

# Cancer treatment: from traditional Chinese herbal medicine to the liposome delivery system

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Received: 27 September 2022; Revised: 8 November 2022; Accepted: 4 December 2022

Published online: 14 December 2022

DOI 10.15212/AMM-2022-0035

## ABSTRACT

Traditional Chinese herbal (TCH) medicines have emerged as a prospective and affordable method to treat various diseases with a broad range of biological activity; however, traditional preparations, like decoctions, are often associated with low bioavailability, thus resulting in limited efficacy against cancer. The drawbacks of active TCH components, including instability, poor permeability, high hydrophilicity or hydrophobicity, undesirable pharmacokinetic profiles, and off-target toxicity, also exist. Most TCH medicines are thus limited to a clinical alternative for the treatment of chronic diseases. A liposomal delivery system is the most common class of FDA-approved nanomedicines, which has improved pharmacokinetics, enhanced targetability, and reduced side effects. Therefore, we anticipate that liposomal delivery technology will help concentrate drugs inside tumors, and fully release the therapeutic potential and reduce the side effects of TCH medicines. The review provides a brief overview of several representative TCH components and related liposome delivery strategies for enhanced cancer therapy. Current challenges associated with liposomal targeting of TCH medicines are also discussed for interested researchers.

**Keywords:** traditional Chinese medicine (TCM), traditional Chinese herbal (TCH) medicines, liposome, targeted delivery, cancer treatment

## 1. INTRODUCTION

Cancer characteristics, including multi-drug resistance, heterogeneity, immunosuppression, and metastasis, are treatment challenges worldwide. According to traditional Chinese medicine (TCM), cancer is recognized as the result of an imbalance between yin and yang, qi stagnation, blood stasis, and the accumulation of dampness, phlegm, and toxins. Thus, a strategy for tonifying the deficiency, coordinating the function of the viscera and eliminating the accumulation of qi, dampness, phlegm, and toxins, is commonly used. For example, Xiaoyao powder combined with a Dahuang Zhechong

pill is a well-known among the compounds of the combined prescription to treat liver cancer with liver stasis and spleen deficiency syndrome. Among them, three types of Chinese drugs have important roles in treating disease. Chai hu (*Bupleurum chinense* DC. or *Bupleurum scorzoniferolium* Wild.) and Dang gui (*Angelica sinensis* (Oliv.) Diels) invigorate qi and soothe the liver, Bai shao (*Paeonia lactiflora* Pall.) tonifies the blood and softens the liver. Moreover, the combination of Fu ling (*Poria cocos* (Schw.) Wolf), Bai zhu (*Atractylodes macrocephala* Koidz.), ginger (*Zingiber officinale* Rosc.), and Gan cao (*Glycyrrhiza uralensis* Fisch., *Glycyrrhiza inflata* Bat. or *Glycyrrhiza glabra* L.) invigorate the spleen and

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stomach. Tian hua fen (*Trichosanthes kirilowii* Maxim or *Trichosanthes rosthornii* Harms), Ban zhi lian (*Scutellaria brabata* D. Don), Zhe chong (*Eupolyphaga sinensis* Walker), Shui zhi (*Whitmania pigra* Whitman, *Hirudo nipponica* Whitman or *Whitmania acranulate* Whitman), Quan xie (*Buthus martensii* Karsch), Bai jiang can [the corpse of the larva of *Bombyx mori* Linnaeus infected with *Beauveria bassiana* (Bals.) Vuillant], San leng (*Sparganium stoloniferum* Buch.-Ham), E zhu (*Curcuma phaeocaulis* Val., *Curcuma kwangsiensis* S.G. Lee et C. F. Liang or *Curcuma wenyujin* Y.H.Chen et C.Ling), and Jiang huang (*Curcuma longa* L.) have shown the effect of detoxification and stasis elimination. Tao ren [*Prunus persica* (L.) Batsch. or *Prunus davidiana* (Carr.) Franch.], Hong hua (*Carthamus tinctorius* L.), Da huang (*Rheum palmatum* L., *Rheum tanguticum* Maxim.ex Balf. or *Rheum officinale* Baill.), and Huang qin (*Scutellaria baicalensis* Georgi) promote blood circulation. All the components work together to combat liver cancer. In addition, Yinchenhao powder, Liu jun zi decoction, Huai jiao pills, and Chai hu Shu gan powder have been successfully

applied for the treatment of liver, lung, colorectal and gastric cancer, respectively (Figure 1). Although promising, the traditional TCH medicine preparations are often associated with poor taste and limited efficacy against cancer due to the low bioavailability. The drawbacks of active TCH components, including instability, poor permeability, high hydrophilicity or hydrophobicity, and off-target toxicity, also exist. Most TCH medicines have thus been limited to clinical alternatives for the treatment of chronic diseases rather than cancer.

Recently, a nanoparticle-based novel drug delivery system that featured improved pharmacokinetics, enhanced targetability, and reduced side effects remains interesting for drug innovation. Especially, a lipid nanoparticle- or liposome-based delivery system emerged as the most common class of FDA-approved nanomedicines [1]. Doxil was the first liposomal-based nanodrug approved by the FDA. With the lipid bilayer structure similar to that of a biological membrane and its inner aqueous core, liposomes can encapsulate hydrophilic and hydrophobic TCH ingredients. In addition, membrane

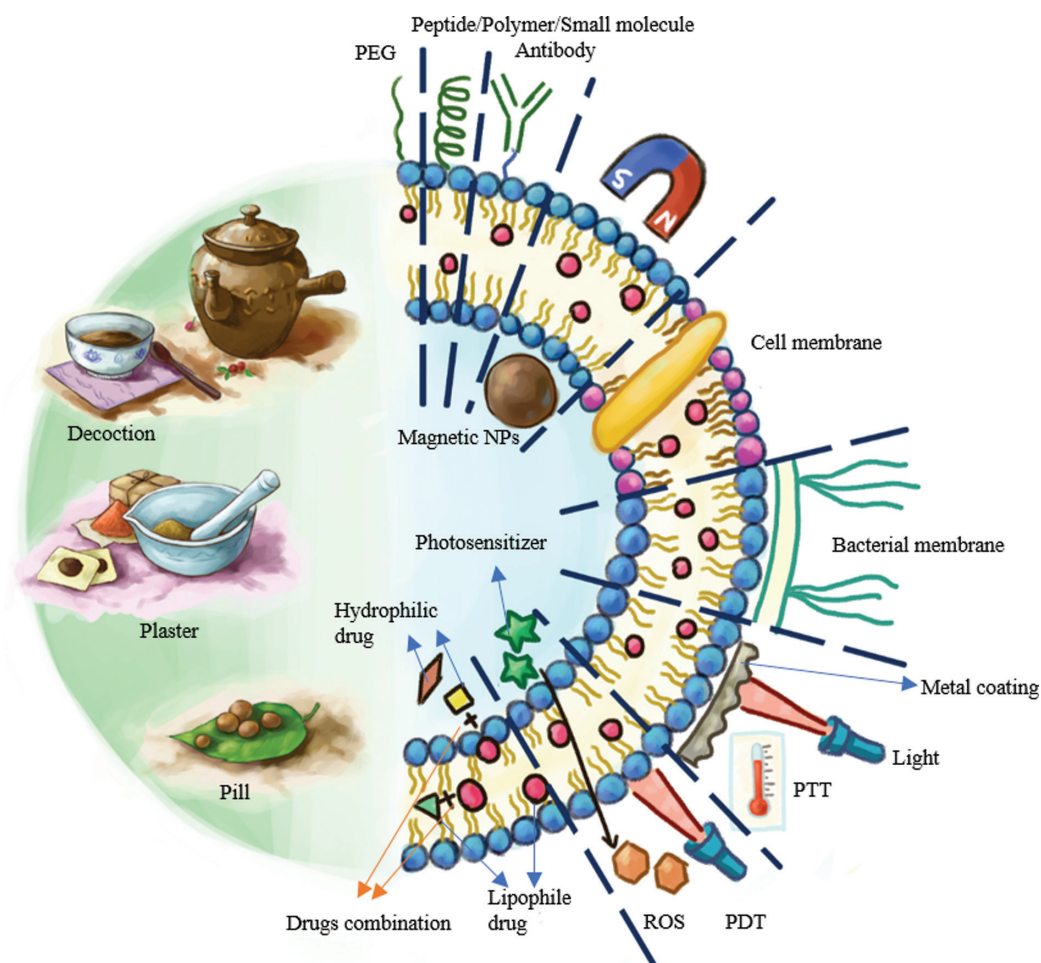


Figure 1 | Illustration of TCH medicines and TCH component-loaded liposomes with emerging strategies for cancer treatment.

fusion allows cargo to be efficiently transported into cells [2, 3] and further escape endosomes or lysosomes [4]. Moreover, the surface charge, lipid structure, and the surface ligand can also be comprehensively adjusted to control drug delivery and bio-distribution profiles. This review highlights the applications of several TCH medicines for cancer treatment and related liposome delivery strategies (Figures 1 & 2). Efforts needed to advance TCH medicines for cancer treatment to clinical trials are also proposed.

## 2. ROLE OF TCH MEDICINES IN CANCER TREATMENT AND STRATEGIES FOR LIPOSOME DELIVERY

TCH medicines, phospholipid composition, drug combinations, improved strategies, disease model route of administration, drug dose, and references are summarized and exemplified in Table 1. Other more detailed content will be discussed in the following text.

### 2.1 Paclitaxel (PTX)

Because Zi shan (*Taxus cuspidata* Sieb. Et Zucc.) causes diuresis and regulates menstruation, Zi shan (*Taxus cuspidata* Sieb. Et Zucc.) was traditionally decocted to treat irregular menstruation, postpartum blood stasis, dysmenorrhea, diabetes, and nephritis-associated edema. PTX is a natural secondary metabolite isolated and purified from the bark of Zi shan. Many studies have confirmed that PTX inhibits the growth of a variety of tumors [55]. The main mechanism of action for PTX is to cause abnormal arrangement of microtubules and the production of microtubule stellates during cell proliferation to hinder cell amplification, inhibit tumor growth and proliferation, induce apoptosis, and enhance innate immunity [56].

