DRUG DELIVERY
2022, VOL. 29, NO. 1, 2130–2161
https://doi.org/10.1080/10717544.2022.2094498

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REVIEW

Nano-drug co-delivery system of natural active ingredients and chemotherapy drugs for cancer treatment: a review

Bingqian Li, Huili Shao, Lei Gao, Huan Li, Huagang Sheng and Liqiao Zhu

College of Pharmacy, Shandong University of Traditional Chinese Medicine, Jinan, China

ABSTRACT

Chemotherapy drugs have been used for a long time in the treatment of cancer, but serious side effects are caused by the inability of the drug to be solely delivered to the tumor when treating cancer with chemotherapy. Natural products have attracted more and more attention due to the antitumor effect in multiple ways, abundant resources and less side effects. Therefore, the combination of natural active ingredients and chemotherapy drugs may be an effective antitumor strategy, which can inhibit the growth of tumor and multidrug resistance, reduce side effects of chemotherapy drugs. Nano-drug co-delivery system (NDCDS) can play an important role in the combination of natural active ingredients and chemotherapy drugs. This review provides a comprehensive summary of the research status and application prospect of nano-delivery strategies for the combination of natural active ingredients and chemotherapy drugs, aiming to provide a basis for the development of anti-tumor drugs.

ARTICLE HISTORY
Received 25 April 2022
Revised 17 June 2022
Accepted 20 June 2022

KEYWORDS
Nano-drug co-delivery system; combination therapy; natural active ingredients; chemotherapy drugs; nanocarrier

1. Introduction

Cancer is a major public health problem worldwide (Siegel et al., 2021). In nearly 100 countries around the world, regardless of the level of development, cancer is one of the highly prevalent malignant diseases which is a major cause of morbidity and mortality. Cancer will become the leading cause of death in every country in the 21st century and the most important obstacle to extending life expectancy (Sarisozen et al., 2016; Bray et al., 2018). The traditional methods of cancer treatment include surgical resection, chemotherapy and radiation therapy. Immunotherapy (Fu et al., 2022) and photothermal therapy (Dai et al., 2022) have also emerged in recent years.

Chemotherapeutics, also known as cytotoxic drugs, have been used in antitumor therapy since the 1940s. They played an important role in tumor treatment. The mechanism of chemotherapeutics is complex, including affecting the chemical structure of DNA, inhibiting nucleic acid synthesis, acting on nucleic acid transcription and DNA replication and interfering with mitotic tubulin synthesis (Xu et al., 2019a). However, the target of chemotherapy drugs is also very important for normal cells, which can cause inevitable damage to the body during chemotherapy, such as hair loss and gastrointestinal toxicity. Therefore, combination, synergistic chemotherapy is a common strategy, and has been recommended for tumor treatment due to its promoted therapeutic effect and reduced systemic toxicity (Wan et al., 2019; Maleki et al., 2021; Liu et al., 2021b). Nevertheless, co-administration therapy may also have additive or synergistic effects resulted from interaction with several distinct targets at reduced administrated doses (Eftekhari et al., 2019). At present, there have been studies on nano-drug delivery system (NDDS) for the co-delivery of chemotherapy drugs with photosensitizers (Xiao et al., 2021; Zhang et al., 2021b), and natural active ingredients.

In recent years, natural products have become the top priority of antitumor drug research and development due to their clear antitumor effectiveness and richness of candidate resources (Yin et al., 2019). Natural drugs are safe and have little side effects (Liu et al., 2020b), which can enhance immunity and improve chemotherapy sensitivity. More attractively, the synergistic combination therapy with natural chemotherapy sensitizers is becoming a promising strategy for conquering multidrug resistance and reducing the side effects of chemotherapy drugs (Wang et al., 2015a). Therefore, the combination of natural active ingredients and chemotherapy drugs may be an effective antitumor strategy. Co-delivery of mutiple drugs via the same vehicle may improve the chemotherapy of tumors by synchronizing their exposure to the drugs and achieving synergistic pharmacological action in the tumor cells (Wan et al., 2019). Additionally, NDDS usually have good biocompatibility (Sun et al., 2021b), low side effects (Zhu et al., 2019), targeting (Lan et al., 2021b), controlled release characteristics (Chen et al., 2020a), which have brought promising prospect in cancer therapies due to their uniquely appealing properties (Maleki et al., 2021; Liu et al., 2021b). To date, advancements in nanotechnology provide

CONTACT Huagang Sheng shenghuagang@163.com; Liqiao Zhu zliqiao@163.com College of Pharmacy, Shandong University of Traditional Chinese Medicine, Daxue Road 4655, Jinan 250355, China

This article was originally published with errors, which have now been corrected in the online version. Please see Correction (http://dx.doi.org/10.1080/10717544.2022.2127213)

more significant improvements and valuable information for drug co-delivery systems (Zhang et al., 2021a), including nanoparticles, liposomes, polymer micelles, polymer drug conjugates (Majidinia et al., 2020). More importantly, the antitumor drug delivery system based on nanocarriers clearly shows the potential to overcome the problems related to traditional chemotherapy (Sohail et al., 2021). In recent years, with the continuous development of nano drug carriers, some of them have been tested in clinical trials or used for disease diagnosis and treatment (Zang et al., 2021). Nano drug co-delivery system (NDCDS), which loads at least two anticancer drugs with different physicochemical and pharmacological properties into a delivery system, is designed for the purpose of clinical combination chemotherapy (Qi et al., 2017). In this paper, the research status and application characteristics of NDCDS of natural active ingredients combined with chemotherapy drugs are reviewed and analyzed, which aim to provide a basis for the research and development of natural active ingredients and chemotherapy drugs for cancer treatment.

2. The effect of natural active ingredients combined with chemotherapy drugs

Studies have confirmed that the combination of natural active ingredients and chemotherapy drugs exert a synergistic antitumor effect through a variety of mechanism. Besides direct antitumor effect, natural active ingredients also can inhibit tumor multidrug resistance (MDR), decrease side effects of chemotherapy drugs, and modulate immune function.

2.1. Induce tumor cell apoptosis and inhibit tumor cell proliferation

Some natural active ingredients, such as schisandrin B (Sch B), β-elemene (β-ELE), betulinic acid (BA), quercetin (Que) and curcumin (CUR), can directly exert antitumor effect through inducing tumor cell apoptosis and inhibiting tumor cell proliferation when combined with chemotherapy drugs. Sch B could inhibit the invasion and metastasis of lung cancer cells by inhibiting vascular endothelial growth factor. At the same time, it could also enhance the cytotoxicity of doxorubicin (DOX) and further promote cell apoptosis (Cai et al., 2020). β-ELE could inhibit cell proliferation, arrest cell cycle and induce apoptosis (Zhai et al., 2019). BA had an effective antitumor effect on paclitaxel (PTX)-resistant human lung cancer cells (H460) through G2/M cell cycle arrest and induced mitochondrial apoptosis (Zhan et al., 2018). BA may also inhibit the proliferation, migration, invasion and tumorigenesis of pancreatic cancer cells by activating AMPK signal, and it combined with gemcitabine (GEM) had an antitumor effect on pancreatic cancer cells (Sun et al., 2019). Que combined with PTX significantly inhibited cell proliferation and increased cell apoptosis, blocked cell cycle at G2/M phase, inhibited cell migration, induced endoplasmic reticulum stress, and increased reactive oxygen species (ROS) production (Zhang et al., 2020b). CUR could improve PTX-induced apoptosis of HPV-positive human cervical cancer cells through NF-κB-p53-caspase-3 pathway, and it combined with PTX may have a better therapeutic effect in the treatment of human cervical cancer (Dang et al., 2015). Cheng et al. (2018) found that CUR could improve the antitumor effect of Cisplatin (CDDP). The mechanism was related to ROS, and the content of ROS was positively correlated with the inhibition of cell proliferation. The combined treatment of RES and 5-fluorouracil (5-FU) could enhance the anti-proliferation effect on colorectal cancer cells (HCT116 and DLD1), induce cell cycle arrest and increase apoptosis in S phase, inhibit pAkt and pSTAT3 signal transduction, and reduce telomerase activity (Chung et al., 2018). RES could activate TRPM2 channels in DBTRG glioblastoma cells to enhance PTX apoptosis and oxidation by increasing intracellular steady-state ROS levels and mitochondrial dysfunction (Ozturk et al., 2019). In addition, β-ELE promoted the anti-proliferation and apoptosis of CDDP in gingival squamous cell carcinoma (GSCC) *in vitro* and *in vivo* by inhibiting STAT3 and blocking JAK2-STAT3 signaling pathway (Huang & Yu, 2017). β-ELE inhibited the proliferation of bladder cancer cells *in vitro* through ROS-5'AMP-activated protein kinase (AMPK) signaling pathway and enhanced CDDP-induced mitochondrial-dependent apoptosis (Gan et al., 2020). Rhein and DOX played a synergistic antitumor effect by reducing mitochondrial energy metabolism in hepatocellular carcinoma cells (Wu et al., 2020a). BCL combined with DTX inhibited tumor growth, increased cell apoptosis, and reduced tumor angiogenesis *in vivo*, and enhanced the antitumor effect of DTX on non-small cell lung cancer (NSCLC) in a β-catenin-dependent manner (Lu et al., 2020a). Oridonin and DOX presented a synergistic cytotoxic effect in osteosarcoma cells. Oridonin increased the accumulation of intracellular DOX and the rate of apoptosis (Kazantseva et al., 2022). Compared with brusatol (BR) or CDDP alone, CDDP and BR could exert synergistic anti-tumor effect by increasing the release of cytochrome c in CT-26 cells, decreasing the expression of caspase-3 and caspase-9, and increasing the ratio of the B-cell lymphoma 2 (Bcl-2)-associated X protein/Bcl-2 (Chen et al., 2018). CDDP and triptolide (TPL) combination treatment could induce apoptosis by increasing the expression of caspase-3, 8 and 9, PARP and cytochrome c (Ho et al., 2015).

2.2. Inhibit tumor multidrug resistance

Tumor multidrug resistance (MDR) refers to the phenomenon that tumor cells are resistant to a series of chemotherapy drugs with different structures and mechanisms when they are resistant to a kind of chemotherapeutic drug, which is an important reason for the failure of chemotherapy in clinic (Kunjachan et al., 2013; Cao et al., 2018). The mechanisms of MDR include elevated metabolism of xenobiotics, enhanced efflux of drugs, growth factors, increased DNA repair capacity, and genetic factors (gene mutations, amplifications, and epigenetic alterations) (Bukowski et al., 2020). Several factors could be associated with drug resistance in cancer such as overexpression of P-glycoprotein (P-gp), cancer stem cells (CSCs), defect in apoptosis, mutation and alteration in DNA repair pathways, angiogenesis, autophagy, and modulation

in metabolic enzymes (Mohammad et al., 2020). One of the advantages of co-loading natural active ingredients with chemotherapy drugs is to reverse MDR. Many natural components, such as resveratrol (RES) (Zhang et al., 2016b), tetrandrine (TET) (Liao et al., 2019; Li et al., 2020e), epigallocatechin gallate (EGCG) (Cheng et al., 2016), pachymaric acid and dehydrotudouic acid (PT) (Li et al., 2020f), quinine hydrochloride (QN) (Shen & Qiu, 2017), β-ELE (Zhang & Guo, 2021), ferulic acid (FA) (Muthusamy et al., 2016), naringin (Jabri et al., 2019), baicalein (BCL) (Li et al., 2018b), Que (Lu et al., 2020b) and Sch B (Wang et al., 2017), could inhibit MDR by inhibiting the ABC transport, including P-gp, BCRP, ABCB1, etc. In addition, natural components can also inhibit MDR effects by inhibiting epithelial-mesenchymal transition through other pathways, such as RES (Buhrmann et al., 2015; Xu et al., 2017b), EGCG (Yuan et al., 2017) and BCL (Yu et al., 2017). At the same time, some natural components can inhibit MDR effects by acting on genetic factors, such as Que (Sang et al., 2014), CUR (Lu et al., 2017a; Xu et al., 2020), RES (Vinod et al., 2015), cinnamaldehyde (CA) (Abbasi et al., 2020) and chrysin (Lee et al., 2021). Rhein could increase the accumulation of DOX in SMMC-7721/DOX cells by inhibiting energy metabolism and inducing the opening of mitochondrial permeability transition pore (mPTP), and reverse the drug resistance of SMMC-7721/DOX cells (Wu et al., 2019a). A summary of the mechanism of reversing MDR of chemotherapy drugs by different natural active ingredients is shown in Table 1.

2.3. Decrease side effects of chemotherapy drugs

Chemotherapy drugs can also damage normal tissues or cells of the body while treating tumors, resulting in toxic and side effects. Natural active ingredients combined with chemotherapy drugs can affect on tumor tissues from multiple targets and pathways, and reduce its toxicity by reducing the dosage of chemotherapy drugs. Zeng et al. (2019) found that β-ELE could replace part of cabazitaxel (CBX) and reduce the dosage of CBX, thereby reducing toxicity. Jiang et al. (2016) found that the antitumor activity of CUR combined with etoposide (ETP) was higher than that of CUR and ETP alone, and the dosage was reduced.

Some natural active ingredients can also directly decrease the side effects of chemotherapy drugs, improve the safety of clinical medication. Many natural active ingredients, such as berberine (BER) (Coelho et al., 2017; Wu et al., 2019b), EGCG (Cheng et al., 2016), honokiol (Huang et al., 2017; Pillai et al., 2017; Huang et al., 2020), RES (Gu et al., 2018), glycyrrhizin (GL) (Figure 1) (Lv et al., 2020), Que (Chen et al., 2019) and Sch B (Thandavarayan et al., 2015; Cai et al., 2020), could reduce DOX-induced cardiotoxicity. In addition, BER (Wang et al., 2021) could reduce irinotecan-induced gastrointestinal toxicity. RES could reduce PTX-induced neuropathic pain (Li et al., 2019c). Chrysin could reduce methotrexate (MTX)-induced Hepatotoxicity (Ali et al., 2014). Angelica polysaccharide (ASP) could protect bone marrow stromal cells from 5-FU chemotherapy damage (Xiao et al., 2017). CUR could improve CDDP-induced spatial learning and memory impairment (Oz et al., 2015) and nerve oxidative damage (Ozkaya & Naziroglu, 2020). CUR (Soetikno et al., 2019) and oleanolic acid (OA) (Potocnjak et al., 2019) could reduce CDDP-induced nephrotoxicity. A summary of the mechanism of natural active ingredients reducing side effects of chemotherapy drugs is shown in Table 2.

2.4. Immunomodulating activity

The immune function of the body has a great influence on the occurrence and development of tumors. Tumor immunotherapy can achieve the purpose of identifying and killing tumor cells by regulating the immune ability of patients, and minimize the toxicity (Zhang et al., 2016c).

The study has shown that natural polysaccharides can activate T lymphocytes, B lymphocytes, macrophages and other immune cells to exert their immune activities (Chen & Huang, 2018). ASP could restore the balance of Th1/Th2 immune response, improve tumor microenvironment immunosuppression and enhance antitumor immune function, resulting in synergistic antitumor effect with DOX (Wang et al., 2020). Astragalus polysaccharides (APS) could exert anti-tumor effects by restoring immune organs, regulating cellular immune response and increasing the levels of cytokines IL-2, TNF-α and IFN-γ. In addition, APS combined with 5-FU could improve the anti-tumor effect accompanied by the immunosuppressive alleviation of 5-FU on immune system, which may be suitable as an immune adjuvant for chemotherapy (Li et al., 2020c). Que could reshape the tumor microenvironment (TM) by reducing the expression of collagen, and promote the penetration of DOX into deep tumor tissues, so as to obtain better antitumor effect (Li et al., 2019b). Quagliariello et al. (2017) found that the combination of rapamycin (RAP) and Que could significantly reduce the levels of IL-8, IL-6 and IL-19 cytokines, suggesting that the combination could regulate the immune state of the body and enhance tumor immunity. Guo et al. (2016) found that andrographolide combined with bleomycin could reduce the levels of IL-1β, TNF-α, IL-6 and TGF-β1 cytokines, regulate the immune state of tumor cells, indicating that andrographolide can be used as an adjuvant drug for bleomycin.

