Acta Pharmaceutica Sinica B 2024;14(4):1525−1541

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

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REVIEW

Nano-formulated delivery of active ingredients from traditional Chinese herbal medicines for cancer immunotherapy

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Received 24 September 2023; received in revised form 15 November 2023; accepted 12 December 2023

KEY WORDS

Chinese herbal medicines;
Nano-formulation;
Active ingredients;
Drug delivery;
Cancer immunotherapy;
Innate immune system;
Adaptive immune system

Abstract Cancer immunotherapy has garnered promise in tumor progression, invasion, and metastasis through establishing durable and memorable immunological activity. However, low response rates, adverse side effects, and high costs compromise the additional benefits for patients treated with current chemical and biological agents. Chinese herbal medicines (CHMs) are a potential treasure trove of natural medicines and are gaining momentum in cancer immunomodulation with multi-component, multi-target, and multi-pathway characteristics. The active ingredient extracted from CHMs benefit generalized patients through modulating immune response mechanisms. Additionally, the introduction of nanotechnology has greatly improved the pharmacological qualities of active ingredients through increasing the hydrophilicity, stability, permeability, and targeting characteristics, further enhancing anti-cancer immunity. In this review, we summarize the mechanism of active ingredients for cancer immunomodulation,

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Peer review under the responsibility of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

https://doi.org/10.1016/j.apsb.2023.12.008

highlight nano-formulated deliveries of active ingredients for cancer immunotherapy, and provide insights into the future applications in the emerging field of nano-formulated active ingredients of CHMs.

1. Introduction

Cancer immunotherapy activates the host's own immune system to induce long-term immunity through defending against tumor invasion, inhibiting tumor progression, and relieving immune tolerance[1]. The innate and adaptive immune system determines the specificity of the anti-tumor response, which is associated with corresponding immune cells and regulatory signal molecules. Innate immune cells like macrophage, dendritic cells (DCs) and natural killer cells (NKs) serve as a natural protective barrier to hinder tumor invasion and eradicate tumor cells, while mediating the initiation of the antigen presentation process for adaptive immune responses[2–4]. In response to tumor-specific antigens, adaptive immune cells (*i.e.*, B and T cells) are activated to induce long-term, specific, and memorable immunity against tumor progression. Additionally, the immunosuppressive tumor microenvironment contains pro-tumor cytokines and immune checkpoint molecules that restrict the systemic immune response resulting in immune resistance[5–7]. Therefore, activating the immune system and tailoring the microenvironment signal molecules to restore immune surveillance are essential to cancer immunotherapy with demonstrated clinical translations. Recently, immune checkpoint antibodies of Ipilimumab, Pembrolizumab and the cellular therapeutic Kymriah are approved for clinical treatment[8]. However, the high costs, off-target effects, and adverse side effects compromised the benefits of patients[9], thus facilitating the development of novel therapeutic strategies.

Chinese herbal medicines (CHMs) originate from natural materials and are considered as a prospective cancer treatment strategy[10–12]. Compared with chemical and biological agents, active ingredients extracted from CHMs with mild and broad-spectrum efficacy avoid potential challenges of high costs, adverse side effects, and multidrug resistance associated with chemotherapeutics, contributing to an improved quality of life and extended patient survival. Active ingredients of CHMs possess superior immunomodulation abilities from multi-channel, multi-target, and multi-level characteristics that have demonstrated tremendous immunotherapeutic potential for cancer immunotherapy and exerting anti-cancer effects[13,14]. These modulate the innate immune response, adaptive immune response and the complicated microenvironment signal to induce long-term and memorable systemic immune response against tumor progression, invasion, and metastasis[15–17]. However, adverse pharmacological properties neutralize its therapeutic efficacy such as hydrophobicity, low stability, inadequate permeability, and a short half-life[18–20]. Leveraging carrier material to maximize the bioavailability and bioactivity of active ingredients of CHMs is a synergizing strategy for cancer immunotherapy.

The emergence of nanotechnology, specifically the integration of nanomaterials and drugs, has revolutionized disease diagnosis and treatment[21,22]. Nanomaterials such as polymers, liposomes, inorganic materials, and nanofibers have attracted widespread attention on clinical translation, facilitating the achievement of precise medicine treatment. By engineering nano-formulated active ingredients of CHMs, the bioavailability and bioactivity of active pharmaceutical agents can be improved through increasing its solubility, stability, permeability, and half-life characteristics[23]. This mode of pharmaceutical transport can also target cancer tissues and cells more effectively, avoiding poor response rates and reducing blood circulation times. Additionally, nano-formulated active ingredients of CHMs are capable of on-demand release in a controlled and sustained manner, collectively minimizing undesirable adverse events and maximizing cancer immunity[24].

In this review, we summarize the modulatory mechanisms of active ingredients of CHMs for cancer immunotherapy through activating the innate immune response, adaptive immune response, and controlling the complicated tumor microenvironment signal (Fig. 1). By introduction of nanomaterials (*i.e.*, polymers, liposomes, inorganic substances, extracellular vesicles, and nanofibers), nano-formulated active ingredients of CHMs contribute to improving the bioavailability and bioactivity. Additionally, the prospects and challenges of nano-formulated active ingredients from CHMs related to process feasibility, industrial production, and safety concerns are discussed in this review.

2. The mechanism of active ingredients from CHMs for cancer immunotherapy

Cancer immunotherapy is a promising strategy to extend patient survival by reeducating the host's immune system and has been used in clinical translation such as CpG 1018, the biological drug in Nivolumab, Kymriah[25,26]. However, low response ratios, severe side effects, and high costs negatively impact the efficacy and availability of immunotherapeutic to patients. CHMs serve as a potential solution to expand patient-centered benefits as they are naturally derived pharmaceutical resources with multi-targeting abilities for disease prevention and treatment[27]. Active ingredients found in CHMs in (Table 1)[3,4,6,7,11,12,16,28–65] such as polysaccharides, flavonoids, saponins, and alkaloids have demonstrated robust immunological activity against tumor cells[44,62,66]. Additionally, CHMs with multi-channel immunomodulatory characteristics can utilize their powerful active ingredients in multiple pathways to eliminate tumor cells, such as modulating the innate and adaptive immune systems, and influencing microenvironment signal molecules.

2.1. *Modulate the innate immune system*

The innate immune system, a first line response to pathogenic invasion, acts as a non-specific and non-memorable protective barrier for defending against infection. Innate immune cells such as macrophages, DCs, and NKs rapidly respond to invading

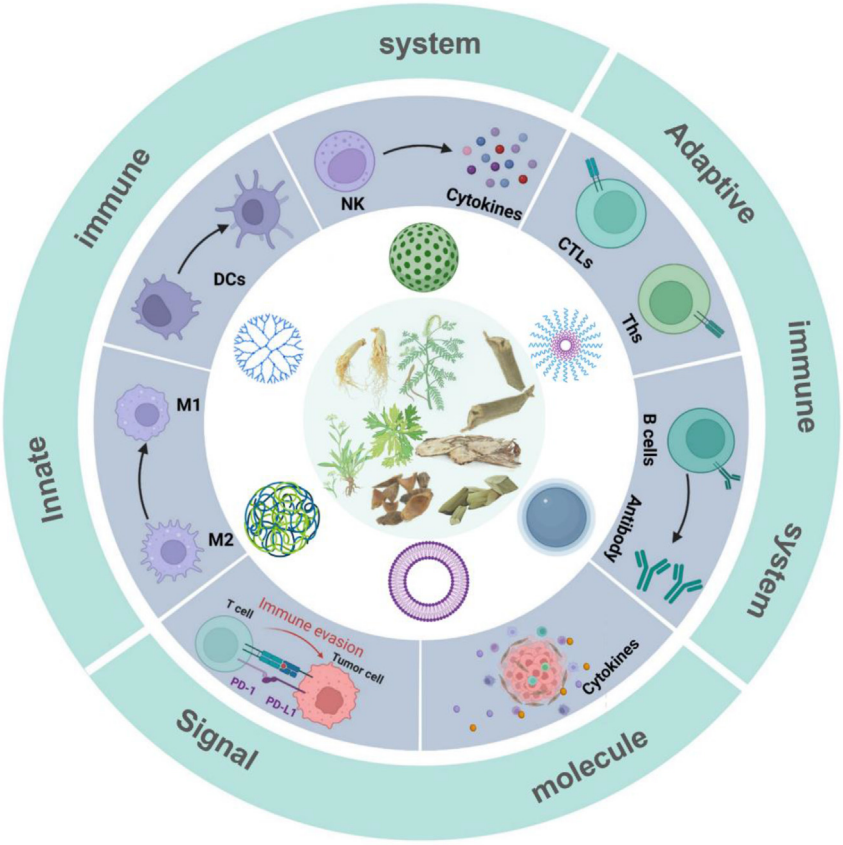

Figure 1 Nano-formulated active ingredients from CHMs demonstrate cancer immunomodulation through interacting with the innate and adaptive immune systems, and modulating the microenvironment signal molecules.

pathogens and further produce non-specific anti-infective immunity[44,45,56,67]. Innate immunity also establishes a foundation and interacts with adaptive immunity through macrophages and DCs presenting pathogen-associated antigens to T cells in acquired immune cells to activate adaptive immune responses[46,48,53].

