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Tumor Immune Regulation by Natural Products: Advances and Challenges

Qianqian Wang[1], Zihan Zhang[2], Zihan Zhang[2], Qiwen Lu[2], Min Li[3,*], Shan Deng[4,*] and Xuan Han[2,*]

[1]*The First Clinical Medical College, Nanjing University of Chinese Medicine, No. 138 Xianlin Avenue, Nanjing, Jiangsu Province, 210023, China*

[2]*School of Integrated Medicine, Nanjing University of Chinese Medicine, No. 138 Xianlin Avenue, Nanjing, Jiangsu Province, 210023, China*

[3]*Oncology Department of Nanjing Municipal Hospital of Traditional Chinese Medicine, No. 157 Daming Road, Nanjing, Jiangsu Province, 210022, China*

[4]*The Third Clinical Medical College, Nanjing University of Chinese Medicine, Nanjing, 210023, People's Republic of China*

***Corresponding Authors:** Shan Deng, The Third Clinical Medical College, Nanjing University of Chinese Medicine, Nanjing, 210023, People's Republic of China, Tel.: 18651811195, E-mail: sharondengs@njucm.edu.cn

Min Li, Oncology Department of Nanjing Municipal Hospital of Traditional Chinese Medicine, No. 157 Daming Road, Nanjing, Jiangsu Province, 210022, China, E-mail: fsyy00340@njucm.edu.cn

Xuan Han, School of Integrated Medicine, Nanjing University of Chinese Medicine, No. 138 Xianlin Avenue, Nanjing, Jiangsu Province, 210023, China, E-mail: hanxuan@njucm.edu.cn

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Abstract

Ethnopharmacological Relevance: Natural products from plants, animals, minerals, and microorganisms are crucial therapeutic resources in traditional and modern medicine. Their extracted active monomers, with definite molecular structures and specific biological activities, have long provided a key material basis for disease treatment, and some have been clinically validated.

Aim of the Review: This review systematically elaborates on the regulatory mechanisms of natural products and their active monomers on key immune cell subsets in the tumor microenvironment (TME), analyzes their pathways in reshaping TME immune status, aiming to inspire future mechanistic studies and accelerate the design of nature-based immunotherapeutics.

Materials and Methods: PubMed and CNKI databases were systematically searched. Existing findings were synthesized, focusing on core TME immune cells to analyze natural products' regulatory mechanisms on these cells' activation, differentiation, cytokine secretion, and signaling pathways.

Results: Natural products regulate TME immune cells via multi-target effects, mildly disrupting immunosuppressive net-

works while awakening latent antitumor immunity. They reshape the tumor niche by modulating key signaling pathways and cellular behaviors, converting cold tumors into immune-hot environments for T lymphocytes infiltration and cytotoxicity. They show synergistic potential alone or with traditional immunotherapies, yet face issues like complex, hard-to-standardize components, poor pharmacokinetics, and insufficient large-scale clinical data.

Conclusions: Natural products have significant potential in tumor immune regulation. Future efforts should integrate multi-omics and AI to elucidate multi-target mechanisms, establish a natural product-immune target database, and combine with strict quality control and clinical trials to accelerate their translation into clinical cancer immunotherapies.

Keywords: Natural products; Immune cells; Tumor microenvironment

Introduction

Critical Immune-Functional Proteins within the Tumor Microenvironment

The tumor microenvironment (TME) constitutes a complex multicellular ecosystem comprising tumor cells, stromal cells, endothelial cells, and dynamically interacting immune populations that collectively regulate tumor progression [1]. Within this landscape, immune cells, including dendritic cells (DCs), myeloid-derived suppressor cells (MDSCs), T and B lymphocytes, natural killer (NK) cells, neutrophils, and tumor-associated macrophages (TAMs) [2] serve as primary effectors that recognize tumor-associated antigens and orchestrate anti-tumor immunity. This bidirectional cellular interplay drives dual outcomes: immune components eliminate malignant cells, while tumors simultaneously develop sophisticated immune evasion strategies such as establishing immunosuppressive niches or exploiting checkpoint pathways [3].

The tumor microenvironment (TME) promotes immune evasion by shielding malignant cells from immunological recognition and attack. Critically, tumor cells exploit immune checkpoint pathways to subvert immune surveillance. Within the TME, cancer cells express programmed death-ligand 1 (PD-L1), which engages programmed death-1 (PD-1) receptors on T lymphocytes to inhibit cytotoxic T cell function [4]. Therapeutic monoclonal antibodies targeting PD-L1 block this interaction, restoring anti-tumor immunity driven by cytotoxic T cells.

Notably, immune checkpoint molecules are expressed beyond tumor cells, including on macrophages, dendritic cells, activated T lymphocytes, and cancer-associated fibroblasts. Regulatory T cells (Tregs), for instance, constitutively express PD-1, enabling PD-L1 binding, which potentiates Treg-mediated immunosuppression and facilitates tumor survival [5].

Similarly, cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) suppresses T cell activation, proliferation, differentiation, and effector functions through ligand binding. This inhibitory receptor competitively binds B7 ligands (CD80/CD86) with greater affinity compared to the co-stimulatory receptor CD28, thereby preventing CD28-mediated co-stimulatory signaling essential for T cell activation [6].

The secretion of diverse cytokines and chemokines by immunosuppressive cells within the TME promotes tumor progression [7]. Furthermore, transforming growth factor-beta (TGF-β) drives tumor metastasis through SMAD signaling activation [8] while impeding T cell recruitment to inflammatory sites [9]. In contrast, interleukin (IL)-10, predominantly secreted by regulatory T cells (Tregs), broadly suppresses immune cell activity yet paradoxically enhances antigen-specific recall responses in memory $CD8^+$ T cells [10].

Interferon-gamma (IFN-γ), a pivotal cytokine in adaptive immunity, enhances MHC-I expression on tumor cells, activates macrophages and dendritic cells, and enhances cross-presentation to $CD8^+$ T cells [11]. Paradoxically, chronic IFN-γ exposure induces PD-L1 upregulation, driving $CD8^+$ T cell exhaustion [12]. IL-12 stimulates IFN-γ production in NK cells and promotes Th1 differentiation during the activation of naïve $CD4^+$ T cells [13]. Emerging evidence indicates that IL-12, IL-15, and

IL-18 collectively reprogram NK cells into memory-like subsets with enhanced anti-tumor functionality [14].

Certain cytokines exhibit dual immunomodulatory roles: tumor necrosis factor-alpha (TNF-α) sensitizes tumor cells to $CD8^+$ T cell cytotoxicity and apoptosis [15]. Conversely, in orthotopic breast cancer mouse models, endogenous TNF-α promotes metastasis and immune-related adverse events [16].

Hypoxic conditions and acidic pH exacerbate immunosuppression by stabilizing hypoxia-inducible factor-1α (HIF-1α), which transactivates immunosuppressive genes [17]. Under cytokine cues (e.g., IL-4, IL-13) and hypoxic stress, tumor-associated macrophages (TAMs) polarize toward immunosuppressive M2-like phenotypes [18]. Concurrently, IL-10, TGF-β, and vascular endothelial growth factor (VEGF) impair DC antigen presentation. Within the TME, chemokines orchestrate pro- or anti-tumor immune responses. For instance, the CCR4-CCL22 axis governs Treg trafficking in breast cancer, the CCR2-CCL2 axis mediates TAM recruitment, and macrophage-derived CCL5 drives leukocyte accumulation at inflammatory sites [19, 20].

Natural Products and Bioactive Monomers

Natural products obtained from multiple sources (plants, animals, minerals, and microorganisms) serve as indispensable therapeutic agents in both traditional and modern medicine for treating human diseases [21, 22].

Bioactive monomers are single chemical entities isolated from natural products, characterized by well-defined molecular structures and specific biological activities. These compounds span diverse chemical classes: alkaloids (e.g., morphine, caffeine), flavonoids (e.g., quercetin, anthocyanins), terpenoids (e.g., menthol, artemisinin), steroids (e.g., cholesterol, progesterone), quinones, coumarins, saponins, and organic acids.

As the fundamental pharmacodynamic basis of natural products, bioactive monomer research provides critical insights for mechanistic elucidation and innovative drug development [23]. For instance, the structural characterization of artemisinin from Artemisia annua L. (sweet wormwood) not only deciphered its anti-malarial mechanism in traditional medicine but also catalyzed the development of optimized derivatives (e.g., artesunate, dihydroartemisinin) with enhanced clinical efficacy [24].

1.3 Targeting Immune Cells in the TME by Natural Products

Targeting specific immune cell subsets to reprogram the tumor microenvironment (TME) into an immunostimulatory milieu represents a key strategy in cancer immunotherapy. Natural products demonstrate significant potential to remodel the TME and enhance immunotherapeutic efficacy by disrupting immunosuppressive barriers through multitarget mechanisms, thereby restoring antitumor immunity.

Natural products modulate the activation, proliferation, and effector functions of T lymphocytes by targeting surface co-stimulatory molecules (e.g., CD28) and co-inhibitory molecules (e.g., CTLA-4, PD-1, PD-L1). In $CD8^+$ T cells, saponin-containing natural products target immune checkpoint molecules, cytokine secretion pathways, and activation/proliferation mechanisms [25]. In $CD4^+$ T cells, polyphenolic-containing compounds regulate differentiation (e.g., suppressing Treg function), restore Th1/Th2 balance, reduce immunosuppression, and enhance helper T cell activity [26].

Polyphenolic-containing natural products reprogram tumor-associated macrophage (TAM) polarization from pro-tumor M2--like to anti-tumor M1-like phenotypes by targeting monoamine oxidase-A (MAO-A)/signal transducer and activator of transcription STAT6 and STAT3 pathways [27]. Saponin-containing agents inhibit TAM-mediated angiogenesis and metastasis via VEGF/matrix metalloproteinase (MMP) signaling blockade, and suppress TAM recruitment by disrupting the CCL2/CCR2 axis and plasminogen activator inhibitor-1 (PAI-1) activity [28].

