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REVIEW

Traditional Chinese medicine-combination therapies utilizing nanotechnology-based targeted delivery systems: a new strategy for antitumor treatment

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Abstract: Cancer is a major public health problem, and is now the world's leading cause of death. Traditional Chinese medicine (TCM)-combination therapy is a new treatment approach and a vital therapeutic strategy for cancer, as it exhibits promising antitumor potential. Nano-targeted drug-delivery systems have remarkable advantages and allow the development of TCM-combination therapies by systematically controlling drug release and delivering drugs to solid tumors. In this review, the anticancer activity of TCM compounds is introduced. The combined use of TCM for antitumor treatment is analyzed and summarized. These combination therapies, using a single nanocarrier system, namely codelivery, are analyzed, issues that require attention are determined, and future perspectives are identified. We carried out a systematic review of >280 studies published in PubMed since 1985 (no patents involved), in order to provide a few basic considerations in terms of the design principles and management of targeted nanotechnology-based TCM-combination therapies.

Keywords: cancer, codelivery, combination therapy, nanotargeted drug-delivery system, tumor targeting, TCM

Introduction

Cancer is the leading cause of disease-associated death in China,[1] and is now the world's leading cause of death.[2] According to the Global Cancer Report 2018 on the trend of 36 cancers in 185 countries worldwide by the WHO, the global burden of cancer is increasing at an alarming rate (one in eight deaths on average are due to cancer). The report also pointed out that the incidence and mortality rate of cancer continues to rise each year, with developing countries accounting for approximately 60% of the world's new cases and 70% of annual deaths. In 2018, nearly half the world's new cases of cancer occurred in Asia, most of which occurred in China.[3] Bray et al[2] provided a status report on the global burden of cancers using GLOBOCAN 2018. It is estimated that there will be 18 million new cases of cancer and 9.6 million cancer deaths in 2018. Lung cancer and breast cancer are the most frequent cancers in men and women, respectively, and the two leading causes of cancer death. Due to the high incidence and mortality rate of cancer, the global health care burden is also increasing rapidly.

Surgical treatment, chemotherapy, and radiotherapy are the primary treatment methods for cancer.[4] If cancer patients are diagnosed early and receive timely surgical

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treatment, the probability of surviving for 5 years after surgery is greatly improved. However, when cancers are diagnosed late, the vast majority of patients are already in the terminal stages, and thus may have lost the opportunity of surgical treatment. In addition, due to adverse reactions caused by radiotherapy, such as fatigue, gastrointestinal reactions, skin damage, bone-marrow suppression, and cardiotoxicity,[5] chemotherapy is still the main method of cancer treatment.

Nevertheless, due to lack of specificity and poor targeting, chemotherapy drugs not only kill tumor cells but also act on normal tissue, causing a reduction in immunity, significant side effects, and low drug efficacy. In addition, cancer patients can develop resistance to a single chemotherapy drug in clinical practice, resulting in a decrease in the subsequent curative effect. Multidrug resistance (MDR) was once considered the leading cause of chemotherapy failure, and may also promote tumor metastasis and recurrence.[6] Based on recent statistics from the American Cancer Society, >90% of cancer patients die from different levels of MDR.

Therefore, the treatment of cancer should be changed from an initial single medication to combination therapy. The combination of two or more active antitumor ingredients plays a crucial role in complementarity and synergy, and has become the preferred scheme in cancer treatment. Notably, the combination of traditional Chinese medicines (TCMs) with chemotherapeutic drugs and the combination of various TCMs, which involves multiple targets and multiple signaling pathways, have improved efficacy compared with drugs with a single molecular target and become a new strategy for tumor therapy in recent years.[7] Due to a great deal of investment and rapid development, nanotechnology is already used in various fields of biomedical science.[8] Novel nanoformulation-based drug-delivery systems, such as liposomes, nanoparticles (NPs), vesicles, mesoporous silica NPs (MSNs), and micelles, provide promise in overcoming current limitations, including poor targeting, insufficient absorption, poor pharmacokinetics and bioavailability, and limited biodistribution.[9–11]

In this review, the anticancer activity of TCM compounds is introduced. The combined use of TCMs for antitumor therapy is analyzed and summarized. These combination therapies using a single nanocarrier system, namely codelivery, are analyzed to determine their potential in prolonging drug duration in vivo, targeting drug delivery, and reducing toxicity (Figure 1). Matters requiring attention and future perspectives in this field are also reviewed, in order to accelerate the clinical application of combination antitumor therapy using targeted nanotechnology.

Antitumor effects of TCMs

Herbs, animals, and minerals are used widely as health foods and medicines to remedy various diseases in Asia, and have been collected and recorded as effective and traditional therapies in the TCM literature. For example, artemisinin was isolated by Youyou Tu at the China Academy of Traditional Chinese Medicine in Beijing, and is now an effective medicine in the treatment of malaria. As a result, Tu won the Nobel Prize in Physiology or Medicine in 2015. In most developing countries, 80% of the population continue to use traditional medicines for primary health care.[12] From 2016 to 2017, the total amount of TCM herbal medicines and other related products exported to the Belt and Road Initiative countries reached US$295 million. In addition, the WHO also recognized traditional medicine in its influential global medical compendium.[13]

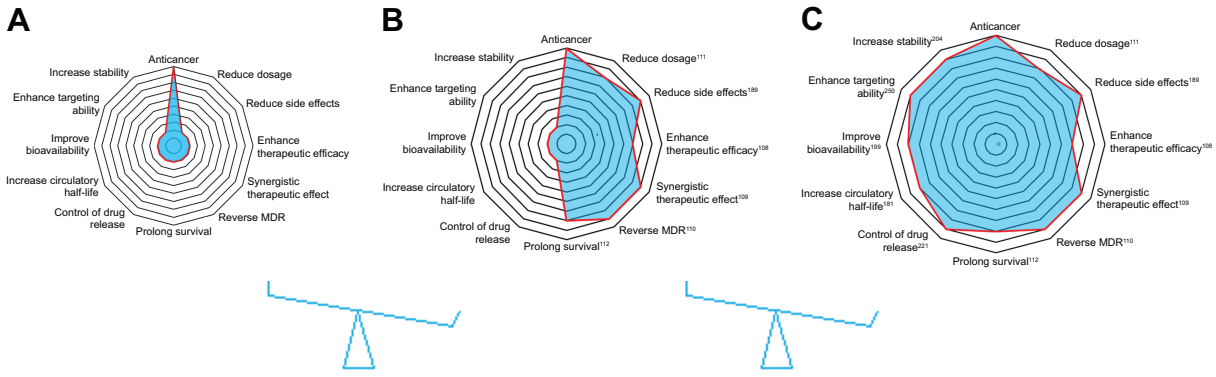

Figure 1 Advantages of targeted nanotechnology-based TCM-combination therapy.
Notes: (**A**) Antitumor effects of TCM; (**B**) antitumor effects of TCM-combination therapy; (**C**) antitumor effects of targeted nanotechnology-based TCM-combination therapy.
Abbreviations: TCM, traditional Chinese medicine; MDR, multidrug resistance.

Worldwide, including in Western countries, TCM has been increasingly used in the past few decades, and is well known for its vital role in cancer prevention and treatment. A number of studies have confirmed that the active ingredients in TCM (curcumin [Cur], gambogic acid, and baicalein [BA], among others) are able to effectively induce apoptosis, interfere with tumor progression, inhibit tumor development, inhibit angiogenesis, cause cell-cycle arrest, and block metastasis. A summary of the antitumor effects of drugs isolated from TCMs is shown in Table 1. Structures of TCM compounds are shown in Figure 2.

Antitumor effects of TCM-combination therapy

Initially, cancer therapy consisted of a single drug, which could involve a single target. However, malignant disease is caused by many complicated factors, and treatment with a single drug is not adequate. Patients are usually susceptible to drug resistance after sequential cycles of therapy with these chemotherapy drugs,[100] and a single medication frequently causes serious side effects. For instance, although cisplatin is clinically effective, it lacks selectivity for tumor tissue, resulting in serious side effects, such as kidney-function damage,[101] neurotoxicity,[102] ototoxicity,[103] and the emergence of MDR, resulting in the failure of chemotherapy.[104] In addition, long-term or high-dose cisplatin treatment can also cause severe anemia.[105] Therefore, the clinical application of single drugs, such as cisplatin, has been greatly restricted.

Cancer therapy urgently requires a new therapeutic approach to overcome these shortcomings. Combination-drug therapy is a new mode of treatment, and has gradually gained the attention of researchers.[106] Combination therapy involves the simultaneous or sequential use of two or more medicines for therapeutic purposes, and gradually plays a meaningful role in a complementary way, has synergistic action, and alleviates adverse reactions. It can not only produce a better therapeutic effect by regulating multiple signaling pathways in abnormal cells and act on multiple targets simultaneously but also reduce the occurrence of MDR and reduce both the dosage and side effects. The combination of two or more active antitumor ingredients is now a vital treatment method for tumors, and has received US Food and Drug Administration (FDA) approval.[107]

Based on classic TCM theory, the combination of antitumor TCMs exhibits promising potential in cancer treatment such as: 1) enhancing the therapeutic efficacy of chemotherapeutic drugs – due to the combined effects of Cur and cisplatin determined in vitro and in vivo, experimental results demonstrate that Cur can enhance the antitumor effect of cisplatin in A549 cells in vitro, the combination markedly inhibiting tumor growth and promoting apoptosis in the A549-xenograft mouse model;[108] 2) achieving synergistic therapeutic effects – resveratrol and Cur synergistically cause apoptosis in breast cancer cells by p2 (Waf/Cip1)-mediated inhibition of the Hedgehog–Gli cascade;[109] 3) reversing drug resistance – the combination of cryptotanshinone and cisplatin leads to cell death and apoptosis, and cryptotanshinone reverses cisplatin resistance in human lung carcinoma A549 cells by downregulating the Nrf2 pathway;[110] 4) reducing the dose of drugs – combination therapy with triptolide and cisplatin completely suppresses tumor growth, suggesting that lower concentrations of cisplatin and triptolide may produce a synergistic anticancer effect;[111] and 5) prolonging survival – As_2O_3 combined with ginsenoside Rg_3 can significantly inhibit the proliferation of NCIH1299 cells and prolong survival of tumor-bearing nude mice, with a significant effect on lung cancer treatment.[112] In addition, TCM-combination therapy results in good prognosis, has fewer adverse reactions, has long-lasting curative effects, regulates the expression of intracellular marker proteins, and reduces the side effects of drugs.[112–115] Further superior effects are shown in Table 2. The anti–lung cancer and anti–breast cancer mechanisms of TCM-combination therapy are shown in Figures 3 and 4. TCM-combination therapy achieves the effects that single chemotherapeutic drugs fail to achieve, and has become the main direction in clinical and experimental research on antitumor therapy.[116]

Nevertheless, there are three possible interactions in drug combinations: antagonistic, additive, and synergistic effects. Therefore, if we do not understand interactions among drugs, blindly combining drugs will not only fail to achieve the desired response but also lead to reduced efficacy and increased toxicity, and even produce drug-borne diseases. For instance, the combination of paclitaxel (Ptx) and BA shows antagonism in breast cancer MCF7 cells,[117] and Liu et al[118] suggested that the combination of gambogic acid and bortezomib should be avoided in patients. In addition, attention should be paid to the proportion and sequence of the two drugs in combination.