2.1.1. *Modulate the macrophages*

Macrophages are highly plastic cells that contain two subtypes, the M1 (anti-tumor) and M2 (pro-tumor), which are driven by surrounding cytokines and the tissular niche[37,65,68]. M1 macrophages predominantly mediate tumor cell death by cytotoxicity, phagocytosis, or vascular damage. Conversely, M2 macrophages, serve as collaborators in tumor progression and immune evasion by secreting anti-inflammatory cytokines, like transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), interleukin-4 (IL-4), and interleukin-10 (IL-10)[51,52,69]. Cancer progression and prognosis are highly associated with the ratio of M1 and M2 macrophages because the predominated M1 macrophage could polarize towards the M2 macrophage with uncontrolled tumor proliferation[40,41]. Therefore, reversing macrophage polarization or increasing the proportion of M1 macrophage is an effective immunological approach against malignancies[32,33,70]. The polyporus polysaccharide, extracted from traditional Chinese medicine *Polyporus umbellatus*, serves as an active ingredient with immunomodulatory, anti-tumor, anti-inflammatory, and hepatoprotective activities[38,39,49]. Liu et al.[71] demonstrated that polyporus polysaccharide promoted the secretion of pro-inflammatory factors interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α) and inducible nitric oxide synthase (iNOS) and increased macrophage markers CD16, CD23, CD86, and CD40, possibly through activating NF-κB/NLRP3 pathways and upregulating the expression of NLRP3, p-P65, p-IκB and p-IKK-α/β in the tumor microenvironment to promote macrophage polarization. This polarization of macrophages in the tumor microenvironment towards the M1-like phenotype effectively inhibited the growth and migration of bladder cancer. In a similar immunomodulatory mechanism, solamargine, an active ingredient of *Solanum nigrum* L. repolarized M2 macrophages to an M1-like phenotype to alleviate the tumor microenvironment in a hepatocellular carcinoma model[61].

2.1.2. *Modulate the dendritic cells*

DCs are the body's most potent, specialized antigen-presenting cells—capable of efficiently ingesting, processing and presenting antigens to link innate and adaptive immune responses. Immature DCs have an excellent capacity for migration and antigen phagocytosis; and these cells can differentiate into mature DCs after being triggered by antigen uptake or an external stimulus[56]. Mature DCs play a pivotal role in initiating the immune response program through activating and sustaining adaptive immune cells and inducing long-term immunological memory; and contain high amounts of major histocompatibility complex and co-stimulatory molecules that stimulate DCs and native T lymphocyte interactions[36,44,72]. Recently, DCs-based vaccines are moving to the forefront of cancer immunotherapy with sipuleucel-T (Provenge) being the first authorized oncologic autologous DCs vaccine for

Table 1 Active ingredients of CHMs and corresponding immunomodulatory mechanisms.

Active ingredient	CHM	Mechanism	Ref.
Artesunate	*Artemisia carvifolia* Buch. Ham. ex Roxb. Hort. Beng.	Tregs reduction TGF-β1, IL-10 reduction	6,28
Angelica polysaccharide	*Angelica sinensis* (Oliv.) Diels	NKs activation Th1/Th2 regulation	29,30
Astragalus polysaccharide	*Astragalus membranaceus*	Macrophage polarization DCs maturation PD-L1 reduction	7,31
Bufalin	Bufo *bufo gargarizans* Cantor	Macrophage polarization NKs activation	32,33
Berberine	*Coptis chinensis* Franch.	CTLs activation PD-L1 reduction	34
Curcumin	*Curcuma longa* L.	Tregs reduction Th1/Th2 regulation	12,35
Cryptotanshinone	*Salvia miltiorrhiza* Bunge	DCs maturation	36
Dioscin	*Discorea nipponica* Makino	Macrophage polarization	37
Dihydroartemisinin	*Artemisia annua* L.	Macrophage polarization	11
Epigallocatechin gallate	*Camellia sinensis*	Macrophage polarization PD-L1 reduction	38,39
Epimedium polysaccharide	*Epimedium pseudowushanense*	DCs maturation	3
Ginsenoside Rh2	*Panax ginseng* C. A. Mey	Macrophage polarization	40,41
Ginsenoside Rg3	*Panax ginseng* C. A. Mey	PD-L1 reduction	16
Ginseng polysaccharides	*Panax ginseng* C. A. Mey.	NKs activation Tregs reduction	42,43
Ganoderma formosanum polysaccharides	*Ganoderma sinense*	DCs maturation	44
Icariin	*Epimedium brevicornu* Maxim.	M2 reduction	45
Luteolin	*Reseda odorata* L.	Tregs reduction	46
Lentinan	*Lentinus edodes*	CTLs activation Tregs, MDSCs reduction	47,48
Lycium barbarum polysaccharides	*Lycium barbarum* L.	Macrophage polarization DCs maturation CTLs activation	49,50
Norcantharidin	*Mylabris phalerata* Pallas	Macrophage polarization Tregs reduction	51,52
Oridonin	*Rabdosia rubescens* (Hemsl.) Hara	Th1/Th2 regulation	53
Resveratrol	*Veratrum album* L.	Tregs reduction PD-1 reduction Macrophage polarization	54,55
Rehmannia glutinosa	*Rehmannia glutinosa* (Gaert.) Libosch. ex Fisch. et M	DCs maturation NKs activation	56,57
Sativan	*Spatholobus suberectus* Dunn	PD-L1 reduction	58
Shikonin	*Lithospermum erythrorhizon* Sieb. et Zucc.	DCs maturation NKs proliferation	59,60
Solamargine	*Solanum nigrum* L.	Macrophage polarization	61
SaikosaponinA	*Bupleurum chinense* DC.	Th1/Th2 regulation	62
Triptolide	*Tripterygium wilfordii* Hook. f.	Tregs reduction PD-L1 reduction	63,64
Tetramethypyrazine	*Ligusticum chuanxiong* Hort	NKs activation	4
β-Elemene	*Curcuma wenyujin* Y.H. Chen & C. Ling	Macrophage polarization	65

prostate cancer[73]. To enhance the efficacy of DCs-based vaccines, various medicinal plants have been used as immunomodulators for the maturation of DCs. As a potential adjuvant for a DCs-based breast cancer vaccine, polysaccharides purified from *Portulaca oleracea* L. have been utilized to promote the activation and maturation of DCs through binding toll-like receptor 4 (TLR4) and further activating nuclear transcription factor kappaB (NF-κB) pathway. The polysaccharide-assisted DCs vaccine reduced the tumor burdens and lung metastases, which might be attributed to accelerating DCs maturation, and improving antigen presentation by altering the TLR4/MyD88/NF-κB pathway by polysaccharides[74]. The CHMs of *Lithospermum erythrorhizon* and *Salvia miltiorrhiza* Bunge demonstrate immunomodulatory activity on DCs, where its active ingredients of shikonin and cryptotanshinone effectively enhanced immunogenicity and elicited anti-proliferative properties against lung cancer and breast cancer, respectively[36,59,60].

2.1.3. *Modulate the natural killer cells*

NKs are innate lymphocytes capable of recognizing and directly killing cancer cells by releasing granzyme B, perforin, and cytokines *via* the antibody-dependent cell-mediated cytotoxicity effect[75,76]. NKs recognize their targets in a human leukocyte antigen-independent manner through germline-encoded receptors that recognize and bind to cell surface ligands, offering a unique advantage for cancer immunotherapy in which cancer cells can be

eliminated without risking T cell-driven inflammatory cytokine storm[29,77,78]. Unlike other innate immune cells, NKs are capable of memory-like properties—after exposure to haptens, viral antigens, or cytokine-induced cell memory—allowing the immune system to respond more effectively to a second pathogen infection[79]. NKs also contribute to influencing acquired immune cells (*i.e.*, B and T cells) by secreting cytokines and chemokines such as interferon-γ (IFN-γ), TNF-α, and CCL3[80,81]. Chuanxiong, a traditional CHM, promoted the cytotoxicity of NKs by upregulating the expression of NKG2D ligands (NKG2DLs), major histocompatibility complex class I-related chains A and B through its active ingredient tetramethypyrazine[4].

Recently, anti-cancer immunotherapy targeting the innate immune system is concentrated on activating innate immune cells such as M1 macrophages, DCs, and NKs through chimeric antigen receptor-macrophages (CAR-M), DCs-based vaccines, and CAR-NK cell immunotherapy, respectively[73,82,83]. However, DCs-based immunotherapy may produce adverse side effects through tumor-associated/tumor specific $CD8^+$/$CD4^+$ T cell responses; and CAR-NK cell therapy present challenges in homing immune cells to tumor tissues and maintaining durable efficacy[84]. Immunomodulatory methods focused on repolarization of tumor-associated macrophages present difficulties with potentially converting macrophages in normal tissues into the proinflammatory M1 phenotype[68]. The discovery of CHMs provides a novel solution for traditional tumor immunotherapy drawbacks where extracted pharmacologically active ingredients can direct the innate immune system and further potentiate adaptive immune system responses.

