Research progress of traditional Chinese medicine in regulating tumor microenvironment

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Abstract
The tumor microenvironment (TME) plays a crucial role in facilitating tumorigenesis and progression. Consequently, there is significant research interest within the oncology community in developing interventions that target the TME. Extensive research has been conducted on the mechanism of traditional Chinese medicine (TCM) in tumor therapy, revealing notable similarities between its theoretical framework and that of the TME. TCM has the ability to regulate various components of the microenvironment, including the modulation of proportions of T cell subsets, enhancement of the quantity and activity of NK cells, regulation of polarization of tumor-associated macrophages, suppression of expression of myeloid-derived suppressor cells, reduction of accumulation of tumor-associated endothelial cells, downregulation of the quantity and function of tumor-associated fibroblasts, and modulation of the architecture of the extracellular matrix. These multifaceted interventions ultimately lead to the attainment of anti-tumor objectives. This comprehensive review encompasses a thorough analysis of relevant literature from both domestic and international sources, with a specific emphasis on elucidating the mechanisms through which TCM compound formulas, single drugs, and monomeric components regulate the TME.

Keywords: tumor; microenvironment; suppression of immunity; traditional Chinese medicine; review
Introduction

Tumor is a significant contributor to mortality rates and poses a substantial threat to human well-being. Recent advancements in cancer research have led to a shift in understanding the tumor, no longer viewing it solely as a cluster of cancer cells, but rather as a dynamic entity encompassing both tumor cells and their surrounding internal and external environments [1]. Presently, there is a transformative shift in anti-cancer strategies, moving away from solely targeting the tumor itself and towards targeting the tumor microenvironment (TME). These novel approaches have demonstrated promising potential in modulating the tumor microenvironment to impede tumor progression and influence therapeutic outcomes [2]. In China, traditional Chinese medicine (TCM) is extensively employed for the prevention and management of tumors. One notable advantage of utilizing TCM for tumor treatment lies in its adherence to a holistic perspective, which enables the application of various treatment methods such as invigorating and removing evil, restoring body balance. By doing so, TCM facilitates the attainment of the body’s environmental homeostasis, thereby inhibiting tumor growth [3, 4]. This approach aligns with contemporary medical concepts aimed at remodeling the TME, thus establishing numerous connections between TCM and modern medicine. Consequently, investigating the mechanism of TCM through the lens of the TME may serve as a promising avenue toward the modernization of TCM. This article aims to present an introduction to the TME and the advancements in TCM interventions targeting the TME. The objective is to offer novel insights and establish a theoretical foundation for the application of TCM in tumor treatment.

The tumor microenvironment

TME refers to the environment in which tumor cells proliferate and reside. This encompasses not only the tumor cells themselves, but also stromal cells that are either resident or recruited, as well as the non-cellular constituents present in the secretory products and extracellular matrix (ECM) of these aforementioned cells [5]. In the initial stages, the microenvironment plays a crucial role in restraining tumor growth and safeguarding the viability of normal cells. However, as tumors advance and expand, the intricate interplay between cells and their surroundings, as well as between cells and non-cellular components, leads to the emergence of a complex environment characterized by biological attributes, such as hypoxia, acidity, chronic inflammation, immunosuppression, and the secretion of numerous cytokines. Ultimately, the TME can collaborate with the tumor to evade immune resistance and serve as a continuous supplier of nutrients and growth factors, facilitating tumor progression [6]. An increasing number of studies have found that the TME plays a crucial role in the immunosuppression, drug resistance, tumor invasion, metastatic growth, and so on of tumors [7, 8].

Mechanisms of TCM in modulating tumor microenvironment

TCM possesses numerous therapeutic attributes, such as its ability to target multiple pathways and targets. Recent evidence has increasingly demonstrated the regulatory effects of TCM on immune cells, stromal cells, and the extracellular matrix within the microenvironment. This study aims to consolidate the roles of different constituents within the TME and emphasize the underlying mechanisms through which TCM interventions can effectively treat tumors (Table 1 and Figure 1).