Flavonoid-containing natural products suppress regulatory B cell (Breg)-mediated immunosuppression by targeting cytokine release (e.g., IL-10), proliferation inhibition, apoptosis induction, and inflammatory response attenuation [29]. The p38/JNK

signaling pathways are critical for dendritic cell (DC) maturation and function [30]. Polysaccharide-containing natural products enhance DC antigen uptake, processing, and presentation capabilities [31]. By modulating IL-2, TNF-α, and IFN-γ levels, these compounds indirectly activate natural killer (NK) cells, augmenting cytotoxicity and tumor infiltration. They also facilitate NK cell recruitment through the CXCL10/CXCR3 axis activation [32, 33].

Polyphenolic-containing natural products inhibit myeloid-derived suppressor cell (MDSC) expansion by targeting arginase-1 and reactive oxygen species (ROS) production, and redirect MDSC differentiation toward dendritic-like phenotypes via Notch/STAT3 pathway modulation [34].

Mechanisms of Natural Product Monomers in Regulating Tumor-Associated Immune Cells

Natural product monomers can regulate multiple functions of immune cells in TME. These findings will be introduced completely in this part and summarized in Table 1.

Table 1: Effects of Natural Compounds on Immune Cell Lineages

Cells	Natural product	Effect	Reference
$CD8^+$ T lymphocytes	Curcumin	Decrease of PD-L1, PD-L2, TIM-3, and Gal-9; Increase of cytotoxicity of $CD8^+$ T lymphocytes; Inhibition of lactic acid metabolism in the tumor microenvironment; MCT1-mediated reduction of lactic acid uptake.	[38, 39, 41, 45, 135]
	Resveratrol	Blocks the interaction between PD-1 and PD-L1; Enhance the infiltration of $CD8^+$ T lymphocytes; Increase the levels of TNF-*α*, IFN-*γ*, IL-12 and IL-2	[40, 45]
	Hesperidin	Activation of $CD8^+$ T lymphocytes; Reduces PD-L1 expression	[41]
	Ginsenoside	Blocks the binding of PD-1 and PD-L1	[46]
	Quercetin	Blocks the binding of PD-1 and PD-L1	[41]
	Apigenin	Decreased expression of PD-L1 on DCs	[41]
	Dendrobium officinale polysaccharide	Decreased expression of PD-1 on $CD8^+$ T lymphocytes	[41]
	Luteolin	Activates $CD8^+$ T lymphocytes and enhances their function; Increases the expression of PD-L1.	[41]
	Paclitaxel	Enhances the response of $CD8^+$ T lymphocytes; Increased proliferation of $CD8^+$ T lymphocytes.	[41]
	Proanthocyadin	Reduces the expression of inhibitory receptors such as PD-1 and TIM-3 on $CD8^+$ T lymphocytes	[41]
	Berberine	Down-regulation of PD-L1 expression on cancer cells; Enhances the cytotoxicity of T cells, the sensitivity of cancer cells to T cells, and the number of $CD8^+$ T lymphocytes	[41, 136]

	Naringenin	Activation of $CD8^+$ T lymphocytes; Increased number of $CD8^+$ T lymphocytes; Increased infiltration of $CD8^+$ T lymphocytes in tumors.	[41]
	6-gingerol	Improves the cytotoxicity of $CD8^+$ T lymphocytes in tumors	[41]
	Ganoderma lucidum polysaccharide	Regulates TGF-β-BCL6 and IL-2-BLIMP1 signaling pathways; Maintains the stem cell-like characteristics of $CD8^+$ T lymphocytes	[41]
	Neem leaf glycoprotein	Increased number of $CD8^+$ T lymphocytes	[41]
$CD4^+$ T lymphocytes	Curcumin	Increases IFN-γ; Reduces IL-10; Reduces FOXP3 expression	[38, 45]
	Ginsenoside	Promotes the differentiation of Th1 and Th17 cells; Reduces Treg cell activity; Regulates the expression of cytokines such as IL-2, IL-6, and TGF-β, and enhances the immune response.	[46]
	Epigallocatechin gallate	Increases the proportion of Th1 cells; Reduces the number of Treg cells, reduces their function; Enhances the anti-tumor activity of $CD4^+$ T cells	[137]
	Resveratrol	Reduces FOXP3 expression; Reduces IL-10 secretion; Attenuates the immunosuppressive effect of Treg cells	[40, 45].
	Ganoderma lucidum polysaccharide	Enhances Th1 cell activity; Reduces the proliferation of Treg cells; Activates dendritic cells; Enhances the anti-tumor effect of $CD4^+$ T cells	[42, 50, 52]
	Astragalus polysaccharide	Promotes the expression of IL-12 and IFN-γ; Enhances the anti-tumor activity of Th1 cells	[138]
	Quercetin	Reduces the secretion of TGF-β and IL-10; Attenuates the immunosuppressive effect of Treg cells.	[139]
	Lycopene	Reduces FOXP3 expression; Weakens the inhibition of Treg cell proliferation; Enhances anti-tumor immune response	[140]
TAMs	Curcumin	Inhibition of M2 polarization of TAMs; Promotes M1 macrophage polarization; Reduces the secretion of pro-tumor factors (such as IL-10, TGF-β)	[27, 141]
	Epigallocatechin gallate	Inhibition of M2 polarization of TAMs; Enhances macrophage phagocytosis; Enhances the ability of antigen presentation.	[64, 142]
	Resveratrol	Inhibition of M2 polarization of TAMs; Improves the balance of inflammatory factors (such as TNF-α, IL-6) in TME.	[59, 61]
	Ginsenoside	Reduces the expression of M2 macrophage markers	[143]

	Andrographolide	Inhibition of TAMs' secretion of pro-inflammatory factors (such as IL-6, IL-1β); Hinders the interaction between tumor cells and TAMs.	[144]
	Quercetin	Inhibition of M2 polarization of TAMs; Promotes the secretion of M1 macrophage-related cytokines (such as IL-12); Weakens the immunosuppressive function of TAMs.	[145]
	Salvianolic acid	Promotes the expression of M1 TAMs markers(CD86, iNOS and IL-1β); Inhibition of M2 TAM markers (Arg-1, CD206 and TGF-β1) expression	[66, 67]
	Ganoderma lucidum polysaccharide	Regulates MAPK / NF-κB signaling pathway; Promotes macrophage M1 polarization	[69]
	Astragalus polysaccharide	Enhances LPS / IFN-γ stimulation; Promotes M1 macrophage polarization; Reduces the M2 polarization of TAMs;Reduces the secretion of IL-4 / IL-13	[73, 74]
	Bufalin	Activation of nuclear factor kappa B (NF-κB) signaling; Reprograms tumor-infiltrating macrophages from M2 phenotype to M1 phenotype	[76-78]
	Dandelion extract	Blocks the IL-10 / STAT3 / PD-L1 signaling pathway; Promotes the expression of M1 macrophage surface markers; Inhibits the expression of M2 macrophage surface markers; Promotes M2 macrophages to M1 polarization	[80]
	Tremella fuciformis polysaccharide	Regulates MAPK and NF-κB signaling pathways; Promotes M1 macrophage polarization	[71]
Dendritic cells	Astragalus polysaccharide	Enhances the antigen-presenting function of DCs; Improves T cell activation ability	[73]
	Ganoderma lucidum polysaccharide	Promotes the expression of CD80, CD86, CD83and other costimulatory molecules	[104]
	Rehmannia glutinosa polysaccharide	Activation of p38, JNK, and ERK signaling pathways; Increases the activity of DCs.	[105]
	Gambogic acid-loaded nanoparticle	Increases the number of mature DCs; Enhances the antigen presentation and T cell activation of DCs	[106]
	Lycium barbarum polysaccharide	Reduces IL-10 and TGF-β; Increases IL-12	[107, 108]
	Pinellia pedatisecta extract	Upregulates the expression of CD80, CD86, and MHCII antigen complex was up-regulated; Activation of CTL and $CD4^+$ T cells	[109]
	Tetrandrine	Upregulates the expression of CCL5 and CXCL10	[110]
NK cells	Curcumin	Enhances NK cell survival via STAT5/Jak3 signaling pathway; Reduces the inhibitory effect of exosomes on NK cells	[112-114]

	Epigallocatechin-3-gallate	Upregulates the levels of IL-2 and IFN-γ; Enhances NK cell toxicity.	[115]
	Rehmannia glutinosa polysaccharide	Increases Ki-67 antigen; Enhances NK cell proliferation activity; Enhances NK cytotoxic activity; Promotes type 1 IFN secretion.	[116]
	Paulownin	Promotes perforin expression; Enhances NK cell toxicity	[117]
	Artemisinin	Activation of ERK 1/2 and Vav-1 pathways; Promotes the expression of CD107a	[118]
	Quercetin	Promotes the expression of NKG2D ligands on the surface of tumor cells; Increases sensitivity of tumor cells to NK cells; Enhances NK cell activity	[119]
	Sarcandra glabra extract	Upregulates the levels of IL-2, TNF-α, and IFN-γ in tumor tissues; Enhances NK cell recruitment and infiltration	[120]
MDSCs	Curcumin	Reduces IL-6, MDSC arginase-1, and ROS; Inhibition of TLR4 / NF-κB signaling pathway and expression of inflammatory factors; Reduces GM-CSF and G-CSF and other regulatory factors.	[124, 125]
	Grifola frondosa polysaccharide	Consumption of MDSC; Activates tumor immune response	[126]
	Cryptotanshinone	Reduces MDSC accumulation; Inhibition of tumor-associated MDSC recruitment and reversal.	[127-129]
	Ganoderma lucidum polysaccharide	Promotes the protein expression of CARD9, p-Syk and p-NF-κB p65 in MDSCs	[132]
	Resveratrol	Attenuates TCDD-mediated PMN-MDSCs induction; Blocks the inhibition of TCDD on the proliferation of some T cells	[133]

Regulation of $CD8^+$ T Lymphocytes by Natural Products

$CD8^+$ T lymphocytes recognize tumor antigens and directly eliminate malignant cells through cytotoxic mediators such as perforin and granzymes. They also secrete cytokines like IFN-γ to amplify anti-tumor immunity by activating other immune cells. Intratumoral infiltration of $CD8^+$ T cells positively correlates with patient prognosis, making them promising targets for cancer immunotherapy [35, 36].