3. Advantages of NDCDS of natural drug active ingredients and chemotherapy drugs

3.1. Increase the capacity of targeting delivery of drugs to tumors

Targeted therapy in cancer is the primary role of NDCDS of natural drug active ingredients and chemotherapy drugs. The efficiency of nano-drug targeting tumor depends on the physical and chemical properties of nanocarriers (such as size and surface chemical properties) and the pathophysiological characteristics of target tissues. At present, the clinical application of nano-drugs mostly relies on passive targeting (Arranja et al., 2017). Additionally, nanocarriers can be modified by surface modification, and target molecules can be combined with receptors with high expression on the surface

Table 1. Mechanism of natural active ingredients reversing MDR of chemotherapy drugs.

Mechanism of natural active ingredients	Chemotherapy drugs	Natural active ingredients	Ref
Inhibit the activation of NF-κB and p38 MAPK signaling pathways to reverse p-Glycoprotein (P-gp)-mediated cellular MDR	Adriamycin	Resveratrol (RES)	(Zhang et al., 2016b)
Down-regulate the expression of ABCB1 transporter to increase the intracellular concentration of chemotherapy drugs	Doxorubicin (DOX), Vincristine, Paclitaxel (PTX)	Tetrandrine (TET)	(Liao et al., 2019)
Inhibit P-gp transport activity to reduce the outflow of DOX in cancer cells	DOX	Epigallocatechin gallate (EGCG)	(Cheng et al., 2016)
Reduce the levels of P-gp and caveolin-1 protein to enhance the sensitivity of DOX to drug-resistant MCF cells	DOX	Pachymaric acid and dehydrotudouic acid	(Li et al., 2020f)
Inhibit the function of P-gp and acting as the sensitizer of DOX to prevent the outflow of DOX from MCF-7/ADR cells	DOX	Quinine hydrochloride (QN)	(Shen & Qiu, 2017)
Inhibit the antioxidant protein peroxiredoxin-1 to reverse DOX resistance of DOX-resistant osteosarcoma cells	DOX	β-elemene (β-ELE)	(Zhang & Guo, 2021)
Inhibit the expression of P-gp and down-regulating the expression of anti-apoptotic protein surviving to increase the intracellular accumulation of DOX	DOX	Schisandrin B (Sch B)	(Wang et al., 2017)
Down-regulating ABCB1 expression to overcome P-gp-mediated MDR	PTX	Ferulic acid (FA)	(Muthusamy et al., 2016)
Inhibit the expression of breast cancer resistance protein (BCRP) to enhance the antitumor activity of PTX in BCRP-mediated MDR	PTX	Naringin	(Jabri et al., 2019)
Reduce the expression of P-gp to increase the accumulation of antitumor drugs	5-fluorouracil (5-FU), Epirubicin	Baicalein (BCL)	(Li et al., 2018b)
Reduce the activation of PI3K/Akt signaling pathway, reducing the expression of P-gp, and reversing the phenotypes of mesenchymal cells and stem cell-like cells to reverse DTX resistance	Docetaxel	Quercetin (Que)	(Lu et al., 2020b)
Sensitize glioblastoma cells to DOX	DOX	Cinnamaldehyde (CA)	(Abbasi et al., 2020)
Improve the sensitivity of rat glioma cell line (C6) cells to TMZ	Temozolomide	Curcumin (CUR)	(Xu et al., 2020)
Inhibit Hsp27 to sensitize glioblastoma cells to TMZ	Temozolomide	Que	(Sang et al., 2014)
Regulate PTEN/Akt signaling pathway to prevent epithelial-mesenchymal transition (EMT), thereby reversing DOX resistance in gastric cancer	DOX	RES	(Xu et al., 2017b)
Stimulate AKT/STAT3 pathway and inhibiting MDR1 signaling pathway to sensitize the apoptosis and autophagy of CDDP-resistant oral cancer CAR cells	Cisplatin (CDDP)	EGCG	(Yuan et al., 2017)
Inhibit epithelial-mesenchymal transition (EMT) and anti-apoptotic genes mediated by PI3K/Akt/NF-κB pathway to reverse CDDP resistance of A549 lung adenocarcinoma cells	CDDP	BCL	(Yu et al., 2017)
Up-regulate intercellular connection and down-regulating NF-κB pathway to inhibit EMT phenotype, chemical sensitizing colorectal cancer cells to enhance the antitumor effect of 5-FU on colorectal cancer cells	5-FU	RES	(Buhrmann et al., 2015)
Inhibit energy metabolism and inducing the opening of mitochondrial permeability transition pore (mPTP) to increase the accumulation of DOX in SMMC-7721/DOX cells	DOX	Rhein	(Wu et al., 2019a)
Reduce microRNA-30c-mediated metastasis-associated gene 1 to increase the sensitivity of PTX -resistant non-small cell lung cancer cells to PTX	PTX	CUR	(Lu et al., 2017a)
Block the G2/M phase to increase the resistance of 5-FU to 5-FU-resistant AGS cells.	5-FU	Chrysin	(Lee et al., 2021)
Block the expression and activation of human epidermal growth factor receptor-2(HER-2) to induce the death of SK-BR-3 cells overexpressing HER-2	Docetaxel	RES	(Vinod et al., 2015)

of tumor cells to achieve the purpose of active targeting delivery of drugs. Common targeted modification molecules include folate (FT) (Hu et al., 2015), hyaluronic acid (HA) (Zhang et al., 2019a), lactoferrin (Lf) (Fang et al., 2014), polypeptide (Yan et al., 2017; Zan et al., 2019; Deng et al., 2020), wheat germ lectin (Wang et al., 2019c), fucoidan (Chu et al., 2019), folic acid (FA) (Rawal et al., 2020a), prostate-specific membrane antigen targeted ligand (Sun et al., 2021a), rituximab (Varshosaz et al., 2021), etc.

Guo et al. developed star-shaped polyester-based folic acid-modified nanoparticles (DOX + CUR-FA-NPs) to co-deliver DOX and CUR to enhance tumor targeting selectivity. *In vitro* and *in vivo* experiments showed (DOX + CUR)-FA-NPs not only had remarkable tumor targeting and anticancer efficacy, but also had less side effects on normal tissues (Guo et al., 2021). Deng et al. (2020) developed a pH-responsive targeting nanosystem modified with T7 peptide, which co-loaded DTX and CUR for the treatment of esophageal cancer. This T7 peptide-modified targeting nanosystem released loaded drugs in the acidic microenvironment of tumor and played a synergistic antitumor effect. Wang et al. (2016) prepared arginine-glycine aspartic acid (RGD) modified lipid-coated

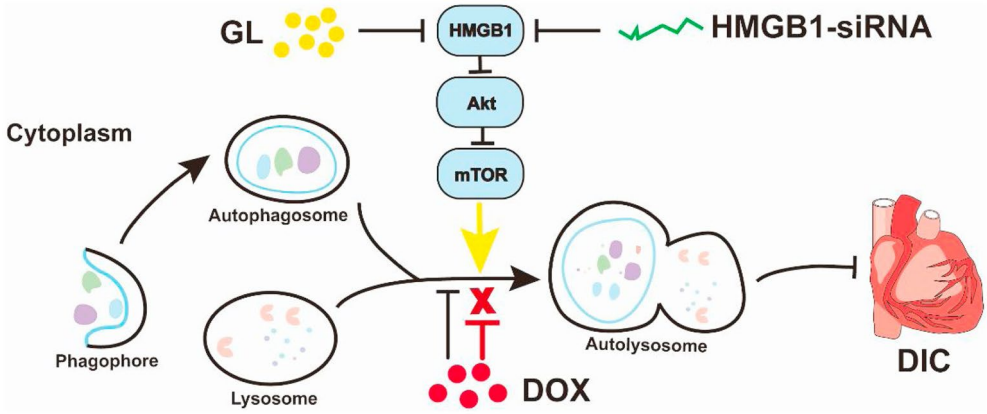

Figure 1. Schematic of GL attenuating DOX-induced cardiotoxicity. Reprinted with permission from Lv et al. (2020).

Table 2. Mechanism of natural active components reducing side effects of chemotherapy drugs.

Side effects	Chemotherapy drugs	Natural active ingredients	Mechanism of natural active ingredients	Ref
Cardiotoxicity	DOX	Berberine (BER)	Reduce oxidative stress and mitochondrial dysfunction, p66Shc mediated by sirtuin 1 (SIRT1) and sirtuin 3 (SIRT3) to protect against DOX-induced cardiotoxicity	(Coelho et al., 2017; Wu et al., 2019b)
Cardiotoxicity	DOX	EGCG	Scavenge ROS produced by DOX and prevent ROS from attacking cardiomyocytes to reduce DOX-induced cardiotoxicity	(Cheng et al., 2016)
Cardiotoxicity	DOX	Honokiol	Mediate the activation of SIRT3, inhibit mitochondrial protein acetylation, enhance cardiac PPARγ activity, inhibit the expression of thioredoxin-interacting protein and the NOD-like receptor family pyrin domain-containing 3 to protect the heart from DOX-induced cardiac injury	(Huang et al., 2017; Pillai et al., 2017; Huang et al., 2020)
Cardiotoxicity	DOX	RES	Block DOX-induced E2F transcription factor 1/AMP-activated protein kinase α2 and E2F1/mammalian rapamycin (RAP) target protein complex 1 in cardiomyocytes to reduce DOX-induced cytotoxicity	(Gu et al., 2018)
Cardiotoxicity	DOX	Glycyrrhizin (GL)	Improve autophagy flux through Akt/mTOR signaling pathway dependent on high mobility group protein 1 to reduce DOX-induced cardiotoxicity	(Lv et al., 2020)
Cardiotoxicity	DOX	Que	Inhibit oxidative stress and up-regulate the expression of 14-3-3γ to protect cardiomyocytes from DOX injury	(Chen et al., 2019)
Cardiotoxicity	DOX	Sch B	Regulate DNA damage, oxidative stress, and inflammation by inhibiting MAPK/p53 signaling pathway to prevent DOX-induced cardiac dysfunction	(Thandavarayan et al., 2015)
Gastrointestinal toxicity	Irinotecan	BER	Reduced the gastrointestinal toxicity caused by irinotecan	(Wang et al., 2021)
Neuropathic pain	PTX	RES	Reduce apoptosis, inhibited inflammation, and alleviate oxidative stress by activating PI3K/Akt and SIRT1/PGC1α signaling pathways to prevent PTX -induced neuropathic pain	(Li et al., 2019c)
Hepatotoxicity	Methotrexate (MTX)	Chrysin	Restore the antioxidant defense function of cells and down-regulate the expression of p53, Bax, and caspases 3 to reduce MTX-induced hepatotoxicity	(Ali et al., 2014)
Bone marrow stromal cells injury	5-FU	Angelica polysaccharide (ASP)	Reduce oxidative damage of stromal cells and improve their hematopoietic function to protect bone marrow stromal cells from 5-FU chemotherapy damage	(Xiao et al., 2017)
Spatial learning and memory impairment	CDDP	CUR	Restore cholinergic function and enhance oxidative state to improve CDDP-induced spatial learning and memory impairment	(Oz et al., 2015)
Nerve oxidative damage	CDDP	CUR	Inhibit mitochondrial ROS production by regulating transient receptor potential melastatin 2 signaling pathway to prevent CDDP-induced optic nerve oxidative damage and cell death	(Ozkaya & Naziroglu, 2020)
Nephrotoxicity	CDDP	CUR	Inhibit inflammation, apoptosis, extracellular regulated kinase 1/2 phosphorylation, and NF-κB expression of oxidative stress	(Soetikno et al., 2019)
Nephrotoxicity	CDDP	Oleanolic acid (OA)	Inhibit oxidative stress, apoptosis, autophagy, and inflammatory response induced by CDDP	(Potocnjak et al., 2019)

PLGA nanoparticles (RGD-SRF-Que NPs) for targeted delivery of sorafenib (SRF) and Que to treat liver cancer. The results showed that the efficacy of SRF combined with Que preparations in both the NPs group and the solution group were better than that of a single drug preparation. And RGD-SRF-Que NPs had a more significant tumor growth

inhibitory effect than non-RGD modified SRF-Que NPs. Chu et al. (2019) used dual nanosystems to jointly deliver EGCG and CUR. A dual targeting system was established by using HA and fucoidan as targeting agents for CD44 on prostate cancer cells and P-selectin in tumor vascular system, respectively. It was found that compared with EGCG/CUR combined solution, EGCG/CUR loaded nanoparticles were more absorbed into prostate cancer cells, resulting in better antitumor efficiency.

3.2. Maintain the optimal proportion of combined drug administration

In combination antitumor therapy, the optimal proportion of drugs has a great influence on the antitumor effect. The inappropriate proportion of drugs may cause antagonism of combined drug administration and reduce the therapeutic effect. NDCDS can change the original pharmacokinetic characteristics of drugs, so as to ensure that the combined drugs enter tumor cells with a constant proportion, which is conducive to the synergy between drugs.

At present, in order to maintain the optimal ratio of combined drug administration, the optimal ratio of the two drugs was first screened through *in vitro* cytotoxicity experiments and calculation of the combination index. Then the nano-formulations are prepared according to the proportions. Finally, *in vitro* release and *in vivo* pharmacokinetic studies were used to verify whether the optimal proportion was maintained in the nano-formulations. Jia et al. (2015) prepared multifunctional mesoporous silica nanoparticles (MSN) co-delivery of PTX and TET. When the molar ratio of PTX/TET was 4.4:1, the drug resistance of MCF-7/ADR cells to PTX was completely reversed, and it was more effective than PTX-CTAB @ MSN or free PTX in inhibiting the growth of tumor cells. Chen et al. (2014) developed PLGA nanoparticles co-delivery of VCR and verapamil (VRP). In multidrug resistant MCF-7/ADR cells, the 1:250 molar ratio of VCR/VRP showed a strong synergistic effect, which could enhance the efficacy of multidrug resistant breast cancer and reduce the toxicity to normal cells. Chen et al. (2017) prepared bovine serum albumin (BSA) coated supermagnetic iron oxide nanoparticles (SPIOs) by co-precipitation method. CUR and sunitinib (Sun) were co-loaded in BSA-SPIOs (denoted as SPIO-SC) to achieve synergistic treatment. The study showed that the proportion range of the initial designed optimal concentration of CUR and Sun was maintained at the tumor target site (Sun:CUR = 0.5–0.25), resulting in the optimal synergistic effect and more effective treatment results. Rawal et al. (2020a) developed FA modified NLCs to promote the targeting and proportional co-delivery of DTX and CUR, namely FA-DTCR-NLCs. In vivo pharmacokinetic study, DTX and CUR showed a synergistic ratio of 1:2 throughout the cycle. The *in vivo* toxicity evaluation of FA-DTCR-NLCs showed that DTX-related side effects were significantly reduced. The results of preclinical studies *in vitro* and *in vivo* proved the excellent therapeutic and safety of FA-DTCR-NLCs in the treatment of NSCLC.

Liposomes can also be used to maintain the required proportion of synergistic drugs and coordinate the release of co-delivery drugs to achieve enhanced antitumor activity *in vivo* (Shen & Qiu, 2017). Cheng et al. (2018) prepared CUR and CDDP co-loaded liposomes (CDDP/CUR-Lip) for the treatment of hepatocellular carcinoma. MTT method and median effect method were used to determine the optimal synergistic drug loading ratio when the molar ratio of CDDP to CUR was 1:8. In vitro release experiments showed that CDDP and CUR had similar release rates within 24 h, indicating that the ratio of the two drugs can remain stable to ensure the optimal synergistic ratio at all time points. *In vivo* pharmacokinetic studies also showed that CDDP/CUR-Lip in plasma at different time points could maintain a synergistic drug ratio of 1:8. Zucker and Barenholz (2010) prepared topotecan and VCR-loaded liposomes (LipoViTo). Pharmacokinetics and biodistribution studies showed that LipoViTo simultaneously delivered two drugs to tumors and released them in a predetermined proportion. LipoViTo were more effective in two mouse tumor models than free drugs and liposomes alone or in combination.

