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REVIEW

Enhanced photodyamic therapy via photosensitizer-loaded nanoparticles for cancer treatment

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Abstract Cancer is one of the most challenging human disease to cure, and has high rate to death. The current major cancer treatments include surgery, chemotherapy and radiation therapy. However, these treatments have a lot of obstacles that included low efficacy, mortality and severe aftereffects. Photodynamic therapy is developing cancer therapy that photosensitizer (PS) transfers energy from light to molecular oxygen damaged to generate reactive oxygen species (ROS). These reactions occur in the immediate locale of the light-absorbing PS. Almost of PSs have obstacle to adjust in human body system. Nanoparticle systems (NS) were used to overcome problems like drug solubility, delivery and low efficacy. Nanoparticles loaded anticancer drug, small molecule drug, biomedicine and PSs. In this review, we summarize the studies that have confirmed the nanoparticle systems loading PSs which are Phthalocyanine 4, Photofrin®, Temoporfin, Levulan® and Foscan® cancer therapy and discuss the future direction for the this novel therapy.

Keywords Nanoparticles · Photodynamic therapy · Photosensitizer · Drug delivery · Tumor

Introduction

Malignant tumors as the major public health problem arise great threats to humans (Wang et al. 2015). The treatments for malignant tumors include surgery, chemotherapy, and radiotherapy, which remain the first choices for most patients (Dy et al. 2013). Among the traditional treatments, the chemotherapy remains unsatisfying due to multidrug-resistance, which has become a major obstacle in cancer treatment (Wang et al. 2016).

Photodynamic therapy (PDT) is an arising alternative approach for improved cancer treatment. The use of PDT is more and more attractive, especially since it has been shown that this therapeutic method can be performed as an alternative or adjuvant to other therapy, such as radiotherapy, surgery and chemotherapy. PDT uses the toxicity of singlet oxygen generated by a reaction between a highly safe photosensitizer (PS) specifically accumulated in tumor cells and light with a specific wavelength that excites the PS. It causes selective damage to the tumor and its surrounding vasculature. Photochemical reactions damage tumor tissues by direct injuries that are necrosis and apoptosis of tumor cells due to the toxicity of singlet oxygen, the occlusion of tumor vessels and secondarily enhanced host immunity (Akimoto 2016). However, the success of PDT is limited by the difficulty in administering PSs with low water solubility, which compromises the clinical use of several molecules (Calixto et al. 2016). Nanoparticles such as gold nanoparticles, solid lipid nanoparticles (SLN) have been widely studied for targeted drug delivery, especially for PSs (He 2015).

Nanoparticles systems

Nanoparticles systems (NS) have received much attention in the field of drug targeting, because it has the high drug loading capacity as well as the unique disposition characteristics (Kataokaa 2000). Nanoparticles could be composed various materials divided organic and inorganic.

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First, representative organic materials include transferrin, H-Ferritin (HFn), SLN, and the like. They loaded HFn nanocage with Doxorubicin (DOX) for tumor-specific drug delivery. HFn nanocages can encapsulate large amounts of foreign molecules (Xiong et al. 2014; Zhao et al. 2015), bind specifically to tumor cells that overexpress transferrin receptor 1 (TfR1), and should be able to efficiently deliver high doses of therapeutic drugs to tumors. These solid colloidal particles consist of a solid lipophilic matrix at body temperature, in which biologically active substances can be dissolved or entrapped (Goto et al. 2017). SLN have many advantages when compared to other colloidal carriers, such as avoidance of organic solvents, low cost materials, drug release profile controlled by modification of the solid matrix, improved stability profile, and the possibility of large scale production (Kakadia et al. 2014).

Other materials to compose nanoparticles are gold and iron which is inorganic. Gold nanoparticles have been highlighted for applications in cancer therapy due to their significant resonance property, which is accomplished by energy excitation derived from application of a specific wavelength of light onto the surfaces of gold nanoparticles (Kim and Lee 2016). There has been considerable interest in iron oxide nanoparticles as multifunctional nano-platforms for imaging and therapy. Since they have unique properties such as biocompatibility, intrinsic ability to enhance magnetic resonance contrast, facile surface modification, and target specificity under external magnetic control, Iron oxide NPs hold a promise as theranostic NPs (Choi et al. 2016).

