Am J Transl Res 2025;17(6):4071-4086
www.ajtr.org /ISSN:1943-8141/AJTR0164011

*Review Article*

# Regulation of the tumor microenvironment by Traditional Chinese Medicine: current progress and future perspectives in oncology

Zhaohong Wang[1], Fei Wang[2], Yongjun Zhang[3]

[1]*Department of Traditional Chinese Medicine, Haiyan County People's Hospital, Jiaxing 314300, Zhejiang, China;* [2]*Department of Gynecology, Haiyan County People's Hospital, Jiaxing 314300, Zhejiang, China;* [3]*Integration of Traditional Chinese and Western Medicine Department, Zhejiang Cancer Hospital, Hangzhou 310022, Zhejiang, China*

Received February 18, 2025; Accepted May 26, 2025; Epub June 15, 2025; Published June 30, 2025

**Abstract:** The microenvironment in which tumor cells thrive constitutes a complex and dynamic system closely intertwined with tumors' occurrence, progression, metastasis, and drug resistance. As research in Traditional Chinese Medicine (TCM) for anticancer purposes advances, the holistic and multi-target regulatory principles of TCM have been proven highly suitable for modulating the tumor microenvironment (TME). Targeted therapy focusing on TME is poised to become a key area in future research on TCM's anticancer properties. This article provides an overview of TME characteristics and the current status of TCM's regulation of TME, offering insights into the application of TCM in anticancer research.

**Keywords:** Tumor microenvironment, Traditional Chinese Medicine, Chinese herbal medicine, tumor, cancer

## Introduction

The tumor microenvironment (TME) represents a bidirectional growth environment where tumor cells interact with the host, encompassing various cellular components (tumor cells, immune cells, fibroblasts, lymphocytes, inflammatory cells, endothelial cells, etc.) and non-cellular components (extracellular matrix, tumor vascular system, cytokines, chemokines, signaling factors, hormones, etc.) [1]. The continuous close interactions between tumor cells and the surrounding TME components promote tumor growth, survival, and metastasis [2]. Alterations in the TME lead to genetic mutations in cells, constituting a significant cause of tumor development. Therapeutic interventions targeting the TME have emerged as one of the most prominent research areas in oncology in recent years. The unique holistic perspective of Traditional Chinese Medicine (TCM) aligns with the concept of TME, resulting in numerous research achievements in improving the TME through various single Chinese herbal medicines, complex active ingredients, and modulation of signaling pathways. Based on the characteristics of TME and principles of TCM, this article summarizes and analyzes the current status of the regulation of TME by active ingredients in Chinese herbal medicine and related signaling pathways, aiming to provide insights and references for future TCM strategies in preventing and treating tumors by intervening in the TME.

## Overview of TME characteristics

### *Inflammatory microenvironment*

"Inflammation" stands as one of the core features of the TME, where persistent chronic inflammatory stimuli lead to the accumulation of numerous inflammatory cells, cytokines, chemokines, and other factors at the local site, fostering an inflammatory microenvironment conducive to the survival of tumor cells [3]. Prolonged infiltration of tissue cells into the inflammatory microenvironment disrupts the stability of the cell genome, potentially causing

https://doi.org/10.62347/NOAI4101

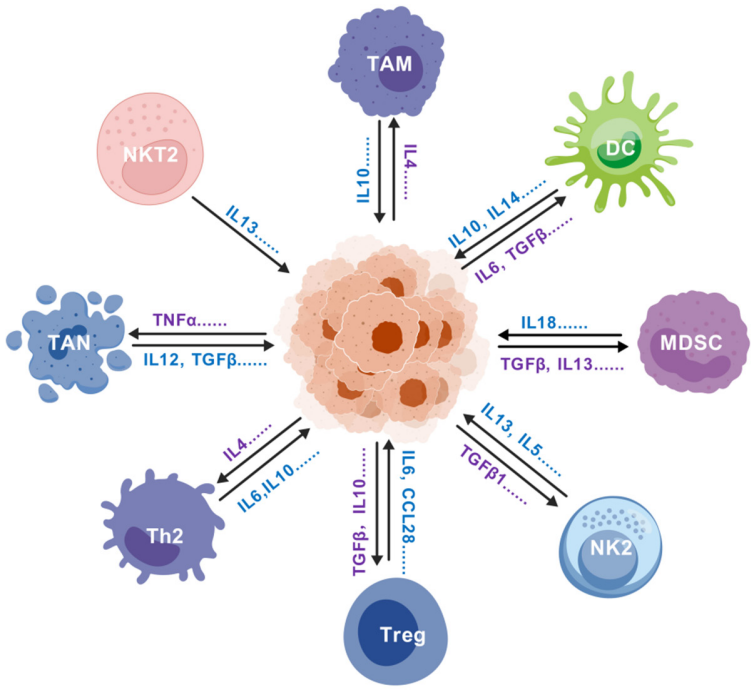


**Figure 1.** Tumor immune microenvironment. Note: TAM, tumor-associated macrophage; TGFβ, transforming growth factor-β; DC, dendritic cell; MDSC, marrow-derived suppressor cell; NK, natural killer cell; Treg, tumor-associated neutrophils, regulatory T cell; CCL28, CC chemokine ligand 28; Th2, T-helper type 2; TAN, tumor associated neutrophil; NKT2, natural killer T 2.

irreversible mutations, thereby shifting inflammation towards an uncontrollable state and promoting the "inflammation-cancer" transformation [4]. Long-term inflammatory stimuli can promote tumor development, while tumors can also induce secondary inflammatory responses, forming a tumor-inflammatory microenvironment that facilitates tumor cell proliferation and contributes to generating an immunosuppressive microenvironment [5].

*Immune microenvironment*

The tumor immune microenvironment comprises both anti-tumor immune effector cells and molecules, as well as immune-suppressive cells and molecules, with its core characteristic being immune suppression. The TME is infiltrated by a plethora of bone marrow-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), tumor-associated neutrophils, regulatory T cells (Tregs), mast cells (MCs), and inflammatory dendritic cells (DCs), among others, which promote tumor growth and development. These tumor-associated immune cells constitute the primary cellular components of the tumor immune suppressive microenvironment, shielding tumor cells from immune system surveillance, recognition, and clearance, consequently allowing tumors to persist, grow progressively, invade, and metastasize [6] (see **Figure 1**).

*Acidic microenvironment*

Under adequate oxygen supply conditions, normal human cells' extracellular pH typically ranges between 7.2 and 7.4. In contrast, the extracellular environment of tumor cells often falls between 6.5 and 6.9, commonly exhibiting acidification. Extensive research indicates that microenvironment acidification is crucial in transforming tumors from non-invasive to malignant infiltrative states [7]. The primary causes of tumor acidic microenvironments are glycolysis and hypoxia, where glycolysis generates lactate and abundant $H^+$, decreasing pH [8]. Even in the presence of oxygen, tumors prefer anaerobic glycolysis, known as the Warburg effect. Hypoxia enhances the expression of hypoxia-inducible factor-1α (HIF-1α) and the inadequate clearance of acidic products like lactate due to poor tissue perfusion [9]. Additionally, the $CO_2$ generated by tumor cell respiration, either spontaneously or facilitated by the overexpressed carbonic anhydrase, catalyzes the reaction between $CO_2$ and $H_2O$ to form carbonic acid, which subsequently dissociates into $H^+$ ions [10].

*Hypoxic microenvironment*

Hypoxia is a prevalent phenomenon in the development of tumors, with oxygen tensions around most tumor cells falling below 7.5 mmHg [11]. The mechanisms contributing to hypoxia involve rapid proliferation and vigorous metabolism of tumor cells, limiting the oxygen diffusion range around tumor cells from capillaries. This leads to uneven oxygen and nutrient supply to tumor tissues, thus creating a hypoxic TME [12]. Furthermore, tumor-associated coag-

ulation and abnormal vascular structures cause local circulation disturbances, resulting in an imbalance between tissue oxygen supply and consumption [13].

## TCM understanding of TME

Although the term "TME" is not explicitly present in TCM, the core of TCM theoretical thinking lies in holism, emphasizing that the human body's internal environment is an organic whole encompassing the environment surrounding the tumor. TCM approaches treatment by differentiating symptoms and signs for the entire body rather than solely targeting tumor cells [14]. TCM follows the principle of reinforcing the body's healthy Qi and expelling pathogenic factors. In light of the multifaceted interactions and dynamic evolution of components within the TME, TCM identifies "phlegm", "stasis", "toxins", and "deficiency" as core pathological factors of tumors.

### *Phlegm*

Some scholars, starting from the TCM concept of "phlegm", suggest that the accumulation of acidic metabolic byproducts or other abnormal cellular components in the TME is essentially a disturbance in the body's fluid metabolism, leading to the formation of "phlegm" due to internal dampness, a key factor in cancer development [15]. There is a correlation between the acidic constitution and the phlegm-dampness constitution in TCM theory based on clinical characteristics and disease susceptibility [16]. From a modern medical perspective, individuals with a phlegm-dampness constitution exhibit a decrease in CD4 cells compared to normal individuals, an increase in CD8 cells, leading to a decreased CD4/CD8 ratio, abnormal lymphocyte apoptosis, and potentially reduced macrophage activity [17]. Individuals with a phlegm-dampness constitution show abnormal levels of inflammatory factors in their peripheral blood, with significantly elevated levels of pro-inflammatory factors like TNF-α and IL-6, which can activate various inflammatory signaling pathways, sustaining a chronic inflammatory state within the body [18]. The TME represents a state of mutual entanglement between phlegm and stasis, fluid metabolism disturbances, Qi and blood obstruction, conflict between pathogenic and healthy forces, and imbalance of Yin and Yang.