Although effective, PTX holds the intrinsic drawbacks of poor water solubility and non-selective cytotoxicity. As a result, a traditional decoction accompanied by oral administration may not be sufficient to fully release the therapeutic potential of PTX. To enhance the solubility, it is reasonable to mix PTX with polyoxyethylated castor oil (PCO) and dehydrated alcohol (1:1) to make an injectable solution; however, severe toxic side effects, including dyspnea, sleepiness, allergies, cardiotoxicity, red blood cell aggregation, nephrotoxicity, and neurotoxicity still suggest the need for novel dosage forms. Therefore, an improved PTX formulation, such as a liposome preparation, that could minimize the PCO-induced adverse effects without diminishing anticancer activity would greatly benefit cancer patients [57].

Luye Pharma's PTX liposomes (Lipusu) have been on the market since 2003 and can be used to treat ovarian and non-small cell lung cancer [58]. Lipusu exhibits a greater safety margin than free PTX. The lethal dose 50 (LD<sub>50</sub>) values for Lipusu and free PTX were calculated to be 69.8 mg/kg (range, 58.9-82.7 mg/kg) and 33.0 mg/kg (range, 30.2-36.1 mg/kg), respectively. Lipusu neither

increases histamine accumulation nor induces severe hypersensitivity reactions in mice more than free PTX; however, both free PTX and Lipusu display robust anti-proliferation activity against human lung adenocarcinoma cells with no significant difference between the two formulations [57]. Moreover, several disadvantages, including rapid clearance *in vivo*, off-target toxicity, and insufficient clinical efficacy, still need to be overcome before achieving broader applications.

The rapid clearance of traditional liposomes *in vivo* is strongly affected by the reticuloendothelial system (RES) [59]. The RES mainly includes liver, spleen, lymph node, lung, peritoneal cavity, and bone marrow macrophages [60]. Xu et al. [5] decorated traditional liposomes with inert and biocompatible polymer polyethylene glycol (PEG) to make stealth liposomes. The protective and hydrophilic layer formed on the surface of liposomes reduces the clearance of liposomes by the cells of the RES and significantly prolongs the half-life of liposomes in the circulation. As a result, stealth liposomes have a much longer half-life (34.2 h) than traditional liposomes (13.7 h), which further increases the enrichment of PTX in tumor sites through an enhanced permanence and retention (EPR) effect, as well as transcytosis [61, 62]. In addition, super-paramagnetic iron oxide nanoparticle (SPIO-NP) incorporation also helps guide PTX liposomes (PTX-LP) to tumor sites through the magnetic force. For example, Ganipineni et al. [6] reported that PTX-SPIO liposomes have a 3-fold increased accumulation with than without SPIO-NPs in brain tumor sites of an orthotopic U87MG glioblastoma mice model 24 h after injection, further leading to a prolonged median survival time (49 days vs. 41 days).

Moreover, ligand decoration is a well-known strategy to boost tumor targeting ability [63]. Karpuz et al. [7] developed a folic acid-modified liposome loaded with PTX (FA-PTX-LP). FA-PTX-LP had significantly higher cytotoxicity towards LLC1 non-small cell lung cancer cells compared with PTX-LP [7]. The half maximal inhibitory concentration (IC<sub>50</sub>) of PTX-LP and FA-PTX-LP was determined to be 35.2 µg/mL and 26.3 µg/mL, respectively [7]. In addition, estrone [8], folic acid (FA) [9], epidermal growth factor receptor [10], and aptamer AS1411 [11] were utilized to target liposomes to breast cancer, non-small cell lung cancer, lung adenocarcinoma, ovarian cancer, melanoma, and cervical cancer cells.

The blood-brain barrier (BBB) increases the extra barrier for liposomes to target tumors in brain tissue [64-66]. To make liposomes penetrate the BBB, Xin et al. [12] prepared PTX-LP modified by rabies virus glycoprotein 15 (RVG15) that specifically binds to nicotinic acetylcholine receptors (nAChRs), which are widely overexpressed in the BBB and on glioma cells. The cellular uptake of RVG15-modified liposomes by rat C6 glioma cells and human brain microvascular endothelial cells (HBMECs) is approximately 1.8 times higher than non-modified liposomes. The cumulative transport efficiency of RVG15-modified PTX liposomes is 1.3 times higher

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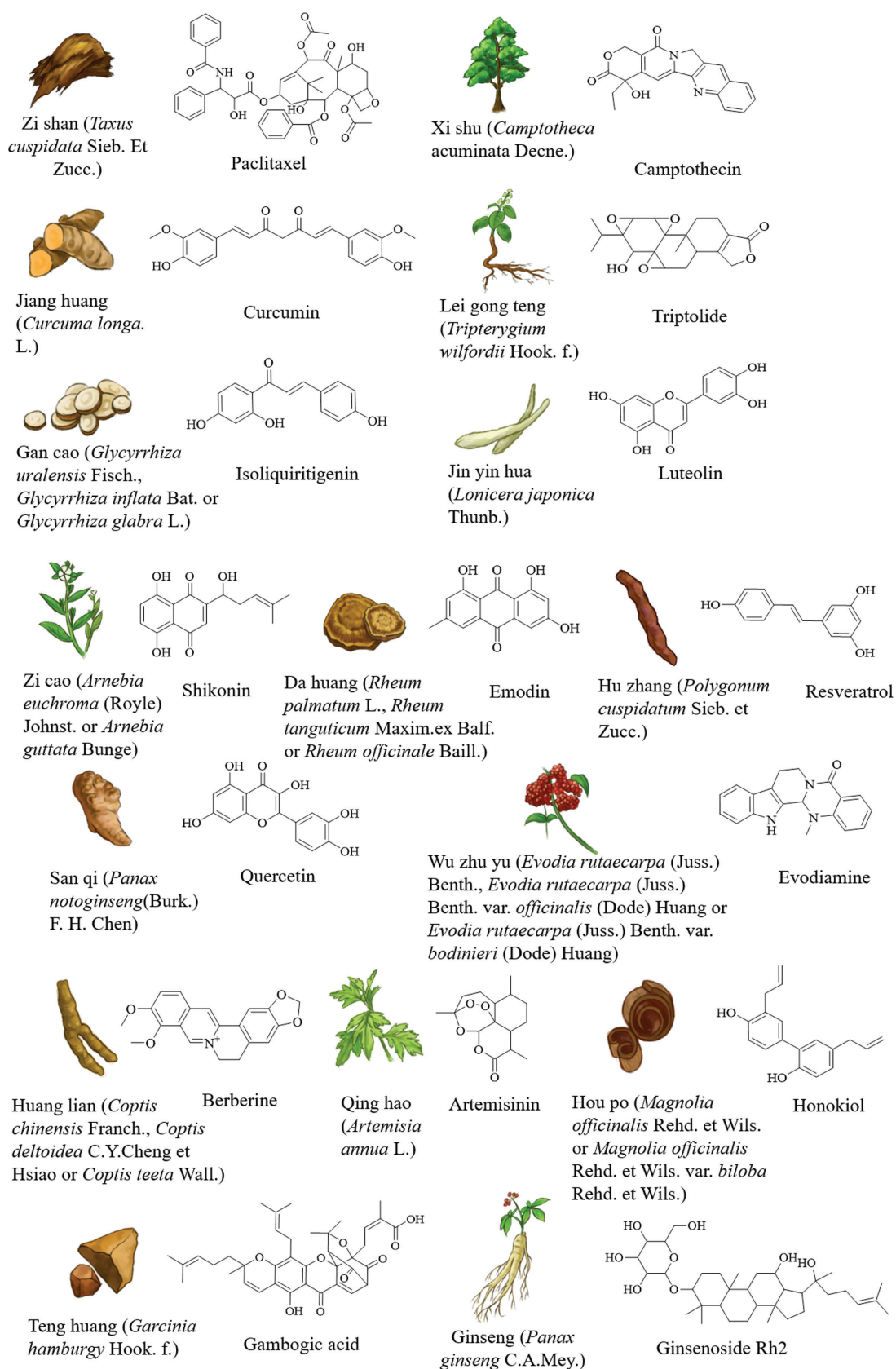


Figure 2 | Photograph of TCH medicine listed in the review and the corresponding chemical structure of the representative TCH components.



**Table 1** | TCH components listed in the review and the corresponding strategies for the liposome delivery

TCH	Phospholipid Composition	Combined Drug	Improving Strategy	Disease Model	Administration Route	Drug Dose	Reference
PTX	SPC, CHOL, PEG (2000)-DSPE, Tocopherol	/	Modified with PEG	Mice bearing tumor xenograft (A549 cell)	Tail-vein injection	5 mg/kg	[5]
PTX	PLGA, PCL-b-PEG, PLGA-b-PEG	/	Load SPIO	Orthotopic U87MG glioblastoma mice	Intravenous injection	5 mg/kg	[6]
PTX	DPPC, DSPE-PEG (2000), Rh-PE	Vinorelbine	Modified with FA	Lewis lung adenocarcinoma cell line male C57BL/6 mice	Intraperitoneal injection	1 mg/kg	[7]
PTX	SPC, CHOL, DSPE-mPEG (2000)	Epirubicin	Modified with estrone	Human breast cancer MCF-7 cell line female BALB/c nude mice	Intraperitoneal injection	10 mg/kg	[8]
PTX	SPC, CHOL, DCP, PEG (2000)-DSPE	/	Modified with FA	Lung adenocarcinoma cell line A549	/	/	[9]
PTX	HSPC, CHOL, TPGS, TPGS-COOH	Piperine	Modified with epidermal growth factor receptor	MDA-MB-231 cells	/	/	[10]
PTX	DOPE, SM, CHOL, DSPE-PEG(2000), DDAB	Polo-like kinase 1 specific siRNA	Modified with aptamer AS1411	Human breast cancer MCF-7 cell line BALB/c nude mice	Tail-vein injection	1.0 µg/kg	[11]
PTX	SPC, CHOL, DSPE-mPEG (2000)	/	Modified with rabies virus glycoprotein (RVG)	Rat C6 glioma cell line male ICR mice	Tail-vein injection	7.5 mg/kg	[12]
PTX	EPC, CHOL, DSPE-PEG (2000)	/	Load SPIO, modified with H <sub>2</sub> K(R) <sub>2</sub>	Human breast carcinoma MDA-MB-231 cell line female BALB/c nude mice	Intravenous injection	15 mg/kg	[13]
PTX	SL (S100), CHOL, DSPE-PEG (2000)	/	Modified with pH-sensitive cell-penetrating peptide and tumor necrosis factor-related apoptosis-inducing ligand	B16F10 melanoma cell line female C57 BL/6 mice	Intravenous injection	8 mg/kg	[14]
PTX	SPC, CHOL	/	Transferred into E.coli	Human lung cancer A549 cell line male sprague-dawley (SD) rats	Intratumorally injected	1 mg	[15]
PTX	SPC, CHOL, DSPE-PEG (2000)	Resveratrol	Transferred into macrophage	Breast cancer 4T1 cell line BALB/C mice	Intravenous injection	1.5 mg/kg	[16]
PTX	DMPC, CHOL, PEG-DSPE	Vactosertib	/	C57BL/6 mice bearing KPC (LSL-KrasG12D/+; LSL-Trp53R172H/+ of pancreatic carcinomas) tumors	Tail-vein injection	400 µL of Gd-liposomes	[17]
PTX	DPPC, CHOL, DSPE-PEG (2000), DSPE-mal	Gemcitabine	/	Pancreatic cancer BxPC3 cell line	/	/	[18]

