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Review

Chitosan- and hyaluronic acid-based nanoarchitectures in phototherapy: Combination cancer chemotherapy, immunotherapy and gene therapy

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ABSTRACT

Cancer phototherapy has been introduced as a new potential modality for tumor suppression. However, the efficacy of phototherapy has been limited due to a lack of targeted delivery of photosensitizers. Therefore, the application of biocompatible and multifunctional nanoparticles in phototherapy is appreciated. Chitosan (CS) as a cationic polymer and hyaluronic acid (HA) as a CD44-targeting agent are two widely utilized polymers in nanoparticle synthesis and functionalization. The current review focuses on the application of HA and CS nanostructures in cancer phototherapy. These nanocarriers can be used in phototherapy to induce hyperthermia and singlet oxygen generation for tumor ablation. CS and HA can be used for the synthesis of nanostructures, or they can functionalize other kinds of nanostructures used for phototherapy, such as gold nanorods. The HA and CS nanostructures can combine chemotherapy or immunotherapy with phototherapy to augment tumor suppression. Moreover, the CS nanostructures can be functionalized with HA for specific cancer phototherapy. The CS and HA nanostructures promote the cellular uptake of genes and photosensitizers to facilitate gene therapy and phototherapy. Such nanostructures specifically stimulate phototherapy at the tumor site, with particle toxic impacts on normal cells. Moreover, CS and HA nanostructures demonstrate high biocompatibility for further clinical applications.

1. Introduction

A multifactorial and chronic disease that results from significant genetic and epigenetic alterations is known as cancer [1,2]. Cancer is asymptomatic in the early stages, and this allows it to gradually grow and disseminate into other parts of the body. Most of the cancer patients

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demonstrate symptoms at the advanced and metastatic stages. Despite the focus on the diagnosis of cancer, there is still a long way to go, and currently, the treatment of cancer should be evolved for the better prognosis and survival of patients. In the initial stages of cancer, the transformation of normal cells into neoplastic cells occurs to achieve several remarkable features, including abnormal proliferation, cell death resistance, and angiogenesis stimulation. At later stages, they acquire the ability to migrate and disseminate in order to survive in the body and develop metastatic colonies in secondary sites. These are known as major hallmarks of cancer and were introduced by Hanahan and Weinberg [3]. Moreover, immune evasion [4], metabolic reprogramming, inflammation, and genomic instability are considered other hallmarks of cancer [5]. The molecular profile of cancer has been understood largely, and despite understanding the role of genomic and epigenetic alterations in its progression, there are still problems in its treatment. The lack of effective cancer therapy results from a majority of factors and cases. Chemotherapy and radiotherapy are the most common conventional therapies for cancer. However, frequent and long-term applications of chemotherapy and radiotherapy can cause changes in the tumor cells and mediate their resistance [6,7]. In fact, the stimulation of alternative molecular pathways has been responsible for the resistance of tumors to therapy. Although immunotherapy has emerged as a new therapy for cancer, the cancer cells have shown the ability to evade and escape from the surveillance of the immune system [8,9]. As a result, new kinds of therapies, including nanoparticles, should be introduced for the eradication of cancer.

Polymer-based nanostructures are among the most applied nanomaterials owing to their advantages, including improving the physicochemical features of drugs and targeting the delivery of cargo into the site of action [10,11]. Therefore, nanocarriers can improve the absorption of the active ingredients and promote their accumulation at the tumor site [12]. Both synthetic and natural polymers can be utilized for the synthesis of polymeric nanostructures. However, natural polymers are recommended for nanomaterial synthesis owing to their absorption in the body and biosafety [13,14]. Although nanomaterials have been developed for precision cancer therapy, the long-term safety of these structures is of importance. Therefore, the fabrication of nanoformulations from biocompatible and biodegradable sources can improve clinical applications. As a result, natural polymers are highly suggested for the development of nanomaterials, as they are biodegradable and their safety has been evaluated [15,16]. Chitosan (CS) and hyaluronic acid (HA) are biodegradable and biocompatible components for the synthesis of nanomaterials and can undergo structural modification to be activated in response to stimuli and release their cargo. A variety of formulations have been developed from CS and HA to provide prolonged release of cargo and improve their potential in the regulation of cancer progression [17–22]. CS- and HA-modified nanoparticles can deliver both drugs and genes in cancer therapy, and they are also promising for the regulation of the immune system [23-29].

In recent years, phototherapy has emerged as a new therapeutic strategy in the treatment of human diseases, especially cancer. Phototherapy can not only mediate the ablation of tumor cells but also increase the sensitivity of tumor cells to traditional therapies. For stimulation of phototherapy, photosensitizers are used. However, the accumulation of photosensitizers at the tumor site is low. Therefore, nanoparticles are explored for the targeted delivery of photosensitizers for effective cancer suppression. Several nanoparticles, such as gold nanostructures, have photo-responsive activity. However, the clinical application of photo-responsive nanoparticles requires them to be biocompatible. Nanoparticle-mediated phototherapy can accelerate tumor ablation, and its combination with chemotherapy [30], immunotherapy [31,32], and gene therapy [33] can significantly enhance the potential in tumor suppression. Therefore, the current review focuses on the application of CS- and HA-based nanocarriers for the specific and targeted treatment of cancer through stimulation of phototherapy to mediate tumor ablation. The features of nanoparticles and their ability to combine phototherapy with other modalities, including chemotherapy and immunotherapy, are also described.

2. The cancer phototherapy: promises of nanoparticles

A long time ago, sunlight-based phototherapy was considered an approach for the treatment of pathological events, especially skin diseases [34]. The belief originated from human society's worship of the sun during that era, and this type of therapy was associated with red light and solar heat [35,36]. Until the middle of the 19th century, heliotherapy was the only commonly used form of phototherapy [37]. Then, advances in phototherapy started, which led to progress and the introduction of optics, electricity, and the invention of artificial light sources [35,37]. A milestone was achieved after the treatment of Lupus vulgaris with filtered sunlight or the electric carbon arc torch-ultraviolet radiation that provided the foundation for modern phototherapy. In 1903, the Nobel Prize was awarded to Finson for his work on advanced and modern phototherapy [37,38]. Then, Theodore H. Maiman developed coherent and monochromatic lasers in 1927–2007 and utilized modern phototherapy for the treatment of skin pathologies [39]. Gerhard Meyer-Schwickerath evaluated the application of natural sunlight for the treatment of retinal diseases [40], and this provided the foundations for the utilization of ophthalmology and the clinical application of phototherapy for neonatal jaundice with the blue light having a range of 460–490 nm [41]. There are two types of phototherapies, including photothermal (PTT) and photodynamic (PDT) therapy.

After the discovery of PDT in a fluorescent dye, Dougherty and colleagues focused on the application of photosensitizers (PSs) and their excitation by light, finally introducing them into the treatment of cancer in the 1970s [42–44]. Currently, there is enough evidence showing that PDT can be utilized for the treatment of different pathologies, including tumors, bacterial infections, skin disorders, and others [45,46]. For the stimulation of PDT, there is a requirement to have three major components, including PS, a light source, and oxygen [47,48]. Tumor therapy by PDT mainly involves the stimulation of direct damage to the cancer cells through the induction of apoptosis, necroptosis, and autophagy. Moreover, PDT is vital for suppressing tumor vasculature and mediating local inflammation to trigger the systemic immunity for cancer therapy. The absorption of PSs mainly occurs by cancer cells, while PSs are poorly accumulated in normal cells and metabolized [49]. When the internalization of PSs in the tumor cells occurs, the light source is utilized, and such irradiation with a specific wavelength can increase the formation of reactive singlet oxygen to affect the major biological mechanisms and molecular pathways in cancer therapy. Noteworthy, normal cells are not affected since they are not sensitive to the detrimental impacts of reactive oxygen species (ROS) [50–52]. Therefore, for the stimulation of PDT in the tumor cells, there should be internalization of PSs in the cancer cells. However, one of the major issues is the lack of specific and targeted delivery of PSs. In this case, nanostructures have been introduced to deliver PSs into the tumor cells, increasing the potential of PDT in tumor suppression. The nanoparticles utilized for the PDT should have high stability in response to radiation, and their photothermal conversion efficiency should be high to significantly enhance singlet oxygen formation in cancer therapy [53]. Such an increase in ROS generation can cause cell death in tumors [54].

Noteworthy, the benefit of nanoparticles is their capability to stimulate PDT without the delivery of PSs. For instance, metal nanostructures can be loaded in metal-organic framework composites to catalyze H_2O_2 into singlet oxygen for stimulation of PDT [55]. Moreover, carrier-free nanostructures have been developed for combining PDT and chemotherapy to stimulate tumor eradication. In this case, the presence of NIR can enhance the release of Cy-I to promote the generation of singlet oxygen for stimulation of PDT [56]. Therefore, the potential of PDT can be significantly improved through the introduction of nanoparticles [57,58].

Another type of phototherapy is PTT, in which the mechanism of

action is different from PDT, but it finally causes cell death in tumors. PTT is mainly preferred over conventional therapeutic strategies due to the low risk of relapse and high efficiency [59]. In the case of PTT, the photothermal factors and structures are loaded into nanoarchitectures that can be PSs or nanoparticles with the ability to cause hyperthermia, such as gold and iron oxide nanoparticles [60]. Then, optical energy is absorbed by the nanoparticles, and such exposure to light irradiation leads to the generation of thermal energy. The mechanism of PTT requires the absorption of light; its transfer occurs through electron-electron and electron-phonon relaxation, generating hot nanoparticle lattices. Then, the nanostructure is cooled by phonon-phonon relaxation, and this promotes heat scattering to enhance the temperature of cancer cells that are near the nanostructures [61].

Nanostructures can mediate cell lysis and enzyme release during PTT and hyperthermia, enhancing necrosis and protein denaturation. However, the application of PTT in the treatment of diseases at the clinical level has its own problems, the most prominent of which is the low penetration of light into deep parts of soft tissues and also the cancers that are present in the bones or those located behind the bones [62]. However, these limitations are being addressed, and in recent years, a significant explosion has occurred in the application of nanostructures for PTT induction and improving their efficacy in cancer eradication. After the accumulation of nanoparticles at the tumor site, the application of laser irradiation and stimulation of PTT can cause apoptosis and necrosis in tumor cells [63]. PSs have poor tissue diffusion, and their cell internalization is low. Moreover, PSs demonstrate concentration-related toxicity, which is another issue [64]. Therefore, the application of nanoparticles allows to reduce the amount of PS utilized while improving tumor eradication ability. Furthermore, nanoparticles can provide a new promise for cancer therapy through the combination of PTT and chemodynamic therapy [65]. Since phototherapy is a new treatment modality for cancer and has high potential for being introduced into clinics, the current review will focus on the CS and HA nanoparticles for stimulation of phototherapy. Fig. 1 demonstrates the use of PTT and PDT in the treatment of cancer.

3. Chitosan: structural, chemistry and biological evaluation

CS is a source of nitrogen for living terrestrial and aquatic organisms [66]. CS is present in the cytoskeleton of arthropods, including insects, spiders, and crustaceans. Moreover, invertebrates' internal structures contain CS [67]. CS is derived from chitin. Structurally, chitin has been comprised of β (1 → 4) linked residues of *N*-acetyl-2-amino-2-deoxy-D-glucose and 2-amino-2-deoxy-D-glucose [68]. The aqueous ability of chitin is poor because of the presence of highly crystalline features resulting from hydrogen binding among the acetamido moieties [69,70]. When chitin undergoes partial deacetylation, it generates a water-soluble compound [71,72]. 10 % is the lowest degree of deacetylation of chitin, in which its molecular weight is 1–2.5 × 10^6 Da, and according to the polymerization degree, there can be about 5000–1000 monomeric residues [73]. The *N*-deacetylation of chitin with hot alkali leads to the generation of CS, the major derivative of chitin [74]. The deacetylation degree of CS can range from 40 % to 98 %, and the molecular weight is in the range of 5 × 10^4 Da and 2 × 10^6 Da [74–76].

When chitin undergoes deacetylation, it generates CS with free amino functional groups capable of being protonated for improving the solubility of polymers or undergoing chemical modification for the generation of new derivatives of CS with improved physico-chemical

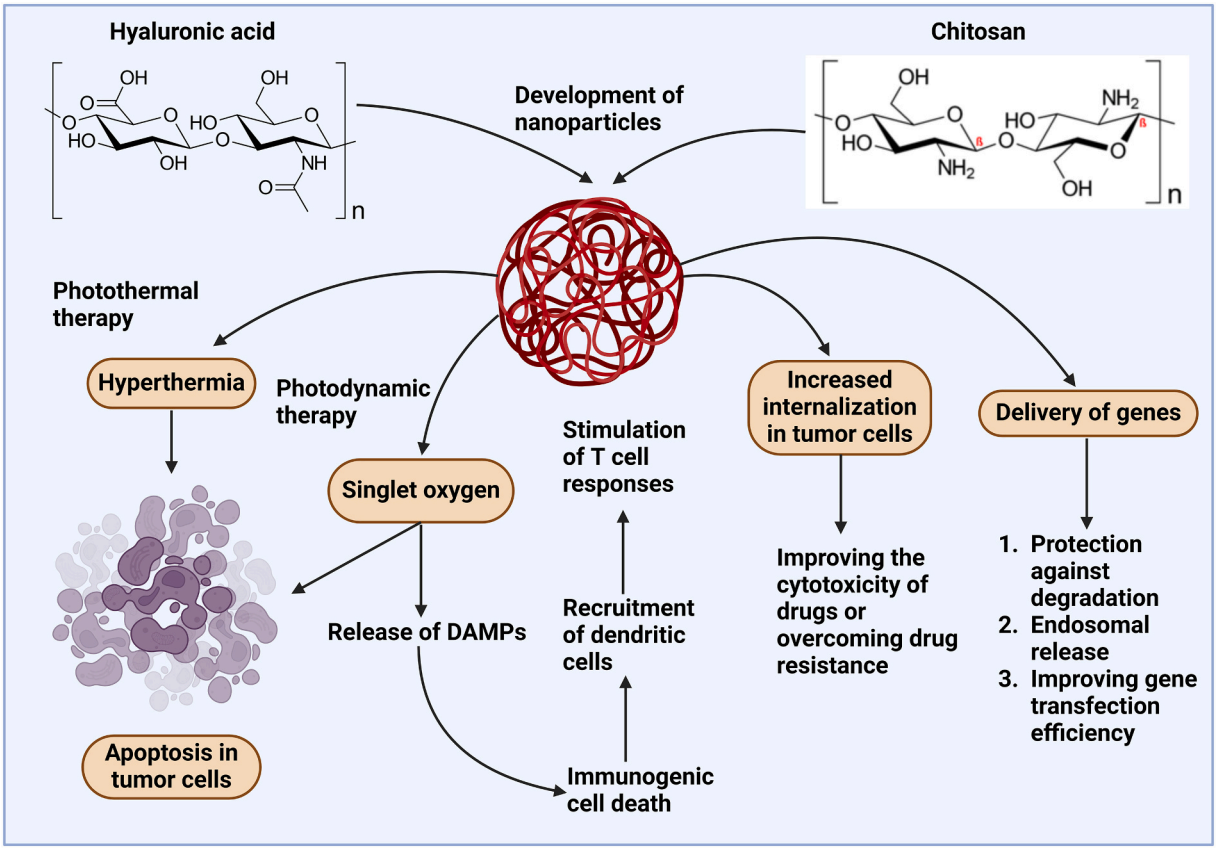

Fig. 1. Chitosan and hyaluronic acid can be used for the development of nanoparticles. These nanoparticles stimulate hyperthermia to induce cell death, known as photothermal therapy. Moreover, they can increase singlet oxygen to mediate photodynamic therapy. Such effects can also induce the release of DAMPs to induce immunogenic cell death through the recruitment of dendritic cells and subsequent activation of T cell responses in cancer immunotherapy. The nanoparticles can also promote the internalization of drugs and genes in the tumor cells to exert a synergistic impact with phototherapy. (Created by Biorender.com).

and biological features. Currently, there are several kinds of CS derivatives with potential features. A number of CS derivatives possess cationic features, including trimethyl CS chloride, N-[(2-hydroxy-3-trimethyl-ammonium)-propyl] CS chloride, N-propyl-*N*,*N*-dimethyl CS, N-furfuryl-*N*,*N*-dimethyl CS, and *N*-diethylmethylamino CS. These derivatives are cationic, and they display desirable film-forming features. Moreover, they can develop complexes with anions, and their aqueous solubility at pH <9 is improved. Their intestinal permeability is high, and they are biodegradable with mucoadhesive features [77–90]. Another type of derivative is N-acylchitosan, including formyl, acetyl, propionyl, and other types. They are also biodegradable, and their hydrogels have high water absorption abilities. They are promising compounds for the delivery of anticancer drugs, and they have strong antibacterial activities, among other good features [81,87,91–94]. *O*-acetylchitosan, N-carboxyalkyl/aryl CS, thiolated CS, and O-carboxyalkyl CS are other derivatives of CS that have been summarized in the review [95]. All these derivatives share a promising feature, which is biodegradability, and some other features, including biocompatibility and important biological mechanisms. Therefore, CS is a promising compound for the development and functionalization of nanoparticles.

