Acupuncture and Herbal Medicine

Priming immunity *via* herbal components and their nanomedicines for the treatment of cancer

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Abstract

Recently, immunotherapy has redefined cancer treatment by promoting the rapid killing of tumor cells through the immune system. Herbal medicines have been increasingly used as adjunct therapies to complement cancer treatment along with chemotherapy and radiotherapy to delay tumor development, reduce pain, and prolong patient survival. However, the potential immunotherapeutic effects of these herbal derivatives are limited by their structural instability, poor membrane permeability, and low bioavailability. To address this issue, nanotechnology has been used to enhance the activity of active compounds. Therefore, this review focuses on the effectiveness of the active ingredients of herbal medicines in suppressing tumor progression by modulating both the innate and adaptive immune systems, challenges in their delivery, and the application of nanocarriers for the effective delivery of these herbal components.

Keywords: Anti-tumor, Herbal components, Immune system, Nanodrug delivery systems

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Introduction

Definition and formation of cancer

In medicine, cancer refers to malignant tumors that most commonly originate in the epithelial tissue[1]. The biological characteristics of cancer include abnormal cell differentiation and proliferation, uncontrolled growth, invasion, and metastasis. Cancer occurrence is related to many factors, including genetics, immunity, and lifestyle[2]. Here, we discuss cancer formation from two perspectives.

Ancient understanding of cancer

Cancer has affected humans since ancient times. A reliable piece of evidence for this is the discovery of tumor chunks in fossilized human bones. The oldest recorded case of disseminated cancer was that of a Scythian king 2,700 years ago who was diagnosed with metastatic prostate carcinoma using modern microscopy and proteomic techniques[3]. The understanding of cancer in China can be traced back to more than 3,500 years, and the earliest records of cancer appeared in oracle bone inscriptions from the Yin and Zhou eras[4]. The earliest written description of human cancer came from an ancient Egyptian manuscript found in the 19th century, which mentioned breast cancer for the first time and described breast tumors as cool to touch and refractory to treatment when they swelled and spread to the breast[5]. For the treatment of tumors, Chinese medicine attaches great importance to mobilizing the internal factors of the body, eliminating the evil and attacking local cancer, and enhancing "right", healthy qi (ie, strengthening the resistance of the body). Based on the understanding of "healthy qi" and "evil disease" fighting each other, it was widely recognized that in the early stage of the disease, treatment should be focused on killing the tumor cells (attack strategy). During the middle stage, treatment should include a combination of attacks and regulations. In the later stages, treatment is adjusted to restore normal body function and consolidate the constitution. The use of Chinese herbs with anticancer activity can improve immune function and systemic conditions in the body[6]. These medical achievements have enhanced our knowledge and provided valuable insights for clinical research on tumor treatment.

Xiang Li, Chenkai Gong, and Abid Naeem contributed equally to this work.

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Modern study of cancer

The incidence and mortality rates of cancer are increasing worldwide and pose serious threats to human health and life. According to the American Cancer Society, 1,958,310 new cases of cancer and 609,820 cancer-related deaths occurred in the United States by 2023[7]. According to the latest data from the National Cancer Registry, approximately one-quarter of new global cancer cases and deaths have been reported in China. Moreover, cancer has the highest incidence and mortality rates in China[8].

Cancer treatment remains challenging for clinicians and researchers worldwide. Studies have shown that tumor development is closely related to the immune system[9,10]. The tumor microenvironment maintains an immunosuppressive state. Several factors contribute to this phenomenon. First, tumor cells hyperactivate immune checkpoints, thereby escaping immune surveillance. Secondly, heterogeneous tumor antigens with high mutation rates prevent the recognition and killing of tumor cells by the surrounding immune system. Third, tumor cells are not immunogenic, and the recognition by antigen-presenting cells is difficult. This evidence suggests that the intrinsic immune system cannot remove tumor cells through the same mechanisms as those used to remove foreign substances[11].

Science listed cancer immunotherapy as one of the top 10 scientific breakthroughs in 2013. This type of therapy has been described as the most promising of the four major approaches to cancer treatment (along with chemotherapy, surgery, and radiotherapy)[12]. This treatment aims to coordinate the immune system so that cancer cells, including those in primary, metastatic, and recurrent tumors, are eliminated from the body. By coordinating the immune system, cancer immunotherapy maximizes efficacy and reduces toxicity while minimizing side effects. Cancer immunotherapy offers advantages over the other three types of treatments that are limited in terms of effectiveness, serious side effects, and tumor recurrence. Furthermore, by adjusting the immune system, the body can develop an immune memory that can identify and reattack tumor cells in the event of tumor recurrence, leading to favorable outcomes[13].

Evolution of traditional herbal medicine (THM) for cancer treatment

Remarkable progress has been made in cancer immunotherapy. However, its use has been limited by safety concerns regarding autoimmune reactions and nonspecific inflammation in most patients, resulting in severe physical trauma and damage to normal tissues[14]. Therefore, it is necessary to identify compounds with high specificity and safety.

THM is a unique diagnostic and therapeutic technique that has been used for thousands of years, particularly in Eastern countries[15,16]. Over the past 50 years, many natural compounds have been identified as highly active at the clinical level (eg, indirubin, artemisinin, ginsenoside Rg3, and paclitaxel). The importance of this point cannot be overstated, as more than 65% of anti-tumor agents are natural compounds, such as paclitaxel, doxorubicin (Dox), and hydroxycamptothecine. These compounds have significantly improved the quality of life of millions of patients with cancer[17].

According to Traditional Chinese Oncology, tumor occurrence is associated with the strength of "vital energy" in the human body, individual physical characteristics, and mental state. In modern medicine, this is closely related to enhanced immunity, which coincides with immunotherapies targeting the immune system. The THM theory has led to the discovery of numerous phytochemicals with anticancer effects and the establishment of combination regimens. The selection of relevant compounds is based on the following six treatment principles: 1) clearing heat and detoxification; 2) promoting blood circulation and transforming addiction; 3) eliminating diseases and dispersing knots; 4) using poison to combat toxins; 5) warming meridians and eliminating accumulation; and 6) strengthening the body and eliminating deficiencies. Examples of plants from which immunity-related compounds have been isolated include *Panax ginseng*, *Poria cocos*, *Rabdasia rubescens*, *Pulsatilla chinensis* (Bunge) Regel, *Glycyrrhiza uralensis* Fisch., and *Radix Inulae racemosae* (Table 1)[45,46,157].

Modern studies have shown that herbs or natural products derived from herbs have an inhibitory effect on the proliferation and metastasis of tumor cells and can interfere with tumor progression by regulating the immune system. However, many polymers are hydrophobic or unstable because of their structure (eg, polycyclic or polyconjugated) and special functional characteristics. These compounds are characterized by poor membrane permeability, low bioavailability, and limited distribution. High doses must be repeatedly administered to achieve therapeutic effects. Consequently, the toxicity associated with high-dose therapy negatively affects patient adherence to treatment regimens[47]. The construction of a natural compound nanotechnology delivery platform can compensate for the limitations of natural compounds in drug formation and delivery, particularly in improving the efficacy of the agents[48]. Nanomedicines designed for THMs provide a better understanding of immunomodulatory mechanisms at each cancer stage[49].

This review aimed to highlight the critical role of natural compounds in cancer immunotherapy (Figure 1) and to provide strategies by which natural products can serve as highly effective and safe cancer immunomodulators.

Regulation of the innate immune system

Innate immunity developed early in human evolution to protect against foreign pathogens and tumor cells. Natural immune cells such as macrophages deliver cytotoxic molecules and perform phagocytosis, thereby inhibiting or killing tumor cells. Dendritic cells (DCs) present antigenic peptides *via* major histocompatibility complex (MHC) molecules to induce naive T cell activation and differentiation to initiate the adaptive immune system. Natural killer (NK) cells selectively recognize and kill tumor cells, and recent studies have shown that NK cells are potential targets for cancer therapy[158]. These cells, which directly or indirectly kill tumor cells through some mechanisms, are called "tumor opponent cells". The cells that have a positive effect on the spread or metastasis of tumor cells are called "tumor accomplice cells".

Table 1

Regulatory effects of the active components of THM on immune cells in different types of cancer

Structure classification	Active components	Herbs	Cancer types or cell lines	Macrophages	MDSCs	NK cells	DCs	CD4+ cells	CD8+ cells	Treg cells	B cells	References
Phenols	Salidroside	Rhodiola rosea	Human breast cancer	Increase of macrophage colony stimulating factor		Increase in the number of NK cells			Increase in the number of $CD8^+$ T cells			[18,19]
	Resveratrol	Veratrum grandiflorum	Lung cancer	Inhibition of M2-like polarization of TAM					Inhibition of PI3K pathway and activation of $CD8^+$ Cytotoxic T cell activity			[20]
			HCC			Activation of NK cells			Regulation of naive $CD8^+$ T cell proliferation	Suppression of Treg cells		[21–23]
	Gastrodin	Gastrodia elata blume	Liver ascites tumor	Stimulation of polarization of M2-like macrophages				Promotion of the immunomodulatory activity of $CD4^+$ T cells	Promotion of the proliferation of $CD8^+$ T cells			[24,25]
	Ferulic acid	Monocotyledons	Lung cancer									[26]
	Curcumin	Turmeric	CRC		Suppression of MDSCs proliferation							[27]
			Pancreatic cancer			Enhancement of NK cytotoxicity	Modulation of bone marrow-derived DC to express ALDH1A1 and IL-10	Regulation of naive $CD4^+$ T cell differentiation				[28,29]
	Echinacea polyphenols	Echinacea	Leukemia	Promotion of the polarization of M1 macrophages		Promotion of the activity of NK cells	Upregulation of MHC-II and Th1 $CD4^+$ T cells					[30–32]
Polysaccharides	Ganoderma polysaccharides	G. lucidum, G. sinense	S-180, CRC	Inhibition of macrophage infiltration		Increase in the number and killing activity of NK cells					Increase in the expression of B cells	[33]

(*Continued*)

