Review Article

Advances in traditional Chinese herbal medicine and their pharmacodynamic mechanisms in cancer immunoregulation: a narrative review

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Background and Objective: The cancer-immunity cycle (CIC) is defined as a series of progressive events that cause an anticancer immune response leading to the killing of the cancer cell. The concept of CIC has important guiding significance for the clinical and basic tumor immunotherapy research. As one of the methods of traditional Chinese medicine (TCM), Chinese herbal medicine (CHM) has shown unique advantages in multitarget and multipathway immune regulation. However, the tumor immune circulation targeted by CHM is generally unclear at present. To provide reference for future clinical and basic research, we systematically reviewed the existing literature on CHM (including CHM monomers, CHM compounds, and CHM patent medicines) and the mechanisms related to its efficacy.

Methods: We searched the PubMed and China National Knowledge Infrastructure (CNKI) databases for relevant Chinese-language and English-language literature published from January 1988 to October 2022. The literature was screened manually at three levels: title, abstract, and full text, to identify articles related to CHM and their mechanism of regulating tumor immunity.

Key Content and Findings: By further classifying the CIC, it was confirmed that CHM can regulate the activation of dendritic cells (DCs) and macrophages and promote the presentation of tumor antigens. Meanwhile, CHM can also reverse tumor-immune escape by enhancing T-cell proliferation and infiltration. In addition, CHM can also enhance the antitumor ability of the body by regulating the killing process of tumor cells.

Conclusions: The theory of a CIC is of guiding significance to regulating tumor immunity via CHM.

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Keywords: Chinese herbal medicine (CHM); tumor; cancer-immunity cycle (CIC); mechanism

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Introduction

According to the International Agency for Research on Cancer (IARC), the global cancer burden was estimated to be 19.3 million new cases and 10.0 million deaths in 2020, and malignant tumors have become the first or second leading cause of death in 112 countries (1). Although the vast majority of initial cancer cells are identified and eliminated by the continuous monitor of the immune system, but some tumor cells manage to evade the monitor of the immune system or are able to limit the extent of immune killing to avoid elimination (2). As early as 2013, Chen *et al.* (3) proposed the concept of the "Cancer-Immunity Cycle (CIC)", which was defined as a series of progressive events that cause an anticancer immune response leading to the killing of the cancer cell, indicating that the immune system kills tumor cells via seven steps: In the first step, neoantigens produced by cancer cells are presented and captured by dendritic cells (DCs) (step 1). Next, DCs present tumor neoantigens captured on molecules of the major histocompatibility complex (MHC)-I and MHC-II to T lymphocytes (step 2) to activate the specific antigenic response of T lymphocytes (step 3). Finally, the aggregated T lymphocytes traffic to (step 4) and infiltrate the tumor bed (step 5) and bind to MHC-I via T cell receptor (TCR) (step 6), so as to specifically recognize and kill cancer cells (step 7). The dying cancer cells will again release antigens for DCs to recognize, completing the immune cycle. The realization of the cancer immune cycle is regulated by a series of stimulatory and inhibitory signals, such as the immune checkpoint proteins programmed death-1 (PD-1) /programmed death-ligand 1 (PD-L1) provide inhibitory signals. Among them, the PD-1/PD-L1 pathway is an essential co-inhibitory molecular pathway mediating tumor immune escape caused by T cell depletion. Moreover, the tumor microenvironment (TME) also plays an important role in the PD-1/PD-L1 pathway. Tumor immune escape mediated by the PD-1/PD-L1 pathway is described as "adaptive resistance", in which T cells recognize the tumor antigen MHC complex and are activated as tumor effector cells (Teff). It reaches the tumor site and becomes tumor-infiltrating lymphocytes (TILs). TILs recognize tumor antigens and produce interferon gamma (IFN-γ) and other molecules to promote the expression of PD-L1 in the tumor environment. After binding with PD-1, PD-L1 transmits anti-apoptotic signals to tumor cells through T cell inhibition signals, resulting in T cell functional inactivation and survival. With the advances in tumor immunology, the value of immune checkpoint inhibitors (ICIs) is increasingly being recognized. Anti-cytotoxic T lymphocyte-associated protein 4 (anti-CTLA-4), antibodies against PD-1 and PD-L1 have demonstrated extension of patients' survival (4). However, the unstable and heterogeneous TME may mediate the immune escape of tumor cells and concurrently inhibit the normal immune function of the body, leading to poor clinical responses to immunotherapy in some patients. Thus, new approaches are under investigation to increase the efficacy of immunotherapy in cancer research. During thousand years' practice, traditional Chinese medicine (TCM) has shown remarkable efficacy in treating malignant tumors. The existing basic researches have shown that TCM has significant effects on inhibiting the growth of tumor cells, enhancing the effect of radiotherapy and chemotherapy, and reducing the side effects of chemotherapy (5-7). TCM includes Chinese herbal medicine (CHM), acupuncture, etc. CHM and acupuncture have been used in cancer treatments, through immune regulation and other pathways. Acupuncture stimulation can regulate the sympathetic and parasympathetic nervous system by regulating the function of NK cells, macrophages and T lymphocytes, and produce a variety of physiological reactions including immune response. Acupuncture simulation can relieve pain, fatigue, nausea and vomiting in the treatment of patients with lung cancer, breast cancer and so on (8,9). Many clinical and basic studies on the role of CHM in regulating tumor immunity have demonstrated that some CHM monomers, CHM compound prescriptions, and CHM patent medicines can regulate the immune function of patients via multiple pathways, including immune cells, immunoactive substances, and immune organs (10,11).

The regulatory effect of CHM on CIC is mainly

Table 1 Summary of the literature search strategy

Items	Specification
Date of search	October 26, 2022, to November 2, 2022
Databases and other sources searched	PubMed and CNKI databases
Search terms used	See Table S1 for details
Timeframe	January 1988 to October 2022
Inclusion and exclusion criteria	Inclusion criteria: original articles and review articles in English and Chinese languages
	Exclusion criteria: (I) publications with duplications or studies with overlapping data from the same author; (II) abstracts, case reports, proceedings, and meta-analyses; and (III) incomplete outcome data
Selection process	Two reviewers included and validated the studies independently. Inconsistencies in the opinions of the two reviewers were resolved by negotiation and discussion by all authors

CNKI, China National Knowledge Infrastructure.

reflected of antigen presentation (step 1), T-cell activation (step 3), T-cell infiltration (step 5) and tumor-cell killing (step 7). This article evaluated the step 1, 3, 5 and 7 of the CIC in terms of CHM monomers, CHM compound prescriptions, and CHM patent medicines and elucidated the research progress on the pharmacodynamic mechanism of CHM in regulating tumor immunity. These represent an attempt to provide new perspectives and insights for further CHM research. We present this article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1983/rc).

Methods

We searched the PubMed and China National Knowledge Infrastructure (CNKI) databases for original research and review articles published in English or Chinese languages between January 1988 and October 2022. The following search terms were employed: "traditional Chinese medicine" or "Chinese medicine", "tumor" or "neoplasm" or "cancer", and "immune" and "immune system". Articles cited in the relevant articles were also examined as potential sources of information. The database resources are summarized in *Table 1* and Table S1.

TCM theories on tumor immunoregulation

The term "immunity" (Mian Yi) in TCM was first seen in the *Mian Yi Lei Fang* (or "Immune Formularies") in the Ming Dynasty (12). It was also stated in the *Notes and interpretations of the inner canon of the yellow emperor-divine pivot* (by Ma Shi of the Ming Dynasty, 1586AD) that "*pathogens may present, just because the vital qi is insufficient and the pathogens take the chance*". From the perspective of TCM, the occurrence and development of diseases are closely related to the status of the human body. Moreover, according to the *Plain questions* of the *Huangdi Neijing*, "*When there is sufficient vital qi inside, the pathogenic qi has no way to invade the healthy body*". When the human body has balanced yin and yang and normal immune function, it can fight against and dispel pathogenic qi, and thus pathogenic qi will not cause harm to the human body. *Plain questions: great theory on the law of primordial qi in nature* proposed the following: "*If there is the relative equilibrium of yin-yang, the essence and spirit will be well governed; and if there is a divorce of yin-yang, the essence and qi will be exhausted*". The balance between yin and yang is the foundation of health. When yin and yang become unbalanced and the vital qi becomes deficient and weak, the body's defenses are reduced, which is reflected as immune dysfunction. As a result, pathogenic qi may afflict the human body. Therefore, a healthy or sick body depends mainly on the rise and fall of vital qi. Here the "vital qi" generally refers to the body's ability to fight against diseases and pathogenic qi. Supposed the vital qi is not sufficient to defend the body from being beset by external pathogens. In that case, diseases will occur or progress, which is in line with the knowledge of immunity in modern medicine (13).