CS nanoparticles cause sustained drug release and can improve the therapeutic index of compounds and drugs in disease therapy [96]. CS can also improve the therapeutic index of natural-based compounds such as curcumin, improving its potential in the treatment of various pathological events, including cancer, neurological disorders, chronic wounds, and microbial infections [97]. The cationic feature of CS allows for the development of nanocarriers complexed with negatively charged factors, such as genes, in cancer therapy [98]. Moreover, CS-based nanostructures can cause a combination of chemotherapy and gene therapy to eradicate cancer. Cinnamon oil can be loaded into CS nanoparticles to enhance levels of caspase-3 and AIP in apoptosis induction and reduce the growth rate of cancer [99]. The chemotherapy drugs utilized for cancer therapy, such as paclitaxel and docetaxel, suffer from low tumor accumulation, which may cause drug resistance [100]. The application of CS nanoparticles can significantly enhance the cytotoxicity of these drugs in cancer therapy [15].

CS can be combined with other types of natural polymers for the development of nanostructures, such as alginate. Such nanocarriers may undergo further functionalization with ligands targeting the folate receptor and EGFR through the ionic gelation method to improve drug delivery ability [101]. CS polymer can be utilized for the development of nanogels, and due to the features of CS, these nanogels can be pH-sensitive for a better and more specified release of drugs at tumor sites [102]. The ability of nanocomposites containing CS has made them promising factors in apoptosis stimulation, inducing nuclear damage, and improving the generation of ROS in cancer therapy [103]. Although the main focus of the current review is on CS-based nanoparticles, it is worth mentioning that hydrogels can also be developed from CS, and they are able to cause ferroptosis for the acceleration of cancer immunotherapy [104].

CS has been utilized for immunization. A co-formulation of CS and IL-12 was administered through the intratumoral route into a breast cancer model to induce immunotherapy and improve long-term tumor-free survival by 67 % [105]. Moreover, CS/γ-PGA nanostructures can exert synergistic impact with radiotherapy and mediate immunotherapy in breast tumor by reducing myeloid cells and increasing the CD4 + IFN-γ + population [106]. Regarding the positive charge of CS, it is beneficial for the purpose of gene therapy, and depending on the cargo, it can reduce (siRNA) and increase (mRNA and pDNA) the expression level of target genes. CS can improve the stability of the genes and protect them against degradation. Moreover, CS induces the endosomal release of genes and enhances their internalization into cells [107].

4. Chitosan nanoparticles: preparation methods and unique properties

4.1. Preparation of chitosan nanoparticles

Multiple strategies are utilized for the synthesis of CS nanostructures; each method has its own benefits, and depending on the situation, one of these strategies could be used. CS nanostructures were first developed in 1994 by Ohya and colleagues, using emulsifying and crosslinking for the synthesis of CS nanostructures to provide intravenous delivery of 5-flourouracil as an anticancer agent [108]. Currently, up to five strategies could be utilized to synthesize CS nanostructures, including ionotropic gelation, microemulsion, emulsification solvent diffusion, polyelectrolyte complexes, and the reverse micellar method [109]. Ionotropic gelation and polyelectrolyte complexes are considered the main strategies for the synthesis of CS nanostructures since they are simple and there is no requirement for the application of organic solvents [110]. The ionotropic gelation was first applied by Calvo and colleagues in 1997, which utilizes the electrostatic interaction between the amine groups of CS and negatively charged groups of polyanion, including tripolyphosphate [111]. The dissolution of CS in the acetic acid is performed, and, in this manner, the stabilizing compounds, including poloxamer, can be utilized. Then, the addition of polyanion is performed, and upon mechanical stirring at room temperature, the synthesis of CS nanostructures occurs.

The microemulsion approach is another strategy for the synthesis of CS nanoparticles that was reported by De and colleagues in 1999 [112], which utilizes dissolved CS in an acetic acid solution and a surfactant dissolved in N-hexane, and then the glutaraldehyde is added to the surfactant/hexane mixture at room temperature under magnetic stirring. The generation of nanostructures occurs in the presence of surfactants. The stirring continues overnight to mediate the process of crosslinking among the amine groups of CS and glutaraldehyde. The emulsification solvent diffusion method is another strategy for the synthesis of CS nanostructures that was first reported by El-Shabouri in 2002 [113], and then it underwent modification by Niwa and colleagues in 1993 using PLGA [114]. After the injection of an organic phase into CS solution with poloxamer as a stabilizer, magnetic stirring is performed, and using high-pressure homogenization, an emulsion is achieved. Then, water is utilized to dilute the emulsion, and because of organic solvent diffusion into the water, polymer precipitation happens to generate the nanostructures. The polyelectrolyte complex is another strategy that is performed by the self-assembly of cationic charged polymers and plasmid DNA. When the DNA solution is added to the CS/acetic acid solution, mechanical stirring at room temperature is performed to synthesize CS nanostructures [115]. The reverse micellar method was first reported by Brunel and colleagues in 2008 [116]. The toxic agents and crosslinkers are not utilized in this method, and this strategy can lead to the generation of nanostructures with low particle sizes. An aqueous solution of CS is added to the organic solvent consisting of surfactant under constant agitation to produce reverse micelles [117].

4.2. Characterization and modification of chitosan

Drug loading in CS nanoparticles can be performed through incorporation and absorption, while drug release from CS nanostructures results from diffusion, swelling, and erosion [118]. Desorption, diffusion, and release are the factors mediating the release of proteins from CS nanostructures. The drug release rate from CS nanostructures originates from the solubility, diffusion, and size of the nanoparticles [119,120]. The zeta potential is an electrical potential that is determined by the mobility of charged particles, and it can be positive, negative, or neutral based on the surface modifications of polymers [121]. CS nanostructures mainly demonstrate a particle size in the range of 100–400 nm. The stability of CS nanostructures affects the therapeutic

index of drugs [122]. The agglomerations of particles, bridging flocculation, and coagulation determine the physical stability of CS nanostructures. Moreover, temperature, pH, formulation composition, and polymer molecular weight determine the chemical stability of nanostructures [123,124].

The cellular uptake of CS nanostructures can be determined based on their size, drug loading and release, zeta potential, and other factors [125]. Two important methods are utilized for the physical modification of CS, including physical and chemical modifications [126]. Blending can be utilized to obtain physical modifications that require the application of and mixing of two or more polymers. Physical modification is a conventional strategy for the modification of CS, and based on the ratio of polymers, the quality and performance of the blend can be different. The physical modification is an affordable way to modify CS for certain applications [127].

PVA, PVP, and PEO are hydrophilic polymers that can be blended with CS to obtain an oral drug delivery system. The CS and PVA mixture significantly improves the mechanical features and barrier properties of CS films [128]. Another method is chemical modification, where the functional groups should be changed. Chemical modification can be performed through chemical compounds, radiation, photochemicals, plasma, and enzymatic grafting strategies [129]. There are amine groups in CS that can undergo chemical modification for various pharmaceutical applications, and reactions with sulfates, citrates, and phosphates can improve the stability and drug encapsulation efficiency [130].

5. Chitosan-based nanoparticles for photothermal therapy

In PTT, PSs are exposed to the light to cause hyperthermia, and this can mediate apoptosis or necrosis depending on the temperature [131]. For the denaturation of proteins or genes, the local temperature should reach >70 °C [132]. Regarding the ability of nanoparticles in photothermal conversion, they can augment the conversion of light irradiation to heat. Therefore, the regions surrounding nanoparticle sites are exposed to photothermal impacts, and the damage is limited to healthy tissues. Organic dyes have facilitated PTT, but their poor photostability poses a restriction. As a result, nanostructures such as gold nanoparticles have been introduced [133]. Gold nanoparticles, especially those with rod shapes, demonstrate a high ability for optical absorption, and therefore, they are promising structures for PTT [134]. Researchers have conjugated CS to gold nanostructures for PTT [135,136]. Gold nanorods can be stabilized by thiolated CS polymers. Upon the preparation of cetyltrimethylammonium bromide (CTAB)-passivated gold nanorods, their surface was functionalized with thiolated CS, and therefore, this significantly decreased the toxicity profile of CTAB, improving the biocompatibility of nanostructures. In addition to stability and biocompatibility, the modification of CS-functionalized gold nanorods with folic acid was conducted to specifically target the colon tumor cells upregulating the folate receptor. These ligand/CS-functionalized gold nanorods demonstrated high photothermal impact under 808 nm NIR laser irradiation [137].

The ability of CS-modified nanoparticles to perform PTT and tumor ablation is significant. Upon application of PTT, the CS/hydroxypropyltrimethyl ammonium chloride and CS/hydroxyapatite/black phosphorus (CS/HC/HA/BP) scaffold eradicated up to 95 % of osteosarcoma cells [138]. Such an impact is highly important for preventing the recurrence of cancer since incomplete and insufficient cancer therapy is not able to remove all tumor cells, and therefore, the remaining cancer cells proliferate and form new colonies to cause cancer relapse. As a result, the PTT can aid in tumor suppression and prevent cancer recurrence. Moreover, even exposure of CS-functionalized gold nanorods to low light intensities can suppress tumor cells in vivo [136].

CS oligosaccharide lactate (COL) is considered a naturally occurring compound with important biological features, including biodegradability, biocompatibility, and cationic nature. The depolymerization of CS leads to the formation of COL, whose average molecular weight is 5000 Da. The application of COL in medicine and pharmacy has improved because of its distinct properties, including water solubility, short chain length, low viscosity, and anticancer function [139,140]. Moreover, owing to the intracellular accumulation and site-specific delivery potential of COL, it has been utilized for the delivery of anticancer drugs and imaging agents [141–143]. The structures developed from COL and ZW800–1 NIR fluorophore (COL-ZW) can be utilized for the PTT of cancer. Furthermore, the theranostic feature of this structure makes it suitable for imaging. In vivo, the temperature of COL-ZW enhanced and reached 62.3 °C, and it was kept for 5 min. After a week of PTT, the tumor size significantly reduced. Moreover, these structures lack toxicity in normal tissues, and no tumor relapse was observed after PTT [144]. The poly(vinyl alcohol)/CS layer-by-layer microneedles have the ability to deliver doxorubicin, and under 808 nm NIR irradiation, they enhance the local temperature up to 12 °C. Since CS has a pH-sensitive feature, the release of drugs is performed at the tumor site, and therefore, the efficacy of PTT and chemotherapy is enhanced [145]. In recent years, the application of microneedles for the treatment of cancer has increased [146–148]. Microneedles can be loaded with nanostructures. Therefore, one strategy could be to develop CS nanostructures for PTT and then load them into microneedles for cancer therapy.

Without exogenous photoabsorbers, PTT's efficacy in tumor ablation is insufficient. A high number of endogenous photoabsorbers are ubiquitous in the body, and therefore, light energy penetration into deep tissues is difficult. For effective PTT and hyperthermia, the application of NIR and exogenous photoabsorbers is suggested. The nanostructure-based photoabsorbers have demonstrated high NIR light absorption and photostability. As a result, various classes of nanostructures, including gold, iron oxide, and melanin nanocarriers, among others, have been developed for PTT [149–152]. The gold nanodot swarms were utilized to develop gold nanostructures functionalized with glycol CS. Gold nanoparticles were complexed with glycol CS through interaction with the amine groups of CS. Exposure to 808 nm laser irradiation enhanced the temperature to 55 °C. The exposure of such nanostructures to thiolated molecules impairs the particle structure of nanocarriers, and then they are no longer able to mediate PTT and convert the light into heat. Moreover, these CS-modified nanocarriers can cause PTT and immunogenic cell death [153].

For improving the ability of tumor ablation, a combination of PDT and PTT has been utilized. Moreover, the CS nanofibers can be developed to cause both PDT and PTT. CS nanofibers have amine groups and are capable of absorbing gold nanostructures for PTT and chlorin e6 for PDT. CS nanofibers have a catonic nature in which they discharge the gold nanostructures attached to a motif with a pH-responsive feature through electrostatic repulsion. Then, CS nanofibers selectively bind to the cancer cells with anionic charge through electrostatic interaction [154]. Since PSs are loaded into the CS nanoparticles for PTT, the encapsulation efficiency of these nanostructures should be high. CS nanostructures usually demonstrate high encapsulation efficiency, for instance, 80.2 % for doxorubicin as an anticancer drug [155].

Trimethyl CS (TMC) can be achieved through the alkylation of CS. TMC is positively charged and enhances cell membrane penetration and lyso-endosomal escape via the proton sponge mechanism. Moreover, TMC can interact with negatively charged materials for the purpose of drug delivery or be utilized for the modification of nanostructures [156–158]. PEG-functionalized TMC-based nanoarchitectures have shown high potential in gene delivery for cancer elimination [159]. IR780 or bufalin was loaded into TMC nanoparticles through ionic gelation. At the next step, the functionalization of nanostructures with human serum albumin was performed through electrostatic absorption. The resulting nanocarriers demonstrated a 30 nm particle size and high photothermal impact. Moreover, they increased mitochondrion localization and promoted phototoxicity. TMC-based nanostructures highly accumulated in the tumor site and impaired 98.46 % of cancer invasion (Fig. 2) [160].

