investigational studies on liposomal PDT, which are promising and further investigation are required for the full understanding and exploring the great potential of this approach.

5.1. Hypericin

Hypericin-loaded liposomes were employed in photodynamic ovarian cancer therapy. Liposomal encapsulation of hypericin can overcome these drug limitations, such as high lipophilic nature and poor bioavailability via weak solubility in an aqueous medium, resulting in greater phototoxicity in human ovarian adenocarcinoma cells (SK-OV-3) [60]. In another study, transferrin-conjugated PEGylated liposomes were used to increase the biological specificity of hypericin and PS uptake. This study reported that in comparison with other liposome categories, MLV ones could load PS as a hydrophobic agent with a higher entrapment efficiency [172].

5.2. Zinc phthalocyanine (ZnPc)

One of the oldest liposome applications in PDT was reported in 1998, when liposomal ZnPc for the treatment of human cervix carcinoma and *in vitro* tests on NHIK 3025 (human cervix carcinoma cell line) demonstrated that liposome improved PS diffusion in the Golgi apparatus and mitochondria [173]. Additionally, doxorubicin/ZnPc co-loaded

mesoporous silica/calcium phosphate/PEGylated liposome (DOX/ZnPc/MSNs/CaP/PEGylated liposomes) has been used as a combination of PDT and chemotherapy for the treatment of liver cancer. Ma et al. [174] synthesized DOX-loaded MSNs as core particles and coated them with CaP to create a pH-triggered passive tumor-targeting, and the cores were encapsulated in ZnPc-loaded PEG-coated liposomes. This approach was tested on H22 liver cancer cells and H22 tumor-bearing mice, as a result, DOX/ZnPc/MSNs/CaP/PEGylated liposomes showed a considerable anticancer effect and excellent passive tumor-targeting therapy [174]. In another study, the PDT efficacy of ZnPc nearly doubled when it was used in a novel endothelium targeted liposomal formulation with co-encapsulation of ZnPc and tirapazamine [175].

5.3. Chlorin e6 (Ce6)

Chlorin e6 (Ce6) is another common second-generation PS used in liposomal PDT applications. Feng et al. compared the effect of Ce6-loaded liposomes with free Ce6 molecules at the same PS concentration on female mice bearing 4 T1 breast cancer tumor and reported high tumor selectivity and minor phototoxicity [176]. They also utilized the same liposome compounds with co-encapsulation of metformin and Ce6 into the inner cavity and outer membrane of liposomes, respectively. Their approach was intravenously administrated to breast cancer tumor mice models, and the results demonstrated significant improvement of PDT efficacy and better modulation of the unfavorable hypoxic tumor microenvironment by reducing oxygen consumption [177]. In another study, liposomes successfully improved the efficiency of Ce6 for the treatment of ovarian cancer [178].