3.3. Control the sequence of drug release

The multi-stage NDDS can control the sequence and process of drug combination therapy by regulating the release response mechanism and release rate of combined drugs under different stimuli, so as to achieve more accurate drug delivery process and improve the effect and specificity of combination. Lin et al. (2019) designed a pH and redox two-stage response nanocarrier for co-delivery of phosphorylated curcumin (p-CUR) and DOX. MSNs nanocarriers (Figure 2) were functionalized by specific cuttable PEGylation and disulfide cross-linked hydrogel coatings: MSNs were encapsulated as core-loaded DOX, p-CUR in hydrogel coatings. In the blood circulation, PEGylated nanocarriers had a longer time. In tumor tissues, polyethylene glycol (PEG) shell was cracked due to its sensitivity to pH, and cationic hydrogel coating was exposed to improve cell uptake. In tumor cells, the hydrogel coating could be lysed and released by glutathione. Thus, the double-response shell endowed the nanocarrier with the cell uptake and specific cancer cell target release triggered by the extracellular pH of tumor cells, and the synergistic effect of p-CUR and Dox enhanced the apoptosis of HeLa cells. In order to kill cancer stem-like cells (CSCs) in tumors, Shen et al. (2021) prepared nanoparticles to co-load all-trans retinoic acid and camptothecin (CPT). All-trans retinoic acid is released under hypoxic conditions, resulting in CSCs differentiation under hypoxic conditions. In differentiated CSCs, ROS levels increased, leading to CPT release and subsequent cell death. This dual strategy could control drug release in stem cells, reduce stem cell-related drug resistance, and enhance chemotherapy response. It could inhibit tumor growth and prevent postoperative tumor recurrence and metastasis in breast tumor mouse models.

3.4. Used as a drug carrier

Some natural active ingredients have not only the same drug encapsulation ability as synthetic nanomaterials, but also better biodegradability, biocompatibility and safety than

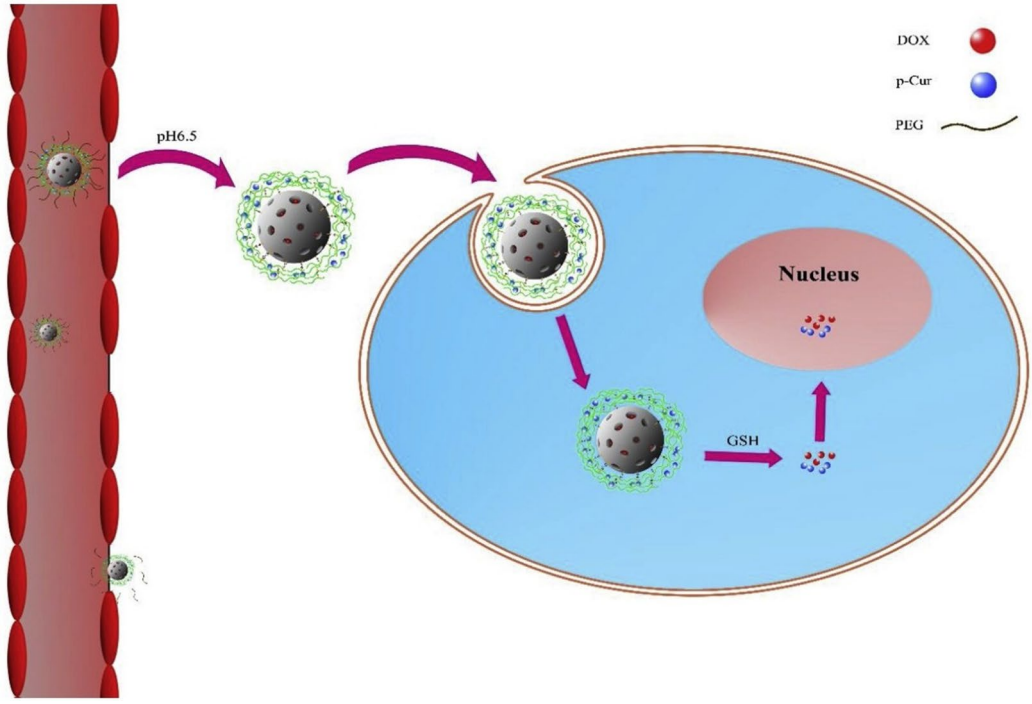

Figure 2. Illustration of the dual responsive nanocarriers for co-delivery p-Cur and Dox. Reprinted with permission from Elsevier (Lin et al., 2019).

synthetic nanomaterials. They can be used as natural drug carrier for nano-drug delivery, which can improve the bioavailability and efficacy of drugs. At present, ASP (Wang et al., 2020), bletilla polysaccharide (Wang et al., 2019a), *Ganoderma lucidum* polysaccharide (Zheng et al., 2021a), ursodeoxycholic acid (MDCA) (Anwar et al., 2018), *Semen Armeniacae Amarum* protein (Lin et al., 2020) have been successfully used for the delivery of DOX, MTX, sulfasalazine and PTX. A summary of the studies of natural active components as drug carriers in NDCDS is shown in Table 3.

4. Types and characteristics of NDCDS

NDCDS have shown strong advantages in the delivery of natural active ingredients and chemotherapy drugs, including high encapsulation efficiency, prolonging circulation time, controlling release and improving therapeutic effect. At present, there are mainly two strategies for NDCDS of natural active ingredients and chemotherapy drugs (Figure 5), physical encapsulation and carrier-linked prodrug delivery system, and physical encapsulation include liposomes, nanoparticles, polymer micelles, polymer drug conjugates, nanosuspensions, nanoemulsions, etc.

4.1. Liposomes

Liposomes have the characteristics of nanoscale, biofilm-like structure, good biocompatibility, and relatively stable. Moreover, their surface modification properties make the application of liposomes truly extend to targeted and environmentally sensitive delivery systems (Li et al., 2019a). The aqueous phase and lipid bilayer of liposomes can contain a variety of drugs. For example, hydrophilic drugs can be encapsulated in the core of hydrophilicity. Hydrophobic drugs can be encapsulated in the lipid membrane. Amphoteric drugs can be located on the phospholipids in the aqueous phase and membrane. A summary of the liposomes used to co-deliver chemotherapy drugs and natural active ingredients is shown in Table 4.

4.1.1. Passive targeting liposomes

The distribution of the passive targeting preparation in the body after it is administered intravenously is determined by the size of the microparticles. Small-size nanoparticles usually have strong tissue permeability and small renal excretion (Sohail et al., 2021).

Jiang et al. (2016) prepared the nano-lipid carrier (ETP-CUR-NLC) containing ETP and CUR, which showed low cytotoxicity in normal tissues and high cytotoxicity in tumor tissue *in vivo*. Meng et al. (2016a) co-encapsulated Res and PTX in PEGylated liposomes, which could produce strong cytotoxicity to drug-resistant MCF-7/ADR tumor cells *in vitro*, and improve the bioavailability of drugs and tumor retention ability *in vivo*.

4.1.2. Active targeting liposomes

Through the modification of the special ligands, liposomes can also achieve active targeting. HA can modify the surface of liposomes to give them targeting. This may be because the specific adhesion of cancer cells to HA ligands is enhanced, and the activity and permeability of HA administration are increased, resulting in the improvement of the efficacy of standard dosage, reduction of side effects, and overcoming drug resistance. Mahira et al. (2019) prepared cationic liposomes of CBX and silibinin (SIL) by ethanol injection method, and performed surface functionalization with

Table 3. Studies of natural active components as drug carriers in NDDS.

Polymers	Types of drug carriers	Cross-linker	Loaded drugs	Target	Specificity	Ref.
ASP-PP-DOX (Figure 3)	Conjugates, nanoparticle	3-(Maleimido) propionic acid N-hydroxysuccinimide ester	DOX, ASP	A549 and MCF-7 cells, spleen cells	Synergistic Antitumor, target tumor tissue, improve tumor microenvironment	(Wang et al., 2020)
Histidine- stearic acid- *Bletilla striata* polysaccharides	Copolymer micelle		DOX	MCF-7 cells	Improve the accumulation of drugs in tumor sites, enhance intracellular absorption	(Wang et al., 2019a)
FA/LA-SSZ-MDCA (Figure 4)	Amphiphilic maltodextrin-based micelle	Carbodiimide	Sulfasalazine (SSZ), RES	HepG2 cells, liver tumor	FA and Lactide dual targeted modification	(Anwar et al., 2018)
SAP-NPs	Nanoparticle	Disulfide bonds	PTX	L-02 and MDCK cells	Encapsulate insoluble compounds and preventing their precipitation	(Lin et al., 2020)
GLP-APBA-MTX	Conjugates, nanoparticle	3-aminophenylboronic acid (APBA)	MTX, 10-hydroxycamptothecin (HCPT)	MCF-7 cells, breast tumor	High drug loading capacity, pH-sensitive	(Zheng et al., 2021a)

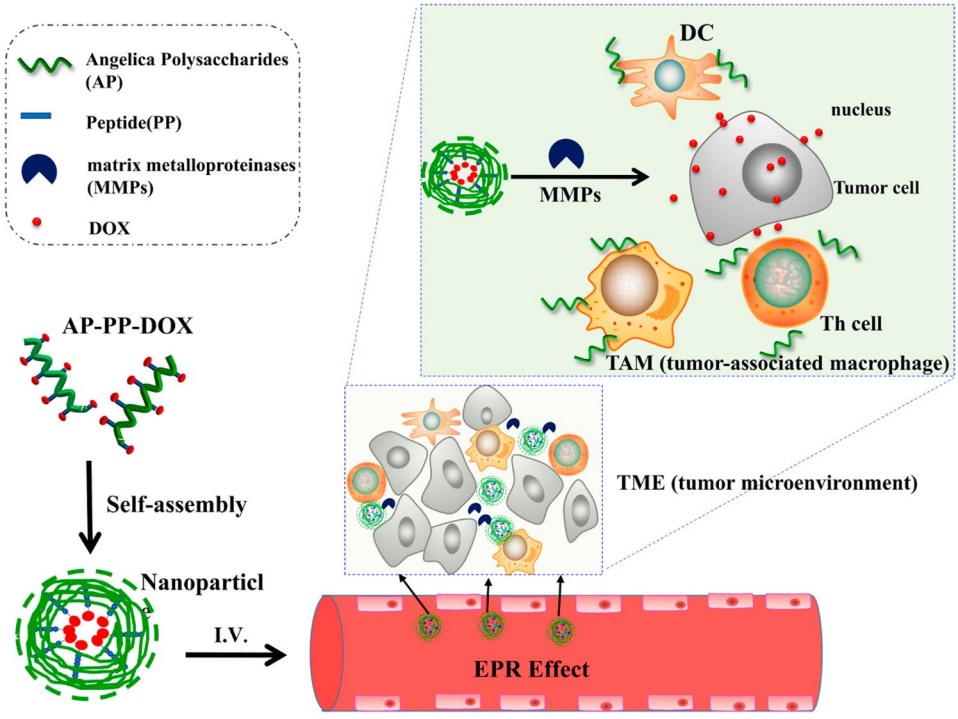

Figure 3. Proposed schematic diagram of AP-PP-DOX (*Angelica* polysaccharide-peptide-doxorubicin) nanoparticles for antitumor drug delivery. Reprinted with permission from Wang et al. (2020).

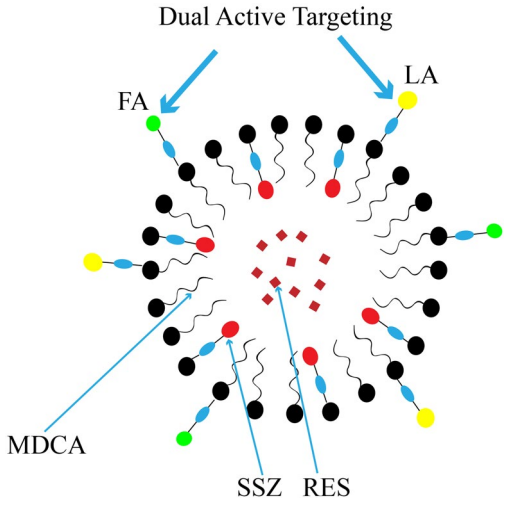

Figure 4. Structure of lactobionic/folate dual-targeted amphiphilic maltodextrin-based micelles for targeted delivery of sulfasalazine and resveratrol. Reprinted with permission from American Chemical Society (Anwar et al., 2018).

anionic HA through electrostatic interaction. The results showed that HA-coated liposomes were more effective, and CBX and SIL showed a synergistic effect on prostate cancer. Liu et al. (2016b) constructed HA modified nanoliposomes (NLCs) as a carrier for co-delivery of BCL and DOX. In vitro cytotoxicity experiments showed that HA-modified NLCs were better than BCL/DOX-NLCs in reducing the activity of breast cancer (MCF-7/ADR) cells, which may be due to the fact that HA ligands on the surface of particles can target HA receptors on the surface of tumor cells, thereby promoting the entry of BCL and DOX into cancer cells. Lu et al. (2017b) prepared the targeted NLCs modified by HA for co-delivery of GEM and BCL precursors by nanoprecipitation technology. In vivo antitumor experiments showed that HA-GEM-BCL NLCs had the strongest antitumor effect on pancreatic cancer animals compared with other liposomes, and had less systemic toxicity to tumor treatment *in vivo*. At the same time, the cell uptake efficiency of HA-GEM-BCL NLCs *in vitro* was significantly higher than that of other NLCs.

4.1.3. pH-sensitive liposomes

When liposomes deliver therapeutic drugs *in vivo*, the change of pH can make some new liposomes release drugs in specific pathological tissues. pH-sensitive liposomes are widely used environmental-sensitive liposomes (Li et al., 2019a). Cao et al. (2019a) developed a pH-sensitive nanostructured lipid carrier (DOX/ELE Hyd NLCs) loaded with DOX and β-ELE for the treatment of lung cancer. When NLCs were transported to acidic tumor sites, acid-sensitive hydrazone bonds may decompose and promote drug release. Compared with non pH-sensitive NLCs and single drug-loaded NLCs, pH-sensitive and double drug-loaded NLCs showed higher cytotoxicity and tumor inhibition rate.

4.1.4. Ultra-deformable liposomes

Liposomes can increase the penetration rate of drugs through the skin, but they are limited by their positioning in the stratum corneum during use. Ultra-deformable liposomes composed of phospholipids and edge activators are used to increase the skin penetration of different biologically active substances, which can achieve obvious drug localization even in the bloodstream. Cosco et al. (2015) co-encapsulated RES

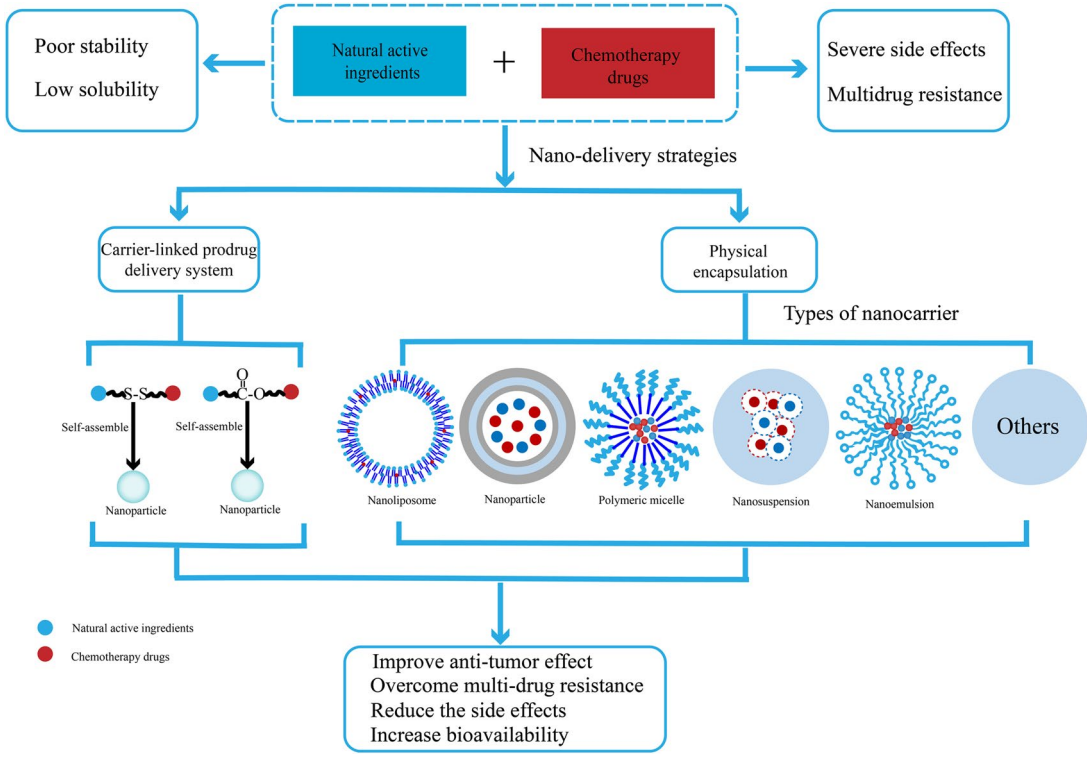

Figure 5. Two strategies for NDCDS of natural active ingredients and chemotherapy drugs: physical encapsulation and carrier-linked prodrug delivery system.

and 5-FU in ultra-deformable liposomes. Compared with the free drug form and a single encapsulant, the ultra-deformable liposomes co-encapsulated by the two drugs had increased antitumor activity in skin cancer cells. This effect may depend on super-deformable liposomes, which may accumulate in deeper skin layers, thereby creating a skin reservoir from which RES and 5-FU can be gradually released.

