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Review article

Antitumour mechanisms of traditional Chinese medicine elicited by regulating tumour-associated macrophages in solid tumour microenvironments

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ABSTRACT

Tumour-associated macrophages (TAMs), particularly M2-TAMs, constitute the largest proportion of immune cells in the solid tumour microenvironment, playing a crucial role in tumour progression and correlating with poor prognosis. TAMs promote the proliferation, invasion, and metastasis of tumour cells by remodelling the extracellular matrix, inhibiting immunity, promoting immune escape and tumour angiogenesis, and affecting cell metabolism. Traditional Chinese medicine (TCM) has been used clinically in China for millennia. Chinese herbs exhibit potent antitumour effects with minimal to no toxicity, substantially contributing to prolonging the lives of patients with cancer and improving their quality of life. TCM has unique advantages in improving the solid tumour microenvironment, particularly in regulating TAMs to further inhibit tumour angiogenesis, reduce drug resistance, reverse immunosuppression, and enhance antitumour immunity. This review highlights the TAM-associated mechanisms within the solid tumour microenvironment, outlines the recent advancements in TCM targeting TAMs for antitumour effects, emphasises the superiority of combining TCM with standard treatments or new nano-drug delivery systems, and evaluates the safety and efficacy of TCM combined with conventional treatments via clinical trials to provide insights and strategies for future research and clinical treatment.

1. Introduction

As of 2017, tumours accounted for 23.3% of global noncommunicable disease deaths, ranking second. Among them, trachea, bronchus, and lung cancers represented the highest proportion, followed by colorectal cancer (CRC) [1]. According to the World Health Organization's International Agency for Research on Cancer (IARC) (Cancer Today (iarc.fr)) statistics, approximately 19.3 million new cancer cases and ~10 million deaths were reported in 2020 worldwide. It is estimated that 28.4 million new cancer cases will be reported by 2040 [2]. Conventional treatments for cancer primarily include surgery, chemotherapy, and radiotherapy. These treatments are usually effective in early-stage cancer while demonstrating limited efficacy in advanced cancers [3]. In addition, the toxicity induced by chemotherapy and radiotherapy considerably affects the quality of life of patients and increases mortality [4–6]. Recently, immunotherapies have developed rapidly, including immune checkpoint blockade (ICB), antibody therapy, cancer vaccines,

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and adoptive cellular immunotherapy. Owing to its advantages, including fewer adverse events, activation of antitumour immunity, and prevention of tumours [7], the remission rate has improved considerably with the administration of combinatorial treatments [8]. Accordingly, this strategy has become indispensable in the treatment of human cancer.

Although immunotherapy has achieved satisfactory results, the specificity of solid tumours poses considerable challenges to current immunotherapies. The antigen heterogeneity of solid tumours has impeded the identification of target genes and contributes to the development of off-target effects and drug resistance. Tumour cells and the tumour microenvironment (TME) constitute the primary components of solid tumours. The complex microenvironment presents physical and chemical barriers, impeding the effective delivery of treatments to the tumour cells. The physical barrier includes tumour neovascularization and the extracellular matrix (ECM), posing challenges to infiltrating $CD8^+$ T cells, NK cells, and other immune cells. Similarly, various therapeutic drugs are prevented from effectively penetrating this barrier. The chemical barrier comprises the hypoxic and low-pH environment, which harbours immunosuppressive cells and molecules [9,10]. These factors induce immunosuppression and immune escape, which jointly promote tumour growth, invasion, and metastasis.

Different components of the TME can promote tumour progression. Tumour-associated macrophages (TAMs), the major immune components within the TME, have become a focal point for research. TAMs originate from the bone marrow-derived circulating lymphocyte antigen 6C $(Ly6C)^+$ monocytes in the spleen. Upon reaching the tumour, monocytes/macrophages are stimulated by pathogens, cytokines, tumour cells, and other signals in the local environment. This leads to their polarisation to different functional phenotypes, including those induced by the classical activation pathway (M1), stimulated by interferon-gamma (IFN-γ) and microbial products like Toll-like receptor (TLR) ligands, as well as those induced by the alternative activation pathway (M2) activated by helper T cell (Th) 2 cytokines, such as interleukin (IL)-4 and IL-13 [11,12]. TAMs are characterised by heterogeneous and plastic features. In the early stages of tumour development, M1 macrophages are considered to inhibit tumour growth. However, as tumour progression advances, the secretion of certain cytokines and transmission of metabolic signals can polarise TAMs towards the M2-phenotype [13]. This promotes neovascularization, tumour spread, and inhibition of localised antitumour immune responses. Hence, exploiting TAMs has become a research strategy for developing treatment modalities, including regulating TAM polarisation, depleting TAMs, and using TAMs for nanoparticle transport. These approaches reshape the immune microenvironment and inhibit tumour progression; however, each method has its own limitations.

The multi-target effects of traditional Chinese medicine (TCM) play an important role in the treatment of haematological and solid tumours. TCM is administered primarily during the postoperative recovery period to patients with tumours, to reduce the toxicity and side effects caused by radiotherapy and chemotherapy. Additionally, it is often combined with immunotherapy to enhance the overall curative effect. Indeed, TCM enhances patient immunity, reduces discomfort, improves the quality of life, and prolongs overall survival. Mechanistically, TCM elicits antitumour effects by enhancing antitumour immunity in the TME. Given that TAMs constitute the largest proportion of the TME, they have become a target for antitumour research in TCM, yielding promising results. In this review, we discuss 1) the future development direction of TCM targeting macrophages in the treatment of solid tumours by clarifying the role of macrophages in the microenvironment, 2) the superiority of combining TCM with conventional treatments or nano-drug delivery systems, and 3) the considerable potential of TCM as a combination therapy in clinical practice to provide insights for improved clinical treatment and future research.

2. Roles of macrophages in the solid tumour microenvironment

Macrophages are innate immune cells primarily derived from blood monocytes produced by bone marrow myeloid progenitor cells, which later differentiate into macrophages in tissues after leaving blood circulation. In the early stages of embryonic development, macrophages primarily originate from the yolk sac or foetal liver and persist as tissue-resident macrophages (TRMs) throughout life. Different sources of macrophages are particularly important in cancer as TRMs and bone marrow-derived TAMs differ between primary and metastatic tumours [14]. Macrophages constantly transfer their functional status to a new metastable state to respond to physiological tissue changes or environmental stress, regulate tissue homeostasis, and participate in cancer progression [15]. TAMs are the most abundant type of immune cells in the TME. Soluble factors and metabolites secreted by tumours into the TME can promote the tumorigenicity of TAMs and inhibit their antitumour properties. Typically, M1 macrophages secrete pro-inflammatory cytokines that support and activate adaptive immune cells during the early stages of cancer. Meanwhile, the M2 phenotype is the primary TAM, immunosuppressive, and related to the poor prognosis of patients with tumours. They are characterised by low major histocompatibility complex (MHC) II and inhibitory molecule expression [16]. These factors are involved in ECM remodelling, immunosuppression, tumour angiogenesis, and TAM or tumour cell metabolic changes. Considering that TAMs have strong plasticity and can produce subsets with different abilities to support tumour growth and metastasis, they represent potential targets for cancer treatment.

2.1. Participation of TAMs in ECM remodelling

The ECM is a highly dynamic structure in all tissues that can be continuously remodelled. The ECM interacts with cells to regulate cell proliferation, differentiation, and migration while maintaining tissue homeostasis. An imbalance in the ECM composition and structure can lead to various pathological states. In solid tumours, the ECM acts as an external environment for the survival of tumours and other cells and transmits growth or apoptosis signals. Additionally, it functions as a robust protective barrier for tumour cells [17]. The ECM is primarily composed of structural proteins (collagen and elastin), glycosaminoglycans, proteoglycans, and adhesion proteins (fibronectin and laminin). Meanwhile, in the TME, the ECM structure is reconstructed, and intercellular signals are destroyed [18].

Under the stimulation of tumour cells or the ECM environment, macrophages can differentiate into different TAMs phenotypes. They mediate ECM remodelling by secreting growth factors, inflammatory cytokines, extracellular matrix-degrading proteases, and activating cancer-associated fibroblasts. Alternatively, they may differentiate into profibrotic phenotypes to promote fibrosis (Fig. 1A). For example, using a pancreatic ductal adenocarcinoma model, Zhu et al. reported that embryonic-derived macrophages exhibit a profibrotic phenotype with upregulation of molecules involved in ECM deposition and remodelling. This includes genes encoding ECM molecules (collagen isomer, nidogen, tenascin C, and elastin), ECM-producing enzymes (hyaluronic acid synthase 2 and 3), and ECM-remodelling molecules (lysine acyl oxidase). Moreover, increased production of collagen I and IV occurs *in vitro* [15]. Although the ECM of pancreatic cancer is collagen-rich, the key step in remodelling the fibrotic ECM is degrading collagen, mediated by extracellular and endocytic pathways. The endocytosis pathway consists of the mannose receptor 1 (MRC1) in macrophages and the endocytic collagen receptor in fibroblasts; these phagocytic cells internalise the proteolytic fragments of collagen, which are subsequently degraded by lysosomal proteases. MRC1-dependent collagen uptake and degradation by TAMs are accompanied by an increase in intracellular arginine levels, leading to upregulated inducible nitric oxide synthase (iNOS) and reactive nitrogen species (RNS) production. Macrophage-derived RNS promotes the synthesis and extracellular deposition of collagen via pancreatic stellate cells through a paracrine mechanism, leading to a considerable increase in tumour fibrosis and promoting ECM remodelling in pancreatic tumours [19].