Regulation of T lymphocytes by TCM

Within the TME, various distinct subsets of T lymphocytes play a significant role in shaping tumor progression. Notably, cytotoxic lymphocytes (CTLs), characterized by the expression of CD8 or CD8+ T cells, are pivotal in exerting anti-tumor effects through the direct elimination of malignant cells via the secretion of perforin, granzymes, and other effector molecules [9]. Moreover, helper T cells (Th), distinguished by the presence of CD4 on their surface, assume a regulatory role in governing the human immune system. Th cells can be classified into distinct subsets, namely Th1, Th2, Th17, and so on, based on their secretion of various cytokines [10]. These subsets of Th cells have been found to have diverse roles in immunity. For instance, Th1 cells contribute to immune responses by releasing interleukin-2 (IL-2) and interferon-γ (IFN-γ), thereby promoting the proliferation and activation of CTLs, macrophages, and natural killer (NK) cells, which are involved in the elimination of tumor cells [11]. Conversely, Th2 cells secrete cytokines such as IL-4, IL-5, IL-10, and IL-13, which exert suppressive effects on the immune system against tumors [12]. In recent years, significant attention has been directed towards regulatory T cells (Tregs), a specific subset of CD4+ T cells known for their robust negative immunoregulatory capabilities. This is achieved through the secretion of various cytokines, including IL-10 and transforming growth factor-β (TGF-β), which effectively hinder the proliferation and cytotoxicity of CD8+ T cells, consequently facilitating tumor growth [13]. Given the crucial functions performed by diverse T cell populations within the TME, the targeting of T cells is widely regarded as a promising therapeutic approach for the treatment of tumors.

TCM has been shown to possess anti-tumor properties through its ability to regulate the differentiation, infiltration number, and activity of T lymphocyte subsets. One notable TCM formula, known as Yupleifeng granule, has been recognized for its effectiveness in enhancing human immunity. In a study conducted by Yao et al. [14], it was observed that Yupleifeng granule mitigated immunosupression in mice with hepatocellular carcinoma. This effect may be attributed to the elevation of the Th1/Th2 ratio and increased expression of IL-2, IL-12, and tumor necrosis factor-α (TNF-α) in tumors and adjacent tissues, while simultaneously reducing the expression of IL-4, IL-5, IL-10, and IL-13. Zhao et al. [15] conducted in vitro and in vivo experiments to demonstrate that Yangyin Wenyang Decoction has the potential to enhance the maturation of dendritic cells and stimulate their secretion of various cytokines, including IFN-γ, IL-1β, IL-2, IL-10, and TNF-α. This, in turn, facilitates the proliferation and differentiation of T cells into Th1 and CTLs, ultimately leading to the manifestation of anti-tumor effects. Xihuang Pill, a commonly prescribed oral Chinese patent medicine for tumor treatment, was investigated by Su et al. [16]. Their findings suggest that Xihuang Pill may inhibit the growth of breast cancer in mice by upregulating the MEK1/Erk1/2/Jnk1/2 pathway, thereby promoting the apoptosis of Tregs within the TME. Furthermore, it has been established that various Chinese herbal components possess the capability to modulate T cells and exhibit anti-tumor properties. For instance, the extract of salidroside [17] has demonstrated the ability to augment the population of CD4+ T and CD8+ T lymphocytes in mice with lung cancer, enhance the cytotoxicity of CTLs, elevate the levels of IL-2, while concurrently reducing the proportion of Treg cells, thereby effectively reshaping the tumor microenvironment. Additionally, quercetin [18] has been found to impede tumor growth by suppressing Treg cells and stimulating the secretion of cytokines from Th1 and Th17 cells.