Table 1
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Structure classification	Active components	Herbs	Cancer types or cell lines	Macrophages	MDSCs	NK cells	DCs	CD4⁺ cells	CD8⁺ cells	Treg cells	B cells	References
			Lung cancer		Regulation of the differentiation and inhibition of MDSCs			Increase in the percentage of $CD4^+$ T cells	Increase in the percentage of $CD8^+$ T cells			[34]
	Miltiorrhizae polysaccharides	Salvia miltiorrhiza	Gastric cancer			Promotion of the function of NK cells		Excitation of cytotoxic T lymphocytes				[35]
	Astragalus polysaccharides	Radix astragali mongolici	Glioblastoma	Excitation of macrophage from the M2 to the M1 phenotype				Stimulation of $CD4^+$ T cell infiltration	Stimulation of $CD8^+$ T cell infiltration			[36]
			Breast cancer	Activation of macrophages to release NO and TNF-α	Reduction of MDSCs proliferation							[37]
	Radix glycyrrhiza polysaccharides	Licorice	Liver cancer				Promotion of the maturation of bone marrow-derived DCs	Reduction of the proportion of Treg cells; increase in the ratio of Th1/Th2 cytokines		Reduction in the number of Treg cells		[38]
Triterpenes and their glycosides	Astragaloside IV	Astragali radix	Lung cancer	Inhibition of IL-13 and IL-4-induced M2 polarization of macrophages								[39,40]
			RAW264.7	Improvement of macrophage phagocytic function		Enhancement of the cytotoxicity of NK cells					Enhancement of the ability of B cells	[41]
			Human uterine leiomyomas, lung cancer	Regulation of macrophage polarization						Inhibition of Treg cells activation by inhibiting IDO1 expression		[39–42]

(*Continued*)

Table 1
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Structure classification	Active components	Herbs	Cancer types or cell lines	Macrophages	MDSCs	NK cells	DCs	CD4⁺ cells	CD8⁺ cells	Treg cells	B cells	References
	Anemoside A3	Pulsatilla chinensis	Breast cancer	Increase of the typical M1 macrophage pro-inflammatory cytokines TNF-α, and IL-12 expression			Downregulation of the expression of certain Th1 and Th17 cytokines in activated T cells stimulated by MOG					[43–44]
	Anemoside B4		HCC					Increase in the percentage of $CD4^+$ cells	Increase in the percentage of $CD8^+$ cells			[45–50]
	Pulsatilla saponin D	Pulsatilla koreana	Pancreatic cancer									[51]
	Ginsenoside F1	Panax ginseng	Gastric cancer			Promotion of the cytotoxic activity of NK cells						[52]
	Ginsenoside Rg3		Colon cancer, B16F10	Increase of the M2 phenotype			Induction of the activation of DC function					[53–55]
			Glioma		Reduction of MDSCs			Enlargement of the T cell population; promotion of T-cell immune response		Reduction of Treg cells		[56]
	Ginsenoside Rh2		Breast cancer			Enhancement of the cytotoxicity of NK cells						[57]
			Pancreatic cancer			Enhancement of the cytotoxicity of NK cells	Upregulation of DC content and increase in tumor invasion by DCs					[58,59]
			NSCLC	Modulation of the crosstalk between TAMs								[60]
	Cucurbitacin B	Cucurbitaceae plants	NSCLC				Enhancement of DC cell anti-tumor activity					[61,62]

(*Continued*)

Table 1
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Structure classification	Active components	Herbs	Cancer types or cell lines	Macrophages	MDSCs	NK cells	DCs	$CD4^+$ cells	$CD8^+$ cells	Treg cells	B cells	References
			CRC	Control of M2 macrophage polarization			Promotion of DC differentiation	Promotion of $CD4^+$ T cells expression	Promotion of $CD8^+$cells expression			[63,64]
	Achyranthes bidentata polysaccharides	Achyranthes bidentata blume	SW480 cells				Promotion of DCs and DCs-CIK cells					[65]
			S-180 sarcoma cells	Enhancement of the cytotoxicity macrophages		Improvement of the activity of NK cells		Increase in the percentage of $CD4^+$ T cells	Increase in the percentage of $CD8^+$ T cells			[66]
	Lupeol	Edible fruits and vegetables	CRC, BGC823, N87, HGC27			Promotion of proliferation; enhancement of the killing effect of NK cells						[67,68]
	Saikosaponin	Radix bupleuri	Breast cancer					Regulation of Th1/ Th2 balance				[69]
			Liver cancer	Improvement of the spread of macrophages and activity of acid phosphatase				Stimulation of T lymphocytes to play a role in immune regulation			Stimulation of B lymphocytes	[70,71]
	Oridonin	Rabdosia rubescens	4T1 cells	Reduction of macrophage infiltration					Promotion of the action of $CD8^+$ T cells	Mitigation of the immunosuppressive ability of Treg cells	Inhibition of BAFF	[72–74]
			Lung cancer			Enhancement of the cytotoxic activity of NK cells						[75,76]
	Ursolic acid	Vegetables and fruits	CRC	Enhancement of macrophage autophagy	Decrease in the number of myeloid suppressor cells					Decrease in the number of Treg cells	Inhibition of B cell differentiation	[77,78]

(*Continued*)

Table 1
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Structure classification	Active components	Herbs	Cancer types or cell lines	Macrophages	MDSCs	NK cells	DCs	CD4+ cells	CD8+ cells	Treg cells	B cells	References
	Asiatic acid	Centella asiatica	Breast cancer; MCF-7 cells			Promotion of NK cells differentiation, maturation, and cytotoxicity against cancer					Activation of B cells transcriptional pathways by indirect nuclear factors	[79,80]
	Paclitaxel	Taxus wallichiana var. chinensis	Non-small cell carcinoma	Guiding of TAMs toward an M1-like anti-tumor phenotype					Promotion of TLR4 and CD8+ T cells			[81–83]
			Human breast cancer	Repolarization of original tumor M2 macrophages into the M1 phenotype	Inhibition of MDSCs							[84,85]
			Mouse renal cell carcinoma					Increase in CD4+ T cells	Improvement of the anti-tumor CD8+ T cells response	Decrease in the number and function of Treg cells		[86]
	Triptolide	Tripterygium wilfordii hook	Colon cancer, glioma	Decrease of tumor-associated macrophages infiltration and M2 polarization			Enhances the phagocytic capacity of DCs	Reversal of T helper cells inhibition				[87,88]
			Human epithelial ovarian cancer			Increase of NK cell-related protein levels in CD16 and CD56						[89]
			Glioma				Induction of differentiation of splenic DCs to CD11c(low) DCs	Reversal of CD4+ T cells inhibition caused by glioma cells				[90,91]

(*Continued*)

Table 1
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Structure classification	Active components	Herbs	Cancer types or cell lines	Macrophages	MDSCs	NK cells	DCs	CD4+ cells	CD8+ cells	Treg cells	B cells	References
	Dihydroartemisinin (DHA)	Artemisinin	Neck squamous cell	Inhibition of M2 macrophage polarization						Control the number of Tregs	Upregulation of apoptosis-related genes leading to a decrease in circulating plasma cells	[58–92]
			Pancreatic cancer	Reduction of the expansion of M2	Decreased the expansion of MDSCs	Increase in the population of NK cells			Increase in the population of $CD8^+$ T cells			[93]
			CRC	Reversal of macrophage infiltration								[94]
	Andrographolide	Andrographis paniculata	Breast cancer	Inhibition of M2-like polarization and enhancement of M1-like polarization in macrophages				Increased the infiltration and function of $CD4^+$ T cells	Enhancement of the function of $CD8^+$ T cells			[95,96]
			MCF-7, K562 cells			Promotion of NK cell proliferation		Stimulation of the production of cytotoxic T lymphocytes				[97,98]
	β-Elemene	Turmeric	Esophageal cancer, lung cancer	Regulation of the polarization of macrophages from M2 to M1			Increase in the number of mature DCs	Increase in the number $CD4^+$ T cells	Increase in the number of $CD8^+$ T lymphocytes and mature DCs			[99,100]
	Pseudolaric acid B	Pseudolarix	Glioma	Inhibition of the phenotypic polarization of macrophage M7						Regulation of the balance of Th1/Th17/Treg cell subsets		[101]
Phenylpropanoids	Esculetin	Fraxinus rhynchophylla hance	LM8 cells	Inhibition of M2 macrophage differentiation and/or G1 arrest in tumor cells								[102,103]

(*Continued*)

Table 1
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Structure classification	Active components	Herbs	Cancer types or cell lines	Macrophages	MDSCs	NK cells	DCs	CD4⁺ cells	CD8⁺ cells	Treg cells	B cells	References
	Silibinin	Silybum marianum	Lung cancer	Reduced infiltration of macrophage-associated cells	Reduction in MDSCs quantity							[104]
			Prostate cancer			Enhancement of the activity of NK cells		Stimulation of cytotoxic T cells				[105]
	Chlorogenic acid	Folium cortex eucommiae	MDA-MB-231, MDA-MB-453 and 4T1 cells					Activate CD4⁺ T lymphocytes by suppressing TLR 4 signal molecules				[106]
	Osthole	Cnidium monnieri	HCC, breast cancer	Promotion of the polarization of M1 macrophages				Promotion of the activation of tumor-infiltrating CD4⁺ T cells	Increase in the proportion and number of spleen CD8⁺ T cells			[107–109]
Quinones	Shikonin	Lithospermum	Colon cancer cells		Decrease of MDSCs		Promotion of DC cells maturation		Enhancement of the cytotoxic effect CD8⁺ T cells			[110,111]
			Melanoma									[112]
	Emodin	Rheum palmatum	4T1, EO771 cells	Inhibition of recruitment and M2 polarization						Regulation of Treg cells production		[113]
			Breast cancer, HCC	Inhibition of the EMT of breast cancer cells induced by macrophages		Increase of NK cell-mediated cancer cell killing power						[96–114]
Flavonoids	Delicaflavone	Selaginella doederleinii	Breast cancer	Increase of M1 phenotype TAMs (M1-TAMs); decreased M2 phenotype TAMs (M2-TAMs)	Decrease of monocytic-MDSCs					Decrease of Treg cells		[115]
	Luteolin	Flowers,herbs, vegetables and spices	Breast cancer	Reduction of JNK expression in macrophages		Enhancement of the activity of NK cells		Boosted the function of CD4⁺ T cells	Enhanced the function of CD8⁺ T cells			[116,117]