Mixed with organic and inorganic materials also could be NS. Lee et al. studied about Rabies virus (RABV) with gold nanoparticles to go through blood–brain barrier. RABV is a prototypical neurotropic virus in the genus *Lyssavirus* in the Rhabdoviridae family that causes hydrophobia accompanied by difficulty swallowing and panic in mammalian hosts (Lee et al. 2017).

Nanoparticles for photodynamic therapy

Photosensitizer

The PS which is key points to PDT transfers energy from light to molecular oxygen, to generate reactive oxygen species (ROS). These reactions occur in the immediate locale of the light-absorbing PS. The life of singlet oxygen was reported to range between 0.04 and 4 μs and the distance of migration between 0.02 and 1 μm, and therefore PDT is considered a less invasive therapy targeting each cell containing the PS alone while preserving the adjacent normal tissues(Akimoto 2016). Various PSs are developed to treat cancer. Some of them are commercialized and on the market. Those mentioned above are Phthalocyanine 4, Photofrin®, Temoporfin and Levulan® (Fig. 1).

Phthalocyanine 4 to treat cancer for photosensitizer by using nanoparticles

Phthalocyanine 4 to treat cancer

Phthalocyanine 4 (Pc 4) (Fig. 2a) is a second-generation PS for PDT discovered and developed at Case Western Reserve University. It is structurally related to the porphyrins and is a on isomeric tetrapyrrole, large macrocyclic ring structure with silicon chelated in the center. The four subunits that comprise the Phthalocyanine ring are linked by nitrogen instead of carbon and hydrogen and each subunit incorporates a benzo group that expands the ring structure. Therefore, some nanoparticles for enhance cytotoxicity and deliver to specific cancer cell were needed to develop. It is summarized in Table 1.

Increasing delivery efficacy using NP systems

PS is usually used via injection. It is unnecessary to delivery to non-target tissue like normal tissue. Wang et al. reported that using fibronectin–mimetic nanoparticles can enhance binding to brain tissue (Wang et al. 2014). Dixit et al. and Chan et al. also reported that how to make better to deliver to brain tissue. They use gold nanoparticles (AuNPs) targeting to transferrin receptor. It also increases deliver to brain. AuNPs can synergistically disrupt cancer tissue. Combination of a contrast agent with a AuNPs formulation can simultaneously identify the location of tumor tissue and destroying the identified tissue (Kim and Lee 2016).