4.2. Nanoparticles

4.2.1. Lipid nanoparticles

Lipid nanoparticles have stable properties, simple preparation, and a certain sustained and controlled release effect, which can reduce the toxicity of drug loading. Targeted lipid nanoparticles with specific modifications can actively target the diseased tissues (Tapeinos et al., 2017). Li et al. (2020g) established an active targeting drug delivery system (FA-LB-MSNs) for FA modified PEGylated lipid bilayer modified mesoporous silica nanoparticles, which jointly delivered PTX and tanshinone IIA (Tan IIA). The bioadhesion between FA and its receptors significantly increased the uptake of FA-LB-MSNs by NB4 cells. Compared with uncoated MSNs, FA-LB-MSNs showed sustained drug release, and PTX and Tan IIA were released synchronously from the carrier. Gao et al. (2019) prepared MSNs with a layer of polyethylene glycol lipid bilayer (PL) on the surface, which was used to co-load PTX and CUR, and to control the release of loaded drugs from the mesoporous. Cell uptake and localization studies showed that MSNs with a layer of polyethylene glycol lipid bilayer could effectively carry drugs into cancer cells with sustained release characteristics, reduce the clinical dosage of the drug, reduce its side effects, and showed good targeting characteristics for breast cancer.

4.2.2. Active targeting nanoparticles

In order to improve the targeting of nanoparticles, researchers have tried to functionalize their surface to better achieve the purpose of active targeting in recent years. Dong et al. (2020) developed mesoporous silica nanoparticles (Figure 6) coated with graphene oxide modified by HA for the combined administration of CA and DOX to enhance their combined therapeutic effect on tumor cells. CA and DOX co-loaded graphene oxide coated mesoporous silica nanoparticles (MSNCA @ GODOX-HA) actively targeted tumor cells through the "ligand receptor" affinity between HA and CD44 receptors, improved the advantages of CA and DOX, limited their shortcomings, so as to achieve effective treatment of cancer. Li et al. (2017c) prepared Tf-modified DTX and BCL loaded solid lipid nanoparticles (Tf-D/B-SLNs) for lung cancer combined chemotherapy, which had better antitumor efficiency than unmodified SLNs and single drug loaded SLNs. Gao et al. (2021) prepared PLGA NPs encapsulated antitumor drugs DOX and CUR by solvent evaporation method. Then, the extracted TE10 cell membrane and DSPE-PEG were self-assembled to wrap the drug-loaded PLGA NPs, so that the drug carrier had homologous targeting function, significantly improved the drug concentration of the target site. The results showed that PMPNs could be specifically taken up by TE10/DOX cells, and exhibited good antitumor effect *in vitro*. At the same time, it had excellent targeting and

Table 4. The researches of liposomes used to co-deliver chemotherapy drugs and natural active ingredients.

Nanocarrier composition	Feature	Drugs	Experimental subject	The role of natural active ingredients	Ref
Phospholipon90® + sodium cholate	Ultradeformable	5-FU/RES	SK-MEL-28, Colo-38 cells	Antioxidant activity	(Cosco et al., 2015)
Glyceryl palmitostearate + Trimyristin + medium-chain triglyceride + Phospholipon90® + PEG 4000 monostearate + stearylamine		Docetaxel/CUR	NCI-H460 cells	Antitumor	(Rawal et al., 2020b)
Compritol®888ATO + Miglyol®812 + Methoxy (polyethylene glycol)2000-hydrazone-1,2-distearoyl-sn-glycero-3-phosphoetha-nolamine + lecithin + Tween® 80	pH-sensitive	DOX/β-ELE	A549 cells, MRC-5 cells, A549/ADR cells, C57BL/6 mice	Induce lung cancer cells apoptosis, reverse MDR, Reduce the toxicity of chemoradiotherapy	(Cao et al., 2019a)
Phosphatidylcholine (PC) + cholesterol (Chol) + 1,2-distearoylsn-glycero-3-phosphoethanolamine-N-[methoxy (polyethylene glycol)] (DSPE-PEG)		CDDP/β-ELE	A549 cells, A549/CDDP cells, LLC cells, C57BL/6 mice, non-obese, severely diabetic combined immune-deficient mice	Induce tumor cells apoptosis, inhibit tumor cells proliferation, reverse MDR	(Cao et al., 2019b)
Chol + 1,2-Dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) + PEG-2000-DSPE	Long-circulating	DOX/CUR	C26 murine colon cancer cells	Reverse MDR, induce tumor cells apoptosis	(Tefas et al., 2017)
1,2-dimyristoyl-sn-glycero-3-phosphocholine + Chol + Polyethylene glycol-distearoyl phosphatidylethanolamine (DSPE-PEG2000)		CDDP/CUR	HepG2 cells, BALB/c nude mice, Kunming mice	Induce tumor cells apoptosis, reduce toxicity	(Cheng et al., 2018)
poloxamer 188 + Glyceryl monostearate + medium chain triglycerides		Temozolomide/CUR	Rat glioma cell line, human brain glial normal cell line, BALB/c nude mice	Reverse MDR, induce tumor cells apoptosis	(Xu et al., 2020)
Glycerol monostearate + soybean phosphatidylcholine (SPC) + oleic acid + dimethyldioctadecylammonium bromide (DDAB)	Tumor targeted	Etoposide/CUR	SGC7901 cells, gastric tumor-bearing BALB/c nude mice	Inhibit tumor cells proliferation, reverse MDR	(Jiang et al., 2016)
Chol + SPC	pH-gradient method	DOX/hydrochloride QN	MCF-7 cell line, MCF-7/ADR cell line	Reverse MDR	(Shen & Qiu, 2017)
Compritol®888ATO + Tween™80 + peanut oil + Triethanolamine + oleic acid		DOX/Sclareol	MDA-MB-231 cells, 4T1 cells, BALB/c mice	Enhance antitumor effect, reduce cardiotoxicity	(Borges et al., 2019)
N-[1-(2,3-dioleoyloxy) propyl] N, N, N-trimethyl ammonium chloride (DOTAP) + Chol + Vitamin E polyethylene glycol succinate (TPGS)	CD44 targeting	Cabazitaxel (CBX)/ Silibinin	PC-3 and DU-145 cells	Targeting CSCs, induce tumor cells apoptosis, inhibit tumor cells proliferation	(Mahira et al., 2019)
Hydrogenated Soybean Phospholipids (HSPC) + Chol + DSPE-MPEG2000		DOX/BER	MDA-MB-231 cells, 4T1 cells, BALB/c mice, Sprague-Dawley rats	Induce tumor cells apoptosis, inhibit tumor cells proliferation, reduce toxicity	(Zhang et al., 2020a)
HSPC + Chol + DSPE-mPEG2k		Irinotecan/BER	BXPC-3 cells, 4T1 cells, BALB/c mice, Sprague-Dawley rats	Induce tumor cells apoptosis, inhibit tumor cells proliferation, reduce toxicity	(Wang et al., 2021)
SPC + Precirol ATO-5 + olive oil + Tween™80 + DDAB	Tumor targeted	Gemcitabine (GEM)/BCL	AsPC1 cells, C57BL/6 mice	Reduce side effects, reverse MDR	(Lu et al., 2017b)
poloxamer 188 + Tween-80 + DSPE-PEG2000 + glyceryl behenate + soy lecithin + Chol		Temozolomide/Que	U87 glioma cells, Sprague-Dawley rats	Induce tumor cells apoptosis, inhibit tumor cells proliferation	(Hu et al., 2016)
SPC + Stearic acid + Glyceryl distearate + Cremophor ELP + DDAB	CD44 targeting	DOX/BCL	MCF-7/ADR cells, Kunming mice	Antitumor effect	(Liu et al., 2016b)
Lecithin + Chol	EPR	DOX/PT	MCF/ADR cells, BALB/c nude mice	Reverse MDR	(Li et al., 2020f)
Chol + DPPC		CDDP/CUR	MCF-7 cells	Induce tumor cells apoptosis, reduce toxicity	(Mahmoudi et al., 2021)
Dynasan 114® + Precirol ATO5® + triglycerides medium-chain (Labrafac lipophile WL 1349) ® + Phospholipon 90 G® + octadecylamine + PEG 4000	Folic acid modification	Docetaxel/CUR	NCI-H460 cells, Sprague-Dawley rats, BALB/c mice	Antitumor effect	(Rawal et al., 2020a)
DPPC + PEG-2000-DSPE + Chol	Long-circulating	DOX/CUR	C26 murine colon carcinoma cells, BALB/c mice	Antitumor effect	(Sesarman et al., 2019)
PC + DSPE-mPEG2000		PTX/RES	MCF-7 or MCF-7/ADR cells, BALB/c nude mice	Reverse MDR, reduce toxicity	(Meng et al., 2016a)
Phospholipid + Chol + DSPE-PEG2000 + DSPE-PEG2000-PFV	PFV modified	DOX/Sch B	A549 cells, BALB/c nude mice	Enhance the cytotoxicity, alleviate the cardio toxicity, inhibit the invasion and metastasis of tumors	(Cai et al., 2020)
^{33}I-α-Phosphatidylcholine + Chol + DSPE-PEG$_{2000}$	Liver-targeted + Glycyrrhetinic acid (GA)–modified	Combretastatin a4 phosphate/CUR	BEL7402 cells, B16 cells, BALB/c mice	Induce tumor cells apoptosis, inhibit tumor cells proliferation	(Jiang et al., 2019)
Chol + soybean phospholipid + TPGS + trehalose		CBX/β-ELE	A549 cells, A549/T cells, BALB/c nude mice	Inhibit tumor cells proliferation, reverse MDR	(Zeng et al., 2019)

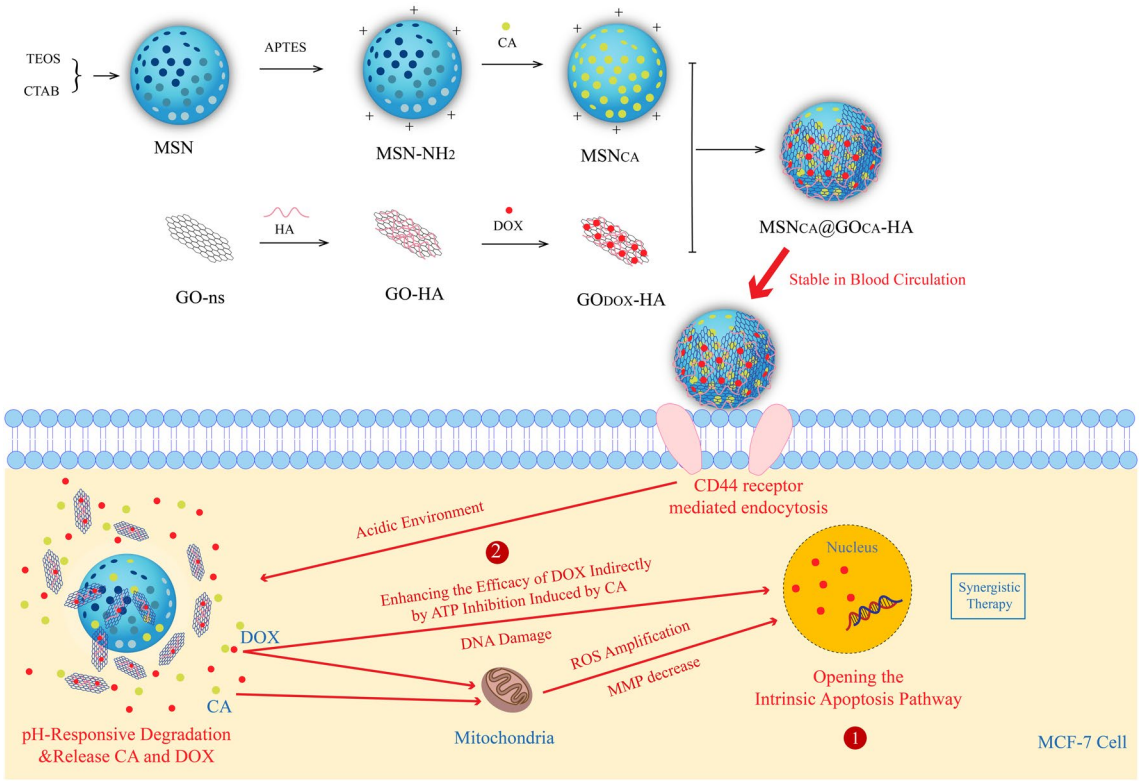

Figure 6. Illustration of the preparation, dual-drugs loading, pH-responsive intracellular release of MSNCA@GODOX-HA nanoparticles and the apoptosis induction in MCF-7 cells. International Journal of Nanomedicine 2020 15 10285-10304' Originally published by and used with permission from Dove Medical Press Ltd.

therapeutic effect in TE10/DOX xenograft mice. Wang et al. (2015b) synthesized PTX and BCL prodrugs containing FA and HA dual targeting ligands, and prepared multifunctional self-assembled nanoparticles for delivery of PTX prodrug and BCL prodrug. HA and FA on the surface of the complex could bind to CD44 receptor and folate receptor respectively. The results showed that PTX-BCL nanoparticles exhibited good antitumor activity in a wide range of drug concentration and had obvious synergistic effect. In addition, nanoparticles with folate receptor (Hiremath et al., 2019; Guo et al., 2021) active targeting and dual targeting (Wang et al., 2015b; Cui et al., 2016) were also studied.

4.2.3. pH-sensitive nanoparticles

The pH-sensitive polymer nanocarriers are developed by using the acidic microenvironment in tumor tissues and tumor cell/lysosomes to achieve the efficient and rapid release of antitumor drugs tumors. Martinez-Edo et al. (2020) prepared a glycyrrhetinic acid (GA)-modified pH-triggered MSN based nanocarrier for the delivery of DOX/CPT-polyethylene glycol(CPT-PEG). GA modified drug delivery system could be selectively absorbed by HepG2 cells. Under acidic conditions (pH = 4), DOX could be rapidly released and CPT-PEG could be gradually released. The results showed that the presence of this system reduced the systemic toxicity of combined treatment, but still maintained the effective cytotoxicity of liver cancer. Gao et al. (2017a) prepared a new type of pH-sensitive prodrug nanoparticles by synthesizing the self-assembly of amphiphilic macromolecular prodrugs for selective co-delivery of DOX and CUR. Compared with the neutral environment (pH = 7.4), CUR-DOX-NPs could release DOX and CUR more effectively in acidic environments (pH = 5.0). CUR-DOX-NPs were easily absorbed by cells, and selectively released drugs into human breast cancer cell line MCF-7 with significant cytotoxicity. Compared with the free DOX at the same level, CUR-DOX-NPs had lower cardiac toxicity and were safer for zebrafish. Khan et al. (2019b) prepared pH-sensitive CDDP/OA calcium carbonate nanoparticles (LCC NPs) by microemulsion method. In vitro release studies showed that LCC NPs released more drugs at acidic pH than at alkaline pH, and it was pH-sensitive and ideal carrier for chemotherapy drugs. Cell viability test and toxicity evaluation showed that CDDP/OA-LCC NPs could not only reduce CDDP-induced hepatotoxicity, but also effectively treat hepatocellular carcinoma. Zeng et al. employed HA-conjugated CUR and D-α-tocopheryl acid polyethylene glycol succinate as selective drug-carrying carriers to deliver dasatinib to cancer cells. The nanoparticles were pH sensitive and could accelerate drug release at low pH conditions. *In vitro* and *in vivo* experiments showed that the nanoparticles had obvious cytotoxicity to HepG2 cells and could inhibit the growth of solid tumors in mice (Zeng et al., 2022).