TCM's understanding of the pathogenesis of a specific disease also guides its treatment. Starting from classic theories such as "harmonizing yin and yang" and

"supporting the vital qi to dispel pathogenic qi", TCM-based treatment of malignant tumors is characterized by its holistic and balanced approaches. Modern research has confirmed that TCM can regulate antitumor immunity. By regulating the TME and reshaping the immunosuppressive cells in the TME, TCM can prevent and treat tumor metastasis/recurrence and enhance the body's immune response (14), ultimately enabling patients to live with tumors.

CHM in regulating antitumor immunity

In China, CHM is an indispensable part of multidisciplinary treatment (MDT) for tumors and can be involved in the whole-process management of patients with tumors. CHM can enhance the efficacy of conventional treatments [e.g., chemotherapy, radiotherapy and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs)] and provide synergy to enhance the sensitivity of chemotherapy drugs, reduce adverse reactions, relieve pain and improve quality of life of patients (15). We have found that most CHM herbs used for regulating antitumor immunity function as restoratives (also known as tonics) or for invigorating blood. CHM compound prescriptions are mainly used for "strengthening vital qi to eliminate pathogenic factor" or "strengthening the spleen and tonifying the kidney". New studies have demonstrated the immune-regulating effects of some of CHM' active ingredients (e.g., polysaccharides, glycosides, and alkaloids). CHM can regulate the tumor immune microenvironment (TIME) and the human body's immunity in a dual manner. Chen *et al.* (3) proposed the concept of the "CIC", indicating that the immune system kills tumor cells via seven steps, with each step being interconnected and iterative. Here, we summarize the currently available studies on CHM (including monomers, CHM compound prescriptions, and proprietary Chinese medicines) in CIC and their pharmacodynamic mechanisms, focusing on their roles in each CIC step.

The roles of CHM in CIC

CHM regulates antigen presentation

DCs are the most potent antigen-presenting cells (APCs) that are widely distributed in the body. However, DCs in tumors are often immature, and the immature DCs need to undergo "activation" of tumor neoantigens as well as phenotypic and functional changes before they become mature and activated. Up to 45 studies in China and abroad have reported that polysaccharides and other ingredients (e.g., ginsenoside Rg3 and curcumin) of CHM, CHM compound prescriptions (e.g., Fei-Liu-Ping ointment), and CHM patent medicines (e.g., Fei-Yan-Ning granules) can upregulate the expressions of MHC-I/II and costimulatory molecules (e.g., CD40, CD80, and CD86) on the surface of DCs through different mechanisms to promote the maturation of DCs. Meanwhile, they can also promote the secretion of cytokines such as interleukin (IL)-6, IL-12, and IL-18 to enhance antitumor activity.

Macrophages (MΦ), an integral component of innate immunity, can differentiate into either a proinflammatory (M1) subtype, also known as a classically activated subtype, or an anti-inflammatory alternatively activated subtype (M2). M1 macrophages play a vital role in promoting type 1 T helper (Th1) response and antitumor function, while M2 macrophages exert anti-inflammatory and protumor growth effects by expressing IL-10, arginase-1 (Arg-1) and other immunosuppressive cytokines (16). Research has shown that CHM monomers (e.g., ginsenoside Rh2), CHM compound prescriptions (e.g., flavored astragalus Jianzhong decoction), and CHM patent medicines (e.g., Fei-Yan-Ning granules) can promote the polarization of macrophages from M2 to M1, thus reducing M2 macrophages and increasing M1 macrophages (*Table 2*). Therefore, CHM can dually regulate M1 and M2 macrophages to suppress tumor cell proliferation and migration and enhance the body's immune function.

CHM herbs regulate T-cell activation

Cytokines affecting antitumor immune response mainly derive from Th cells (including Th1 and Th2) and macrophages, among which the imbalance between Th1 and Th2 affects the growth and metastasis of various tumors (58). Upregulated expression of Th1 and downregulated expression of Th2 are associated with enhanced cellular immunity, which facilitates T-cell proliferation, activation, and infiltration and is conducive to tumor cell clearance. Some CHM including CHM monomers (e.g., polysaccharides, icariin, and Huaier extract), CHM compound prescriptions (e.g., Anfei decoction and compound yin-nourishing and yang-warming recipe), and CHM patent medicines (e.g., Xihuang pills) can induce the transformation of the immune balance and enhance antitumor immunity. In addition, the regulatory

Table 2 CHM herb regulation of APCs

Type of CHM herb	Active ingredients	DC			Macrophage	Mechanism/pathway findings	Reference
		Proliferation	Antigen-presentation capacity	Secretion of costimulating molecules and cytokines	Macrophage M1/M2 polarization		
CHM monomers	Polyporusus Bellatus	√		√	√	Promoted myeloid DC proliferation; promoted the secretion of IL-1β and TNF-α; promoted the transformation of M2 subtype to M1 subtype and significantly reduced the expression level of M2 macrophage-specific marker CD206	Jiang *et al.* (17)
	Honey-processed Astragalus polysaccharides			√		Increased the release and expressions of HSP70, CRT, MHC-I, CD86, CD80, and ATP	Sha *et al.* (18)
	Ginseng polysaccharide	√		√		Increased the expression of APCs and upregulated the expressions of TNF-α, IL-1, IL-6, and NO	Wang *et al.* (19)
	Lycium barbarum polysaccharides		√	√		Induced the maturation of murine DCs via TLR2- and/or TLR4-mediated NF-κB signaling pathways and upregulated the expressions and release of CD11c, I-A/I-E, and IL-12	Zhu *et al.* (20)
	Rehmannia glutinosa polysaccharide		√	√		Upregulated the expressions of CD40, CD80, CD83, CD86, and MHC II	Zhang *et al.* (21)
	Pueraria lobata polysaccharide		√			Induced the phenotypic and functional maturation of DCs via TLR4	Kim *et al.* (22)
	Platycodon grandiflorus polysaccharide		√			Induced DC phenotypic maturation by activating MAPK and NF-κB signaling pathways downstream of TLR4	Park *et al.* (23)
	Glossy ganoderma polysaccharide			√		Upregulated the expressions of CD40, CD80, and CD86	Zhu *et al.* (24)
	Polysaccharide isolated from seeds of Plantago asiatica L.		√	√		Induced DC maturation by activating MAPK and NF-κB signaling pathways downstream of TLR4; upregulated the expressions of MHC II, CD86, and CD80	Jiang *et al.* (25)
	Eucommia ulmoides polysaccharides		√			Upregulated the expressions of MHC I/II, IL-12, and TNF-α	Feng *et al.* (26)
	Radix Glycyrrhiza polysaccharide		√			Upregulated the expressions of MHC I/II, IL-12, and TNF-α	Li *et al.* (27)
	Epimedium koreanum polysaccharides		√	√		Promoted the secretion of IL-6, TNF-α, IL-12 and other antitumor immune factors; induced Th-cell differentiation	Wang (28)
	Total saponins of Achyranthes bidentata			√		Initiated the JAK/STAT signaling pathway in DCs	Chen *et al.* (29)
	Achyranthes bidentata polysaccharides			√		Initiated the JAK/STAT signaling pathway in DCs	Chen *et al.* (29)
	Platycodin D	√				Regulated the BiP-IRE1α-XBP1 and PI3K-AKT-mTOR pathways	Zhang (30)
	Ginsenoside Rh2				√	Upregulated the expression levels of VEGF, MMP-2, and MMP-9	Li *et al.* (31)
	Dioscin				√	Reduced the amount of M2 macrophages in tumors	Cui *et al.* (32)
	Pulchinenoside A3				√	Targeted the TLR4/NF-κB/MAPK signaling pathways	Yin *et al.* (33)
	PA (an active component of Pulsatilla chinensis)				√	Targeted the TLR4/NF-κB/MAPK signaling pathways in macrophages	Liu *et al.* (34)
	Ganoderma lucidum spores	√		√		Stimulated the differentiation and maturation of myeloid DCs and increased CD11a and CD86 expressions	Sun *et al.* (35)
	Triterpenoids from Ganoderma lucidum			√		Upregulated the expressions of IL-6 and TNF-α	Feng *et al.* (36)
	Extract of Pinellia pedatisecta Schott			√		Upregulated the expressions of CD80, CD86, and IL-12; induced the expressions of CD107a, GZMB and perforin in CTL	Wang *et al.* (37)
	A lipid-soluble extract of Pinellia pedatisecta Schott			√		Upregulated the expressions of MHC II, CD80, and CD86 on TADC; induced the secretion of IL-12	Wang *et al.* (37)
	Taraxacum mongolicum extract				√	Promoted macrophage M1/M2 polarization	Deng *et al.* (38)
	Huaier extract	√			√	Promoted DC maturation by regulating the MAPK and PI3K/AKT signaling pathways; regulated the polarization of macrophages and reduced M2 polarization	Li *et al.* (39)
	Gastrodin			√		Upregulated the expressions of CD80, CD86, and MHC I	Liu *et al.* (40)
	Proanthocyanidins			√		Upregulated the expressions of CD80, CD86, and MHC I/II	Zhang (41)
	Baicalein			√		Upregulated the expressions of CD80, CD86, and MHC I/II	Zhang (41)
	Apigenin			√		Upregulated the expressions of CD80, CD86, and MHC I/II	Zhang (41)
	Dihydroartemisinin				√	Remodeled TAM into the M1 phenotype	Li *et al.* (42)
	Emodin				√	Targeted inhibition of IRF4, STAT6, and 5CEBPβ signaling	Iwanowycz *et al.* (43)
	Flavonoids from Scutellaria barbata			√		Upregulated the expressions of CD86, CD40, caspase-3 and caspase-8	Liao (44)
	Salidroside			√		Upregulated the expressions of MHC II and CD80	He *et al.* (45)
	Flavonoids				√	Regulated via the JAK2-STAT1 pathway	Guo *et al.* (46)