Matrix metalloproteinases (MMPs) can degrade all components of the ECM and are markedly upregulated in malignant tumours. MMP family members positively correlate with tumour invasion and metastasis [20]. Kang et al. found that the expression of MMP11 in tumour cells and fibroblasts is not related to patient survival. Furthermore, enhanced expression of MMP11 in breast cancer cells does not promote cell proliferation or migration. However, macrophages overexpressing MMP11 increase the migration of $HER2^{+}$ breast cancer cells via the CCL2/CCR2/MAPK pathway [21]. High expression of MMP11 in TAMs is associated with poor prognosis in patients with breast cancer. Meanwhile, macrophage-derived MMP9 and MMP2 are closely related to fibrous capsule (FC) rupture in hepatocellular carcinoma (HCC), leading to the migration and invasion of tumour cells to adjacent tissues. Consequently, it is necessary to expand the tumour resection range for patients with a ruptured FC during surgical resection to reduce the risk of recurrence and metastasis of HCC [22]. In addition, Zhu et al. found that TAMs with high CD155 expression are present in the tumour and adjacent tissues of patients with CRC. CD155 knockout in mice and the transfection of RAW264.7 macrophages with sh-CD155 expression vectors confirmed that $CD155^{+}$ TAMs induce STAT3 activation via high TGF-β expression. This mediates the release of MMP2 and MMP9 in CRC cells, leading to invasion and metastasis [23].

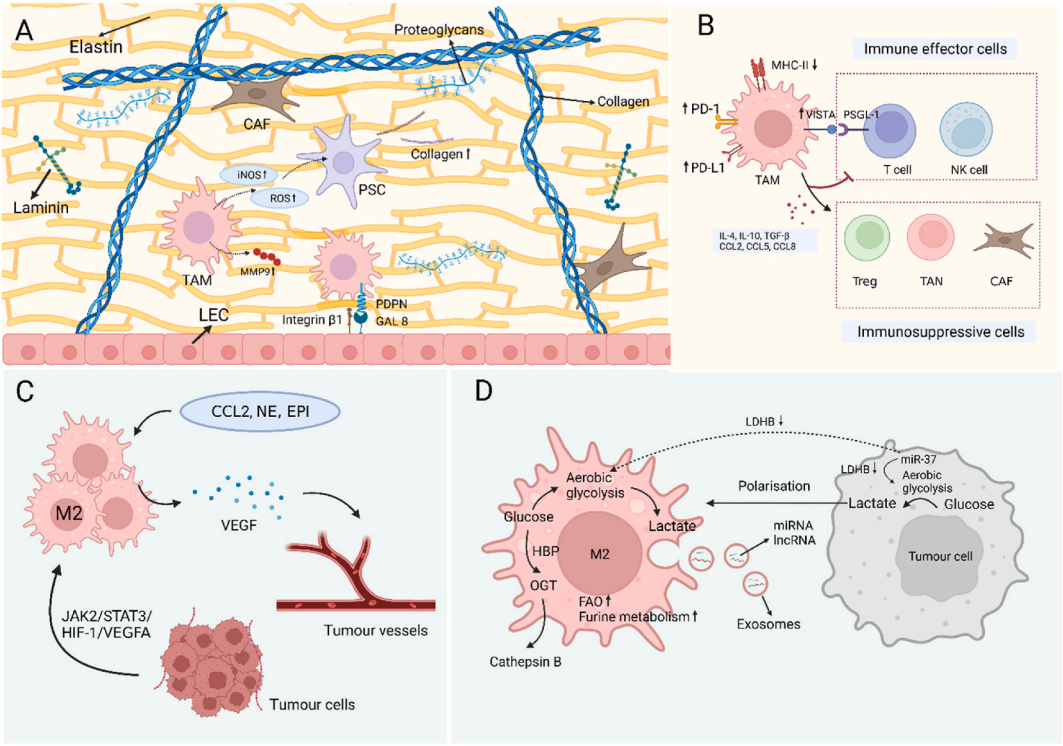

Fig. 1. TAMs in the solid tumour microenvironment. (A) Remodelling of the ECM: Collagen is deposited, and tumour fibrosis is supported; MMPs and PDPN are expressed to foster tumour cell invasion and metastasis. (B) Immunosuppression mediation: Immune checkpoints (PD-1, PD-L1, VISTA) are upregulated, immunosuppressive molecules (IL-4, IL-10, CCL2, etc.) are secreted to inhibit immune effector cells and promote immunosuppressive cell infiltration. (C) M2 macrophages promote tumour angiogenesis by expressing VEGF. (D) Metabolic changes in TAMs and tumour cells; and M2-related exosomes promote tumour progression.

In patients with breast cancer, TAMs with high podoplanin (PDPN) expression promote lymphatic vessel and distant metastasis. These TAMs adhere to endothelial cells while PDPN binds to galectin 8 (GAL8) derived from lymphatic endothelial cells (LECs) in a glycosylation-dependent manner. This interaction activates pro-migratory integrin β1, stimulating local matrix remodelling, promoting vascular growth, and facilitating lymphatic invasion. Therefore, inhibiting *anti*-integrin β1, PDPN, and GAL8 expression could hinder the adhesion of TAMs to LECs and prohibit the proliferation of cancer cells [24]. In gliomas, matrix remodelling-associated protein 8 (MXRA8) has been identified as a new prognostic indicator with markedly upregulated expression that promotes glioma progression. MXRA8 positively correlates with the macrophage marker colony-stimulating factor 1 receptor (CSF1R); its knockdown in glioma cells reduces M2 macrophage infiltration [25]. Moreover, tumour cell-derived spondin 2 (SPON2) is an ECM glycoprotein that positively correlates with M2-TAM infiltration and poor prognosis in patients with CRC. SPON2 promotes cytoskeleton remodelling and the transendothelial migration of monocytes by activating the integrin β1/PYK2 axis. M2 polarisation is indirectly induced by upregulating the expression of cytokines IL-10, CCL2, and CSF1 in tumour cells. Meanwhile, blocking the SPON2/integrinβ1/PYK2 axis impairs the transendothelial migration of monocytes and the cancer-promoting function of TAMs *in vivo* [26].

Remodelling of the ECM by TAMs is closely associated with tumour invasion and metastasis. Hence, targeting TAMs to reverse ECM remodelling can improve the immune microenvironment and inhibit tumour progression. A comprehensive understanding of the composition and structural characteristics of the ECM in cancer is essential for the discovery of therapeutic targets and diagnostic markers.

2.2. Involvement of TAMs in immunosuppression and immune escape

TAMs constitute the largest proportion of the TME. Tumour-promoting TAMs have immunosuppressive properties, including low MHC II expression, high immune checkpoint expression (programmed cell death protein (PD)-1, PD-L1, etc.), and secretion of immunosuppressive cytokines (IL-4, IL-10, transforming growth factor (TGF)-β, and arginase (Arg)-1) and chemokines (CCL-2, CCL-5, CCL-8, etc.). These features inhibit macrophage phagocytosis, inflammasome activation, and effector factor function, weakening the antitumour immunity of immune effector cells such as T cells and NK cells. Consequently, there is an augmented infiltration of immunosuppressive cells, such as Treg, TAN (tumour-associated neutrophil), tumour-associated fibroblasts, tumour-associated mesenchymal cells, and other immunosuppressive cells, ultimately promoting the tumour cell immune escape (Fig. 1B).

TAMs exhibit high heterogeneity and polarise towards different subtypes within the TME depending on the solid tumour type. Wang et al. classified HCC tumours from patients in The Cancer Genome Atlas (TCGA) into three subtypes: S1, S2, and S3. Notably, S3 had the worst prognosis and the highest expression of immunosuppressive genes, including cytotoxic T lymphocyte-associated protein-4 (CTLA-4) and TIGIT. Moreover, the myeloid-derived suppressor cell-like macrophage subtype (mMφ) overexpressed the immunosuppressive gene *IL10* and further inhibited the immune response of T cells via NECTIN2–TIGIT axis [27]. Meanwhile, using single-cell RNA sequencing, Yang et al. identified two common immunosuppressive TAMs ($CCL18^+$ and $SPP1^+$) with unique functional and metabolic characteristics in the TME of non-small cell lung carcinoma (NSCLC), in which $CCL18^+$ macrophages exert immunosuppressive effects by inhibiting inflammatory factor production [28].

TAMs promote the immune escape of tumour cells by upregulating immune checkpoints in the TME. The increased expression of V-domain immunoglobulin suppressor of T cell activation (VISTA), activated by immune checkpoint T cells on the TAM membrane, binds to the co-inhibitory receptor P-selectin glycoprotein ligand-1 (PSGL-1) at acidic pH, leading to T cell inhibition. In the TME, elevated levels of histamine and histamine receptor H1 (HRH1) activate macrophages, polarise them to the M2-like phenotype, upregulate VISTA expression, and induce T cell dysfunction. Meanwhile, *HRH1* knockout and antihistamine therapy can reverse macrophage immunosuppression, restore the cytotoxic function of T cells, and restore the responsiveness to ICB immunotherapy [29,30].

Antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent phagocytosis (ADCP) play important roles in antitumour therapy; however, following ADCP, AIM2 is recruited into phagosomes via FcgR signalling, activated by tumour DNA. This activation leads to the cleavage of cGAS and upregulation of PD-L1 and IDO, inhibiting NK cell-mediated ADCC and T cell-mediated cytotoxicity in breast cancer and lymphoma [31]. Overexpression of B7–H3 in TAMs leads to decreased collagen fibres and enhanced angiogenesis in breast cancer [32]. In addition, in high-grade serous ovarian cancer, B7–H3 overexpression mediates immunosuppression and tumour progression via the CCL2–CCR2–M2 macrophage axis. Patients with tumours exhibiting high B7–H3 expression have reduced $IFN\gamma^+CD8^+$T cells and poor prognosis [33]. Therefore, targeting B7–H3 may simultaneously improve the ECM, reduce angiogenesis, and increase $CD8^+$ T-cell infiltration into tumour tissues. The transcription factor c-MAF is highly expressed in TAMs, promoting M2-like macrophage polarisation and mediating T-cell suppression [34].