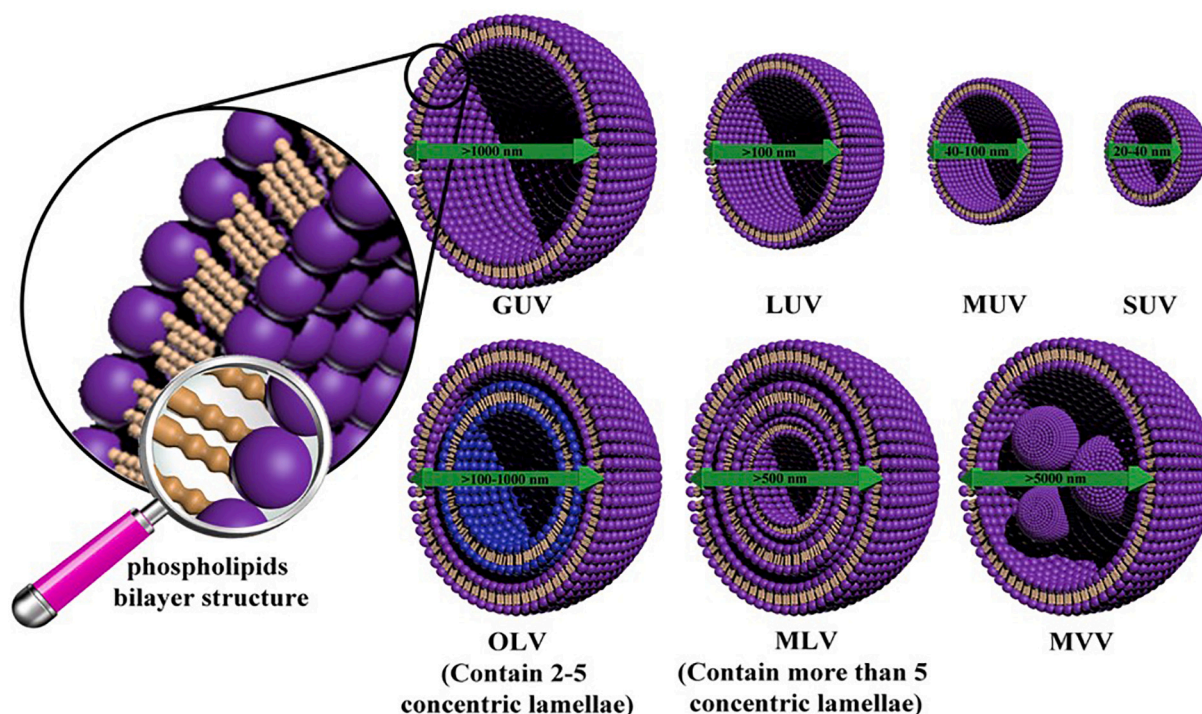


Fig. 6. Seven categories of liposomes based on their structure and size, GUV: giant unilamellar vesicle; LUV: large unilamellar vesicle; MUV: medium-sized unilamellar vesicle; SUV: small unilamellar vesicle; OLV: Oligolamellar vesicle; MLV: multilamellar large vesicle; MVV: multivesicular vesicle.

5.4. Al(III) phthalocyanine chloride tetrasulfonic acid (AlPcS4)

As a promising PS, AlPcS4 has several advantages, such as considerable penetration into tissue, high quantum yields, low photobleaching, and suitable photostability. However, it shows low penetration into cancer cells due to its little release efficiency and high binding affinity to serum albumin. To improve this limitation, cationic liposomes have been used. Indeed, Rocha et al. studied dog breast cancer treatment and demonstrated that the safety and efficiency of AlPcS4 can be increased when it loads in liposomes [179]. Additionally, Xin et al. reported that AlPcS4 loading in liposomal DDSs can increase PDT efficiency and reduce PSs' binding affinity to serum proteins [27]. In another study, the formulation of AlPcS4-loaded transferrin-conjugated PEG-liposomes was compared to free and non-targeted liposomal AlPcS4, showing higher tumor-selective accumulation in bladder tumor tissues [180]. Besides, Gijssens et al. had successfully used the same AlPcS4-loaded transferrin-conjugated PEG-liposomes formulation for the treatment of cervix carcinoma [28].

5.5. Advantages and disadvantages of PS-loaded liposomes

Liposomes are employed as highly potential vesicular DDS because of their various advantages, including biocompatibility, biodegradability, and ability to be used as a targeted DDS and transport drug molecules into cells, decreasing drug side effects and consequently enhancing tissue/cell-specificity. As mentioned in Section 2.3, one of the most significant drawbacks of many PSs is their poor solubility in an aqueous biologic medium, which causes their tendency to self-aggregation, poor bioavailability, and off-target activation. In this regard, liposomes, which are suitable for the delivery of lipophilic, amphipathic, and hydrophilic drugs due to their ability to entrap water-soluble agents in their aqueous core and hydrophobic molecules into their bilayers, can load hydrophobic PSs and make a homogeneous suspension in aqueous solutions. Moreover, they can protect encapsulated PSs from the effect of biological reactions, increasing the PSs' stability and improving their pharmacological properties [186,187].

Additionally, liposomes can easily be functionalized for surface modification due to various functional groups on phospholipids' hydrophilic heads. Therefore, they can be conjugated with targeting agents, molecules with a high specific affinity for biomolecules over-expressed in targeted tumor cells [188,189]. Therefore, targeted PDT by using liposomal PSs is attracting attention, and many studies are using targeted liposomal PDT for the treatment of various types of cancer [190–193].

