



Review

Cyclodextrin-Based Nanoplatfoms for Tumor Phototherapy: An Update

Xingjie Wu ^{1,2,*} , Ying Chen ^{1,2}, Qianqian Guo ^{1,2}, Ling Tao ^{1,2}, Yang Ding ³, Xiangguang Ding ^{4,*} and Xiangchun Shen ^{1,2,*} 

- ¹ The State Key Laboratory of Functions and Applications of Medicinal Plants, School of Pharmaceutical Sciences, Guizhou Medical University, University Town, Guiyan New District, Guiyang 550025, China; ychen1214@163.com (Y.C.); guoqqsci@126.com (Q.G.); tl15285581860@163.com (L.T.)
 - ² High Efficacy Application of Natural Medicinal Resources Engineering Center of Guizhou Province, School of Pharmaceutical Sciences, Guizhou Medical University, University Town, Guiyan New District, Guiyang 550025, China
 - ³ State Key Laboratory of Natural Medicines, Department of Pharmaceutics, China Pharmaceutical University, Nanjing 210009, China; dingypharm@cpu.edu.cn
 - ⁴ Key Laboratory for Organic Electronics and Information Displays & Jiangsu Key Laboratory for Biosensors, Nanjing University of Posts and Telecommunications, Nanjing 210023, China
- * Correspondence: wxj_gmu@126.com (X.W.); iaxmxgding@njupt.edu.cn (X.D.); shenxiangchun@126.com (X.S.)

Abstract: Tumor phototherapies are light-mediated tumor treatment modalities, which usually refer to tumor photothermal therapy (PTT) and photodynamic therapy (PDT). Due to the outstanding spatial-temporal control over treatment through light irradiation, tumor phototherapies display extremely low side effects during treatment and are believed to be a tumor treatment method with a clinical translation potential. However, current tumor phototherapy nanoplatfoms face obstacles, including light irradiation-induced skin burning, tumor hypoxia microenvironments, limited light penetration depth, et al. Therefore, one important research direction is developing a tumor phototherapy nanoplatfom with multifunctionality and enhanced pharmacological effects to overcome the complexity of tumor treatment. On the other hand, cyclodextrins (CDs) are starch-originated circular oligosaccharides with negligible toxicity and have been used to form supermolecular nanostructures through a host–guest interaction between the inner cavity of CDs and functional biomolecules. In the past few years, numerous studies have focused on CD-based multifunctional tumor phototherapy nanoplatfoms with an enhanced photoeffect, responsive morphological transformation, and elevated drug bioavailability. This review focuses on the preparation methods of CD-based tumor phototherapy nanoplatfoms and their unique physiochemical properties for improving anti-tumor pharmacological efficacy.

Keywords: cyclodextrin; supermolecular assembly; photothermal therapy; photodynamic therapy



Citation: Wu, X.; Chen, Y.; Guo, Q.; Tao, L.; Ding, Y.; Ding, X.; Shen, X. Cyclodextrin-Based Nanoplatfoms for Tumor Phototherapy: An Update. *Pharmaceutics* **2022**, *14*, 1375. <https://doi.org/10.3390/pharmaceutics14071375>

Academic Editors: Denisa Laura Circioban, Iulia Pinzaru and Cristina Trandafirescu

Received: 2 June 2022

Accepted: 27 June 2022

Published: 29 June 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Cancer phototherapy is a highly specific tumor treatment modality developed in the past decade. The two most intensively investigated cancer phototherapies are PTT and PDT, which are activated by light irradiation to generate heat or reactive oxygen species (ROS), respectively. For PTT, the generated heat can promote localized temperature elevation to cause cancer cell membrane disintegration and protein denaturation, which would further induce cell apoptosis and necrosis [1–4]. Such temperature elevation-induced cell inhibition can be dramatically intensified due to the insufficient circulating system inside tumor tissues. For PDT, the light irradiation-generated ROS can destroy subcellular structures, such as cell membrane and organelle membrane, by the rapid oxidation of biomolecules, in a localized manner [5–7], as ROS are extremely active with a short diffusion radio. More importantly, cancer phototherapy showed a synergistic effect with other

cancer therapies by promoting a cargo release upon laser irradiation. For example, PTT-induced temperature elevation can accelerate a chemotherapy drug's release by accelerating molecule diffusion within a nanoparticle [8,9]. Similarly, PDT-generated ROS can be applied as a drug release trigger when ROS-responsive materials are used to construct drug-loaded nanocarriers [10–14]. Owing to those unique features, both PTT and PDT were used to develop advanced anti-cancer nanoplateforms with low normal tissue toxicity and enhanced pharmacological efficacy.

CDs are a kind of non-toxic and biocompatible cyclic-oligosaccharides consisting of α -1,4-glucosidic bonds linked to D-glucose [15]. Depending on the number of D-glucose unites, CDs have six, seven, and eight D-glucose units, respectively nominated as α -, β -, and γ -CD. CDs possess a rigid 3-D structure with a hydrophobic inner cavity, allowing the supermolecular inclusion of various biomolecules with appropriate size and hydrophobicity. In addition, the hydrophilic outside surface of CDs can endow the inclusion complex with water solubility. Therefore, CDs have been widely applied as a drug solubilizer for optimizing drug bioavailability and a building block for developing a hierarchy self-assembly nanostructure [16–19]. Nowadays, CDs and their derivative-based cancer phototherapy nanoplateforms are drawing greater attention in both academic and industrial societies. In this review, we first introduce the preparation of CD-based PTT and PDT nanoplateforms. Then, we discuss the roles CD played in those nanoplateforms and the mechanism underlying their unique physicochemical performance (Figure 1). Finally, the *in vivo* anti-tumor performance of CD-based nanoplateforms is evaluated to elucidate their advantages and challenges in future clinical translations.

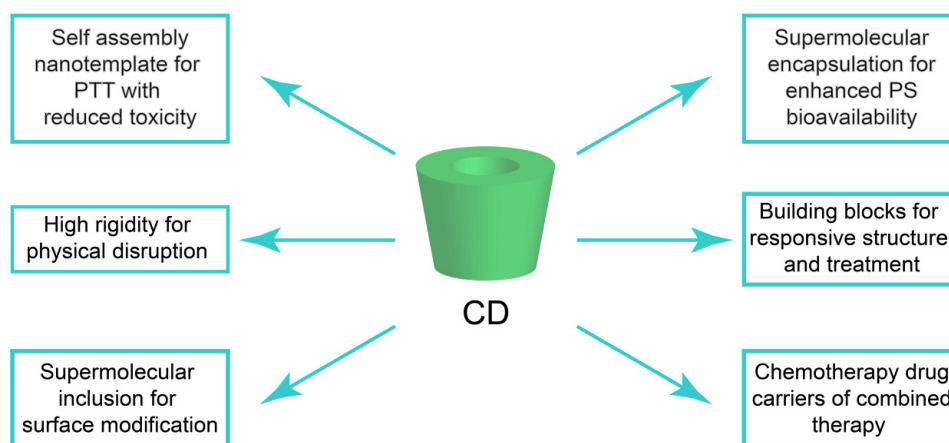


Figure 1. CD functionalities in tumor phototherapy nanoplateforms.

2. CD-Based Nanoplateforms for PTT and Its Combined Therapies

Photothermal agents (PTAs) refer to materials capable of converting light to heat and are the key functional component of PTT nanoplateforms [3,20]. As the light at near infra-red I (NIR-I, 750–850 nm) and NIR-II (900–1200 nm) regions are considered safe windows for clinical treatment by the US Food and Drug Administration, various materials, including gold nanomaterials, 2-D materials, carbon nanomaterials, and conducting polymers were heavily investigated as NIR-I and/or NIR-II PTAs for anti-tumor PTT [21–24]. Note that the NIR-II region is believed to be less of an irritant and more transparent than the NIR-I region; as a result, PTAs with high NIR-II photothermal conversion efficiency (PCE) are drawing more and more attention. However, the clinical translations of current PTT technologies were severely impeded by the following factors: 1. The non-biocompatible nanotemplate and toxic surfactant used during PTA synthesis; 2. A light overdose due to an insufficient PCE; 3. A lack of multifunctionality. In this section, we introduce the synthesis and preparation of CD/PTA hybridization and discuss how CD/PTA hybridization nanostructures overcame the aforementioned problems (Table 1).

Table 1. A summary of the CD-based PTT nanoplatform.

Guest Molecule	PTA Type	Combined Therapy	Cell or Tumor Type	References
PEG	Gold nanoshells	Chemotherapy	HeLa cell	[25]
None	Gold nanotriangles, gold nanoflowers	None	A673 cell	[26]
Pyridine-2-imine	AuNP aggregation	None	MCF-7 tumor.	[27]
Azobenzene	GO	Mitochondrial physical disruption	S180 tumor	[28]
Cyclohexylalanine	AuNR	Mitochondrial physical disruption	A549 tumor	[29]
Camptothecin	GO	Chemotherapy	BEL-7402 tumor	[30]
Paclitaxel	Polydopamine	Chemotherapy	MDA-MB-231 cell	[31]
10-hydroxy camptothecin	Palladium nanosheet	Chemotherapy	H-22 tumor	[32]
AD	Mesoporous platinum nanoparticle	Chemotherapy	MCF-7 tumor	[33]
None	Quaterrylene bisimide derivative	None	HepG2 tumor	[34]
PEG	Perylene diimide	Chemotherapy	HeLa tumor, A549 tumor	[35]
AD	AuNR	Chemotherapy	S180 tumor	[36]
PEG	AuNR	Chemotherapy	4T1 tumor	[37]
PEG	AuNR	Chemotherapy	MDA-MB-231 tumor	[38]
AD	AuNR	Immunotherapy, genetherapy	B16-F10 tumor	[39]
AD	Copper sulfide nanoparticles	Chemotherapy	HeLa cell	[40]
AD	AuNR	Chemotherapy, genetherapy	C-6 tumor	[41]
AD	Fe ₃ O ₄ nanoparticle	Genetherapy, magnetolytic therapy	4T1 tumor	[42]