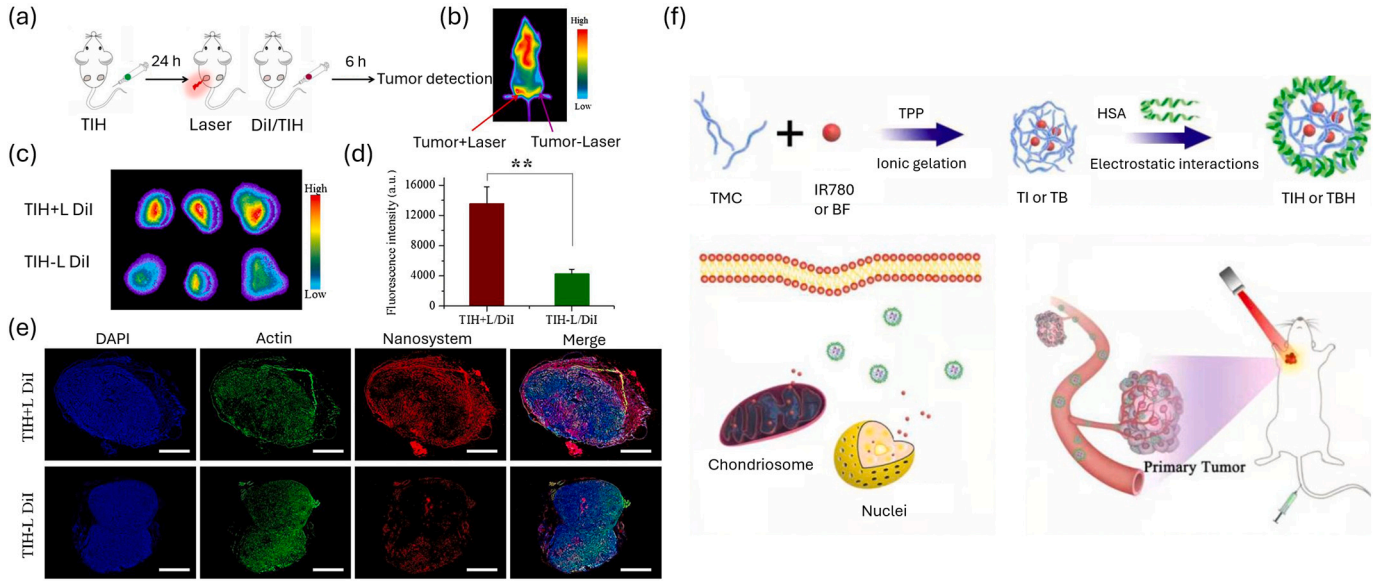

Fig. 2. The effect of the irradiation on the cancer site accumulation of TMC-based nanostructures. a) Treatment schedule; b) The distribution of nanoparticles; b) Ex vivo imaging; d) The fluorescent intensity; e) The deep penetration in tumor tissue; f) The synthesis of nanoparticles and their mechanism of action. Reprinted with permission from Elsevier [160].

The Pluronic F127 application has been approved by the FDA, and this synthetic structure is considered a thermo-sensitive block *co*-polymer that can be utilized for the encapsulation of IR780 dye. The Pluronic F127 can be deployed for the synthesis of self-assembled micelles through its amphiphilic triblock structure consisting of PEO (poly-(ethylene oxide)), PPO (poly-(propylene oxide)), and PEO (poly-(ethylene oxide)) to deliver the hydrophobic molecules [161–163]. The nanocapsules were prepared from Pluronic and CS, and then their functionalization with folate was conducted to improve their ability in the selective delivery of IR780 to ovarian tumor cells overexpressing the folate receptor, causing PDT and PTT and imaging (theranostic application) [164]. The Cu_2Se nanostructures were functionalized with CS, and they displayed high stability, water solubility, thermostability, and the ability to convert NIR light into heat. They demonstrated high cellular uptake in the tumor cells, and exposure to 808 nm laser irradiation enhanced their antitumor activity up to 400 % to mediate apoptosis through intrinsic and extrinsic pathways [165].

An important aspect of CS-based nanostructures utilized for PTT is their ability in imaging. Several imaging strategies have been combined with CS nanostructures during cancer therapy, including computed tomography, magnetic resonance imaging, dark field imaging, and fluorescence imaging [166–170]. Among the various kinds of imaging techniques, fluorescence imaging has emerged as a promising modality because of its sensitivity, simple conduction, and affordability [171–175]. Furthermore, red fluorescence imaging compounds have high priority in imaging applications since the red emission can eliminate the interference of bio-autofluorescence and provide deep penetration into biosystems [176–178]. In this regard, Bi_2S_3 nanoparticles were loaded in CS nanospheres for PTT and fluorescent imaging applications. These nanostructures can provide green and red luminescence emission, and there is no need to apply fluorescent dye because of the crosslinking present between CS and glutaraldehyde. The photothermal efficiency of nanoparticles in 808 nm laser irradiation was high, and they caused optical imaging-guided PTT in cancer therapy (Fig. 3) [179].

CuS quantum dots can also be applied for imaging and PTT of cancer. However, the targeting ability and biocompatibility of such structures are poor. Therefore, functionalization and modification of CuS quantum dots by CS and folic acid can be performed to increase the potential of imaging and PTT in cancer [180]. Therefore, CS-modified nanostructures have high potential in PTT and the imaging (theranostic) of cancer [181]. The anticancer activity of CS-modified nanostructures for PTT has been evaluated using 2D monolayers. However, in order to improve the insight into their cancer suppression potential, 3D spheroids of cancer could be utilized that mimic the tumor microenvironment, and even in this case, they demonstrate high potential in tumor elimination [182].

6. Chitosan-based nanoparticles for photodynamic therapy

3D crosslinked networks of polymer chains are known as hydrogels, which can absorb large amounts of water. Physical or chemical crosslinking agents can be utilized for the development of hydrogels [183]. In recent years, much attention has been directed towards the application of physically crosslinked gels that can occur through hydrogen bonding, hydrophobic association, and chain aggregation. In chemical crosslinking, covalent bonds are required. However, one of the main restrictions of chemical crosslinking agents is their poor biocompatibility, limiting their biomedical applications [184,185]. There are several types of hydrogels, including solid molds, liquids, membranes, and films. The solvent evaporation can be utilized for the generation of films, possessing the benefits of both hydrogels and films [185]. In this regard, ZnPc liposomes and CS were combined on a hybrid matrix in PDT induction. The hydrogel films function as delivery systems, and then ZnPC liposomes were embedded into the hydrogels. This system augmented PDT and reduced the viability of tumor cells by >95 % [186]. In addition to the application of CS for the functionalization of nanoparticles, several studies loaded CS into nanostructures. In an experiment, CS and garlic were loaded into CdO-TiO2 nanostructures and used for cancer therapy via the PDT action [187]. The synthesis of CS nanoparticles can be performed through various methods; one of them is the combination of CS and TPP with a mass ratio of 5:1 in 1 % *v*/v acetic acid at pH 5.5, and then obtaining nanostructures with a size of 200–300 nm for PDT induction and elimination of 98 % of tumor cells [188].

One of the most common PSs with wide application in clinics is 5-aminolevulinic acid (5-ALA) [189,190]. Protoporphyrin IX (PpIX) is the metabolic product of 5-ALA that is also an efficient and potential PS and has the ability to evoke mitochondria in cancer cells [191,192]. The application of 5-ALA through topical or systemic methods for the induction of PDT and the elimination of cancer cells has increased

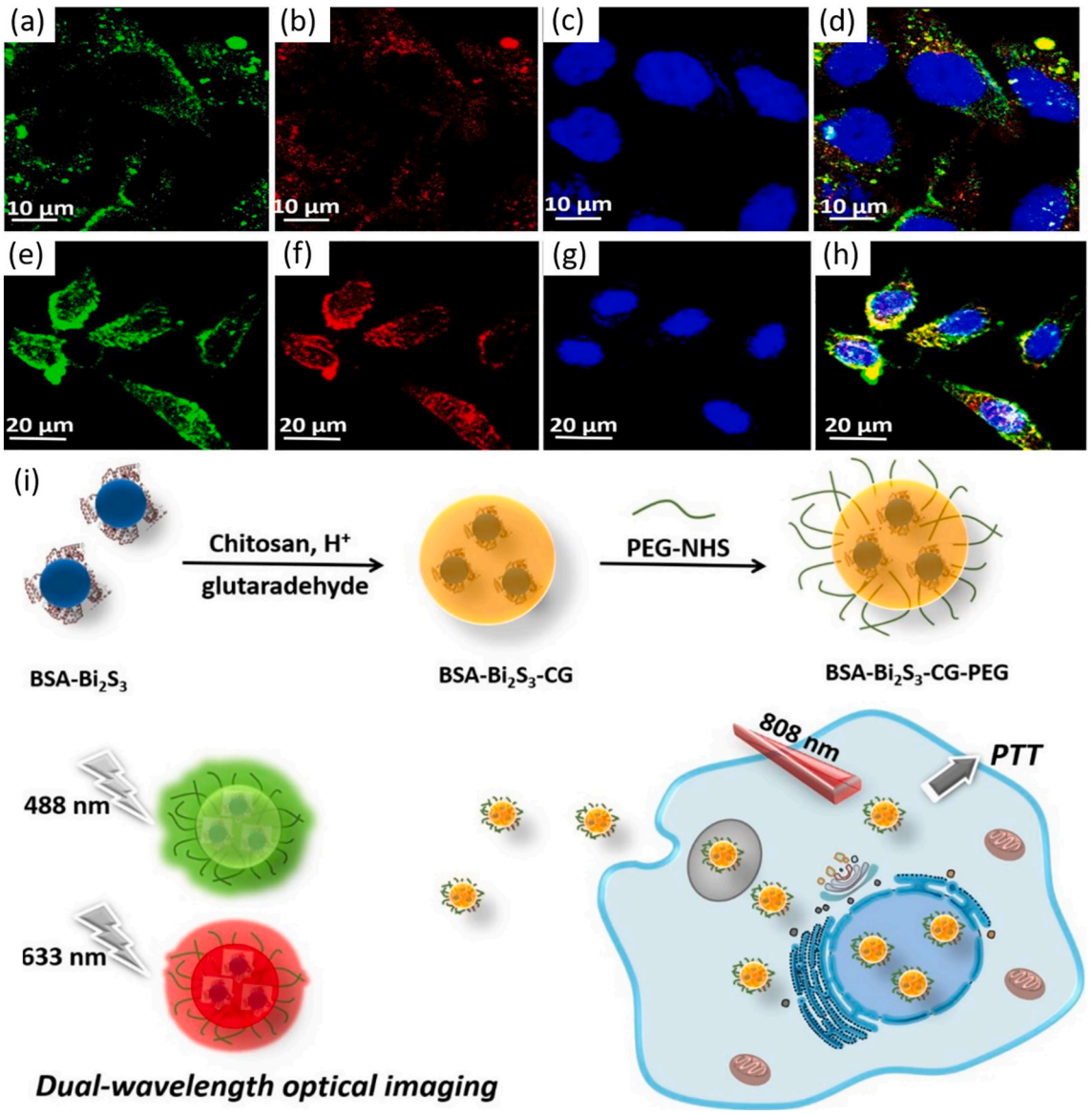

Fig. 3. a-h) CLSM images of the HepG2 cells after incubation with BSA-Bi_2S_3-CG-PEG nanostructures; i) The synthesis of nanoparticles and then their modification with chitosan and PEG for PTT induction and imaging, providing the theranostic application of nanocarriers. Reprinted with permission from Elsevier [179].

[193–198]. However, the cellular uptake and tumor accumulation of 5-ALA are low because of its hydrophobic nature and non-specificity towards cancer cells [199,200]. As a result, nanoparticles have been developed for the delivery of 5-ALA, including micelles, gold nanostructures, and mesoporous silica nanocarriers [201–204]. CS nanostructures have been applied for the delivery of IR780 and 5-ALA for PTT and PDT, respectively. These nanocarriers were deployed for noninvasive oral administration, and they demonstrated high stability at an acidic pH, confirming their potential and promises for the oral delivery of such drugs. This combination causes a synergistic impact to mediate both PTT and PDT in increasing ROS levels, causing oxidative damage, and suppressing tumorigenesis (Fig. 4) [205].

Lipid nanostructures were developed from stearic acid and glycerol monostearate, and then they were loaded and functionalized with chloroaluminum phthalocyanine and CS, respectively. The particle size of nanostructures was in the range of 131.5–231.5 nm, and their zeta potential was between −24.30 and + 19.96 mV. These nanoparticles displayed encapsulation efficiency of >96 %, and despite being non-toxic for the fibroblasts (showing their biocompatibility), they suppressed the survival rate of melanoma [206]. Another kind of PS for the induction of PDT is porphyrins and their derivatives [207,208]. The porphyrins demonstrate several properties, making them suitable for the PDT. The chemical purity of porphyrins is appropriate, and because of their high triplet state, they can increase reactions with molecular oxygen to promote the generation of singlet oxygen. Moreover, porphyrins lack action and cytotoxicity in the dark, and they can be cleared rapidly from the body [209–212]. The biopolymeric films were prepared from CS, PEG, and gelatin, and then the porphyrins were loaded into these biofilms. These PS-loaded CS-based films were able to enhance the generation of singlet oxygen, and they suppressed cervical cancer [213].