### *Stasis*

In TCM, "blood stasis" is considered a crucial pathological factor in the formation of accumulations. Tumors depend on neovascularization, and the structure and function of new blood vessels in the TME differ from normal vessels, exhibiting changes such as twisting, dilation, and pouch formation. Vascular twisting increases vascular resistance, slowing blood flow. As blood, a shear-thinning fluid slows down, viscosity increases, further reducing blood flow, resulting in a lower overall blood perfusion rate in tumors compared to normal tissues, manifesting as a state of "blood stasis" [19]. Blood-activating and stasis-resolving herbal medicines aim to eliminate stasis toxins, improve the hypoxic microenvironment in tumor patients, and inhibit tumor vessel formation and cancer thrombus formation.

### *Toxins*

The ancient Chinese medical text "Jin Gui Yao Lue Xin Dian" states, "Where there is firmness, there must be lurking Yang". In a state of "lurking Yang", the function of Yang Qi is disrupted, leading to a breakdown in defense mechanisms, weakened propulsive force, abnormal Qi transformation, accumulation of pathological products, prolonged stagnation transforming into heat toxins, creating a pathological microenvironment conducive to tumor formation and progression [20]. Renowned Chinese medicine expert Professor Zhou Zhongying proposed the "cancer toxin theory", suggesting that cancer toxins can directly lead to organ dysfunction, inducing conditions resembling phlegm-dampness, blood stasis, and heat toxins, similar to inflammatory pathological factors in modern medicine [21]. Some scholars propose that the abundance of inflammatory cells and cytokines in the TME shares similarities with phlegm, stasis, dampness, and toxins in TCM's theory of cancer toxins, suggesting a mutual causality and transformation among these pathological factors, collectively contributing to the disease [22]. The different stages of cancer toxins accompany the formation and transformation of the TME, driving the onset and progression of tumors.

### *Deficiency*

The development and changes in tumors result from a complex interplay of multiple factors

and steps, with the primary pathological mechanism being "spleen and stomach weakness, deficiency of healthy Qi". According to TCM theory, the spleen governs transformation and transportation, serving as a primary source for converting absorbed essence from grains and water into Qi, blood, essence, and body fluids to nourish the entire body. When the spleen and stomach are weak, the generation of Qi and blood becomes inadequate. This aligns with the observation that tumor cells predominantly convert glucose to lactate through glycolysis rather than completely oxidizing it aerobically into $CO_2$ and $H_2O$, resulting in insufficient energy production [23]. Weakness in the spleen and stomach leads to a deficiency of healthy Qi in the body, causing dysfunction in organ functions. The "Huang Di Nei Jing" states, "When the healthy Qi is stored within, evils cannot intrude". A deficiency of healthy Qi corresponds to immunosuppression in modern medicine. The TME represents the battleground between healthy and pathogenic forces, with dynamic changes in the microenvironment reflecting the fluctuations in the balance of these forces, where the tumor's immunosuppressive microenvironment manifests the localized deficiency of healthy Qi in the primary or secondary tumor lesions [24].

## Influence of TCM on TME

TCM can positively regulate the number and function of immune killer cells. It also downregulates the number and function of immune suppressive cells. Furthermore, TCM modulates tumor growth signaling pathways, inhibits tumor cell growth, migration, and invasion, and enhances the anticancer immune response of tumors. To some extent, these effects improve TME, potentially leading to reduced tumor size, improved patient prognosis, and enhanced quality of life. This section analyzes the regulatory effect of TCM on TME from the following perspectives: TCM monomers, single Chinese herbs, compound herbal preparations, and other dosage forms.

### *TCM monomers*

*Flavonoids:* Flavonoids are polyphenolic compounds that can be extracted from TCM and have been extensively studied for their antitumor activities. The expression of Wnt16 in tumor-associated fibroblasts (TAFs) is a key factor in promoting malignant tumor drug resistance [25]. Hu et al. [26] reported that quercetin can inhibit the expression of Wnt16 in activated fibroblasts, thereby reducing the TME stromal barrier and reversing drug resistance. Li et al. [27] discovered that quercetin can reduce programmed death-ligand 1 (PD-L1) in tumor cells by inhibiting the phosphorylation of Janus kinase-2 (JAK2) and signal transducer and activator of transcription 3 (STAT3) and reshaping the extracellular matrix (ECM) by downregulating alpha-smooth muscle actin (α-SMA) fibroblasts in tumors. In their study, Li et al. [28] observed that quercetin can enhance anti-tumor immunity by modulating the tumor immune microenvironment, increasing M1 macrophages, CD8+/CD4+ T lymphocytes, promoting CD8+ T cells to secrete IL-2 and interferon-gamma (IFN-γ), thereby inhibiting melanoma growth.

Luteolin inhibits the growth, migration, and invasion of glioblastoma and colon cancer cells by suppressing the immune microenvironment and the IL6/STAT3 signaling pathway [29, 30]. It also inhibits cervical cancer HeLa cell proliferation by inhibiting the protein kinase B (Akt)/mammalian target of Rapamycin (mTOR) and mitogen-activated protein kinase (MAPK) pathways, inducing apoptosis [31]. Additionally, luteolin induces apoptosis and cell cycle arrest by altering the expression of Bax, Caspase 3, and Caspase 9 in A549 lung cancer cells while reducing Bcl-2 expression, leading to apoptosis and cell cycle arrest [32]. Luteolin inhibits the MAPK/AKT/Phosphoinositide 3-kinase (PI3K) pathway and JAK2/STAT3 signaling pathways in multiple tumor cell lines, exerting anti-inflammatory and anticancer effects [33, 34].

Curcumin has been shown to regulate various signaling pathways, including JAK/STAT [35], PI3K/Akt/mTOR [36], Wnt/β-catenin [37], vascular endothelial growth factor (VEGF)/vascular endothelial growth factor receptor (VEGFR) [38], and genes such as cyclin D1, TP53, BAX, BCL-2, human telomerase reverse transcriptase (hTERT), and matrix metalloproteinases (MMPs) [39-41], thereby affecting tumor cell proliferation, migration, invasion, cell cycle, and apoptosis. Curcumin can also enhance the anticancer immune response, reshape the tumor immune suppressive microenvironment, impact lymphocyte infiltration, and improve the immune status of the TME [42].

Silybin induces G0/G1 cell cycle arrest and apoptosis by mediating the JAK2/STAT5 and PI3K/AKT pathways, inhibits tumor angiogenesis, and suppresses Non-small cell lung cancer (NSCLC) cell proliferation, migration, and invasion; it also inhibits the formation of the STAT5/PD-L1 complex, suppressing tumor immune escape mechanisms [43]. Silybin increases ROS levels, induces cell death, and downregulates extracellular signal-regulated kinase (ERK) and Akt in ovarian cancer cells, inhibiting tumor growth [44].

Rutin inhibits the mRNA and protein expression of Notch-1 and Hes-1 in colon cancer cells, suppressing cell proliferation mediated by the Notch signaling pathway [45]. Rutin regulates key proteins in the PI3K/Akt and nuclear factor κB (NF-κB) signaling pathways, inhibiting oxidative damage and cell apoptosis in liver cells [46]. Rutin stimulates autophagy and apoptosis in glioblastoma cells through the Akt/Creb/miR-20b-5p/Atg7 signaling pathway, inhibiting glioblastoma cell proliferation [47].

Genistein [48], chrysin [49], epigallocatechin-3-gallate (EGCG) [50], nobiletin [51, 52], and myricetin [53], among other flavonoids, exhibit multi-target characteristics by modulating various signaling pathways, exerting anti-tumor effects on proliferation, invasion, migration, and promoting apoptosis. For detailed information on their action pathways and mechanisms, see **Table 1**.

*Terpenoids:* Terpenoids are the most widely found monomers in medicinal plants. Paclitaxel is a highly efficient, low-toxicity, broad-spectrum natural anticancer drug that induces G2/M phase arrest and apoptosis in tumor cells by targeting microtubules, exhibiting anti-tumor activity [54].

Parthenolid can inhibit the NF-κB pathway, reduce the expression of TNF-α, IL-1, IL-6, intercellular adhesion molecular (ICAM), cyclooxygenase-2 (COX-2), and block the inflammatory response positively [55]. It can also inhibit the JAK/STAT pathway, leading to the downregulation of several anti-apoptotic molecules in the Bcl-2 family downstream [56].

Triptolide inhibits gastric cancer MGC803 cell proliferation, invasion, and migration by inhibiting the AKT/glycogen synthase kinase-3β (GSK-3β) signaling pathway [57]. It also regulates p53 expression and acetylation by inhibiting Sirtuin type 1 (SIRT1), thereby controlling the SIRT1/p53 signaling pathway to suppress HepG2 liver cancer cell proliferation and migration [58].

Artesunate inhibits tumor progression by blocking receptor tyrosine kinase-like orphan receptor 1 (ROR-1)-induced STAT3 activation [59], regulating VEGF and MMP-2/-9 to inhibit angiogenesis [60], modulating cell cycle protein kinases to reshape the TME, improving tumor immunotherapy [61], inhibiting lymphoma cell proliferation by suppressing AKT and ERK [62].