TAMs promote the immune escape of tumour cells through various mechanisms. Indeed, the administration of immune checkpoint inhibitors (ICIs) targeting TAMs has proven effective for various solid tumours. Research in this direction may provide additional opportunities for human tumour immunotherapy.

2.3. Roles of TAMs in promoting tumour angiogenesis

A primary characteristic of tumour cells is the induction of tumour angiogenesis to meet the rapid growth requirements of tumour cells; TAMs are intimately involved in this process (Fig. 1C). Vascular endothelial growth factor (VEGF) is a key regulator of angiogenesis in solid tumours [35]. TAMs can promote tumour angiogenesis by upregulating VEGF levels through various pathways. Calmodulin 2 is highly expressed in gastric cancer tissues and promotes macrophage M2 polarisation by regulating the JAK2–-STAT3–HIF-1–VEGFA axis, resulting in increased angiogenesis [36]. Currently, the VEGF antibody, bevacizumab, represents a common combination therapy drug included in most clinical first-line antitumour treatment regimens. However, TAMs can promote

resistance to bevacizumab treatment. TAMs promote the expression of VEGF via CCL-2, whereas the CCL2 inhibitor mNOX-E36 blocks macrophage recruitment and angiogenesis and improves the efficacy of anti-angiogenic therapy for glioblastoma multiforme (GBM) [37]. Elevated catecholamine levels in the TME direct macrophages towards the M2 phenotype and promote tumour progression. Norepinephrine and epinephrine act on the adrenergic receptors and stimulate VEGF secretion. The use of 6OHDA to eliminate sympathetic nerve function or propranolol to block adrenergic signalling and compete with adrenergic receptor agonists significantly inhibits stress-induced lung cancer growth. In addition, IL-10 is markedly upregulated after catecholamine treatment, whereas IL-6 and IL-12 levels are reduced, promoting the immune escape of tumour cells [38]. The nervous system regulates the tumour immune microenvironment. Vasculogenic mimicry (VM) is an important component of tumour blood vessels. Tumour-promoting $F4/80^{+}$ TAMs regulate tumour angiogenesis via direct contact with endothelial cells or pericytes in time and space and form original, non-endothelial VM channels within *in vivo* tumour models to increase blood perfusion [39]. Therefore, anti-vascular therapy targeting VEGF alone fails to completely prevent tumour angiogenesis and is prone to drug resistance. However, multi-channel and multi-target combination therapy may enhance the efficacy of anti-vascular therapy.

Macrophage hypoxia is a key factor in angiogenesis. REDD1—a negative regulator of mTOR complex 1 (mTORC1)—plays a key role in the metabolic switch of hypoxic TAMs, impairing TAM glycolysis and leading to abnormal angiogenesis [40]. Hypoxia promotes macrophage M2 polarisation and VEGF secretion by upregulating hypoxia-inducible factor-1α (HIF-1α), consequently activating the PI3K–AKT–NRF2 pathway to promote GBM cell proliferation, epithelial–mesenchymal transition (EMT), glioblastoma stem cell characteristics, and temozolomide (TMZ) resistance [41].

2.4. The roles of TAM and tumour cell metabolism and metabolites in cancer development

As an important nutrient, carbohydrates are closely related to tumour cell metabolism. Tumour cells promote their own proliferation, angiogenesis, metastasis, immune escape, and drug resistance via aerobic glycolysis [42–46]. The glucose metabolism of TAMs and tumour cells exhibits interconnected interactions (Fig. 1D). On the one hand, the glucose metabolism of tumour cells influences and exploits TAMs to promote cancer progression. Tumour cells accumulate extracellular lactate via aerobic glycolysis and promote M2 polarisation. For example, ZEB1 ectopically expressed in breast cancer cells produces lactate in an acidic tumour environment, promoting the malignant progression of breast cancer by stimulating the PKA–CREB signalling pathway to induce an alternatively activated macrophage phenotype [47]. Tumour cells also release miR-37 to downregulate lactate dehydrogenase B, increasing aerobic glycolysis and enhancing lactate production in TAMs to meet the energy requirements of tumour cells [48]. In contrast, the reprogramming of glucose metabolism in TAMs promotes tumour cell growth. M2 markers in TAMs are upregulated in patients with type 2 diabetes (T2DM) patients and CRC. Mechanistically, the enhanced glucose flow through the hexosamine biosynthetic pathway increases O-GlcNAc glycosylation in TAMs and promotes cancer progression and immune escape [49]. Additionally, M2-like TAMs exhibit enhanced glucose uptake in the TME. This contributes to lysosome-localised O-GlcNAc transferase-mediated glycosylation of cathepsin B in macrophages. The increased secretion of cathepsin B in the TME promotes tumour metastasis and chemotherapy resistance [50].

Lipids are the primary components of cell and organelle membranes and participate in cell metabolic activities. Lipid accumulation and metabolism in TME maintain immunosuppressive cell survival [51–53]. In HCC, enhanced fatty acid metabolism in TAMs, particularly fatty acid oxidation (FAO; Fig. 1D), induces M2-TAM polarisation. Mechanistically, RIPK3 deficiency in TAMs promotes macrophage fatty acid metabolism and M2-TAM activation via the ROS–caspase1–PPAR pathway [54]. The increase in lipid uptake by macrophages in the TME upregulates scavenger receptor CD36 levels and lipid accumulation, replacing glycolysis with FAO as a means of generating cellular energy. TAMs express higher levels of molecules that are conducive to tumour proliferation and progression [55, 56]. These studies highlight the importance of lipid metabolism in promoting TAM differentiation and function in the TME. Therefore, TAM FAO is a potential target for cancer treatment.

Amino acids can be transformed into other metabolites involved in cellular regulation, including purines, pyrimidines, and pigments. Li et al. found that purine metabolism may be a key metabolic feature of tumour-promoting TAMs and is associated with the poor therapeutic effect of ICB [57]. Additionally, based on a comprehensive analysis of GEO datasets and amino acid metabolic pathways in CRC, Jiang et al. identified eight key enzymes involved in amino acid metabolism in colonic TAMs. The tumours of *Acads*-deficient mice grew faster, and the number of M2 macrophages increased. The absence of ACADS is speculated to regulate the metabolism of TAMs, induce the polarisation of M2 macrophages, and promote CRC progression [58]. However, studies on the involvement of amino acid metabolism in the immunosuppressive functions of TAMs remain limited.

2.5. Roles of TAM-related exosomes in promoting tumour progression

Exosomes are extracellular vesicles with a diameter of 40–150 nm secreted by most cells, naturally present in body fluids. They achieve intercellular signal transduction by transmitting mRNA, miRNA, DNA, and proteins [59]. M2 macrophage-derived exosomes (MDE) promote tumour progression (Fig. 1D). In pancreatic cancer, MDE miR-155-5p and miR-221-5p target E2F2 to induce angiogenesis in mouse aortic endothelial cells, promote subcutaneous tumour growth, and increase vascular density [60]. Similarly, in lung adenocarcinoma (LUAD), the infiltration of M2 macrophages positively correlates with miR-942 expression and LUAD metastasis. Exosomal miR-942 promotes LUAD cell migration, invasion, and angiogenesis by regulating FOXO1 expression in LUAD cells [61]. Generally, exosomes exist in the TME and are involved in the signal transduction between TAMs and tumour cells. Hence, targeting TAM-related exosomes or using them as carriers to regulate tumour progression represents a promising treatment approach.

3. Regulatory effects elicited by TCM on TAMs in different solid tumours

As previously mentioned, modern medical treatments for most solid tumours have not achieved the desired results. However, combined treatment with TCM can prolong the survival time of patients and improve their quality of life. TCM originates from natural products with a rich diversity. Numerous TCMs exhibit antitumour effects by directly preventing tumour cell proliferation, promoting apoptosis, and inhibiting invasion, metastasis, and angiogenesis by improving the TME (Fig. 2). Combining TCM with chemotherapy, targeted therapy, and immunotherapy has also elicited considerable antitumour effects. This approach holds promise to evolve into a novel adjuvant therapy for cancer. However, the mechanisms of action of several TCMs remain unclear. Studies on TCM targeting TAMs have shown positive results in different solid tumours. The following sections introduce the mechanisms of action employed by TCM, combined chemotherapy, and immunotherapy against TAMs.

3.1. The regulatory role of monomers or compounds in Chinese herbs in common solid tumours

3.1.1. Lung cancer

According to IARC statistics, lung cancer ranks first in cancer-related mortality, and its 5-year survival rate remains low [2,62]. Numerous studies have been performed to elucidate the anti-lung cancer mechanisms of herbs, revealing that some improve the TME by regulating macrophages to enhance the overall antitumour therapeutic effect.

Atractylenolide II (AT-II) is a sesquiterpene monomer isolated from the dried rhizomes of *Atractylodes macrocephala* (BaiZhu). AT-II can inhibit the proliferation of gastric cancer, prostate cancer, and melanoma cells by promoting apoptosis [63–65]. It also reverses the chemotherapeutic resistance of CRC cells while increasing sensitivity [66]. Regarding lung cancer, Zhang et al. discovered that AT-II inhibits the expression of the M2 phenotype marker CD206 by blocking the STAT6 signalling pathway, downregulating ARG-1, IL-10, and TGF-β mRNA levels. Meanwhile, the proportion of M2 macrophages in subcutaneous tumours and metastatic lung nodules in mice is considerably reduced, indicating that AT-II can reduce TAM-mediated lung cancer cell metastasis [67].