2.1. CD-Based Supermolecular Nanostructure as a Functional Nanotemplate for PTA

Non-spherical gold nanomaterials, such as gold nanoshells, gold nanorods (AuNR), and gold nanotriangles, were intensively applied as PTAs due to their localized surface plasmon resonance (LSPR) peak at the NIR light region [3,4,21]. As gold nanomaterials' PCE was correlated with their morphology, CD-based self-assembly with a predesigned nanostructure can be applied as a biocompatible nanotemplate to enhance the PCE. For example, Wu et al. synthesized biodegradable poly(ethylene glycol)-b-polycysteine (PEG-b-PC) and further prepared polyrotaxane-b-PC micelle through the supermolecular interaction between the PEG segment and α -CD [25]. As polyrotaxane is highly hydrophobic, a PC segment with abundant thiol moieties was located at the micelle surface. Using this biocompatible micelle as a nanotemplate, thickened gold nanoshells with an elevated PCE can be formed through the strong thiol-Au complexation. In another report, a nitroaniline type NO generator-tethered β -CD was copolymerized with β -CD and epichlorohydrin. Under 420 nm light irradiation, the tethered NO generator can produce an NO capable of reducing Au³⁺ to Au⁰ to form gold nanotriangles or nanoflowers in situ [26]. This method provided a biofriendly synthesis route without gold seed, toxic reductant, and surfactant. The aggregation of small gold nanoparticles can red-shift its LSPR peak to induce photothermal conversion in the NIR region. Inspired by this, Yu et al. developed a pH-responsive PTT nanoplatform using α -CD as the steric hindrance. This nanoplatform consisted of two gold nanoparticles (AuNP) separately decorated with a pair of complementary DNA sequences at their surface. The 3'-end of the DNA sequence was covalently modified with α -CD

through a pH-responsive linker, pyridine-2-imine. The conjugated α -CD can act as a steric hindrance to prevent AuNP's aggregation in a neutral physiological environment, while a large AuNP aggregation with a high PCE at the NIR region can be in situ formed in acid tumor microenvironments (TMEs) due to the release of α -CD from AuNP's surface [27]. The self-fabricated gold aggregation can also enhance an in vivo photoacoustic signal by a 3.5-fold and keep a high signal level within 24 h.

A CD-based self-assembly nanostructure was reported to have shape transformation abilities under the help of stimuli-responsive moieties. Due to the structural rigidity of CD, the shape transformation of CD-based self-assembly can physically disrupt the subcellular structure. Zhang et al. modified the tumor-targeting protein transferrin with the mitochondrion-targeting peptide and PEG, whose terminals were further linked with azobenzene. After being bound with a cancer cell mitochondrion through a mitochondrion-targeting peptide, the light-responsive azobenzene at the transferrin's surface can be used as a guest to form a supermolecular inclusion with β -CD-modified graphene oxide (GO) under 520 nm light irradiation (Figure 2). The in situ supermolecular assembly further caused mitochondrion aggregation and mitochondrial dysfunction, which significantly promoted the pharmacological efficacy of GO-based PTT against the S180 tumor-bearing mice [28]. In a similar work, a mitochondrion-targeting peptide-tethered magnetic nanoparticle and lipoic acid-modified AuNR were hybridized with each other through an amidation reaction. Under the guidance of a geomagnetic field, the magnetic nanoparticle-AuNR hybrid nanostructure and β -CD-modified hyaluronic acid can self-assemble to form photothermal nanofibril along the direction of the magnetic field, which can physically damage the cancer cell's mitochondrion and clear the A549 cell for suppressed tumor metastasis after a PTT treatment [29].

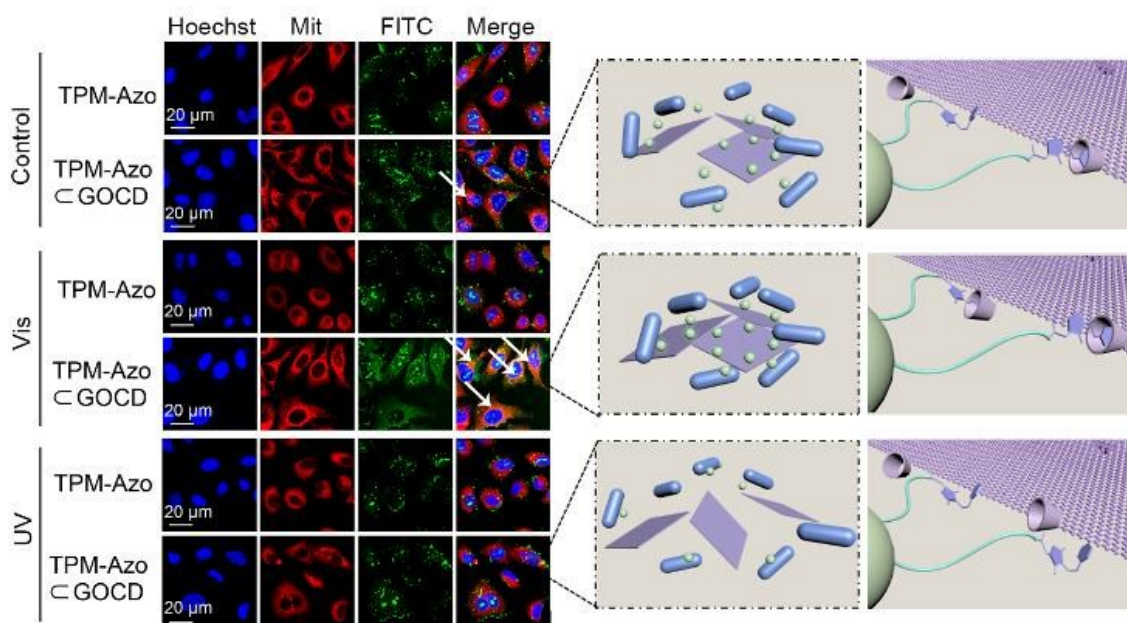


Figure 2. Light-controlled intracellular mitochondrial disruption by azobenzene and mitochondrion-targeting peptide-modified transferrin and CD-modified GO. Mitochondrial disruption (white arrows) after visible-light irradiation (Vis, 520 nm) but not after UV irradiation (UV, 365 nm). The effect of azobenzene and mitochondrion-targeting peptide-modified transferrin and CD-modified GO on intracellular mitochondrial dynamics was investigated by confocal microscopy. (Adapted with permission from Ref. [28]. Copyright 2019, Royal Soc. Chemistry).

2.2. CDs as Drug Carriers for Combined PTT and Chemotherapy

PTA, such as AuNR, magnetic nanoparticles, CuS nanocrystals, et al. are solid nanomaterials lacking the ability to encapsulate anti-cancer drugs. Thus, the CDs were coated at their surface to load the anti-cancer drugs through a host–guest interaction [30,31,43–47]. Furthermore, CD-encapsulated drugs can display a photothermal-triggered release due to the localized temperature elevation during PTT treatment. In one recent report, a magnetic nanoparticle was in situ-synthesized at GO's surface and was further covalently modified with β -CD and cholic acid-modified hyaluronic acid. Then, the anti-cancer drug, camptothecin, was loaded at a high loading capacity of 442 mg/g by adsorbing at GO's surface through π - π interaction and encapsulating within the β -CD cavity. As graphene and its derivatives are excellent NIR light PTAs, this hybrid GO nanoplatform displayed a photothermal-triggered camptothecin release profile and enhanced an anti-tumor efficacy under NIR light irradiation [30]. To further endow nanoparticles with a multi-responsive release profile, another research group grafted β -CD onto the HA chain through a pH- responsive linker, boronic acid. After covalently decorating β -CD at the fluorescent polydopamine nanoparticles' surface, the anti-cancer drug paclitaxel was loaded into the β -CD cavity through a host–guest interaction. This multifunctional polydopamine nanoparticle can achieve a pH and NIR light dual-stimuli-triggered drug release and fluorescence imaging-guided chemo-photothermal therapy [31].

Simultaneously loading two anti-cancer drugs with opposite hydrophilicity in a single nanocarrier has been an extremely difficult task for the traditional drug delivery system. To overcome this, drugs were loaded within different sectors of a CD-based Janus nanostructure for programmed release [32,48]. Zhang et al. selectively decorated one side of a palladium nanosheet with the zeolitic imidazolate framework-8 for loading the hydrophobic anti-cancer drug, 10-hydroxycamptothecin (Figure 3), while the other side was decorated with β -CD for loading the hydrophilic drug, doxorubicin (DOX). The obtained Janus nanoparticle displayed a pH and photothermally-triggered dual-drug release profile and enhanced in vivo anti-tumor therapeutic efficacy [32]. In addition, the palladium nanosheet displayed strong absorbance at the NIR-II region and endowed this hybrid nanoplatform with a deep tumor treatment potential.

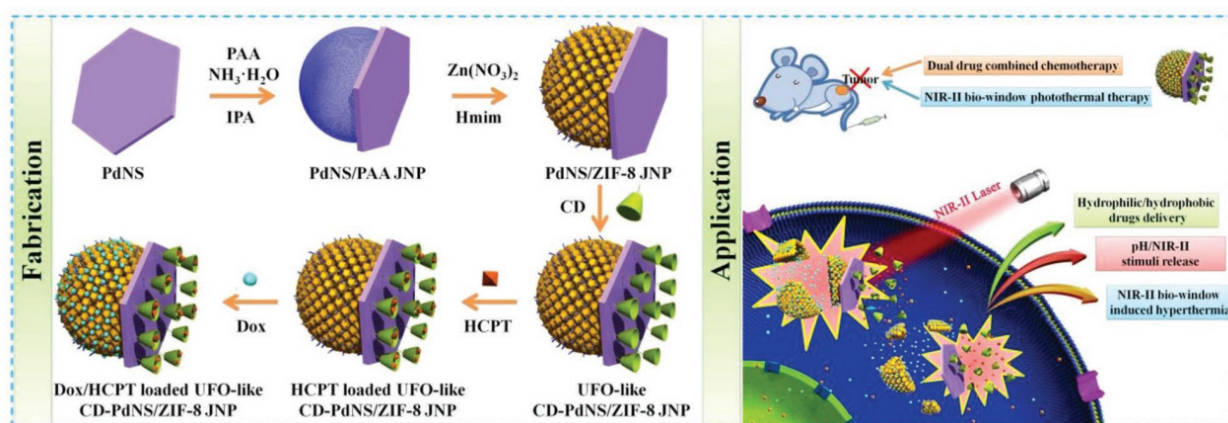


Figure 3. Schematic diagram of preparing the Janus nanoparticle for an in vitro and in vivo pH and NIR-II (1064 nm) dual-triggered synergistic dual-drug chemotherapy and photothermal therapy in the NIR-II biowindow. (Adapted with permission from Ref. [32]. Copyright 2018, Wiley).

