International Journal of Nanomedicine

Dovepress
Taylor & Francis Group

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REVIEW

Nanodelivery of Traditional Chinese Medicine Monomers: An Emerging Strategy to Reprogram the Immunosuppressive Tumor Microenvironment

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Abstract: The tumor microenvironment (TME), a highly complex and dynamic system, plays a central role in tumor progression and resistance to immunotherapy. Key immunosuppressive cell populations within the TME, including tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs), contribute to immune evasion through complex cytokine signaling and cellular crosstalk. These factors significantly limit the therapeutic efficacy of immune checkpoint inhibitors and other immunotherapies, particularly in "cold" tumors with poor immune infiltration. Traditional Chinese medicine (TCM) monomers have emerged as promising immunomodulatory agents due to their multi-target capability, favorable safety profiles, and ability to remodel the immune landscape. TCM compounds such as curcumin, berberine, resveratrol, and ginsenosides can modulate the recruitment, polarization, or function of TAMs, MDSCs, and Tregs. However, their clinical translation is hindered by the central challenge of poor solubility, low bioavailability, and limited tumor targeting capability. Nanotechnology provides a breakthrough strategy to address this core issue. Recent advances in nanotechnology offer effective solutions by enabling the encapsulation of TCM monomers into nano-delivery systems such as liposomes, polymeric nanoparticles, inorganic carriers, and biomimetic vesicles which enhance drug stability, promote tumor-specific accumulation, and allow controlled release. These integrated systems potentiate the pharmacological effects of TCM agents. Moreover, they help overcome immune resistance mechanisms within the TME. This review systematically examines the immunosuppressive roles of TAMs, MDSCs, and Tregs, summarizes the immunoregulatory actions of TCM monomers, and highlights cutting-edge nano-formulations developed to optimize their delivery. Together, these insights offer a novel framework for developing TCM-based nanomedicine strategies aimed at reprogramming the immunosuppressive TME and enhancing cancer immunotherapy.

Keywords: traditional Chinese medicine monomer, nano-delivery systems, tumor microenvironment

Introduction

Despite significant advancements in immunotherapeutic strategies such as immune checkpoint inhibitors (ICIs) and chimeric antigen receptor T (CAR-T) cell therapy, Clinical outcomes remain suboptimal for cancer patients. Durable responses are predominantly observed in a subset of individuals with high tumor mutational burden, while the majority exhibit limited benefit. The presence of "cold" tumors characterized by poor immune cell infiltration substantially hinders the broader clinical applicability of ICIs.[1–4] These limitations highlight the urgent need for novel approaches that can sensitize tumors to immunotherapy and mitigate associated toxicities.

https://doi.org/10.2147/IJN.S576928
Received: 26 October 2025
Accepted: 26 January 2026
Published: 7 April 2026

Recent studies have illuminated the complex and heterogeneous nature of immune cell infiltration across different tumor types, emphasizing its critical role in determining treatment responses. Single-cell sequencing technologies have revealed that the density and composition of immune infiltrates serve as predictive biomarkers for immunotherapeutic efficacy. For instance, tumors enriched with $CD8^+$ cytotoxic T lymphocytes tend to respond more favorably to ICIs, whereas those with dominant infiltration by regulatory T cells (Tregs) and tumor-associated macrophages (TAMs) are typically associated with immunosuppressive phenotypes and resistance.[5] These immunological characteristics are orchestrated within the tumor microenvironment (TME), which is a highly dynamic and complex ecosystem composed of tumor cells, stromal cells, immune cells, cytokines, and extracellular matrix (ECM) components. The TME is characterized by hypoxia, acidosis, and metabolic dysregulation.[6,7] Hypoxic conditions within the TME not only promote tumor cell survival and metastasis but also facilitate immune evasion by recruiting immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs), TAMs, and Tregs, while concurrently upregulating immune checkpoint pathways like PD-1/PD-L1.[8] In parallel, the acidic microenvironment further impairs immune cell activity and poses a physical barrier to therapeutic penetration through ECM remodeling.[9]

To overcome the immunosuppressive barriers of the TME, increasing attention has been directed toward the immunomodulatory potential of traditional Chinese medicine (TCM) monomers. These bioactive compounds exhibit multi-target pharmacological effects, low systemic toxicity, and favorable immunoregulatory properties. Specifically, they can also modulate cytokine profiles, enhance immune cell activation and suppress chronic inflammation.[10–12] However, the clinical translation of TCM monomers is significantly hampered by inherent pharmacokinetic drawbacks, including poor aqueous solubility, low bioavailability, rapid metabolism, and insufficient tumor-specific accumulation.[13–15] These challenges prevent the attainment of therapeutic concentrations at the tumor site, limiting their practical efficacy.

Nanomedicine offers a promising strategy to address these pharmacokinetic and delivery challenges. By employing passive and active targeting mechanisms, nanocarriers can enhance the stability, tumor selectivity, and controlled release of TCM monomers, thereby minimizing off-target effects.[16,17] For example, pH-responsive nanoparticles can release immune-activating agents such as IL-12 within the acidic TME, effectively reconditioning the immunosuppressive milieu by reprogramming tumor-associated macrophages from an M2-like to an M1-like phenotype, thereby enhancing pro-inflammatory signaling and T cell activation.[18] Moreover, multifunctional nanocarriers enable the co-delivery of chemotherapeutics and immunomodulators, enhancing antigen presentation and amplifying anti-tumor immunity.[19–21] For example, a folate-modified nanosystem co-delivering doxorubicin and calcium overload inducers was shown to induce immunogenic cell death (ICD) and activate dendritic cells, thereby enhancing long-term T cell memory responses. This “kill-then-activate” synergistic antitumor strategy effectively promotes durable antitumor immunity.[22]

Therefore, the integration of TCM monomers with advanced nano-delivery platforms represents a transformative dual-targeting approach. This combination not only potentiates the intrinsic immunomodulatory pharmacology of TCM agents but also equips them with the capability to precisely dismantle key immunosuppressive mechanisms within the TME. This review aims to provide a comprehensive overview of the immunoregulatory roles of TAMs, MDSCs, and Tregs within the TME. We further summarize the emerging evidence on TCM monomers that target these immunosuppressive cells and discuss recent progress in nanotechnology-based delivery systems designed to improve therapeutic precision. These insights offer valuable directions for the development of TCM-based nanomedicine strategies in the context of cancer immunotherapy (Figure 1 and Table 1).

Targeting TAM with Chinese Herbal Monomer

TAMs are critical immune cells within the TME, originating from either resident tissue macrophages or bone marrow-derived monocytes.[98] TAMs exhibit functional and phenotypic heterogeneity due to the complexity of the TME and the plasticity of macrophages. They are broadly categorized into two subtypes: M1 macrophages (tumor-suppressive) and M2 macrophages (tumor-promoting). M1 macrophages are activated by interferon-gamma (IFN-γ) and lipopolysaccharide (LPS), secreting pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-12, and tumor necrosis factor-alpha (TNF-α), which contribute to anti-tumor immunity.[99,100] In contrast, M2 macrophages are induced by IL-4, IL-10, and IL-13, and produce anti-inflammatory mediators like IL-10, transforming growth factor-beta (TGF-β), and vascular endothelial growth factor (VEGF), facilitating tumor progression through immunosuppression and angiogenesis.[101–103]

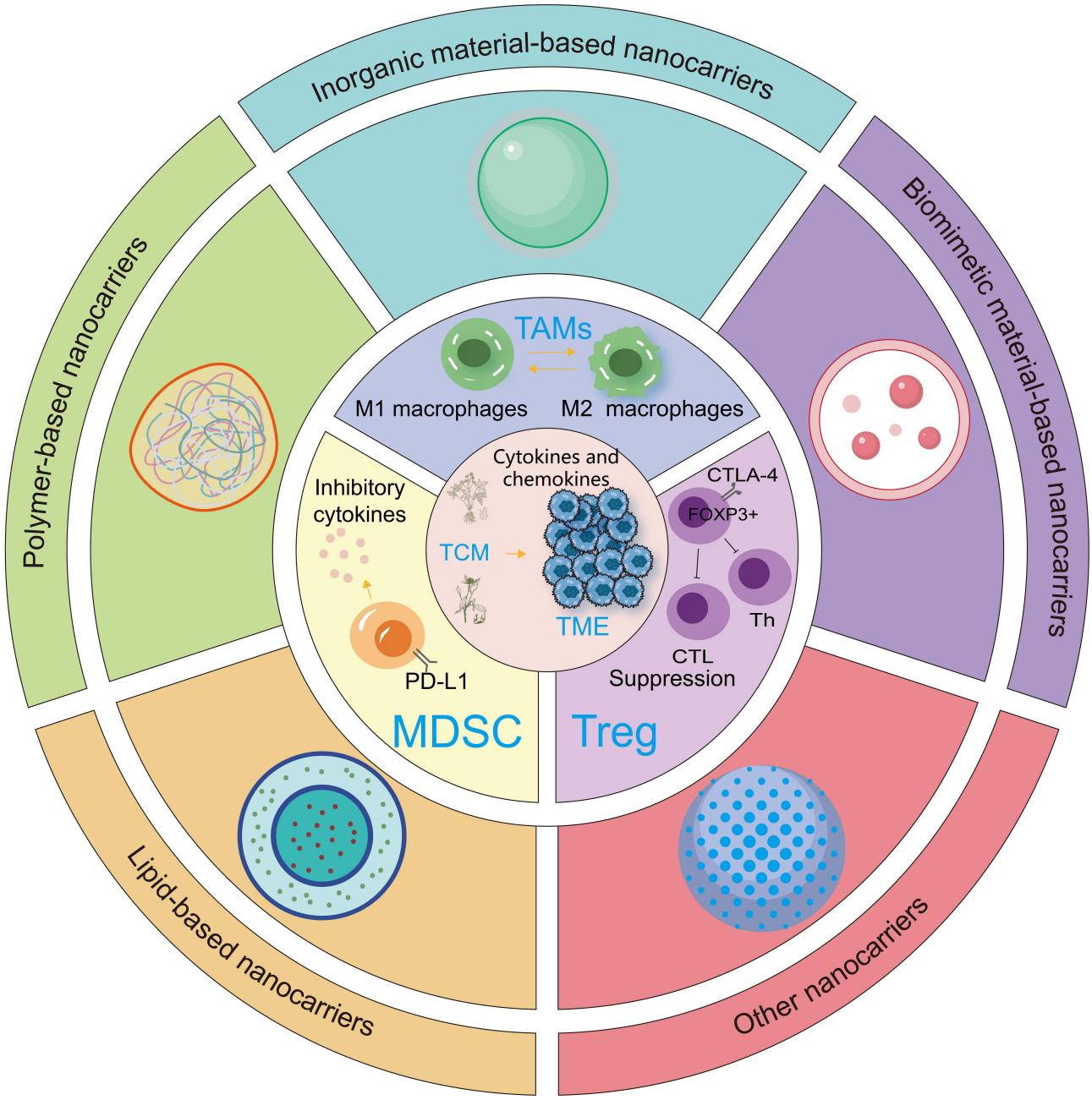

Figure 1 Diagrammatic representation of immune system modification and the several nanocarriers utilized in TCM active ingredient nano-delivery systems.

TAMs exhibit bidirectional regulatory interactions, such as M1 macrophages inhibiting M2 polarization via Smad2/3 phosphorylation, while M2-derived exosomes promote M2 phenotype conversion by activating arginase-1 (Arg-1) and suppressing inducible nitric oxide synthase (iNOS) expression. Additionally, TAMs contribute to the TME by secreting cytokines like IL-6, IL-10, IL-1β, CCL18, CXCL8, and TGF-β, as well as producing angiogenic factors such as VEGF, basic fibroblast growth factor (bFGF), PDGF-β, and WNT family members. Initially, TAMs exhibit M1 polarization and exert anti-tumor effects. However, as tumors progress, they shift toward the M2 phenotype, promoting tumor cell proliferation, invasion, and metastasis through the secretion of immunosuppressive cytokines like IL-10 and TGF-β. TAMs also induce gene mutations in tumor cells via oxidative stress and nitrosation-related molecules, activating oncogenic pathways such as STAT3 and NF-κB, thereby enhancing tumor survival and proliferation (Figure 2).

https://doi.org/10.2147/IJN.S576928

Table 1 Active Ingredients of CHMs and Corresponding Immunomodulatory Mechanisms

Active Ingredients	TCM	Effects	Cancer/Tumor Types	Refs
Achyranthes bidentata polysaccharides	Achyranthes bidentata Bl	↑DCs	Colorectal cancer	[23]
Angelica sinensis polysaccharide	Angelica sinensis (Oliv). Diels	↑NKs	Liver cancer	[24–26]
		↑CTLs	Breast cancer	
		↑Th1/Th2 ratio	Lung cancer	
Apigenin	Apium graveolens L	↓Tregs	Breast cancer	[27, 28]
		↓PD-L1	Melanoma	
		↑CTLs	Lung cancer	
		↑Th1/Th2 ratio	Pancreatic cancer	
		↑M1 macrophages		
Artesunate	Artemisia carvifolia Buch. Ham. ex Roxb. Hort. Beng.	↓Tregs	Cervical cancer	[29–31]
		↓TGF-β1, IL-10	Colorectal cancer	
		↓Integrins	Bladder cancer	
Asiatic acid	Centella asiatica (L). Urb	↓Tregs	Breast cancer	[32, 33]
		↓PD-L1	Melanoma	
		↑CTLs	Lung cancer	
		↑NKs		
Astragalus polysaccharide	Astragalus membranaceus	↓Tregs	Breast cancer	[34, 35]
		↓MDSCs	Liver cancer	
		↓PD-L1	Lung cancer	
		↑DCs	Ehrlich ascites carcinoma	
		↑M1 macrophages	Gastric cancer	
			Colorectal cancer	
			Cervical cancer	
Astragaloside III	Astragalus membranaceus (Fisch). Bunge	↑NKs	Colorectal cancer	[36, 37]
		↓M2 macrophages	Lung cancer	
Astragaloside IV	Astragalus membranaceus (Fisch). Bunge	↓M2 macrophages	Colorectal cancer	[38, 39]
		↓TGF-β, IL-10	Lung cancer	
			Ovarian cancer	
Baicalin	Scutellaria baicalensis Georgi	↓M2 macrophages	Liver cancer	[40, 41]
		↓PD-L1		
		↓TGF-β, IL-10		
Berberine	Coptis chinensis Franch	↓Tregs	Lung cancer	[42, 43]
		↓MDSCs		
		↓PD-L1		
Betulinic acid	Betula platyphylla Suk	↓MDSCs	Breast cancer	[44–46]
		↑CTLs	Glioblastoma	
		↓M2 macrophages	Liver cancer	
Calceolarioside B	Akebiae Fructus	↓M2 macrophages	Liver cancer	[47]
Celastrol	Tripterygium wilfordii Hook. F	↓M2 macrophages	Breast cancer	[48]
Cryptotanshinone	Salvia miltiorrhiza Bunge	↑DCs	Lung cancer	[49, 50]
		↑M1 macrophages	Ovarian cancer	
Curcumin	Curcuma longa L	↓Tregs	Colorectal cancer	[51–53]
		↓TGF-β, IL-10	Leukemia	
		↓CTLA4	Lung cancer	
		↑CTLs	Tongue squamous cell carcinoma	
		↑Th1/Th2 ratio		
Dihydroartemisinin	Artemisia annua Linn	↓Tregs	Breast cancer	[54–59]
		↓PD-1	Pancreatic cancer	

(*Continued*)

Table 1 (Continued).

Active Ingredients	TCM	Effects	Cancer/Tumor Types	Refs
		↓M2 macrophages ↑CTLs ↑Th1/Th2 ratio	Melanoma Lung cancer Head and neck squamous cell carcinoma	
Epimedium polysaccharides	Epimedium koreanum Nakai	↓MDSCs ↑M1 macrophages ↑DCs ↑CTLs	Lung cancer	[60–63]
Gambogic acid	Garcinia hanburyi Hook.f	↓Tregs ↓MDSCs ↓M2 macrophages ↓PD-1 ↑CTLs	Colorectal cancer Nasopharyngeal carcinoma Oral squamous cell carcinoma	[64–66]
Ganoderma lucidum polysaccharides	Ganoderma lucidum	↓Tregs ↓MDSCs ↑M1 macrophages ↑Th1/Th2 ratio ↑CTLs	Breast cancer Liver cancer Lung cancer	[62, 67, 68]
Ginsenoside Rg3	Panax ginseng C. A. Meyer	↓Tregs ↓MDSCs ↓PD-L1 ↑Th1/Th2 ratio ↑CTLs	Liver cancer Lung cancer	[69–71]
Glycyrrhizic acid	Glycyrrhiza uralensis Fisch	↓Tregs ↓MDSCs ↑Th1/Th2 ratio	Melanoma	[72, 73]
Icariin	Epimedium brevicornum Maxim	↓MDSCs ↓TGF-β, IL-10 ↓PD-L1 ↓M2 macrophages ↑CTLs	Breast cancer Pancreatic cancer Cervical cancer Mastocytoma Melanoma	[60, 74–76]
Lentinan	Lentinus edodes	↓Tregs ↓MDSCs ↓TGF-β, IL-10 ↑NKs ↑Th1/Th2 ratio ↑CTLs	Bladder cancer Breast cancer Lung cancer	[77–79]
Lobeline	Lobelia	↓M2 macrophages ↑M1 macrophages	Colorectal cancer	[151]
Luteolin	Reseda odorata L	↓Tregs ↓PD-L1 ↑Th1/Th2 ratio ↑CTLs	Lung cancer Melanoma	[152,153]
Matrine	Sophora flavescens Aiton	↓M2 macrophages ↑DCs ↑CTLs	Lung cancer	[80–82]
Norcantharidin	Mylabris phalerata Pallas	↓Tregs ↓TGF-β, IL-10	Liver cancer Prostate cancer	[83–85]

(*Continued*)

https://doi.org/10.2147/IJN.S576928

Table 1 (Continued).

Active Ingredients	TCM	Effects	Cancer/Tumor Types	Refs
		↑M1 macrophages	Gastric cancer	
		↑CTLs		
Oridonin	Rabdosia rubescens (Hemsl). Hara	↓Tregs	Bladder Cancer	[86–88]
		↓PD-L1	Breast cancer	
		↓TGF-β, IL-10		
		↑CTLs		
Resveratrol	Veratrum album L	↓Tregs	Breast cancer	[89–93]
		↓MDSCs	Leukemia	
		↓PD-L1	Liver cancer	
		↓TGF-β, IL-10	Lung cancer	
		↑NKs	Melanoma	
		↑DCs	Oral squamous cell carcinoma	
		↑CTLs	Osteosarcoma	
			Renal cell carcinoma	
Salvianolic acid B	Salvia miltiorrhiza Bunge	↓PD-1	Breast cancer	[94, 95]
		↑CTLs	Liver cancer	
Tetramethylpyrazine	Ligusticum chuanxiong Hort	↑Th1/Th2 ratio	Lung cancer	[96, 97]
		↑NKs	Renal cell carcinoma	
		↓Tregs	Breast cancer	
Triptolide	Tripterygium wilfordii Hook. f	↓TGF-β, IL-10	Leukemia	[154,155]
		↓PD-L1	Melanoma	
			Oral squamous cell carcinoma	
			Ovarian cancer	

Notes: "↑": indicates a significant increase. "↓": indicates a significant decrease.