However, within the TME, persistent antigen exposure, hypoxia, nutrient deprivation, and inhibitory cytokines (e.g., IL-10, TGF-β) drive exhaustion of $CD8^+$ T cells. This dysfunctional state is characterized by proliferation impairment, diminished cytotoxic activity, and reduced cytokine production, ultimately compromising antitumor efficacy [37]. Exhausted $CD8^+$ T cells exhibit elevated expression of immune checkpoint receptors such as PD-1 and Tim-3, a hallmark associated with tumor progression and poor clinical outcomes [36].

Notably, $CD8^+$ T cells play dual roles: mediating tumor clearance while being prone to exhaustion. Natural product monomers counteract this exhaustion by targeting multiple regulatory pathways, enhancing $CD8^+$ T cell functions. This approach may constitute novel therapeutic strategies to overcome immunotherapy resistance.

Activation

Multiple natural products activate $CD8^+$ T lymphocytes to enhance their anti-tumor efficacy. A prominent example is curcumin, which augments the cytotoxicity of $CD8^+$ T cells by increasing their secretion of cytotoxic mediators such as IFN-γ, granzyme B, and perforin. The underlying mechanism for curcumin's enhancement of $CD8^+$ T cell cytotoxicity involves its regulation of T cell signaling pathways. Mechanistically, curcumin enhances T cell receptor (TCR) signaling via STAT5 phosphorylation, thereby potentiating tumor cell lysis. *In vitro* studies demonstrate that curcumin-treated $CD8^+$ T cells exhibit significantly elevated cytotoxic activity against esophageal carcinoma cells, with a 2.3-fold increase in tumor cell apoptosis compared to untreated controls [38]. In vivo, combinatorial therapy of curcumin with adoptive T cell therapy in murine T lymphoma models synergistically enhances intratumoral $CD8^+$ T cell infiltration (by 58%) and IFN-γ production (by 3.1-fold), resulting in marked tumor regression [39]. This synergy is attributed to curcumin's ability to counteract PD-1-mediated exhaustion while augmenting mitochondrial biogenesis in $CD8^+$ T cells.

Resveratrol enhances the cytotoxic activity of $CD8^+$ T lymphocytes, thereby facilitating more effective tumor cell elimination. This polyphenolic compound also significantly promotes the proliferation of $CD8^+$ T cells through modulation of cell cycle regulatory proteins. *In vitro* studies demonstrate that physiologically relevant concentrations of resveratrol (10-50μm) increase the proliferation of $CD8^+$ T cells by 1.8- to 2.5-fold, correlating with upregulated cyclin D1 expression and downregulated p27 levels [40]. The mechanism underlying resveratrol's effect on $CD8^+$ T cell proliferation involves its regulation of mitochondrial biogenesis. Mechanistically, resveratrol activates Silent information regulator 1 (SIRT1)-dependent mitochondrial biogenesis, which sustains T cell metabolic fitness during clonal expansion. *In vivo* evidence from murine tumor models reveals that resveratrol administration (100 mg/kg/day) elevates systemic populations of $CD8^+$ T cells by 40-60%, particularly enhancing tumor-infiltrating lymphocytes through CXCR3 upregulation. This expansion provides an enlarged effector cell pool for anti-tumor immunity [40].

Ganoderma lucidum polysaccharides enhance the infiltration of $CD8^+$ T lymphocytes and the proliferation of T lymphocytes in the spleen of tumor-bearing rats. In murine melanoma models, ganoderma lucidum polysaccharides administered at 20–100 mg/kg significantly boost $CD8^+$ T lymphocyte activity by inducing the differentiation of cytotoxic T lymphocytes (CTLs), which elevates granzyme B and perforin production, thereby intensifying cytotoxicity against melanoma cells [41, 42].

Apigenin suppresses IFN-γ-induced PD-L1 protein expression in breast cancer models by inhibiting STAT1 phosphorylation at tyrosine 701, thereby blocking PD-L1 upregulation and restoring T cell-mediated tumor lysis. Additionally, apigenin potentiates HPV DNA vaccine efficacy by enhancing IFN-γ-driven $CD8^+$ T cell responses, demonstrating synergistic anti-tumor effects in cervical cancer both *in vitro* and *in vivo* studies [43].

Paclitaxel promotes $CD8^+$ T lymphocyte proliferation, expanding their population in non-small cell lung cancer patients after treatment. This expansion enhances immune surveillance and cytotoxic clearance of malignant cells, effectively curbing tumor progression. Lau et al. further demonstrated that paclitaxel treatment increases T lymphocyte infiltration in ovarian cancer patients, facilitating better immune-mediated tumor control and therapeutic outcomes [44].

Immune Checkpoints Modulation

Natural products regulate $CD8^+$ T lymphocyte function by targeting immune checkpoint pathways, counteracting tumor-induced immunosuppression.

$CD8^+$ T cells' exhaustion contributes to poor cancer immunotherapy. The use of Curcumin reverses its exhausted phenotype by downregulating immune checkpoint ligands (e.g., PD-L1) and restoring NF-κB activity. It simultaneously inactivates TNF-α signaling to rebalance CTLs and Tregs infiltration, thereby expanding intratumoral $CD8^+$ T cells' populations. In murine melanoma models, curcumin synergizes with vaccine therapy to significantly enhance intratumoral $CD8^+$ T cell infiltration and anti-tumor immunity [39].

Resveratrol enhances tumor antigen recognition by $CD8^+$ T lymphocytes through TCR signal amplification, improving tumor cell targeting specificity. This is evidenced by the increased efficiency of tumor cell lysis across multiple preclinical models following resveratrol treatment [40].

Hesperidin potentiates the cytotoxicity of $CD8^+$ T cells via phosphatidylinositol-3-kinase (PI3K)-protein kinase B (Akt) pathway activation while suppressing PD-L1 expression in triple-negative breast cancer (TNBC) through Akt/NF-κB axis inhibition. This dual mechanism restricts melanoma progression and enhances immune-mediated tumor clearance [41].

Berberine sensitizes tumors to immune checkpoint blockade by downregulating PD-L1 expression and augmenting the functionality of $CD8^+$ T cells. It elevates IFN-γ secretion, MHC-II antigen presentation, and CD40 co-stimulatory signaling, creating a pro-immunogenic tumor microenvironment [41].

Paclitaxel induces the responses of $CD8^+$ T cells by promoting neoantigen presentation and TCR diversification. In ovarian cancer patients, paclitaxel enhances T cell infiltration into tumor beds, sustaining long-term immune surveillance and tumor suppression [44].

Cytokine Secretion Modulation

Natural products regulate $CD8^+$ T lymphocyte function by reprogramming cytokine secretion profiles.

Curcumin suppresses immunosuppressive cytokines (e.g., IL-10, TGF-β) to alleviate $CD8^+$ T cells inhibition while promoting pro-inflammatory cytokine secretion (e.g., IL-2, IFN-γ) to enhance cytotoxicity. Clinical studies in colorectal cancer patients reveal that curcumin treatment increases peripheral Th1 cell populations (IL-2/IFN-γ producers) and reduces Treg frequencies, synergistically augmenting $CD8^+$ T cell-mediated anti-tumor responses [45].

Resveratrol enhances the secretion of cytotoxic mediators by $CD8^+$ T cells (IFN-γ, granzyme B, perforin) and restricts tumor-derived immunosuppressive cytokines (e.g., IL-10, TGF-β), thereby reducing Treg-mediated suppression [45]. In renal cell carcinoma models, resveratrol-treated $CD8^+$ T cells exhibit 2.1-fold higher tumor cell lysis capacity. Moreover, studies on melanoma further demonstrate its ability to remodel TME, increasing intratumoral $CD8^+$ T cells infiltration by 45% compared to controls [40].

Ginsenoside Rg3 elevates serum IFN-γ and IL-2 levels in H22 hepatoma-bearing mice. IFN-γ potentiates $CD8^+$ T cells' cytotoxicity, while IL-2 drives clonal expansion and functional persistence. This dual cytokine modulation results in a 3.2-fold increase in tumor-specific $CD8^+$ T cell activity, significantly suppressing tumor growth [46].

Regulation of $CD4^+$ T Lymphocytes by Natural Products

$CD4^+$ T lymphocytes play a central regulatory role in immune responses by aiding B lymphocytes in the production of antibodies, enhancing $CD8^+$ T lymphocyte activity, and regulating macrophage functions. In tumor immunity, they promote immunoglobulin class switching and somatic hypermutation in B lymphocytes, thereby strengthening the body's immune response against tumor cells. $CD4^+$ T lymphocytes can differentiate into various subtypes, including Th1, Th2, Th17, Tfh, and Tregs.

Th1 cells activate macrophages and CTLs through IFN-γ secretion, enhancing tumor cell killing capacity [47]. Th2 cells secrete cytokines such as IL-4, IL-5, and IL-13, engaging in humoral immunity and allergic reactions, while demonstrating complex roles in tumor immunity. Th17 cells produce IL-17 and other cytokines involved in inflammatory responses and immune defense, exhibiting dual effects on tumors. Tfh cells assist B lymphocytes in antibody production within germinal centers, modulating antibody generation and class switching in tumor immunity. Tregs suppress tumor-specific immune effector cells through inhibitory cytokines, such as TGF-β and IL-10, facilitating tumor immune evasion [48, 49].

Natural products, with their diverse sources and components, demonstrate multifaceted regulatory effects on $CD4^+$ T lymphocyte-related pathways, revealing unique advantages and potential in cancer treatment.