Regulation of NK cells by TCM

NK cells are primarily derived from hematopoietic stem cells in the bone marrow and exhibit a strong association with anti-tumor activity [19]. The targeting mechanism of NK cells towards tumor cells can be primarily attributed to three pathways [20]. Firstly, NK cells enhance cell membrane permeability through the release of perforin and granzymes, leading to cell lysis. Secondly, NK cells induce cell death by expressing the Fas ligand, TNF ligand, and TNF-related apoptosis-inducing ligand, which bind to their respective death receptors on the surface of tumor cells. Lastly, NK cells transmit signals via various cytokines, such as IFN-γ, thereby promoting the death of cancer cells. However, within the TME, NK cells often exhibit characteristics of diminished expression of activating receptors and heightened expression of inhibitory receptors, impeding their ability to effectively function as “anti-cancer pioneers.” In recent times, the...
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†, Up-regulated or enhanced; ↓, Down-regulated or inhibited.
targeting of NK cells for tumor treatment has emerged as a prospective avenue with promising prospects [21]. Several studies have demonstrated that TCM has the ability to impede the progression of tumors by enhancing the quantity and functionality of NK cells. Jinfukang, a specific formulation of TCM primarily designed for lung cancer treatment, exhibits notable efficacy in terms of preventing tumor metastasis and enhancing the overall quality of patient survival. Que et al. [22] conducted an investigation into the impact of Jinfukang on both circulating tumor cells and NK cells, thereby confirming its anti-metastatic effects in lung cancer. This phenomenon can be attributed to the promotion of circulating tumor cells to express and secrete chemokine CXCL1, which subsequently enhances the number and cytotoxicity of NK cells. In their study, Mao et al. [23] demonstrated that the administration of Yanghe decoction resulted in the upregulation of NK cells, CTLs, IFN-γ, and phosphorylated-signal transducers and the activator of transcription 1(p-stat1) in the TME, thereby enhancing the anti-tumor immune responses in a mouse model of breast cancer. Additionally, Nkp46, an activating receptor expressed in NK cells, has played an important role in the recognition of tumors [24]. Du et al. [25] observed that the use of Shiquan Dabu Decoction led to an increase in Nkp46 expression and the proportion of activated NK cells, resulting in the inhibition of primary tumor metastasis in mice with colon cancer. Furthermore, the effectiveness of certain Chinese herbal ingredients in enhancing the cytotoxicity of NK cells against tumors has been demonstrated. Zhu et al. [26] have extensively focused on researching anti-tumor immunity in traditional Chinese medicine. They previously published findings indicating that rocaglamide (RocA) can enhance the activity of NK cells in autophagy, resulting in anti-tumor effects. Subsequent investigations have demonstrated that RocA facilitates the release of mitochondrial DNA (mtDNA) into the cytosol of tumor cells, subsequently activating the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) signaling pathway. Activation of this signaling pathway leads to the upregulation of chemokines such as chemokines CCL5 and CXCL10, ultimately facilitating the recruitment of NK cells to the tumor microenvironment and consequently exerting anti-tumor effects [27]. Astragaloside III, derived from Astragalus membranaceus, has the capability to upregulate the expression of NKG2D and IFN-γ, thereby stimulating the activation of NK cells in various anatomical locations such as tumor sites, lymph nodes, and spleen [28]. Consequently, augmenting the quantity and functionality of NK cells may represent a significant mechanism through which TCM Formulas and their active constituents exert immunomodulatory effects on tumors.

**Regulation of tumor-associated macrophages by TCM**

Macrophages are integral constituents of the innate immune response and can be categorized into two distinct types, namely the pro-inflammatory M1 type and the anti-inflammatory M2 type, based on their respective functions [29]. The macrophages that infiltrate tumor tissue are referred to as tumor-associated macrophages (TAMs) and constitute over 50% of the immune cells present in the TME [30]. TAMs predominantly exhibit the phenotype and functionality of M2 macrophages, which exert their influence on tumor growth promotion and immune suppression through various pathways [31]. Firstly, TAMs possess the capability to secrete a diverse range of cytokines, including epidermal growth factor (EGF) and platelet-derived growth factor (PDGF), among others, which facilitate the proliferation of tumors. Secondly, TAMs exhibit the ability to express vascular endothelial growth factor (VEGF), thereby contributing to the formation of tumor vasculature. TCM has been shown to possess the ability to impede tumor growth and development by modulating TAMs through various mechanisms, including TAMs depletion, TAM recruitment reduction, and M2 to M1 macrophage conversion. Haimufang Decoction, a clinical patent formula derived from traditional Chinese medicine, has been specifically designed for the treatment of lung cancer. In a study conducted by Ma et al. [32], in vitro experiments demonstrated that Haimufang Decoction effectively influences mouse monocyte macrophages, inducing their polarization towards the M1 phenotype. And this polarization could enhance the anti-cancer properties and phagocytic capacity of macrophages. IL-33 is known to have a significant impact on the inflammatory response following tissue injury and has the ability to facilitate the development of M2 macrophages. In a study conducted by Jiang et al. [33], Lewis lung cancer mice were treated with Jiawei Huangqi Jiazhong Decoction, resulting in a decrease in IL-33 levels in both blood and tumor tissues. Additionally, there was an increase in M1 macrophage cell levels and a decrease in M2 macrophages, suggesting that this formula may possess an inherent mechanism for combating cancer. Similarly, Some Chinese herbal ingredients exhibit immunomodulatory activities. For instance, Astragaloside IV has been shown to inhibit the M2 type polarization of macrophages and increase the proportion of M1 type cells in the TME through the downregulation of the AMPK pathway. This, in turn, reduces the proliferation of lung cancer A549 and H1299 cells [34]. Additionally, Jia et al. [35] discovered that Homogeneous polypos polysaccharide can hinder the proliferation and progression of bladder cancer by polarizing macrophages towards the M1 phenotype. They suggested that this effect may be attributed to the downregulation of JAK2/NF-κB signaling pathways. Xu et al. [36] conducted a study to investigate the anti-tumor effect and mechanism of arabinogalactan (ptps-1-2), a potent constituent in traditional Chinese medicine dandelion, on colon cancer RKO cells through the regulation of TAM polarization. The findings demonstrated that ptps-1-2 effectively activates the NF-κB signaling pathway, leading to the polarization of macrophages towards the M1 phenotype. Furthermore, the study revealed that the conditioned medium derived from macrophages pre-treated with ptps-1-2 exhibited significant anti-tumor properties by suppressing RKO cell proliferation and inhibiting cell colony formation. In recent years, the relationship between TAMs and tumor metabolism was further revealed, and the regulation of metabolic reprogramming by TCM is a direction that deserves intensive investigation in the future.