4.2.4. Redox-responsive nanoparticles

In addition to pH-responsive nanoparticles, redox-responsive nanoparticles were also used for the co-delivery of natural active ingredients and chemotherapy drugs. Xue et al. prepared citronellol-cabazitaxel conjugate self-assembled

nanoparticles (CSNPs) by conjugating cabazitaxel with citronellol via the disulfide bond that was redox-sensitive to the high concentration of glutathione within tumor cells (Xue et al., 2016). CSNPs could rapidly release cabazitaxel in tumor cells. The *in vivo* pharmacokinetics of CSNPs could be apparently improved, and CSNPs had a target effect for accumulating at the tumor site. Li et al. developed a novel pH and redox dual-sensitive polypeptide-calcium phosphate hybrid nanoparticles (Li et al., 2021b). With the disulfide-crosslinked interlayer and the Calcium phosphate (CaP) shell, the polypeptide-calcium phosphate hybrid nanoparticles encapsulated CUR into the hydrophobic core of micelles and loaded DOX on the hydrophilic segment of micelles as well as CaP shell. The premature leakage of drugs from the nanoparticles at physiological pH was efficiently restrained because of the enhanced structure integrity, whereas at acidic and hypoxia microenvironment the release of both drugs was promoted due to the rapid dissolution of the CaP shell and the break of the disulfide crosslinked network.

A summary of the researches of nanoparticles used to co-deliver chemotherapy drugs and natural active ingredients is shown in Table 5.

4.3. Polymeric micelles

Polymeric micelles are a macromolecular assembly formed by synthetic block copolymer or graft copolymer, which have a two-phase structure of a spherical core and a shell (Yokoyama, 2014). Polymer micelles have core-shell structures. Hydrophobic nuclei are commonly used to encapsulate poorly water-soluble or hydrophobic drugs, which can improve the solubility and bioavailability of encapsulated drugs and avoid rapid degradation of drugs *in vivo*. Hydrophilic shells can prolong circulation time and improve spatial stability by reducing hydrolysis in blood circulation. Polymeric micelles can selectively and effectively accumulate in tumors by enhancing the permeability and retention (EPR) effect, thus improving the therapeutic effect of chemotherapy drugs. A summary of the researches of polymer micelles used to co-deliver chemotherapy drugs and natural active ingredients is shown in Table 6.

4.3.1. Passive targeting polymer micelles

Sabzi et al. (2020) synthesized a novel biodegradable polyε-caprolactone-co-maleic anhydride grafted citric acid copolymer micelles (PCL-co-P(MA-g-CA)) for co-delivery of DOX-CUR to eradicate MDA-MB231 cells. The unique micelle structure allowed the simultaneous loading of hydrophilic DOX and hydrophobic CUR, and the loading efficiency of each drug was above 98 %. DOX@CUR loaded micelles showed synergistic effect, and the combined treatment of DOX and CUR nanoparticles enhanced the cytotoxicity of MDA-MB231 cells by promoting apoptosis. Lv et al. (2016b) prepared polyethylene glycol-bock-polylactic acid micelles for co-delivery of DOX and CUR to multidrug-resistant breast cancer (MCF-7/ADR) cells. In vitro experiments showed that (DOX + CUR)-micelles could reduce the DOX efflux rate through the inhibitory effect of CUR on P-gp, significantly increase the uptake of DOX by MCF-7/ADR cells, thereby enhancing the *in vitro* cytotoxicity of DOX. In vivo experiments showed that compared with (DOX)-micelles, (CUR)-micelles, free (DOX + CUR), free DOX, and free CUR, (DOX + CUR)-micelles had more tumor accumulation and better antitumor effect in drug-resistant MCF-7/ADR xenograft model. Zheng et al. (2021b) developed a polymer nano micelle for co-delivery of TPL and an antitumor chemotherapeutic drug SN38. Amphiphilic SN38 prodrug polymeric micelles (PSN38) and encapsulated the hydrophobic esterase-responsive prodrug of TPL, TPL-naphthalene sulfonamide (TPL-nsa), were synthesized to form PSN38@TPL-nsa nanoparticles. PSN38@TPL-nsa showed strong antitumor effect and reshaped tumor microenvironment in cancer-related fibroblasts-rich peritoneal disseminated tumor and patient-derived xenograft model of gastric cancer.

4.3.2. Active targeting polymer micelles

The polymer micelles are surface modified to achieve the active targeting of tumor sites. Sarisozen et al. (2016) developed PEG-PE-based polymeric micelles modified with single-chain fragment variable region of glucose transporter-1 antibody as ligand for the synergistic delivery of DOX and CUR for the treatment of glioblastoma to promote blood-brain barrier transport and glioblastoma targeting. Sabra et al. (2018) prepared a new type of natural self-assembly micelles with hydrophilic Lf as the micelle corona to co- deliver RAP and wogonin (WOG). Lf corona enhanced tumor targeting and prolonged the cycling of nanocarriers. This combined NDDS maximized the synergistic cytotoxicity of RAP and WOG in tumor inhibition of MCF-7 breast cancer cells and Ehrlich ascites tumor animal models.

4.3.3. pH-sensitive polymeric micelles

Multistage pH-responsive micelles can better control drug release in tumor sites. Yang et al. (2017b) synthesized a pH-sensitive polymer polyethylene glycol-benzoic acidimine-poly(γ-benzyl-L-aspartate)-b-poly (1-vinylimidazole) block copolymer (PPBV), and developed a pH-responsive micelle system (Figure 7) for PTX and CUR co-delivery and synergistic removal of breast cancer stem cells (bCSCs) and non-bCSCs. The results of *in vitro* release experiments showed that the benzoic acid-imine bond was relatively stable in neutral medium, and the hydrophilic PEG layer prevented the outward diffusion of hydrophobic drugs and limited the drug release. However, in the acidic extracellular environment of tumor cells, the PEG layer gradually separated from the PPBV micelles and the volume of the PPBV micelles was reduced. The EPR effect was used to effectively target breast tumors, thereby promoting their cellular uptake and tumor deep penetration, and triggering the rapid release of PTX and CUR. These advantages were also conducive to the maximum efficacy of the combined treatment of PTX and CUR, achieving superior tumor inhibitory activity and effective bCSCs killing ability *in vivo*. Qi et al. (2018) developed a novel pH and redox dual-sensitive nanocarrier loaded with CUR

Table 5. The researches of nanoparticles used to co-deliver chemotherapy drugs and natural active ingredients.

Nanocarrier type	Nanocarrier composition	Feature	Drugs	Experimental subject	The role of natural active ingredients	Ref
Fructose-tethered lipid-polymeric hybrid nanoparticle	DSPE-PEG + polylactic acid (PLA) + Stearoyl polyoxyl-32 glycerides + stearyl amine + Pluronic F-127	EPR	MTX/beta carotene	MCF-7 cells, female Wistar rats	Ameliorate MTX-induced hepatic and renal toxicity, antitumor	(Jain et al., 2017)
PLA-based nanoparticle	Maleimide-poly (ethylene glycol)-poly (lactic acid) + Methoxy-poly (ethylene glycol)-poly (lactic acid) (MPEG-PLA)		Sorafenib (SRF)/ Plantamajoside	HepG2 cells, tumor bearing-mice	Reverse MDR	(Zan et al., 2019)
Nanoparticle	Folate (FT)-Polyethylene Glycol (PEG)–poly(lactide-co-glycolide) (PLGA)	Folate modified	Docetaxel/CUR	A549 cells, HeLa cells, S180 cell line, S180 bearing mice	Inhibit tumor cells proliferation	(Hu et al., 2015)
MPEG-PLA Nanoparticle	MPEG-PLA		DOX/Honokiol	A2780s cells	Induce tumor cells apoptosis, reverse MDR	(Wang et al., 2010)
Polyester nanosponge particle	The oxidized poly (vl/evl) linear polymer		Tamoxifen/Que	4T1 cells	Alleviate the hepatotoxicity generated throughout the course of treatment, improve the uptake of TAM	(Lockhart et al., 2015)
Nanoparticle	D-α-tocopheryl polyethylene glycol 1000-block-poly (β-amino ester) copolymer	pH-sensitive	DOX/CUR	SMMC 7721 cells, nude mice	Induce tumor cells apoptosis, reduce toxicity	(Zhang et al., 2017a)
Polymer nanoparticle	3mPEG-bP (Glu-co-Phe)	EPR	DOX/CUR	Raji cells, human Burkitt's lymphoma cells, BJAB cells, Pfeiffer cells, male SCID mice, male Kunming mice	Antitumor effect, reduce toxicity	(Guo et al., 2020b)
Supermagnetic iron oxide nanoparticles (SPIOs)	Bovine serum albumin (BSA)-SPIOs	EPR	sunitinib/CUR	MCF-7 cells, HeLa cells, female BALB/c nude mice	Reverse MDR	(Chen et al., 2017)
Lipid-polymer hybrid nanoparticle	Chitosan + Soybean lecithin (LIPOID S75)		CDDP/CUR	MCF-7 breast cell lines, A2780 ovarian cell lines	Inhibit tumor cells proliferation, improve sensitivity to drug-resistant cancer cells, reduce nephrotoxicity and ototoxicity caused by CDDP	(Khan et al., 2020)
Hybrid lipid-polymer nanoparticle	1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine + DOTAP + DSPE-PEG2000 + Chol	EPR	PTX/CUR	MCF-7 cells, B16F10 carcinoma cells	Induce tumor cells apoptosis, improve sensitivity to drug-resistant cancer cells, enhance the effect of PTX	(Ruttala & Ko, 2015)
Hybrid nanoparticle	$CaCl_2$ + $(NH_4)_2CO_3$	Cancer cell membrane decorated	CDDP/OA	MGC-803 cells, NIH3T3 cells, tumor-bearing mice	Induce tumor cells apoptosis, reduce side effects, reverse MDR	(Li et al., 2020a)
Calcium carbonate nanoparticle	HSPC + Chol + DSPE-PEG-2000	pH-dependent	CDDP/OA	HepG2 cells, Kunming mice	Induce tumor cells apoptosis, reduce side effects	(Khan et al., 2019b)
Wrapped mesoporous silica nanoparticle	Cetyltrimethylammonium bromide (CTAB) + triethanolamine + Graphene oxide + hyaluronic acid (HA)	Modified with HA, pH-responsive release	DOX/CA	MCF-7 cells, H9c2 cells	Antitumor effect, improve the efficacy of DOX	(Dong et al., 2020)
Glycol chitosan nanoparticle	N, N-dimethylformamide (DMF) + Glycol chitosan	EPR	retinoic acid Chlorochalcone/ Gambogic acid	MG63 cells	Induce tumor cells apoptosis, Inhibit tumor cells proliferation	(Liu et al., 2016a)
Albumin nanoparticle	BSA	EPR	PTX/RES	A549 cells, A549/PTX cells, female BABL/c mice	Improve the sensitivity of multidrug-resistant cancer cells to chemotherapeutics	(Zhao et al., 2020a)
Mesoporous silica nanoparticle	CTAB + sodium hydroxide + Tetraethyl orthosilicate (TEOS) + ChS	CD44 receptor-mediated active targeting	PTX/Que	MCF-7/ADR cells, female BALB/c mice	Reverse MDR	(Liu et al., 2020a)
PLGA Nanoparticle	PLGA-N-Hydroxysuccinimide (NHS)		DOX/BER	MD-MBA-231 and T47D breast cancer cells, Sprague Dawley rats (male)	Antitumor effect, reduce the toxicity of DOX	(Khan et al., 2019a)
Hybrid nanoparticle	PLGA + HA + n-hexadecylamine	bCSC-targeted, HA-modified	PTX/CUR	MCF7 cells, female nude BALB/c mice	Reverse MDR	(Yang et al., 2017a)

(*Continued*)

Table 5. Continued.

Nanocarrier type	Nanocarrier composition	Feature	Drugs	Experimental subject	The role of natural active ingredients	Ref
Lipid-polymer hybrid nanoparticle	Epidermal growth factor-PEG-SA + mPEG-PLA	EGFR targeted	Docetaxel/RES	HCC827 cells, NCIH2135cells, HUVEC cells, BALB/c nude mice	Reverse MDR, regulate the tumor microenvironment	(Song et al., 2018)
Dual-targeted nanoparticles	PEG-NH2 + PLGA-PEG-Mal + PLGA-PEG-NH2	EGFR peptide (GE11) targeted, pH-sensitive	Docetaxel/CUR prodrug	LNCaP cells	Antitumor effect	(Yan et al., 2017)
PLGA – PEG polymer nanoparticle	PLGA + polyvinyl alcohol (PVA)		GEM/Betulinic acid (BA)	Panc1 cell line	Induce tumor cells apoptosis	(Saneja et al., 2019)
Nanoparticle	Grafting nitroimidazole + HA polysaccharide		All-trans retinoic acid/Camptothecin (CPT)	MCF-7 SP cells, TNBCs (HCC70, HCC1937 and SUM159PT cells)	Reverse MDR	(Shen et al., 2021)
PLA nanoparticle	PLA + PVA + chitosan + Succinic anhydride acetone		Daunorubicin/ glycyrrhizic acid	K562/A02 cells	Induce tumor cells apoptosis, inhibit tumor cells proliferation	(Zhang et al., 2019b)
Dual-Targeted Nanoparticle	HA + fucoidan + poly (ethylene glycol)-gelatin	HA and fucoidan targeting	EGCG/CUR	LucPC3 cells	Inhibit tumor cells proliferation	(Chu et al., 2019)
Mesoporous silica nanoparticle	NaOH + CTAB + TEOS	Folic acid modified	PTX/Tanshinone IIA	NB_4 cells	Induce tumor cells apoptosis, reduce side effects	(Li et al., 2020g)
Nanoparticle	Maleic anhydride + N, N′-dicyclohexyl-carbodimide (DCC) + 4-dimethylaminopyridine (DMAP)	Transferrin-targeted, pH-sensitive	DOX/CUR	MCF-7 cells	Reverse MDR, Enhance the efficacy of DOX	(Cui et al., 2017)
PLGA nanoparticle	PLGA + CHO-hyd-PEG-AA		DOX/RES	MCF-7/ADR cells, MBA-MD-231/ADR cell	Improve the sensitivity of tumor cells to chemotherapeutics, reduce side effects	(Zhao et al., 2016)
Mesoporous silica nanoparticle	TEOS + NH4F + CTAB	pH-responsive release	PTX/TET	MCF-7 cells, MCF-7/ADR cells	Reverse MDR	(Jia et al., 2015)
PLGA nanoparticle	PLGA + DSPE-PEG-2000 + Lecithin		Docetaxel/Gambogic Acid	MCF-7 cells, MCF-7/ADR cells	Induce tumor cells apoptosis, reverse MDR	(Xu et al., 2016)
Solid lipid nanoparticle	mPEG-hz + Histidine + DCC + DMAP + GMS + Injectable soya lecithin (ISL) + Poloxamer 188	pH-sensitive, Tf modification	Docetaxel/Baicalin	A549 cells, A549/DTX cells	Induce tumor cells apoptosis, reverse MDR	(Li et al., 2017c)
Nanoparticle	Methanol + chloroform	biotin-decorated	DOX/Que	MCF-7 cells, MCF-7/ADR cells	Inhibit the expression of P-gp gene, enhance the cytotoxicity of chemotherapeutics	(Lv et al., 2016a)
Mesoporous silica nanoparticle	CTAB + TEOS + NaOH + ethanol + soybean phospholipid + Chol + PEG-2000		PTX/CUR	7364 cells	Reverse PTX multidrug resistance	(Lin et al., 2018)
PLGA nanoparticle	NH 2-PEG-MAL + T7 peptide + N-diisopropylcarbodiimide + NHS + PLGA-NHS + NH 2-PEG-T7	T7-modified, magnetic-guided	PTX/CUR	U87 glioma cells, mouse brain endothelial cells	Antitumor effect	(Cui et al., 2016)
Janus-type magnetic mesoporous silica nanoparticle	[1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC) + NHS + HA	HA-grafted	DOX/BER	HepG2 cells, H22 cells, HL-7702 cells, NIH-3T3 cells	Inhibit cancer cell reproliferation	(Zhang et al., 2019a)
Mesoporous silica nanoparticle	CTAB + NaOH + TEOS + soybean phospholipid + PEG-2000 + Chol		PTX/CUR	7364 cells, 4T1 cells	Induce tumor cells apoptosis, chemical sensitizer	(Gao et al., 2019)
Lipid-polymer hybrid nanoparticle	PLGA + dimethylsulfoxide + Lecithin + DSPE-PEG	EPR	CDDP/CUR	HeLa cells	Induce tumor cells apoptosis, reverse multidrug resistance in cancer cells, reduce the nephrotoxicity of CDDP	(Li et al., 2017a)
Self-assembled nanoparticle	DSPE – PEG2000 + citronellol – CBX conjugate	Redox-sensitive	CBX/Citronellol	PC3 cells, A549 cells	Increase the activity of other antitumor drugs, Improve the immune function of cancer patients and their ability to fight cancer	(Xue et al., 2016)
Lipid-polyacrylic acid-calcium carbonate nanoparticle	CaCl2 + Egg lecithin + DOTAP + DSPE-PEG + Na2CO3 + polyacrylic acid (PAA)	pH-sensitive	DOX/CUR	HepG2 cells	Reverse MDR, Reduce side effects	(Peng et al., 2017)

(*Continued*)

Table 5. Continued.