Although PDT is considered a potential strategy for cancer suppression, it has the ability to induce a hypoxic environment, which stimulates the prodrugs [214]. In this case, liposomes have been introduced for inducing PDT and stimulation of AQ4N as a hypoxia-activated prodrug in breast cancer therapy [215]. Liposomes were functionalized with CS, and TH302 as a hypoxia-activated prodrug was embedded into the nanostructures. Such nanoparticles possessed high biocompatibility and targeting abilities. Moreover, they have fluorescence imaging capacity, induce PDT, and impair tumorigenesis in breast cancer [216]. Therefore, similar to the CS nanostructures for PTT, these nanoparticles

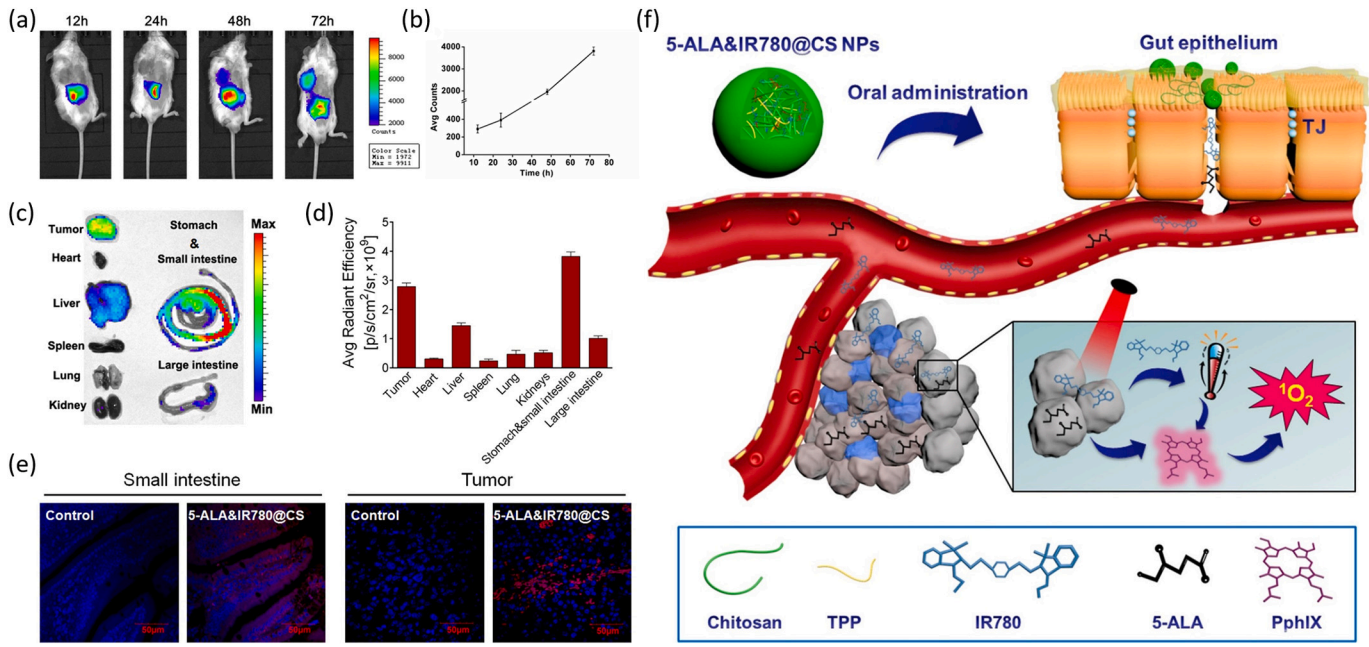

Fig. 4. The imaging of 5-ALA/IR780/CS nanoparticles in the tumor tissues. a) IR780 fluorescence images and b) fluorescence analysis; c) Ex vivo fluorescence images and d) fluorescence analysis of major organs and tumors; e) IR780 fluorescence imaging of the small intestine; f) The structures used for the synthesis of nanoparticles and loading drugs for oral delivery. Reprinted with permission from Elsevier [205].

utilized for PDT can also provide imaging. Notably, CS nanostructures can provide both MRI and PDT. The conjugation of CS with octadecanoic acid (OA) generates glycolipid polymers (CS-OA) with an amphipathic nature. Then, conjugation of gadopentetic acid (GA) to CS-OA was performed to produce Gd-CS-OA nanostructures for MRI. These polymers self-assemble into the micellar nanostructures in an aqueous solution, and chlorin e6 molecules can be loaded into their hydrophobic cores. Via the EPR effect, they accumulate in tumor sites, and MRI can be used to provide new insights regarding metabolism and the targeted delivery of cancer cells. The laser irradiation can induce PDT to impair cancer survival (Fig. 5) [217]. Furthermore, CS-based nanostructures possess stealth features [218], and they can be utilized for the treatment of various cancers, including gastrointestinal tumors [219]. Table 1 is an overview of CS-based nanostructures for cancer phototherapy. Fig. 6 is a summary of CS-based nanoparticles in cancer PDT and PTT.

7. Hyaluronic acid: structural, chemistry and biological evaluation

John W. Palmar and Karl Mayer first isolated HA from bovine vitreous humor [240,241]. HA is abundantly found in the extracellular matrix (ECM), and its physiological functions have been of importance for the systems and organs in the body. HA can also be found in synovial fluid, intra-articular cartilage, and aqueous humor. HA has an anionic and non-sulfated nature; this non-protein polysaccharide is comprised of disaccharides of d-glucuronic acid (GlcA) linked with *N*-acetyl-glucosamine (GlcNAc) by a glucuronidic β (1 → 3) bond. There are two types of HA: low-molecular-weight HA (20–500 kDa) and high-molecular-weight HA (>1 MDa). Moreover, the HA with a few kDa of molecular weight is known as the oligosaccharide HA [242–245]. The low-molecular-weight HA can improve tissue regeneration and penetrate the epidermal layer of skin tissue to transport the bioactive compounds for accelerating healing [246,247]. HA can serve as an antiadhesive compound during abdominal surgical resection. Owing to the large size, hygroscopicity, and viscoelasticity of HA, it has the capacity to be utilized for the regulation of skin hydration, osmotic balance, and ECM [248].

HA also has the ability to absorb water, even 1000 times higher than its volume [249]. Vital physiological and biological mechanisms, including proliferation, cell adhesion, and even differentiation, can be controlled by HA. The application of HA in tissue engineering has been improved, especially along with alginate, collagen, and gelatin. HA possesses a few osteogenic features for bone repair, but it can be used as a delivery system for bioactive compounds, where it binds to the CD44 receptor on the surface of cells to regulate molecular-related pathways [250].

Other kinds of nanostructures can be functionalized with HA to improve their targeting ability, such as cubosomes, and they selectively target tumor cells with upregulation of CD44 [251]. The important biological mechanisms participating in tumorigenesis and cancer metastasis, such as EMT, can be targeted by HA-functionalized Fe_3O_4 nanocubes [252]. Because HA has the ability to bind to the CD44 receptor, the nanoparticles can be designed in a way to provide both imaging and therapy for tumors [253]. The yeast β-glucan particles can be functionalized with HA to deliver doxorubicin, and through binding to the CD44 receptor, the accumulation of drugs increases, impairing cancer progression [254]. The polymeric micelles functionalized with HA can deliver paclitaxel, and such nanoparticles provide targeted and sustained release of chemotherapy drugs while their size is low and appropriate for tumor internalization and cancer eradication [255]. Similar to the CS that can be utilized for the development of hydrogels, HA also has the ability to be used in hydrogel development. The HA-based hydrogels have the potential to accelerate immunotherapy [256], suppress cancer relapse [257], and theranostic applications (delivery and bioimaging) [258].

HA has shown great promise for cancer immunotherapy. Redox-sensitive nanohydrogels have been developed from HA to deliver oncolytic viruses. Upon release, the oncolytic virus undergoes replication and finally stimulates apoptosis in tumor cells [259]. In this effort, copper-doped mesoporous polydopamine (CP) nanozyme was functionalized with HA and triphenylphosphine (TPP) to enhance oxidative damage and mediate apoptosis. Moreover, such nanosystems can stimulate damage-associated molecular patterns due to their mild photothermal activity and mediate tumor eradication [260]. The potential of HA in gene delivery has been promising for tumor suppression, as conjugation of PD-L1 siRNA into HA and targeting CD44-overexpressed tumor cells can improve siRNA potential in PD-L1 downregulation and

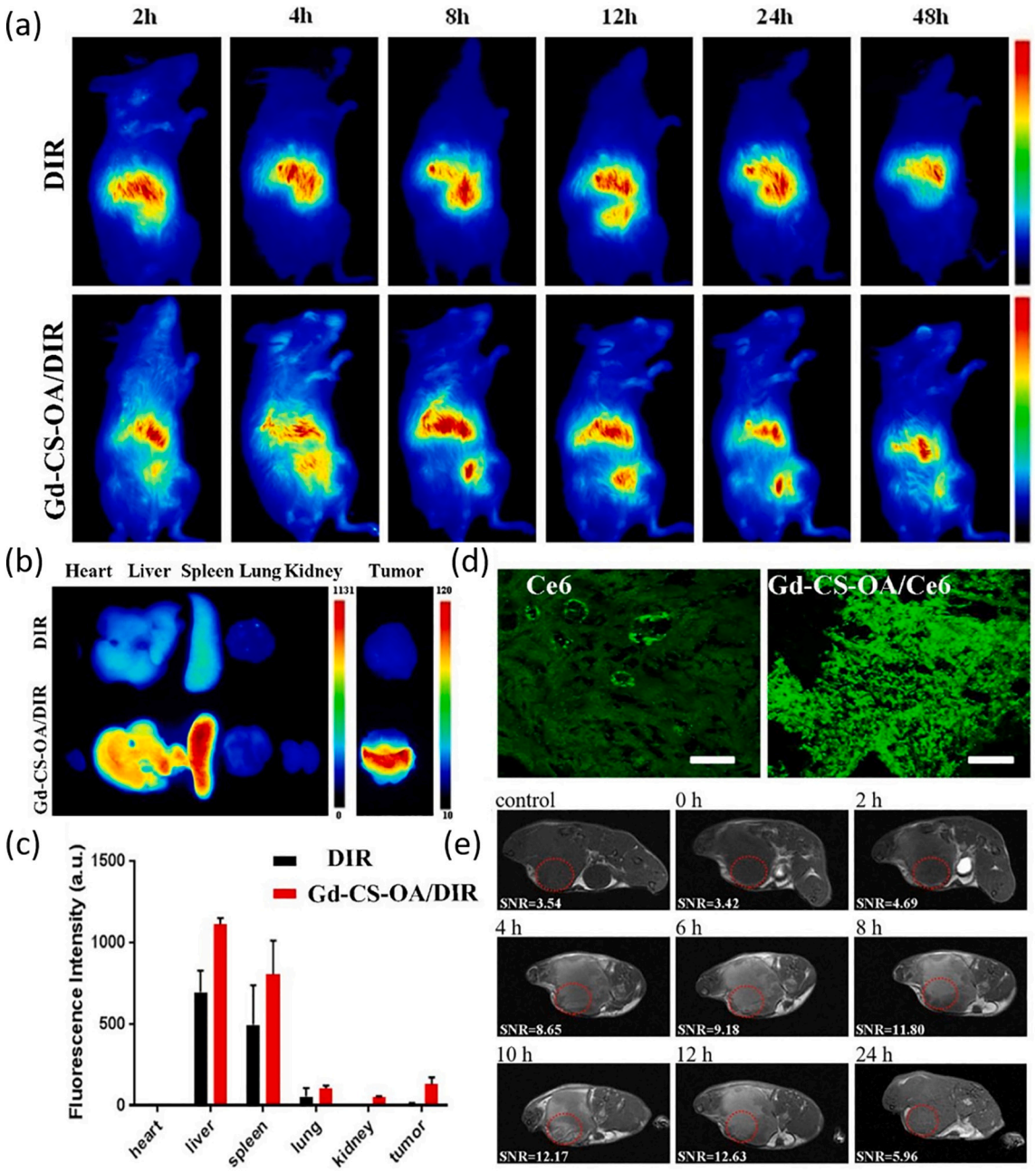

Fig. 5. a) In vivo distribution of DIR and Gd-CS-OA/DIR in 4 T1 tumor-bearing mice model. b) Representative ex vivo organ distribution of DIR and Gd-CS-OA/DIR at 48 h post injection. c) Quantification (mean fluorescent intensity) of ex vivo organ distribution. Data were presented as standard deviation ($n = 3$). d) The distribution of Ce6 and Gd-CS-OA/Ce6 (NPs/Ce6) at the tumor site at 24 h post injection. Scale bar: 100 μm. e) In vivo T1 weighted MRI images of 4 T1 tumor bearing mice model obtained at different time points after intravenous administration of Gd-CS-OA/Ce6. Reprinted with permission from Elsevier [217].

promote T cell-related responses in cancer eradication [261]. The modification of nanoparticles with HA can selectively target tumor cells and enhance the delivery of the p53 gene [262]. HA can be deployed for the synthesis of hydrogels and particles that are important for gene delivery. The next sections evaluate the great potential of HA-based carriers in PTT and PDT.

8. Rational for hyaluronic acid application in biomedicine and pharmaceutics

Recent years have witnessed the application of HA and its derivatives as delivery systems for steroid drugs, polypeptides, protein drugs, and antitumor therapeutics [263,264]. HA-based delivery systems significantly improve drug retention at the administration site, diminish the requirement for frequent administrations, improve the pharmacokinetic profile, and decrease the adverse impacts [265]. For entering the therapeutics into the cells, HA and polycation conjugates improve serum stability, and through binding to related receptors on the surface of cells, they mediate receptor-mediated endocytosis, increasing their penetration through the cell membrane [266]. The HA utilized for biomedical applications is obtained through microbial fermentation [267]. Moreover, HA extraction can be performed from roster combs and umbilical cords [268]. The depolymerization of HA can occur in batch cultures through enzymatic reactions or applications of physical and chemical degradations [269–271]. The linkage of HA to drugs can occur chemically. There are a high number of benefits regarding the application of

Table 1
CS-based nanostructures for cancer phototherapy.

Nanostructure	Therapy	Highlights	Refs
RGDyK-functionalized CS-wrapped upconversion nanostructures	PDT	Targeting the glioblastoma cells upregulating integrin receptor High phototoxicity at 980 nm irradiation	[220]
CS-LDH nanocomposites	PDT	Improving the stability of PSs to increase PDT Coating with CS increases PDT activity	[221]
Glycol chitosan nanostructures	PDT	The presence of intracellular reductive condition causes the improved photoreactivity of nanoparticles EPR effect Causing PDT-mediated tumor suppression	[222]
CS/TPP nanostructures	PDT	Loading curcumin in nanostructures and specific targeting of EGFR receptor PDT induction Increasing ROS generation Decreasing survival of tumor cells	[223]
Lipid-coated CS nanostructures	PDT	High cytotoxicity mediated by PDT and reducing viability of tumor cells	[224]
Glycol CS nanostructures	PDT	The compact structure of nanocarrier after cellular internalization decreases to enhance fluorescence signal and promote generation of singlet oxygen during irradiation Improving blood circulation and increasing targeting ability	[225]
Carboxymethyl CS nanostructures	PDT	Co-delivery of crose Bengal and oxymatrine and release in response to glutathione PDT induction and increasing singlet oxygen levels	[226]
CS hybrid nanospheres	PDT PTT	180 nm size with spherical shape Stimulation of hyperthermia Increasing ROS levels	[227]
Alginate-folic acid-functionalized CS nanostructures	PDT	The detection of intestinal neoplasms by photodynamic effect	[228]
PEG/CS/iron oxide hybrid nanoassemblies	PDT PTT	Increasing heat and singlet oxygen generation under NIR irradiation to induce damge in tumor cells	[229]
CS oleate-coated PLGA nanostructures	PDT	Association of indocyanine green with the nanoparticles Reduction in viability of tumor cells	[230]
CS-modified gold nanorods	PTT microRNA detection	A probe for the detection of miR-21 in breast cancer PTT effect in killing tumor cells	[231]
CS/fucoidan-coated nanorods	PTT	51.87 nm size and increasing temperature to 54.4 °C after laser irradiation PTT-mediated tumor killing	[232]
CS oligosaccharide-functionalized gold nanorods	PTT	The strong absorption peak at 838 nm and ability of PTT induction to suppress breast tumor	[233]
Glycol CS/iron oxide/polypyrrole nanoclusters	PTT Chemodynamic	The accumulation in tumor site and enhancing ROS generation through inducing Fenton reaction Limiting the side impacts	[234]
Palladium nanoparticles	PTT	Modification with folic acid-conjugated CS Increasing cellular uptake	[235]
Gold nanorods	PTT	Functionalization with CS and folic acid PTT effect at 808 nm laser irradiation and reducing viability of cervical cancer	[236]
Mesoporous silica nanostructures	PTT Chemotherapy	Modification of nanostructures with galactosylated CS Loading nedaplatin in the nanoparticles to mediate PTT and chemotherapy Apoptosis induction	[237]
CS/carbon dot hybrid nanogels	PTT Chemotherapy	High colloidal stability and high doxorubicin loading Drug release in response to pH and NIR light PTT and reducing growth of tumor cells	[238]
CS-functionalized gold nanocarriers	PTT Chemotherapy	Delivery of 5-flourouracil with 72 % loading efficiency Combination of chemotherapy and PTT by irradiation in hepatocellular carcinoma therapy	[239]

Abbreviations: RGDyK, Pyropheophorbide A and c; CS, chitosan; LDH, layered double hydroxide; PS, photosensitizer; EPR, enhanced permeation and retention; TPP, tripolyphosphate; EGFR, epidermal growth factor receptor; PDT, photodynamic therapy; PTT, photothermal therapy; PEG, polyethylene glycol; PLGA, poly lactic-*co*-glycolic acid.

