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Review Article

Targeting ferroptosis and immune surveillance in gastric cancer with traditional Chinese medicine monomers: a dual-targeted strategy for epithelial-mesenchymal transition and angiogenesis

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Abstract: Gastric cancer (GC) is a highly prevalent and lethal malignancy worldwide. Tumor progression is driven by epithelial-mesenchymal transition (EMT) and aberrant angiogenesis, which collectively facilitate invasion, metastasis, and immune evasion. Ferroptosis, a form of programmed cell death induced by iron-dependent lipid peroxidation, has recently emerged as a promising mechanism to eliminate GC cells, overcome apoptosis resistance, and inhibit migration. Remodeling the tumor immune microenvironment to enhance immune surveillance represents another advanced therapeutic strategy. Natural compounds derived from traditional Chinese medicine (TCM), such as quercetin and curcumin, exert multi-targeted anti-tumor effects by modulating ferroptosis, EMT, angiogenesis, and the immune microenvironment. This review synthesizes evidence from both in vitro and in vivo studies supporting the role of TCM monomers in co-regulating ferroptosis and immune surveillance in GC. Furthermore, it proposes a dual-target approach against EMT and angiogenesis to advance the theoretical framework and promote the clinical application of TCM in precision oncology, thereby guiding the development of novel, low-toxicity, and high-efficacy anti-cancer agents.

Keywords: Traditional Chinese medicine, gastric cancer, ferroptosis, immune surveillance, epithelial-mesenchymal transition

Introduction

Gastric cancer (GC) is one of the most common malignancies of the gastrointestinal tract worldwide. In 2020, approximately 1.089 million new cases were reported, making it one of the leading cancer types globally [1]. Recent advances in multimodal treatment strategies, including surgical resection, chemotherapy, targeted therapy, and immunotherapy, have significantly reduced GC mortality. Nonetheless, overall survival remains suboptimal, and patients with advanced disease continue to encounter challenges such as drug resistance and recurrence [2]. Consequently, the development of novel combination treatment strategies to overcome drug resistance and metastasis has become a major focus of GC research.

Epithelial-mesenchymal transition (EMT) and tumor angiogenesis are critical drivers of GC progression, contributing to tumor invasion, metastasis, and nutrient supply, and are major determinants of treatment failure. These processes warrant investigation as dual targets for combination therapy. EMT endows tumor cells with mesenchymal characteristics, enabling detachment, extracellular matrix invasion, and dissemination to distant organs via blood or lymphatic circulation. This process markedly increases the risk of recurrence and metastasis and is strongly associated with chemotherapy resistance and poor prognosis [3]. Similarly, angiogenesis is indispensable for tumor growth and metastasis, as tumor-secreted pro-angiogenic factors stimulate neovascularization, ensuring sufficient oxygen and nutrient

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supply for rapid cell proliferation while also providing additional routes for metastasis [4]. Consequently, simultaneous targeting of EMT and angiogenesis has emerged as a promising research strategy in GC treatment.

In recent years, ferroptosis and immune surveillance have emerged as critical tumor-suppressive mechanisms. Ferroptosis is an iron-dependent form of programmed cell death initiated by lipid peroxidation, ultimately resulting in cancer cell death [5]. Immune surveillance eliminates tumor cells through the antitumor activity of the immune system. Increasing evidence suggests that regulating ferroptosis in conjunction with activating immune surveillance can synergistically suppress tumor progression [6]; however, research on these mechanisms in GC remains in its early stages.

Natural monomers derived from traditional Chinese medicine (TCM) are bioactive compounds capable of targeting multiple pathways. These monomers exhibit low toxicity and minimal side effects at effective doses, and they can be combined with chemotherapy, targeted therapy, and immunotherapy to enhance therapeutic efficacy. Certain TCM monomers not only modulate the tumor microenvironment but also inhibit tumor cell proliferation and promote apoptosis. Nonetheless, significant knowledge gaps remain regarding the integration of ferroptosis, immune surveillance, EMT, and angiogenesis in GC. This study investigates the potential mechanisms by which TCM monomers regulate ferroptosis and immune surveillance, as well as their anti-EMT and anti-angiogenic effects, based on the concept of "dual-target synergistic therapy", thereby providing new theoretical perspectives and therapeutic targets for GC.