2.2. *Modulate the adaptive immune system*

Adaptive immunity is the ability of the host to resist infection through exposure to invading pathogens or artificial vaccination, and consequently triggering a precise immune response to specific antigens primarily through T and B lymphocytes[34,35]. Active ingredients of CHMs demonstrate immunomodulatory activity and induce durable long-term immunological memory to resist tumor invasion and metastasis through effectively augmenting the infiltration and proliferation of adaptive immune cell types (including cytotoxic T lymphocytes, helper T cells, regulatory T cells, and B cells)[30,53,85]. T cells coordinate cellular immunity through cytotoxic T lymphocytes (CTLs, $CD8^+$ T cells), helper T cells (Ths, $CD4^+$ T cells), and regulatory T cells (Tregs); and these cells also undertake a vital supporting role in humoral immune system to promote the proliferation and differentiation of B cells[64,86].

2.2.1. *Modulate the T cells*

CTLs directly destroy infected cells through secreting perforin, TNF-α and FASL-mediating antitumor cytotoxicity by initiating apoptosis of tumor cells[47,48,87]. Ths direct the immune process through an adjuvant role with predominant subtypes of Th1 and Th2; in which Th1 cells secrete cytokines IFN-γ and TNF-α that activate tumor cell surface death receptors and induce epitope spreading on antigen-presenting cells, and Th2 cells secrete cytokines IL-4, IL-5, and IL-10 that primarily induce humoral immune responses and exacerbate cancer progression through inhibiting IFN-γ secretion[62,88]. Notably, human cytokine activities are associated with the Th1/Th2 balance, and antigen-presenting cells can influence the direction of polarization of Ths[54,55,89]. $CD4^+CD25^+Foxp3^+$ Tregs avoid excess immune activation from self-antigens, but further accelerate tumor proliferation by inducing immune resistance when infiltrated into the tumor microenvironment[43,90,91]. Active ingredients of CHMs have achieved promising results on tumor immunomodulation through interacting with tumor related T cells consisting of these different mechanisms of action. To identify the individual active ingredient contributing to CTLs cytotoxicity, 594 small molecules originating from CHMs were screened and atractylenolide I was identified to augment tumor-associated antigen presentation through binding to proteasome 26S subunit non-ATPase 4, increasing antigen-processing ability of immunoproteasome and consequently elevating the systemic immune response against tumors[92]. To regulate the balance of Th1 and Th2 subtypes, saikosaponin A purified from Bupleurum Radix-elicited the Th1 dominant response leading to an increase in CTLs and Ths infiltration within the tumor microenvironment to reduce breast cancer growth *in vivo*[62] and ginsenoside purified from *Panax ginseng* C. A. Mey demonstrated antitumor effects through modulating the proportion of CTLs[93]. Extracts derived from Astragalus demonstrated a polarization of Th2 predominant cells to Th1 cells to elicit antitumor effects in patients with cervical cancer, increasing the populations of $CD4^+IFN\text{-}\gamma^+$ cell and $CD4^+IL\text{-}4^+$ cell in total $CD4^+$ cells[94]. Additionally, the active ingredients of scutellarin from flavonoid could directly inhibit activation and expansion of Tregs by disrupting the interaction of tumor necrosis factor (TNF)-tumor necrosis factor receptor type II (TNFR2), subsequently inhibiting the phosphorylation of p38 MAPK, a downstream signaling component of TNFR2 expressed on Tregs, and down-regulating the activity of $TNFR2^+$ Treg[95].

2.2.2. *Modulate the B cells*

Naïve B cells directly recognize and clear tumor-associated antigens in a Ths-independent activation; whereas, B cells receptor-antigen and co-stimulation signal of CD40 and CD40L expressed on Ths are required to activate the humoral immunity response. In addition to antibody production, B cells can function as antigen presentation cells for activating cellular immune response and alter the response mode of T cells by secreting tumor-specific antibodies and inflammatory cytokines[96]. The two polysaccharide fractions, CDA-1A and CDA-3B, were derived from the cold-water extracts of the valuable CHMs *Cistanche deserticola* Y. C. Ma; and *in vitro* immunological testing showed that these polysaccharide fractions displayed potent bioactivity on B cells proliferation[97].

2.3. *Modulate the microenvironment signal molecule*

The occurrence and development of tumors are affected by the dynamic network of stromal cells, immune cells, blood vessels, and signal molecules through positive and negative feedback interactions. Inflammatory cytokines dominate antitumor immunity, whereas inhibitory molecules (such as PD-1/PD-L1) hinder the infiltration and proliferation of immune cells to induce immune evasion[54,58,98].

2.3.1. *Modulate the cytokines*

Of note, cytokines are pertinent signaling molecules that activate the systemic immune response, regulating interactions between cell populations within the immune system and between the immune system and surrounding cells. Cytokine levels can be used as an indicator for the assessment of tumor diagnosis, efficacy, and prognosis due to a tumor's pro-inflammatory and pro-angiogenic properties[99]. These molecules can be targeted to preferentially

localize and activate anticancer immunity, in which the cytokines of interferon-α (IFN-α), interleukin-2 (IL-2) have been approved by the US Food and Drug Administration (FDA) in the United States for treatment of various malignant cancer types[100]. Despite their ability to elicit an anti-tumor immune response, cytokine therapies are often associated with poor patient response rates due to severe adverse side effects from non-antigen-specific toxicities[101]. CHMs extracted from nature with moderate medicinal property and multi-target effect have shown excellent efficacy on tumor immunomodulation[28]. Ginseng berry polysaccharide (GBPP), an immunostimulant extracted from natural medicine *P. ginseng*, significantly promoted the secretion of anti-melanoma cytokines (including IL-6, IL-12, IFN-γ, and TNF-α) by activated peritoneal macrophages in dose-dependent fashion, for a potential treatment of lung cancer model established by intravenously injected with B16-BL6 melanoma cells[102].

2.3.2. *Modulate the immune checkpoint*

The interaction of immune cells and tumors within tumor microenvironment determines the amplitude and mechanism of immune response interactions; however, overexpressed immune checkpoint molecule restricts immune activation and can result in immune tolerance. The PD-1/PD-L1 immune checkpoint axis in which programmed cell death 1 (PD-1) binds to programmed cell death ligand 1 (PD-L1) on tumor cells to establish immunologic escape[103]. Blocking the PD-1/PD-L1 axis *via* biological agents, such as Nivolumab and Pembrolizumab, has limited clinical efficacy rates due to a high prevalence of immune-related adverse events in patients[104]. The natural medicine *Platycodon grandiflorum* is widely used in the field of biomedicine with immunomodulation, anti-inflammatory, antitumor, expectorant and cough, hypoglycemic, and anti-obesity effects. Recent investigation indicated *P. grandiflorum* effectively restricted the expression of PD-1 on CTLs within the tumor microenvironment, locally increasing the T cells responses while avoiding over-activation of systemic immunity in an *in vivo* non-small cell lung cancer model[105]. Combining active ingredients of CHMs with chemical or biological agents is a promising strategy to assist cancer immunotherapy. Mice treated with curcumin and sildenafil reduced the PD-L1 expression on CT26 tumors, and significantly improved tumor inhibition when combined with anti-PD-1 antibody or 5-flurouracil[106]. Therefore, the active ingredient of CHMs can be regarded as a neoadjuvant to enhance tumor immunotherapy and achieve amplified immunomodulatory effects in combination therapies[31,50].

3. Nano-formulated active ingredients of CHMs for improving bioavailability

Despite evidence of CHMs possessing antitumor characteristics, active ingredients purified from CHMs may possess limited clinical applications due to undesirable pharmaceutical properties, such as hydrophobicity, poor stability, restricted circulation, poor targeting capabilities, and insufficient permeability[107,108]. The introduction of nanotechnology is expected to improve the active ingredient's bioavailability through increasing solubility and stability, extending half-life, optimizing targeting, and enhancing permeability. By engineering nano-formulated active ingredients of CHMs, these compounds can individually regulate host immune responses or be incorporated with chemotherapy, surgery and/or radiotherapy to maximize antitumor efficacy, proving novel clinical oncology treatments.

3.1. *Increased solubility and stability*

The poor solubility and stability of active ingredients in CHMs result in suboptimal bioavailability, which affects oral absorption and injectable administration. With the assistance of nanomaterials, active ingredients of CHMs can be loaded onto carrier materials in the form of absorption and/or encapsulation—to increase the drug's solubility and avoid direct exposure in the recipient. Polymeric nanomicellular systems for the delivery of baicalin, a hydrophobic active ingredient from the root of *Scutellaria baicalensis* Georgi, enhanced the compound's solubility and stability by encapsulating baicalin within a hydrophobic cavity constructed of conjugated stearic acid and pluronic F68. This nano-formulation exhibited monodisperse nano-sized particles with a high entrapment efficiency, that significantly mediated A549 human lung cancer cell cytotoxicity through modulating the chemical moieties of hydrophobic CHMs[15].