Applications of targeted nanotechnology in TCM-combination therapy

During the early 20th century, Paul Ehrlich proposed the concept of targeted drugs, which consisted of three

Table 1 Antitumor effects of traditional Chinese medicine

Monomer composition	Source (Chinese name)	Anticancer category	Anticancer property
Curcumin ($C_{21}H_{20}O_6$)	*Curcuma longa* (*jiang huang*)	Breast cancer, neurological cancers, lymphoma, lung cancer, melanoma, sarcoma, leukemia, gastrointestinal cancers, ovarian cancer, genitourinary cancers[14]	It can inhibit the initiation step of cancer and malignant-cell proliferation during the promotion and progression of carcinogenesis.[15]
Arsenic trioxide (As_2O_3)	Arsenic (*pi shuang*)	Acute promyelocytic leukemia,[16] renal cancer, prostate cancer, hepatocellular carcinoma,[17–19] lung cancer[20,21]	As_2O_3 can induce the accumulation of cellular ROS, causing DNA damage and leading to cell-cycle arrest and apoptosis in various solid tumors.[17–19]
Resveratrol ($C_{14}H_{12}O_3$)	*Polygonum cuspidatum* (*hu zhang*)	Osteosarcoma cells,[22] breast cancer,[23] colon cancer,[24] cervical cancer, blood cancer, kidney cancer, liver cancer, bladder cancer, thyroid cancer, esophageal cancer, prostate cancer, brain cancer, gastric cancer, bone cancer, ovarian cancer[25]	It can induce apoptosis and inhibit proliferation by modulating the PI3K–Akt–mTOR and MAPK pathways.[22,26,27]
Ginsenoside Rg_3 ($C_{42}H_{72}O_{13}$)	*Panax ginseng* (*ren shen*)	Breast cancer cells,[28] colorectal tumor,[29] ovarian cancer[30]	Ginsenoside Rg_3 can inhibit tumor development by inhibiting tumor angiogenesis, regulating apoptosis of tumor cells, controlling the proliferation, invasion, and metastasis of tumor cells, and inhibiting multidrug resistance.[28–30]
Baicalein ($C_{15}H_{10}O_5$)	*Scutellaria baicalensis* (*huang qin*)	HCT116 human colon cancer,[31] pancreatic cancer stem cells,[32] bladder cancer,[33] breast cancer,[34] gastric cancer,[35] hepatocellular carcinoma[36]	It can inhibit a variety of cyclins or cyclin-dependent kinases, regulate the cell cycle,[37] scavenge oxidative radicals, weaken MAPK, Akt, or mTOR activities,[38] inducing apoptosis[39] and inhibiting the invasion and metastasis of tumors.[40]
Gambogic acid ($C_{38}H_{44}O_8$)	*Garcinia hanburyi* (*teng huang*)	Gastric cancer,[41] prostate cancer,[42] lung cancer,[43] pancreatic cancer,[44] hepatocarcinoma[45]	Gambogic acid can induce apoptosis,[46] enhance the accumulation of ROS,[47] and inhibit telomerase activity.[41,43]
Gambogenic acid ($C_{38}H_{46}O_9$)	*Garcinia hanburyi* (*teng huang*)	Human nasopharyngeal carcinoma CNE1 cells,[48] U251 glioblastoma cells,[49] breast cancer,[50] lung cancer[51]	Gambogenic acid is associated with inhibition of proliferation of A549 cells by apoptosis induction and cell-cycle arrest,[48,52,53] and can mediate apoptosis in human nasopharyngeal carcinoma CNE1 cells.[49]
Quercetin ($C_{15}H_{10}O_7$)	*Hypericum ascyron* (*hong han lian*)	Melanoma,[54] prostate cancer,[55] breast cancer,[56] human leukemia HL60 cells[57]	Quercetin can induce cancer-cell apoptosis by modulating signaling pathways and blocking cell-cycle progression,[58] as well as actively suppress cancer proliferation and cancer metastasis.[59]
Triptolide ($C_{20}H_{24}O_6$)	*Tripterygium wilfordii* (*lei gong teng*)	Medulloblastoma,[60] lung cancer cells,[61] blood cancer cells, colon cancer cells, breast cancer cells, brain cancer cells, ovary cancer cells, kidney cancer cells, prostate cancer cells[62,63]	Triptolide can inhibit cell proliferation and arrest the cell cycle,[64] increase LC3α expression levels,[65] and inhibit the PI3K–Akt–mTOR pathway. While ERK1/2 is activated, autophagy of cell death is induced.[66,67]
Berberine ($C_{20}H_{18}NO_4$)	*Coptis chinensis* (*huang lian*)	Human malignant pleural mesothelioma NCIH2452 cells,[68] human colon cancer cells,[69] hepatocellular carcinoma,[70] breast cancer cells,[71,72] human HSC3 oral cancer cells,[73] human epidermoid carcinoma A431 cells[74]	It can inhibit cancer-cell proliferation, induce cell-cycle arrest at the G_1/G_0 phase, induce apoptosis in cancer cells,[69] cause cell-growth inhibition, and suppress cell migration and invasion.[71–74]
Cryptotanshinone ($C_{19}H_{20}O_3$)	*Salvia miltiorrhiza* (*dan shen*)	Prostate cancer,[75] breast carcinoma,[76] lung cancer[77]	It inactivates STAT3 activity,[75] arrests the cell cycle in the G_1/G_0 phase, and inhibits expression of cyclin D1.[76]

Tetramethylpyrazine ($C_8H_{12}N_2$)	*Ligusticum striatum* (*chuan xiong*)	Lung cancer,[78] osteosarcoma[79]	It can reduce activities of COX2 and MMP2/TIMP2,[78] upregulate cytosolic NFκB p65 expression, and downregulate protein expression of nuclear NFκB p65, BCL2, and cyclin D1.[79]
Dihydroartemisinin ($C_{15}H_{24}O_5$)	*Artemisia annua* (*huang hua hao*)	Pancreatic cancer,[80] osteosarcoma,[81] liver cancer,[82] leukemia[83,84]	It can activate caspase 3, caspase 8, and caspase 9, upregulate the expression of Fas, cyclin D1, and Bax, downregulate the expression of CDC25B, Bcl2, and cyclin B1, and inhibit NFκB activity.[85]
Ginsenoside Rh_2 ($C_{36}H_{62}O_8$)	*Panax ginseng* (*ren shen*)	Breast cancer,[86] ovarian cancer,[87] prostate cancer,[88] leukemia,[89] colorectal cancer,[90] hepatocellular carcinoma[91]	Some signaling pathways, such as TNFα,[92] EGFR,[93] JAK–STAT3,[94] and PI3K–Akt[95] have been implicated in the regulatory process of Rh_2 in cancer cells.
Plumbagin ($C_{11}H_8O_3$)	*Plumbago zeylanica* (*bai hua dan*)	Prostate cancer,[96] breast cancer cells,[97] melanoma cells[98]	It can induce apoptosis and autophagy, destroy the cell cycle, inhibit invasion and metastasis, and prevent angiogenesis, with anticancer potential in different cancer cells in vitro and in vivo.[99]

components: the drug, targeting moiety, and drug carrier. The main aim was to deliver the drug to the specific target organ under the specific guiding mechanism.[168] Targeted preparations are characterized by increasing the intensity of pharmacological action in target tissue, controlling drug release, and decreasing systemic adverse reactions. Targeted drug-delivery systems have become one of the important high-profile topics in modern pharmacy. Nanotargeted drug-delivery systems have remarkable advantages in improving the bioavailability of drugs, enhancing the targeting ability of drugs, improving the distribution and pharmacokinetic properties of antitumor drugs in vivo and in vitro, increasing the stability of drugs, solubilizing poorly soluble drugs, protecting drugs from degradation in vivo, intelligently regulating the release of components, enhancing efficacy, and reducing toxicity.[169–172] Moreover, metastasis of neoplastic cells is the major cause of death in cancer patients,[173,174] and nanosize drug-delivery systems also provide an encouraging strategy for lymphatic metastases.[175] In 2004, the National Cancer Institute (NCI) launched the NCI Cancer Nanotechnology Alliance, which aims to use nanotechnology to combat cancer.[176]

In recent years, many types of nanopreparations of TCMs, which involve the combination of nanotargeted drug-delivery systems and the advantages of TCM components in the treatment of tumors, have been reported.[177–179] Simultaneously, nanotargeted drug-delivery systems are also promising multidrug carriers and allow the development of drug combinations by systematically controlling drug release and delivering drug to solid tumors.[180] Codelivery of multiple antitumor agents in a single well-designed nanocarrier has significant advantages over monotherapy.[181,182] Generally, drug targeting can be classified into three categories: passive targeted preparations, active targeted preparations, and other physicochemical targeted drug-delivery systems.