(*Continued*)

Table 1
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Structure classification	Active components	Herbs	Cancer types or cell lines	Macrophages	MDSCs	NK cells	DCs	CD4⁺ cells	CD8⁺ cells	Treg cells	B cells	References
			Prostate cancer, lung cancer	Reduction of the expression of M2-related genes						Inhibition of the differentiation of Treg cells		[105–118]
	Isoliquiritigenin	Licorice	CRC	Downregulation of PGE2 and IL-2 blockage of M6 macrophage polarization						Enhancement of immune suppression of Treg cells		[119,120]
			Pancreatic cancer, mouse ascites tumor			Inhibition of GSK-65 in NK cells						[121,122]
	Baohuoside I	Epimedium koreanum nakai	Breast cancer	Inhibition of M2 phenotypic polarization		Enhancement of the dynamism of NK cells				Regulation of Th17/ Treg cell balance	Inhibition of B-cell proliferation	[123,124]
	Quercetin	Flowers, vegetables	MCF-7				Reduction of DCs adhesion		Increase in the number of CD8⁺ T cells			[125–127]
			CRC	Regulation of M1/M2 macrophage polarization and oxidation/anti-oxidant balance	Significant reduction in the number of MDSCs	Increase the number of NK cells	Increase of costimulatory signals (MHC class II and CD86) on dendritic cells					[46]
	Gambogic acid	Garcinia hanburyi tree	Large B cell lymphoma, mouse hepatocarcinoma cells	Inhibition of LPS-induced pro-inflammatory cytokine production in macrophages				Activation of CD4⁺ T cell lymphocytes			Promotion of apoptosis of activated B-cell-like DLBCL	[128–130]
	Puerarin	Pueraria lobata	Cervical cancer, NSCLC	Inhibition of macrophage polarization to the M2 phenotype								[77–132]
	Epigallocatechin gallate (EGCG)	Green tea	CRC	Reduction and regulation of macrophage polarization				Increase in the proportion of CD4⁺ CD25⁺ regulatory T lymphocytes in spleen				[133–135]

(*Continued*)

Table 1
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Structure classification	Active components	Herbs	Cancer types or cell lines	Macrophages	MDSCs	NK cells	DCs	CD4⁺ cells	CD8⁺ cells	Treg cells	B cells	References
	Wogonin	Scutellaria baicalensis	Human malignant neuroblastoma	Regulation of the activation of macrophage surface markers				Enhancement of effector T cell function		Suppression of Treg cells		[136–138]
			Gastric cancer	Promotion of NK cell recruitment to tumor tissue	Promotion of DCs recruitment to tumor tissue		Promotion of T cells recruitment to tumor tissue					[139]
	Apigenin	Vegetables and fruits	Human breast cancer	Mediation of the polarization of macrophages		Stimulation of the proliferation and activation of NK cells			Stimulation of the proliferation and activation of CD8⁺ T cells lymphocytes			[140,141]
			Pancreatic cancer			Promotion of NK cells proliferation and enhancement of the cytotoxicity of NK cells				Elimination of Treg cells activity		[142,143]
Steroids	Periplocin	Periplocae cortex	Liver cancer		Reduction of MDSCs recruitment			Increase in the number of CD4⁺ T cells and the CD4⁺/CD8⁺ ratio				[144,145]
Alkaloids	Matrine	Sophora	Acute lymphoblastic leukemia			Enhancement of NK cells toxicity					Promotion of the apoptosis of B cells	[146,147]
			Lung cancer	Inhibition of EMT induced by M2-like macrophages				Promotion of CD4⁺ T cells expression	Promotion of CD8⁺ T cells expression			[148]
	Berberine	Coptis chinensis franch	Ovarian cancer, breast cancer	Increase in the content of M1-like macrophages		Increase in the infiltration of NK cells				Regulation of the Treg/Th17 balance		[149,150]
			Melanoma cells	Increase in M1-like macrophages				Increase in CD4⁺ T cells				[151]

(*Continued*)

Table 1 (Continued)

Structure classification	Active components	Herbs	Cancer types or cell lines	Macrophages	MDSCs	NK cells	DCs	$CD4^+$ cells	$CD8^+$ cells	Treg cells	B cells	References
			DLBCL	Enhancement of the phagocytosis of macrophages								[152]
	Aconitine	Aconitum	Ovarian cancer, HCC	Elevation in the number of macrophages			Decrease in the expression of DC-STAMP	Increase in spleen $CD4^+$ T cells	Increase in $CD8^+$ T cells in the mouse spleen			[153–155]
	Chelerythrine	Toddalia asiatica	Dalton lymphoma, melanoma			Activation of NK cells	Prevention of the transformation of naive $CD4^+$ T cells					[145–156]

4T1: Mouse breast cancer cells; ALDH1A1: Aldehyde dehydrogenase 1A1; B cells: B lymphocytes; BGC823/N87: Human gastric cancer cells; B16F10: Mouse cutaneous melanoma cells; CD4+/8+/16: Cluster of differentiation 4+/8+/16; CD56: Nerve cell adhesion molecule 1; CD86: Cluster of differentiation 86; CRC: Colorectal cancer; DCs: Dendritic cells; DCs-CIK: Dendritic cells-cytokine induced killers; DC-STAMP: Dendritic cell-specific transmembrane protein; DLBCL: Diffuse large B-cell lymphoma; EMT: Epithelial–mesenchymal transition; GSK-65: Glycogen synthase kinase; HCC: Hepatocellular carcinoma; HGC27: Human gastric cancer cells, undifferentiated; IDO: Indoleamine 2,3-dioxygenase; IL-12/13/14: Interleukin-12/13/14; K562: Human chronic myelogenic leukemia cells; LPS: Lipopolysaccharide; MCF-7: Michigan cancer foundation-7; MDSCs: Myeloid-derived suppressor cell; MHC-II: Major histocompatibility complex II; MOG: Mixed of Gaussian function; NFATc2: Nuclear factor of activated T cells 2; NK cells: Natural killer cells; NO: Nitrous oxide; NSCLC: Non-small cell lung carcinoma; PGE2: Prostaglandin E2; PI3K: Phosphatidyl inositol 3-kinase; RAW264.7: Mouse mononuclear macrophages cells; TAMs: Tumor-associated macrophages; Th1/2/17: T helper cell 1/2/17; TLR4: Toll-like receptor 4; TNF-α: Tumor necrosis factor alpha; Treg cells: Regulatory T cells.

Anti-tumor cells

NK cells

NK cells are a class of natural lymphocytes that rapidly recognize and clear infected cells. These cells are essential for immune surveillance and subsequent host defense against viral infections and cancer cells as part of the natural immune system[159]. NK cells account for 8% to 20% of the circulating lymphocytes in the human body. Numerous experimental and clinical studies have demonstrated the effectiveness of anti-tumor immunotherapy using NK cells[160].

NK cells play a crucial role in cancer cell metastasis and proliferation. They target differentiated tumor stem cells or undifferentiated tumor cells by secreting interferon-γ (IFN-γ) and membrane-binding tumor necrosis factor-α, thus reshaping the tumor microenvironment to inhibit tumor growth[161]. Several experimental and clinical studies have shown that immunotherapies based on NK cell functions and product expression reduce cancer-related mortality[162,163].

Studies have reported that, within a certain concentration range, lupeol improves the proliferation rate of NK cells. Moreover, at concentrations ranging from 50 to 200 μg/mL, it exerts inhibitory effects on gastric cancer cell lines BGC823, N87, and HGC27. When the concentration of lupeol reached 200 μg/mL, the inhibition rate of gastric cancer cell line BGC823 reached approximately 70% in 72 h in the treatment group compared with that in the control group. IFN-γ is mainly produced by the activation of T cells and NK cells and has antiviral, anti-tumor, and immunomodulatory functions[164], which can enhance the activity of NK cells[165]. Culturing with lupeol upregulated the expression of perforin (PFP), IFN-γ, and CD107a in NK cells, indicating greater damage to gastric cancer cells. NK cells co-cultured with lupeol exerted significant cytotoxic effects on differentiated gastric cancer cells. The mechanism underlying this effect may be related to the promotion of NK cell proliferation and upregulation of the expression of PFP, CD107a, and IFN-γ[68].

Ginsenosides are active components of ginseng. Ginsenosides have been widely studied as promising drug molecules for adjuvant cancer therapy because of their efficacy and safety. In addition, they have been shown to improve the efficacy of cancer chemotherapeutic drugs. Ginsenosides can act on and enhance the functioning of the immune system[166,167].

The de-sugar metabolite of G-Rg1 (G-F1) significantly enhances the functions of NK cells, such as cytotoxicity and IFN-γ production, thereby enhancing their negative effects on cancer cells. Moreover, G-F1 enhances the cytotoxicity of NK cells through various activating receptors (eg, immunoreceptor tyrosine-based activation motifs and non-immunoreceptor tyrosine-based activation motif-coupled receptors), thus enhancing their cytotoxic effects on various cancer cells expressing NK-activated receptors[52].