Table 2 (*continued*)

Table 2 (*continued*)

Type of CHM herb	Active ingredients	DC			Macrophage	Mechanism/pathway findings	Reference
		Proliferation	Antigen-presentation capacity	Secretion of costimulating molecules and cytokines	Macrophage M1/M2 polarization		
CHM compound prescriptions	Fei-Liu-Ping ointment		√			Regulated the BiP-IRE1α-XBP1 and PI3K-AKT-mTOR pathways	Zhang (30)
	Compound yin-nourishing and yang-warming recipe		√	√		Promoted DC maturation via the MAPK and NF-κB signaling pathways; promoted the release of cytokines including IFN-β, IL-1β, IL-2, IL-12, and TNF-α	Zhao *et al.* (47)
	Qi-lowering decoction		√			Targeted the IL-17 signaling pathway	Zhang *et al.* (48)
	Liujunzi decoction (decoction of six ingredients)			√		Upregulated the expressions of CD80, CD86, and CD1a	Wu *et al.* (49)
	Qige powder (diaphragm-arousing powder)			√		Promote the expressions and secretion of CD80, CD86, CD1a, and IL-12 through the STAT3 signaling pathway	Wu *et al.* (49)
	Jianpi Bushen decoction (spleen- and kidney-invigorating decoction)			√		Upregulated the expressions of MHC I/II	Li *et al.* (50)
	Shengyu decoction		√			Promoted the differentiation and maturation of mouse spleen DCs; induced the differentiation of T lymphocytes to CTLs and increased cytolytic killing of CTLs	Sun *et al.* (51)
	Compound Changtai decoction			√	√	Promoted the expression and secretion of cytokines such as CD86, CD40, TNF-α, IL-6, MCP-1, and IL-1β; activated M1 macrophages	Li *et al.* (52)
	Fuzheng Jiedu formula				√	Promoted the phenotypic transformation of macrophages; inhibited the TAM-mediated PI3K/AKT/TSC1/Rheb/mTOR signaling pathway; reduced the expression of relevant angiogenic factors	Song (53)
	Zhou's Kejinyan formula				√	Downregulated the expressions of TNF-α, IFN-γ, IL-6, IL-4, and IL-13 in TME	Chen *et al.* (54)
	Flavored Astragalus Jianzhong decoction			√	√	Upregulated the expression of CD86; promoted the phenotypic transformation of macrophages	Jiang *et al.* (55)
CHM patent medicines	A Tai oral liquid			√		Upregulated the serum levels of IL-2, IL-4, and IFN-γ	Zhang (56)
	Fei-Yan-Ning granules				√	Increased the amount of M1 macrophages; regulated TAM and its secreted cytokines through the NF-κB signaling pathway	Si *et al.* (57)

CHM, Chinese herbal medicine; APCs, antigen-presenting cells; DC, dendritic cell; CRT, calreticulin; IL, interleukin; TNF, tumor necrosis factor; HSP70, heat shock protein 70; ATP, adenosine triphosphate; NO, nitric oxide; TLR, Toll-like receptor; NF-κB, nuclear factor-κB; MHC, major histocompatibility complex; MAPK, mitogen-activated protein kinase; JAK, Janus kinase; STAT, signal transducer and activator of transcription; VEGF, vascular endothelial growth factor; MMP, matrix metalloprotein; GZMB, granzyme B; TADC, tumor-associated dendritic cell; TAM, tumor-associated macrophage; CTL, cytotoxic T lymphocyte; MCP, monocyte chemoattractant protein; IFN, interferon; TME, tumor microenvironment.

T cells (Tregs) can inhibit APCs through cytotoxic T lymphocyte antigen-4 (CTLA-4); by secreting inhibitory cytokines [e.g., IL-10, tumor growth factor-beta (TGF-β), and IL-35], expressing granzyme/perforin, and consuming IL-2, Tregs exert their immunosuppressive function, and are thus one of the major mechanisms of tumor escape from the immune system (59). Some CHM monomers and compound prescriptions can also inhibit the expression of Tregs (*Table 3*).

CHM herbs regulate T-cell infiltration into tumors

After the naive T lymphocytes in the lymph nodes are stimulated and activated by tumor antigens presented by APC, they begin to migrate to tumor cells through blood circulation via penetration and infiltration, to complete subsequent tumor cell recognition and killing. The key to cytotoxic T lymphocyte (CTL) infiltration within tumor bed lies in the capture, rollover, adhesion, and transendothelial migration of activated T cells, which depend on the interactions between specific adhesion molecules (e.g., selectins and integrins) and chemokines [e.g., C-X-C motif chemokine ligand (CXCL)9, CXCL10, and CXCL11] expressed on the vascular lumen and CTL surface (101). However, vascular endothelial growth factor (VEGF)-induced signaling leads to a decrease in the expressions of adhesion molecules and T cell-attracting chemokines (e.g., CXCL10 and CXCL11) by inhibiting nuclear factor-κB (NF-κB) activation in endothelial cells (102), thereby preventing T-cell migration and reducing their invasion within the tumor bed. Antiangiogenic agents can reverse this negative regulatory effect. In fact, CHM herbs can reverse the negative regulatory effect of VEGF on CTL infiltration within tumor beds by downregulating VEGF or its ligands. Zhai *et al.* (103) and Zhang *et al.* (104) have demonstrated that the turmeric extract β-elemene can downregulate VEGF; in addition, it can enhance CTL invasion within tumor beds by regulating the estrogen receptor-α (ERα)/metastasis-associated protein 3 (MTA3)/snail family transcriptional repressor 1 (SNAI1) pathway. Wang *et al.* (105) and Dai *et al.* (106) found that ginsenosides Rh2 and Rg3, two effective extracts of ginseng, downregulated VEGF and its ligand VEGF receptor (VEGFR) to reverse the negative regulation of CTL infiltration. Similarly, CHM monomers/extracts (e.g., tanshinone IIA, silybin, and *Solanum nigrum* L. extract) and CHM compound prescriptions (e.g., Xiaotan Sanjie decoction) can downregulate VEGF or VEGFR expression through different mechanisms. In particular, *Solanum nigrum* L. extract can upregulate the expression level of vascular endostatin (ES) and concurrently exert its antiangiogenetic effect, further strengthening CTL infiltration within the tumor bed (103) (*Table 4*).