Passive targeted drug-delivery systems

In a passive targeted drug-delivery system, lipids, adipoids, proteins, and biodegradable high-molecular-weight polymers are mainly used as carriers, and the drug is encapsulated or embedded into various colloidal systems, forming stable structures, such as polymeric NPs (PNPs), micelles, nanovesicles, and liposomes, to increase drug concentration in tumor cells, decrease drug distribution in blood and other organs, and prevent toxicity and adverse reactions. This spontaneous accumulation, or "passive" targeting, is particularly effective against tumors, due to leaky angiogenic vessels and poor lymphatic drainage of the tumor, which is currently

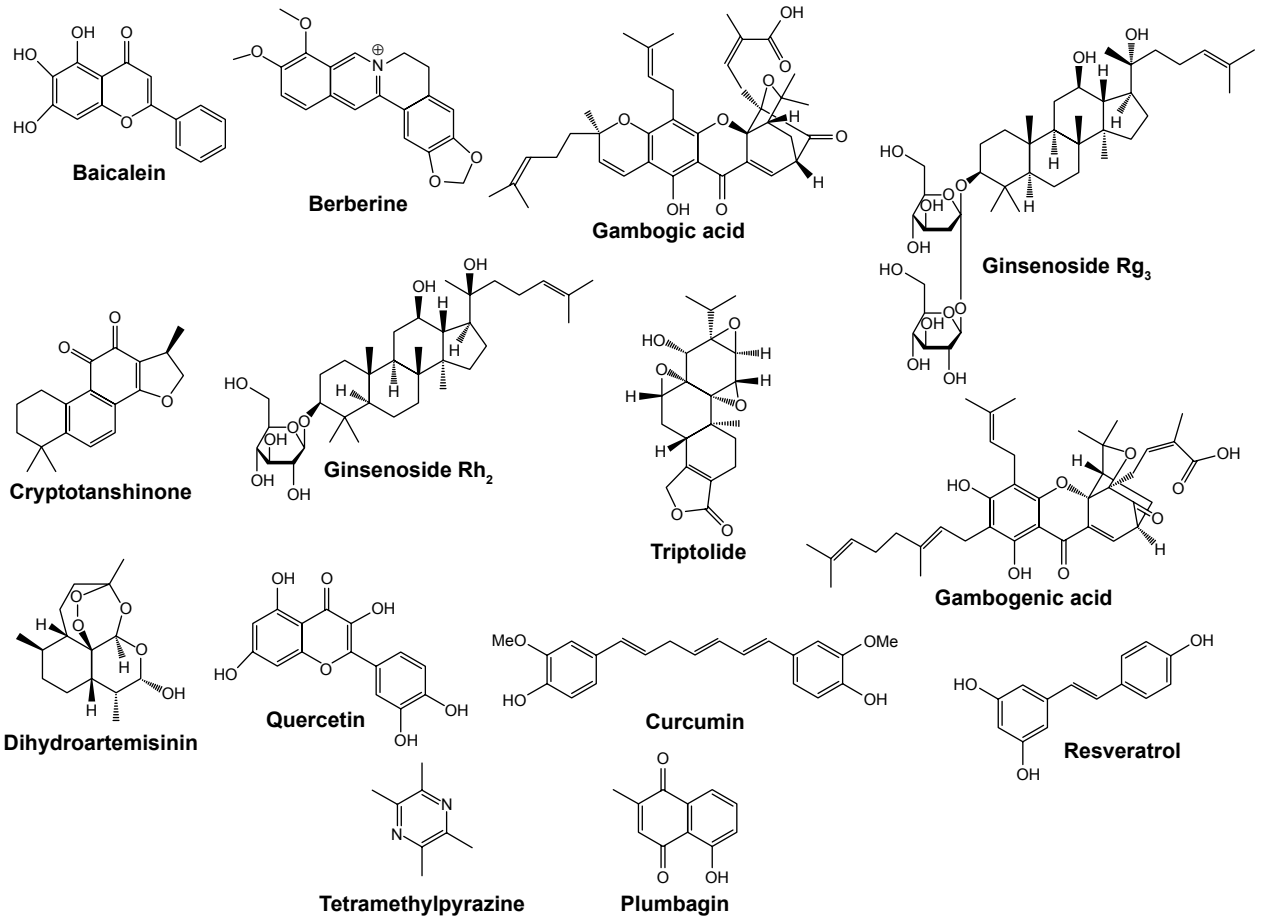

Figure 2 Chemical structures of the active components in traditional Chinese medicine.

referred to as the enhanced permeability and retention (EPR) effect. That is to say, the high permeability of tumor blood vessels allows nanosystems to enter the interstitial spaces of the tumor, while impaired lymphatic filtration allows these nanosystems to remain there. This phenomenon does not exist in normal tissue. Currently, EPR-mediated drug delivery is considered effective in delivering drugs into tumors, especially nanocarriers (Figure 5). The size of the particles is also closely related to their distribution.[183] The different sizes of these nanosystems decide the in vivo distribution behavior. Nanopreparations of <100 nm can be slowly accumulated in bone marrow; nanocarriers of 100–200 nm are apt to become enriched in the solid-tumor site; nanosystems of 0.2–3 μm are taken by macrophagocytes in the liver and spleen and particles of >7 μm are often intercepted by pulmonary capillary beds and enter the pulmonary tissues or alveoli.[184]

Liposomes

Liposomes are microvesicles with one or more aqueous cavities formed by the encapsulation of one or two amphiphilic molecular double-layer membranes, and the drug is encapsulated or embedded into the liposomes to form the liposome drug. Due to the similarity between the structure and the biological membrane, the encapsulation of water-soluble and fat-soluble drugs can reduce the drug dose, lower drug toxicity, delay release, lower in vivo elimination speed, change in vivo distribution of the drug, and achieve targeted release. Due to these advantages, liposome drugs have attracted considerable attention, and many studies have been carried out on them.[185]

Plumbagin is a quinonoid isolated from the roots of *Plumbago zeylanica* (*bai hua dan* in Chinese).[186] It has high antiproliferative activity against a variety of tumor cell lines,[187,188] and its anticancer properties have also been demonstrated in vivo.[186] Celecoxib and plumbagin are two antitumor drugs that synergistically kill melanoma cells instead of normal cells. The combined use of these two agents in traditional approaches was not possible, due to their poor bioavailability and toxicity concerns. In order to circumvent these challenges, Raghavendra et al[182] developed a nanoliposome containing celecoxib and plumbagin, named CelePlum 777, which has good stability and can release these two drugs

Table 2 Antitumor effects of TCM-combination therapy

Monomer composition	Combination therapy	Cellular, animal levels	Advantages of combination therapies	Reference
Curcumin (Cur)	Cur + cisplatin	Human non-small-cell lung cancer (NSCLC) A549, A549-xenograft mouse model	Cur can strengthen the antitumor effect of cisplatin in A549 cells in vitro. Cur combined with cisplatin can inhibit tumor growth and promote apoptosis in xenograft mouse model.	108
	Cur + paclitaxel	Breast cancer cell line MCF7, MCF7-xenograft mouse model	Cur combined with paclitaxel can inhibit the growth of MCF7 cells synergistically, induce significant apoptosis in MCF7 cell lines, and exert increased antitumor efficacy in mouse models.	117
	Cur + Rsv	Breast epithelial MCF10A-Tr, tumor xenograft in mice	Cur and Rsv causes apoptosis synergistically in breast cancer cells by p2 Waf/Cip1-mediated inhibition of Hedgehog–Gli cascade.	109
		Colon cancer HCT116 (wild type) cells, xenografts in SCID mice	The combination of Cur and Rsv has stronger inhibitory effects on the growth of p53-positive (wild type) and p53-negative (HCT116) colon cancer cells in vitro and in vivo than either agent alone.	119
	Cur + Rsv–diallyl disulfide	Malignant rhabdoid (SJRH4, RD/18) and osteosarcoma (SAOS2) cell lines	Cur induces apoptosis in rhabdomyosarcoma and osteosarcoma cells, which is potentiated when Cur is combined with Rsv or diallyl disulfide.	120
	Cur + As_2O_3/Ionidamine	U937 and HL60 human acute myeloid leukemia cells, K562 chronic myelogenous leukemia cells	Cur plus As_2O_3 or Ionidamine stimulates events typical of the mitochondrial executioner pathway. Cotreatment with Cur may be an effective way to improve the efficacy of As_2O_3 and Ionidamine as antineoplastic agents for myeloid leukemia cells.	121
	Cur + vesicular stomatitis virus	PC3 prostate cancer cells, mouse model of prostate cancer	Cur makes prostate cancer cells sensitive to the oncolytic effects of vesicular stomatitis virus through modulating antiviral responses and components of the intrinsic apoptotic pathway.	122
	Cur + Qct	Human gastric cancer MGC803 cells	The combination of Cur and Qct has a significant inhibitory effect on cell proliferation and a stronger effect on gastric cancer MGC803 cells than individual therapy.	123
Arsenic trioxide (ATO)	ATO + artesunate	Human K562 cell lines	Artesunate combined with ATO can significantly promote apoptosis of K562 cells induced by artesunate.	124
	ATO + dihydroartemisinin	A549 cells	Dihydroartemisinin effectively sensitizes A549 cells to ATO, increasing the effectiveness of ATO-induced cell death, and can cooperate with ATO to exert synergistic effects in promoting apoptosis in A549 lung cancer cells.	85
	ATO + cisplatin–doxorubicin (Dox)	HepG2 cell lines, hepatic cancer stem cells	This study was critical in realizing the potential for synergy between ATO and chemotherapeutic protocols, such as cisplatin and Dox.	125
		Human hepatoma BEL7402 cells, mouse hepatoma HepA	Low-dose cisplatin or Dox and ATO in combination can increase the antihepatocarcinoma effect.	126
	ATO + Dox	SGC7901/S human GC cell line, Dox-resistant SGC7901/ADM cell line	ATO can reverse MDR to Dox in human GC cells. This may be relevant to decreased Pgp expression.	127
	ATO + matrine	Myeloma cell lines RPMI 8226 and U266	Matrine shows an antimyeloma effect by inducing apoptosis, and ATO combined with matrine enhances apoptosis induced by matrine, having synergistic effects.	128