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Table 1 Continued

TCH	Phospholipid Composition	Combined Drug	Improving Strategy	Disease Model	Administration Route	Drug Dose	Reference
PTX	SPC, CHOL, DSPE-PEG (2000)	Curcumin	Modified with RGD (cyclo [Arg-Gly-Asp-D-Tyr-Cys])	Lung adenocarcinoma cell line A549 BALB/c nude mice	Tail-vein injection	10 mg/kg	[19]
PTX	PLGA, DSPE-mPEG5000, ISL	Triptolide	/	Lung adenocarcinoma cell line A549 BALB/c nude mice	Intravenous injection	5 mg/kg	[20]
PTX	PC, CHOL	Photosensitizer	Combined with photodynamic therapy (PDT)	Prostatic cancer cell PC3 male BALB/c nude mice	Intratumorally injected	6 mg/kg	[21]
PTX	???	Anti-CD47	Combined with immunotherapy	???	???	???	[22]
IRI	CHOL, HSPC, DSPE-Mpeg (2000)	Berberine	/	Breast cancer 4T1 cell line female BALB/c nude mice	Tail-vein injection	4 mg/kg	[23]
IRI	Lecithin, CHOL, DSPE-PEG (2000), DSPE-PEG (2000)-NHS	JO1 (a small molecule inhibitor of bromoamine and extraterminal protein)	/	Murine colon cancer cell line CT26 female BALB/c mice	Tail-vein injection	45 mg/kg	[24]
CUR	Lecithin, CHOL, DSPE-PEG (2000)	/	Modified with Z <sub>4</sub> -HER2-34261 (an antibody molecule that specifically targets HER2)	Breast cancer MCF-7 cell line	/	/	[25]
CUR	SPC, CHOL	/	/	Male albino mice inoculated with Ehrlich ascites's carcinomas cells	Intratumorally injected	20 mg/kg	[26]
CUR	DPPC, CHOL, Dipalmitoyl-GRGDSPA	/	Modified with RGD (cyclo [Arg-Gly-Asp-D-Tyr-Cys])	Breast cancer MCF-7 cell line	/	/	[27]
CUR	GMS or lecithin, Oleic acid or labrafac	Imatinib	Modified with rituximab	Non-Hodgkin lymphoma Jurkat T cells	/	15 mg/kg	[28]
CUR	PC, CHOL, DSPE-PEG (2000)	Capsaicin	Modified with Glycyrrhethinic acid and Galactose	mouse hepatoma H22 cell line female BALB/c mice	Tail-vein injection	5 mg/kg	[29]
CUR	DMPC, CHOL, DSPE-PEG(2000)	Cisplatin	/	Human hepatocellular carcinoma HepG2 xenograft tumor bearing Balb/c nude mice	Tail-vein injection	9.8 mg/kg	[30]
CUR	EPC, CHOL, DSPE-PEG (2000)	Combretastatin A-4 phosphate	Modified with Glycyrrhethinic acid and Galactose	H22 hepatoma-bearing BALB/c mice	Tail-vein injection	5 mg/kg	[31]
CUR	DOTAP, DOPE, C6 ceramide, SC	STAT3 (signal transducer and activator of transcription 3) siRNA	/	Melanoma tumor B16F10 cell line female C57BL/6 mice	Administered topically	3 mg/kg	[32]

Table 1 Continued

TCH	Phospholipid Composition	Combined Drug	Improving Strategy	Disease Model	Administration Route	Drug Dose	Reference
TPL	CHOL, DSPG, Egg yolk lecithin (PC-98T)	Photosensitizer chlorin e6 (Ce6)	Combined with PDT therapy	Subcutaneous patient-derived xenograft (PDX) BALB/C nude mice model of HCC	Intravenous injection	0.4 mg/kg	[33]
TPL	SPC, DSPE-PEG (2000)	/	Modified with carbonic anhydrase IX antibodies	Lung adenocarcinoma cell line A549 male BALB/c nu/nu mice	Via pulmonary delivery	0.15 mg/kg	[34]
TPL	DMPC, CHOL, DSPE-PEG (2000)	/	Modified with cell membrane protein	Liver cancer Huh-7 cell line male BALB/C nude mice	Intravenous injection	100 µg/kg	[35]
TPL	CHOL, SL	/	Coated with platinum/gold bimetallic-nanoshell	Breast cancer U14 tumor female Kunming mice	Intratumorally injected	1.4 mg/kg	[36]
ISL	SC, CHOL, IPM	/	/	Colorectal cancer cell line HCT116	/	25, 50 and 100 µM	[37]
ISL	SP, CHOL, SC, IPM, TPGS	/	Modified with D-α-Tocopherol polyethylene glycol 1000 succinate (TPGS)	Sprague-Dawley rats	Take orally	200 mg/kg	[38]
LUT	CHOL, Lecithin	/	/	Murine CT26 colorectal carcinoma cell line BALB/c mice	Intravenous injection	50 mg/kg	[39]
LUT	DOPC, CHOL, DSPE-PEG (2000)	/	Modified with programmed death ligand-1 (PD-L1) mAb	Liver cancer Huh-7 cell line	/	/	[40]
SHK	HSPC, CHOL, DSPE-PEG (2000)	/	/	Melanoma tumor B16F10 cell line female C57BL/6 mice	Intravenous injection	2 mg/kg	[41]
SHK	EPC, CHOL, DSPE-PEG (2000)	/	Modified with RGD	Breast cancer MDA-MB-231 and MCF-7 cell cell lines	/	/	[42]
EMO	Lecithin, CHOL	/	Load SPIO	4T1 breast cancer female BALB/c mice	Intravenous injection	3 mg per mL * 150 µL	[43]
EMO	EPC, CHOL, DSPE-PEG(2000)	Daunorubicin loaded	Modified with R <sub>g</sub> GD	Breast cancer MDA-MB-4355 cell line BALB/c nude mice	Tail-vein injection	9 mg/kg	[44]
RS	SL, CHOL, Stearylamine	/	Cationic liposome	Liver cancer Huh-7 cell line male Wistar albino rats	Intraperitoneal injection	20 mg/kg	[45]
QR	SPC, DSPE-PEG (2000), CHOL	/	Modified with transferrin peptide	Lung adenocarcinoma cell line A549 BALB/c nude mice	Pulmonary aerosol administration	10 mg/kg	[46]
BER and EVO	SL, CHOL	/	/	Murine melanoma B16 cell line	Skin permeation	/	[47]

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Table 1 Continued

TCH	Phospholipid Composition	Combined Drug	Improving Strategy	Disease Model	Administration Route	Drug Dose	Reference
DHA	Phospholipid S100, Alkyl glucoside	/	Modified with alkyl glycoside	Human hepatoma carcinoma HepG2 cell line specific-pathogen-free ICR mice	Intraperitoneal injection	70 mg/kg	[48]
ART	CHOL, SPC, DSPE-PEG (2000)	/	Modified with cell penetrating peptide HE-R6	Breast cancer 4T1 cell line female BALB/c mice	Intravenous injection	10 mg/kg	[49]
ART	DOPE, CHEMS, DSPE-PEG (2000)	/	Modified with transferrin peptide	Human hepatoma carcinoma HepG2 cell line specific-pathogen-free female BALB/c nude mice	Tail-vein injection	0.9 mg/kg	[50]
HNK	EPC, DOPE, DOTAP, CHOL	/	Modified with hyaluronic acid	Breast cancer 4T1 cell line female BALB/c mice	Intravenous injection	20 mg/kg	[51]
GA	DSPC, CHOL, DSPE-PEG (2000)	Retinoic acid	/	Mouse breast cancer cell line 4T1 BALB/c mice	Tail-vein injection	8 mg/kg	[52]
GA	HSPC, CHOL	/	Modified with nuclear targeting peptide CB5005N (NF- $\kappa$ B nuclear localization /sequence)	Breast cancer 4T1 cell line female BALB/c mice	Tail-vein injection	2 mg/kg	[53]
GRH2	CHOL, DOTAP, Span 60	/	/	PC3 prostate cancer cell line	/	/	[54]