As demonstrated in Table 3, the PS incorporation molar percentage is less than 13% for commercial PS-loaded liposomes. However, since higher PS ratios may cause vesicle aggregation, the extrusion technique could be applied, which includes pushing the final liposomal suspension through some membrane with well-defined pore sizes. However, this technique is not easy to scale up for commercial quantities.

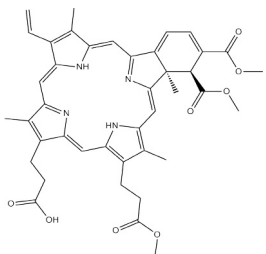
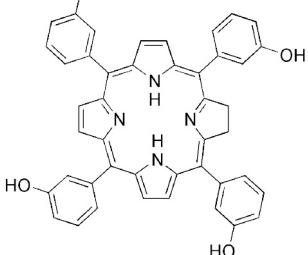
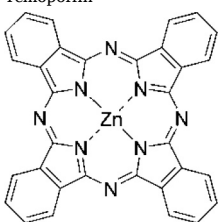
On the other hand, an ideal nanoparticle for PSs would be a highly purified chemical that could be analyzed for quality control while having minimal manufacturing costs and high storage stability. In this regard, liposomes are limited by their high production cost, phospholipids oxidation, and hydrolysis-like reaction possibilities. In addition, compared to other polymeric NPs, liposomes demonstrate relatively less stability and may cause quick uptake nearby reticuloendothelial system (RES), but as mentioned above, the functionalization ability of liposomes make them able to be modified by some agents (usually polyethylene glycol (PEG)), evading RES to increase their blood lifetime and have a much higher chance for drug delivery in the blood vessels surrounding cancer tumors [194–196]. Altogether, despite some drawbacks, the unique favorable properties of liposomes make them attractive NPs in nanomedicine.

5.6. Other applications for liposomal PSs

In addition to photodynamic cancer therapy, PS-encapsulated liposomes have other applications. Verteporfin, a standard second-generation PS, has been successfully encapsulated in cationic liposomes for choroidal neovascularization (CNV) treatment [197], and hypericin-encapsulated liposomes have been utilized for anti-microbial

Table 3

Clinically and preclinically approved Ps-loaded liposomes (updated data obtained from the USA National Institute of Health clinical trials website).

Approach	Loaded PS	Administration Route	Formulation Components	Size (nm)	PS incorporation	Clinical	Preclinical	Approving Organization	Ref.
Visudyne®		Intravenous	DMPC:EPG (3:5 M ratio)	150–300	12.5% (molar)	AMD, Pathologic myopia, CNV	BCC and nevoid BCC syndrome, OHS, Glioblastoma	FDA	[165,166]
Foslip®		Intravenous	DPPC:DPPG (9:1 mass ratio)	111	8% (molar)	HNSCC, NSCLC	Cholangiocarcinoma, Klatskin Tumor	EMA	[168]
Fospeg®			DPPC:DPPG:DSPE-PEG (9:1:1 mass ratio)	114					
CGP55847®	 ZnPc	Intravenous	POPC:DOPS (9:1 mass ratio)	70–80	1% (mass)	SCC	–	Switzerland	[169,171]

Abbreviations: FDA: USA Food and Drug Administration; EMA: European Medicines Agency; AIClPc: aluminum-chloride-phthalocyanine; DMPC: dimyristoyl-phosphatidylcholine; ZnPc: Zinc phthalocyanine; AMD: age related-macular degeneration; OHS: ocular histoplasmosis syndrome; BCC: Basal cell carcinoma; CNV: choroidal neovascularization; NSCLC: non-small cell lung cancer; HNSCC: head and neck squamous cell carcinoma; SCC: squamous cell carcinoma.