Dihydroartemisinin (DHA), a derivative of *Artemisia annua* (*QingHao*), is a sesquiterpene lactone extract that represents and effective anti-malarial drug. DHA elicits evident cytotoxic effects on various tumour cells, with minimal effects on normal tissue cells. Xiao et al. discovered that DHA increases the levels of M1 phenotype-related molecules CD86, iNOS, and COX-2 via the AKT/mTOR signalling pathway, demonstrating that DHA promotes TAM polarisation to the M1 phenotype in a dose-dependent manner, increases the production of pro-inflammatory cytokines IL-1β, IL-6, TNF-α, and MCP-1, and enhances the RAW264.7 cell phagocytosis. In addition, DHA reduces the expression of CD206 and ARG-1 and reprogrammes M2 to M1. Meanwhile, rapamycin markedly reduces DHA-induced M1-related phenotypic expression of pro-inflammatory cytokines [68].

Marsdenia tenacissima (Roxb.) Wight et Arn (TongGuanTeng) is primarily used to treat rheumatism, respiratory tract infections, and

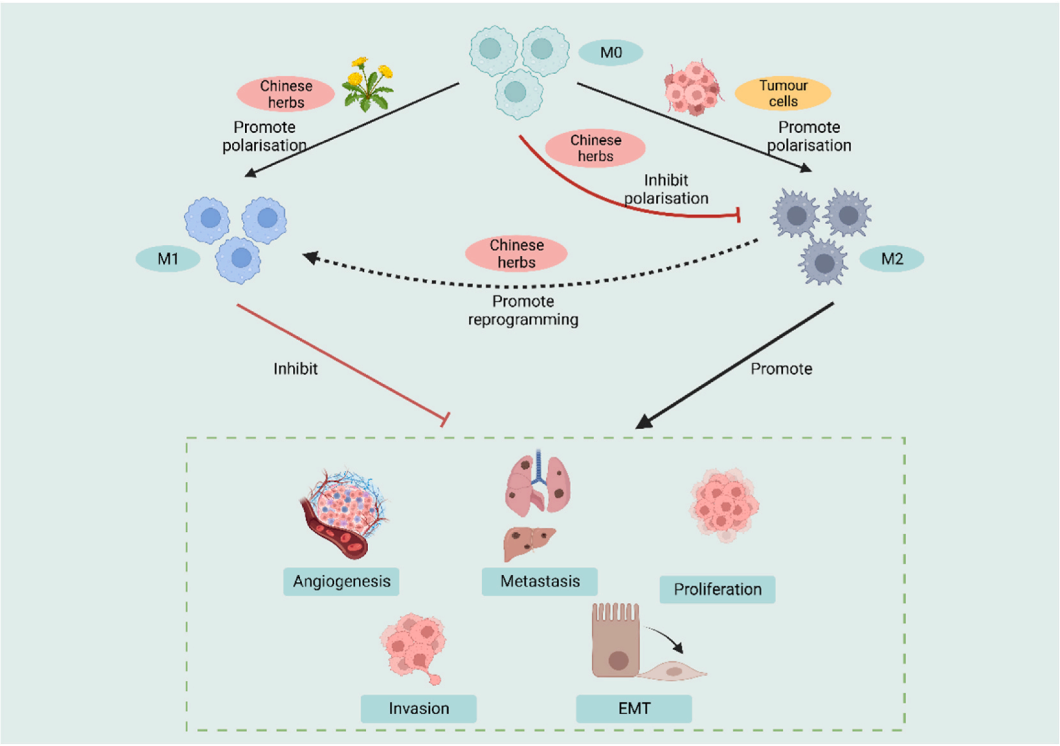

Fig. 2. Macrophages polarisation under the effects of TCM and tumour cells. The roles of M1 and M2 in tumour progression are shown.

cystitis. *Marsdenia tenacissima* extract (MTE) is the water-soluble component of *M. tenacissima* and exhibits antitumour effects in various cancers by promoting tumour cell apoptosis and autophagy [69], inhibiting tumour angiogenesis [70], reversing multidrug resistance [71], and enhancing chemotherapy and targeted drug efficacy [72,73]. However, the regulatory effect of MTE on the TME is unclear. Hepatoma-derived growth factor (HDGF) is highly expressed in NSCLC and is associated with tumour cell invasion. Fu et al. first confirmed that HDGF induces macrophage M2 polarisation via the IL-4/JAK1/STAT3 signalling pathway by constructing HDGF-overexpressing PC-9 and H292 cells. Subsequently, MTE markedly inhibits the migration and invasion of NSCLC cells stimulated by HDGF-induced M2 macrophages. Simultaneously, tumours in mice were inhibited, accompanied by a decrease in plasma HDGF levels and M2 macrophage infiltration of tumours and an increase in M1 macrophages [74].

Astragaloside IV (AS-IV) is an extract of *Astragali radix* (HuangQi) that has anti-inflammatory, anti-cancer, anti-oxidative, and immunoregulatory effects. Xu et al. confirmed that AS-IV blocks the M2 polarisation of macrophages by inhibiting the AMPK signalling pathway, partially reducing the expression of metastasis-related genes *CCL7*, *MMP9*, *MMP10*, and *MMP14* in A549 and H1299 cells treated with M2-CM, and inhibiting the mRNA expression of angiogenesis-promoting genes *VEGFA*, *ICAM-1*, *IGF-1*, and *CCL2*. Notably, AS-IV has no toxic effects on mouse myeloid cells or liver and kidney functions [75]. Astragalus polysaccharide (PG2) inhibits the migration and invasion of lung cancer cells. Mechanistically, PG2 inhibits MIF to restore AMPK activation while inhibiting EMT in lung adenocarcinoma cells. Moreover, the protein levels of MMP-13, AXL, and vimentin become markedly decreased after PG2 treatment. In severely combined immunodeficient mice injected with A549 cells via the tail vein, intraperitoneal injection of PG2 reduced lung and abdominal metastases [76].

Various TCM compounds have exhibited good antitumour effects in repeated clinical applications; however, the underlying mechanisms are complex and lack clear evidence. Nevertheless, the roles of some TCM compounds have been verified through preliminary research.

The KeJinYan decoction is an empirical prescription comprising 13 herbs and produced by Professor Zhongying Zhou, a master of national TCM in China. It is widely used in the treatment of lung cancer. Chen et al. performed RNA sequencing of C57BL/6 Lewis lung cancer mouse tumours, and identified the 'metabolic pathway' as the most important pathway regulated by KeJinYin decoction. Moreover, a significant decrease in the levels of tumour-infiltrating F4/80 macrophages and GLUT1 was noted. Hence, the KeJinYin decoction can reduce the number of TIMs and glucose metabolism in the TME while promoting the transformation of macrophages to the M1 phenotype [77]. Additionally, the HaiMu decoction (HMF) is a clinically patented prescription for the treatment of advanced lung cancer. In fact, HMF effectively and safely inhibits the growth of transplanted lung cancer cells in mice. *In vitro*, HMF activates RAW264.7 macrophages, increases phagocytic activity, and directs RAW264.7 towards M1 polarisation in a concentration-dependent manner [78].

3.1.2. Colorectal cancer

CRC is the second leading cause of cancer-related death worldwide. The 'immune tolerance' phenotype (microsatellite stability) of patients with CRC is considered non-responsive to ICIs, lacks immune cell infiltration, and has a low tumour mutation load, reducing the likelihood of benefiting from immunotherapy. Meanwhile, TCM can target TAMs and are expected to improve the immunosuppressive microenvironment of CRC, representing a potential combinatorial treatment strategy [79].

Cucurbitacin B (CuB) is a triterpenoid compound extracted from *Cucurbitaceae* plants, such as melons, and has various pharmacological antitumour and anti-metastatic functions. The activation of JAK/STAT3 in macrophages enhances macrophage proliferation and survival and increases the EMT of colon cancer cells to promote tumour metastasis [80]. In contrast, CuB inhibits M2 polarisation by regulating the JAK2/STAT3 pathway and further inhibits the migration and invasion of CRC cells. *In vivo*, 0.5 and 1 mg/kg of CuB markedly inhibit Ki-67 in tumour tissues, increase calpain-I, and effectively induce apoptosis. Additionally, the CD206 expression in the TME decreases, and the number of T cells increases. Collectively, CuB inhibits M2-like polarisation and alleviates TAM-mediated immunosuppression [81].

Inflammatory bowel disease is a known risk factor for CRC. Colitis-associated cancer (CAC) accounts for approximately 5% of CRC cases [82]. Therefore, alleviating intestinal inflammation is crucial in controlling the morbidity and mortality of CRC.

Dioscin is a natural active ingredient found in various *Dioscorea* plants, including *Dioscorea nipponica* Makino (ShanYao). Xun et al. found that dioscin inhibits CAC and tumourigenesis in an AOM/DSS mouse model. Specifically, NF-κB phosphorylation is inhibited, the mRNA expression of pro-inflammatory factors (TNF-α, IL-6, and IL-1β) is decreased, the anti-inflammatory factor IL-10 increases, and the intestinal barrier function improves. Moreover, dioscin promotes the differentiation of MDSCs into M1-like macrophages and inhibits their differentiation into the M2-like phenotype [83]. This suggests that dioscin reshapes the immune microenvironment and improves intestinal barrier function, preventing CAC.

YTE-17 is extracted from the fruit of *Garcinia yunnanensis* (YunNanTengHuang). Sui et al. discovered that YTE-17 reduces the incidence and number of colon adenomas in AOM/DSS-induced and $Apc^{Min}/^{+}$ mouse models. Mechanistically, YTE-17 inhibits the STAT3, JNK, and ERK pathways in RAW 264.7 cells, downregulates the expression of M2 markers, and upregulates the expression of M1 markers. The consumption of macrophages by clodronate reduces the tumour burden and inhibits tumorigenesis. Moreover, YTE-17 demonstrates favourable oral bioavailability without inducing significant damage to the liver or kidneys of mice [84].