\*TCH: Traditional Chinese herbal, PTX: Paclitaxel, IRI: Irinotecan, CUR: Curcumin, TPL: Triptolide, ISL: Isoliquiritigenin, LUT: Luteolin, SHK: Shikonin, EMO: Emodin, RS: Resveratrol, QR: Quercetin, BER: Berberine, EVO: Evodiamine, DHA: Dihydroartemisinin, ART: Artemisinin, HNK: Honokiol, GA: Gambogic acid, GRH2: Ginsenoside Rh2, SPC: Soybean phosphatidylcholine, CHOL: Cholesterol, DSPE-PEG(2000): 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[(poly-ethylene glycol)-2000], DSPE-mPEG (2000): 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(poly-ethylene glycol)-2000], PLGA: Poly-lactic-co-glycolic acid, PCL: Polycaprolactone, PCL-b-PEG: Poly(e-caprolactone)-b-poly(ethylene glycol), PLGA-b-PEG: Poly(lactic-co-glycolic acid)-b-poly(ethylene glycol), DPPC: Dipalmitoyl phosphatidylcholine, Rh-PE: Rhodamine-phosphatidylethanolamine, DCP: Di-hexadecyl-phosphate, HSPC: Hydrogenated soy phosphatidylcholine, TPGS: D- $\alpha$ -tocopherol polyethylene glycol 1000 succinate, DOPE: Di-oleoyl-phosphatidylethanolamine, SM: Sphingomyelin, DDAB: Di-decyl-dimethyl-ammonium bromide, EPC: Egg phosphatidylcholine, SL: Soybean lecithin, DMPC: 1,2-dimyristoyl-sn-glycero-3-phosphocholine, ISL: Injectable soybean lecithin, PC: l- $\alpha$ -phosphatidylcholine, GMS: Glycerol monostearate, DOTAP: 1,2-dioleoyl-3-trimethylammonium-propane, SC: Sodium cholate, IPM: Isopropyl myristate, SP: Soybean phospholipid, DOPC: 1,2-dioleoyl-sn-glycero-3-phosphocholine, CHEMS: Cholesteryl hemi-succinate, DSPC: Di-stearoyl-phosphatidyl-choline, FA: Folate.



than non-modified PTX liposomes, further leading to the much lower  $IC_{50}$  value of 0.1  $\mu\text{g}/\text{mL}$  (4.6  $\mu\text{g}/\text{mL}$  for non-modified PTX liposomes).

Apart from receptor-mediated endocytosis, the tumor microenvironment can also affect the fate of liposomes *in vivo*. Zheng et al. [13] designed a cell-penetrating peptide [ $H_7K(R_2)_2$ ] that has a specific response to the tumor acidic environment and prepared an  $H_7K(R_2)_2$ -decorated PTX-loaded liposome [ $H_7K(R_2)_2$ -PTX-LP]. Due to the higher acidity of solid tumor tissues (pH 6.0-7.0) than the neutral environment of normal organs (pH 7.4), Zheng et al. [13] achieved the effect of selective penetration and produced the effect of targeting tumor tissues. The cellular uptake of liposomes without  $H_7K(R_2)_2$  modification was almost the same as the liposomes modified by  $H_7K(R_2)_2$  at pH 7.4, but approximately 1.5 times higher than at pH 6.8. An *in vitro* cytotoxicity study showed similar trends in the MDA-MB-231 cell line. Interestingly, the  $IC_{50}$  value of the  $H_7K(R_2)_2$ -PTX-LP group at pH 6.8 (7.2  $\mu\text{M}$ ) was significantly lower than the PTX-LP group (32.0  $\mu\text{M}$ ). Increased melanoma cell internalization of PTX-LP was also achieved using the same strategy. The core method relied on liposome surface modification of a stearyl chain-fused, pH-sensitive, cell-penetrating peptide [14].

Because bacteria play an important role in the tumor hypoxic microenvironment [67], Zheng et al. [15] transferred PTX-LP into *Escherichia coli* to make a PTX-in-liposome-in-bacteria (PTX-LP@BP) hybrid delivery system. PTX-LP@BP was shown to be ingested by A549 cells much faster with than without bacteria coating (0.5 h vs. 4 h). As a result, compared to mice with lung cancer treated with PTX-LP, a large number of tumor nodules, obvious bleeding, significant angiogenesis, and a large inflammatory cell infiltrate in the lung tissues of rats were alleviated after PTX-LP@BP treatment.

Recurrence after tumor resection is associated with postoperative inflammation and tumor cell residue [68]. A series of inflammatory factors aggregate in the resection wound, which quickly recruits monocytes / macrophages [69-71]. Qiu et al. [16] designed a macrophage cell membrane-coated liposome to encapsulate PTX (PTX-LP-MP). With the help of inflammatory gradients, macrophage-mediated vectors penetrated to the deep site of 4T1 tumor spheroids at a depth of 100  $\mu\text{m}$ . In a mouse breast cancer postoperative model, the tumor growth rate of the PTX-LP-MP treated mice was 2.5  $\text{mm}^3$  per day, which was significantly slower than PTX-LP+MP (physical mixture, 12.7  $\text{mm}^3$  per day). The results showed that macrophage membrane-coated liposomes with higher drug delivery efficiency exhibited the potential to prevent the recurrence of triple-negative breast cancer after surgery.

Due to the heterogeneity of tumors, the delivery efficiency of liposomes is often hindered by a dense extracellular matrix (ECM) [72]. To overcome this problem, Zhao et al. developed a transforming growth factor- $\beta$ 1 receptor kinase inhibitor (vactosertib [VAC]) and PTX

(VAC/PTX-LP) co-loaded liposome. VAC was chosen to inhibit the proliferation of tumor fibers in ECM, thus facilitating PTX penetration into pancreatic ductal adenocarcinoma tumor xenografts. The antitumor efficacy of PTX-LP was increased greatly after combination with VAC, with a tumor inhibition rate of 67.5% in the VAC/PTX-LP group, while PTX-LP showed no significant antitumor effect [17]. At present, the combination of two or more chemotherapy drugs is widely used for cancer treatment [62]. Thus, Yang et al. [18] developed gemcitabine (GEM) and PTX co-loaded liposomes (GEM/PTX-LP) to treat pancreatic cancer. The  $IC_{50}$  values of GEM, PTX, and GPL were 5.9  $\mu\text{g}/\text{mL}$ , 4.2  $\mu\text{g}/\text{mL}$ , and 1.9  $\mu\text{g}/\text{mL}$ , respectively. The results showed that a combination strategy benefitted the cellular toxicity against cancer cells [18]. In addition, the combination of PTX and other TCH medicines (resveratrol [16], curcumin [19], triptolide [20], and piperine [10]), Polo-like kinase 1-specific siRNA [11], chemotherapy drugs (oxaliplatin [73], camrizumab [74], apatinib [75], and vinorelbine [7]), and antibodies were also shown to improve anti-tumor efficacy.

Along with surgery and chemotherapy, radiation therapy remains an important form used in cancer treatment by destroying chromosomes [76]. Chen et al. [77] retrospectively analyzed the clinical data of 38 patients with locally advanced lung squamous cell carcinoma (LSCC) and evaluated the efficacy and safety of PTX-LP and carboplatin combined with radiotherapy. The weekly PTX-LP and carboplatin concurrent chemoradiotherapy (total dose, 60.0 Gy) exhibited a remarkably longer median survival time of 29.0 months than drug-loaded liposomes without radiation therapy (range, 12.0-16.0 months) [77]. Maximizing the radiation dose in the tumor site while minimizing the exposure to normal cells is the ongoing challenge to make chemoradiotherapy more feasible and well-tolerated.

Phototherapy, including photodynamic therapy (PDT), has emerged as an alternative to tumor ablation, which could also be combined with TCH medicine-based liposomal therapy. For example, Wang et al. [21] encapsulated the photosensitizer, TPCI, and PTX into liposomes (TPCI/PTX-LP) for PC3 prostate cancer therapy. The irradiated TPCI/PTX-LP (460 nm, 1  $\text{mW}/\text{cm}^2$ , 10 min) remarkably enhanced the efficacy of both PTX and TPCI. The  $IC_{50}$  values of both drugs was reduced 30-fold in treating PC3 cells compared to sole chemotherapy (PTX-LP) or PDT (TPCI-LP). Light and photosensitizers are two critical elements for PDT therapy and may directly impede tumor cell propagation by destroying the tumor cell membrane and promoting drug absorption in tumors, thus enhancing the effect of chemotherapy; however, light intensity and tissue penetration ability as well as photosensitizer potential cytotoxicity to normal tissue need to be optimized to minimize the side effects.

The strategy of restarting the normal tumor immune cycle and restoring the anti-tumor immune response makes immunotherapy an efficient method of anti-tumor therapy [78, 79]. Chen et al. [22] modified

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anti-CD47 on the surface of PTX-LP (CD47-PTX-LP) to combine chemotherapy and immunotherapy. Anti-CD47 monoclonal antibodies (mAbs) promote tumor-associated macrophages (TAMs) in triple-negative breast cancer (TNBC) to polarize from the M2-like phenotype to the M1-like phenotype. M2-like TAMs are alternating activated macrophages that promote tumor growth and are related to tumor invasion, metastasis, T cell inhibition, and adverse clinical results, while M1-like TAMs are typical activated macrophages that have an anti-tumor role by presenting antigen and dissolving cancer cells [80, 81]. After treatment with CD47-PTX-LP, the number of M2 macrophages (F4/80<sup>+</sup>CD11b<sup>+</sup>CD206<sup>+</sup>) in mice was significantly decreased compared with PTX-LP-treated mice, while the number of M1 macrophages (F4/80<sup>+</sup>CD11b<sup>+</sup>CD80<sup>+</sup>) were significantly increased, further resulting in 2.3-, 2.8-, and 1.5-fold lower migration rates, IC<sub>50</sub> values, and apoptosis rates, respectively, in MDA-MB-231 cells. Moreover, the CD47-PTX-LP-treated mice had 15.3-fold fewer lung metastatic nodules than PTX-LP-treated mice. In general, CD47-PTX-Lip significantly inhibits cell migration and proliferation, and induces excellent antitumor effects *in vitro*.

### 2.2 Irinotecan (IRI)

Xi shu (*Camptotheca acuminata* Decne.) is a relatively newly-developed TCH medicine. The whole plant contains camptothecin. Xi shu has been used in treating various cancers, including acute and chronic leukemia, psoriasis, and hepatosplenomegaly caused by schistosomiasis. The anti-tumor effect of Xi shu has been recorded in various Chinese medicine books.

IRI, a semi-synthetic water-soluble camptothecin derivative, is a first-line chemotherapy drug for colorectal cancer, which improves the water insolubility of camptothecin [82]. IRI inhibits the release of DNA strands by acting on the topoisomerase I-DNA complex, resulting in double-stranded DNA breakage and cell death. Moreover, IRI induces immunogenic cell death (ICD), which will help increase the immune response of tumor-specific antigen or increase damage-related molecular patterns [83].