**Regulation of myeloid-derived suppressor cells by TCM**

Myeloid-derived suppressor cells (MDSCs) represent a diverse group of cells. Typically, Hematopoietic stem cells initially undergo differentiation into common myeloid pro-genitor (CMPs), which then promptly differentiate into fully developed granulocytes, dendritic cells, and macrophages, subsequently entering tissue organs to carry out immune functions. Nevertheless, within the TME, the maturation process of CMPs is impeded, resulting in their arrest at different stages of differentiation, ultimately leading to the formation of MDSCs possessing immunosuppressive capabilities [37]. Clinical observation revealed a significant correlation between breast cancer typing and the presence of MDSCs, whereby a higher proportion of MDSCs in
patients' blood was associated with poorer healing outcomes [38]. The promotion of tumor growth and development by MDSCs primarily occurs through the inhibition of CTLs activation and function, impairment of NK cell-mediated cell killing, and facilitation of tumor angiogenesis and metastasis [39].

The identification of MDSCs has expanded the possibilities for tumor treatment, with current beliefs suggesting that TCM approaches may have various impacts, including the elimination of MDSCs and the suppression of their recruitment and activity within tumor sites. In a prospective clinical study conducted by Zhang et al. [40], the clinical effectiveness of Jiedu Sanjie Prescription was observed in patients with advanced non-small cell lung cancer. The finding demonstrated that Jiedu Sanjie Prescription effectively and safely suppressed the presence of MDSCs and Tregs in the patients' bloodstream. In their study, Tian et al. [41] discovered that the administration of Shugan Jinji Decotion resulted in a decrease in the specific gravity of MDSCs in the spleens of mice with tumors. This decrease subsequently led to the restoration of the anti-tumor immune response of CD8+ T cells, potentially through the regulation of the TLR-4/MyD88/NF-kB pathway. Similarly, Wang et al. [42] conducted an evaluation of the anti-tumor efficacy of ganoberberidi radix polysaccharide (GLP) in mice with Lewis lung cancer. Their findings indicated that GLP could prevent lung carcinogenesis by promoting the differentiation of MDSCs and inhibiting their aggregation via the CARPS-NF-κB-IDO pathway. Zhang et al. [43] conducted a study demonstrating the potential of ginseng polysaccharides in enhancing immune function and mitigating chemotherapy-related adverse effects in patients with advanced non-small cell lung cancer undergoing chemotherapy. The investigation revealed a significant reduction in the peripheral blood levels of MDSCs and Tregs following treatment with ginseng polysaccharides. This observation suggests that the immunomodulatory effects of ginseng polysaccharides may be attributed to the suppression of MDSCs and Treg cells, thereby improving the immune status of patients. It is worth noting that certain Chinese herbs have been identified to stimulate the proliferation and activation of MDSCs, which contrasts with the beneficial effects of ginseng polysaccharides in this context. Chen et al. [44] conducted experiments to demonstrate the enhancing effects of Angelica polysaccharide on murine MDSCs through both in vitro and in vivo approaches. In vivo, Angelica polysaccharide was found to increase the proportion of MDSCs in the spleen and peripheral blood of mice. Similarly, in vitro experiments revealed that Angelica polysaccharide promoted the proliferation and differentiation of mouse MDSCs. These findings imply that certain Chinese herbs have the potential to augment the quantity and functionality of MDSCs, and physicians should consider rational compatibility to minimize adverse effects.