3.2. *Extended half-life*

When exposed to systemic circulation, active ingredients of CHMs tend to be eliminated by immunosurveillance systems that recognize and clear exogenous substances, leading to an unfavorable half-life and poor bioavailability. Nano-formulated CHMs extend the half-life of active pharmacological agents by preventing the exogenous drug from being recognized by the immune system. To further extend the CHM's half-life, PEGylated nanocarriers have been used to alter the active pharmaceutical agent's metabolic properties, prolonging the retention and circulation time in physiological environments—thus promoting its aggregation in tumor target sites[109,110]. The piperine extracted from the seeds of Piperaceae has previously demonstrated adjuvant characteristics for breast cancer chemotherapy by eliciting reversing drug resistance and anti-metastatic bioactivities; however, piperidine's hydrophobicity leads to poor bioavailability at high concentrations[111]. Piperine-loaded aptamer-functionalized polyethylene glycol polylactide-*co*-glycolide nanoparticles (APT-P-PEG-PNP) effectively prolonged the retention of piperine in circulation and enhanced its antiproliferative activity against MCF-7 cells in combination with paclitaxel by inhibiting P-gp activity[112].

3.3. *Optimized targeting*

Targeted drug delivery systems prolong and localize pharmacological compounds to specific cells, tissues, and organs in a dose-dependent manner. Although nano-drug delivery systems such as polymeric nanoparticles, liposomes, inorganic materials, and nanofibers demonstrate excellent targeting abilities in preclinical models with a size-controlled manner, these targeted drug delivery systems often result in negligible clinical outcomes[113]. According to the characteristics of tumor microenvironments, nano-formulated delivery systems can be optimized by modified ligands binding to receptors overexpressed on tumor cells such as: transferrin-receptors, epidermal growth factor receptors, and folate receptors. Alternately, nano-formulations can be functionalized as tumor microenvironment responsive delivery systems by introducing pH-sensitive, redox-sensitive, and enzyme-sensitive linkers to achieve on-demand drug release[114]. A targeted and redox-responsive nano-formulation containing camptothecin conjugated to lactose (CPT-S-S-LA) promoted the CPT accumulation in tumor cells through the interaction of lactose with sialoglycoprotein receptors on the hepatocellular carcinoma cells surface[115]. These interactions significantly enhanced the antitumor ability and

alleviated the toxic side effects by promoting a responsive release of the drug as a response to high glutathione levels.

3.4. Enhanced permeability

The primary prerequisite for drug treatment is that sufficient active ingredients accumulate at target cells. However, active ingredients of CHMs encounter penetration obstacles in the tumor tissues due to high-density tumor cells, a dense extracellular matrix, and interstitial fluid pressure within the tumor microenvironment[116]. Engineering nanosized delivery systems with penetration-assisted peptides or multifunctional transformable properties can help increase the prevalence of drugs within the tumor microenvironment. A biomimetic, targeted nano-formulation of icariin functionalized with an internalized RGD peptide (iRGD, sequence c(CRGDK/RGPDC)) to enhance the water solubility and biocompatibility of icariin. The iRGD could bind to $\alpha v\beta$ integrins expressed on the surface of tumor-associated endothelial cells and then generates CRGDK/R fragments, which further interacts with neuropilin-1 (NRP-1) receptors on tumor cells, eventually penetrating inside the tumor cells in the NRP-1-dependent endocytosis manner. Indeed, this nano-formulation improved tumor penetration in an A549 lung cancer cell model and increased the efficacy of icariin[117]. Enzyme-activated drug−protein conjugates have also been investigated to enhance the permeability of nanoparticle delivery systems across the tumor microenvironment. A membrane γ-glutamyl transpeptidase-triggered charge reversal CPT-polymer conjugate infiltrated the tumor microenvironment *via* caveolae-mediated endocytosis and transcytosis, significantly augmenting CPT-triggered tumor regression[118].

4. Nano-formulated delivery of active ingredients from CHMs for cancer immunotherapy

Engineered nanomaterials can help protect the active ingredients from direct contact with blood by means of carrier adsorption, encapsulation, or conjugation, leading to increased drug efficacy[119]. Nano-formulated active ingredients of CHMs tend to enhance the retention, accumulation, and penetration of active ingredients in tumor sites, in addition to facilitating a controlled release of active ingredients in the tumor extracellular matrix or tumor cells. Notably, nanomaterials allow for synergistic treatment by loading multiple components, overcoming drug resistance, and activating immune responses through multiple pathways against tumors (Table 2)[120–147].

4.1. Polymer-assisted nano-formulation

4.1.1. Polymeric nanoparticles

Polymeric nanoparticles (PNPs) delivery systems consist of synthetic or naturally-occurring polymeric materials that agglomerate

Table 2 Nano-formulated active ingredients originated from CHMs for cancer immunotherapy.

Active ingredient	Carrier type	Loading method	Tumor model	Ref.
Astragaloside III	Mesoporous silica nanoparticle	Hydrophobic interaction	CT26 colon cancer	120
Angelica sinensis polysaccharide	Nanoparticle	Esterification reaction	MCF-7 human breast cancer	121
Astragalus polysaccharide	Nanoparticle	Esterification reaction	4T1 breast cancer	122
	Gold nanoparticle	Hydrophobic interaction	4T1 breast cancer	123
Celastrol	Polymeric nanoparticle	Hydrophobic interaction	D4M, BPD6 melanoma	124
	Nanoemulsion	Hydrophobic interaction	B16F10 melanoma	125
Curcumin	Nanofiber	Amidation reaction	LLC lung cancer	126
	Liposome	Hydrophobic interaction	C26 colon carcinoma	127
Camptothecin	Nanofiber	Esterification reaction	GL-261 brain cancer	128
Dihydrotanshinone I	Biomimetic nanoparticle	Hydrophobic interaction	Huh7, Hepa1-6 liver cancer	129
Epigallocatechin-3-*O*-gallate	Polymeric nanoparticle	Esterification reaction	4T1 breast cancer	130
Ginsenoside Rg3	Liposome	Hydrophobic interaction	C6 glioma	131
Ginsenoside Rg3, quercetin	Cyclodextrin nanoparticle	Hydrophobic interaction	CT26, HCT116 colorectal cancer	132
Ganoderma lucidum polysaccharide	Gold nanoparticle	Au-SH interaction	4T1 breast cancer	133
Icaritin	Polymeric nanoparticle	Hydrophobic interaction	Huh7, Hepa1-6 liver cancer, B16 melanoma	134
Norcantharidin	Liposome	Hydrophobic interaction	H22 liver cancer	135
Puerarin	Nanoemulsion	Hydrophobic interaction	4T1 breast cancer	136
Podophyllotoxin	Lipid nanoparticle	Amidation reaction	H460 lung cancer	137
Quercetin, alantolactone	Polymeric micelle	Hydrophobic interaction	CT26-FL3 colorectal cancer	138
Silybin	Liposome	Hydrophobic interaction	4T1 breast cancer	139
Shikonin	Lactoferrin nanoparticle	Hydrophobic interaction	CT26 colon cancer	140
	Liposome	Hydrophobic interaction	B16F10 melanoma	141
	Polymeric micelle	Hydrophobic interaction	CT26 colon cancer	142
Silibinin	Polymeric nanoparticle	Hydrophobic interaction	4T1 breast cancer	143
Salvianolic acid B	Liposome	Hydrophobic interaction	4T1 breast cancer	144
Ursolic acid	Liposome	Hydrophobic interaction	4T1 breast cancer	145
	Excipient-free nanodrug	Hydrophobic, $\pi-\pi$ stacking interactions	A549 lung cancer, Hela cervical cancer	146
Ursolic acid, lentinan	Excipient-free nanodrug	Hydrogen bond, van der Waals force	CT26 colon cancer	147

into nano-sized PNPs to load active ingredients in their inner core or covalently link functional groups on active ingredients[121−123]. By introducing targeting ligands or pH-sensitive linkers, PNPs can more effectively modulate the cancer immune environment[120,124,130,137]. A polymeric nanoparticle composed of poly lactic-*co*-glycolic acid-polyethylene glycol-aminoethyl anisamide (PLGA-PEG-AEAA)-encapsulated icaritin and doxorubicin was formulated for hepatocellular carcinoma treatment[134]. The icaritin moiety activated the autophagy pathway, potentiating tumor immunogenicity synergistically with doxorubicin, to serve as an immune activator (Fig. 2A).