Onivyde was the first commercialized IRI liposome that is mainly used to treat metastatic pancreatic cancer [84]. Although effective in improving the pharmacokinetics and tumor biological distribution of IRI, Onivyde is still prone to gastrointestinal toxicity and delayed diarrhea. It has been reported that berberine (BER) combined with cytotoxic drugs has a beneficial role in alleviating intestinal mucositis and producing synergistic anticancer effects [85, 86]. Therefore, Wang et al. [23] constructed liposomes co-loaded with IRI and BER (BER/IRI-LP). BER/IRI-LP exhibited a stronger inhibitory effect on BXP-3 pancreatic cancer cells with an IC<sub>50</sub> of 29.5 µg/mL, thus surpassing Onivyde and BER-LP plus IRI-LP (39.2 and 33.4 µg/mL, respectively). In contrast to the severe colon damage and diarrhea caused by Onivyde, BER/IRI-LP causes slight deformation of crypts, almost

no mucosal epithelial detachment, and mild diarrhea, which indicates that BER protects colon tissue damage caused by IRI and reduces gastrointestinal toxicity. To further boost the anticancer effect of IRI, drug combination strategy has been widely performed. He et al. developed liposomes to co-deliver IRI and JQ1, a small molecule inhibitor of bromoamine and extraterminal protein. IRI induces immunogenic cell death, while JQ1 acts as a PD-L1 inhibitor to activate the anticancer immunity against murine colon cancer cell line CT26 and reshape the tumor immune microenvironment, thus activating the host immune system and prevent tumor growth [24, 87, 88].

### 2.3 Curcumin (CUR)

In the field of TCH medicine, Jiang huang (*Curcuma longa*. L.) invigorates qi, invigorates the circulation of blood, restores menstrual flow, and is used for treating blood stasis caused by bruises. CUR, the main active component of Jiang huang, is widely used in the food industry as a common natural pigment and edible spice. In the medical field, CUR inhibits nuclear factors [nuclear factor-κB (NF-κB), activator protein-1, and other transcription factors], which induce differentiation of malignant tumor cells, induces apoptosis of tumor cells, and inhibits the growth of tumors at various stages without apparent side effects [89, 90]. In practical applications, however, CUR is insoluble in water and it is difficult to achieve a high-efficiency anticancer effect in the traditional decoction using oral administration. The drug is directly transported to the gastrointestinal tract by pill powder, which partially overcomes the limitation of CUR insolubility in water; however, it is easy to transform CUR into glucuronic acid and sulfonic acid complexes in the intestine, with fast metabolism and a short half-life. These problems contribute to the low bioavailability of CUR. Therefore, a novel formulation of CUR, liposomal CUR, may emerge as a promising alternative to improve water solubility and bioavailability.

No CUR liposome (CUR-LP) has been clinically used for cancer treatment until now. Based on the antitumor potential of CUR, there are still many studies aimed at developing and improving CUR-LP formulations. For example, Moballegh-Nasery et al. [25] showed that CUR-LP is more cytotoxic towards breast cancer MCF-7 cell lines than free CUR. Specifically, the number of apoptotic MCF-7 cells induced by CUR-LP was 3.6 times that of free CUR [25].

Under 450 nm light excitation, CUR has been shown to produce singlet oxygen and can be effectively used as a photosensitizer in PDT, except as a chemotherapy drug. To verify the therapeutic effect of CUR as a photosensitizer, Fadel et al. [26] prepared CUR-LP and demonstrated its light-enhanced anticancer capacity as well. CUR-LP under light irradiation (200 mW/cm<sup>2</sup>) showed higher cytotoxicity in the solid Erlich tumor model than in the dark, and had a prolonged survival time of

72 days compared with CUR-LP without irradiation (65 days) [26].

Drug accumulation in the CUR-LP tumor site without targeted modification is still limited. Therefore, many studies aim to increase CUR-LP targeting to enhance the anticancer effect. Integrin  $\alpha\beta 3$  has a high level of expression in various cancer types (breast cancer, lung cancer, and activated vascular endothelial cells), while integrin  $\alpha\beta 3$  shows low or no expression in other endothelial cells and most non-cancerous organs [91]. In a study conducted by Mahmoudi et al. [27], RGD (cyclo [Arg-Gly-Asp-D-Tyr-Cys]), which has a high binding affinity for  $\alpha\beta 3$  [92], was directly conjugated to CUR-LP (RGD-CUR-LP). Compared to CUR-LP (cell survival rate = 48.0%), RGD-CUR-LP (cell survival rate = 18.4%) displayed significantly improved cytotoxicity to MCF-7 breast cancer cells [27]. In addition, Z<sub>HER2:342</sub> [25], an affibody molecule that specifically targets HER2, RGD [19], and rituximab [28], has also been reported to enhance the targetability of CUR-LP in breast cancer cells (SKBR3 and MCF-7 cells), A549 lung adenocarcinoma cancer cells, and Ramos b non-Hodgkin's lymphoma cancer cells, respectively.

To achieve better tumor selectivity and more efficient target cell uptake of CUR-LP, dual-targeted nanotherapeutics that selectively target two different cancer biomarkers have been developed. Qi et al. [29] modified CUR-LP with glycyrrhetic acid (GA, which specifically binds to the overexpressed GA receptor on liver cancer cells [93]) and galactose (GAL, which can target to the special lectin as a protein receptor on liver cell membranes [94]) [29]. Compared with the GA-CUR-LP group, the GA/GAL-CUR-LP group exhibited a 12% higher tumor inhibition rate in H22 tumor-bearing mice [29].

A combined administration strategy further enhances the killing effect of CUR on tumor cells. For example, prominent cytotoxicity of cisplatin (CDDP) and CUR co-loaded liposomes (CDDP/CUR-LP) against HepG2 cells was achieved and demonstrated by the IC<sub>50</sub>, in contrast to CUR-LP (0.6  $\mu$ M vs. 20.3  $\mu$ M) [30]. In addition, CUR/imatinib [28] and CUR/combretastatin A-4 phosphate [31] co-loaded liposome systems have also been reported to exhibit enhanced anti-tumor efficacy against non-Hodgkin's lymphoma and liver cancer than CUR-LP. The complexity of the tumor microenvironment also contributes to the failure of CUR-LP treatment. The liver cancer microenvironment is composed of activated hepatic stellate cells (aHSCs), immune system cells, and cytokines [95]. aHSCs not only produce a large number of cytokines to stimulate tumor proliferation, but also promote tumor angiogenesis, extracellular matrix remodeling, and epithelial mesenchymal transformation, thus leading to drug resistance as well as tumor invasion and metastasis [96]. Capsaicin (CAPS) has been shown to have a significant anti-fibrosis effect by inhibiting the proliferation of aHSCs [97]. CAPS and CUR co-loaded liposomes exhibit greater cytotoxicity and stronger inhibition of lung metastasis in a HepG2 liver tumor model than

CUR-LP [29]. Apart from small molecular drugs (siRNAs), such as STAT3 (signal transducer and activator of transcription 3), siRNAs have also been combined with CUR for cancer therapy. For example, liposome co-delivery of CUR and STAT3 siRNAs into the murine melanoma cell, B16F10, resulted in a higher B16F10 cell growth inhibition of 76.3 % than CUR-LP (51.1%) [32].

## 2.4 Triptolide (TPL)

Lei gong teng (*Tripterygium wilfordii* Hook. f.) dispels wind and removes dampness, activates blood circulation and dredges collaterals, reduces swelling, and relieves pain, and has been widely used in China to treat various immunologic diseases, such as rheumatoid arthritis, lupus erythematosus, nephritis, psoriatic arthritis, and Henoch-Schonlein purpura [98]. Lei gong teng can be administered in a variety of ways, including slow fire and long-term decoction for oral use, powdered and encapsulated, powdered or mashed, or made into tincture and ointment for external use.

The main extracts of Lei gong teng are TPL and celastrol. TPL is a diterpene tricyclic oxide that has an effective anticancer effect on a variety of cancers, such as liver cancer, leukemia, breast cancer, pancreatic cancer, and lung cancer [99]. TPL inhibits tumor growth and metastasis by inhibiting the HSP70 gene and the generation of vascular endothelium, thus inducing S-phase arrest, activating apoptosis related proteins in tumor cells [99]. Due to the low solubility of TPL in water; however, oral administration will lead to severe systemic toxicity and rapid clearance in the body but the clinical application is limited [33]. Although TPL and its analogues have shown effective biological activities against various cancers, inflammation, and autoimmune diseases, none have been approved for clinical use. Minnelide and LLDT8, two analogues of TPL, overcame the problem of low TPL solubility and entered phase II clinical trials [100]; however, the reduction in side effects warrants further study. The strategy involving liposome transport provides a way to reduce side effects. It is of great significance to control the targeting and release site of TPL-LP before meeting the standards required for clinical application.

Carbonic anhydrase IX is a well-known gene in response to hypoxia. Thus, carbonic anhydrase IX is over-expressed on the surface of various cancer cells, including lung cancer cells. TPL-LP with surfaces modified by carbonic anhydrase IX antibodies exhibit stronger tumor growth inhibition and longer median survival time (90 days) in an A549 lung cancer model compared to non-targeted TPL-LP (71 days) [34].

In addition to the strategy of targeting ligand modification, the transmembrane domain of cell membrane protein (MP) has also been used for surface modification of liposomes to enhance tumor targeting ability [101]. Zheng et al. [35] modified MP on the surface of TPL-LP (MP-TPL-LP) to target Huh-7 liver cancer cells. MP-TPL-LP is internalized by Huh-7 cells in 1 h, but it takes  $\geq 2$  h

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for TPL-LP, which further leads to a higher drug accumulation at the tumor site. *In vivo* experiments in mice have also shown that the MP-TPL-LP group tumor volume was only one-half of the TPL-LP group.