Approximately half of the patients with CRC have colorectal liver metastases (CRLM), resulting in poor prognosis and high mortality [85]. Multiple compounds showed good therapeutic effects in the CRLM mouse model. The DaHuang ZheChong pill (DZP) is widely used in the clinical treatment of liver fibrosis, reducing liver collagen levels, ECM production, and TGF-β1 levels. Chen et al. speculated that DZP may improve the premetastatic TME to inhibit liver metastasis. MC38-EGFP cells were injected into the splenic capsules of C57BL/6J mice. The results indicated that DZP treatment blocks the recruitment and polarisation of liver macrophages mediated by tumour-associated exosomal CCL2, primarily manifested by the upregulation of the M1-TAMAs ratio and downregulation

Table 1
The targets and effects of TCM on macrophages in the TME.

Cancer type	Chinese herbal monomer	Chinese name of plant/animal	Latin binomial	Target(s)	Effect(s)	Study type	Reference
Lung cancer	Atractylenolide II	BaiZhu	*Atractylodes macrocephala Koidz.*	STAT6	Inhibit M2 polarisation, the migration and invasion of A549 cells	*In vivo* and *in vitro*	[67]
	Dihydroartemisinin	QingHao	*Artemisia annua*	Akt/mTOR	1. Promote M1 polarisation and the reprogramming of M2 to M1 2. Increase the secretion of pro-inflammatory factors IL-1β, IL-6, TNF-α and MCP-1	*In vivo* and *in vitro*	[68]
	Marsdenia tenacissima extract	TongGuanTeng	*Marsdenia tenacissima (Roxb.) Wight et Arn.*	HDGF/IL-4/ JAK1/STAT3	Inhibit the infiltration of M2 and promote the reprogramming of M2 to M1	*In vivo* and *in vitro*	[74]
	Astragaloside IV	HuangQi	*Astragalus membranaceus (Fisch.) Bunge*	AMPK	1. Inhibit M2 polarisation, 2. Down-regulate metastasis-related genes CCL7, MMP9, MMP10 and MMP14.3 . Down-regulate angiogenesis promoting genes *VEGFA*, *ICAM-1*, *IGF-1* and *CCL2*	*In vivo* and *in vitro*	[75]
	Astragalus Polysaccharide	HuangQi	*Astragalus membranaceus (Fisch.) Bunge*	MIF/AMPK	Decrease MMP-13, AXL and vimentin	*In vivo* and *in vitro*	[76]
	Ginsenoside	RenShen	*Panax ginseng C. A. Mey*		Promote the reprogramming of M2 to M1, decrease VEGF-C, MMP2 and MMP9	*In vivo* and *in vitro*	[93]
	Chinese herbal compound	**Composition**		**Target(s)**	**Effect(s)**	**Study type**	**Reference**
	KeJinYan decoction	*Semen Benincasae* (DongGuaZi), *Arisaema Cum Bile* (DanNanXing), *Houttuynia Cordata* (YuXingCao), *Rhizoma Fagopyri Dibotryis* (JinQiaoMai), *Cremastra Appendiculata* (WangBuLiuXing), *Herba et Gemma Agrimoniae* (XianHeCao), *Carthami Flos* (HongHua), *Lignum Sappan* (SuMu), *Rhizoma Pinelliae* (BanXia), *Radix Ranunculi Ternati* (MaoZhuaCao), *Radix Adenophorae* (ShaShen), *Radix Ophiopogonis* (MaiDong), *and Rhizoma Polygonati Odorati* (YuZhu)			1. Promote the reprogramming of M2 to M1 2. Regulate glucose metabolism	*In vivo*	[77]
	HaiMu decoction	*Sargassum* (HaiZao), *Ostreae Concha* (MuLiKe), *Menispermi Rhizome* (BeiDouGen), *Solani Nigri Herba* (LongKui)			Induce M1 polarisation	*In vitro*	[78]
Colorectal cancer	**Chinese herbal monomer**	**Chinese name of plant/animal**	**Latin binomial**	**Targets**	**Effects**	**Study type**	
	Cucurbitacin B	GuaDi	Cucumis melo L.	JAK-2/STAT3	Inhibit M2 polarisation and alleviate TAM-mediated immunosuppression	*In vivo* and *in vitro*	[81]
	Dioscin	ShuYu	Dioscorea nipponica Makino	pNF-κB	Promote the differentiation of bone marrow cells into M1 and inhibit differentiation into M2	*In vivo* and *in vitro*	[83]
	YTE-17	YunNanTengHuang	Garcinia yunnanensis Hu	STAT3, JNK and ERK	Down-regulate M2 markers and up-regulate M1 markers	*In vivo* and *in vitro*	[84]

(*continued on next page*)

Table 1 (*continued*)

Cancer type	Chinese herbal monomer	Chinese name of plant/animal	Latin binomial	Target(s)	Effect(s)	Study type	Reference
	Chinese herbal compound	**Composition**		**Targets**	**Effects**		
	DaHuang ZheChong Pill			CCL2	Increase M1 proportion and decrease M2 proportion in the liver	*In vivo*	[86]
	XiaoYaoSan	*Bupleurum chinense DC.* (ChaiHu), *Angelica sinensis (Oliv.) Diels.* (DangGui), *Paeonia lactiflora Pall.* (ShaoYao), *Atractylodes macrocephala Koidz.* (BaiZhu), *Poria cocos Wolf.* (FuLing), *Glycyrrhiza uralensis Fisch* (GanCao), *Mentha haplocalyx Briq.* (BoHe), *Zingiber officinale Rosc.* (Shengjiang)			Reduce TAMs recruitment and decrease TGF-β, IL-6, MMP-9, VEGF and CD31	*In vivo*	[94]
Breast cancer	**Chinese herbal monomer**	**Chinese name of plant/animal**	**Latin binomial**	**Target(s)**	**Effect(s)**	**Study type**	**Reference**
	Baohuoside I	YinYangHuo	*Epimedia brevicornum Maxim*	TAMs/CXCL1	Reverse M2 polarisation and reduce CXCL1	*In vivo* and *in vitro*	[88]
	Emodin	DaHuang, HuZhang	*Rheum palmatum, Polygonum cuspidatum*	TGF-β1/TGFβRI	1. Inhibit EMT and CSC key transcription genes in breast cancer cells 2. Reduce cancer-promoting macrophages	*In vivo* and *in vitro*	[89]
	Cordyceps sinensis extract	DongChongXiaCao	*Cordyceps*	NF-κB	1. Promote M1 polarisation 2. Increase the mRNA levels of TNF-α, iNOS, CCL-4, IL-1-β, IL-12 and CD38	*In vivo* and *in vitro*	[95]
	RYP extract	Ruyiping (RYP) formula: *Iphigenia indica Kunth* (ShanCiGu), *Curcuma phaeocaulis Valeton* (EZhu), *Nidus Vespae* (FengFang), *Akebiae Fructus* (YuZhiZi) and *Coix lacryma-jobi L.* (YiYiRen)		STAT6	1. Inhibit M2 polarisation, the migration and invasion of breast cancer cells 2. Increase alveolar ventilation	*In vivo* and *in vitro*	[96]
	Total glucose of paeony	ShaoYao	*Paeonia lactiflora*	NF-κB	1. Promote T cell infiltration and reduce TAMs 2. Down-regulate IL-6, IL-25, IL-20, CCL2, CCL3, CCL7, VEGF, MMP9 and MMP12	*In vivo* and *in vitro*	[97]
	Chinese herbal compound	**Composition**		**Target(s)**	**Effect(s)**	**Study type**	**Reference**
	AiDuQing formula	*Oldenlandia diffusa* (BaiHuaSheSheCao), *Curcuma phaeocaulis Valeton* (EZhu), *Astragalus membranaceus* (HuangQi), *and Glycyrrhiza uralensis Fisch.* (GanCao)		TAM/CXCL1/ Treg	1. Decrease TAMs infiltration and M2 polarisation 2. Decrease the secretion of CXCL1 3. Inhibit the chemotaxis and differentiation of naive $CD4^+$ T cells to Tregs 4. Enhance the infiltration and cytotoxicity of $CD8^+$ T cells	*In vivo* and *in vitro*	[98]
Liver cancer	**Chinese herbal monomer**	**Chinese name of plant/animal**	**Latin binomial**	**Target(s)**	**Effect(s)**	**Study type**	**Reference**

(*continued on next page*)

Table 1 (*continued*)

Cancer type	Chinese herbal monomer	Chinese name of plant/animal	Latin binomial	Target(s)	Effect(s)	Study type	Reference
	Bufalin	ChanSu		p50 NF-κB	1. Promote macrophage recruitment 2. Reprogramme M2-TAMs into M1 type 3. Promote T cell immune response	*In vivo* and *in vitro*	[92]
	Terminalia bellirica	PiLiLe	*Terminalia bellirica (Gaertn.) Roxb*		1. Promote the reprogramming of M2 to M1 2. Enhance the infiltration of T cells	*In vivo* and *in vitro*	[99]
	Bombyx batryticatus	BaiJiangChan	*B. batryticatus*	AKR1C3, SPP1 (VIR), NR1I2, CYP1A2, CYP3A4 (NVIR)	Act on different targets and regulate M1 in VIR and NVIR	*In vivo* and *in vitro*	[100]
	Ganoderma lucidum Spore Polysaccharide	LingZhi-BaoZi	*G. lucidum spore polysaccharide*	PI3K/Akt/mTOR	1. Promote the reprogramming of M2 to M1 2. Increase the proportion of M1/M2 3. Promote the apoptosis of H22 cells	*In vitro*	[101]
Gastric cancer	**Chinese herbal compound**	**Composition**		**Target(s)**	**Effect(s)**	**Study type**	**Reference**
	JianPi YangZheng Decoction	*Radix astragali* (HuangQi), *Radix codonopsis pilosulae* (DangShen), *Rhizoma Sparganii* (SanLeng) *and Rhizoma Curcumae* (EZhu)		PI3Kγ	1. Promote the reprogramming of M2 to M1 2. Increase M1 proportion and inhibit EMT	*In vivo* and *in vitro*	[102]
Head and neck squamous cell carcinoma	**Chinese herbal monomer**	**Chinese name of plant/animal**	**Latin binomial**	**Target(s)**	**Effect(s)**	**Study type**	**Reference**
	Dihydroartemisinin	QingHao	*Artemisia annua*	STAT3	Inhibit M2 polarisation and angiogenesis	*In vitro*	[103]
Prostate cancer	**Chinese herbal compound**	**Composition**		**Target(s)**	**Effect(s)**	**Study type**	**Reference**
	QiLing decoction	*Astragalus mongholicus* Bunge (HuangQi), *Rabdosia rubescens* (DongLingCao), *Rehmannia glutinosa* (DiHuang), *Psoralea corylifolia* (BuGuZhi), *Leonurus* (YiMuCao), *Turmeric* (JiangHuang) *and Glycyrrhiza uralensis Fisch.* (GanCao)		IL-6/STAT3	1. Down-regulate M2 markers and up-regulate M1 markers 2. Induce M1 polarisation	*In vitro*	[104]

of the M2-TAMAs ratio, and improved exosome-induced liver metastasis [86].

