Journal of Nanobiotechnology

REVIEW

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Integration of active ingredients from traditional Chinese medicine with nano-delivery systems for tumor immunotherapy

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Abstract

Tumor immune escape presents a significant challenge in cancer treatment, characterized by the upregulation of immune inhibitory molecules and dysfunction of immune cells. Tumor immunotherapy seeks to restore normal anti-tumor immune responses to control and eliminate tumors effectively. The active ingredients of traditional Chinese medicine (TCM) demonstrate a variety of anti-tumor activities and mechanisms, including the modulation of immune cell functions and inhibiting tumor-related suppressive factors, thereby potentially enhancing anti-tumor immune responses. Furthermore, nano-delivery systems function as efficient carriers to enhance the bioavailability and targeted delivery of TCM active ingredients, augmenting therapeutic efficacy. This review comprehensively analyzes the impact of TCM active ingredients on the immune system and explores the synergistic application of nano-delivery systems in combination with TCM active ingredients for enhancing tumor immunotherapy.

Keywords Tumor immunotherapy, TCM, Active ingredients, Drug delivery, Nanocarriers

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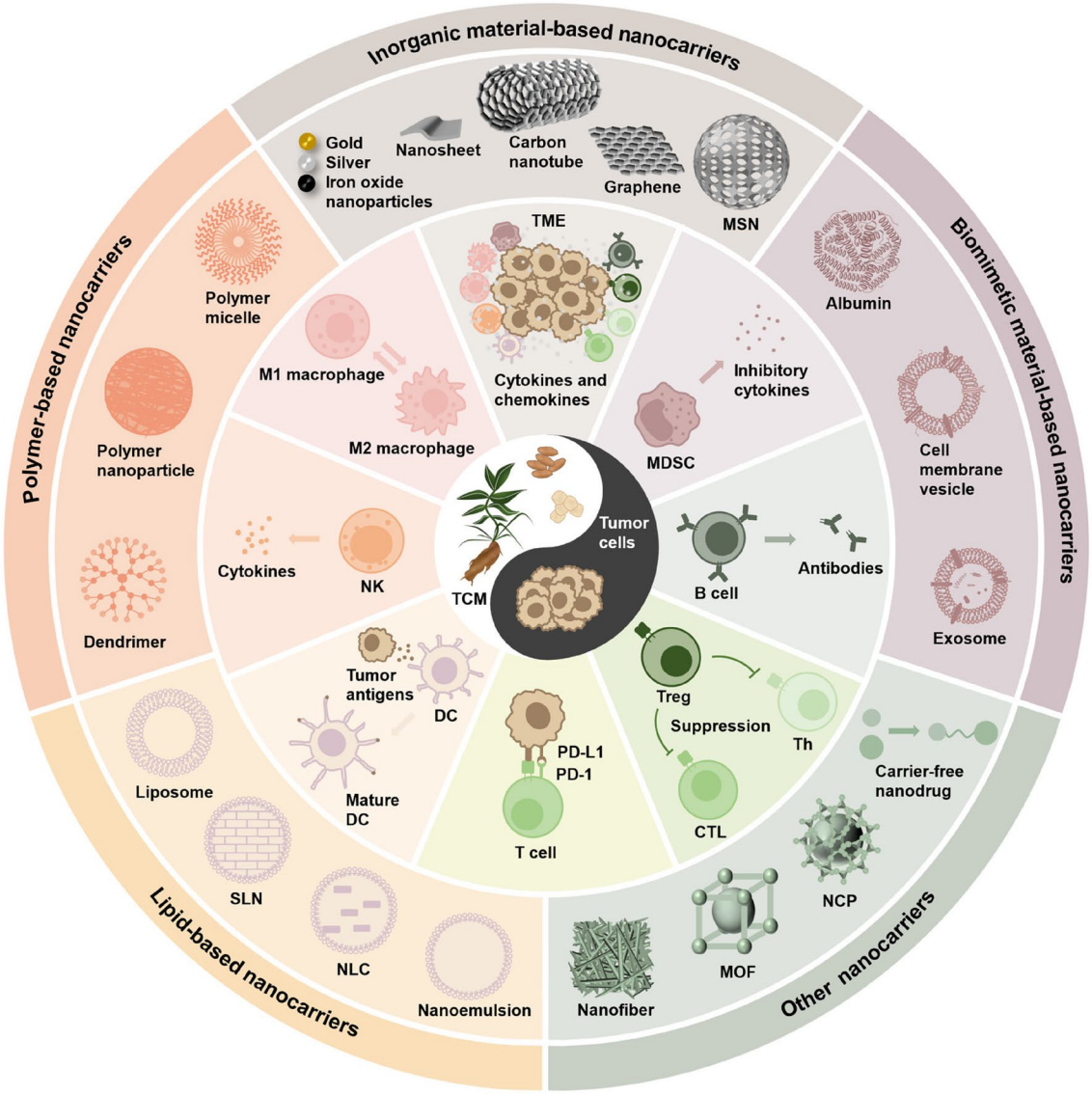
Graphical abstract



Introduction

Tumor cells evade immune recognition and attack through various mechanisms, enabling their survival and proliferation within the body. Tumor immunotherapy employs immunological principles to activate immune cells and bolster the body's anti-tumor response, inhibiting tumor growth and overcoming immune tolerance. Notably, tumor immunotherapy is characterized by minimal side effects and significant treatment efficacy, positioning it as a promising frontier in cancer treatment. It is increasingly recognized as the fourth major modality in oncology, alongside surgery, radiotherapy, and chemotherapy [1].

TCM has been developed over thousands of years, encompassing a comprehensive theoretical framework, distinctive diagnostic methods, and an extensive treatment system. In recent decades, TCM has gained recognition as a promising approach for cancer prevention and treatment [2]. There are numerous active ingredients in TCM with complex mechanisms that exert various effects on tumor occurrence, development, metastasis, and immune regulation. The immunomodulatory effects of TCM active ingredients mainly include enhancing the

functions of the immune system, as well as alleviating the immunosuppressive state caused by cancer and its treatment. These mechanisms highlight TCM's potential in tumor immunotherapy [3].

The clinical application of TCM active ingredients is hindered by their undesirable drug characteristics, such as low water solubility, poor stability, low bioavailability, short retention time, and insufficient permeability and targeting ability, leading to unmet expectations [4]. The emergence of nanotechnology, specifically the integration of nanomaterials with drugs, has attracted significant attention in cancer treatment. Nano-drug delivery systems offer potential solutions to overcome these limitations and expedite the modernization of TCM. By engineering nano-delivery systems for TCM active ingredients, it becomes feasible to enhance drug solubility, stability, half-life, permeability, targeting ability, bioavailability, and pharmacological activity while minimizing side effects [5]. Thus, this combination can play a more potent immunomodulatory and anti-tumor role in immunotherapy.

In this review, we explore how TCM active ingredients modulate the immune response to enhance anti-tumor effects, providing insights for the development of novel immunotherapeutic drugs. Furthermore, the article examines current research advancements for integrating TCM active ingredients with nano-delivery systems in tumor immunotherapy, which provides a theoretical basis for clinical practice (Fig. 1).

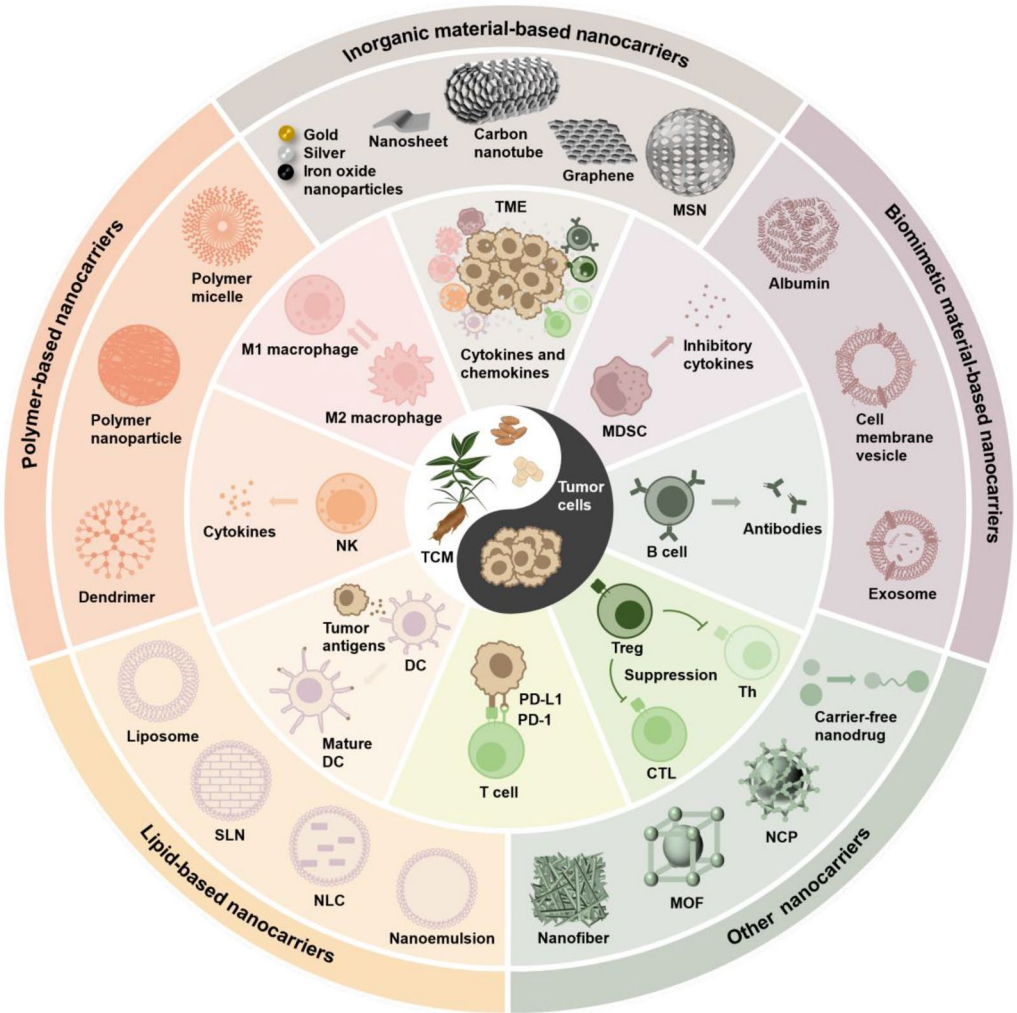


Fig. 1 Schematic illustration of the modulation of the immune system and the various nanocarriers used in nano-delivery systems for active ingredients in TCM

Effects of active ingredients of TCM on the immune system

Immune cells, such as lymphocytes, macrophages, natural killer cells (NKs) and dendritic cells (DCs), play an essential role in the immune system (Fig. 2). However, the dynamic and complex interactions between tumors and the immune system often allow them to avoid immune surveillance, resulting in immune escape and ultimately increased malignancy and metastasis [6, 7]. TCM encompasses the characteristics of multi-components, multi-targets, and multi-pathways, which not only directly kill tumor cells but also effectively regulate a variety of immune cells and improve anti-tumor immunity (Table 1) [8–115].

Regulation of macrophages

Tumor cells evade macrophage clearance through the expression of anti-phagocytic signaling proteins. CD47 on tumor cells interacts with the inhibitory receptor signal regulatory protein α (SIRPα) on macrophages, inhibiting immune response [116–118]. It is overexpressed in numerous cancers, including human lung cancer, breast cancer, and epithelial ovarian cancer. Gambogic acid (GA) is a resin secreted by the *Garcinia hanburyi* tree that can improve anti-tumor immunity. Ren et al. discovered that GA could markedly diminish the increased CD47 expression induced by chemotherapy [45]. Many tumors, such as triple-negative breast cancer (TNBC) and bladder cancer, also express high levels of CD24, which binds to sialic acid-binding Ig-like lectin 10 (Siglec-10) on tumor-associated macrophages (TAMs), aiding in immune evasion by the tumor cells [119].