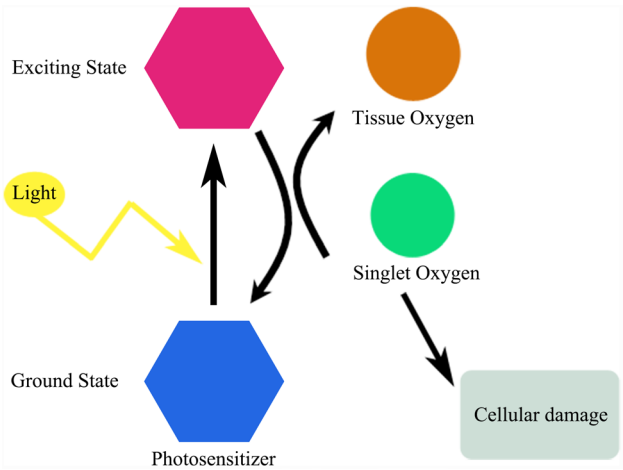

Fig. 1 Mechanism of photodynamic therapy

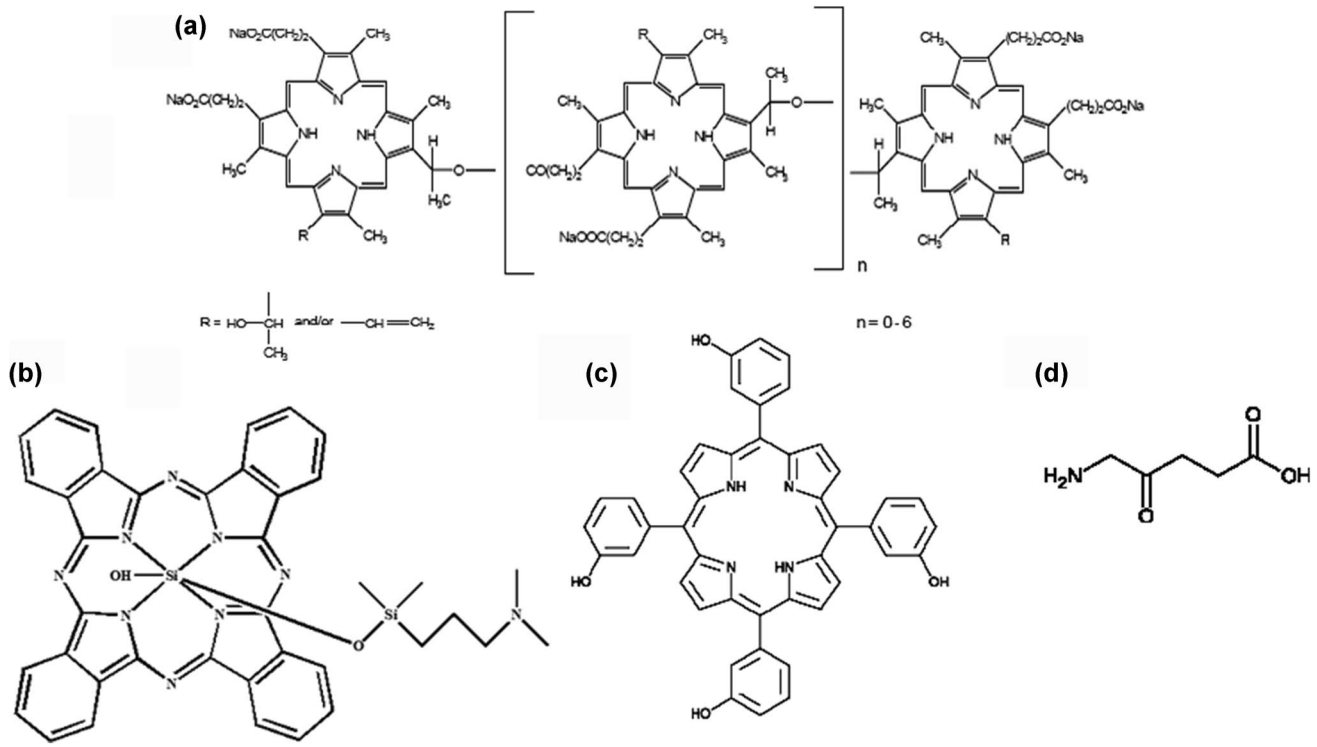

Fig. 2 Chemical structure of photosensitizer. **a** Phthalocyanine 4, **b** Photofrin, **c** Temoporfrin, and **d** Levulan

Table 1 Nanoparticles loading Pc 4 to treat cancer

Photosensitizer	Nanoparticle	Result	Target	Reference
Zinc phthlaocyanine	Au–SiO_2	Enhancement of light extinction and extension of spectrum	Brain	Kavelin et al. (2017), Seoudi et al. (2006)
Phthalocyanine 4	Gold NP, transferrin Rc-Target	Specific delivery to the brain	Brain	Dixit et al. (2015a), Chan et al. (2017)
Phthalocyanine 4	Fibronectin–mimetic peptide, Iron-oxide	Enhancement of effect and binding	Brain	Wang (2014)
Aluminium phthalocyanine disulfonate	Iron oxide, Macrophage	Significant increasing of uptake	Brain	Madsen et al. (2013)
Phthalocyanine 4	Gold NP	Enhancement of cellular association and increasing cytotoxicity	Brain	Dixit et al. (2015b)
Aluminum chloride phthalocyanine	Solid lipid nanoparticles	Outstanding photo-toxicity effects	Melanoma	Goto et al. (2017)