Nanocarrier type	Nanocarrier composition	Feature	Drugs	Experimental subject	The role of natural active ingredients	Ref
Lipid nanoparticle	Precirol ATO 5 + Labrafac Lipophile WL 1349 + Lipoid S75 + Polyoxyl 40 Hydrogenated Castor Oil + glycerin		DOX/CUR	BEL 7402 cells, BEL 7402/5-FU cells	Induce tumor cells apoptosis, reverse MDR	(Zhao et al., 2015a)
Multifunctional lipid nanoparticle	Glyceryl monostearate + TPGS + Tween 80 + 2-hydroxypropyl-β-cyclodextrin + conjugated stearic acid + folate	Folate-conjugated	PTX/CUR	MCF-7/ADR cells	Reverse MDR	(Baek & Cho, 2017)
Copolymer nanoparticle	(branched polyethyleneimine (PEI)- Stearic acid) HA	HA modified	PTX/CUR	SKOV3 cells, SKOV3-TR30 cells	Induce tumor cells apoptosis, inhibit tumor cells proliferation, reverse MDR	(Zhao et al., 2019)
Silver nanoparticle	TCEP·HCl + BSA solution + silver seed solution + glucose solution + $AgNO_3$	Albumin-coated	Albendazole/ Trichosanthin	HCT8 cells, A549 cells, HCT8/ ADR cells, A549/T cells	Induce tumor cells apoptosis, reverse MDR	(Tang et al., 2017)
Mesoporous silica nanoparticle	Triton X-100 + cyclohexane + n-hexanol + TEOS + N-(2-aminoethyl)-3-ami nopropyltrimethoxysilane + NH_4OH + HA-SiLN	HA-modified	DOX/Que	SGC7901/ADR cells, NIH3T3 cells	Induce tumor cells apoptosis, inhibit tumor cells proliferation, reverse MDR	(Fang et al., 2018)
PLGA nanoparticle	HA-PEG-PLGA	CD44 receptor-mediated active targeting	Salinomycin/CUR	MCF-7 cells	Inhibit CSCs' viability and their stemness, anti-metastasis, induce tumor cells apoptosis	(Zhao et al., 2020b)
Self-assembled nanoparticle	MPEG5000-b-PAMAMG3X	pH-sensitive	DOX/HCPT	HepG2 cells, MCF-7 cells	Antitumor effect	(Zhang et al., 2013)
Lipid coated PLGA nanoparticle	Arginine-glycineaspartic acid (RGD)-PEG-DSPE + PLGA + DSPE + DMSO	RGD modified	SRF/Que	HepG2 cells	Induce tumor cells apoptosis, inhibit tumor cells proliferation	(Wang et al., 2016)
Iron oxide nanoparticle	PF127 + Pluronic-F127FA + Fe(III) + Fe(II) + ammonia + oleic acid	Folic acid modified	PTX/CUR	MCF-7 cells	Inhibit tumor cells proliferation, reverse MDR	(Hiremath et al., 2019)
PLGA nanoparticle	PLGA		MTX/CUR	SK-Br-3 cells	Antitumor effect	(Vakilinezhad et al., 2019)
Co-delivery nanoparticle	HA-ethylenediamine– Poly(aspartic acid)-Tyrosine	EPR, pH-sensitive, HA-modified	DOX hydrochloride/ CUR	HCT-116 cells	Inhibit tumor cells proliferation, reverse MDR, myocardial protective effect	(Li et al., 2021a)
Polypeptide-calcium phosphate hybrid nanoparticle	Crosslinked methoxy poly (ethylene glycol)-g-poly (aspartic acid)-g- tyrosine @CaP	pH and redox dual-sensitive	DOX hydrochloride/ CUR	A549 cells	Induce tumor cells apoptosis, inhibit tumor cells proliferation, reverse MDR, myocardial protective effect	(Li et al., 2021b)
Lipid nanoparticle	GMS + HA + Lactoferrin (Lf) + PEG400	Hyaluronate/lactoferrin layer-by-layer-coated	RAP/BER	A549 cells	Inhibit tumor cells proliferation	(Kabary et al., 2018)
Prodrug nanoparticle	Oxidized sodium alginate + DMSO	pH-sensitive	DOX/CUR	MCF-10A cells, MCF-7 cells	Antitumor effect	(Gao et al., 2017a)
PEGylated nanoparticle	PEG400	EPR	PTX/ Dihydroartemisinin	HT-29 cells	Induce tumor cells apoptosis, reverse MDR	(Phung et al., 2020)
PLGA–PEG–PLGA nanoparticle	PLGA–PEG–PLGA + Hydrogenated soybean lecithin + Chol + ultrapure water + PVA		Tamoxifen/Salidroside	4T1 cells	Antitumor effect, neuroprotective and cardiovascular protective effect	(Yu et al., 2020)
Biodegradable polymeric nanoparticle	Poly-ε-caprolactone (PCL)-PEG-PCL	EPR	PTX/CUR	MCF-7 cells	Induce tumor cells apoptosis	(Xiong et al., 2020)
PLGA-PEG-PLGA polymeric nanoparticle	PLGA-PEG-PLGA		5-FU/Chrysin	HT-29 cells	Induce tumor cells apoptosis, reduce the toxicity of 5-FU	(Khaledi et al., 2020)
Carboxymethyl chitosan nanoparticle	Carboxymethyl chitosan	EPR	DOX/Rose Bengal	Cal-27 cells	Antitumor effect	(Zhang et al., 2019c)
Self-assembled nanoparticle	2-hydroxyethyl disulfide + triethylamine (TEA) + DMAP + triphosgene + anhydrous dichloromethane + DMSO	EPR	GEM/CPT	HeLa cells, MCF-7 cells	Antitumor effect	(Hou et al., 2017)
Lactosylated nanoparticle	Lactosylated -ADH-PEG-PCL	pH-sensitive	SRF/CUR	HepG2 cells, LO2 cells	Induce tumor cells apoptosis	(Bian & Guo, 2020)

(*Continued*)

Table 5. Continued.

Nanocarrier type	Nanocarrier composition	Feature	Drugs	Experimental subject	The role of natural active ingredients	Ref
PEGylated gelatin nanoparticle	PEG-P ((N, N-di-methylamino) ethyl methacrylate-co-Itaconic acid) + gelatin + glutaraldehyde	pH-sensitive	DOX/betanin	MCF-7 cells	Induce tumor cells apoptosis, reduce side effects	(Amjadi et al., 2019)
Mesoporous silica nanoparticle	PEG@ mesoporous silica nanoparticle-GA	Glycyrrhetinic acid modified	DOX/CPT	HepG2 cells	Antitumor effect	(Martinez-Edo et al., 2020)
PLGA nanoparticle	PLGA + PVA205	EPR	Verapamil/Vincristine	MCF-7 cells, MCF-7/ADR cells	Antitumor effect	(Chen et al., 2014)
Magnetic-amphiphilic gelatin nanoparticle	Amphiphilic gelatin-iron oxide@calcium phosphate	pH-sensitive	DOX/CUR	SKBr3 cells, MCF-7 cells	Antitumor effect, reverse MDR	(Li et al., 2015b)
Polylactic-co-glycolic acid–polyethyleneimine nanoparticle	PLGA-PEI-HA	HA-modified	Docetaxel/Que	4T1 cells	Prevent breast cancer metastasis	(Li et al., 2017b)
Self-assembled nanoparticle	PEG	pH-sensitive	DOX/CUR	HepG 2 cells, HeLa cells	Antitumor effect	(Zhang et al., 2016d)
PLGA nanoparticle	PLGA		RAP/piperine	MDA-MB-231 cells	Reverse MDR	(Katiyar et al., 2016)
Mesoporous silica nanoparticle	Triton X-100 + cyclohexane + n-hexanol + TEOS + NH_4OH	EPR	CDDP/OA	A549/CDDP cells	Immunomodulatory effect	(Zhang et al., 2021c)
Targeted nanoparticle	HA/PEG-Gelatin	HA-modified	DOX/EGCG	MKN45 cells	Reverse MDR, increase the accumulation of DOX	(Mi et al., 2018)
Lipid–polymer hybrid nanoparticle	1,2-Distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy (polyethylene glycol)-5000] + ISL + PLGA		PTX/triptolide (TPL)	A549 cells, A549/PTX cells	Induce tumor cells apoptosis, inhibit tumor cells proliferation, reverse MDR	(Liu et al., 2018)
Combination nanoparticle	NH_4F + TEOS + CTAB + lipid mixture	EPR	Axitinib/celastrol	SCC7 cells, SH-SY5Y cells, BT-474 cells	Antitumor effect	(Choi et al., 2016)
Self-assembled nanoparticle	NHS-FA + HA + PLGA + poloxamer 188	Folate (FA) and HA modified	PTX/BCL	A549 cells, A549/PTX cells	Induce tumor cells apoptosis, reverse MDR	(Wang et al., 2015b)
Self-Assembled Nanoparticles	3-aminophenylboronic acid + *Ganoderma lucidum* polysaccharides	pH-Sensitive	MTX/HCPT	MCF-7 cells, 4T1 cells, female BALB/C mice	Antitumor effect	(Zheng et al., 2021a)
PLGA Nanoparticles	PLGA + Polyvinyl alcohol + TE10 cell membrane + DSPE-PEG15000	PEGylated Cancer Cell Membrane Coated	DOX/CUR	TE10 cells, L02 cells, A549 cells, TE10/DOX cells, female BALB/C nude mice	Reduce side effects of DOX, reverse MDR	(Gao et al., 2021)
Layer-by-layer nanoparticles	PLGA + PVA + lecithin + Glyceryl monostearate		CDDP/oridonin	A549/CDDP cells, mice bearing A549/CDDP cells xenografts	Antitumor effect, reverse MDR	(Fan et al., 2021)

Table 6. The researches of polymeric micelles used to co-deliver chemotherapy drugs and natural active ingredients.

Nanocarrier type	Nanocarrier composition	Feature	Drug	Experimental Subject	The role of natural active ingredients	Ref
Drug-Loaded Micelles	Amphiphilic block copolymers were prepared by triphenylphosphine -oHSM	pH and redox dual-sensitive	Antitumor Polypeptide/ CUR	MDA-MB-231 cells, MCF-7 cells, MDA-MB-231 (CD44-overexpressing) xenograft-bearing mice	Antitumor effect	(Qi et al., 2018)
Micelles of a polymeric prodrug	Amphiphilic phosphorylcholine polymers or SN38 polymeric prodrug + TEA		7-Ethyl-HCPT/DOX	MCF-7 cells, 4T1 cells, Sprague Dawley rats, 4T1 tumor-bearing BALB/c mice	Antitumor effect	(Wu et al., 2020b)
Polymeric micelle	Triethylamine + DSPE-PEG 2000 + TPGS 1000		DOX/rhein	SKOV3 cells, L02 cells, HOSE cells, SKOV3/DOX cells, BALB/c athymic nude mice	Reverse MDR, improve the effect of PTX	(Han et al., 2018)
Conjugate micelle	mPEG-PLA-NHNH2 + DMF + mPEG-PLA + TEA	pH-labile	DOX/CUR	HepG2 cells	Antitumor effect, chemosensitization	(Li et al., 2015a)
Polyion complex micelle	Poly (ethylene glycol)-block-poly(L-lysine) + 3-fluoro-4-carboxy-phyenylboronic acid	pH responsiveness	DOX/(-)-Epigallocatechin-3-O-gallate	MCF-7 Cells, MCF-7/ADR Cells, H9C2 cells, BALB/c mice	Prevent cardiotoxicity caused by DOX, chemosensitization	(Cheng et al., 2016)
Biodegradable self-assembling micelles	MPEG-PCL diblock copolymer	EPR	DOX/Honokiol	C6 glioma cells, Tg(flk:EGFP) transgenic zebrafish, BALB/c nude mice	Inhibit tumor cells proliferation	(Gao et al., 2017b)
Responsive Micellar System	mPEG-PBLA-Poly(1-vinylimidazole) triblock copolymer	pH-sensitive	PTX/CUR	MCF7 cells, female nude BALB/c mice	Induce tumor cells apoptosis, inhibit tumor cells proliferation, reverse MDR	(Yang et al., 2017b)
Amphiphilic Copolymeric Micelle	PEG-PLA	EPR	DOX/CUR	MCF-7 cells, MCF-7/ADR cells, female BALB/c nude mice	Reverse MDR	(Lv et al., 2016b)
Polymeric Micelle	Triethylamine + Di-tocopherol polyethylene glycol2000 succinate + PEG2000-DSPE	EPR	DOX/CUR	MCF-7 cells, MCF-7/ADR cells, Sprague-Dawley rats, female BALB/c mice	Inhibit tumor cells proliferation, reverse MDR, reduce side effects	(Wang et al., 2015a)
Copolymeric micelle	Methoxy poly (ethylene glycol)-ε-poly(caprolactone) diblock copolymers		RAP/CUR	T98G glioblastoma cells	Induce tumor cells apoptosis, inhibit tumor cells proliferation	(Mohanty & Mohanta, 2015)
Novel Bottlebrush Copolymer-based Micelle	NB-PEG + methylene chloride + Grubbs second generation initiator + NB-Br		PTX/CUR	A549 cells, HeLa cells	Induce tumor cells apoptosis, inhibit tumor cells proliferation, overcoming PTX resistance	(Yao et al., 2017)
Nanomicelle	MPEG-PLA copolymers		Docetaxel/CUR	A2780 cells, female BALB/c athymic nude mice	Reverse MDR, improve the bioavailability of docetaxel	(Hu et al., 2020)
Polymeric micelle	mPEG-PDLA block copolymer		Docetaxel/RES	MCF-7 cells, Sprague-Dawley rats	Reverse MDR	(Guo et al., 2019)
Mixed polymeric micelle	MeO-PEO_{5k}-b-PCL	EPR	PTX/Naringin	MCF-7 cells	Reverse MDR	(Jabri et al., 2019)
Polymeric prodrug micelle	PEG – Fmoc-Lys-$(NH2)_2$	EPR	PTX/Capsaicin	HepG2 cells, 4T1 cells, A549 cells, female BALB/c mice, ICR mice	Chemoprevention properties, enhance the effect of PTX	(Lan et al., 2019)
PEG-PE-based polymeric micelle	pNP-PEG_{3400}-pNP + 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine + chloroform + TEA + 1,2-distearoyl-sn-glycerol-3–phosphoethanolamine-N-[methoxy (polyethylene glycol) 2000] (PEG-PE) + anti-GLUT-1 single chain variable fragment	Decorated with single chain fragment variable (scFv)	DOX/CUR	U87MG cells	Induce tumor cells apoptosis, inhibit tumor cells proliferation, Reverse MDR	(Sarisozen et al., 2016)
Rod-shaped nano-micelle	NH2-PEG2000-NH2 + 4-carboxyphenylboronic acid	4-Carboxyphenylboronic acid-decorated + redox-sensitive	GEM/CPT	MCF-7/ADR cells, 4T1 cells, female BABL/c nude mice	Antitumor effect	(Xu et al., 2019b)
Zein-Lf micelle	Zein-Lf co-polymer	EPR	RAP/wogonin	MCF-7 cells, female Albino Swiss CD1 mice	Induce tumor cells apoptosis, reduce side effects	(Sabra et al., 2018)
Poly (ε-caprolactone) based micelle	PCL-co-P(maleic anhydride-g- Citric Acid)	pH-responsive	DOX/CUR	MDA-MB-231 cells	Antitumor effect	(Sabzi et al., 2020)

(*Continued*)

Table 6. Continued.