Similar to the strategy of paclitaxel combined with PDT, Yu et al. [33] designed photoactivated liposomes combined with the photosensitizer, chlorin e6 (Ce6), and TPL (Ce6/TPL-LP) for synergistic PDT therapy in the treatment of liver cancer. Compared with chemotherapy alone (TPL-LP), near-infrared radiation combined with Ce6/TPL-LP significantly reduced the tumor tissue volume in mice [33]. Unlike PDT, which mainly causes chemical damage to cancer cells, PTT often results in thermal damage at the target tumor site. Luo et al. [36] designed a platinum / gold bimetallic nano-shell-coated TPL-LP (Pt/Au-TPL-LP) for the treatment of breast cancer. Under the irradiation of an 808-nm laser with a power density of 2 W/cm<sup>2</sup>, the tumor temperature of mice in the Pt/Au-TPL-LP group increased from below 39 °C to 62.6 °C, and the tumor tissue inhibition rate reached 90.7%, while the tumor tissue in the Pt/Au-TPL-LP group showed clear growth.

### 2.5 Isoliquiritigenin (ISL)

Gan cao (*Glycyrrhiza uralensis* Fisch., *Glycyrrhiza inflata* Bat. or *Glycyrrhiza glabra* L.) is considered to invigorate qi, relieve pain, strengthen the spleen and stomach, resolve phlegm, and relieve cough. A large number of studies have shown that Gan cao has many pharmacologic activities, such as antiviral, anti-inflammatory, anti-tumor, antibacterial, and many other activities [102]. The extracts of Gan cao mainly include glycyrrhizin (GL) and ISL. ISL plays an anti-tumor role by inhibiting proliferation, inducing apoptosis and/or autophagy, and inhibiting the migration and invasion of various cancer cells [103]. GA produced by GL hydrolysis also has anti-tumor activity [104], but GA is often used as the targeting ligand of liposomes [29]. ISL inhibits angiogenesis, inhibits inflammatory and oxidative stress via the regulation of the Nrf2 and NF-κB signaling pathways, and modulates cyclin B1-CDK1 for G2/M arrest and apoptosis to inhibit tumor growth and metastasis [103].

Liposome potentially overcomes the inherent drawbacks of ISL, including poor water solubility and low bioavailability, thus promoting the clinical application of ISL; however, no pharmaceutical ISL liposomes are in clinical trials. Wang et al. [37] wrapped ISL in liposomes (ISL-LP) to enhance water solubility, thereby enhancing ISL bioavailability and the inhibitory effect on HCT-116 colon cancer cells. In *in vitro* cell studies, compared to cells treated with free ISL (59.2 %), ISL-LP treatment significantly increased the apoptotic rate of HCT-116 cells (79.7%). To further boost the targeting performance, Liu et al. [38] used D-α-tocopherol polyethylene glycol 1000 succinate (TPGS) to modify ISL-Lip. TPGS exhibits liver-targeting ability and has strong anti-oxidant activity. The area under the curve (AUC) and the C<sub>max</sub> of TPGS-ISL-LP were shown to be 1.3 and 1.9 times higher

than ISL-LP. The concentrations of ISL from ISL-TPGS-LP were higher in the liver and showed a statistically significant difference when compared to an ISL-LP suspension. The experimental results verified the targeting and antioxidant capacity of TPGS.

### 2.6 Luteolin (LUT)

LUT, a flavonoid polyphenol compound, exists in many natural medicinal materials [Jin yin hua (*Lonicera japonica* Thunb.), Jing jie (*Schizonepeta tenuifolia* Briq.), and Huang qin (*Scutellaria baicalensis* Georgi), Zi su ye (*Perilla frutescens* (L.)Britt.)], vegetables (cabbage, cauliflower, broccoli, carrots, celery, and sweet peppers), and fruits. Using Jin yin hua as an example, Jin yin hua has the function of heat-clearing and detoxifying and is often used to treat dysentery or other diseases with heat syndrome or wind-warm syndrome. In recent years, many experiments and clinical studies have proved that heat-clearing TCH medicines have good anti-inflammatory effects [105]. LUT has a variety of pharmacologic activities, such as anti-inflammation, anti-allergic, anti-tumor, anti-bacterial, and anti-virus activity [106]. LUT also blocks cancer development *in vitro* and *in vivo* by inhibiting the proliferation of tumor cells, protecting against carcinogenic stimuli, activating cell cycle arrest, and inducing apoptosis via different signal pathways [107]; however, the bioavailability of LUT is very low after oral administration, and it is difficult to administer intravenously or intraperitoneally due to its poor water solubility, so many drug delivery strategies have been used to improve the bioavailability of LUT in the human system, especially liposomes [106]. Moreover, the exact pharmacologic mechanism and dosage of LUT have not been established [106], and there is no LUT liposome for clinical use.

Therefore, Wu et al. [39] used liposome-encapsulated LUT to increase solubility and bioavailability, and compared the antitumor effect on colorectal cancer with free LUT. *In vitro* studies showed that compared with free LUT, LUT-LP had a significantly greater inhibitory effect on the growth of the murine colorectal cancer cell line, CT26. The extent of apoptosis in the LUT-LP group was significantly higher than the free LUT group. *In vivo* studies showed that the LUT-LP group tumor weight was only 47% of the free LUT group after 22 days of treatment in a CT26 tumor model. Cao et al. [40] used programmed death ligand-1 (PD-L1) mAbs anchored to the surface of LUT-LP to further boost the targetability to HepG2 cells. Owing to the high expression of PD-L1 on the surface of HepG2 cells, PD-L1-LUT-Lip was associated with a higher inhibitory rate (47.9%) than non-targeting LUT-LP (31.3%).

### 2.7 Shikonin (SHK)

Zi cao (*Arnebia euchroma* (Royle) Johnst. or *Arnebia guttata* Bunge) cools blood, activates the blood circulation, detoxifies, and promotes eruption of rashes. So, Zi cao is often used for the treatment of blood-heat



syndrome, measles impervious, sores, eczema, and empyrosis. When treating traumatic skin injuries, Zi cao is usually formulated as an ointment for application, while other diseases are treated with an oral decoction. SHK is a highly-lipophilic naphthoquinone isolated from Zi cao. The anti-cancer mechanism underlying SHK has been extensively studied and it has been shown that SHK inhibits proliferation by reducing tumor-derived exosome inhibition of estrogen signaling transduction, inhibits migration and invasion by preventing epithelial mesenchymal transition and matrix metalloproteinase-9 secretion, induces apoptosis and necrosis by regulating the expression of apoptosis-related proteins and reducing reactive oxygen species, and regulates the activation of STAT-3, focal adhesion kinase, and steroid receptor coactivator, which have important roles in tumor progression [108]. In addition, SHK induces strong ICD, which not only has a cytotoxic effect on tumors, but also stimulates the immune response by promoting antigen production, recognition, and processing, and activation of immune cells, thereby killing tumors [41]. The multiple inhibitory effects of SHK on tumors suggest that SHK may be a good candidate drug for cancer treatment; however, SHK has low solubility, a low lethal dose, and a wide range of first-pass elimination, so it has not been used in the clinical treatment of cancer.

To overcome these shortcomings and release the anti-cancer potential of SHK, Li et al. [41] investigated the anti-cancer performance of SHK-loaded liposomes in B16F10 tumor-bearing C57BL/6 mice. The  $C_{max}$  and  $AUC_{0-t}$  of the SHK-LP group were 85.0- and 148.6-fold higher than the free SHK group, indicating that liposome encapsulation improves the stability and pharmacokinetics of SHK [41]; however, the side effects of SHK should be reduced by optimizing its targetability. Therefore, Wen et al. [42] studied the effect of RGD-modified SHK-LP by  $\alpha v\beta 3$ -positive breast cancer MDA-MB-231 cells. In MDA-MB-231 cells, RGD-SHK-LP showed a higher uptake rate (higher fluorescence intensity) and cytotoxicity ( $IC_{50}$ : 7.2  $\mu M$  vs. 10.9  $\mu M$ ) than SHK-LP [42].

## 2.8 Emodin (EMO)

Da huang (*Rheum palmatum* L., *Rheum tanguticum* Maxim. ex Balf. or *Rheum officinale* Baill.) was first recorded in *Shen Nong's Herbal* and was used in the medical field for approximately 2000 years. Da huang can clear heat, cool blood, detoxify damp heat poisoning, and eliminate blood stasis. Thus, Da huang is used for constipation, blood stasis, diarrhea, discomfort, and damp heat jaundice. Chengqi decoction is a classic prescription with Da huang as the main component, and has an excellent effect in removing intestinal stasis. Da huang can be orally decocted or ground into powder, then mixed with water or vinegar and applied to the skin. When used externally, Da huang has anti-inflammatory, detumescence, and hemostasis effects. With the rapid development of modern society, a large number of scientific reports have shown that Da huang has many

pharmacologic activities, such as diarrhea, anti-inflammation, anti-cancer, liver protection, and cholagogic [109]. EMO is a naturally-occurring anthraquinone derivative and the active ingredient of many Chinese herbal medicines, including Da huang, Hu zhang, He shou wu (*Polygonum multiflorum* Thunb.), Lu hui (*Aloe barbadensis* Miller or *Aloe ferox* Miller), and Jue ming zi [110]. EMO regulates a variety of signal pathways, including popaidlininsial 3-hydroxy Kinase/Akt, transforming growth factor-B (TGF-B), adenosine monophosphate-activated protein kinase (AMPK), mammalian target of rapamycin (mTOR), mitogen-activated protein kinase (MAPK), and nuclear factor kappa B (NF- $\kappa$ B), and inhibits the growth of tumor cells [111]. Furthermore, EMO exerts potential therapeutic action on many chronic diseases, such as myocardial infarction, atherosclerosis, diabetes, and Alzheimer disease [112]. The lack of targeting and disadvantages of nephrotoxicity, hepatotoxicity, genotoxicity, and low biological activity of oral administration limits the clinical cancer treatment effect of EMO [112], therefore EMO liposomes are not available for clinical use. Song et al. [43] co-encapsulated EMO and SPIO-NPs into liposomes to prepare magnetic nanoparticles (SPIO/EMO-LP) and increase the enrichment of EMO at the 4T1 breast cancer tumor site. In the presence of an external magnetic field, the accumulation (fluorescence intensity) of SPIO/EMO-LP at the tumor site of the orthotopic 4T1 breast cancer mouse model was significantly higher than that of SPIO/EMO-LP without the presence of an external magnetic field, which further reduced the tumor weight of mice. In addition, the ligand modification strategy also enhanced targeting of EMO-LP. The experiments of Fu et al. [44] showed that arginine<sub>8</sub>-glycine-aspartic acid (R<sub>8</sub>GD)-modified EMO-LP had stronger targeting and cytotoxicity to breast cancer MDA-MB-4355 cells compared with EMO-LP without R<sub>8</sub>GD modification. Specifically, the cellular internalization,  $IC_{50}$  value of tumor cells, and tumor volume of tumor-bearing mice were 1.3-, 0.6-, and 0.8-fold that of EMO-LP [44]. To further enhance the killing effect on breast cancer MDA-MB-4355 cells, EMO-LP combined with daunorubicin-loaded LP increased the apoptosis rate by 12.6% and reduced the tumor volume by 14.2% compared with EMO-LP alone [44].

