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Chitosan-based advanced materials for docetaxel and paclitaxel delivery: Recent advances and future directions in cancer theranostics

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Abstract

Paclitaxel (PTX) and docetaxel (DTX) are key members of taxenes with high anti-tumor activity against various cancer cells. These chemotherapeutic agents suffer from a number of drawbacks and it seems that low solubility in water is the most important one. Although much effort has been made in improving the bioavailability of PTX and DTX, the low bioavailability and minimal accumulation at tumor sites are still the challenges faced in PTX and DTX therapy. As a consequence, biomaterial-synthesized NPs have attracted much attention due to unique properties. Among them, chitosan (CS) is of interest due to its great biocompatibility. CS is a positively charged polysaccharide with the capability of interaction with negatively charged biomolecules. Besides, it can be processed into the sheet, micro/nano-particles, scaffold, and is dissolvable in mildly acidic pH similar to the pH of the tumor microenvironment. Keeping in mind the different applications of CS in the preparation of nanocarriers for delivery of PTX and DTX, in the present review, we demonstrate that how CS functionalized-nanocarriers and CS modification can be beneficial in enhancing the bioavailability of PTX and DTX, targeted delivery at tumor site, image-guided delivery and co-delivery with other anti-tumor drugs or genes.

Keywords: Chitosan, Chemotherapy, Nanoparticles, Paclitaxel, Docetaxel, Delivery

Abbreviations:

CS, chitosan;

PTX, paclitaxel;

DTX, docetaxel;

FDA, Food and Drug Administration;

NPs, nanoparticles;

CRC, colorectal cancer;

PLGA, poly-(lactic-co-glycolic acid);

PLL, polycaprolactone;

EE, entrapment efficiency;

ss-pLG, star shaped poly (d,1-lactide)-b-gelatin;

PLA, poly (lactic acid);

CHN, CS hollow NPs;

NOSC, N-octyl-O-sulfate CS;

P-gp, P-glycoprotein;

PTX-M, PTX-coated CS micelles;

GNR, gold nanorods;

CPNPs, CS-coated polymer NPs;

OCBCS, N-octyl-N-(2-carboxylbenzoyl) CS;

MC, mesoporous carbon nanomatrix;

CCS, carboxymethyl CS;

DTX-C-G/P, DTX-loaded thermos-responsive CS/b-glycerophosphate hydrogel;

GSH, glutathione;

FA, folic acid;

DA, deoxycholic acid;

OCMC, o-carboxymethylated CS;

FACC, FA-cholesterol-CS;

TF, transferrin;

TFRs, TF receptors;

HA, hyaluronic acid;

EGFR, epidermal growth factor receptor;

BI, biotinylated;

NC, nanocochleates;

PSMA, prostate-specific membrane antigen;

GC, gastric cancer;

miR, microRNA;

siRNA, short interfering RNA;

LNA, locked nucleic acid;

pDNA, plasmid DNA;

DOX, doxorubicin;

Alg, alginate;

ACHC, Alg coated CS hollow nanosphere;

CNT, carbon nanotube;

BB, berbamine;

LDL, low density lipoprotein;

NSC, N-succinyl CS;

LA, lipoid acid;

IGF-1R, insulin-like growth factor receptor-1;

MUC1, mucin-1;

CS-AuNPs, CS-stabilized gold NPs;

PAI, photoacoustic imaging;

DMC, 3,6-O,O′-dimyristoyl CS;

SLNs, solid lipid NPs;

CDs, cyclodextrins.

1. Introduction

Driven from the second most abundant polysaccharide, chitin, chitosan (CS) is a low-cost biomaterial which its favorable characteristics have turned in into one of the most explored biomaterials. CS-based materials have been used in the versatile area including biological medicine [1-3]. The first mention of the inveterate extraction of chitin backed to 1799 by Hatchett, but its discovery attributed to Braconnot, twelve years later, who extracted it from fungi [4]. Chitin has been extracted mostly from crustaceans and fungi, but its extraction from insects and vertebrates are also reported [5]. The research by Rouget in 1859 resulted in the discovery of CS, the most important derivative of chitin, which is obtained by the deacetylation of chitin, removing the acetamido groups leaving the free amino groups. CS is regarded as a random co-polymer of ɣ-glucosamine and N-acetyl-ɣ-glucosamine units linked with β(1,4) - glycosidic bonds, providing the polymer with two functional groups, hydroxyl, and amine, and overall positive charge. It is dissolvable in mild acidic condition, naturally gellable with pH, can be processed into sheet, micro/nano-particles, scaffold, can be chemically modified via its functional groups, can interact with negatively charged biomolecules and cell surface because of its positive charge [6, 7], enzymatically degradable [8], generally non-cytotoxic, biocompatible and having antibacterial effects. Owing to its bio-friendly characteristics, CS-based materials have been applied in multiple fields of medicine including replacement/ supplemental to tissue (dental, bone and cartilage, wound healing, regenerative medicine) [9-11], as carrier and delivery vehicle for biomolecule cargo (targeted drug delivery, stimuli-response release) [12, 13], cell encapsulation/ cell delivery [14], and 3D bioprinting [15]. As drug carriers, CS-based materials have been developed as micro/nano-particles based on crosslinking the CS in the presence of cargo. This process can be approached via developing surfactant-stabled CS droplets in water/oil emulsion followed by crosslinking CS, coacervation of aqueous acidic CS solution in alkaline, spray-drying of CS solution, ionotropic gelation of CS in a bath of polyanion solution, and reverse micellar methods [16, 17]. Crosslinking could be performed either covalently, e.g. using glutaraldehyde [18], or physically, e.g. using polyanions [19]. The size and size distribution of NPs being controlled by the concentration and molecular weight of reactants, stirring speed, duration of process, pH and temperature of solutions [20, 21].

2. Paclitaxel and docetaxel

Finding an effective way to cure cancer, the leading cause of death on a worldwide scale, is still a challenge [22]. The rate of cancer incidence is significantly increased for the past few years, probably due to the exposure to potentially toxic agents [23-26]. However, nanotechnology techniques and methods can help to increase the efficiency of the drug delivery and releasing control in the tumor sites [27]. The conventional chemotherapeutic agents such as paclitaxel (PTX) (PubChem CID: 36314) [28] and docetaxel (DTX) (PubChem CID: 148124) [29] have been loaded on nanostructures to improve their potential in chemotherapy [30, 31]. PTX with chemical formula of C47H51O41 (figure 1) [32] is one of the most common therapeutic compounds extensively applied for treatment of a number of cancers such as lung cancer [33], ovarian cancer [34], brain tumors [35], cervical cancer [36], breast cancer [37] and colorectal cancer [38]. The discovery of PTX returns to 1963 when it was isolated from the bark of the pacific yew *Taxus brevifolia* [39]. in 1992, the Food and Drug Administration (FDA) confirmed the application of PTX for cancer therapy [40]. As a semisynthetic plant alkaloid, PTX belongs to the category of Taxanes s that restabilize the microtubule cytoskeleton against depolymerization (figure 2) [41]. As one of the key members of the cytoskeleton, microtubules play a remarkable role in a variety of biological processes including preservation of cell shape, molecular signaling pathways, contributing in the transportation of cell organelles and more import the antly, generation of the mitotic spindle for ensuring the progression of the cell cycle [42-45]. PTX impacts the cell division via promoting the polymerization of the tubulin proteins and production of non-functional microtubules [46]. DTX, another member of taxanes, is extensively used for cancer treatment as well (figure 1) [47-51]. This chemotherapeutic compound was first introduced in 1990 from the European yew tree, *Taxus baccata* [52]. Similar to PTX, DTX also stabilizes the microtubules and disrupts the microtubule dynamics which leads to mitosis prevention and cell proliferation [53]. FDA approved the application of DTX for the treatment of cancer in 1996 [54]. Despite its potential of anti-tumor activities, DTX is a lipophilic agent with low solubility in water which restricts its efficiency [47, 55, 56]. The current formulation of the DTX contains ethanol has an adverse impact on its bioavailability [47, 55, 56]. In this context, nano-techniques can be a promising approach to improve the bioavailability of DTX with no side effects on healthy cells or tissues. In spite of the efficient benefits of phytoconstituents, they show some of the challenges such as limited knowledge of pharmacokinetic profiles and the requirement of high doses that are usually associated with toxicity [57, 58]. Over recent years, the use of new drug delivery systems such as encapsulation of herbal ingredients with nanoparticles would likely affect the stability and

pharmacokinetics of the carried compounds [59]. In the case of PTX and DTX, there are some challenges such as low water solubility (0.3 μg/mL), presystemic metabolism, high protein binding, high affinity to P-glycoprotein (P-gp), and some adverse effects which lead to their low bioavailability [60, 61]. In this study, a broad range of biocompatible, biodegradable, and nontoxic polymeric nanoparticles, micelles, and nanotubes were introduced to improve the pharmacokinetic profiles of DTX and PTX to increase the solubility, bioavailability, and intracellular accumulation to tumors cells.

3. Chitosan nanocarriers

3.1. Chitosan nanoparticles for PTX delivery

Glioblastoma is a malignant brain tumor with high prevalence and surgery is considered as the best option in glioblastoma therapy [62]. However, patients with glioblastoma have a low survival time (< 2 years). The possibility of recurrence is at the highest rate in glioblastoma and anti-tumor drugs should effectively eliminate cancer cells. In order to provide efficient anti-glioblastoma therapy, targeted delivery of chemotherapeutic agents such as PTX is of interest. PTX-loaded CS NPs have demonstrated great potential in the treatment of glioblastoma by providing a prolonged release of the drug, improving drug bioavailability, enhancing hemocompatibility and more importantly, exerting more cytotoxic effect compared to the PTX alone [63]. Higher cellular uptakes/efficacy of the nanoformulation of PTX elucidated that 1,3β-Glucan shell of the core NPs actively targeted various overexpressed receptors on both glioma stem cell lines (C6) and glioma cancer cell line (LN-18). Due to the dose-dependent toxicities of PTX [64], nanocarriers can provide a platform for enhancing the anti-tumor activity of PTX and simultaneously, reducing its toxicity by loading a low amount of drug on NPs [65]. Making an increase in the EE% and loading efficiency of PTX in NPs are obtained via developing novel strategies in the synthesis of NPs. It appears that the emulsification-crosslinking method in a W/O emulsion system can be considered as a smart strategy in preparation of CS NPs [66], as the resulting NPs demonstrated excellent loading efficiency (8.55%) and EE% (94.01%) with high biocompatibility.