**Regulation of cancer associated fibroblasts by TCM**

Cancer associated fibroblasts (CAFs) are mainly formed by the transition of fibroblasts upon stimulation by various inflammatory cytokines produced by cancer cells, host immune cells, and so on [45]. Furthermore, CAFs can also arise from epithelial cells within tumor tissue, bone marrow mesenchymal stem cells, and other cell types. In comparison to normal fibroblasts, CAFs exhibit not only larger morphological characteristics but also heightened metabolic activity and robust secretion [46]. These attributes empower CAFs to significantly contribute to the modulation of the tumor microenvironment, thereby evading immune surveillance. In general, CAFs contribute to the establishment of an immunosuppressive microenvironment through three main mechanisms. Firstly, CAFs can inhibit the activation of immune cells by secreting various cytokines, including VEGF and IL-6. Secondly, CAFs can modulate the ECM by secreting fibronectin and other molecules, thereby creating a physical barrier that hinders the infiltration of immune cells and anti-tumor drugs. Lastly, CAFs can generate metabolites such as pyruvate and lactate through glycolysis, leading to the formation of an acidic microenvironment that dampens T cell activity. Consequently, there has been a rapid exploration and development of CAF-targeted cancer therapies in recent years [47].

Based on recent research findings, it has been determined that certain TCM Formulas and ingredients possess efficacy in enhancing the TME through their ability to selectively eliminate CAFs, weaken CAFs function, and impede CAFs generation. In their in vivo and in vitro experiments, Zhu et al. [48] demonstrated that Fuzheng Jiedu Formula may hinder the TGF-β1/Smad2/3 pathway, thereby reducing CAFs generation and subsequently impeding the progression of gastric cancer. Additionally, Ruan et al. [49] discovered that Jiedu Sangen Decotion, through the inhibition of Ki67 α- SMA protein expression, activation of CAFs, tumor neovascularization, and subsequent regulation of tumor cell invasion, exerts its effects. In their study, Wu et al. [50] discovered that Astragalus polysaccharide possesses the ability to impede α-Smooth muscle actin and its associated activators, thereby impeding the proliferation of CAFs and subsequently inhibiting the progression of lung cancer. Considering the significant role of CAFs within the microenvironment, it is anticipated that rectifying the hypoxic and acidic microenvironment through TCM could serve as a crucial concept for the advancement of drug combination strategies in the future.

**Regulation of tumor-associated endothelial cells by TCM**

Tumor-associated endothelial cells (TECs) constitute the inner layer structure of tumor blood vessels and have emerged as pivotal contributors to tumor angiogenesis [51]. In contrast to normal endothelial cells, TECs exhibit substantial functional and phenotypic disparities. Notably, TECs not only facilitate proliferation and invasion but also confer resistance to anti-cancer agents in cancer cells [52]. Furthermore, TECs exert influence on the immune system's ability to eliminate tumor cells by diminishing leukocyte adhesion, releasing diverse immunosuppressive factors, and promoting apoptosis in activated T cells [53]. Recently, the role of tumor vascular endothelial cell metabolism in the process of angiogenesis has garnered increasing attention through extensive research.