DCs

DCs are important antigen-presenting cells widely distributed in various tissues. They have dual functions in

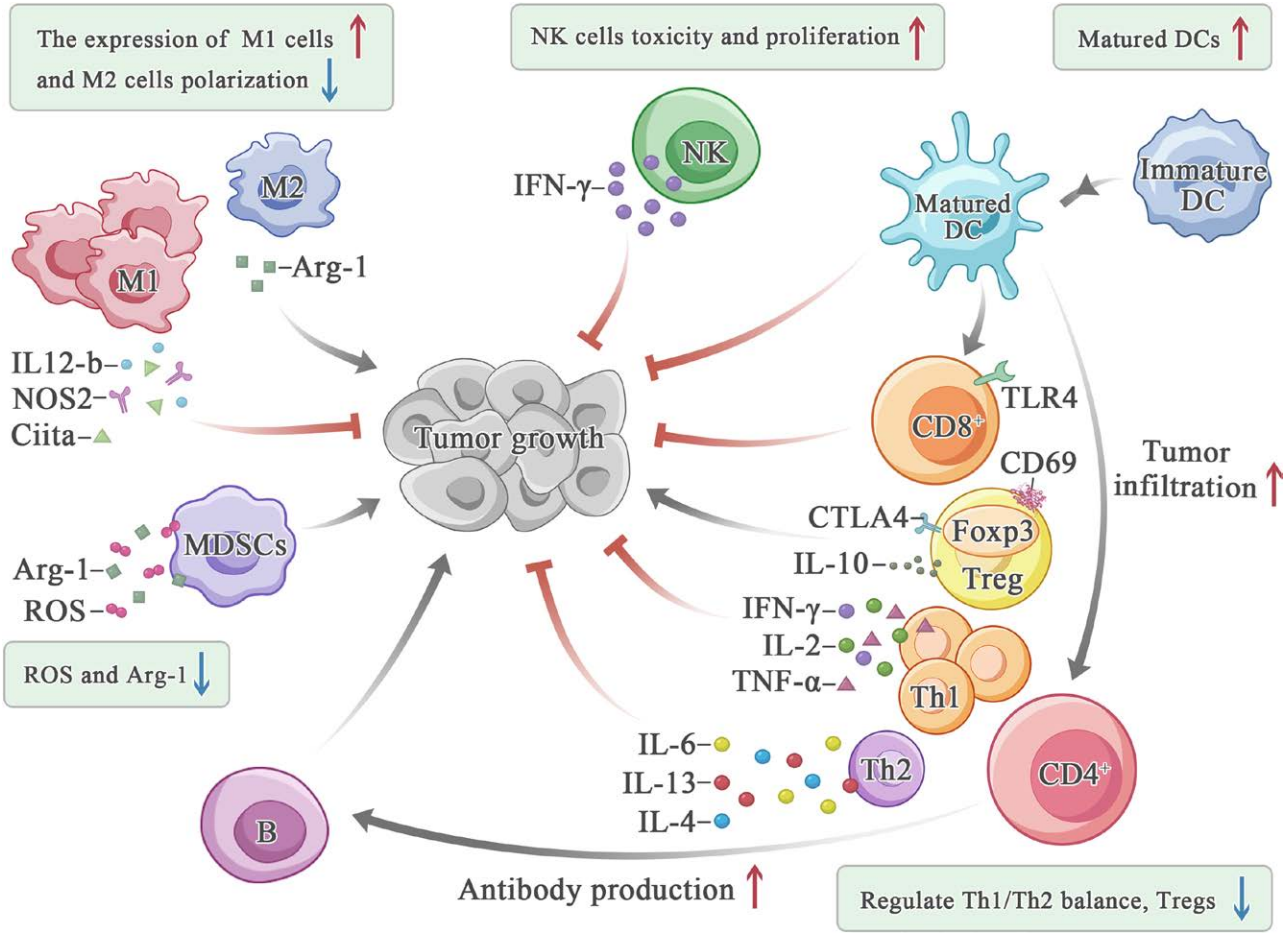

Figure 1. Immunotherapeutic mechanism of active THM components. Arg-1: Arginase-1; DC: Dendritic cell; IFN-γ: Interferon-γ; IL: Interleukin; NK: Natural killer; ROS: Reactive oxygen species; Th: T helper cell; THM: Traditional herbal medicine; TLR4: Toll-like receptor 4; TNF-α: tumor necrosis factor-alpha.

antigen presentation and immune regulation and play a crucial role in inducing immune responses against exogenous and endogenous pathogenic microorganisms and anti-tumor immune responses[168].

There are two main types of DCs, transtypic and non-transtypic, with different forms and functions. Following the detection of invasion by a foreign pathogen, DCs use antigen-presenting molecules on their surface (eg, MHC-II) to bind and present microbe-specific antigens to T cells, thereby activating the immune system[169].

In addition, DCs exhibit immune surveillance and tumor clearance abilities. Through their special antigen-presenting and immunomodulatory functions, DCs can transmit antigen-mediated information on the surface of tumor cells to specific immune cells, thereby activating the immune system and playing an anti-tumor role. Furthermore, DCs can regulate immune IFN production and cytokine expression, as well as the function of T cells as sensitive cells, and provide this information to other cells[170]. Therefore, they have a profound significance in the prevention and treatment of various pathogens, cancers, and other diseases.

Astragalus membranaceus (Huang Qi), a herbal medicine commonly used in clinical practice, is mainly derived from the roots of *Astragalus* leguminous plants such as *Astragalus*, Sichuan *Astragalus*, and Rye *Astragalus*. In recent years, many studies have found that polysaccharides, saponins, amino acids, and other active ingredients in *Astragalus* exhibit various immunomodulatory and anti-tumor effects. In particular, highly enriched *Astragalus* polysaccharides kill tumor cells by regulating immune function.

DCs treated with *Astragalus* and *Codonopsis* polysaccharides promote the proliferation of $CD4^+$ and $CD8^+$ T cells in mice. Moreover, a mouse 4T1 breast cancer vaccine prepared using DCs effectively enhanced anticancer effects against metastatic cancer in mice[61]. In addition, the expression levels of CD40, CD80, CD86, and other immune molecules on the surface of DCs significantly increased following treatment with *Astragalus* and *Codonopsis* polysaccharides, thereby enhancing the immune-stimulatory function of DCs. These findings suggest that *Astragalus* and *Codonopsis* are potential immunomodulators for cancer therapy. *Astragalus* polysaccharide induced the differentiation of splenic DCs into CD11chigh and CD45RBow DCs and the transformation of T helper type 2 (Th2) cells into Th1 cells. These effects enhance the immune functions of T lymphocytes[171].

Therapy with tumor lysate-pulsed recombinant interleukin (IL)-15-activated DCs and cucurbitacin I significantly prolonged the survival of tumor-bearing mice. Additional treatment of vaccinated mice with recombinant IL-15 significantly improved therapeutic efficacy and provided a lifelong cure without recurrence. DCs

from surviving vaccinated mice restored their anti-tumor potential against lymphoma cells in terms of growth inhibition and cytotoxicity[172].

It has been reported that the combination of B16 tumor cell lysate and alkannin can activate DCs to a highly mature state. This leads to high expression levels of CD86 and MHC-II on the surface of DCs, thereby activating Th1 cells and enhancing their function. A DC vaccine supported by alkannin and tumor cell lysate strongly induced cytotoxicity against tumor cells in spleen cells, delayed tumor growth, and improved the survival rate of experimental mice[173].

Tumor-supporting cells

Myeloid-derived suppressor cells (MDSCs)

MDSCs are produced by the bone marrow of tumor-carrying hosts. Subsequently, they are recruited to peripheral lymphatic organs and tumors to participate in the formation of the tumor microenvironment. MDSCs inhibit tumor development and metastasis[84]. They can be divided into two subgroups: monocytes and neutrophils[174,175].

In the lung cancer microenvironment, MDSCs are associated with poor prognosis and negative effects of chemotherapy and immunotherapy[176]. As an important group of regulatory immune cells in the tumor microenvironment, MDSCs play a key role in promoting the growth and metastasis of cancer cells and weakening the effects of MDSCs unrelated to anticancer immunotherapy. This suggests that MDSCs serve as indicators of tumor progression and are targets for cancer immunotherapy[177].

Curcumin (Cur), a compound extracted from turmeric roots, is used to prevent and treat various human diseases. It has been demonstrated that Cur exerts anti-infective, anti-oxidant, anti-thrombotic, anti-inflammatory, and other effects[178,179]. In recent years, Cur has been shown to inhibit the growth of various tumor cells[180].

Cur treatment significantly inhibits MDSC expansion in tumor-bearing mice. Moreover, the volume and absolute number of tumors in the spleen tissue of Cur-treated mice were significantly lower than those in the control group. For example, the average tumor volume in mice treated with Cur for 23 days was 1,000 $mm^{3,}$ smaller than that observed in the control group. In addition, Cur treatment reduced the positive correlation between the frequency and absolute number of MDCSs and the tumor load. Cur inhibits the activity of MDSCs in tumor-bearing mice by downregulating the expression of arginase-1 (Arg-1) (an important factor for MDSC activation) and reducing reactive oxygen species (ROS)[181].

Macrophages (M2)

Macrophages are commonly found at the growth sites of solid tumors, and a large body of evidence has shown that tumor-associated macrophages (TAMs) play an important role in tumor angiogenesis and metastasis[182]. Macrophages can be classified into classically activated macrophages (M1) and replacement-activated macrophages (M2) based on their different immune microenvironments. The former type is dependent on IFN-γ and lipopolysaccharides, while the latter is activated by IL-4. M1 macrophages secrete nitric oxide synthase 2, a class II MHC transactivator (Ciita), and IL-12b, whereas M2 macrophages secrete Arg-1, chitinase-like 3, and resistin-like alpha[183].

In addition, studies have shown that macrophages continuously secrete cytokines during wound site healing and that exposure to these cytokines leads to tumor cell proliferation. The formation of TAMs is closely related to the polarization of M2[184]. Various transcription factors are involved in M1/M2 polarization; specifically, signal transducer and activator of transcription (STAT)1, nuclear factor-κB, and IFN regulatory factor 5 are involved in M1 polarization, whereas STAT6, MYC, IFN regulatory factor 4, KLF transcription factor 4, and peroxisome proliferator-activated receptor γ regulate M2 polarization[185]. Macrophages with M2 phenotype occupy a dominant position in TAMs and play a key role in promoting tumor growth, invasion, and metastasis. Switching TAM polarization from M2 to M1 may trigger an anti-tumor-specific immune response and inhibit tumor metastasis[186]. Enhancing the expression of M1 macrophages and inhibiting M2-type macrophages have become important anti-tumor strategies.