Overview of ferroptosis and immune surveillance

Basic mechanisms of ferroptosis

Ferroptosis is a distinct, iron-dependent form of programmed cell death characterized by the accumulation of lipid peroxides. Like apoptosis, it maintains cellular membrane integrity while preventing further intracellular cytotoxicity to other cells or organisms. The central mechanism involves the accumulation of polyunsaturated lipid peroxides beyond the antioxidant capacity of glutathione peroxidase 4 (GPX4), leading to disruption of membrane structure [7]. Lipid peroxidation serves as the primary execution signal of ferroptosis and is primarily driven by iron-dependent reactive oxygen species (ROS). Polyunsaturated fatty acids (PUFAs) serve as the main substrates involved in lipid peroxidation. Under iron catalysis, ROS attack PUFA, forming lipid radicals that initiate a chain reaction, ultimately producing phospholipid hydroperoxides (PLOOH) [8]. Excessive accumulation of PLOOH compromise membrane integrity and culminates in cell death through both enzymatic and non-enzymatic mechanisms [9]. Dysfunction of the antioxidant defense system represents another critical factor in the initiation of ferroptosis, primarily involving the depletion of glutathione (GSH) or inactivation of GPX4. GPX4 requires GSH as a cofactor to neutralize lipid peroxidation, while GSH biosynthesis depends on cystine uptake mediated by the system Xc- transporter. Impairment of this axis results in uncontrolled lipid peroxidation and ferroptotic cell death [10].

In summary, ferroptosis is a form of cell death induced by factors such as iron metabolism imbalance, exacerbated lipid peroxidation, and dysfunction of the antioxidant system, with oxidative stress as its hallmark (**Figure 1**).

Tumor immune surveillance and escape mechanisms

Immune surveillance refers to the ability of the immune system to recognize and eliminate newly formed cancer cells. Its principal effectors are cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells [11]. Tumor cells use multiple methods to evade immune attack. For instance, they evade recognition by $CD8^+$ T cells by downregulating major histocompatibility complex class I (MHC-I) molecules, thus impairing $CD8^+$ T-cell recognition and reducing tumor antigen presentation [12]. In addition, tumor cells frequently overexpress immune checkpoint molecules, such as PD-L1, which engage PD-1 receptors on T cells to inhibit their activation, proliferation, and cytotoxicity, thus promoting immune escape [13]. Metabolic reprogramming further supports tumor survival while impairing immune cell function. For instance, excessive glucose uptake by tumor cells deprives T cells of essential energy substrates, leading to functional exhaustion [14].