Macrophages undergoing M2 polarization can promote tumor cell growth, which facilitates the expression of arginase-1 (Arg-1) and vascular endothelial growth factor (VEGF), supporting extracellular matrix formation and cell proliferation [120–122]. Additionally, M2-like macrophages release lots of anti-inflammatory cytokines like TGF-β, IL-4, IL-10, and chemokines such as C-C motif chemokine ligand (CCL)1, CCL17, CCL18, ultimately causing immune suppression [123–125]. Celastrol, a pentacyclic triterpenoid compound derived from *Tripterygium wilfordii* Hook F., exhibits a range of pharmacological activities. Yang et al. observed a dose-dependent inhibition of CD206 expression in both RAW264.7 cells and TAMs following treatment with celastrol [26]. Celastrol inhibits cancer metastasis by blocking M2 polarization through the signal transducer and activator of transcription (STAT)6 signaling pathway. Dihydroartemisinin (DHA) is an active metabolite of artemisinin and its derivatives, which has better water solubility and more robust antimalarial activity than artemisinin. Chen et al. demonstrated that DHA inhibits the migration and invasion of head and neck squamous cell carcinoma by impeding STAT3 phosphorylation and preventing M2 polarization in the tumor microenvironment (TME) [33]. Epigallocatechin-3-gallate (EGCG) is the predominant catechin in green tea, and it has anti-bacterial, anti-virus, and anti-tumor effects. Jang et al. reported that EGCG increases the

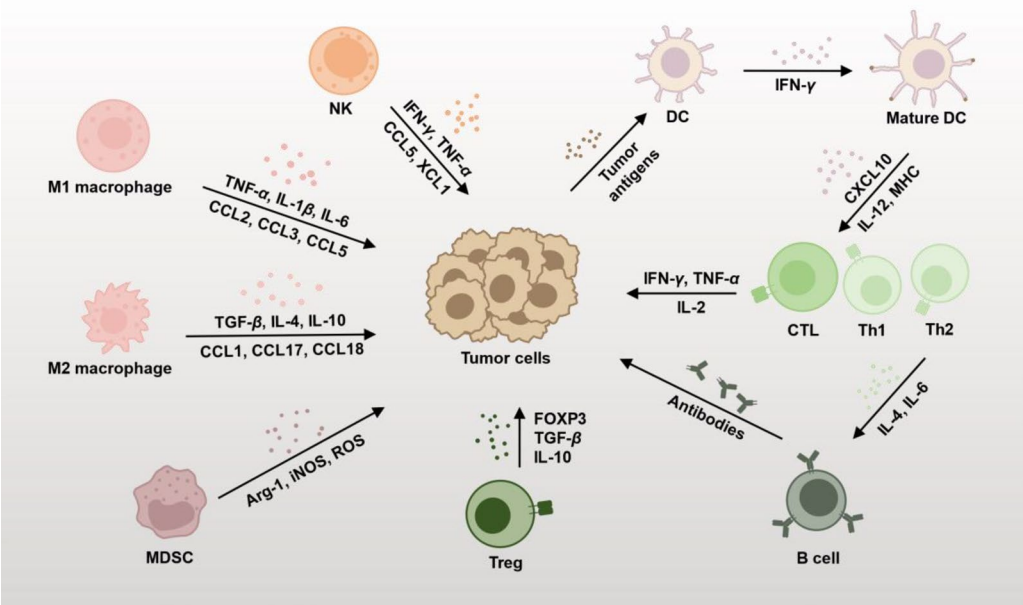


Fig. 2 Schematic diagram of the regulatory mechanisms of immune cells

Table 1 Active ingredients of TCM and their mechanisms in tumor immunotherapy

Active ingredients	TCM	Effects	Cancer/tumor types	Refs.
Achyranthes bidentata polysaccharides	*Achyranthes bidentata* Bl	↑DCs	Colorectal cancer	[8]
Angelica sinensis polysaccharide	*Angelica sinensis* (Oliv.) Diels	↑NKs ↑CTLs ↑Th1/Th2 ratio	Melanoma	[9, 10]
Apigenin	*Apium graveolens* L	↑CTLs ↑Th1/Th2 ratio ↑M1 macrophages ↓PD-L1 ↓Tregs	Breast cancer Melanoma Lung cancer Pancreatic cancer	[11]
Artesunate	*Artemisia annua* Linn	↓TGF-*β*, IL-10 ↓Tregs	Colorectal cancer Cervical cancer	[12, 13]
Asiatic acid	*Centella asiatica* (L.) Urb	↑NKs ↑CTLs ↓Tregs ↓PD-L1	Breast cancer Melanoma Lung cancer	[14, 15]
Astragaloside III	*Astragalus membranaceus* (Fisch.) Bunge	↑NKs	Colorectal cancer	[16]
Astragaloside IV	*Astragalus membranaceus* (Fisch.) Bunge	↓M2 macrophages ↓TGF-*β*, IL-10	Colorectal cancer Lung cancer Ovarian cancer	[17]
Astragalus polysaccharide	*Astragalus membranaceus* (Fisch.) Bunge	↑M1 macrophages ↑NKs ↑DCs ↑CTLs ↓Tregs ↓PD-L1 ↓MDSCs	Lung cancer Breast cancer Ehrlich ascites carcinoma Gastric cancer Colorectal cancer Cervical cancer	[18]
Baicalin	*Scutellaria baicalensis* Georgi	↓M2 macrophages ↓PD-L1	Liver cancer	[19, 20]
Berberine	*Coptis chinensis* Franch	↑CTLs ↓PD-L1 ↓MDSCs ↓Tregs	Lung cancer	[21]
Betulinic acid	*Betula platyphylla* Suk	↓MDSCs ↓M2 macrophages	Breast cancer Liver cancer	[22, 23]
Bufalin	Bufo *bufo gargarizans* Cantor	↑NKs ↑M1 macrophages	Liver cancer	[24, 25]
Celastrol	*Tripterygium wilfordii* Hook. f	↓M2 macrophages	Breast cancer	[26]
Cryptotanshinone	*Salvia miltiorrhiza* Bunge	↑DCs ↑M1 macrophages	Lung cancer	[27, 28]
Curcumin	*Curcuma longa* L	↑CTLs ↑Th1/Th2 ratio ↓Tregs ↓TGF-*β*, IL-10 ↓CTLA4	Lung cancer Colorectal cancer Leukemia Tongue squamous cell carcinoma	[29, 30]
Dihydroartemisinin	*Artemisia annua* Linn	↑CTLs ↑Th1/Th2 ratio ↓Tregs ↓PD-L1 ↓M2 macrophages	Breast cancer Pancreatic cancer Melanoma Lung cancer Head and neck squamous cell carcinoma	[31–33]
Dioscin	*Dioscorea polystachya* Turczaninow	↑M1 macrophages	Melanoma Lung cancer	[34, 35]
Echinacea polysaccharides	*Echinacea purpurea* (L.) Moench	↑M1 macrophages	Liver cancer Colorectal cancer	[36]
Epigallocatechin-3-gallate	*Camellia sinensis* (L.) O. Kuntze	↓M2 macrophages ↓PD-L1	Breast cancer Melanoma	[37, 38]
Epimedium polysaccharides	*Epimedium koreanum* Nakai	↑M1 macrophages ↑DCs ↑CTLs	Lung cancer	[39, 40]

Table 1 (continued)

Active ingredients	TCM	Effects	Cancer/tumor types	Refs.
Fucoidan	*Laminaria japonica* Aresch	↑DCs ↓M2 macrophages ↓PD-L1	Melanoma Tongue squamous cell carcinoma Liver cancer Fibrosarcoma	[41–43]
Gambogic acid	*Garcinia hanburyi* Hook.f	↑CTLs ↓PD-1 ↓Tregs ↓MDSCs ↓M2 macrophages	Oral squamous cell carcinoma Nasopharyngeal carcinoma Colorectal cancer	[44–46]
Ganoderma formosanum polysaccharides	*Ganoderma formosanum*	↑CTLs ↑Th1/Th2 ratio ↑NKs	Sarcoma Melanoma Colorectal cancer Lung cancer	[47, 48]
Ganoderma lucidum polysaccharides	*Ganoderma lucidum*	↑M1 macrophages ↑Th1/Th2 ratio ↑CTLs ↓Tregs ↓MDSCs	Liver cancer Breast cancer Lung cancer	[49–51]
Ganoderma sinense polysaccharides	*Ganoderma sinense*	↑CTLs ↑DCs	Liver cancer Lung cancer Esophageal cancer Colorectal cancer Leukemia	[52, 53]
Genistein	*Glycine max* (L.) Merr	↑CTLs ↓Tregs	Breast cancer	[54]
Ginseng polysaccharides	*Panax ginseng* C. A. Meyer	↑CTLs ↑NKs ↑Th1/Th2 ratio ↓Tregs	Melanoma Nasopharyngeal carcinoma Lung cancer Colorectal cancer Liver cancer Gastric cancer	[55]
Ginsenoside F1	*Panax ginseng* C. A. Meyer	↑NKs	Lymphoma Melanoma	[56]
Ginsenoside Rg3	*Panax ginseng* C. A. Meyer	↑CTLs ↑Th1/Th2 ratio ↓PD-L1	Liver cancer Lung cancer	[57, 58]
Ginsenoside Rh2	*Panax ginseng* C. A. Meyer	↑CTLs ↑M1 macrophages ↑NKs ↓PD-L1 ↓Tregs	Lung cancer Breast cancer Melanoma Leukemia Ovarian cancer Liver cancer Colorectal cancer	[59–62]
Glycyrrhetinic acid	*Glycyrrhiza uralensis* Fisch	↑CTLs	Lung cancer	[63]
Glycyrrhiza polysaccharide	*Glycyrrhiza uralensis* Fisch	↑CTLs ↑Th1/Th2 ratio ↓Tregs ↓TGF-β, IL-10	Liver cancer Colorectal cancer	[64, 65]
Glycyrrhizic acid	*Glycyrrhiza uralensis* Fisch	↑Th1/Th2 ratio ↓Tregs ↓MDSCs ↓CTLA4	Melanoma	[66, 67]
Icariin	*Epimedium brevicornum* Maxim	↑CTLs ↓M2 macrophages ↓PD-L1 ↓MDSCs ↓TGF-β, IL-10	Breast cancer Pancreatic cancer Cervical cancer Mastocytoma Melanoma	[68]

Table 1 (continued)

Active ingredients	TCM	Effects	Cancer/tumor types	Refs.
Icaritin	*Epimedium brevicornum* Maxim	↑CTLs ↓PD-L1 ↓MDSCs	Breast cancer Liver cancer Lung cancer Melanoma Prostate cancer Colorectal cancer	[69]
Lentinan	*Lentinus edodes*	↑CTLs ↑Th1/Th2 ratio ↑NKs ↓MDSCs ↓Tregs ↓TGF-β, IL-10	Lung cancer Bladder cancer	[70, 71]
Lupeol	*Lupinus polyphyllus* Lindl	↑NKs ↓M2 macrophages	Gastric cancer Lung cancer	[72]
Luteolin	*Reseda odorata* L	↑CTLs ↑Th1/Th2 ratio ↓Tregs ↓PD-L1	Melanoma Lung cancer	[73, 74]
Lycium barbarum polysaccharides	*Lycium barbarum* L	↑CTLs ↑DCs	Sarcoma Colorectal cancer	[75, 76]
Matrine	*Sophora flavescens* Aiton	↑CTLs ↑DCs ↓M2 macrophages	Lung cancer	[77, 78]
Norcantharidin	*Mylabris phalerata* Pallas	↑CTLs ↑M1 macrophages ↓Tregs ↓CTLA4 ↓TGF-β, IL-10	Liver cancer Prostate cancer	[79, 80]
Notoginsenoside Ft1	*Panax notoginseng* (Burk.) F. H. Chen	↑CTLs	Colorectal cancer	[81]
Oridonin	*Rabdosia rubescens* (Hemsl.) Hara	↑CTLs ↓Tregs ↓PD-L1 ↓TGF-β, IL-10	Breast cancer Bladder Cancer	[82, 83]
Plumbagin	*Plumbago zeylanica* L	↑CTLs	Lung cancer	[84]
Poria cocos polysaccharide	*Poria cocos* (Schw.) Wolf	↑CTLs ↑NKs	Ehrlich ascites carcinoma	[85]
Puerarin	*Pueraria lobata* (Willd.) Ohwi	↑Th1/Th2 ratio ↓M2 macrophages ↓TGF-β, IL-10	Lung cancer	[86]
Red ginseng acidic polysaccharides	*Panax ginseng* C. A. Meyer	↑M1 macrophages	Melanoma	[87]
Rehmannia glutinosa polysaccharide	*Rehmannia glutinosa* (Gaert.) Libosch. ex Fisch. et C. A. Mey	↑NKs	Colorectal cancer	[88]
Resveratrol	*Veratrum album* L	↑CTLs ↑DCs ↑NKs ↓M2 macrophages ↓Tregs ↓MDSCs ↓PD-L1 ↓TGF-β, IL-10	Lung cancer Osteosarcoma Thymoma Oral squamous cell carcinoma Breast cancer Liver cancer Melanoma Renal cell carcinoma Leukemia	[89, 90]
Saikosaponin A	*Bupleurum chinense* DC	↑CTLs ↑Th1/Th2 ratio	Breast cancer	[91]
Saikosaponin D	*Bupleurum chinense* DC	↑CTLs ↑NKs ↓M2 macrophages ↓MDSCs	Pancreatic cancer	[92]

