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REVIEW

Application of active targeting nanoparticle delivery system for chemotherapeutic drugs and traditional/herbal medicines in cancer therapy: a systematic review

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Abstract: Patients treated with conventional cancer chemotherapy suffer from side effects of the drugs due to non-selective action of chemotherapeutic drugs to normal cells. Active targeting nanoparticles that are conjugated to targeting ligands on the surface of nanoparticles play an important role in improving drug selectivity to the cancer cell. Several chemotherapeutic drugs and traditional/herbal medicines reported for anticancer activities have been investigated for their selective delivery to cancer cells by active targeting nanoparticles. This systematic review summarizes reports on this application. Literature search was conducted through PubMed database search up to March 2017 using the terms nanoparticle, chemotherapy, traditional medicine, herbal medicine, natural medicine, natural compound, cancer treatment, and active targeting. Out of 695 published articles, 61 articles were included in the analysis based on the predefined inclusion and exclusion criteria. The targeting ligands included proteins/peptides, hyaluronic acid, folic acid, antibodies/antibody fragments, aptamer, and carbohydrates/polysaccharides. In vitro and in vivo studies suggest that active targeting nanoparticles increase selectivity in cellular uptake and/or cytotoxicity over the conventional chemotherapeutic drugs and non-targeted nanoparticle platform, particularly enhancement of drug efficacy and safety. However, clinical studies are required to confirm these findings.

Keywords: active targeting, nanoparticles, ligands, chemotherapy, natural active compounds, cancer

Introduction

Cancer remains one of the major causes of deaths worldwide. In 2017, approximately 1.7 million new cases and 600 thousand deaths were estimated to occur in the USA.[1] Most patients treated with conventional chemotherapy suffer from serious side effects due to non-selective action of chemotherapeutic drugs to normal cells. For a few decades, nanoparticles have been developed as a drug delivery system of various chemotherapeutic drugs to enhance drug efficacy and safety.[2–4] Nanoparticles play an important role in increasing drug concentration in cancer cells by enhancing drug accumulation by passive and active targeting mechanisms as well as by decreasing drug efflux from cancer cells. The passive targeting nanoparticle is the mechanism by which the drugs leak from blood vessels supplying cancer cells and accumulate in the cells by enhanced permeability and retention (EPR) effect.[5] The active targeting nanoparticles, on the other hand, target ligands conjugated on the surface of nanoparticles, resulting in increasing cellular uptake by receptor-mediated endocytosis and therefore increased

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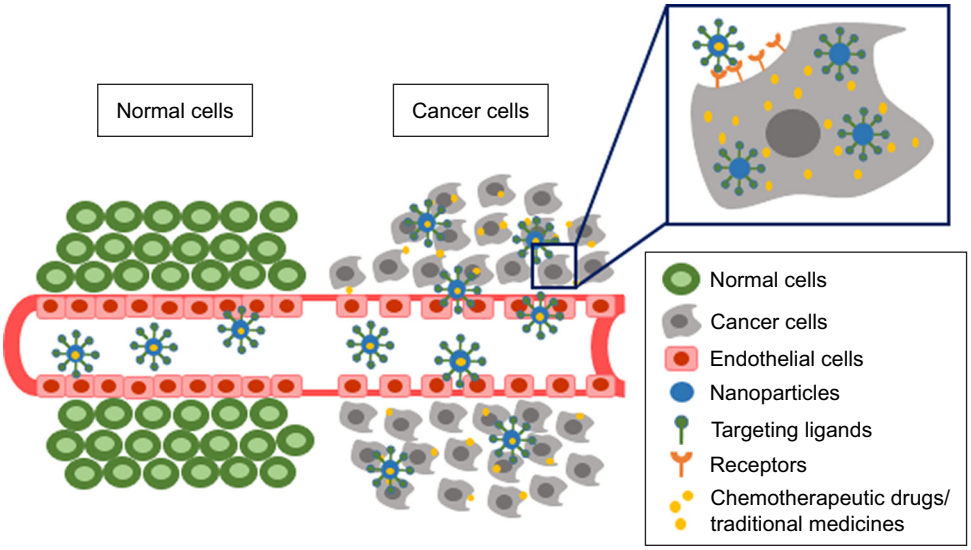

Figure 1 Passive targeting and active targeting mechanisms of nanoparticles.

drug accumulation in cancer cells. This mechanism relies on the interaction between tumor ligands conjugated on the surface of nanoparticles and cell-surface receptors or antigens on cancer cell surfaces (Figure 1).[5] Nanoparticles acting via both mechanisms have been shown to increase drug concentration in cancer cells. Active targeting nanoparticles have been shown in various studies to be more efficient in increasing drug accumulation in cancer cells and therefore play important role not only in modern cancer chemotherapy, but also in cancer therapy with traditional/herbal medicines.[6–11] A number of nanoparticle formulations derived from these active compounds have been developed for active targeting purpose to improve anticancer efficacy and to reduce side effects. The objective of this current review is to summarize the research articles relating to the application of active targeting nanoparticles delivering system for chemotherapeutic drugs derived from chemical synthesis as well as natural sources.

Materials and methods

Study selection and inclusion and exclusion criteria

This systematic review was conducted through the search from PubMed database up to March 2017. The following keywords were used: nanoparticle, chemotherapy, traditional medicine, herbal medicine, natural medicine, natural compound, cancer treatment, and active targeting. Inclusion criteria for selection of the searched articles were 1) articles in full text and written in English; 2) articles with in vitro or in vivo investigations of effects of nanoparticles delivering chemotherapeutic drugs or traditional/herbal medicines on efficacy and/or safety; and 3) articles with investigations of targeting and receptor/antigen. The articles with insufficient data for extraction or those with application for radiotherapy, gene therapy, photodynamic therapy, or for diagnostic purpose, or duplicate articles, or review articles were excluded from the analysis.

Data extraction and collection

The titles and abstracts of articles searched from PubMed database using the above mentioned keywords were initially screened to obtain relevant original research articles according to the eligibility criteria. Thereafter, the full texts of all relevant articles were carefully examined in details to confirm their compliance with the defined eligibility criteria. The studies of active targeting nanoparticles applied for both chemotherapeutic drugs and traditional/herbal medicines for cancer were classified according to the types of targeting ligands.