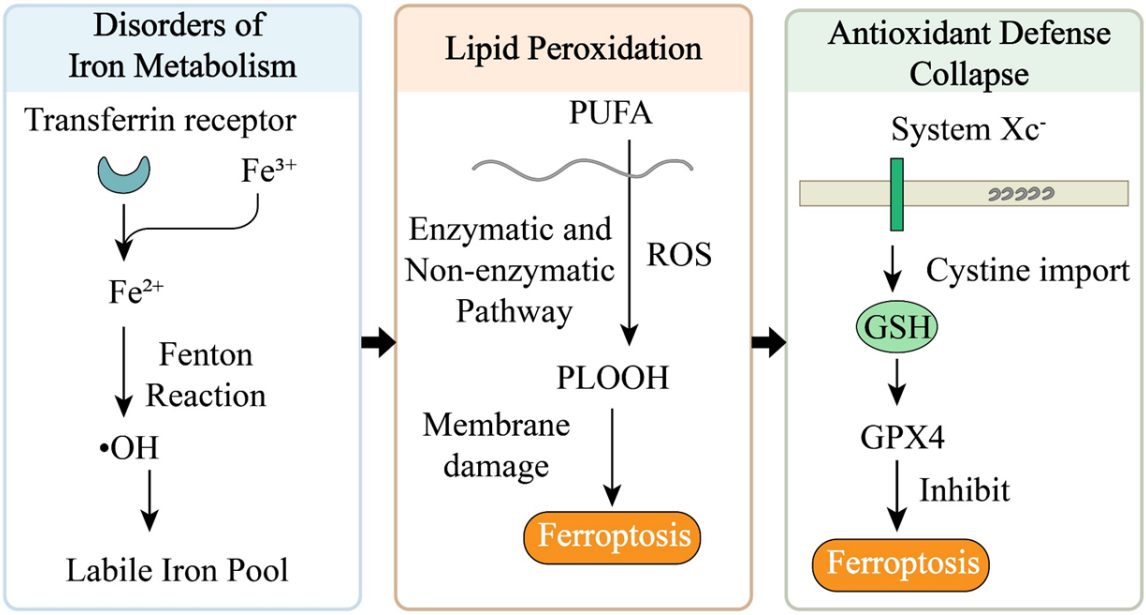

Figure 1. Schematic representation of the ferroptosis mechanism.

Hypoxia is an essential stressor in the tumor microenvironment, which drives immune escape and remodels immune responses by activating hypoxia-inducible factors (HIFs) [15]. Wu et al. [16] showed that activation of HIF-1α and HIF2α in tumor cells inhibits cytotoxic T-cell activity and recruits regulatory T-cells, thus crippling anti-tumor immunity.

Interaction between ferroptosis and immune surveillance

Ferroptosis plays a critical role in tumor immune escape. On one hand, it enhances immune surveillance by inducing tumor cell death, releasing damage-associated molecular patterns (DAMPs), and activating both innate and adaptive immunity. For instance, in the GC microenvironment, ferroptosis promotes dendritic cells (DCs) maturation, enhances antigen presentation, and facilitates the recruitment and activation of effector $CD8^+$ T cells, thereby strengthening tumor immune surveillance [17]. On one hand, ferroptosis may also contribute to immune escape under certain conditions. For instance, in complex tumor microenvironments such as GC, ferroptosis may induce the release of immunosuppressive factors, impair DC maturation, and thereby weaken the anti-tumor immune response [18]. Moreover, ferroptosis has been associated with upregulation of PD-L1 expression, which induces T cell exhaustion through the PD-1/PD-L1 axis, promoting immune tolerance and tumor escape [19]. Furthermore, immune cells can induce ferroptosis in tumor cells to facilitate their elimination. For example, in B-cell lymphoma, cytotoxic T lymphocytes induce ferroptosis in tumor cells by releasing ROS and disrupting iron metabolism, thereby enhancing the anti-tumor immune response [20].

In summary, ferroptosis and immune surveillance are interconnected processes that reciprocally regulate tumor immunity through complex molecular mechanisms (**Figure 2**). Understanding this crosstalk provides novel targets and strategies for cancer immunotherapy.

The key role of EMT and angiogenesis in the progression of GC

GC is a highly aggressive and heterogeneous malignancy, whose development involves the coordinated regulation of multiple biological processes. Among these, EMT and angiogenesis play pivotal roles in facilitating tumor cell invasion and metastasis. Within the tumor microenvironment, these processes are often co-activated, collectively driving malignant progression and contributing to therapeutic resistance.