Table 1 (continued)

Active ingredients	TCM	Effects	Cancer/tumor types	Refs.
Salidroside	*Rhodiola rosea* L	↑CTLs ↑DCs ↓Tregs ↓TGF-β, IL-10	Lung cancer	[93, 94]
Salvia miltiorrhiza polysaccharides	*Salvia miltiorrhiza* Bunge	↑CTLs ↑NKs	Gastric cancer	[95]
Salvianolic acid A	*Salvia miltiorrhiza* Bunge	↓M2 macrophages	Breast cancer	[96]
Salvianolic acid B	*Salvia miltiorrhiza* Bunge	↑CTLs ↓PD-1	Breast cancer	[97]
Sativan	*Spatholobus suberectus* Dunn	↓PD-L1	Breast cancer	[98]
Shikonin	*Lithospermum erythrorhizon* Sieb. et Zucc	↑DCs ↑NKs	Ovarian cancer Breast cancer Colorectal cancer	[99–101]
Solamargine	*Solanum nigrum* L	↑DCs ↓M2 macrophages ↓MDSCs ↓PD-L1	Liver cancer Lung cancer	[102, 103]
Soyasapogenols	*Glycine max* (L.) Merr	↓M2 macrophages	Glioblastoma Osteosarcoma	[104]
Tanshinone IIA	*Salvia miltiorrhiza* Bunge	↑CTLs ↑DCs ↑M1 macrophages ↓Tregs	Lung cancer Liver cancer Colorectal cancer	[105–107]
Tetramethylpyrazine	*Ligusticum chuanxiong* Hort	↑Th1/Th2 ratio ↑NKs	Lung cancer Renal cell carcinoma	[108, 109]
Triptolide	*Tripterygium wilfordii* Hook. f	↑NKs ↓Tregs ↓TGF-β, IL-10 ↓PD-L1	Melanoma Breast cancer Oral squamous cell carcinoma Ovarian cancer Leukemia	[110–112]
β-elemene	*Curcuma wenyujin* Y. H. Chen et C. Ling	↑DCs ↓M2 macrophages	Lung cancer Pancreatic cancer	[113–115]

expression of microRNA (miR)-16 in tumor cells, which is then transferred to TAMs via exosomes [37]. This transfer leads to reduced TAM infiltration and M2 polarization.

In contrast, M1-like macrophages secrete large amounts of co-stimulatory molecules and highly express major histocompatibility complex (MHC) class II molecules. They release matrix metalloproteinases (MMPs), inducible nitric oxide synthase (iNOS), and reactive oxygen species (ROS) [126]. M1 macrophages are characterized by their strong antigen presentation and the secretion of pro-inflammatory cytokines like TNF-α, IL-1β, IL-6, and chemokines such as CCL2, CCL3, CCL5, which stimulate a strong anti-tumor immune response [127, 128]. In the early stages of tumor development, TAMs predominantly exhibit an M1 phenotype; however, as the tumor progresses, they shift to the M2 phenotype and then become dominant among TAMs [129]. Astragaloside IV (ASIV) has been shown to exert cytotoxic effects on tumor cells by altering the polarization of TAMs in the TME [17]. ASIV partially blocks M2 macrophage polarization and reduces M2 macrophage proangiogenic activity via the AMP-activated protein kinase (AMPK) signaling pathway. Additionally, ASIV promotes the polarization of M2 macrophages to M1 macrophages by decreasing IL-4 and TGF-β expression and inhibiting the AMPK pathway. Dioscin is a steroidal saponin extracted from the roots of *Dioscorea* plants. Kou et al. demonstrated that dioscin can inhibit tumor progression by polarizing RAW264.7 cells towards the M1 type through the connexin-43 (Cx43) channel [34]. Additionally, Cui et al. reported that dioscin inhibits M2 macrophages and promotes their transformation to M1 type by downregulating the STAT3 and Jun N-terminal kinase (JNK) pathways in lung cancer [35].

Regulation of NKs

Research has consistently highlighted the crucial role of NKs in regulating tumor metastasis and proliferation by releasing IFN-γ and TNF-α, which alter the TME and impede tumor growth [130–132]. Conversely, Freeman

et al. identified that genes involved in antigen presentation and IFN-γ signaling could protect tumor cells from NK cell-mediated killing [133]. Tumors lacking these genes are more sensitive to NKs but resistant to $CD8^+$ T cells [134]. Additionally, NKs express NK receptor group 2 member D (NKG2D), which recognizes MHC class I molecules and participates in the killing of tumor cells [135]. NKs produce CCL5 and X-C motif chemokine ligand (XCL)1, recruiting type 1 conventional DCs to the TME. Böttcher et al. revealed that prostaglandin E2 (PGE2) from tumor cells diminishes NK cell activity and chemokine production, which also impairs DC responsiveness [136]. *Angelica sinensis* polysaccharides (ASP) are among the primary active components of *Angelica sinensis*. ASP treatment resulted in increased levels of IL-2, IL-6, IL-12, and IFN-γ in macrophages, T helper (Th) cells, and NKs. IL-12 is crucial for the activation of NK and natural killer T (NKT) cells [9]. Kim et al. demonstrated that ASP enhanced the anti-cancer activity of NK and NKT cells in vivo, leading to increased cytotoxicity against murine B16 melanoma cells [10]. Chen et al. reported that astragaloside III significantly augmented the production of NKG2D, Fas, and IFN-γ in NKs, thereby enhancing their capacity to eliminate tumors [16]. Bufalin, a major active ingredient from the dry skin gland secretion of *bufo gargarizans*, has been shown to possess significant anti-liver cancer effects. Besides directly inhibiting the proliferation of liver cancer cells and inducing apoptosis, bufalin also modulates the immune response to exert cytotoxic effects. Fu et al. found that bufalin enhances the killing efficacy of NKs by regulating MHC class I chain-related protein A (MICA) and a disintegrin and metalloproteinase 9 (ADAM9) [24]. Bufalin potentially downregulates ADAM9 expression, thereby impeding MICA shedding and promoting NK-mediated cytotoxicity against tumor cells.

Regulation of DCs

DCs are specialized in antigen presentation and play a crucial role in $CD8^+$ T cell activation. In addition to the mentioned PGE2, tumor cells inhibit DC function via multiple pathways, including β-catenin upregulation, which affects cell adhesion, gene expression, and immune evasion. For instance, β-catenin downregulates chemokines like CCL5, CCL17, CCL20, CCL28, CXC chemokine ligand (CXCL)1, and CXCL10 in liver cancer, leading to impaired DC recruitment and immune escape [137]. In melanoma, activated β-catenin upregulates activating transcription factor 3 (ATF3) while reducing CCL4, thereby preventing migration of DCs into the TME [138]. Additionally, Wnt proteins, such as Wnt1 in lung cancer, indirectly inhibit $CD8^+$ T cells by affecting tumor-infiltrating DCs [139]. Cryptotanshinone, a component of *Salvia miltiorrihiza* Bunge, exhibits a range of therapeutic and biological activities. Liu et al. reported that cryptotanshinone displayed anti-tumor activity by inhibiting cell proliferation and enhancing immune response in a mouse model of Lewis lung cancer [27]. Cryptotanshinone enhanced the maturation of DCs, leading to increased expression of MHC and co-stimulatory molecules, which in turn induced the production of TNF-α and IL-1β from DCs. Cryptotanshinone promoted DC maturation by activating the myeloid differentiation primary response protein 88 (MyD88) and nuclear factor kappa B (NF-κB) signaling pathway, resulting in the inhibition of IL-10 secretion. Marine algae are one of the most abundant natural resources in the ocean. Fucoidan, a polysaccharide derived from marine algae, exhibits a range of immune-modulating and anti-tumor properties. Studies have demonstrated that intravenous or intraperitoneal administration of fucoidan induces the activation of DCs, NKs, and T cells in mice. For example, fucoidan serves as an adjuvant in B16-OVA murine models, effectively augmenting DC maturation and function while stimulating antigen-specific T cell immune responses [41]. Matrine, an alkaloid found in *Sophora flavescens* Aiton, is widely used to treat various inflammatory diseases and cancers. Clinical studies have demonstrated that matrine dramatically improves the immune function of patients and exerts anti-tumor effects. Wang et al. revealed the mechanisms underlying matrine's anti-tumor effects on DCs [78]. Matrine increases the mRNA and protein expression of toll-like receptors (TLRs), especially TLR7 and TLR8, and promotes the expression of a series of downstream signaling molecules, ultimately activating IL-6, IL-12, and TNF-α secretion. These cytokines facilitate DC maturation and further enhance antigen presentation.

Regulation of T cells

Immune checkpoints such as cytotoxic T lymphocyte (CTL)-associated antigen 4 (CTLA4) and programmed death protein 1 (PD-1) are popular in the study of immunotherapy [140]. CTLA4, expressed on CTLs and regulatory T cells (Tregs), acts as an immunosuppressive receptor with a higher affinity for B7 molecules on antigen-presenting cells (APCs) than CD28 [141]. It functions as a competitive antagonist of CD28-B7 interaction, blocking T cell-APC co-stimulation and inhibiting T cell activation [142]. CTLA4 signaling reduces IL-2 secretion, inhibits IL-2 receptor expression, and regulates the cell cycle, thereby restricting T cell proliferation and cytokine secretion [143]. It has also been reported that CTLA4 is expressed on some tumor cells (such as melanoma cells), which contributes to immune escape [144].

PD-1 expression increases on activated T cells, while PD-1 ligand (PD-L1) is similarly upregulated on tumor cells [145]. These two molecules combine and generate inhibitory signals that suppress the proliferation of $CD8^+$ T cells and the release of pro-inflammatory cytokines [146]. IL-21 from $CD4^+$ T cells promotes CTL generation, but exhausted $CD4^+$ T cells can lead to dysfunction in $CD8^+$ T cells, which PD-1/PD-L1 blockade cannot fully reverse. Additionally, PD-1 expression is elevated in B cells, macrophages, DCs, and monocytes, with mutations in tumor cells further enhancing PD-L1 expression through various mechanisms, which promote cancer metastasis and immunosuppression [147, 148]. Berberine, a compound extracted from *Coptis chinensis*, is renowned for its medicinal properties in addressing cancers, bacterial infections, diabetes, and cardiovascular issues. Liu et al. discovered that berberine effectively counteracts immunosuppression in lung cancer [21]. Mechanistically, berberine specifically binds to constitutive photomorphogenic 9 signalosome 5 (CSN5) and uses its deubiquitination activity to inhibit the PD-1/PD-L1 axis. This leads to the ubiquitylation and degradation of PD-L1, thereby increasing CTL activity and cytotoxicity against cancer cells. In addition, DHA reduces PD-L1 expression and counteracts immune evasion in lung cancer by modulating the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT), TGF-β, and STAT3 signaling pathways. This intervention effectively overcomes resistance to radiation therapy and improves its efficacy by enhancing radiation sensitivity [32]. Furthermore, Ravindran Menon et al. showed that EGCG treatment suppressed the PD-L1 and PD-L2 expression induced by IFN-γ and inhibited Janus kinase (JAK)-STAT signaling, thereby enhancing CTL responses [38]. 18β-glycyrrhetinic acid (GLA), the principal metabolite of glycyrrhizic acid (GL) extracted from licorice root, is noted for its antiviral, anticancer, and immunomodulatory properties. Ma et al. demonstrated that GLA suppresses lung cancer by enhancing $CD8^+$ T cell activation [63]. Additionally, GLA prevents arachidonic acid-mediated apoptosis of $CD8^+$ T cells by inhibiting CD36 expression, thereby strengthening the immune response.

