Chinese Journal of Natural Medicines

Traditional Chinese medicine–based drug delivery systems for anti–tumor therapies

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Citation: Ling YANG, Yani WANG, Xietao YE, Qiaoming LIU, Ding QU, Yan CHEN, Traditional Chinese medicine–based drug delivery systems for anti–tumor therapies, Chinese Journal of Natural Medicines, 2024, 22(12), 1177–1192. doi: 10.1016/S1875–5364(24)60746–6.

View online: https://doi.org/10.1016/S1875–5364(24)60746–6

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Chinese Journal of Natural Medicines

"Natural-derived drug carriers (NDDCs) for precision therapy"Special Issue

•Review•

Traditional Chinese medicine-based drug delivery systems for anti-tumor therapies

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[ABSTRACT] The treatment of tumors continues to be significantly challenging. The presence of multiple modalities, including surgery, radiation, chemotherapy and immunotherapy, the therapeutic outcomes remain limited and are often associated with adverse effects and inconsistent efficacy across cancer types. Recent studies have highlighted the potential of active components from traditional Chinese medicine (TCM) for their anti-cancer properties, which are attributable to multi-targeted mechanisms and broad pharmacological actions. Despite this potential, TCM-derived compounds are commonly limited by poor water solubility, low bioavailability, and suboptimal targeting. Currently, it is believed that advances in nanotechnology could address these limitations. Nanoparticles (NPs), which possess properties such as enhanced bioavailability, controlled release and precise targeting, have been used to improve the therapeutic efficacy of TCM components in cancer therapy. This review discusses the use of NPs for the delivery of active TCM compounds *via* organic-inorganic nanocarriers, highlighting innovative strategies that enhance the effectiveness of TCM-based anti-tumor components to provide insights into improving clinical outcomes while advancing the modernization and global application of TCM in oncology.

[KEY WORDS] Traditional Chinese medicine; Nano drug delivery systems; Organic-inorganic nanocarriers

[CLC Number] R944 **[Document code]** A **[Article ID]** 2095-6975(2024)12-1177-16

Introduction

Tumors pose a substantial threat to global health, and the latest data from the International Agency for Research on Cancer (IARC) of the World Health Organization indicates a continued rise in cancer incidence worldwide [1-3]. Current clinical approaches to cancer treatment include surgery, radiotherapy, chemotherapy, and immunotherapy [4]. While these treatments can improve therapeutic outcomes to some extent, their effectiveness is often hindered by challenges such as high toxicity and side effects, drug resistance, limited efficacy, and immune regulation difficulties. Given these limitations, there is an urgent need for new strategies to enhance the effectiveness of cancer treatment.

In recent years, traditional Chinese medicine (TCM) has become an integral part of modern medicine, especially in anti-tumor therapy [5]. Advances in isolation and purification techniques and understanding of pharmacological mechanisms have enabled active TCM components to become promising medicines in cancer treatment [6]. Compared to synthetic chemotherapeutic drugs, natural active ingredients in TCM offer several distinctive advantages, including multi-target activity, reduced toxic side effects, potential to circumvent drug resistance, and collectively improving therapeutic outcomes [7]. However, despite these benefits, the clinical application of TCM-derived components still faces multiple challenges.

Foremost, some TCM compounds with low solubility and permeability have low bioavailability [8]. Additionally,

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[Received on] 10-Aug.-2024

[Research funding] This work was supported by the National Natural Science Foundation of China (Nos. 82374045, 82173985), the Jiangsu Province Leading Talent Project (No. CZ2023SLJ0302), the National Natural Science Foundation of China (No. 82173980), Jiangsu Province Key Research and Development Program for Social Development Project (No. BE2023788), and the Jiangsu Clinical Innovation Center of Digestive Cancer of Traditional Chinese Medicine (No. 2021.6).

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These authors have no conflict of interest to declare.

the efficacy of single TCM compound is often limited, necessitating combination therapies to achieve optimal effects [9]. Furthermore, TCM encounters challenges in precisely targeting tumor sites and delivering sustained therapeutic effects [10-11]. As a result, how to efficiently transport active components of TCM to tumor tissues while also addressing the difficulties of multi-component co-loading and high drug loading have emerged as critical techniques for improving traditional Chinese medicine's anti-tumor efficacy [12a-b].

Nanocarriers, including polymers, dendrimers, liposomes, microemulsions and various metal and inorganic nanoparticles, represent a promising drug delivery platform in treatment of cancer [13]. Compared to conventional drug preparations, nanoparticles can improve the pharmacokinetics and biodistribution, increasing drug concentration at the target site and thereby minimizing systemic toxicity. Recently, both organic and inorganic nanocarriers have attracted considerable attention, each type displaying distinct properties beneficial for TCM formulations [14]. Organic carriers, such as liposomes, polymer nanoparticles, and biomacromolecules, are characterized by good biocompatibility and biodegradability, which helps evade immune recognition and clearance [15]. Additionally, their structure and function can be easily modified, allowing for targeted delivery and controlled release through surface modifications [16]. In contrast, inorganic carriers, including metal-organic frameworks (MOFs), mesoporous silica nanoparticles (MSNs), and carbon nanotubes, offer unique physical and chemical properties, such as high surface area, porous structure, and exceptional thermal stability [14]. These attributes make inorganic carriers highly effective for drug loading and controlled release. Nonetheless, inorganic carriers often face limitations related to biocompatibility and biodegradability.

This review provides an overview of recent research progress and applications of both organic and inorganic carriers in TCM delivery systems (Figure 1). By comparing the advantages and limitations of each type of carrier, we discuss their suitability and potential future directions for TCM formulations and innovative strategies for the efficient delivery of TCM-derived anti-tumor drugs to promote the modernization and global integration of TCM in oncology.

Organic Nano-sized Systems for the Delivery of TCM

Organic drug delivery systems (ODDS) , such as liposomes , microemulsions, micelles, solid lipid nanoparticles, utilize organic materials as carriers to deliver TCM compounds to tumor sites. Significant progress has been made in ODDS in recent years by entering cells *via* endocytosis and other cellular uptake processes, ODDS can improve drug penetration across membrane barriers, facilitate transdermal absorption, and enhance cellular efficacy [17]. ODDS also possess strong targeting capabilities, allowing for selective recognition of cancer cells, which highlights their considerable potential in tumor therapy.

Despite the advantages of organic drug delivery methods, some limitations remain in practical application. The stability and safety of drug carriers must be thoroughly assessed, as some organic materials may provoke immune or toxic reactions *in vivo*, potentially compromising patient health [18]. Secondly, the low drug-loading capacity of organic carriers limits the broader application of TCM. Moreover, the complex and costly preparation methods of drug carriers restrict their scalability for large-scale production [19]. Thus, targeting precision also requires further refinement to ensure that drugs reach the intended site and exert therapeutic effects.