Results

Study description

Twenty out of 695 research articles were initially excluded from the analysis during title screening for duplicate articles. The titles together with abstracts of the remaining articles were further checked for eligibility criteria and a total of 597 articles were excluded from the analysis. Finally, 61 out of 78 articles were included in the analysis, 17 articles being excluded due to unclear/inadequate information. The flow diagram of the search process is presented in Figure 2, and the

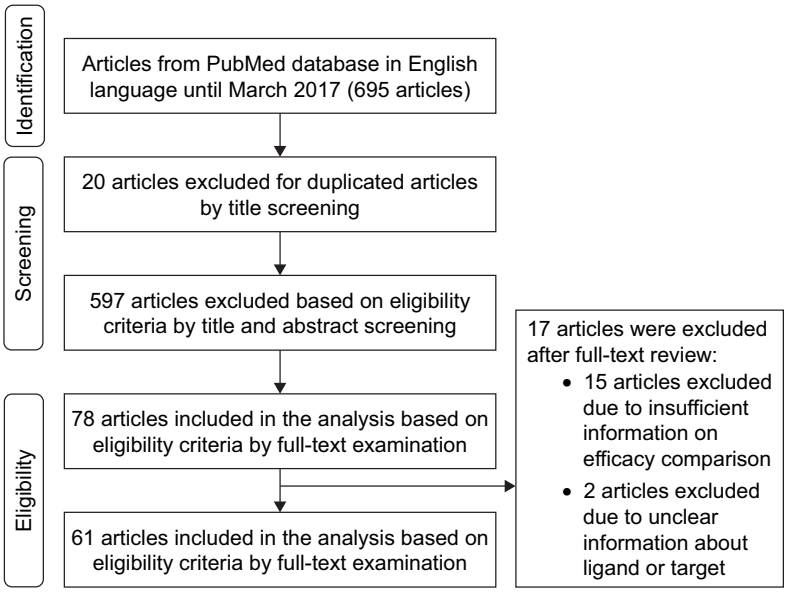

Figure 2 Flow diagram showing the different phases of the systematic review.

effects of active targeting nanoparticles delivering modern chemotherapeutic drugs and traditional/herbal medicines for cancer are summarized in Tables 1 and 2.

Of the 61 articles included in the analysis, 54 (88.5%) investigated nanoparticles delivering modern chemotherapeutic drugs; the majority was doxorubicin (40.7%), followed by paclitaxel (8.5%). Types of targeting ligand platforms used included proteins or small peptides (15 articles), hyaluronic acids (HAs; 10 articles), folic acids (9 articles), antibodies (5 articles), aptamers (5 articles), carbohydrates or polysaccharide (5 articles), and other molecules (5 articles). Seven articles (11.5%) investigated nanoparticles delivering traditional/herbal medicines; the majority was curcumin (42.9%). The ligand platforms used were proteins or small peptides (2 articles), HA (1 article), folic acid (1 article), antibody (1 article), aptamer (1 article), and other molecule (1 article).

Discussion

Ligands for nanoparticle platform

Proteins or small peptides

Various types of proteins or small peptides were used to conjugate on the surface of nanoparticles to improve selectivity of chemotherapeutic drugs or traditional/herbal medicines to cancer cells. Transferrin, a serum glycoprotein, was one of the widely used targeting ligands. It plays a role in transferring iron from blood stream into the cells by binding to transferrin receptor on the cell surface. Upregulation of transferrin receptor has been reported in metastatic and drug-resistant cancer cells.[67] The transferrin-conjugating nanoparticles delivering chemotherapeutic drugs have been shown to improve cellular uptake of the drugs by cancer cells and enhance in vitro and in vivo cytotoxicity. For instance, the transferrin-conjugated polyethylene glycol (PEG) nanoparticle delivering hydroxycamptothecin was shown to provide longer retention time of drug in blood circulation, higher drug accumulation in cancer cells, and higher in vivo growth inhibitory activity against S180 tumor compared with non-targeted nanoparticles.[16] In the study of transferrin-conjugated chitosan-PEG nanoparticles delivering paclitaxel, the targeted nanoparticles also exhibited higher cytotoxic activity to transferrin-overexpressing human non-small cell lung cancer cells (HOP-62). The respective half-maximal inhibitory concentrations (IC_{50}) were 0.3 μM and 2.0 μM.[17] Apart from transferrin, arginine–glycine–aspartic acid (RGD) peptide has been used as targeting ligand to conjugate on the surface of nanoparticles to specifically target integrin $\alpha_v\beta_3$ receptor. This receptor is expressed on the surface of tumor vessels and various types of cancer cells and plays important roles in tumor growth promotion, metastasis, and angiogenesis.[18] A number of RGD-conjugated nanoparticles delivering chemotherapeutic drugs or traditional/herbal medicines have been developed and demonstrated to promote their delivery to the cancer cells. The cyclic arginine–glycine–aspartic acid–tyrosine–lysine c(RGDyK)-conjugated poly(trimethylene carbonate)-PEG micellar nanoparticle delivering paclitaxel was shown to enhance cytotoxic activity of the drug to integrin $\alpha_v\beta_3$-overexpressing human glioblastoma cells

Table 1 Summary of research articles that investigated active targeting NPs delivering chemotherapeutic drugs in cancer therapy