Regulation of other immune cells

Tregs, a subgroup of $CD4^+$ T cells, are essential for maintaining immune homeostasis and can inhibit T lymphocyte functions after activation. Macrophages in the TME secrete chemokines to recruit Tregs from peripheral blood to the tumor site, leveraging their immunosuppressive functions to evade immune detection [149]. Artesunate is a water-soluble derivative of artemisinin, which has been found to possess a variety of anti-tumor mechanisms, including the reversal of tumor immunosuppression. Zhang et al. discovered that artesunate can significantly inhibit the production of PGE2 by suppressing the expression of cyclooxygenase-2 (COX-2) in cervical cancer cells [13]. This leads to a reduction in the expression of forkhead box protein P3 (FOXP3) in T cells and a decrease in the percentage of $CD4^+CD25^+$ Tregs in peripheral blood. *Ganoderma lucidum* polysaccharides (GLPS) are among the most important bioactive compounds in *Ganoderma lucidum*. Li et al. demonstrated that GLPS treatment inhibits the Notch1 signaling pathway and FOXP3 expression by upregulating miR-125b [50]. This results in a reduction in the accumulation and activity of Tregs, thereby inhibiting liver cancer growth.

Th1 and Th2 cells are other $CD4^+$ T cell subsets. Th1 cells primarily secrete cytokines like IFN-γ, TNF-α, and IL-2, which facilitate the CTL-mediated anti-tumor responses. Conversely, Th2 cells produce cytokines such as IL-4, IL-6, and IL-13 to support B cells in generating antigen-specific antibodies and participating in humoral immunity [150]. Normally, there exists a delicate balance between Th1 and Th2 cells due to their cytokine secretion, but cancers often skew this balance towards Th2, which contributes to tumor immune evasion [151]. Curcumin is the principal active component of a yellow pigment extracted from the root of *Curcuma longa*. It is recognized as a potent anti-cancer medicine and a potential immune adjuvant. In general, curcumin exerts its anti-tumor immune functions by enhancing $CD4^+$ and $CD8^+$ T cell populations within the TME and redirecting the Th2 cells towards Th1 cells. This results in an increased Th1-mediated immune response and enhanced secretion of IFN-γ [29]. Saikosaponin A (SSA), a triterpenoid glycoside derived from *Radix Bupleuri*, is known for its anti-inflammatory, immunomodulatory, and anti-tumor effects. Zhao et al. conducted a study demonstrating SSA's inhibitory effect on breast cancer [91]. Their results indicated that SSA significantly enhanced the anti-tumor immune response, as evidenced by increased infiltration of $CD4^+$ and $CD8^+$ T cells in the TME and a shift in the Th1/Th2 balance towards a Th1 response. SSA was shown to upregulate the expression of IL-12, IL-12 receptor, and STAT4, thereby facilitating Th1 differentiation. This was corroborated by elevated serum levels of IFN-γ and IL-12 and lowered levels of IL-4 and IL-10.

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous group of cells originating from the bone marrow, serving as precursors to DCs, macrophages, and granulocytes. MDSCs suppress immune responses through various mechanisms and pathways, including inhibiting T cell activation, inducing T cell anergy, suppressing NK cell cytotoxicity, and promoting

tumor-supportive macrophages. They secrete Arg-1, iNOS, and ROS to hinder T cell activity and enhance Tregs' immunosuppressive effects [152]. Studies by Bu et al. demonstrated that GLPS could assist gemcitabine against tumors [51]. They observed that GLPS significantly reduced the chemotherapy-induced increase of MDSCs in breast and lung cancers, decreased the proportion of M2 macrophages while increasing M1 macrophages, promoted the proliferation and differentiation of Th1 cells and CTLs, and reversed gemcitabine-induced T cell depletion. GL is a glycoside composed of two molecules of glucuronic acid that decompose into GLA in the body. Juin et al. reported that GL inhibited melanoma growth by inducing apoptosis. Meanwhile, GL inhibited phospho-STAT3-mediated immune suppression by Tregs and MDSCs in melanoma. Notably, FOXP3, glucocorticoid-induced TNF receptor (GITR), and CTLA4 were downregulated in Tregs, while COX-2, PGE2, and Arg-1 were inhibited in MDSCs [66, 67].

Integration of nano-delivery systems and TCM active ingredients in tumor immunotherapy

Nano-drug delivery systems are technologies that deliver drugs to the body through a variety of nanocarriers, such as lipids, polymers, inorganic materials, and biomimetic materials. The combination of nano-delivery systems with active ingredients in TCM offers several advantages, including enhanced drug stability, prolonged circulation time in the bloodstream, controlled and sustained drug release, and targeted accumulation at tumor sites. This integration not only bolsters the immune system's response against tumor cells but also improves overall treatment outcomes (Table 2) [153–229].

Lipid-based nano-delivery systems with TCM active ingredients

Lipid-based nano-delivery systems are a widely used and effective platform for drug delivery. They utilize the biocompatibility and structural characteristics of lipids to encapsulate and transport drugs.

Liposomes

Liposomes, characterized by their phospholipid bilayer structure, offer unique advantages for TCM delivery due to their dual loading capacity—encapsulating hydrophilic compounds within the aqueous core and hydrophobic actives within the lipid bilayers [230]. Their excellent biocompatibility, derived from endogenous phospholipid components, minimizes immunogenicity risks while enabling penetration through biological barriers [231]. Notably, this biomimetic design has been leveraged to co-deliver synergistic TCM active ingredients and other drugs for enhanced anti-tumor effects. However, liposomes are rapidly cleared and physically unstable in vivo, so they are often modified to overcome these limitations. Zhu et al. replaced cholesterol with ginsenoside Rg3 as a liposomal membrane material, allowing the liposomes to target cancer cells and the TME through recognition of glucose transporter 1 (GLUT1) [191, 192]. Utilizing this functional liposome loaded with paclitaxel (Rg3-PTX-LPs) significantly promotes tumor cell apoptosis, reshapes immunosuppressive TME, and reverses multidrug resistance (MDR). The glucose chains present in ginsenoside Rg3 exhibit a specific affinity towards the GLUT1 located within the blood–brain barrier (BBB), thereby facilitating the increased translocation of liposomes into the brain. This indicates that Rg3-PTX-LPs have the potential for treating glioma. Xu et al. substituted cholesterol with GL and loaded triptolide into the lipid bilayer, resulting in TP/GLLNP [200]. GL not only enhances the stability and fluidity of liposomes but also binds to GL receptors on the surface of liver cancer cells. The co-loaded drugs of TP/GLLNP exhibit enhanced cellular uptake, cytotoxicity, and immune activation. Additionally, Xin et al. designed thermosensitive liposomes with specific structure and function (Fig. 3A) [208]. Surface modification with CXCL10 greatly reduces the capture of liposomes by leukocytes. As a chemokine, CXCL10 can activate immune cells, thereby enhancing their response against tumors. Furthermore, the incorporation of hyaluronic acid (HA)-conjugated oridonin on the liposome surface, combined with hyperthermia, synergistically enhances the anti-tumor efficacy of CXCL10.

Solid lipid nanoparticles and nanostructured lipid carriers

Solid lipid nanoparticles (SLNs) consist of solid-state natural or synthetic lipids, such as phospholipids and triglycerides, that encapsulate drugs to form a solid gel drug delivery system. SLNs offer advantages, including controlled drug release, prevention of drug degradation or leakage, and improved targeting ability [232, 233]. However, SLNs tend to form structures with perfect crystals, which restrict the loading and release of drugs. To overcome these limitations, researchers have developed nanostructured lipid carriers (NLCs) based on SLNs. NLCs are composed of a mixture of liquid and solid lipids with an irregular crystal structure. The addition of liquid lipids significantly enhances drug encapsulation efficiency and loading capacity while also providing better stability and controlled release characteristics [234, 235].

Table 2 Applications of active ingredients from TCM using nano-delivery systems in tumor immunotherapy

Active ingredients	Carrier Type	Features	Effects	Cancer/tumor types	Refs.
Angelica sinensis polysaccharide	Carrier-free nanodrug	Enzyme-sensitive	↑Th1/Th2 ratio	Lung cancer Breast cancer	[153]
Artesunate	Biomimetic nanoparticle	Redox-sensitive Photothermal	↑DCs ↑CTLs	Breast cancer	[154]
Artesunate	Biomimetic nanoparticle	ROS-sensitive Tumor targeting	↓M2 macrophages	Colorectal cancer	[155]
Artesunate	Nanoparticle	pH-sensitive	↑DCs	Breast cancer	[156]
Astragaloside IV and tanshinone IIA	Metal–organic framework	Improve solubility	↑CTLs	Liver cancer	[157]
Astragaloside III	Mesoporous silica nanoparticle	Photosensitive	↑NKs ↑CTLs	Colorectal cancer	[158]
Astragaloside IV and oxymatrine	Biomimetic nanoparticle	Tumor targeting Magnetic targeting	↑CTLs	Liver cancer	[159]
Astragaloside IV and ursolic acid	Nanoparticle	Tumor targeting	↑NKs ↑CTLs	Lung cancer	[160]
Astragalus polysaccharide	Carrier-free nanodrug	Abscopal effect	↑DCs ↑CTLs	Breast cancer	[161]
Astragalus polysaccharide	Carrier-free nanodrug	Improve solubility	↑CTLs	Liver cancer	[162]
Astragalus polysaccharide	Nanoparticle	Photoacoustic imaging	↑DCs ↑CTLs	Breast cancer	[163]
Baicalin	Nanoparticle	TAMs targeting	↓M2 macrophages	Melanoma	[164]
Celastrol	Nanoemulsion	Abscopal effect	↑DCs ↑NKs ↑CTLs ↑Th1/Th2 ratio ↓PD-L1 ↓MDSCs ↓Tregs	Melanoma	[165]
Celastrol	Nanoparticle	Tumor targeting	↑DCs ↑CTLs ↓MDSCs ↓Tregs ↓M2 macrophages ↓TGF-β, IL-10	Melanoma	[166]
Curcumin	Liposome	Tumor targeting	↑Th1/Th2 ratio	Colorectal cancer	[167]
Curcumin	Nanofiber	Improve solubility	↑CTLs ↓MDSCs	Lung cancer	[168]
Curcumin	Nanoparticle	pH/ROS-sensitive Tumor targeting	↑NKs ↓M2 macrophages ↓MDSCs ↓Tregs	Lung cancer	[169]
Curcumin	Nanoparticle colloidal dispersion	Improve solubility	↑CTLs ↑DCs	Esophageal cancer	[170]
Curcumin and camptothecin	Liposome	Across the BBB	↓PD-L1 ↓Tregs	Glioma	[171]
Curcumin and shikonin	Carrier-free nanodrug	Enhance therapeutic efficacy	↑DCs ↑CTLs ↓Tregs	Colorectal cancer	[172]
Curcumin, glycyrrhetic acid, and *Angelica sinensis* polysaccharide	Biomimetic nanoparticle	Liver targeting Redox-sensitive	↑CTLs	Liver cancer	[173]
Dihydroartemisinin	Nanoscale coordination polymer	Redox-sensitive	↑CTLs ↑DCs ↑M1 macrophages	Colorectal cancer	[174]
Dihydroartemisinin	Biomimetic nanoparticle	Redox-sensitive Sonodynamic Photoacoustic imaging	↑CTLs ↑DCs ↓Tregs	Liver cancer	[175]

Table 2 (continued)

Active ingredients	Carrier Type	Features	Effects	Cancer/tumor types	Refs.
Dihydroartemisinin	Layered double hydroxide	pH-sensitive	↑CTLs ↑DCs	Breast cancer	[176]
Dihydroartemisinin	Nanoscale coordination polymer	Redox-sensitive	↑CTLs ↑DCs ↑NKs	Colorectal cancer	[177]
Dihydroartemisinin	Nanosheet	Redox-sensitive	↑CTLs ↑DCs ↑M1 macrophages ↓Tregs	Liver cancer	[178]
Epigallocatechin-3-gallate	Gold nanoparticle	Reduce side effects	↑NKs	Bladder cancer	[179]
Epigallocatechin-3-gallate	Nanoparticle	pH-sensitive	↑CTLs ↑DCs ↓PD-L1	Breast cancer	[180]
Fucoidan	Iron oxide nanoparticle	Magnetic targeting	↑CTLs ↓Tregs ↓M2 macrophages ↓PD-L1	Breast cancer Colorectal cancer	[181]
Fucoidan	Nanomicelle	Tumor targeting	↑DCs ↑CTLs ↓Tregs ↓MDSCs ↓TGF-β, IL-10	Breast cancer	[182]
Fucoidan	Nanoparticle	Inhibit MDR	↑M1 macrophages	Colorectal cancer	[183]
Gambogic acid	Biomimetic nanoparticle	Tumor targeting	↑DCs ↑CTLs ↓PD-1/PD-L1	Colorectal cancer	[184]
Gambogic acid	Nanomicelle	pH-sensitive Tumor targeting	↑CTLs ↓Tregs	Melanoma	[185]
Gambogic acid	Nanoparticle	Photothermal	↑DCs ↑CTLs ↓Tregs	Breast cancer	[186]
Ganoderma lucidum polysaccharide	Gold nanoparticle	Enhance therapeutic efficacy	↑DCs ↑CTLs	Breast cancer	[187]
Ganoderma lucidum polysaccharide	Nanoparticle	Radiosensitization	↑DCs ↑CTLs ↑Th1/Th2 ratio	Breast cancer	[188]
Ginsenoside Rg3	Biomimetic nanoparticle	Tumor targeting	↑DCs ↑CTLs	Breast cancer	[189]
Ginsenoside Rg3	Carbon nanotube	Enhance therapeutic efficacy	↑CTLs ↓PD-1/PD-L1	Breast cancer	[190]
Ginsenoside Rg3	Liposome	Across the BBB Tumor targeting	↑CTLs ↓M2 macrophages ↓MDSCs ↓Tregs	Glioma	[191]
Ginsenoside Rg3	Liposome	Inhibit MDR Tumor targeting	↓M2 macrophages ↓MDSCs ↓PD-L1	Breast cancer	[192]
Ginsenoside Rg3	Nanoparticle	Mitochondrial targeting Enhance penetration	↑DCs ↑CTLs ↑Th1/Th2 ratio ↓Tregs ↓PD-L1	Breast cancer	[193]
Ginsenoside Rg3 and quercetin	Cyclodextrin nanoparticle	Tumor targeting	↑DCs ↑CTLs ↓M2 macrophages ↓MDSCs ↓Tregs	Colorectal cancer	[194]
Ginsenoside Rh2	Biomimetic nanoparticle	pH/redox-sensitive Tumor targeting MRI	↑DCs ↑CTLs ↓Tregs	Osteosarcoma	[195]