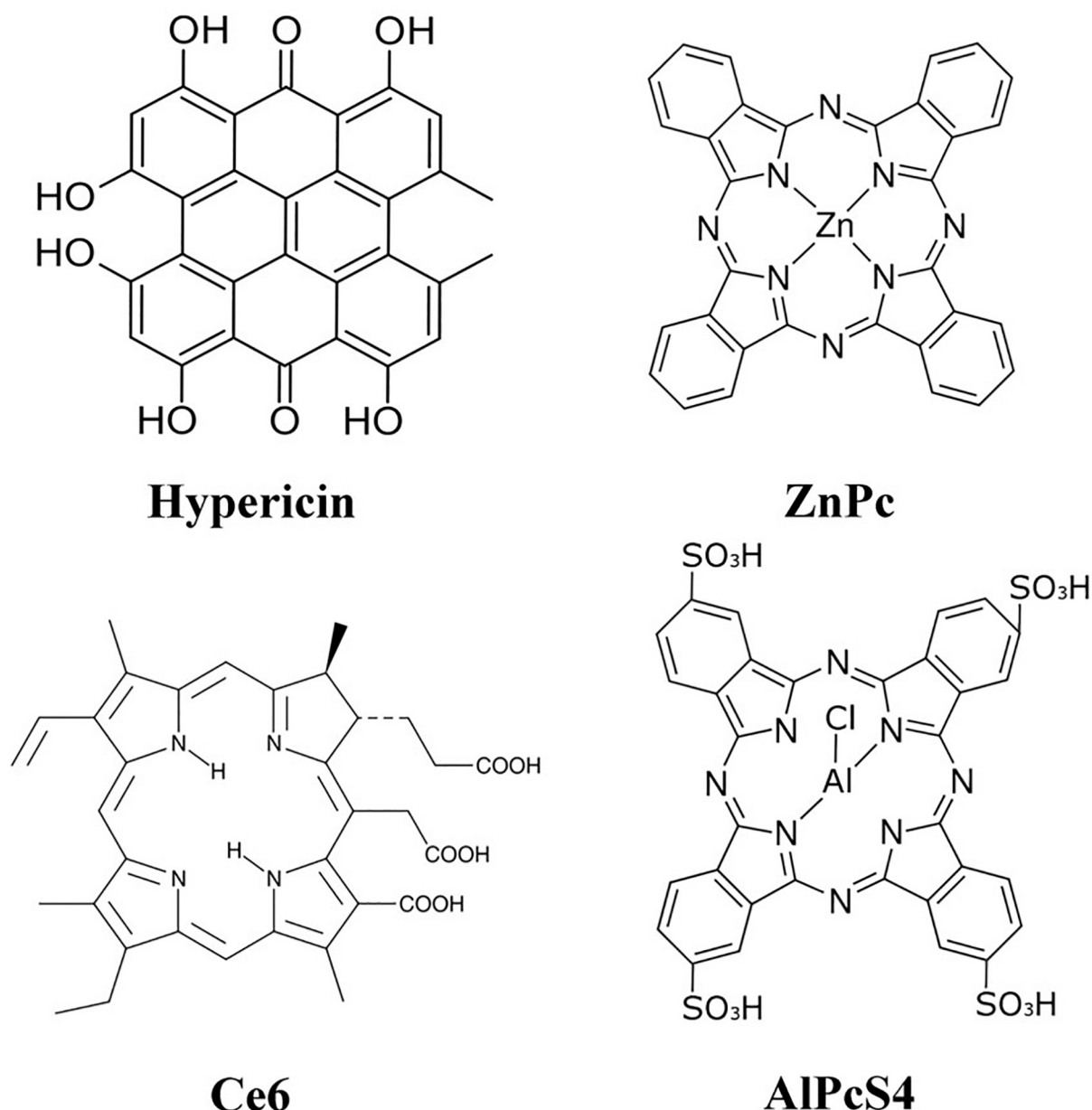


Fig. 7. Chemical structure of hypericin, ZnPc, Ce6 and AlPcS4.

PDT of gram-positive bacteria. This approach has also been used as an artificial model of biological light sensors [198,199].