Despite the photothermal effect-triggered drug release, combined PTT and chemotherapy still face a drug leaky release due to a large dilution volume in the circulation system. Therefore, premature drug release remains one major obstacle to highly specific and efficient tumor treatments. To fight against this, CDs or CD-modified PTAs were used to cap the pores of the drug-loaded mesoporous nanoparticle as the gatekeepers [33,49,50]. Compared to gold nanomaterials, mesoporous platinum nanoparticles are reported to have

a stable NIR light PCE and enhanced biocompatibility. Inspired by this, Zhao et al. capped the pores of DOX-loaded mesoporous platinum nanoparticles with β -CD. As platinum can be oxidized to Pt^{2+} in the acid TME, these β -CD-capped mesoporous platinum nanoparticles exhibited both a photothermal effect and acid TME-triggered DOX release with the minimum leaky release [33].

Organic PTAs are a type of small molecule with a high NIR light PCE and biocompatibility, which can be either encapsulated within the CD cavity or covalently linked to CD for elevated bioavailability and biosafety [34,35,51–53]. After covalently linked to β -CD, organic PTA quaterylene bisimide exhibited enhanced photostability, NIR light absorptivity, and photoacoustic imaging ability. More importantly, the β -CD modification of quaterylene bisimide was reported to promote its renal clearance pathway, which is believed to have reduced long-term side effects and minimized toxicity [34]. Due to the mechanically interlocked molecule structure of polyrotaxane, polyrotaxanes at the polymer micelles' surface also showed a drug gatekeeper effect. To prepare this type of micelle, the ends of polyrotaxanes were, respectively, modified with organic PTA perylene diimide and a targeting ligand cyclic-RGD peptide as the stoppers. Due to the π - π interaction between perylene diimide, a core-shell structure with polyrotaxanes at the surface was formed. After being crosslinked by N-hydroxysulfosuccinimide ester-activated disulfide moieties, the micelle displayed a 24 h cumulative release of 61.6% for paclitaxel under NIR light and a 10 mM glutathione treatment, which was increased by 10-fold compared to micelle without any treatment (6.27% within 24 h) [35].

Compared with oral or intravenous administration, drug administration through an injectable hydrogel implant can have better control over drug biodistribution and prolonged drug retention in tumor tissue. Using CDs as crosslinkers or building blocks, injectable hydrogels with a sustained drug release profile can be further obtained for tumor treatment without repeated drug administration [36–38]. Recently, adamantane (AD)-modified DOX was supermolecularly conjugated to the methacrylated poly- β -CD macromer, which was further used to form composite hydrogel with encapsulated AuNR through the radical copolymerization with N-isopropylacrylamide. The composite hydrogel displayed reversible drug release behavior due to the photothermally-induced hydrogel collapse and hydrogel swelling in a dark state [36]. Further in vivo experiments showed that hydrogel can achieve a 21-day DOX retention with a single hydrogel injection, which significantly reduced the discomfort of patients during treatment.

2.3. CDs as Connecting Moieties for Sophisticated Surface Modification

In order to prepare a PDT nanoplatform with multifunctionality, sophisticated surface modifications were performed to construct nanolayers with the required structure. Utilizing the specificity of a supermolecular interaction, CDs are ideal, connecting moiety for anchoring biomolecules at the PTT's nanoplatform surface. For example, the heat-inducible promoter-loaded CRISPR/Cas9 plasmid and polyethyleneimine-modified β -CD were conjugated to the NIR-II type's AuNR surface. Then, guanidyl, capable of promoting deep tissue penetration and Cas9 plasmid delivery, was decorated to AuNR's surface through an inclusion effect between AD and β -CD. With the help of guanidyl ligands, photothermally-activated immune checkpoint blockade therapy was achieved for reduced tumor metastasis and prolonged immune memory effects [39]. In another report, the surface of a CuS nanocrystal, a kind of metallic compound nanocomposite with photothermal conversion properties at the NIR region, was sequentially modified with a poly(maleic anhydride)-based amphiphilic polymer and β -CD. As β -CD was further conjugated with an AD-modified RGD peptide, the obtained CuS nanocrystal displayed a tumor integrin-targeted PTT under the guidance of photoacoustic imaging [40].

Besides targeting ligands, positively charged biopolymers capable of loading a DNA sequence for combined PTT and gene therapy can also be introduced by CDs' supermolecular interaction. After loading quantum dot and DOX at its mesoporous silica shell, polycation poly(glycidyl methacrylate)-modified β -CD was coated at the surface of the

core-shell AuNR. The β -CD not only acted as a gatekeeper for the triggered DOX release but also introduced polycation for antioncogene p53 loading and AuNR *in vivo* stabilization. The obtained hetero-AuNR can perform synergistic photothermal-chemo-gene therapy with enhanced specificity under the guidance of tomography, fluorescence, and PA imaging [41]. Zhao et al. prepared a 1-D nanofibril prepared from dextran and Fe_3O_4 and decorated poly(glycidyl methacrylate)- β -CD at the nanofibril surface through a β -CD and AD interaction. Compared to its spherical counterpart, the 1-D nanofibril exhibited a significantly accelerated cell uptake rate under the magnetic field treatment, which further led to substantially enhanced gene transfection efficiency. Moreover, the 1-D nanofibril would rotate under an alternating magnetic field, which can cause cancer cell destruction due to the rotary shear force. Therefore, combined gene/photothermal/magnetolytic therapy with synergistic treatment against a 4T1 tumor was observed for this 1-D nanofibril [42].

3. CD-Based Nanoplatform for PDT and Its Combined Therapies

PDT relies on the cytotoxicity of ROS generated by photosensitizers (PS). Ideal PS should accumulate in tumor tissues and possess a high photostability. However, most PS display low bioavailability and a hampered ROS-producing efficacy as a result of their hydrophobic nature and potential aggregation in the physiological condition. Furthermore, PDT is limited by hypoxic TME and a short tissue penetration depth of visible light [54,55]. In this section, we first introduce the conjugation of PS with CDs for enhanced bioavailability and photostability. Then, we discuss CDs' hierarchy self-assembly nanostructure-based PDT nanoplatform for enhanced tumor treatment efficacy (Table 2).

Table 2. A summary of the CD-based PDT nanoplatform.

Guest Molecule	PS Type	Combined Therapy	Cell or Tumor Type	References
Chlorophyll a	Chlorophyll a	None	HT-29 cell	[56]
AD	Porphyrin	None	4T1 tumor	[57]
AD	Porphyrin	None	4T1 tumor	[58]
Ce6	Ce6	None	MDA-MB-231 cell	[59]
Ce6	Ce6	PTT	MDA-MB-231 tumor	[60]
PEG	Ce6	None	LM3 tumor	[61]
AD	Indocyanine green	PTT	MCF-7 tumor	[62]
None	Purpurin 18	Chemotherapy	4T1 tumor	[63]
AD	Porphyrin	Chemotherapy	4T1 tumor	[64]
AD	Polypyridyl ruthenium	None	A549 cell	[65]
Ce6	Ce6	Immunotherapy	4T1 tumor	[66]
ferrocene	Ce6	None	4T1 tumor	[67]
PEG	Ce6	None	MCF-7 tumor	[68]
Camptothecin	Ce6	Chemotherapy	HepG2 tumor	[69]

3.1. CD and Photosensitizer Conjugation

Porphyrin and its derivatives are the most intensively investigated PS in clinical trials [55]. Due to its cyclic structure formed through the π - π conjugation of four pyrrole rings, porphyrin is quite hydrophobic and displays an aggregation-induced quenching after being intravenously administered. Utilizing the hydrophilic surface of CDs, porphyrin solubility can be promoted without hampering its ROS-generating ability [56,70–73]. Ikeda et al. reported that porphyrin derivatives and trimethyl- β -CD could readily form a water-soluble supermolecular complex. Importantly, aniline- and phenol- substitutions of

β -CD were found to have promoted PDT's performance against the HeLa cell due to their electrostatically accelerated cell internalization rate [70]. Another group found that the inclusion of a porphyrin derivative, (5,10,15,20-tetrakis(3-hydroxyphenyl) chlorin (mTHPC), within trimethyl- β -CD can strongly restrict the rotation of mTHPC's phenol rings, which further led to an elevated fluorescence quantum yield. As a result, the fluorescence of the mTHPC and trimethyl- β -CD complex can be used to monitor the in vitro delivery and release of mTHPC [71]. In another work, β -CD modified with the hydrophilic group 2-hydroxypropyl was observed to promote the water solubility and fluorescence quantum yield of chlorophyll a, which is a highly hydrophobic porphyrin derivative extracted from plants. In consequence, the chlorophyll-encapsulated 2-hydroxypropyl- β -CD displayed a higher cellular uptake rate and enhanced PDT's performance against HT-29 colorectal cancer cells [56]. Besides being directly encapsulated within CDs, PS were also modified with moieties having a strong interaction with the CDs for indirect supermolecular inclusion [57,58,74]. Recently, one group reported that the bis-AD-modified porphyrin and β -CD dimer could be used to prepare an ABA tri-block type amphiphilic supramolecular polymer with an AD- modified PEG at both terminals. The obtained supermolecular polymer can self-assemble in water to form a spherical porphyrin-loaded nanostructure for enhanced porphyrin biocompatibility and solubility (Figure 4). In addition, the alternating structure can reduce the aggregation-induced quenching of porphyrin by the steric hindrance of β -CD, which significantly promotes the in vivo PDT's performance of porphyrin [57].