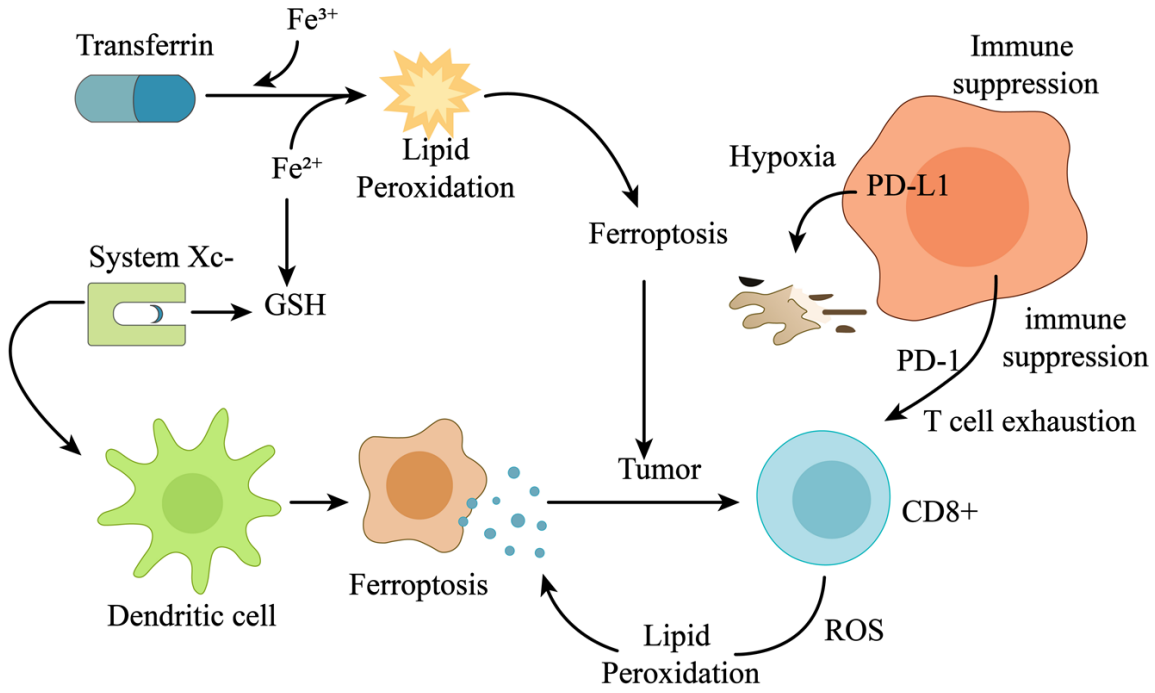

Figure 2. Schematic representation of the interaction between ferroptosis and immune surveillance.

Physiological mechanisms and functions of EMT

EMT is a complex cellular process in which epithelial cells acquire mesenchymal phenotypes and functions through distinct morphological and molecular changes. Physiologically, EMT plays a critical role in embryonic development, tissue repair, and various pathological conditions, including cancer [21]. Hallmarks of EMT include the loss of cell polarity, intercellular junctions, and epithelial adhesion to the basement membrane, along with the acquisition of mesenchymal characteristics, such as spindle-shaped morphology, increased motility, and increased invasiveness [22]. At the molecular level, EMT is characterized by a shift in marker expression, with downregulation of E-cadherin and the upregulation of N-cadherin, vimentin, and fibronectin [23]. Multiple signaling pathways are involved in the activation of EMT. One key pathway is the transforming growth factor-β (TGF-β)/Smad signaling cascade. Upon ligand binding, TGF-β receptors I and II (TGFβRI and TGFβRII) phosphorylate Smad2 and Smad3, which then form a complex with Smad4. This Smad complex translocates to the nucleus, where it upregulates EMT-related transcription factors such as Snail family transcriptional repressor 1 (Snail), Slug, and zinc finger E-box binding homeobox 1 (ZEB1), thereby repressing E-cadherin transcription, remodeling the cytoskeleton, and enhancing cellular motility [24-26]. The Wnt/β-catenin pathway is also critical in GC-associated EMT. Activation of Wnt signaling results in β-catenin accumulation in the cytoplasm and subsequent nuclear translocation. Nuclear β-catenin binds T-cell and lymphoid enhancer factors to activate EMT-related genes. This pathway intersects with and potentiate other signaling cascades, such as Notch and Hedgehog signaling, fostering stem cell-like properties and enhancing drug resistance in tumor cells [27]. EMT represents the initial step in cancer metastasis, enabling tumor cells to migrate and invade distant organs [28]. Furthermore, EMT is associated with resistance to chemotherapy and radiotherapy. Xu et al. [29] demonstrated that EMT-related transcription factors activate pro-survival cascades such as phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT), upregulating multidrug resistance proteins and thereby reducing tumor cell sensitivity to drug-induced apoptosis.