HA-drug conjugates, HA-associated colloidal carriers, and HA-functionalized nanocarriers. The most prominent benefit of HA is that it improves and makes it easier to associate drugs with polysaccharides, either directly or through a carrier. Consequently, it resolves solubility-related issues. HA can improve the half-life of drugs in plasma and reduce their clearance, demonstrating a similar function to PEG [272].

In the case of cancer therapy, the application of HA can improve the specific targeting ability. HA-drug conjugates or HA-functionalized carriers demonstrate an EPR effect vital for improving the distribution of drugs in cancer tissues [273,274]. Regarding the upregulation of CD44 on tumor cells, circulating cancer cells, and stem cells, HA functionalization significantly improves the possibility of cancer targeting [275,276]. Furthermore, HA can be utilized to reverse multidrug resistance mediated by hyperactivation of P-glycoprotein [277]. The biological activities of HA have made it a promising compound for delivery systems. In fact, when the nanostructures are functionalized with HA, not only their targeting ability is improved, but also a number of biological activities is increased [278]. HA fragments have the ability to regulate inflammation, tumor metastasis, and drug resistance [279,280]. The fragments of HA with 25–50 disaccharide units demonstrate accumulation at the inflammation site, and through functioning as danger signals, they can reflect oxidative stress on tissue [281]. The macrophage expression of chemokines, cytokines, and growth factors can be altered by HA oligosaccharides, and these impacts reduce the proliferation of endothelial, fibroblast, and smooth muscle cells [282]. Therefore, HA and its derived or functionalized nanostructures could be significantly utilized in biopharmaceutics.

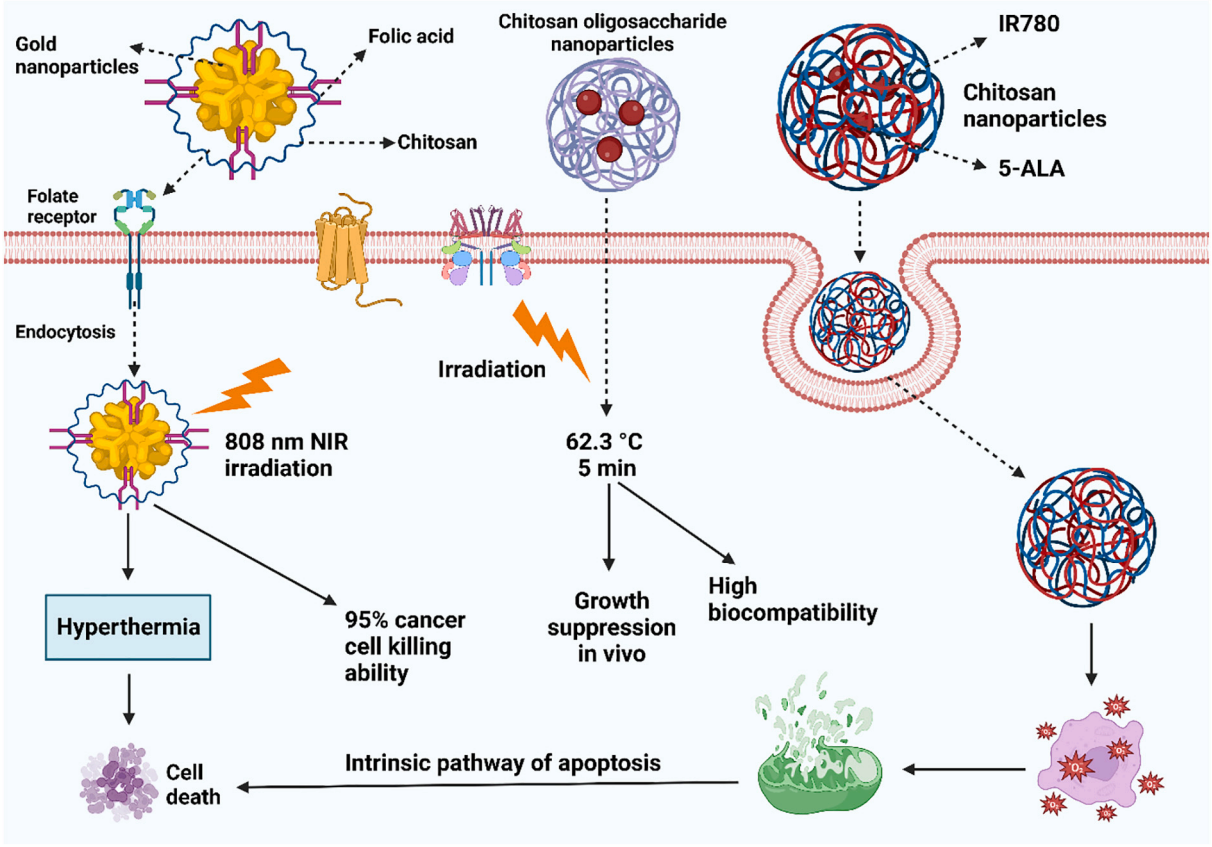

Fig. 6. The application of CS nanoparticles for cancer PDT and PTT. Different kinds of nanostructures can be utilized. Some of them, such as gold nanoparticles, have the ability to absorb light, so there is no need to utilize photosensitizers. Functionalization with ligands such as folic acid can increase internalization in tumor cells through endocytosis, and this causes hyperthermia in cell death induction. Moreover, chitosan oligosaccharide nanocarriers impair tumorigenesis in vivo. In photodynamic therapy, the nanoparticles increase the levels of ROS to induce mitochondrial dysfunction and mediate apoptosis. (Created by Biorender.com).

9. Hyaluronic acid-based nanoparticles for photothermal therapy

The modification of nanostructures with HA has been considered a promising way to improve the potential of PTT in tumor eradication. Similar to CS-modified nanostructures, HA-functionalized nanostructures can also be utilized for the eradication of cancer. HA was conjugated to boron dipyrromethene (BODIPY), which could self-assemble in the generation of BODIPY-HA nanocarriers. These nanostructures performed the actions of PTT and PDT by increasing temperature at the tumor site and promoting ROS generation [283]. The benefit of such a combination is not only related to the synergistic impact, but sometimes the cancer cells change the expression levels of heat shock proteins to obtain resistance to phototherapy. Therefore, combination therapy can prevent resistance to phototherapy. Gold nanostructures have a local surface plasmon resonance effect that can be utilized for light absorption and scattering [284]. The change and conversion of light by gold nanostructures can increase the temperature, making them promising candidates for PTT [285]. Gold nanostructures were prepared by glutathione, and then their shielding with SiO_2 was performed to increase the biocompatibility index. Moreover, HA modification of nanocarriers was performed to improve the targeting ability towards tumor cells overexpressing CD44. The photothermal conversion efficiency of nanostructures was 47.6 %, and within 200 s, these nanocarriers increased the temperature of tumor site from 38.5 °C to 57.6 °C, causing photothermal ablation of gastrointestinal cancers [286]. HA can be utilized for the modification of various nanostructures for the purpose of cancer PTT. Reduced graphene oxide (rGO) can result from GO through the application of chemical, thermal, or electrochemical methods. rGO is preferred to GO for the purpose of cancer therapy because of its large surface area, high drug loading efficiency, NIR light photothermal conversion efficiency, and capacity to be conjugated with other compounds and structures [287,288]. Both doxorubicin and IR780 was loaded on rGO nanostructures, and their functionalization with HA was performed. These structures released the cargo at a pH similar to the pH of the tumor microenvironment. Moreover, they increased the temperature at the tumor site, and the upregulation of HSP70 and ROS was observed. These nanostructures have high biocompatibility, and they can stimulate apoptosis and necrosis in tumor cells [289]. GO is a 2D carbon material possessing a graphitic lattice and having various oxygen functional groups, including epoxy, hydroxyl, or carboxyl groups, capable of absorbing NIR light [290,291]. When GO is transformed into rGO, its ability to absorb NIR increases due to recovering the aromatic lattice of this material, improving the photothermal potential of this structure [292]. The generation of rGO is mainly performed by the application of hydrazine hydrate [293,294]. However, such a kind of rGO is toxic [294], and therefore, new strategies for its application should be followed. The response of HA nanostructures to the light depends on the cargo that they carry. Cy5.5-conjugated HA nanomaterials were loaded with copper sulfide (CuS). The fluorescence potential of CuS was quenched by loading in the nanostructures. The presence of hyaluronidase in the tumor microenvironment can degrade the nanocomposite to release CuS for emitting fluorescent signals, and CuS causes hyperthermia via PTT, and is also interesting for photoacoustic imaging [295]. In another experiment, HA–hybridized polyaniline (HA–PANI) nanomaterials were developed for specific targeting of cancer cells upregulating CD44 receptor. The nanostructures were prepared using one-step oxidative polymerization. HA with a negative charge was

conjugated into PANI as a cationic polymer. Their average hydrodynamic diameter was 100 nm, and after exposure to an 808 nm NIR laser, they induced PTT and suppressed tumorigenesis [296].

Two problems regarding rGO should be addressed, including the toxicity of the agents used for its synthesis and the poor water solubility and selectivity towards tumor cells. Green synthesized rGO can be functionalized with HA to increase cancer therapy. The green reduction of GO can be performed by L-ascorbic acid, and functionalization with HA can increase the specificity towards tumor cells, targeting the tumor cells overexpressing CD44, increasing tumor accumulation, and causing PTT in tumor ablation (Fig. 7) [297].

HA-functionalized nanostructures can be internalized in cancer cells through CD44-mediated endocytosis [298]. In treating breast cancer, the HA-functionalized platinum nanostructures show a high ability to bind cells and a high PTT in eliminating tumors [299]. Furthermore, there are two kinds of HA with low and high molecular weights. Both can be utilized for the synthesis and modification of nanostructures, and the final impact on the PTT could be evaluated. The internalization of nanostructures modified with high molecular weight HA into cancer cells is higher compared to those functionalized with low molecular weight HA. Besides, the PTT impact of nanostructures modified with high molecular weight HA is higher compared to low molecular weight HA [300].

Similar to CS, HA is also applied in hydrogel synthesis. Although the scope of this paper is on the application of HA-based nanostructures in cancer therapy, it is worth mentioning that HA-based hydrogels can be utilized for suppressing the relapse of cancer. Injectable hydrogels were synthesized from HA, and they were embedded with gold nanostructures and ATRA to impair cancer stem cells (CSCs). The application of HA can be utilized to target CD44 upregulation on CSCs [301]. A micellar nanostructure was synthesized from HA and oleic acid with cystamine for ATRA loading that is redox-sensitive. CS was utilized for the synthesis and stability of gold nanostructures, causing cancer PTT. Then, both ATRA micellar nanostructures and gold nanocarriers were incorporated into CS to develop HA hydrogels. The HA-based hydrogels can cause the differentiation of CSC through the release of gold nanostructures and ATRA, suppressing cancer relapse and invasion. These hydrogels stimulate PTT and impair tumorigenesis through the eradication of CSCs, disrupting relapse and invasion (Fig. 8) [302].

HA nanostructures can be ROS-responsive for PTT-mediated cancer ablation. HA nanocarriers have a ROS-responsive thioketal moiety linker that is present between methotrexate and HA. Because they are hydrophobic and stack up against each other, these nanostructures were used to deliver IR780. These nanocarriers are ROS-responsive, have high targeting ability, and can cause tumor suppression up to 70.95 % [303]. This provides the notion that HA-modified nanostructures can be developed in a way to be responsive to both endogenous and exogenous nanocarriers. CuS nanostructures were loaded with doxorubicin, and GO was conjugated to these nanocarriers through the COOH functional group. To improve the targeting ability of cancer cells, the modification of nanoparticles with HA was performed to enhance CD44-targeting. These nanoparticles can extravasate the blood vessels after intravenous administration, and they release the cargo in response to pH and NIR to enhance the intracellular and nucleus accumulation of drugs for

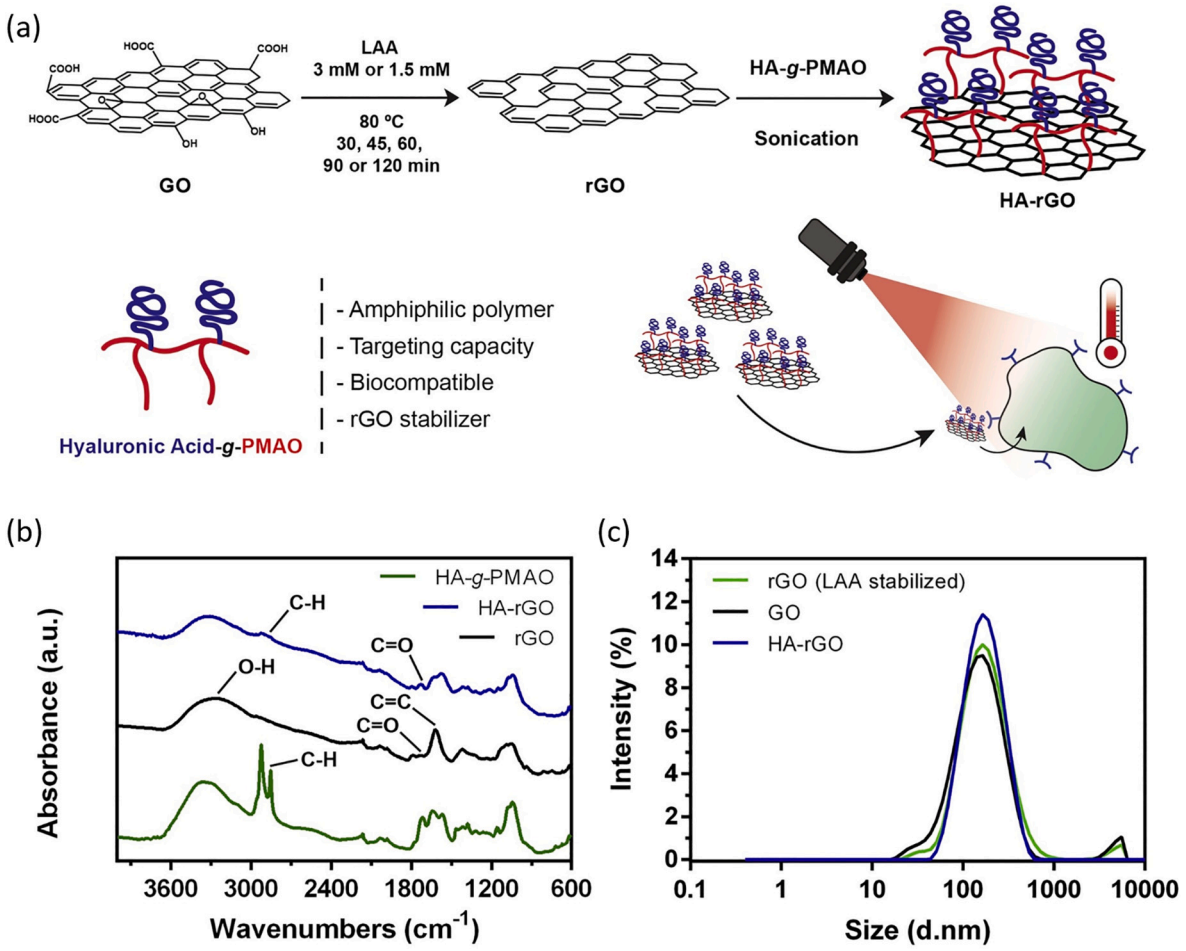

Fig. 7. Preparation and characterization of HA-rGO. Schematic representation of the reduction and functionalization of rGO with HA-g-PMAO and its application in cancer photothermal therapy (a). FTIR spectra of rGO, HA-g-PMAO, and HA-rGO (b). DLS size distribution of GO, rGO (LAA stabilized), and HA-rGO (c). Reprinted with permission from Elsevier [297].