## 2.9 Resveratrol (RS)

Hu zhang (*Polygonum cuspidatum* Sieb. et Zucc.) eliminates wind, dampness, and blood stasis, and dredges channels and collaterals. Hu zhang is mainly used to treat rheumatic myalgia, rheumatic osteodynia, damp heat jaundice, amenorrhea, postpartum cachexia, hemorrhoids, and blood leakage, and scald. RS exists in peanuts, grapes, berries and other foods, as well as in various herbal medicines, such as Hu zhang, Jue ming zi (*Cassia obtusifolia* L. or *Cassia tora* L.), and Li lu (*Veratrumnigrum* L.) [113].

RS has anti-oxidant, anti-tumor, anti-inflammatory, and anti-aging effects, improves obesity, controls



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diabetes, and is cardioprotective in clinical treatment [114]. In research involving the anti-cancer mechanism, RS has been shown to downregulate the expression of  $\beta$ -catenin and block  $\beta$ -catenin nuclear translocation through perturbation of the long non-coding RNA, MALAT1. RS suppresses TGF- $\beta$ /Smad-induced epithelial-mesenchymal transition and the transcription factor, Snail. RS lowers the expression of IKK-induced TNF- $\beta$ , thus leading to inhibition of cancer cell proliferation through deactivation of NF- $\kappa$ B. RS inhibits p-PI3K/p-AKT-mediated FOXO3a nuclear accumulation, suppresses the phosphorylation of Src-STAT3, and induces apoptosis of cancer cells [115]. RS is absorbed orally and excreted through the urine and feces after metabolism [114]; however, the rapid metabolism and rapid clearance from the systemic circulation results in low bioavailability (<1% of oral activity) and a low biological half-life (30-45 min) [116]. Therefore, Jagwani et al. [45] loaded RS into the hydrophilic core of cationic liposomes (RS-LP) to delay drug metabolism and clearance time to increase the toxicity of RS against tumors. Cations targeted the anionic charge generated by phosphatidylserine in liver cancer cells (HepG2 cells). The cellular uptake of free RS and RS-LP was 54.2% and 75.0%, respectively. Compared with the free RS group, the IC<sub>50</sub> value of RS-LP in HepG2 cells was further reduced (42.3 vs. 68.2  $\mu$ g/mL). Unfortunately, there are no RS-LP clinical trials in progress.

### 2.10 Quercetin (QR)

San qi [*Panax notoginseng* (Burk.) F. H. Chen] is a commonly used and powerful hemostatic drug in clinical Chinese medicine. The efficacy of San qi in hemostasis, eliminating blood stasis, detumescence, and relieving pain makes San qi useful in treating hematemesis, hemoptysis, blood dysentery, metrorrhagia, persistent lochia, and other internal bleeding. In addition to oral usage, San qi powder is frequently used in skin wounds. QR, a natural flavonoid widely distributed in nature, is found in many fruits and vegetables, such as apples, cherries, berries, onions, asparagus, and red leaf lettuce. In addition, approximately 100 kinds of medicinal plants, such as San qi, Ce bai ye [*Platycladus orientalis* (L.) Franco], Gao liang jiang (*Alpinia officinarum* Hance), Kuan dong hua (*Tussilago farfara* L.), and Sang ji sheng [*Taxillus chinensis* (DC.) Danser] contain this ingredient [117].

Modern studies have shown that QR has an anti-cancer role by scavenging oxygen-free radicals, inhibiting the expression of heat shock proteins, suppressing the activity of matrix metalloproteinases (MMPs), inhibiting the proliferation of cancer cells, restraining the expression of mutant p53 genes, chemoprevention, and enhancing the role of anticancer drugs [118, 119]. The low water solubility, low bioavailability, and rapid plasma clearance of QR limit its clinical application. To overcome this issue, Riaz et al. [46] encapsulated QR into liposomes (QR-LP). QR-LP exhibited

higher cytotoxicity (63.5  $\mu$ M) against A549 cells than free QR (107.5  $\mu$ M), as revealed by the IC<sub>50</sub> [46]. To further enhance the anti-tumor effect of QR-LP, Riaz et al. [46] also modified transferrin (TF) peptide on the surface of QR-LP (TF-QR-LP). TF peptide specifically targets the transferrin receptor (TFR), which is overexpressed approximately 100-fold in many cancers, such as ovarian, brain, breast, and prostate cancer, and lung adenocarcinoma, due to an increased demand for iron [120]. Hence, TF-QR-LP exhibited higher cytotoxicity (40.5  $\mu$ M) against A549 cells than QR-LP (63.5  $\mu$ M), as revealed by the IC<sub>50</sub> [46]. QR liposome testing has only been completed in laboratory animals, and there is no research data on the use of QR liposome in patients.

### 2.11 Berberine (BER) and Evodiamine (EVO)

Huang lian (*Coptis chinensis* Franch., *Coptis deltoidea* C.Y.Cheng et Hsiao or *Coptis teeta* Wall.) has been used to treat various diseases caused by inflammation for a thousand years. According to TCM theory, Huang lian clears heat, eliminates dampness, and detoxifies dampness and fire. The medicinal value of this plant was first recorded in *Shen Nong's Herba* in the Han Dynasty. Huang lian is involved in > 32,000 Chinese herbal formulas. Huang lian is often used in combination with other TCH medicines. For example, Zuojin pill is a prescription composed of Huang lian and Wu zhu yu, and is mostly used to treat liver-gallbladder damp-heat. Wu zhu yu [*Evodia rutaecarpa* (Juss.) Benth., *Evodia rutaecarpa* (Juss.) Benth. var. *officinalis* (Dode) Huang or *Evodia rutaecarpa* (Juss.) Benth. var. *bodinieri* (Dode) Huang] can dispels cold, relieves pain, stops vomiting, and stops diarrhea, and has been used to treat gastrointestinal diseases, headaches, amenorrhea, and postpartum hemorrhage for a long time [121].

BER and EVO were the typical ingredients of Huang lian and Wu zhu yu, respectively. Modern studies have shown that BER has a wide range of pharmacologic activities, including antibacterial, alleviating hepatic steatosis, delaying myocardial ischemia, improving reperfusion injury, alleviating arrhythmias, delaying diabetes progression, atherosclerosis, and hypertension, as well as anti-inflammatory, anti-oxidation, and anti-tumor effects [122]. BER reduces adhesions between cancer cells and the extracellular matrix, inhibits the proliferation of cancer cells, and blocks the cancer cell cycle [123]. While EVO induces apoptosis, inhibits cancer cell proliferation, changes the cell cycle, inhibits the formation and invasion of human umbilical vein endothelial cells, and inhibits the effects of various carcinogens and activates inflammatory factors on NF- $\kappa$ B activation to have an anti-tumor effect [124]. BER is poorly absorbed after oral administration. After injection, BER quickly enters various organs and tissues. BER is widely distributed, but the blood drug concentration is maintained for a short period and BER remains in the tissues for a short time, leaving only a trace after 24 h. Therefore, BER has not been used in the treatment of clinical cancer [125]. At

the same time, the water-insoluble nature of EVO also limits the clinical application of EVO [124].

Inspired by the Zuojin pill, Lin et al. [47] studied the therapeutic effect of the combination of BER-LP and EVO-LP on B16 melanoma cells (BER-LP + EVO-LP). It can be seen from the intensity and distribution of fluorescence that the transmission of BER-LP + EVO-LP in the skin basal layer is clearly better than BER and EVO solutions. In addition, BER-LP and EVO-LP exhibit stronger cytotoxicity (cell viability: 28.4% and 45.0%, respectively) than BER and EVO solutions (cell viability: 52.5% and 87.6%, respectively). Thus, LP improves the penetration of BBR and EVO through the stratum corneum, and thus improves the anti-tumor effect.

### 2.12 Artemisinin (ART)

Records related to Qing hao (*Artemisia annua* L.) were first recorded in 52 *Disease Prescriptions for the Treatment of Hemorrhoids*. Ge Hong mentioned in the *Emergency Prescription Manual* that Qing hao is used to treat fever and shivering related to malaria. Currently, Qing hao has been officially recognized as a medicinal plant and listed in the Chinese Pharmacopoeia. Qing hao eliminates heat, intercepts malaria, and is recommended for the treatment of intermittent fevers, tuberculosis, wound scabies, dysentery, bone transpiration, and fevers [126]. ART is a famous natural drug extracted from Qing hao. ART and its derivatives, such as dihydroartemisinin (DHA), have anti-tumor effects by releasing oxygen-free radicals to destroy the membrane structure of tumor cells, alkylate biomacromolecules, and interfere with the formation of proteins. DHA also inhibits cancer cell proliferation by regulating glycolysis [127].

Although ART and DHA have broad application prospects in anti-tumor effects, the lack of tumor targeting ability is limiting. To overcome this shortcoming, Shen et al. [48] prepared liposomes containing DHA and modified by alkyl glycosides (AG) to target liver tumor cells (HepG2 cell line). AG targets a glucose transporter, which is observed in many malignant cells. After intraperitoneal injection of AG-DHA-LP, the fluorescence signal is significantly enriched to tumor tissues in the abdomen of mice, further leading to an increase in the tumor growth inhibition rate, which was reported to be 15.8% higher than DHA-LP. In addition, ART-LP surface modified by cell penetrating peptides (HE-R6 [49] and TF [50]) also display higher anti-tumor effects against murine breast cancer 4T1 cells and murine liver cancer HepG2 cells than none-targeted controls. At present, there are no ART liposomes approved for clinical cancer treatment.