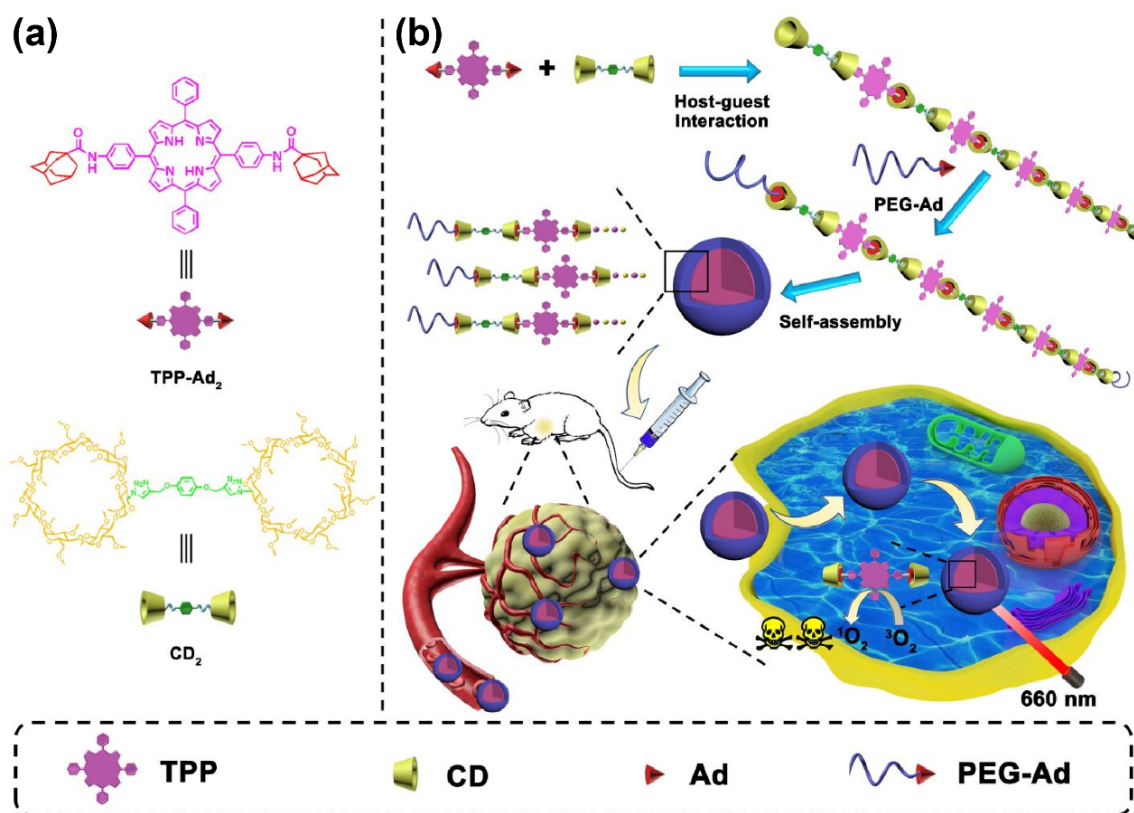


Figure 4. (a) The chemical structures of the adamantyl-modified tetraphenyl porphyrin and the cyclodextrin dimer. (b) Illustration of the formation of nanoparticles from linear supramolecular polymers with an alternating porphyrin/cyclodextrin structure by the host–guest interaction and self-assembly, and the enhanced PDT process. (Adapted with permission from Ref. [57]. Copyright 2020, Amer. Chemical Soc.).

3.2. CD-Based Nanoplatform for Responsive PDT

$^1\text{O}_2$ produced by the direct energy transfer from the PS triplet state to oxygen is one of the most active ROS and can oxidate a variety of biomolecules, such as lipids, polysaccharides, and amino acids, to induce cytotoxicity. Therefore, $^1\text{O}_2$ can irreversibly damage cell membranes and subcellular structures, such as the mitochondria and Golgi apparatus and plays a major role in tumor inhibition under PDT treatment [54,55]. However, $^1\text{O}_2$ displays an extremely low maximum active radius (<20 nm), indicating that the accumulation of PS in tumor tissue is a prerequisite for a highly specific and efficient PDT. To increase PS' delivery specificity, Yoon et al. conjugated γ -CD with PEG and a pH-responsive moiety, 3-(diethylamino)propylamine (DEAP). Due to the hydrophobicity of the DEAP in the neutral solution, the modified γ -cyclodextrin self-assembled in water to form a porous nanoparticle with the ability to encapsulate PS chlorin e6 (Ce6) through supermolecular interactions. After reaching the tumor tissue, the DEAP moiety was dramatically protonated in the acid TME, leading to the disassembly of porous nanostructures and the specific release of Ce6 for an enhanced PDT against the MDA-MB-231 tumor [59]. In another work, AuNP's surface was coated with a primary amine-modified γ -CD, which was further electrostatically complexed with a 2,3-dimethylmaleic acid-modified γ -CD. In the acid TME, the complex at AuNP's surface was destabilized due to the decoupling of the 2,3-dimethylmaleic acid. As a result, the cell uptake rate of positively charged AuNP was significantly accelerated for enhanced PTT and highly specific PDT [74].

The host-guest interaction of CDs makes them ideal candidates for developing anti-cancer nanoplatforms with programmed responsiveness [61,62,75]. In a recent report, the pH-responsive molecule benzimidazole, capable of supermolecularly conjugating with β -CD, was introduced to the side chain of PEG-b-polylysine. Then, an obtained polypeptide was sequentially mixed with the (2-hydroxypropyl)- β -CD and Ce6-modified α -CD to obtain polyrotaxane as the hydrophobic segment and (2-hydroxypropyl)- β -CD-capped polylysine as the hydrophilic segment for forming negatively charged supermolecular nano-assemblies in water. The negative surface charge of the obtained nanoassembly can prevent the undesired retention of normal tissues in the circulation system, while benzimidazole and β -CD detached from the polylysine backbone to convert the nanoassembly surface to a positive charge and promote its cell internalization rate [61]. As Ce6 was linked to α -CD through disulfide bonds, the loaded Ce6 could be released for an enhanced PDT after being internalized by cancer cells. Indocyanine green, as an FDA-approved PS for tumor PDT therapy, was loaded to the porous silica layer of AuNR@MSN (Figure 5). The pores of MSN were covalently capped by the CDs as a gatekeeper to prevent the leaky release of indocyanine green, which was further conjugated with an AD-modified peptide possessing membrane penetration and mitochondrion targeting abilities [62]. Then, the charge-reversible polymer 2,3-dimethylmaleic anhydride and PEG-modified chitosan were introduced to AuNR@MSN's surface through its electronic interaction with the peptide. Once reaching the tumor tissue, the acid TME could dissociate the modified chitosan from the nanoparticle surface to re-expose the targeting peptide, which could enhance the binding of AuNR@MSN to mitochondrion for a highly efficient PDT treatment.

Due to the high reactivity of ROS, there are a variety of moieties that are sensitive to ROS and can undergo bond cleavage or hydrophilicity transfer under ROS treatment. Nanostructures with ROS-responsive moieties as crosslinkers or hydrophobic blocks display photodynamic-triggered cargo release profiles, which were heavily applied to develop nanoplatforms with a combined PDT and chemotherapy. Jia et al. covalently decorated β -CD with PEG and a 4-(hydroxymethyl) phenylboronic acid pinacol ester, which was used to form DOX and a purpurin 18-loaded nanoassembly. Under 660 nm light irradiation, ROS, produced by purpurin 18, not only caused tumor tissue damage but also induced the hydrophobic to the hydrophilic transfer of phenylboronic acid to trigger DOX's release. This dual drug-loaded micelle exhibited good permeability within solid tumor tissue under confocal microscopy analysis and displayed a synergistic PDT and chemotherapy against the 4T1 tumor on a nude mouse under 660 nm light irradiation for 5 min [63]. Tian et al.

mixed a thioketal-linked AD dimer, triphenylphosphine-modified AD, PEG-modified AD, and tetra β -CD-modified porphyrin in water to form a DOX-loaded self-assemble nanostructure with mitochondria targeting ability. Due to the cleavage of thioketal under the ROS treatment, the in vivo distribution of DOX and porphyrin can be readily adjusted by 660 nm light irradiation to achieve highly specific combinational PDT and chemotherapy [64].