Regulation of Differentiation and Cytokine Secretion

In the TME, the Th1/Th2 balance is disrupted with a predominance of Th2-type immune responses, which suppress the body's anti-tumor immunity. Curcumin modulates this imbalance by promoting $CD4^+$ T cell differentiation into Th1 cells. Specifically, it upregulates Th1-associated cytokines (e.g., IFN-γ) while suppressing Th2-type mediators including IL-4, IL-10, and TGF-β. Administration of curcumin to tumor-bearing mice significantly increases serum IFN-γ levels while decreasing IL-4, IL-10, and TGF-β levels, shifting the Th1/Th2 balance toward Th1 dominance and enhancing anti-tumor immune responses [45]. This immunomodulatory effect activates immune cells such as macrophages, NK cells, and $CD8^+$ T lymphocytes, thereby improving their tumor-killing capacity.

Resveratrol promotes the secretion of Th1-type cytokines (e.g., IFN-γ) while inhibiting Th2-type cytokines (e.g., IL-4, IL-10), thereby polarizing immune responses toward Th1 dominance [38]. This regulatory mechanism enhances anti-tumor immunity by activating Th1-associated immune cells, including macrophages, NK cells, and $CD8^+$ T lymphocytes, to eliminate tumor cells. In renal cell carcinoma mouse models, resveratrol treatment significantly elevated IFN-γ levels and reduced IL-4/IL-10 levels in TME, restoring the Th1/Th2 balance toward Th1 and strengthening anti-tumor immune responses [40, 45]

Ganoderma lucidum polysaccharides facilitate the differentiation of $CD4^+$ T lymphocytes into Th1 cells, amplifying Th1-type immune responses. Cytokines secreted by Th1 cells (e.g., IL-2, TNF-α, IFN-γ) enhance the cytotoxicity of macrophages and the antigen-presenting functions of DCs, contributing to tumor cell elimination. In colorectal cancer mouse models, ganoderma lucidum polysaccharides treatment markedly increased Th1 cytokine levels in TME and elevated the proportion of Th1 cells among $CD4^+$ T lymphocytes [50]. This suggests that Ganoderma lucidum polysaccharides may enhance anti-tumor immunity by modulating relevant signaling pathways to promote Th1 differentiation.

Ginsenosides act on DCs to improve their capacity for tumor antigen uptake, processing, and presentation, thereby driving naïve T lymphocytes differentiation toward Th1 cells. As a $CD4^+$ T cell subset, Th1 cells secrete cytokines (e.g., TNF-α, IFN-γ, IL-2) that enhance immune functions and facilitate activation of other immune cells. Specifically, IFN-γ activates macrophages and NK cells to amplify immune responses, while IL-2 promotes T lymphocyte proliferation/differentiation to strengthen tumor-targeting capabilities. Studies demonstrate that ginsenoside Rg3 significantly elevates serum IFN-γ and IL-2 levels in H22 tumor-bearing mice. This further promotes Th1 differentiation of $CD4^+$ T cells, enhances Th1-mediated immune functions, improves their capacity to activate immune cells and regulate immune responses, and ultimately boosts anti-tumor immunity [46].

Inhibition of Treg Function and Differentiation

Curcumin promotes the proliferation and activation of $CD4^+$ T lymphocytes to enhance their anti-tumor activity. In tumor-bearing mouse models, curcumin treatment elevates the infiltration of activated $CD4^+$ T lymphocytes within tumor tissues[45]. These activated cells secrete elevated levels of cytokines such as IL-2 and IFN-γ, further activating other immune cells and strengthening immune surveillance and tumor-killing capacity [51]. Additionally, curcumin suppresses the function and differentiation of Tregs, reducing their proportion in TME. Studies indicate that curcumin inhibits the immunosuppressive activity of Tregs by downregulating Foxp3 expression. In colorectal cancer patients, curcumin treatment decreases the number of $Foxp3^+$ Tregs in peripheral blood while increasing Th1 cell populations, which promotes the conversion of Tregs to Th1 cells. This alleviates Treg-mediated suppression of immune cells and enhances anti-tumor immunity [38].

Resveratrol inhibits the proliferation of Tregs and their function, reducing their abundance in TME. Research shows that resveratrol downregulates Foxp3 expression in Tregs, diminishing their immunosuppressive effects and enhancing anti-tumor im-

mune responses. In breast cancer and melanoma mouse models, resveratrol treatment significantly reduces Treg infiltration in tumors, increases the Th1 subset within $CD4^+$ T lymphocytes, and suppresses tumor growth [40, 45].

Ganoderma lucidum polysaccharides impair Tregs' function and proliferation, limiting their accumulation in TME. In hepatocellular carcinoma mouse models, administration of Ganoderma lucidum polysaccharides markedly decreases Treg proportions in tumor tissues while elevating Th1 cell ratios among $CD4^+$ T lymphocytes. Mechanistic studies suggest that these polysaccharides may inhibit the PI3K/Akt/ mammalian target of rapamycin (mTOR) signaling pathway, thereby disrupting Treg proliferation and function, reducing their tumor infiltration, and enhancing $CD4^+$ T cell-mediated anti-tumor activity [42, 52]. The mechanisms of action of certain natural compounds on T Lymphocytes are illustrated in Figure 1.

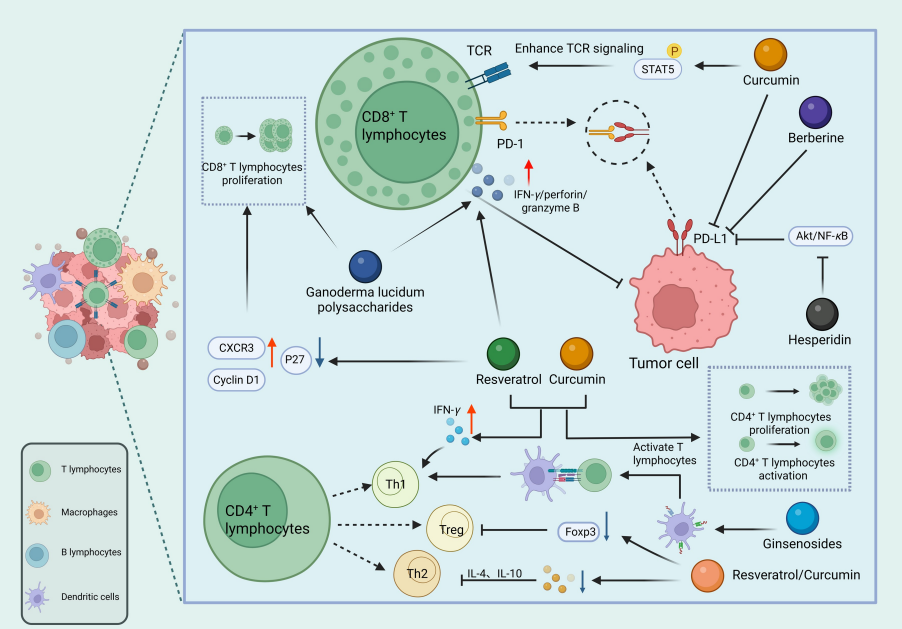

Figure 1: Mechanisms of Natural Products Targeting T Lymphocytes

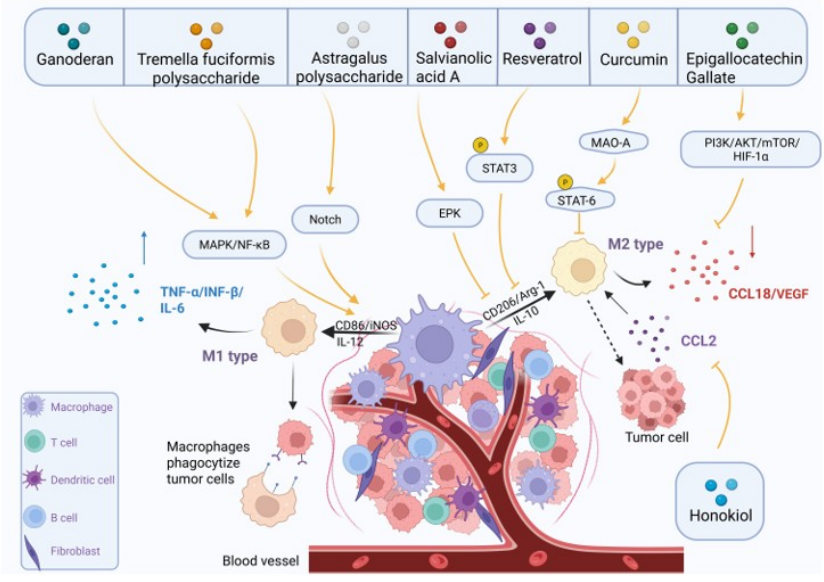

Figure 2: Mechanisms of natural compounds targeting TAMs

Regulation of Macrophages by Natural Products

Macrophages are recognized as key drivers of cancer-associated inflammation. Studies indicate that TAMs can be polarized into pro-tumorigenic (M2-like macrophages) or anti-tumorigenic (M1-like macrophages) phenotypes depending on the different

TME. M1-like macrophages secrete pro-inflammatory cytokines and exhibit tumor-suppressive functions, whereas M2-like macrophages produce anti-inflammatory cytokines and support tumor progression [53, 54]. Most current research focuses on M2-like macrophages, which primarily promote tumor growth, with tumor-associated M2-polarized macrophages considered the dominant TAM subtype. However, some studies reveal that M1-like macrophages exhibit dual roles in tumors, both inhibiting and promoting malignancy. For instance, M1-like macrophages may secrete cytokines such as IL-1β, TNF-α, and IL-6, which directly or indirectly stimulate the proliferation of blood vessels and potentially facilitate tumor metastasis [53, 55].