Liposomes

Liposomes are nanoscale vesicles composed of lipid molecules, primarily phospholipids and cholesterol, which form a structure that closely resembles the biological cell membrane. This structure possesses an aqueous core surrounded by lipid bilayers, which allows liposomes to encapsulate both water-soluble and lipophilic components, accommodating the complex composition of TCM. Conventional drug delivery methods are often limited due to low bioavailability and high toxicity, but liposomes can tackle these issues through their unique structural properties: (a) Biocompatibility: Liposomes have a composition similar to cell membranes, providing high biocompatibility and enabling cellular recognition and uptake in *vivo*. (b) Biodegradability: Liposomes' primary components, phospholipids and cholesterol, degrade naturally in organisms without prolonged accumulation. (c) Targeting: Surface modifications or specific designs enable liposomes to target particular cells or tissues, thereby enhancing therapeutic efficacy. (d) Sustained release: Liposomes can control drug release rates, supporting prolonged and controlled drug deliv-

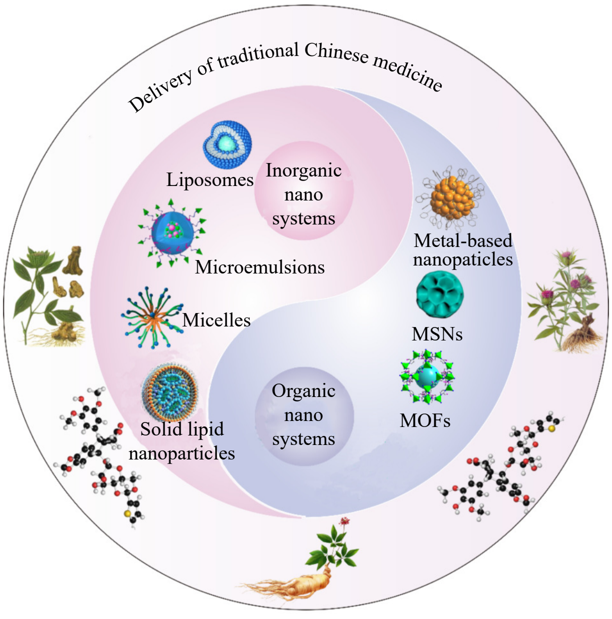

Fig. 1 Schematic overview of significant research on nano-systems in traditional Chinese medicine, including organic and inorganic nano-systems.

ery, which extends the duration of therapeutic effects. (e) Synergistic potential: Liposomes can maintain an optimal balance of synergistic drugs, complementing sustained-release properties to enhance overall therapeutic outcomes.

Here, we summarize the use of liposome carriers for different types of TCM, including poorly soluble, water-soluble, and multi-component co-loaded formulations, as follows.

Hydrophobic traditional medicine components-based liposomes

Baicalin (BA), the main effective constituent isolated from the roots of the herb scutellaria baicalensis, has low solubility due to the presence of glycosyl groups in its molecular structure. Its oral bioavailability is only 2.2%, limiting its clinical application [20]. Liposomes have been shown to enhance the solubility and bioavailability of BA. For example, Yu Long [21] developed BA-loaded liposomes (BA-LPs) using a reverse evaporation technique to increase drug lipophilicity and concentration in brain tissue, achieving an encapsulation efficiency of 42.0% ± 1% .

Curcumin, a diketone compound extracted from the turmeric plant, exhibits various biological and pharmacological properties, such as anti-inflammatory, anticancer, and antiviral properties, and has broad clinical application prospects due to its low toxicity. However, its extremely low water solubility and rapid intestinal and liver metabolism result in poor systemic bioavailability, limiting its oral use. Therefore, Chen *et al*. [22] selected soybean phospholipids (SPC), egg yolk phospholipids (EPC), and hydrogenated soybean phospholipids (HSPC) to construct different types of phospholipids composed of curcumin loaded liposomes: C-SSPC-L (curcumin loaded SPC liposomes), C-EPC-L (curcumin loaded EPC liposomes), and C-HSPC-L (curcumin loaded HSPC liposomes). Subsequent *in vitro* skin penetration studies have shown that C-SPC-L significantly promotes drug penetration and deposition in all loaded liposomes, and exhibits the greatest ability to inhibit the growth of B16BL6 melanoma cells. Further pharmaceutical studies have demonstrated that the tumor inhibition rate of the C-SPC-L group compared to the blank control group was 43.6% ± 3.6%, which is 1.74 times higher than that of the curcumin solution group.

Elemene, a low-toxicity anticancer substance isolated from curcuma wenyujin, contains 85% β-elemene. However, elemene's hydrophobicity and low bioavailability limit its clinical application. Xie *et al.* [23] developed a long-circulation liposome of β-elemene with polyethylene glycol. The liposome effectively prolonged the circulation time of the drug *in vivo*, significantly improved the bioavailability of β-elemene, and enhanced its anticancer effect in a bladder cancer model. In addition, compared with elemene injection with a tumor inhibition rate of 33.01%, β-elemene has a tumor inhibition rate as high as 45.67%.

Hydrophilic traditional medicine components-based liposomes

Oxymatrine (OM) is an water-soluble component of the Chinese medicinal herbal sophora flavescens, which can balance the synthesis and degradation of extracellular matrix and control the deposition of collagen in the liver. However, the physicochemical properties and non selective biological distribution of OM limit its application in reversing epithelial mesenchymal transition, so OM requires suitable drug delivery [24]. Guo *et al*. [25] designed a new cysteine terminal FH peptide (CFH) (CFHKHKSPALSPVGGG) and decorated it on the surface of OM loaded liposomes (CFH/OM-L). CFH/OM-L has high affinity for tenascin-C overexpressed on the surface of CAF, reversing the EMT process, reducing collagen deposition, decreasing CAF abundance, creating a favorable environment for deep penetration of nanoparticles, and activating TME to enhance anti-liver cancer efficacy.

Liposomes can also encapsulate polysaccharides in their aqueous cores or membranes, which enhance bioavailability, therapeutic efficacy, and targeted delivery of TCM components. For instance, APS-liposomes have been shown to increase phagocytic activity in macrophages and improve dendritic cell (DC) ability to stimulate T cell proliferation, thereby enhancing antigen development compared to non-encapsulated APSs [26].