Jiang et al. have examined the efficacy of CS hollow NPs (CHN) for the delivery of PTX in lung cancer [67]. The limited space of a nanometer-scale hollow structure was used in

order to enhance the water solubility, preventing drug crystallinity, and diminishing the particle size. Notably, the resulting CHN had a diameter size of about 200 nm that was lower compared to the previously reported particle sizes. The high biodegradability of CHN led to the release of PTX after their uptake by A549 cells, resulting in apoptotic cell death and consequently, reduced viability and malignancy of cancer cells. While PTX has been applied for the treatment of a variety of cancer, its dose-dependent toxicity is still a challenge which could be addressed using nanocarriers as they can enhance the targeted delivery of PTX to the tumor site by delivering a low amount of the PTX hence reduces the toxicity side effects in healthy neighbor cells. To date, the prepared CS NPs for delivery of PTX have demonstrated excellent properties in terms of biocompatibility, targeted delivery, biodegradability at the tumor site and cellular uptake. Besides, PTX-loaded CS NPs have dramatically diminished the viability, proliferation, and migration of cancer cells by induction of apoptotic cell death [68-79].

3.2. Chitosan nanoparticles for DTX delivery

Breast cancer with high malignancy and recurrence, which are two important features of this condition, is one of the most life-threatening threatening illnesses in women [80-83]. CS NPs can improve the chemotherapeutic efficiency of DTX due to its excellent drug entrapment (65-76%) and sustained-release behavior of CS which significantly inhibits the viability and proliferation of MDA-MB-231 breast cancer cells [84]. Moreover, breast cancer cells treated with encapsulated DTX in CS NPs showed a higher ratio of Bax (an apoptotic factor) over the BCL-2 (a down regulator of anti-apoptotic) compared to the cells treated with non-capsulated DTX [85].

Colorectal cancer (CRC), is another lead life-threatening illness in Europe and Asia [86, 87]Therefore, improving the efficacy of chemotherapy is of importance in improving the survival time of patients with CRC. Badran et al have investigated the anti-tumor activity of DTX CS-coated poly (lactic-co-glycolic acid) (PLGA)/polycaprolactone (PCL) NPs [88]. These nanocarriers have demonstrated significant drug entrapment efficiency (EE%) (PCL NPs: 67.1% and PLGA NPs: 76.2%), increasing the cytotoxicity potential of DTX, as well as the decreasingthe cell growth up to 50%. Moreover, PLGA/PCL NPs can increase the bioavailability of the DTX by about 4 times higher. One of the most challenging problems in the delivery of chemotherapeutic agents in the low biocompatibility of

synthesized NPs which was addressed by Balavigneswaran et al. through conjugation of star-shaped poly (d, 1-lactide)-b-gelatin (ss-pLG) into biodegradable poly (lactic acid) (PLA). On the other hand, the ss-pLG scaffold provides the burst release of DTX [89]. CS NPs demonstrate high EE% and prolonged-release behavior, and simultaneously, improve the intestinal permeation of DTX [90].

4. Chitosan micelles for PTX delivery

It has been shown that micelles are potential candidates in enhancing the bioavailability of drugs with low aqueous solubility [91, 92]. As core-shell NPs spontaneously generated in water from amphiphilic molecules, micellar NPs are able to protect drugs from degradation [93, 94]. These excellent properties have led to the extensive application of micelles for delivery of PTX, an anti-tumor compound with low water solubility. CS micellar NPs are capable of releasing PTX in prolonged-release behavior [95]. PTX-loaded CS micelles remarkably enhance the anti-cancer effect of PTX without influencing its cytotoxicity and simultaneously, improve the distribution of PTX in tissues including liver, spleen, lung, and kidney [96]. However, it has been reported that the levels of CS micellar NPs are higher in the liver and spleen compared to the heart and kidney [97].

The resistance of cancer cells to chemotherapy is still a challenge. Recently, Jin et al have investigated the potential of PTX-loaded N-octyl-O-sulfate CS (NOSC) micelles for decreasing the viability and proliferation of resistant tumor cells [98]. It was found that PTX-loaded NOSC micelles: 1) increase the accumulation of PTX at the tumor site, and 2) enhance the residence time of PTX. High accumulation of PTX at the tumor site is a result of using NOSC, so that NOSC exerts an inhibitory impact on the P-glycoprotein (P-gp) by induction of P-gp ATPase to suppress the binding of PTX with P-gp, leading to the entering of PTX into cancer cells and simultaneously, decrease the fluidity of cell membrane. P-gp is involved in the inhibition of entering of chemotherapeutic agents into cells [99] and P-gp inhibition by NOSC facilitates the entering of PTX into tumor cells. Moreover, an increase in the incidence time of PTX by NOSC micellar NPs is due to the efficacy of these nanocarriers in intracellular delivery, drug loading, tumor targetability and increasing the stability of the drug. These excellent properties have led to the enhanced cytotoxicity of PTX-loaded NOSC micellar NPs against resistant hepatocellular carcinoma cells. In order to promote the targetability of NOSC NPs, a polyethylene glycol (mPEG) group can be added. Besides, the mPEG group

leads to a decrease in the removal of CS micellar NPs by the reticuloendothelial system (RES) [100]. These studies highlight this fact that PTX has a low bioavailability which restricts its anti-tumor activity and enhancing the dose of PTX is associated with increased toxicity of PTX. Moreover, using a high amount of a chemotherapeutic agent such as PTX elevates the chance of resistance of cancer cells that consequently, decreases the efficacy of chemotherapy. It seems that CS micellar NPs are potential candidates to improve the bioavailability and anti-tumor potential of PTX. Besides, CS micelles are capable of diminishing the toxicity of PTX by loading a low amount of PTX on NPs. In contrast to CS NPs, CS micelles have been designed based on targeting tumor receptors such as P-gp or integrin receptors to promote the entering of PTX into cancer cells [101-110]. However, more studies are required to develop CS micelles targeting surface receptors and this capability should be considered for CS NPs.

5. Chitosan microstructures for PTX and DTX delivery

Various therapeutic agents with different sizes can be loaded on microspheres to improve their bioavailability [111-113]. A variety of strategies are applied in order to administer therapeutic-loaded microspheres. However, microspheres are mainly delivered through subcutaneous and intramuscular routes [114-116]. Microspheres are particles with the size at the range of 5-15 □m and the development of microsphere induced a dramatic evolution in enhancing the bioavailability of anti-tumor drugs by providing a prolonged-release behavior [117]. Moreover, decreasing adverse impacts and providing targeted delivery are among the other beneficial effects of using microspheres for drug delivery [118]. Wang and colleagues have investigated the potential of DTX-loaded CS microspheres for the delivery of the drug to the lungs [119]. A water-in-oil emulsification method was used to synthesize glutaraldehyde crosslinked microspheres. The resulting microspheres demonstrated excellent properties such as spherical shape, smooth surface, high EE% (88.1%) and drug loading (18.7%). These carriers had excellent biocompatibility with the capability of releasing a drug in a sustained-release behavior. In the case of PTX, the efficacy of CS-modified PLGA NPs with the capability of transient formation of microaggregates has been evaluated for lung delivery [120]. The modification of NPs by CS led to remarkable alterations in the properties of PLGA NPs so that after contacting plasma, the particle size of NPs enhanced from 200-300 nm to 2670 nm. However, this increase was reversed after 5 min and the mean particle size of CS-modified PLGA NPs returned to 350.7nm.

Besides, CS modification provided a positive zeta potential, high cellular uptake and enhanced cytotoxicity against lung cancer cells (A549 cells). The in vivo experiment manifested a significant change in the CS-modified PLGA NPs so that upon the administration of NPs through the tail vein, an increase in trapping in lung capillaries and uptake by endothelial cells occurred due to the formation of microaggregates in the bloodstream. To date, two studies have examined the potential of CS-modified microspheres for delivery of PTX and DTX, demonstrating that there is still a long way for further investigations [119]. The incredible role of CS modification is undeniable, so that conjugation of CS is associated with high cellular uptake and cytotoxicity against cancer cells.

6. Chitosan hydrogels for PTX delivery

A three-dimensional network generated from hydrophilic agents is defined as hydrogels [121, 122]. The aim of the production of hydrogels is to form insoluble polymer matrices. These water-swollen networks are capable of loading a high concentration of water without being dissolved in water. Hydrogels have a number of benefits such as adjustable stiffness and excellent biocompatibility, leading to their tremendous applications in biomedicine [123-125]. Notably, CS-modified hydrogels have demonstrated great potential in releasing drugs in a prolonged-release behavior, resulting in their usefulness for the delivery of chemotherapeutic agents such as PTX in cancer therapy [126, 127]. An essential advantage of hydrogels is providing a nanocomposite to load other therapeutics. This strategy diminishes the need for the anti-tumor drug, and by reducing the concentration of the medicine, the chance of resistance decreases, while the inhibitory effect on the growth and viability of cancer cells is high. In line with this strategy, Zhang and colleagues designed nanocomposite hydrogel for loading gold nanorods (GNR) and PTX-loaded CS micelles (PTX-M) in photothermal-chemotherapy [128]. The synthesized thermo-sensitive hydrogel matrix effectively delivered GNR and PTX-M at the tumor site. Exposing to laser ablation produced GNR-mediated photothermal damage. However, some tumor cells may rescue from photothermal therapy. In order to maximize the anti-tumor treatment, the PTX-M was loaded on nanocomposite hydrogel. These nanocarriers released PTX in a sustained-release behavior, resulting in the elimination of cancer cells evaded from photothermal ablation.