Another application of liposomal PSs is the anti-microbial PDT, which is an alternative method for destroying bacterial cells to overcome antibiotic resistance of microorganisms. Yang et al. reported a novel anti-microbial peptide (AMP)-modified liposomal temoporfin as a bacteria targeted therapy system, showing that this approach can promisingly increase the efficiency of photodynamic anti-microbial chemotherapy in local infections against both gram-positive and gram-negative bacteria [200]. In another study, rhodamine 6G (R6G) as a hydrophilic PS was loaded in liposomes for anti-microbial PDT application. As a result, photoefficacy and singlet oxygen quantum yield of R6G in liposomes were much higher than free R6G [201].

In addition, PSs can be loaded in the liposome's bilayer to make "photosensitive" liposomes, which are usually interested when a hydrophilic cargo is loaded in the core of the liposome and can be released at a higher rate as soon as be exposed to proper irradiation [202–204]. Recently, Zhu et al. studied photosensitive DOX-loaded liposomes by

protoporphyrin IX co-loading [182]. The result shows a successful omission of the MCF-7 tumor growth in nude mice within two weeks due to the PS effect, which was not only used as a combination of PDT and chemotherapy but also as the "gates" in the liposomal lipidic bilayer to trigger the release of the chemo-agent [182]. This strategy can be combined with targeted cancer therapy by specific antibodies for more selectivity. For example, Li et al. designed the Her2-targeting ICG-DOX-loaded liposome as a targeted photodynamic-chemo therapy system to treat osteosarcoma, breast, and lung cancer [183].

6. Conclusion and future perspectives

Nowadays, cancer therapy is one of the most challenging topics for research, and nanomedicine and photodynamic therapy combination can provide a plethora of promising approaches in this area. Based on numerous advantages of liposomes for PSs, they have been widely used as a high potential carrier for the PDT applications, improving the PDT effect via increasing PS half-life, increasing bioavailability, preventing

Table 4

Recent studies on photosensitizer-loaded liposomes for PDT application and cancer treatment.