Inhibition of TAM Recruitment

The CCL2/CCR2 axis plays a central role in macrophage recruitment to the TME. Disrupting this chemokine signaling pathway not only reduces monocyte infiltration but also promotes macrophage repolarization and enhances cytotoxic $CD8^+$ T lymphocyte (CTL) activation, thereby improving anti-tumor immunity.[104,105] Curcumin, a polyphenolic compound from turmeric, suppresses CCL2 expression in tumor cells and stromal components by inhibiting the NF-κB pathway, thereby impairing monocyte chemotaxis and limiting TAM accumulation in preclinical cancer models.[51,106–108] Total glucosides of peony (TGP) inhibit TAM recruitment by targeting the NF-κB/CCL2 pathway, reducing CCL2 secretion and reshaping the tumor microenvironment.[109] Targeting the CCL2/CCR2 axis with TCM monomers like curcumin and TGP presents a promising strategy to reduce the immunosuppressive TAM pool at the source. However, the clinical translation of this approach requires overcoming the complex redundancy of chemokine networks in the TME and ensuring precise spatiotemporal inhibition to avoid disrupting homeostatic immune functions.

Depletion and Inhibition of TAM

TAMs reduce immunity by activating oncogenic signaling pathways (STAT3 and MAPK) via pro-inflammatory cytokines like IL-6 and IL-1β, which promote tumor development and metastasis. Strategies targeting TAM depletion or functional inhibition show promise in enhancing tumor immune responses. Quercetin, a flavonoid from multiple traditional Chinese medicinal plants, induces TAM apoptosis by modulating Bcl-2/Bax signaling, leading to TAM reduction in the TME.[110,111] Andrographolide, a diterpenoid from *Andrographis paniculata*, inhibits macrophage activation and cytokine production, modulating M1 and M2 phenotypes, and targeting the Wnt5a/β-catenin pathway to suppress M2 macrophage activity.[112–115] Matrine, an alkaloid from *Sophora flavescens*, inhibits TAM activation and

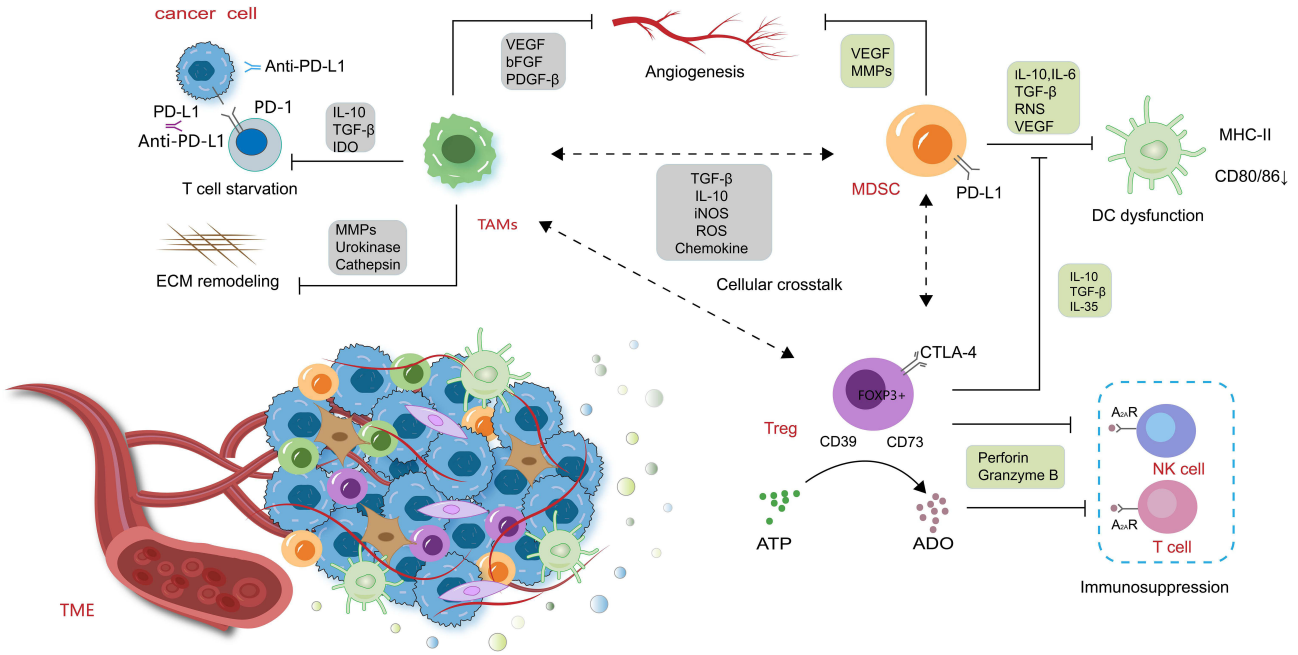

Figure 2 Overview of tumor microenvironment (TME). It mainly includes tumor cells, immune cells, epithelial cells and stromal cells. This picture highlights three key immunosuppressive immune cells-tumor-associated macrophages (TAMs), myelosuppressive cells (MDSCs) and regulatory T cells (Tregs), and depicts their interactions and their core roles in shaping the immunosuppressive microenvironment.

survival by suppressing M2 polarization and the mTOR/PI3K/Akt pathway, reducing anti-inflammatory cytokines and M2 markers without affecting M1 polarization.[80,89] Resveratrol, a polyphenolic compound from *Polygonum cuspidatum*, exhibits dose-dependent effects on macrophage polarization, promoting M1 polarization at moderate concentrations and favoring M2 polarization at higher doses, highlighting the importance of precise dosing.[90,116] Lobeline, an alkaloid from the herbal medicine lobelia, promotes polarization of TAMs toward M1-like TAMs while inhibiting their polarization toward M2-like TAMs.[151] Calceolarioside B, a major compound in Akebiae Fructus, regulates M2-like TAMs polarization and infiltration to impede HCC progression by targeting MMP12.[47] Directly depleting or functionally inhibiting TAMs with monomers such as quercetin and matrine offers a rapid means to alleviate TAM-mediated immunosuppression. A key challenge lies in achieving tumor-selective effects to spare resident tissue macrophages essential for normal physiology, and in carefully managing the dose-response relationships, as exemplified by resveratrol, to avoid paradoxical outcomes.

Reprogramming the Phenotype of TAMs

Monomers derived from traditional Chinese medicine have been shown to regulate TAM polarization and function, thereby modulating anti-tumor immune responses and inhibiting tumor progression. Berberine, a bioactive isoquinoline alkaloid from *Coptis chinensis*, effectively downregulates M2 macrophage markers, including CD206 and Arg-1, while upregulating major histocompatibility complex class II (MHC-II) and CD40 expression. The decrease of IL-10 production and inhibition of STAT3 phosphorylation in B16F10 melanoma cells treated with recombinant IL-6 (rIL-6) mediate this phenotypic change. Moreover, berberine enhances the secretion of pro-inflammatory cytokines such as IL-1β, IL-12, and TNF-α in response to tumor antigens, thereby promoting CTL activity and expanding the population of IFN-γ-producing $CD4^+$ T cells. By disrupting M2 polarization and suppressing the immunosuppressive cytokines IL-10 and TGF-β, berberine effectively restores T cell-mediated anti-tumor cytotoxicity within the tumor microenvironment.[42]

Ganoderic acid A (GAA), a bioactive triterpenoid compound derived from *Ganoderma lucidum*, has demonstrated potent anti-tumor effects in both orthotopic and subcutaneous hepatocellular carcinoma (HCC) mouse models. The anti-HCC activity of GAA is mediated, at least in part, by enhancing macrophage-mediated immune responses, including increased phagocytic activity against HCC cells, promotion of M1-type macrophage polarization, and suppression of M2-

type polarization. These immunomodulatory effects are associated with the downregulation of colony-stimulating factor 1 receptor (CSF1R) expression in macrophages, as observed in both in vitro experiments and in vivo animal models.[117] Astragaloside IV, a bioactive saponin compound derived from *Astragalus membranaceus*, has been investigated for its anti-tumor properties in a murine model injected with CT26 colon carcinoma cells. This compound significantly inhibited tumor growth by modulating cytokine expression and promoting M1-type reprogramming of TAMs. It downregulates anti-inflammatory cytokines such as TGF-β, IL-10, and VEGF-A, while upregulating pro-inflammatory cytokines such as IFN-γ, IL-12, and TNF, contributing to enhanced anti-tumor immune responses.[38]

Astragaloside III (AS-III) has been reported to inhibit lung cancer metastasis and angiogenesis, while inducing apoptosis of lung cancer cells in both in vitro and in vivo models. These anti-tumor effects are primarily attributed to the inhibition of M2-type macrophage polarization and the induction of M1 phenotypic transformation, mediated by suppression of the mitogen-activated protein kinase (MAPK) signaling pathway. Additionally, AS-III modulates the Akt/mammalian target of rapamycin (Akt/mTOR) pathway, further contributing to its tumor-suppressive activity. These findings highlight the potential of AS-III to reprogram TAMs and reshape the TME, thereby enhancing anti-tumor immunity.[36] Dihydroartemisinin (DHA), a derivative of artemisinin, modulates TAM polarization by increasing M1 markers and decreasing M2 markers, enhancing anti-tumor immune responses in murine models.[54]

Reprogramming TAMs towards an anti-tumor M1 phenotype using TCM monomers (eg., berberine, astragalosides) represents a highly desirable approach to convert foes into allies within the TME. The primary hurdles include ensuring stable and sustained phenotypic switching in the face of strong M2-polarizing signals in the TME, and delivering effective intratumoral concentrations of these agents to exert reprogramming effects.

Activation of the Phagocytic Function of TAMs

Phagocytosis is a critical immune function of TAMs, enabling them to engulf and eliminate tumor cells or debris. This process is tightly regulated and represents a key immunotherapeutic target for anti-tumor immunity. Schisandrin B (Sch B), a lignan compound derived from *Schisandra chinensis*, has demonstrated tumor-suppressive effects through its modulation of TAM function. Sch B inhibits the phosphorylation of signal transducer and activator of transcription 3 (STAT3), thereby suppressing tumor growth and metastasis. While Sch B induces autophagy in hepatocellular carcinoma cells by elevating intracellular reactive oxygen species (ROS) levels, its primary role in activating TAM phagocytosis remains unclear and warrants further investigation.[118,119]

Baicalin, the principal bioactive flavonoid from *Scutellaria baicalensis*, promotes M2c macrophage polarization, enhancing phagocytic activity through MERTK receptor upregulation. M2c macrophages exhibit increased expression of genes such as interferon regulatory factor 4 (IRF4), IL-10, and pentraxin 3 (PTX3), while reducing pro-inflammatory cytokines like TNF-α and IL-6. This polarization state distinguishes M2c macrophages from classical M2 macrophages, which exhibit elevated Arg-1 and CD206 expression.[40] Ginsenoside Rg3, a bioactive saponin isolated from *Panax ginseng*, augments macrophage phagocytic capacity through activation of the extracellular signal-regulated kinase 1/2 (ERK1/2) and p38 mitogen-activated protein kinase (MAPK) signaling cascades. This activation promotes Fc gamma receptor (FcγR)-mediated phagocytosis, suggesting its potential role in enhancing macrophage-mediated anti-tumor responses.[69]

In summary, the modulation of TAM function and activation of their phagocytic activity represent promising approaches to enhance anti-tumor immunity. By targeting TAM polarization, recruitment, and function, Chinese herbal monomers offer unique advantages in reshaping the TME. However, further research is needed to optimize dosing, enhance bioavailability, and explore nano-delivery systems to maximize their therapeutic potential in clinical settings.

Targeting MDSCs with Chinese Herbal Medicine Monomers

MDSCs represent a heterogeneous population of immature myeloid cells with potent immunosuppressive functions. These cells primarily originate from bone marrow progenitors and are classified into two main subsets: polymorphonuclear MDSCs (PMN-MDSCs), resembling neutrophils, and monocytic MDSCs (M-MDSCs), sharing features with monocytes. MDSCs play a critical role in tumor-induced immunosuppression, actively regulating immune responses

within TME and contributing to immune evasion by suppressing anti-tumor immunity, particularly through inhibition of T cell activation and effector functions.

The expansion and activation of MDSCs are regulated by multiple cytokines and signaling molecules, such as IL-13, IL-14, and IFN-γ. MDSCs release immunosuppressive mediators, including arginase, iNOS, TGF-β, and IL-10, and they facilitate the expansion of Tregs, further contributing to tumor immune escape. Consequently, MDSCs have become a pivotal target in cancer immunotherapy research, with increasing attention on the potential of Chinese herbal monomers to modulate their proliferation, differentiation, and immunosuppressive functions, offering novel therapeutic strategies to enhance anti-tumor immunity.

Inhibition of MDSC Recruitment

Curcumin, a polyphenolic compound from turmeric, has demonstrated effective reduction of MDSC accumulation in both spleen and tumor tissues, promoting their maturation and differentiation within the TME in a Lewis lung carcinoma (LLC) syngeneic mouse model. Furthermore, curcumin inhibits the immunosuppressive activity of MDSCs by downregulating the expression of Arg-1 and reactive oxygen species (ROS) in purified MDSCs isolated from tumor tissues. In tumor-bearing mice, curcumin significantly attenuates MDSC-mediated immune suppression by lowering IL-6 levels in tumor tissues and serum, restricting MDSC expansion and functional activity.[120]

To enhance curcumin's therapeutic potential, novel nanoformulations have been developed. Wang et al created a curcumin formulation by conjugating it with the FFE-ss-EE peptide, achieving a high drug-loading efficiency of approximately 40%. This nanostructure, termed nano-curcumin (nano-Cur), exhibits enhanced biological activity, evidenced by downregulation of ARG-1 and iNOS, suppression of ROS generation, and inhibition of IL-10 secretion, contributing to reduced tumor burden by impeding MDSC recruitment and differentiation within the TME.[121] Kang et al developed a reactive oxygen species (ROS)- and glutathione (GSH)-responsive drug delivery system, termed CUR/miR155@DssD-Hb nanoparticles (NPs), for the co-delivery of curcumin (CUR) and microRNA-155 (miR-155). This nanoplatform effectively inhibits tumor cell proliferation, enhances dendritic cell (DC) maturation, activates $CD8^+$ cytotoxic T lymphocytes, and reduces the presence of immunosuppressive cells, including MDSCs, Tregs, M2-type TAMs, and exhausted T cells, promoting sustained antitumor immune responses and decreasing pulmonary metastasis, offering a promising strategy for melanoma and triple-negative breast cancer (TNBC) treatment.[122]

Silibinin, a natural flavonoid from Silybum marianum seeds, significantly prolonged the survival of tumor-bearing mice and reduced tumor volume in a 4T1-luciferase murine breast cancer model. It decreases the accumulation of $CD11b^+Gr\text{-}1^+$ MDSCs in peripheral blood and tumor tissues and enhances T cell infiltration into the TME, indicating its potential to reverse tumor-induced immunosuppression.[123]

Inhibiting the recruitment of MDSCs to the TME with agents like curcumin and silibinin is a strategic front-line intervention to prevent the establishment of an immunosuppressive niche. A significant challenge is the systemic nature of MDSC expansion and recruitment, necessitating treatments that maintain effective drug levels over time to continuously block multiple chemokine axes (eg., CXCR2) involved in this process.

MDSC Depletion from Circulation and Tumor Infiltration

Resveratrol (RSV), a polyphenolic compound from Polygonum cuspidatum, significantly reduces both the abundance and immunosuppressive function of MDSCs in a murine model exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). TCDD induces a marked reduction of $F4/80^+$ macrophages and increases $CD11c^+$ dendritic cells, effects reversible by RSV treatment. Mechanistically, TCDD upregulates CXCR2 and ARG-1, promoting MDSC generation and immunosuppressive activity. RSV counteracts these molecular alterations, suggesting its potential as a therapeutic agent to mitigate MDSC-mediated immunosuppression.[91] Depleting existing MDSCs from the circulation and tumor, as demonstrated by resveratrol, can provide a rapid reduction in immunosuppressive pressure. The transient nature of this effect poses a challenge, as the bone marrow can continuously replenish MDSCs. Therefore, achieving sustained depletion likely requires prolonged or combination therapy targeting both MDSCs and their upstream production signals.

Targeted MDSC Generation and Differentiation

Chinese herbal medicine monomers inhibit MDSC differentiation from bone marrow precursors and promote their maturation into functional myeloid lineages. Ganoderma lucidum polysaccharide (GLP), derived from Ganoderma lucidum, restores the expression of caspase recruitment domain-containing protein 9 (CARD9), phosphorylated spleen tyrosine kinase (p-Syk), and phosphorylated p65 (p-p65), while increasing indoleamine 2,3-dioxygenase (IDO) levels in MDSCs isolated from Lewis lung carcinoma (LLC) tumor-bearing mice. These molecular changes suggest that GLP regulates MDSC differentiation through the CARD9–NF-κB–IDO signaling axis, contributing to its antitumor effects.[64]

Ginsenoside Rg3 indirectly modulates immune cells in the bone marrow by inhibiting the biological activity of endothelial progenitor cells (EPCs), attenuating tumor angiogenesis and exerting its immunoregulatory and antitumor effects. Icariin and its derivative icaritin (ICT) promote MDSC differentiation into dendritic cells or macrophages by inhibiting the S100A8/9, STAT3, and AKT signaling pathways, suggesting an effective strategy for reversing MDSC-mediated immunosuppression in the TME.[74,124] Xuanhusuo Powder, a traditional Chinese medicinal formula composed of Rhizoma Zedoariae and Rhizoma Corydalis, inhibits MDSC differentiation by downregulating granulocyte colony-stimulating factor (G-CSF), a key cytokine involved in MDSC expansion within the TME, offering anti-breast cancer effects.[125]

In conclusion, targeting MDSC recruitment, depletion, and differentiation represents a promising approach to enhance anti-tumor immunity. By leveraging Chinese herbal monomers and advanced nano-delivery systems, it is possible to modulate MDSC functions more effectively, offering novel therapeutic strategies in cancer immunotherapy. However, further research is needed to optimize dosing, enhance bioavailability, and explore combination therapies to maximize therapeutic efficiency in clinical settings.