Ursolic acid (UA) can regulate the activity of key cell signaling pathways involving AKT, mTOR, STAT, NF-κB, and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) [63]. In nature, UA has very low solubility and is typically prepared as nanocrystals, solid dispersions, and loaded into nanoparticles. Zhang et al. [64] found that UA liposomes can effectively correct tumor-mediated immune suppression by inhibiting STAT5 phosphorylation and IL-10 secretion, effectively regulating CD4+CD25+Foxp3+ T cells from 4T1 tumor-bearing mice. This suggests that UA liposomes alone can effectively correct the immune suppressive microenvironment mediated by tumors, halting tumor growth.

Kaempferol's anti-tumor mechanism primarily involves arresting cancer cells in the S phase and inducing apoptosis [65]. Zhang et al. [66] observed that kaempferol inhibits lung adenocarcinoma cell proliferation by suppressing cell division and cycle-related protein 5 (CDCA5) expression, promoting cell apoptosis.

Gastrodin, through the reprogramming of long noncoding RNAs to regulate autophagy and activate the cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA)/G protein-coupled receptor kinase type 2 (GRK2) pathway, inhibits cell proliferation and induces apoptosis in brain glioma cells [67]. Gastrodin can directly bind and inhibit AKT, downregulate hexokinase 2 (HK2) at the transcriptional level, suppress HK2-mediated glucose metabolism, promote apoptosis in oral squamous cell carcinoma (OSCC) cells, and may serve as an effective candidate drug for OSCC treatment [68]. The

**Table 1.** Modulatory effects of flavonoids on tumor TME

| TCM monomer | Source | Mode of Action | References |
|---|---|---|---|
| Quercetin | Bupleurum<br>Mulberry leaves<br>Hawthorn<br>Pagoda tree fruit | Decreases Wnt16 in TAFs; Inhibits JAK2 and STAT3 phosphorylation, PD-L1 downregulation, α-SMA+ fibroblasts downregulation; Increases M1 macrophages, CD8+/CD4+, IL-2, and IFN-γ | [26-28] |
| Luteolin | Abelia<br>Honeysuckle<br>Baikal skullcap<br>Dandelion | Inhibits immune microenvironment, IL6/STAT3, Akt/mTOR, MEK-ERK, MAPK/AKT/PI3K, JAK2/STAT3 signaling pathways | [29-34] |
| Curcumin | Turmeric<br>Mustard<br>Curcuma<br>Turmeric | Modulates JAK/STAT, PI3K/Akt/mTOR, Wnt/β-catenin, VEGF/VEGFR signaling pathways; Modulates cyclin D1, TP53, BAX, BCL-2, hTERT, and MMPs gene expression; Enhances immune response | [35-42] |
| Silybin | Milk thistle | Mediates JAK2/STAT5 and PI3K/AKT pathways, induces G0/G1 cell cycle arrest, apoptosis, inhibits tumor angiogenesis, increase ROS, decrease ERK, AKT | [43, 44] |
| Rutin | Tangerine peel Pagoda tree fruit<br>Astragalus<br>Kudzu root | Downregulates Notch-1, Hes-1, Notch pathway inhibition; Regulates PI3K/AKT, NF-κB pathways; Regulates AKT/Creb/miR-20b-5p/Atg7 pathway | [45-47] |
| Genistein | Kudzu root<br>Soybean<br>Pagoda tree flower | Inhibits the G2/M cell cycle phase, promotes apoptosis, suppresses proliferation and migration | [48] |
| Chrysin | Poplar buds<br>Passion flower | Inhibits the PI3K/AKT/mTOR/NF-κB pathway, induces cell apoptosis, enhances autophagy, reduces the production of inflammatory mediators, and improves TME | [49] |
| EGCG | Tea leaves<br>Green tea | Activates anti-tumor immune responses in the tumor microenvironment, targeting multiple upregulated metabolic reprogramming pathways | [50] |
| Nobiletin | Tangerine peel<br>Orange peel | Inhibits the AKT/ERK/Nrf2 pathway, reverses paclitaxel resistance; upregulates SLFN5, regulates the PTEN/Akt pathway, inhibits renal cancer cell proliferation, and promotes apoptosis | [51, 52] |
| Myricetin | Bayberry bark, leaves, and roots | Regulates the JAK-STAT-IRF1 signaling pathway, inhibiting immune evasion | [53] |

Note: TCM, traditional Chinese medicine; TAFs, tumor-associated fibroblasts; JAK, Janus kinase; STAT, signal transducer and activator of transcription; PD-L1, programmed death-ligand 1; α-SMA, alpha-smooth muscle actin; IFN-γ, interferon-gamma; Akt, protein kinase B; mTOR, mammalian target of Rapamycin; MEK, mitogen-activated extracellular signal-regulated kinase; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; BAX, Bcl-2 associated X protein; BCL-2, B-cell lymphoma 2; hTERT, human telomerase reverse transcriptase; MMP, matrix metalloproteinase; ROS, reactive oxygen species; Hes-1, hairy and enhancer of split 1; NF-κB, nuclear factor κB; Creb, cyclic-AMP response element binding protein; Atg7, autophagy-related protein 7; TME, tumor microenvironment; Nrf2, Nuclear factor erythroid 2-related factor 2; SLFN5, schlafen family member 5; PTEN, phosphatase and tensin homolog; IRF1, interferon regulatory factor 1.

intervention pathways and mechanisms of terpenoids in the TME are detailed in **Table 2**.

*Alkaloids compounds:* Berberine is an isoquinoline alkaloid compound extracted from the TCM Coptis chinensis, with anti-inflammatory, anti-tumor, and anti-fibrotic effects. Studies [69] have shown that berberine significantly upregulates the expression of Bax and cyclin D1 mRNA in gemcitabine-resistant pancreatic ductal adenocarcinoma cells while downregulating the expression of Bcl-2, survivin, PI3K, AKT, and p-Akt proteins, indicating that berberine exerts its anti-pancreatic cancer effects by inhibiting the PI3K/AKT signaling pathway.

Sinomenine, extracted from the Chinese herb Sinomenium acutum, is a compound that induces apoptosis, reverses drug resistance, and exhibits anti-angiogenic properties in various cancers. Research has shown that sinomenine induces cell apoptosis by activating the AMP-dependent protein kinase (AMPK)-mTOR pathway [70] and inhibits the growth of rheumatoid arthritis fibroblast-like synoviocytes (RA-FLS) cells by inhibiting AMPK phosphorylation, without affecting normal macrophages in autoimmune disease models.

Dictamnine, extracted from the dried root bark of the Rutaceae plant Dictamnus dasycarpus,

**Table 2.** Modulatory effects of terpenoids on tumor TME

| TCM monomer | Source | Mode of Action | References |
|---|---|---|---|
| Paclitaxel | Yew Schisandra | Block G2/M cell cycle, activate p53, ↓Cyclin, ↓BCL-XL, promote apoptosis | [54] |
| Parthenolid | Chrysanthemum | Inhibit NF-κB pathway, anti-inflammatory; Inhibit JAK/STAT pathway, promote apoptosis | [55, 56] |
| Triptolide | Thunder god vine | Inhibit AKT/GSK-3β, SIRT1/p53 pathways, inhibit proliferation, invasion, migration, promote apoptosis | [57, 58] |
| Artesunate | Artemisia annua Sweet wormwood | Inhibit STAT3, regulate VEGF and MMP-2/-9, suppress cell cycle proteins, inhibit AKT/ERK, inhibit proliferation | [59-62] |
| Ursolic acid | Hawthorn Cornelian cherry Hedyotis diffusa Willd Prunella vulgaris | Regulate key cell signaling pathways involving AKT, mTOR, STAT, NF-κB, TRAIL | [63, 64] |
| Kaempferol | Melia azedarach L. Meliae Cortex | Block S phase, promote apoptosis; ↓CDCA5, promote apoptosis, inhibit proliferation | [65, 66] |
| Gastrodin | Gastrodia elata | Regulate autophagy, activate cAMP/PKA/GRK2 pathway; Inhibit Akt, ↓HK2, inhibit glycolysis, promote apoptosis | [67, 68] |

Note: TME, tumor microenvironment; TCM, traditional Chinese medicine; BCL-XL, B-cell lymphoma x long; NF-κB, nuclear factor κB; JAK, Janus kinase; STAT, signal transducer and activator of transcription; AKT, protein kinase B; GSK-3β, glycogen synthase kinase-3β; SIRT1, Sirtuin type 1; VEGF, vascular endothelial growth factor; MMP, matrix metalloproteinase; ERK, extracellular signal-regulated kinase; mTOR, mammalian target of Rapamycin; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; GRK2, G protein coupled receptor kinase type 2; HK2, hexokinase 2.

inhibits cancer cell growth in vitro and in vivo by downregulating the PI3K/AKT/mTOR and MAPK signaling pathways through the inhibition of c-Met receptor tyrosine kinase phosphorylation and activation, suppressing cancer cell proliferation [71].

*Other TCM monomers:* Resveratrol, derived from the traditional Chinese herb Polygonum cuspidatum, is a polyphenolic compound known to modulate the tumor immune microenvironment and cell communication [72] to enhance the therapeutic effects against tumors. It regulates various signaling pathways by stimulating or inhibiting certain cell mediators, such as chemokines, cytokines, miRNAs, and death signals, and modulating signaling pathways like NF-κB, Wnt, PI3K/AKT/mTOR, among others [73].