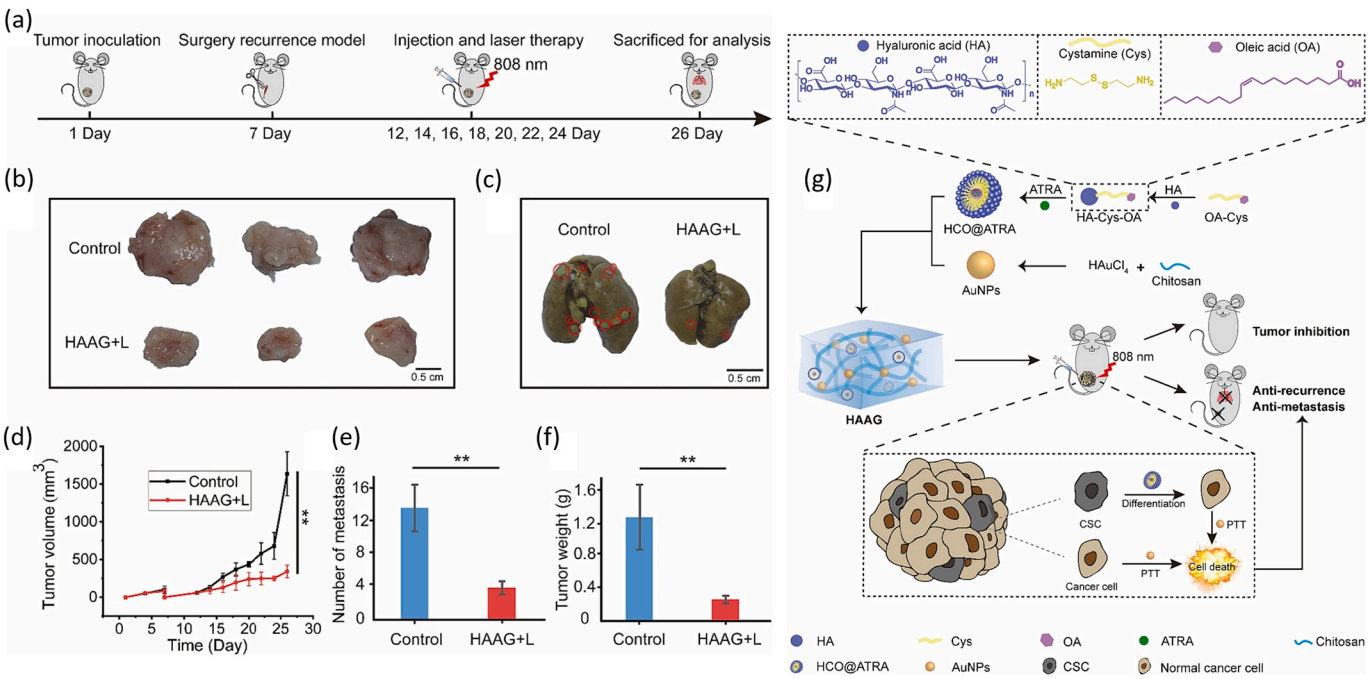

Fig. 8. Anti-recurrence and anti-metastasis inhibition in vivo ($n = 3$). a) Illustration of the therapeutic schedule of the recurrence-metastasis mouse model. b) Tumor images (scale bar: 0.5 cm). c) Photographs of lung metastatic nodules (scale bar: 0.5 cm). The metastatic nodules were labeled with red circles. d) Tumor volume growth curves after tumor implantation, subsequent surgery, and therapy. e) The number of lung metastatic nodules in each group. f) Final mean tumor weights. All data are shown as mean ± SD. $^*p < 0.05$, $^{**}p < 0.01$. g) Schematic illustration of composite hydrogel preparation, tumor inhibition, and anti-recurrence/metastasis through eliminating both CSCs and non-CSCs by combining differentiation of ATRA and PTT of AuNPs. Reprinted with permission from Elsevier [302].

cancer therapy [304].

Nanocarriers can be utilized for imaging and PTT simultaneously. In a study, after the preparation of PEI-Ag nanostructures, hydrothermal synthesis was performed to increase Fe_3O_4@Ag seeds. Then, their modification with PEI-SH was conducted. The nanoparticles were functionalized with HA through EDC/NHS to increase their targeting ability. These nanostructures were internalized by tumor cells, and they not only induced PTT but also provided MR and CT imaging of cancer [305]. Such ability for PTT and imaging can be obtained through the conjugation of HA to quantum dot nanostructures to provide theranostic applications [306]. The conjugation of HA to different kinds of nanostructures, such as GO, can be performed to induce PTT [307]. Therefore, such experiments demonstrate that functionalization of nanostructures with HA can significantly increase their internalization into tumor cells overexpressing CD44, which enhances the PTT impact in tumor ablation [308–310].

10. Hyaluronic acid-based nanoparticles for photodynamic therapy

Biomedical imaging has achieved significant progress owing to advances in the chemistry of molecular imaging nanoprobes. However, it is vital to develop molecular imaging nanoprobes that can specifically target cancer cells. Due to its high resolution and lack of radiation exposure requirements, MRI has gained widespread application [311–314]. PLGA nanostructures were applied for the delivery of chlorin e6, and their functionalization with HA was performed. The presence of HA provides the carboxylate groups capable of providing chelation with gadolinium ions for MRI imaging. These nanostructures can specifically target the CD44 receptors upregulated on the surface of tumor cells, and they delay cancer progression [315]. Tumor hypoxia refers to a situation in which the oxygen supply is not enough, which can commonly occur in solid tumors [316,317]. The hypoxic and normoxic tissues display heterogeneity in their TME, and therefore, the pressure of oxygen can be utilized for tumor-specific delivery [318,319]. As a result, hypoxia-responsive nanogels are utilized for imaging and PDT. AZO-CDI is utilized as a hypoxia-responsive linker and can be prepared by HA-functionalized groups. When the oxygen level is high enough, the quenching of the fluorescence of Ce6 conjugated to the nanoparticles is performed, and even after irradiation, the ROS generation is low. However, when hypoxia is present in TME, the dissociation of nanoparticles occurs, and the fluorescent activity of Ce6 is achieved to enhance ROS generation after irradiation. Owing to the modification with HA, they specifically target the tumor cells, upregulating CD44, and their intracellular accumulation in cancer is high [320].

In an experiment, HA-ceramide nanostructures were developed for the co-delivery of paclitaxel and hypocrellin B. The nanoparticles suppressed tumorigenesis (lung cancer) in vitro and in vivo. They were able to selectively target tumor cells (binding to the CD44 receptor), and through stimulation of PDT, they exerted a synergistic impact with chemotherapy [321]. The delivery of chlorin e6 by the HA nanostructures can cause PDT [322]. The HA nanostructures were self-assembled through the chemical conjugation of aminated 5β-cholanic acid, polyethylene glycol (PEG), and black hole quencher3 (BHQ3) to the HA polymers. The dialysis method was utilized to load Ce6 into HA nanoparticles with a loading efficiency of 80 %. The nanoparticles were stable and could rapidly internalize into cancer cells. The hyaluronidase in the cytoplasm of cancer cells degraded HA nanoparticles to release Ce6 into cells. In vivo experiments confirmed the accumulation of nanostructures at the tumor site, and laser irradiation was able to produce fluorescence due to the Ce6 release, generating single oxygen for PDT [322].

It can be understood from the studies that, despite the promising potential of PDT in tumor suppression, the low specificity towards cancer cells is one of the main problems of PDT, which can be solved through functionalization of nanostructures with HA [323]. The conjugation or loading of hydrophobic drugs into HA-based nanostructures can increase the water solubility, and until now, several kinds of drugs, including doxorubicin, paclitaxel, and PSs, have been conjugated to HA [324,325]. The functionalization of HA with glycodendron and

pyropheophorbide-a (Ppa) was performed to prepare nanostructures with high cellular uptake in tumor cells capable of causing mitochondrial dysfunction and increasing ROS generation upon laser irradiation. These nanoparticles showed a dendritic structure, and they had a higher molecular weight compared to the linear polymer, causing high cellular uptake and prolonged blood circulation. These nanostructures can disrupt the growth of tumor cells, and the elimination of almost 60 % of tumors upon irradiation was observed [326]. Due to the unique features of carbon-based nanocarriers, significant attention has been paid to their functionalization with HA. HA-derived carbon dots can be prepared using the hydrothermal method, and they can target tumor cells overexpressing CD44. These nanocarriers are also PSs, and under 650 nm irradiation, they display photoluminescence emission, providing imaging and PDT of tumor cells [327].

Nanoparticles can impair CSCs in tumor therapy. Ce6-Olaparib micelles were functionalized with HA, and they can impair cancer progression through stimulation of PDT and prevention of DNA damage repair. These nanoparticles can stimulate immunogenic cell death since PDT can increase ROS generation. Then, maturation of dendritic cells occurs to reduce the infiltration of MDSCs and overcome CSC resistance [328]. The PDT potential of HA-ceramide nanostructures increases when both paclitaxel and hypocrellin B are loaded into the nanocarriers [329]. This is because these drugs can also exert anticancer activity, and therefore, PDT-mediated tumor ablation is improved. In recent years, the application of stimuli-responsive nanocarriers for cancer eradication has improved significantly [330]. The intelligent drug delivery systems can respond to endogenous and exogenous stimuli, including temperature [331,332], pH [333,334], redox [335,336], light [337,338] or enzyme [339,340], that are ideal candidates for delivery applications. These nanocarriers minimize premature drug release, and they can release cargo at the tumor site in exact response to the site and time [341].

Gold nanostructures functionalized with HA are promising candidates for the treatment of breast cancer through stimulation of both PDT and PTT, and they can respond to triple stimuli. Gold nanorods were functionalized with HA, bearing the hydrazine and thiol groups through Au—S bonds. Then, their chemical modification through conjugation with 5-aminolevulinic acid (ALA), Cy7.5, and an anti-HER2 antibody onto the HA moiety was performed to induce PDT, specific targeting, and fluorescence imaging. These nanostructures demonstrated uniform size and desirable dispersion, and they could respond to pH, redox, and HAase (enzyme). The internalization of nanostructures into the tumor cells significantly increases due to the modification of the HER2 and CD44 receptors. Moreover, NIR irradiation can significantly enhance ROS generation and heat, causing PDT and PTT in breast cancer ablation. The nanoparticles demonstrated a 1.9 h half-life, and their accumulation at the tumor site was 12.8 %. Besides, the nanostructures caused PDT and PTT along with imaging, lacking adverse impacts (Fig. 9) [342]. Fig. 10 is an overview of using HA-based nanoparticles in cancer phototherapy.

11. Chitosan- and hyaluronic acid-based nanoparticles in phototherapy and immunotherapy

11.1. Chitosan nanoparticles

Immunotherapy is the process of immune system regulation aimed at improving the reactions of immune cells and, therefore, reversing the mechanisms responsible for immune evasion [343,344]. Immune checkpoint inhibitors, cytokines, cancer vaccines, and CAR-T cells, among others, can be utilized for immune system induction [345]. However, the function of the immune system has been restricted because of poor responses and a lack of targeted delivery of immunomodulators. The combination of immunotherapy and phototherapy has been used for cancer eradication. The hollow CuS nanostructures can be coated with CS, and then they assemble with immunoadjuvant