Table 2 (continued)

Active ingredients	Carrier Type	Features	Effects	Cancer/tumor types	Refs.
Ginsenoside Rh2	Nanoparticle	Photothermal	↑DCs ↑M1 macrophages	Breast cancer	[196]
Glycyrrhetinic acid	Biomimetic nanoparticle	Tumor targeting	↑CTLs	Leukemia Colorectal cancer	[197]
Glycyrrhizic acid	Biomimetic nanoparticle	Photosensitive MRI	↑DCs ↑CTLs ↑M1 macrophages ↓Tregs ↓PD-L1	Melanoma	[198]
Glycyrrhizic acid and tanshinone IIA	Biomimetic nanoparticle	Across the BBB Tumor targeting	↑DCs ↑CTLs ↓M2 macrophages ↓Tregs	Glioblastoma	[199]
Glycyrrhizic acid and triptolide	Liposome	Tumor targeting	↓M2 macrophages	Liver cancer	[200]
Icaritin	Mesoporous silica nanoparticle	Tumor targeting Detect fluorescence	↑CTLs	Liver cancer	[201]
Icaritin	Nanoparticle	Enhance therapeutic efficacy	↑CTLs	Gastric cancer	[202]
Icaritin	Nanoparticle	Tumor targeting	↑DCs ↑CTLs ↓Tregs ↓MDSCs ↓M2 macrophages ↓TGF-β, IL-10	Liver cancer Melanoma	[203]
Lentinan and ursolic acid	Carrier-free nanodrug	Improve solubility Enhance therapeutic efficacy	↑DCs ↑CTLs ↑M1 macrophages	Colorectal cancer	[204]
Lentinan, pachymaran and *Tremella* polysaccharides	Nanosheet	pH-sensitive Photothermal	↑NKs	Breast cancer	[205]
Lycium barbarum polysaccharides	Nanoparticle	Photothermal Reduce side effects	↑Th1/Th2 ratio	Breast cancer	[206]
Norcantharidin	Nanoparticle	pH-sensitive	↑DCs ↑CTLs ↓Tregs ↓PD-L1	Breast cancer	[207]
Oridonin	Liposome	Tumor targeting Thermosensitive	↑NKs ↑CTLs ↑Th1/Th2 ratio ↑M1 macrophages	Melanoma	[208]
Oridonin	Nanoparticle	Tumor targeting Reduce side effects	↑Th1/Th2 ratio	Esophageal cancer	[209]
Oridonin	Nanoparticle	Tumor targeting pH/redox-sensitive	↑DCs ↓PD-L1	Breast cancer	[210]
Plumbagin and dihydrotanshinone I	Biomimetic nanoparticle	Tumor targeting pH-sensitive	↑DCs ↑NKs ↑CTLs ↑M1 macrophages ↓Tregs ↓MDSCs ↓TGF-β, IL-10	Liver cancer	[211]
Puerarin	Nanoemulsion	Tumor targeting	↑CTLs ↑Th1/Th2 ratio ↓Tregs ↓MDSCs ↓M2 macrophages	Breast cancer	[212]
Resveratrol	Nanoparticle	Enhance therapeutic efficacy	↓PD-L1	Oral cancer	[213]

Table 2 (continued)

Active ingredients	Carrier Type	Features	Effects	Cancer/tumor types	Refs.
Salvianolic acid B	Liposome	Enhance therapeutic efficacy	↑CTLs ↑Th1/Th2 ratio ↑M1 macrophages ↓Tregs ↓MDSCs ↓TGF-β, IL-10	Breast cancer	[214]
Salvianolic acid B	Nanoparticle	Photothermal Photoacoustic imaging Tumor targeting	↑DCs ↑CTLs ↑M1 macrophages ↓Tregs ↓MDSCs ↓TGF-β, IL-10	Breast cancer	[215]
Shikonin	Biomimetic nanoparticle	Tumor targeting Photothermal	↑DCs ↑CTLs ↑M1 macrophages ↓Tregs ↓MDSCs	Breast cancer Melanoma	[216]
Shikonin	Biomimetic nanoparticle	Tumor targeting TAMs targeting	↑DCs ↑CTLs ↓Tregs ↓PD-L1 ↓M2 macrophages	Colorectal cancer	[217]
Shikonin	Liposome	Redox-sensitive	↑CTLs	Breast cancer	[218]
Shikonin	Liposome	pH/redox-sensitive Reduce side effects	↑DCs ↑CTLs ↑Th1/Th2 ratio ↓Tregs ↓TGF-β, IL-10	Melanoma	[219]
Shikonin	Metal-phenolic network	Redox-sensitive	↑DCs ↑NKs ↑CTLs ↑Th1/Th2 ratio ↑M1 macrophages ↓Tregs	Breast cancer	[220]
Shikonin	Nanoparticle	Tumor targeting	↑DCs ↑CTLs ↓Tregs	Breast cancer	[221]
Shikonin	Nanomicelle	Tumor targeting pH-sensitive	↑DCs ↑CTLs ↓Tregs ↓PD-L1 ↓M2 macrophages ↓TGF-β, IL-10	Colorectal cancer	[222]
Shikonin	Nanoparticle	Tumor targeting	↑DCs ↑CTLs ↑NKs ↓MDSCs	Colorectal cancer	[223]
Solamargine	Biomimetic nanoparticle	Tumor targeting pH-sensitive	↑NKs ↑DCs ↑CTLs ↑M1 macrophages ↓MDSCs ↓TGF-β, IL-10	Prostate cancer	[224]
Tetramethylpyrazine	Liposome	Tumor targeting	↑CTLs	Lung cancer	[225]
Triptolide	Biomimetic nanoparticle	Redox-sensitive Tumor targeting Reduce side effects	↑DCs ↑CTLs	Melanoma	[226]
Triptolide	Biomimetic nanoparticle	Tumor targeting Inhibit MDR Reduce side effects	↑M1 macrophages	Ovarian cancer	[227]

Table 2 (continued)

Active ingredients	Carrier Type	Features	Effects	Cancer/tumor types	Refs.
Triptolide	Dendrimer	Across the BBB TAMs targeting Reduce side effects	↑M1 macrophages	Glioblastoma	[228]
β-elemene	Nanosheet	Enhance therapeutic efficacy	↑DCs ↑CTLs ↑M1 macrophages ↓TGF-*β*, IL-10	Melanoma	[229]

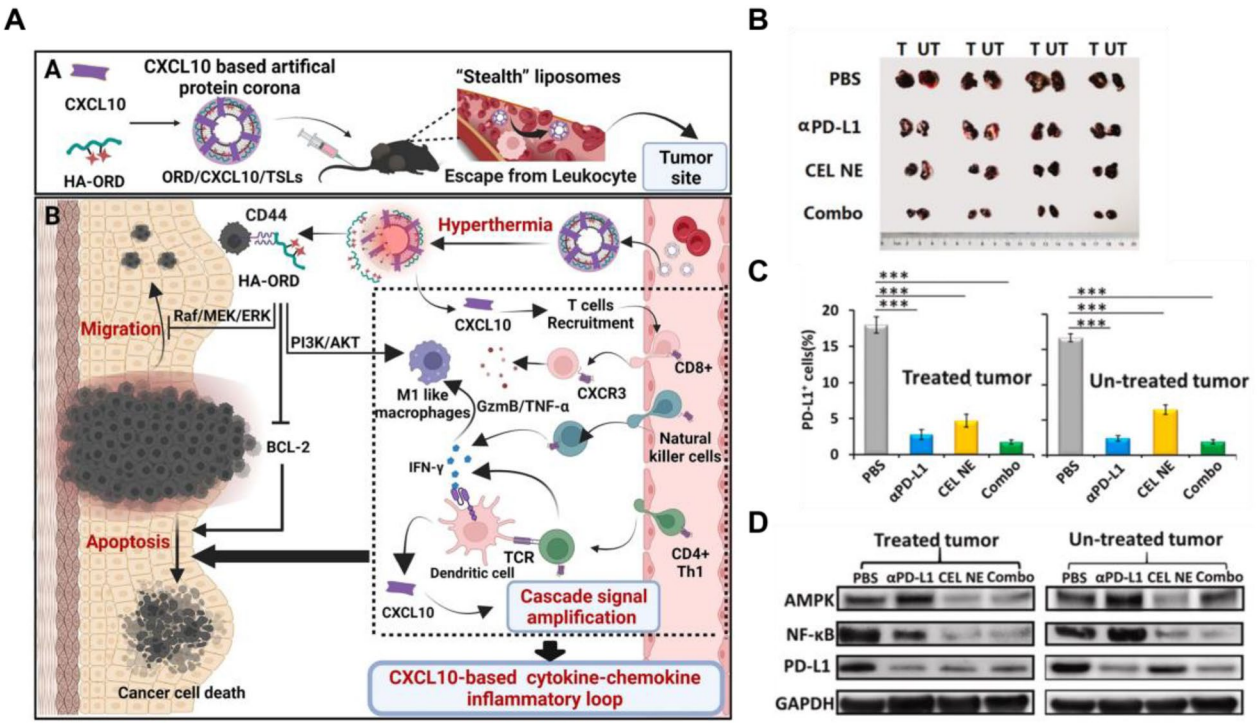


Fig. 3 Lipid-based nano-delivery systems with TCM active ingredients. **A** Schematic diagram of thermosensitive liposomes for melanoma chemoimmunotherapy. Reproduced with permission of Ref. [208]. Copyright © 2022 Elsevier. **B** Tumor images, **C** flow cytometry analysis and quantitation, and **D** western blot analysis of CEL NE treatment on B16F10 bilateral tumor model. Reproduced with permission of ref. [165]. Copyright © 2020 Elsevier

Nanoemulsions, microemulsions and self-microemulsifying drug delivery systems

Nanoemulsions and microemulsions overcome critical limitations of traditional emulsions in TCM delivery through nanoscale droplet sizes, enabling enhanced physical–chemical stability and bioavailability for poorly soluble active ingredients [236]. Their thermodynamic stability eliminates phase separation during long-term storage, particularly advantageous for TCM formulations containing volatile oils [237]. The self-microemulsifying drug delivery system comprises surfactants, co-surfactants, and oil phases, which can spontaneously disperse in water to form microemulsions [238]. Persistent challenges include gastrointestinal irritation from high surfactant or co-surfactant and limited targeting specificity. Emerging strategies employ TCM-derived biocompatible surfactants to mitigate toxicity. Qiu et al. used an ultrasonic emulsification method to prepare a celastrol nanoemulsion (CEL NE), which enhanced the immunogenicity in melanoma treatment [165]. CEL NE effectively induced tumor immunogenic cell death (ICD) and improved both local and distant therapeutic effects by reducing PD-L1 expression (Fig. 3B–D). Xu et al. chose soybean lecithin, noted for its good biocompatibility, as the primary emulsifier to prepare a nanoemulsion carrying puerarin (nanoPue) [212]. The surface of nanoPue was modified with a targeting

ligand aminoethyl anisamide (AEAA), which targets the sigma-1 receptor, facilitating efficient uptake of the nanoparticles by tumor cells. NanoPue improves the solubility and bioavailability of puerarin, effectively reshapes the immune microenvironment, and serves as a promising adjuvant for chemotherapy and checkpoint blockade immunotherapy.