3.1.3. Other solid tumours

Female breast cancer became the leading cause of cancer worldwide in 2020, with an estimated 2.3 million new cases, accounting for 11.7 % of all cancer cases [2]. The XiaoPi formula (XPF) has been widely used in clinical practice as an adjuvant therapy for treating breast hyperplasia and preventing breast cancer since the 1980s. Wang et al. analysed the network pharmacology of XPF, which consists of 10 herbs containing 105 active compounds, regulating 806 potential targets, of which 81 correlate with breast cancer [87]. They screened the active ingredient of XPF, baohuoside I (BHS), using bioactivity-guided fractionation and purification, chemical structure identification, and biological verification approaches. Furthermore, BHS can reshape the TME via the TAMs/CXCL1 pathway and inhibit breast cancer cell metastasis [88]. Emodin is an anthraquinone derivative isolated from various Chinese herbal medicines, such as *Rheum palmatum* L. (DaHuang) and *Polygonum cuspidatum* (HuZhang). Fan et al. reported that emodin exerts anti-breast cancer effects by directly killing cancer cells and acting on macrophages and breast cancer cells, reducing macrophage recruitment to tumours and lungs and inhibiting their M2-like polarisation [89,90]. In a mouse model of orthotopic breast tumours, short-term administration of emodin prior to surgical resection of breast tumours reduces cancer-promoting macrophages and inhibits EMT and cancer stem cells in primary tumours [89].

Primary liver cancer includes HCC (75–85%) and intrahepatic cholangiocarcinoma (10–15%). Treatments for liver cancer include tumour resection or ablation, transcatheter arterial chemoembolisation, liver transplantation, and a tyrosine kinase inhibitor (sorafenib) [91]. However, HCC is typically diagnosed in the late stages of the disease, and treatment options are often limited to palliative care. The liver contains abundant macrophages, including Kupffer cells. Therefore, TAM-targeting TCM may effectively improve responsiveness to advanced liver cancer treatment. Bufalin is the primary active ingredient in ChanSu and is a steroid derivative extracted from the skin and parotid venom glands of toads. It has antitumour effects against various cancers, including HCC. Yu et al. discovered that the antitumour activity of bufalin depends on the immune response and induces M1 polarisation by inhibiting p50 NF-κB factor overexpression to stimulate the immune response of $CD8^+$ T cells, effectively improving the immunosuppressive TME. Additionally, bufalin combined with an *anti*-PD-1 antibody enhances the therapeutic effect in HCC [92].

In general, diverse monomers and compounds have antitumour effects on solid tumours, including gastric cancer, bladder cancer, and head and neck squamous cell carcinoma. The mechanisms underlying the regulation of TAMs are similar. The targets and effects of TCM on macrophages in the TME are shown in Table 1.

3.2. Combination of TCM with chemotherapy or immunotherapy in cancer treatments

TCM alone is insufficient to inhibit cancer progression. Instead, its advantages are reflected in its clinical use as a combination or adjuvant therapy, making TCM more suitable for advancing innovative cancer therapies, including chemotherapy and immunotherapy. The combined mode-and-effect results are listed in Table 2.

Ginsenoside Rh2 (Rh2) combined with *anti*-PD-L1 can reprogramme M2-like macrophages into M1-like macrophages, considerably increase the ratio of $CD8^+$ T/Tregs, increase the expression of the T cell chemokine CXCL10, and further increase T cell infiltration and activation in the TME. Rh2 enhances the efficacy and safety of *anti*-PD-L1 immunotherapy [105].

Compound KuShen injection (CKI) is extracted from the roots of Radix *Sophorae flavescentis* (KuShen) and *Rhizoma Smilacis glabrae* (TuFuLing). The main bioactive alkaloids are oxymatrine, matrine, oxysophocarpine, and sophocarpine. CKI is primarily used alone or in combination with conventional chemotherapy to enhance the associated antitumour efficacy and reduce the toxicity. Unresectable liver cancer enhances the therapeutic efficacy of transarterial chemoembolisation [108]. In HCC treatment, only 30% of the patients benefit from sorafenib owing to its severe adverse reactions, acquired resistance, and immunosuppressive microenvironment. Yang et al. explored the potential efficacy of CKI combined with chemotherapeutic drugs for the treatment of HCC. They found that combining CKI with low-dose sorafenib reduces the proportion and polarisation of M2-TAMs in the TME and enhances the distribution and polarisation of M1-TAMs. CKI-induced macrophages reduce the immunosuppressive effects on $CD8^+$ T cells, promote the proliferation and cytotoxic activity of $CD8^+$ T cells, and reduce the depletion of $CD8^+$ T cells. CKI transforms M2 to M1 via the TNFR1/NF-κB and MAPK axes, enhances the therapeutic effect of HCC on the subclinical dose of sorafenib, and reduces tumour recurrence, without eliciting significant toxicity [107]. Hence, combining CKI with sorafenib enhances anticancer activity by regulating the TME and targeting tumour cells to inhibit HCC.

Jin-Fu-An decoction (JFAD) is used for treating patients with advanced NSCLC, spleen deficiency, and phlegm dampness. Tang et al. discovered that *CTNNB*1 (β-catenin) expression was upregulated in various cancers across different databases. In particular, it was increased in mononuclear macrophages and malignant tumour cells. Treating LLC mice with JFAD and cisplatin caused the protein and gene expression of β-catenin to decrease, M1 macrophages in tumour tissue and the spleen to increase, and the level of CD206 in tumours to decrease. However, the proportion of M2 macrophages in the spleen did not change. Subsequent immunohistochemical analysis revealed increased infiltration of $CD8^+$ T cells in the tumours of the combined treatment group [106].

Collectively, these studies have shown that TCM combined with chemotherapy or immunotherapy reduces toxic reactions *in vivo* and effectively activates innate and adaptive immunity.

3.3. Combination of TCM with new nano-drug delivery systems in cancer treatments

Currently, the emerging core nano-drug loading technology can address the poor solubility and absorption of herbs and improve conventional drug administration methods. Additionally, it offers the advantage of biosafety, providing an important pathway for TCM

Table 2
Use of TCM as a combination or adjuvant therapy to remodel the TME.

Cancer type	Chinese herbal monomer		Combination therapy	Study type	Target(s)	Effect(s)	Reference
Lung cancer	Ginsenoside Rh2		*Anti*-PD-L1	*In vivo* and *in vitro*	TBK1-IRF3	1. Rh2 enhances the efficacy of *anti*-PD-L1 immunotherapy and is safe. 2. Combination treatment slightly reduces the number of Tregs but increases the ratio of $CD8^+$ T cells/Tregs. 3. Increase the expression of T cell chemokine CXCL10, T cell infiltration, and activation in TME. 4. Reprogramme M2-like to M1-like macrophages.	[105]
Cancer type	Chinese herbal compound	Composition	Combination therapy	Study type	Targets	Effects	**Reference**
Lung cancer	Jin-Fu-An decoction	*Pseudostellaria heterophylla* (Miq.) Pax (TaiZiShen), *Cremastra appendiculata* (D. Don) Makino (ShanCiGu), *Coix lacryma-jobi* L. (YiYiRen), *Salvia miltiorrhiza* Bunge (DanShen), *Gecko* (BiHu), *Prunus persica* (L.) Batsch (XinRen), *Phragmites australis* subsp. *altissimus* (Benth.) Clayton (LuWeiJing), *Fritillaria thunbergii* Miq (ZheBeiMu), Unprocessed *Pinellia ternata* (Thunb.) Makino (ShengBanXia), and Unprocessed *Arisaema heterophyllum* Blume (ShengNanXing)	Cisplatin	*In vivo* and *in vitro*	β-catenin	1. Down-regulate the expression of β-catenin and up-regulate iNOS in LLC tumours. 2. Increase M1 macrophages and $CD8^+$T cells. 3. Combination with cisplatin reduces the adverse reactions and prolongs the survival time of mice.	[106]
Liver cancer	Compound KuShen injection	Radix *Sophorae flavescentis* (KuShen) and *Rhizoma Smilacis glabrae* (TuFuLing)	Low-dose sorafenib	*In vivo* and *in vitro*	TNFR1	1. Combination with low-dose sorafenib enhances the antitumour effect, reduces recurrence and toxicity. 2. Combination with low-dose sorafenib also promotes the infiltration of total immune cells in the TME, the proportion of M1 increases and M2 decreases. 3. CKI reduces the immunosuppression of $CD8^+$ T cells and enhances tumour cytotoxicity and antitumour memory effect.	[107]

Table 3
Combining TCM with new nano-drug delivery systems to treat cancer.