Punicalagin (PUN) is a polyphenolic compound extracted from pomegranate. Huang et al. [74] reported that PUN reduces TNF-α oxidative stress, regulates the immune microenvironment by promoting polarization of M2 macrophages, and alleviates oxidative stress by activating the Nuclear factor erythroid 2-related factor 2 (Nrf2)/hemoxygenas-1 (HO-1) pathway.

Oridonin, the main active compound extracted from the Chinese herb Isodon rubescens, regulates apoptosis through various pathways and exhibits anti-tumor effects. Oridonin can inhibit pyroptosis by suppressing caspase-1 and nucleotide-binding oligomerization domain-like receptor pyrin domain-containing 3 (NLRP3), activate pyroptosis by activating caspase-3 and caspase-8, and regulate pyroptosis by inhibiting noncoding RNA (ncRNA) and the NLRP3 pathway [75].

Ginsenosides, important chemical components of ginseng, improve the TME by inhibiting cancer cell stemness tumor angiogenesis, promoting anti-tumor immunity, enhancing the efficacy of chemotherapy drugs against cancer, inhibiting cell growth, proliferation, migration, and promoting apoptosis. They also regulate signaling pathways like PI3K/AKT, CCAAT/enhancer-binding proteins β (C/EBPβ)/NF-κB, Wnt/β-catenin, Notch-Hes1, to prevent and treat tumors [76].

Lycium barbarum polysaccharides (LBPs) significantly reshape the TME by modulating the functions of TAMs [77] and protecting the extracellular matrix, thereby inhibiting tumor cell metastasis and slowing down tumor progression [78].

*Single Chinese herbs*

Astragalus, with its sweet taste and slightly warm nature, is a crucial herb in TCM for tonifying Qi. It can regulate tumor immunity, as astragalus polysaccharides have been shown to inhibit tumor-associated macrophages' M2 polarization, increase cytotoxic T lymphocyte infiltration, promote dendritic cell maturation, enhance natural killer (NK) cell function, and activate immune cells such as Treg cells, macrophages, NK cells, and DC to activate the immunosuppressive TME [79]. Additionally, it can downregulate the expression of PD-L1 on the surface of tumor cells such as colorectal cancer, breast cancer, melanoma, and cervical cancer, enhancing T cell anti-tumor immune responses [80]. Astragalus affects tumor cell proliferation, invasion, migration, and apoptosis. Studies have shown that astragalus polysaccharides can intervene in the transition of human gastric cancer MKN45 and MGC-803 cells from the G1 phase to the S phase, inhibiting gastric cancer cell proliferation [81].

Hedyotis diffusa Willd (HDW), also known as Bai Hua She She Cao, contains active anti-tumor components, mainly including flavonoids (such as quercetin), terpenoids (such as UA), anthraquinones, and polysaccharides [82]. Studies have reported that HDW can arrest the cell cycle of rat glioma C6 cells in the S phase, inhibit C6 glioma cell growth, and induce apoptosis [83]. Furthermore, HDW has been shown to suppress the migration of lung cancer H1975 cells by downregulating MMP-2 and MMP-9 and upregulating tissue inhibitors of the MMP-2 (TIMP-2) [84].

Prunellae Spica is known for its effects on clearing heat, improving vision, and dispersing nodules. Modern pharmacological studies have revealed that extracts of Prunellae Spica possess various pharmacological effects, including antiviral, immunosuppressive, antioxidant, and anti-tumor activities [85]. Its mechanisms involve inducing cell apoptosis, inhibiting cell invasion and migration, suppressing cell proliferation, inducing autophagy, anti-tumor angiogenesis, reversing tumor multidrug resistance, and regulating immune function through miRNA and various signaling pathways such as Wnt/β-catenin, AMPK/mTOR/UNC-51-like kinase 1 (ULK1), PI3/Akt, receptor activator of Nuclear factor-kappa B Ligand (RANKL)/receptor activator of nuclear factor-kappa B (RANK)/osteoprotegerin (OPG) [86].

Salvia miltiorrhiza is recognized for its ability to invigorate blood circulation, resolve blood stasis, clear the heart, relieve restlessness, cool blood, and dissipate swellings. Its active component, tanshinone, has been shown to inhibit tumor cell growth and proliferation, suppress tumor cell invasion and migration, inhibit tumor angiogenesis, induce tumor cell autophagy, and exert anticancer effects by regulating immune-related cells (such as macrophages, NK cells, CD4 cytotoxic cells, and dendritic cells) through NF-κB, MAPK, JAK, and STAT4 signaling pathways [87]. Tanshinone can also regulate the cell cycle to induce cancer cell apoptosis and inhibit cancer cell invasion and migration by suppressing the MMP-2 and MMP-9 signaling pathways [88].

*Compound Chinese medicine preparations*

*Decoctions:* The modified Buzhong Yiqi decoction, in animal experiments, significantly prolongs the survival of mice with immune-competent pre-gastric cancer cell xenografts, increases CD4+ T cell infiltration in tumors, and enhances the CD4+/CD8+ T cell ratio in peripheral blood while reducing the proportion of CD8+PD-1+ T cells and PD-1+ Treg cells. In vitro experiments have shown that this formulation promotes the proliferation, activation, and cytotoxicity of T lymphocytes and suppresses gastric cancer PD-L1 expression via the PI3K/AKT pathway [89]. The modified Jianpi Yangzheng decoction inhibits the phosphoinositide 3-kinase γ (PI3K) and NF-κB signaling pathways, reduces the transformation of M2 macrophages to M1 in the TME, and induces TAM reprogramming to inhibit cancer growth and metastasis [90]. Danggui Buxue decoction blocks the protective effect of M2 macrophages on gemcitabine by inhibiting excessive deoxycytidine secretion and reducing cytidine deaminase overexpression [91]. The Jianpi Yangzheng Xiaozheng decoction suppresses tumor PD-L1 expression through the IL-6/JAK2/STAT3 pathway, reduces PD-L1 levels in tumor-derived exosomes, inhibits MDSC proliferation, and reshapes the immunosuppressive TME [92]. In vitro experiments have shown that this

decoction can inhibit aerobic glycolysis in gastric cancer cells [93].

*Pills:* The Xihuang pill has been shown to inhibits the migration and invasion abilities of U251 glioma cells, while downregulating the expression of VE-cadherin, MMP14, and laminin γ2 proteins. It regulates the activation of the HIF-1α/VEGFA/VEGFR2 signaling pathway, inhibits the mimicry of glioma cell angiogenesis, and exerts anti-angiogenic effects [94]. The Biejia Jian pill is a classical formula for reducing the incidence of hepatocellular carcinoma (HCC). It inhibits the expression of vascular endothelial growth factor A (VEGF-A) and hepatocyte growth factor (HGF) in cancer-associated fibroblasts (CAFs) by downregulating platelet-derived growth factor receptor β (PDGFRβ) signaling, thereby inhibiting the progression of HCC [95]. The Shuyu pill has demonstrated the ability to regulate M1/M2 polarization of tumor-associated macrophages, thereby alleviating the immune-suppressive state within the colorectal cancer TME and inhibiting the growth of colon cancer xenografts [96].

*Injections:* The Shenqi Fuzheng injection mainly consists of Codonopsis and Astragalus extracts, known for their tonifying and invigorating properties. Clinical studies have shown that the Shenqi Fuzheng injection tonifies Qi, invigorates the spleen, increases the patient's vital energy, and enhances cellular immune function. In treating postoperative chemotherapy patients with rectal cancer, it has been found to improve immune function by increasing CD4+ and CD8+/CD8+ T cell levels and related cytokines, thereby prolonging progression-free survival [97]. The injection can also elevate IL-2, IFN-γ, and CD40 levels in tumor tissue and reduce transforming growth factor-β1 (TGF-β1) levels while increasing the activation of CD4+ T cells in tumor tissue, promoting glycolysis in CD4+ T cells, improving the tumor immune microenvironment [98].

The compound Kushen injection, composed of Sophora flavescens and Poria extracts, possesses anti-inflammatory, antioxidant, and immune-enhancing effects. Animal experiments have shown that the compound Kushen injection can improve acute radiation-induced oral mucositis in rats by inhibiting M1 polarization of macrophages, suppressing the expression of pro-inflammatory cytokines IL-6 and TNF-α, and promoting M2 polarization of macrophages, increasing the expression of anti-inflammatory cytokines TGF-β and IL-10 [99]. The Kangai injection, containing Ginseng, Astragalus, and Sophora alkaloid extracts, has been shown in various studies to induce tumor cell apoptosis, inhibit tumor cell proliferation, invasion, and migration, increase sensitivity to chemotherapy drugs, reduce chemotherapy-related adverse events, and enhance immune function. Research has demonstrated that the Kangai injection lowers tumor necrosis factor receptor 2 (TNFR2), tumor necrosis factor receptor-associated factor 2 (TRAF2), PI3K, AKT, and inhibitor of nuclear factor kappa-B (IκBα) mRNA levels in gastric cancer cells, inhibits PI3K, AKT, and IκBα phosphorylation, and suppresses cell proliferation [100].