Multi-traditional medicine components-based liposomes

Single TCM component often has limited efficacy in anticancer treatment, while its combination with chemotherapy drugs can effectively reduce the toxicity of these drugs and enhance overall anticancer efficacy. This synergistic effect not only improves treatment outcomes but may also enhance patient tolerance, making the treatment regimen safer and more effective. Through this combination strategy, the unique active components of TCM can play an auxiliary role, providing patients with more comprehensive treatment options [27]. Paclitaxel (PTX), a taxane-class chemotherapeutic, induces immunogenic cell death (ICD), which activates an anti-tumor immune response [28]. Cryptotanshinone (CTS), a bioactive compound from *Salvia miltiorrhiza*, inhibits the signal transducer and activator of transcription 3 (STAT3) pathway by blocking phosphorylation at Tyr705 [29]. These findings suggest that the co-administration of PTX and CTS can modulate the tumor microenvironment favorably. Luo *et al.* [30] developed dual-targeting liposomes co-loaded with PTX and CTS, which demonstrated superior anti-tumor efficacy in mouse models of triple-negative breast cancer (TNBC) and effectively suppressed lung metastasis.

Chlorogenic acid (CA), a phenolic compound derived from in plants such as honeysuckle flower and eucommia ulmoides, functions as an anti-tumor immune modulator by promoting the transition of TAMs from the pro-tumorigenic M2 phenotype to the anti-tumorigenic M1 phenotype [31]. This effect is mediated through the activation of STAT1 and inhibition of STAT6, effectively restraining glioma cell proliferation [32]. DOX, a widely used anthracycline Chemical drugs, is limited in clinical application due to adverse effects, including bone marrow suppression and cardiotoxicity. To enhance efficacy and reduce toxicity, Zhu *et al*. [33]developed sialic acid-octadecylamine conjugate-modified liposomes (CA-DOX-SAL) co-loaded with CA and DOX. This modification leverages the Siglec-1 receptor on TAMs to enhance targeted drug delivery. Pharmacodynamic studies demonstrated that CA-DOX-SAL effectively inhibited B16F10 melanoma growth by facilitating the transition of M2-type TAMs to M1-type TAMs and by directly killing tumor cells. Although this section highlights several representative studies, numerous other related investigations have also yielded valuable insights. A comprehensive summary of these studies is presented in Table 1.

Microemulsions

Microemulsions, also known as nanoemulsions, are transparent or translucent systems with low viscosity and thermodynamic stability, composed of surfactants, cosurfactants, an oil phase, and water in precise proportions [29]. According to Bancroft's law, hydrophilic surfactants favor the formation of oil-in-water (o/w) emulsions, while hydrophobic surfactants promote w/o emulsions. These structural characteristics provide microemulsions with unique advantages, such as enhanced drug solubility, long-term stability, and improved biocompatibility [30]. Unlike liposomes, which contain easily oxidized phospholipid components, microemulsions form spontaneously based solely on the drug excipient formula, without requiring heat, simplifying the preparation process and enhancing the potential for industrialization. Additionally, the oil phase in microemulsions can incorporate TCM components, reflecting an effective combination of drugs and excipients [31]. This characteristic gives microemulsions broad application potential in drug delivery [31].

Microemulsions based on TCM ingredients

Ginsenoside Rg3 is a triterpenoid glycoside extracted from ginseng, known for its significant anticancer activity and Rhein is an anthraquinone derived extract from rhubarb, commonly used in the treatment of malignant tumors. However, their limited solubility and bioavailability restrict their injectable applications [50]. To address this limitation, Zhang *et al.* [51] developed a nanoemulsion containing g-Rg3 and Rhein and showed that they could significantly suppress tumor growth in tumor-bearing mice. Notably, when combined with an α PD-L1 antibody, the g-Rg3/Rhein nanoemulsion substantially reduced tumor volume and demonstrated a superior therapeutic effect compared to other groups. This innovative delivery system offers promising new avenues for the clinical application of g-Rg3 and Rhein in oncology.

Coix seed polysaccharides are the main active ingredients in Coix seed extracts. However, coix seed ester has the disadvantage of oral absorption. Liu *et al.* [52] synthesized butyryl galactose ester (Butt Gal) and prepared butyryl galactose ester modified Coix seed ester component micro lotion (Butt Gal CMEs). As a targeted nano carrier for the treatment of liver cancer, the prepared Butt Gal CMEs showed the characteristics of small particle size, narrow PDI and neutral potential. In the study of cell apoptosis, treatment with But Gal CMEs (50 μg·mL^{-1}) resulted in a 1.34-fold increase in total apoptotic cells in HepG2 compared to CMEs.

Traditional medicine components-constructed microemulsions

Although microemulsion formulations offer significant advantages in enhancing drug absorption, their application in

Table 1 Applications of traditional Chinese medicine component liposomal systems in tumor treatment

Carrier	Traditional medicine	Disease	References
SpHL-UA Lips	Ursolic acid	Prostate (LNCaP) cancer	[34]
CS/LyP-1-PC Lips	Paclitaxel and cryptotanshinone	Triple-negative breast cancer	[35]
A15-CUR LiPs	Curcumin	Prostate cancer	[36]
Doc/Res-LP	Docetaxel and resveratrol	Prostate cancer	[37]
HA-DOPE@Lips/HNK)	Honokiol	Osteosarcoma	[38]
Rg3-Lip/DTX	Ginsenoside and docetaxel	Triple-negative breast cancer	[39]
MP-TPL-LP	Triptolide	Liver cancer	[40]
ISL-LP	Isoliquiritigenin	Colorectal cancer	[41]
LUT-LP	Luteolin	Colorectal cancer	[42]
SHK-LP	Shikonin	Colorectal cancer	[43]
SPIO/EMO-LP	Emodin	Breast cancer	[44]
PR-lipo@GA	Glycyrrhizic acid/platycodin /ginsenoside	Lung cancer	[45]
Cel-LPs	Celastrol	Colorectal cancer	[46]
RI-LP-M	Muscone/RI7217	Blood-brain barrier	[47]
Cel/Rg$_3$-LPs	Ginsenoside Rg$_3$/celastrol	Triple negative breast cancer	[48]
TPL-LA-lip	Triptolide	Pancreatic cancer	[49]

TCM still faces common challenges, similar to other nanotechnology-based formulations. These challenges include high excipient requirements, low drug loading capacity, and limitations in achieving multi-component drug loading [53]. Some TCM components not only possess specific therapeutic activities but can also function as drug carriers due to their unique physicochemical properties, supporting the transport of various therapeutic agents such as anti-cancer drugs, DNA/RNA, and antibodies. This dual role can reduce the quantity of excipients needed, enabling multi-component drug loading while enhancing efficacy [54].

Coix seed oil, extracted from Coix seeds, contains glycerides, fatty acids, and other nutrients that support immune function. It exhibits anti-tumor effects and pharmacological activities, such as immune enhancement, with relatively low toxicity and minimal side effects [55]. However, Coix seed oil faces challenges such as poor water solubility and limited oral absorption. Formulating Coix seed oil into microemulsions as the oil phase can reduce the need for excipients, improve bioavailability, enhance therapeutic effects, and facilitate the effective combination of drugs and excipients.