Chinese Medicine Monomer Targeting Tregs

Tregs, a specialized subset of $CD4^+$ T cells, play a pivotal role in maintaining immune homeostasis by suppressing excessive T cell activation. Within TME, TAMs, secrete chemokines that recruit Treg precursor cells (TPCs) from the peripheral circulation to the tumor site. These recruited Tregs exert potent immunosuppressive functions, facilitating tumor progression by inhibiting effective antitumor immune responses.[126]

Li et al demonstrated that Ganoderma lucidum polysaccharides (GLPS) inhibit the Notch1 signaling pathway and downregulate FOXP3 expression by upregulating microRNA-125b (miR-125b). This leads to reduced accumulation and functional activity of Tregs, thereby suppressing liver cancer progression.[127]

Similarly, artesunate, a flavonoid compound derived from Artemisia annua L., effectively inhibits cyclooxygenase-2 (COX-2) expression in cervical cancer cells, thereby reducing prostaglandin E2 (PGE2) production. This suppression ultimately lowers FOXP3 expression in T cells and decreases the proportion of $CD4^+CD25^+$ T cells in peripheral blood.[29]

Glycyrrhizic acid, a major bioactive compound in licorice, suppresses phosphorylated signal transducer and activator of transcription 3 (p-STAT3)-mediated immunosuppressive signaling in both Tregs and myeloid-derived suppressor cells (MDSCs) in melanoma. Specifically, it downregulates FOXP3, glucocorticoid-induced TNF receptor (GITR), and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) in Tregs, while inhibiting COX-2, PGE2, and Arg-1 in MDSCs.[72] Additionally, astragalus polysaccharides (APS) exhibit dual action in immunoregulation, targeting both Treg/Th17 balance and TAMs. In late-stage cancer, APS suppresses hyperactivated Tregs, significantly reduces the IL-10/TGF-β1 ratio, and restores the Treg/Th17 equilibrium. Furthermore, APS inhibits M2 macrophage polarization and promotes M1 phenotype conversion in liver cancer models, thereby contributing to tumor cell proliferation suppression.[34]

Collectively, these TCM monomers demonstrate the feasibility of targeting Tregs to alleviate their immunosuppressive stranglehold on the TME. However, a central challenge is achieving selective modulation or depletion of tumor-infiltrating Tregs without compromising the vital role of peripheral Tregs in maintaining systemic immune tolerance and preventing autoimmunity. Furthermore, the plasticity and compensatory expansion of Tregs demand strategies that can durably suppress their function.

Application of Traditional Chinese Medicine Monomer and Nano-Delivery System in Tumor Immunotherapy

A nano-drug delivery system represents an advanced drug delivery technology that utilizes various nanocarriers, such as lipids, polymers, inorganic materials, and biomimetic structures, to enable targeted and controlled delivery of therapeutic agents within the body.[128–130] While TCM monomers have demonstrated significant potential in tumor immunotherapy, their clinical application is often constrained by pharmacokinetic limitations. These include poor water solubility, resulting in low bioavailability; structural instability, leading to rapid metabolism and degradation; and limited target specificity, increasing the risk of off-target toxicity to normal tissues. The emergence of nano-drug delivery systems presents a promising solution to overcome these challenges by enhancing solubility, improving stability, and enabling precise tumor targeting, thereby optimizing the therapeutic efficacy of TCM-based interventions.[131]

Nano-delivery systems possess unique physicochemical characteristics, typically in the particle size range of 1–100 nm. Their advantages in drug delivery are multifaceted: a, Enhanced Solubility and Stability: By encapsulating or adsorbing TCM monomers onto nanocarriers, these systems improve the solubility of hydrophobic compounds, protect the drug from environmental degradation, and extend pharmacological activity. b, Controlled Release: Nanodelivery platforms enable sustained release of therapeutic agents in vivo, allowing for precise modulation of drug release rates and site-specific delivery. This ensures effective drug concentrations are maintained within tumor tissues, thereby enhancing therapeutic efficacy. c, Targeting Capabilities: Functionalization of nanocarriers with targeting ligands—such as antibodies, peptides, or aptamers—permits selective recognition of specific receptors or antigens overexpressed on tumor cells. This enables precise delivery of TCM monomers to tumor sites while minimizing off-target effects on healthy tissues (Table 2).

Table 2 Application of TCM Effective Component Nanodelivery System in Tumor Immunotherapy

Carrier Type	Active Ingredients	Features	Effects	Cancer/Tumor Types	Refs
Liposome	Curcumin	Tumor targeting	↑Th1/Th2 ratio	Colorectal cancer	[132]
	Curcumin and camptothecin	Across the blood–brain barrier	↓Tregs	Glioma	[133]
			↓PD-L1		
	Celastrol and ginsenoside Rg3	Enhance therapeutic efficacy	↑CTLs	Melanoma	[134]
			↑DCs		
	Ginsenoside Rg3	Across the blood–brain barrier	↓MDSCs	Glioma	[135]
		Tumor targeting	↓Tregs		
			↓M2 macrophages		
			↑CTLs		
	Ginsenoside Rg3	Inhibit drug resistance	↓MDSCs	Breast cancer	[136]
		Tumor targeting	↓PD-L1		
			↓M2 macrophages		
	Glycyrrhizic acid and triptolide	Tumor targeting	↓M2 macrophages	Liver cancer	[137]

(*Continued*)

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Table 2 (Continued).

Carrier Type	Active Ingredients	Features	Effects	Cancer/Tumor Types	Refs
	Salvianolic acid B	Enhance therapeutic efficacy	↓Tregs	Breast cancer	[138]
			↓MDSCs		
			↓TGF-β, IL-10		
			↑M1 macrophages		
			↑Th1/Th2 ratio		
			↑CTLs		
	Silybin	Tumor targeting	↑CTLs	Breast cancer	[139]
Polymeric nanoparticle	Celastrol	Tumor targeting		Melanoma	[140]
	Silibinin	Enhance therapeutic efficacy	↓Tregs	Breast cancer	[141]
			↓MDSCs		
Biomimetic nanoparticle	Artesunate	Tumor targeting	↓M2 macrophages	Colorectal cancer	[142]
	Artesunate	Redox-sensitive	↑DCs	Breast cancer	[143]
		Photothermal	↑CTLs		
	Tanshinone IIA and glycyrrhizic acid	Across the blood–brain barrier	↑M1 macrophages	Glioblastoma	[144]
			↑DCs		
	Angelica polysaccharide glycyrrhetic acid and curcumin	Enhance therapeutic efficacy	↑M1 macrophages	Liver cancer	[145]
		Tumor targeting	↑CTLs		
	Ginseng-derived	Tumor targeting	↑M1 macrophages	Melanoma	[146]
Inorganic material	Astragaloside IV and tanshinone IIA	Improve solubility	↑CTLs	Liver cancer	[147]
	Ganoderma lucidum polysaccharide	Enhance therapeutic efficacy	↑DCs	Breast cancer	[148]
			↑CTLs		
Other	Curcumin and shikonin	Enhance therapeutic efficacy	↓Tregs	Colorectal cancer	[149]
			↑CTLs		
			↑DCs		
	Lentinan and ursolic acid	Enhance therapeutic efficacy	↑M1 macrophages	Colorectal cancer	[150]
			↑DCs		
			↑CTLs		

Notes: "↑": Indicates a significant increase or increase in data. "↓": Indicates that the data is significantly reduced or reduced.

Lipid Nano-Delivery System Combined with Chinese Herbal Monomer

Lipid-based nanoparticles, including liposomes and lipid nanoparticles, feature diverse substructures but commonly comprise at least one lipid bilayer enclosing an aqueous core.[77,152] Their favorable biocompatibility, enhanced bioavailability, and tunable physicochemical properties confer significant advantages in drug delivery.[156–158] (Table 3).

Rg3-LPs Liposomes

Zhu et al showed that ginsenoside Rg3-loaded liposomes (Rg3-LPs) significantly improve cellular uptake and glioma penetration in vitro and enhance intratumoral delivery in vivo compared to cholesterol-based liposomes. Paclitaxel-loaded Rg3-LPs (Rg3-PTX-LPs) exhibit stronger antiproliferative effects on C6 glioma cells and induce M2-to-M1 macrophage repolarization. In vivo, Rg3-PTX-LPs significantly prolong median survival in glioma-bearing mice by modulating the immune microenvironment, including increasing $CD8^+$ T cells, enhancing the M1/M2 ratio, and reducing Tregs and MDSCs[136] (Figure 3Ai–iv). Shuang et al discovered that Rg3-LNPs employ the Rg3 ligand to anchor antigens onto the surface of tumor cells with high Glut1 expression, thereby enhancing recognition by CTLs. Additionally, these nanoparticles accumulate in lymph nodes, where they activate DCs and promote antigen presentation, ultimately priming and expanding CTLs. Furthermore, Rg3-LNPs can synergize with GM-CSF to remodel the tumor immune microenvironment, consequently augmenting the tumor-killing capacity of CTLs.[159]

Glycyrrhizic Acid (GL)-Lipid Hybrid Nanoplatform (GLLNP)

Xu et al developed a glycyrrhizic acid (GL)-lipid hybrid nanoplatform (TP/GLLNP) loading triptolide (TP) for HCC immunochemotherapy. GL replaced cholesterol as lipid membrane skeleton, endowing nanocarriers with enhanced stability, tumor targeting via GL receptors, and M2-to-M1 macrophage polarization regulation. TP/GLLNP exhibited superior cellular uptake, cytotoxicity, and apoptosis induction in HepG2 cells compared to traditional liposomes. In H22 tumor-bearing mice, it showed enhanced tumor accumulation and synergistic anti-HCC efficacy by combining TP-mediated chemotherapy and GL-mediated immunomodulation, without systemic toxicity. This "three-birds-with-one-stone" strategy provides a novel dual-drug co-delivery system for combined cancer therapy[137] (Figure 3B).

Table 3 Representative Lipid-Based Nano-Formulations for TCM Monomer Delivery and TME Remodeling

Nano-Formulation	TCM Monomer(s) (Role)	Key Structural/Functional Feature	Primary Mechanism of TME Remodeling	Tumor Model (Ref)
Rg3-PTX-LPs	Ginsenoside Rg3 (Membrane material replacing cholesterol)	Rg3 integrates into the liposomal bilayer, enhancing glioma penetration.	M2-to-M1macrophage repolarization; Increases $CD8^+$ T cells; Reduces Tregs & MDSCs.	C6 Glioma[136]
TP/GLLNP	Glycyrrhizic Acid, GL (Membrane skeleton); Triptolide, TP (Payload)	GL replaces cholesterol, conferring stability and GL receptor-mediated targeting.	GL drives M2-to-M1 polarization; TP induces chemotherapy. Synergistic immunochemotherapy.	H22 HCC[137]
PEG-SAB-Lip	Salvianolic Acid B, SAB (Payload)	PEGylated liposome for enhanced circulation.	Downregulates TGF-β1 to suppress CAFs; Promotes M2-to-M1 polarization; Limits Treg infiltration.	Breast Cancer[138]
CR-Lip	Ginsenoside Rg3 (Membrane component); Celastrol, CEL (Payload)	Rg3 in bilayer with surface-exposed glycosyl groups for potential GLUT1 targeting.	Induces ICD; Inhibits metabolic reprogramming; Boosts DC maturation and $CD8^+$ T cell infiltration.	Melanoma (obesity-associated)[134]
SLN/LIP	Silybin (Payload)	Standard liposomal encapsulation.	Increases IFN-γ/IL-12, decreases TGF-β/IL-6; Promotes CTL infiltration ("cold" to "hot" tumor conversion).	Combined with DOX/LIP[139]

Abbreviations: Rg3-PTX-LPs, Paclitaxel-loaded Rg3-LPs; TP/GLLNP, a glycyrrhizic acid (GL)-lipid hybrid nanoplatform loading triptolide; PEG-SAB-Lip, PEGylated salvianolic acid B-loaded liposomes; CR-Lip, a multifunctional liposomal delivery platform (CR-Lip) to encapsulate celastrol (CEL); SLN/LIP, a liposomal formulation of silybin; CAFs, Cancer-associated fibroblasts; DC, Dendritic cell; HCC, Hepatocellular carcinoma; ICD, Immunogenic cell death.

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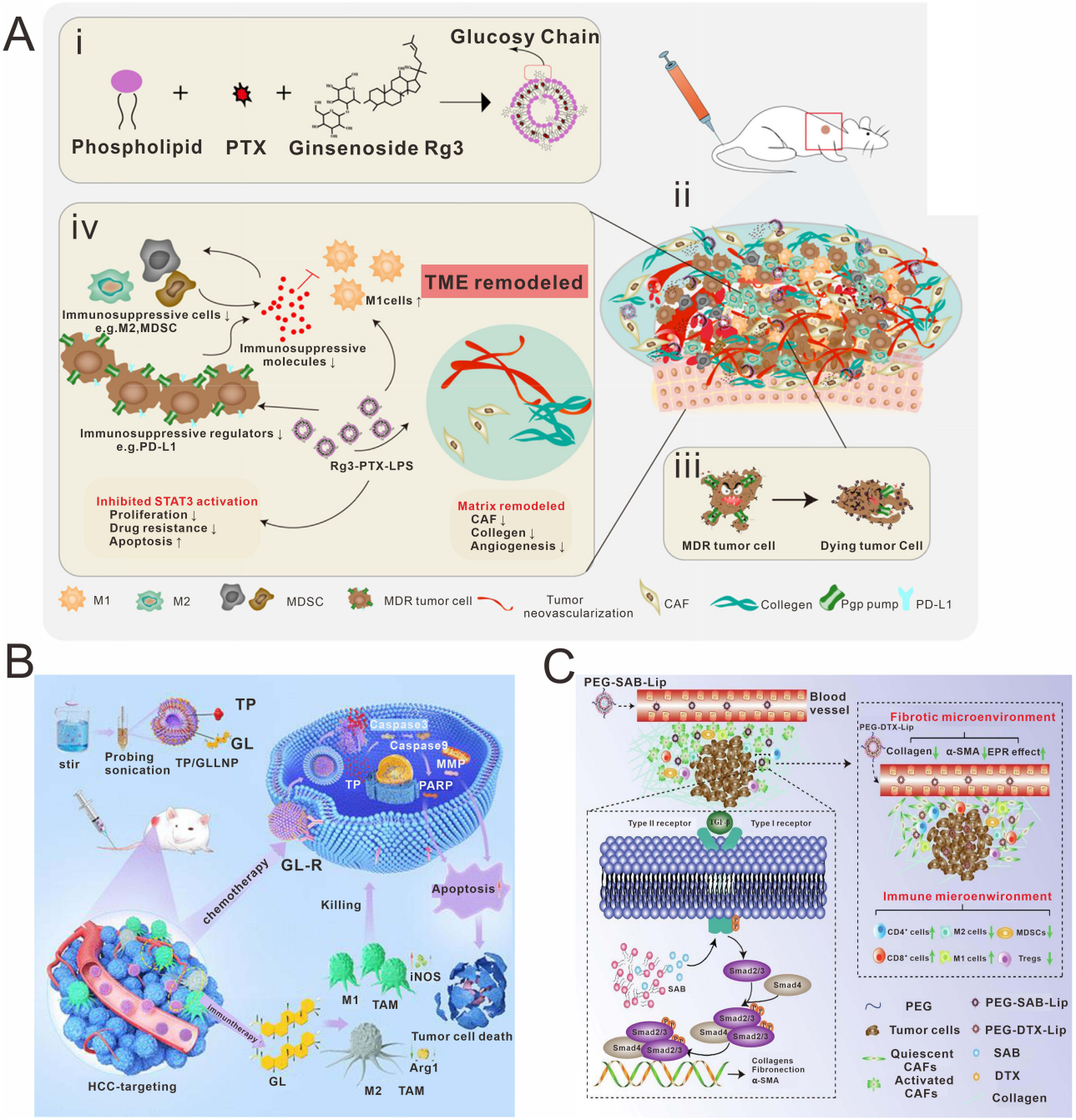

Figure 3 Lipid nano-drug delivery system containing effective components of TCM. (**A**) Schematic representation of Rg3-PTX-LPs overcoming cancer drug resistance. (i) Ginsenoside Rg3 is incorporated as a membrane component in place of cholesterol during liposome preparation. (ii) Depiction of an immunosuppressive and chemoresistant tumor microenvironment. (iii) Rg3-PTX-LPs decrease Pgp expression, limiting PTX efflux from cells. (iv) By inhibiting IL-6/STAT3/p-STAT3 activation, Rg3-PTX-LPs reprogram the TME: shifting macrophages from M2 to M1 phenotype, reducing MDSCs and TAFs, lowering collagen fiber content, and inhibiting angiogenesis. Reprinted by reference.[136] Copyright 2023, The authors. (**B**) Schematic diagram of anti-H22 effect of triptolide (TP/GLLNP) loaded on glycyrrhizic acid (GL)- lipid mixed nano-platform. Reprinted by reference.[137] Copyright 2023, American Chemical Society. (**C**) Schematic diagram of PEG-SAB-Lip loaded with salvianolic acid B remodeling tumor microenvironment. Reprinted with permission of reference.[138] Copyright 2022, Elsevier Ltd.

PEG-SAB-Lip Nanoparticles

Yunna et al reported that PEG-SAB-Lip suppresses tumor-associated fibroblast activation by downregulating TGF-β1 secretion. This inhibition reduces collagen deposition, enhances intratumoral nanoparticle permeability, reverses the tumor microenvironment through M2-to-M1 macrophage polarization, and limits Treg infiltration. Furthermore, this nanocarrier augments the antitumor efficacy of docetaxel-loaded PEG-liposomes[138] (Figure 3C).