*Other formulations:* The Shenling Baizhu formula can reduce the expression of peripheral blood CD4+CD25+Tregs and monocyte Foxp3 mRNA in stage IV gastric cancer patients, decrease the concentrations of the inhibitory cytokines IL-10 and TGF-β1, correct the immunosuppressive microenvironment, and improve the inhibitory status of tumor-specific T lymphocytes in gastric cancer patients [101]. The modified Huoluo Xiaoling formulation intervenes in colorectal cancer through multiple targets and signaling pathways. In cell experiments, the modified Huoluo Xiaoling formulation regulates the Wnt/β-catenin signaling pathway, inhibiting the proliferation, invasion, and migration of colorectal cancer cells [102]. The Zilongjin tablet, used as a TCM for treating lung cancer, exerts immune modulation effects on lung cancer, both positively and negatively regulating inflammatory responses to suppress the excessive proliferation of immune cells or inflammatory factors, thereby inhibiting excessive inflammatory responses and promoting positive immune response, avoiding immunosuppression [103]. The Fei Liu Ping ointment, a paste formulation of the Yifei Qinghua granule, has been shown to downregulate HIF-1α expression, thereby inhibiting the expression of proteins involved in tissue glycolysis such as glucose transporter type 4 (GLUT4), HK, glucose-regulated protein 78Kd (GrP78), carbonic anhydrase (CA)-IX and intracellular pH regulation, reducing lactate production, improving the tumor's acidic environment [104]. Furthermore, it has been observed that the combination of

**Table 3.** Regulatory effects of compound Chinese medicine preparations on the tumor TME

| TCM compound | Composition | Mode of Action | References |
|---|---|---|---|
| Modified Buzhong Yiqi decoction | Astragalus, Angelica, Atractylodes, Licorice, etc. | CD4+/CD8+↑, CD8+PD-1/PD-1+ Treg↓, inhibition of tumor PD-L1 expression via the PI3K/AKT pathway | [89] |
| Modified Jianpi Yangzheng decoction | Astragalus, Codonopsis, Polygonatum, Turmeric | Inhibition of PI3Kγ and NF-κB signaling pathways, reduction of M2 macrophage transformation to M1 in the TME, induction of TAMs reprogramming | [90] |
| Danggui Buxue decoction | Astragalus, Angelica | Deoxyguanosine↓, cytidine deaminase↓, blocking the protective effect of M2 macrophages on gemcitabine | [91] |
| Jianpi Yangzheng Xiaozheng decoction | Codonopsis, Astragalus, Atractylodes, Paeonia, Curcuma, Hedyotis diffusa, etc. | Downregulation of IL-6/JAK2/STAT3 pathway, inhibition of PD-L1 expression, PD-L1↓, inhibition of MDSCs proliferation; inhibition of aerobic glycolysis | [92, 93] |
| Xihuang pill | Cow bezoar, Musk, Frankincense, Myrrh | VE-cadherin, MMP14, laminin γ2↓, regulation of HIF-1α/VEGFA/VEGFR2 signaling pathway, anti-angiogenesis | [94] |
| Biejia Jian pill | Soft-shelled turtle shell, Donkey-hide gelatin, Beeswax, Earthworm, etc. | Downregulation of CAFs-mediated PDGFRβ signaling to exert anticancer effects | [95] |
| Shu Yu pill | Dioscorea, Licorice, Angelica, Cinnamomum, etc. | Regulation of M1/M2 polarization of tumor-associated macrophages, improvement of immune-suppressive state in TME | [96] |
| Shenqi Fuzheng injection | Codonopsis, Astragalus, etc. | CD4+, CD8+/CD8+ T cell levels↑, enhancement of immune function; IL-2, IFN-γ, CD40↑, TGF-β1↓, improvement of immune microenvironment | [97, 98] |
| Compound Kuchan injection | Sophora flavescens, Poria, etc. | Regulation of M1/M2 polarization of tumor-associated macrophages, improvement of radiation-induced mucositis | [99] |
| Kangai injection | Ginseng, Astragalus, etc. | TNFR2, TRAF2, PI3K, AKT, IκBα mRNA↓, inhibition of PI3K, AKT, IκBα phosphorylation, inhibition of cell proliferation | [100] |
| Shenling Baizhu formula | Ginseng, Atractylodes, Poria, Amomum, Platycodon, etc. | CD4+CD25+Tregs, Foxp3 mRNA, IL-10, TGF-β1↓, improvement of immune suppression | [101] |
| Huoluo Xiaoling formulation | Angelica, Salvia, Frankincense, Myrrh, etc. | Multi-target, multi-pathway anti-tumor effects; regulation of Wnt/β-catenin signaling pathway, inhibition of proliferation, invasion, and migration of colorectal cancer | [102] |
| Zilongjin tablet | Astragalus, Angelica, Solanum lyratum thunb, Salvia, etc. | Immune modulation, improvement of immune suppression | [103] |
| Fei Liu Ping ointment | Astragalus, American ginseng, Adenophora stricta, Ophiopogon, etc. | Combination with cyclophosphamide, HIF-1α, GLUT4, HK, GRP78, CA-IX↓, lactate↓, inhibition of T cell differentiation into Treg cells, immune suppression, promotion of immune escape | [104] |

Note: TME, tumor microenvironment; TCM, traditional Chinese medicine; Treg, tumor-associated neutrophils, regulatory T cell; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; PI3Kγ, phosphoinositide 3-kinase γ; NF-κB, nuclear factor κB; TME, tumor microenvironment; TAMs, tumor-associated macrophages; JAK2, Janus kinase-2; STAT3, signal transducer and activator of transcription 3; MDSCs, marrow-derived suppressor cells; VE-cadherin, vascular endothelial-cadherin; MMP14, matrix metalloproteinase 14; HIF-1α, hypoxia-inducible factor-1α; VEGFA, vascular endothelial growth factor A; VEGFR2, vascular endothelial growth factor receptor 2; CAFs, cancer-associated fibroblasts; PDGFRβ, platelet-derived growth factor receptor β; IFN-γ, interferon-gamma; TGF-β1, transforming growth factor-β1; TNFR2, tumor necrosis factor receptor 2; TRAF2, tumor necrosis factor receptor-associated factor 2; IκBα, inhibitor of nuclear factor kappa-B; Foxp3, forkhead box P3; GLUT4, glucose transporter type 4; HK, hexokinase; GRP78, glucose regulated protein 78Kd; CA-IX, carbonic anhydrase-IX.

Fei Liu Ping ointment and cyclophosphamide chemotherapy can suppress IL-2 expression and inhibit T cell differentiation into Treg cells, ultimately inhibiting immunity and promoting immune escape. For detailed information on the pathways and mechanisms through which compound Chinese medicine preparations intervene in the TME, see **Table 3**.

## Conclusion and prospects

As research on the TME deepens and expands, it is increasingly evident that the occurrence and development of tumors are closely related to the TME. The physical and chemical characteristics of the TME, with its heterogeneity and pathogenicity, are not only pathological features but also correspond to the etiology and pathogenesis of TCM. The low oxygen acidity characteristic of the TME corresponds to the phlegm-dampness pattern in Chinese medicine, emphasizing the importance of eliminating phlegm-dampness in treatment. Immune suppression in the TME corresponds to the struggle between the nourishing Qi and defensive Qi in TCM against cancer pathogens, highlighting the need to tonify the body's vital energy and expel pathogenic factors while focusing on nourishing the body's defense mechanisms. Increasingly, studies at the molecular and cellular levels have validated the effectiveness of TCM in combating cancer. With its complex composition, multiple targets, pathways, and

minimal adverse effects, TCM may not precisely target and destroy tumors. Still, its combination with modern multidisciplinary diagnostic and therapeutic models plays an irreplaceable role in reducing toxicity and enhancing efficacy. Through the compilation and summarization of existing literature, this study has suggested that active components of single Chinese herbs and compound Chinese medicine preparations can inhibit the formation and development of the TME through various pathways, thereby preventing and treating tumors. These pathways include (1) blocking the cell cycle, inhibiting tumor cell growth, invasion, and migration, inducing apoptosis and autophagy; (2) inhibiting tumor angiogenesis, promoting vascular normalization; (3) regulating the polarization of M1/M2 tumor-associated macrophages, improving the immune-suppressive state in the TME; (4) regulating tumor-infiltrating lymphocytes, enhancing immune responses, improving immune suppression, and reshaping the immune microenvironment; (5) regulating aerobic glycolysis energy metabolism, improving the acidic microenvironment; (6) inhibiting the secretion of inflammatory cytokines, improving the inflammatory microenvironment, and more. Given the current need for comprehensive cancer treatment, targeting the TME for treatment will undoubtedly become a heated topic in future research on TCM's anti-tumor effects.

The regulation of TME in TCM has been proven to play a crucial role in the formation, occurrence, development, and treatment of various tumors, offering novel strategies and therapeutic approaches for cancer management. In recent years, studies on the regulatory effect of TCM, compound medicine, traditional Chinese patent medicines, and simple injections of TME have primarily focused on modulating immune cell function within the TME. However, based on the current literature review, most studies investigating the impact of TCM on the TME remain preclinical or experimental, with limited large-scale, multicenter, registered clinical trials and low rates of translational success. This limitation may be attributed to the inherent complexity, networked interactions, and dynamic nature of the TME. Anti-tumor TCM therapies possess unique advantages, such as high safety profiles, minimal adverse reactions, strong patient compliance, and the principle of "supporting the body without retaining evil, eliminating evil without harming the body". Its concept of "nourishing the body and strengthening the foundation, supporting the body and eliminating evil" aims to prevent and treat tumors by regulating the host's immune system. This aligns closely with the core idea of modern tumor immunology and warrants further in-depth investigation. More clinical and experimental studies are expected to continuously explore the pharmacological mechanisms, active ingredients, dosage, administration time, and toxicological pathology of TME. Continued exploration of these aspects will help unlock the full potential of TCM in regulating TME for the treatment of tumors. This will provide a basis and possibility for developing new drugs characterized by high safety, strong specificity, stability, and efficacy.