The pro-tumorigenic effects of M2-like macrophages can be categorized into three aspects: the enhancement of angiogenesis, the amplification of immunosuppression, and the promotion of tumor metastasis. Meanwhile, M2-like macrophages hinder anti-tumor immunity by limiting antigen presentation and reducing CTL activation [56]. Notably, TAMs exhibit high plasticity, critically influencing tumor initiation, progression, and prognosis [57].

Macrophage Polarization Modulation

Curcumin has been widely studied in macrophages as well. Experimental evidence highlights its abilities to reprogram macrophage polarization in TME, notably inducing the transition of M2-like macrophages to an M1-like phenotype, thereby improving TME. In *in vitro* co-culture systems, curcumin promotes the polarization of TAMs toward the M1-like phenotype. Flow cytometry analyses reveal elevated expression of CD86 (an M1-like surface marker) and reduced CD206 (an M2-like surface marker) in these macrophages. Researchers propose that curcumin may drive M1-like polarization by suppressing the MAO-A/STAT6 pathway, as curcumin-treated M2-like macrophages exhibit decreased MAO-A activity, reduced ROS levels, and diminished STAT6 phosphorylation [27].

Resveratrol has demonstrated anti-tumor effects in numerous in vitro and in vivo studies, particularly through its modulation of macrophages [58]. It likely exerts anti-tumor activity by inhibiting M2-like macrophage polarization, thereby attenuating the pro-inflammatory and pro-survival functions of TAMs. In a study by Sun et al., resveratrol-treated human monocyte-derived macrophages in a co-culture model showed significantly reduced surface expression of IL-10, a marker associated with M2-like polarization. Additionally, resveratrol treatment in mouse tumor models suppressed M2-like polarization in lung cancer by inhibiting STAT3 activity, leading to tumor regression [59]. However, resveratrol's clinical application is limited by poor pharmacokinetics and low absorption efficiency. Therefore, to address this, recent studies focus on combining resveratrol with nanoparticles to enhance efficacy [60]. For example, nanoparticle-encapsulated resveratrol was shown to downregulate cytokines (e.g., TNF-α, IL-6, IL-1β) and reduce metastatic markers in tumors. Xenograft mouse models further confirmed its anti-tumor effects, demonstrating that resveratrol nanoparticles selectively target macrophages, suppress cytokine release, and inhibit angiogenesis and tumor invasion [61].

Catechins, the primary active components in green tea and major constituents of tea polyphenols, exhibit antioxidant, anti-inflammatory, and immunomodulatory properties [62]. Accumulating evidence suggests that catechins may influence various human diseases and act as tumor immunomodulators, with epigallocatechin gallate being the most abundant and bioactive catechin in green tea [63]. A study demonstrated that epigallocatechin gallate reverses leptin-enhanced proliferation, migration, and invasion of A549 lung cancer cells by suppressing leptin-induced expansion of M2-like macrophage subsets and downregulating CD86 and CD80 expression. Mechanistically, epigallocatechin gallate triggers ferroptosis via the STAT1-SLC7A11 pathway, thereby inhibiting lung cancer progression [64]. These findings suggest that epigallocatechin gallate exerts anti-tumor effects by attenuating M2-like macrophage polarization.

Salvianolic acids, the water-soluble components of Dan-Shen Root, include salvianolic acid A to I, with salvianolic acid A and salvianolic acid B being the most abundant and bioactive ones. Both compounds exhibit anti-cancer, anti-inflammatory, and cardioprotective effects [65]. Specifically, salvianolic acid A and salvianolic acid B demonstrate significant anti-tumor activity against lung, breast, and colorectal cancers [66]. In a TNBC model, Tang et al. found that salvianolic acid A treatment upregulated M1-like TAMs markers (CD86, iNOS, and IL-1β) while suppressing M2-like macrophages' markers (Arg-1, CD206, and

TGF-β1) and p-ERK protein levels. Further studies revealed that the ERK pathway mediates salvianolic acid A's dual effects, including the inhibition of M2-like macrophages' polarization and the reprogramming of M2-like macrophages toward the M1--like phenotype [67].

Polysaccharides, a class of natural medicinal compounds, regulate TAMs through multifaceted mechanisms. They promote macrophage polarization toward the M1-like phenotype (enhancing antigen presentation and tumor-killing activity) while suppressing the pro-tumorigenic M2-like polarization. Below, we focus on three polysaccharides, including Ganoderma lucidum polysaccharides, Tremella fuciformis polysaccharides, and Astragalus polysaccharides.

Ganoderma lucidum polysaccharides are bioactive polysaccharides extracted from the fruiting bodies, mycelia, or fermentation broth of Ganoderma lucidum [68]. They exhibit diverse bioactivities, including activation of immune cells and anti-tumor effects via immunomodulation, immune system activation, and tumor cell apoptosis induction. Sheng et al. demonstrated that Ganoderma lucidum polysaccharides treatment upregulates M1-like phenotype markers (CD86, iNOS) and pro-inflammatory cytokines (IL-12a, IL-23a, IL-27, TNF-α), while downregulating M2-like markers (CD206, Arg-1) and inflammation-related cytokines (IL-6, IL-10). This suppresses M2-like macrophage polarization and enhances phosphorylation of mitogen-activated protein and extracellular regulated protein kinases, suggesting Ganoderma lucidum polysaccharides modulate M1-like polarization through the mitogen-activated protein kinase (MAPK)/NF-κB signaling pathway [69].

Tremella fuciformis polysaccharides, heteropolysaccharides primarily composed of β-(1→3)-D-mannans with β-(1→6)-linked side chains, are the main bioactive constituents of Tremella fuciformis [70]. Tremella fuciformis polysaccharides exhibit immunostimulatory, antioxidant, anti-tumor, and metabolic regulatory properties. In a co-culture system of macrophages and melanoma cells, Tremella fuciformis polysaccharides promote M1-like markers (iNOS, CD80) and enhance macrophage phagocytosis and migration. Mechanistically, Tremella fuciformis polysaccharides likely regulate M1-like polarization via the MAPK and NF-κB pathways, contributing to its anti-tumor activity [71].

Astragalus Polysaccharides, extracted from the roots of Astragalus membranaceus, are immunomodulatory polysaccharides with prominent anti-cancer potential [72]. Bamodu et al. elucidated their role in macrophage regulation. Astragalus polysaccharides enhance LPS/IFN-γ-induced M1-like polarization while suppressing IL-4/IL-13-driven M2-like polarization. Notably, Astragalus polysaccharides prioritize M1-like activation over M2-like suppression, positioning it as a potential immunomodulator for M1-polarized macrophage-based therapies [73]. Furthermore, Wei et al. identified another Astragalus polysaccharide that upregulates Notch ligands, indicating its regulation of M1-like polarization via the Notch pathway to exert anti-tumor effects [74].

Bufalin, a bioactive compound extracted from toads and the primary active ingredient in the traditional Chinese medicine Chan Su (toad venom), exhibits significant anti-tumor activity and holds broad therapeutic potential in oncology [75]. Yu et al. demonstrated that bufalin recruits macrophages to TME and reprograms tumor-infiltrating macrophages from the M2-like to M1-like phenotype by activating the nuclear factor kappa B (NF-κB) signaling pathway. This shift reduces protumorigenic cytokine and signaling protein production, thereby enhancing anti-tumor immunity. Furthermore, combining bufalin with anti-PD-1 antibodies synergistically improves anti-hepatocellular carcinoma efficacy by modulating cytokine expression and activating macrophage- and T lymphocyte-mediated anti-tumor responses [76]. Current studies reveal multiple mechanisms underlying bufalin's macrophage regulation. In one study, researchers hypothesized that bufalin suppresses hepatocellular carcinoma cell proliferation and malignant transformation via the Wnt1/β-catenin pathway. Experimental results confirmed that bufalin treatment directly reduces Wnt1 secretion by M2-like macrophages and induces tumor regression in mouse models, validating its inhibitory effects on hepatocellular carcinoma [77]. In another study, Tang et al. reported that bufalin inhibits TAM--mediated colorectal cancer metastasis through the SRC-3/IL-6 pathway and attenuates IL-6-driven M2-like polarization of Kupffer cells in the liver [78]. These findings provide a foundation for leveraging bufalin to enhance tumor immunotherapy.

Dandelion (Taraxacum officinale), a perennial herb in the Asteraceae family, is traditionally used in Chinese medicine for its heat-clearing and detoxifying properties. Modern studies have identified key bioactive compounds such as triterpenes, saponins, phenolic acids, and sterols, which are recognized as contributors to its anti-tumor effects. [79]. Deng et al. discovered that dandelion extract inhibits STAT3 and PD-L1 expression in TNBC cells within a TAM-enriched microenvironment. By suppressing the IL-10/STAT3/PD-L1 signaling axis, the extract upregulates M1-like macrophage markers (e.g., CD86, iNOS) and downregulates M2-like markers (e.g., CD206, Arg-1), and thereby repolarizes M2-like macrophages to the M1-like phenotype. This reprogramming effectively inhibits TNBC cell proliferation, migration, and invasion in TAM-conditioned medium [80].

Inhibition of TAM Recruitment and Pro-tumor Functions

Tumor-associated macrophages (TAMs) dynamically regulate the tumor microenvironment (TME) through phenotypic polarization, transitioning from pro-inflammatory M1-like phenotypes in early stages to immunosuppressive M2-like dominance during tumor progression [81]. This polarization shift enables M2-like TAMs to secrete anti-inflammatory cytokines (e.g., IL-10, TGF-β, CCL18) and pro-angiogenic factors (e.g., VEGF), driving immune evasion through T/NK cell suppression, Treg recruitment, extracellular matrix remodeling, and pathological angiogenesis [82, 83]. All hallmarks of malignant progression. Notably, the accumulation of M2-like TAMs in the TME not only facilitates tumor invasion and metastasis but also establishes a self-reinforcing loop through chemokine production (e.g., CCL2/CSF-1) that recruits additional macrophages. Studies indicate that inhibition of chemokine signaling pathways can effectively block macrophage recruitment into the TME [84, 85].