### 2.13 Honokiol (HNK)

Hou po (*Magnolia officinalis* Rehd. et Wils. or *Magnolia officinalis* Rehd. et Wils. var. *biloba* Rehd. et Wils.) eliminates dampness and phlegm, promotes the circulation of qi, and is mainly used to treat spleen and stomach discomfort, such as abdominal distension, abdominal

pain, vomiting, and diarrhea, as well as asthma and depression. Hou po has a major role in the treatment of ancient classic TCM prescriptions, such as Xiaochengqi decoction, and Huoxiang Zhengqi dropping pill; Hou po also has an effect when administered alone [128].

HNK is a lignan compound isolated from the dry, root, and branch bark of Hou po and has anti-angiogenesis and anti-inflammatory effects, limits oxidation, eliminates cancer, and has no apparent toxicity. HNK induces apoptosis and cell cycle arrest by triggering mitochondrial dysfunction and endoplasmic reticulum stress, and suppresses tumors by inhibiting epidermal growth factor receptor, NF- $\kappa$ B, and the Ras-extracellular signal-regulated kinase and PI3K/AKT/mTOR pathways [129]. The disadvantages of poor water solubility and low bioavailability of HNK limit its clinical application.

Jiye launched the clinical research of HNK-loaded liposome (HNK-LP) lyophilized powder for injection in the treatment of advanced non-small cell lung cancer in 2017. Although promising, there is no commercialized HNK-LP for clinical use.

To further boost the targetability of HNK-LP, Wang et al. [51] modified the surface of HNK-LP with hyaluronic acid (HA) for the purpose of targeting CD44 receptor overexpressed cancer cells. Compared with the non-targeting HNK-Lip group, HA-HNK-Lip exhibited 1.9-fold higher cell internalization in the 4T1 tumor 3D sphere model, which further resulted in an improved inhibition rate of tumor growth (13.4%) [51]. Therefore, HA modification is a feasible strategy to enhance the targeting and cytotoxicity of HNK-LP.

### 2.14 Gambogic acid (GA)

*Bencao Biandu* indicated that Teng huang (*Garcinia hamburgy* Hook. f.) is fried and refined with rattan juice. Teng huang kills insects and attacks poisons with poisons, all of which are external treatments. Therefore, Teng huang is often used in medicines for carbuncles and sores, which has the effect of qu-fu-sheng-xin and astringent wounds. The first records and interpretations of qu-fu-sheng-xin [130, 131] are in the *Compendium of Materia Medica*; it is an important mechanism by which TCH medicines directly kill tumor tissues. If a TCM has the function of qu-fu-sheng-xin, the TCM is corrosive and kills most living cells, including cancer cells, before helping the wound recover.

GA naturally exists in the dried resin of Teng huang. Modern research has shown that GA inhibits nuclear factors via the NF- $\kappa$ B signal pathway and controls the growth of tumor vascular endothelial cells to inhibit the proliferation of cancer cells [132]. Teng huang has good multi-target antitumor activity in a variety of tumors, but its low water solubility, instability to light and heat, low oral bioavailability, and rapid plasma clearance hinder its clinical application [133]. The pharmacokinetic parameters of GA can be significantly increased by packaging GA in a lipophilic bilayer into LP (GA-LP) [52]. Compared with GA solution, the AUC of GA after

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administration of GA-LP increased by 33.3 times, further leading to a significant reduction in tumor volume of BALB/c mice carrying 4T1 murine cancer. To further enhance the anti-tumor effect of GA, Na et al. [52] co-loaded GA and retinoic acid (RA) in LP (RA/GA-LP). Compared with GA-LP, the  $IC_{50}$  value of RA/GA-LP in 4T1 cells decreased by 52.5% [52]; however, the lack of targeting is still a problem that needs to be resolved.

Dang et al. [53] linked the nuclear targeting peptide, CB5005N (NF- $\kappa$ B nuclear localization sequence), to the liposome surface (NTP-GA-LP) to improve the anti-tumor effect of GA-LP on 4T1 and MDA-MB-231 breast cancer. The uptake (fluorescence intensity) of NTP-GA-LP in cells was significantly higher than GA-LP, and the cell death rate was significantly higher than GA-LP [53]. In addition, after 13 days of treatment, the tumor size in BALB/c female mice in the NTP-GA-LP group was significantly reduced compared with the GA-LP group; the percentage of tumor tissue growth inhibition also increased by 22% [53].

### 2.15 Ginsenoside Rh2 (GRH2)

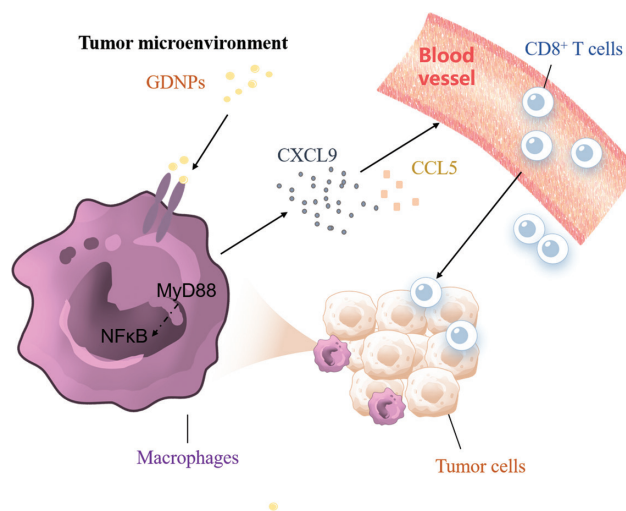
Ginseng (*Panax ginseng* C.A.Mey.) plays an important role in TCH medicine, and can be traced back to approximately 2000 years ago, as recorded in *Shen Nong's Herbal*, the oldest comprehensive herbal classic text. There are two main processing methods for primitive ginseng. Ginseng can be dried into white ginseng or steamed into red ginseng. Based on TCM theory, ginseng is generally a rich and energetic substance influenced by qi. Ginseng improves any defect and prevents any loss of proper influence (positive energy) [134].

The bioactive compounds in ginseng include approximately 30 triterpene glycosides, called ginsenosides (Rb1, Rb2, Rg1, Rg2, Rg3, Rc, Rd, Re, Rh1, Rh2, etc.) [135, 136]. Among the glycosides, Rg3, Rd, and Rh2 have anti-tumor activity. GRH2 has been shown to possess anticancer properties against various cancerous cells, including colorectal, breast, skin, ovarian, prostate, and liver cancer, by killing tumor cells in the proliferative stage, inducing cancer cells to differentiate into normal cells, significantly improving the activity of IL-2, improving the function of T cells and macrophages, and enhancing the killing activity of natural killer (NK) cells [137, 138]. The poor bioavailability, low stability in gastrointestinal systems, and fast plasma elimination limit further clinical applications of GRH2 for cancer treatment. At present, GRH2-LP has not been approved for clinical use. For this reason, Zare-Zardini et al. [54] loaded GRH2 into the lipophilic bilayer of LP, and the inclusion rate reached 93.5%. The anticancer study involving the PC3 prostate cancer cell line showed that the administration of GRH2 in the form of LP enhanced the cytotoxic activity of PC3 prostate cancer cell line cells compared with free GRH2 solution ( $IC_{50}$  values 31.2 vs. 62.7  $\mu$ g/mL) [54]. The content of GRH2 in ginseng root is extremely low [139]. Therefore, higher utilization of GRH2 warrants further study.

### 3. CONCLUSION

The multi-component and -target characteristics of TCH medicines have shown splendid clinical efficacy in the treatment of various chronic diseases, such as pain, liver fibrosis, myocardial ischemia, coronary heart disease, and gastric ulcer, but the control of malignant tumors has been insufficient. Thoroughly investigated and active components of TCH medicines with high hydrophilicity or hydrophobicity are prone to fast clearance, thus leading to low bioavailability. In addition, the instability, poor permeability, and inevitable off-targeting toxicity of TCH components also accounts for the novel drug delivery platform. Currently, liposomes have been used for TCH component delivery in the treatment of cancer. Surface modification of PEG and coating with platelet membranes has successfully improved the pharmacokinetics of liposome-based nano-medicine. Liposomes decorated with small molecules, peptides, antibodies, and cell membranes or incorporated with magnetic nanoparticles often have an improved tumor targetability. Moreover, great efforts have also been made to investigate the synergistic effect of different drugs and therapeutics combination to overcome the complexity of the tumor microenvironment. Although several TCH component-loaded liposomes have entered the clinical or preclinical phase, the stability, drug loading efficiency, off-targeting toxicity, as well as long-term carrier safety still need to be addressed.

TCM prescriptions are clinically used with TCH medicine combinations, which may serve as the impetus for improving the liposome loading system to maximize the efficacy and minimize the side effects. In recent years, nanoparticles prepared from fresh TCH sources, such as ginseng (Figure 3) [140, 141] and ginger [142], have



**Figure 3 | Illustration of 'Ginseng-derived nanoparticles (GDNPs) and its underlying mechanism of combating the cancer'.**



been certified with similar structures as liposomes, but with higher biocompatibility and mass production ability along with the internal pharmacologic activities. In the future, TCH component-loaded liposomes would be better quantified to analyze the stability, drug-loading efficiency, off-targeting toxicity, as well as long-term carrier safety in patients which have not been addressed.

As a result, it is reasonable to combine the clinical experience with current cutting-edge technologies to facilitate the clinical translation of more TCH medicine-based liposome drugs.

#### ACKNOWLEDGEMENTS

This work was supported by Distinguished Professor Grant in Nanjing University of Chinese Medicine (No. 013038019015), Grants from the National Natural Science Foundation of China (No. 82204696), and Support Grant in Nanjing University of Chinese Medicine (No. XPT82204696). The illustrations were created by Xingyu Li from Soochow University.

#### CONFLICTS OF INTEREST

The authors declare no competing interests.

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