7. Stimuli-responsive chitosan nanoparticles for PTX and DTX delivery

7.1. pH-responsive chitosan nanoparticles

Stimuli-responsive NPs have opened a new perspective in cancer therapy. This is due to the alteration of pH in the tumor microenvironment. CS-functionalized NPs coated with polymers are able to release PTX in a prolonged-release behavior (figure 3) [129]. These CS-coated polymer NPs (CPNPs) have a PLGA core, to load and retain drugs, covered by a polydopamine. In order to functionalize NPs, CS modification was performed through the polydopamine layer to functionalize NPs. CPNPs released PTX in a sustained release behavior so that 80% of PTX was released during 48 h. Because of the mild acidic nature of CS (PKa of 6.5), the CPNPs are in non-ionized form at mild acidic pHs (of around 6.5) hence relatively soluble and diffusive through the lipidic membrane of cells. Due to this fact, CPNPs demonstrated higher delivery of drugs at a mildly acidic pH of the tumor microenvironment (pH=6) compared to the slightly basic extracellular environment of normal tissues (pH=7.4) [130]. There is a difference in the pH of the tumor microenvironment (pH=6.3-6.8) and endosomes or lysosomes (pH=5) [131]. It seems that pH-responsive NPs start releasing the drug after entering to the tumor microenvironment. So, it is necessary to release the drug in a sustained release behavior to ensure the delivery of the drug into cancer cells. N-octyl-N-(2-carboxylbenzoyl) CS (OCBCS) can produce micellar NPs with the capability of encapsulating PTX and delivering at a prolonged release behavior [132]. The pH-responsive NPs play a more important role during oral administration of anti-tumor drugs. These NPs should be able to effectively release a drug in the intestine while protecting the drug from degradation in the stomach. Carboxymethyl CS/phospholipid bilayer-capped mesoporous carbon NPs are useful nanocarriers in the delivery of anti-tumor drugs such as DTX [133]. These nanocarriers are composed of three individual parts: A) a mesoporous carbon nano matrix [131] for drug loading; B) a positively charged phospholipid (PL) layer providing the sustained release of a drug and C) a negatively charged carboxymethyl CS (CCS) provides pH-responsive drug release. pH=1.2 and pH=6.8 were selected to mimic the pH of gastric and intestinal fluids, respectively. Up to 80% of DTX release occurred in pH=6.8, demonstrating the potential of these nanocarriers for oral delivery. The slight decline in the pH of the tumor extracellular environment (6.5) and its similarity to the pKa of CS made CS-based materials suitable for

drug carriers in chemotherapy for targeted delivery into cancerous tissues. The carrier can be engineered to release the drug when exposed to the pH gradient of the tumor not normal tissue.

7.2. Thermo-responsive chitosan nanoparticles

Thermo-responsive nanocarriers are another great option for the delivery of PTX and DTX. One of the difficulties in PTX therapy is the formation of PTX crystals associated with decreased anti-tumor potential of PTX. The application of PLGA microparticles and CS thermo-responsive gels is beneficial in the inhibition of PTX crystallization [134]. It has been demonstrated that in order to provide high anti-tumor activity, the lowest concentration of PTX should be used [135]. A combination of CS gel and PLGA microparticles allows the application of a low amount of PTX with high anti-tumor activity against mammary adenocarcinoma cells. More importantly, the in vivo experiment on tumor-bearing mice revealed that CS NPs have anti-tumor activity and loading PTX significantly diminishes the tumor growth and volume. In contrast, Li and colleagues prepared DTX-loaded thermo-responsive CS/b-glycerophosphate hydrogel (DTX-C-/P) [136]. The results of this study demonstrated that C-G/P has no anti-tumor effect (H22 tumor bearing-mice). This discrepancy is needed to be considered in subsequent studies. The second issue is the biodistribution of DTX-C-G/P so that these hydrogels are distributed in the heart, spleen, liver, lung, and kidney. Hence, a low amount of chemotherapeutic agent should be used to minimize adverse impacts. Besides, the resulting nanocarriers need to have great biocompatibility. It appears that the absorption of thermal-sensitive nanocarriers occurs by electrostatic-mediated endocytosis [137]. The high absorption and sustained-release behavior result in the great anti-tumor activity of thermo-responsive nanocarriers [138].

7.3. Redox-responsive chitosan nanoparticles

Another intracellular signaling is oxidative stress and there have been attempts to design nanocarriers with the capability of releasing a drug in response to oxidation [139]. Among these nanocarriers, micellar NPs are of interest due to the redox-triggered release of drugs [140, 141]. Notably, this redox-mediated release depends on disulfide bonds found in the matrix crosslink or in auxiliary chains. A high oxidative environment leads to the stabilization of bonds, while the degradation of these bonds occurs in an environment containing antioxidant agents such as glutathione (GSH). The redox-responsive CS micelles have high properties in terms of intracellular release of PTX and high cytotoxicity against tumor

cells [142]. An important point is an increase in average particle size after exposing to GSH so that it seems that in the highly reducing environment, the micellar structure is hardly found [143]. However, the tumor microenvironment has a partial impact on the size distribution of CS micelles. A high concentration of GSH stimulates the release of PTX from redox-responsive micelles. These nanocarriers demonstrated anti-tumor activity in a time-dependent manner due to accumulation in the cytoplasm.

8. Chitosan nanocarriers for targeted delivery

8.1. Chitosan nanoparticles for targeted PTX delivery

The enhanced incidence rate of cancer has forced to develop novel methods in cancer therapy. Targeted drug delivery is a smart strategy in combating cancer cells. The identification of receptors on the surface of cancer cells is of importance in the following targeting by nanocarriers. Folate receptors undergo upregulation in tumor cells, while their expression is low in normal cells [144]. There have been efforts to promote the potential of nanocarriers by targeting folate receptors [145]. It appears that CS-folic acid (FA)-deoxycholic acid (DA) micelles are able to mediate the receptor-targeted delivery of PTX (figure 4) [146]. Exposing breast cancer cells (MCF-7) into CS-FA-DA micelles led to a significant decrease in their viability due to increased internalization of micelles through folate receptor-mediated endocytosis. One of the challenges in preparation of CS micelles is the high molecular weight of CS that leads to its poor solubility and consequently, diminishes the biomedical application. The application of water-soluble CS resolves this pitfall due to its low molecular weight [107]. For instance, o-carboxymethylated CS (OCMC) is an amphiphilic derivative of CS with the capability to be used in the synthesis of micelles [147]. The same strategy has been made by Cheng and colleagues [148]. They prepared FA-cholesterol-CS (FACC) micelles for delivery of PTX in the treatment of cervix cancer. The importance of this study was the pH-triggered release of PTX at the mildly acidic pH of the tumor microenvironment. Taking everything into account, using CS nanocarriers with the capability of targeting folate receptors is beneficial in terms of improving the delivery of PTX into cancer cells. This delivery is induced by folate receptor-mediated endocytosis [149-151]. Another important surface receptor is transferrin (TF). TF receptors (TFRs) stimulate iron absorption via endocytosis and exocytosis [152]. The upregulation of TFRs manifests the high cellular growth [153], and a variety of nanocarriers have been designed to target these surface receptors. TF/PEG/OCMC/fatty acid/PTX (TPOCFP) micelles have been developed for targeting TFRs [154]. TPOCFP micelles

remarkably enter the nucleus by binding into surface receptors. The high cellular uptake and prolonged-release behavior lead to the high cytotoxicity of TF-functionalized NPs against cancer cells [155]. Attachment of glycol chain into CS produces NPs with high cellular uptake through clathrin-mediated endocytosis, caveola and macropinocytosis that is in favor of delivery of chemotherapeutic agents like PTX and enhancing anti-tumor activity [156]. In order to improve the delivery efficiency of glycol-CS NPs and generate composite NPs, anionic heparin can be used to interact with positively charged glycol CS, leading to the high anti-tumor activity and targeted drug delivery [157]. Another major importance of heparin modification is cytotoxicity concern. Polycation NPs suffer from a number of drawbacks and it seems that low biocompatibility is the most important one. Neutralizing this positive charge can resolve this difficulty and heparin modification (negative charge) is the best option. Although other negatively charged agents can be applied in neutralizing the positive charge, the interest into heparin emanates from this fact that heparin modification provides the targeted delivery of NPs by tumor cells overexpressed heparanase [158].

Hyaluronic acid (HA) receptors, known as CD44, are exclusively overexpressed on cancer cells [159]. As one of the most malignant cancer cells, the incubation of breast cancer cells with CS-hyaluronan-coated solid lipid NPs led to decreased viability and proliferation of cancer cells. This high anti-tumor activity is a consequence of the great cellular uptake of these nanocarriers by HA receptors. Overall, targeted delivery systems are able to improve the anti-tumor efficacy of PTX exponentially [160].

8.2. Chitosan nanoparticles for targeted DTX delivery

The same strategy is used for DTX delivery. Targeted delivery is of importance in lung cancer therapy due to its high malignancy [161]. Epidermal growth factor receptor (EGFR) is responsible for the invasion and metastasis of lung cancer cells. Besides, the upregulation of EGFR occurs in lung cancer and further targeting is of interest in terms of diminishing the viability and proliferation of cancer cells [162, 163]. The DTX-loaded CS NPs targeting EGFR are capable of significantly reducing the malignancy of lung cancer cells by induction of G2/M phase arrest and stimulation of apoptosis and necrosis via diminishing the mitochondrial membrane potential [164]. This great anti-tumor activity is a consequence of high cellular uptake of NPs through EGFR.

In a study, Poudel and colleagues designed novel biotinylated CS-decorated DTX-loaded nanocochleates (BI-CHI-DTX-NCs) for breast cancer therapy [165]. The NCs are a kind of liposomes that phospholipid is affected by divalent cation, leading to the formation of a roll of stacked sheets [166]. NCs have great properties in terms of high biocompatibility, great potential in drug delivery and affordable synthesis [167, 168]. On the other hand, BI receptors undergo upregulation in various cancers such as breast cancer [169]. So, BI-CHI-DTX-NCs should have a combination of the mentioned properties. Surprisingly, NCs demonstrated high efficiency in encapsulating DTX by making hydrogen-binding. Besides, NCs exhibited a pH-dependent release of DTX at mildly acidic pH (pH=5.3) similar to the acidic pH of the tumor microenvironment. BI-CHI-DTX-NCs had high anti-tumor activity against MCF-7 breast cancer cells. Notably, in addition to the potential role of BI in enhancing the cellular uptake of NPs, NC has a remarkable effect itself by providing direct interaction with the cell membrane of cancer cells or phagocytosis [170].