(*Continued*)

Table 2 (*Continued*)

Monomer composition	Combination therapy	Cellular, animal levels	Advantages of combination therapies	Reference
Resveratrol (Rsv)	Rsv + cisplatin	A549 cells	Rsv combined with cisplatin synergistically induced apoptosis by modulating autophagic cell death in A549 cells.	104
	Rsv + Dox	MCF7 and MDA-MB231 cell lines, Ehrlich ascitic carcinoma–bearing mice	Rsv combined with Dox can inhibit tumor volume and prolong the life of Ehrlich ascitic carcinoma cell–bearing mice.	129
	Rsv + paclitaxel	HepG2 human liver cancer cells	Rsv can enhance the anticancer effect of paclitaxel on HepG2 cells and be used as a sensitizer of paclitaxel.	130
		NSCLC cell line A549	Rsv enhances the anticancer effects of paclitaxel in A549 cells, and thus Rsv might be used as an excellent sensitizer for paclitaxel.	131
	Rsv + temozolomide	Human glioblastoma U87 MG and GBM8401 cell lines, GBM-SKH (GBM) cell line, orthotopic xenograft model	Rsv can enhance temozolomide-mediated antitumor effects in glioblastoma multiforme in vitro and in vivo by ROS-dependent AMPK–TSC–mTOR signaling pathway.	132
	Rsv + Qct	Human hepatoblastoma HepG2 cells	Rsv plays different roles in autophagy according to cellular energy state, and can represent a promising strategy to sensitize cancer cells to Qct therapy.	133
	Rsv + As_2O_3	HeLa, MCF7, and NB4 cells, HeLa-cell mouse model	Rsv can significantly raise the antitumor effect induced by As_2O_3 in vitro, and As_2O_3 combined with Rsv can significantly inhibit tumor growth and angiogenesis in nude mice.	134
Ginsenoside Rg_3	Rg3 + As_2O_3	NCIH1299 lung cancer cells, nude mice bearing hepatoma	As_2O_3 combined with Rg_3 can dramatically inhibit proliferation of NCIH1299 cells and prolong the survival of nude mice bearing tumors, having a significant effect on lung cancer therapy.	112
	Rg_3 + paclitaxel	Triple-negative breast cancer lines MDA-MB231, sMDA-MB453, BT549, mouse MDA-MB231-xenograft model	Rg_3 promotes cytotoxicity and apoptotic effects of paclitaxel on triple-negative breast cancer through inhibition of NFκB activity and regulating Bax/Bcl2 expression.	113
	Rg_3 + paclitaxel/cisplatin	Mouse tumor-xenograft models	The combined use of Rg_3 can remarkably raise the inhibitory effects of chemotherapy on tumor growth, and expression levels of Ki67 in the chemotherapy + Rg_3 group were significantly lower than in the other groups (Rg_3 alone, paclitaxel alone, and cisplatin alone).	114
	Rg_3 + docetaxel	Colon cancer (HCT116 and SW620) cells	Compared to treatment with Rg_3 or docetaxel alone, combination therapy can inhibit the growth of cancer cells and induce apoptosis of cancer cells more effectively, accompanied by significant inhibition of NFκB activity.	135
Baicalein (BA)	BA + taxol	Human ovarian cancer A2780 cells, SKOV3 cells, and OVCAR cells	BA combined with taxol at low concentrations can play a synergistic antitumor role via the Akt–β-catenin signaling pathway and mitochondria-mediated cell apoptosis in ovarian cancer cells.	136
	BA + 10-hydroxycamptothecin (Hcpt)	BGC823, MCF7, and SMMC7721 cells, mice xenografted with BGC823 tumors	In BGC823, MCF7, and SMMC7721 cells, BA significantly enhances the anticancer activity of Hcpt at an atoxic dose. Hcpt with BA is a novel and effective combination therapy, which synergistically target Topo I and upregulate p53 to induce cell-cycle arrest and cell apoptosis.	115

Gambogic acid (GA)	GA + cisplatin	Human NSCLC A549, NCIH460, and NCIH1299 cell lines	GA synergizes the growth-inhibitory activity of CDDP and enhances the apoptosis-induced effect of CDDP on NSCLC cells, meanwhile sensitizing lung cancer cells to CDDP in vitro and in vivo.	137
	GA + gemcitabine	PANC1 and BxPC3 cells, mouse xenograft model of human pancreatic cancer	GA inhibits the activation of ERK–E2F1–RRM2 signaling pathway to sensitize pancreatic cancer cells to gemcitabine in vitro and in vivo.	138
	GA + sunitinib	Renal carcinoma cell lines 786O and CAKI1, mouse xenograft models	Therapy of 786O and CAKI1 cells with GA or sunitinib can reduce the proliferation of tumor cells, especially when combined with the two medicines. The combination of GA and sunitinib has greater antitumor efficacy than either drug alone.	139
Gambogenic acid (GNA)	GNA + adriamycin (Adr)	MCF7 cell lines, MCF7/ADR cell lines	GNA can increase the chemosensitivity of breast cancer cells to Adr. This modulatory role is mediated by suppression of the PTEN–PI3K–Akt pathway, leading to apoptosis in MCF7/ADR cells.	140
	GNA + bortezomib (Btz)	Myeloma MM1S cells, tumor-xenograft models	Btz and GNA have strong synergistic effect in combination therapy, inducing apoptosis of MM.1S cells. The combination of Btz and GNA is superior to single drug on MM.1S-xenograft models.	141
Quercetin (Qct)	Qct + tamoxifen	Prostate-tumor xenografts in mice	Tamoxifen combined with Qct can effectively delay the occurrence of tumors, inhibit the final volume of tumors, and reduce the weight of the end-point tumor ($P<0.05$).	142
	Qct + metformin	PC3 and LNCaP cells, prostate cancer xenografts in nude mice	Combined application of metformin and Qct has a significantly stronger effect on apoptosis of prostate cancer cells than monotherapy, and combination therapy can inhibit the VEGF–Akt–PI3K signaling pathway to play a synergistic antitumor effect.	143
	Qct + trichostatin A	Mouse xenograft model of A549 cells	Qct enhances the antitumor effect of trichostatin A and prevents trichostatin A-induced muscle wasting.	144
	Qct + Hcpt	MCF7, BGC823, and HepG2 cells, MCF7 xenograft in nude mice	The combination of Qct and Hcpt can inhibit Topo I in MCF7 cells, which synergistically induces cell-cycle arrest and apoptosis by triggering DNA damage.	145
	Qct + irinotecan–SN38	The AGS human gastric adenocarcinoma cell line, AGS xenograft mouse model	Qct combined with irinotecan has a superior regulatory effect on angiogenesis and EMT-related factors. Qct may enhance the efficacy of irinotecan–SN38 in the human AGS cell line.	146
Triptolide (TL)	TL + sorafenib	Huh7 and PLC/PRF/5 cells, Huh7 tumor-xenograft mouse model	Sorafenib combined with TL is superior to single-drug therapy in increasing cell death and apoptosis in vitro.	147
	TL + cisplatin	Human gastric adenocarcinoma SCM1 cells, xenografts in SCID mice	TL can raise the cytotoxicity of cisplatin to SCM1 cells, and the combined therapy can significantly inhibit the growth of tumors.	111
		Urothelial cancer cells, PC3 prostate cancer cell line, mouse xenograft model	Cancer-specific enhancement of cisplatin-induced cytotoxicity with TL by the interaction of inactivated GSK3β with p53.	148
	TL + oxaliplatin	Colon cancer cell line SW480, nude mouse model	Combination therapy with TL and oxaliplatin exerts synergistic antitumor effects at low concentrations in colon cancer cells, with less cytotoxicity, which exhibits high potency for clinical applications.	149

(*Continued*)

Table 2 (*Continued*)

Monomer composition	Combination therapy	Cellular, animal levels	Advantages of combination therapies	Reference
	TL + fluorouracil	Colon carcinoma HT29 cells, tumor xenografts in nude mice	The combined effects of TL and fluorouracil on the growth of colon carcinoma are better than that of single drug, whether in vitro or in vivo. TL combined with fluorouracil has synergistic effects at lower concentrations and promotes apoptosis, but the side effects of chemotherapy are not increased.	150
	TL + gemcitabine	Pancreatic cancer BxPC3 and PANC1 cell lines	TL can increase gemcitabine-induced cell-growth inhibition and apoptosis synergistically. When TL is combined with gemcitabine, the potential for therapy of pancreatic cancer increases markedly.	151
Berberine (Bbr)	Bbr + Dox	Human breast cancer MCF7/MDR cells, tumor xenografts in the BALB/c nu/nu mice	Bbr can increase the sensitivity of drug-resistant breast cancer to Dox chemotherapy and can directly induce apoptosis in vitro and in vivo by dose-orchestrated AMPK signaling.	152
		NSCLC NCIH460, NCIH1975 cells	Bbr inhibits Dox-mediated STAT3 activation and enhances the cytotoxic effect in lung cancer cells of Dox treatment.	153
	Bbr + evodiamine	Human breast cancer MCF7 cells, mice with MCF7 human breast cancer xenografts	Bbr combined with evodiamine plays a synergistic role in inhibiting the proliferation of MCF7 cells through inducing cell-cycle arrest and apoptosis.	154
	Bbr + galangin	ECA9706 cells, nude mice with xenograft tumors	Galangin combined with Bbr synergistically exerts cell-growth inhibition, apoptosis, and cell-cycle arrest in esophageal carcinoma cells and also exhibits outstanding synergistic anticancer role in vivo.	155
	Bbr + tamoxifen	MCF7 and MCF7/TAM cells	Bbr combined with tamoxifen is more effective than tamoxifen alone in inducing cell-growth inhibition, inducing G_1-phase arrest and activating cell apoptosis.	156
	Bbr + sorafenib	SMMC7721 and HepG2 cells	The combination of Bbr and sorafenib exhibits a synergistic inhibitory effect on the proliferation of SMMC7721 and HepG2 cells.	157
Allicin (AN)	AN + IL2	BXPC3 cell line, pancreatic cancer xenograft in mice	The combination of AN and IL2 can inhibit the growth of tumors and prolong survival, possibly by activation of $CD4^+$ T, $CD8^+$ T, and NK cells.	158
	AN + fluorouracil	SK-Hep1 and BEL7402 cell lines, hepatocellular carcinoma-xenograft models in nude mice	By ROS-mediated mitochondrial pathway, AN can increase the sensitivity of hepatocellular carcinoma cells to fluorouracil-induced-apoptosis. Combination of AN and fluorouracil can be used as a novel chemotherapeutic regimen for hepatocellular carcinoma.	159
Dihydroberberine (Dhb)	Dhb + sunitinib	Human NSCLC NCIH460, NCIH460 cell-xenografted nude mice	Sunitinib shows synergistic effects on proliferation, colony formation, and growth of transplantable tumors of NCIH460 cells, suggesting that Dhb can increase the sensitivity of lung cancer to sunitinib.	160
Oxymatrine (Omt)	Omt + oxaliplatin	Colon cancer lines (HT29 and SW480), SW480 xenograft mouse model	A combined index value <1 for Omt and oxaliplatin has a synergistic effect. Compared with oxaliplatin or Omt alone, combination therapy has more effective inhibition on tumor weight and volume of SW480-xenotransplant mice.	161
	Omt + NM3	Human gastric cancer cell lines SGC7901, MKN45, MKN74, human gastric cancer xenografted in mice	Omt combined with NM3 can synergistically inhibit the growth of human gastric cancer cell line SGC7901 in vitro and the growth of xenograft human gastric cancer cell line SGC7901 in vivo.	162
Tetraarsenic oxide (TAO)	TAO + cisplatin	Human cervical carcinoma cell line HPV16, CaSki cells, mice bearing CaSki-cell tumors	TAO can induce apoptosis. Combined with cisplatin, it can significantly increase the number of apoptotic cells, exerting a synergistic role.	163