Enhanced cytotoxicity of Pc 4 using NP system in tumor

Increasing cytotoxicity of Pc 4 by loading AuNPs with transferrin peptide is reported by Dixit et al (2015a). $T_f$pep-AuNPs-Pc 4 is more efficacious than free Pc 4 and AuNPs-Pc 4 at lower concentrations (100 nM). This results in a reduced therapeutic dose for glioma treatments, which could potentially decrease unintended side effects of the drug in vivo. AuNP with SiO_2 loaded Pc4 enhanced light extinction and extension of spectrum (Kavelin et al. 2017). We can use broad spectrum of light to PDT by using these nanoparticles. SLN targeting melanoma also were enhancing phototoxicity effects (Goto et al. 2017). SLN containing Aluminum chloride phthalocyanine (ClAlPc) showed better phototoxicity than free CIAIPc at same dose. Madsen et al. supposed that iron oxide-loaded rat alveolar macrophages with aluminium phthalocyanine disulfonate had shown higher uptake. (Madsen et al. 2013) These might be an attractive solution to the specific and efficient cancer therapies by using Pc 4.

Photofrin® to treat cancer for photosensitizer by using nanoparticles

Photofrin® to treat cancer

Photofrin (Fig. 2b), a complex mixture of porphyrin oligomers, is first developed PS and one of the most efficient PSs approved for PDT of cancer (Reddy et al. 2006). The development of Photofrin arose from an initial discovery in 1983 by Thomas Dougherty, who showed that crude hematoporphyrin contains a range of different porphyrins. However, PDT is often accompanied by long lasting skin toxicity, which is a major limitation in the clinical application (Felsher 2003; Nishiyama et al. 2009). Therefore, some nanoparticles for reduce side effect and dose to PDT were needed to develop. It is summarized in Table 2.

Reducing phototoxicity of Photofrin® using NP systems

Skin damage is major side effect of PDT by using Photofrin®. Ionic dendrimer porphyrin was effective to significant reduce the skin phototoxicity.(Nishiyama et al. 2009) F3 is a 31-amino acid sequence of the NH2-terminal fragment of human high-mobility group protein 2, which was discovered using phage-displayed cDNA libraries.(Porkka et al. 2002) F3 has been reported to have cell-penetrating properties. F3-targeted nanoparticles derived the result of meaningful improvement in survival rate. F3-targeted nanoparticles providing a significantly increased survival time over that of non-targeted Photofrin® encapsulated nanoparticles or Photofrin® alone.(Reddy et al. 2006) If solved problem of phototoxicity, Photofrin® can be used broad.

Increasing delivery efficacy using NP systems

Delivery efficacy of PSs depends on several factors such as uptake and localization of the PS, mode of light delivery, physiological status of the cells or the target tissue, and photophysical properties of the sensitizer like singlet and triplet quantum yields and lifetimes (Gupta et al. 2011). Selective damage to the tumor can be achieved by increased accumulation and retention of the sensitizer in the tumor (B.A. GoWf 1994). Newly designed mixed polymeric micelles based on Pluronics P123 and F127 could improve delivery of Photofrin®. Specific distribution and release in MCF-7/WT cells are higher than control (Lamch et al. 2014).

Enhanced cytotoxicity of Photofrin using NP systems in tumor

Pluronic micelles loaded with Photofirin II enhanced cytotoxicity in tumor cell. For the doxorubicin-sensitive MCF-7/WT line we observed 20—40% improved cell viability in comparison to the free form of Photofrin II®. Furthermore, cell survival significantly decreased after irradiation of both, MCF-7/WT and SKOV-3 lines, treated with the loaded nanocarriers in contrast to those incubated with the native Ph II® molecules. Therefore, enhanced photoinducted effect of the encapsulated PS was successfully detected (Lamch et al. 2014).

Temoporfin to treat cancer for photosensitizer by using nanoparticles

Temoporfin to treat cancer

Temoporfin (structure is shown in Fig. 2c) (metatetra (hydroxyphenyl) chlorin, m-THPC) is a highly lipophilic, second generation PS. (Reshetov et al. 2013) Temoporfin is a hydrophobic porphyrin derivative approved as the PS for PDT (O'Connor et al. 2009) of squamous cell carcinoma of the head and neck. (Brezaniova et al. 2016) It has some weakness to use PS for PDT. Low bioavailability caused its water solubility and limited skin penetration caused its high molecular weight inhibits the development of the