Chen *et al*. [56] prepared a co-loaded microemulsion of Coix lacryma oil and Triptolide coloaded microemulsions with a transferrin modification (Tf-CT-MEs) to improve the treatment of cervical cancer. Tf-CT-MEs exhibited good stability in serum and enhanced tumor targeting, facilitating deeper drug penetration and significantly slowing tumor growth. Moreover , icaritin (IC) is an active ingredient of prenylflavonoids obtained from epimedium, known for its isoprenylflavonoid compounds. However, its poor solubility and oral bioavailability limit its anticancer efficacy. They have developed a microemulsion formulation (IC-MEs) that incorporates icariin using coix seed oil as a carrier. The preparation technique for IC-MEs was optimized through a Box-Behnken design to facilitate industrial-scale production. The IC-MEs significantly improved the bioavailability of icariin, enhanced pharmacokinetics, and enhanced the efficacy of anti liver cancer treatment [57]. Qu *et al*. developed a multi-component microemulsion ECGMEs containing etoposide (a chemotherapeutic agent), coix seed oil (serving as both the oil phase and an anti-cancer agent), G-Rh2 (a P-glycoprotein inhibitor, simulated surfactant, and anti-cancer agent), RH40 (surfactant), and PEG400 (cosurfactant) for the oral treatment of multidrug-resistant (MDR) tumors related Breast cancer [58]. Moreover, Huang *et al*. developed a microemulsion incorporating Triptolide and coix seed oil, utilizing coix seed oil and coix seed polysaccharides as functional excipients. This formulation minimized the reliance on synthetic surfactants and cosurfactants, thereby enhancing antitumor efficacy through the synergistic effects of the combined components. Additionally, the inclusion of coix seed polysaccharides reduced liver toxicity associated with Triptolide-based therapies [59].Other studies on the applications of microemulsions in tumors are summarized in Table 2.

Micelles

The formation of micelles is primarily driven by the hydrophobic interactions of the hydrophobic segments of the amphiphilic copolymers, resulting in a structure with a hydrophobic core surrounded by a hydrophilic shell. The hydrophobic cores of micelles facilitates the solubilization and encapsulation of hydrophobic small molecules, while hydrophilic molecules, particularly relatively large proteins, are

Table 2 Applications of traditional Chinese medicine component microemulsions systems in tumor treatment

Preparations	Traditional medicine	Disease	References
GLP-M	Ganoderma lucidum polysaccharide	Colorectal cancer	[60]
Gal-C-MEs	Coix seed oil and coix seed polysaccharide	Liver cancer	[61]
ECG-MEs	Ginsenoside Rh2	Liver cancer	[62]
MG-SMDDS	Magnolol	Liver cancer	[63]
NG-C	Curcumin	Liver cancer	[64]
Cop-Gin-SMEDDS	Coptidis Rhizoma and Zingiberis Rhizoma	Ulcerative colitis	[65]
HN-SMEDDS	Rhubarb and *Astragalus membranaceus*	Chronic kidney disease	[66]
GA-IL-ME	Glycyrrhizic acid	Skin disease	[67]
Evo-PC-SMEDDS	Evodiamin	Gastric ulcer	[68]
Cur-MEs	Curcumin	Colorectal cancer	[69]
CSE	Coicis Semen lipid	Pancreatic cancer	[70]
Sch B-T-ME	Schisandrin B	Liver cancer	[71]
M.EO-ME	*Mesona chinensis* polysaccharide	Malignant melanoma	[72]
Astragaloside IV-(β-elemene) MEs	Astragaloside Iv and β-elemene	Malignant melanoma	[73]
Rg3-PC-SME	Ginsenoside Rg3	Colorectal cancer	[74]

usually loaded into the micelles through physical interactions or covalent coupling [75-77].

Micelles enhance the solubility of poorly soluble drugs, improve bioavailability, and enable targeted delivery through surface modification, thereby increasing therapeutic efficacy. These features highlight the potential of micelles in drug delivery. TCM active ingredients can be loaded into micelles through several mechanisms [78-80]: (a) Hydrophobic interactions: Many TCM components are hydrophobic, enabling encapsulation within the micellar core *via* hydrophobic interactions. (b) Electrostatic interactions: Somes TCM compounds can adsorb onto micelle surfaces *via* electrostatic interactions. (c) Hydrogen bonding: Stable hydrogen bonds may form between TCM molecules and micelles, promoting effective encapsulation. (d) Hydrophobic/Hydrophilic equilibrium: The balance between hydrophobic and hydrophilic parts of TCM compounds and the micelle's hydrophobic core and hydrophilic shell [81].

Micelles based on TCM ingredients

Based on the unique properties of micelles, such as enhancing the solubility, stability, and bioavailability of hydrophobic TCM compounds, TCM micelles show great potential in anti-tumor therapy [82-86]. Xia *et al*. employed SolutolVR HS15 and TPGS to prepare self-assembled micelles loaded with ginsenoside Rh2 using a thin-film dispersion method to improve the solubility of ginsenoside Rh2 and thus enhance its anti-tumor effects. *In vitro* and *in vivo* studies demonstrated that Rh2-micelles increased drug uptake by tumor cells, efficiently transported the drug to the tumor site, prolonged retention time, and significantly improved the anti-tumor efficacy of Rh2 [9]. Similarly, ursolic acid (UA), a TCM compound effective in cancer therapy, faces clinical application challenges due to its hydrophobic nature [87]. Zhou *et al*. addressed this limitation by loading UA into polymeric micelles, thereby enhancing UA's therapeutic effect in hepatocellular carcinoma [88]. Additionally, Rui *et al*. [89] synthesized a polyethylene glycol-poly(lactic-co-glycolic acid) (PEG-PLGA) copolymer modified with ASN-Gly-Arg (NGR) peptide and used a solvent evaporation method to create curcumin-loaded NGR-PEG-PLGA micelles (Cur-NGR PM). The Cur-NGR PM had a particle size of 139.70 ± 2.51 nm and a drug loading efficiency of 14.37% ± 0.06%. Animal studies further confirmed that Cur-NGR PM had a substantial inhibitory effect on liver cancer growth while demonstrating favorable biological safety.