Ligand-receptor interactions direct the targeting of drug delivery systems, promoting drug enrichment in target sites and avoiding undesirable side effects on healthy tissues. To target hepatocellular carcinoma cells, a mannose-coated poly (D,L-lactic-*co*-glycolic acid) (PLGA)-based nanoparticle was designed to deliver two CHMs, plumbagin (PLB) and dihydrotanshinone I (DIH), as shown in Fig. 2B. This nano-formulation effectively increased the half-life and tumor enrichment capacity of CHMs, reprogramming the "cold-tumor" by inducing tumor immunogenic cell death and activating systemic immune responses[129]. Additionally, a folate-coated polyethylene glycol (PEG)-modified cyclodextrin nanoparticle was utilized to co-encapsulate natural medicines ginsenoside Rg3 and quercetin for cancer chemo-immunotherapy[132]. Quercetin activated reactive active oxygen species to enhance the ginsenoside Rg3-induced tumor immunogenicity, thus activating innate-adaptive immunity against tumor growth and prolonging survival rates in combination with PD-L1 antibodies (Fig. 2C).

4.1.2. *Polymeric micelles*

Polymeric micelles are promising drug delivery systems formed by the self-assembly of amphiphilic block copolymers in aqueous solutions above the critical micelle concentration[148]. Polymeric micelles possess unique core−shell architectures with a hydrophilic outer shell and a hydrophobic inner core, imparting multiple biological properties. The hydrophobic inner core serves as an ideal compartment for embedding lipophilic drugs, protecting active ingredients from degradation, and enhancing solubilization. Meanwhile, the hydrophilic exterior creates a tight protective shell that reduces protein and cell adhesion, prolongs blood circulation times, and increases the drug's half-life. Polymeric micelles consisted of FDA-approved polymers, TPGS and DSPE-PEG2000, were investigated for the codelivery of quercetin (originated from *Inula racemosa* Hook. F) and alantolactone (isolated from *Inula helenium* L.) with a specific drug ratio of 1:4. Combined with alantolactone, the quercetin strengthened the tumor immunogenicity and induced a tumor surveillance with durable memory[138].

Hybrid micelles are also an encouraging strategy for maximizing cancer immunomodulatory potential through the co-delivery of therapeutic agents. Hybrid polymeric micelles co-delivering shikonin (SK, originated from the *L. erythrorhizon* plant) and indoleamine 2,3-dioxygenase-1 (IDO-1) knockdown siRNA (siIDO1) effectively induced anticancer immune response by remodeling the tumor microenvironment[142]. These hybrid polymeric micelles (SK/siIDO1-HMs) were prepared using polyethylene glycol-polycaprolactone (PEG-PCL) and polyethyleneimine-polycaprolactone (PEI-PCL),

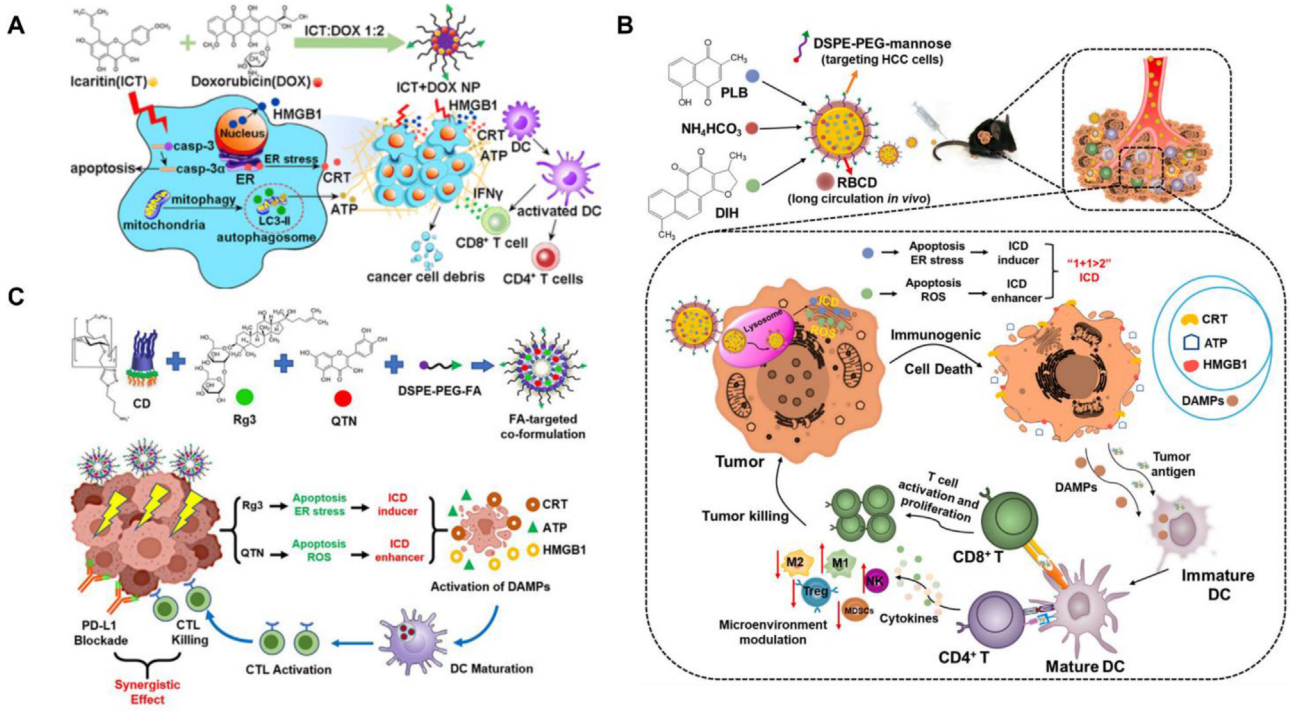

Figure 2 The polymeric nanoparticle delivery of active ingredient from CHMs to induce anticancer immune responses. (A) Schematic illustration of ICT + DOX NPs for provoking immunogenic cell death and activating adaptive immunity. Reprinted with the permission from Ref. 134. Copyright © 2020 American Chemical Society. (B) Schematic illustration of Comb-NP for targeting hepatocellular carcinoma cells and remodeling the immunosuppressive microenvironment. Reprinted with the permission from Ref. 129. Copyright © 2022 Elsevier. (C) Schematic illustration of FA-targeted co-formulation co-delivery of ginsenoside Rg3 and quercetin to exert synergic chemo-immunotherapy. Reprinted with the permission from Ref. 132. Copyright © 2022 Elsevier.

where PCL constituted the hydrophobic core to encapsulate SK while PEI with positive charges adsorbed the siIDO1 (Fig. 3A). The SK/siIDO1-HMs prolonged the circulation time to favor intratumoral accumulation such that SK moiety promoted DCs maturation and increased the proportions of infiltrating CTLs in tumor sites. The IFN-γ cytokines secreted by CTLs upregulated the expression of inhibitory molecule IDO1, leading to immune resistance (Fig. 3B−E). Following IDO pathway blockade by siIDO1, the SK/siIDO1-HMs displayed a remarkable anti-tumor efficacy in reducing tumor volume and extending survival rate (Fig. 3F−I).

4.2. *Lipid-assisted nano-formulations*

4.2.1. *Liposomes*

Liposomal drug delivery systems are formed by phospholipid bilayer membranes encapsulating drug molecules; and these nanoparticles possess superior biocompatibility and lower immunogenicity due to their structural similarity to biological membranes[127,149,150]. Owing to its unique lipid bilayer structure, liposomes have various applications for delivery of both hydrophobic and hydrophilic molecules alike[135,151]. Their internal water cavity is suitable for loading hydrophilic drugs, while possessing lipophilic drugs between the bilayers of lipid molecules[141]. PEG-modified liposomes have been incorporated to entrap hydrophilic salvianolic acid B (which originated from *S. miltiorrhiza* Bunge) in the liposome's inner cavity to prolong its biological half-life time *in vivo* (Fig. 4A). When accumulated in tumor sites, salvianolic acid B reversed the tumor microenvironment through converted M2 macrophages into M1 macrophages and inhibited Tregs infiltration (Fig. 4B). Moreover, this nano-formulation improved the chemotherapeutic efficacy exerted by docetaxel-loaded PEG-modified liposomes[144]. Liposomes composed of hydrogenated soy phosphatidyl-choline, cholesterol and 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[methoxy(polyethylene glycol)-2000] have been utilized to increase the solubility and control the release dynamics of a natural herb, ursolic acid (UA), for tumor microenvironment modulation[145]. The UA liposomes effectively ameliorated the tumor immunosuppressive state through down-regulating the percentage of Tregs and myeloid-derived suppressor cells residing in the tumor tissues, further strengthened the immune response against 4T1 triple negative breast cancer cells.