Cryptotanshinone (Cts)	Cts + cisplatin	A549 cells, A549/DDP cells	Compared with cisplatin monotherapy, the combination of Cts and cisplatin induces cell death and apoptosis by increasing the sensitivity of A549/DDP cells to cisplatin. Cts can reverse the resistance of human lung cancer A549 cells to cisplatin by downregulating the Nrf2 pathway.	110
Tetramethylpyrazine (Tmp)	Tmp + cisplatin (CDDP)	Lewis lung cancer mice	The inhibitory effect of Tmp combined with DDP on tumor growth is enhanced compared to Tmp- or CDDP-alone treatment. Tmp with CDDP had additional or synergistic effects to inhibit tumor growth effectively.	164
Catechin (RQC)	RQC + gefitinib	Human metastatic breast cancer cell line MDA-MB231, hairless SCID female mice	Combination of RQC and gefitinib can significantly reduce the viability of gefitinib-resistant breast cancer cells. Compared with RQC or gefitinib alone, it can significantly inhibit the growth and metastasis of breast tumors in nude mice.	165
Dihydroartemisinin (Dha)	Dha + gemcitabine	BxPC3 and PANC1 cell lines, BALB/c nude mice	Dha significantly enhances the inhibition and apoptosis of gemcitabine on BxPC3 and PANC1 cell lines in vitro. Combination therapy can significantly enhance the antitumor effect of gemcitabine.	80
Epigallocatechin-3-gallate (EGCG)	EGCG + Dox	Human prostate-cell lines, mouse tumor modeling with PC3ML cells	EGCG can be effectively used to improve the efficacy of Adr through improving its ability to eradicate highly aggressive, metastatic, or primary tumors.	166
		Human HCC cell line BEL7404/Dox, xenograft mouse model	EGCG can enhance Dox-induced cytotoxicity and increase the sensitivity of drug-resistant hepatocellular carcinoma cells to Dox at an atoxic dose.	167
Ginsenoside Rh_2	Rh_2 + paclitaxel–mitoxantrone	LNCaP prostate-tumor cells, human LNCaP-tumor xenograft	Rh_2, combined with paclitaxel shows stronger inhibition and synergistic effect on growth in a cultured LNCaP cell line.	88

Abbreviations: SCID, severe combined immunodeficiency; MDR, multidrug resistance; CDDP, *cis*-diamminedichloroplatinum; EMT, epithelial–mesenchymal transition.

at optimal proportion to achieve the maximum synergistic killing effect. Compared to nanoliposomes containing individual drugs, CelePlum 777 can enhance the inhibition of melanoma-cell proliferation in vitro and reduce the growth of melanoma tumors, with negligible systemic toxicity in nude mice. The goal of loading different individual drugs into a nanoliposome that releases the drugs at synergizing ratios was realized.

Previous studies have shown that Cur can reduce side effects caused by cisplatin (*cis*-diamminedichloroplatinum [CDDP]), including ototoxicity,[189] nephrotoxicity,[190] and neurotoxicity.[191] In addition, Cur can also overcome resistance to CDDP and improve the sensitivity of hepatocellular carcinoma cells to CDDP.[192] However, due to poor water-solubility and the different pharmacokinetics of CDDP and Cur,[193] the cocktail of both drugs controlling the drug proportions and dose regimen at target cancer cells would be challenging. Based on a previous approach and advantages of the liposome, Cheng et al[194] developed a liposomal delivery system using a reverse-microemulsion and film-dispersion method, which coencapsulated CDDP and Cur and transplanted them into hepatocellular carcinoma cells. The antitumor activity of CDDP-Cur liposomes against HepG2 cells was higher than that of free drug or encapsulated-monodrug therapy, and retention was prolonged ($t_{½}$=2.38 hours). Therefore, coloaded liposomes can be used as an effective treatment for tumors, with great clinical application potential.

Polymeric nanoparticles

NPs are solid colloid particles 10–100 nm in size formed by drug dissolution, encapsulation, or adsorption on macromolecular materials. NPs within the particle-size range of 10–100 nm can hide the physicochemical characteristics of the drug, and the in vivo process of the drugs depends on the physicochemical characteristics of the carriers.[195] NPs are characterized by a relatively simple preparation process, a significant solubilization effect on active components, significantly improved drug targeting to tumors, and proneness to surface modification. They can improve drug stability, reduce digestive tract stimulation, achieve sustained release or controlled release,[196] effectively overcome multiple physiological barriers encountered in vivo, and achieve accurate, safe, efficient, and targeted therapeutic effects. Coating the surface of NPs with polyethylene glycol (PEG), or "PEGylation", is a commonly used approach to improve the efficiency of drug delivery to target cells and tissue. PEGylation is capable of achieving prolonged blood circulation of nanocarriers, and can improve colloidal stability by providing steric

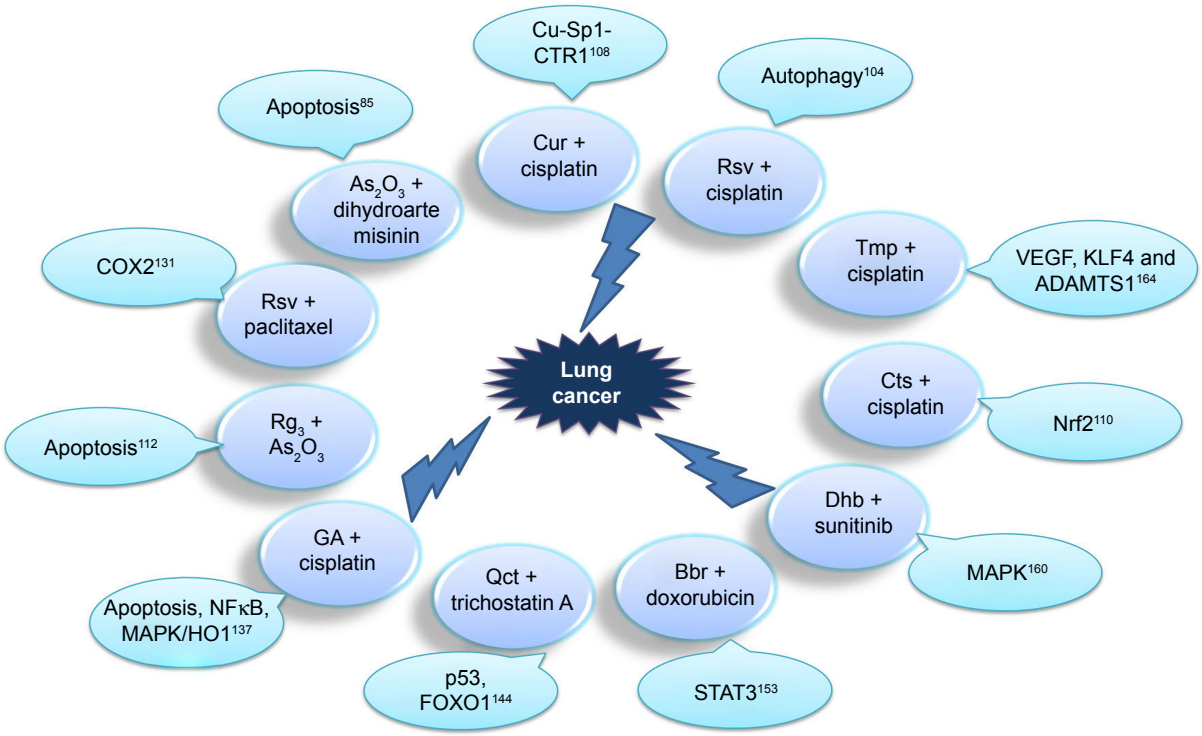

Figure 3 Anti–lung cancer mechanism of TCM-combination therapy.
Abbreviations: Cur, curcumin; Rsv, resveratrol; Tmp, tetramethylpyrazine; Cts, cryptotanshinone; Qct, quercetin; Bbr, berberine; Dhb, dihydroberberine; GA, gambogic acid.