In conclusion, EMT is a dynamic and tightly regulated process with dual physiological and pathological roles (**Figure 3**), making it a crucial therapeutic target in cancer treatment.

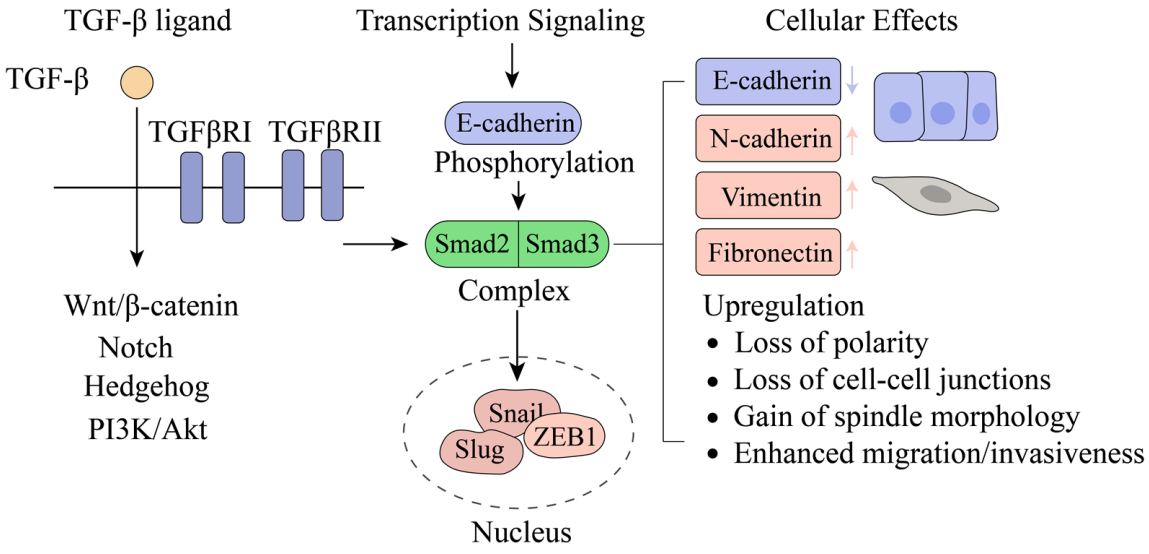

Figure 3. Schematic representation of the EMT mechanism.

Driving factors and regulatory networks of GC angiogenesis

Angiogenesis supplies oxygen and nutrients to GC cells and is essential for tumor growth and metastasis. Vascular endothelial growth factor (VEGF) is the primary driver of GC angiogenesis, activating endothelial cell proliferation and new vessel formation. VEGF expression is significantly elevated in GC tissues compared with normal gastric mucosa and is positively correlated with microvessel density, tumor stage, and lymphatic metastasis [30]. Angiogenesis Hypoxia in the tumor microenvironment further accelerates angiogenesis through HIF-1α. Under low oxygen conditions, HIF-1α inhibits ubiquitination-mediated protein degradation and induces the transcription of pro-angiogenic genes, including VEGF, angiopoietin-2 (Ang2), and platelet-derived growth factor (PDGF) [31]. In addition, inflammatory mediators such as interleukin-8 (IL-8) and the chemokine C-X-C motif chemokine ligand 12 (CXCL12) act on vascular endothelial cells through their respective receptors, C-X-C motif chemokine receptor 2 (CXCR2) and C-X-C motif chemokine receptor 4 (CXCR4), to promote angiogenesis and recruit immunosuppressive cells, thereby creating a tumor-supportive microenvironment [32]. The PI3K/AKT/mammalian target of rapamycin (mTOR) pathway plays a central regulatory role in GC angiogenesis by activating downstream effectors that promote endothelial cell proliferation and survival. Moreover, the PI3K/AKT pathway interacts with other signaling cascades, including Wnt/β-catenin and Hedgehog, to cooperatively regulate angiogenesis [33, 34].