Polymer-based nano-delivery systems with TCM active ingredients

The polymer-based nano-delivery systems represent cutting-edge delivery methods that enhance drug stability and solubility while also featuring easy modification and biodegradability.

Polymer micelles

Polymer micelles are generated by the self-assembly of amphiphilic block copolymers in water. The hydrophobic core shields lipophilic TCM compounds from degradation and improves solubility, while the hydrophilic shell helps avoid clearance by the reticuloendothelial system (RES) and extends blood circulation time. Through the enhanced permeability and retention (EPR) effect, polymer micelles can accumulate in tumor tissues, thereby boosting drug efficacy. Additionally, the hydrophilic segments can be functionalized with specific antibodies, ligands, peptides, or other stimulus-responsive elements to enable targeted delivery and controlled release [239, 240]. Key limitations in polymer micelles include poor biodegradability and limited drug loading of polar components. Guo et al. developed a functionalized doxorubicin-loaded micelle using fucoidan (FD/DOX), which can effectively bind to activated platelets via P-selectin, enabling the tracking of tumor tissues and circulating tumor cells [182]. FD/DOX is capable of inhibiting TGF-β expression, reversing immunosuppressive microenvironment, and demonstrating excellent anti-tumor and anti-metastatic efficacy. Deng et al. designed a self-assembling nanomedicine constructed from an amphiphilic conjugate F3 peptide-low molecular weight heparin (LMWH)-hydrazone-GA (FLG) [185]. The F3 peptide targets tumor vascular endothelial cells and acts as a ligand for FLG. The hydrophilic LMWH and hydrophobic drugs, acting as VEGF/VEGF receptor 2 inhibitors, can be released under acidic conditions to induce vascular normalization. Additionally, when combined with CCL5/C-C motif chemokine receptor (CCR)5 pathway blockers, FLG further promotes vascular repair and TME remodeling. Li et al. utilized two materials, folic acid-conjugated 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-poly(ethylene glycol) (DSPE-PEG) and polyethyleneimine (PEI)-polycaprolactone (PCL), to co-deliver shikonin and PD-L1 small interfering RNA (siRNA) (Fig. 4A) [222]. The PCL component forms a hydrophobic core that encapsulates shikonin, while the PEI segment is employed for loading PD-L1 siRNA. This co-delivery system enhances tumor immunotherapy by simultaneously inducing ICD, repolarizing M2-like TAMs, and suppressing PD-L1 expression (Fig. 4B and C).

Polymer nanoparticles

Polymer nanoparticles are solid spherical particles composed of polymer materials obtained through monomer polymerization, polymer dispersion, or self-assembly of amphiphilic polymers [241, 242]. Polymer nanoparticles possess the advantage of biodegradability, which is essential for the sustained release of TCM active ingredients. Their surface engineering versatility enables controlled drug release and active tumor targeting, particularly in cancer treatment, where they hold significant application value [243]. Xu et al. explored a HA-modified polydopamine (PDA) nanocarrier loaded with ursolic acid and ASIV for combined chemotherapy, immunotherapy, and photothermal therapy of lung cancer (Fig. 4D–F) [160]. HA targets the CD44 receptor on tumor cell surfaces, enhancing drug accumulation within the tumor. This nanoparticle not only releases drugs to inhibit tumor growth and improve antitumor immunity but also enhances treatment efficacy through photothermal effects. Xiong et al. constructed PEGylated poly(lactic-co-glycolic acid) (PLGA) nanoparticles encapsulating *Astragalus* polysaccharide and gold nanorods, combined with focused ultrasound technology for breast cancer treatment [163]. The study demonstrated that these nanoparticles not only effectively delivered drugs to tumor sites but also served as contrast agents for tumor detection. Zhu et al. developed a T7 peptide-modified nanoparticle based on carboxymethyl chitosan (CMCS) for co-delivery of docetaxel and curcumin, aiming to enhance the chemoimmunotherapy against lung cancer [169]. This nanoparticle specifically targets the transferrin receptor (TfR) overexpressed on lung cancer cells and precisely releases drugs in response to pH and ROS levels.

Dendrimers

Dendrimers are synthetic polymers with a tree-like three-dimensional structure characterized by a central small molecule core, multiple branching units, and numerous functional groups on the periphery. The cavities of dendrimers can be utilized for drug encapsulation, effectively overcoming challenges related to drug solubility, permeability, and biocompatibility [244, 245]. Liaw et al. designed a generation-4 hydroxyl-terminated

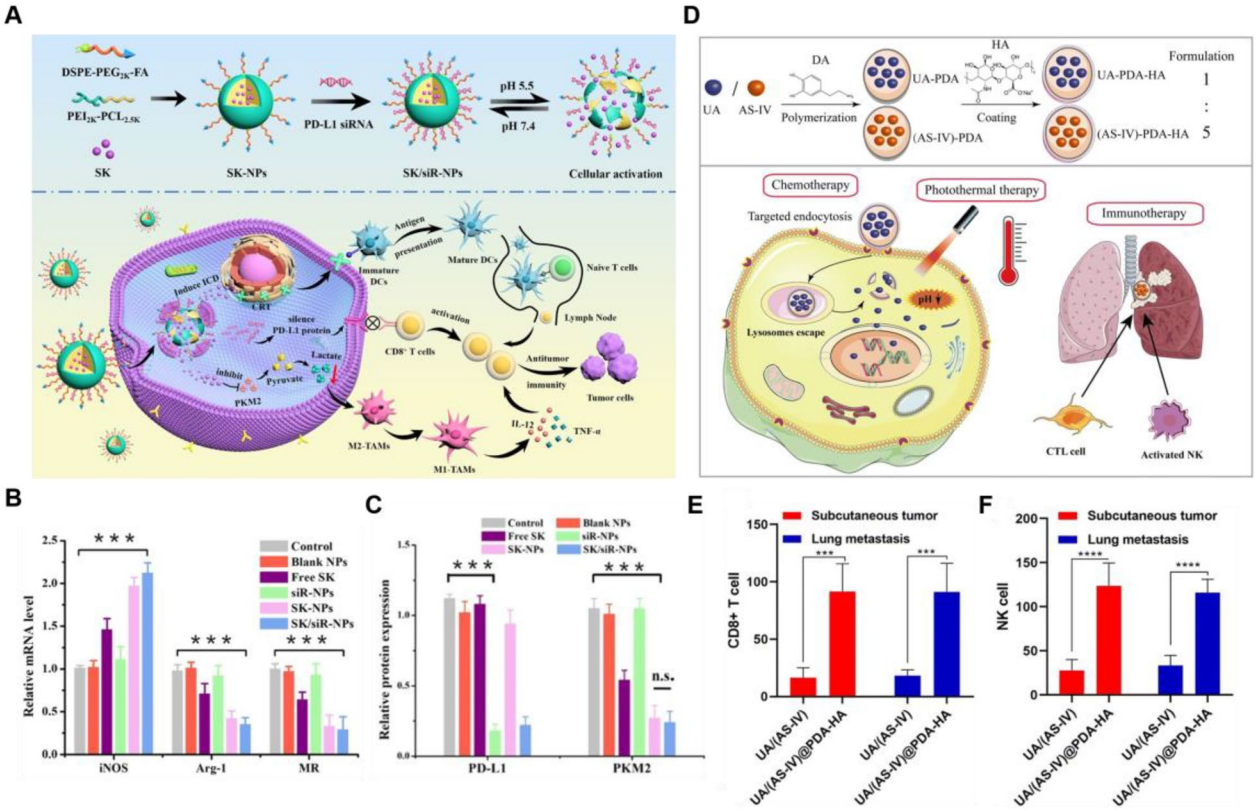


Fig. 4 Polymer-based nano-delivery systems with TCM active ingredients. **A** Schematic diagram of co-delivery polymer micelles to improve immunosuppressive TME. **B** mRNA levels of M1-TAM and M2-TAM markers and **C** PD-L1 and PKM2 expression after treatment in vitro. Reproduced with permission of Ref. [222]. Copyright © 2020 American Chemical Society. **D** Schematic illustration of drug-loaded PDA-HA nanoparticle in combination with chemo-immuno-photothermal therapy. **E** The corresponding quantification of the number of $CD8^+$ T cells and **F** NK cells. Reproduced with permission of Ref. [160]. The copyright is owned by the author under the Creative Commons Attribution-NonCommercial 3.0 Unported Licence

polyamidoamine dendrimer-triptolide conjugate that can penetrate the damaged BBB and selectively target brain tumors and TAMs [228]. The dendrimers significantly reduce the systemic toxicity of triptolide, promoting its induction of anti-tumor immunity.

Inorganic material-based nano-delivery systems with TCM active ingredients

Inorganic nanomaterials have emerged as promising candidates in biomedicine compared to organic nanomaterials. They have the advantages of simple preparation process, high controllability of shape and size, and easy surface modification. Additionally, these materials exhibit unique optical, electrical, and magnetic properties, which enable potential functions such as imaging enhancement, targeted delivery, and synergistic drug therapy [246]. However, inorganic materials may not be biodegradable in some cases and may cause toxicity problems with long-term use.

Metal and metal compound nanoparticles

Gold nanoparticles are the most widely used type of metal nanomaterial, with applications in hyperthermia and photothermal therapy, drug delivery systems for cancer treatment, and the development of biosensors and diagnostic tools. A key characteristic of gold nanoparticles is their ease of surface modification and binding, which facilitates non-covalent TCM loading while maintaining good stability and biocompatibility [247]. The use of EGCG attached to gold nanoparticles (EGCG-pNG) is more effective in treating bladder cancer compared to free EGCG [179]. EGCG-pNG inhibits tumor cell growth by inducing apoptosis and enhances anti-tumor immunity (Fig. 5A–C). Furthermore, EGCG-pNG can prevent liver damage caused by high doses of EGCG.

Silver nanoparticles possess excellent antibacterial properties and optical characteristics, which make them widely used in fields such as antimicrobial coatings for medical supplies and the treatment of infectious diseases.