Ligand	Receptor/antigen	Drug-NP platform	Types of study	Outcome		References
				Compared to non-targeted	Side effect	
Proteins/peptides						
H2009.1 peptide	Integrin $\alpha_v\beta_6$	Doxorubicin-liposome	In vivo: human non-small cell lung cancer cell lines (H2009) xenograft	No difference in tumor targeting and tumor growth inhibition rate	No significant change in body weight	12
IL-13 peptide	IL-13Rα2 receptor	Docetaxel-PEG-PCL	In vitro: human glioblastoma cell lines (U87)	Higher cellular uptake; 1.1-fold higher cellular apoptosis	Not evaluated	13
			In vivo: cell lines U87 orthotopic xenograft	Higher tumor growth inhibition rate; 1.73-fold higher tumor targeting		
AP-1 peptide	IL-4 receptor	Paclitaxel-cyclodextrin	In vivo: human breast adenocarcinoma cell lines MDA-MB-231 xenograft	Specifically targeting tumor site; higher tumor growth inhibition rate	Low nonspecific toxicity	14
Peptide CVKTPAQSC	CD133+ receptor	Docetaxel-PLA	In vitro: human lung cancer cell lines (A549)	30.5% higher cellular uptake ratio	No significant change in body weight	15
			In vivo: cell lines A549 xenograft	Higher anti-metastatic efficacy		
Transferrin	Transferrin receptor	Hydroxycamptothecin-PEG	In vivo: murine sarcoma cell lines (S180) xenograft	9.03-Fold higher tumor accumulation; 1.85-fold higher tumor growth inhibition rate	No significant change in body weight	16
Transferrin	Transferrin receptor	Paclitaxel-PEG-chitosan	In vitro: non-small cell lung cancer cell lines (HOP-62)	Higher cellular uptake; 6.67-fold higher cytotoxicity	Not evaluated	17
cRGDyK	Integrin $\alpha_v\beta_3$	Paclitaxel-PEG-PTMC	In vitro: human glioblastoma – astrocytoma, epithelial-like cell lines (U87MG)	36.6% higher cellular uptake; 2.3-fold higher cytotoxicity; higher cellular apoptosis	Not evaluated	18
RGDS	Integrin $\alpha_v\beta_3$	Doxorubicin-PEG-MIONP	In vitro: human cervical carcinoma cell lines (HeLa)	11-Fold higher cellular uptake; higher cytotoxicity	Not evaluated	19
cRGDyK	Integrin $\alpha_v\beta_3$	Paclitaxel-micelle	In vitro: human prostate cancer cell lines (PC-3)	1.93-Fold higher cellular uptake; 1.26-fold higher cytotoxicity	No significant change in body weight	20
			In vivo: cell lines PC-3 xenograft	Higher tumor growth inhibition rate		
RGD	Integrin $\alpha_v\beta_3$ receptor	Doxorubicin-dendritic poly-L-lysine-gelatin	In vitro: mouse mammary breast tumor cell lines (4T1)	Higher cytotoxicity	No significant change in body weight	21
			In vivo: cell lines 4T1 xenograft	1.18-Fold higher tumor accumulation; 10.6% higher tumor growth inhibition rate		
Bombesin peptide	Gastrin-releasing peptide receptor	Docetaxel-PLGA	In vitro: human breast adenocarcinoma cell lines (MDA-MB-231)	4-Fold higher cytotoxicity	Not evaluated	22
NR7 peptide	EGFR	Doxorubicin-PLGA-PEG	In vitro: human ovarian carcinoma cell lines (SKOV3)	3-Fold higher cellular uptake; 62.4-fold higher cytotoxicity	Low nonspecific toxicity	23
			In vivo: cell lines SKOV3 xenograft	2.6-Fold higher tumor accumulation		
LHRH peptide	LHRHR	Methotrexate-HSA	In vitro: human breast carcinoma cell lines (T47D)	71.5% higher cellular uptake; 8.5-fold higher cytotoxicity	Not evaluated	24

Angiopep-2	LRP	Doxorubicin-dendritic poly-L-lysine-gelatin NP	In vitro: mouse mammary breast tumor cell lines (4T1) In vivo: cell lines 4T1 xenograft	Higher cellular uptake; higher cellular apoptosis Higher accumulation of NP in tumor; higher tumor growth inhibition rate	Low side effect to normal tissue	25
TbFGF peptide	FGFR	Paclitaxel-micelle	In vitro: murine Lewis lung carcinoma cell lines (LL/2), human hepatocellular liver carcinoma cell lines (HepG2), human lung cancer cell lines (A549), murine colorectal cancer cell lines (C26)	18-Fold higher cytotoxicity to LL/2; higher cellular uptake by 6.6-fold for HepG2, 6.2-fold for A549, 2.9-fold for C26, and 2.7-fold for LL/2	Not evaluated	26
Hyaluronic acid						
Hyaluronic acid	CD44 receptor	Topotecan hydrochloride-dendrimer	In vitro: human colorectal cancer cell lines (HCT-116) In vivo: cell lines HCT-116 xenograft	Higher cellular uptake; 3-fold higher cytotoxicity compared to free drug Higher tumor growth inhibition rate; 3.6-fold and 1.7-fold higher drug accumulation in tumor compared to kidney and liver	Not evaluated	8
Hyaluronic acid	CD44 receptor	Paclitaxel-micelle	In vitro: human breast adenocarcinoma cell lines (MCF-7) In vivo: murine hepatic carcinoma cell lines (Heps) xenograft	4.1-Fold higher cellular uptake 2.80-Fold higher tumor accumulation; 31.89% higher tumor growth inhibition rate; higher median survival time	No significant change in body weight	27
Hyaluronic acid	CD44 receptor	Cisplatin-chitosan	In vitro: human lung cancer cell lines (A549)	Higher cellular uptake; 8-fold higher cytotoxicity	Not evaluated	28
Hyaluronic acid	CD44 receptor	Rapamycin-LbL-LCNP	In vitro: human breast adenocarcinoma cell lines (MCF-7 and MDA-MB-231)	Higher cytotoxicity, 1.35-fold for MDA-MB-231, and 1.1-fold lower cytotoxicity to MCF-7	No significant change in body weight	29
Hyaluronic acid	CD44 receptor	Doxorubicin-PBLG	In vivo: Ehrlich ascites tumor-bearing mice	Higher tumor growth inhibition rate; higher survival time	Not evaluated	30
Hyaluronic acid	CD44 receptor	Methotrexate-lipid-based NP	In vivo: murine melanoma cell lines (B16F10) xenograft	Higher tumor accumulation; higher tumor growth inhibition rate	Not evaluated	31
Hyaluronic acid	CD44 receptor	Doxorubicin-hydroxylapatite	In vitro: human hepatocellular carcinoma cell lines (HepG2) In vivo: cell lines HepG2 xenograft	Higher cellular uptake; 46.3% higher cytotoxicity compared to free drug Higher in tumor targeting; lower tumor volume	No significant change in body weight	32
Hyaluronic acid	CD44 receptor	Doxorubicin- HACE-PEG	In vitro: murine squamous cell carcinoma cell lines (SCC7) and mouse embryo fibroblast cell lines (NIH3T3) In vivo: cell lines SCC7 xenograft	Higher cellular uptake in CD44 overexpressing (SCC7) compared to CD44 negative (NIH3T3); no difference in cellular uptake compared to free drug 30% higher tumor growth inhibition rate compared to free drug	No significant change in body weight	33

(*Continued*)

Table 1 (*Continued*)