Nanocarrier type	Nanocarrier composition	Feature	Drug	Experimental Subject	The role of natural active ingredients	Ref
Complex polymeric micelle	mPEG–PCL–N-t-butoxycarbonyl-phenylalanine	EPR	DOX/CUR	H9C2 cells, A549 cells, male Sprague Dawley rats, inbred female C57BL/6J mice	Reduce side effects, antioxidant	(Zhang et al., 2018a)
Novel P(HEMA-LA-MADQUAT) micelle	P(2-Hydroxyethyl methacrylate (HEMA)-LA-MADQUAT)	EPR	MTX/Chrysin	MCF-7 cells	Induce tumor cells apoptosis, reduce side effects	(Davaran et al., 2018)
Amphiphilic maltodextrin-Based micelles	Maltodextrin + Ursodeoxycholic acid + FA + LA	Lactobionic/folate dual-targeted	SSZ/RES	HepG2 cells, male mice	Induce tumor cells apoptosis, inhibit tumor cells proliferation	(Anwar et al., 2018)
Prodrug polymeric micelles	PSN38 + TPL-nsa		SN38/TPL	Gastric cancer cell lines MKN45, BGC-823, SGC7901, and AGS, female BALB/c athymic nude mice	Remodel tumor microenvironment	(Zheng et al., 2021b)
PCM micelles	ROS-cleavable thioketal linker	ROS-sensitive	PTX/cucurbitacin B	BGC-823 cells, SGC7901 cells, BGC-823 xenograft model	Increase intracellular ROS level	(Pang et al., 2022)

and antitumor peptide (AP). Amphiphilic block copolymers were prepared by triphenylphosphine (TPP)/oligomeric hyaluronic acid (oHA)/disulfide-menthone 1,2-glycerolone (SM), referred to as TPP-oHSM. In vitro release and cellular uptake experiments showed that C/A@TM targeted mitochondria and CD44 receptors, and it was sensitive to pH and redox. In addition, C/A@TM showed satisfactory cytotoxicity to MDA-MB-231 cells and MCF-7 cells. Finally, it showed good therapeutic effect in clinical application.

4.3.4. Redox-responsive self-assembled polymer micelles

Self-assembled micelles can adjust the ratio of the two drugs and optimize the synergistic effect of drug combinations by using a simple co-assembly strategy, which is simple and feasible. Xu et al. (2019b) prepared redox-sensitive rod-like micelles by co-assembly of CPT-disulfide bond-PEG2000-4-carboxyphenylboronic acid and CPT-disulfide bond-GEM to achieve controllable redox and tumor-targeted synergistic self-delivery of CPT and GEM. In vitro drug release studies verified the redox triggering and synchronous rapid release of CPT and GEM by the co-assembled nano micelles. Nano micelles had obvious synergistic anti-proliferation effect on MCF-7/ADR and 4T1 cells *in vitro*. In addition, biodistribution nano micelles preferentially aggregated in the breast tumor site, which could improve the therapeutic effect and reduce the side effects of nonselective antitumor drugs.

4.4. Polymer-drug conjugates

Polymer-drug conjugates are designed to release drugs in tumor tissues or cells. They are mostly designed and manufactured to release drugs in tumor tissues or cells triggered by different stimuli to reduce systemic toxicity of parent drugs and improve their therapeutic effects (Feng & Tong, 2016). Polymer-drug conjugates remain stable in the process of transport in the body. Through the reasonable design of the connecting group, the physiological environment such as pH value, enzyme, temperature, and magnetic sensitivity is obtained, so as to realize the effective release of drugs in tumor targeting sites. A summary of the researches of polymer-drug conjugates used to co-deliver chemotherapy drugs and natural active ingredients is shown in Table 7.

4.4.1. Passive targeting

Graft copolymers have the characteristics of easy preparation, high drug loading, good stability, and tumor accumulation, which are often used as delivery carriers of antitumor drugs. Tai et al. (2014) designed a new graft copolymer, which can form polymer nanocarriers similar to protein folding for co-delivery of CPT and DOX. CPT was polymerized on the catenary segment of the graft polymer, while DOX was non-covalently wrapped in the hydrophobic core. In vivo studies have shown that compared with free drugs, nanocarriers show strong accumulation in tumor sites, and have significant antitumor activity in lung cancer xenograft mouse models. Huo et al. (2020) successfully prepared a dextran-deoxycholic acid (Dex-DOCA) amphiphilic polymer for co-delivery of PTX and silybin (SB). Dex-DOCA had good encapsulation efficiency for PTX and SB, and the drug loading was adjustable. The release of PTX and SB at a fixed dose ratio was consistent with the initial drug loading ratio of co-donor nanoparticles (PTX:SB = 1:1.4), which was conducive to the generation of synergistic effect. In vivo studies showed that co-loaded nanoparticles could effectively accumulate in the tumor site through passive targeting, and ultimately improve the permeability of nanoparticles to tumors in the A549 xenograft model by enhancing the intratumoral permeability and the sensitization of SB to PTX. Zou et al. (2017) used one-step nanoprecipitation method to co-load PTX and natural compound Borneol (BNL) in the prepared PEG-PAMAM NPs, denoted as PB/NPs. The results showed that PB/NPs and P/NPs + BNL had high cellular uptake and cytotoxicity on A2780/PTX cells, and could improve the apoptosis rate. More importantly, although PB/NPs and P/NPs + BNL showed similar tumor accumulation in tumor-bearing mice, PB/NPs could significantly decrease tumor growth of A2780/PTX tumor-bearing mice, in comparison to P/NPs + BNL.

4.4.2. Active targeting polymer-drug conjugates

When nanoparticles are modified with various ligands, they can specifically target components in the tumor microenvironment, including dendritic cells, macrophages, fibroblasts, tumor vascular system (Yang et al., 2021). In recent years, polymer dendrimers have been widely used for targeted delivery of antitumor drugs due to their homogeneity and biocompatibility. Anbazhagan et al. (2021) prepared

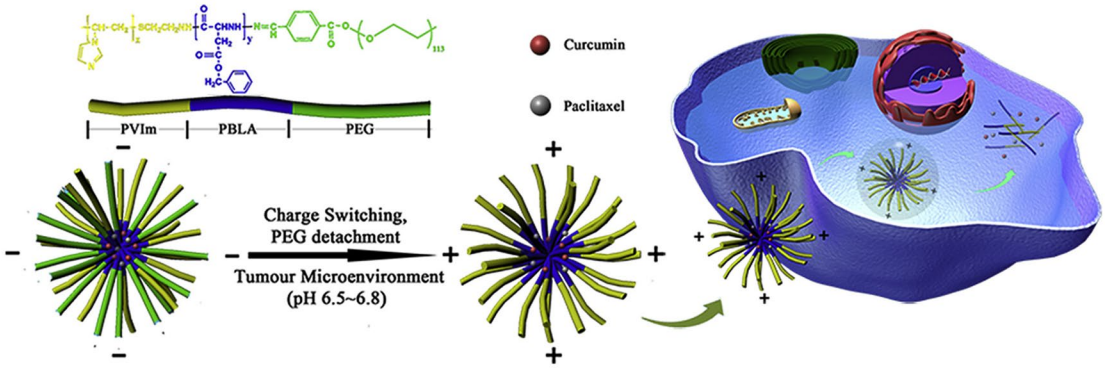

Figure 7. Schematic illustration of pH multistage responsive PTX and CUR-loaded PPBV micelles with the PEG detachment and charge-switching function for enhanced cellular uptake and tumor penetration. Reprinted with permission from Elsevier (Yang et al., 2017b).

Table 7. The researches of polymer-drug conjugates used to co-deliver chemotherapy drugs and natural active ingredients.

Nanocarrier type	Nanocarrier composition	Feature	Drug	Experimental subject	The role of natural active ingredients	Ref
RGD-PAMAM-FP nanoaggregate	RGD-PAMAM (PAMAM G 4.5) + RGD peptide + cystamine)	RGD targeting	PTX/FA	KB-CHR 8-5 cells	Improve the utilization of PTX in the cell, reverse MDR	(Anbazhagan et al., 2021)
Folding graft copolymer	Tris (2-aminoethyl) amine + Boc2O + TFA + BSA + triphosgene + DIPC + Et3N + DMAP	EPR	DOX/CPT	A549 cells, female naive athymic nude mouse	Antitumor effect	(Tai et al., 2014)
PEG-PAMAM nanoparticle	mPEG + PAMAM dendrimer		PTX/Silybin	A2780 cells, A2780/PTX cells	Reverse MDR	(Zou et al., 2017)
Dextran-based amphiphilic polymer	Dex-DOCA	EPR	PTX/borneol	A549 cells	Induce tumor cells apoptosis, inhibit tumor cells proliferation, sensitize tumor cells to PTX	(Huo et al., 2020)
Lipid-polymer hybrid nanoparticle	HA-PEG-DSPE + lecithin + acetone + PCL polymer	HA modified	DOX/gallic acid	HL-60 cells, K562 cells, HL-60/ADR cells, K562/ADR cells	Induce apoptosis, scavenge free radicals	(Shao et al., 2019)

Table 8. The researches of carrier-free NDCDS of natural active ingredients and chemotherapy drugs.

Nanocarrier type	Feature	Drugs	Experimental Subject	The role of natural active ingredients	Ref
Self-assembled nanofibers	EPR	PTX/Succinic acid	A549 cells, nude mice	Antitumor effect	(Xu et al., 2017a)
Nanoparticle	EPR	Cytarabine/CPT	Human umbilical vein endothelial cells (HUVEC), B16F10 cells, B16F10 tumor-bearing mice	Antitumor effect	(He et al., 2017)
Janus nano-prodrug	Redox-sensitive	GEM/CPT	A549 cells, NCI-H460 cells, MCF-7/ADR cells, HCT116 cells, HT-29 cells	Antitumor effect	(Xu et al., 2018)
Nanoparticle	Redox-sensitive	GEM/CPT	HeLa cells, MCF-7 cells, KM mouse model	Antitumor effect	(Hou et al., 2017)
Nanoparticle	Targeting folate receptor	MTX/CPT	HeLa cells, MCF-7 cells, A549 cells, HeLa tumor-bearing BALB/c nude mice	Induce tumor cells apoptosis, inhibit tumor cells proliferation	(Li et al., 2017d)
Nanoparticle	EPR	Erlotinib/CUR	BxPC-3 cells, NIH-3T3 cells, female nude mice	Antitumor effect	(Cheng et al., 2020)
Nanofiber	EPR	PTX/TET	MGC-803 gastric tumor cells, female nude mice	Induce tumor cells apoptosis	(Li et al., 2020d)
Nanoparticle	Targeting folate receptor	MTX/Ursolic acid	MCF-7 cells, BALB/c nude mice	Antitumor effect	(Lan et al., 2021a)
Nanoparticle		Aspirin/Ursolic acid	B16F10 cells, HeLa cells, HepG2 cells, MCF-7 cells, male KM mice	Anti-metastasis effect	(Li et al., 2018a)
Nanoparticle	EPR	5-FU/CA	HepG2 cells, H22 cells, ICR mice	Antitumor effect	(Fang et al., 2021)
Nanoparticle	EPR	PTX/Semen Armeniacae Amarum protein	L-02 cells, MDCK cells	Used as drug carrier	(Lin et al., 2020)
Self-assembled nanoparticle	EPR	PTX/CPT	LLC cells, A549 cells, MEF cells	Antitumor effect	(Gao et al., 2020)

polyamidoamine (PAMAM) dendrimers co-loaded FA and PTX coupled with arginine-glycine-aspartic acid (RGD) to overcome the multidrug resistance of oral cancer cells overexpressing P-gp. In vitro drug uptake data showed that RGD-PAMAM-FP could deliver more PTX than PAMAM-FP in KB CH-R8-5 cells. This indicated that RGD promoted the accumulation of intracellular PTX through active targeting on multidrug-resistant KBCH-R8-5 cells. *In vitro* toxicity experiments showed that when FA and PTX were loaded on RGD-PAMAM nanocarriers, more KBCH-R8-5 cell apoptosis might be induced than loaded on PAMAM nanocarriers. Zhang et al. (2017b) prepared iRGD peptide modified lipid-polymer hybrid nano system (LPN) to couple PTX and TET in a 1:1 ratio. PTX was conjugated to the PLGA polymer core through disulfide bonds, and TET was encapsulated in the hydrophobic polymer core. Due to the enhanced TET-mediated cellular uptake and P-gp inhibition, the accumulation of PTX in A2780/PTX cells treated with PTX+TET/iRGD LPNs was significantly higher than that in free drugs or non-iRGD modified LPNs. PTX+TET/iRGD LPNs had the highest cytotoxicity to A2780/PTX cells, especially promoting ROS production, enhancing apoptosis, and cell cycle arrest.

4.5. Nanosuspension

Nanosuspensions are nanoscale, heterogeneous aqueous dispersions of insoluble drug particles stabilized by surfactants (Jacob et al., 2020). Nanosuspension technology is the only alternative when many disadvantages of drug molecules such as the inability to form salt, high molecular weight, and dosage hinder the development of appropriate dosage forms. This technique is attractive due to the reduced use of excipients, which usually cause toxicity or side effects. NS made from hydrophobic drugs have the advantages of increasing drug loading, improving solubility, improving bioavailability (Sahu et al., 2016), and reducing side effects (Wang et al., 2019d).

Wang et al. (2019d) prepared PTX-BA hybrid nanosuspension to induce early apoptosis of MCF-7 cells through the decrease of mitochondrial membrane potential (Jiang et al., 2015). Compared with PTX-NS and BA-NS, PTX-BA-NS has the strongest effect on MCF-7 cell apoptosis, which may be partly attributed to the enhanced accumulation of PTX-BA-NS in cells and the synergistic effect of PTX and BA. Sahu et al. (2016) prepared nanosuspension of poorly water-soluble CUR and DTX by precipitation homogenization technology, and modified it with polyethylene glycol to increase its solubility and bioavailability, thereby improving the efficacy. Chen et al. (2015) and Zhao et al. (2015b) chose 10-hydroxycamptothecin (HCPT) and DOX to prepare HD nanoparticles (HD NPs) by "green" and convenient self-assembly method, which successfully improved the water solubility of HCPT. Due to the higher chemical sensitization and improving intracellular drug accumulation induced by DOX/HCPT combination, HD NPs showed synergistic therapeutic effect and enhanced inhibitory effect on breast cancer cells and drug-resistant cancer cells *in vitro*. Liu et al. (2021a) prepared multifunctional nanosuspension of CUR and irinotecan hydrochloride by precipitation using carrier-free self-assembly strategy, which showed better antitumor effect on gastric cancer cells.

4.6. Nanoemulsion

Nanoemulsions (NM) usually include aqueous and oil phases, which can overcome the shortcomings of low drug solubility by improving bioavailability, increasing drug stability, and reducing side effects when used as drug carriers (Yukuyama et al., 2017). Guo et al. (2020a) developed a novel NM as an oral 5-FU and CUR synergistic delivery system (CUR/5-FU-NM) for synergistic treatment of liver cancer. The comprehensive

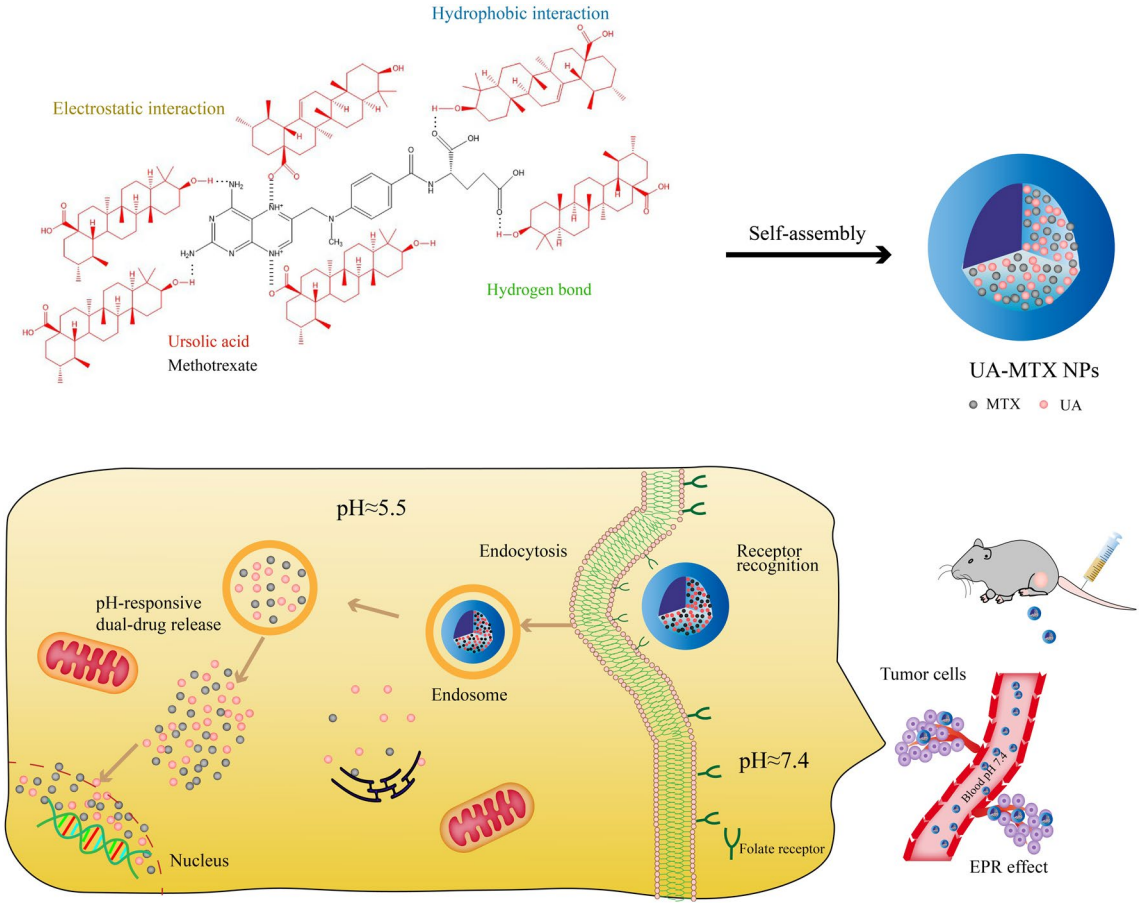

Figure 8. Schematic representation of the carrier-free nanoparticles (NPs) via co-assembly between UA and MTX. International Journal of Nanomedicine 2021 16 1775-1787′ Originally published by and used with permission from Dove Medical Press Ltd.