CR-Lip Liposomal Platform

Zhang et al developed a multifunctional liposomal delivery platform (CR-Lip) to encapsulate celastrol (CEL) for reprogramming the obesity-associated tumor microenvironment and enhancing cancer immunotherapy. In this system, ginsenoside Rg3 (Rg3) is distributed within the phospholipid bilayer, with glycosyl groups exposed on the liposome surface, potentially facilitating preferential accumulation in tumor tissues via interaction with overexpressed glucose transporter 1. Following accumulation at the tumor site, CR-Lip induces immunogenic cell death (ICD), upregulates PHD3, and inhibits metabolic reprogramming, increasing fatty acid availability. In vivo studies in an obesity-associated melanoma model demonstrated that CR-Lip boosts proinflammatory cytokine secretion, promotes dendritic cell maturation, enhances $CD8^+$ T cell infiltration, and synergizes with aPD-1 therapy to achieve a tumor inhibition rate of 82.1%.[134]

Silybin Liposomal Formulation

Wu et al designed a liposomal formulation of silybin (SLN/LIP), exhibiting spherical morphology and 75.2 nm particle size, with tumor-specific accumulation and robust immune modulation capabilities. SLN/LIP increased IFN-γ and IL-12 levels, decreased TGF-β, SDF-1, IL-6, and TNF-α, and promoted CTL infiltration, effectively converting "cold" tumors into "hot" ones. Combined with liposomal doxorubicin (DOX/LIP), an inducer of ICD, this system significantly enhances antitumor immunity and overall survival.[139]

Polymer Nano-Delivery System Combined with Traditional Chinese Medicine Monomer

Polymeric nanoparticles, including nanocapsules and nanospheres, can be further classified into polymers, micelles, and dendrimers. These nanoparticles are synthesized through various techniques such as nanoprecipitation, ionic gelation, and emulsification.[160,161] Polymeric nanoparticles are regarded great candidates for drug delivery owing to their biodegradability, water solubility, biocompatibility, biomimicry, non-toxicity, and simplicity of functionalization.[162]

GLP-APBA-MTX/HCPT Nanoparticles

Zheng et al developed a novel pH-responsive nanoparticle system (GLP-APBA-MTX/HCPT) by conjugating β-glucan-rich Ganoderma lucidum polysaccharides (GLP) with methotrexate (MTX) via 3-aminophenylboronic acid (APBA). The conjugate was coupled with 10-hydroxycamptothecin (HCPT) via nanoprecipitation to create nanoparticles. Compared to free MTX and HCPT, GLP-APBA-MTX/HCPT nanoparticles did not significantly alter IgE levels or leukocyte counts, indicating reduced systemic toxicity. Additionally, the formulation demonstrated potent inhibition of MCF-7 and 4T1 tumor cell viability and achieved a tumor inhibition rate of 73.68%, highlighting its promise as an effective and low-toxicity anti-cancer therapy.[163]

SK/siIDO1-HMs Micelles

Li et al designed hybrid micelles (SK/siIDO1-HMs) for the co-delivery of shikonin (SK) and small interfering RNA targeting indoleamine 2,3-dioxygenase 1 (siIDO1). To elucidate the antitumor mechanism of SK/siIDO1-HMs, we assessed intratumoral IDO-1 (Figure 4A). Western blot revealed that SK/siIDO1-HMs markedly decreased IDO-1 protein levels compared to SK-HMs (Figure 4B). Concurrently, SK/siIDO1-HMs effectively suppressed IDO-1 activity, as shown by the reduced kynurenine/tryptophan ratio (Figure 4C). Furthermore, this treatment significantly diminished the infiltration of immunosuppressive Tregs (Figure 4D). These results indicate that SK/siIDO1-HMs confer synergistic antitumor efficacy by inducing ICD and mitigating IDO1-mediated immunosuppression. These micelles exhibited prolonged systemic circulation, enhanced tumor accumulation, and rapid cytoplasmic release, thereby triggering immune responses through remodeling of the tumor immune microenvironment.[164]

Nano-Delivery System of Chinese Medicine Monomer Combined with Inorganic Material

Inorganic nanoparticles, such as gold, iron, and silica, exhibit unique magnetic, radioactive, and photothermal properties.[165,166] These physicochemical characteristics make them highly valuable for applications in cancer detection,

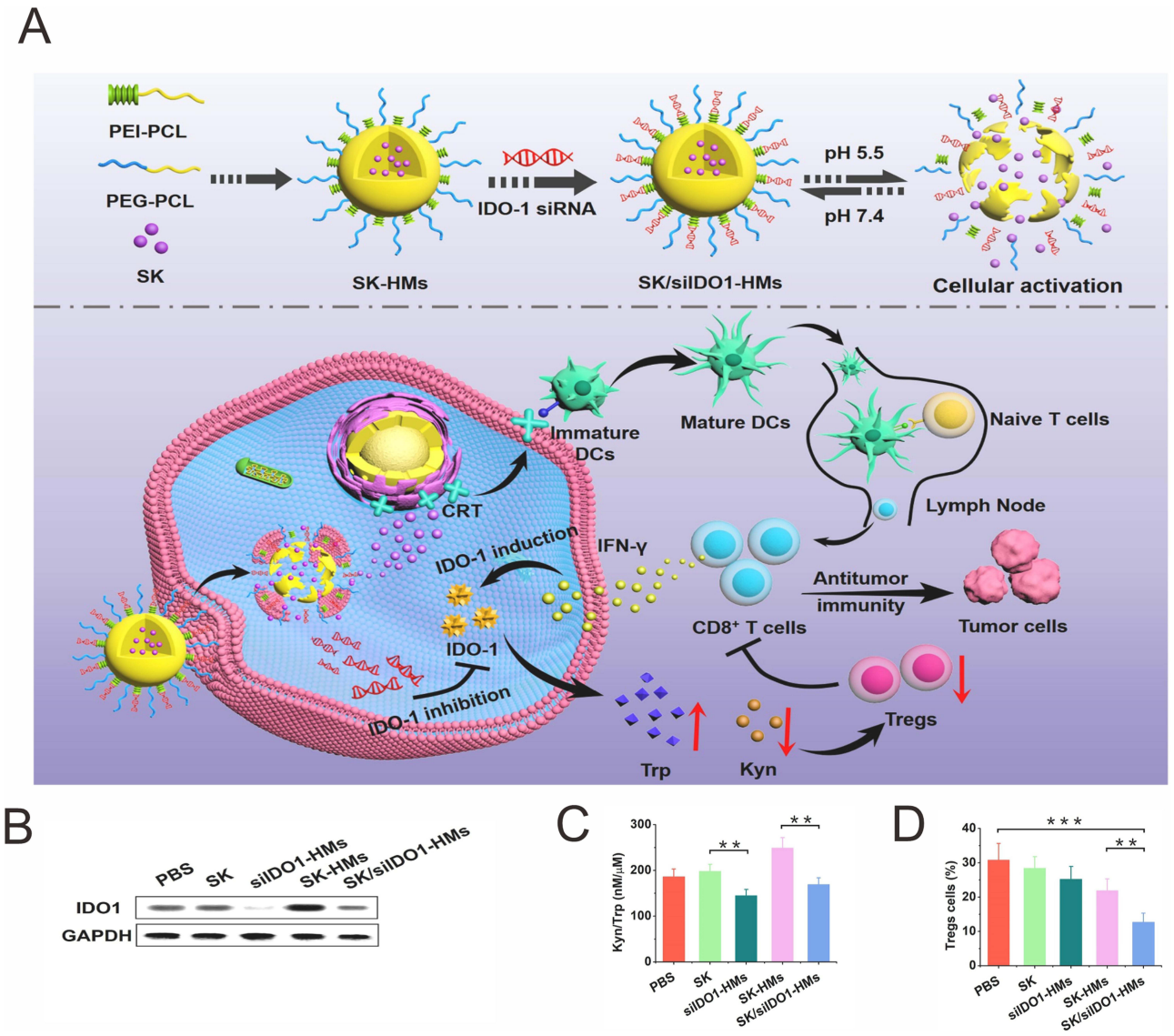

Figure 4 Polymer nano-drug delivery system containing TCM active ingredients. (**A**) Schematic depiction of SK/siIDO1-HMs demonstrating anticancer effectiveness by promoting tumor cell ICD and eliminating IDO-1-triggered immunosuppression. (**B**) Western blot analysis of IDO-1 proteins. (**C**) The intratumoral kynurenine (Kyn) to tryptophan (Trp) ratio. (**D**) Treg infiltration measured by FCM. Data are presented as mean ± SD. **p < 0.01, ***p < 0.001. Reprinted with permission of reference.[164] Copyright 2021, Elsevier Ltd.

imaging, and photothermal therapy in both preclinical and clinical settings. A major advantage of gold nanoparticles lies in their facile surface modification and strong binding affinity, enabling non-covalent loading of TCM monomers while preserving stability and biocompatibility.[167]

EGCG-Png Gold Nanoparticles

Gold nanoparticle-conjugated EGCG (EGCG-png) demonstrates superior therapeutic efficacy compared to free EGCG in bladder cancer treatment. EGCG-png exerts antitumor effects by inducing apoptosis and enhancing immune responses, while also mitigating EGCG-associated hepatotoxicity at high doses.[168]

GLP-Au Gold Nanocomposite

Hang et al developed a *Ganoderma lucidum* polysaccharide-coated gold nanocomposite (GLP-Au) that effectively promotes DC activation (Figure 5A–D). Combining GLP-Au-stimulated DCs with T cells leads to increased T cell proliferation and a higher fraction of $CD4^+/CD44^+$ memory T cells when paired with doxorubicin (Figure 5E–L).[148]

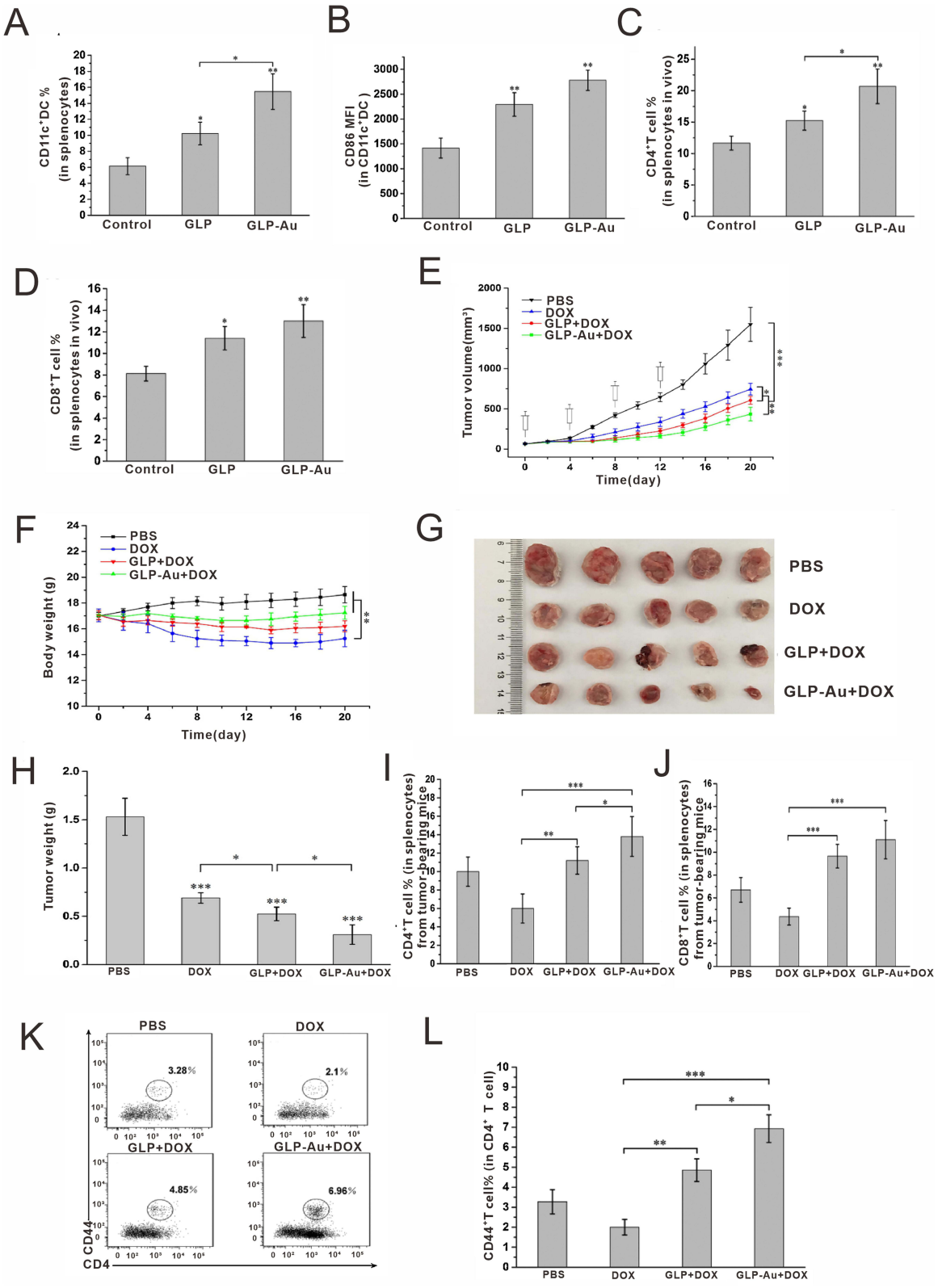

Figure 5 Nano-drug delivery system of inorganic materials containing TCM active ingredients. DC differentiation/maturation and T cell proliferation in the spleen following a 5-day therapy with GLP or GLP-Au at 30 mg/kg. (**A**) Frequency of CD11c$^+$ DCs among splenocytes. (**B**) Mean fluorescence intensity (MFI) of CD86 on CD11c$^+$ DCs. (**C**) Proportion of CD4$^+$ T cells in splenocytes. (**D**) Proportion of CD8$^+$ T cells in splenocytes. (**E**) Tumor growth curves over time. Syringe icons indicate intravenous tail vein injection time points. (**F**) Body weight changes of mice throughout the study starting from the first day post-injection. (**G**) Representative photographs of excised tumors from each group at the endpoint. (**H**) Tumor weight comparison across groups, represented as a bar chart corresponding to (**G**). (**I**) Proportion of CD4$^+$ T cells in splenocytes. (**J**) Proportion of CD8$^+$ T cells in splenocytes. (**K**) Representative dot plots of CD4 vs CD44 expression in splenocytes from groups treated with PBS, DOX, GLP+DOX, and GLP-Au+DOX. (**L**) Quantification of CD4$^+$CD44$^+$ T cells, shown as a histogram. Data are presented as mean ± SD, *p < 0.05**p < 0.01, ***p < 0.001. Reprinted with permission of reference.[148] Copyright 2018, Elsevier Ltd.

https://doi.org/10.2147/IJN.S576928

Magnetic Nanoparticles (MNPs)

Magnetic nanoparticles have gained prominence due to their small size, excellent colloidal stability, favorable biocompatibility, tumor-targeting capacity, and efficient heat generation under magnetic fields.[169] Chiang et al proposed a magnetically guided therapeutic platform combining a fucosan-dextran-based nanocarrier (IO@FuDex 3) with checkpoint blockade (anti-PD-L1) and T cell co-stimulation (anti-CD3 and anti-CD28). This strategy reactivates tumor-infiltrating lymphocytes and targets tumors via magnetic guidance, reducing off-target effects. Notably, treatment with IO@FuDex 3 extended median survival from 32 to 63 days, significantly outperforming soluble anti-PD-L1 at subtherapeutic doses (<1%).[170]

Nano-Delivery System of Traditional Chinese Medicine Monomer Combined with Bionic Material

Biomimetic nano-delivery systems are nanocarriers designed to mimic the structure and biological functions of endogenous substances, offering excellent biocompatibility, precise targeting, and controlled drug release. Representative biomimetic materials include cell membrane-derived vesicles, such as those sourced from red blood cells or tumor cells. These materials facilitate immune evasion, extend systemic circulation time, and enable tumor-specific delivery via homologous membrane targeting.[171,172]

Exosome-Based Delivery

Exosomes are nanoscale extracellular vesicles originating from endosomal compartments, characterized by small size and complex biochemical composition and structure.[173] Cui et al employed tanshinone IIA (TanIIA) and glycyrrhizic acid (GL), both traditional Chinese medicine-derived STAT3 inhibitors, to formulate self-assembled TanIIA-GL nanomicelles (TGM). These nanomicelles were encapsulated using endogenous serum-derived exosomes, and CpG oligonucleotides -agonists of Toll-like receptor 9 were functionalized onto the exosome surface, forming immune exosomes loaded with TCM-based nanomicelles (CpG-exo/TGM). The resulting CpG-exo/TGM demonstrated the ability to evade mononuclear phagocyte system (MPS) clearance, penetrate the blood-brain barrier via transferrin receptor-mediated endocytosis, and enable efficient intratumoral drug release. Co-administration of CpG-exo/TGM with temozolomide significantly enhanced antitumor efficacy and reduced the risk of postoperative recurrence.[144]

Exosome-Like Nanoparticles Derived from Dipsacus Asper (DAELNs)

Lu et al investigated the effects of exosome-like nanoparticles derived from Dipsacus asper (DAELNs) on osteosarcoma in both in vitro and in vivo models. In vitro, DAELNs suppressed proliferation, migration, and invasion of osteosarcoma cells, while promoting apoptosis. In xenograft nude mouse models, DAELNs markedly inhibited tumor growth. Mechanistically, DAELNs induced apoptosis via activation of the P38/JNK signaling cascade. Biodistribution studies with DiD-labeled DAELNs confirmed tumor-specific accumulation and demonstrated minimal hepatotoxicity and nephrotoxicity upon histological examination.[174]

Cell Membrane Vesicles

Cell membrane vesicles are nanoscale structures derived from various membrane sources, including single-cell types (eg, stem cells, immune cells, blood cells, and bacterial membranes), hybrid membranes, or membranes fused with liposomes. These vesicles exhibit intrinsic biocompatibility, targeting ability, and therapeutic potential. They can transport therapeutic agents such as drugs, genes, or signaling molecules that interact with target cell receptors, enabling immune evasion and precise drug delivery.[175]

GACS-Cur@RBCm Nanoparticles

Guo et al synthesized glycyrrhizic acid (GA)-aps-disulfide bond (DTA)-curcumin nanoparticles (GACS-Cur) using a dialysis-based self-assembly method. To prolong systemic circulation and enhance immune evasion, GACS-Cur was encapsulated in erythrocyte membranes (GACS-Cur@RBCm). Upon encountering the glutathione-rich tumor microenvironment (TME), GACS-Cur disassembles, releasing its cytotoxic payload into HCC cells. Additionally, this

encourages the invasion of CD8+ T cells and triggers the release of TNF-α, IFN-γ, and IL-2. The formulation demonstrates precise tumor targeting and robust antitumor activity in liver cancer models.[145]

GDNPs Exosomal Nanoparticles

Cao et al isolated ginseng-derived extracellular vesicle-like nanoparticles (GDNPs) from ginseng roots and used them as immunostimulants to reprogram M2 macrophages, implicating anti-melanoma activity via TLR4 and MyD88 signaling pathways. This reprogramming led to enrichment of M1 macrophages and T cells within the tumor, enhancing antitumor immunity and confirming GDNPs' macrophage-dependent mechanism in melanoma suppression.[146]

Mannose-Modified Red Blood Cell Membranes Nanoparticles

Han et al developed PLGA nanoparticles co-loaded with PLB, DIH, and NH_4HCO_3, a pH-sensitive adjuvant. To produce a targeted nanoformulation, these nanoparticles were further functionalized using red blood cell membranes modified with mannose. As shown in the study (n=6), the combination nanoformulation (Comb-NP) effectively suppressed HCC progression over a 20-day period, extending median survival from 28 days (PBS group) to over 90 days (Figure 6A–C). Analysis of tumors on day 18 revealed an increase in immunostimulatory cells and a decrease in immunosuppressive cells, demonstrating the strategy's efficacy in reversing the immunosuppressive tumor milieu (Figure 6D–G). This design markedly improved pharmacokinetic behavior and tumor selectivity of traditional Chinese medicine payloads. It modulates the "cold" tumor microenvironment by inducing ICD and triggering systemic immune responses. Consequently, this chemoimmunotherapy strategy reverses the immunosuppressive tumor milieu.[176]