Prostate-specific membrane antigen (PSMA) is a potential target in prostate cancer therapy due to its overexpression and relation with invasion and malignancy [171-174]. Glycol-CS micelles targeted PSMA have high anti-tumor activity due to their great cellular uptake through receptor-mediated endocytosis [175]. Another option in cancer therapy is targeting angiogenesis. It has been demonstrated that angiogenesis is associated with the high proliferation of tumor cells. Drug delivery systems have been designed for the inhibition of angiogenesis [176]. Studies have shown that GX1 can be beneficial in the inhibition of human gastric cancer (GC) angiogenesis [177, 178]. This inhibitory impact is exerted by specific binding of GX1 to endothelial cells and stimulation of apoptosis [179, 180]. It seems that DTX-loaded CS NPs containing GX1 can be applicable for favorable treatment of GC by both exerting anti-tumor activity and suppressing angiogenesis [181].

One of the challenges faced in the delivery of DTX is the low stability of synthesized CS nanocarriers. In order to overcome this problem, binding a glycol chain into CS is associated with the great stability of CS NPs [182]. Overall, it appears that more attempts have been made in targeted delivery of DTX compared to the PTX with more kinds of receptors. Efforts have been directed into synthesizing CS NPs with great biocompatibility and high cellular uptake [183, 184]. However, the high average particle size of CS NPs is a major problem, resulting in their low efficacy and also high clearance by phagocytosis system.

9. Chitosan as co-delivery system

Using a combination of several of anti-tumor drugs is currently common in cancer therapy. On one hand, this strategy diminishes the chance of resistance of tumor cells. On the other hand, it enhances the anti-tumor potential. In addition to the co-delivery of anti-tumor drugs, gene therapy can be considered as a potential candidate. In respect to the gene mutations in cancer progression, co-delivery of an anti-tumor drug and gene seems beneficial [185, 186]. DNA, RNA, short interfering RNA (siRNA), microRNA (miR), locked nucleic acid (LNA) and plasmid DNA (pDNA) can be loaded on NPs [187]. One of the commonly used combinations in cancer therapy is the application of PTX and doxorubicin (DOX). It is noteworthy to mention that alginate (Alg) coated CS hollow nanosphere (ACHN) is able to remarkably improve the anti-tumor potential of PTX and DOX [188]. ACHN has great biocompatibility so that ACHN a the concentration of 5 □g/ml to 500 □g/ml is well-tolerated and just diminishes the viability of cells by 20%. Besides, the co-delivery of PTX and DOX by ACHN has higher anti-tumor activity compared to the PTX-DOX. This great anti-tumor activity is a result of high cellular uptake by cancer cells and synergistic impact of PTX and DOX. Carbon nanotubes (CNTs) have opened a novel perspective in medicine because of their characteristic features. Currently, they are extensively applied in gene delivery, cellular imaging, biosensor, cancer therapy and so on [189, 190]. There have been efforts to use CS functionalized-CNTs for co-delivery of PTX and DOX in order to promote their anti-tumor activity [191]. Notably, both PTX and DOX drugs can be loaded on CNTs. The attachment of DOX is performed by binding to the aromatic surface of the CNTs via **it-it** stacking, while PTX binds to the benzene ring via **it-it** stacking. One of the challenges in the functionalization of CNTs is the adverse effects on the stability and biocompatibility [192]. CS functionalization offers no harmful effect on the stability and functionalization of CNTs by providing noncovalent functionalization. At the tumor microenvironment, the release of DOX and PTX occurs due to the protonation of CS that in turn, weakens the attachment of DOX and PTX. It appears that CS functionalized-CNTs have the efficiency of delivery of anti-tumor drugs (figure 5). Plant-derived chemicals are extensively used in chemotherapy due to their great physiological activities [27, 193, 194]. Berbamin (BB) is a naturally occurring nutraceutical compound with high anti-tumor activity. DTX- and BB-loaded CS NPs have demonstrated great capability in the stimulation of apoptotic cell death and down-regulation of survivin. This is due to the higher bioavailability of DTX and BB [195]. The studies suggest that CS functionalization not only improves the

biocompatibility of NPs but also may provide a pH-triggered release. So, CS can be considered as a potential candidate in the delivery of PTX and DTX [196-198]. Gene delivery can be applied for enhancing the cellular uptake of PTX-loaded CS NPs. Such a strategy can be achieved by co-delivery of MDR1 siRNA and PTX using low density lipoprotein (LDL)-coupled N-succinyl CS (NSC) lipoid acid (PTX-siRNA/LDL-NSC-LA) micelles [199]. Breast cancer cells have a high expression of LDL-receptor and have great sensitivity to LDL micelles. The carboxyl group of NSC-LA provides a reaction with LDL, leading to its attachment to micelles. Although the role of LDL is great, MDR1 siRNAs also plays a remarkable role in cellular uptake of PTX. As it was mentioned, P-gp inhibits the entering of chemotherapeutic agents into cancer cells. MDR1 siRNA results in down-regulation in the expression of mdr1 and P-gp, improving the cellular uptake of PTX. Another privilege of CS is providing a platform for conjugation of aptamers. As newly introduced synthetic DNA or RNA molecules, aptamers have demonstrated excellent specificity towards target [200]. Aptamer-conjugated CS NPs enhance the co-delivery of DTX and insulin-like growth factor receptor 1 (IGF-1R) siRNA into breast cancer cells [201]. Anti-mucin 1 (MUC1) was applied as an aptamer due to the upregulation of MUC1 on the breast epithelial cells [202]. CS is not only associated with the biocompatibility of these nanocarriers but also provides a platform for conjugation of the aptamer. By improving the targeted delivery of DTX and IGF-1R siRNA, high cellular uptake of DTX significantly diminishes the viability and proliferation of breast cancer cells and a decrease in cell growth and survival is observed due to inhibition of IGF-1R. Taking everything into account, it seems that CS modification of NPs has two major advantages: A) improving the biocompatibility of NPs, and B) providing a platform for attachment of drugs and genes [203-205].

10. Imaging and theranostics applications of chitosan here

NPs have attracted much attention in the field of imaging [186]. Simultaneous imaging and drug delivery are of interest in cancer therapy and NPs provide minimally invasive imaging [206]. In line with this strategy, Bano and colleagues synthesized PTX-loaded magnetic nanocomposites with folate modified CS/carboxymethyl surface [207]. CS served as a platform for loading PTX and folate improved the cellular uptake of NPs through receptor-mediated absorption. Besides, CS provided the stability and protection of drug against degradation or oxidation. It seems that the external magnetic field enhances the anti-tumor activity of these nanocarriers. It is likely that this improvement was caused by controlling the directional

movement of magnetic carriers via the external field as also reported by Xue et al. [208]. Nevertheless, this finding demonstrates that these NPs have a magnetically guided drug delivery function. Notably, it was found that the high labeling potential of these nanocarriers is a consequence of high cellular uptake due to using CS and folate. CS-stabilized gold NPs (CS-AuNPs) are able to be applied for photoacoustic imaging (PAI) of cancer cells [209]. CS-AuNPs served as contrast agents and PAI effectively provided image-guided cancer therapy (figure 6). This strategy has demonstrated satisfactory results while using PTX for chemotherapy.

11. Chitosan nanoparticles for oral delivery of PTX and DTX

Protection against degradation and improving absorption are two major goals in the oral administration of chemotherapeutic agents such as PTX and DTX by CS nanocarriers (figure 7) [210]. CS-functionalized micelles promote the cellular uptake of PTX through clathrin- and caveolae-mediated endocytosis [173]. Application of amphiphilic CS derivatives such as N- deoxycholic acid-N, O-Hydroxyethyl CS or carboxymethyl CS is beneficial in the development of NPs for delivery of PTX due to their low molecular weight, resulting in NPs with great properties such as high biocompatibility and excellent potential for drug delivery [211, 212]. Designing N-octyl-N'-phthalyl-O-phosphoryl CS micelles improve the accumulation of PTX in Caco-2 cells through caveolin-mediated endocytosis [213]. However, one of the most challenges of CS NPs is their low cellular uptake in animal models. It seems that 3,b-O, O'-dimyristoyl CS (DMC) is not beneficial in improving the absorption of PTX upon oral administration. This drawback is due to the mucoadhesive feature of CS so that DMC NPs make a tough attachment with the mucus layer secreted by HT29-MTX cells, leading to the inhibition of penetration of PTX-loaded CS NPs into cell monolayer [214]. These formulations significantly increase the bioavailability of PTX and subsequently, result in higher anti-tumor activity compared to the PTX alone [215-221]. The same story occurs in DTX delivery. Thiolated CS-functionalized NPs are potential candidates in delivery of DTX [222, 223]. These nanocarriers are associated with enhanced cellular uptake of DTX by opening tight junctions. It is noteworthy to mention that solid lipid NPs (SLNs) enhance the penetration of drugs into the intestinal epithelial layer [224, 225]. With respect to the capability of CS in opening the tight junctions between cells [226, 227], CS-functionalized SLNs are able to incredibly promote the permeabilization of DTX [228]. Notably, in vivo experiments confirm the higher anti-tumor activity of DTX-loaded CS NPs compared to the DTX alone, while these nanocarriers have minimal adverse impacts

[229]. Conjugation of cyclodextrins (CDs) into CS is an efficient strategy in enhancing the delivery of DTX. This is due to the potential role of CDs in improving the solubility of DTX and protection against degradation, whereas CS opens tight junctions to elevate cellular uptake of DTX [230].