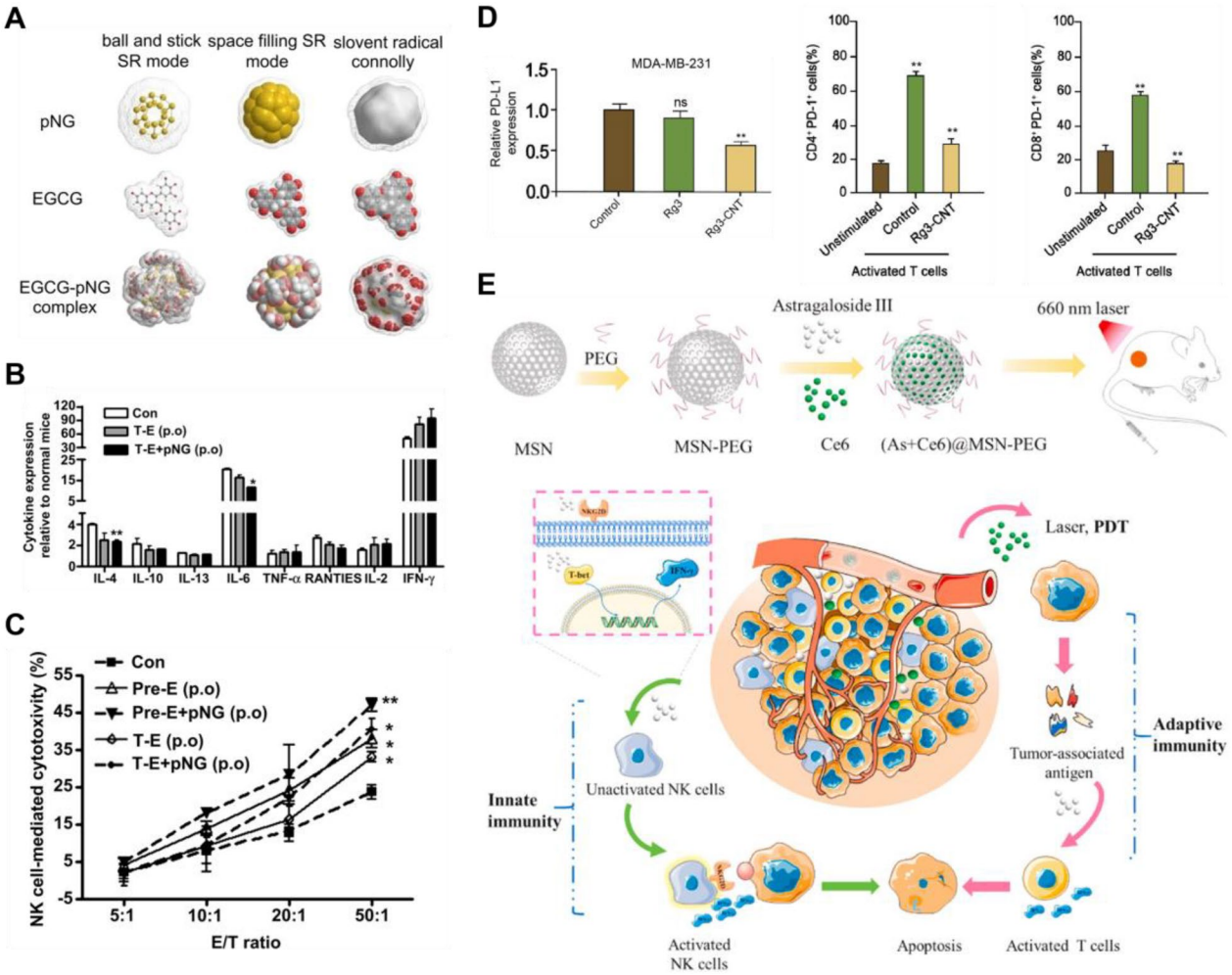


Fig. 5 Inorganic material-based nano-delivery systems with TCM active ingredients. **A** Prediction of EGCG-pNG complex assembly. **B** Serum cytokine levels and **C** NK cytotoxicity in tumor-bearing mice after treatment. Reproduced with permission of Ref. [179]. Copyright © 2011 Elsevier. **D** Ginsenoside Rg3-loaded carbon nanotubes suppress the PD-1/PD-L1 pathway in TNBC. Reproduced with permission of ref. [190]. The copyright is owned by the author under the Creative Commons Attribution License. **E** Schematic representation of synergistic antitumor immunotherapy mechanism of MSN nanoparticles. Reproduced with permission of Ref. [158]. Copyright © 2021 Elsevier

Their surface properties and chemical modifications enable additional drug delivery functions, allowing them to act as carriers or stabilizers in nano-delivery systems to improve drug solubility and stability [248].

Iron oxide exists in two primary forms: Fe_2O_3 and Fe_3O_4. The magnetic properties of Fe_3O_4, particularly as magnetic nanoparticles, allow for targeted treatment of tumors via external magnetic fields. Iron oxide nanoparticles have been extensively utilized in magnetic resonance imaging (MRI), targeted drug delivery, and thermal therapy [249]. Chiang et al. developed a magnetic nanomedicine composed of superparamagnetic iron oxide nanoparticles, fucoidan, and aldehyde-functionalized dextran (IO@FuDex) [181]. Magnetic navigation effectively directs IO@FuDex to tumor sites, reducing off-target effects. Dextran can be conjugated with various antibodies to maximize the restoration of tumor-infiltrating lymphocyte vitality, particularly when coupled with immune checkpoint inhibitors and T-cell activators.

Zinc oxide and titanium dioxide nanoparticles exhibit excellent photothermal and photodynamic properties, which can significantly enhance the drug-controlled release and therapeutic effects [250, 251].

Carbon-based nanomaterials

Carbon dots, which are zero-dimensional nanomaterials with particle sizes smaller than 10 nm, exhibit notable photoluminescent properties. They are easy to synthesize, highly stable, biocompatible, and low-toxicity,

making them suitable for applications in anti-tumor, antibacterial, and central nervous system diseases [252].

Carbon nanotubes are hollow cylindrical structures composed of carbon atoms arranged in a hexagonal pattern and curled into tube-like shapes. Due to their high specific surface areas and drug-loading capacity, carbon nanotubes have been used as TCM delivery carriers, allowing for controlled release and improving therapeutic effects [253]. Luo's research shows that loading ginsenoside Rg3 onto carbon nanotubes further enhances its inhibitory effect on TNBC cell growth through suppression of the PD-1/PD-L1 axis (Fig. 5D) [190].

Graphene oxide is a two-dimensional carbon material derived from the oxidation of graphene. It retains a hexagonal arrangement of carbon atoms similar to graphene but contains oxygen-containing functional groups. These groups impart good water solubility and chemical reactivity to graphene oxide [254].

Silicon-based nanomaterials

Mesoporous silica nanoparticles (MSNs) feature controllable pore sizes and distributions, allowing TCM active ingredients to be loaded inside the pores via physical adsorption or chemical modification. In addition, MSNs possess good biocompatibility, stability, and ease of modification, enabling controlled release and targeted delivery of drugs [255]. Wu et al. prepared PEGylated MSNs loaded with astragaloside III and chlorin e6 (Ce6) to serve as anti-tumor immune activators and photosensitizers (Fig. 5E) [158]. Ce6 is known for its anti-tumor activities, effectively inducing tumor apoptosis and promoting immune cell infiltration into tumors, thereby enhancing the anti-tumor function of $CD8^+$ T cells. Xiang et al. constructed a multifunctional nanocarrier consisting of MSNs loaded with AS1411 aptamer, icaritin, and fluorescein isothiocyanate (FITC) [201]. Given that nucleolin is overexpressed in various malignant tumors, the AS1411 aptamer can specifically bind to nucleolin on the cell membrane surface, leading to the release of FITC and icaritin from the MSNs for combined detection and therapy purposes.

Biomimetic material-based nano-delivery systems with TCM active ingredients

Biomimetic nanomaterials represent a novel class of carriers derived from living organisms. They are designed to mimic the natural biological characteristics and functions of cells and are known for their high biocompatibility. These materials offer substantial advantages in targeted drug delivery, including enhanced therapeutic efficacy and reduced adverse effects [256]. The limitations are the difficulty of standardized extraction and preparation of bionic materials and the possible problem of insufficient encapsulation for TCM active ingredients.

Albumin

Albumin, the most abundant protein in plasma, is distinguished by its excellent biocompatibility and biodegradability and has shown safety and reliability in clinical applications. Its structural properties enable it to bind effectively with a wide range of TCM active ingredients, potentially protecting these drugs from degradation and metabolism in the body, thereby optimizing their pharmacokinetic properties. Additionally, albumin's ability to bind to receptors overexpressed in tumor tissues and cells provides a unique advantage for active targeted cancer therapy [257]. Xiong et al. synthesized a platinum-based prodrug containing two artesunate molecules (A-Pt), which can be reduced to cisplatin and artesunate under high levels of glutathione (GSH) [154]. They further encapsulated A-Pt and near-infrared-II photothermal agent IR1048 with human serum albumin (HSA) to form nanoparticles (Fig. 6A). IR1048 enables mild hyperthermia therapy and enhances the therapeutic efficacy of A-Pt. Du et al. developed a nanocomplex with multiple immune activation functions consisting of hollow MnO_2 nanoparticles loaded with GL and Ce6-modified DNAzyme, encapsulated within bovine serum albumin (BSA) [198]. Upon entering the TME, the released Mn^{2+} ions catalyze the cleavage of PD-L1 mRNA by DNAzyme, activating the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) signaling pathway and improving MRI quality in the tumor region. Additionally, the ICD induced by GL and photodynamic therapy further enhances the efficacy of immunotherapy.

Cell membrane vesicles

Cell membrane vesicles derived from cells inherit the surface characteristics and functional properties of their parental cells, resulting in excellent biocompatibility, low immunogenicity, and prolonged circulation times. Utilizing various cell membrane vesicles as coating materials for nanocarriers not only enables evasion of immune surveillance but also effectively enhances targeted precision therapy [258]. Guo et al. designed a curcumin-loaded nanomicelle incorporating glycyrrhetic acid-*Angelica sinensis* polysaccharide-disulfide bond-curcumin (GACS-Cur) to demonstrate superior targeting ability and anti-tumor effects in liver cancer treatment [173]. To further enhance long-term circulation, GACS-Cur was shielded with red blood cell membranes to evade immune system clearance. In the presence of high levels of GSH in the TME, GACS-Cur dissociates,

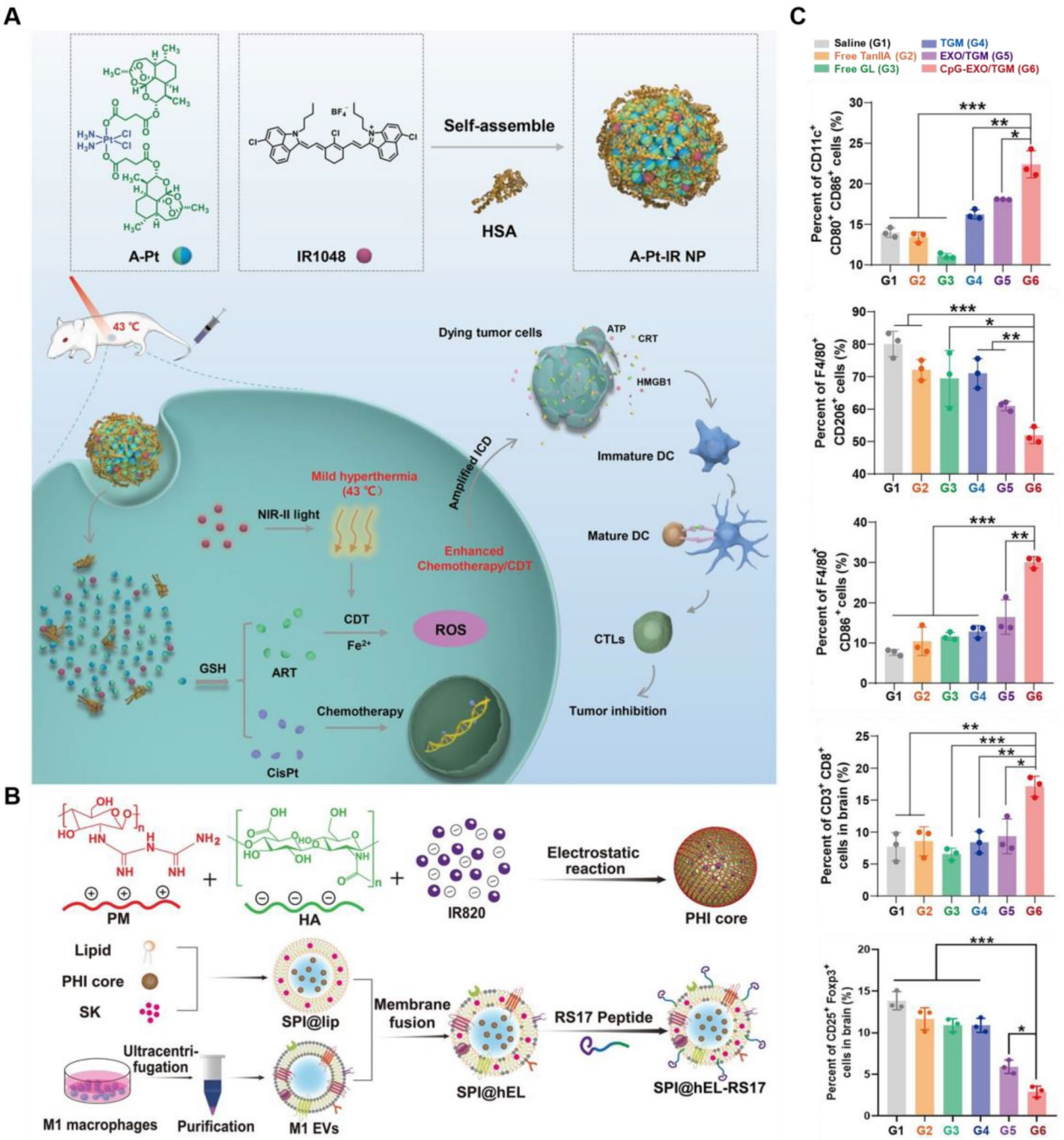


Fig. 6 Biomimetic material-based nano-delivery systems with TCM active ingredients. **A** Schematic diagram of hyperthermia enhanced chemotherapy and immunotherapy with HSA nanoparticles. Reproduced with permission of Ref. [154]. Copyright © 2022 Wiley–VCH GmbH. **B** Preparation of hEL-RS17. Reproduced with permission of Ref. [216]. Copyright © 2023 Wiley–VCH GmbH. **C** Flow cytometry analysis of mature DCs, M2-TAMs, M1-TAMs, CTLs, and Tregs in glioblastoma tissues. Reproduced with permission of Ref. [199]. Copyright © 2023 American Chemical Society

releasing the drug to directly kill liver cancer cells, as well as increase the infiltration of $CD8^+$ T cells and the expression of IL-2, IFN-γ, and TNF-α. Zhang et al. encapsulated ginsenoside Rg3 in PLGA nanoparticles and coated them with tumor cell-derived microvesicles, resulting in Rg3-PLGA@TMVs [189]. Due to their homologous targeting properties, Rg3-PLGA@TMVs are precisely delivered to specific tumors, significantly enhancing anti-tumor immunity. Moreover, Rg3-PLGA@TMVs can improve the efficacy of chemotherapy while

reducing toxic side effects. Tang et al. developed a hybrid nanoplatform called hEL-RS17 (Fig. 6B) [216]. Derived from M1 macrophage extracellular vesicles and decorated with RS17 peptide, hEL-RS17 specifically binds to CD47 on tumor cells. It blocks the CD47-SIRPα signaling pathway, facilitating active targeting of tumor cells and reshaping the TAM phenotype. Additionally, hEL-RS17 co-encapsulates shikonin, photosensitizer IR820, and polymetformin, synergistically exerting potent anti-tumor effects.