In an endometrial cancer study, epigallocatechin gallate reduced CXCL12 secretion, suppressed the infiltration of TAMs and tumor angiogenesis, and inhibited VEGFA production by TAMs via the PI3K/AKT/mTOR/HIF1α pathway [86].

Glycyrrhetinic Acid, a bioactive compound from licorice (Glycyrrhiza glabra), exhibits anti-tumor effects. Ceng et al. demonstrated that Glycyrrhetinic Acid suppresses TAM-mediated angiogenesis and metastasis by downregulating pro-angiogenic molecules (VEGF, MMP9, MMP2) and anti-inflammatory cytokines (IL-10) secreted by M2-like macrophages. In the experimental studies, Glycyrrhetinic acid treatment significantly suppressed Arg-1 protein expression in IL-4/IL-13-stimulated RAW264.7 macrophages. Furthermore, it effectively attenuated both IL-4/IL-13-induced 4T1 cell migration and HUVEC tube formation. Notably, the observed inhibitory effects were reversed upon administration of a JNK inhibitor, demonstrating that the JNK signaling pathway plays a critical regulatory role in glycyrrhetinic acid-mediated suppression of macrophage M2 polarization. In vitro, Glycyrrhetinic Acid counteracted M2-like macrophage-induced proliferation of HUVECs and 4T1 cells. In tumor-bearing mouse models, Glycyrrhetinic Acid inhibited breast cancer growth and metastasis, confirming its dual suppression of TAM-driven angiogenesis and metastasis [87].

Triptolide, a natural compound from Tripterygium wilfordii, exhibits potent anti-inflammatory and anti-angiogenic properties. In vitro, it dose-dependently inhibited VEGF-induced cell migration and angiogenesis. In a choroidal neovascularization model, triptolide suppressed VEGF and inflammation-related molecules, highlighting its dual targeting of pathological angiogenesis and inflammatory microenvironments, a mechanism highly relevant to tumor progression [88]. Additionally, its derivative ZT01 demonstrated improved safety and efficacy in mouse models, reducing LPS-induced IL-6 and TNF-α production in RAW264.7 macrophages and alleviating macrophage-mediated sepsis. Experimental results demonstrated that ZT01 significantly suppressed JNK phosphorylation and reduced the levels of phosphorylated TAK1 and MKK4 in LPS-stimulated peritoneal macrophages. These findings suggest that ZT01 likely mediates its anti-inflammatory activity through modulation of the TAK1/MKK4/JNK signaling cascade [89].

Honokiol, a natural compound derived from Magnolia officinalis, exhibits anti-tumor and anti-angiogenic properties. It demonstrates the potential to inhibit TAMs' recruitment into the TME. CCL2 signaling, a key mechanism driving macrophage recruitment and tumor metastasis [90], is downregulated by honokiol. In tumor-bearing mouse models, honokiol treatment reduces CCR2 expression on M2-like macrophages, confirming its suppression of macrophage recruitment and accumulation via the CCL2/CCR2 axis [91].

Lupeol, a phytochemical with anti-inflammatory and anti-cancer activities, inhibits tumor initiation and progression by blocking macrophage recruitment. In co-culture systems, lupeol significantly decreases macrophage migration toward the TME. Cytokine array analyses identify PAI-1 as a critical factor stimulating macrophage chemotaxis. Lupeol suppresses cancer cell-derived PAI-1 production, thereby attenuating macrophage migration toward tumors [92].

The dichloromethane extract of Morus alba root bark exhibits dose-dependent inhibition of the recruitment and migration of TAMs. The dichloromethane extract downregulates PAI-1 mRNA expression in H1299 cells at the transcriptional level, reducing macrophage chemotaxis. Src, a molecular target of MEMA in H1299 cells, is typically phosphorylated by phorbol myristate acetate. The dichloromethane extract inhibits Src phosphorylation, and transfection with constitutively active Src rescues PAI-1 expression. Conversely, dasatinib (a Src inhibitor) reduces PAI-1 levels, confirming that the dichloromethane extract suppresses macrophage recruitment via Src-mediated PAI-1 regulation [93].

TNBC, the most aggressive breast cancer subtype with poor prognosis, shows increased infiltration of M2-like macrophages. In co-culture systems, TGF-β1 and p-ERK expression are upregulated in human TNBC cells. SAA treatment significantly reduces macrophage numbers, inhibiting TCM-TNBC-induced migration and invasion of M2-like macrophages [67].

The natural CCR2 antagonist Abies georgei extract 747 disrupts the CCL2/CCR2 axis, which drives macrophage infiltration and tumor metastasis. Its anti-tumor effects correlate with reduced infiltration of TAMs and expanded $CD8^+$ T lymphocyte populations, which are key effectors suppressed by TAMs. Combining 747 with low-dose sorafenib enhances tumor cell death and $CD8^+$ T cells cytotoxicity without significant toxicity [94].

The mechanisms of action of certain natural compounds on TAMs are illustrated in Figure 2.

Regulation of B Lymphocytes by Natural Products

B lymphocytes play dual roles in TME, either promoting or suppressing tumor progression. Specifically, they can inhibit anti--tumor immunity by producing immunosuppressive factors like IL-10 and promoting Treg generation. Conversely, B lymphocytes also exert anti-tumor effects by producing tumor-specific antibodies and enhancing T cell activation [95, 96]. Their functional heterogeneity is evident in melanoma models, where B cells correlate with immune checkpoint inhibitor (ICI) response by recruiting and activating PD-1^+ T lymphocytes [97]. Regulatory B Cells (Bregs), an immunosuppressive B cell subset, suppress anti-tumor immunity through multiple mechanisms, including inhibiting Th1/Th17 differentiation of $CD4^+$ T cells, blocking pro-inflammatory cytokine production by effector T cells, suppressing TNFα secretion by monocytes, and impairing the responses of cytotoxic $CD8^+$ T cells [98].

Additionally, Bregs promote apoptosis of effector T cells via FASL expression, drive $Foxp3^+$ Tregs and Tr1 cell differentiation, modulate the cytokine profiles of DCs, and sustain regulatory iNKT cell populations. Natural Products target B Lymphocytes through multiple mechanisms, playing pivotal roles in reshaping the TME.

Suppression of Proliferation and Apoptosis

Nobiletin, a polymethoxyflavone derived from Citrus reticulata, exerts dual antitumor effects in the TME by targeting B lymphocytes. Studies in lymphoma cell lines demonstrate that it significantly inhibits B cell proliferation through disruption of cell cycle regulation, specifically by altering the balance of cyclin-dependent kinases and cyclins, which induces cell cycle arrest at specific phases and suppresses uncontrolled division[99, 100]. Additionally, nobiletin promotes apoptosis in TME-associated B lymphocytes by activating caspase-dependent pathways (caspase-3, -8, -9), initiating an intracellular apoptotic cascade. This dual mechanism not only reduces protumor B cell populations but also modulates cytokine dynamics, downregulating tumor-promoting factors like IL-10 while enhancing antitumor cytokines such as IL-6. Collectively, these actions restore immune equilibrium in the TME, curbing tumor progression through both antiproliferative and proapoptotic pathways [99, 100].

Triptolide targets Bruton's tyrosine kinase, a critical regulator of BCR signaling. It inhibits malignant B cell proliferation in chronic lymphocytic leukemia and synergizes with ibrutinib to overcome drug resistance [89].

Breg's Function Modulation

Resveratrol suppresses STAT3 and TGF-β expression in Bregs, blocks the conversion of *naïve* $CD4^+CD25^-$ T cells into Tregs, and disrupts the positive interaction between Tregs and Bregs, thereby inhibiting breast cancer metastasis [101]. Experimental studies in breast cancer models reveal that resveratrol treatment reduces immunosuppressive cytokine release from Bregs, suppresses the infiltration of Tregs, and partially restores $CD8^+$ T cells and NK cells' functions. These findings demonstrate resveratrol's efficacy in alleviating the immunosuppression mediated by Bregs and enhancing anti-tumor immunity [40].

Curcumin modulates B cell differentiation, suppressing IL-10-producing Bregs while enhancing antibody-secreting plasma cells. In colorectal cancer models, curcumin reshapes the B cell repertoire by regulating specific signaling pathways, thereby creating a more favorable environment for anti-tumor immunity [45].

Regulation of Cytokine Release

Resveratrol indirectly influences B lymphocyte function through modulating cytokine networks in the TME. Studies demonstrate that it promotes the secretion of anti-tumor cytokines such as IFN-γ and TNF-α to enhance immune cell activation, including B cells, while inhibiting pro-tumor cytokines like IL-1 and IL-6 to disrupt their immunosuppressive signaling. Co-culture experiments confirm that resveratrol treatment significantly elevates IFN-γ/TNF-α levels, reduces IL-1/IL-6 expression, and enhances B cell activity, thereby improving tumor immune surveillance through dual regulatory mechanisms [40].

Nobiletin suppresses the excessive secretion of pro-tumor cytokines (e.g., IL-10) by B lymphocytes while promoting anti-tumor cytokines (e.g., IL-6). This rebalancing of cytokine profiles reshapes the TME, strengthening immune surveillance and anti-tumor attack mechanisms [99, 100].

Regulation of Dendritic Cells by Natural Products

DCs, derived from myeloid-lineage antigen-presenting cells, play critical roles in the tumor immunity cycle by recognizing and presenting antigens while recruiting T lymphocytes to the TME [102]. WDFY4- and SEC22B-dependent cross-presentation by DCs enables efficient processing of exogenous and endogenous antigens associated with dead cells, and enhances antigen capture. DC-mediated cross-presentation sustains cytotoxic immune responses in naïve $CD8^+$ T cells, underscoring the importance of understanding DC-T lymphocyte interactions in the TME to improve cancer immunotherapies [103].