12. Conclusion and remarks

At the present review, we described the various CS functionalized-NPs for the delivery of PTX and DTX (table 1,2). NPs can be considered as potential candidates in the delivery of PTX and DTX and have demonstrated great potentials such as high biocompatibility, drug loading, EE and anti-tumor activity. Although the particle size distribution of synthesized CS NPs is uniform, the average particle size should be considered in the following studies. Self-assembled CS micelles can protect PTX and DTX against degradation and release these potent chemotherapeutic agents in a prolonged-release behavior. Similarly, microstructures provide the sustained release of PTX and DTX. It appears that the development of stimuli-responsive NPs provided dramatic progress in cancer therapy and until now, pH-, redox- and thermos-responsive CS NPs have been designed for the delivery of PTX and DTX. An important strategy in enhancing the anti-tumor potential of PTX and DTX is using targeted delivery systems. Folate, TF, and CD44 receptors have been targeted by CS NPs and findings have disclosed satisfactory results in terms of elevating cellular uptake of PTX and DTX. Unfortunately, we have witnessed a significant decrease in the anti-tumor activity of PTX and DTX due to the resistance of cancer cells. As a consequence, CS NPs have been developed in order to simultaneously deliver PTX and DTX with other anti-tumor drugs or genes. One of the most interesting strategies was the application of the MDR1 gene that down-regulated P-gp, leading to the high cellular uptake of PTX and DTX by cancer cells. Minimally invasive image-guided delivery and image-guided cancer therapy using PAI are other applications of CS NPs. Besides, CS NPs are of importance in oral delivery of PTX and DTX by protection against degradation at the stomach, sustained-release in intestinal fluid and improving cellular uptake by opening tight junctions. However, more studies are needed to evaluate the efficiency of CS NPs for the delivery of PTX and DTX.

Conflict of interest:

The authors declare no conflict of interest.

Figure captions

Figure 1: The chemical structure of PTX and DOX.

Figure 2: The mechanism of action of PTX and DTX. During the physiological condition, there is a balance in entering and eliminating of tubulin proteins from microtubules. Upon administration of PTX or DTX, this balance is interrupted, and microtubules obtain a stabilized form, resulting in inhibition of mitosis and apoptotic cell death.

Figure 3: Stimuli-responsive CS NPs for delivery of PTX and DTX, and their mechanism of action.

Figure 4: Various CS-functionalized NPs applied in the delivery of PTX and DTX.

Figure 5: CNTs as potential candidates in the delivery of PTX and DTX.

Figure 6: The application of CS-functionalized NPs in cancer imaging and theranostics.

Figure 7: Protection against degradation in the stomach and enhancing the absorption of PTX and DTX through the intestine by CS NP

Table 1: Chitosan-based delivery systems for PTX.

Components	**Structures**	**Loading capacity**	**Release properties**	**Targeting agents**	**Co-delivered agents**	**Cancer cell lines/*in vivo***	**Major outcomes**	**Refs**
Deoxycholic acid-O-carboxymethylated CS–FA	Micelle	33.61%	100% of the nonencapsulated drug was released after 24 hours	FA		MCF-7 cells,	Cytotoxicity of the micelles contain folate was considerably more than the micelles without folate or the injection of PTX (commercially available)	[147]
N Octyl O sulfate CS	Micelles	40%	Sustained release (30.67 ± 2.50 μg/mg)			Human hepatocellular carcinoma (HepG2)/ mice.	High stability, drug-loading efficiency, targetability of tumor and the valuable intracellular delivery of PTX- Micelles by NOSC polymer	[98]

CS-Ceramide Nanoparticle	Polymeric nanoparticle	Loading efficiency =96.9% and Loading capacity= 12.1%.	30% PTX is released after 48 h.			B16F10 and MCF-7	The polymeric nanoparticle of CS-CE could be used as a nanocarrier for oral delivery of hydrophobic drugs.	[220]
CS stabilized multilayered liposomes	Multilayered liposomes	10 wt%	42% in 1 h and 69% in 4 h.			HeLa	The prepared multilayered liposomes induced cytotoxicity in cancer cells compared to PTX-liposomes	[231]
CS/β-Glycerophosphate	Hydrogel		The release of the 1 mg/mL loaded gel was 92.85%, 4 mg/mL loaded			Murine H22 hepatoma cells/ Male ICR mice	Administration of prepared hydrogel was an effective targeting treatment strategy for tumor.	[136]

			gel was 76.68% (After 21 days)					
Trimethyl CS	Polymeric nanoparticle	~30%	~70% for 96 h			NCI-N87 and SGC-7901/ mice	Polymeric nanoparticle showed a prominent 50-60% G2/M phase arrest in cancer cell lines.	[73]
CS nanoparticles	Nanoparticles	8–12%	68–83% of the drug within 12 h			MDA-MB-231 as a model breast cancer cell line	An increase of 20% growth inhibition by docetaxel loaded CS nanoparticles compared to the free drug after 72 h.	[84]
CS-g-poly(ε-caprolactone) polymer			Steady release				Release rates were improved for implants modified with CP (CS-g-poly(ε-caprolactone) additives, Drug release kinetics showed that	[232]

							Fick diffusion was the dominant release mechanism. the profiles of drug release were significantly affected by implant modification.	
CS nanoparticles	Nanoparticles	9.6%	Sustained-release (37.8% within the first 0.5 hour)			Rat	Significant increase in area under the curve at 24h (AUC0→24h) significantly improved controlled release and delivery of the PTX as poorly water-soluble drug and also its derivatives	[75]
Linoleic acid-modified glycol chitosan (LAGC)	Nanoparticle	4.35%	85.5% after 48 hours			HepG2, H22	Prepared nanoparticles showed stronger antitumor effects	[79]
Low molecular weight chitosan (LMWC) coated			~80% release in 48 hours			SKOV-3		[129]

polymeric nanoparticles	Polymeric nanoparticle s						The polymeric nanoparticles indicated less phagocytic uptake	
N-succinyl-palmitoyl- palmitoyl-CS decorated with peptide	Micelle	11.2%	50% at pH7.4 and 65% at pH 5.3, after 80h			A549 /mice	Micelles showed higher cytotoxicity and more cellular uptake, the micelles mostly accumulated in the tumor mass	[108]
α-tocopherol succinate-modified CS	Micelles	7.4%	Sustained manner			MCF-7 cells ((human breast cancer	PTX-loaded micelles showed superior antitumor effect but yielded less toxicity as indicated by the results of antitumor efficacy study and survival	[97]

						cells)/ mice.	study in U14 tumor-bearing mice.	
CS /carboxymethyl cellulose (CMC) with folate	Magnetic nanocomposites	83%	24% After 24 h release in pH 5.4 PBS			MCF 7 cell line	Magnetic nanocomposites enhanced the release of PTX and tumor inhibition	[207]
CS-based polymeric	Micelle	28.2%	20–30% within 20 h and approximately completed after 160 h	Tocopherol succinate - polyethylene glycol-folic acid		4T1/ mice	PTX/TS-CS-PEG-FA prolonged the systemic circulation time of PTX and increased the AUC of Vd, T1/2ß, and MRT, the micelles increased PTX accumulation in tumor mass	[149]
O, N-	Micelles	>30%	70% after 160h			MDA-MB-	The potential of redox-sensitive	[142]

hydroxyethylchitosan-octylamine						231/ mice	micelles for intracellular transportation of lipophilic anticancer drugs	
CS oligosaccharide-stabilized gold nanoparticles	Nanoparticles	82.71%	19% in the first 3 h			MDA-MB-231	Use of prepared nanoparticles for drug delivery and also photoacoustic imaging of cancer cells.	[209]
CS Nanoparticles	Nanoparticles					MCF-7and human fibroblast primary cell	The decrease in BAX and BCL-2 gene expressions in nanoparticle treated cells in comparison to intact cells, elevating the BAX/BCL-2 ratio compared with free drug-treated cells.	[85]
CS-PEG nanoparticles	Nanoparticles	over 50%	67.14 ± 0.9 and 69.64 ± 0.5% up to 48 h in PBS	Transferrin recept		HOP-62/ rat	Prepared nanoparticles enhanced the therapeutic action, showed sustained release profile, higher	[155]

			7.4 and pH4.0, respectively	or			intracellular uptake, progress cell cytotoxicity and prolonged systemic circulation time	
Nanocomposite hydrogel contain paclitaxel-loaded CS micelles and gold nanorods	Nanocomposite	34.8%				Mice	Nanocomposite showed prolonged tumor retention along with the sustained release of drug to efficiently kill the remaining cancer cells that survive after the photothermal ablation	[128]
N-octyl-N-trimethyl CS micelles coated with heparin sodium and sodium carboxymethyl	Micelles	24%				HeLa and NIH-3T3 cells /Rat	The micelles were effective and safe tumor-targeting carriers for anti-cancer drug delivery	[158]

cellulose (anionic polymers)								
CS-hyaluronan-coated solid lipid nanoparticles	Nanoparticles	35.64%	The 24-h release percentage stood at 25.56 ± 2.8 and 38.46 ± 3.6% for pH 7.4 and 6.0, respectively.			MCF-7	The prepared nanoparticles facilitated the cellular uptake, targeting, and the dose - and - time-controlled release and delivery of PAX, enhancing chemotherapeutic activities	[159]
Carboxymethyl CS/ phospholipid bilayer-capped mesoporous carbon nanoparticles	Nanoparticles	25.9%	Around 80% during 24 h at pH 6.8.			Caco-2	Nanoparticles had a great mucoadhesiveness, and improve intracellular drug delivery.	[133]
hydroxypropyl	Nanoparticl	2.55%	22%, 60 % at pH			Rats	Nanoparticles enhanced oral	[228]

trimethyl ammonium chloride CS-modified solid lipid nanoparticles	es		1.2 was lower than that at pH 6.8 after 24 h				bioavailability of DTX	
Vitamin E succinate-grafted-CS oligosaccharide RGD-conjugated D-alpha-tocopheryl PEG	Micelles	5.92%	27% after 4h			U87MG	The prepared micelles have non-toxic on normal cells. The tumor inhibitory rate of the prepared micelles and free drug in the treatment tumor was 88.4% and 49.3%, respectively.	[102]
FA-cholesterol-CS micelles	Micelles	9.1%	Almost 85% at pH 5.0 and 76% at pH 7.4			Hela	The cytotoxic effect of prepared micelles was higher than that of free Taxol.	[148]
CS nanoparticle	Nanoparticl	0.345	60% release			MDA-MB-	Treatment with nanoparticles	[70]

	e		within 24 h.			231	enhanced cell apoptosis (nearly double) compared to paclitaxel	
PTX conjugated trimethyl CS and FA		10.5%	41.3% at pH 7.4, after 48h			Mice	The PTX conjugated trimethyl CS and FA improved the and intestinal transport of PTX, mucoadhesion, and could increase blood retention and enhance the accumulation of PTX in tumor mass compared to PTX injection	[218]
3,6-O,O'-dimyristoyl CS micelles	Micelles	100%				Caco-2 and HT29-MTX cells	The prepared micelles improved the PTX intestinal absorption of.	[214]
Endostatin-loaded CS nanoparticles	Nanoparticles	9.76%	44.15% at pH 7.4 and 54.75% at pH 5, within 3 days			Mice	ES-NPs could overcome the shortcomings of free Endostatin, enhanced the antitumor effect of Endostatin	[197]