Traditional Chinese Medicine Monomer Combined with Other Nano-Delivery Systems

Mesoporous Microfibers (SMF) Vaccine Scaffolds

Astragaloside IV (AS-IV) can be formulated into mesoporous microfibers (SMF) without excipients. These injectable SMFs self-aggregate in vivo to form macroporous three-dimensional scaffolds. Such scaffolds recruit DCs into the inter-fiber pores and facilitate their maturation through NLRP3 pathway activation. AS-IV-based scaffold vaccines, lacking toxic or costly adjuvants, show strong immunostimulatory activity in melanoma and breast cancer models, eliciting potent antitumor immune responses. These scaffolds further enhance therapeutic efficacy when combined with approved TLR-4 agonists and immune checkpoint inhibitors.[177]

NRA Quantum Dots

Realgar, a traditional mineral medicine, possesses notable anticancer properties and is a promising adjuvant in oncology. Its clinical translation is limited by poor solubility and low bioavailability. Wang et al developed realgar quantum dots (NRA QDs) conjugated with 6-AN and encapsulated them in a hyaluronic acid-modified, pH-sensitive dextran hydrogel (DEX-HA gel) for improved delivery. The resulting NRA@DH gel exerts chemotherapeutic effects and acts as a sustained ROS generator. It inhibits the pentose phosphate pathway (PPP), reducing NADPH levels by blocking GSSG-to-GSH conversion. As a result, intracellular GSH is depleted, promoting ROS accumulation and enhancing radiotherapy efficacy. In tumor-bearing mice, NRA@DH gel inhibited proliferation, migration, and tumor growth, improved motor coordination, and extended survival via combined chemo-radiotherapy.[178]

LNT-UA Nanopharmaceutical

Mao et al formulated LNT-UA, a carrier-free nanopharmaceutical derived from ursolic acid (UA) and lentinan (LNT), using a simple nanoprecipitation method for colorectal cancer immunotherapy. In CT26 CRC models, LNT-UA modulated the immunosuppressive TME and activated both innate and adaptive immunity to suppress tumor progression. LNT-UA significantly inhibited primary and metastatic tumor growth, doubling median survival in bilateral tumor models. In a spontaneous colorectal cancer model, sequential administration of LNT-UA and αCD47 markedly reduced tumor burden and nodule size.[150]

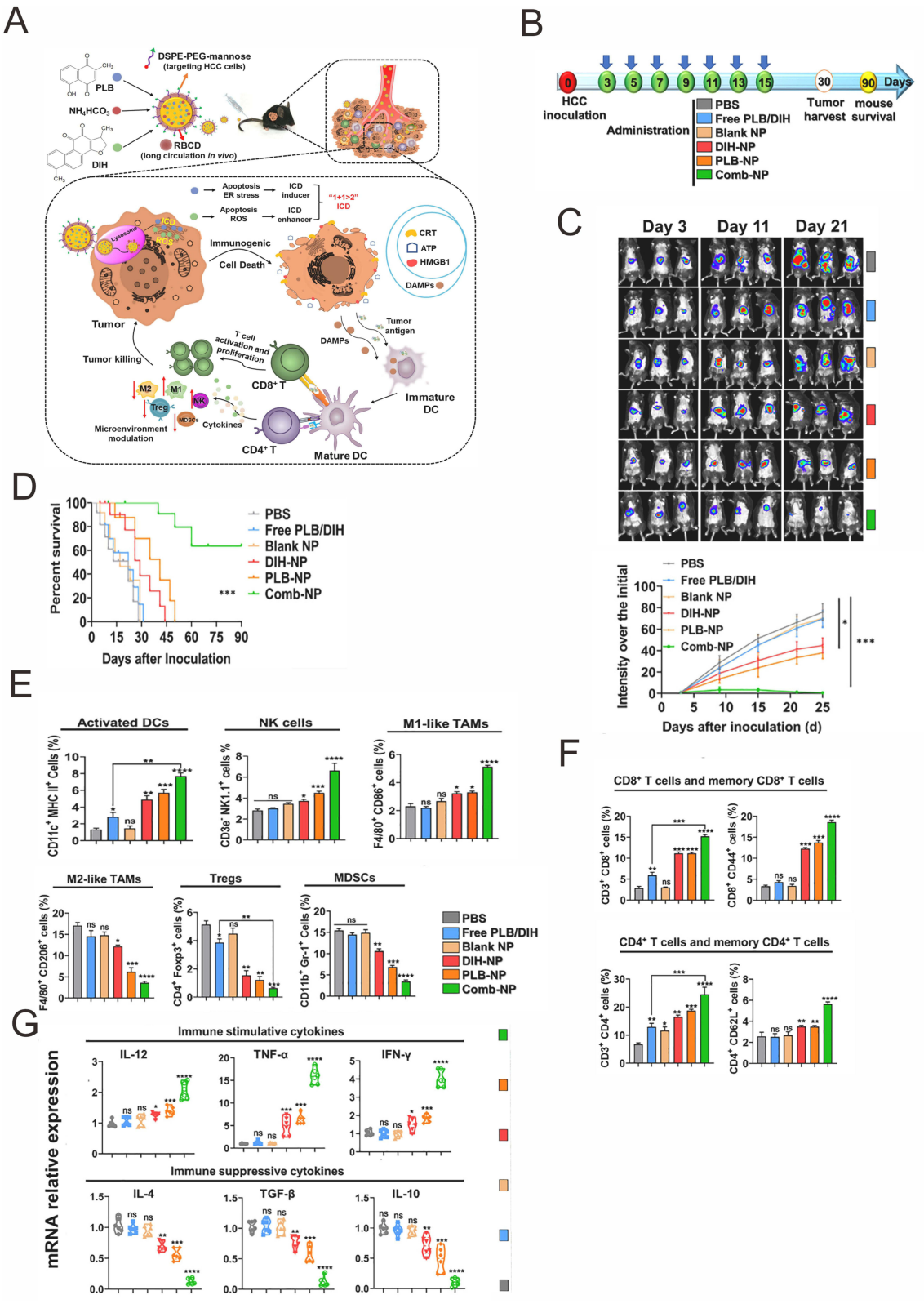

Figure 6 Nano-drug delivery system of bionic material containing TCM active ingredients. (**A**) Reversing immunosuppressive TME in HCC by co-delivering plumbagin and dihydrotanshinone I utilizing a biomimetic nanoformulation. The immunosuppressive TME of HCC was altered by the biomimetic nanoformulation, which also produced an anticancer impact. (**B**) Treatment and inoculation plan for tumors (n = 6). (**C**) The evolution of the HCC over a 20-day span. (**D**) Animal survival (median survival: 28 days for PBS, 31 days for Free PLB/DIH, 29 days for Blank NP, 44 days for DIH-NP, 50 days for PLB-NP, and 90 days for Comb-NP). (**E**) On Day 18, immunostimulatory cells in tumors. (**F**) On Day 18, immunosuppressive cells in tumors. (**G**) Immunostimulatory and immunoinhibitory cytokine mRNA expression in tumors on Day 18. (ns: $p > 0.05$, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ and ****$p < 0.0001$). Reprinted with permission of reference.[176] Copyright 2022, Elsevier Ltd.

https://doi.org/10.2147/IJN.S576928

Comparative Analysis of Nano-Delivery Platforms

The preceding sections have detailed a variety of nano-delivery systems designed to enhance the therapeutic efficacy of TCM monomers. A critical comparative analysis of their fundamental characteristics, strengths, and weaknesses is essential to guide rational platform selection for future research and clinical translation.

Lipid Nano-delivery System are among the most clinically advanced nanocarriers. Their primary advantages include excellent biocompatibility, proven ability to encapsulate both hydrophilic and hydrophobic drugs, and a well-established, scalable manufacturing process (eg., extrusion, microfluidics). Functionalization with PEG (stealth coating) or targeting ligands further enhances their circulation time and tumor accumulation.[179] However, their limitations include potential drug leakage during storage, batch-to-batch variability, and sometimes insufficient drug loading capacity for certain TCM compounds.[180] Lipid Nano-delivery System benefits from decades of research, with multiple FDA-approved products (eg., Doxil®, Onpattro®). Their safety profiles are relatively well-understood, and Good Manufacturing Practice (GMP) production is feasible. The successful integration of TCM monomers like ginsenoside Rg3 and glycyrrhizic acid as both membrane components and active agents (eg., Rg3-PTX-LPs, TP/GLLNP) demonstrates a highly innovative and translatable strategy that leverages the intrinsic properties of TCM compounds.

Polymer Nano-delivery System offer high design flexibility. Their key advantages are controllable biodegradation rates, sustained drug release profiles, and the capacity for precise surface engineering.[181] Systems like SK/siIDO1-HMs demonstrate the potential for co-delivering small molecules and nucleic acids. The main challenges involve the potential toxicity of polymer degradation products, complex synthesis/purification steps that can affect reproducibility, and relatively lower drug loading efficiency compared to some lipid systems.[182,183]

Inorganic Nano-delivery System (eg., gold, silica, magnetic NPs) possess unique physicochemical properties. Their strengths lie in their exceptional stability, ease of surface modification, and multifunctionality (eg., imaging contrast, photothermal therapy). GLP-Au nanocomposites, for instance, combined immunotherapy with potential diagnostic capabilities. Three types of rod-like gold-mesoporous silica nanoparticles (termed bare AuNPs, core-shell Au@mSiO2NPs, and Janus Au@mSiO2NPs) were specially designed, and the effects of these AuNPs on cellular uptake, toxic behavior, and mechanism were then systematically studied. The results showed that bare AuNPs were more toxic to human breast cancer cells. The significant drawbacks that hinder clinical translation are concerns regarding long-term toxicity and biodistribution (potential for organ accumulation), uncertain biodegradation pathways, and generally more complex and costly synthesis.[184,185]

Biomimetic Nano-delivery System (eg., exosome, cell membrane-coated NPs) represent a cutting-edge strategy. Their greatest advantage is superior biocompatibility and innate ability to evade immune clearance, leading to prolonged circulation and enhanced targeting. Platforms like CpG-exo/TGM and mannose-modified RBC membrane NPs show impressive blood-brain barrier penetration and tumor-specific accumulation. The primary limitations are the technical challenges in scalable production with consistent quality, difficulties in achieving high and standardized drug loading, and the complexity of fully characterizing these biologically derived components.[186,187]

Discussion

In recent years, immunotherapy has changed the landscape of cancer treatment with its significant improvement in patient outcomes. However, its efficacy remains limited to a subset of patients, largely due to intrinsic resistance mechanisms and the immunosuppressive characteristics of TME.[188,189] While ICIs and CAR-T cell therapy have demonstrated success, challenges such as low immune infiltration ("cold" tumors), T cell exhaustion, and immune-related adverse events continue to constrain their broader application.[190] The TME plays a central role in shaping therapeutic outcomes and regulating tumor immune escape and therapy resistance.[191,192] Immunosuppressive populations such as TAMs, MDSCs, and Tregs contribute to T cell dysfunction through cytokine secretion, immune checkpoint upregulation, and ECM remodeling.[99,193–195] Consequently, effective strategies that modulate the TME are critical for enhancing immunotherapy responsiveness.

TCM monomers have shown potential in remodeling the immune landscape of the TME. Compounds like curcumin, ginsenosides, berberine, and triptolide exert multi-target immunomodulatory effects, such as reprogramming TAMs,

reducing MDSC accumulation, and restoring T cell function.[196,197] However, their clinical application is hampered by poor solubility, low bioavailability, and inadequate tumor targeting, which limit effective concentrations within the tumor site. In this context, nanotechnology offers promising solutions to these delivery challenges. By improving pharmacokinetics, stability, and tumor accumulation, nano-delivery systems enhance the therapeutic efficacy of TCM monomers. For instance, pH-sensitive nanocarriers can facilitate site-specific release in the acidic TME, while ligand-modified systems enable active targeting of immune cells or tumor sites.[198–200] Additionally, co-delivery strategies integrating TCM compounds with ICIs or chemotherapeutics have demonstrated synergistic effects by modulating the TME and promoting immunogenic cell death.[201–203]

Nevertheless, the clinical translation of TCM-based nanomedicine still faces several challenges. First, the heterogeneity of TCM monomers, including variability in purity, source, and preparation, may affect formulation reproducibility and pharmacodynamics. Second, the safety and long-term toxicity of certain nanomaterials require comprehensive evaluation, especially regarding immune compatibility. Third, large-scale production, cost-effectiveness, and regulatory approval remain major hurdles that must be addressed before widespread clinical application. The future research should focus on the rational design of multifunctional nanoplatforms tailored for specific TCM compounds and tumor types. Integration of advanced technologies such as artificial intelligence, bioinformatics, and single-cell sequencing may guide the personalized selection of TCM agents and predict therapeutic responses. Moreover, combination regimens incorporating TCM-nanoformulations with ICIs, cancer vaccines, or adoptive cell therapies could offer synergistic benefits and expand the responder population in immunotherapy.

Looking forward, the next frontier in TCM-based nanomedicine lies in the rational design of more intelligent and adaptive delivery systems. Emerging nanotechnological strategies offer compelling solutions to current challenges. First, the development of "cascade-responsive" or logic-gated nanocarriers is promising. These systems can be engineered to sequentially respond to multiple, specific TME stimuli (eg., overexpressed enzymes followed by acidic pH), ensuring highly precise spatiotemporal drug release only at the intended site, thereby maximizing therapeutic efficacy and minimizing systemic toxicity.[204] Second, biomimetic technologies are advancing beyond simple cell membrane coating. By leveraging synthetic biology tools, future nanosystems can be endowed with dynamic, bioinspired functions—such as surfaces that mimic the recruitment signals of specific immune cells—to achieve active, context-dependent homing to immunosuppressive niches within the TME.[205,206] Furthermore, the convergence of nanomedicine with real-time sensing could pave the way for closed-loop therapeutic systems. These "smart" platforms would not only deliver TCM monomers but also monitor local biomarkers (eg., cytokine levels) and adaptively adjust their payload release to maintain an optimal immunomodulatory state, representing a paradigm shift towards personalized and adaptive cancer immunotherapy.[207] The integration of these sophisticated strategies with the multi-targeting philosophy of TCM holds transformative potential for robustly and intelligently reprogramming the immunosuppressive TME.

To bridge the promising preclinical findings discussed herein to tangible clinical benefits, a focused effort on translational science is imperative. The key steps for this transition must be systematically addressed. First, the scalable and reproducible production of TCM-based nano-formulations under Good Manufacturing Practice (GMP) standards is a fundamental prerequisite to ensure consistent quality, stability, and safety for human use. Second, beyond proof-of-concept models, rigorous validation in immunocompetent, patient-derived xenograft (PDX) models or humanized mouse models that better recapitulate the human immune system and tumor heterogeneity is crucial for predicting clinical efficacy. Third, comprehensive pharmacokinetic and pharmacodynamic (PK/PD) studies, including detailed assessments of biodistribution, organ-specific accumulation, and clearance pathways, are essential to understand the in vivo fate of these nanosystems. Finally, thorough toxicological evaluation—extending beyond acute toxicity to include chronic toxicity, immunotoxicity, and potential off-target effects—must be conducted in relevant animal species to establish a safety profile that supports Investigational New Drug (IND) application. Addressing these translational pillars with the same rigor applied to mechanistic discovery will be critical for advancing TCM-based nanomedicine from the bench to the bedside.

In conclusion, the immunosuppressive TME remains a formidable barrier to effective cancer immunotherapy. TCM monomers represent a valuable reservoir of bioactive compounds capable of reprogramming the immune landscape, yet their clinical utility is constrained by delivery limitations. Nanotechnology-based delivery systems offer a powerful

platform to overcome these barriers, enabling precise, controlled, and targeted modulation of the TME. Continued interdisciplinary research integrating traditional medicine, nanoscience, and immuno-oncology will be critical to translating these innovations into clinical reality.

Conclusion

This review systematically elucidates the critical roles of immunosuppressive cell populations TAMs, MDSCs, and Tregs in fostering a tumor-promoting microenvironment and contributing to immunotherapy resistance. We have comprehensively summarized the compelling evidence that numerous TCM monomers, such as curcumin, berberine, ginsenoside Rg3, and glycyrrhizic acid, can directly target these cells to reverse immunosuppression, offering a unique multi-target and low-toxicity approach to "heat up" cold tumors.

However, the inherent pharmacokinetic drawbacks of these compounds—including poor solubility, instability, and non-specific biodistribution—severely limit their clinical translation and therapeutic efficacy. The integration of advanced nano-delivery systems (eg., liposomes, polymeric nanoparticles, inorganic carriers, and biomimetic vesicles) emerges as a transformative strategy. These systems not only overcome the delivery barriers but also enhance the immunomodulatory potency of TCM monomers through improved tumor targeting, controlled release, and intelligent responsiveness to the TME. The reviewed nano-formulations demonstrate synergistic potential in reprogramming the immune landscape, promoting immunogenic cell death, and enhancing the efficacy of conventional therapies.

Looking forward, the convergence of TCM and nanotechnology represents a promising frontier in cancer immunotherapy. To advance this field, future efforts must prioritize: (1) the rational design of multifunctional and tumor-microenvironment-responsive nanoplatforms tailored to specific TCM agents; (2) rigorous investigation into the long-term safety, biocompatibility, and potential immunotoxicity of these complex nano-formulations; and (3) the exploration of personalized combination regimens that integrate TCM-based nanomedicines with immune checkpoint inhibitors, adoptive cell therapies, or conventional modalities. By fostering deeper interdisciplinary collaboration among pharmacologists, material scientists, and clinical oncologists, the translation of these sophisticated TCM-nano strategies from bench to bedside can be accelerated, ultimately providing new hope for overcoming tumor immunosuppression and improving patient outcomes.

Abbreviations

Akt/mTOR, the Akt/mammalian target of rapamycin; APBA, 3-aminophenylboronic acid; APS, astragalus polysaccharides; Arg-1, activating arginase-1; AS-III, Astragaloside III; AS-IV, Astragaloside IV; bFGF, basic fibroblast growth factor; CARD9, caspase recruitment domain-containing protein 9; CAR-T, chimeric antigen receptor T; CEL, celastrol; COX-2, cyclooxygenase-2; CSF1R, colony-stimulating factor 1 receptor; CTL, cytotoxic $CD8^+$ T lymphocyte; CTLA-4, cytotoxic T lymphocyte-associated antigen 4;DAELNs, Dipsacus asper; DC, dendritic cell; DHA, Dihydroartemisinin; EPCs, endothelial progenitor cells; ERK1/2, extracellular signal-regulated kinase 1/2; FcγR, Fc gamma receptor;GAA, Ganoderic acid A; GDNPs, ginseng-derived extracellular vesicle-like nanoparticles; GL, glycyrrhizic acid; GLP, Ganoderma lucidum polysaccharide;HCC, hepatocellular carcinoma; HCPT, 10-hydroxycamptothecin;ICD, immunogenic cell death; ICIs, immune checkpoint inhibitors; ICT, icaritin; G-CSF, granulocyte colony-stimulating factor; IDO, indoleamine 2,3-dioxygenase; IFN-γ, interferon-gamma; IL-1, interleukin-1; iNOS, inducible nitric oxide synthase; IRF4, interferon regulatory factor 4;LLC, Lewis lung carcinoma; nano-Cur, nano-curcumin; LNT, lentinan; LPS, lipopolysaccharide;MAPK, mitogen-activated protein kinase; MDSCs, myeloid-derived suppressor cells; MHC-II, major histocompatibility complex class II; miR-125b, microRNA-125b; M-MDSCs, monocytic MDSCs; MPS, mononuclear phagocyte system;PGE2, prostaglandin E2;PMN-MDSCs, polymorphonuclear MDSCs; p-p65, phosphorylated p65; PPP, pentose phosphate pathway; p-Syk, phosphorylated spleen tyrosine kinase;PTX3, pentraxin 3;Rg3, ginsenoside Rg3; Rg3-PTX-LPs, Paclitaxel-loaded Rg3-LPs; rIL-6, recombinant IL-6; ROS, reactive oxygen species; RSV, Resveratrol;Sch B, Schisandrin B; SK, shikonin; SLN/LIP, a liposomal formulation of silybin; STAT3, signal transducer and activator of transcription 3;TAMs, tumor-associated macrophages; TanIIA, tanshinone IIA; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; TCM, Traditional Chinese medicine; TGF-β, transforming growth factor-beta; TGM, TanIIA-GL nanomicelles; TGP, Total glucosides of peony; TME, The tumor microenvironment; TNBC, triple-negative breast

cancer;TNF-α, tumor necrosis factor-alpha; TPCs, Treg precursor cells;UA, ursolic acid; VEGF, vascular endothelial growth factor. GMP, Good Manufacturing Practice; PDX, patient-derived xenograft; PK/PD, pharmacokinetic and pharmacodynamic; IND, Investigational New Drug.