Tumor necrosis factor (TNF) and IFN-γ, two proinflammatory cytokines, can conduce the senescence of tumor cells expressing cytokine receptors; meanwhile, they release the antiangiogenic chemokines CXCL9 and CXCL10, which ultimately leads to dormant tumors with degraded vascular supply (102). CHM monomers (e.g., polysaccharides such as licorice polysaccharides and triterpenoids from *Ganoderma lucidum*), CHM compound prescriptions (e.g., compound yin-nourishing and yang-warming recipe), and CHM patent medicines (e.g., Fuzheng Yiliu granules) can upregulate the secretion of TNF-α, whereas CHM monomers (e.g., β-elemene), CHM compound prescriptions (e.g., Yangyinwenyang formula), and CHM patent medicines (e.g., Huisheng oral liquid) can upregulate IFN-γ (*Table 4*). All of them can enhance CTL infiltration within the tumor bed by upregulating antiangiogenic chemokines.

CHM herbs regulate tumor-cell killing

The last step in CIC is killing tumor cells by immune cells. Studies have shown that CHM herbs have an absolute superiority in quantity when regulating this CIC step (73 studies; see *Table 5*).

CTLs are the main effector cells in this step. They are mainly derived from the direct activation of $CD8^+$ T cells and have a specific killing effect on tumor cells (14). A variety of CHM polysaccharides (e.g., *Epimedium koreanum* polysaccharides), CHM monomers (e.g., cycloastragol), CHM compound prescriptions (e.g., Anfei decoction), and CHM patent medicines (e.g., *Ganoderma applanatum* polysaccharide injection) can positively regulate the killing of tumor cells by CTL in the immune circulation by upregulating $CD8^+$ T cells or enhancing CTL killing ability (*Table 5*). CTL mainly kills tumor cells through the perforin/granzyme pathway and the death receptor pathways [Fas/Fas ligand (FasL) and TNF-α/TNF receptor]. Among them, the death receptor pathway refers to the binding of the FasL expressed by the effector CTL to the receptor (Fas receptor) on the surface of tumor cells; alternatively, the TNF-α secreted by CTL binds to TNF receptors on the surface of tumor cells, activating the signaling pathway in the cells and further inducing

Table 3 CHM herb regulation of naïve lymphocyte activation in lymph nodes

Type of CHM herb	Active ingredients	T cells		Mechanism/pathway findings	Reference
		Enhances cellular immunity	Inhibits the immune escape of cancer cells		
CHM monomers	Lentinan		√	Decreased the induction of CD4, CD25, and Tregs; increased the expressions of IFN-γ, TNF-α, and IL-12	Wang *et al.* (60)
	Astragalus polysaccharides		√	Downregulated the expression of PD-L1 on the cell surface via the AKT/mTOR/p70S6K pathway	Lee *et al.* (61)
	Epimedium polysaccharides		√	Significantly decreased the expression of IDO in tumor tissue; increased the levels of immune cytokines IL-2 and IFN-γ; and restored peripheral blood $CD4^+/CD8^+$ ratio	Wang *et al.* (62)
	Angelica sinensis polysaccharide	√		Promoted a Th2→Th1 switch	Luo *et al.* (63)
	Ginseng polysaccharide	√		Promoted a Th2→Th1 switch	Luo *et al.* (63)
	Lycium barbarum polysaccharides	√		Promoted a Th2→Th1 switch	Luo *et al.* (63)
	Glossy ganoderma polysaccharide	√		Promoted a Th2→Th1 switch	Luo *et al.* (63)
	Thymopeptide	√		Promoted a Th2→Th1 switch	Luo *et al.* (63)
	Asparagus juice	√		Promoted the transformation and proliferation of peripheral blood T lymphocytes	Li *et al.* (64)
	Emodin	√		Increased T cell activation	Choudhari *et al.* (65)
	Icariin	√	√	Participated in regulating Th1/Th17 or Th2 balance and Th17/Treg, and NK proliferation	Shen *et al.* (66)
	Peptide fraction from the larvae of Musca domestica	√		Initiated Th1-mediated immunity	Sun *et al.* (67)
	Ethanol extract of Nakai		√	Inhibited the expressions of PD-L1, Foxp3, and TGF-β	Yao *et al.* (68)
	SA		√	Increased Bax expression and decreased Bcl-2 protein levels; inhibited PD-L1 in the activated TNBC cells in EMT by upregulating miR-200c and concurrently inhibited the EMT process and PD-L1	Peng *et al.* (69)
	Erianin		√	Inhibited PD-L1 expression and induced lysosomal degradation of PD-L1	Yang *et al.* (70)
	Huaier extract	√		Stimulated the proliferation of allogeneic active CD4 T cells, driving their differentiation into Th1 subsets	Pan *et al.* (71)
	Huaier extract	√		Increased the levels of CD4 T, CD4 T/CD8 T, and Th1 cytokines; downregulated the mRNA expressions of key genes PI3KR1, Wnt1, and Notch1 in the PI3K/AKT, Wnt/β-catenin and Notch pathways; downregulated Bcl-2 protein expression; upregulated Bax protein expression	Sun (72)
	Yam extract	√		Increased the levels of CD4 T, CD4 T/CD8 T, and Th1 cytokines; downregulated the mRNA expressions of key genes PI3KR1, Wnt1, and Notch1 in the PI3K/AKT, Wnt/β-catenin, and Notch pathways; downregulated Bcl-2 protein expression; upregulated Bax protein expression	Sun (72)
	Cinobufotalin	√		Increased T lymphocyte subset	He (73)
CHM compound prescriptions	Aiduqing formula		√	Inhibited the expression and secretion of CXCL1 by TAMs; suppressed the chemotaxis and differentiation of naïve CD4 T cells into Tregs; enhanced the cytotoxic effect of CD8 T cells	Li *et al.* (74)
	Anfei decoction	√		Enhanced the immune function of Th1 cells to correct the immune imbalance; increased the amounts of $CD4^+$ and $CD8^+$ T lymphocytes	Ren (75)
	Compound yin-nourishing and yang-warming recipe	√		Promoted T cell differentiation into Th1 and CTL; increased the Th1/Th2 ratio (IFN-γ/IL-4)	Zhao *et al.* (47)
	Gehua Jiecheng decoction		√	Downregulated Tregs, TAM cells, and MDSCs; decreased the expressions of angiogenesis-related molecules CD31 and VEGF	Cheng *et al.* (76)
	Wuji pill	√		Ginsenosides promoted the proliferation of T cells	Zhou *et al.* (77)
	Detoxification method by tonifying kidney and lung		√	Enhanced the body's antitumor immune response by reducing the levels of $CD4^+CD25^+$Treg cells, Foxp3, and B7-H3	Lin *et al.* (78)
	Liuwei Dihuang pills	√		Reduced Th2 cells to regulate the balance of Th1/Th2 and Th17 cells	Zou (79)
	A self-designed CHM prescription	√		Increased $CD4^+$ and decreased $CD8^+$, and therefore elevated the $CD4^+/CD8^+$ ratio	Zhou *et al.* (80)
	Modified Sijunzi decoction	√		Increased $CD4^+$ and decreased $CD8^+$, and therefore elevated the $CD4^+/CD8^+$ ratio	Wang *et al.* (81)

Table 3 (*continued*)

Table 3 (*continued*)