N-deoxycholic acid-N, O-hydroxyethyl CS	Micelles	~30 wt%	1.5% during 2 h in an artificial gastric juice at pH 1.2 and 5.0% within 22 h in the intestinal fluid at pH 6.8			Caco-2 cells/Rat	Micelles overcame the low bioavailability- the most prominent barrier to oral PTX efficacy.	[217]
N Succinyl Hydroxyethyl CS Film	Film		10% of PTX in the first 2 weeks			Rabbit	PTX SHEC film effectively inhibits the myofibroblast proliferation and extracellular matrix over deposition during the the healing process of biliary reconstruction	[233]
CS-grafted-polycaprolactone micelles	Micelles	Almost 5%				Caco-2, HT29-MTX	Permeability of PTX was higher in prepared micelles compared with monolayer due to the mucoadhesive	[101]

							character of micelles; it acts as a substrate to deliver PTX at the absorption sites.	
N-mercapto acetyl-N′-octyl-O, N″-glycol CS	Micelles	31.81%	4.5% of PTX during 2 h after administration (artificial gastric juice) and around 8.0% within 22 h (artificial intestinal fluid)			Caco-2 cells/Rat	Enhancing the bioavailability of PTX when delivered by prepared micelles compared to non-sulfhydrylated OGC micelles or Taxol and increasing intestinal retention	[221]
CS functionalized Single-Walled Carbon Nanotubes	Carbon Nanotubes				DOX		the ability of co-loading and releasing of DOX and PTX. The two anti-cancer drugs bind with pristine SWCNT in a similar	[191]

							stability	
Amphiphilic polymer of -tocopherol succinate modified glycol CS	Micelles	10.9%				MCF-7 /rabbit	The PTX-loaded prepared micelles showed low toxicity and increased dose, the polymer improved the delivery properties as a carrier of PTX	[106]
Olate-grafted copolymer of PEG and CS	Nanoparticles	4.6% (w/w)	70% within 24 h			HeLa M109 HiFR /mice	The copolymer showed suitable pharmacokinetic profile	[150]
Poly (lactide-co-glycolide) microparticles loaded with PTX and included in a CS thermosensitive	Gels	7.8–9.4%	≥*85%* after 196h			M234-p /mice	The Gels contain PTX showed more long-term effect in the site of action, and inhibition in tumor size	[234]

gelling solution								
PTX–cholesterol complex-loaded lecithin–CS nanoparticles	Nanoparticles	195.06µg/mL	64.4% at pH at 47.7% at pH 7.4 after 48h.			4T1	The prepared formulation significantly inhibited the growth of cancer cells and metastasis to other organs and effectively improved the rate of survival of cancer mice	[69]
N-octyl-N'-phthalyl-O-phosphoryl CS derivative	Micelles	51.23% (wt %)	less than 20% after 24h			Caco-2 cells	Efficient accumulation and transport of prepared micelles loading rhodamine-123 or PTX into the cells by clathrin/cavelin-mediated endocytosis	[213]
Glycol CS nanoparticles	Nanoparticles		Slow-release			HeLa cells	PTX-loaded nanoparticles with 400 nm particle size, low PDI and positive charge. They could be internalized by cell lines, probably by endocytosis	[72]

Carboxymethyl CS- polymeric micelles	Micelles	35.24%	19.62% of the loaded PTX in simulated gastric fluid / intestinal fluid and 66.14% in PBS during 48 h			MCF-7 and Caco-2 cells/rat	Prepared micelles were favorable for oral delivery of water-insoluble anticancer drugs.	[212]

Table 2: CS-based delivery systems for DTX.

Components	**Structures**	**Loading capacity**	**Release properties**	**Targeting agents**	**Co-delivered agents**	**Cancer cell lines**	**Major outcomes**	**Refs**
CS cross-linked ɣ-poly (glutamic acid) nanoparticles	biopolymeric nanoparticles			Epidermal growth factor	Cetuximab (CET)	A549 (Non-small- cell lung carcinoma) and NIH3T3 (mouse embryonic fibroblasts cells)	A G2/M phase cell cycle arrest in The A549 cells treated with nanoparticles, reduction of mitochondrial membrane potential, induction of necrosis and apoptosis leads to an increase in cancer cell death.	[164]
CS Microspheres	Microsphere	18.7	sustained-			Rats and	By using the microsphere	[119]

			release (80% in the first 12 h)			mice	DTX accumulates in the target site while decreasing the drug accumulation in healthy tissue	
CS/Sulfobutylether-β-Cyclodextrin Nanoparticles	Nanoparticles	0.36%	40% in the first 12		Berbamine (A natural isoquinoline alkaloid)	MCF-7 (Human breast cancer cells) /Rat	A better controlled-release property and an enhanced intestine absorption property of the dual-drug CD/CS NPs. higher cellular uptake, cytotoxicity and apoptosis rate	[195]
CS nanoparticles	Nanoparticles	12.01	73.79% over a period of			Breast cancer (MDA-	Improving therapeutic effects and reducing toxicity	[235]

			24 h			MB-231)		
CS coated hyaluronic acid-docetaxel	Nanoparticles	62.78 %		HA		MCF-7 and T1 cell lines	The prepared nanoparticles were more effective against cancer cells in comparison with free DTX.	[236]
CS-functionalized single-walled carbon nanotube	Carbon nanotube	32.04%	(68%) at pH 5.0 and (49%) at pH 7.4.			A549 tumor cells/ mice	Carbon nanotube showed high drug loading, pH-responsive drug release, Significant antitumor effect as well as good safety to the body.	[184]
Biotinylated CS	Nanocochleates		57% after 72 h.			Breast cancer MCF-7 cells	Increasing bioavailability of DTX from prepared Nanocochleates by 10-folds with longer circulation time and slower speed of	[165]

							elimination accompanied by low tissue distribution as compared to free DTX	
CS-Coated Flexible Liposomes	Liposomes	11.85%	70% released within 12 h			Human colon cancer (HT-29) cells /rat	The prepared liposomes effect on the pharmacokinetic parameters cytotoxic efficiency compared with those of the uncoated ones	[237]
Glycol CS-lipoic acid	Micelles	7.5%	71.6% for 36 h.	PSMA		LNCaP and PC-3 cell lines/ mice	The prepared micelles showed stronger anti-tumor effects than DTX injection. Developing a new method for hydrophobic drug delivery in cancer therapy.	[175]

CS nanoparticle	Nanoparticle		50% of their contents (siRNA or DTX) in the first 36 h.	Anti-MUC1 aptamer	IGF-1R Silencer siRNA	SKBR3 cells	Aptamer-conjugated NPs dramatically reduced the genetic expression of IGF-1R, matrix metalloproteinase-9, STAT3, and VEGF.	[201]

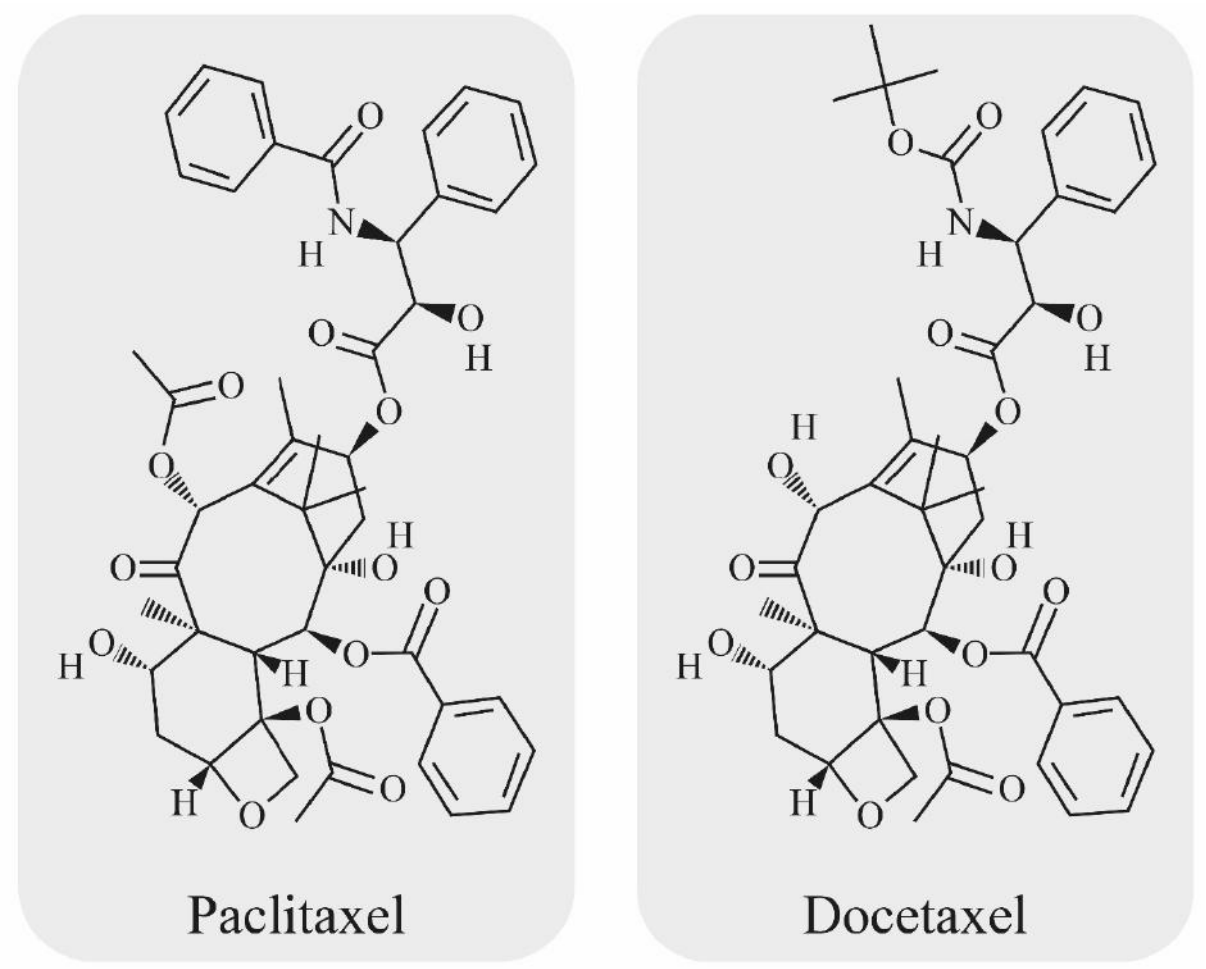

Figure 1: The chemical structure of PTX and DOX.