In the TME, DCs often exhibit impaired anti-tumor potential due to immunosuppressive factors released by tumor cells, leading to reduced antigen uptake and processing capacity and diminished co-stimulatory molecule expression. Consequently, DCs fail to effectively activate T cell-mediated tumor killing. Natural products can counteract these limitations through multifaceted mechanisms, including enhancing antigen uptake and processing, upregulating co-stimulatory molecule expression such as CD80 and CD86, and restoring DC-mediated T cell activation to amplify anti-tumor immune responses.

Activation

Astragalus polysaccharides enhance DCs' functionality in the TME. A study demonstrated that astragalus polysaccharides, either alone or combined with granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-4, boost the generation of functional myeloid DCs in breast, colon, ovarian, liver, gastric, and brain cancers, highlighting their potential in DC-mediated tumor suppression [73].

Ganoderma lucidum polysaccharides promote the activation and maturation of immature DCs. Polysaccharides with β-(1→6)-linked glucans alter the morphology and phenotype of DCs and play a role in the activation process by upregulating surface

markers (CD80, CD86, CD83, CD40, CD54, MHC-II, HLA-DR) and enhancing IL-12 production (subunits p70, p35, p40). Furthermore, Ganoderma lucidum polysaccharides combined with GM-CSF/IL-4 induce the differentiation of monocytic leukemia cells (THP-1) into immunostimulatory DCs with regulatory functions. The maturation of dendritic cells (DCs) induced by Ganoderma lucidum polysaccharides appears to be mediated through activation of three key MAPK signaling pathways (p38, ERK1/2, and P46/54 JNK) within DCs. Furthermore, Toll-like receptor 4 (TLR4) signaling was identified as a critical regulator of DC cytokine secretion during this process [104].

Rehmannia glutinosa polysaccharides, bioactive polysaccharides from Rehmannia glutinosa, activate monocyte-derived DCs via the p38, JNK, and ERK signaling pathways, with p38 playing a dominant role [105]. In one study, rehmannia glutinosa polysaccharides treatment significantly upregulated pro-inflammatory cytokines (e.g., TNF-α, IL-6) and co-stimulatory molecules (e.g., CD80, CD86), indicating its ability to activate DCs, promote T cell priming, and reshape the TME toward anti--tumor immunity [30].

Huang et al. recently developed gambogic acid-loaded nanoparticles (CCM-PLGA/GANPs) that effectively modulate the TME. In animal models, CCM-PLGA/GANPs treatment significantly increased mature DC populations, demonstrating their capacity to activate the maturation of DCs and establish an immunostimulatory TME [106].

Enhancement of DC-Mediated CTL Cytotoxicity

Lycium barbarum polysaccharides, extracted from the traditional herb Lycium barbarum, exhibit diverse bioactivities. Studies show that treatment with lycium barbarum polysaccharides enhances DC-mediated CTLs killing of colon cancer cells (CT26-WT) while promoting IFN-γ production by CTLs. Lycium barbarum polysaccharides reduce IL-10 and TGF-β levels in the supernatants of DCs while increasing IL-12, suggesting their role in driving the activation of CTLs and functional differentiation through cytokine modulation [107]. Furthermore, lycium barbarum polysaccharides - encapsulated liposomes improve antigen uptake by DCs, serving as effective antigen-delivery adjuvants. Experimental results demonstrate that LBP-encapsulated liposomes induced modest upregulation of TLR4, MyD88, TRAF6, and NF-κB mRNA levels. These findings suggest that the nanoparticles enhance dendritic cell activation through the TLR4/NF-κB signaling axis [108].

Pinellia pedatisecta Extract, a liposoluble extract from Pinellia pedatisecta, demonstrates anti-tumor activity. Pinellia pedatisecta Extract treatment promotes the infiltration of DCs into tumor tissues and upregulates co-stimulatory molecules (CD80, CD86) and MHC-II complexes on DCs. Activated DCs prime CTLs and $CD4^+$ T cells via MHC-antigen recognition, co-stimulatory signaling, and cytokine polarization. In vitro, Pinellia pedatisecta Extract induces potent antigen-specific responses of CTLs in a dose-dependent manner. SOCS1 negatively regulates tumor-associated immune cells by inhibiting JAK/STAT signaling. In cervical cancer, Pinellia pedatisecta extract downregulated SOCS1 and increased p-JAK2, activating the JAK/STAT pathway [109].

Regulation of Migration and Infiltration

DCs, as central hubs bridging innate and adaptive immunity, rely on precisely balanced migration and tissue infiltration to maintain immune homeostasis. In pathological microenvironments, DCs navigate chemokine gradients and integrate receptor signaling to migrate from antigen-capturing sites to secondary lymphoid organs. Dysregulation of this process may drive immune evasion or chronic inflammatory cascades. Natural products, with their multi-component synergy and multi-target intervention capabilities, have emerged as key tools for modulating DCs migration and infiltration.

Tetrandrine, a primary bioactive alkaloid from Stephania tetrandra, inhibits tumor proliferation and angiogenesis. In a mouse non-small cell lung cancer model, Tetrandrine treatment suppressed tumor growth and significantly increased macrophage infiltration and the infiltration of DCs. However, this anti-tumor effect was abolished by STING pathway inhibitors, accompanied by downregulated phosphorylated STING levels and reduced expression of downstream chemokines CCL5 and CX-

CL10. These findings indicate that tetrandrine enhances the infiltration of macrophages and DCs into the TME through STING pathway activation, thereby exerting anti-tumor effects [110].

Regulation of NK Cells by Natural Products

NK cells possess intrinsic tumor-killing potential, but tumor cells evade their activity through mechanisms such as releasing immunosuppressive factors and altering surface ligand expression, thereby impairing NK cells' recognition and cytotoxicity [111]. Natural products significantly impact NK cells in the TME. Some enhance the cytotoxicity and proliferation of NK cells via signaling pathway activation, boosting immune surveillance. Others reshape the TME to alleviate immunosuppressive constraints on NK cells, restoring their anti-tumor function.

Reversal of Immunosuppression

Curcumin mitigates tumor-derived exosomes-induced suppression of NK cells and enhances the anti-tumor activity of NK cells. Tumor-derived exosomes are internalized by or interact with NK cells, suppressing their recruitment, migration, proliferation, survival, cytotoxicity, and cytokine secretion while altering receptor/molecular expression patterns [112]. Mechanistically, curcumin potentiates the survival of NK cells via the STAT5/JAK3 signaling pathway, contributing to its anti-tumor effects [113].

Enhancement of Cytotoxicity

Curcumin increases phosphorylation of STAT4 and STAT5 in NK cells, enhancing their cytotoxicity and suppressing pro-survival genes (e.g., PI3K, ERK) in cancer cells [114].

Epigallocatechin gallate enhances NK cell-mediated tumor killing across multiple cancer models. In mouse bladder cancer, both free epigallocatechin gallate and epigallocatechin gallate nanoparticles amplify NK cytotoxicity, correlating with elevated IL-2 and IFN-γ levels. Similarly, in WEHI-3 leukemia models, epigallocatechin gallate significantly boosts the activity of NK cells. Its metabolic derivative, EGC-M5, also upregulates NK cytotoxicity [115].

Rehmannia glutinosa polysaccharides treatment elevates the proliferation marker Ki-67 in murine hepatic and splenic NK cells, promoting their activation and cytotoxic activity. Rehmannia glutinosa polysaccharides also stimulate type I IFN secretion, further enhancing anti-tumor effects through NK cell-mediated cytotoxicity. The mechanism may be related to TLR4 stimulation [116].

Paulownin, a natural compound from Paulownia tomentosa, activates splenic NK cells in mouse models, increasing cytotoxicity against YAC-1 cells and suppressing melanoma growth. JNK inhibitors block paulownin-induced perforin upregulation and cytotoxicity, indicating its reliance on the JNK signaling pathway [117].

Artemisinin directly enhances the lytic activity of NK cells. At 0.1 μM, it doubles the cytotoxicity of NK-92MI cells, accompanied by increased CD107a degranulation and ERK expression. Mechanistically, artemisinin activates the ERK1/2 and Vav-1 pathways to stimulate NK cells' cytotoxicity and granule exocytosis [118].

Quercetin sensitizes tumor cells to killing by NK cells by upregulating NKG2D ligands on tumor surfaces. In mouse models, combining quercetin with cyclophosphamide synergistically enhances the activity of T and NK cells compared to quercetin alone [119].

Promotion of Infiltration and Recruitment

NK cells serve as a critical defense line in anti-tumor immunity due to their ability to rapidly kill tumor cells without prior sensitization. However, tumor-induced immune evasion often impedes the infiltration of NK cells and recruitment into tumor tis-

sues, severely limiting their anti-tumor efficacy. Natural products, with their diverse components and unique mechanisms, offer promising strategies to enhance the trafficking of NK cells, providing innovative avenues for cancer immunotherapy.

Sarcandra glabra extract significantly promotes the recruitment and infiltration of NK cells by remodeling the tumor immune microenvironment. Experimental studies in Lewis lung carcinoma-bearing mice revealed that Sarcandra glabra treatment markedly increases the populations of NK cells in peripheral blood and tumor tissues, particularly at low-to-medium doses. Mechanistically, Sarcandra glabra extract elevates IL-2 levels in tumor tissues, indirectly activating and enhancing the anti-tumor activity of NK cells. Furthermore, high-dose treatment upregulates pro-inflammatory cytokines (TNF-α, IFN-γ), synergistically amplifying immune responses. Immunohistochemical staining confirmed enhanced IL-2 expression in tumors, correlating with increased NK cell infiltration. These findings demonstrate that Sarcandra glabra reshapes immune cell and cytokine networks to activate NK cell-mediated anti-tumor immunity [120].