Type of CHM herb	Active ingredients	T cells		Mechanism/pathway findings	Reference
		Enhances cellular immunity	Inhibits the immune escape of cancer cells		
	Recipe for strengthening vital qi to eliminate pathogenic factor	√		Slightly increased the $CD3^+$, $CD4^+$, NK cell levels, and $CD4^+/CD8^+$ ratio	Liu *et al.* (82)
	CHM herbs for invigorating spleen and kidneys	√		Improved immune indicators, such as CD3, CD4, CD4/CD8, and NK cells	Jiang *et al.* (83)
	Xiao'ai Jiedu prescription	√		Improved $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ ratio, and NK cell activity	Zhou *et al.* (84)
	Fuzheng Feiliu formula		√	Decreased peripheral blood $CD4^+/CD25^+$/Treg cells	Wang (85)
	A combination of herbs for benefiting qi, invigorating spleen, and clearing heat	√		$CD3^+$/HLA-DR^+ (activated T lymphocytes)	Liu *et al.* (86)
	Fuzheng Pingxiao decoction	√		Increased the levels of Th1, IL-2, and IFN-α	Wang (87)
	CHM herbs for invigorating spleen and regulating qi		√	Reduced the amount of Treg cells in the microenvironment and increased the amount of $CD4^+$ T cells	Lu (88)
	CHM herbs for invigorating qi, clearing heat, and nourishing yin	√		Regulated Th1/Th2 balance	Han *et al.* (89)
	CHM herbs for invigorating qi, nourishing essence, detoxifying, and resolving hard mass		√	Improved the Treg/Th17 cell imbalance	Yin (90)
	A method for invigorating qi and nourishing yin	√		Increased the expression of a Th1-specific transcription factor T-bet; decreased the expression of a Th2 transcription factor GATA-3; reversed the Th1/Th2 drift in older adult patients with non-small cell lung cancer	Wang (91)
CHM patent medicines	Xihuang pill	√		Regulated the peripheral blood Th1/Th2 balance in rats with precancerous lesions of the breast	Li *et al.* (92)
	Pingfei mixture	√		Suppressed tumors in mouse models; changed cell proliferation cycle; stimulated splenic lymphocyte proliferation; increased serum IL-2 level	Xu *et al.* (93)
	Qilian Fuzheng capsule	√		Improved $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ ratio, and NKT cell activity	Wang (94)
	Feiji No.1 recipe	√		Increased thymus index and spleen index; improved $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ ratio; downregulated $CD8^+$ level	Lv *et al.* (95)
	Compound Kushen injection	√		Increased $CD3^+$ and $CD4^+$ levels and decreased $CD8^+$ level	Gong *et al.* (96)
	Kang'ai injection	√		Improved CD4 and CD4/CD8 and decreased CD8	Wang *et al.* (81)
	Compound E-zhu oil capsules	√		Significantly increased peripheral blood $CD4^+/CD8^+$	Jiang *et al.* (97)
	Shengxue granules	√		Increased $CD3^+$ and $CD4^+$ levels and $CD4^+/CD8^+$ ratio and decreased $CD8^+$ level	Ji *et al.* (98)
	Fuzheng Yiliu granules	√	√	Suppressed the expression of Tregs; increased the levels of CD3, CD4, and NK cells and the concentration of TNF-α	Cao (99)
	Ultramicro-Yupingfeng Pilular	√		Increased the proportion of T lymphocytes	Cai *et al.* (100)

CHM, Chinese herbal medicine; IFN, interferon; TNF, tumor necrosis factor; IL, interleukin; PD-L1, programmed death-ligand 1; Th, T helper; NK, natural killer; TGF, tumor growth factor; SA, sativan; TNBC, triple-negative breast cancer; EMT, epithelial-to-mesenchymal transition; CXCL, C-X-C motif chemokine ligand; TAMs, tumor-associated macrophages; CTL, cytotoxic T lymphocyte; MDSCs, myeloid-derived suppressor cells; VEGF, vascular endothelial growth factor; HLA-DR, human leukocyte antigen-DR; NKT, natural killer T.

Table 4 CHM herb regulation of T-cell infiltration into tumor tissue

Type of CHM herb	Active ingredients	Type of mechanism		Mechanism/pathway findings	Reference
		Negatively regulate tumor angiogenesis	Adhesion molecules, chemotactic factors, and others		
CHM monomers	β-elemene	√	√	Regulated the expressions of several key molecules involved in tumor angiogenesis and metastasis, such as VEGF, MMP, E-cadherin, N-cadherin, and vimentin	Zhai *et al.* (103)
	β-elemene		√	Upregulated the expression of E-cadherin by regulating the ERα/MTA3/SNAI1 pathway	Zhang *et al.* (104)
	Ginsenoside Rh2		√	Enhanced $CD4^+$ and $CD8a^+$ T lymphocyte infiltration in tumors	Wang *et al.* (105)
	Ginsenoside Rg3	√		Inhibited the expressions of VEGF-C, VEGF-D, and VEGFR-3 in an orthotopic mouse model of human gastric cancer	Dai *et al.* (106)
	Ginsenoside	√		Regulated transcription and suppressed the expressions of VEGF and VEGF2 by inhibiting the Wnt/β-catenin signaling pathway, thereby inhibiting AKT phosphorylation	Han *et al.* (107)
	Tanshinone IIA	√		Reduced HIF-1α level and inhibited the secretion of VEGF and bFGF	Sui *et al.* (108)
	Silybin	√		Downregulated the mTOR/p70S6K/4E-BP1 signaling pathway; and upregulated p-AKT to downregulate VEGF expression	García-Maceira *et al.* (109)
	Solanum nigrum L. extract	√		Increased $CD4^+$, $CD4^+/CD8^+$, and ES levels and decreased $CD8^+$ and VEGFR levels	Yu (110)
	Ethanol extract from Amomum tsao-ko	√		Downregulated p-STAT3, NF-κB, IL-6, and VEGF	Chen *et al.* (111)
CHM compound prescription	Fuzheng Jiedu formula	√		Inhibited the TAM-mediated PI3K/AKT/TSC1/Rheb/mTOR signaling pathway and unfolded protein response; reversed the formation of immunosuppressive TME; reduced the expression of relevant angiogenic factors in the TME	Song (53)
	Fuzheng Jiedu formula	√		Downregulated the expressions of immunosuppressive factors (Arg-1 and IL-10) and upregulated the expressions of antiangiogenic factors (TNF-α and COX-2); inhibited angiogenesis in the TIME	Zhang (112)
	Fuzheng Jiedu formula	√		Baicalein, dioscin, and quercetin: downregulated VEGF-A expression Quercetin: inhibited VEGFR2 expression from suppressing tumor angiogenesis Kaempferol: inhibited HIF-1α and VEGFR2 in endothelial cells by suppressing the PI3K/AKT/mTOR signaling pathway	Shi *et al.* (113)
	Recipes for strengthening the spleen and tonifying the kidney	√		Downregulated VEGF-A expression; and upregulated the expression of HB-EGF	Zheng *et al.* (114)
	Shugan Jianpi recipe	√		Upregulated NKT expression and remodeled its immune function; downregulated negative immune regulators including IL-6, IL-4, IL-13, and IFN-γ; upregulated $CD4^+/CD8^+$ ratio and downregulated TGF-β and VEGF expressions	He (115)
	Bufei Xiaoji drink	√		Effectively reduced the secretion of immunosuppressive cells (e.g., sCD44v6, VEGF, TGF-β1, and $CD4+CD25^+$ Tregs)	Rong *et al.* (116)
	Water extract of Yupingfeng powder	√		Downregulated VEGF, TSLP, and p-STAT3	Yuan *et al.* (117)
	Shiquan Yuzhen decoction	√		Downregulated VEGF-A and HIF-1α; and upregulated $CD8^+$ T and Treg cells	Sun *et al.* (118)
	Xiaotan Sanjie decoction	√		Downregulated Notch-1, Hes1, VEGF, and VEGFR1/2	Shi *et al.* (119)
	Jiedu recipe	√		Downregulated VEGFR, p-AKT, p-Erk, p-NF-kB, and HIF-1	Lin *et al.* (120)
	Gehua Jiecheng decoction	√		Downregulated the expressions of angiogenesis-related molecules CD31 and VEGF	Zhou *et al.* (77)

CHM, Chinese herbal medicine; VEGF, vascular endothelial growth factor; MMP, matrix metalloprotein; ERα, estrogen receptor-α; MTA3, metastasis-associated protein 3; SNAI1, snail family transcriptional repressor 1; VEGFR, VEGF recepto ; bFGF, basic fibroblast growth factor; TAM, tumor-associated macrophages; TME, tumor microenvironment; Arg-1, arginase-1; IL, interleukin; TNF, tumor necrosis factor; TIME, tumor immune microenvironment; HB-EGF, heparin-binding epidermal growth factor; NKT, natural killer T; TGF, tumor growth factor; HIF-1, hypoxia-inducible factor-1; NF-κB, nuclear factor-κB.