Exosomes

Exosomes, a type of extracellular vesicles, are formed in endosomes and possess a smaller size with a relatively complex composition and structure [259]. Cui et al. constructed self-assembled tanshinone IIA-GL nanomicelles, which were subsequently encapsulated with endogenous serum exosomes [199]. CpG oligonucleotide (CpG-ODN), an immune adjuvant, was then inserted into the exosome membrane to obtain CpG-EXO/TGM. CpG-EXO/TGM can evade phagocytosis by the mononuclear phagocyte system (MPS) and cross the BBB through TfR-mediated transcytosis, ultimately achieving efficient drug release within tumor cells (Fig. 6C). Li et al. prepared biomimetic hybrid nanoparticles (miR497/TP-HENPs) consisting of tumor-derived exosomes expressing CD47 and liposomes modified with the tumor-targeting peptide cRGD for the co-delivery of miR497 and triptolide [227]. The results demonstrated that miR497/TP-HENPs synergistically induced cell apoptosis by inhibiting the PI3K/AKT/mammalian target of rapamycin (mTOR) signaling pathway and overcame drug resistance in ovarian cancer by modulating macrophage polarization.

Other nano-delivery systems with TCM active ingredients

Carrier-free nanodrugs refer to drugs that possess sufficient biological activity and cell permeability, allowing them to enter cells directly without the assistance of nanocarriers. Wang et al. have developed an enzyme-sensitive tumor-targeting nanodrug delivery system called *Angelica sinensis* polysaccharide-peptide-doxorubicin (AP-PP-DOX) [153]. In this system, doxorubicin and polysaccharide can be rapidly released from AP-PP-DOX in the presence of MMP2. The polysaccharides not only serve as carriers but also act as effectors to improve the TME, enhance immune functions, and produce synergistic effects with chemotherapy drugs. Yan et al. designed self-delivering nanoparticles with a potent inducible ICD effect [172]. Curcumin and shikonin can self-assemble into nanoparticles through π–π stacking and hydrophobic interactions, exhibiting excellent stability, cellular uptake, and tumor accumulation.

Organic–inorganic hybrid materials combine the characteristics of both organic and inorganic materials. Guo et al. developed a nanoplatform based on a magnetic metal–organic framework (MOF) and platelet membrane coating (PmMN@Om&As) [159]. This platform facilitates the simultaneous delivery of oxymatrine and ASIV to the microenvironment of liver cancer. PmMN@Om&As features a large drug-carrying capacity and can evade clearance by the MPS, as well as target liver cancer tissues under a magnetic field. Duan et al. developed self-assembling nanoscale coordination polymer (NCP) core–shell nanoparticles (OxPt/DHA), with oxaliplatin prodrug in the core and dihydroartemisinin prodrug in the shell [174]. These nanoparticles could reduce uptake by the MPS and selectively release drugs within the TME, thereby activating immune responses and exerting anti-tumor effects. In mouse models, OxPt/DHA combined with anti-PD-L1 antibody was able to eradicate colorectal tumors, providing new strategies and experimental foundations for combination immunotherapy. Shi et al. constructed aluminum hydroxyphosphate nanoparticles loaded with CpG-ODN, covered by Fe-shikonin metal-phenolic networks (MPNs), for tumor vaccines [220]. After entering tumor cells, the MPN shell decomposes and effectively induces ICD. Subsequently, the aluminum nanoparticles absorb tumor cell lysates and activate anti-tumor immunity in conjunction with CpG-ODN.

Conclusions

The active ingredients of TCM can enhance anti-tumor immune responses by activating immune cells, regulating cytokine levels, and inhibiting immunosuppressive cells. They foster an immune microenvironment conductive to tumor elimination. Crucially, nanotechnology augments TCM's therapeutic potential through two distinct paradigms: TCM delivered by nano-system and TCM as part of the nano-system. In the former strategy, nano-delivery systems overcome inherent pharmaceutical limitations of TCM active ingredients by enhancing solubility, prolonging systemic circulation, and enabling tumor-targeted accumulation through both passive and active targeting mechanisms. In the latter approach, TCM-derived bioactive molecules serve as functional building blocks for nano-constructs, imparting intrinsic biocompatibility and synergistic therapeutic effects. Importantly, nano-formulated TCM demonstrates superior pharmacokinetic profiles compared to free counterparts, with marked improvements in bioavailability, tumor penetration depth, and immunomodulatory activity [214, 219, 226, 229]. The synergistic combination of TCM active ingredients with nano-delivery systems provides a viable guide for the development of next-generation immunotherapies with

higher efficacy and lower toxicity. It is a transformative strategy for overcoming the limitations of current cancer immunotherapies.

Despite the identification of tens of thousands of active ingredients in TCM, there is a limited number of reported ingredients with documented antitumor immunomodulatory effects. Several factors contribute to this. Firstly, current research predominantly emphasizes on the traditional uses and well-established components of TCM. Concurrently, the antitumor immunomodulatory effects of many ingredients remain underexplored or undiscovered, and systematic studies in this area are still needed. Additionally, the complex chemical compositions and multifaceted mechanisms of action of TCM make it challenging to elucidate their specific antitumor immunomodulatory effects [260–262]. For instance, the effects of active ingredients in TCM may vary according to doses, drug interactions, and tumor heterogeneity, thus affecting their immunomodulatory efficacy. Last but not least, challenges related to standardization, validation, clinical trials, and resources further hinder the research in this field. However, with ongoing advancements in scientific research technologies and more comprehensive studies (such as high-throughput screening and precision medicine), it is anticipated that future research will reveal additional TCM active ingredients for tumor immunotherapy.

Nanomedicine is a promising frontier in medical research. The integration of nano-delivery systems with TCM active ingredients has demonstrated enhanced and reliable therapeutic effects, encompassing nanosized TCM active ingredients and TCM active ingredients combined with other nanomedicines. Certain nanoparticles with unique physicochemical properties can not only respond to multiple stimuli for precise drug delivery but also integrate phototherapy, thermotherapy, and ultrasound therapy for improved immune-modulating and anti-tumor effects [263, 264]. Additionally, combinations of TCM active ingredients with chemotherapy, targeted therapy, and immunotherapy drugs often exhibit superior efficacy compared to monotherapy approaches [265]. Recent research has explored combining TCM active ingredients with gene therapies (such as siRNA, mRNA, and CRISPR-Cas9), offering promising, precise cancer treatments [266]. While nano-delivery systems offer numerous advantages, it is imperative to consider their stability, biocompatibility, toxicity, immunogenicity, drug release and targeting capabilities, as well as production costs and clinical translatability to ensure their safety and effectiveness. Future research should focus on optimizing nanocarrier design, discovering potential combination therapies, and validating clinical feasibility to pave the way for novel tumor immunotherapy.

Abbreviations

TCM	Traditional Chinese medicine
NKs	Natural killer cells
DCs	Dendritic cells
SIRP*α*	Signal regulatory protein *α*
GA	Gambogic acid
TNBC	Triple-negative breast cancer
Siglec-10	Sialic acid-binding Ig-like lectin 10
TAMs	Tumor-associated macrophages
Arg-1	Arginase-1
VEGF	Vascular endothelial growth factor
CCL	C-C motif chemokine ligand
STAT	Signal transducer and activator of transcription
DHA	Dihydroartemisinin
TME	Tumor microenvironment
EGCG	Epigallocatechin-3-gallate
miR	MicroRNA
MHC	Major histocompatibility complex
MMPs	Matrix metalloproteinases
iNOS	Inducible nitric oxide synthase
ROS	Reactive oxygen species
ASIV	Astragaloside IV
AMPK	AMP-activated protein kinase
Cx43	Connexin-43
JNK	Jun N-terminal kinase
NKG2D	NK receptor group 2 member D
XCL	X-C motif chemokine ligand
PGE2	Prostaglandin E2
ASP	*Angelica sinensis* Polysaccharides
Th	T helper
NKT	Natural killer T
MICA	MHC class I chain-related protein A
ADAM9	A disintegrin and metalloproteinase 9
CXCL	CXC chemokine ligand
ATF3	Activating transcription factor 3
MyD88	Myeloid differentiation primary response protein 88
NF-κB	Nuclear factor kappa B
TLRs	Toll-like receptors
CTL	Cytotoxic T lymphocyte
CTLA4	CTL-associated antigen 4
PD-1	Programmed death protein 1
Tregs	Regulatory T cells
APCs	Antigen-presenting cells
PD-L1	PD-1 ligand
CSN5	Constitutive photomorphogenic 9 signalosome 5
PI3K	Phosphoinositide 3-kinase
AKT	Protein kinase B
JAK	Janus kinase
GLA	18*β*-Glycyrrhetinic acid
GL	Glycyrrhizic acid
COX-2	Cyclooxygenase-2
FOXP3	Forkhead box protein P3
GLPS	*Ganoderma lucidum* Polysaccharides
SSA	Saikosaponin A
MDSCs	Myeloid-derived suppressor cells
GITR	Glucocorticoid-induced TNF receptor
GLUT1	Glucose transporter 1
MDR	Multidrug resistance
BBB	Blood–brain barrier
HA	Hyaluronic acid
SLNs	Solid lipid nanoparticles
NLCs	Nanostructured lipid carriers
ICD	Immunogenic cell death
AEAA	Aminoethyl anisamide
RES	Reticuloendothelial system
EPR	Enhanced permeability and retention
LMWH	Low molecular weight heparin

CCR	C-C motif chemokine receptor
DSPE-PEG	1,2-Distearoyl-sn-glycero-3-phosphoethanolamine-poly(ethylene glycol)
PEI	Polyethyleneimine
PCL	Polycaprolactone
siRNA	Small interfering RNA
PLGA	Poly(lactic-co-glycolic acid)
PDA	Polydopamine
CMCS	Carboxymethyl chitosan
TfR	Transferrin receptor
MRI	Magnetic resonance imaging
MSNs	Mesoporous silica nanoparticles
Ce6	Chlorin e6
FITC	Fluorescein isothiocyanate
GSH	Glutathione
HAS	Human serum albumin
BSA	Bovine serum albumin
cGAS	Cyclic GMP-AMP synthase
STING	Stimulator of interferon genes
CpG-ODN	CpG oligonucleotide
MPS	Mononuclear phagocyte system
mTOR	Mammalian target of rapamycin
MOF	Metal–organic framework
NCP	Nanoscale coordination polymer
MPNs	Metal-phenolic networks

Acknowledgements
The authors would like to express our gratitude to the National Natural Science Foundation of China, Fujian Research and Training Grants for Young and Middle-aged Leaders in Healthcare, and the Medical Innovation Project of Fujian Provincial Health Commission for their invaluable support.

Author contributions
N.K., L.G. and T.X. conceived the overall framework of this review. H.Z. and Y.C. wrote the original draft. W.L., S.H., M.S., M.L. and C.W. reviewed and edited the draft. All authors read and approved the final manuscript.

Funding
This study was supported by the National Natural Science Foundation of China (Grant No. 82122076 to N.K.), Fujian Research and Training Grants for Young and Middle-aged Leaders in Healthcare (minweirenhan2023, No. 26), and the Medical Innovation Project of Fujian Provincial Health Commission (Grant No. 2022CXA052).

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
All authors declare full consent for publication.

Competing interests
The authors declare no competing interests.

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Received: 7 January 2025 Accepted: 7 April 2025
Published online: 17 May 2025

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