Assembly of TCM in micelles

The combination of TCM micelles with conventional clinical drugs for tumor treatment is gaining substantial interest, as numerous studies have shown that herbal micelles enhance anti-tumor efficacy through synergistic mechanisms [90-94]. For instance, Liu *et al*. developed curcumin-polyethylene glycol (Cur-PEG) micelles that can remodel the tumor microenvironment and amplify vaccine efficacy. The study demonstrated a synergistic anti-tumor effect when Cur-PEG was combined with vaccine therapy, showing significant improvement over monotherapy alone ($P < 0.001$) by causing notable downregulation of immunosuppressive factors, including reductions in myeloid-derived suppressor cells, regulatory T-cells (Tregs), and levels of IL-6 and chemokine ligand 2. Additionally, there was an increase in pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and CD8$^+$ T-cells [95]. The use of traditional chemotherapeutic agents has been associated with significant limitations, such as multidrug resistance (MDR) and severe adverse effects, and co-delivery systems using herbal compounds as synergistic agents have emerged as effective strategies to overcome these limitations. Ma *et al*. co-encapsulated DOX and CUR into HA-vitamin E succinate (HA-VES) copolymer micelles ((DOX + Cur)-PMs). Their study showed that (DOX + Cur)-PMs displayed the highest cytotoxicity and apoptosis-inducing activity against DOX-resistant MCF-7/Adr breast cancer cells. The concurrent delivery of DOX and CUR enhanced the therapeutic efficacy of DOX in resistant tumor cells [96]. Similarly, Guo *et al*. developed polymeric micelles for the co-delivery of resveratrol and DOX, successfully improving treatment outcomes for drug-resistant breast tumors [97].

Solid lipid nanoparticles (SLNs)

SLNs are solid colloidal drug delivery systems created by loading drugs into solid natural or synthetic lipid matrices. Derived from o/w emulsions, SLNs replace the liquid lipid component with a solid lipid matrix, which remains stable at body temperature and is stabilized with surfactants [98]. Due to the favorable properties and excellent biocompatibility of lipid materials, SLNs are suitable for delivering a variety of molecules, including small molecules, peptides, and biologics [99]. The increased use of SLNs is largely attributed to their numerous advantages: (a) Biodegradability and biocompatibility: The lipid matrix in SLNs is typically composed of biodegradable and biocompatible lipids, such as stearic acid and triglycerides. These materials reduce immune responses and toxicity, making SLNs suitable for drug delivery. (b) Drug stability protection: Encapsulation within a solid lipid matrix protects drugs from environmental degradation (*e.g.*, light, heat, and enzymes) during storage and delivery, thus preserving drug activity and stability. (c) Extended half-life and shelf life: SLNs' sustained-release properties allow for prolonged drug circulation time in the body, extending the half-life and shelf life of the formulation. (d) Controlled release: By adjusting the type and ratio of lipid matrix and surfactant, the drug release rate can be precisely controlled, providing a slow and sustained release beneficial for maintaining effective drug concentrations in the body. (e) Enhanced absorption and bioavailability: The small particle size of SLNs and lipid carrier properties improve drug interactions with biological membranes, enhancing dissolution rates and transmembrane absorption, thereby increasing bioavailability. (f) Simplified production and commercial potential: SLNs are relatively straightforward to manufacture, making them suitable for large-scale production and easy to sterilize, which supports commercial viability.

SLNs based on TCM ingredients

Hawthorn acid (MA), a plant-derived compound with anti-tumor properties, exhibits low water solubility, which limits its oral bioavailability. To address this, MA was formulated into SLNs to improve its dissolution and absorption profile. Studies showed that SLNs increased the solubility of MA to 7.5 mg·mL^{-1}, maintained stability across a wide pH range, and enhanced MA bioavailability following *in vitro* gastrointestinal (GI) digestion. These SLNs facilitated MA delivery through an *in vitro* intestinal barrier model using Caco-2 and mucus-producing Caco-2/HT29-MTX co-culture, supporting its potential for oral administration [100].

Esophageal squamous cell carcinoma (ESCC) is a highly malignant tumor with significant incidence and mortality rates in China. The application of standard chemotherapy drugs for ESCC is limited by high toxicity and multiple drug resistance (MDR). Recently, the TCM artemisinin has attracted attention for its anti-cancer effects, which include low toxicity, high efficacy, and MDR-reversal potential. Xia *et al*. [101] developed SLNs loaded with artesunate (SLNART) to address artemisinin's poor water solubility and bioavailability, thereby enhancing the efficiency of artemisinin in the treatment of esophageal squamous cell carcinoma.

Nanostructured lipid carriers (NLC)

Nanostructured lipid carriers (NLCs) are a type of nanodrug delivery system composed of solid and liquid lipids, designed to enhance drug permeability and increase bioavailability. NLCs exhibit a high drug-loading capacity, enabling them to encapsulate greater drug volumes compared to traditional solid lipid nanoparticles (SLNs). Additionally, NLCs have lower moisture content, improved drug retention, and reduced leakage during storage, making them a more efficient and stable delivery platform [102-103].

NLCs assembly with TCM ingredients

Triptolide, derived from *Tripterygium wilfordii*, is a bioactive compound known for its inhibitory effects on proteasome and NF-κB activity. However, its poor water solubility leads to inadequate absorption in the gastrointestinal tract and low oral bioavailability. Furthermore, high-dose oral administration of Triptolide can induce significant side effects such as gastrointestinal toxicity, hepatotoxicity, and nephrotoxicity, limiting its therapeutic potential. To address these challenges, Chen *et al.* [104] developed a novel oral drug delivery system by constructing a CPP-coated Triptolide-loaded nanostructured lipid carrier (CT-NLC) using a unique cell-penetrating peptide (CPP), Ste-R6L2. The incorporation of CPP into NLC significantly enhances the membrane permeability and oral bioavailability of Triptolide. *In vitro* and *in vivo* studies on prostate cancer models demonstrated that CT-NLC effectively accumulates in tumor tissues, reduces the toxicity of Triptolide to normal cells, prolongs survival in mouse models, and enhances anti-tumor efficacy.

For organic nano-sized systems, we have discussed liposomes, microemulsions, micelles, solid lipid nanoparticles, and nanostructured lipid carriers. Each of these carriers presents unique advantages and disadvantages, which are summarized as shown in Table 3.