Table 5 CHM herb regulation of tumor-cell killing

Types of CHM herbs	Active ingredients	Mechanism								Mechanism/pathway findings	Reference
		CTL		NK/MΦ		Reverses immunosuppression					
		Upregulates amount and function of $CD8^+$ T cells	Enhances the tumor cell-killing ability of CTL	Directly upregulates the amount/function of cells	IFN-γ/ IL-12	Treg	MDSC	TGF-β1/ IL-10	PD-1/ PD-L1		
CHM monomers	Radix Glycyrrhizae polysaccharide	√								Increased the thymus index, spleen index, and amount of T lymphocytes; increased the levels of cytokines IL-2, IL-6, and IL-7; lowered the protumor cytokine TNF-α	Ayeka *et al.* (121)
	Astragalus polysaccharides								√	Downregulated the expression of PD-L1 via the AKT/mTOR/p70S6K pathway	Sun *et al.* (67) and Liao *et al.* (122)
	Astragalus polysaccharides				√				√	Increased the levels of IL-2 and IFN-γ; downregulated PD-1 protein and mRNA expressions; down-regulated the expression of PD-L1 and PD-L2 proteins and PD-L2 mRNA	Wang *et al.* (123)
	Novel acidic polysaccharide RPAPS			√						Promoted the activation of macrophages and lymphocytes; stimulated the proliferation of splenocytes	Zhang *et al.* (124)
	Lentinan	√	√	√	√	√		√		Upregulated the proportions of $CD3^+$ and $CD8^+$ cytotoxic T cell subsets and the levels of $CD3^+$, $CD56^+$, and NK cells; reduced $CD4^+$ and $CD25^+$ Treg induction; downregulated IL-10 and TGF-β1 secretion; and upregulated IFN-γ, TNF-α, and IL-12 secretion	Wang *et al.* (60)
	Epimedium koreanum polysaccharides		√							Induced Th cell differentiation and enhanced its immune-mediated antitumor activity; promoted the proliferation of $CD4^+$ T cells, increased the level of IFN-γ, and enhanced the tumor cell-killing capability of T cells	Wang (28)
	Lycium barbarum polysaccharides	√		√		√	√		√	Downregulated the expression level of PD-1 molecules in T cells in tumor tissues; lowered the proportions of $PD\text{-}1^+CD25^-CD4^+$ Tregs and $PD\text{-}1^-CD25^+CD4^+$ Tregs; enhanced the antitumor activities of splenocytes (mainly NK), TDLN cells (mainly CTL), and macrophages	Deng (125)
	Astragalus polysaccharides				√				√	Increased the levels of IL-2 and IFN-γ; downregulated PD-1 protein and mRNA expressions; down-regulated the expression of PD-L1 and PD-L2 proteins and PD-L2 mRNA	Wang *et al.* (123)
	Polyporusus bellatus							√		Regulated the secretion of immunosuppressive molecule TGF-β1	Cui *et al.* (126-128)
	Fomes officinalis Ames polysaccharide		√		√					Increased the proportions of $CD3^+$ T and $CD4^+$ T cells and decreased the proportion of $CD8^+$ T cells, thereby increasing $CD4^+/CD8^+$ ratio; elevated cytokines such as TNF-α, IL-2, and IFN-γ	Shabiti (129)
	Gastrodin	√								Promoted CD8 T cell response by enhancing T-cell proliferation and proinflammatory cytokine expression	Liu *et al.* (40)
	Prim-O-glucosylcimifugin						√		√	Inhibited the proliferation, metabolism, and immunosuppressive ability of PMN-MDSCs by suppressing arginine metabolism and TCA cycle; enhanced the antitumor activity of PD-1 inhibitors by enhancing the anti-PD-1 immune checkpoint blockade	Gao *et al.* (130)
	Extract of Pinellia pedatisecta Schott				√	√				Increased the proportion of Th1 cell subset (characterized by IFN-γ production and transcription factor Tbet) and decreased the proportions of Th2 cells (characterized by IL-4 production and transcription factor GATA3) and Th17 cells (characterized by IL-17 production and transcription factor RoRγt)	Huang *et al.* (131)
	Triterpenoids from Ganoderma lucidum		√							Upregulated the expressions of IL-6 and TNF-α	Feng *et al.* (36)
	Ganoderma lucidum spore oil				√					Increased the serum IFN-γ level	Jiang *et al.* (132)
	Ginsenoside Rh2	√							√	Promoted the killing effect of lymphocytes on tumor cells and enhanced the inhibitory effect of anti-PD-1 antibodies on tumor cells	Qiang (133)
	Tanshinone IIA			√						Enhanced the killing effect of NK cells on tumor cells; upregulated DR5 and ULBP1 expressions on the surface of tumor cells	Sun (134)
	Cycloastragenol	√								Enhanced the killing function of $CD8^+$ T cells by promoting the presentation of tumor cell surface antigens	Deng *et al.* (135)
	Rediocide-A			√						Downregulated CD155 expression to block tumor resistance to NK cells	Ng *et al.* (136)
	Arsenic trioxide							√		Regulated the secretion of immunosuppressive molecules TGF-β1 and IL-10	Cui *et al.* (126-128)
	Tetramethylpyrazine							√		Regulated the secretion of immunosuppressive molecules TGF-β1 and IL-10	Cui *et al.* (126-128,137)

Table 5 (*continued*)

Table 5 (*continued*)