Regulation of MDSCs by Natural Products

MDSCs, a group of pro-tumor immune cells in the TME, are categorized into polymorphonuclear MDSCs and monocytic MDSCs (M-MDSCs) [121]. MDSCs promote tumor metastasis by secreting cytokines such as TGF-β, IL-10, VEGF, and GM-CSF [122]. Additionally, MDSC-derived exosomes carry tumor-promoting factors. For example, exosomal miR-93-5p from MDSCs drives the differentiation of M-MDSCs into M2-like macrophages while downregulating STAT3 activity in M-MDSCs [123].

MDSCs suppress anti-tumor immunity through multiple mechanisms. Natural products exert diverse effects on MDSCs in the TME. They reduce their abundance by inhibiting expansion and chemotaxis, redirecting their differentiation towards immunostimulatory cell types such as DCs or macrophages, and blocking the release of immunosuppressive molecules like arginase-1 and ROS, thereby restoring immune cell function.

These actions collectively reshape the TME into an immunologically active state, enhancing anti-tumor immune responses.

Inhibition of Proliferation and Recruitment

Curcumin suppresses tumor cell proliferation and survival by targeting MDSCs. In Lewis lung carcinoma models, curcumin reduces arginase-1 expression and ROS production in MDSCs. Curcumin treatment decreases IL-6 levels in tumor tissues and serum, thereby inhibiting MDSCs' recruitment and expansion. Similar effects are observed in colon and gastric cancer xenograft models, where curcumin attenuates IL-6 release. Since MDSC-derived IL-6 is regulated by inflammatory mediators like STAT3 and NF-κB, curcumin likely modulates tumor immunity by suppressing IL-6-mediated MDSC dynamics [124]. Another study demonstrates that curcumin reduces the populations of MDSCs in tumor-bearing mice by blocking the TLR4/NF-κB pathway and downregulating inflammatory factors (IL-6, IL-1β, PGE2, COX-2). Curcumin also inhibits secretion of MDSC-regulating cytokines, including GM-CSF and granulocyte colony-stimulating factor (G-CSF), highlighting its potential as a TLR4/NF-κB-targeted therapeutic strategy [125].

Grifola frondosa polysaccharides, bioactive polysaccharides from the fungus Grifola frondosa, exhibit anti-tumor effects in TNBC models. Li et al. showed that grifola frondosa polysaccharides treatment significantly reduces PMN-MDSCs accumulation in the spleen, blood, and tumor tissues. Grifola frondosa polysaccharides deplete MDSCs, reactivate $CD8^+$ T cell-mediated immunity, and suppress tumor growth by reducing the infiltration of MDSCs. TIGIT is an inhibitory immune checkpoint, and MDSCs modulate T cell activity via the TIGIT/CD155 axis. Grifola frondosa polysaccharides downregulate TIGIT expression at both mRNA and protein levels in tumors, leading to the depletion of MDSCs and restoration of $CD8^+$ T cell-mediated immunity [126].

Cryptotanshinone, a bioactive diterpenoid, modulates MDSC-mediated immunosuppression. In endometriosis and pulmonary fibrosis models, cryptotanshinone inhibits the accumulation of MDSCs via the JAK2/STAT3 pathway, reduces STAT3 phosphorylation, and attenuates inflammation in a dose-dependent manner [127, 128]. These findings suggest that STAT3 targeting is a

viable strategy for MDSCs regulation. Cryptotanshinone may also reverse tumor-associated MDSCs recruitment and immunosuppression through ROS-dependent STAT3 inhibition, aligning with recent advances in cancer immunotherapy [129].

Ursolic Acid, a pentacyclic triterpenoid found in fruits and vegetables, exhibits poor solubility and bioavailability. Studies focus on Ursolic Acid derivatives, such as CDDO-Me, which effectively counteract the immunosuppression of MDSCs *in vitro*. Ursolic Acid-loaded liposomes induce phenotypic shifts in peripheral and tumor-infiltrating MDSCs, which may provide a promising delivery strategy for modulating MDSCs' function in the tumor microenvironment [130].

Neobavaisoflavone, an active isoflavone from Psoralea corylifolia, inhibits tumor growth and metastasis. In 4T1 tumor-bearing mice, Neobavaisoflavone promotes the differentiation of MDSCs into mature myeloid cells and reduces their immunosuppressive activity by downregulating arginase-1 and ROS levels. STAT3 signaling is critical for Neobavaisoflavone's suppression of the expansion of MDSCs. Neobavaisoflavone synergizes with anti-PD-1/PD-L1 therapies to enhance anti-tumor immunity by further inhibiting the activation of MDSCs [131].

MDSCs Differentiation Modulation

Studies demonstrate that ganoderma lucidum polysaccharides, resveratrol, and the macromolecular α-glucan YM-2A from Grifola frondosa can reprogram MDSCs differentiation to enhance anti-tumor immunity.

Wang et al. reported that treatment with ganoderma lucidum polysaccharides in mouse tumor models reduces tumor growth and proliferation marker PCNA expression. Ganoderma lucidum polysaccharides upregulate protein levels of CARD9, p-Syk, and p-NF-κBp65 in MDSCs, suggesting its regulation of MDSCs differentiation and immunosuppression via the CARD9-NF-κB-IDO pathway [132].

Resveratrol acts as an aryl hydrocarbon receptor antagonist. The carcinogen 2,3,7,8-tetrachlorodibenzo-p-dioxin activates aryl hydrocarbon receptor to induce highly immunosuppressive MDSCs. Resveratrol treatment counteracts 2,3,7,8-tetrachlorodibenzo-p-dioxin-mediated induction of PMN-MDSCs and reverses 2,3,7,8-tetrachlorodibenzo-p-dioxin-induced suppression of T cell proliferation. Notably, resveratrol downregulates arginase-1, a key immunosuppressive enzyme in MDSCs. This downregulation indicates its potential to reverse MDSC-driven immunosuppression [133].

The macromolecular α-glucan YM-2A from Grifola frondosa selectively reduces the accumulation of M-MDSCs by promoting their differentiation into immunostimulatory M1-like macrophages rather than immunosuppressive M-MDSCs. Dectin-1 was expressed in splenic PMN-MDSCs from CT26 tumor-bearing mice. YM-2A treatment abrogated the suppressive effect of M-MDSCs on T cell proliferation and activation in a Dectin-1-dependent manner. Furthermore, YM-2A upregulated F4/80, MHC-II, and CD80 expression in M-MDSCs, suggesting Dectin-1-mediated differentiation into M1-like macrophages. This shift enhances the efficacy of cancer immunotherapy [134].

Discussion

This article systematically reviews the potential of natural products and their bioactive monomers in regulating the tumor immune microenvironment, with a focus on discussing their regulatory effects on key immune cell subsets, including $CD8^+$ T lymphocytes, $CD4^+$ T lymphocytes, TAMs, DCs, NK cells, MDSCs, and B lymphocytes. Studies have shown that natural bioactive components often act synergistically on the immune network through multiple targets and pathways, rather than being limited to a single cell type. For instance, curcumin can simultaneously enhance the cytotoxicity of $CD8^+$ T lymphocytes via STAT5, and inhibit Tregs through the MAO-A/STAT6/Foxp3 axis, thereby promoting the polarization of macrophages toward the M1 phenotype. In contrast, resveratrol and Ganoderma lucidum polysaccharides regulate Treg cell function via the STAT3 and PI3K/Akt/mTOR signaling pathways, respectively. This "one-drug-multiple-effects" characteristic highlights the unique advantages of natural products in immune regulation. However, current studies mostly focus on the verification of a single mech-

anism, lacking horizontal comparisons between different drugs and in-depth analysis of their application scenarios. This limitation has restricted the systematic understanding of their role in tumor microenvironment regulation and their clinical application.

Although natural products exhibit broad prospects in anti-tumor immune regulation, and existing studies have combined them with conventional therapies to enhance therapeutic efficacy and reduce toxicity, with examples including ginsenosides used as an adjuvant to cisplatin-based chemotherapy, they still face numerous challenges during clinical translation [146]. These challenges specifically include difficulties in standardization caused by component complexity, poor pharmacokinetic properties such as low bioavailability and rapid metabolism, and unclear mechanisms of action. All these issues have severely restricted their further development. Of particular importance is the lack of necessary longitudinal comparisons in current research among multiple natural product drugs that exert the same immunomodulatory effect. No clear comparative evaluation criteria have been established, neither in terms of differences in the efficiency of regulating the same immune cell subsets nor in practical application dimensions such as drug preparation costs and feasibility of large-scale production. Most existing preclinical studies focus on verifying the activity of a single drug, but fail to conduct systematic comparative analysis of identified candidate drugs with consistent targets or similar mechanisms under uniform experimental conditions. This makes it impossible to clarify the advantages and disadvantages of different drugs in terms of efficacy, economy and other aspects, and this research gap hinders the screening of optimal drugs with both high efficiency and practicality. Identifying the commonalities of drugs that can effectively target the same cells and pathways is of great importance, as this provides better insights and foundations for the development of new drugs and the optimization of small-molecule drugs in the future. In addition, the scarcity of large-scale and high-quality clinical research data has also hindered the recognition and application of natural products.

Looking ahead, efforts should focus on overcoming the bottlenecks faced by natural products in drug delivery, mechanism elucidation, and clinical validation. Specific approaches include: developing new delivery systems such as nanoparticle formulations and biomaterials to enhance targeting ability and bioavailability; integrating multi-omics technologies, single-cell sequencing, and artificial intelligence methods to systematically dissect the multi-target mechanisms of action of drugs in the tumor microenvironment and the immune regulatory networks involved. Of particular note is the potential to introduce artificial intelligence and big data technologies to construct a multidimensional database encompassing natural products, immune targets, and tumor types. Using machine learning, this database can predict drug synergistic effects and optimize combination regimens, enabling a shift from "experience-driven" to "data-driven" drug screening and repurposing, thereby accelerating the development of highly effective and low-toxicity immunotherapeutic combinations. Ultimately, through the in-depth integration of traditional medicine, modern pharmacology, and data science, and with the support of strict quality control and clinical trials, natural products are expected to play a more crucial role in the field of cancer immunotherapy.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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