Numerous studies have shown that herbs can inhibit the growth, invasion, and metastasis of tumor cells by regulating M1/M2 macrophages[48]. Emodin is an anthraquinone derivative isolated from several herbs, including rhubarb and knotweed. Transforming growth factor-β (TGF-β) is the dominant factor in the process of epithelial-mesenchymal transformation (EMT), and rheum emodin blocks the EMT of TGF-β1-induced breast cancer cells in macrophages and cancer cells. In one study, primary macrophages isolated from mice were pretreated with tumor cell-conditioned medium (TCCM) to generate TAM-like macrophages. Macrophages have been used to treat breast cancer cells. By detecting EMT, emodin was found to significantly reduce N-cadherin expression. The expression of fibroin and basic metalloproteinases (MMPs) was reduced (ie, the expression of N-cadherin, vimentin, MMP2, and MMP9 decreased by 50%, 50%, 80%, and 33%, respectively). In addition, the expression of CD206 in macrophages treated with TCCM reached 300 pg/mL and decreased to 100 pg/mL after emodin treatment. Moreover, TGF-β1 production and TGF-β1-induced Arg-1 expression were inhibited in macrophages treated with TCCM[96]. Some studies have found that the expression of Arg-1 is directly related to the immunosuppressive ability of TAMs[187].

Triptolide is a bioactive compound extracted from *Tripterygium wilfordii* (Leigong Teng). Triptolide treatment of colon cancer cells inhibited macrophage infiltration and polarization of M2 cells[87]. In one study, Raw264.7 cells (a mouse macrophage cell line) were inoculated with fresh complete medium obtained from a mouse colon cancer cell line (CT26). The cells were treated with different concentrations of triptolide in complete medium for 24 h. The results showed that the chemotaxis of Raw264.7 cells was inhibited in a dose-dependent manner. Compared with the blank group, the LU values of treated Raw264.7 cells treated with triptolide at concentrations of 20, 40, and 80 nM were reduced by 50,000, 75,000, and 100,000 units, respectively. Additionally, anti-inflammatory M2 macrophages were co-cultured with CT26 cells treated with

different concentrations of triptolide (20, 40, and 80 nM) for 48 hours. Analysis of mRNA expression showed that the expression of anti-inflammatory M2 macrophage-related markers (Arg-1, CD206, and IL-10) was significantly inhibited. Specifically, Arg-1 expression decreased by 30%, 40%, and 60%, CD206 expression decreased by 50%, 60%, and 75%, and IL-10 expression decreased by 40%, 50%, and 55%, respectively, compared with the control group. These data suggest that triptolide can reshape the colon cancer microenvironment and delay macrophage infiltration and polarization[87].

Regulation of the adaptive immune system

The innate immune system is a key mechanism for the rapid detection and elimination of pathogens. Adaptive immunity has evolved to provide broader and more refined recognition of self- and non-self-antigens[188]. Adaptive immune responses mediated by T and B cells play an important role in protective immunity against pathogens and tumors[189]. In addition, several studies have shown that the active ingredients of THM play anti-tumor roles by regulating T cell subgroup differentiation and cytokine secretion[35,38,190].

Anti-tumor cells

CD4⁺ cells

CD4⁺ T cells can differentiate into the following functional subsets: Th1, Th2, Th17, Th9 cells, T follicular helper cells, and regulatory T (Treg) cells. Th1 cells primarily secrete cytokines (eg, IFN-γ, tumor necrosis factor-αα, and IL-2) and help produce cytotoxic T lymphocytes, thus playing an important role in anti-tumor immunity. Th2 cells participate in humoral immunity by secreting cytokines (eg, IL-4, IL-6, and IL-13) and assisting B lymphocytes in producing specific antibodies. Th1/Th2 balance plays an important role in maintaining homeostasis. Th17 cells produce IL-17 and IL-22, which are involved in the development of autoimmune diseases. In various malignancies, such as acute lymphoblastic leukemia and multiple osteomas, the number of Th1 cells is significantly reduced, whereas that of Th2 cells is increased[191]. According to clinical data, patients with cancer suffer from a Th1/Th2 imbalance characterized by an increased release of cytokines by Th2 cells. Th1-led responses in patients are associated with higher survival and lower cancer recurrence rates. Therefore, developing new treatment strategies to alter the Th1/Th2 balance may help control cancer[192].

Studies have shown that resveratrol stimulates the polarization of CD4⁺ T cells and macrophages in cancer cells and reduces the infiltration and polarization of immunosuppressive cells. Additionally, it can sensitize cancer cells to death signals released by anticancer immune cells[193].

Saikosaponin A (SSa) is isolated from the dried roots of calamus, an herb with high anti-tumor activity. In one study, the tumor volume was significantly reduced in tumor-bearing rats treated with SSa. The investigators concluded that SSa significantly inhibited tumor growth and proliferation. SSa enhances anti-tumor immunity by increasing the number of infiltrating CD4⁺ and CD8⁺ T cells in the tumor. SSa transfers the Th2/Th1 balance to Th1, thereby elevating the serum levels of IFN-γ and IL-4 while decreasing those of IL-10 and IL-12. SSa increases the expression of IL-12 and IL-4 receptors and phosphorylates STAT1 to promote Th1 differentiation. In summary, SSa can inhibit breast cancer growth by shifting the Th2/Th1 balance toward Th1[69].

Oridonin is a natural terpenoid found in *Rabdosia rubescens*[194]. Recently, advances have been made in exploring the pharmacological effects of oridonin (eg, anti-inflammatory[195], anticancer[196], antibacterial, and antiseptic effects). A previous study revealed that oridonin reduces lung metastasis in the breast cancer cell line 4T1[72]. In addition, a reduction in Tregs and an increase in IFN-γ⁺CD8⁺ T cells were observed in the lung tumor-infiltrating lymphocytes of mice injected with oridonin. These results indicated that oridonin exerts its anti-tumor activity by targeting T cells. Previous studies have demonstrated that Tregs have powerful immunosuppressive functions and express many inhibitory molecules, such as cytotoxic T-lymphocyte-associated protein 4 and CD69[197,198]. In addition, Tregs also exert their immunosuppressive effects by producing cytokines TGF-β1 and IL-10. Oridonin inhibits the expression of cytotoxic T-lymphocyte-associated protein 4 and CD69 and affects the immunosuppressive ability of Tregs. It also reduces the secretion of TGF-β1 and IL-10. Furthermore, oridonin inhibits Treg differentiation by reducing the levels of TGF-β receptor protein. In conclusion, oridonin limits the immunosuppressive ability of Tregs and plays an anti-tumor role. In addition, the combination of oridonin and an anti-programmed cell death 1 (PD-1) vaccine exerts a better effect on tumor regression in breast cancer than monotherapy with oridonin or anti-PD-1[72].

Gastrodin, derived from the herb *Gastrodia*, is used to treat stroke, convulsions, dizziness, headache, and numbness of the extremities. As a key subgroup of immune cells mediating anti-tumor immune defense, stabilization of the number of CD4⁺ T cells against tumor cells plays a positive role in cancer. CD4⁺ T cells target tumor cells through various pathways[199]. However, it has been shown that cancer cells are able to induce CD4⁺ T cell apoptosis, which contributes to immune escape during tumor progression[200]. Gastrodin enhances the lytic activity of CD8⁺ T cells in H22 liver cancer cells. The percentage of CD4⁺ T cells in the lymph nodes and spleen decreased after H22 liver tumor cell transplantation compared with that in the control group. In addition, administration of gastrodin mitigated the H22 tumor cell transplant-induced reduction in CD4⁺ T cells in a dose-dependent manner, suggesting that gastrodin ameliorated tumor-induced immune deficiency. Similarly, after transplantation of H22 tumor cells, the serum levels of Th1 cytokines, including IFN-γ and IL-2, were downregulated; in contrast, the representative Th2 cytokine IL-4 levels were upregulated. The cytotoxic activities of CD8⁺ T and NK cells against H22 cells were also impaired. Following the administration of gastrodin, the serum levels of IFN-γ and IL-2 increased, whereas those of IL-4 decreased. Gastrodin treatment consistently increased the cytotoxic activity of NK and CD8⁺ T cells against H22 cells. These events salvage the systemic immunosuppressive environment induced by

tumor transplantation and stimulate the host anticancer immune response, which is closely related to the *in vivo* anticancer activity of gastrodin[24].

CD8⁺ T cells

CD8⁺ T cells, also known as cytotoxic or killer T cells, play a key role in the immune response against viruses, bacteria, and other harmful cells. These cells are important for long-term immunity because they can remember previous contacts with infectious agents and thus respond more rapidly and effectively to subsequent infections. CD8⁺ T cells play a key role in eliminating intracellular infections and malignant cells and provide long-term protective immunity[201].

An increase in the number of peripheral and infiltrating CD8⁺ T lymphocytes is beneficial for tumor therapy[202]. Infiltration of CD8⁺ T cells into the tumor area is a strong predictor of good prognosis, and its density has prognostic value[203]. However, CD8⁺ T lymphocytes are very sensitive to genotoxic treatments such as radiation and traditional chemotherapy drugs[204]. Increased ROS production and the induction of DNA damage can lead to the apoptosis of CD8⁺ T lymphocytes. A reduction in peripheral blood and infiltrating CD8⁺ T lymphocytes leads to a low response to treatment and high mortality in patients with cancer[205,206]. The release of damage-associated molecular patterns after immune cell death can induce CD8⁺ T lymphocyte activity. CD8⁺ T lymphocytes detect damage-associated molecular patterns *via* several receptors, specifically Toll-like receptors (TLRs)[207].

Studies have shown that the treatment of ovarian cancer cells with paclitaxel induces immune cell death and TLR4 upregulation[81]. Additionally, paclitaxel may enhance the anticancer effects of other drugs by stimulating immune cell death. Another clinical study confirmed that the use of paclitaxel to treat patients with non-small cell lung cancer increases the number of peripheral CD8⁺ T lymphocytes[82]. Clinical evaluations have shown that increased infiltration of CD8⁺ T lymphocytes after paclitaxel treatment and radiotherapy is associated with a better response and higher survival rates[208]. An increase in the number of infiltrating CD8⁺ T lymphocytes after paclitaxel treatment has also been observed in patients with cervical cancer[209]. Together, these results indicate that paclitaxel promotes the proliferation of CD8⁺ T lymphocytes by inducing immune cell death in tumors. In addition to the increased infiltration of CD8⁺ T lymphocytes into tumors, the study found that carboplatin/paclitaxel treatment modulates the function of CD8⁺ T lymphocytes in patients with ovarian cancer. The study showed that, although cancer cells inhibit the activity of CD8⁺ T lymphocytes, carboplatin/paclitaxel treatment can induce CD8⁺ T lymphocyte function and IFN-γ production[210].