Plant-derived liposomes have been investigated to help improve the safety and fluidity of liposomes[152]. For example, ginsenoside Rg3, derived from *P. ginseng* roots, may serve as a substitute for cholesterol in liposomal drug delivery systems[131]. This molecule demonstrated brain cell-targeting capabilities through crossing the blood−brain barrier, which is attributed to the interaction of Rg3 glucosyl residues with glucose transporters located on cancer cells. The multifunctional Rg3-based liposomal system also exhibited synergic efficacy when combined with chemotherapeutic drugs (Fig. 4C). The paclitaxel-loaded Rg3-liposome significantly strengthened innate and adaptive immune

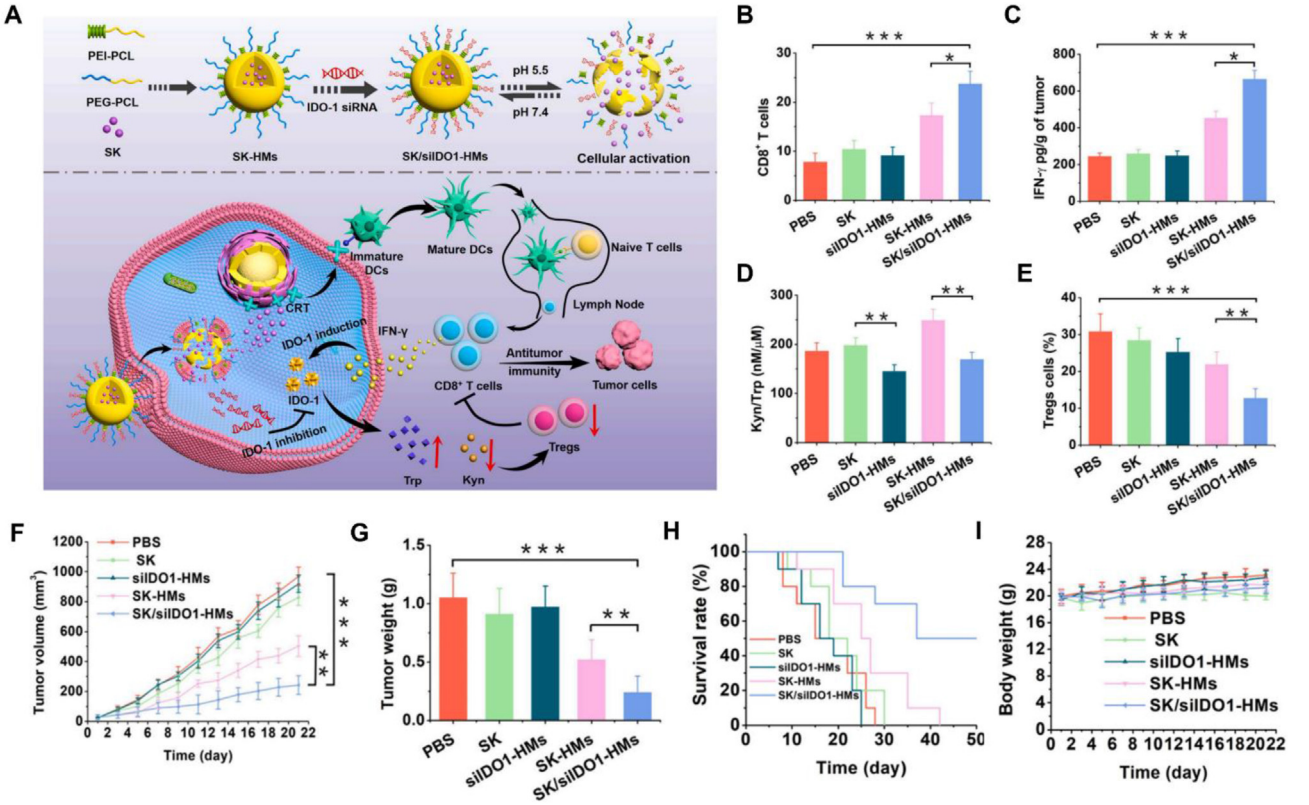

Figure 3 The polymeric micelles delivery of active ingredients from CHMs to induce anticancer immune responses. (A) Schematic illustration of the SK-siIDO1-HMs remolded tumor immunosuppressive microenvironment and enhanced antitumor immunity. (B) Quantitative measurement of immunofluorescence of intratumoral $CD8^+$ T cells. (C) Detection of intratumoral IFN-γ secretion. (D) Evaluation of the IDO effect under corresponding treatments. (E) The infiltration of intratumoral Tregs. (F) The change of tumor volume. (G) Tumor weight following corresponding treatments. (H) Survival ratio curve. (I) Body weight in various treatments. Reprinted with the permission from Ref. 142. Copyright © 2021 Elsevier.

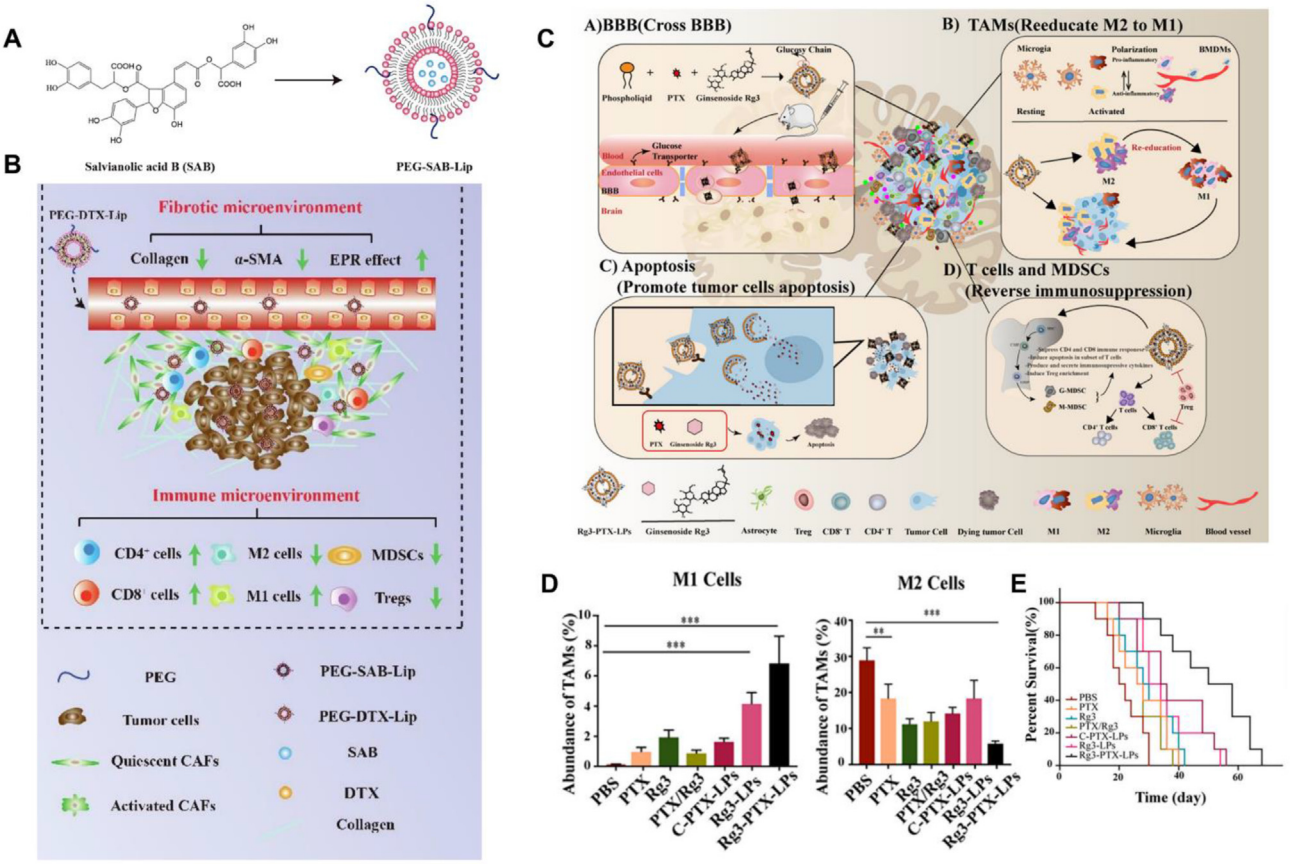

Figure 4 The liposomal delivery of active ingredients from CHMs to induce anticancer immune responses. (A) Schematic diagram of PEG-SAB-Lip. (B) Schematic illustration of PEG-SAB-Lip for immune microenvironment modulation. Reprinted with the permission from Ref. 144. Copyright © 2022 Elsevier. (C) Schematic illustration of the multifunctional Rg3-PTX-LPs for glioma targeting chemo-immunotherapy. (D) Determination of tumor tissue-resident M1 and M2-type macrophages in tumor tissues. (E) *In vivo* survival ratios following corresponding treatments. Reprinted with the permission from Ref. 131. Copyright © 2021 Elsevier.

responses through enhancing the M1/M2 ratio and expanded CTLs against glioma growth, resulting in prolonged median survival rates (Fig. 4D and E).

4.2.2. *Nanoemulsions*

Nanoemulsions are formed by water, oil, surfactant and co-surfactant in appropriate proportions to construct a low viscosity, thermodynamically stable, transparent and heterogeneous dispersion drug delivery system[125]. They are comprised of two incompatible phases: a discontinuous phase and continuous phase. Based on the composition and relative distribution of the dispersed and continuous phases, nanoemulsions can be classified as two-phase (O/W or W/O) or multi-phase (W/O/W). In addition to being an effective solubilizing carrier, nanoemulsions can also improve the bioavailability and control the release of insoluble active ingredients[153,154]. For example, puerarin nanoemulsions (nanoPue) utilize lecithin as the main emulsifier to improve the solubility of puerarin (Fig. 5A). The active ingredient of puerarin, an isoflavone derivative originating from the kudzu root, has the capacity to regulate the tumor stromal microenvironment. The nanoPue formulation significantly improved the CHM's solubility and therapeutic efficacy through remodeled stromal microenvironment, enhanced M1/M2 ratio, and reduced Tregs infiltration (Fig. 5B–E). NanoPue can be treated as an adjuvant to paclitaxel and anti-PD-L1 antibodies, with demonstrated tumor inhibition and prolonged median survival rates in a 4T1 tumor model[136].