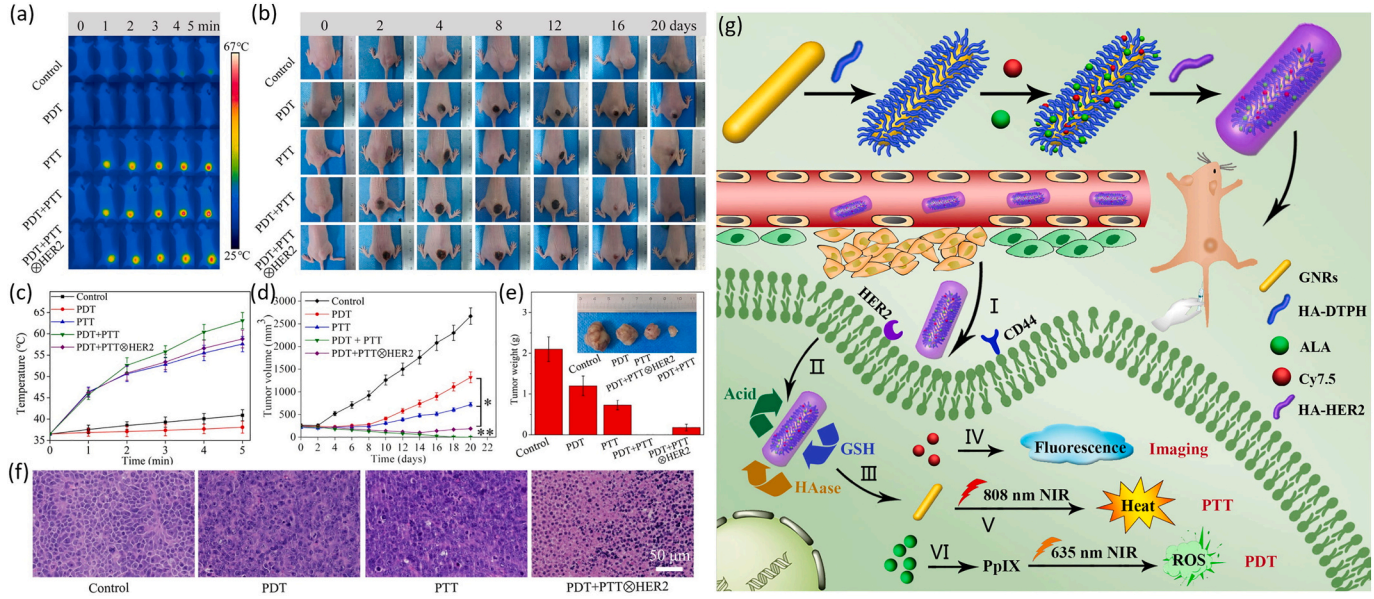

Fig. 9. In vivo antitumor study in nude mice xenograft models with MCF-7 breast cancer. a) Photothermal photographs of the mice received different treatments: PDT (GNR-HA − ALA/Cy7.5-HER2 + 635 nm NIR irradiation), PTT (GNR-HA − ALA/Cy7.5-HER2 + 808 nm NIR irradiation), PDT + PTT (GNR-HA − ALA/Cy7.5-HER2 + 635 nm and 808 nm NIR irradiation), PDT + PTT ⊗ HER2 (GNR-HA − ALA/Cy7.5 + 635 nm and 808 nm NIR irradiation). b) Typical digital photos of mice bearing tumors at different treatment stages. Changes in c) tumor temperature, d) tumor volume, and e) tumor weight of mice received different treatments. Inset: Representative photograph of excised tumors. ($n = 5$, $^{*}p < 0.05$, $1 - \beta = 90.2$ %; $^{**}p < 0.01$, $1 - \beta = 83.2$ %). f) H&*E*-stained micrographs of tumor tissues from different groups; g) Schematic representation of the processes for preparing GNR-HA − ALA/Cy7.5-HER2 with triple-responsive drug release and its application for HER2/CD44 dual-targeted and fluorescence imaging-guided combined PDT/PTT treatment of breast cancer. (I) GNR-HA − ALA/Cy7.5-HER2 accumulates at the tumor site through the EPR effect. (II) GNR-HA − ALA/Cy7.5-HER2 is recognized by CD-44 and HER2 receptors and then internalized into tumor cells. (III) The release of ALA is triggered by an acidic intracellular microenvironment. HA is degraded by GSH and HAase. The Cy7.5, GNRs, and ALA liberated from the nanoplatform are used for (IV) fluorescence imaging, (V) PTT, and (VI) PDT of HER2-positive breast cancer, respectively. Reprinted with permission from Elsevier [342].

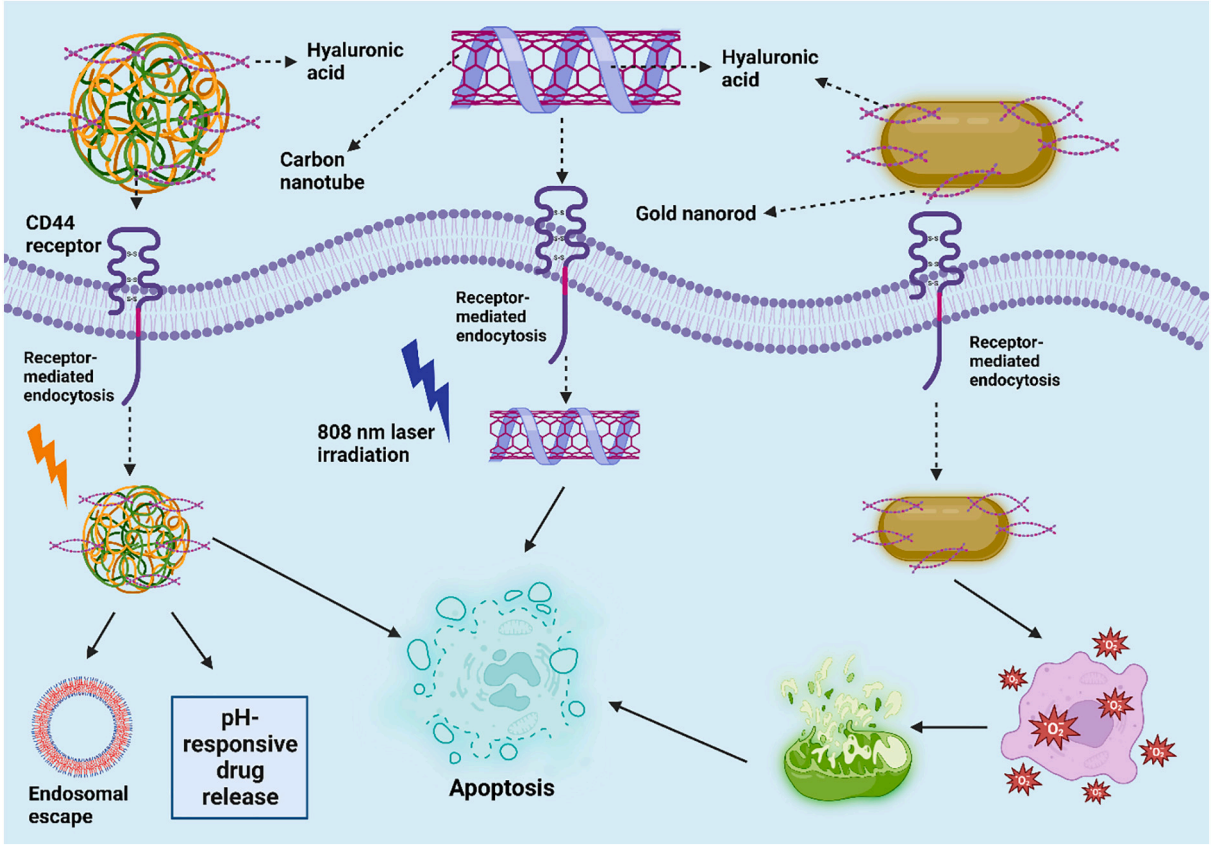

Fig. 10. Hyaluronic acid can functionalize different kinds of nanostructures, including gold nanorods, carbon nanotubes, and PLGA nanoparticles. The benefit of gold and carbon nanoparticles is their ability to convert light; therefore, there is no need for the application of photosensitizers. They can release their cargo in response to pH, and through stimulation of hyperthermia and increasing ROS levels, they induce apoptosis. Moreover, the internalization of HA-functionalized nanoparticles in tumor cells occurs through binding the CD44 receptor and mediating endocytosis. (Created by Biorender.com).

oligodeoxynucleotides consisting of CpG motifs. The laser irradiation causes the breakdown of nanoparticles, and they reassemble and are transformed into polymer complexes capable of tumor retention for the purpose of cancer immune oncology. The immunoadjuvants accelerate the immune reactions, while PTT-induced cancer ablation delays tumorigenesis and reduces the tumor antigens [346]. Although the concept of this paper is on CS nanoparticles, it should be briefly mentioned that CS-based hydrogels can cause PTT, and through the delivery of STING agonists, they transform the immunosuppressive TME into a tumoricidal microenvironment [347]. This concept can guide future studies for the application of CS nanoparticles in a way to impair immunosuppressive TME.

11.2. Hyaluronic acid nanoparticles

HA-based micellar nanostructures have been utilized for the co-delivery of IDO inhibitors, known as NLG919 and Ce6 as PS. These nanocarriers cause PDT to mediate immunogenic cell death, and through the delivery of NLG919, they regulate the tryptophan metabolic pathway in tumor ablation. Moreover, singlet oxygen generation by PDT of nanoparticles stimulates an immune response to induce the maturation of dendritic cells. Immunosuppressive TME can be reversed by NLG919 by enhancing the activity and cytotoxicity of T cells and decreasing the infiltration of Treg cells [348]. In the new strategies, the nanostructures could be applied for triple therapy using chemotherapy, immunomodulation, and phototherapy. Polydopamine nanostructures were functionalized with HA, and applied for the delivery of ursolic acid and astragaloside IV. The aqueous solubility and targeting ability of loaded drugs increased with HA-functionalized nanostructures. Moreover, they induce PTT, mediate immune system, and suppress proliferation and invasion of lung tumor cells through triple therapy [349].

However, there are still some other aspects that should be considered in this combination therapy. The macrophages present in the TME possess a high ability for tumor acceleration when they have M2 polarization [350]. Recent studies have highlighted the role of M2-polarized macrophages in accelerating cancer progression [351,352]. Therefore, CS and HA nanostructures should be used for inducing M1 polarization in macrophages. Moreover, the PD-L1/PD-1 axis has been considered as a mechanism for causing immune evasion [351,353,354], while the efficacy of CS and HA nanoparticles for phototherapy and immunotherapy in regulating PD-1 should be evaluated.

12. Chitosan- and hyaluronic acid-based nanoparticles in phototherapy and chemotherapy

12.1. Chitosan nanoparticles

Drug resistance has been a major reason for therapy failure among patients [355]. Studies have shown that there are two categories of resistance, including acquired and intrinsic drug resistance. In both types, the stimulation of alternative molecular mechanisms participates in tumorigenesis. As a result, the combination of phototherapy and chemotherapy has been suggested to overcome drug resistance. CS nanoparticle complexes with tetraphenylchlorin as PS were used for the delivery of mertansine or cabazitaxel. CS nanoparticles containing 10 % of side chains consisting of PS had high drug loading ability and stability. These nanostructures demonstrated high cytotoxicity against

breast cancer and combined chemotherapy and PDT [356]. The carboxymethyl cellulose and CS nanostructures were loaded with polypyrrole nanostructures and 5-flourouracil. These nanostructures had a shell of carboxymethyl cellulose crosslinked with disulfide, providing the redox-sensitive feature of nanocarriers. The presence of GSH, acidic pH, and NIR irradiation caused the release of cargo from these nanoparticles, and after internalization in liver cancer cells, they impaired tumorigenesis and reduced the growth of tumor [357]. For loading both PSs and chemotherapy drugs into CS nanoparticles, the mesoporous structure of CS and electrostatic interaction are beneficial [358]. The ionic gelation of tripolyphosphate was utilized to develop CS nanostructures, and 6-mercaptopurine was loaded into gold nanostructures and encapsulated by CS nanocarriers. The encapsulation efficiency of nanocarriers was suggested to be 57 %, and through a combination of PTT and chemotherapy, they significantly decreased the progression and survival of breast cancer [359].

12.2. Hyaluronic acid nanoparticles

HA-based nanostructures can combine phototherapy and chemotherapy for synergistic suppression of tumors. The oxygen-deficient molybdenum oxide hybridized HA hollow nanostructures known as MoO_3-x@HA HNSs can be prepared through a one-stop strategy, and the HA moiety provides the specific and selective targeting of tumor cells, while the MoO_3-x component provides the TME-responsive feature of nanocarriers for phototherapy. Under 808 nm laser irradiation, these nanocarriers stimulate PDT and chemotherapy, and they can be specifically absorbed by the tumor cells for phototherapy and imaging simultaneously [360].

Carbon nanotubes (CNTs) have been recognized as rolled graphene sheets, with both ends providing hollow cylindrical structures. CTNs can be single-walled or multi-walled, and their properties are various. CNTs can be functionalized with HA for the treatment of colon cancer. Single-walled CNTs are functionalized with HA and Ce6. These nanocarriers internalize in the colon tumor cells, and through the application of chemotherapy and PDT, they sufficiently suppress cancer [361]. Fe_3O_4 nanostructures can be coated with porous carbon, and their functionalization with HA can be conducted. The preparation of these nanostructures can be performed through the solvothermal method, and the reason for functionalization with HA is to improve cancer selectivity, cause tumor site PTT, and facilitate chemotherapy [362].

One of the most common drugs in cancer therapy is doxorubicin [363]. However, the dysregulation of biological and molecular pathways in the tumor cells causes doxorubicin resistance. HA nanoparticles can deliver both doxorubicin and IR780 with high internalization in breast tumor cells to cause both PTT and chemotherapy for tumor suppression [364]. Therefore, the application of CS and HA nanostructures in combination with chemotherapy and phototherapy can introduce new concepts in tumor eradication. These kinds of strategies provide significant insights into the application of nanostructures. The first insight pertains to the heightened intracellular accumulation of anticancer drugs, which can significantly escalate their cytotoxicity. Moreover, the application of nanoparticles for phototherapy can cause DNA damage and cell death, which are the main mechanisms for enhancing the chemosensitivity of tumor cells.

13. Chitosan- and hyaluronic acid-based nanoparticles in phototherapy and gene therapy

13.1. Chitosan nanoparticles

A new type of cancer treatment modality has emerged: gene therapy. Chemotherapy is a conventional cancer treatment modality, and its frequent application can cause cancer cells to become resistant. Although the introduction of the immunomodulation concept significantly improved the insight towards the treatment of cancer, and it was considered an alternative for chemotherapy or in combination, further analysis and investigations revealed that the tumor cells can also stimulate the oncogenic mechanisms causing immune evasion. Furthermore, TME interactions can cause immunosuppression and impair the immune system's function. Therefore, researchers have introduced gene therapy to target specific mechanisms and pathways in cancer treatment. Gene therapy may alter resistance to other therapies by changing a specific pathway. However, the major pathways and mechanisms in gene therapy should be targeted, such as those related to DNA damage, cell death, and the progression of tumor cells. Despite the significant hope of gene therapy in the treatment of cancer, it was further demonstrated that this kind of therapy requires more modification since the genetic tools have off-targeting and, during blood circulation, they may undergo degradation, providing insight for the introduction of nanostructures in the delivery of genetic tools [365].

CS-modified gold nanostructures have the potential to suppress cancer. Researchers have utilized polycationic CS nanospheres to functionalize PEGylated gold nanorods. In addition to their high cellular uptake and causing both PTT and gene therapy, such nanocarriers can mediate imaging, providing promises for theranostic application [366]. 5-minolevulinic acid (ALA) is one of the clinically used PSs for treating oral cancer [367]. However, ALA has difficulties in fusion with the cancer cell membrane, and the tumor cells can develop resistance to ALA [191,368]. The CS/tripolyphosphate (TPP) nanostructures have been utilized for the delivery of ALA and MTHFD1L-shRNA. They were 145 nm in size, and this co-delivery significantly enhanced the antitumor activity through apoptosis induction, ROS overgeneration, and impaired cancer progression [369]. In addition, the upregulation of GBAS can accelerate the progression of oral tumors. Loading ALA in CS nanoparticles was performed through the ionic crosslinking method, and the loading of shRNA was conducted by electrostatic interaction. These nanostructures demonstrated a spherical structure with good dispersion and stability. The combination of PDT and gene therapy significantly improved oral tumor suppression [370]. CS nanoparticles are promising candidates for gene therapy since they have a cationic charge and can form complexes with negatively charged genes. Furthermore, functionalizing DNA-complexed CS nanoparticles with HA can enhance their specificity for inducing gene therapy and phototherapy.