It has been established that TCM possesses a distinctive capability to hinder tumor angiogenesis, potentially achieved by impeding the proliferation or facilitating the apoptosis of tumor vascular endothelial cells. In their study, Zhong et al. [54] demonstrated the ability of ginsenosides to normalize tumor vascular structure and inhibit tumor neovascularization in vivo. Additionally, they found that ginsenosides could inhibit the migration ability of TECs in vitro. Feng et al. [55] established an in vitro co-culture model between colon cancer cells and human umbilical vein endothelial cells (HUVECs). Their findings revealed that curcumin could inhibit tumor angiogenesis in colon cancer, potentially through the inhibition of proliferation in both human colon cancer cells and HUVECs. Recent experiments have demonstrated that salvianolic acid B possesses the ability to restore endothelial barrier function through the regulation of the interaction between tumor cells and TECs. Additionally, it has been observed to normalize tumor vessels, thereby delaying the invasion and metastasis of breast cancer [56]. Furthermore, tumor cells possess the capability to assume characteristics of endothelial cells through self-organization, resulting in the formation of tubular structures that facilitate blood transportation, commonly referred to as vasculosogenic mimicry. Zhu et al. [57] conducted a study that revealed that celastrol exhibits inhibitory effects on glioma growth, angiogenesis, and the formation of vasculosogenic mimicry. The underlying mechanism behind these effects is believed to be associated with the PI3K/Akt/mTOR pathway. Tumor angiogenesis is a complex process influenced by multiple factors, and current research on TCM and its effects on anti-tumor angiogenesis primarily focuses on angiogenic signaling proteins. However, if future studies delve into the metabolism of TECs in greater detail, it may offer a novel theoretical foundation for understanding the mechanism underlying TCM's anti-vascular action.

**Regulation of by extracellular matrix TCM**

ECM primarily comprises non-cellular constituents, including collagens, proteoglycans, and network junction proteins, which serve
as sources of biochemical components and fundamental structural support for tumor cells [58]. It is presently recognized that intact stromal architecture plays a crucial role in maintaining internal homeostasis, and an imbalance in ECM degradation, either excessive or insufficient, can facilitate the progression of cancer [59]. For instance, an excessive accumulation of ECM can function as a physical hindrance surrounding tumor cells, impeding the proximity of CTLs. Furthermore, the presence of biochemical signals within the ECM conspicuously facilitates the proliferation and survival of tumor cells [60]. Consequently, the targeting of the ECM is being regarded as a novel approach to enhance the effectiveness of immunotherapy.

Current evidence suggests that the regulation of the ECM may serve as one of the mechanisms by which TCM treats tumors. Matrix metalloproteinases (MMPs) have the ability to degrade the ECM, thereby dismantling the barrier that impedes the invasion of tumor cells into neighboring tissues [61]. In their study, Hu et al. [62] observed a reduction in the protein levels of MMP-2 and MMP-9 in lung cancer cells following treatment with Pien Tze Huang. Consequently, they concluded that the suppression of MMP-9 and MMP-2 synthesis could potentially sole as a mechanism by which Pien Tze Huang inhibits lung cancer metastasis. Similarly, Ye et al. [63] investigated the impact of Yangzhen Xiaoji capsules on ECM adhesion in various tumor cells. The findings of this study indicate that the capsule may have the potential to reduce the adhesion of ECM and consequently hinder the metastatic capabilities of tumors by inhibiting the PI3K/Akt signaling pathway. Currently, there is limited research available regarding the regulation of ECM by TCM. However, we are optimistic about the prospects of investigating TCM’s multi-target and multi-pathway regulation of the tumor microenvironment, starting from the perspective of ECM, as it holds promise for future advancements.

**Conclusion**

The tumor and its microenvironment are intrinsically interconnected, akin to the concept of the “seed and soil” relationship. The tumor microenvironment serves as a crucial nurturing ground for tumor growth and facilitates evasion of treatment. We posit that by targeting the “tumor microenvironment” as a therapeutic strategy, rather than solely eliminating factors within the microenvironment that promote tumor initiation and progression, one can exploit the remodeling of diverse components within the microenvironment to restore tumor cells to their normal state. Despite the notable advancements in anti-tumor research within TCM in China, a comprehensive understanding of its underlying mechanism remains elusive. The emergence of the tumor microenvironment doctrine presents a novel avenue to employ contemporary scientific and technological approaches in elucidating the principles governing TCM’s efficacy, thereby facilitating the promotion of TCM’s high-quality development. Current investigations have demonstrated that TCM Formulas, single drugs, and individual components possess the ability to partially remodel the immune microenvironment; however, numerous areas for improvement persist. We advocate for the promotion of clinical studies with substantial sample sizes in future research endeavors to establish clinical evidence supporting the anti-tumor properties of TCM through its modulation of the microenvironment. Concurrently, there is a need to intensify the investigation of the active constituents within TCMs and employ contemporary research methodologies to elucidate the multifaceted mechanisms of action involving multiple targets and pathways. These efforts aim to enhance the overall efficacy of TCMs within the realm of anti-tumor research.

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