4.3. *Inorganic material-assisted nano-formulations*

Inorganic drug delivery systems such as gold nanoparticles (AuNP), magnetic nanoparticles, and mesoporous silica nanoparticles demonstrate great potential in cancer immunotherapies due to their high surface area, size tunability, unique optical, and magnetic properties[155]. AuNP are considered to be the most widely used metal nanoparticles in the field of drug delivery due to their biocompatibility, unique optical properties, high surface area, and excellent surface modifiability[156]. These nanoparticles can load targeting ligands or drug molecules in various ways to facilitate drug release kinetics including electrostatic interactions, hydrophobic interactions, and covalent binding[157]. As shown in Fig. 5F, AuNPs were conjugated to the natural herbal *Ganoderma lucidum* polysaccharide (GLP) to elicit immunoregulatory functions to inhibit 4T1 tumor growth[133]. The GLP-Au nano-formulation promoted the GLP accumulation in tumor tissues and up-regulated the expression of CD80 and CD86 on DCs, thus inducing DCs maturation and T cells proliferation. Additionally, the GLP-Au nano-formulation increased the proportion of $CD4^+$/$CD44^+$ memory T cells in synergy with the chemotherapeutic

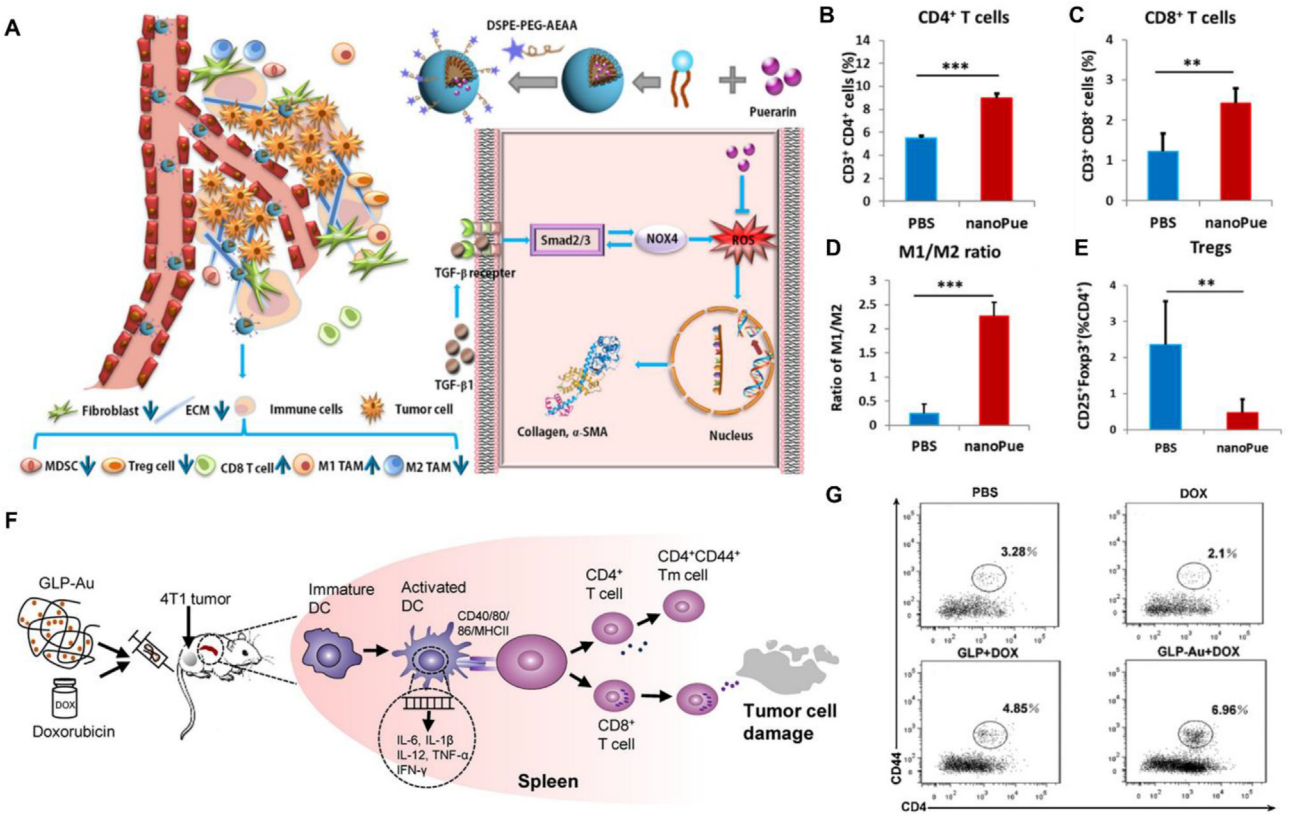

Figure 5 The nano-emulsion and inorganic nano-formulation delivery of active ingredients from CHMs to induce anticancer immune response. (A) Schematic diagram of the nano-puerarin regulated tumor microenvironment and boosted cancer immunotherapy. (B) The percentages of infiltrated $CD4^+$ and (C) $CD8^+$ T cells in tumor tissues. (D) The M1/M2 ratio in therapeutic and control groups. (E) The populations of Tregs in tumor tissues. Reprinted with the permission from Ref. 136. Copyright © 2020 Elsevier. (F) Schematic diagram of GLP-Au + DOX for activating DCs and memory T cells. (G) The percentages of $CD4^+CD44^+$ T cells under corresponding experimental groups. Reprinted with the permission from Ref. 133. Copyright © 2019 Elsevier.

doxorubicin (Fig. 5G). Thus, immunoreactive active ingredients of CHMs can be formulated with inorganic-materials for improving the compound's bioactivity; however, potential long-term toxicity and clearance rates of inorganic materials *in vivo* should be fully considered.

4.4. *Other nano-formulations*

4.4.1. *Excipient-free nanodrugs*

Biomaterial-assisted nano-formulations increase the drug's accumulation in target sites and prolong the drug's release behavior, thus avoiding unexpected side effects on healthy tissues. Unfortunately, this nano-formulation requires repeated dosing due to its insufficient drug-loading efficiency. To maximum the drug efficacy, nanodrug-based nanoparticles utilize self-assembly by prodrugs or amphiphilic drug−drug conjugates that lead to an increased drug-loading capacities and have the potential to release drugs as a response to a stimulus[158]. Recent studies indicated that the active ingredients of CHMs can spontaneously form stable excipient-free nanodrug structures under certain conditions, favorably reducing multiple dosing and improving biocompatibility[159]. Fig. 6A demonstrates an LNT-UA nanodrug composed of ursolic acid (UA) and lentinan (LNT) *via* hydrogen bond and van der Waals force[147]. This nanodrug without additional carrier material effectively improved the bioavailability of the naturally active ingredient UA, which initiated the immune response program to reverse the tumor immunosuppressive microenvironment. Combined with immune checkpoint inhibitor anti-CD47 antibody, this nanodrug reinforced systemic immunity against tumor growth and metastases as demonstrated in bilateral and spontaneous colorectal cancer models.

4.4.2. *Extracellular vesicles*

Extracellular vesicles (EVs) within bilayer lipid membranes are nano-scaled membrane vesicles secreted by cells, containing genetic information and regulatory molecules, to modulate intracellular communication[160]. EVs are recognized as a natural drug delivery system with low immunogenicity, homologous targeting abilities, and high biocompatibility; and can serve as excellent carriers for drug delivery in cancer immunotherapies. Ginseng-derived EVs was extracted and purified from the roots of *P. ginseng* C. A. Mey; and demonstrated immunomodulatory mechanisms against melanoma through altering M2 macrophage polarization and skewing the M1/M2 rate towards the M1-like phenotype, which tend to associate with TLR4 and myeloid differentiation antigen 88 signaling pathways (Fig. 6B)[161]. Subsequently, the tumor tissues were enriched in M1 macrophages and T cells, enhancing the immune response in the tumor microenvironment, which validated the macrophage-