Ligand	Receptor/antigen	Drug-NP platform	Types of study	Outcome		References
				Compared to non-targeted	Side effect	
Hyaluronic acid	CD44 receptor	Doxorubicin-hyaluronic acid-Lys-LA10	In vitro: doxorubicin-resistant human breast adenocarcinoma cell lines (MCF-7/ADR)	Higher cellular uptake compared to free drug; no difference in cytotoxicity	No significant change in body weight and low nonspecific toxicity	34
			In vivo: cell lines MCF-7/ADR xenograft	Lower relative tumor volume; higher median survival time		
Hyaluronic acid	CD44 receptor	Doxorubicin-PBLG-LA	In vitro: human breast adenocarcinoma cell lines (MCF-7)	10-Fold higher in cellular DOX level; higher cytotoxicity	No significant change in body weight and low nonspecific toxicity	35
			In vivo: cell lines MCF-7 xenograft	No difference in tumor growth inhibition rate; higher survival time		
Folate						
Folic acid	Folate receptor	Docetaxel-PEG-PLGA	In vitro: human cervical carcinoma cell lines (HeLa)	26.7-Fold higher cellular uptake; 12-fold higher cytotoxicity compared to free drug	Not evaluated	36
			In vivo: cell lines HeLa xenograft	Higher tumor targeting; higher tumor growth inhibition rate		
Folic acid	Folate receptor	Doxorubicin-dendrimer	In vitro: human epidermal carcinoma cell lines (KB)	1.4-Fold higher cellular uptake; 2.2-fold higher cytotoxicity	Not evaluated	37
Folic acid	Folate receptor	Gemcitabine-BSA	In vitro: human ovarian cancer cell lines (Ovcar-5) and human breast adenocarcinoma cell lines (MCF-7)	2-Fold higher cellular uptake by MCF-7; higher cytotoxicity – 1.4-fold for MCF-7 and 1.6-fold for Ovcar-5; higher cellular apoptosis	No significant change in body weight	38
			In vivo: Ehrlich ascites carcinoma tumor cell-bearing mice	Higher tumor growth inhibition rate		
Folic acid	Folate receptor	Carboplatin-PLGA-chitosan	In vitro: human cervical carcinoma cell lines (HeLa)	Higher cellular uptake in time-dependent manner; 1.67-fold higher cytotoxicity; higher cellular apoptosis	Not evaluated	39
Folic acid	Folate receptor	Doxorubicin-polymeric NP	In vivo: human epidermal carcinoma cell lines (KB) xenograft	1.6-Fold higher tumor growth inhibition rate	Not evaluated	7
Folic acid	Folate receptor	Doxorubicin-PEG	In vitro: human epidermal carcinoma cell lines (KB), human lung cancer cell lines (A549) and human hepatocellular carcinoma cell lines (HepG2)	Higher cellular uptake by KB cell; higher cytotoxicity – 1.2-fold for A549, 3.5-fold for KB, and 2.1-fold for HepG2	No significant change in body weight and less cardiotoxicity	40
			In vivo: cell lines KB xenograft	Higher tumor targeting; higher tumor growth inhibition rate; higher survival time		
Folic acid	Folate receptor	Cisplatin-PEG-MSN	In vitro: human cervical carcinoma cell lines (HeLa)	Higher cellular uptake	Not evaluated	41

Folic acid	Folate receptor	Doxorubicin-β-cyclodextrin	In vitro: human placenta choriocarcinoma cell lines (JAR), human colon adenocarcinoma cell lines (HT-29), human breast adenocarcinoma cell lines (MCF-7), and mouse fibroblast cell lines (3T3)	Higher cellular uptake – 2.09-fold by HT-29, 1.98-fold by MCF-7, and 7.31-fold by JAR; higher cytotoxicity – 12.39-fold for JAR, 6.73-fold for HT-29, and >1.5-fold for 3T3	Not evaluated	42
Folic acid	Folate receptor	Paclitaxel-PEG-PLGA	In vitro: human endometrial carcinoma cell lines (HEC-1A)	Higher cellular uptake; 2.6-fold higher in cytotoxicity; 12% higher cellular apoptosis	Not evaluated	43
			In vivo: cell lines HEC-1A xenograft	16.48% higher tumor growth inhibition rate		
Antibody						
Anti-Fas mAb	Fas receptor	Camptothecin-PLGA	In vitro: human colorectal cancer cell lines (HCT116)	Higher cellular uptake; 58.9-fold higher cytotoxicity compared to free drug	Not evaluated	44
Anti-CD20 mAb	CD20 receptor	Doxorubicin-DSPE-PEG2000	In vitro: human Burkitt's lymphoma cell lines (Raji)	Selectively targeting CD-20-overexpressing cells (Raji)	Low nonspecific toxicity	45
Anti-CD47 mAb	CD47 receptor	Gemcitabine-MIONP	In vitro: human pancreatic ductal adenocarcinoma primary cells (Panc215 and Panc354)	Higher cellular uptake; higher cytotoxicity	Not evaluated	46
EGFR antibody	EGFR	Rapamycin-PLGA	In vitro: human breast adenocarcinoma cell lines (MCF-7)	13-fold higher cellular uptake; higher cytotoxicity; 2.4-fold higher cellular apoptosis	Not evaluated	47
PR81 mAb	MUC1 receptor	5-fluorouracil-BSA	In vitro: human breast adenocarcinoma cell lines (MCF-7)	Higher cytotoxicity	Not evaluated	48
Aptamer						
Aptamer AS1411	Nucleolin receptor	Doxorubicin-HPAEG	In vitro: human breast adenocarcinoma cell lines (MCF-7)	2-fold higher cellular uptake; 1.7-fold higher cytotoxicity	Not evaluated	6
Aptamer AS1411	Nucleolin receptor	Gemcitabine-PEG-PLGA	In vitro: human lung cancer cell lines (A549)	36% higher cellular uptake; 5.9-fold higher cytotoxicity	Not evaluated	49
Aptamer AS1411	Nucleolin receptor	Methotrexate-UnTHCPSi-PEI	In vitro: human breast adenocarcinoma cell lines (MDA-MB-231)	1.6-fold and 4.7-fold higher cellular uptake for 3 h and 12 h, respectively; higher cytotoxicity	Not evaluated	50
Aptamer AS1411	Nucleolin receptor	Docetaxel-mannitol-PLGA-TPGS	In vitro: human cervical carcinoma cell lines (HeLa)	Higher cellular uptake; 20-fold higher cytotoxicity	Not evaluated	51
			In vivo: cell lines HeLa xenograft	24.44% life time extended		
Aptamer AS1411	Nucleolin receptor	Doxorubicin-polymersome	In vitro: human breast adenocarcinoma cell lines (MCF-7)	1.73-fold higher cellular uptake compared to mutated aptamer conjugates; 1.75-fold higher cytotoxicity compared to mutated aptamer conjugates	No significant change in body weight	52
			In vivo: cell lines MCF-7 xenograft	1.75-fold higher tumor targeting; 21.8% higher tumor growth inhibition rate compared to mutated aptamer conjugated		

(*Continued*)

Table 1 (*Continued*)