B lymphocytes

B cells are the main immune cells that mediate fluid immunity. However, their role in tumor immunity remains unclear. Most investigations have focused on the role of T cell responses in anti-tumor immunity; however, research on the role of B cells in solid tumors is limited. The recent clinical success of cancer immune checkpoint blockade has highlighted the relationship between the quality of T cell, NK cell, and B cell responses in the tumor microenvironment. Recent studies have shown that B lymphocytes play a key role in immunotherapy[211]. Their presence improves the prognosis of different cancer types, including breast cancer, melanoma, renal cell carcinoma, colorectal cancer (CRC), hepatocellular carcinoma (HCC), and head and neck squamous cell carcinoma[212–215]. However, the tumor-promoting effects of B cells have been widely described[216–218].

Research has demonstrated that tumor-infiltrating B cells can also secrete IFN-γ and toxic cytokines, such as granzyme B, which can directly or indirectly kill tumor cells by promoting tumor-specific secretion of immune-stimulating cytokines by T cells[219].

Gambogic acid, a small molecule extracted from licorice, exhibits anti-tumor activity against a wide range of human cancer cells[220]. Studies have found that gambogic acid exerts growth inhibition and apoptosis effects on diffuse large B-cell lymphoma tumor cells[128]. Tanshinone-IIA is the major compound extracted from Danshen. It is involved in the anti-tumor activity against various types of cancers, such as colon cancer[221], malignant melanoma[222], lung cancer[223], and HCC[224]. Tanshinone-IIA was found to significantly induce cell proliferation by inducing G2/M phase arrest, promoting cell apoptosis by altering the balance of B-cell lymphoma 2/B-cell lymphoma 2-related X proteins, inhibiting cell migration by reducing the phosphorylation of focal adhesion kinase, and blocking the expression of vascular endothelial growth factor[225].

Tumor-supporting cells

Tregs are a subset of CD4⁺ T cells that regulate autoimmune responses and maintain immune homeostasis. Activated Tregs actively inhibit the immune function of T lymphocytes. The transcription factor forkhead box P3 (FOXP3) is essential for the Treg function[226]. It is closely related to Treg cell development, peripheral expression, and functional maintenance and is the main regulator of Treg cells[227,228]. Owing to their ability to inhibit their own antigen response, Tregs may hinder anti-tumor immune responses. A high ratio of Treg cells to CD8⁺ T cells in the tumor tissue indicates poor prognosis. An increase in FOXP3 expression in tumor tissues is strongly linked to better prognosis in CRC[229]. During tumor development, tumor cells and macrophages in the local tumor microenvironment secrete chemokines that recruit Tregs from peripheral blood into the tumor. This results in the evasion of the host immune system owing to the immunosuppressive function of Treg cells[230]. Experiments have shown that specific depletion or functional changes in Tregs can evoke effective tumor immunity. Moreover, *in vivo* treatment measures targeting Tregs are beneficial for anti-tumor immunity[231].

Herbal medicines can enhance anti-tumor immunity and inhibit the growth and metastasis of tumor cells by reducing the number and function of Treg cells and secreting immunosuppressive cytokines. *Astragalus membranaceus* (Huang Qi) is a leguminous plant. According to the Chinese Pharmacopoeia, the medicinal

part of *Astragalus membranaceus* (Huang Qi) is its dry root. *Astragalus* polysaccharides are important natural active ingredients in *Astragalus membranaceus* (Huang Qi). An increasing number of pharmacological studies have shown that *Astragalus* polysaccharides have various biological activities, such as regulation of blood sugar and blood lipid levels, anticancer and anti-aging effects, and immune regulation. Immune regulation is its most important activity[232]. Studies have shown that *Astragalus* polysaccharides can inhibit Treg proliferation in a dose- and time-dependent manner. This effect may be related to the restoration of cytokine balance and the reduction in FOXP3 expression in the HCC microenvironment[233].

In the microenvironment of human HCC, *Astragalus* polysaccharides (10–200 μg/mL) can inhibit the growth, proliferation, and migration of Treg cells by inhibiting the activation of the chemokine (C-X-C motif) receptor 4/C-X-C motif chemokine ligand signaling pathway, blocking chemokine matrix derived factor-1 and its receptors, and restoring the cytokine balance (ie, increase in IFN-γ expression and reduction of IL-4 and IL-10 expression)[234]. *Astragalus* polysaccharides can promote the proliferation of T and B lymphocytes, increase the secretion of related cytokines, inhibit the activity of Treg cells, improve immune suppression, and enhance tumor immunity[235].

Herbal nanomedicines for tumor immunotherapy

The active compounds described in the previous sections have demonstrated encouraging effects on tumor immunotherapy through different pathways. However, the clinical application of these effects is limited by biopharmaceutical constraints. The chemical stabilities and solubilities of compounds vary widely because of the differences in their molecular weights, functional groups, and polarities[236].

Nanomedicine has been developed to solve the problems associated with traditional therapies. Nanomedicine refers to pharmaceutical products inspired by nanotechnology and used for therapeutic, diagnostic, and palliative purposes[237]. The main types of nanomedicines include liposomes, nanocrystals, micelles, and nanoparticles (NPs)[238].

In recent years, NP-based delivery systems have shown considerable promise because of their ability to overcome critical challenges associated with conventional phytomedicine, including low solubility, low bioavailability, and drug resistance (Figure 2)[239].

Ideally, NPs should deliver the active compound alone or in combination with chemicals, genes, and other active compounds, taking advantage of the *in vivo* release, accumulation, and stability profiles of nanocarriers (Table 2). This process should eventually result in improving the immunotherapeutic effect in the body[251].

Lipid-based NPs

Liposomes, which are characterized by high biocompatibility, have been used as anticancer therapeutic carriers for many years to deliver hydrophilic and lipophilic drugs. Liposome-associated stability problems have been overcome by modulating the liposome size, surface charge, lipid composition, and surface functionalization. Conventional and new forms of liposomes, such as niosomes, are commonly used to deliver phytocompounds directly to cancer cells. Niosomes are preferred over conventional liposomes owing to their superior stability. Surface modification is a method for delivering bioactive compounds to specific locations and prolonging their circulation in the body[252]. Nanoliposomes modified with hyaluronic acid and glycyrrhetinic acid simultaneously delivered Cur to HCC and stellate cells. Nanoliposomes can inhibit tumor metastasis and alter the tumor microenvironment[240].

In a study, *Ganoderma lucidum* polysaccharides (GLP) and ovalbumin (OVA) were encapsulated in liposomes (GLPL/OVA) and administered to mice as vaccines. This approach showed a more potent ability to induce antigen-specific immune responses than the administration of single components. Mice immunized with GLPL/OVA exhibited higher levels of antigen-specific immunoglobulin G antibodies, better splenocyte proliferation, increased levels of cytokine production by splenocytes, and higher numbers of $CD3^+CD4^+$ and $CD3^+CD8^+$ T cells than other mice. GLPL may be an effective method for delivering vaccines to improve immune responses by enhancing DC activation and maturation in draining lymph nodes[253].

Researchers have successfully used liposomal NPs to deliver flavonoids in cancer treatments that target the tumor microenvironment. Accordingly, Sesarman et al.[254] observed enhanced anti-tumor effects in colon carcinoma after the co-encapsulation of Cur with Dox in long-circulating liposomes. This enhancement was largely due to the suppressive effect of long-circulating liposomes-Cur-Dox on tumor microenvironmental processes, specifically inflammation, oxidative stress, angiogenesis, and Th cell dysregulation[254].

Therefore, future cancer treatments using liposomal nanodrug delivery systems may employ multiple strategies. Li et al.[45] developed a targeted liposomal cyclic arginylglycylaspartic acid formulation for delivering programmed cell death ligand 1 (PD-L1) small interfering RNA (siRNA) with anemoside B4 (AB4) and AB4/siP-c-Land tested its anticancer effects in mouse models of LLC and 4T1. Co-delivery of siP and AB4 in AB4/siP-c-L caused silencing of the PD-L1 gene and altered the tumor-suppressive immune microenvironment, thereby increasing the immunological response against cancer and improving long-term memory. The combination of AB4 and PD-L1 siRNA into targeted nanovesicles has great potential for clinical applications and provides an excellent testbed for studying the effects of combining herbal monomers with different immunotherapies[45].