Synergistic promotion of EMT and angiogenesis and their clinical significance

EMT and angiogenesis are two interrelated processes that jointly drive tumor progression, as illustrated in **Figure 4**. The TGF-β signaling pathway has been reported to induce EMT and promote angiogenesis through the upregulation of VEGF [35]. In addition, EMT further enhances angiogenesis by stimulating the secretion of pro-angiogenic factors such as matrix metalloproteinase-9 (MMP-9), which degrades the extracellular matrix and releases angiogenic signals. Conversely, basic fibroblast growth factor (bFGF), produced by endothelial cells of newly formed blood vessels and the surrounding matrix, along with epidermal growth factor (EGF), can induce EMT in tumor cells, forming a reciprocal “tumor-vessel” network [36, 37]. The combined impact of EMT and angiogenesis within the tumor microenvironment is substantial: EMT endows cancer cells with enhanced migratory and invasive capabilities, while angiogenesis provides essential nutrients and oxygen, facilitating distant metastasis [38]. Moreover, elevated EMT markers and angiogenesis are associated with poor prognosis. Patients with high EMT expression and microvessel density exhibit signifi-

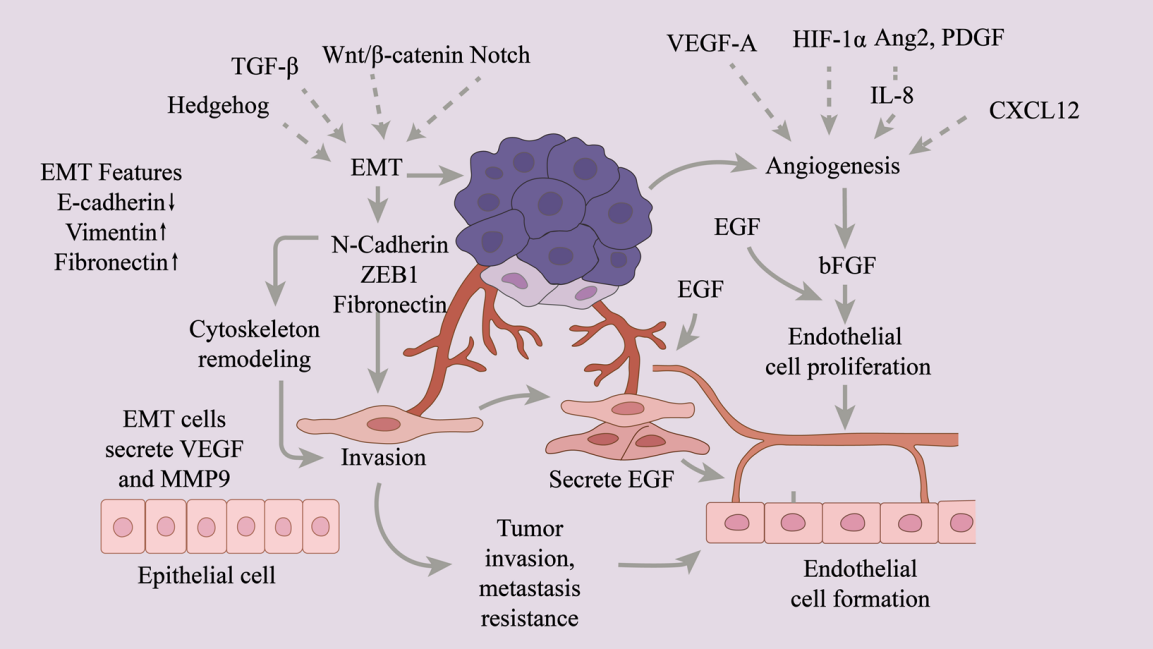

Figure 4. Schematic representation of the synergistic mechanism between EMT and angiogenesis.

cantly reduced overall and progression-free survival [39], underscoring the prognostic significance of both EMT expression and microvessel density in GC progression.