Data Sharing Statement

The datasets generated and analyzed during the current study are available from the corresponding author [Peng Zhao] upon reasonable request.

Ethics Approval and Consent to Participate

This study was a systematic review of published studies that did not involve individual human data. Ethical approval or consent to participate was not required.

Author Contributions

Conception and design: L.Z., M.X., J.Y. Literature search, investigation, data acquisition, analysis, and interpretation: L. Z., M.X., J.Y., X.S., X.D., X.B. Drafting of the original manuscript: L.Z., M.X., J.Y. Critical revision of the manuscript for important intellectual content: All authors (L.Z., M.X., J.Y., X.S., X.D., X.B., C.H., J.H., J.L., P.Z.). Visualization and figure preparation: L.Z., X.S., X.D., X.B. Supervision: J.L., P.Z. Final approval of the version to be submitted: All authors. Accountability for all aspects of the work: All authors are accountable for the work's integrity and accuracy. L. Z., M.X., and J.Y. contributed equally to this work.

Funding

This work received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Disclosure

The authors declare that they have no competing interests.

References

1. Kennedy LB, Salama AKS. A review of cancer immunotherapy toxicity. *CA Cancer J Clin*. 2020;70(2):86–104. doi:10.3322/caac.21596
2. Wu B, Zhang B, Li B, Wu H, Jiang M. Cold and hot tumors: from molecular mechanisms to targeted therapy. *Signal Transduct Target Ther*. 2024;9(1):274. doi:10.1038/s41392-024-01979-x
3. Blum SM, Rouhani SJ, Sullivan RJ. Effects of immune-related adverse events (irAEs) and their treatment on antitumor immune responses. *Immunol Rev*. 2023;318(1):167–178. doi:10.1111/imr.13262
4. Andersen MH. Novel immunotherapeutic combinations moving forward: the modulation of the immunosuppressive microenvironment. *Semin Immunopathol*. 2023;45(2):159–161. doi:10.1007/s00281-023-00991-7
5. Zhang Y, Zhang Z. The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications. *Cell Mol Immunol*. 2020;17(8):807–821. doi:10.1038/s41423-020-0488-6
6. Huang Y, Kim BYS, Chan CK, Hahn SM, Weissman IL, Jiang W. Improving immune-vascular crosstalk for cancer immunotherapy. *Nat Rev Immunol*. 2018;18(3):195–203. doi:10.1038/nri.2017.145
7. Chen Z, Han F, Du Y, Shi H, Zhou W. Hypoxic microenvironment in cancer: molecular mechanisms and therapeutic interventions. *Signal Transduct Target Ther*. 2023;8(1):70. doi:10.1038/s41392-023-01332-8
8. Chang WH, Lai AG. The hypoxic tumour microenvironment: a safe haven for immunosuppressive cells and a therapeutic barrier to overcome. *Cancer Lett*. 2020;487:34–44. doi:10.1016/j.canlet.2020.05.011
9. Liao S, Wu G, Xie Z, et al. pH regulators and their inhibitors in tumor microenvironment. *Eur J Med Chem*. 2024;267:116170. doi:10.1016/j.ejmech.2024.116170
10. Zhang J, Feng J, Huang Y, Zhou B, Li B, Zhang R. Ginseng Polysaccharide Enhances the Humoral and Cellular Immune Responses to SARS-CoV-2 RBD Protein Subunit Vaccines. *Vaccines*. 2023;11(12):1833. doi:10.3390/vaccines11121833
11. Wang H, Wei L, Mao D, et al. Combination of oxymatrine (Om) and astragaloside IV (As) enhances the infiltration and function of TILs in triple-negative breast cancer (TNBC). *Int Immunopharmacol*. 2023;125(Pt A):111026. doi:10.1016/j.intimp.2023.111026
12. Li XM, Yuan DY, Liu YH, et al. Panax notoginseng saponins prevent colitis-associated colorectal cancer via inhibition IDO1 mediated immune regulation. *Chin J Nat Med*. 2022;20(4):258–269. doi:10.1016/s1875-5364(22)60179-1
13. Bharali DJ, Siddiqui IA, Adhami VM, et al. Nanoparticle delivery of natural products in the prevention and treatment of cancers: current status and future prospects. *Cancers*. 2011;3(4):4024–4045. doi:10.3390/cancers3044024
14. Andreani T, Cheng R, Elbadri K, et al. Natural compounds-based nanomedicines for cancer treatment: future directions and challenges. *Drug Deliv Transl Res*. 2024;14(10):2845–2916. doi:10.1007/s13346-024-01649-z
15. Liu G, Yang L, Chen G, et al. A Review on Drug Delivery System for Tumor Therapy. Review. *Front Pharmacol*. 2021;12:735446.

16. Blanco E, Shen H, Ferrari M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. *Nat Biotechnol*. 2015;33(9):941–951. doi:10.1038/nbt.3330
17. Azevedo C, Macedo MH, Sarmento B. Strategies for the enhanced intracellular delivery of nanomaterials. *Drug Discov Today*. 2018;23(5):944–959. doi:10.1016/j.drudis.2017.08.011
18. Silveira MJ, Martins C, Cardoso AP, et al. Immunostimulatory effects of IL-12 targeted pH-responsive nanoparticles in macrophage-enriched 3D immuno-spheroids in vitro model. *Drug Deliv Transl Res*. 2025;15(12):4775–4794. doi:10.1007/s13346-025-01896-8
19. Chen H, Jiang C, Yu C, Zhang S, Liu B, Kong J. Protein chips and nanomaterials for application in tumor marker immunoassays. *Biosens Bioelectron*. 2009;24(12):3399–3411. doi:10.1016/j.bios.2009.03.020
20. Abd Elkodous M, El-Sayyad GS, Abdelrahman IY, et al. Therapeutic and diagnostic potential of nanomaterials for enhanced biomedical applications. *Colloids Surf B Biointerfaces*. 2019;180:411–428. doi:10.1016/j.colsurfb.2019.05.008
21. Chen Y, Xianyu Y, Jiang X. Surface Modification of Gold Nanoparticles with Small Molecules for Biochemical Analysis. *Acc Chem Res*. 2017;50(2):310–319. doi:10.1021/acs.accounts.6b00506
22. Tang Y, Huang J, Cui C, et al. Folate-Modified Smart Responsive Nanosystems for Enhancing Anti-Tumor Therapy Through Calcium Overload and Chemotherapy. *Int J Nanomed*. 2025;20:10233–10249. doi:10.2147/ijn.S523621
23. Zhou ZD, Xia DJ. Effect of Achyranthes bidentata polysaccharides stimulated dendritic cells co-cultured with cytokine induced killer cells against SW480 cells. *Zhongguo Zhong Yao Za Zhi*. 2013;38(7):1056–1060.
24. Yang T, Jia M, Meng J, Wu H, Mei Q. Immunomodulatory activity of polysaccharide isolated from Angelica sinensis. *Int J Biol Macromol*. 2006;39(4–5):179–184. doi:10.1016/j.ijbiomac.2006.02.013
25. Kim SH, Lee SW, Park HJ, et al. Anti-cancer activity of Angelica gigas by increasing immune response and stimulating natural killer and natural killer T cells. *BMC Complement Altern Med*. 2018;18(1):218. doi:10.1186/s12906-018-2277-7
26. Zhang Y, Zhou T, Wang H, Cui Z, Cheng F, Wang KP. Structural characterization and in vitro antitumor activity of an acidic polysaccharide from Angelica sinensis (Oliv.) Diels. *Carbohydr Polym*. 2016;147:401–408. doi:10.1016/j.carbpol.2016.04.002
27. Yan X, Qi M, Li P, Zhan Y, Shao H. Apigenin in cancer therapy: anti-cancer effects and mechanisms of action. *Cell Biosci*. 2017;7(1):50. doi:10.1186/s13578-017-0179-x
28. Zhou Y, Yu Y, Lv H, et al. Apigenin in cancer therapy: from mechanism of action to nano-therapeutic agent. *Food Chem Toxicol*. 2022;168:113385. doi:10.1016/j.fct.2022.113385
29. Zhang LX, Liu ZN, Ye J, et al. Artesunate exerts an anti-immunosuppressive effect on cervical cancer by inhibiting PGE2 production and Foxp3 expression. *Cell Biol Int*. 2014;38(5):639–646. doi:10.1002/cbin.10244
30. Cui C, Feng H, Shi X, et al. Artesunate down-regulates immunosuppression from colorectal cancer Colon26 and RKO cells in vitro by decreasing transforming growth factor β1 and interleukin-10. *Int Immunopharmacol*. 2015;27(1):110–121. doi:10.1016/j.intimp.2015.05.004
31. Vakhrusheva O, Zhao F, Markowitsch SD, et al. Artesunate Inhibits Metastatic Potential in Cisplatin-Resistant Bladder Cancer Cells by Altering Integrins. *Cells*. 2025;14(8):570. doi:10.3390/cells14080570
32. Lian GY, Wang QM, Tang PM, Zhou S, Huang XR, Lan HY. Combination of Asiatic Acid and Naringenin Modulates NK Cell Anti-cancer Immunity by Rebalancing Smad3/Smad7 Signaling. *Mol Ther*. 2018;26(9):2255–2266. doi:10.1016/j.ymthe.2018.06.016
33. Zhu Z, Cui L, Yang J, et al. Anticancer effects of asiatic acid against doxorubicin-resistant breast cancer cells via an AMPK-dependent pathway in vitro. *Phytomedicine*. 2021;92:153737. doi:10.1016/j.phymed.2021.153737
34. Li C, Pan XY, Ma M, Zhao J, Zhao F, Lv YP. Astragalus polysacharin inhibits hepatocellular carcinoma-like phenotypes in a murine HCC model through repression of M2 polarization of tumour-associated macrophages. *Pharm Biol*. 2021;59(1):1533–1539. doi:10.1080/13880209.2021.1991384
35. Bamodu OA, Kuo KT, Wang CH, et al. Astragalus polysaccharides (PG2) Enhances the M1 Polarization of Macrophages, Functional Maturation of Dendritic Cells, and T Cell-Mediated Anticancer Immune Responses in Patients with Lung Cancer. *Nutrients*. 2019;11(10):2264. doi:10.3390/nu11102264
36. Sun Y, Liu JQ, Chen WJ, et al. Astragaloside III inhibits MAPK-mediated M2 tumor-associated macrophages to suppress the progression of lung Cancer cells via Akt/mTOR signaling pathway. *Int Immunopharmacol*. 2025;154:114546. doi:10.1016/j.intimp.2025.114546
37. Chen X, Chen X, Gao J, et al. Astragaloside III Enhances Anti-Tumor Response of NK Cells by Elevating NKG2D and IFN-γ. *Front Pharmacol*. 2019;10:898. doi:10.3389/fphar.2019.00898
38. Liu F, Ran F, He H, Chen L. Astragaloside IV Exerts Anti-tumor Effect on Murine Colorectal Cancer by Re-educating Tumor-Associated Macrophage. *Arch Immunol Ther Exp*. 2020;68(6):33. doi:10.1007/s00005-020-00598-y
39. Wang Y, Zhang Z, Cheng Z, Xie W, Qin H, Sheng J. Astragaloside in cancer chemoprevention and therapy. *Chin Med J*. 2023;136(10):1144–1154. doi:10.1097/cm9.0000000000002661
40. Lai YS, Putra R, Aui SP, Chang KT. M2(C) Polarization by Baicalin Enhances Efferocytosis via Upregulation of MERTK Receptor. *Am J Chin Med*. 2018;46(8):1899–1914. doi:10.1142/s0192415x18500957
41. Ke M, Zhang Z, Xu B, et al. Baicalein and baicalin promote antitumor immunity by suppressing PD-L1 expression in hepatocellular carcinoma cells. *Int Immunopharmacol*. 2019;75:105824. doi:10.1016/j.intimp.2019.105824
42. Shah D, Challagundla N, Dave V, et al. Berberine mediates tumor cell death by skewing tumor-associated immunosuppressive macrophages to inflammatory macrophages. *Phytomedicine*. 2022;99:153904. doi:10.1016/j.phymed.2021.153904
43. Liu Y, Liu X, Zhang N, et al. Berberine diminishes cancer cell PD-L1 expression and facilitates antitumor immunity via inhibiting the deubiquitination activity of CSN5. *Acta Pharm Sin B*. 2020;10(12):2299–2312. doi:10.1016/j.apsb.2020.06.014
44. Zeng AQ, Yu Y, Yao YQ, et al. Betulinic acid impairs metastasis and reduces immunosuppressive cells in breast cancer models. *Oncotarget*. 2018;9(3):3794–3804. doi:10.18632/oncotarget.23376
45. Guo L, Pei H, Yang Y, Kong Y. Betulinic acid regulates tumor-associated macrophage M2 polarization and plays a role in inhibiting the liver cancer progression. *Int Immunopharmacol*. 2023;122:110614. doi:10.1016/j.intimp.2023.110614
46. Fernandes S, Vieira M, Prudêncio C, Ferraz R. Betulinic Acid for Glioblastoma Treatment: reality, Challenges and Perspectives. *Int J Mol Sci*. 2024;25(4):2108. doi:10.3390/ijms25042108
47. Cao L, Shao M, Gu Y, et al. Calceolarioside B targets MMP12 in the tumor microenvironment to inhibit M2 macrophage polarization and suppress hepatocellular carcinoma progression. *Phytomedicine*. 2025;142:156805. doi:10.1016/j.phymed.2025.156805