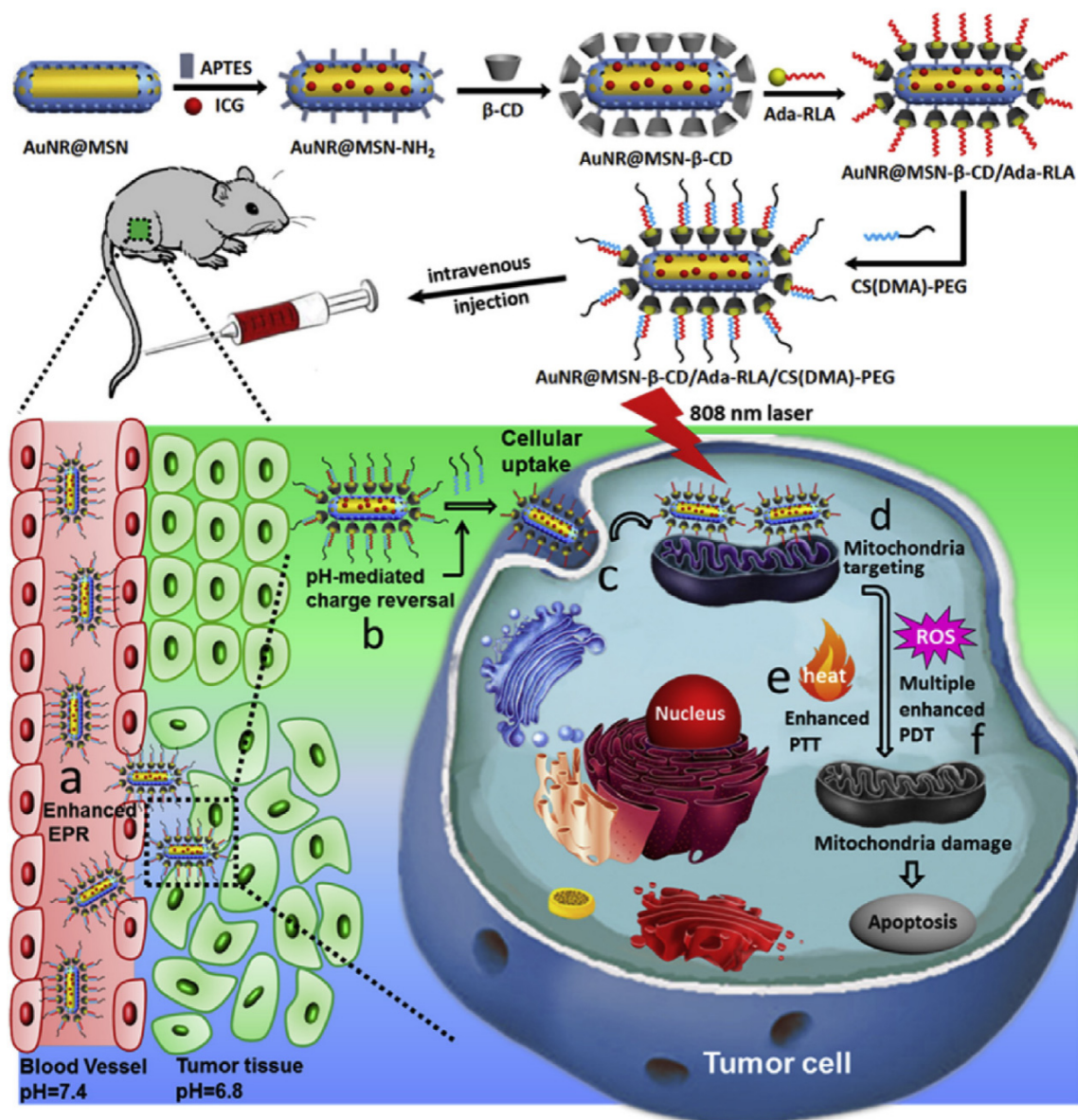


Figure 5. Schematic illustration of the preparation of the AuNR@MSN-based multifunctional nanoplateform and its work process in vivo: (a) tumor accumulation of nanosystem via the EPR effect; (b) removal of PEG-modified chitosan by slight acidity and exposure of the functional [RLARLAR]₂ peptide; (c) peptide-mediated internalization and (d) mitochondrial targeting; (e) NIR light-mediated enhanced photothermal and (f) photodynamic therapy. (Adapted with permission from Ref. [62]. Copyright 2018, Elsevier).

Another research direction for enhancing PDT specificity has been focused on developing PS with stimuli activable ROS and/or ¹O₂ generating ability. Dai et al. synthesized diarylethene-bridged β -CD dimer and AD-modified PS polypyridyl ruthenium, which could form a supermolecular nanoassembly in water with β -CD grafted to HA. Under 245 nm light irradiation, the diarylethene moiety was transformed to a closed ring struc-

ture, which triggered the energy transfer from polypyridyl ruthenium to diarylethene and quenched its $^1\text{O}_2$ generating ability. The closed ring structure can be reopened under a long wavelength (>490 nm) light irradiation to activate $^1\text{O}_2$ generation for the tumor PDT treatment (Figure 6). This reversible PDT nanoplatform, in its activated state, displayed an A549 cancer cell inhibition rate 4.4 times higher than its quenched state and is suitable for minimizing inadvertent PS activation during PDT treatment [65].

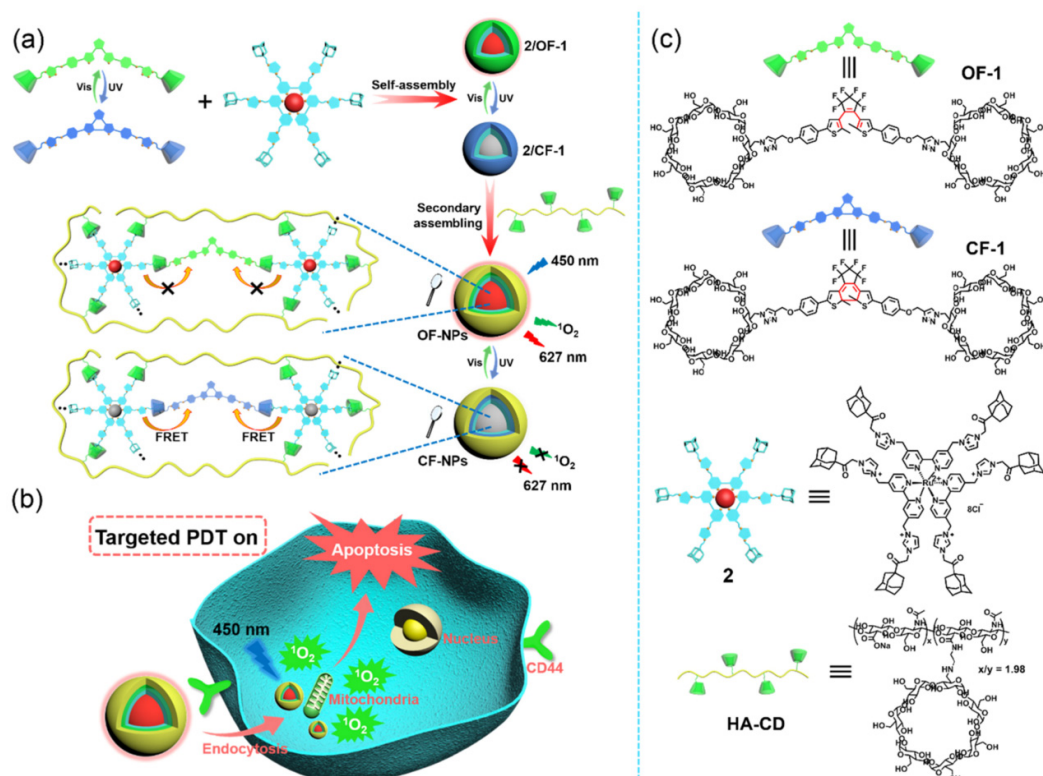


Figure 6. (a) Schematic diagram of the formation of CD secondary assemblies with the controllable $^1\text{O}_2$ generation ability and (b) their application for targeted PDT; (c) the chemical structures of diarylethene-bridged CD in its ring-opened form OF-1 and ring-closed form CF-1; AD polypyridyl ruthenium photosensitizer (2) and β -CD-grafted hyaluronic acid. (Adapted with permission from Ref. [65]. Copyright 2020, Amer. Chemical Soc.).

3.3. CD-Based Nanoplatform for Multifunctional PDT

In this section, we introduce the CD-based PDT multifunctional nanoplatform dedicated to removing PDT obstacles, such as tumor hypoxia and insufficient light penetration depth. As PDT consumes O_2 to produce ROS during treatment, the hypoxia TME dramatically restricted the application of PDT tumor therapy. To alleviate tumor hypoxia during PDT, PEG-modified Cu_{2-x}Se nanoparticles were decorated at the Ce6-loaded β -CD surface. Utilizing the Fenton reaction between Cu^+ and H_2O_2 to produce O_2 , the abundant H_2O_2 in TME acted as an O_2 reservoir to promote the ROS' generation during PDT treatment. Furthermore, the Fenton reaction can shift the sensitive wavelength of Ce6 to the NIR region and generate a large quantity of ROS with the help of Ce6 for potential deep tumor treatment. An *in vivo* experiment revealed that those Cu^+ - and Ce6-generated ROS not only prohibited the primary tumor growth but also suppressed tumor metastasis due to the ROS-induced immunogenic cell death [66]. Ferrocene is another frequently used Fenton reaction agent and can be encapsulated within the β -CD cavity through a host-guest interaction. Qin et al. prepared ferrocene and a PEG-modified FFVLG₃C peptide, which further formed linear supermolecular nanostructures with Ce6-modified β -CD. The amphiphilic linear supermolecular structure was self-assembled to a spherical

micelle with enhanced permeability and retention effect-induced passive tumor targeting. Under 650 nm light irradiation, ferrocene can be oxidized to ferrocene⁺ by Ce6-generated ROS and dissociate from the β -CD cavity. Therefore, the micelle would reshape to the ferrocene-loaded peptide nanofibril with enhanced tumor retention and a Ce6-loaded smaller micelle with deeper tissue penetration, respectively. A further *in vivo* experiment showed that the ferrocene accumulated in tumor tissues could efficiently relieve tumor hypoxia to allow PDT with a positive feedback loop [67]. As the cancer cells overexpressed glutathione, the ROS' consumption by intracellular glutathione seriously hampered PDT's therapeutic efficacy. NO is a bio-signal molecule involving a variety of physiological and pathological processes. Like ROS, NO, as a kind of oxidant, can damage mitochondria and the DNA structure and can react with glutathione to promote PDT's efficacy. More importantly, NO can cause tumor vasculature relaxation, leading to an elevated blood flow rate and O₂ supply. Inspired by this, Deng et al. conjugated α -CD with an NO generator *s*-nitrosothiol and Ce6, respectively (Figure 7). The obtained α -CD-Ce6 and α -CD-NO can form a supermolecular micelle with PEG-*b*-poly(2-methacryloyloxyethyl phosphorylcholine). After being internalized by cancer cells, the *s*-nitrosothiol moiety was activated by intracellular glutathione to generate a large quantity of NO, which in turn depleted the glutathione and explosively amplified PDT's efficacy [68].