Table 2 Nanoparticles loading Photofrin® to treat cancer

Photosensitizer	Nanoparticle	Result	Target	Reference
Photofrin®	F3 peptide, PEG	Significant improvement in survival rate	Brain	Reddy et al. (2006)
HpD	Liposomes, conjugated to a monoclonal antibody to anti-CEA	Enhance the efficacy	Brain	Gupta et al. (2011)
Photofrin®	Dendrimer	Efficacy in vitro and in vivo, and also significantly reduced the skin phototoxicity	Brain	Nishiyama et al. 2009)
Hematoporphyrin monomethyl ether	Hyaluronic acid-derivatized carbon nanotubes	Inhibition of cell growth	Melanoma	Shi et al. (2013)
Photofrin®	Polymeric micelles based on Pluronics P123 and F127	Enhanced delivery, cytotoxicity and pro-apoptotic activity	Breast, ovarian	(Lamch et al. 2014)

effectiveness of Temoporfin. Nanoparticles for solving the above obstacles are summarized Table 3.

Reducing phototoxicity of Temoporfin using NP systems

Hinger et al. prepared Lipidot loaded Temoporfin to reduce its phototoxicity. Lipidot were chosen an advanced in vitro cancer spheroid model to investigate for the first time PDT effects of these particles (called M-Lipidots) at the cellular level and compare it to effects of free Temoporfin. Encapsulation of Temoporfin into Lipidots resulted in a significantly reduced dark toxic effect without tumor cells (Hinger et al. 2016).

Increasing delivery efficacy using NP systems

Temoporfin is also used for skin cancer. Skin is the outermost organ of the human body with the main task to protect it from external materials (Bolzinger et al. 2012). Due to its role, many chemical products targeted skin disease have limitation into the skin. Therefore, a large amount of compounds is used to penetrate skin layer. However, nanogel-peptide conjugates with unique properties constitute novel drug delivery systems through skin layer (Zabihi et al. 2016). 1-tetradecanol-based thermo-responsive SLN could also result in controlled release (Brezaniova et al. 2016).

Enhanced cytotoxicity of Temoporfin using NP systems in tumor

Study used Temoporfin-loaded 1-tetradecanol-based thermo-responsive SLN could result in higher phototoxicity against the tumor cells (Brezaniova et al. 2016). It showed higher effect to human breast carcinoma MDA-MB-231. When irradiated with same exposure of light, SLN studied by Navarro et al. enhance its phototoxicity (Navarro et al. 2014). Its lipid core was surrounded by a lecithin layer, in association with a PEG coating ensuring a strong colloidal stability of SLN in an aqueous buffer such as PBS. Moreover, water solubility was higher than normal Temoporfin. Lipid-based nanoparticles appear as suitable carriers for poor soluble drugs like Temoporfin.

Levulan® to treat cancer for photosensitizer by using nanoparticles

Levulan® to treat cancer?

Levulan® (5-ALA) (structure is shown in Fig. 2d), which can be converted to PS protoporphyrin IX (PpIX) intracellularly, has attracted increasing attention owning to its low toxicity and rapid metabolization from biological systems (Abd-Elgaliel et al. 2013). Levulan® is documented as the starter in biosynthesis of the heme. The produced intracellular protoporphyrin IX (PpIX) following 5-ALA administration has been widely used in PDT for a range of malignant and nonmalignant lesions. Since malignant tissue has been found to preferentially accumulate PpIX after the administration of 5-ALA, this compound has been utilized in PDT of human cancers (Mohammadi et al. 2013) (Table 4).

Increasing delivery efficacy using NP systems

The skin permeation of Levulan® was evaluated using Franz diffusion cells by Zhang et al. (2011). The Confocal laser scanning microscopic (CLSM) fluorescence of the accumulated protoporphyrin IX observed Levulan® application can give an indication of the spatial distribution. They showed that soybean oil systems promoted Levulan® permeation to deeper layers of the skin from ~100 to ~140 µm, which would be beneficial for treating subepidermal and subcutaneous lesions. Ligand folic acid (FA)-functionalized hollow mesoporous silica nanoparticles (HMSNPs) also could use to deliver PS to targeted cell. Folic acid is a widely used cancer-targeting ligand, which has high affinity to folic acid