48. Yang Y, Cheng S, Liang G, Honggang L, Wu H. Celastrol inhibits cancer metastasis by suppressing M2-like polarization of macrophages. *Biochem Biophys Res Commun*. 2018;503(2):414–419. doi:10.1016/j.bbrc.2018.03.224
49. Ashrafizadeh M, Zarrabi A, Orouei S, et al. Recent advances and future directions in anti-tumor activity of cryptotanshinone: a mechanistic review. *Phytother Res*. 2021;35(1):155–179. doi:10.1002/ptr.6815
50. Liu S, Han Z, Trivett AL, et al. Cryptotanshinone has curative dual anti-proliferative and immunotherapeutic effects on mouse Lewis lung carcinoma. *Cancer Immunol Immunother*. 2019;68(7):1059–1071. doi:10.1007/s00262-019-02326-8
51. Ameer SF, Mohamed MY, Elzubair QA, Sharif EAM, Ibrahim WN. Curcumin as a novel therapeutic candidate for cancer: can this natural compound revolutionize cancer treatment? *Front Oncol*. 2024;14:1438040. doi:10.3389/fonc.2024.1438040
52. Shafabakhsh R, Pourhanifeh MH, Mirzaei HR, Sahebkar A, Asemi Z, Mirzaei H. Targeting regulatory T cells by curcumin: a potential for cancer immunotherapy. *Pharmacol Res*. 2019;147:104353. doi:10.1016/j.phrs.2019.104353
53. Paul S, Sa G. Curcumin as an Adjuvant to Cancer Immunotherapy. *Front Oncol*. 2021;11:675923. doi:10.3389/fonc.2021.675923
54. Xiao X, Li Y, Wang Y, et al. Dihydroartemisinin inhibits Lewis Lung carcinoma progression by inducing macrophages M1 polarization via AKT/mTOR pathway. *Int Immunopharmacol*. 2022;103:108427. doi:10.1016/j.intimp.2021.108427
55. Chen R, Lu X, Li Z, Sun Y, He Z, Li X. Dihydroartemisinin Prevents Progression and Metastasis of Head and Neck Squamous Cell Carcinoma by Inhibiting Polarization of Macrophages in Tumor Microenvironment. *Onco Targets Ther*. 2020;13:3375–3387. doi:10.2147/ott.S249046
56. Zhang H, Zhou F, Wang Y, et al. Eliminating Radiation Resistance of Non-Small Cell Lung Cancer by Dihydroartemisinin Through Abrogating Immunity Escaping and Promoting Radiation Sensitivity by Inhibiting PD-L1 Expression. *Front Oncol*. 2020;10:595466. doi:10.3389/fonc.2020.595466
57. Dai X, Zhang X, Chen W, et al. Dihydroartemisinin: a Potential Natural Anticancer Drug. *Int J Biol Sci*. 2021;17(2):603–622. doi:10.7150/ijbs.50364
58. Zhang H, Zhuo Y, Li D, et al. Dihydroartemisinin inhibits the growth of pancreatic cells by inducing ferroptosis and activating antitumor immunity. *Eur J Pharmacol*. 2022;926:175028. doi:10.1016/j.ejphar.2022.175028
59. Li Y, Zhang W, Shi N, et al. Self-assembly and self-delivery of the pure nanodrug dihydroartemisinin for tumor therapy and mechanism analysis. *Biomater Sci*. 2023;11(7):2478–2485. doi:10.1039/d2bm01949c
60. de Haas N, de Koning C, Spilgies L, de Vries IJ, Hato SV. Improving cancer immunotherapy by targeting the STATe of MDSCs. *Oncoimmunology*. 2016;5(7):e1196312. doi:10.1080/2162402x.2016.1196312
61. Wang C, Feng L, Su J, et al. Polysaccharides from Epimedium koreanum Nakai with immunomodulatory activity and inhibitory effect on tumor growth in LLC-bearing mice. *J Ethnopharmacol*. 2017;207:8–18. doi:10.1016/j.jep.2017.06.014
62. Wang Y, Fan X, Wu X. Ganoderma lucidum polysaccharide (GLP) enhances antitumor immune response by regulating differentiation and inhibition of MDSCs via a CARD9-NF-κB-IDO pathway. *Biosci Rep*. 2020;40(6):1170. doi:10.1042/bsr20201170
63. Ke L, Duan X, Cui J, et al. Research progress on the extraction technology and activity study of Epimedium polysaccharides. *Carbohydr Polym*. 2023;306:120602. doi:10.1016/j.carbpol.2023.120602
64. Ren T, Bai XY, Yang MZ, et al. Gambogic acid suppresses nasopharyngeal carcinoma via rewiring molecular network of cancer malignancy and immunosurveillance. *Biomed Pharmacother*. 2022;150:113012. doi:10.1016/j.biopha.2022.113012
65. Chen X, Chen DR, Liu H, et al. Local delivery of gambogic acid to improve anti-tumor immunity against oral squamous cell carcinoma. *J Control Release*. 2022;351:381–393. doi:10.1016/j.jconrel.2022.09.010
66. Xu H, Zhang D, Wei R, et al. Gambogic Acid Induces Pyroptosis of Colorectal Cancer Cells through the GSDME-Dependent Pathway and Elicits an Antitumor Immune Response. *Cancers*. 2022;14(22):5505. doi:10.3390/cancers14225505
67. Song M, Li ZH, Gu HS, et al. Ganoderma lucidum Spore Polysaccharide Inhibits the Growth of Hepatocellular Carcinoma Cells by Altering Macrophage Polarity and Induction of Apoptosis. *J Immunol Res*. 2021;2021:6696606. doi:10.1155/2021/6696606
68. Bu Y, Liu Q, Shang Y, et al. Ganoderma lucidum spores-derived particulate β-glucan treatment improves antitumor response by regulating myeloid-derived suppressor cells in triple-negative breast cancer. *Int J Biol Macromol*. 2024;270(Pt 1):131949. doi:10.1016/j.ijbiomac.2024.131949
69. Xin C, Quan H, Kim JM, et al. Ginsenoside Rb1 increases macrophage phagocytosis through p38 mitogen-activated protein kinase/Akt pathway. *J Ginseng Res*. 2019;43(3):394–401. doi:10.1016/j.jgr.2018.05.003
70. Wu R, Ru Q, Chen L, Ma B, Li C. Stereospecificity of ginsenoside Rg3 in the promotion of cellular immunity in hepatoma H22-bearing mice. *J Food Sci*. 2014;79(7):H1430–5. doi:10.1111/1750-3841.12518
71. Jiang Z, Yang Y, Yang Y, et al. Ginsenoside Rg3 attenuates cisplatin resistance in lung cancer by downregulating PD-L1 and resuming immune. *Biomed Pharmacother*. 2017;96:378–383. doi:10.1016/j.biopha.2017.09.129
72. Juin SK, Ghosh S, Majumdar S. Glycyrrhizic acid facilitates anti-tumor immunity by attenuating Tregs and MDSCs: an immunotherapeutic approach. *Int Immunopharmacol*. 2020;88:106932. doi:10.1016/j.intimp.2020.106932
73. Zhang Y, Sheng Z, Xiao J, et al. Advances in the roles of glycyrrhizic acid in cancer therapy. *Front Pharmacol*. 2023;14:1265172. doi:10.3389/fphar.2023.1265172
74. Waldron TJ, Quatromoni JG, Karakasheva TA, Singhal S, Rustgi AK. Myeloid derived suppressor cells: targets for therapy. *Oncoimmunology*. 2013;2(4):e24117. doi:10.4161/onci.24117
75. Zheng X, Li D, Li J, et al. Optimization of the process for purifying icariin from Herba Epimedii by macroporous resin and the regulatory role of icariin in the tumor immune microenvironment. *Biomed Pharmacother*. 2019;118:109275. doi:10.1016/j.biopha.2019.109275
76. Bi Z, Zhang W, Yan X. Anti-inflammatory and immunoregulatory effects of icariin and icaritin. *Biomed Pharmacother*. 2022;151:113180. doi:10.1016/j.biopha.2022.113180
77. Xu H, Qi Z, Zhao Q, et al. Lentinan enhances the antitumor effects of Delta-like 1 via neutrophils. *BMC Cancer*. 2022;22(1):918. doi:10.1186/s12885-022-10011-w
78. Sun M, Bu R, Zhang B, Cao Y, Liu C, Zhao W. Lentinan Inhibits Tumor Progression by Immunomodulation in a Mouse Model of Bladder Cancer. *Integr Cancer Ther*. 2020;19:1534735420946823. doi:10.1177/1534735420946823
79. Zhao C, Yan H, Pang W, et al. Lentinan combined with cisplatin for the treatment of non-small cell lung cancer. *Medicine*. 2021;100(12):e25220. doi:10.1097/md.0000000000025220

80. Wang H, Wang X, Zhang Q, Liang Y, Wu H. Matrine reduces traumatic heterotopic ossification in mice by inhibiting M2 macrophage polarization through the MAPK pathway. *Biomed Pharmacother*. 2024;177:117130. doi:10.1016/j.biopha.2024.117130
81. Wang JK, Zhao BS, Wang M, et al. Anti-tumor and Phenotypic Regulation Effect of Matrine on Dendritic Cells through Regulating TLRs Pathway. *Chin J Integr Med*. 2021;27(7):520–526. doi:10.1007/s11655-020-3433-8
82. Zhao B, Hui X, Wang J, et al. Matrine suppresses lung cancer metastasis via targeting M2-like tumour-associated-macrophages polarization. *Am J Cancer Res*. 2021;11(9):4308–4328.
83. Ren J, Li G, Zhao W, Lin L, Ye T. Norcantharidin combined with ABT-737 for hepatocellular carcinoma: therapeutic effects and molecular mechanisms. *World J Gastroenterol*. 2016;22(15):3962–3968. doi:10.3748/wjg.v22.i15.3962
84. Mo L, Zhang X, Shi X, et al. Norcantharidin enhances antitumor immunity of GM-CSF prostate cancer cells vaccine by inducing apoptosis of regulatory T cells. *Cancer Sci*. 2018;109(7):2109–2118. doi:10.1111/cas.13639
85. Zhai Y, Zhang F, Zhou J, et al. Mechanism of norcantharidin intervention in gastric cancer: analysis based on antitumor proprietary Chinese medicine database, network pharmacology, and transcriptomics. *Chin Med*. 2024;19(1):129. doi:10.1186/s13020-024-01000-1
86. Wu J, Ding Y, Chen CH, et al. A new oridonin analog suppresses triple-negative breast cancer cells and tumor growth via the induction of death receptor 5. *Cancer Lett*. 2016;380(2):393–402. doi:10.1016/j.canlet.2016.06.024
87. Guo J, Chen T, Ma Z, et al. Oridonin inhibits 4T1 tumor growth by suppressing Treg differentiation via TGF-β receptor. *Int Immunopharmacol*. 2020;88:106831. doi:10.1016/j.intimp.2020.106831
88. Liu S, Wang X, Sun X, et al. Oridonin inhibits bladder cancer survival and immune escape by covalently targeting HK1. *Phytomedicine*. 2024;126:155426. doi:10.1016/j.phymed.2024.155426
89. Wang P, Li Z, Song Y, Zhang B, Fan C. Resveratrol-driven macrophage polarization: unveiling mechanisms and therapeutic potential. *Front Pharmacol*. 2024;15:1516609. doi:10.3389/fphar.2024.1516609
90. Zong Y, Sun L, Liu B, et al. Resveratrol inhibits LPS-induced MAPKs activation via activation of the phosphatidylinositol 3-kinase pathway in murine RAW 264.7 macrophage cells. *PLoS One*. 2012;7(8):e44107. doi:10.1371/journal.pone.0044107
91. Neamah WH, Rutkovsky A, Abdullah O, et al. Resveratrol Attenuates 2,3,7,8-Tetrachlorodibenzo-p-dioxin-Mediated Induction of Myeloid-Derived Suppressor Cells (MDSC) and Their Functions. *Nutrients*. 2023;15(21):4667. doi:10.3390/nu15214667
92. Talib WH, Alsayed AR, Farhan F, Al Kury LT. Resveratrol and Tumor Microenvironment: mechanistic Basis and Therapeutic Targets. *Molecules*. 2020;25(18):4282. doi:10.3390/molecules25184282
93. Mu Q, Najafi M. Resveratrol for targeting the tumor microenvironment and its interactions with cancer cells. *Int Immunopharmacol*. 2021;98:107895. doi:10.1016/j.intimp.2021.107895
94. Qian C, Yang C, Tang Y, et al. Pharmacological manipulation of Ezh2 with salvianolic acid B results in tumor vascular normalization and synergizes with cisplatin and T cell-mediated immunotherapy. *Pharmacol Res*. 2022;182:106333. doi:10.1016/j.phrs.2022.106333
95. Xu M, Zheng Y, Chen J, et al. CLDN4 palmitoylation promotes hepatic-to-biliary lineage transition and lenvatinib resistance in hepatocellular carcinoma. *Cell Rep Med*. 2025;6(7):102208. doi:10.1016/j.xcrm.2025.102208
96. Wei H, Sun R, Xiao W, et al. Type two cytokines predominance of human lung cancer and its reverse by traditional Chinese medicine TTMP. *Cell Mol Immunol*. 2004;1(1):63–70.
97. Luan Y, Liu J, Liu X, et al. Tetramethypyrazine inhibits renal cell carcinoma cells through inhibition of NKG2D signaling pathways. *Int J Oncol*. 2016;49(4):1704–1712. doi:10.3892/ijo.2016.3670
98. Murray PJ, Allen JE, Biswas SK, et al. Macrophage activation and polarization: nomenclature and experimental guidelines. *Immunity*. 2014;41(1):14–20. doi:10.1016/j.immuni.2014.06.008
99. Noy R, Pollard J. Pollard Jeffrey W. Tumor-Associated Macrophages: from Mechanisms to Therapy. *Immunity*. 2014;41(1):49–61. doi:10.1016/j.immuni.2014.06.010
100. Cassetta L, Pollard JW. A timeline of tumour-associated macrophage biology. *Nat Rev Cancer*. 2023;23(4):238–257. doi:10.1038/s41568-022-00547-1
101. Martinez FO, Gordon S. The M1 and M2 paradigm of macrophage activation: time for reassessment. *F1000Prime Rep*. 2014;6:13. doi:10.12703/p6-13
102. Pollard JW. Tumour-educated macrophages promote tumour progression and metastasis. *Nat Rev Cancer*. 2004;4(1):71–78. doi:10.1038/nrc1256
103. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature*. 2008;454(7203):436–444. doi:10.1038/nature07205
104. Iwamoto H, Izumi K, Mizokami A. Is the C-C Motif Ligand 2-C-C Chemokine Receptor 2 Axis a Promising Target for Cancer Therapy and Diagnosis? *Int J Mol Sci*. 2020;21(23):9328. doi:10.3390/ijms21239328
105. Li X, Yao W, Yuan Y, et al. Targeting of tumour-infiltrating macrophages via CCL2/CCR2 signalling as a therapeutic strategy against hepatocellular carcinoma. *Gut*. 2017;66(1):157–167. doi:10.1136/gutjnl-2015-310514
106. Karin M. Nuclear factor-kappaB in cancer development and progression. *Nature*. 2006;441(7092):431–436. doi:10.1038/nature04870
107. Dhillon N, Aggarwal BB, Newman RA, et al. Phase II trial of curcumin in patients with advanced pancreatic cancer. *Clin Cancer Res*. 2008;14(14):4491–4499. doi:10.1158/1078-0432.Ccr-08-0024
108. Zong H, Wang F, Fan QX, Wang LX. Curcumin inhibits metastatic progression of breast cancer cell through suppression of urokinase-type plasminogen activator by NF-kappa B signaling pathways. *Mol Biol Rep*. 2012;39(4):4803–4808. doi:10.1007/s11033-011-1273-5
109. Jin L, Guo Y, Mao W, et al. Total glucosides of paeony inhibit breast cancer growth by inhibiting TAMs infiltration through NF-κB/CCL2 signaling. *Phytomedicine*. 2022;104:154307. doi:10.1016/j.phymed.2022.154307
110. Shang HS, Lu HF, Lee CH, et al. Quercetin induced cell apoptosis and altered gene expression in AGS human gastric cancer cells. *Environ Toxicol: Int J*. 2018;33(11):1168–1181. doi:10.1002/tox.22623
111. Almatroodi SA, Alsahli MA, Almatroudi A, et al. Potential Therapeutic Targets of Quercetin, a Plant Flavonol, and Its Role in the Therapy of Various Types of Cancer through the Modulation of Various Cell Signaling Pathways. *Molecules*. 2021;26(5):1315. doi:10.3390/molecules26051315
112. Wang W, Wang J, Dong SF, et al. Immunomodulatory activity of andrographolide on macrophage activation and specific antibody response. *Acta Pharmacol Sin*. 2010;31(2):191–201. doi:10.1038/aps.2009.205

113. Islam MT, Ali ES, Uddin SJ, et al. Andrographolide, a diterpene lactone from Andrographis paniculata and its therapeutic promises in cancer. *Cancer Lett*. 2018;420:129–145. doi:10.1016/j.canlet.2018.01.074
114. Raman S, Murugaiyah V, Parumasivam T. Andrographis paniculata Dosage Forms and Advances in Nanoparticulate Delivery Systems: an Overview. *Molecules*. 2022;27(19):6164. doi:10.3390/molecules27196164
115. Li L, Yang LL, Yang SL, et al. Andrographolide suppresses breast cancer progression by modulating tumor-associated macrophage polarization through the Wnt/β-catenin pathway. *Phytother Res*. 2022;36(12):4587–4603. doi:10.1002/ptr.7578
116. Sun L, Chen B, Jiang R, Li J, Wang B. Resveratrol inhibits lung cancer growth by suppressing M2-like polarization of tumor associated macrophages. *Cell Immunol*. 2017;311:86–93. doi:10.1016/j.cellimm.2016.11.002
117. Lu J, Zhang T, Jiang C, et al. Ganoderic acid A regulates CSF1R to reprogram tumor-associated macrophages for immune therapy of hepatocellular carcinoma. *Int Immunopharmacol*. 2025;161:114989. doi:10.1016/j.intimp.2025.114989
118. Tan S, Zheng Z, Liu T, Yao X, Yu M, Ji Y. Schisandrin B Induced ROS-Mediated Autophagy and Th1/Th2 Imbalance via Selenoproteins in Hepa1-6 Cells. *Front Immunol*. 2022;13:857069. doi:10.3389/fimmu.2022.857069
119. He L, Chen H, Qi Q, et al. Schisandrin B suppresses gastric cancer cell growth and enhances the efficacy of chemotherapy drug 5-FU in vitro and in vivo. *Eur J Pharmacol*. 2022;920:174823. doi:10.1016/j.ejphar.2022.174823
120. Liu D, You M, Xu Y, et al. Inhibition of curcumin on myeloid-derived suppressor cells is requisite for controlling lung cancer. *Int Immunopharmacol*. 2016;39:265–272. doi:10.1016/j.intimp.2016.07.035
121. Wang T, Wang J, Jiang H, et al. Targeted regulation of tumor microenvironment through the inhibition of MDSCs by curcumin loaded self-assembled nano-filaments. *Mater Today Bio*. 2022;15:100304. doi:10.1016/j.mtbio.2022.100304
122. Li K, Wang J, Xie Y, et al. Reactive oxygen species/glutathione dual sensitive nanoparticles with encapsulation of miR155 and curcumin for synergized cancer immunotherapy. *J Nanobiotechnology*. 2024;22(1):400. doi:10.1186/s12951-024-02575-5
123. Forghani P, Khorramizadeh MR, Waller EK. Silibinin inhibits accumulation of myeloid-derived suppressor cells and tumor growth of murine breast cancer. *Cancer Med*. 2014;3(2):215–224. doi:10.1002/cam4.186
124. Kim JW, Jung SY, Kwon YH, et al. Ginsenoside Rg3 attenuates tumor angiogenesis via inhibiting bioactivities of endothelial progenitor cells. *Cancer Biol Ther*. 2012;13(7):504–515. doi:10.4161/cbt.19599
125. Mao Y, Liu X, He K, Lin C, He B, Gao J. Xuanhusuo powder has an anti-breast cancer effect by inhibiting myeloid-derived suppressor cell differentiation in the spleen of mice through down-regulating granulocyte colony stimulating factor. *Zhejiang Da Xue Xue Bao Yi Xue Ban*. 2023;52(1):88–100.doi:10.3724/zdxbyxb-2022-0353
126. Tanaka A, Sakaguchi S. Regulatory T cells in cancer immunotherapy. *Cell Res*. 2017;27(1):109–118. doi:10.1038/cr.2016.151
127. Li A, Shuai X, Jia Z, et al. Ganoderma lucidum polysaccharide extract inhibits hepatocellular carcinoma growth by downregulating regulatory T cells accumulation and function by inducing microRNA-125b. *J Transl Med*. 2015;13(1):100. doi:10.1186/s12967-015-0465-5
128. Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, Langer R. Engineering precision nanoparticles for drug delivery. *Nat Rev Drug Discov*. 2021;20(2):101–124. doi:10.1038/s41573-020-0090-8
129. Shahzad A, Teng Z, Yameen M, et al. Innovative lipid nanoparticles: a cutting-edge approach for potential renal cell carcinoma therapeutics. *Biomed Pharmacother*. 2024;180:117465. doi:10.1016/j.biopha.2024.117465
130. Imani S, Moradi S, Faraj TA, et al. Nanoparticle technologies in precision oncology and personalized vaccine development: challenges and advances. *Int J Pharm X*. 2025;10:100353. doi:10.1016/j.ijpx.2025.100353
131. Ma Z, Wang N, He H, Tang X. Pharmaceutical strategies of improving oral systemic bioavailability of curcumin for clinical application. *J Control Release*. 2019;316:359–380. doi:10.1016/j.jconrel.2019.10.053
132. Sesarman A, Tefas L, Sylvester B, et al. Co-delivery of curcumin and doxorubicin in PEGylated liposomes favored the antineoplastic C26 murine colon carcinoma microenvironment. *Drug Deliv Transl Res*. 2019;9(1):260–272. doi:10.1007/s13346-018-00598-8
133. Wang Z, Wang X, Yu H, Chen M. Glioma-targeted multifunctional nanoparticles to co-deliver camptothecin and curcumin for enhanced chemo-immunotherapy. *Biomater Sci*. 2022;10(5):1292–1303. doi:10.1039/d1bm01987b
134. Zhang H, Huang J, Li Y, et al. Celastrol-loaded ginsenoside Rg3 liposomes boost immunotherapy by remodeling obesity-related immunosuppressive tumor microenvironment in melanoma. *Acta Pharm Sin B*. 2025;15(5):2687–2702. doi:10.1016/j.apsb.2025.03.017
135. Zhu Y, Liang J, Gao C, et al. Multifunctional ginsenoside Rg3-based liposomes for glioma targeting therapy. *J Control Release*. 2021;330:641–657. doi:10.1016/j.jconrel.2020.12.036
136. Zhu Y, Wang A, Zhang S, et al. Paclitaxel-loaded ginsenoside Rg3 liposomes for drug-resistant cancer therapy by dual targeting of the tumor microenvironment and cancer cells. *J Adv Res*. 2023;49:159–173. doi:10.1016/j.jare.2022.09.007
137. Xu Z, Huang Y, Wu Y, et al. Glycyrrhizic Acid-Lipid Framework Nanovehicle Loading Triptolide for Combined Immunochemotherapy. *ACS Appl Mater Interfaces*. 2023;15(35):41337–41350. doi:10.1021/acsami.3c08003
138. Chen Y, Hu M, Wang S, et al. Nano-delivery of salvianolic acid B induces the quiescence of tumor-associated fibroblasts via interfering with TGF-β1/Smad signaling to facilitate chemo- and immunotherapy in desmoplastic tumor. *Int J Pharm*. 2022;623:121953. doi:10.1016/j.ijpharm.2022.121953
139. Wu S, Liu D, Li W, et al. Enhancing TNBC Chemo-immunotherapy via combination reprogramming tumor immune microenvironment with Immunogenic Cell Death. *Int J Pharm*. 2021;598:120333. doi:10.1016/j.ijpharm.2021.120333
140. Liu Q, Chen F, Hou L, et al. Nanocarrier-Mediated Chemo-Immunotherapy Arrested Cancer Progression and Induced Tumor Dormancy in Desmoplastic Melanoma. *ACS Nano*. 2018;12(8):7812–7825. doi:10.1021/acsnano.8b01890
141. Jiang M, He K, Qiu T, et al. Tumor-targeted delivery of silibinin and IPI-549 synergistically inhibit breast cancer by remodeling the microenvironment. *Int J Pharm*. 2020;581:119239. doi:10.1016/j.ijpharm.2020.119239
142. Peng J, Zhou J, Sun R, et al. Dual-targeting of artesunate and chloroquine to tumor cells and tumor-associated macrophages by a biomimetic PLGA nanoparticle for colorectal cancer treatment. *Int J Biol Macromol*. 2023;244:125163. doi:10.1016/j.ijbiomac.2023.125163
143. Xiong G, Huang D, Lu L, et al. Near-Infrared-II Light Induced Mild Hyperthermia Activate Cisplatin-Artemisinin Nanoparticle for Enhanced Chemo/Chemodynamic Therapy and Immunotherapy. *Small Methods*. 2022;6(9):e2200379. doi:10.1002/smtd.202200379
144. Cui J, Wang X, Li J, et al. Immune Exosomes Loading Self-Assembled Nanomicelles Traverse the Blood-Brain Barrier for Chemo-immunotherapy against Glioblastoma. *ACS Nano*. 2023;17(2):1464–1484. doi:10.1021/acsnano.2c10219