PS	Approach	The goal of using liposomes	Basic compounds	Liposome size (nm)	Experiment	Conclusion	Ref.
Hypericin	Hyp-HPbCD-loaded liposomes	Treatment of ovarian carcinoma: to achieve a safer and more selective cancer therapy system	DSPC DPPC TEL	127–212	<i>In vitro</i> tests in SK-OV-3	Achieved formulations showed no dark toxicity on SK-OV-3 cells, but a considerable phototoxicity effect after irradiation	[60]
	Hypericin-loaded transferrin-conjugated PEG-liposomes	Cervical cancer therapy: to reduce side effects and improve hypericin specificity	DSPC PEG CH	~146	<i>In vitro</i> tests in human epithelial cervix carcinoma cells (HeLa)	PS liposome encapsulation increased drug hydrophilicity, and in comparison with non-targeted PEG-liposomes or free hypericin, transferrin-conjugated PEG-liposomes demonstrated higher affinity.	[172]
AlPcS4	Clip-AlPcS4	Gastric cancer therapy: to provide a more effective PDT compared to free PS, PS-conjugated gold NPs and micelle	DPPC DSPE-PEG CH	~150	<i>In vitro</i> tests using SGC-7901 cells	AlPcS4-PDT modified clip showed effective inhibition of cancer cell proliferation, optimal AlPcS4 drug delivery efficiency and low binding affinity to serum proteins	[27]
	Tf-Lip-AlPcS4	Treatment of bladder cancer: to provide a more efficient treatment	DSPE-PEG DSPC CH	~146	<i>In vitro</i> tests with human AY-27 transitional-cell carcinoma cells and <i>in vivo</i> tests with orthotopic rat models	Tf-Lip-AlPcS4 showed a promising potential for targeted PDT for superficial bladder tumors	[180]
	Tf-Lip-AlPcS4	Cervical cancer therapy: to enhance the efficiency of PDT	DSPE-PEG DSPC CH	~146	<i>In vitro</i> tests with HeLa cells	Tf-Lip-AlPcS4 formulation demonstrated a higher efficiency compared to free AlPcS4. It could also uptake PS more selectively in transferrin receptor medium	[28]
Ce6	Ce6/DOTAP/TELS liposomes	Ovarian cancer therapy: to control Ce6 release and obtain a more efficient PDT	DPPC DOTAP TEL	98–168	<i>In vitro</i> tests using mouse neuro-blastoma (Neuro-2a) and SK-OV-3 and chick chorioallantoic membrane (CAM) model for <i>in situ</i> cytotoxicity test	DOTAP improved Ce6 entrapment in liposomal bilayer and formulation neglected dark toxicity. CAM model showed effective localized vascular destruction while sparing quiescent non-irradiated ones	[178]
	DiR-hCe6-liposome	Breast cancer therapy: to reduce PDT side effects on skin and increase efficiency	DPPC DSPE PEG CH	~150	<i>In vitro</i> tests with 4 T1 cancer cells and breast-tumor-bearing female mice for <i>in vivo</i> tests	Phototoxicity test on mouse skin showed that the approach yielded an excellent skin protection ability and improved treatment selectivity	[176]
	Met-HCe6-Liposomes	Breast cancer therapy: to reduce tumor cell oxygen consumption more effectively	DPPC DSPE-PEG CH	~232	<i>In vitro</i> tests with murine breast cancer 4 T1 cells and <i>in vivo</i> tests with mice bearing 4 T1 tumors	Significant improvement of PDT efficacy and tumor oxygenation modulation	[177]
ZnPc	DOX-ZnPc-MSNs-CaP-PEGylated liposomes	Liver cancer therapy: as a system for combining PDT and chemotherapy	SPC PEG CH	~122	<i>In vitro</i> tests with H22 liver cancer cells and H22 tumor-bearing mice for <i>in vivo</i> tests	<i>In vitro</i> study demonstrated a great anticancer effect and <i>in vivo</i> fluorescence imaging indicated an excellent passive tumor-targeting therapy	[174]
	TPZ-ZnPc-ETL	Skin cancer therapy: to improve PS biodistributive properties and enhance PDT efficiency	DPPC DC-CH DSPE-PEG	~111	<i>In vitro</i> tests with human epidermoid A431 carcinoma cells	<i>In vitro</i> study: TPZ and ZnPc co-encapsulation in liposomes could nearly double the PDT efficacy and also circumvent the unfavorable pharmacokinetics	[175]
PpIX	Protoporphyrin IX loaded PC-liposomes	Cervical cancer therapy: to increase PDT efficiency and intracellular distribution	PC DOTAP SOPS	117–148	<i>In vitro</i> tests with HeLa cells	Incorporation of PS into PC-liposomes could increase PS internalization efficiency and improved PS' distribution within cells	[181]
	PpIX/Dox liposomes	Treatment for breast cancer by a combination of photodynamic-chemo therapy strategies	HSPC, DSPE-PEG- OMe CH	~56	<i>In vitro</i> study with carcinoma cell lines (MCF-7 and A549) and breast-tumor-bearing mice for <i>in vivo</i> tests	Significant improvement in cellular uptake, <i>in vivo</i> study, demonstrated that the combination of liposomal DOX with PDT could eradicate Dox-resistant MCF-7/ADR tumors	[182]
ICG-ODA	Her2-I&D-LSL	Treatment for breast and lung cancer and osteosarcoma: as a targeted photodynamic-chemo therapy system	DSPE-PEG PLsPC CH	~128	<i>In vitro</i> and <i>in vivo</i> (mouse bearing MCF7, A549 or S180) tests of their cell lines (MCF7, A549, S180)	<i>In vitro</i> study indicated a stronger inhibition effect on cells compared with PDT (I-LSL) and chemotherapy alone (D-LSL). <i>In vivo</i> study also showed that targeted therapy caused more LSL accumulation in tumors	[183]
AlEgen-lipid	AlEsomes			~150			[184]

(continued on next page)

Table 4 (continued)