Types of CHM herbs	Active ingredients	Mechanism								Mechanism/pathway findings	Reference
		CTL		NK/MΦ		Reverses immunosuppression					
		Upregulates amount and function of $CD8^+$ T cells	Enhances the tumor cell-killing ability of CTL	Directly upregulates the amount/function of cells	IFN-γ/IL-12	Treg	MDSC	TGF-β1/IL-10	PD-1/PD-L1		
	Oxymatrine							√		Regulated the secretion of immunosuppressive molecule IL-10	Cui *et al.* (126-128,137)
	Artesunate							√		Regulated the secretion of immunosuppressive molecule TGF-β1	Cui *et al.* (126-128,137)
	Proteins extracted from mycelia of Omphalia lapidescens				√					Increased serum IFN-γ level, decreased serum IL-4 content, and increased spleen index	Chen *et al.* (138)
	Anemone raddeana Regel extracts		√		√					Increase the levels of cytokines such as TNF-α and IL-12 secreted by macrophages	Zhao (139)
	Sativan								√	Inhibited PD-L1 in the activated TNBC cells in EMT and concurrently inhibited the EMT process and PD-L1	Peng *et al.* (69)
	Erianin	√							√	Inhibited PD-L1 expression and induced lysosomal degradation of PD-L1; enhanced the activity of CTLs	Yang *et al.* (70)
	Huaier extract	√								Activated Th1 immune response by regulating the MAPK and PI3K/AKT signaling pathways	Pan *et al.* (71)
	Yam extract	√								Upregulated $CD4^+$ T cells, $CD4^+/CD8^+$ T cells, and Th1 level	Sun (72)
	Panax japonicus	√		√						Increased the proportions of peripheral blood NK cells, B cells, neutrophils, and T lymphocyte subsets and increased the spleen index and thymus index	Huang (140)
	Proanthocyanidins	√	√							Promoted the secretion of perforin, IFN-γ, and TNF-α, and the expression of $CD8^+$ T cells	Zhang (41)
	Baicalein	√	√							Promoted the secretion of perforin, IFN-γ, and TNF-α, and the expression of $CD8^+$ T cells	Zhang (41)
	Apigenin	√	√							Promoted the secretion of perforin, IFN-γ, and TNF-α, and the expression of $CD8^+$ T cells	Zhang (41)
	Extract of Ginkgo biloba exotesta		√				√			Upregulated the Fas mRNA expression in tumor cells, downregulated the expression of FasL mRNA and DcR3 Mrna expressions in tumor cells, and decreased the proportion of Tregs	Wang (141)
	Hydroxysafflor yellow A						√			Lowered the proportion of $CD4^+CD25^+Foxp3^+$ T cells in splenocytes and reduced the Foxp3 mRNA and protein expressions in tumor tissues	Wang (142)
	Fomes fomentarius ethanol extract	√	√	√						Stimulated the proliferation of spleen lymphocytes and increased the phagocytic ability of phagocytes	Zhao *et al.* (143)
	Cinobufotalin			√						Increased the activity of NK cells and the proportion of the T lymphocyte subset	He (73)
	β-elemene				√					Stimulated IFN-γ secretion	Ni (144)
CHM compound prescriptions	Qi-lowering decoction	√								Activated $CD8^+$ T cells to promote the apoptosis of tumor cells	Zhang *et al.* (48)
	Shiquan Yuzhen decoction	√	√	√						Upregulated the thymus and spleen indexes; upregulated the expressions and secretion of CD3, CD4, IL-2, IFN-β, and TNF-α in leukocytes and lymphocytes; upregulated the amounts of NK cells and lymphocytes	Sun *et al.* (118)
	Gansui root–Pinellia tuber decoction									Downregulated AKT/STAT3/ERK signaling pathway and inhibited IL-1β and IFN-γ	Feng *et al.* (145)
	Anfei decoction	√								Enhanced the immune function of Th1 cells; increased the amounts of $CD4^+$ and $CD8^+$ T lymphocytes	Ren (75)
	Gegen Qinlian decoction		√	√						Raised the proportions of $CD4^+$ T cells and NKT cells and downregulated the expression levels of NF-κB and TNF-α	Li *et al.* (146)
	Compound yin-nourishing and yang-warming recipe	√	√		√					Promoted the maturation of DCs through the MAPK and NF-κB signaling pathways; promoted the DCs to release cytokines, including IFN-γ, IL-1β, IL-2, IL-12, and TNF-α; enhanced the proliferation of T cells; promoted T-cell differentiation into Th1 and CTL; increased the proportions of Th1/Th2 (IFN-γ/IL-4)	Zhao *et al.* (47)

Table 5 (*continued*)

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Types of CHM herbs	Active ingredients	Mechanism								Mechanism/pathway findings	Reference
		CTL		NK/MΦ		Reverses immunosuppression					
		Upregulates amount and function of $CD8^+$ T cells	Enhances the tumor cell-killing ability of CTL	Directly upregulates the amount/function of cells	IFN-γ/IL-12	Treg	MDSC	TGF-β1/IL-10	PD-1/PD-L1		
	Gehua Jiecheng decoction		√	√						Raised the proportions of $CD4^+$ T cells and NKT cells and downregulated the expression levels of NF-κB and TNF-α	Zhou *et al.* (77)
	Erdong Gao			√						Increased macrophage activity and decreased serum TNF-α level	Guo *et al.* (147)
	Liuwei Dihuang pills	√			√					Increased total T cells and total B cells, decreased IL-1β, increased IL-2 and IFN-γ levels, and decreased $CD4^+/CD8^+$ ratio	Zou (79)
	Sijunzi decoction					√				Reduced Th17 and Th17/Treg and reduced Th2 cells to regulate the Th1/Th2 balance	Zou (79)
	Lingjia anticancer medicine	√	√	√		√		√		Reduced the proportion of Treg cells and downregulated the levels of TGF-β and IL-10; promoted the proliferation of spleen lymphocytes; increased the levels of IL-2, IFN-γ, perforin, and granzyme B, and increased the proportion of NK cells	Pan *et al.* (148)
	Yiliu drink	√		√						Reversed the inhibitory effect of S180 xenografts on NK cell activity, transformation index, IL-2 activity, and proportions of $CD4^+$ and $CD8^+$ cells in mouse splenocytes	Yang *et al.* (149)
	Shugan Jianpi Recipe			√				√		Upregulated NKT expression and remodeled its immune function; downregulated negative immune regulators including IL-6, IL-4, IL-13, and IFN-γ; upregulated $CD4^+/CD8^+$ ratio, and downregulated TGF-β and VEGF expressions	He (115)
	Recipe for strengthening vital qi to eliminate pathogenic factors			√						Improved $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ ratio and NK cell activity	Liu *et al.* (82)
	Detoxification method by tonifying kidney and lung						√			Decreased the levels of $CD4^+CD25^+$Tregs, Foxp3, and B7-H3 in peripheral blood and tumor xenografts	Lin *et al.* (78)
	Immunopotentiation decoction							√		Inhibited TGF-β1 production and upregulated IL-10 expression	Cui *et al.* (150)
CHM patent medicines	Jinfukang			√						Enhanced the clearance of tumor cells in peripheral blood by NK cells	Que *et al.* (151)
	Quxie capsule	√								Increased the amount of Th cells	Sun *et al.* (152)
	Huisheng liquid			√	√					Improved macrophage function and promoted IL-12 and IL-18 secretion	Xiao (153)
	Ganoderma applanatum polysaccharide injection	√		√						Increased the amounts of $CD4^+$ and $CD8^+$ T cells in peripheral blood, the serum IL-2 level, and the phagocytosis rate and phagocytosis index of macrophages	Guan (154)
	Astragalus injection	√		√						Promoted ConA-stimulated splenocyte transformation, IL-2 production, and IL-2Rα expression; improved NK activity and IL-2 responsiveness of CTL-2 cells	Yang (155)
	Polyporusus Bellatus injection	√		√						Promoted ConA-stimulated splenocyte transformation, IL-2 production, and IL-2Rα expression; improved NK activity and IL-2 responsiveness of CTL-2 cells	Yang (155)
	Fuzheng Yiliu granules		√	√		√				Inhibited the expression of Treg cells, increased the proportions of CD3 and CD4 cells and NK cells, and increased the serum TNF-α level	Cao (99)

CHM, Chinese herbal medicine; CTL, cytotoxic T lymphocyte; NK, natural killer; IFN, interferon; IL, interleukin; MDSC, myeloid-derived suppressor cell; TGF, tumor growth factor; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TNF, tumor necrosis factor; TDLN, tumor-draining lymph node; PMN, polymorphonuclear; TCA, tricarboxylic acid; Th, T helper; EMT, epithelial-to-mesenchymal transition; DCs, dendritic cells; Treg, regulatory T cell; VEGF, vascular endothelial growth factor; NKT, natural killer T.

apoptosis of tumor cells. However, if FasL is highly expressed on the surface of tumor cells and Fas is highly expressed on the surface of CTL, CTL will become the target cell and then be killed (156). Wang *et al.* (37) and Pan *et al.* (148) confirmed that some herbal extracts and CHM compound prescriptions could regulate the antitumor immune response by regulating the expressions of perforin and granzyme. Wang *et al.* (141) reported that the extract of *Ginkgo biloba* exotesta upregulated Fas messenger RNA (mRNA) expression and downregulated FasL mRNA expression in tumor cells. In addition, there are CHM monomers, CHM compound prescriptions, and CHM patent medicines that can upregulate TNF-α secretion and thus enhance the tumor-killing effect of CTL (*Table 5*). In addition, Zhang (41) demonstrated that four CHM monomers (proanthocyanidins, gastrodin, baicalein, and apigenin) can promote not only the secretion of TNF-α but also enhance the killing of tumor cells by CTL through the induced expressions of perforin and granzyme.

In addition, the antibody-dependent cell-mediated cytotoxicity (ADCC) of macrophages (MΦ) and natural killer (NK) cells is another significant means of killing tumor cells and thus has become an important supplement to the final step of CIC. Immunoglobin G (IgG) mediates this effect through IgG Fc receptors on the surface of macrophages and NK cells. The ADCC effect of NK cells can be significantly enhanced by activating cytokines such as IFN-γ and IL-12 (136). Many CHM monomers (e.g., tanshinone IIA), CHM compound prescriptions (e.g., the recipe for strengthening vital qi to eliminate pathogenic factor), and CHM patent medicines (Liuwei Dihuang pill) can directly increase the amount or function of macrophages or NK cells to enhance their ADCC effect. In contrast, a variety of CHM monomers (e.g., β-elemene), CHM compound prescriptions (e.g., Yangyinwenyang formula), and CHM patent medicines (e.g., Huisheng oral liquid) can indirectly enhance the ADCC effect of NK cells by upregulating the expression of IFN-γ and IL-12 (*Table 5*).