Cancer type	Chinese herbal monomer	Combination regimen(s)	Advantages	Study type	Target(s)	Effect(s)	Reference
Glioblastoma	Tanshinone IIA and Glycyrrhizic acid	1. Self-assembled tanshinone IIA and glycyrrhizic acid into tanshinone IIA-GL nanobody (TGM), encapsulated in serum exosome membranes, anchored with CpG oligonucleotides. 2. Combination with TMZ in treatment.	1. Longer blood circulation time 2. Good blood barrier penetration and tumour targeting ability 3. Decrease haemolysis 4. Good safety *in vivo*	*In vivo* and *in vitro*	STAT3	1. Improve drug entry into the tumour and induces apoptosis 2. Promote DC maturation, increase antigen presentation, and polarise M2 to M1 to activate the immune response. 3. Combining with TMZ provides a synergistic effect.	[109]
Colorectal cancer	Ursolic acid and lentinan	1. Stable nano-drug (LNT-UA) developed from the self-assembly of LNT and UA without additional carriers using a nanoprecipitation method 2. Combined with αCD47 immunotherapy.	1. No carrier is required 2. Good stability in aqueous solution and high drug loading rate. 3. Compared with free drugs, it is more easily taken up by tumour cells and better improves immunogenicity.	*In vivo* and *in vitro*	Related to the increased tumour cell immunogenicity.	1. Induce ICD reaction and increase tumour immunogenicity. 2. Activate DCs, polarise TAMs to M1, recruit effector T cells, and increase the level of antitumour related cytokines. 3. Combining LNT-UA with αCD47 effectively inhibits tumour growth and metastasis.	[110]
Colorectal cancer	Resveratrol	1. Adopted cell membrane coating nanotechnology 2. Erythrocyte membranes coated with RSV-containing poly (ε-caprolactone)–polyethylene glycol (PCL-PEG) nanoparticles 3. Coupled with a tumour-penetrating peptide iRGD	1. Good biocompatibility and biodegradability 2. Avoid macrophage phagocytosis 3. With long cycle effect 4. Easier to penetrate solid tumours	*In vivo* and *in vitro*	SLC7A11, GPX4	Induce ferroptosis and improve the biosafety of RSV.	[111]
Melanoma	Emodin and glycyrrhizin	1. Emodin and glycyrrhizic acid subjected to ultrasonic-combined extrusion to form nanoparticles 2. Fused erythrocyte and macrophage to form a hybrid membrane and encapsulated nanoparticle. 3. Combined with photodynamic therapy (PDT)	1. Glycyrrhizin enhances the solubility of emodin. 2. Nanoparticles with high encapsulation efficiency and high drug loading capacity. 3. Promote the selectivity and effectiveness of PDT	*In vivo* and *in vitro*	BAX, BCL2	1. Induce early apoptosis and senescence of B16 cells 2. Combining with PDT improves the efficiency of local photothermal heating and tumour tissue ablation	[112]
Breast cancer	Gambogic acid	The GA-loaded folate (FA)-conjugated arginine-based polys nanoparticles was prepared using a dialysis method	Improve drug targeting, reduce off-target damage	*In vivo* and *in vitro*	Cleaved PARP, cleaved caspase-3, cleaved caspase-6, cleaved caspase-7, cleaved caspase-8, and cleaved caspase-12	1. Increase endogenous and exogenous apoptosis. 2. Combining with FA increases the uptake of nanocarriers by TNBC cells. 3. ARG-based nanoparticles make the surface positive and regulate TAM polarisation.	[113]

Table 4
Completed and ongoing clinical trials for TCM in combination with conventional treatments.

	Registrationnumber	Studytype	Cancertype	Chineseherbalmonomer/compound	Majorcomponents/activeingredients	Combinationtherapy	Mechanism(s)/target(s)	Effect(s)	Reference
Completed clinical trials	NCT00076609	Open-label, phase II safety and efficacy clinical trial	Hepatocellular Carcinoma	PHY906	*Scutellaria baicalensis Georgi* (HuangQin), *Glycyrrhiza uralensis Fisch.* (GanCao), *Paeonia lactiflora Pall.* (ShaoYao), *and Ziziphus jujuba* var. *spinosa* (Bunge) (SuanZaoRen)	Capecitabine	1. Targeting on multidrugresistant protein, CYP450, tachykinin NK-1, opiate δ receptors, acetylcholinesterase, NF-κB, MMP, HIF-α, and Fos/Juk pathway 2. Activate M1 macrophages	1. The disease stability rate increases, the median progression-free survival and median overall survival prolongs. 2. The incidence of nausea and vomiting in combination therapy is lower than that in capecitabine monotherapy.	[114]
	/	Retrospective cohort study		Fufang Banmao Capsule, Huaier Granule, Jinlong Capsule, Kanglixin Capsule and Ganfule Capsule	Cantharidin, Huaier polysaccharide, Gecko peptides, Hesperidin, costunolide, Emodin	Conventional therapy	PP2A, P53, caspase-3, etc.	1. TCM treatment is an independent protective factor for 5-year survival rate of HCC patients. 2. The overall survival rate and progression-free survival rate of Chinese medicine users are higher than those of non-Chinese medicine users.	[115]
	ChiCTR2000033941	Randomised controlled clinical trial		Fuzheng Jiedu Xiaoji formulation	*Codonopsis pilosula* (Franch.) Nannf. (DanShen), *Astragalus mongholicus* Bunge (HuangQi),	TACE and standard treatment	AKT1	1. Combination therapy reduces the incidence of complications, prolongs 1-year OS and FPS, and	[116]

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Table 4 (*continued*)

	Registration number	Study type	Cancer type	Chinese herbal monomer/ compound	Major components/ active ingredients	Combination therapy	Mechanism(s)/target(s)	Effect(s)	Reference
					Atractylodes macrocephala (BaiZhu), *Poria cocos* (Schw.) Wolf (FuLing), *Adenophora stricta* Miq. (ShaShen), *Ophiopogon japonicus* (Thunb.) Ker Gawl. (MaiDong), *Angelica sinensis* (Oliv.), etc.			reduces overall mortality, especially in patients with BCLC stage A and B. 2. FZJDXJ inhibits cell proliferation, migration and invasion, and promotes apoptosis through AKT/ Cyclin D1/p21/p27 pathway.	
	2015EC117-05	Phase II randomised, double-blind, placebo-controlled clinical trial	Non-small cell lung cancer	Reishi & Privet Formula	*Ganoderma lucidum* (Curtis) P. Karst. (LingZhi) and *Ligustri Lucidi Fructus* (NuZhenzi)	Paclitaxel plus cisplatin or paclitaxel plus carboplatin		1. A higher QoL score 2. RPF may alleviate chemotherapy-induced fatigue. 3. Good tolerance and less related adverse events.	[117]
	NCT03712969	Multicentre, two-arm, open-label, parallel randomised controlled superiority trial		Shenlingcao oral liquid	American ginseng polysaccharide, ginsenoside, Ganoderma lucidum polysaccharides, cordyceps polysaccharide, cordycepin, adenine, protocatechuic acid, hyperoside, rutin, and gallic acid	Adjuvant chemotherapy and usual care	FAK, MAPK, NF-kB, PI3K, AKT, TLR4	1. Improve the physical, role, emotional function, lung cancer related symptoms (dyspnea, cough, alopecia, fatigue, nausea/vomiting, pain) of patients. 2. Active ingredients promote macrophage proliferation, activate T, B lymphocytes, and NK cells.	[118]
	ChiCTR-IOR-16009733	Double-blind, block randomised, placebo controlled clinical trial.	Metastatic Colorectal Cancer	Quxie Capsule	*Tetradium ruticarpum* (WuZhuYu), *Rhizoma Zingiberis* (GanJiang), etc.	Conventional therapy (chemotherapy, radiotherapy, targeted therapy and supportive care)	Foxo1	1. OS is longer than the control group. 2. Quxie capsule increases Th cells in patients and the abundance of beneficial bacteria in the intestine.	[119,120]

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Table 4 (*continued*)

	Registration number	Study type	Cancer type	Chinese herbal monomer/ compound	Major components/ active ingredients	Combination therapy	Mechanism(s)/target(s)	Effect(s)	Reference
	0228463	Pilot randomised controlled trial	HER2-Positive breast cancer	/	*Poria cocos* (Schw.) Wolf (FuLing), *Atractylodes macrocephala* (BaiZhu), *Fritillaria thunbergii* Miq (ZheBeiMu), etc.	Trastuzumab plus paclitaxel regimen after surgery	/	1. Protect the heart, liver, and reduce bone marrow suppression 2. Enhance the anti-cancer effect CEA, CA125 and CA153 are lower than those in the control group after 6 weeks of treatment.	[121]
	Registration number	**Study type**	**Cancer type**	**Chinese herbal monomer/ compound**		**Combination therapy**		**Research objective**	**Address**
Ongoing clinical trials	NCT05834413	Prospective, multicentre, randomised controlled clinical study	Driver Gene Negative II-IIIa Lung Cancer	TCM		Chemotherapy and Immune Checkpoint Inhibitors		Offer proof for establishing and optimizing a new model of postoperative staged TCM with adjuvant chemo-immunotherapy for lung cancer.	https://www.clinicaltrials.gov/study/NCT05834413?cond=cancer&term=Chinese%20Medicine&start=2022-06-01_&page=2&rank=12
	NCT05641506	Open-label, single-Arm , phase II clinical trial	Ovarian Cancer	YangZhengXiaoJi Capsule		Niraparib		Investigate the Chinese patent medicine Yangzheng Xiaoji Capsule for improving the adverse reaction, nausea, in Niraparib in the first-line maintenance therapy in advanced ovarian cancer	https://www.clinicaltrials.gov/study/NCT05641506?cond=cancer&term=Chinese%20Medicine&start=2022-06-01_&page=2&rank=14
	NCT05897749	Prospective, multicentre, randomised controlled clinical trial	Advanced Colorectal Cancer	Brucea Javanica Oil Emulsion Injection		Best palliative treatment		Assess the safety and efficacy of *Brucea javanica* oil emulsion injection in patients with advanced CRC who lack access to multi-line treatment	https://www.clinicaltrials.gov/study/NCT05897749?cond=cancer&term=Chinese%20Herbal%20Medicine&start=2022-06-01_&rank=7