13.2. Hyaluronic acid nanoparticles

The process of gene therapy and phototherapy has also been performed by the application of HA nanostructures. The gold nanorod-PGED was functionalized with HA for improving blood circulation time and increasing efficacy in photoacoustic imaging. The results demonstrated that cloaking with HA improves the stability, biocompatibility, and circulation time of nanocarriers. Moreover, there are Schiff base bonds in the structure that are pH-responsive and can enhance endosomal and lysosomal escape. Moreover, this nanostructure can cause PTT and gene therapy [371]. Table 2 provides an overview of HA nanostructures for cancer phototherapy.

14. Clinical application of chitosan and hyaluronic acid

In recent years, the clinical applications of CS and HA have increased. These agents are biocompatible and biodegradable. Notably, HA has been utilized for the purposes of cancer radiotherapy and immunotherapy. The clinical application of CS for wound dressing has been confirmed. CS has also been used for weight loss in clinical studies. The AGE (advanced glycation endproducts) levels demonstrate association with the process of carcinogenesis. Therefore, regulation of AGE levels can change the process of tumorigenesis. CS has been applied for the regulation of AGE levels in prostate cancer (phases I and II) (NCT03712371), and therefore, future studies can provide more insights regarding the application of CS in the modulation of AGE levels in other kinds of tumors. To alleviate cancer pain in outpatients, oral morphine is

Table 2
The application of hyaluronic acid nanostructures in cancer phototherapy.

Nanostructure	Therapy	Highlights	Refs
HA-functionalized PLGA magnetic nanocarriers	Chemotherapy PTT	pH-sensitive drug release, accelerated cellular uptake and endosomal escape and mediating cisplatin sensitivity by PTT	[372]
Self-assembled HA nanostructures	PTT	808 nm laser irradiation causes PTT and specific targeting of tumor cells upregulating CD44 in bladder cancer therapy	[373]
HA-functionalized carbon nanotubes	PTT	NIR laser irradiation mediates PTT to induce apoptosis and reduce proliferation of tumor cells	[374]
HA-functionalized hollow Prussian blue nanostructures	PTT Chemotherapy	Delivery of 10-hydroxycamptothecin and induction of PTT Specific binding to CD44 receptor	[375]
Injectable hydrogel based on Bi_2Se_3 nanosheets and HA	PTT Chemotherapy	Response to the acidic pH and sustained delivery of doxorubicin NIR irradiation mediates PTT	[376]
MoS_2-HA-DTPA-Gd/Gef nanostructures	PTT Chemotherapy	PTT-mediated tumor ablation Apoptosis induction Downregulation of PI3K/Akt Suppressing proliferation	[377]
Magnetic HA micellar nanoparticles	PTT Chemotherapy MRI	Internalization in cancer cells through receptor-mediated endocytosis Converting light into heat Stimulation of PTT-mediated tumor ablation	[378]
HA-RGD mesoporous silica-coated gold nanorods	Chemotherapy PTT	High PTT impact High drug loading (20.16 %) pH-enzyme sensitive Targeting CD44 and integrin receptors for endocytosis in tumor cells	[379]
HA-modified mesoporous carbon-copper peroxide	PTT Chemotherapy	Stimulation of PTT and causing chemotherapy through doxorubicin delivery Stimulation of chemodynamic therapy through Cu^{2+} release and catalysing OH in the presence of H_2O_2	[380]
HA-coated lipid nanocarriers	PTT Chemotherapy	Delivery of doxorubicin in breast cancer chemotherapy Internalization in tumor cells through endocytosis Lysosomal escape	[381]
TPGS/HA dual functionalized PLGA nanostructures	PTT Chemotherapy	Active targeting of mitochondria due to functionalization with HA and TPGS to deliver paclitaxel Upregulation of caspase-3 and downregulation of survivin and MMP-9 Suppressing tumor progression in vitro and in vivo	[382]
β-Cyclodextrin-cholic acid-HA polymer coated Fe_3O_4-graphene oxide nanocarriers	PTT Chemotherapy	Loading camptothecin in nanostructures to cause chemotherapy MGO responds to the NIR and causes PTT to accelerate apoptosis	
HA-modified gold nanorods	PTT Chemotherapy	Improving the biocompatibility of nanostructures through modification with low molecular weight HA Aggregation at acidic TME Suppressing cancer growth	[383]
HA nanogels	PTT Chemotherapy	Size of 77 nm and good colloidal stability Endocytosis in tumor cells Synergistic tumor suppression	[384]
HA-functionalized gold nanorods	PDT PTT	Inducing hyperthermia and increasing singlet oxygen generation to cause PTT and PDT Enhancing cellular uptake and mediating endo/lysosomal escape	[349]
HA-functionalized liposomes	PTT Chemotherapy	Citric acid-coated magnetic nanostructures have been loaded in aqueous cores, while docetaxel was added to the hydrophobic layers of liposomes High cellular uptake PTT and chemotherapy-mediated tumor suppression	[385]
HA nanostructures	PDT Chemotherapy	Delivery of Ce6 and DHA in cancer PDT and chemotherapy Suppressing microtubule deolymerization Impairing cell cycle progression Increasing ROS generation	[386]
HA nanogels	PDT Chemotherapy	Delivery of doxorubicin in cancer chemotherapy Ce6 stimulates PDT Providing MRI	[387]
HA-modified hollow mesoporous silica nanostructures	PDT Chemotherapy	pH-responsive feature 170 nm size High drug loading for doxorubicin and ICG PDT and breast cancer suppression	[388]
HA-Ce6-Hemin@DNA-Protamine nanostructure	PDT	Co-delivery of PS and DNA Release of Ce6 in response to GSH Increasing oxygen generation to ameliorate hypoxia Apoptosis induction	[389]
HA-modified mesoporous silica nanocarriers	PDT	More efficiency that non-modified nanostructures Specific targeting of CD33 receptor and increasing PDT High levels of HA can impair PDT	[390]

Abbreviations: HA, hyaluronic acid; PTT, photothermal; PLGA, Poly(Lactic-*co*-Glycolic Acid); Gd, gadolinium; Gef, gefitinib; DTPA, diethylenetriaminepentaacetic acid; MRI, magnetic resonance imaging; TPGS, α-Tocopheryl polyethylene glycol succinate; MGO, Fe_3O_4-graphene oxide; TME, tumor microenvironment; PDT, photodynamic therapy; Ce6, chlorin e6; DHA, docosahexaenoic acid; ICG, indocyanine green; PS, photosensitizer; Ato, atovaquone.

used, and as an alternative, future studies can also utilize nasal ketamine spray with CS for the amelioration of cancer pain (NCT02591017). Notably, CS has the potential to be utilized for the prognosis of cancer patients. The pH-sensitive CS can be used to investigate the cell detachment ratio to be used as a prognostic tool in lung tumors (NCT04218188). Even after axillary dissection for breast cancer, a mixed solid of poloxamer, gelatin, and CS can be used as a safe anti-adhesive factors (NCT02967146). Moreover, glycated CS can be considered an immune stimulant to induce antigen-presenting cells and enhance the uptake of tumor antigens, triggering the patient's immune system (NCT03202446). On the other hand, HA has been extensively deployed during radiotherapy (NCT00882232, NCT01787630, NCT02165020). These studies highlight the fact that CS and HA have made their way into the clinic. However, the CS- and HA-based nanomaterial applications in cancer therapy are in their early stages. For

future clinical studies, the efficacy of CS- and HA-based nanomaterials in tumor suppression should be compared, along with investigating their route of administration.

15. Conclusion, limitations, and clinical perspectives

The introduction of phototherapy for cancer treatment can significantly improve the potential for tumor eradication. Despite the significant promises made by phototherapy, there are still limitations that can be problematic in clinical trials and also reduce the potential of preclinical investigations. The process of phototherapy can be mediated through two strategies, including the delivery of PSs or the application of nanostructures such as gold nanorods that can respond to the irradiation. A significant problem with the nanostructures is their low biocompatibility. Even for a highly efficient nanostructure for phototherapy-mediated tumor ablation, clinical application is suggested when biocompatibility and long-term safety have been highlighted and confirmed. Therefore, the synthesis of nanoparticles from green and safe sources is suggested, or further functionalization is recommended. The present review highlights the potential of CS- and HA-synthesized or functionalized nanoparticles in cancer phototherapy. The CS and HA nanostructures can deliver PSs to the cancer site, improving phototherapy. The CS improves the biocompatibility and stability of nanostructures, while HA specifically binds to the CD44 receptor, providing specific cancer targeting. Therefore, it is suggested to use both CS and HA for the functionalization of nanostructures in cancer phototherapy. A number of structures, including gold nanorods and quantum dots, possess photo-responsive activity, and therefore, their modification with CS and HA has been beneficial in improving their potential in PDT and PTT induction. Furthermore, the current studies have evaluated the potential of CS- and HA-mediated phototherapy in combination with chemotherapy, immunotherapy, and gene therapy. Despite significant efforts, there are still some limitations that should be addressed, and the suggestions for future studies are as follows:

A) Until now, multiple types of nanostructures, including organic and inorganic materials, have been modified with CS and HA for phototherapy and combination therapy. However, nanoparticles with the highest possibility of clinical application are preferred. Lipid-based nanoparticles, especially liposomes, have been commonly applied in clinical trials; the most recent one is the application of liposomal nanoparticles in the Pfizer vaccine. Therefore, more focus should be directed towards the modification and synthesis of novel kinds of liposomes based on CS and HA to facilitate phototherapy and combination therapy in cancer patients.

B) Recently, there has been an acceleration in the application of biomimetic nanostructures in cancer therapy [391–394]. The rationale for the application of biomimetic nanoparticles is their stealth properties and their ability to mimic the features and properties of normal cells. Therefore, they are not considered foreign structures. One of the potentials that have been ignored in the application of CS and HA nanoparticles in phototherapy is the lack of their functionalization and coating with membranes derived from tumor cells, macrophages, and other sources to improve their circulation, biocompatibility, and internalization in tumor cells. Therefore, this strategy should also be applied in further studies.

C) Researchers have suggested the application of CS and HA nanostructures for combination immunomodulation and phototherapy. Current studies have a simple analysis of immune-related reactions, evaluating T cell function and cytotoxicity, as well as transforming immunosuppressive TME into a tumoricidal TME. However, a significant factor inducing immune evasion has been ignored: the PD-L1/PD-1 axis. The pharmacological and genetic inhibitors of PD-L1 can be utilized for a combination of immunomodulation and phototherapy. Moreover, factors causing immunogenic cell death, such as sulfasalazine, can be applied along with PSs for delivery to induce immune reactions, and PDT can also accelerate the activation of the immune system in a synergistic way. The M2 polarized macrophages impair immune function, and therefore, the CS and HA nanoparticles could be utilized for the reeducation of macrophages and phototherapy.

D) For the combination of chemotherapy and phototherapy, efforts have shown promise in this combination cancer therapy. However, some of the major mechanisms have been ignored. The regulation of P-glycoprotein as a factor mediating chemoresistance requires investigation. Moreover, the major biological mechanisms dysregulated during cancer progression and drug resistance are apoptosis, ferroptosis, autophagy, and DNA damage repair mechanisms that a combination of phototherapy and chemotherapy should focus on targeting. Regarding the regulation of autophagy, it has both carcinogenic and tumor-suppressor functions [395,396], and therefore, its regulation requires more caution.

E) The problems for cancer gene therapy are internalization and protection against degradation, among others. The siRNA and shRNA have been delivered by CS and HA nanostructures for a combination of phototherapy and gene therapy. The capacity of these nanostructures for the encapsulation of the CRISPR/Cas9 system in more powerful gene therapy and phototherapy should be evaluated.

F) In recent years, self-assembled nanostructures have received much attention in the treatment of cancer [363,397,398]. Therefore, more studies regarding the ability of self-assembled nanoparticles from CS and HA or their functionalization with these polymers for phototherapy should be performed. Moreover, it is suggested that a comparison of phototherapy efficacy with different classes of nanostructures modified with CS and HA for cancer therapy be provided to further improve the knowledge and insights towards such nanocarriers in cancer therapy.

G) Further investigation regarding the endocytosis of CS and HA nanostructures by tumor cells are needed, and the impact of size, shape, and zeta potential on their internalization and efficacy of phototherapy should be evaluated.

The key points and directions for the future studies can be summarized as 1) emphasizing on the development of more novel stimuli-responsive CS and HA nanostructures, 2) further functionalization with membranes obtained from cancer cells, macrophages and other cells to endow the stealth property, 3) loading natural products with anticancer activity in these nanoparticles to sensitize tumor cells to phototherapy, 4) loading other kinds of genetic tools in these nanostructures including the CRISPR/Cas9 system, 5) highlighting other factors in immune system modulation and combination with phototherapy such as PD-L1/PD-1 axis, M2 polarized macrophages, cancer-associated fibroblasts and recruitment of dendritic cells, and 6) revealing the internalization of the nanoparticles and providing more insights regarding increase in the crossing over cell membrane via endocytosis to better deliver the PSs.

Based on the search on ClinicalTrials.gov, both CS and HA have been applied in clinical studies for the treatment of cancerous and non-cancerous diseases. However, the interesting point is that there is no report regarding the application of CS and HA nanoparticles for phototherapy in cancer. Therefore, it can be suggested that, owing to the efficacy and biocompatibility of HA and CS nanostructures, they can be utilized for phototherapy in cancer suppression. However, the clinical application of nanostructures requires their large-scale production, which can affect the physico-chemical properties of nanoparticles. It is quite difficult to yield nanoparticles with determined physico-chemical features in large-scale production, as they may aggregate or change in size, zeta potential, and other characteristics. These changes can

ultimately affect the biocompatibility and efficacy of patient treatment.

There are several benefits to using CS and HA nanoparticles in regulating tumor cells' response to chemotherapy, modulating the immunosuppressive tumor microenvironment, and phototherapy. PSs have a poor pharmacokinetic profile, but nanostructures improve tumor accumulation. Nanoparticles, on the other hand, should be biocompatible and biosafe, which HA and CS can provide. With the help of CS and HA nanoparticles, phototherapy can be combined with other common treatments, such as anticancer drugs and immunomodulatory drugs, to improve the effects in the area around the tumor.

Regarding the clinical application, there are still several points that require further clarification. The biological safety of CS and HA nanoparticles should be evaluated accurately, and the mechanisms responsible for their clearance and their degradation into other structures should be understood. At the clinical level, these nanoparticles should be produced at high levels, and therefore, the large-scale production of these structures may affect several of their properties, including particle size, zeta potential, drug and gene loading, and aggregation, affecting the therapeutic index. Therefore, a simple method for the large-scale production of such nanoparticles should be adopted.

CRediT authorship contribution statement

Zheng Wang: Writing – original draft, Visualization, Conceptualization. **Shuo Pang:** Writing – original draft, Visualization. **Xiaoli Liu:** Writing – original draft, Visualization. **Zi Dong:** Writing – original draft, Visualization. **Yu Tian:** Writing – original draft, Visualization. **Milad Ashrafizadeh:** Writing – original draft, Visualization. **Navid Rabiee:** Writing – review & editing, Conceptualization. **Yavuz Nuri Ertas:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Ying Mao:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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