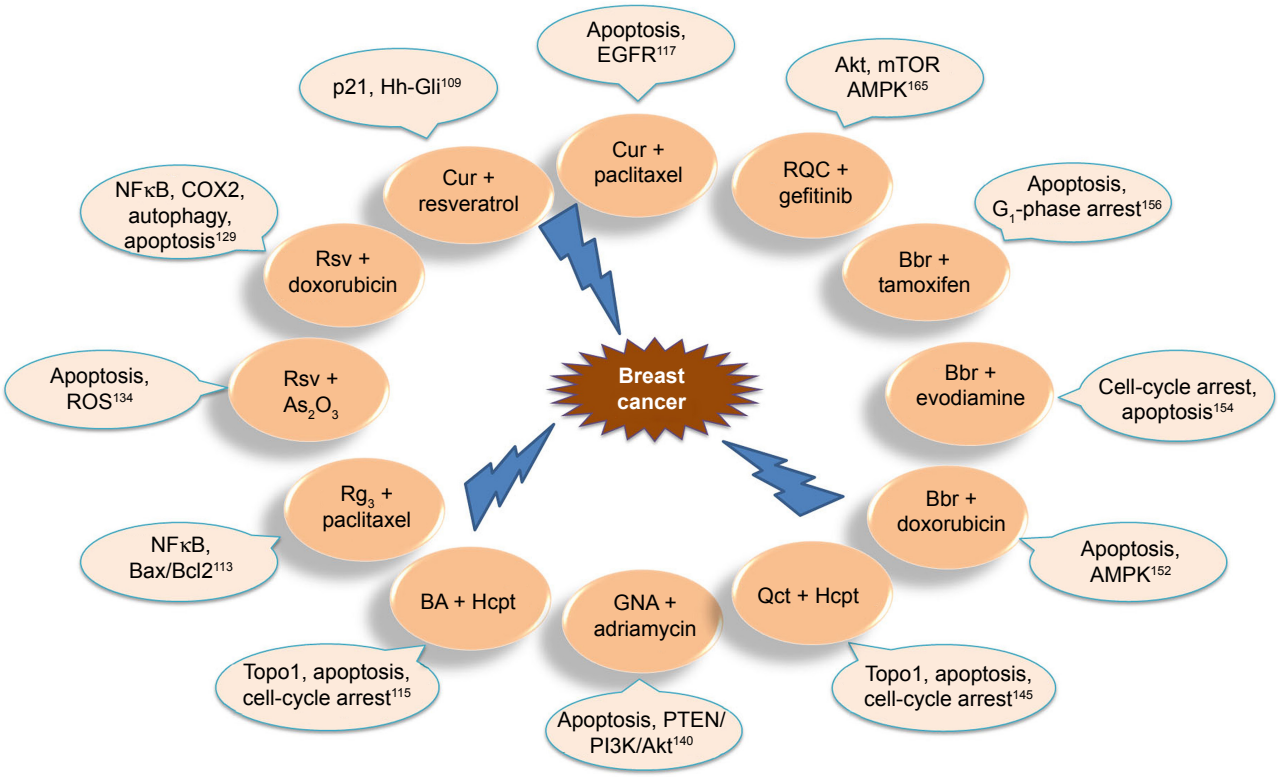

Figure 4 Anti–breast cancer mechanism of TCM-combination therapy.
Abbreviations: Cur, curcumin; Rsv, resveratrol; Bbr, berberine; Hcpt, hydroxycamptothecin; Qct, quercetin; GNA, gambogenic acid; BA, baicalein.

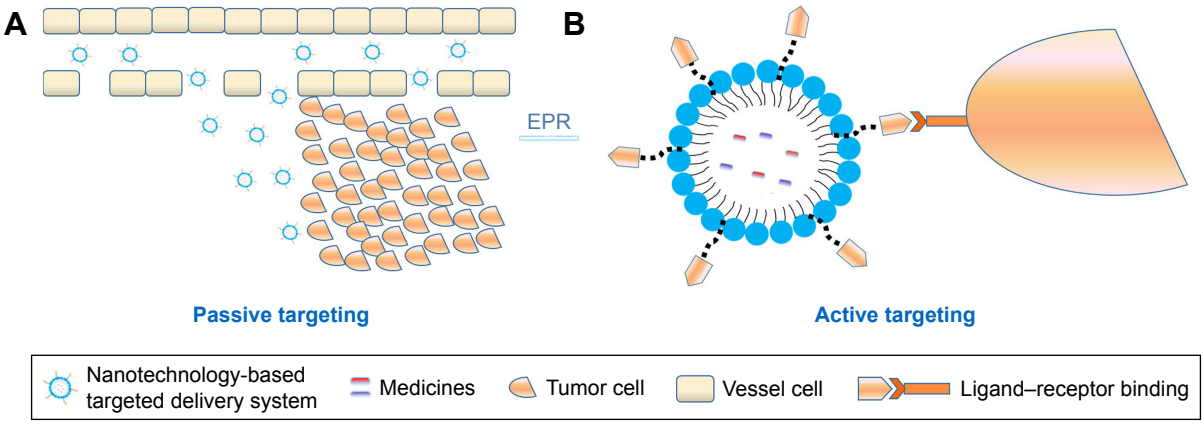

Figure 5 Passive (**A**) and active (**B**) targeting of tumors.
Abbreviation: EPR, enhanced permeability and retention.

surface hindrance. In addition, it has the ability to improve particle dispersion and decrease hemolysis.[197,198] Polylactic-*co*-glycolic acid (PLGA), a biodegradable polymer, is atoxic to final degradation products and has been approved by the FDA.[181,199] The antitumor effects of codelivered PNPs in TCM combinations are shown in Table 3.

Lipid–polymer hybrid nanoparticles

As indicated, it has been demonstrated by the increasing numbers of research reports that biodegradable PNPs and liposomes have become the two main types of active TCM nanocarriers. Lipid–polymer hybrid NPs (LPNs) are nuclear-shell NPs formed by polymer core–lipid/lipid–PEG shells[206,207] that have the advantages of biodegradable PNPs and bionic liposomes.

Li et al[208] prepared LPNs and PNPs loaded with cisplatin and Cur. Results indicated that LPNs had higher anticancer efficacy than PNPs and free drugs. Cytotoxicity was highest in vitro and antitumor effect best in vivo. Therefore, LPNs can be used as a targeted and synergistic nanodrug codelivery system for tumor chemotherapy. In a similar study, Zhu et al[209] developed vincristine–quercetin (Qct) dual-loaded LPNs. The experimental results proved that the LPNs loaded with both drugs exhibited better antitumor efficacy in vitro and in vivo.

Ruttala et al[210] developed nanocarriers loaded with Ptx and Cur using a method different from the previously mentioned studies. Ptx-loaded albumin NPs were prepared and encapsulated in PEGylated hybrid liposomes containing Cur by a thin-film hydration method. This combination guaranteed the release of Ptx and Cur in a sustained and sequential manner. Compared with a cocktail combination, the dual-drug-loaded nanocarrier had a better cytotoxic effect at a lower dose. Therefore, such coloading drug-delivery systems can be used as a promising treatment method to improve clinical efficacy in various malignant tumors. NPs containing genistein and Ptx have also showed similar experimental results.[211]

Nanostructured lipid carriers

Nanostructured lipid carriers (NLCs) are novel lipid NPs and mixtures of solid and liquid lipids, which have the advantages of excellent drug-loading capacity and sustained-release properties. Jiang et al[212] prepared etoposide (Etp)- and Cur-loaded NLCs by the solvent-injection technique. Etp-Cur NLCs had the highest cytotoxicity in vitro and higher accumulation in tumor tissues in vivo compared with other preparations, including Etp NLCs, Etp + Cur solution, Etp solution, and NLCs. In addition, Etp-Cur NLCs displayed low cytotoxicity in normal tissue in vivo, suggesting that NLCs could serve as a promising therapeutic strategy in the treatment of tumors.

Mesoporous silica nanoparticles

MSNs have attracted much attention due to their potential biomedical applications. MSNs possess many attractive features for application in the delivery of TCMs, such as the size of tuning particles/pores, large surface, large pore volume, high loading capacity, mass producibility, biocompatibility, and chemical inertia.[213,214] TCMs can be dissolved in surfactant micelles, simultaneously hydrolyzed, and concentrated with silica to form NPs.

Jia et al[215] prepared NPs using the self-assembly in situ drug-loading approach, in order to deliver the anticancer

Table 3 Polymeric nanoparticles (NPs) for codelivery of antitumor agents

Codelivery ingredients	Delivery-system materials	Method	Advantages	Reference
Epigallocatechin gallate (EGCG) + paclitaxel (Ptx)	Polylactic-*co*-glycolic acid (PLGA)–casein polymer–protein hybrid NPs	Emulsion precipitation	The core–shell nanoconstruct sequentially released EGCG followed by Ptx, which was sustained for 7 and 12 days, respectively. Compared with the bare drugs, dual-loaded NPs significantly increased plasma concentration, residence time, and circulatory half-life of nanoencapsulated Ptx and EGCG.	181
Camptothecin (CA) + ABT737	PEGylated polymeric NPs	Nanoencapsulation	Dual-loaded NPs exerted synergistic cytotoxic effects against HCT116 cells, RKO cells, and HT29 cells at a range of NP concentrations.	200
Gambogic acid (GA) + docetaxel (Dtx)	PLGA NPs	Nanoprecipitation	GA and Dtx were released synchronously in blood from the NPs in vivo. Compared with the saline control group, free Dtx solution and free Dtx-GA solution, the cocarrier NP-preparation group had the strongest inhibitory effect on the MCF7/ADR human breast-tumor xenograft.	201
Quercetin (Qct) + tamoxifen (Tmx)	PLGA NPs	Emulsion–diffusion solvent evaporation	NPs coencapsulated with Tmx and Qct had higher cellular uptake, cytotoxicity, and tumor suppression in female rats compared to free Tmx citrate, free Qct, and their combination.	202
Piperlongumine (PL) + Ptx	PLGA and D-α-tocopheryl PEG succinate NPs	Organic solvent evaporation	Compared with free Ptx, the double-loaded NPs had a sustained drug-release rate, showing increased cytotoxicity and cellular uptake in vitro. Ptx/PL-PT NPs suppressed tumor growth more efficiently with less toxicity than Ptx solution.	203
Qct + etoposide (Etp)	PLGA NPs	Single-emulsification (oil in water) solvent evaporation	With sustained release shown by NP pharmacokinetic parameters, bioavailability increased gradually. Cytotoxicity assays showed that the IC_{50} values of Etp-loaded NPs and Etp + Qct double-loaded NPs were nine- and elevenfold lower than free Etp.	199
Piperine + rapamycin	PLGA NPs	Nanoprecipitation	Dual-loaded NPs exhibited sustained release, with potential for long-term therapeutic action with less dosing frequency, and would result in a reduction of dosing and improved bioavailability compared to single-drug administration.	204
Vincristine (VI) + verapamil (VE)	PLGA NPs	Oil-in-water emulsion-solvent evaporation	The toxicity of coencapsulated NPs was lower than that of the free VI–VE combination. Compared with normal saline, free VI, free VI–VE combination, and single-drug NP combination, the coencapsulated NP group had the best tumor growth–inhibition effect in the MCF7/ADR human breast-tumor xenograft.	205