Inorganic Nano-sized Systems for Delivery of TCM

Inorganic nano-sized systems are nanostructures composed of inorganic materials, which are widely utilized in drug delivery, imaging, diagnostics, and therapy. These systems primarily include metal nanoparticles, mesoporous silica nanoparticles, metal-organic frameworks (MOFs). Inorganic

Table 3 Summary of the advantages and disadvantages of organic nano-sized systems for the delivery of TCM

TCM nano-drug delivery system	Advantages	Disadvantages	References
Liposomes	(1) Biocompatibility and biodegradability. (2) Ability to encapsulate both hydrophilic and hydrophobic drugs (3) Enhance drug solubility and stability (4) Targeted delivery through modification of surface characteristics	(1) Potential instability in physiological conditions (2) Difficulties in large-scale production (3) Costly to produce	[21, 25]
Microemulsions	(1) High stability and low interfacial tension. (2) Enhanced solubilization capacity for hydrophobic drugs (3) Ability to enhance drug bioavailability	(1) Dependence on surfactants, which can lead to toxicity (2) Complexity in formulation and stability issues under certain conditions	[30, 32]
Micelles	(1) Simple and cost-effective production (2) Ability to solubilize hydrophobic compounds (3) Enhanced drug solubility and stability	(1) Limited drug loading capacity (2) Stability can be affected by dilution or changes in temperature	[49, 50, 51]
Solid Lipid Nanoparticles	(1) Controlled drug release (2) Biocompatibility and safety (3) Increased bioavailability	(1) Limited drug loading capacity (2) Complex production (3) Potential for drug crystallization	[69, 70]
Nanostructured Lipid Carriers	(1) Controlled drug release (2) Improve drug permeability, (3) Improve drug loading capacity	(1) Poor long-term stability (2) High cost and complex preparation process	[73, 74]

nano-sized systems typically exhibit unique physical and chemical properties, such as exceptional chemical stability, high drug-loading capacity, controlled drug release, and the potential for multifunctionalization. These characteristics make them highly promising for applications in anti-tumor therapy. Compared to organic nanocarriers, inorganic nano-sized systems offer superior drug-loading capacity, which not only enhances the bioavailability of drugs but also opens up new possibilities for the use of multi-component traditional Chinese medicines in tumor treatment [105-108].

Metal-based nanoparticles

Metal nanoparticles (NPs), generally sized between 1–100 nm [109], are composed primarily of dense metals such as gold, silver, and iron oxide. They exhibit unique characteristics due to their small size, large surface area, and high-energy surfaces, which allow for precise control over their optical, electronic, and catalytic properties [110-111], and make metal NPs versatile across multiple fields, including catalysis, imaging, and drug delivery [112-115].

The unique physical, chemical, and biological properties of metal nanoparticles provide significant advantages [116]. Key benefits of metal nanoparticles as following [117-121]: (1) High surface area: The high surface area of metal NPs enhances reactivity, making them efficient as both catalysts and drug carriers. (2) Unique optical properties: Metal NPs such as gold exhibit strong light absorption and scattering, making them particularly useful in imaging and photothermal therapy. (3) High modifiability: The size, shape, and surface characteristics of NPs can be precisely adjusted, allowing customization for specific applications. (4) Multifunctionality: Metal NPs can serve dual functions in tumor diagnosis and therapy, with specific types tailored to various oncology applications. For instance, gold nanoparticles are used for tumor imaging and photothermal therapy, while iron oxide nanoparticles are employed in magnetic resonance imaging (MRI) for tumor detection. Drug loading onto metal nanoparticles can be achieved through several mechanisms [122-127a-b]: (1) Surface adsorption: Drugs attach to the nanoparticle surface *via* electrostatic, hydrogen, or hydrophobic interactions. (2) Covalent bonding: Drugs can be covalently bound to the NP surface, enhancing both stability and targeted delivery.

Composite of TCM and Metal nanoparticles

Parthenolide (PTL), a sesquiterpene lactone derived from feverfew, possesses cytotoxic effects against tumor cells but faces limitations due to low bioavailability, non-specific targeting, and uncontrolled release *in vivo*. To enhance its efficacy, researchers have developed a PTL-liposome@chitosan@gold nanoshell (PTL-Lips@CS@GNS) system responsive to both acidic tumor environments and near-infrared (NIR) light [128]. This system utilizes the localized surface plasmon resonance (LSPR) effect of gold nanoshells to generate heat under NIR light, triggering PTL release by converting liposomes from a gel to a liquid crystal state. Additionally, under mildly acidic conditions (pH 6.5), the chitosan layer undergoes protonation and depolymerization, further releasing PTL. This metal-enhanced TCM delivery approach demonstrates the potential of chemo-photothermal therapy for targeted anti-tumor applications.

Curcumin (Cur) is a phenolic compound derived from turmeric. It has shown potential in modulating tumor immunity and suppressing the breast cancer tumor microenvironment. However, its clinical application is limited due to its low water solubility and poor bioavailability *in vivo*. Researchers have developed a folic acid-curcumin loaded gold-polyvinylpyrrolidone nanoparticles (FA-CurAu-PVP NPs) based nanoconjugate (NC) for targeted delivery in a breast cancer model system. This carrier features a pH-responsive drug release system, favorable cytocompatibility, and folate receptor-mediated targeting, enabling selective killing of tumor cells while minimizing damage to normal cells [129].

Self assembly of TCM and Metal ions

Glycyrrhizin (GA) and triptolide (Cel) are derived from licorice and *Tripterygium wilfordii*, respectively, and are widely used in cancer chemotherapy due to their potent anti-tumor and immune-modulatory properties. However, their clinical translation is hindered by issues such as poor water solubility and inherent molecular toxicity. Copper ions (Cu^{2+}), as a redox-active metal, can dynamically modulate the tumor microenvironment (TME) through the copper-dependent chemotherapy (CDT) mechanism and induce copper-mediated apoptosis. Although conventional approaches such as organic solvents, drug carriers, and structural modifications have partially mitigated these challenges, they simultaneously introduce additional complexities in preparation, elevate treatment costs, and may lead to unforeseen risks. In this context, the emergence of a carrier-free natural small molecule self-assembly technique provides an effective solution to overcome these challenges. Researchers have developed a stable, carrier-free nanomaterial by self-assembling glycyrrhizin (GA), copper ions (Cu^{2+}), and triptolide (Cel) through metal coordination. The group treated with Cel hydrogel displayed remarkable inhibitory capacity (77.89% ± 7.29%), the chemo-immuno combined combo group exhibited exceptional inhibitory effects, with an inhibition rate of 91.24% ± 3.95%.This nanomaterial demonstrates strong anti-tumor efficacy, offering a promising approach for cancer treatment [130].

Mesoporous silica nanoparticles (MSNs)

MSNs are versatile silica-based materials distinguished by their well-organized pore structures and high specific surface areas [131]. With pore sizes typically ranging from 2 to 50 nm and specific surface areas up to 1000 $m^2 \cdot g^{-1}$, MSNs can accommodate substantial amounts of guest molecules [132]. Their unique structural and physicochemical properties have drawn significant attention in the biomedical sector in recent years, especially in drug delivery applications.

As drug delivery carriers, MSNs offer distinct advantages, particularly for transporting TCM compounds, and their nanoscale pore channels can encapsulate diverse molecules, including small drugs, proteins, and nucleic acids [133-135]. MSNs also allow for chemical surface modifications through silane coupling agents, which enable the introduction of hydrophobic or hydrophilic functional groups that facilitate drug adsorption and controlled release [136-138]. Tailored drug release profiles can be achieved by modulating MSN pore size, wall properties and surface functionalization, supporting release mechanisms such as sustained, pH-responsive, temperature-responsive, or receptor-mediated delivery [139-142]. In addition, encapsulation within MSNs further enhances drug stability by shielding active molecules from external environmental factors, thus prolonging their systemic circulation. Moreover, their excellent biocompatibility ensures stability and safety within biological systems [143-144].