Ligand	Receptor/antigen	Drug-NP platform	Types of study	Outcome		References
				Compared to non-targeted	Side effect	
Carbohydrates/polysaccharides						
Lactose	ASGPR	Doxorubicin-lactose	In vitro: human hepatocellular carcinoma cell lines (SMMC-7721)	No difference in cytotoxicity and cellular apoptosis; higher cellular uptake in time-dependent manner	Low nonspecific toxicity	53
			In vivo: cell lines SMMC-7721 xenograft	Higher tumor targeting; no difference in tumor growth inhibition rate		
Galactose	ASGPR	Doxorubicin-LPL	In vitro: human liver cancer cell lines (SK-HEP-1)	Higher cellular uptake; higher cytotoxicity in dose-dependent manner; higher cellular apoptosis	No significant change in liver enzyme	54
			In vivo: cell lines SK-HEP-1 orthotopic xenograft	Higher tumor growth inhibition rate		
Galactose	ASGPR	5-Fluorouracil-pectin	In vitro: human hepatocellular carcinoma cell lines (HepG2)	Higher cellular uptake; 2.6-fold higher cytotoxicity compared to free drug	Not evaluated	55
Galactosamine	ASGPR	Paclitaxel-γ-PGA-PLA	In vitro: cell lines HepG2	Higher cytotoxicity	Not evaluated	56
Galactose	Lecithin receptor	Doxorubicin solid lipid NP	In vitro: human lung cancer cell lines (A549)	1.5-Fold higher cellular uptake; higher cytotoxicity	Not evaluated	57
Other molecules						
EGF	EGFR	Gemcitabine-stearoyl	In vitro: human breast adenocarcinoma cell lines (MDA-MB-468, MDA-MB-231, and MCF-7)	Higher cellular uptake in MDA-MB-468; higher cytotoxicity	Not evaluated	58
			In vivo: cell lines MDA-MB-468 xenograft	Higher tumor growth inhibition rate; higher survival time		
			Ex vivo: MDA-MB-468 tumor	Higher tumor accumulation		
EGa1	EGFR	Doxorubicin-micelle	In vitro: human mouth squamous cell carcinoma cell lines UM-SCC 14C	Higher cellular uptake; higher cytotoxicity	Not evaluated	59
			In vivo: cell lines UM-SCC 14C xenograft	Higher tumor targeting; higher tumor growth inhibition rate; higher median survival time		
CSA	CD44 receptor	Doxorubicin-chondroitin sulfate A-deoxycholic acid	In vitro: human breast adenocarcinoma cell lines (MDA-MB-231)	Higher cellular uptake compared to free drug; 1.67-fold higher cytotoxicity compared to free drug	Not evaluated	60
Folic acid and bovine serum albumin	Folate receptor and SPARC	Paclitaxel-lipid	In vitro: human breast adenocarcinoma cell lines (MCF-7)	1.9-Fold higher cellular uptake	No significant change in body weight	61
Hyaluronic acid and glycyrrhetinic acid	CD44 and glycyrrhetinic acid receptor	Paclitaxel-glycyrrhetinic acid-graft-hyaluronic acid	In vitro: human hepatocellular carcinoma cell lines (HepG2) and murine melanoma cell lines (B16F10)	Higher cellular uptake compared to free drug; higher cytotoxicity to HepG2	Not evaluated	62

Abbreviations: ASGPR, asialoglycoprotein receptor; BSA, bovine serum albumin; cRGDyK, cyclic arginine-glycine-aspartic acid-tyrosine-lysine; DSPE-PEG2000, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-methoxy polyethylene glycol-2000; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; HACE, hyaluronic acid-ceramide; HSA, human serum albumin; HPAEG, hyperbranched poly(2-((2-(acryloyloxy) ethyl)disulfanyl)ethyl 4-cyano-4-(((propylthio)-carbonothioyl)-thio)-pentanoate-co-polyethylene glycol methacrylate; IL, interleukin; LbL-LCNP, layer-by-layer-liquid crystalline nanoparticle; LHRH, luteinizing hormone-releasing hormone; LHRHR, luteinizing hormone-releasing hormone receptor; LPL, lithocholic acid-polyethylene glycol-lactobionic acid; LRP, low density lipoprotein-receptor related protein; Lys-LA10, L-lysine methyl ester-lipoic acid; mAb, monoclonal antibody; MIONP, magnetic iron oxide nanoparticle; MSN, mesoporous silica nanoparticle; NP, nanoparticle; γ-PGA-PLA, poly(gamma-glutamic acid)-poly(lactic acid); PBLG, poly(γ-benzyl L-glutamate); PBLG-LA, G-poly(c-benzyl-L-glutamate)-lipoic acid; PCL, polyethylene glycol-poly(ε-caprolactone); PEG; polyethylene glycol; PEI, polyethylenimine; PLGA, poly(lactic-co-glycolic acid); PTMC, poly(trimethylene carbonate); RGD, arginine–glycine–aspartic acid peptide; RGDS, arginine–glycine–aspartic acid–serine peptide; SPARC, secreted protein, acidic and rich in cysteine; TbFGF, truncated basic fibroblast growth factor; TPGS, tocopheryl polyethylene glycol 1000 succinate; UnTHCPSi, undecylenic acid modified, thermally hydrocarbonized porous silicon.

Table 2 Summary of research articles that investigated active targeting NP delivering traditional/herbal medicines in cancer therapy

Ligand	Receptor/antigen	Drug-NP platform	Types of study	Outcome		References
				Compared to non-targeted	Side effect	
Proteins/peptides						
cRGD	Integrin $\alpha_v b_3$	Tanshinone IIA-mPEG-PLGA-PLL	In vitro: human hepatocellular carcinoma cell lines (Hep G2)	Higher cellular uptake; increase in cytotoxicity	No significant change in body weight	9
			In vivo: cell lines Hep G2 bearing mice	Higher tumor growth inhibition rate; higher accumulation of drug in tumor; 2.5-fold higher life-extended rate		
RGD	Integrin $\alpha_v b_3$	Curcumin-lipid-shell-polymer-core hybrid	In vitro: murine melanoma cell lines (B16)	No difference in cytotoxicity for B16; 19.6% higher cellular apoptosis compared to free drug	No significant change in body weight	10
			In vivo: cell lines B16 xenograft	Higher tumor growth inhibition rate		
Hyaluronic acid						
Hyaluronic acid	CD44 receptor	3,4-difluorobenzylidene curcumin-styrene maleic acid	In vitro: human pancreatic cancer cell lines (MiaPaCa-2, AsPC-1)	Higher cellular uptake in time-dependent manner; higher cytotoxicity – 1.75-fold for MiaPaCa-2 and 2-fold for AsPC-1	Not evaluated	63
Folate						
Folic acid	Folate receptor	Honokiol-PCEC	In vitro: human nasopharynx carcinoma cell lines HNE-1	Higher cellular uptake; 2.1-fold higher cytotoxicity compared with free drug; 15.2% higher percent of cell apoptosis	Not evaluated	11
			In vivo: cell lines HNE-1 tumor-bearing mice	1.3-fold delay in tumor growth compared with free drug; 1.7-fold higher median survival time		
Antibody						
Anti-annexin A2 antibody	Annexin A2 receptor	Curcumin-PLGA	In vitro: human breast adenocarcinoma cell lines (MDA-MB-231)	Higher cellular uptake	Not evaluated	64
Aptamer						
EpCAM aptamer	EpCAM protein	Curcumin-lipid-PLGA-lecithin hybrid	In vitro: human colon adenocarcinoma cell lines (HT29) and human embryonic kidney cell lines (HEK293T)	64-fold higher cellular uptake; higher cytotoxicity compared to EpCAM-negative HEK293T	Not evaluated	65
Other molecules						
HACE and AMPB	CD44 receptor and salicylic acid	Manassantin B-AMPB-HACE	In vitro: human breast adenocarcinoma cell lines (MDA-MB-231)	Higher cellular uptake compared to HACE conjugates alone; higher cytotoxicity compared to HACE conjugates alone	No significant change in body weight	66
			In vivo: cell lines MDA-MB-231 xenograft	2.4-fold higher tumor targeting compared to HACE conjugates alone; higher tumor growth inhibition rate		