ratio analysis showed that when the molar ratio of CUR:5-FU was 2:1, CUR and 5-FU had the greatest synergistic effect. CUR /5-FU-NM enhanced the solubility and permeability of CUR and 5-FU, and improved the oral bioavailability of CUR and 5-FU, thereby enhancing the anti-hepatocellular carcinoma effect of CUR and 5-FU *in vitro* and *in vivo*. Meng et al. (2016b) encapsulated PTX and BCL in nanoemulsion (PTX/BA NM) to treat breast cancer. The experiment showed that the synergistic effect of PTX and BA in combination with the weight ratio of 1:1 was the strongest. In vitro cytotoxicity test and *in vivo* antitumor study showed that PTX/BA NM had better antitumor effect on MCF-7/Tax cells than other PTX preparations. Pangeni et al. (2018) designed an oral co-administration system of pemetrexed (PMX) and Que based on oil-in-water NM (PMX/N$^{\alpha}$-deoxycholyl-L-lysyl-methylester (DCK)-Que-NM). PMX/DCK-QCN-NE had good intestinal permeability and increased cell absorption of PMX/DCK and Que. In vivo experiments showed that compared with free PMX and QCN, the oral bioavailability of PMX and QCN in rats was significantly improved, and PMX/DCK-QCN-NE had the strongest inhibitory effect on tumor growth in A549 tumor-bearing mice.

4.7. Carrier-free NDCDS

Carrier-free NDCDS is a kind of covalent binding prodrug delivery system, and two identical or different drug molecules can be coupled together through chemical bonds to form the inactive precursor of the drug. When it reaches the tumor site, drug activation or biotransformation through environmental stimulation can prevent drug leakage in the process of *in vivo* circulation. Carrier-free NDCDS can improve drug loading, drug stability, and bioavailability, and increase drug safety, so as to achieve high flexibility in drug response release and synergistic combination therapy (Huang et al., 2021; Karaosmanoglu et al., 2021). A summary of the researches of carrier-free NDCDS used to co-deliver chemotherapy drugs and natural active ingredients is shown in Table 8.

Some natural active ingredients and chemotherapy drugs can be coupled together via ester bonds or acetal bonds to form carrier-free nano-systems to obtain high drug loading and synergistic antitumor effects, such as PTX and succinic acid (SA) (Xu et al., 2017a), 5-FU and CA (Fang et al., 2021), MTX and ursolic acid (UA) (Figure 8) (Lan et al., 2021a). Additionally, natural active ingredients can also be coupled with chemotherapy drugs through disulfide bonds to form redox-sensitive carrier-free nano-system to achieve the controlled release of drugs in tumor-specific microenvironment, such as CPT and arabinoside (Ara-C) (He et al., 2017), CPT and GEM (Hou et al., 2017), CPT and PTX (Gao et al., 2020).

What is more, carrier-free NDCDS can maintain the optimal ratio of natural active ingredients and chemotherapy drugs. For example, one mole of the natural active ingredients and one mole of the chemotherapeutic drug can be linked together

Table 9. The researches of other nanocarriers used to co-deliver chemotherapy drugs and natural active ingredients.

Nanocarrier type	Nanocarrier composition	Feature	Drug	Experimental Subject	The role of natural active ingredients	Ref
T7-targeting nanosystem	CM-β-CD-PEI-PEG-T7	T7-Modified + pH-Responsive	Docetaxel/CUR	Het-1a cells, KYSE150, KYSE510, Eca9706, and CaES-17 cells, male BALB/c mice	Antitumor effect, chemosensitization	(Deng et al., 2020)
Gold nanocages	PVP + Ag nanocubes + tetradecanol + Biotin-PEG-SH	Near-infrared (NIR)-responsive	DOX/Que	MCF-7/ADR cells	Inhibit the overexpression of P-gp	(Zhang et al., 2018b)
Nanogel	P(NIPAA-co-N, N-dimethyl-aminoethyl methacrylate (DMAEMA)) + tetraethylene glycol dimethacrylate + N-Isopropylacrylamide (NIPAAm))	pH/thermo-responsive	DOX/CUR	HT-29 cells	Antitumor effect, reverse MDR	(Abedi et al., 2021)
Mesoporous silica-based nanoplatform	CTAB + tetramethylorthosilicate + 3-aminopropyltriethoxysilane + perfluorodecyltriethoxysilane + NH4OH	pH-responsive	DOX/CUR hydrochloride	HepG2 cells, female nude mice	Antitumor effect	(He et al., 2020)
Hydrogel	Dichloromethane + ethylacetate + PLAR + PCLR copolymer	Thermosensitive	oxaliplatin/tannic acid	CT26 cells	Reduce side effects	(Ren et al., 2019)
Prodrug nanogel	A bioresponsive crosslinking agent with disulfide bond and two nitrophenyl groups (DBHD) + PEG	Glutathione-sensitive	DOX/mannose	4T1 cells, female BALB/c mice, female Kunming mice	Cause an anti-tumor immune response	(Ma et al., 2022)
Nanoparticle-loaded gelatin system	PEG-b-PCL block copolymers + gelatin powder	EPR	PTX/TET	BGC-823 cells, SGC-7901 cells, BALB/c athymic nude mice	Induce tumor cells apoptosis, enhance the cytotoxicity of PTX	(Zhang et al., 2016a)
Polymeric microspheres	Chitosan + oleic acid + hydroxypropyl-β-cyclodextrin + lactose + mannitol	pH-responsive	PTX/Que	Wistar rats	Reverse MDR	(Liu et al., 2017)
Nanodroplets	Tween 20 + perfluorohexane + $CaCl_2$ solution	EPR	DOX/CUR	A2780 cells, A2780 ADR cells, female BALB/c mice	Chemosensitization	(Baghbani & Moztarzadeh, 2017)
Core–Shell Nanocapsules	Fe + 1,2-hexadecanediol + oleic acid + oleylamine + benzyl ether + PVA + chloroform + PAA	Magnetic guidance and incorporation of Lf ligands	DOX/CUR	RG2 cells, BALB/c female nude mice	Reverse MDR	(Fang et al., 2014)
Nanocomposite	H6R6-CS-g-PNVCL	pH-responsive, thermosensitive	DOX/OA	SKOV3 cells, HUVEC cells, female nude mice,Sprague-Dawley rats	Antitumor effect, reverse MDR	(Chen et al., 2020b)
Nanobiocomposite	Graphene oxide-CS-FA	Folic acid decorated	3,3′-Diindolylmethane/CPT	MCF-7 cells, female albino wistar rats	Antitumor effect	(Deb et al., 2018)
Nanoconjugate	DMAP + EDC + S-S + NHS + TPGS	EPR	Docetaxel/ dihydroartemisinin	4T1 cells, female BALB/c mice, Sprague-Dawley rats	Induce tumor cells apoptosis, reverse MDR	(Li et al., 2020b)
Nanocomposite	Poloxamer 188 + HPMC + Tween 80 + methanol + ChS solution + Lf solution	EPR	DOX/ellagic acid	A549 lung cancer cells, male BALB/c mice	Antitumor effect	(Abd Elwakil et al., 2018)
Nanocarrier	MSN-NH_2 + bPEG + acrylamide + APMAAm	Bio-responsive	DOX/CUR	HeLa cells	Antitumor effect, reduce side effects, improve the effect of chemotherapy	(Lin et al., 2019)
Nanocomposite	Chitosan + palladium acetate + sodium tripolyphosphate + sodium borohydride	EPR	5-FU/CUR	HT-29 cells	Antitumor effect, reverse MDR	(Dhanavel et al., 2017)
Thermosensitive copolymeric nano-platform Hep-F127	Pluronic F127 + 1,4-diaminobutane + 4-nitrophenyl chloroformate	Temperature-responsive	CDDP/CUR	MCF-7 cells, Mus musculus var. albino mice	Induce tumor cells apoptosis	(Nguyen et al., 2018)
Lipid-polymer hybrid Nanosystem	PLGA-3,3′-dithiodipropionic acid + iRGD peptide	iRGD peptide-modified	PTX/TET	A2780 cells, A2780/PTX cells	Reverse MDR, antitumor effect	(Zhang et al., 2017b)
Nanocapsule	PCL + PEG6000 + span 80 + tween 80		MTX/CUR	Calu-3 cells	Antitumor effect, reverse MDR	(Rudnik et al., 2020)
Nanogel particle	Sodium alginate + Span 80 + Tween 80 + Paraffin oil + $CaCl_2$		DOX/GL	HepG2 cells, Kunming mice	Antitumor effect, reduce side effects	(Wang et al., 2019b)
Albumin sub-microspheres	p-Biguanylbenzoic acid + Ursodeoxycholic acid + albumin	The biguanide and ursodeoxycholic acid dual-modified	nintedanib/Bufalin	HepG2 cells, male ICR mice	Inhibit proliferation and invasion, relieved the tumor microenvironment	(Xu et al., 2021)
Nanocarrier vesicle	DPPC + Chol + DSPE-PEG		six different kinase inhibitors/Ursolic acid	HCC827 cells, H358 cells, HCT116 cells, SW480 cells, A431 cells, A431 OATP cells and A431 ABCG2 cells	Antitumor effect, reverse MDR	(Lőrincz et al., 2021)

by ester bonds or disulfide bonds. Carrier-free nano-systems coupled by ester or disulfide bonds can release drugs in a fixed proportion, which have better antitumor effect. Li et al. (2017d) coupled CPT and MTX by ester bond to synthesize MTX-CPT conjugates. In the tumor/lysosomal environment, the ester bond in the conjugate can be rapidly lysed by acid hydrolysis and/or enzymatic hydrolysis, and the dual drugs can be released synchronously at a fixed proportion. *In vitro* and *in vivo* studies suggested that the MTX-CPT NPs exhibited a superior synergistic effect, and could improve the therapeutic efficiency significantly with reduced toxicity compared to either individual free drug or a combination of both free drugs. Xu et al. (2018) prepared a novel redox-sensitive Janus nanoprecursor drug synthesized by disulfide bond connection to achieve self-administration and synergistic anti-proliferation of CPT and GEM. Due to the hydrophobicity of CPT and the hydrophilicity of GEM, the prepared amphiphilic prodrug CPT-SS-GEM can self-assemble into organized nanoparticles to realize the self-delivery of CPT and GEM without additional materials. At the same time, the dose ratio of CPT and GEM was always 1:1 when CPT-SS-GEM was degraded by high concentration of glutathione in tumor cells, resulting in synergistic antitumor effect.

4.8. Other nanocarriers

In recent years, studies have shown that Graphene (Deb et al., 2018), gold nanocages (Zhang et al., 2018b), hydrogels (Ren et al., 2019; Wang et al., 2019b; Abedi et al., 2021), prodrug nanogel (Ma et al., 2022), microspheres (Liu et al., 2017; Xu et al., 2021) and nanoclusters (He et al., 2020) can also be used for the co-delivery of natural active ingredients of and chemotherapy drugs. A summary of the researches of other nanocarriers used to co-deliver chemotherapy drugs and natural active ingredients is shown in Table 9.

5. Discussion

With the deepening of the research on the mechanism of tumorigenesis and development, drug combination therapy shows obvious advantages in tumor treatment, and the development of nanotechnology in the field of pharmaceutics has brought broad application prospects. NDCDS of natural active ingredients and chemotherapy drugs also have advantages and limitations in tumor treatment.

Firstly, natural products are a key source for the development of innovative anti-cancer medicines that may be used both preventively and therapeutically, and natural active ingredients have effects on cellular processes and signaling pathways (Chavda et al., 2022), which can directly or indirectly affect tumor cells. Therefore, the natural active ingredients can play a synergistic role in combination with chemotherapy drugs. However, the potential regulation mechanism of some natural active components on tumor microenvironment is still in the preliminary research stage. A better understanding of the synergistic antitumor effect of natural active ingredients and chemotherapy drugs can develop more effective anti-tumor drugs. Secondly, although the combination of natural active ingredients and chemotherapy drugs can reduce the side effects of chemotherapy drugs by reducing the intake of chemotherapy drugs and directly acting on certain targets, the nanocarrier itself can also cause toxicity, and the toxicological properties of nanomaterials have gradually been paid attention to. Therefore, the biodegradable and biocompatibility materials will become the first choice for nanocarriers in the future, and the carrier-free NDCDS will also become the focus of attention. In addition, due to the limitations of safety, the complexity of the preparation process, and the controllability of precise drug release, the co-delivery nanocarrier preparations of natural active ingredients and chemotherapy drugs have not yet entered the clinical stage. Before the clinical stage, the formulation or technology of nanopreparations faces great challenges in achieving universal applicability and achieving effective loading, targeted delivery and sustained release of the two drugs at the required proportion, and there are several problems to be considered in formulating an ideal NDCDS.

First, the optimal ratio of natural active ingredients and chemotherapy drugs is the primary issue. Some studies have not determined the optimal ratio of natural active ingredients and chemotherapy drugs, others had carried out to investigate on the optimal ratio of natural active ingredients and chemotherapy drugs by *in vitro* cell tests, but it is often difficult to obtain the optimal ratio *in vivo*.

Second, selecting appropriate nano carriers to realize the effective encapsulation of natural active ingredients and chemotherapy drugs is the important procedure. A suitable nano carrier can maintain the ratio of the multiple drugs constant and deliver them stably to the tumor tissue. At present, multifunctional mesoporous silica nanoparticles, PLGA nanoparticles, bovine serum albumin-coated superparamagnetic iron oxide nanoparticles, liposomes, and carrier-free NDCDS help to control proportional release. At the same time, due to the fact that at least two drugs are loaded on NDCDS, and the water-solubility and physicochemical characteristics of drugs are different, so the procedure for drug loading needs to be carefully considered in preparation. In addition, during the preparation process, the loading of one drug may affect the encapsulation efficiency and drug loading of another drug.

Third, how to achieve the targeted delivery of multiple drugs requires precise design, which puts forward higher requirements for the complex structure of carriers. A delivery system with multi-target modified and multiple environmental responses is designed by encapsulating two or more stimulus response units, which is expected to achieve higher targeting efficiency and improve the efficacy.

Fourth, sequential and precise drug release *in vivo* is another impactful parameter of determining the synergistic action of co-delivery drugs. However, many studies had carried out to investigate on the drug release of NDCDS in model microenvironment with pH buffer of normal body fluid, or tumor tissue and cell, which is difficult to show the real extent of drug release *in vivo*.

Fifth, although NDCDS of natural active ingredients and chemotherapy drugs works well in the experiment, the clinical efficacy is still limited. More in-depth and effective pharmacodynamic evaluation methods are needed to explain the

rationality of the combined use of natural active ingredients and chemotherapy drugs in NDCDS.

Although faced with many difficulties, it is believed that with the continuous revelation of the mechanism of action of natural active ingredients and the continuous development of nanotechnology, the NDCDS of natural active ingredients and chemotherapy drugs will show a promising prospect in antitumor therapy.

Disclosure statement

The authors report there are no competing interests to declare.

Funding

This work was supported by the Medical and Health Science and Technology Development Plan of Shandong Province, China (No. 202113020512), Shandong Provincial Natural Science Foundation, China (No. BS2014YY047).

ORCID

Huagang Sheng http://orcid.org/0000-0003-2299-7553

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