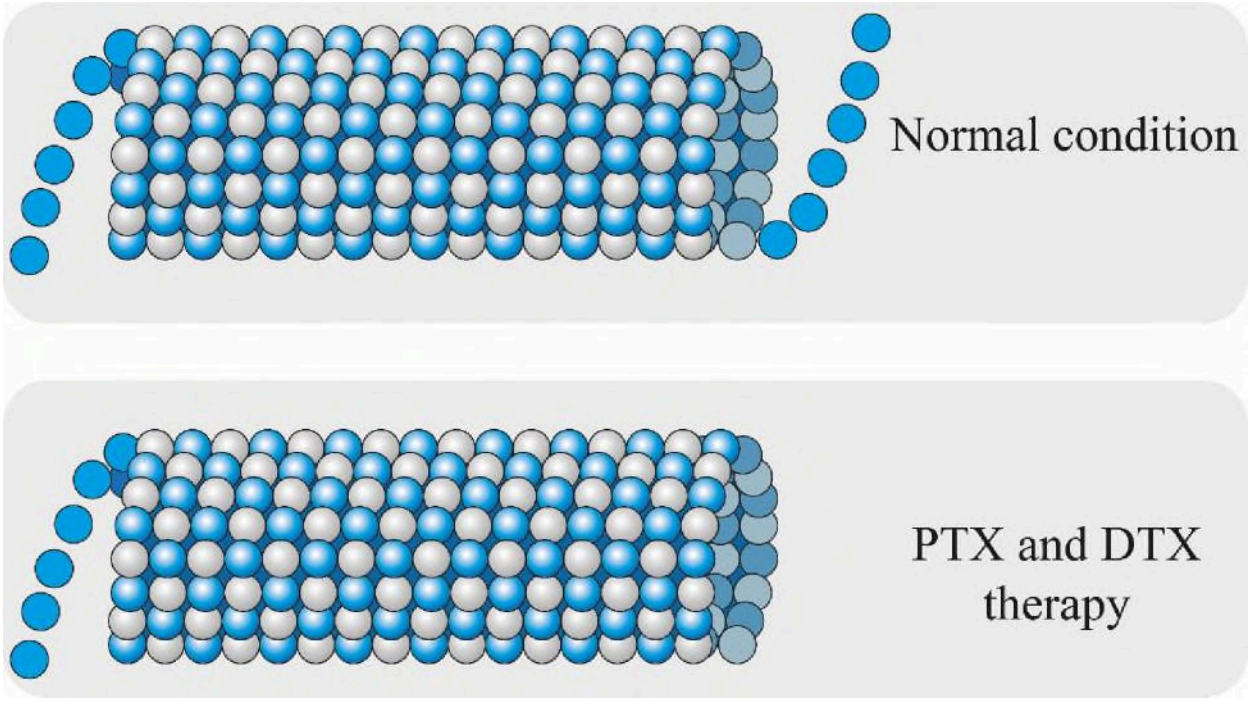

Figure 2: The mechanism of action of PTX and DTX. During the physiological condition, there is a balance in entering and eliminating of tubulin proteins from microtubules. Upon administration of PTX or DTX, this balance is interrupted, and microtubules obtain a stabilized form, resulting in inhibition of mitosis and apoptotic cell death.

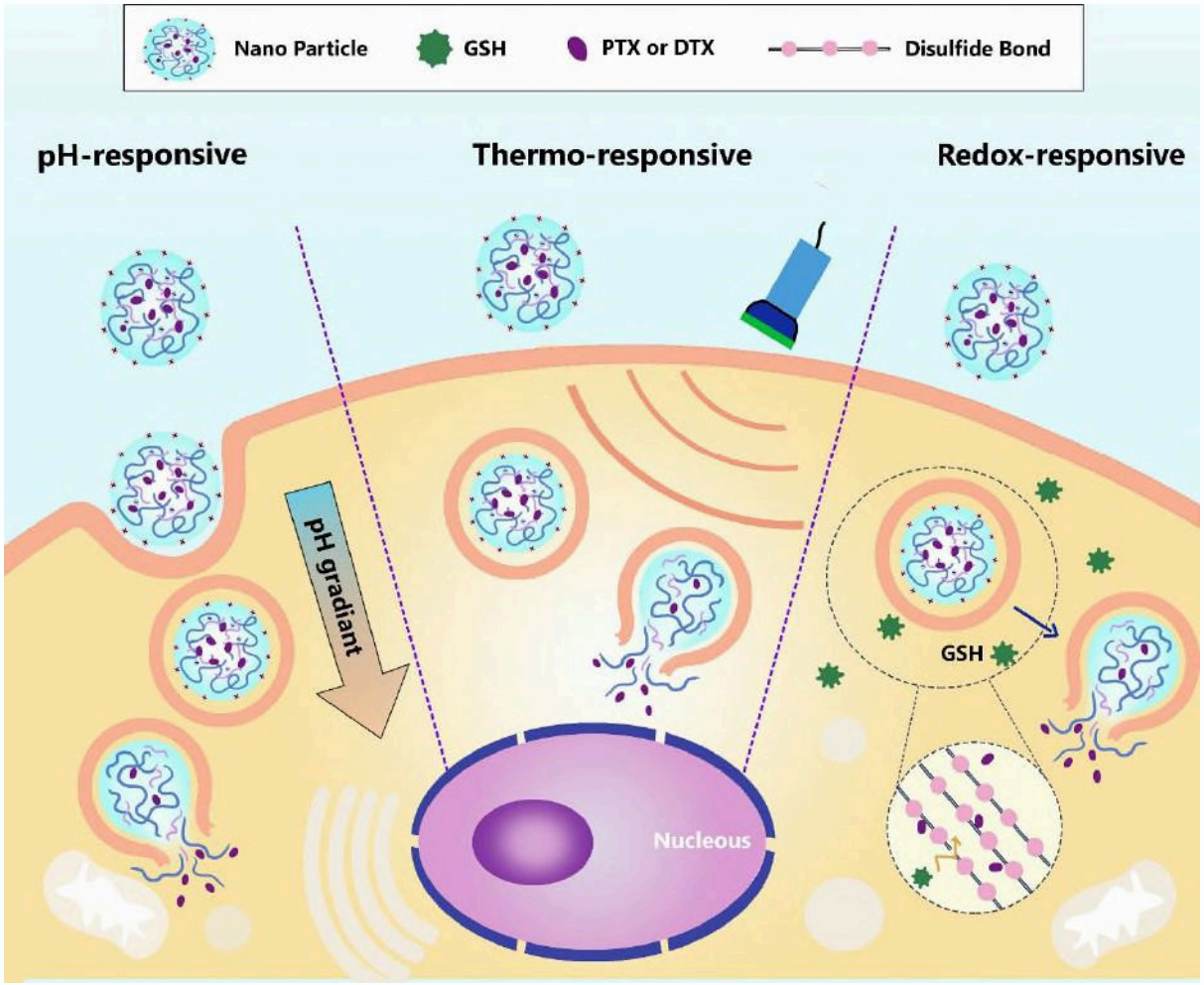

Figure 3: Stimuli-responsive CS NPs for delivery of PTX and DTX, and their mechanism of action.