Targeting either EMT or angiogenesis alone is often insufficient for effective cancer therapy. Recent studies have investigated dual inhibition strategies, such as concurrent blockade of TGF-β and VEGFR, which show potential clinical value [40]. Further comprehensive investigations into the regulatory networks of these processes may yield novel therapeutic strategies for cancer treatment.

Anti-GC effects and mechanisms of representative TCM monomers

In recent years, increasing attention has been given to the roles of ferroptosis and immune surveillance in GC progression and treatment response. Monomers derived from TCM, with multi-target regulatory effects, show potential for the coordinated modulation of ferroptosis and the tumor immune microenvironment. Numerous studies have demonstrated that several bioactive TCM compounds not only induce ferroptosis and enhance immune surveillance but also significantly inhibit EMT and angiogenesis, thereby suppressing tumor invasion and metastasis (**Table 1**).

Quercetin

Quercetin is a plant-derived flavonoid with potent antioxidant and anti-inflammatory qualities, showing anti-proliferation and anti-metastasis efficacy in cancers [41]. In GC, quercetin induces ferroptosis by targeting the amino acid transporter solute carrier family 1 member 5 (SLC1A5). Upon binding to SLC1A5, quercetin increases intracellular iron levels, promotes iron-dependent lipid peroxidation, and subsequently triggers ferroptosis [42]. Quercetin also disrupts the PD-1/PD-L1 interaction, hence enhancing cytotoxic activity and cytokine secretion of $CD8^+$ T cells and improving anti-tumor immunity [43]. Quercetin also downregulates Family with Sequence Similarity 198 Member B (FAM198B) expression and inhibits the Mitogen-Activated Protein Kinase (MAPK) signalling pathway, thereby suppressing cell proliferation, migration and the process of EMT [44]. Moreover, in GC, quercetin exerts anti-angiogenic effects by downregulating VEGF-A expression and its receptor VEGFR-2 [45].

Curcumin

Curcumin, a natural polyphenol extracted from plants of the Zingiberaceae family, possesses potent antioxidant, anti-inflammatory, and anti-cancer properties. Several studies have shown

Table 1. Natural compounds targeting ferroptosis, immunomodulation, EMT, and angiogenesis in gastric cancer

Compound	Ferroptosis Mechanism	Immune Modulation	EMT Inhibition Mechanism	Anti-angiogenic Activity
Quercetin	Iron ↑ → Lipid peroxidation ↑	CD8+ T cell ↑	VEGF-A ↓ → VEGFR-2 ↓	VEGF-A ↓ → VEGFR-2 ↓
Curcumin	HO-1 ↑ → Ferroptosis activation	T cells ↑, M1 macrophages ↑	TGF-β↓ → E-cadherin ↑	VEGF ↓ → HGF ↓ → VEGFR1/2 ↓
Oleanolic Acid	GSH ↓ → Lipid peroxidation ↑	Treg/Th17 balance ↑	E-cadherin ↑ → EMT ↓	VEGF-A ↓ → bFGF ↓
Berberine	ROS ↑ → Lipid peroxidation ↑	DCs ↑	E-cadherin ↑ → EMT ↓	VEGF ↓
Resveratrol	Lipid peroxidation ↑	CD8+ T cell ↑	Snail ↓ → E-cadherin ↑	VEGF ↓ → VEGFR2 ↓
Baicalin	ROS ↑ → Ferroptosis ↑	NF-κB ↑→ Apoptosis ↑	E-cadherin ↑→ EMT ↓	VEGF ↓ → HIF-1α↓
Tanshinone IIA	ROS ↑→ Lipid peroxidation ↑	p53 ↑ → ROS ↑	E-cadherin ↑→ EMT ↓	VEGF ↓ → STAT3 ↓
Ginsenoside Rg3	Lipid peroxidation ↑	NF-κB ↓ → Immune response ↑	EMT ↓ → E-cadherin ↑	VEGF ↓ → COX-2 ↓ → HIF-1α ↓