Abbreviations: AMPB, (3-aminomethylphenyl)boronic acid; cRGD, cyclic arginine–glycine–aspartic acid peptide; HACE, hyaluronic acid-ceramide; mPEG-PLGA-PLL, methoxy polyethylene glycol-poly(lactic-co-glycolic acid)-poly-L-lysine; NP, nanoparticle; PCEC, poly(ε-caprolactone)-polyethylene glycol-poly (ε-caprolactone); PLGA, poly(lactic-co-glycolic acid); RGD, arginine–glycine–aspartic acid peptide.

(U87MG) compared with non-targeted nanoparticles and free drugs (mean IC_{50}: 0.022 μg/mL, 0.051 μg/mL, and 0.058 μg/mL, respectively). The targeted nanoparticles also exhibited greater activity on cell apoptosis (11.23% vs 8.31% and 8.03% vs 5.38% inhibition, for early and late apoptosis, respectively). The percentages (mean values) of free drug were 6.67% and 4.32%, respectively. In addition, cellular drug uptake by U87MG cells was significantly increased.[18] Superior cytotoxic potency against integrin $\alpha_v\beta_3$-overexpressing human cervical carcinoma cells (HeLa) together with increased cellular uptake was also demonstrated with RGD-conjugated magnetic iron oxide nanoparticles (MIONPs)-PEG delivering doxorubicin compared with free drug and non-targeted MIONPs.[19] In another study, improved cytotoxic activity by the cRGDyK-conjugated poly(2-ethyl-2-oxazoline)-poly(D,L-lactide) nanoparticles delivering paclitaxel over the non-targeted nanoparticles and free drug was reported (mean IC_{50}: 51.16 ng/mL, 64.53 ng/mL, and 62.95 ng/mL, respectively). The enhanced activity was through direct targeting of the integrin $\alpha_v\beta_3$-overexpressing prostate cancer cells (PC-3), as well as increasing of cellular uptake by PC-3 cells. Moreover, the targeted nanoparticle was also shown to enhance in vivo tumor growth inhibition rate in PC-3 tumor-bearing mice.[20]

Other types of peptides that have been applied for conjugation on the surface of nanoparticles to increase selectivity of chemotherapeutic drugs to cancer cells include bombesin peptide-conjugated poly(lactic-co-glycolic acid) (PLGA) and NR7 peptide-conjugated PLGA-PEG nanoparticles. Bombesin-conjugated nanoparticles delivering docetaxel specifically bind to gastrin-releasing peptide receptor, which is overexpressed on cell surfaces of prostate, breast, ovarian, pancreatic, and colorectal cancers.[22,68] This targeted nanoparticle was shown to enhance cytotoxic activity of the drug to the gastrin-releasing peptide receptor overexpressing human breast cancer cells (MDA-MB-231) compared with non-targeted nanoparticles (mean IC_{50}: 35.53 ng/mL and 142.23 ng/mL, respectively).[22] The NR7 peptide-conjugated PLGA-PEG nanoparticle delivering doxorubicin was used for specific drug binding to epidermal growth factor receptor (EGFR) on the cancer cell surface.[23] The EGFR is a known receptor that is overexpressed on various types of cancer cell surfaces including head and neck, renal, ovarian, breast, and non-small-cell lung cancer.[47,69] Activation of this receptor results in inhibition of cell apoptosis, promotion of cell proliferation, triggering of angiogenesis, and enhancement of tumor survival and metastasis. Therefore, inhibition of the function of this receptor would be expected to benefit cancer treatment. The NR7 peptide-conjugated PLGA-PEG nanoparticles exhibited higher cytotoxic activity against human ovarian carcinoma cells (SKOV3) compared with non-targeted nanoparticles (mean IC_{50}: 0.05 μg/mL and 3.12 μg/mL, respectively).[23] Although most studies demonstrated satisfactory outcomes of peptide- or protein-conjugated nanoparticles on targeting cancer cells, one study reported that H2009.1 peptide-conjugated liposome delivering doxorubicin to cancer cells expressing integrin $\alpha_v\beta_6$ receptor could not improve the efficacy of the drug. This was due to the liposome platform preventing the targeting ligand from binding to the receptor on the cancer cell surface, and resulted in relatively low drug accumulation in cancer cells.[12]

Hyaluronic acid

HA is a negatively charged linear glycosaminoglycan that consists of D-glucuronic acid and N-acetyl-D-glucosamine. It can specifically bind to CD44 receptor that is overexpressed on the cell surface of various types of cancer including lung, breast, colon, prostate, gastric, and head and neck cancers.[70] HA is a widely used targeting ligand to conjugate on the surface of nanoparticles to improve selectivity of chemotherapeutic drugs to cancer cells and enhance drug efficacy and safety. In one study, HA with the two molecular weights, ie, 9.5 kDa and 35 kDa, was used to conjugate polymeric micelles delivering paclitaxel. The conjugate using 9.5 kDa HA was found to effectively increase drug cellular uptake by CD44-overexpressing human breast adenocarcinoma cells (MCF-7) compared with 35 kDa HA. In murine hepatic carcinoma (Heps), it also exhibited tumor growth inhibition at a higher rate and greater accumulation at the tumor site compared with other nanoparticle formulations.[27] These results suggest that the molecular weight of HA directly influenced the efficacy of drug-loaded active targeting nanoparticles. The HA-conjugated chitosan nanoparticle delivering cisplatin was shown to increase drug cellular uptake by CD44-positive human lung cancer cells (A549) and effectively enhance cytotoxic activity of the drug, compared with non-targeted nanoparticles.[28] The HA-conjugated liquid crystalline nanoparticle delivering rapamycin was reported to increase cytotoxic activity of the drug to CD44-overexpressing human breast adenocarcinoma cells (MDA-MB-231) compared with non-targeted nanoparticles (mean IC_{50}: 18 μg/mL and 24.3 μg/mL, respectively). Moreover, the targeted nanoparticles also enhanced in vivo tumor growth inhibition rate in Ehrlich ascites tumor-bearing mice.[29]