TCM components can be incorporated into MSNs using two primary strategies: adsorption, suitable for drugs with inherent affinity for MSN surfaces or pore channels, and covalent bonding, which requires specific cross-linkers or activators to fortify the stability of drug-MSN interactions [145-146].

MSNs for TCM ingredients delivery

Feng *et al.* [147] developed a novel redox-responsive MSN system by conjugating polyethyleneimine-folic acid (PEI-FA) or HA to the MSN surface *via* disulfide bonds. This functionalized MSN system effectively delivered curcumin to tumor sites, significantly inhibiting tumor growth *in vivo*.

Echinacoside (ECH), a phenylethanoid glycoside from cistanche deserticola with anti-hepatocellular carcinoma activity, suffers from poor absorption and low bioavailability, restricting its therapeutic use. Xia *et al.* [148] created an MSN-based drug delivery system for ECH, conjugating galactose (GAL) and polyethylene glycol diglycidyl ether (PEGDE) to target HepG2 cells (ECH@ Au@MSN-PEGDE-GAL). ECH suppressed ubiquitin-protein ligase E3 component n-recognin 5 (UBR5) expression in HCC, promoting apoptosis and inhibiting glycolysis, with a high drug-loading capacity and a sustained release profile over time.

MSNs-based complexes

Evodiamine (EVO) and berberine (BBR), sourced from evodia rutaecarpa and coptis chinensis, respectively, have been demonstrated to exhibit synergistic anti-tumor effects; however, their clinical potential is constrained by poor solubility and potential side effects. To tackle this, Wu *et al.* [149] designed a temperature- and pH-responsive MSN system, MSN@p(NIPAM-co-MA), encapsulated within a DSPE-PEG2000 lipid bilayer, to enable tumor-targeted drug release. This system enabled controlled EVO and BBR release under tumor-specific conditions, significantly inhibiting tumor cell proliferation, migration, invasion, and angiogenesis *in vitro* while effectively suppressing tumor growth *in vivo*.

Multimodal therapies such as chemotherapy with immunotherapy can significantly improve therapeutic efficacy. In this regard, Chang *et al.* [150] developed PEGylated MSNs loaded with astragaloside III (As) and the photosensitizer Ce6, enabling real-time tracking of nanoparticles, enhancing adaptive immunity through photodynamic therapy (PDT) and boosting innate immunity *via* as release. Ce6 induces apoptosis and potentiates CD8$^+$T cell-mediated anti-tumor activity, while as promotes NK cell activation by upregulating NKG2D and IFN-γ expression. The (As + Ce6)@MSN-PEG system was shown to activate NK and CD8$^+$ T cells within lymph nodes and the spleen, facilitating a robust anti-tumor immune response.

Metal-organic frameworks (MOFs)

MOFs are crystalline materials formed through coordination bonds between metal ions and organic ligands, increasingly utilized in drug delivery applications [151]. Commonly, metal ions such as iron, zinc and manganese, as well as Fe_3O_4 nanoparticles, act as metal nodes within MOFs. The flexibility to vary metal nodes and organic ligands facilitates the design of diverse MOF configurations [152]. Prominent series such as MIL (Materials of Institut Lavoisier), ZIF (Zeolitic Imidazolate Frameworks), and UiO (Universitetet i Oslo) are extensively applied in drug delivery research [153]. MOFs offer unique advantages for delivering TCM nanoparticles: (1) Their highly ordered structures protect TCM components from degradation [154]; (2) They enhance TCM component solubility, thereby improving bioavailability [155]; (3) MOFs have versatile synthesis methods that can be tailored to the specific properties of TCM components [156]; (4) MOFs allow for easy functionalization, facilitating targeted delivery and minimizing side effects [157]. MOFs enable various drug-loading mechanisms for TCM components: (a) Their large surface areas and porous structures allow for physical adsorption of drug molecules on the surface or within the pores, ensuring efficient drug loading [158]; (b) The metal ions and organic ligands of MOFs support ion exchange with drug molecules, promoting stability and controlled release [159]; and (c) Functional groups or chemical bonds can be introduced to increase interactions between MOFs and drug molecules, optimizing drug loading [151]. Additionally, MOFs' tunable pore size, shape, and surface properties allow for the co-loading of different TCM component types, such as flavonoids [160], alkaloids, and saponins [161].

MOFs for delivery of TCM ingredients

Zeng *et al.* [160] developed pH-sensitive MOFs loaded with bufalin and functionalized with folic acid (FA-MOF/Buf) for breast cancer therapy. This formulation targeted folate receptors on tumor cells, promoting accumulation in tumor tissues and enabling drug release in response to the acidic environment, thereby enhancing cytotoxicity against breast cancer cells. Similarly, Zhou *et al.* [159] utilized ZIF-8 loaded with celastrol and conjugated with biotin (CEL@ZIF-8@PEG-BIO) for ovarian cancer treatment. CEL@ZIF-8@PEG-BIO exhibited improved water solubility and a high drug-loading capacity (31.60% ± 2.85%), inducing cancer cell apoptosis through the P38/JNK MAPK signaling pathway.

MOFs-based complexes

Guo *et al.* [152] developed magnetic MOFs coated with platelet membranes, co-loading oxymatrine and astragaloside IV with α-PD-1 for liver cancer treatment. This construct, PmMN@Om&As, targeted HCC tissues under a magnetic field and released Om and As, which enhanced TIL levels and activity by modulating CAF and TIL mitochondrial functions. The combination of PmMN@Om&As with *α*-PD-1 achieved an 84.15% tumor inhibition rate in mice, extending their survival. Guo *et al*. [161] further created magnetic MOFs coated with tumor cell membranes (Hm), co-loading tanshinone IIA and astragaloside IV (Hm@TSA/As-MOF) with *α*-PD-1 for liver cancer treatment. The Hm coating and magnetic responsiveness enabled homotypic magnetic dual-targeting, reducing ascitic tumor cell interference and improving the precision targeting of solid tumors. The HCC microenvironment accelerated the release of TSA and As from Hm@TSA/As-MOF, increasing TIL abundance and activity, and thereby enhancing the efficacy of PD-1 antibody therapy in HCC.

For inorganic nano-sized systems, we have discussed metal-based nanoparticles, mesoporous silica nanoparticles, and metal-organic frameworks. Each of these carriers has distinct advantages and disadvantages, as outlined in Table 4.