## Disclosure of conflict of interest

None.

**Address correspondence to:** Yongjun Zhang, Integration of Traditional Chinese and Western Medicine Department, Zhejiang Cancer Hospital, No. 1 Banshan East Road, Gongshu District, Hangzhou 310022, Zhejiang, China. E-mail: 15700079482@163.com

## References

[1] Tiwari A, Trivedi R and Lin SY. Tumor microenvironment: barrier or opportunity towards effective cancer therapy. J Biomed Sci 2022; 29: 83.

[2] Liu W, Wang B, Zhou M, Liu D, Chen F, Zhao X and Lu Y. Redox dysregulation in the tumor microenvironment contributes to cancer metastasis. Antioxid Redox Signal 2023; 39: 472-490.

[3] Luo YL, Zhou XT, Wei BJ, Liu YQ, Ma Y, Li CH and Li Y. Understanding of traditional Chinese medicine on inflammatory microenvironment and malignant transformation of inflammation. Lishizhen Med Materia Med Res 2022; 33: 1966-1968.

[4] Qian S, Golubnitschaja O and Zhan X. Chronic inflammation: key player and biomarker-set to predict and prevent cancer development and progression based on individualized patient profiles. EPMA J 2019; 10: 365-381.

[5] Niu T and Zhou F. Inflammation and tumor microenvironment. Zhong Nan Da Xue Xue Bao Yi Xue Ban 2023; 48: 1899-1913.

[6] Guo Q, Li J and Lin H. Effect and molecular mechanisms of traditional Chinese medicine

on regulating tumor immunosuppressive microenvironment. Biomed Res Int 2015; 2015: 261620.
[7] Bergers G and Fendt SM. The metabolism of cancer cells during metastasis. Nat Rev Cancer 2021; 21: 162-180.
[8] Wang BS and Jin C. Research progress on the mechanism of hepatocellular carcinoma under tumor acidic microenvironment. Chin J Hepatobiliary Surg 2022; 28: 632-636.
[9] Vaupel P, Schmidberger H and Mayer A. The Warburg effect: essential part of metabolic reprogramming and central contributor to cancer progression. Int J Radiat Biol 2019; 95: 912-919.
[10] Mookerjee SA, Goncalves RLS, Gerencser AA, Nicholls DG and Brand MD. The contributions of respiration and glycolysis to extracellular acid production. Biochim Biophys Acta 2015; 1847: 171-181.
[11] Casazza A, Di Conza G, Wenes M, Finisguerra V, Deschoemaeker S and Mazzone M. Tumor stroma: a complexity dictated by the hypoxic tumor microenvironment. Oncogene 2014; 33: 1743-54.
[12] Yin G, Tang DC, Zhao F, Qi ZC, Gu JF, Cang WH and Tan XY. Research ideas on reshaping the tumor hypoxic microenvironment by tonifying qi and activating blood circulation drugs. Chin J Trad Chin Med Pharmacy 2022; 37: 650-654.
[13] Jafari R, Rahbarghazi R, Ahmadi M, Hassanpour M and Rezaie J. Hypoxic exosomes orchestrate tumorigenesis: molecular mechanisms and therapeutic implications. J Transl Med 2020; 18: 474.
[14] Liu TH, Tao WC, Xiao Y, Chen WH, Liang QE, Chen XD and Chen LG. Connotation of traditional Chinese medicine holistic concept from the perspective of microenvironment. Chin J Trad Chin Med Pharmacy 2020; 35: 3718-3720.
[15] Lan S, Zheng C, Zhu J, Yan R and You FM. Discussion on inflammatory-cancer transformation based on the theory of "Jin Ye" in traditional Chinese medicine. J Basic Chin Med 2018; 24: 614-615, 619.
[16] Ling HZ, Zi WS, Yuan YG, Mei YL, Yi Z, Ruo XY, Qi W and Ling RL. Differences in vascular endothelial function and serum proteome between obese people with phlegm-dampness constitution and balanced constitution. J Tradit Chin Med 2024; 44: 188-196.
[17] Wu J, Li ZY, Cui N, Zhou R, Xu KY and Wu Y. Exploration of the role of invigorating the spleen and resolving phlegm method in colorectal cancer based on tumor microenvironment. Glo Trad Chin Med 2024; 17: 854-857.
[18] Ren S, Liu YT and Zhang J. Analysis of the essence of phlegm-dampness in modern medicine. J Basic Chin Med 2021; 27: 1515-1518.
[19] He W, Hu Y and Tong YJ. Pathogenesis of tumor immune suppression and inflammatory microenvironment in traditional Chinese medicine. Modern Chin Med 2022; 42: 1-5.
[20] Dai YN, Li HJ and Li XR. Formation and intervention of tumor microenvironment based on the theory of "Pi Jian Zhi Chu, Bi You Fu Yang". J Trad Chin Med 2023; 64: 2275-2281.
[21] Cheng HB and Wu MH. Analysis of professor zhou zhongying's academic thought on "Cancer Toxin". Chin J Trad Chin Med 2010; 25: 866-869.
[22] Wen DT and Zhou HP. Understanding of tumor microenvironment based on the theory of "Cancer Toxin". J Practical Med 2023; 39: 2556-2560.
[23] Li B, Guo K, Zeng L, Zeng B, Huo R, Luo Y, Wang H, Dong M, Zheng P, Zhou C, Chen J, Liu Y, Liu Z, Fang L, Wei H and Xie P. Metabolite identification in fecal microbiota transplantation mouse livers and combined proteomics with chronic unpredictive mild stress mouse livers. Transl Psychiatry 2018; 8: 34.
[24] Zhong Y Wang ZY, Zheng YF and Wang N. Scientific connotation of chronic psychological stress regulation of tumor microenvironment based on "Liver-Spleen" metabolic immune dialogue. Chin Arc Trad Chin Med 2024; 42: 99-103.
[25] Xiang L, Song Z and Rong G. Taxotere-induced WNT16 expression in carcinoma-associated fibroblasts might associate with progression and chemoresistance of breast cancer. Ann Clin Lab Sci 2020; 50: 205-212.
[26] Hu K, Miao L, Goodwin TJ, Li J, Liu Q and Huang L. Quercetin remodels the tumor microenvironment to improve the permeation, retention, and antitumor effects of nanoparticles. ACS Nano 2017; 11: 4916-4925.
[27] Li L, Zhang M, Liu T, Li J, Sun S, Chen J, Liu Z, Zhang Z and Zhang L. Quercetin-ferrum nanoparticles enhance photothermal therapy by modulating the tumor immunosuppressive microenvironment. Acta Biomater 2022; 154: 454-466.
[28] Li X, He X, Lin B, Li L, Deng Q, Wang C, Zhang J, Chen Y, Zhao J, Li X, Li Y, Xi Q and Zhang R. Quercetin limits tumor immune escape through PDK1/CD47 axis in melanoma. Am J Chin Med 2024; 52: 541-563.
[29] Zong S, Li X, Zhang G, Hu J, Li H, Guo Z, Zhao X, Chen J, Wang Y and Jing Z. Effect of luteolin on glioblastoma's immune microenvironment and tumor growth suppression. Phytomedicine 2024; 130: 155611.
[30] Jiang J, Zhu F, Zhang H, Sun T, Fu F, Chen X and Zhang Y. Luteolin suppresses the growth of colon cancer cells by inhibiting the IL-6/STAT3 signaling pathway. J Gastrointest Oncol 2022; 13: 1722-1732.