For traditional/herbal medicines, HA has also been used for conjugation on the surface of nanoparticles delivering

3,4-difluorobenzylidene curcumin resulting in increased cellular uptake and cytotoxic activity of the drug against human pancreatic cancer cells (MiaPaCa-2 and AsPC-1) compared with non-targeted nanoparticles (mean IC_{50}: 140 nM, 160 nM, and 245 nM, respectively). Interestingly, when the CD44 receptor was blocked by free soluble HA, the cytotoxic activity to MiaPaCa-2 cells was comparable between the targeted and non-targeted nanoparticles (mean IC_{50}: 234 nM and 245 nM, respectively).[63] These results confirm that targeting ligand-conjugated nanoparticles enhances drug efficacy by improving cellular uptake through receptor-mediated endocytosis mechanism.

Folate

Folate or vitamin B9 is a stable and poorly immunogenic water-soluble vitamin. It is essential for DNA synthesis and replication, methylation, cell division and growth, and cell survival, particularly in rapidly dividing cells or cancer cells.[71] Folic acid receptor is overexpressed on several cancer cell surfaces including ovarian, cervical, breast, lung, kidney, colorectal, and brain cancers.[71] Using folic acid as cancer cell targeting of chemotherapeutic drug nanocarriers has been demonstrated in various studies to improve drug efficacy and safety profiles. The folic acid-conjugated PEG-PLGA nanoparticle delivering docetaxel was shown to increase drug cellular uptake by human cervical carcinoma cells (HeLa) with enhanced cytotoxic activity compared with free drug (mean IC_{50}: 0.69 μg/mL and 8.29 μg/mL, respectively). It also significantly inhibited tumor growth in HeLa tumor-bearing mice.[36] The folic acid-conjugated albumin nanoparticle delivering gemcitabine was shown to enhance cytotoxic activity of the drug against folic acid receptor-overexpressing human breast adenocarcinoma cells (MCF-7) compared with non-targeted nanoparticles (mean IC_{50}: 0.175 μM and 0.240 μM, respectively). Similarly, in folic acid receptor-overexpressing human ovarian cancer cells (Ovcar-5), the targeted nanoparticles exhibited superior cytotoxic activity over the non-targeted nanoparticles (mean IC_{50}: 0.173 μM and 0.279 μM, respectively). On the other hand, activity of the targeted nanoparticles was found similar to that of non-targeted nanoparticles against folate receptor expressing human pancreatic cancer cells (MIAPaCa-2) (mean IC_{50}: 0.166 μM and 0.169 μM, respectively).[38] In one study, the folic acid-conjugated PEG-PLGA nanoparticle delivering paclitaxel was shown to increase drug cellular uptake by folic acid-overexpressing human endometrial carcinoma cells (HEC-1A) with superior cytotoxic activity over the non-targeted nanoparticle (mean IC_{50}: 3.43 μg/mL and 8.81 μg/mL, respectively). Moreover, it also produced significantly higher cell apoptotic activity compared with non-targeted and free drug (35.94%, 23.97% and 19%, respectively). In vivo, it produced significant tumor growth inhibition in HEC-1A tumor-bearing mice.[43] For traditional/herbal medicines, folic acid-conjugated poly(epsilon-caprolactone)-PEG-poly (epsilon-caprolactone) nanoparticle delivering honokiol, a traditional Chinese medicine, was shown to increase compound cellular uptake by folic acid-overexpressing human nasopharynx carcinoma cells (HNE-1) with enhanced cytotoxic activity compared with free drug (mean IC_{50}: 18.41 μg/mL and 38.59 μg/mL, respectively). Furthermore, the targeted nanoparticles also resulted in significant cell apoptotic activity compared with non-targeted nanoparticles (86.07% and 70.89%, respectively) and prolongation of median survival time compared with non-targeted nanoparticles and free drug (median survival time: 57.5 days, 42.5 days, and 34 days, respectively).[11]

Antibodies or antibody fragments

Antibodies or antibody fragments are one of the first targeting ligands used for conjugation on the surface of nanoparticles to target cancer cells due to their potential to specifically bind to antigens or receptors on cancer cell surfaces with high affinity. Various types of antibodies or antibody fragments have been used as targeting agents including anti-CD20 monoclonal antibody, anti-CD47 monoclonal antibody, EGFR antibody, and anti-Fas monoclonal antibody. These targeted nanoparticles have been shown to improve cellular uptake by cancer cells and enhance cytotoxic activity of the drugs to cancer cells. For instance, anti-CD20 monoclonal antibody-conjugated 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-methoxypolyethylene-glycol-2000 delivers doxorubicin active carbon nanoparticles to the target CD20 receptor. It exhibited higher cytotoxic activity against CD20-positive human Burkitt's lymphoma cells (Raji) compared with non-targeted nanoparticles.[45] The anti-CD47 monoclonal antibody-conjugated iron oxide magnetic nanoparticle delivering gemcitabine to the target CD47 receptor was shown to increase drug cellular uptake by human pancreatic ductal adenocarcinoma cells (Panc215 and Panc354). Their cytotoxic activity was also significantly enhanced.[46] The EGFR antibody-conjugated PLGA nanoparticle delivering rapamycin was shown to exhibit higher cellular uptake by EGFR-overexpressing human breast adenocarcinoma cells (MCF-7) with enhanced cell apoptotic activity against all cell stages.[47] For traditional/herbal medicines, the anti-annexin A2 antibody-conjugated PLGA nanoparticle delivering

curcumin was shown to significantly increase compound cellular uptake by human breast adenocarcinoma cells (MDA-MB-231).[64]