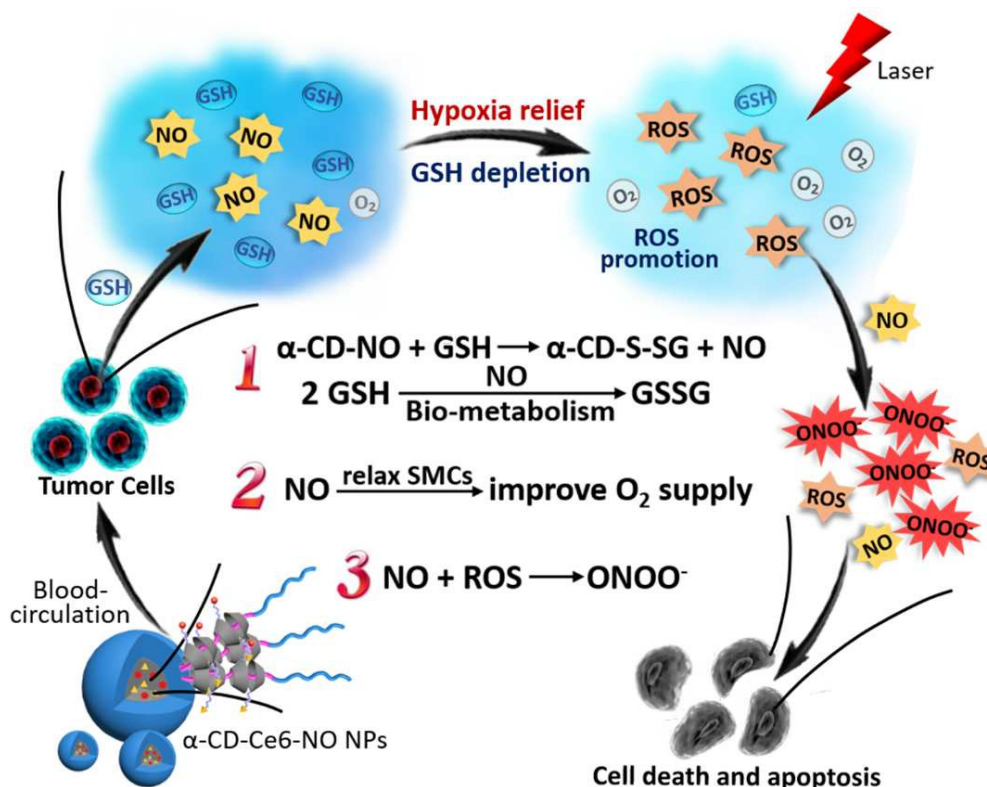


Figure 7. Multiple synergistic effects between NO and PDT generated from the supramolecular nanoparticles α -CD-Ce6-NO nanoparticles to improve therapeutic efficacy. (Adapted with permission from Ref. [68]. Copyright 2018, Elsevier).

Despite a great effort in optimizing its performance in PDT, most PS under clinical trials are only sensitive to visible light. Due to the scattering and absorption of visible light by the human body, visible light-sensitive PS are not suitable for deeper tumor treatments. To overcome this, upconverting a nanoparticle capable of converting NIR light to visible light was co-loaded with PS. Yao et al. synthesized an upconverting nanoparticle with a layer of mesoporous silica at its surface. After loading camptothecin within the mesoporous silica layer, PS 1,8-dihydroxy-3-methylanthraquinone were loaded at the silica layer's surface through a UV-activable bond. Then, lactobionic acid and PEG-modified β -

CD were conjugated with 1,8-dihydroxy-3-methylanthraquinone through a supermolecular interaction for asialoglycoprotein receptor targeting. Under NIR light irradiation, the dual emissive upconverting nanoparticle can convert 980 nm of light to 360 nm of light, activating camptothecin's release, and 480 nm of light can trigger ROS' generation, which could significantly enhance tumor treatment efficacy [69].

4. Conclusions and Future Perspectives

CDs can be readily used to promote the photoeffect of tumor phototherapy by constructing an ideal nanoplatform for PTT with enhanced PCE or PDT with an elevated PS bioavailability and quantum yield. In addition, various bioactive cargoes can be loaded within the cavity of CDs with a photothermally- or photodynamically-triggered release profile. As a result, CDs' hybridization showed great promise in developing tumor phototherapy nanoplatforms in combination with other tumor therapies in a synergistic manner. Particularly, CDs can be used to prepare a tumor phototherapy nanoplatform with responsive morphological change, which can cause the physical disruption of subcellular structures. Furthermore, this type of responsive nanoplatform can be used to achieve a cell membrane and organelle dual-targeting delivery in a sequential manner.

However, most combinational therapies in this area focus on the combination of chemotherapy with PTT or PDT, and more effort is deserved to investigate CD-based tumor phototherapy nanoplatforms in combination with immunotherapy, as immunotherapy is considered the most promising tumor treatment modality. The long-term toxicity of inorganic PTAs is an unpredictable hurdle for the clinical translation of PTT. Therefore, using CD-based nanoassembly as a nanotemplate would be a promising route to develop a biocompatible PTT nanoplatform. For PDT, porphyrin and its derivatives were the most investigated PS with their excitation wavelength in the visible light region. Thus, there is a great need to developing an NIR type PS and encapsulating the NIR type PS with CDs to enhance their bioavailability would be a hot topic in the coming future. Overall, CDs' hybridization can dramatically promote the anti-tumor efficacy of tumor phototherapy and is especially valuable in developing a multifunctional phototherapy nanoplatform to conquer current obstacles in tumor treatment.

Author Contributions: Conceptualization, X.W., X.D. and X.S.; writing-original draft preparation, X.W., Y.C. and Q.G.; writing-review and editing, L.T., Y.D. and X.D.; supervision, X.W. and X.S.; project administration, X.W. and X.S.; funding acquisition, X.W. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the National Natural Science Foundation of China (Grant No. 32001000) and the Guizhou Provincial Department of Education (Grant No. QJHKY [2021]178).

Institutional Review Board Statement: Not Applicable.

Informed Consent Statement: Not Applicable.

Data Availability Statement: Not Applicable.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

AD: adamantane; AuNP: gold nanoparticles; AuNR: gold nanorods; Ce6: chlorin e6; CD: cyclodextrins; DEAP: 3-(diethylamino)propylamine; DOX: doxorubicin; GO: graphene oxide; LSPR: localized surface plasmon resonance; NIR: near infra-red; MSN: mesoporous silica nanoparticle; mTHPC: (5,10,15,20-tetrakis(3-hydroxyphenyl) chlorin; PCE: photothermal conversion efficiency; PEG-b-PC: poly(ethylene glycol)-b-polycysteine; PDT: photodynamic therapy; PTA: photothermal agents; PTT: photothermal therapy; PS: photosensitizers; ROS: reactive oxygen species; TME: tumor microenvironment.

References

1. Kumari, S.; Sharma, N.; Sahi, S.V. Advances in cancer therapeutics: Conventional thermal therapy to nanotechnology-based photothermal therapy. *Pharmaceutics* **2021**, *13*, 1174. [[CrossRef](#)]
2. Liang, P.; Mao, L.; Dong, Y.; Zhao, Z.; Sun, Q.; Mazhar, M.; Ma, Y.; Yang, S.; Ren, W. Design and application of near-infrared nanomaterial-liposome hybrid nanocarriers for cancer photothermal therapy. *Pharmaceutics* **2021**, *13*, 2070. [[CrossRef](#)]
3. Du, C.; Wu, X.; He, M.; Zhang, Y.; Zhang, R.; Dong, C.-M. Polymeric photothermal agents for cancer therapy: Recent progress and clinical potential. *J. Mater. Chem. B* **2021**, *9*, 1478–1490. [[CrossRef](#)]
4. Wu, X.; Gao, Y.; Dong, C.-M. Polymer/gold hybrid nanoparticles: From synthesis to cancer theranostic applications. *RSC Adv.* **2015**, *5*, 13787. [[CrossRef](#)]
5. Yang, Y.-L.; Lin, K.; Yang, L. Progress in nanocarriers codelivery system to enhance the anticancer effect of photodynamic therapy. *Pharmaceutics* **2021**, *13*, 1951. [[CrossRef](#)]
6. Mihoub, A.B.; Larue, L.; Moussaron, A.; Youssef, Z.; Colombeau, L.; Baros, F.; Frochot, C.; Vanderesse, R.; Acherar, S. Use of Cyclodextrins in Anticancer Photodynamic Therapy Treatment. *Molecules* **2018**, *23*, 1936. [[CrossRef](#)]
7. Aghajanzadeh, M.; Zamani, M.; Kouchi, F.R.; Eixenberger, J.; Shirini, D.; Estrada, D.; Shirini, F. Synergic anti-tumor effect of photodynamic therapy and chemotherapy mediated by nano drug delivery systems. *Pharmaceutics* **2022**, *14*, 322. [[CrossRef](#)]
8. Wu, X.; Zhou, L.; Su, Y.; Dong, C.-M. Plasmonic, targeted, and dual drugs-loaded polypeptide composite nanoparticles for synergistic cocktail chemotherapy with photothermal therapy. *Biomacromolecules* **2016**, *17*, 2489–2501. [[CrossRef](#)]
9. Wu, J.; Zhou, L.; Su, Y.; Dong, C.-M. A polypeptide micelle template method to prepare polydopamine composite nanoparticles for synergistic photothermal-chemotherapy. *Polym. Chem.* **2016**, *7*, 5552–5562. [[CrossRef](#)]
10. Saravanakumar, G.; Kim, J.; Kim, W.J. Reactive-oxygen-species-responsive drug delivery systems: Promises and challenges. *Adv. Sci.* **2017**, *4*, 1600124. [[CrossRef](#)]
11. Dariva, C.G.; Coelho, J.F.J.; Serra, A.C. Near infrared light-triggered nanoparticles using singlet oxygen photocleavage for drug delivery systems. *J. Control. Release* **2019**, *294*, 337–354. [[CrossRef](#)] [[PubMed](#)]
12. Waglewska, E.; Pucek-Kaczmarek, A.; Bazylińska, U. Novel surface-modified bilosomes as functional and biocompatible nanocarriers of hybrid compounds. *Nanomaterials* **2020**, *10*, 2472. [[CrossRef](#)] [[PubMed](#)]
13. Jain, M.; Bouilloux, J.; Borrego, I.; Cook, S.; Bergh, H.; Lange, N.; Wagnieres, G.; Giraud, M.-N. Cathepsin B-cleavable polymeric photosensitizer prodrug for selective photodynamic therapy: In vitro studies. *Pharmaceutics* **2022**, *5*, 564. [[CrossRef](#)]
14. Osuchowski, M.; Osuchowski, F.; Latos, W.; Kawczyk-Krupka, A. The use of upconversion nanoparticles in prostate cancer photodynamic therapy. *Life* **2021**, *4*, 360. [[CrossRef](#)]
15. Liu, Z.; Ye, L.; Xi, J.; Wang, J.; Feng, Z. Cyclodextrin polymers: Structure, synthesis, and use as drug carriers. *Prog. Polym. Sci.* **2021**, *118*, 101408. [[CrossRef](#)]
16. Bognanni, N.; Viale, M.; Distefano, A.; Tosto, R.; Bertola, N.; Loiacono, F.; Ponassi, M.; Spinelli, D.; Pappalardo, G.; Vecchio, G. Cyclodextrin polymers as delivery systems for targeted anti-cancer chemotherapy. *Molecules* **2021**, *26*, 6046. [[CrossRef](#)]
17. Rasheed, A.; Ashok Kumar, C.K.; Sravanthi, V.V.N.S.S. Cyclodextrins as drug carrier molecule: A review. *Sci. Pharm.* **2008**, *4*, 567–598. [[CrossRef](#)]
18. Chen, Y.; Yao, Y.; Zhou, X.; Liao, C.; Dai, X.; Liu, J.; Yu, Y.; Zhang, S. Cascade-reaction-based nanodrug for combined chemo/starvation/chemodynamic therapy against multidrug-resistant tumors. *ACS Appl. Mater. Interfaces* **2019**, *11*, 46112–46123. [[CrossRef](#)]
19. Wang, Y.; Han, Y.; Tan, X.; Dai, Y.; Xia, F.; Zhang, X. Cyclodextrin capped gold nanoparticles (AuNP@CDs): From synthesis to applications. *J. Mater. Chem. B* **2021**, *9*, 2584–2593. [[CrossRef](#)]
20. Jahangiri-Manesh, A.; Mousazadeh, M.; Taji, S.; Bahmani, A.; Zarepour, A.; Zarrabi, A.; Sharifi, E.; Azimzadeh, M. Gold nanorods for drug and gene Delivery: An overview of recent advancements. *Pharmaceutics* **2022**, *14*, 664. [[CrossRef](#)]
21. Riley, R.S.; Day, E.S. Gold nanoparticle-mediated photothermal therapy: Applications and opportunities for multimodal cancer treatment. *WIREs Nanomed. Nanobiotechnol.* **2017**, *9*, 10. [[CrossRef](#)] [[PubMed](#)]
22. Wu, X.; Zhou, L.; Su, Y.; Dong, C.-M. An autoreduction method to prepare plasmonic gold-embedded polypeptide micelles for synergistic chemo-photothermal therapy. *J. Mater. Chem. B* **2016**, *4*, 2142–2152. [[CrossRef](#)]
23. Liu, S.; Pan, X.; Liu, H. Two-dimensional nanomaterials for photothermal therapy. *Angew. Chem. Int. Ed.* **2020**, *59*, 5890–5900. [[CrossRef](#)] [[PubMed](#)]
24. Lagos, K.J.; Buzzá, H.H.; Bagnato, V.S.; Romero, M.P. Carbon-based materials in photodynamic and photothermal therapies applied to tumor destruction. *Int. J. Mol. Sci.* **2022**, *23*, 22. [[CrossRef](#)] [[PubMed](#)]
25. Wu, X.; Tian, M. Fabrication of α -cyclodextrin/polypeptide micellar gold nanoshell for synergistic photothermal-chemotherapy. *J. Nanopart. Res.* **2018**, *20*, 217. [[CrossRef](#)]
26. Nocito, G.; Petralia, S.; Malanga, M.; Beni, S.; Calabrese, G.; Parenti, R.; Conoci, S.; Sortino, S. Biofriendly route to near-infrared-active gold nanotriangles and nanoflowers through nitric oxide photorelease for photothermal applications. *ACS Appl. Energy Mater.* **2019**, *2*, 7916–7923. [[CrossRef](#)]
27. Yu, Z.; Wang, M.; Pan, W.; Wang, H.; Li, N.; Tang, B. Tumor microenvironment-triggered fabrication of gold nanomachines for tumor-specific photoacoustic imaging and photothermal therapy. *Chem. Sci.* **2017**, *8*, 4896–4903. [[CrossRef](#)] [[PubMed](#)]
28. Zhang, B.; Yu, Q.; Zhang, Y.-M.; Liu, Y. Two-dimensional supramolecular assemblies based on β -cyclodextrin-grafted graphene oxide for mitochondrial dysfunction and photothermal therapy. *Chem. Commun.* **2019**, *55*, 12200–12203. [[CrossRef](#)]