[31] Raina R, Pramodh S, Rais N, Haque S, Shafarin J, Bajbouj K, Hamad M and Hussain A. Luteolin inhibits proliferation, triggers apoptosis and modulates Akt/mTOR and MAP kinase pathways in HeLa cells. Oncol Lett 2021; 21: 192.
[32] Meng G, Chai K, Li X, Zhu Y and Huang W. Luteolin exerts pro-apoptotic effect and anti-migration effects on A549 lung adenocarcinoma cells through the activation of MEK/ERK signaling pathway. Chem Biol Interact 2016; 257: 26-34.
[33] Kong XL, Huo GT, Li J, Wang YN, Chen W and Jiang DX. Luteolin inhibits p65 NF-KB, promotes p85 PI3K to regulate VCAM-1 expression in microvascular endothelial cells. Prog Biochem Biophys 2020; 47: 675-684.
[34] Hui XL, Shu J, Li JL, Zhao J and Guo J. Effects of luteolin on proliferation, migration and AKT/STAT3 pathway of human ovarian cancer A2780 cells. J Tropical Med 2020; 20: 1292-1295, 1307.
[35] Su J, Liu X, Zhao X, Ma H, Jiang Y, Wang X, Wang P, Zhao M and Hu X. Curcumin inhibits the growth of hepatocellular carcinoma via the MARCH1-mediated modulation of JAK2/STAT3 signaling. Recent Pat Anticancer Drug Discov 2025; 20: 145-157.
[36] Ahmad I, Hoque M, Alam SSM, Zughaibi TA and Tabrez S. Curcumin and plumbagin synergistically target the PI3K/Akt/mTOR pathway: a prospective role in cancer treatment. Int J Mol Sci 2023; 24: 6651.
[37] Vallée A, Lecarpentier Y and Vallée JN. Curcumin: a therapeutic strategy in cancers by inhibiting the canonical WNT/β-catenin pathway. J Exp Clin Cancer Res 2019; 38: 323.
[38] Fu Z, Chen X, Guan S, Yan Y, Lin H and Hua ZC. Curcumin inhibits angiogenesis and improves defective hematopoiesis induced by tumor-derived VEGF in tumor model through modulating VEGF-VEGFR2 signaling pathway. Oncotarget 2015; 6: 19469-82.
[39] Kumar A, Hegde M, Parama D and Kunnumakkara AB. Curcumin: the golden nutraceutical on the road to cancer prevention and therapeutics. A clinical perspective. Crit Rev Oncog 2022; 27: 33-63.
[40] Sadeghzadeh H, Pilehvar-Soltanahmadi Y, Akbarzadeh A, Dariushnejad H, Sanjarian F and Zarghami N. The effects of nanoencapsulated curcumin-Fe3O4 on proliferation and hTERT gene expression in lung cancer cells. Anticancer Agents Med Chem 2017; 17: 1363-1373.
[41] Pereira BP, Silva AO, Awata WMC, Pimenta GF, Ribeiro JM, de Faria Almeida CA, Antonietto CRK, Dos Reis LFC, Esteves A, Torres LHL, de Araújo Paula FB, Ruginsk SG, Tirapelli CR, Rizzi E and Ceron CS. Curcumin prevents renal damage of l-NAME induced hypertension in by reducing MMP-2 and MMP-9. Cell Biochem Funct 2024; 42: e4119.
[42] Wang Y, Lu J, Jiang B and Guo J. The roles of curcumin in regulating the tumor immunosuppressive microenvironment. Oncol Lett 2020; 19: 3059-3070.
[43] Rugamba A, Kang DY, Sp N, Jo ES, Lee JM, Bae SW and Jang KJ. Silibinin regulates tumor progression and tumorsphere formation by suppressing PD-L1 expression in Non-Small Cell Lung Cancer (NSCLC) cells. Cells 2021; 10: 1632.
[44] Cho HJ, Suh DS, Moon SH, Song YJ, Yoon MS, Park DY, Choi KU, Kim YK and Kim KH. Silibinin inhibits tumor growth through downregulation of extracellular signal-regulated kinase and Akt in vitro and in vivo in human ovarian cancer cells. J Agric Food Chem 2013; 61: 4089-96.
[45] Gao R, He DN, Wang YD, Li Q and Chen SX. Rutin inhibits colon cancer cell proliferation via the notch signaling pathway. Chin J Gerontology 2019; 39: 1192-1194.
[46] Jin FD, Zhang T, Zhang Z, Yin XZ and Quan JS. Protective effect of rutin on oxidative stress damage in hepatocytes and its mechanism. J Jilin Univ 2020; 46: 1117-1123+1345.
[47] Wang M, Liu K, Bu H, Cong H, Dong G, Xu N, Li C, Zhao Y, Jiang F, Zhang Y, Yuan B, Li R and Jiang J. Purple sweet potato delphinidin-3-rutin represses glioma proliferation by inducing miR-20b-5p/Atg7-dependent cytostatic autophagy. Mol Ther Oncolytics 2022; 26: 314-329.
[48] He WD, Su WQ, Wei KH, Quan L, Wang S, Gong XM, Yang XN and Liao JH. Inhibitory effect of genistein on the growth of nasopharyngeal cancer CNE1 cells and prediction of targets. China Pharmacy 2021; 32: 1196-1204.
[49] Yu X, Zhang D, Hu C, Yu Z, Li Y, Fang C, Qiu Y, Mei Z and Xu L. Combination of diosmetin with chrysin against hepatocellular carcinoma through inhibiting PI3K/AKT/mTOR/NF-κB signaling pathway: TCGA analysis, molecular docking, molecular dynamics, in vitro experiment. Chem Biol Drug Des 2024; 104: e70003.
[50] Li D, Cao D, Sun Y, Cui Y, Zhang Y, Jiang J and Cao X. The roles of epigallocatechin gallate in the tumor microenvironment, metabolic reprogramming, and immunotherapy. Front Immunol 2024; 15: 1331641.
[51] Feng SL, Tian Y, Huo S, Qu B, Liu RM, Xu P, Li YZ and Xie Y. Nobiletin potentiates paclitaxel anticancer efficacy in A549/T xenograft model: pharmacokinetic and pharmacological study. Phytomedicine 2020; 67: 153141.
[52] Du Wei and Sun Wei. Nobiletin regulates renal cell carcinoma cells through upregulation of SLFN5 to control the PTEN/Akt pathway. CJITWN 2022; 23: 781-785+848.

[53] Zhang YJ, Li JH and Si YG. Effects of myricetin on immune escape of nasopharyngeal cancer cells by regulating the JAK-STAT-IRF1 signaling pathway. Hebei Med J 2023; 45: 3717-3721.
[54] Zhu Y, Wang A, Zhang S, Kim J, Xia J, Zhang F, Wang D, Wang Q and Wang J. Paclitaxel-loaded ginsenoside Rg3 liposomes for drug-resistant cancer therapy by dual targeting of the tumor microenvironment and cancer cells. J Adv Res 2023; 49: 159-173.
[55] Dawood M, Ooko E and Efferth T. Collateral sensitivity of Parthenolide via NF-κB and HIF-α inhibition and epigenetic changes in drug-resistant cancer cell lines. Front Pharmacol 2019; 10: 542.
[56] Liu M, Xiao C, Sun M, Tan M, Hu L and Yu Q. Parthenolide inhibits STAT3 signaling by covalently targeting Janus kinases. Molecules 2018; 23: 1478.
[57] Ma LL, Lv LL, Du YM, Yu JR and Wang DD. Effects of triptolide on the proliferation, invasion, and migration of MGC803 cells via the serine-threonine protein kinase/glycogen synthase kinase-3β pathway. China Pharmaceuticals 2024; 33: 61-66.
[58] Zhou XY and Dai GY. Inhibition of HepG2 cell proliferation and migration by triptolide through regulation of the silencer information regulator 1/p53 pathway. Chin J Gastroenterol Hepatol 2022; 31: 1178-1182.
[59] Li Y, Sun H, Bai C, Hu Y, Tang J, Zhang Y, Chen J, Zhong Z, He Y, Hu K and Yang J. Dihydroartemisinin inhibits tumor progress via blocking ROR1-induced STAT3-activation in non-small cell lung cancer. Int Immunopharmacol 2024; 133: 112157.
[60] Rao Q, Yu H, Li R, He B, Wang Y, Guo X, Zhao G and Wu F. Dihydroartemisinin inhibits angiogenesis in breast cancer via regulating VEGF and MMP-2/-9. Fundam Clin Pharmacol 2024; 38: 113-125.
[61] Zhou Z, Lei J, Fang J, Chen P, Zhou J, Wang H, Sun Z, Chen Y and Yin L. Dihydroartemisinin remodels tumor micro-environment and improves cancer immunotherapy through inhibiting cyclin-dependent kinases. Int Immunopharmacol 2024; 139: 112637.
[62] Yuan-Ce L, Qi Z, Hong-Yang Z, Yan-Wen W, Yu-Mei S, Bi-Juan Y and Jun-Lin Y. Artesunate, as an Hsp90 inhibitor, inhibits the proliferation of Burkitt's lymphoma cells by inhibiting AKT and ERK. Front Pharmacol 2023; 14: 1218467.
[63] Bian Z, Liu H, Xu F and Du Y. Ursolic acid protects against anoxic injury in cardiac microvascular endothelial cells by regulating intercellular adhesion molecule-1 and toll-like receptor 4/MyD88/NF-κB pathway. Hum Exp Toxicol 2022; 41: 9603271221093626.
[64] Zhang N, Liu S, Shi S, Chen Y, Xu F, Wei X and Xu Y. Solubilization and delivery of Ursolic-acid for modulating tumor microenvironment and regulatory T cell activities in cancer immunotherapy. J Control Release 2020; 320: 168-178.
[65] Ali R, Mir HA, Hamid R, Shah RA, Khanday FA and Bhat SS. Jasplakinolide attenuates cell migration by impeding Alpha-1-syntrophin protein phosphorylation in breast cancer cells. Protein J 2021; 40: 234-244.
[66] Zhang ZC, Su LX, Meng RL, Guan WJ and Li HQ. Kaempferol inhibits the growth of lung adenocarcinoma cells by regulating CDCA5 expression. Chin J Clin Pharmacol 2024; 40: 994-998.
[67] Hua XT, Hong WM, Zhang CY and Wang B. The effect of gastrodin on the proliferation and apoptosis of glioma cells via the cAMP/PKA/GRK2 signaling pathway. Acta Med Univ Sci Technol Huazhong 2022; 51: 607-611.
[68] Xie L, Liao J, Liu W, Wang R, Li X, Li W and Zhou Z. Gastrodin overcomes chemoresistance via inhibiting Skp2-mediated glycolysis. Cell Death Discov 2023; 9: 364.
[69] Okuno K, Xu C, Pascual-Sabater S, Tokunaga M, Han H, Fillat C, Kinugasa Y and Goel A. Berberine overcomes gemcitabine-associated chemoresistance through regulation of Rap1/PI3K-Akt signaling in pancreatic ductal adenocarcinoma. Pharmaceuticals (Basel) 2022; 15: 1199.
[70] Li RZ, Guan XX, Wang XR, Bao WQ, Lian LR, Choi SW, Zhang FY, Yan PY, Leung ELH, Pan HD and Liu L. Sinomenine hydrochloride bidirectionally inhibits progression of tumor and autoimmune diseases by regulating AMPK pathway. Phytomedicine 2023; 114: 154751.
[71] Yu J, Zhang L, Peng J, Ward R, Hao P, Wang J, Zhang N, Yang Y, Guo X, Xiang C, An S and Xu TR. Dictamnine, a novel c-Met inhibitor, suppresses the proliferation of lung cancer cells by downregulating the PI3K/AKT/mTOR and MAPK signaling pathways. Biochem Pharmacol 2022; 195: 114864.
[72] Mu Q and Najafi M. Resveratrol for targeting the tumor microenvironment and its interactions with cancer cells. Int Immunopharmacol 2021; 98: 107895.
[73] Chhabra G, Singh CK, Amiri D, Akula N and Ahmad N. Recent advancements on immunomodulatory mechanisms of resveratrol in tumor microenvironment. Molecules 2021; 26: 1343.
[74] Huang L, Lu S, Bian M, Wang J, Yu J, Ge J, Zhang J and Xu Q. Punicalagin attenuates TNF-α-induced oxidative damage and promotes osteogenic differentiation of bone mesenchymal