Aptamers

Aptamers are short single-stranded DNA or RNA sequences that can fold to three-dimensional structure and bind to specific targets on the cancer cell surfaces that express specific targets for different aptamers. For instance, nucleolin receptor is specific for AS14111 aptamer and EpCAM protein is specific for EpCAM aptamer. The aptamer AS14111-conjugated PEG-PLGA nanoparticle delivering gemcitabine to target nucleolin receptor was shown to increase drug cellular uptake (36%) by nucleolin-overexpressing human lung cancer cells (A549) compared with non-targeted nanoparticles, with enhanced cytotoxic activity (IC_{50}: 4.9 µg/mL and 28.9 µg/mL, respectively).[49] The AS14111-conjugated undecylenic acid modified, thermally hydrocarbonized porous silicon (UnTH-CPSi) nanoparticle delivering methotrexate was shown to increase drug cellular uptake by nucleolin-overexpressing human breast adenocarcinoma cells (MDA-MB-231) with enhanced cytotoxic activity compared with non-targeted nanoparticles and nucleolin-negative fibroblasts cells (NIH 3T3).[50] The aptamer AS14111-conjugated polymersome delivering doxorubicin was shown to increase drug cellular uptake by nucleolin-overexpressing human breast adenocarcinoma cells (MCF-7) with enhanced cytotoxic activity compared with mutated aptamer-conjugated nanoparticles (mean IC_{50}: 210.9 ng/mL and 369.4 ng/mL, respectively). In addition, it also produced significant tumor growth inhibition in MCF-7 tumor-bearing mice compared with mutated aptamer-conjugated nanoparticles.[52] For traditional/herbal medicines, the EpCAM aptamer-conjugated lipid-polymer-lecithin hybrid delivering curcumin was shown to increase compound cellular uptake by EpCAM-overexpressing human colon adenocarcinoma cells (HT29) compared with EpCAM-negative human embryonic kidney cells (HEK293T), (58.9%±2.6% and 72.4%±1.3%, respectively.[65]

Carbohydrates or polysaccharides

Galactose is one of targeting ligands in group of carbohydrates that is widely used as a targeting agent for nanoparticles. It is specifically recognized by the asialoglycoprotein receptor (ASGPR), which is overexpressed on liver cancer cell surface.[54] The galactose-conjugated lithocholic acid-PEG-lactobionic acid nanoparticles delivering doxorubicin was shown to increase drug cellular uptake by human liver cancer cells (SK-HEP-1) leading to massive cell death and tumor growth inhibition compared with non-targeted nanoparticles.[54] The galactose-conjugated pectin nanoparticle delivering 5-fluorouracil was shown to increase drug cellular uptake by human hepatocellular liver carcinoma cells (HepG2) with enhanced cytotoxic activity compared with free drug (mean IC_{50}: 0.17×10^{-4} mol/L and 0.45×10^{-4} mol/L, respectively). Moreover, the targeted nanoparticle also improved pharmacokinetic profile of the drugs.[55] On the other hand, the lactose-conjugated nanoparticle delivering doxorubicin was shown to improve drug efficacy, but not as good as galactose.[53] The galactose conjugates not only specifically bind to ASGPR but also to lectin receptor, which is overexpressed on the alveolar macrophages, liver endothelial Kupffer cells, splenic macrophages, peritoneal macrophages, and macrophages of brain. The galactose-conjugated solid lipid nanoparticles delivering doxorubicin specifically targeted human lung cancer cells (A549) resulting in higher cellular uptake, enhanced cytotoxic activity, and improved pharmacokinetic profiles compared with non-targeted nanoparticles and free drug.[57]

Controlled drug release of active targeting nanoparticles

Controlled drug release is a property of drug delivery systems in cancer therapy. Drugs are delivered and released at specific location to avoid side effects to normal cells.[72] Most studies included in this review showed biphasic characteristics of drugs released from both targeted and non-targeted nanoparticles, ie, initial burst release, followed by sustained release. For instance, about 48% and 46% of gemcitabine were released from folic acid-conjugated bovine serum albumin nanoparticles and non-targeted nanoparticles during the first 2 hours, respectively. Sustained release of up to 99% and 94% was observed at 36 hours and pH 7.4 after burst release of targeted and non-targeted nanoparticles, respectively.[38] About 22% and 29% of doxorubicin were shown to release from galactose-conjugated solid lipid nanoparticles and non-targeted nanoparticles during the first 8 hours, respectively. After burst release, sustained released was observed up to 76% and 93% at 144 h and pH 7.4 for targeted and non-targeted nanoparticles, respectively.[57] Moreover, in some cases, the amount of drug released from nanoparticles at endolysosomal environment (pH 5.5) or cancer cell environment (pH 6.8) was shown to be higher than that from physiological environment (pH 7.4). Up to 60% of doxorubicin was released from anti-CD20-conjugated active carbon nanoparticles and non-targeted nanoparticles at 12 hours and at pH 5.5. At pH 7.4, on the other hand, the release

from nanoparticles was only 20%.[45] Similarly, about 28% and 24% of gemcitabine burst were released during the first 24 hours from AS1411 aptamer-conjugated PEG-PLGA nanoparticles and non-targeted nanoparticles, respectively. After burst release, up to 44% and 41% sustained release were observed in both formulations at 120 hours and pH 5.5 for targeted and non-targeted nanoparticles, respectively. Only 30% release was observed at pH 7.4.[49] In another study, doxorubicin released from chondroitin sulfate A-deoxycholic acid at day 6 was 92%, 53%, and 34% for pH 5.5, 6.8, and 7.4, respectively.[60] These results suggested that conjugation of targeting ligands on the surface of nanoparticles did not affect drug release from nanoparticles. Furthermore, higher amount of drug released at acidic pH would benefit the delivery of cancer chemotherapeutic agents to cancer cells with lower side effects to normal cells.

Conclusion

Active targeting nanoparticles of chemotherapeutic drugs or traditional/herbal medicines have been demonstrated in various studies both in vitro and in vivo to improve selectivity of cellular uptake of drugs to cancer cells through receptor-mediated endocytosis and/or cytotoxicity. They provide several advantages over the conventional chemotherapeutic drugs and non-targeted nanoparticle platform, particularly in regard to enhancement of drug efficacy and safety. Active targeting nanoparticles possess several advantages in cancer therapy including enhancement of selectivity of drugs to cancer cells to avoid side effects to normal cells, enhancement of drug accumulation and anticancer activity in cancer cells, and efficiency in control of drug release. Nevertheless, some disadvantages of active targeting nanoparticles include their limitation of clinical uses in only certain types of cancer that express specific receptors on the cell surfaces. Moreover, manufacturing of nanoparticle platforms is costly and requires sophisticated technology. Selection of the types of targeting nanoparticles is determined by the types of target proteins or receptors expressed on cancer cell surfaces. Clinical studies are required to confirm their application in cancer patients.

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Disclosure

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