29. Yu, Q.; Zhang, Y.-M.; Liu, Y.-H.; Liu, Y. Magnetic supramolecular nanofibers of gold nanorods for photothermal therapy. *Adv. Therap.* **2019**, *2*, 1800137. [[CrossRef](#)]
30. Wen, C.; Cheng, R.; Gong, T.; Huang, Y.; Li, D.; Zhao, X.; Yu, B.; Su, D.; Song, Z.; Liang, W. β -Cyclodextrin-cholic acid-hyaluronic acid polymer coated Fe₃O₄-graphene oxide nanohybrids as local chemo-photothermal synergistic agents for enhanced liver tumor therapy. *Colloids Surf. B Biointerfaces* **2021**, *199*, 111510. [[CrossRef](#)]
31. Kim, S.H.; In, I.; Park, S.Y. pH-Responsive NIR-absorbing fluorescent polydopamine with hyaluronic acid for dual targeting and synergistic effects of photothermal and chemotherapy. *Biomacromolecules* **2017**, *18*, 1825–1835. [[CrossRef](#)]
32. Zhang, L.; Li, S.; Chen, X.; Wang, T.; Li, L.; Su, Z.; Wang, C. Tailored surfaces on 2D material: UFO-like cyclodextrin-Pd nanosheet/metal organic framework janus nanoparticles for synergistic cancer therapy. *Adv. Funct. Mater.* **2018**, *28*, 1803815. [[CrossRef](#)]
33. Zhao, W.; Li, Z.; Yang, H.; Ren, C.; Lv, F.; Gao, S.; Ma, H.; Jin, Y.; Ge, K.; Liu, D.; et al. Mesoporous platinum nanotherapeutics for combined chemo-photothermal cancer Treatment. *ACS Appl. Bio Mater.* **2019**, *2*, 3269–3278. [[CrossRef](#)] [[PubMed](#)]
34. Luo, Y.-L.; Rong, R.-X.; Li, J.-M.; Chen, X.; Wang, S.-S.; Li, X.-L.; Wang, K.-R. Effective renal clearance and photothermal therapy of a cyclodextrin-modified quaternary derivative. *ACS Appl. Bio Mater.* **2020**, *3*, 3390–3400. [[CrossRef](#)] [[PubMed](#)]
35. Yu, G.; Yang, Z.; Fu, X.; Yung, B.C.; Yang, J.; Mao, Z.; Shao, L.; Hua, B.; Liu, Y.; Zhang, F.; et al. Polyrotaxane-based supramolecular theranostics. *Nat. Commun.* **2018**, *9*, 766. [[CrossRef](#)] [[PubMed](#)]
36. Xu, X.; Huang, Z.; Huang, Z.; Zhang, X.; He, S.; Sun, X.; Shen, Y.; Yan, M.; Zhao, C. Injectable, NIR/pH-responsive nanocomposite hydrogel as long acting implant for chemo-photothermal synergistic cancer therapy. *ACS Appl. Mater. Interfaces* **2017**, *9*, 20361–20375. [[CrossRef](#)]
37. Liu, M.; Huang, P.; Wang, W.; Feng, Z.; Zhang, J.; Deng, L.; Dong, A. Injectable nanocomposite hydrogel co-constructed by gold nanorods and paclitaxel-loaded nanoparticles for local chemo-photothermal synergetic cancer therapy. *J. Mater. Chem. B* **2019**, *7*, 2667–2677. [[CrossRef](#)]
38. Ruan, C.; Liu, C.; Hu, H.; Guo, X.-L.; Jiang, B.-P.; Liang, H.; Shen, X.-C. NIR-II light-modulated thermosensitive hydrogel for light-triggered cisplatin release and repeatable chemo-photothermal therapy. *Chem. Sci.* **2019**, *10*, 4699–4706. [[CrossRef](#)] [[PubMed](#)]
39. Tang, H.; Xu, X.; Chen, Y.; Xin, H.; Wan, T.; Li, B.; Pan, H.; Li, D.; Ping, Y. Reprogramming the tumor microenvironment through second-near-infrared-window photothermal genome editing of PD-L1 mediated by supramolecular gold nanorods for enhanced cancer immunotherapy. *Adv. Mater.* **2021**, *33*, 2006003. [[CrossRef](#)] [[PubMed](#)]
40. Lu, F.; Wang, J.; Tao, C.; Zhu, J.-J. Highly monodisperse beta-cyclodextrin-covellite nanoparticles for efficient photothermal and chemotherapy. *Nanoscale Horiz.* **2018**, *3*, 538–544. [[CrossRef](#)]
41. Duan, S.; Yang, Y.; Zhang, C.; Zhao, N.; Xu, F.-J. NIR-responsive polycationic gatekeeper-cloaked hetero-nanoparticles for multimodal imaging-guided triple-combination therapy of cancer. *Small* **2017**, *13*, 1603133. [[CrossRef](#)]
42. Zhao, N.; Yana, L.; Xue, J.; Zhang, K.; Xu, F.-J. Degradable one-dimensional dextran-iron oxide nanohybrids for MRI-guided synergistic gene/photothermal/magnetolytic therapy. *Nano Today* **2021**, *38*, 101118. [[CrossRef](#)]
43. Silva, N.; Riveros, A.; Yutronic, N.; Lang, E.; Chornik, B.; Guerrero, S.; Samitier, J.; Jara, P.; Kogan, M. Photothermally controlled methotrexate release system using β -cyclodextrin and gold nanoparticles. *Nanomaterials* **2018**, *8*, 985. [[CrossRef](#)] [[PubMed](#)]
44. Ma, X.; Li, X.; Shi, J.; Yao, M.; Zhang, X.; Hou, R.; Shao, N.; Luo, Q.; Gao, Y.; Du, S.; et al. Host-guest polypyrrole nanocomplex for three-stimuli responsive drug delivery and imaging-guided chemo-photothermal synergetic therapy of refractory thyroid cancer. *Adv. Healthc. Mater.* **2019**, *8*, 1900661. [[CrossRef](#)] [[PubMed](#)]
45. Das, M.; Nariya, P.; Joshi, J.; Vohra, A.; Devkar, R.; Seshadri, S.; Thakor, S. Carbon nanotube embedded cyclodextrin polymer derived injectable nanocarrier: A multiple faceted platform for stimulation of multi-drug resistance reversal. *Carbohydr. Polym.* **2020**, *247*, 116751. [[CrossRef](#)]
46. Liang, W.; Huang, Y.; Lu, D.; Ma, X.; Gong, T.; Cui, X.; Yu, B.; Yang, C.; Dong, C.; Shuang, S. β -Cyclodextrin-hyaluronic acid polymer functionalized magnetic graphene oxide nanocomposites for targeted photo-chemotherapy of tumor cells. *Polymers* **2019**, *11*, 133. [[CrossRef](#)]
47. Salazar, S.; Yutronic, N.; Kogan, M.J.; Jara, P. Cyclodextrin Nanosponges Inclusion compounds associated with gold nanoparticles for potential application in the photothermal release of melphalan and cytoxan. *Int. J. Mol. Sci.* **2021**, *22*, 6446. [[CrossRef](#)]
48. Lia, S.; Zhang, L.; Liang, X.; Wang, Y.; Chen, X.; Liu, C.; Lib, L.; Wang, C. Tailored synthesis of hollow MOF/polydopamine Janus nanoparticles for synergistic multi-drug chemo-photothermal therapy. *Chem. Eng. J.* **2019**, *78*, 122175. [[CrossRef](#)]
49. Guo, X.; Zhu, M.; Yuan, P.; Liu, T.; Tian, R.; Bai, Y.; Zhang, Y.; Chen, X. The facile formation of hierarchical mesoporous silica nanocarriers for tumor-selective multimodal theranostics. *Biomater. Sci.* **2021**, *9*, 5237–5246. [[CrossRef](#)]
50. Li, Q.-L.; Wang, D.; Cui, Y.; Fan, Z.; Ren, L.; Li, D.; Yu, J. AIEgen-functionalized mesoporous silica gated by cyclodextrin modified CuS for cell imaging and chemo-photothermal cancer therapy. *ACS Appl. Mater. Interfaces* **2018**, *10*, 12155–12163. [[CrossRef](#)]
51. Chen, M.; Perez, R.L.; Du, P.; Bhattarai, N.; McDonough, K.C.; Ravula, S.; Kumar, R.; Mathis, J.M.; Warner, I.M. Tumor-targeting NIRF nanoGUMBOS with cyclodextrin-enhanced chemo/photothermal anti-tumor activities. *ACS Appl. Mater. Interfaces* **2019**, *11*, 27548–27557. [[CrossRef](#)] [[PubMed](#)]
52. Dong, X.; Liang, J.; Yang, A.; Qian, Z.; Kong, D.; Lv, F. Fluorescence imaging guided CpG nanoparticles-loaded IR820-hydrogel for synergistic photothermal immunotherapy. *Biomaterials* **2019**, *209*, 111–125. [[CrossRef](#)]
53. Zhang, Y.; Yang, D.; Chen, H.; Lim, W.Q.; Phua, F.S.Z.; An, G.; Yang, P.; Zhao, Y. Reduction-sensitive fluorescence enhanced polymeric prodrug nanoparticles for combinational photothermal-chemotherapy. *Biomaterials* **2018**, *163*, 14–24. [[CrossRef](#)]