In a previous study, extracellular vesicle-like ginseng-derived NPs (GDNPs) were isolated and characterized from *Panax ginseng*. In mouse melanoma cells treated with GDNPs, phenotypic polarization from M2 to M1 and the production of total ROS were significantly enhanced, resulting in increased apoptosis. Moreover, ceramide lipids and proteins found in GDNPs may play important roles in macrophage polarization through TLR4 signaling. A significant reduction in melanoma growth was observed following the treatment of

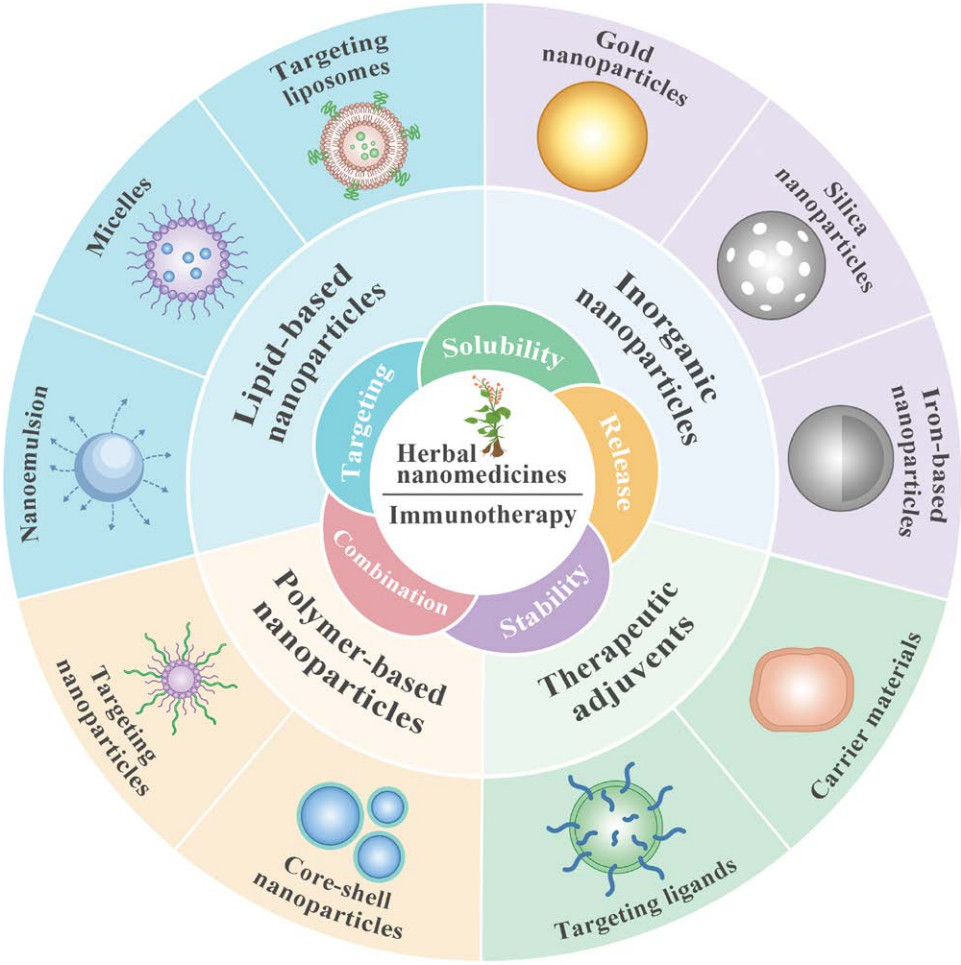

Figure 2. Strategies of immunotherapy-related THM nanodelivery. THM: Traditional herbal medicine.

tumor-bearing mice with GDNPs. In addition, M1 macrophages were detected in tumor tissues following treatment with GDNPs[255].

Solid lipid NPs are second-generation lipid-based nanocarriers currently available for clinical use. The most recently produced NPs of this type are the coronavirus disease 2019 vaccines. These NPs are colloidal particles with sizes ranging between 50 and 200 nm that consist of biodegradable lipids such as triglycerides, fatty acids, and waxes[256]. Solid lipid NPs possess properties like those of liposomes, including the ability to encapsulate hydrophilic and lipophilic molecules, non-toxicity, and bioavailability. However, they are more stable than liposomes because of their rigid cores.

Zhu et al.[257] developed an innovative nanolipid carrier preparation (NCNLC) that incorporated coix seed oil as a liquid lipid, loaded it with naringenin, and diluted *via* ultrasonic melt emulsion. NCNLC exerted more pronounced antiproliferative effects (ie, promoting apoptosis and inhibiting tumor cell proliferation) than nanostructured lipid carriers derived from free naringenin, oleic acid, and neodecanoic triglyceride. The combination of naringenin and coix seed oil upregulated the expression of IL-6 and IL-10 in the serum of tumor-bearing mice and significantly increased the spleen index, suggesting that they work in conjunction to produce the desired effects[257].

Zhang et al.[46] developed a micellar preparation containing a combination of quercetin and alantolactone for the treatment of CRC. Nanotherapy stimulated the host immune system to induce long-term tumor destruction and memory tumor surveillance, which resulted in a 1.3-fold increase in the median survival time compared with phosphate-buffered saline and free drugs. The combined delivery of quercetin and alantolactone induced a synergistic therapeutic effect capable of reactivating anti-tumor immunity by promoting immunogenic cell death (ICD), increasing cell toxicity, and modifying the immunosuppressive microenvironment. The combined immunotherapeutic effects of quercetin and alantolactone, delivered *via* a simple and safe nanodelivery system, may lead to scalable production and clinical applications.

Xu et al.[241] have developed an innovative puerarin nanoemulsion (nanoPue) with enhanced solubility and bioavailability. Compared to the phosphate-buffered saline control, nanoPues significantly reduced stromal microenvironment activity (eg, a six-fold reduction in tumor-associated fibroblasts). As a result of the removal of the physical barrier, there was a two-fold increase in the intratumoral infiltration of cytotoxic T cells. This activation of the immune microenvironment results in synergistic effects when nanoPues are combined with PD-L1 blockade therapy[241].

Table 2

Advantages of herbal nanomedicine for tumor immunotherapy

Types	Dosage forms	Agents	Advantages of the dosage forms	Ref.
Lipid-based NPs	Liposomes	APR and CUR	High biocompatibility and stability; controlled release (the cumulative release after 47 h is 27.76% for CUR and 43.48% for APR); achievement of the cellular uptake by both tumor cells and tumor-associated fibroblasts	[240]
	Micelles	Quercetin (Q) and alantolactone (A)	High entrapment efficiency; improved tumor tissue accumulation; modulation of tumor immune microenvironment; elevated memory tumor surveillance with a 1.3-fold increase	[46]
	Nanoemulsion	Puerarin	Improvement of the solubility and bioavailability of puerarin; reduced tumor-associated fibroblasts; improved safety	[241]
Polymer-based NPs	Targeting nanoparticles	Inulin acetate	Controlled loading and release; stimulation of the long-lasting anti-tumor immunity; prolonged the release cycle of pathogen-mimicking vaccine delivery system antigen to 20 days	[242]
	Core-shell nanoparticles	OxPt and DHA	Avoid of uptake by the mononuclear phagocyte system; better biodistribution and tumor uptake; induction of immunogenic cell death; attenuation of the development of tumors	[243,244]
Inorganic NPs	Gold nanoparticles	Hesperidin	Good biocompatibility; targeted drug delivery; reduced damages and histopathological abnormalities	[245]
	Silica nanoparticles	Colchicine	Reduced cytotoxicity with targeted delivery conjugated with folic acid; Inhibition of PD-1 expression	[246]
	Iron-based nanoparticles	Ginsenosides Rg3	Excellent coupling effect; significantly prolonged survival of HCC mice	[48, 247,248]
Therapeutic adjuvants	Enzyme-sensitive nanodrug delivery system	Angelica polysaccharide/ doxorubicin	Angelica polysaccharide was not used as carriers, but also to enhance immune function; realization of the combination with doxorubicin; quick release of agents at the presence of matrix metalloproteinase 2	[249]
	Self-assembling NPs fabricated by Radix pseudostellariae protein and polysaccharide	Doxorubicin	Targeted drug delivery; pH-sensitive controllable release of doxorubicin; elevated cytotoxicity of doxorubicin on HepG2 cells	[250]

APR: Aprepitant; CUR: Curcumin; HCC: Hepatocellular carcinoma; NP: Nanoparticle; OxPt: Oxaliplatin; PD-1: Programmed cell death 1.

Polymer-based NPs

Polymer-based NPs can be prepared using naturally occurring, synthetic, or partially synthetic materials that can be used to regulate the particle size (25–500 nm), surface properties, and shape. Plant bioactive compounds are loaded and released depending on the surface charge density of NPs. NPs with a positive charge are more likely to be taken up by cells than particles with a negative charge (eg, polyethylene glycol (PEG)-ylated particles). Nevertheless, a high density of surface charges can damage cell membranes, resulting in cell toxicity[258].

In a previous study, polylactic-co-glycolic acid-PEG-aminoethyl anisamide (PLGA-PEG-AEAA) NPs for the co-delivery of icaritin and Dox effectively induced an immune response in mice at an early stage of the disease. This activation was achieved by remodeling the immunosuppressive microenvironment of the tumor tissue and stimulating the immune function. Overall, these findings suggested that icaritin influences mitophagy, potentiates the ICD effect, and provides a potential treatment strategy for HCC that relies on an immune-based approach[259].

Han et al.[260] used PLGA-based NPs to co-encapsulate dihydrotanshinone I and two other drugs capable of reversing the immunosuppressive tumor microenvironment. There was a significant increase in the survival rate of mice with HCC without any signs of toxicity[260]. Kumar et al.[242] designed a PLGA delivery platform containing a bioactive polymer (ie, inulin acetate) to create a pathogen-mimicking vaccine delivery system. Pathogen-mimicking vaccine delivery systems of this type facilitate persistent antigen delivery to antigen-presenting cells. Moreover, it primes and activates TLR4, which triggers cell-mediated immunity in mice, thereby preventing tumor progression[242].

Duan et al.[244] designed a polymer core-shell nanoplatform for delivering and stabilizing prodrug molecules, such as OxPt and dihydroartemisinin (DHA). The core of the NP was a prodrug based on OxPt/Zn, whereas its shell contained DHA and a cholesterol lipid conjugate linked by disulfide bonds. Because of this lipid bilayer, the conjugate was protected from degradation in systemic circulation by both reductants and water. A significant increase in ICD was observed in tumor cells treated with OxPt/DHA *versus* those treated with OxPt/DHA alone, as indicated by a greater ratio of calreticulin expression on the tumor surface and a greater release of high mobility group box 1. The findings demonstrated that this core-shell nanoplatform confers long-lasting anti-tumor immunity based on its ability to stimulate

both the innate and adaptive immune systems; furthermore, the effectiveness of this nanoplatform was enhanced following a combination with the anti-tumor agent α-PD-L1[243].

Xiao et al.[261] developed dual pH-responsive NPs that were coated with PD-1 (αPD-1) antibodies *via* an ammonolysis reaction and loaded with Cur. The surfaces of the NPs were changed from a negative charge to a positive charge, thus increasing PD-1 inhibition on T cells through αPD-1 as well as enhancing tumor cell uptake of the NPs. The pH-responsive nanomedicine disassembled following endocytosis into the lysosomes of tumor cells, resulting in the rapid release of encapsulated Cur. This combination simultaneously blocked the PD-1/PD-L1 pathway and mitigated the immunosuppressive effects of Tregs, resulting in significant anti-tumor responses[261].