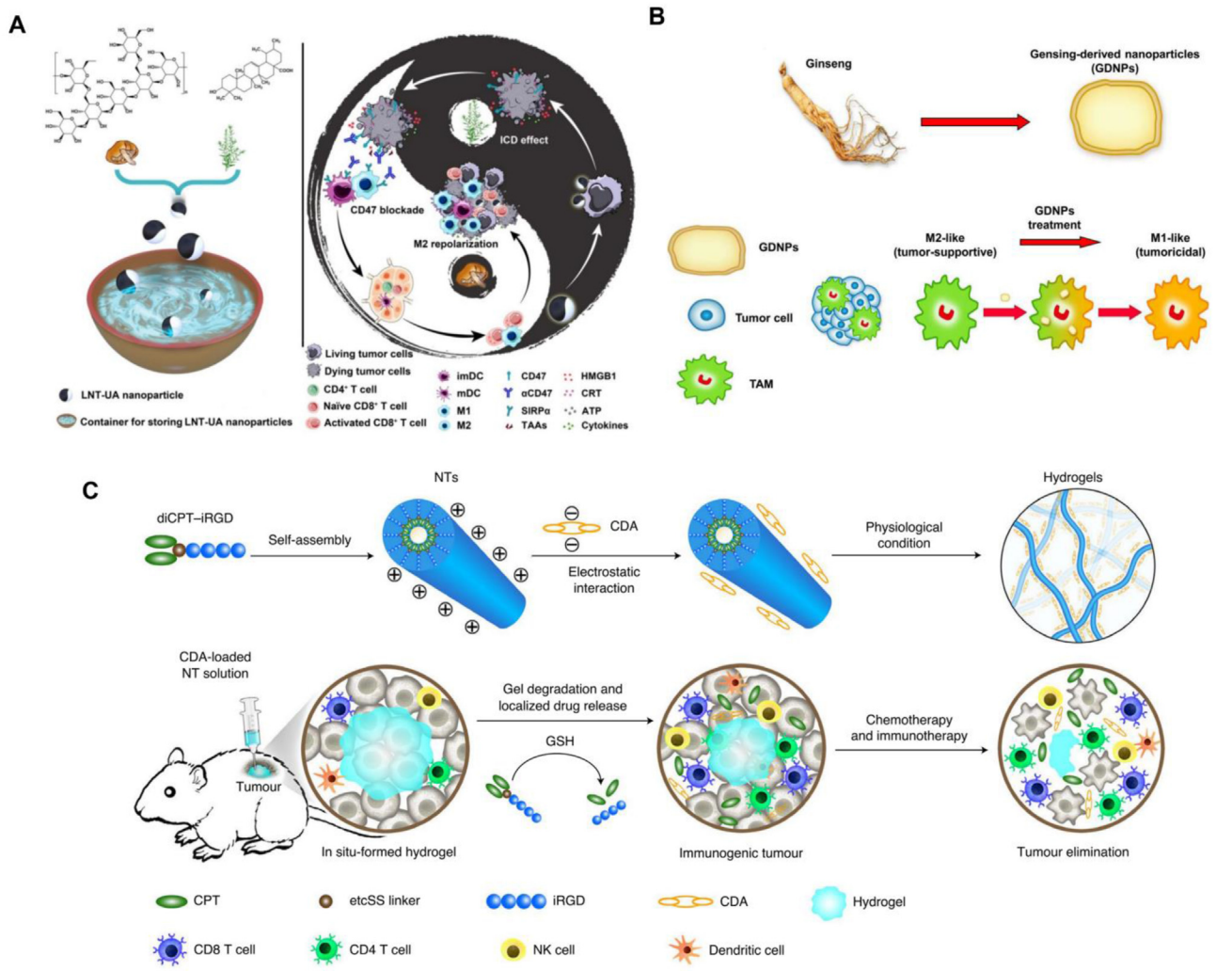

Figure 6 The various nano-formulation delivery of active ingredients from CHMs to induce anticancer immune response. (A) Schematic diagram of excipient-free nanodrug LNT-UA for modulating macrophages and facilitated CD47 antibody-mediated anticancer immunity. Reprinted with the permission from Ref. 147. Copyright © 2022 Ivyspring International Publisher. (B) Schematic diagram of extracellular vesicles for modulating tumor-associated macrophages. Reprinted with the permission from Ref. 161. Copyright © 2019 BMJ Publishing Group Ltd. (C) Schematic diagram of diCPT-iRGD nanofibers for modulated innate-adaptive immune responses against tumors. Reprinted with the permission from Ref. 128. Copyright © 2020 Springer Nature.

dependent mechanism of ginseng-derived EVs on melanoma growth inhibition.

4.4.3. Nanofibers

Nanofibers have shown promising application prospects in the field of tissue engineering and drug delivery due to their high surface-to-volume ratio, high porosity, and low density. Currently, most nanofibers are prepared by synthetic polymers, which may pose safety and degradability issues[126,162]. Notably, peptides with excellent biocompatibility and degradability have the potential to form nanofiber structures through self-assembly processes. Nanofiber delivery systems, constructed with peptide−drug conjugates, enable drug self-delivery. For example, a series of peptide−drug conjugate platforms constructed with tumor penetration peptide iRGD and camptothecin (CPT) derived from the seeds or root bark of *Camptotheca acuminata* decne were investigated[163−165]. The peptide−drug conjugate could self-assemble into nanofibers within a positively charged aqueous environment, with the potential to exert the "drug delivery by drug" strategy through coating negatively charged medicines such as interferon genes (STING) agonist CDA (Fig. 6C)[128]. CPT-induced tumor cell death and resulted in the release of DNA fragments into the cytoplasm, thus initiating STING-dependent activity to transform the tumor immunosuppressive microenvironment into an immunostimulatory microenvironment. Notably, this nanofiber could entangle in the physiological environment and subsequently form a hydrogelator after charge screening.

5. Conclusions and future prospects

In this review, we briefly introduce the integration of nanomaterials and CHMs to construct nano-formulated active ingredients extracted from CHMs for cancer immunotherapy. CHMs exhibit multi-channel, multi-target, and multi-level immunomodulatory activities and their active ingredients may be a promising alternative to traditionally used chemical and biological agents. With the adjuvant of nanomaterials such as polymeric nanoparticles, liposomes, inorganic carriers, and nanofibers, the

bioavailability and bioactivity of active ingredients from CHMs are significantly improved through an increased solubility and stability, extended half-life, optimized targeting abilities, and enhanced penetration[139,140,143,146]. The active ingredients, extracted from natural CHMs, exert multiple immune effects by editing immune response mechanisms from modulating innate and adaptive immune response systems, and tumor microenvironment signal molecules. Through these multiple pathways, these active ingredients establish tumor-specific immunity, inhibit tumor progression, and alleviate immune resistance.

Despite the potential advantages of active ingredients from CHMs, there are many challenges that can hamper clinical translation, such as concerns related to quality control, large-scale processing, reproducibility, biocompatibility, and biosafety[166−168]. CHMs have a multi-potency effect and the extracts determine the disease and quality of treatment. Due to its active ingredients being derived from natural materials, its purity is constrained by the quality of the raw material and the choice of purification reagents, thus precise control of the extraction and purification process is a prerequisite to ensure reproducibility and large-scale processing. Notably, nanomaterial-adjuvant active ingredients of CHMs can address undesirable pharmacological characteristics such as hydrophobicity, short half-life, poor tumor targeting, and penetration, favoring improved therapeutic efficacy and reduced toxic side effects[42,57,63]. Although promising in mice model, the large differences between patients and mice models limit the generalization of results from mice to patients. Therefore, the more representative animal models such as orthotopic xenografts, genetically engineered animal model, and patient-derived xenografts are encouraged to carefully evaluate therapeutic efficacy and monitor toxic side effects in preclinical trials. Importantly, the biosafety and compatibility in clinical applications must be considered. The therapeutic effect in the clinic is significantly attenuated by immune-related adverse events, involving immune-associated pneumonia, cardiotoxicity, digestive tract toxicity, etc., which may be due to the over-activation of the immune system by the active ingredients to attack healthy organs. Combination therapy is a promising approach through the co-administration of Immunotherapeutic agents. The contraindications, drug ratio, administration order present new challenges for immunotherapy. Moreover, active targeting of the site of active ingredients action is expected to reduce immune-related adverse events through conjugation of targeting ligands or modification of nanomaterials. To avoid the additional effect of carrier materials, optimizing nanomaterials characteristics or selecting authorized biomaterials to deliver active ingredients of CHMs are amenable to benefit patients and avoid excessive side effects from foreign carrier materials. Overall, integrating biocompatible nanomaterials and purifying active ingredients derived from CHMs is critical to construct nano-formulated active ingredients for novel cancer immunotherapy solutions.

Acknowledgments

This work is supported by National Key Research and Development Program of China (No. 2022YFC3501905); Key project at central government level: The ability establishment of sustainable use for valuable Chinese medicine resources (No. 2060302); National Natural Science Foundation of China (NSFC, No. 82104076); Science and Technology Commission of Shanghai Municipal (STCSM, No. 22S21902400, China); and Medicine-Engineering joint foundation of Shanghai Jiao Tong University (No. YG2022QN025 and YG2022QN050, China).

Author contributions

Qi Shang and Wandong Liu collected the related papers, drafted the original manuscript. Faith Leslie, Jiapei Yang, Mingmei Guo, and Mingjiao Sun collected the related papers and revised the manuscript. Guangji Zhang, Qiang Zhang, and Feihu Wang proposed and outlined this review, revised and finalized the manuscript. All of the authors have read and approved the final manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

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