(*continued on next page*)

Table 4 (*continued*)

	Registration number	Study type	Cancer type	Chinese herbal monomer/ compound	Major components/ active ingredients	Combination therapy	Mechanism(s)/target(s)	Effect(s)	Reference
	NCT05378334	Double-blind, randomised controlled study	Lung cancer patients with bone metastases	Bone-protecting and Mass-dispersion Decoction		Immune Checkpoint Inhibitors		Validate the safety and efficacy of HGXJT in combination with ICI-based standard therapy in lung cancer patients with bone metastases.	Study Details | Efficacy and Safety of HGXJT in Bone Metastatic NSCLC Patients | ClinicalTrials.gov
	NCT02781285	Observational (Real world study)	Advanced Gastric Cancer	TCM		/		Determine the role of TCM in the treatment of advanced gastric cancer through clinical trials and practical studies	https://www.clinicaltrials.gov/study/NCT02781285?cond=cancer&term=Real-world%20Study&intr=Traditional%20Chinese%20medicine&rank=1
	ChiMCTR2000003662	Randomised, parallel, controlled study (real world study)	Stage III colorectal cancer	Tenglong Buzhong Decoction		/		Provide support for the clinical application of Tenglong Buzhong decoction in preventing CRC metastasis, and lay a foundation for its further research and development.	https://www.chictr.org.cn/showproj.html?proj=59201

to move towards internationalisation and modernisation.

Gui et al. loaded tanshinone IIA (TanIIA) and glycyrrhizic acid (GL) into TanIIA-GL nanomicelles, encapsulated in serum exosome membranes, anchored with CpG oligonucleotides, and combined with temozolomide to treat GBM. Through drug loading, drugs can more readily traverse the blood–brain barrier to reach tumours. In addition, it promotes DC maturation, increases antigen presentation, and reprogrammes M2 macrophages to the M1 phenotype [109]. Gui et al. designed a stable nanodrug (LNT-UA) via self-assembly from lentinan (LNT) and ursolic acid (UA) without additional carriers using the nanoprecipitation method. Compared with free drugs, LNT-UA is more easily taken up by tumour cells, induces ICD reactions, and increases tumour immunogenicity. It can also activate DCs, polarise TAMs to the M1 type, recruit effector T cells, and increase the levels of antitumour-related cytokines. Meanwhile, combining LNT-UA with αCD47 effectively inhibits tumour growth and metastasis [110]. Other excellent drug delivery technologies are presented in Table 3, along with their effects and therapeutic advantages.

4. TCM clinical trial results

Recently, to assess the antitumour efficacy of TCM in clinical practice, numerous clinical trials have been performed, primarily in combination therapies. Real-world study (RWS) methods have received increasing attention in TCM, the results of which have confirmed that comprehensive treatment with TCM can enhance sensitivity to chemotherapy, reverse drug resistance, reduce adverse reactions and toxicity, relieve pain, and improve quality of life. The completed and ongoing clinical trials are summarised in Table 4. These existing clinical trials provide real data for basic research, compensate for the shortcomings of *in vitro* and *in vivo* studies, and, to some extent, provide support for the use of TCM in treating cancer. However, high-level clinical evidence remains deficient.

Additionally, randomised controlled trials have high operating costs and difficult implementation. Hence, meeting the requirements for absolute control and reflecting the characteristics and advantages of TCM has proven challenging. RWS is based on the patient's wishes, combined with the actual situation of the intervention, and aligns with the principle of 'treatment based on syndrome differentiation' in TCM. However, owing to the openness of its research methods, certain uncertainties persist in the associated conclusions. Therefore, it is necessary to formulate more stringent observation indicators and research programs to achieve more reliable results.

5. Conclusion

TCM has been used in China for millennia. In the clinical treatment of solid tumours, combining TCM with modern medicine can reduce toxicity, increase efficiency, and reverse drug resistance. However, the antitumour mechanisms of most TCMs remain unclear and lack evidence-based medical evidence. Recently, research into the mechanisms underlying the activity of TCM has made significant strides, revealing improvements in the TME via TAM regulation. This includes investigations into Chinese medicine monomers, compounds, and new nano-drug delivery systems. In the studies evaluating the targeting of TAMs by TCM that were summarised in this review, the antitumour mechanism of TCM is primarily achieved by regulating the dynamic balance between M1 and M2 TAMs and activating $CD8^+$ T cells. Additionally, to avoid the risk of direct macrophage depletion, TCM can also be used to achieve antitumour effects and compensate for the shortcomings of current Western medicine. However, the main active ingredients of certain drugs and compounds require further investigation. Moreover, TCM is primarily administered orally for the treatment of tumours, which may lead to poor absorption and unclear metabolism. New drug-loading technology can compensate for these shortcomings and enhance the targeting capacity and blood circulation time; however, it also encounters challenges such as high cost and difficult popularisation.

Although the therapeutic effects of TCM monomers and compounds have been confirmed in multiple clinical trials, the patient base is typically within Asian nations. Hence, in future studies, broader studies within other regions of the world are needed.

Generally, the existing research explains certain mechanisms by which TCM regulates the antitumour effect of TAMs. Specifically, TCM improves immunosuppression and immune escape by inhibiting M2-TAMs, promoting M1-TAM polarisation, and shifting M2-TAMs to M1-TAMs. This further induces T cell immunity and antitumour angiogenesis, inhibits ECM remodelling, and regulates glucose metabolism. Hence, this work provides a basis for subsequent research to inform the design of novel combinatorial clinical treatment strategies for different cancer types.

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CRediT authorship contribution statement

Jiamin Gao: Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Weishan Tan:** Writing – review & editing. **Luyun Yuan:** Writing – review & editing. **Haoyue Wang:** Methodology, Conceptualization. **Junkai Wen:** Writing – review & editing. **Kexiang Sun:** Methodology, Conceptualization. **Xin Chen:** Conceptualization. **Shuyun Wang:** Conceptualization. **Wanli Deng:** Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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List of Abbreviations

TAM	Tumour-associated macrophage
TCM	Traditional Chinese Medicine
IARC	International Agency for Research on Cancer
ICB	Immune checkpoint blockade
TME	Tumour microenvironment
ECM	Extracellular matrix
Ly6C	Lymphocyte antigen 6C
TLR	Toll-like receptor
Th	Helper T cell
BM	Bone marrow
TRMs	Tissue-resident macrophages
MRC1	Mannose receptor 1
iNOS	Inducible nitric oxide synthase
RNS	Reactive nitrogen
MMPs	Matrix metalloproteinases
FC	Fibrous capsule
HCC	Hepatocellular carcinoma
CRC	Colorectal cancer
PDPN	Podoplanin
GAL8	Galectin 8
LECs	Endothelial cells
MXRA8	Matrix Remodelling-Associated Protein 8
SPON2	Spondin 2
TAN	Tumour-associated neutrophil
CTLA-4	Cytotoxic T-lymphocyte-associated protein-4
TCGA	The Cancer Genome Atlas
NSCLC	Non-Small Cell Lung Cancer
scRNA-seq	Single-cell RNA sequencing
VISTA	V-domain immunoglobulin suppressor of T cell activation
PSGL-1	P-selectin glycoprotein ligand-1
HRH1	Histamine receptor H1
ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody-dependent phagocytosis
HGSOC	High-grade serous ovarian cancer
ICIs	Immune checkpoint inhibitors
VEGF	Vascular endothelial growth factor
GBM	Glioblastoma multiforme
VM	Vasculogenic mimicry
mTORC1	mTOR complex 1

HIF-1α	Hypoxia-inducible factor-1α
EMT	Epithelial-mesenchymal transition
GSC	Glioblastoma stem cell
TMZ	Temozolomide
LDHB	Lactate dehydrogenase B
T2DM	Type 2 diabetes
FAO	Fatty acid oxidation
MDE	Macrophage-derived exosomes
LUAD	Lung adenocarcinoma
SCLC	Small-cell lung carcinoma
AT-II	Atractylenolide II
DHA	Dihydroartemisinin
LLC	Lewis lung cancer
MTE	*Marsdenia tenacissima* extract
MDR	Multidrug resistance
HDGF	Hepatoma-derived growth factor
AS–IV	Astragaloside IV
PG2	*Astragalus* Polysaccharide
SCID	*Severe* combined immunodeficiency
G-Rh2	Ginsenoside Rh2
HMF	*HaiMuFang* decoction
MSS	Microsatellite stability
CuB	Cucurbitacin
CAC	Colitis-associated colon cancer
MD*SCs*	*Myeloid-derived suppressor cells*
DZP	*DaHuang ZheChong Pill*
XYS	*XiaoYaoSan*
TNBC	*Triple-negative breast cancer*
XPF	*XiaoPi formula*
BHS	*Baohuoside I*
ALDH	*Aldehyde dehydrogenase*
ADQ	*AiDuQing formula*
CKI	*Compound KuShen injection*
HNSCC	*Head and neck squamous cell carcinoma*
VEGFA	*Vascular endothelial growth factor A*
TanIIA	*Tanshinone IIA*
GL	*Glycyrrhizic acid*
LNT	*Lentinan*
UA	*Ursolic acid*
RWS	*Real-world stu*dy

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