54. Xie, J.; Wang, Y.; Choi, W.; Jangili, P.; Ge, Y.; Xu, Y.; Kang, J.; Liu, L.; Zhang, B.; Xie, Z.; et al. Overcoming barriers in photodynamic therapy harnessing nano-formulation strategies. *Chem. Soc. Rev.* **2021**, *50*, 9152–9201. [[CrossRef](#)]
55. Huang, L.; Zhao, S.; Wu, J.; Yu, L.; Singh, N.; Yang, K.; Lan, M.; Wang, P.; Kim, J.S. Photodynamic therapy for hypoxic tumors: Advances and perspectives. *Coord. Chem. Rev.* **2021**, *438*, 213888. [[CrossRef](#)]
56. Semeraro, P.; Chimienti, G.; Altamura, E.; Fini, P.; Rizzi, V.; Cosma, P. Chlorophyll a in cyclodextrin supramolecular complexes as a natural photosensitizer for photodynamic therapy (PDT) applications. *Mater. Sci. Eng. C* **2018**, *85*, 47–56. [[CrossRef](#)]
57. Tian, J.; Xia, L.; Wu, J.; Huang, B.; Cao, H.; Zhang, W. Linear alternating supramolecular photosensitizer for enhanced photodynamic therapy. *ACS Appl. Mater. Interfaces* **2020**, *12*, 32352–32359. [[CrossRef](#)]
58. Xia, L.; Wu, J.; Huang, B.; Gao, Y.; Tian, J.; Zhang, W. Enhanced photodynamic therapy through supramolecular photosensitizers with adamantyl-functionalized porphyrin and cyclodextrin-dimer. *Chem. Commun.* **2020**, *56*, 11134–11137. [[CrossRef](#)]
59. Yoon, S.; Noh, G.J.; Youn, Y.S.; Oh, K.T.; Lee, E.S. Development of pH-responsive cyclodextrin nanoparticles for tumor-specific photodynamic therapy. *Polym. Adv. Technol.* **2020**, *31*, 3228–3237. [[CrossRef](#)]
60. Koo, M.; Oh, K.T.; Noh, G.; Lee, E.S. Gold nanoparticles bearing a tumor pH-sensitive cyclodextrin cap. *ACS Appl. Mater. Interfaces* **2018**, *10*, 24450–24458. [[CrossRef](#)]
61. Hu, H.; Dai, W.; Zhang, Y.; Huang, Y.; Qian, J.; Jin, Q.; Ji, J.; Tang, Z. Fabrication of programmed photosensitizer-conjugated nanoassemblies by dual supramolecular self-assembly for photodynamic therapy of orthotopic hepatoma. *Chem. Eng. J.* **2022**, *435*, 134930. [[CrossRef](#)]
62. Liu, J.; Liang, H.; Li, M.; Luo, Z.; Zhang, J.; Guo, X.; Cai, K. Tumor acidity activating multifunctional nanoplatform for NIR-mediated multiple enhanced photodynamic and photothermal tumor therapy. *Biomaterials* **2018**, *157*, 107–124. [[CrossRef](#)]
63. Jia, D.; Ma, X.; Lu, Y.; Li, X.; Hou, S.; Gao, Y.; Xue, P.; Kang, Y.; Xu, Z. ROS-responsive cyclodextrin nanoplatform for combined photodynamic therapy and chemotherapy of cancer. *Chin. Chem. Lett.* **2021**, *32*, 162–167. [[CrossRef](#)]
64. Tian, J.; Huang, B.; Cui, Z.; Wang, P.; Chen, S.; Yang, G.; Zhang, W. Mitochondria-targeting and ROS-sensitive smart nanoscale supramolecular organic framework for combinational amplified photodynamic therapy and chemotherapy. *Acta Biomater.* **2021**, *130*, 447–459. [[CrossRef](#)]
65. Dai, X.; Dong, X.; Liu, Z.; Liu, G.; Liu, Y. Controllable singlet oxygen generation in water based on cyclodextrin secondary assembly for targeted photodynamic therapy. *Biomacromolecules* **2020**, *21*, 5369–5379. [[CrossRef](#)]
66. Wang, T.; Zhang, H.; Han, Y.; Liu, H.; Ren, F.; Zeng, J.; Sun, Q.; Li, Z.; Gao, M. Light-enhanced O₂-evolving nanoparticles boost photodynamic therapy to elicit anti-tumor immunity. *ACS Appl. Mater. Interfaces* **2019**, *11*, 16367–16379. [[CrossRef](#)]
67. Qin, Y.; Tong, F.; Zhang, W.; Zhou, Y.; He, S.; Xie, R.; Lei, T.; Wang, Y.; Peng, S.; Li, Z.; et al. Self-delivered supramolecular nanomedicine with transformable shape for ferrocene-amplified photodynamic therapy of breast cancer and bone metastases. *Adv. Funct. Mater.* **2021**, *31*, 2104645. [[CrossRef](#)]
68. Deng, Y.; Jia, F.; Chen, S.; Shen, Z.; Jin, Q.; Fu, G.; Ji, J. Nitric oxide as an all-rounder for enhanced photodynamic therapy: Hypoxia relief, glutathione depletion and reactive nitrogen species generation. *Biomaterials* **2018**, *187*, 55–65. [[CrossRef](#)]
69. Yao, X.; Li, M.; Li, B.; Xue, C.; Cai, K.; Zhao, Y.; Luo, Z. Tumor-targeted upconverting nanoplatform constructed by host-guest interaction for near-infrared-light-actuated synergistic photodynamic-/chemotherapy. *Chem. Eng. J.* **2020**, *390*, 124516. [[CrossRef](#)]
70. Ikeda, A.; Satake, S.; Mae, T.; Ueda, M.; Sugikawa, K.; Shigeto, H.; Funabashi, H.; Kuroda, A. Photodynamic activities of porphyrin derivative-cyclodextrin complexes by photoirradiation. *ACS Med. Chem. Lett.* **2017**, *8*, 555–559. [[CrossRef](#)]
71. Aslanoglu, B.; Yakavets, I.; Zorin, V.; Lassalle, H.-P.; Ingrosso, F.; Monari, A.; Catak, S. Optical properties of photodynamic therapy drugs in different environments: The paradigmatic case of temoporfin. *Phys. Chem. Chem. Phys.* **2020**, *22*, 16956–16964. [[CrossRef](#)]
72. Lim, W.Q.; Yang, G.; Phua, S.Z.F.; Chen, H.; Zhao, Y. Self-assembled oxaliplatin(IV) prodrug-porphyrin conjugate for combinational photodynamic therapy and chemotherapy. *ACS Appl. Mater. Interfaces* **2019**, *11*, 16391–16401. [[CrossRef](#)]
73. Fu, H.-G.; Chen, Y.; Yu, Q.; Liu, Y. A Tumor-targeting Ru/polysaccharide/protein supramolecular assembly with high photodynamic therapy ability. *Chem. Commun.* **2019**, *55*, 3148–3151. [[CrossRef](#)]
74. Dai, X.; Zhang, B.; Zhou, W.; Liu, Y. High-efficiency synergistic effect of supramolecular nanoparticles based on cyclodextrin-prodrug on cancer therapy. *Biomacromolecules* **2020**, *21*, 4998–5007. [[CrossRef](#)]
75. Yuan, G.; Wang, Q.; You, Z.; Chen, X.; Xue, J.; Jia, X.; Chen, J. A novel hierarchical targeting and controllable smart nanoparticles for enhanced in situ nuclear photodynamic therapy. *Nano Res.* **2022**, *5*, 4212–4223. [[CrossRef](#)]