Abbreviation: PEG, polyethylene glycol.

drug Ptx and the MDR-reversal agent tetrandrine (Tet) to increase the intracellular concentration of Ptx, enhance its antitumor effect, and minimize the exposure of normal cells to Ptx and Tet. The study demonstrated that Tet significantly increased the accumulation of NPs in cells. Furthermore, Ptx-Tet–cetyltrimethylammonium bromide MSNs suppressed tumor-cell growth more efficiently than the delivery of Ptx (Ptx–cetyltrimethylammonium bromide MSNs) or free Ptx alone. The prepared NPs released the drugs easily in the acidic environment of tumors, and thus, side effects and toxicity in normal tissue and organs were reduced. This nanocarrier may have important potential in clinical applications to avoid MDR by codelivering multiple TCMs. Solid self-nanoemulsifying drug-delivery systems containing tamoxifen and Qct have also shown similar experimental results.[216]

PEGylated lipid bilayer–supported mesoporous silica nanoparticles

The anticancer drug axitinib (Axt) is a small-molecule tyrosine kinase–receptor inhibitor of VEGFR1, -2, and -3.[217,218] Another anticancer drug, celastrol (Cst), can induce the suppression of angiogenesis[219] and enhance the antitumor activity of standard chemotherapeutic drugs.[220] Choi et al[221] loaded Cst into an MSN carrier and subsequently coated it with a lipid bilayer containing Axt, denoted by "ACML", to increase the synergistic efficacy of the two agents. The difference in drug loading resulted in a sequential-release pattern where Axt was released first to exert its anticancer effect, and then Cst was released to further induce a synergistic effect. The experimental results showed that the synergistic apoptotic effect of ACML against cancer cells was stronger than the Axt-Cst cocktail. Moreover, ACML had a greater tumor-inhibitory effect than either drug administered alone in a tumor-xenograft mouse model. It has been proved that PEGylated lipid bilayer–supported MSNs have the potential to be used as an effective therapeutic strategy for malignant tumors.

Micellar systems

Self-assembled polymeric micelles have been studied widely, due to their excellent role in cancer treatment. Polymeric micelles have a core–shell structure, where hydrophobic drugs are soluble and remain stable in the hydrophobic core of the micelles, and the hydrophilic shell can prolong internal circulation and improve spatial stability by reducing opsonization during blood circulation. Furthermore, polymeric micelles can selectively and effectively accumulate in tumor tissues due to the EPR effect, thus enhancing the therapeutic effects of the loaded chemotherapeutic drugs. As such, codelivery micellar systems have attracted considerable attention.[222,223]

Doxorubicin (Dox) has extensive antitumor activity against various solid tumors, including lung cancers, melanoma, neurological cancers, sarcoma, leukemia, lymphoma, gastrointestinal cancers, genitourinary cancers, breast cancers, and ovarian cancers.[14] Due to the rapid elimination of drugs in vivo, the cocktail combination of free Dox and Cur often fails to provide enough antitumor efficacy or low systemic toxicity. Furthermore, the combination of Dox and Cur has not been realized clinically. In recent years, a few studies have proposed that codelivering Dox and Cur may result in less toxicity, good drug-release profiles, and improved drug distribution in tumor tissue.[224–226] Zhang et al[223] prepared dual-loaded micelles with coencapsulated Dox and Cur. The experimental results showed that Dox delivered by this method prolonged systemic circulation and increased its accumulation in the tumor, resulting in a lower level of the toxic metabolite doxorubicinol in heart tissue than free Dox alone or the cocktail combination. In addition, Gu et al[225] assembled micelles loaded with Dox and Cur. The micelles prolonged the circulation of Dox or Cur when compared with the individual administration of either, and exhibited strong inhibition of tumor growth and reduced Dox side effects.

Ptx has a broad spectrum of activity against various tumors. It has been used clinically for more than two decades. However, it is poorly soluble and has considerable limitations in clinical applications. In addition, Ptx extravasation of cancer cells caused by Pgp activity is also a main factor limiting its clinical efficacy.[227,228] Abouzeid et al[229] prepared micelles loaded with Ptx and Cur using the thin-film hydration method. Cur–Ptx-loaded micelles released the entrapped drugs with a slow pattern, and resulted in a threefold inhibition of tumors in vitro. The combination of Cur and Ptx was shown to reverse MDR in a resistant human ovarian adenocarcinoma model. Therefore, these combinations of micelles have significant advantages in vitro and in vivo over individual drug treatment, especially in drug-resistant tumors.

Microemulsions

A microemulsion is a transparent or semitransparent oil–water system with low viscosity, isotropism, and thermodynamic stability, and is spontaneously formed by an oil phase, water phase, emulsifier, and coemulsifier. As an ideal drug carrier, it has the advantages of solubilizing components with different solubility properties, good dispersibility, excellent absorbability, and increased bioavailability.[230]

BA is one of the most commonly used traditional chemotherapeutic drugs for the treatment of various cancers, including HCT116 human colon cancer,[31] pancreatic cancer stem cells,[32] and bladder cancer.[33] It is known that BA has the ability to inhibit the function of Pgp.[231] Meng et al[230] developed nanoemulsions (NEs) coencapsulating Ptx and BA using rotary evaporation. The research showed that compared with other Ptx preparations, Ptx-BA NEs had a better antitumor effect on MCF7/Tax cells. Studies on cellular uptake have shown that Ptx-BA NEs accumulate effectively in cancer cells. More importantly, Ptx-BA NEs have a higher antitumor effect than other Ptx formulations used in antitumor in vivo studies. The combined delivery of Ptx and BA by NEs may provide a potential combination-treatment strategy to overcome MDR.

Nanovesicles

Nanovesicles are microvesicles with a quasiliposome dual-layer structure formed by the self-assembly of synthesized or naturally modified amphiphilic polymers and cholesterol in hydrophilic media. In contrast to other micromolecular vesicles, the polymer vesicle is characterized by good molecular designability, high intensity of the vesicle, excellent stability, and strong permeability.[232,233] As a TCM carrier, it can improve histocompatibility and cell permeability and encapsulate hydrophilic drugs or lipophilic drugs.

Alemi et al[234] loaded both Cur and Ptx into cationic PEGylated niosomal formulations using thin-film hydration method to enhance efficacy in MCF7 human breast adenocarcinoma cells. The combination of Ptx and Cur, particularly in the nanoniosome formulations, improved the effectiveness of cancer therapy. The novel cationic PEGylated niosome delivery of combined Ptx and Cur is an effective strategy in the treatment of breast cancer.

Schematic illustrations of these nanosystems for drugs are shown in Figure 6. In addition, graphene oxide,[235] carbon nanotubes,[236,237] nanorods,[238] nanosponges,[239] solid lipid NPs,[240] nanometal–organic frameworks,[241] metallosupramolecular nanogels,[242] and microspheres[243] all provide new opportunities for the antitumor effects of TCM-combination therapy.

Despite the EPR effect, most nanosystems fail to find their way toward tumor sites.[244] Under most circumstances, 90% or more of the administered nanosystems end up in the liver or spleen, increasing adverse systemic reactions and causing low therapeutic efficacy.[245,246]

Active targeted drug-delivery systems

An active targeting preparation is a drug-delivery system which can utilize the modified drug carrier as a "missile" and deliver the drug selectively to the target area to allow the drug to accumulate and exert its efficacy. The mechanism of active targeting is that after surface modification with the specific targeted antibody or ligand via covalent or noncovalent binding, the nanodelivery system can avoid recognition and phagocytosis by macrophages and change

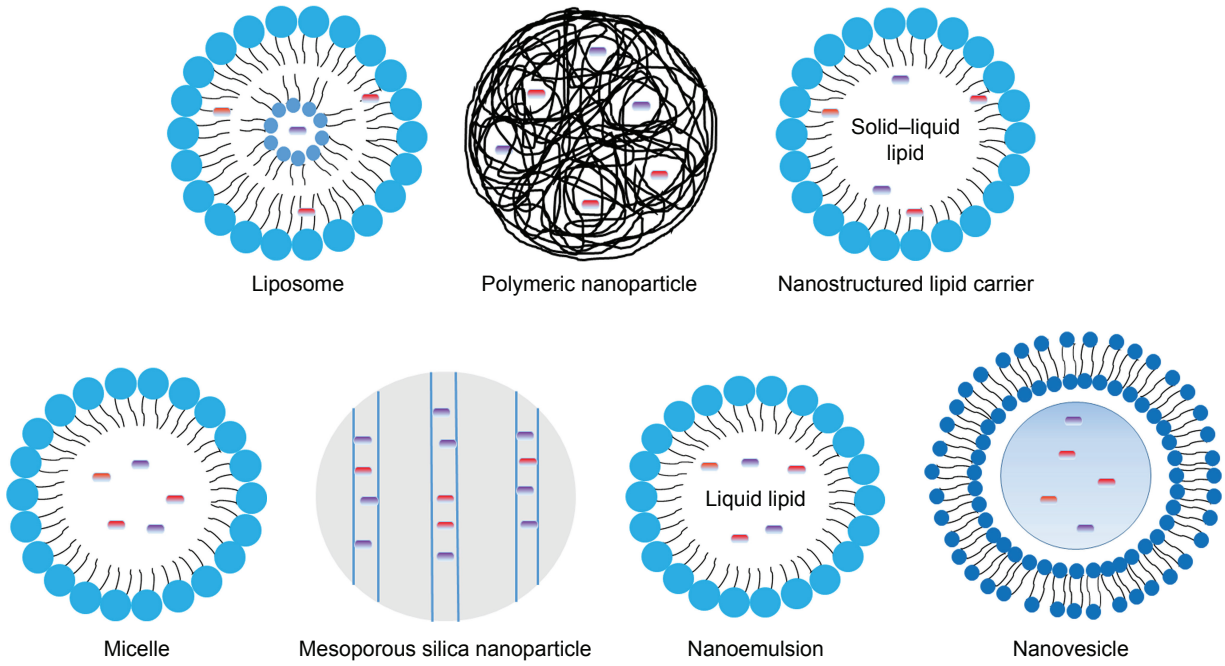

Figure 6 Schematic illustrations of several nanosystems for drugs.

natural in vivo distribution, so as to deliver the drug to the targeted tumor site and exert its active tumor-targeting effects.[247] For instance, due to the difference between tumor cells and normal cells in terms of receptor expression or other biological characteristics, the tumor-targeted drug-delivery system has been developed to ensure that the drug acts only on tumor cells[248] and induces the off-target effect in normal tissue, which has become a high-profile topic in studies on drug-delivery systems.