145. Guo C, Hou X, Liu Y, et al. Novel Chinese Angelica Polysaccharide Biomimetic Nanomedicine to Curcumin Delivery for Hepatocellular Carcinoma Treatment and Immunomodulatory Effect. *Phytomedicine*. 2021;80:153356. doi:10.1016/j.phymed.2020.153356
146. Cao M, Yan H, Han X, et al. Ginseng-derived nanoparticles alter macrophage polarization to inhibit melanoma growth. *J Immunother Cancer*. 2019;7(1):326. doi:10.1186/s40425-019-0817-4
147. Li X, Guo H, Mao DX, Liu YP, Chen Y. Preparation of two tanshinone II_A-astragaloside IV co-loaded nano-delivery systems and in vitro antitumor activity comparison. *Zhongguo Zhong Yao Za Zhi*. 2023;48(3):672–680. doi:10.19540/j.cnki.cjcmm.20221127.302
148. Zhang S, Pang G, Chen C, et al. Effective cancer immunotherapy by Ganoderma lucidum polysaccharide-gold nanocomposites through dendritic cell activation and memory T cell response. *Carbohydr Polym*. 2019;205:192–202. doi:10.1016/j.carbpol.2018.10.028
149. Yan C, Zhao Y, Liu X, et al. Self-Delivery Nanobooster to Enhance Immunogenic Cell Death for Cancer Chemoimmunotherapy. *ACS Appl Mater Interfaces*. 2024;16(26):33169–33181. doi:10.1021/acsami.4c06149
150. Mao Q, Min J, Zeng R, et al. Self-assembled traditional Chinese nanomedicine modulating tumor immunosuppressive microenvironment for colorectal cancer immunotherapy. *Theranostics*. 2022;12(14):6088–6105. doi:10.7150/thno.72509
151. Zhao M, Zhou L, Zhang Q, et al. Targeting MAPK14 by Lobeline Upregulates Slurp1-Mediated Inhibition of Alternative Activation of TAM and Retards Colorectal Cancer Growth. *Adv Sci*. 2025;12(10):e2407900. doi:10.1002/advs.202407900
152. Jiang ZB, Wang WJ, Xu C, et al. Luteolin and its derivative apigenin suppress the inducible PD-L1 expression to improve anti-tumor immunity in KRAS-mutant lung cancer. *Cancer Lett*. 2021;515:36–48. doi:10.1016/j.canlet.2021.05.019
153. Tian L, Wang S, Jiang S, et al. Luteolin as an adjuvant effectively enhances CTL anti-tumor response in B16F10 mouse model. *Int Immunopharmacol*. 2021;94:107441. doi:10.1016/j.intimp.2021.107441
154. Liang M, Fu J. Triptolide inhibits interferon-gamma-induced programmed death-1-ligand 1 surface expression in breast cancer cells. *Cancer Lett*. 2008;270(2):337–341. doi:10.1016/j.canlet.2008.05.025
155. Liu B, Zhang H, Li J, et al. Triptolide downregulates Treg cells and the level of IL-10, TGF-β, and VEGF in melanoma-bearing mice. *Planta Med*. 2013;79(15):1401–1407. doi:10.1055/s-0033-1350708
156. Allen TM, Cullis PR. Liposomal drug delivery systems: from concept to clinical applications. *Adv Drug Deliv Rev*. 2013;65(1):36–48. doi:10.1016/j.addr.2012.09.037
157. Bobo D, Robinson KJ, Islam J, Thurecht KJ, Corrie SR. Nanoparticle-Based Medicines: a Review of FDA-Approved Materials and Clinical Trials to Date. *Pharm Res*. 2016;33(10):2373–2387. doi:10.1007/s11095-016-1958-5
158. Shah S, Dhawan V, Holm R, Nagarsenker MS, Perrie Y. Liposomes: advancements and innovation in the manufacturing process. *Adv Drug Deliv Rev*. 2020;154-155:102–122. doi:10.1016/j.addr.2020.07.002
159. Liang S, Gao S, Fu S, et al. Screening Natural Cholesterol Analogs to Assemble Self-Adjuvant Lipid Nanoparticles for Antigens Tagging Guided Therapeutic Tumor Vaccine. *Adv Mater*. 2025;37(27):e2419182. doi:10.1002/adma.202419182
160. Jurak M, Wiącek AE, Ładniak A, Przykaza K, Szafran K. What affects the biocompatibility of polymers? *Adv Colloid Interface Sci*. 2021;294:102451. doi:10.1016/j.cis.2021.102451
161. Le Z, Chen Y, Han H, et al. Hydrogen-Bonded Tannic Acid-Based Anticancer Nanoparticle for Enhancement of Oral Chemotherapy. *ACS Appl Mater Interfaces*. 2018;10(49):42186–42197. doi:10.1021/acsami.8b18979
162. Subhan MA, Torchilin VP. Biocompatible Polymeric Nanoparticles as Promising Candidates for Drug Delivery in Cancer Treatment. In: Hussain CM, Thomas S, editors. *Handbook of Polymer and Ceramic Nanotechnology*. Springer International Publishing; 2021:855–872.
163. Zheng D, Zhao J, Li Y, et al. Self-Assembled pH-Sensitive Nanoparticles Based on Ganoderma lucidum Polysaccharide-Methotrexate Conjugates for the Co-delivery of Anti-tumor Drugs. *ACS Biomater Sci Eng*. 2021;7(8):3764–3773. doi:10.1021/acsbiomaterials.1c00663
164. Li J, Zhao M, Xu Y, Hu X, Dai Y, Wang D. Hybrid micelles codelivering shikonin and IDO-1 siRNA enhance immunotherapy by remodeling immunosuppressive tumor microenvironment. *Int J Pharm*. 2021;597:120310. doi:10.1016/j.ijpharm.2021.120310
165. Lin G, Mi P, Chu C, Zhang J, Liu G. Inorganic Nanocarriers Overcoming Multidrug Resistance for Cancer Theranostics. *Adv Sci*. 2016;3(11):1600134. doi:10.1002/advs.201600134
166. Tong F, Hu H, Xu Y, et al. Hollow copper sulfide nanoparticles carrying ISRIB for the sensitized photothermal therapy of breast cancer and brain metastases through inhibiting stress granule formation and reprogramming tumor-associated macrophages. *Acta Pharm Sin B*. 2023;13(8):3471–3488. doi:10.1016/j.apsb.2022.11.003
167. Chang X, Wang H, Chen X. Tumor Diagnosis and Treatment Based on Stimuli-Responsive Aggregation of Gold Nanoparticles. *Exploration*. 2025;5(3):270006. doi:10.1002/exp.70006
168. Huang D, Xu D, Chen W, et al. Fe-MnO(2) nanosheets loading dihydroartemisinin for ferroptosis and immunotherapy. *Biomed Pharmacother*. 2023;161:114431. doi:10.1016/j.biopha.2023.114431
169. Dongsar TT, Dongsar TS, Abourehab MAS, Gupta N, Kesharwani P. Emerging application of magnetic nanoparticles for breast cancer therapy. *Eur Polym J*. 2023;187:111898. doi:doi:10.1016/j.eurpolymj.2023.111898
170. Chiang CS, Lin YJ, Lee R, et al. Combination of fucoidan-based magnetic nanoparticles and immunomodulators enhances tumour-localized immunotherapy. *Nat Nanotechnol*. 2018;13(8):746–754. doi:10.1038/s41565-018-0146-7
171. Xuan M, Shao J, Zhao J, Li Q, Dai L, Li J. Magnetic Mesoporous Silica Nanoparticles Cloaked by Red Blood Cell Membranes: applications in Cancer Therapy. *Angew Chem Int Ed Engl*. 2018;57(21):6049–6053. doi:10.1002/anie.201712996
172. Wang S, Cheng K, Chen K, et al. Nanoparticle-based medicines in clinical cancer therapy. *Nano Today*. 2022;45:101512. doi:doi:10.1016/j.nantod.2022.101512
173. Bai C, Liu J, Zhang X, et al. Research status and challenges of plant-derived exosome-like nanoparticles. *Biomed Pharmacother*. 2024;174:116543. doi:10.1016/j.biopha.2024.116543
174. Lu J, Chen J, Ye J, et al. Dipsacus Asperoides-Derived Exosomes-Like Nanoparticles Inhibit the Progression of Osteosarcoma via Activating P38/JNK Signaling Pathway. *Int J Nanomed*. 2024;19:1097–1108. doi:10.2147/ijn.S446594
175. Walker S, Busatto S, Pham A, et al. Extracellular vesicle-based drug delivery systems for cancer treatment. *Theranostics*. 2019;9(26):8001–8017. doi:10.7150/thno.37097
176. Han S, Bi S, Guo T, et al. Nano co-delivery of Plumbagin and Dihydrotanshinone I reverses immunosuppressive TME of liver cancer. *J Control Release*. 2022;348:250–263. doi:10.1016/j.jconrel.2022.05.057

177. Huo J, Zou J, Ma H, et al. Astragaloside IV microfibers assembling into injectable 3D-scaffolds with intrinsic immunoactivity for enhanced tumor vaccine efficacy. *Chem Eng J*. 2024;498:155511. doi:doi:10.1016/j.cej.2024.155511
178. Chang L, Chang R, Shen J, et al. Self-healing pectin/cellulose hydrogel loaded with limonin as TMEM16A inhibitor for lung adenocarcinoma treatment. *Int J Biol Macromol*. 2022;219:754–766. doi:10.1016/j.ijbiomac.2022.08.037
179. Jeon JH, Zhu H, Qin J, et al. Lipid Nanoparticles Formulated with a Novel Cholesterol-Tailed Ionizable Lipid Markedly Increase mRNA Delivery Both in vitro and in vivo. *Int J Nanomed*. 2025;20:9389–9405. doi:10.2147/ijn.S527822
180. Ma Y, Fung V, VanKeulen-Miller R, et al. A Metabolite Co-Delivery Strategy to Improve mRNA Lipid Nanoparticle Delivery. *ACS Appl Mater Interfaces*. 2025;17(18):26202–26215. doi:10.1021/acsami.4c22969
181. Yilma AN, Sahu R, Subbarayan P, et al. PLGA-Chitosan Encapsulated IL-10 Nanoparticles Modulate Chlamydia Inflammation in Mice. *Int J Nanomed*. 2024;19:1287–1301. doi:10.2147/ijn.S432970
182. Machado FR, Bortolotto VC, Araujo SM, et al. Toxicological analysis of chronic exposure to polymeric nanocapsules with different coatings in Drosophila melanogaster. *Comp Biochem Physiol C Toxicol Pharmacol*. 2024;283:109939. doi:10.1016/j.cbpc.2024.109939
183. Iureva AM, Nikitin PI, Tereshina ED, Nikitin MP, Shipunova VO. The influence of various polymer coatings on the in vitro and in vivo properties of PLGA nanoparticles: comprehensive study. *Eur J Pharm Biopharm*. 2024;201:114366. doi:10.1016/j.ejpb.2024.114366
184. Oh JY, Villaseñor KE, Kian AC, Cormode DP. Advances in Ultrasmall Inorganic Nanoparticles for Nanomedicine: from Diagnosis to Therapeutics. *ACS Appl Mater Interfaces*. 2025;17(20):28982–29001. doi:10.1021/acsami.5c02810
185. Liu G, Li Q, Ni W, et al. Cytotoxicity of various types of gold-mesoporous silica nanoparticles in human breast cancer cells. *Int J Nanomed*. 2015;10:6075–6087. doi:10.2147/ijn.S90887
186. Liu Y, Ling Y, Tai W. Mechanical Extrusion of the Plasma Membrane to Generate Ectosome-Mimetic Nanovesicles for Lung Targeting. *Mol Pharm*. 2025;22(1):304–315. doi:10.1021/acs.molpharmaceut.4c00927
187. Chen Y, Douanne N, Wu T, et al. Leveraging nature's nanocarriers: translating insights from extracellular vesicles to biomimetic synthetic vesicles for biomedical applications. *Sci Adv*. 2025;11(9):eads5249. doi:10.1126/sciadv.ads5249
188. Spotlight on cancer immunotherapies. *Nat Biotechnol*. 2025;43(4):453–454. doi:10.1038/s41587-025-02645-5
189. Hinshaw DC, Shevde LA. The Tumor Microenvironment Innately Modulates Cancer Progression. *Cancer Res*. 2019;79(18):4557–4566. doi:10.1158/0008-5472.Can-18-3962
190. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. *Science*. 2018;359(6382):1350–1355. doi:10.1126/science.aar4060
191. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144(5):646–674. doi:10.1016/j.cell.2011.02.013
192. Fridman WH, Zitvogel L, Sautès-Fridman C, Kroemer G. The immune contexture in cancer prognosis and treatment. *Nat Rev Clin Oncol*. 2017;14(12):717–734. doi:10.1038/nrclinonc.2017.101
193. Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. *Nat Rev Immunol*. 2009;9(3):162–174. doi:10.1038/nri2506
194. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. 2012;12(4):252–264. doi:10.1038/nrc3239
195. Veglia F, Sanseviero E, Gabrilovich DI. Myeloid-derived suppressor cells in the era of increasing myeloid cell diversity. *Nat Rev Immunol*. 2021;21(8):485–498. doi:10.1038/s41577-020-00490-y
196. Luo H, Vong CT, Chen H, et al. Naturally occurring anti-cancer compounds: shining from Chinese herbal medicine. *Chin Med*. 2019;14:48. doi:10.1186/s13020-019-0270-9
197. Miao K, Liu W, Xu J, Qian Z, Zhang Q. Harnessing the power of traditional Chinese medicine monomers and compound prescriptions to boost cancer immunotherapy. *Front Immunol*. 2023;14:1277243. doi:10.3389/fimmu.2023.1277243
198. Lee NK, Kim SN, Park CG. Immune cell targeting nanoparticles: a review. *Biomater Res*. 2021;25(1):44. doi:10.1186/s40824-021-00246-2
199. Paurević M, Šrajer Gajdošik M, Ribić R. Mannose Ligands for Mannose Receptor Targeting. *Int J Mol Sci*. 2024;25(3):1370. doi:10.3390/ijms25031370
200. Yang C, Yang Z, Wang S, et al. Berberine and folic acid co-modified pH-sensitive cascade-targeted PTX-liposomes coated with Tween 80 for treating glioma. *Bioorg Med Chem*. 2022;69:116893. doi:10.1016/j.bmc.2022.116893
201. Xiao Z, Su Z, Han S, Huang J, Lin L, Shuai X. Dual pH-sensitive nanodrug blocks PD-1 immune checkpoint and uses T cells to deliver NF-κB inhibitor for antitumor immunotherapy. *Sci Adv*. 2020;6(6):eaay7785. doi:10.1126/sciadv.aay7785
202. Xu H, Zhang D, Zhang Y, et al. TMTP1-modified nanocarrier boosts cervical cancer immunotherapy by eliciting pyroptosis. *Theranostics*. 2025;15(11):5420–5439. doi:10.7150/thno.108357
203. Guo W, Song Y, Song W, et al. Co-delivery of Doxorubicin and Curcumin with Polypeptide Nanocarrier for Synergistic Lymphoma Therapy. *Sci Rep*. 2020;10(1):7832. doi:10.1038/s41598-020-64828-1
204. Pan Y, Luan X, Zeng F, et al. Logic-gated tumor-microenvironment nanoamplifier enables targeted delivery of CRISPR/Cas9 for multimodal cancer therapy. *Acta Pharm Sin B*. 2024;14(2):795–807. doi:10.1016/j.apsb.2023.09.016
205. Yu B, Xue X, Yin Z, Cao L, Li M, Huang J. Engineered Cell Membrane-Derived Nanocarriers: the Enhanced Delivery System for Therapeutic Applications. *Front Cell Dev Biol*. 2022;10:844050. doi:10.3389/fcell.2022.844050
206. Cubillos-Ruiz A, Guo T, Sokolovska A, et al. Engineering living therapeutics with synthetic biology. *Nat Rev Drug Discov*. 2021;20(12):941–960. doi:10.1038/s41573-021-00285-3
207. Fu Q. Harnessing Biomarker Activatable Probes for Early Stratification and Timely Assessment of Therapeutic Efficacy in Cancer. *Exploration*. 2025;5(3):20240037. doi:10.1002/exp.20240037