PS	Approach	The goal of using liposomes	Basic compounds	Liposome size (nm)	Experiment	Conclusion	Ref.
		Breast cancer therapy: as a targeted system to optimized PDT	DSPE-PEG DSPC CH		<i>In vitro</i> tests with 4 T1 cancer cells for and breast-tumor-bearing mice for <i>in vivo</i> tests	<i>In vitro</i> : AIEsomes generated ROS more efficiently than the widely used NPs with core-shell structures. <i>In vivo</i> : AIEsomes exhibited good tumor targeting and imaging efficacies	
PheoA	GDPL	Treatment of cholangiocarcinoma: as photomediated immune modulator for cholangiocarcinoma treatment	DSPE-PEG DOPE DPPC CH	~102	<i>In vitro</i> study with carcinoma cell line (HuCCT-1) and tumor-bearing xenograft mice for <i>in vivo</i> tests	<i>In vivo</i> studies demonstrated that GDPL triggers robust immune activation and T cell response	[185]
Photofrin	PF-PEG-Lip	Treatment of ovarian sarcoma: to prolong PS retention and increase its phototoxicity	DMPC DMPG PEG CH	~114	<i>In vitro</i> tests with M5076 ovarian sarcoma cells	PEGylation prolonged PS retention time in the liposome bilayer. PF-PEG-Lip phototoxicity was the highest compared to free PF and liposomal PF	[57]

Abbreviations: Ce6: Chlorin e6; AlPcS4: Al(III) phthalocyanine chloride tetrasulfonic acid; ZnPc: zinc phthalocyanine; PpIX: Protoporphyrin IX; DSPC: 1,2-dioctadecanoyl-sn-glycero-3-phosphocholine; DPPC: 1,2-dipalmitoyl-sn-glycero-3-phosphatidylcholine; TEL: tetraether lipid; DSPE: 1,2-distearoyl-sn-glycero-3-phosphoethanolamine; PEG: polyethylene glycol; CH: cholesterol; DOPE: dioleoylphosphatidyl-ethanolamine; DSPE-PEG-OME: 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000]; PLSPC: 1-(1z-octa- decenyl)-2-oleoyl-sn-glycero-3-phosphocholine; PC: phosphatidylcholine; DOTAP: 1,2-dioleoyl-3-trimethylammonium-propane; SOPS: 1-stearoyl-2-oleoyl-sn-glycero-3-[phospho-L-serine]; DMPC: 1- α -Dimyristoylphosphatidylcholine; DMPG: 1- α -dimyristoylphosphatidyl-dl-glycerol; Hyp-HPBCD: hypericin-hydroxypropyl- β -cyclodextrin inclusion complex; Her2-I&D-LSL: Her2 antibody conjugated/ICG-ODA and DOX loaded liposomes; ICG-ODA: indocyanine green-octadecylamine; DC-CH: 3 β -[N-(N',N'-dimethylaminoethane)-carbimoyl]cholesterol; TPZ-ZnPc-ETL: tirapazamine-zinc phthalocyanine-endothelium targeted liposome; GDPL: gemcitabine-loaded PS-conjugated liposomes; PheoA: pheophorbide A; Clip-AlPcS4: AlPcS4-loaded cationic liposome; Tf-Lip-AlPcS4: AlPcS4-loaded transferrin-conjugated PEG-liposomes; Ce6/DOTAP/TELS liposomes: chlorin e6/1,2-dioleoyl-3-trimethylammonium-propane/tetraether lipids liposomes; EE%: encapsulation efficiency; DiR-hCe6-liposome: liposomes containing DiR as a lipophilic near-infrared dye and exylamine conjugated chlorin e6 as PS; hCe6: hexylamine conjugated Ce6; PF-PEG-Lip: polyethyleneglycol modified photofrin loaded liposome.

their tendency to be aggregated, augmenting cell/tissue-specificity, and decreasing unwanted side effects. In addition to loading hydrophobic agents, like PSs with high entrapment efficiency, because of the functional groups on phospholipids' hydrophilic head, liposomes are also able to be coated with specific antibodies' conjugation and used as targeted PDT. Moreover, release-triggering liposomes by using various kinds of liposomal PSs can be an exciting topic for other research areas, such as the controlled release application in tissue engineering where growth factors/hormones/nucleotides need to be available in the matrix following a combination of both immediate and sustained release profiles in different time points. In conclusion, this review indicates that liposomal PSs with their variety based on PS types, liposomal formulation, and modification agents have a great and yet untapped potential in photodynamic cancer therapy. There are too many promising ideas that need to be investigated to understand their preclinical/clinical potential fully.

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