Inorganic NPs

The sizes of the metal NPs approved for cancer treatment commonly range from 5 to 50 nm. These NPs decompose under physiological conditions *via* several metabolic pathways without harming the healthy tissues[262]. They can reach tumor cells when exposed to external stimuli, such as heat, light, magnetic fields, and lasers[263]. Numerous metallic NPs can induce oxidative stress in tumor cells. Metallic NPs may be targeted and regulated by certain conditions within the tumor microenvironment (eg, changes in pH, reduced oxygen levels, and oxidative stress)[264].

Gold NPs

A recent study has shown that Au NPs containing hesperidin possess anticancer properties[245]. Sulaiman et al.[245] demonstrated that gold hesperidin NPs directly interfered with tumor cells, affecting Ehrlich ascites tumor growth during the early stages of treatment. This effect was attributed to the stimulation of macrophages, which resulted in the remarkable eradication of tumor cells[245]. Several studies have reported that Cur gold NPs are characterized by low bioavailability, poor solubility, and poor stability. Furthermore, in another study, Cur-loaded core-shell nanostructures of gold NPs and chitosan (nanogels) rapidly released the drug in acidic environments and were readily internalized by Huh7 and MCF-7 cells[265].

Iron-based NPs

As multifunctional carriers, Fe-based NPs have significant advantages in terms of biocompatibility and autologous targeted drug delivery[266]. Ginsenoside Rg3, isolated from ginseng, induces cellular autophagy and sensitizes liver cancer cells to adriamycin[267]. Fe@Fe3O4 NPs were synthesized and coupled with ginsenoside Rg3 to develop a novel nanomedicine (NpRg3). Rg3 suppresses cancer angiogenesis by regulating vascular endothelial growth factor activity, whereas iron-based NpRg3 circulates in the body for a long time and may be an effective therapy for circulating tumor cells by activating the immune system[48,247].

Silica NPs

Silica NPs (SNPs) were first developed in 1992. The United States Food and Drug Administration recognizes SNPs as generally safe. Recently, the potential use of SNPs for drug delivery in cancer treatment has attracted considerable attention[268]. This interest is primarily based on the wide range of advantages offered by SNPs, such as biocompatibility, the ability to modify their shape, and diversity. In addition, they can be customized in terms of their size and surface chemistry to increase their specificity. The biodegradability of these materials has led to their widespread acceptance in biomedicine[269].

AbouAitah et al.[246] developed a novel drug delivery system that involved loading colchicine into spherical mesoporous SNPs, which were subsequently modified with phosphonate groups and coated with a chitosan-glycine complex conjugated with folic acid, which acted as a ligand for targeting cancer cells. This approach fully inhibited HCT116 colon cancer cells but exhibited negligible cytotoxicity against normal cells. This response was mediated by strong anti-mitotic effects that induce apoptosis (intrinsic). This system revealed novel effects on the regulation of genes and immune responses to cancer, significantly inhibiting the expression of metastasis-associated lung adenocarcinoma transcript 1, mir-205, Ang-2, and PD-1[246].

Nanoemulsions

Celastrol nanoemulsions were also designed to stimulate ICD and reduce PD-L1 expression in tumor cells[270]. Intratumorally administered celastrol nanoemulsions with high drug concentrations effectively activated the immune system. This led to simultaneous growth arrest of both the treated tumor and the adjacent untreated tumor (ie, the abscopal effect). Evidence indicates that these nanoemulsions are cost-effective novel strategies for melanoma chemotherapy-induced immunotherapy.

Therapeutic adjuvants

An enzyme-sensitive nanodrug delivery system (*Angelica sinensis* polysaccharide-peptide-Dox) was constructed for tumor targeting. In addition to acting as drug carriers in tumor tissues, polysaccharides improve the tumor microenvironment and stimulate the immune system, thereby enhancing the anticancer effects of chemotherapy. Dox exhibits significant anti-tumor properties *in vitro*. The release of the *Angelica* polysaccharide moiety increased the expression of IL-2 but decreased that of IL-10. These results suggest that this approach can restore the balance of Th1/Th2 immunity within the tumor microenvironment[249].

Angelica sinensis (Dang Gui) polysaccharide-coated core-shell NPs were also synthesized. Cur was loaded into positively charged chitosan oligosaccharides with mitochondria-targeting capabilities, and the negatively charged shells were wrapped around the nuclear surface with *Angelica sinensis* (Dang Gui) polysaccharides. As a result, a pH-sensitive borate bond was formed between the shell and the core. When mitochondria-targeting nucleocapsid NPs were placed in an acidic tumor microenvironment, their charge was reversed, leading to the

release of an increased amount of Cur. Lysosomal escape was successfully achieved once Cur entered the tumor cells and was more readily transferred to the mitochondria. In addition, core-shell NPs enhanced drug delivery to the tumor site and ensured their presence in the tumor tissue for a longer duration[271].

Studies have explored the anti-tumor immune responses in T cells and Tregs induced by nanosized ginseng-derived exosome-like NPs (GENs) containing phospholipids and various bioactive compounds[272]. The improved targeting capability of GENs has resulted in significant therapeutic effects and effectiveness in the recruitment of M1 macrophages to the tumor microenvironment. GENs have demonstrated promising results in the treatment of glioma, both *in vitro* and *in vivo*, indicating that they can inhibit disease progression and control TAMs.

GLP also has anticancer properties and is an excellent adjuvant for immunosuppressive conditions. The hydroxyl groups in GLP generate hydrophilic chains, whereas rutin and DHA create hydrophobic chains that are interconnected by disulfide bonds and borates. These NPs are pH- and redox-reactive, allowing for the release of anticancer drugs in a controlled and programmable manner. Furthermore, it has been shown that RCGDDH-NPs are effective in killing tumor cells and inhibiting tumor growth with limited side effects. Therefore, pH- and redox-reactive RCGDDH-NPs are promising candidates for tumor treatment[273].

Cai et al.[250] used the protein-polysaccharide complex of *Radix Pseudostellariae* (Taizi Shen) as a basis for self-assembling NPs (CP3) after heat treatment and pH adjustment. pH-sensitive release patterns were observed in CP3 loaded with Dox NPs when tested in an acidic environment that simulated the tumor microenvironment and endosomal pH. Dox uptake by CP3-DOX NPs in HepG2 cells was significantly enhanced (1.56-fold greater than Dox internalization by free Dox NPs). CP3-DOX NPs inhibited the function of p-glycoprotein truffle pumps through cypermethrin-dependent endocytosis in HepG2 cells[250].

Conclusion and outlook

Based on evidence obtained from preclinical studies, immunotherapy may be associated with the long-term success of cancer treatment. Consequently, cancer immunotherapy is considered an effective treatment approach for both primary and metastatic cancers owing to its ability to establish immune memory in patients[274].

THM contain various chemical components, such as polysaccharides, amino acids, flavonoids, saponins, and alkaloids. These components have been used to treat diseases for thousands of years, and many have the potential to treat cancers. In this article, we reviewed the active compounds present in THM. We focused on their complex and varied regulatory effects on the immune system, which affect immune cells through specific mechanisms, and their inhibitory effects on tumor cell growth. However, only a few herbs have been linked to immune system regulation. The active ingredients in many herbal medicines used for the clinical treatment of cancer have not yet been fully identified. Additionally, the rate of international recognition for the clinical use of herbal medicines is low. Therefore, it is necessary to investigate the anticancer mechanisms further to identify the active ingredients in herbal medicines. Herbal medicines have great potential for use in anti-tumor immunotherapy.

Plant-derived bioactive compounds exhibit different physicochemical characteristics depending on their source species. Therefore, there are different requirements for their administration, *in vitro* and *in vivo*. The use of NP-based carrier systems to deliver plant bioactive compounds allows for more precise control of drug release, preservation of unstable compounds, and high bioavailability. Therefore, we focused on promising nanocarriers for immunotherapy using THM monomers as pharmacological agents and carrier materials. All aspects of the formulation process, including safety, efficacy, immunogenicity, and biodegradability, must be considered. Therefore, the selected carrier system must be compatible with the physicochemical characteristics and efficacy of phytochemicals.

However, the design of plant-derived nanomedicines is complex. Hence, such nanomedicines do not always meet the clinical demands owing to their diverse chemical structures and capability to form NPs. One type of nanoencapsulation process may not be suitable for encapsulating other phytochemical compounds if the same type of polymer-, lipid-, or metal-based nanocarrier is used. Polymers and lipids interact differently with phytochemical compounds during NP fabrication under various environmental conditions. Consequently, a detailed understanding of the molecular configurations and intermolecular interactions of phytochemicals and their synthesis parameters is important to tailor the nanoencapsulation process for each type of phytochemical. It is also crucial to control the stability and functionality of the NPs by adjusting their surface charge. For example, cationic nanocarriers have gained considerable attention over the past few years primarily because of their ability to interact with anionic phosphatidylserine residues found in tumor cells. Several critical parameters must be considered for nanocarrier systems, such as formulation characteristics (ie, water solubility, crystallinity, polarity, partition coefficients, and dissolution rates), safety, and reproducibility. The development of new carriers and nanomedicines derived from plants may lead to novel anti-tumor treatments, particularly if tumor heterogeneity is better understood. The combination of herbal medicines and materials science may lead to significant advances, particularly in the integration of active ingredients of herbal medicines with NPs. Further research is necessary to develop effective cancer therapies using herbal monomeric compounds in combination with other immunotherapeutic agents using targeted nanocarrier systems.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Xiang Li and Jing Zhang conceived and supervised this study. Xiang Li, Chenkai Gong and Abid Naeem participated in literature search, screening and writing original draft. Jing Liu, Ming Yang and Hongming Shang participated in writing-review and polishing the language of the manuscript. Jing Zhang and Xiang Li participated in writing, editing and funding acquisition. All authors have read and agreed to the published version of the manuscript.

Ethical approval of studies and informed consent

Not applicable.

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Data availability

All data generated or analyzed during this study are included in this published article.

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