Table 3 Nanoparticles loading Temoporfin to treat cancer

Photosensitizer	Nanoparticle	Result	Target	Reference
Temoporfin	Thermoresponsive solid lipid nanoparticles	Higher phototoxicity against the tumor cells and controlled release	breast adenocarcinoma	Brezaniova et al. (2016)
Temoporfin	Conjugated nanogel-peptide (Ac-QFFLFFQGG-COOH)	Enhance the penetration to the viable skin layers	Skin	Zabihi et al. (2016)
Temoporfin	Lipidot, novel lipid nanostructured carrier	Nontoxic and enhance effect	Tongue squamous cell carcinoma	Hinger et al. (2016), Delmas et al. (2011)
Temoporfin	Loaded hybrid liposomes	Inhibition tumor growth, while combined treatment completely eradicated the tumor	Ovarian cancer	Di Corato (2014), Navarro et al. (2014)

Table 4 Nanoparticles loading Levulan® to treat cancer

Photosensitizer	Nanoparticle	Result	Target	Reference
Levulan®	Hydrazone-containing ALA to gold nanoparticles	Enhanced by RGD moieties and exhibited better photodynamic cytotoxicity	Human Lung Adenocarcinoma	Wu et al. (2017)
Levulan®	Targeting ligand folic acid (FA)-functionalized hollow mesoporous silica nanoparticles (HMSNPs)	5-ALA exhibited high photocytotoxicity to the cancer cells in vitro	Melanoma	Ma et al. (2015)
Levulan®	Fullerene Nanoparticles	Exhibited no detectable toxicity	Melanoma	Li et al. (2014)
Levulan®	Gold nanoparticle	Higher cell death rate	Melanoma	Mohammadi et al. (2013)
Levulan®	Oil in water emulsion	Highest skin permeation	Franz diffusion cells	Zhang et al. (2011)

receptor (Ma et al. 2015). NPs loaded PS enabled selective endocytosis of Levulan® loaded HMSNPs into B16F10.

Enhanced cytotoxicity of Levulan® using NP systems in cancer cells (or tumor)

Various NS system were used to enhance cytotoxicity of Levulan® such as gold nanoparticles (Mohammadi et al. 2013; Wu et al. 2017), fullerene nanoparticles (Li et al. 2014). Mohammadi, et al. studied that protoporphyrin IX induction into the cells showed a significant increase after incubation with the conjugate in comparison to Levulan® alone. Also, the conjugate resulted in a two times higher cell death rate compared to free group. Gold nanoparticles loaded Levulan® could combine some additional materials like zwitter-ionic stealth peptide and hydrazone (Mohammadi et al. 2013; Wu et al. 2017). Recently, zwitter-ionic materials have been demonstrated to be a promising candidate to design non-fouling surfaces which can effectively reduce non-specific protein adsorption (Jin et al. 2014). The cellular internalization could be greatly enhanced by RGD moieties. MTT results demonstrated that Levulan® prodrug nanoparticles exhibited better photodynamic cytotoxicity than free Levulan® after light irradiation, suggesting enhanced photodynamic therapeutic efficacy. The dark cytotoxicity study of fullerene-Levulan® on B16-F10 cells was carried out at different concentrations of fullerene-Levulan® to determine the systemic toxicity of the nanoparticles. This study indicated fullerene-Levulan®/630 nm laser enhanced cell-killing effect, thus, a synergistic therapeutic effect of PDT induced by fullerene-Levulan® was observed in B16-F10 cells (Li et al. 2014).

Conclusion

In this review, we discussed different PS that could be loaded various nanoparticles. PDT has been around for the several years and has been an experimental clinical trial for the last two decades. It has the potential of being a primary therapy, depending on the specific indication. In the future, it is expected that PDT will continue to be used as a stand-alone modality or in combination with chemotherapy or surgery. Nanoparticle system is one of key step to adjust PDT to overcome its obstacles. PS loaded NPs is widely accepted to combat against tumors. Nanoparticle systems are used to be beyond limitation and deliver to specific cells of PS and improve phototoxicity in a certain period. More research and development about NPs were demanded though above success.

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Compliance with ethical standards

Conflict of interest All authors (G. Jeon, Y. T. KO) declare that they have no conflict of interest.

Statement of human and animal rights This article does not contain any studies with human and animal subjects performed by any of the authors.

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