Transferrin (Tf)-modified nanocarriers

The Tf receptor is commonly present in normal cells and tumor cells. However, expression of the Tf receptor is approximately four to five times that on the surface of tumor cells than on normal cells.[249] Transferrin can bind with the Tf receptor and be internalized into the cells under mediation by the receptors to reach the targeted site.

Cui et al[250] designed Tf-decorated NPs (Tf-PEG Cur–Dox NPs) to codeliver Cur and Dox for breast cancer therapy. Results showed that the combination of Tf-PEG-Cur and Dox NPs exerted higher cytotoxicity in MCF7 cells compared with Tf-PEG-Cur NPs alone. Higher accumulation of Tf-PEG Cur–Dox NPs was observed in tumors compared to the Cur-Dox injection. Therefore, Tf-PEG Cur–Dox NPs displayed higher efficiency in vitro and in vivo, and resulted in efficient tumor-targeted drug delivery, reduced cytotoxicity, and a stronger antitumor effect.

Folic acid–modified nanocarriers

Similarly to distribution of the Tf receptor on surfaces of tumor-cell membrane, folic acid receptors on tumor cells are overexpressed compared with normal cells, and their activity is also significantly higher than that on normal cells. In addition, folic acid is characterized by low immunogenicity, high modifiability, and high storability. Utilization of the difference in folic acid–receptor expression between tumor sites and normal tissue can achieve targeted delivery of a folic acid–modified drug to cancer cells.[251,252]

Prodrugs of Ptx and baicalein containing dual-targeted ligands of folate and hyaluronic acid have been synthesized. NPs loaded with these prodrugs (Ptx–baicalein) have also been prepared and the synergistic antitumor effect evaluated in vitro and in vivo. The results showed that the Ptx–baicalein NP drug-delivery system delivered Ptx–baicalein prodrugs to drug-resistant human lung cancer cells, and the delivery was proven to be effective. In addition, Ptx–baicalein NPs exerted an enhanced synergistic anticancer effect, which also overcame MDR to Ptx.[253]

Low-density lipoprotein–modified nanocarriers

The low-density lipoprotein (LDL) receptor is widely present on the surface of various cells and tissue types, but is overexpressed in tumor cells. LDL is an endogenous NP with good biocompatibility, good biodegradability, and low immunogenicity, and can avoid being recognized and cleared by the in vivo endogenous reticuloendothelial system.[254,255] Therefore, LDL is an ideal potential ligand for tumor targeting.

A novel nanocarrier containing Ptx-loaded micelles and siRNA-loaded LDL has been developed. Results showed that the delivery system delivered siRNA and Ptx directly to cancer cells, enhancing the intracellular release of drugs and genes, increasing intracellular drug concentration, decreasing drug efflux, prolonging circulation, and reversing MDR.[256,257]

Cell-penetrating/tumor-targeting peptide–modified nanocarriers

Nanocarriers using cell-penetrating and/or tumor-targeting peptides for functionalization are a promising strategy, and have attracted the attention of researchers. In our previous report, we reviewed the classification of polypeptide- and polypeptide-modified nanocarriers in detail.[258] In this report, recent research progress is summarized in the following paragraphs.

Epigallocatechin-3-gallate (EGCG), a major polyphenol in green tea, has been widely studied as a potential anticancer drug. Narayanan et al[259] prepared targeted drug-loaded core–shell NPs using anti-EGFR and anti-HER2 antibodies, and entrapped a combination of Ptx and EGCG at different doses in the core and shell, respectively, using emulsion precipitation. Cellular uptake in MDA-MB231 cells was higher for targeted NPs than untargeted NPs at 24 hours. The sequential release of EGCG followed by Ptx from this core–shell nanocarrier sensitized Ptx-resistant MDA-MB231 cells to Ptx, induced their apoptosis, and inhibited NFκB activation. In addition, EGFR-peptide (GE11)-targeted, pH-sensitive docetaxel Dtx–Cur NPs[260] and arginylglycylaspartic acid–modified lipid-coated PLGA NPs targeting delivery of both sorafenib and Qct[261] achieved significant inhibition of tumor growth in vitro and in vivo.

In addition, galactosamine can recognize and bind to the asialoglycoprotein receptor on the surface of hepatocellular carcinoma cells, and a galactosamine-mediated drug-delivery carrier was significant for targeted liver cancer therapy.[262,263] Glycyrrhizin, glycyrrhetinic acid, and mannose can serve as the guiding group in liver-targeted drug-delivery systems, with good potential.[264–270] As natural endogenous ligands, bile acids have good biocompatibility and are ideal routes for targeting hepatocellular cancer.[271] In addition, sialic acid,[272]

human Nanog,[273] and hyaluronic acid[274] are excellent targets in cancer therapy. Vapreotide is a somatostatin analogue and can be also used as a ligand for targeted drug delivery based on its high affinity to somatostatin receptors, which are overexpressed in many tumor cells.[275] Several studies have shown that double-modified nanocarriers have also attracted considerable attention in anticancer drug research.[276,277] Dual or multiple targeting also provides a new approach for antitumor therapy.

Physicochemical targeted drug-delivery systems

Physicochemical targeting refers to the binding of magnetic, pH-sensitive, temperature-sensitive, or electromagnetic wave–responsive materials onto the surface of drug-delivery systems (such as NPs and liposomes) to make them respond to various stimuli in vitro and in vivo (such as pH, temperature, applied magnetic fields, ultrasonic waves, infrared rays, and electromagnetic radiation) to ensure that the drug acts directly on the target area, increases drug concentration at the lesion site, and reduces adverse reactions. Most studies have used magnetic NPs, temperature-sensitive NPs, and pH-sensitive NPs.

NPs that are pH-sensitive have been designed to promote uptake in tumor cells[278] and accelerate drug release at tumor sites, as the extracellular pH (6.5–7.2) of the tumor is different to that of normal tissue.[216] Zhang et al[278] developed a codelivery system for Dox and Cur using pH-sensitive NPs. Enhanced release in the acidic environment of cancer cells and enhanced cellular internalization of the cargoes delivered from Dox–Cur NPs were observed in SMMC7721 cells and human umbilical vein endothelial cells compared to the free drugs. Therefore, pH-sensitive NPs can provide a promising strategy for the effective inhibition of cancer in a synergistic manner. Danafar et al[279] achieved codelivery of Cur and sulforaphane (SF) with PEGylated gold-coated Fe_3O_4 magnetic NPs as an effective and promising antitumor agent. Results showed that SF–Cur coloaded Fe_3O_4@Au NPs caused a decrease in cell viability and induced apoptosis by increasing the Bax:Bcl2 ratio. Moreover, photosensitizer NPs,[280] thermosensitive NPs,[281] and redox-sensitive NPs[282] also provide new opportunities for nanosystems with antitumor TCM combinations.

Conclusion

The significant challenge posed by cancers, as well as adverse reactions and drug resistance induced by long-term treatment of a single drug, compels us to change our focus from a single target to the regulation of networks in vivo. Many complex factors cause cancer; therefore, it is rational that treatment should involve multiple components, genes, systems, and target pathways. The combination of drugs has resulted in a new approach to cancer treatment. Rational combinations of drugs not only result in synergy but also reduce the occurrence of drug resistance and adverse reactions, which has resulted in combination therapy, thus becoming a significant antitumor treatment in the clinic and in research. As such, this significant research direction may allow medical researchers to identify a chemotherapeutic combination regimen with high efficacy and low toxicity.

The combination of TCMs for clinical therapy has increased. TCM combinations can exert improved synergistic antitumor effects by adjusting the multiple signaling pathways of tumor cells. Compared with single-drug therapy, combinations of TCMs can reduce the toxicity and side effects of chemotherapy drugs and increase the antitumor effect of drugs. Simultaneously, TCM combinations and chemical drugs can improve immunofunction, relieve clinical symptoms, improve patient survival and quality of life, and improve the efficacy of chemotherapy drugs.

It should be noted that there are usually three approaches in targeted nanotechnology-based TCM-combination-therapy: nanodrugs combined with conventional preparations, coloading of two or more anticancer drugs in a single nanocarrier system (recorded as codelivery), and combined administration of different nanosystems. The loading of two drugs into a single well-designed nanocarrier synchronizes the pharmacokinetic and biological distribution of different drugs to achieve a synergistic effect, which has distinct advantages. This method has been summarized in detail. An increasing number of studies have shown that dual nanosystems have distinct advantages in antitumor treatment and can provide drugs for different targets or sites of action, as they are administered flexibly using different dose/time schedules. Consequently, the remaining two methods urgently require further investigation. In addition, with further comparative analyses of these three research methods, the most suitable form of drug use for cancers can be identified to provide basic considerations in terms of design principles and management progress.

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Disclosure

The authors report no conflicts of interest in this work.

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