stem cells by activating the Nrf2/HO-1 pathway. Exp Cell Res 2023; 430: 113717.
[75] Li GQ, Gao SX, Wang FH, Kang L, Tang ZY and Ma XD. Anticancer mechanisms on pyroptosis induced by Oridonin: new potential targeted therapeutic strategies. Biomed Pharmacother 2023; 165: 115019.
[76] Hu QH, Lu X, Fan ZK, Li SS and Zhang T. Research progress on the mechanism of ginsenoside Rg3 in the treatment of colon cancer. Pharmacol Clin Chin Materia Med 2023; 39: 123-129.
[77] Liu MQ, Bao CJ, Liang XF, Ji XY, Zhao LQ, Yao AN, Guo S, Duan JL, Zhao M and Duan JA. Specific molecular weight of Lycium barbarum polysaccharide for robust breast cancer regression by repolarizing tumor-associated macrophages. Int J Biol Macromol 2024; 261: 129674.
[78] An XL, Lu JY, Dong H and Meng X. Research progress on the regulation of tumor microenvironment by Chinese medicine polysaccharides. Drugs & Clinic 2022; 37: 2142-2147.
[79] Wang YN, Qu LP, Zhang ZK, Cao YJ, Shi CD, Zhang XF and Gao F. Research progress on the role of astragalus polysaccharide in tumor immunotherapy. Chin J Mod Appl Pharm 2023; 40: 3452-3458.
[80] Chang HL, Kuo YH, Wu LH, Chang CM, Cheng KJ, Tyan YC and Lee CH. The extracts of Astragalus membranaceus overcome tumor immune tolerance by inhibition of tumor programmed cell death protein ligand-1 expression. Int J Med Sci 2020; 17: 939-945.
[81] Gui Z, Shao ZG and Jin D. Inhibition mechanism of astragalus polysaccharide on human gastric cancer MKN45 and MGC-803 cell growth. Acta Chin Med 2018; 33: 525-528.
[82] Li ZM, Zhang JY, Li F, Fu LN, Zhu ZM and Wang G. Research progress on anti-tumor chemical components and pharmacological effects of hedyotis diffusa. Infor Trad Chin Med 2021; 38: 74-79.
[83] Wang DH, Yue W, Shi HZ, Li JS and Wang C. Combined application of photodynamic therapy and hedyotis diffusa on C6 glioma cells in rats. Chin J Laser Med Surg 2005; 14: 279-284.
[84] Wu K, Wu X, Liang Y, Wang T, Wu D, Li L and Wang Z. Inhibitory effects of total triterpenoids isolated from the Hedyotis diffusa willd on H1975 cells. Front Pharmacol 2022; 13: 922477.
[85] Feng L, Jia XB, Chen Y and Li X. Research progress on chemical components and anti-tumor mechanisms of prunella vulgaris. Chin J Trad Chin Med Pharmacy 2008; 23: 428-434.
[86] Li MQ, Shi Y, Yang SY, Li JY, Hu Y, Sun WX and Li LJ. Research progress on anti-tumor active components and mechanisms of prunella vulgaris. Chin J Mod Appl Pharm 2024; 41: 716-726.
[87] Chen Z, Zhu R, Zheng J, Chen C, Huang C, Ma J, Xu C, Zhai W and Zheng J. Cryptotanshinone inhibits proliferation yet induces apoptosis by suppressing STAT3 signals in renal cell carcinoma. Oncotarget 2017; 8: 50023-50033.
[88] Xu H, Guo NN, Zhu CY, Ye LY, Yan XY, Liu YQ, Zhang ZY, Zhang G and Hussain L. Diterpenoid tanshinones can inhibit lung cancer progression by improving the tumor microenvironment and downregulation of NF-κB expression. ACS Omega 2024; 9: 7230-7238.
[89] Xu R, Wu J, Zhang X, Zou X, Li C, Wang H, Yuan M, Chen M, Sun Q and Liu S. Modified Buzhong-yi-qi decoction synergies with 5 fluorouracile to inhibits gastric cancer progress via PD-1/PD- L1-dependent T cell immunization. Pharmacol Res 2020; 152: 104623.
[90] Yuan M, Zou X, Liu S, Xu X, Wang H, Zhu M, Xie X, Wang H, Wu J and Sun Q. Modified Jian-pi-yang-zheng decoction inhibits gastric cancer progression via the macrophage immune checkpoint PI3Kγ. Biomed Pharmacother 2020; 129: 110440.
[91] Zhan X, Xu X, Zhang P, Wang X, Hu Z, Zhao W, Hang T and Song M. Crude polysaccharide from Danggui Buxue decoction enhanced the anti-tumor effect of gemcitabine by remodeling tumor-associated macrophages. Int J Biol Macromol 2023; 242: 125063.
[92] Chen Y, Liu J, Chen Y, Zhang R, Tao J, Chen X, Wang H, Sun Q, Wu J and Liu S. Jianpi Yangzheng Xiaozheng decoction alleviates gastric cancer progression via suppressing exosomal PD-L1. Front Pharmacol 2023; 14: 1159829.
[93] Tao HY, Liu YJ, Li JP, Zeng SH, Zhang Y, Liu SL and Zou X. Effects of jianpi yangzheng xiaozheng on proliferation and stem cell properties of gastric cancer HGC-27 cells by inhibiting aerobic glycolysis. Chin J Exp Trad Med Formulas 2023; 29: 82-88.
[94] Zhang QH, Yu ZL, Fan HW, Pan J, Wang X and Xu HB. Xihuang pill downregulates the HIF-1α/VEGFA/VEGFR2 signaling pathway to inhibit pseudoangiogenesis in glioma cells. Acta Pharm Sinica 2023; 58: 1256-1266.
[95] Chen W, Yang X, Sun J, Chen Y, Zhao W, He C, An H, Pang J, Xu W, Wen B, Sun H and He S. Biejiajian pill inhibits progression of hepatocellular carcinoma by downregulating PDGFRβ signaling in cancer-associated fibroblasts. J Ethnopharmacol 2023; 301: 115825.
[96] Ren FM, Yang C, Zeng JJ, Guo YH and Zhang QF. Shuyu pill regulates the polarization of M1/M2 tumor-associated macrophages to inhibit the progression of colorectal cancer. Chin J Exp Trad Med Formulas 2023; 29: 20-26.

[97] Liu LZ, Xie JL and Liang JX. Evaluation of the effect of shenqi fuzheng injection on the anesthetic recovery and analgesic effect of laparoscopic radical surgery for rectal cancer in elderly patients with Qi deficiency. Chin Arch Trad Chin Med 2024; 1-8.

[98] Ma WB, Ma Y, Fan FT, Zhang YH, Chang JW and Zhou ZH. Intervention of shenqi fuzheng injection in low-sugar-mediated immune-suppressive microenvironment and its mechanism. Chin J Clin Pharmacol Therapeutics 2022; 27: 136-143.

[99] Dong KC, Zhang M, Liang Y, Li S, Liu D and Fei XX. Compound kushen injection improves acute radiation-induced oral mucositis in rats by regulating macrophage polarization. Liaoning J Trad Chin Med 2024; 51: 200-204+226.

[100] Qiu Y, Huang S and Zhu M. The molecular targets of Kangai injection in gastric cancer by in silico network pharmacology approach and experiment confirmation. J Appl Biomed 2023; 21: 150-159.

[101] Zhou B and Dai FY. Effect of shenling baizhu fomula on peripheral blood CD4+CD25+Tregs in stage IV gastric cancer patients. J Hunan Univ Chin Med 2015; 35: 50-52.

[102] Jiang W, Zhao QP, Huang L, Jiang JW, Li ML, Chen XC, Xu Y, Wang GJ, Deng L, Zhang LC and Li ZM. Mechanism of modified huoluo xiaoling pills against colorectal cancer based on network pharmacology, molecular docking, and experimental validation. Zhongguo Zhong Yao Za Zhi 2024; 49: 3657-3667.

[103] Yang W, Zhang Y, Gao J, Hu P, Yang Y and Xu X. A meta-analysis of the Zilongjin tablets for non-small cell lung cancer and its network pharmacology of action against NSCLC and COVID-19. Front Med (Lausanne) 2023; 10: 1080121.

[104] Geng L, Lv J and Fan J. Effect of fei-liu-ping ointment combined with cyclophosphamide on lung cancer cell proliferation and acidic microenvironment. Beijing Da Xue Xue Bao Yi Xue Ban 2020; 52: 247-253.