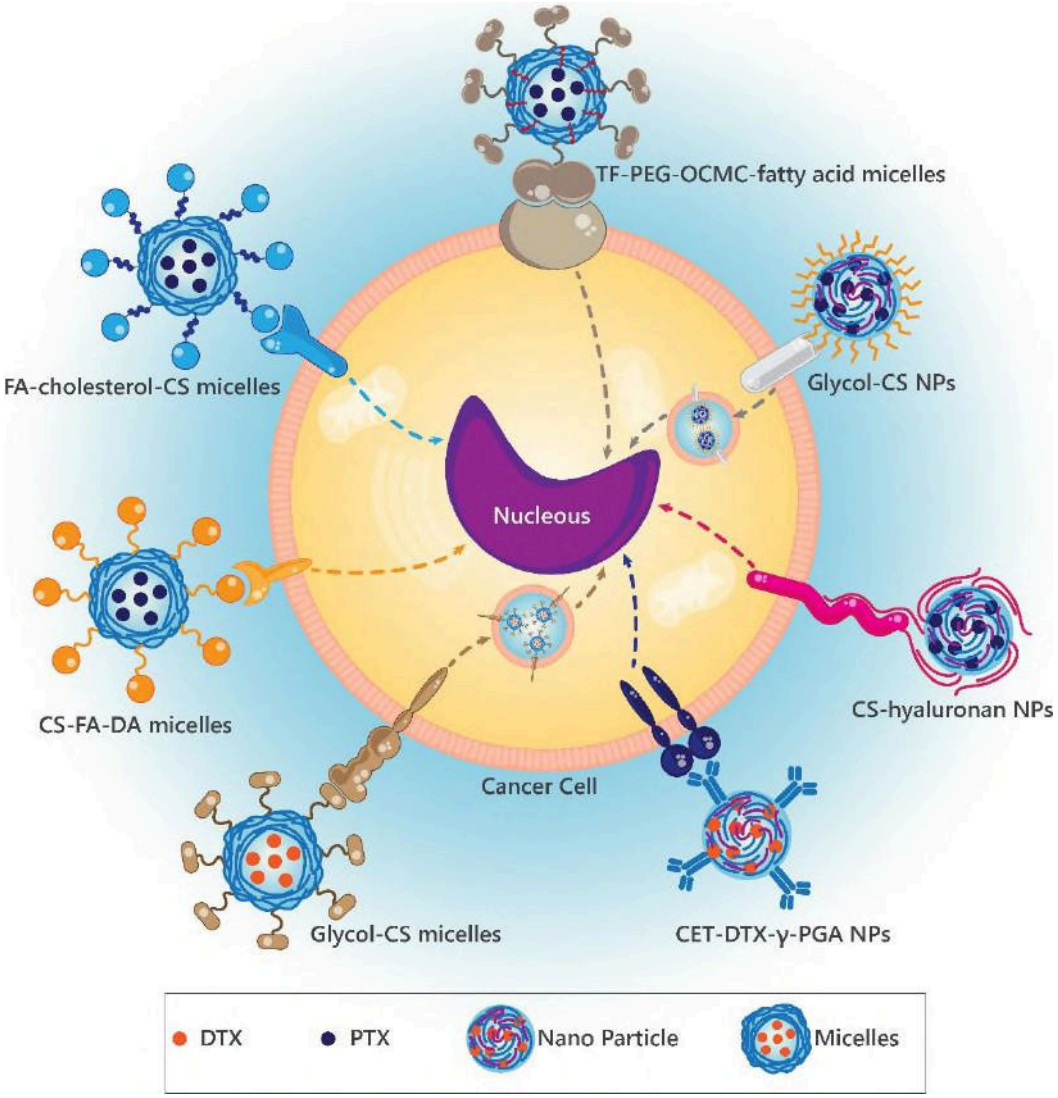

Figure 4: Various CS-functionalized NPs applied in the delivery of PTX and DTX.

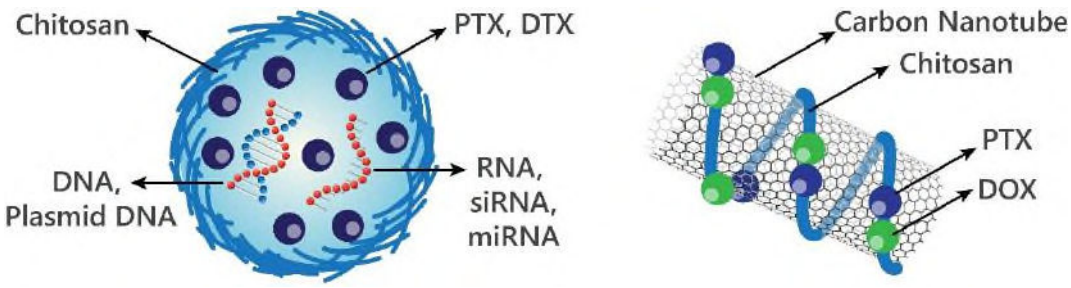

Figure 5: CNTs as potential candidates in the delivery of PTX and DTX.

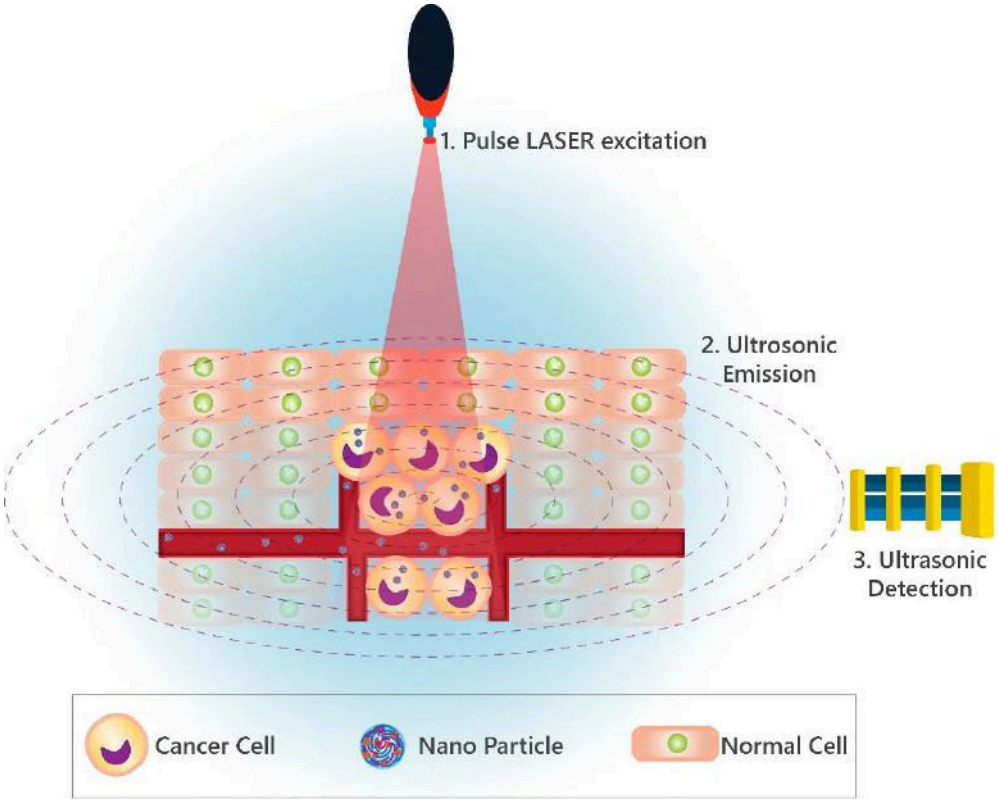

Figure 6: The application of CS-functionalized NPs in cancer imaging and theranostics.

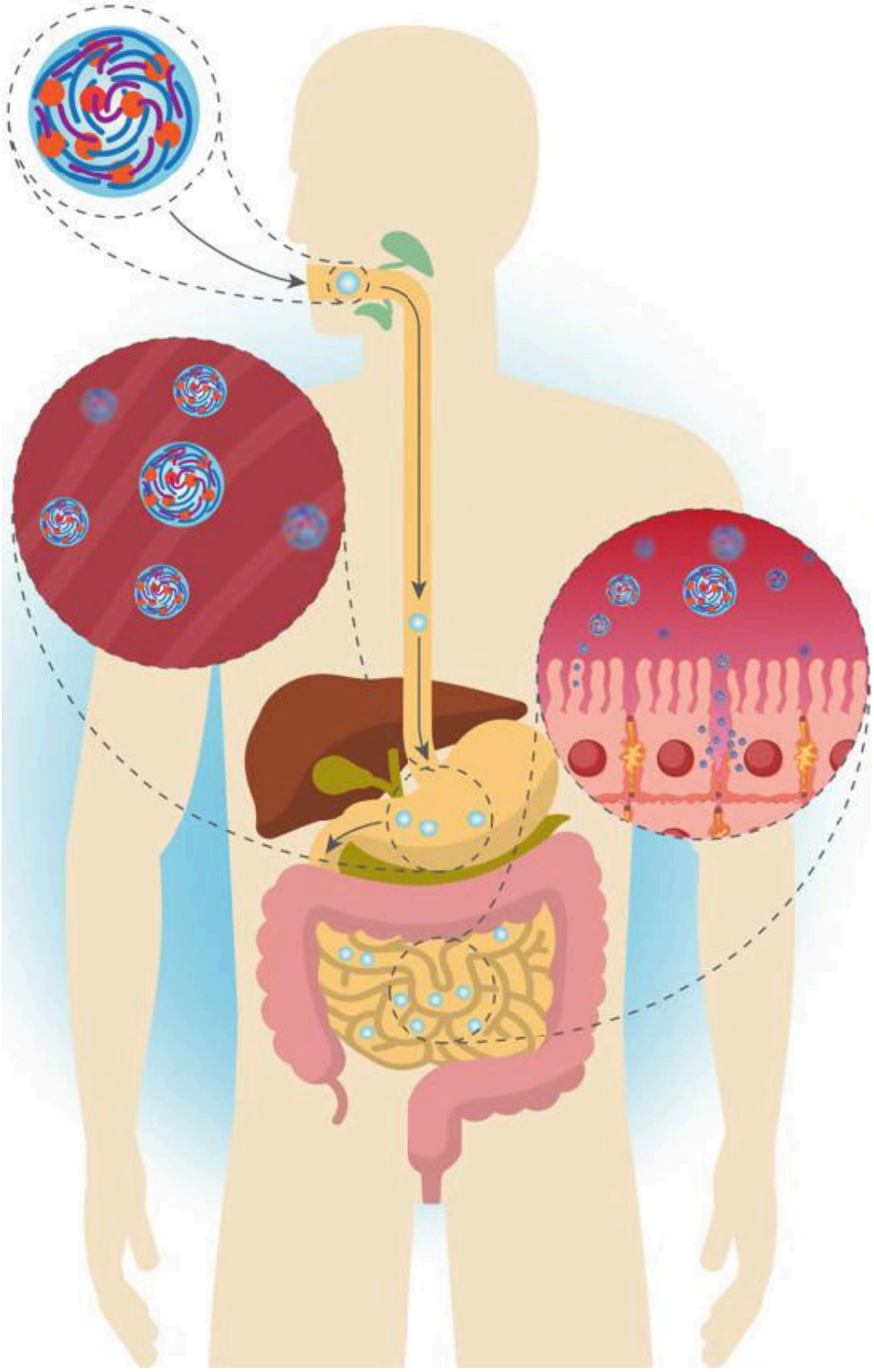

Figure 7: Protection against degradation in the stomach and enhancing the absorption of PTX and DTX through intestine by CS NPs.

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