Tumor cells can inhibit the body's killing of tumor cells by actively inducing tumor-bearing bodies to produce Tregs and myeloid-derived suppressor cells (MDSCs), achieved mainly by secreting immunosuppressive factors such as TGF-β1 and IL-10 (157). CHM monomers/compounds, CHM compound prescriptions, and CHM patent medicines, represented by lentinan, Gansui root-Pinellia tuber decoction, and Fuzheng Yiliu granules, respectively, can reverse such immunosuppression by downregulating the amount or function of Tregs or MDSCs. Meanwhile, CHM monomers and CHM compound prescriptions can directly downregulate the secretion of immunosuppressive factors TGF-β1 and IL-10, as demonstrated by Cui *et al.* in a series of studies (126-128,137) (*Table 5*).

The interaction between PD-1 and PD-L1 on T cells can lead to T cell anergy, exhaustion, and apoptosis. For one, the activation of PD-1/PD-L1 signaling pathway transmits inhibitory signals to tumor cells, promoting tumor cells to resist immune effector cell-mediated apoptosis (158); for another, it suppresses the immune cell secretion of proinflammatory factors such as IFN-γ, promotes the secretion of immunosuppressive molecules such as IL-10 to suppress T-cell immune response (159,160), and even induces apoptosis (161), thereby mediating immune escape. Blocking PD-L1/PD-1 binding can relieve the inhibition of the effector T cells (14). A total of 6 studies (*Table 5*) reported that CHM herbs (mainly CHM monomers) regulate PD-1/PD-L1 expression through multiple pathways, thereby regulating the killing of tumor cells by the immune system.

Discussion

The studies listed in *Tables 2-5* have proven that CHM and its active ingredients can enhance the body's immune function, reduce toxicities, and increase efficiency through the second, third, fifth and seventh steps in CIC. As can be seen from the above tables, different CHM can act on different receptor cells and result in different effects. Heat-clearing and detoxicating medicine plays a role in anti-tumor by regulating cancer-associated fibroblasts and extracellular matrix. Supplementing medicine exerts its anti-tumor effect by targeting tumor-associated immune cells in the TME, while qi-rectifying and blood-invigorating medicine targets the hypoxic and acidic environment in TME. However, the currently available studies have the following limitations: First, most of the research focused on the roles of CHM herbs in regulating immune cells and the expressions of immune factors, and the specific CIC steps targeted by CHM herbs were poorly investigated. Therefore, it is important to carry out research on the targets and mechanisms of CHM herbs regulating CIC. Second, most studies on the regulation of CIC by CHM herbs were performed on the level of systemic immunity, with little evidence of local immunity. In fact, CHM antitumor therapies are based on the combination of holistic view and syndrome differentiation, which emphasizes the importance of pathological changes of local zang-fu while

pursuing the balance between yin and yang in the whole body. Therefore, new and innovative CHM theories of immune balance are urgently required to guide the research on the pharmacodynamic mechanisms through which CHM regulate tumor immunity. Third, most relevant studies focused on the restoratives (e.g., ginseng and astragalus) while fewer studies have explored the roles of CHM for clearing heat and removing toxicity and those for activating blood circulation. One of the principles of CHM in treating malignant tumors is "strengthening vital qi to eliminate pathogenic factors". Indeed, eliminating pathogenic factors also functions to strengthen vital qi. CHM for eliminating pathogenic factors (including CHM for clearing heat and removing toxicity and those for activating blood circulation) can be used in combinations based on the of the individual patient's specific condition. Therefore, pharmacological research on antitumor CHM herbs should be further carried out to enrich the database of CHM herbs for tumor immunomodulation. Fourth, most of the currently available research focused on the pharmacodynamic mechanisms of CHM monomers or natural compounds, while few studies have investigated the effects of CHM compound prescriptions on CIC. Therefore, multiomics technologies, such as network pharmacology, botanomics, metabolomics, and bioinformatics, should be used to explore the optimal combinations of CHM targeting multiple steps in CIC so as to further identify new directions in CHM antitumor immunotherapy.

Since its introduction, the concept of CIC has been widely applied in clinical application and basic research. CHM is a critical part of traditional Chinese culture. The value of CHM and their active ingredients and that of CHM compound prescriptions in treating malignant tumors is being increasingly recognized. The intervention of CHM on immune cells and angiogenic cells is a hot research topic at present, but with the continuous development of tumor biology and tumor immunology, tumor-related fibroblasts and extracellular matrix will be a hot research topic in the future. Future research on CIC and CHM pharmacology will further clarify the mechanisms through which CHM regulate tumor immunity. Accordingly, the advantages of CHM in regulating tumor immunity will be additionally recognized, and there will be a broader platform for finding the optimal combinations of CHM herbs for antitumor immunotherapy.

Conclusions

The mechanisms underlying CHM antitumor are complex. On the one hand, CHM (e.g., ginseng and astragalus) can enhance the activity of positive immune cells to improve the body's anti-tumor immunity. On the other hand, CHM (e.g., tripterygium wilfordii and sophora flavescens) can inhibit the polarization of negative immune cell so as to alleviate the state of immune suppression. TIME includes a variety of immune cells, stromal cells, cytokines and so on. Although the currently available studies have shed light on some antitumor mechanisms, future research is needed to elucidate better the targets (e.g., PD-L1) and mechanisms of CHM regulating CIC. This review clarifies the current progress and creates optimism for CHM's role in regulating the tumor immunity.

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Supplementary

Table S1 Detailed search strategy of the PubMed and CNKI databases

Items	Database	Number of results
((((((((((((((((((tumour(Title/Abstract)) OR (Tumor(Title/Abstract))) OR (Neoplasm(Title/Abstract))) OR (Tumors(Title/Abstract))) OR (Neoplasia*(Title/Abstract))) OR (Cancer*(Title/Abstract))) OR (Malignant Neoplasm(Title/Abstract))) OR (Malignancy(Title/Abstract))) OR (Malignancies(Title/Abstract))) OR (Malignant Neoplasms(Title/Abstract))) OR (Neoplasm, Malignant(Title/Abstract))) OR (Neoplasms, Malignant(Title/Abstract))) OR (Benign Neoplasms(Title/Abstract))) OR (Benign Neoplasm(Title/Abstract))) OR (Neoplasms, Benign(Title/Abstract))) OR (Neoplasm, Benign(Title/Abstract))) AND ((((((((((((((traditional Chinese medicine(Title/Abstract)) OR (Zhong Yi Xue(Title/Abstract))) OR (Chung I Hsueh(Title/Abstract))) OR (Hsueh, Chung I(Title/Abstract))) OR (Chinese Medicine, Traditional(Title/Abstract))) OR (Chinese Traditional Medicine(Title/Abstract))) OR (Traditional Chinese Medicine(Title/Abstract))) OR (Traditional Medicine, Chinese(Title/Abstract))) OR (Traditional Tongue Diagnosis(Title/Abstract))) OR (Tongue Diagnoses, Traditional(Title/Abstract))) OR (Tongue Diagnosis, Traditional(Title/Abstract))) OR (Traditional Tongue Diagnoses(Title/Abstract))) OR (Traditional Tongue Assessment(Title/Abstract))) OR (Tongue Assessment, Traditional(Title/Abstract))) OR (Traditional Tongue Assessments(Title/Abstract)))) AND ((((immune(Title/Abstract)) OR (Immune Systems(Title/Abstract))) OR (System, Immune(Title/Abstract))) OR (Systems, Immune(Title/Abstract)))	PubMed	499
(theme=traditional Chinese medicine) AND (theme=tumor) AND (theme=immune)	CNKI	12,532

CNKI, China National Knowledge Infrastructure.

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