Summary and Outlook

Nanomedicines, owing to their unique advantages in tumor therapy, have achieved partial clinical application. However, only a limited number of organic nanocarrier formulations, such as liposomes, microemulsions, and micelles with good biocompatibility, have been licensed for commercial usage, primarily for chemically synthesized antitumor drugs (Table 6). Currently, the only authorized TCM and natural product formulations are *β*-elemene liposome injection and paclitaxel microemulsion (Table 5). The clinical transformation of TCM nanomedicines mainly confronts several significant challenges: (1) Most active components of TCM exhibit moderate potency, often requiring higher concentrations or synergistic combinations to achieve significant therapeutic effects, necessitating high drug-loading capacities to meet therapeutic requirements. However, the drug-loading capacity of currently approved organic nanocarriers remains relatively low. (2) TCM often requires synergistic effects of multiple components for therapeutic efficacy, but the physical and chemical properties of multiple components are often different, which complicates the design of combined drug loading, and it is difficult for conventional nanocarriers to achieve efficient co-loading of multiple components. (3) Compared to conventional formulations, the preparation of nanomedicines is more complex. This complexity is particularly pronounced during scale-up and pilot production, where issues such as reproducibility and stability become critical. Furthermore, the absence of a comprehensive quality control system hinders the production of stable and controllable formulations. (4) The *in vivo* processes of TCM nanomedicines are intricate, with limited understanding of their pharmacokinetics, biodistribution, and safety profiles. These unresolved issues significantly impede the industrialization and clinical translation of TCM nanomedicines.

With the advancement of drug delivery technologies, the

Table 4 Summary of the advantages and disadvantages of inorganic nanocarriers for Traditional Chinese Medicine

TCM nano-drug delivery system	Advantage	Disadvantage	References
Metal nanocarriers	(1) Optical properties; (2) High surface area; (3) Versatility; (4) Physical stability	(1) Toxicity issues; (2) Poor biodegradability; (3) Immune response; (4) Complex preparation	[109, 114, 115]
Mesoporous Silica Nanoparticles	(1) Large pore volume; (2) Regulatability; (3) Biocompatibility; (4) Sustainability	(1) Potential toxicity; (2) Poor biodegradability; (3) Difficult to produce on a large scale; (4) Surface modification dependence	[131, 133]
Metal organic frameworks	(1) High porosity and extensive surface area; (2) Structural diversity; (3) Controlled release; (4) Functionalization capability	(1) Poor solubility; (2) Toxicity issues; (3) Complex preparation; (4) Uncertain behavior *in vivo*	[132, 133]

Table 5 Various Nanocarriers licensed of TCM for clinical applications

Formulations	Products	API	Therapeutic modalities
Liposomes	Paclitaxel	Paclitaxel	Ovarian cancer; non-small cell lung cancer; melanoma
	Marqibo	Vincristine sulfate	Leukemia
	Onivyde	Irinotecan hydrochloride (Camptothecin)	Pancreatic cancer
	Elemene liposomes	*β*-Elemene	Lung cancer; brain tumor; breast cancer
Microemulsion	Paclitaxel microemulsion	Paclitaxel	Breast cancer; ovarian cancer; non-small cell lung cancer
	Brucea Javanese Oil (Submicroemulsion)	Brucea Javanese Oil	Lung cancer; lung cancer brain metastasis; gastrointestinal tumors; and liver cancer

Table 6 Various Nanocarriers licensed for clinical applications

Formulations	Products	Therapeutic modalities	References
Liposomes	Doxil® (Liposomal Doxorubicin)	Treatment of multiple types of cancer	[162]
	Myocet® (Non-pegylated Liposomal Doxorubicin)	Reduce the skin toxicity associated with Doxil®	[163]
	DaunoXome® (Liposomal Daunorubicin)	Enhance stability and therapeutic effectiveness	[164]
	Inflexal® V (Influenza Vaccine)	Enhance the immunogenicity of the vaccine	[165]
	Exparel® (Liposomal Bupivacaine)	Provide durable pain relief for up to 72 hours	[166]
	Arikayce® (Liposomal Amikacin)	increase the concentration of the drug in the lung	[167]
	Ambisome® (Liposomal Amphotericin B)	Reduce the renal toxicity of the drug	[168]
Microemulsion	Estrasorb® (Estradiol Topical Emulsion)	Treats symptoms of menopause and increases the skin permeability	[169]
	Neoral® (Cyclosporine Oral Solution)	Use for preventing organ transplant rejection and treating autoimmune diseases	[170]
	Nizoral® (Ketoconazole Shampoo)	Enhances local concentration and therapeutic efficacy	[171]
	Restasis® (Cyclosporine Ophthalmic Emulsion)	Micromelectal system-enhanced circulin for prolonged retention and efficacy in dry eye treatment	[172]
	Kaletra® (Lopinavir/Ritonavir Oral Solution)	Improves the solubility and bioavailability of lopinavir and lithonavir	[173]
Micelle	Doxil® (Pegylated Liposomal Doxorubicin)	Enhances circulation time and minimizes toxic side effects	[174]
	Genexol-PM® (Polymeric Micellar Paclitaxel)	Enhances solubility and bioavailability.	[175]

application prospects of TCM nanomedicines are becoming increasingly promising. The interdisciplinary integration of artificial intelligence, new materials, and other emerging technologies are expected to further propel the research and development of TCM nanomedicines. By leveraging artificial intelligence, machine learning, and computational techniques in combination with pharmacological and molecular biology approaches, it is possible to identify highly active TCM components, thereby reducing the challenges associated with nanomedicine development. For drug combinations requiring synergistic multi-component action, strategies such as self-assembly or drug-excipient integration can be employed to achieve efficient co-loading of TCM components, ultimately enhancing drug-loading capacity. Moreover, the development of innovative materials, such as improving the biocompatibility of inorganic nanomaterials, can address the requirements for multi-component systems with high drug-loading capacity. The application of intelligent manufacturing technologies in TCM production lines and the development of novel formulation techniques, such as microfluidics for liposome preparation, have significantly improved production efficiency and formulation stability. Through comprehensive quality control across the entire production process, these advancements facilitate large-scale industrial production and ensure the stability and controllability of formulation products. Additionally, the evolution of visualization technologies and *in vivo* qualitative and quantitative drug analysis has enabled a deeper understanding of the dynamic transportation processes of nanomedicines within the body, elucidating their efficacy and safety profiles.

In summary, the continuous progress in nanotechnology is expected to accelerate the modernization and globalization of TCM, fully unlocking the therapeutic potential of its nanomedicine formulations.

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Cite this article as: YANG Ling, WANG Yani, YE Xietao, *et al*. Traditional Chinese medicine-based drug delivery systems for anti-tumor therapies [J]. *Chin J Nat Med*, 2024, **22**(12): 1177-1192.