that curcumin activates both classical and non-classical ferroptosis pathways by upregulating heme oxygenase-1 (HO-1) expression and downregulating GPX4 expression, thereby inhibiting GC proliferation and survival [46]. Curcumin also modulates the tumor immune microenvironment. It reduces the expression of immune checkpoint molecules, including PD-L1 and cytotoxic T-lymphocyte antigen 4 (CTLA-4), thus liberating T cells from inhibitory signaling [47]. In addition, curcumin remodels the immunosuppressive microenvironment by restoring NF-κB activity in T cells, inhibiting Treg cell function, and upregulating IFN-γ. In addition, it promotes the polarization of macrophages from the M2 to the M1 phenotype, thereby enhancing the activity of NK cells and cytotoxic T lymphocyte (CTLs) [48]. Moreover, curcumin inhibits TGF-β-induced EMT and upregulates E-cadherin expression, while downregulating transcription factors Snail and Slug, which reduces tumor cell invasion and migration [49]. Curcumin also exerts anti-angiogenic effects by inhibiting the expression of VEGF and hepatocyte growth factor (HGF), as well as the activity of VEGFR1/2. These changes collectively impair the proliferation and lumen formation of tumor endothelial cells, thereby suppressing angiogenesis [50].

Oleanolic acid

Oleanolic acid, a triterpenoid compound found in various plants, is widely used in TCM. Studies have shown that oleanolic acid induces ferroptosis in GC cells by downregulating solute carrier family 7 member 11 (SLC7A11), depleting GSH, and inhibiting GPX4 expression, thereby causing lipid peroxide accumulation [51]. In terms of immune regulation, oleanolic acid suppresses the IL-1β/NF-κB/TET3 signaling pathway, which reduces DNA methylation of the PD-L1 gene and downregulates PD-L1 expression, ultimately enhancing T-cell cytotoxicity [52]. It also targets IL-6 via miR-98-5p, inhibiting its secretion and restoring the balance between Treg and T helper 17 (Th17) cells, thereby strengthening anti-tumor immunity [53]. Furthermore, oleanolic acid counteracts TGF-β1-induced EMT by promoting inducible nitric oxide synthase (iNOS) dimerization, preventing the downregulation of E-cadherin and the upregulation of N-cadherin and vimentin [54]. This mechanism contributes to the inhibition of GC cell invasion and migration. In addition, oleanolic acid suppresses key angiogenic signaling pathways, including the signal transducer and activator of transcription 3 (STAT3) pathway and the Sonic Hedgehog pathway, leading to reduced secretion of angiogenic factors such as VEGF and bFGF [55].

Berberine

Berberine is a natural isoquinoline alkaloid found in a variety of plants used in TCM, with diverse biological activities. It has attracted considerable interest in both basic and clinical oncology research. Mechanistically, berberine inhibits mitochondrial complex I and activates complex II, leading to excessive ROS production and lipid peroxidation. It also suppresses GPX4 and GSH, thereby inducing Parkin/PTEN-induced kinase 1 (PINK1)-mediated mitophagy and promoting ferroptosis [56]. In terms of immune regulation, berberine promotes maturation of DCs, suppress Treg expansion, downregulate PD-L1 expression, and restores the cytotoxic activity of $CD8^+$ T cells against GC [57]. It also inhibits the polarization of tumor-associated macrophages (TAMs) into M2 type while promoting their conversion to the M1

type, thereby reducing the secretion of immunosuppressive cytokines and remodeling of tumor immune microenvironment [58]. Du et al. [59] demonstrated that berberine binds directly to TGFβRI/II, blocking the TGF-β/Smad pathway. This results in downregulation of Snail, Slug, and Vimentin, accompanied by upregulation of E-cadherin, thereby reversing EMT in GC cells. In addition, berberine significantly reduces angiogenesis in GC tissues by downregulating VEGF expression and inhibiting vascular endothelial cell proliferation, significantly reducing tumor vascularization [60].

Resveratrol

Resveratrol, a naturally occurring polyphenolic compound derived from *Polygonum cuspidatum*, is widely used in TCM. Mechanistically, resveratrol reduces intracellular GSH synthesis by inhibiting the activity of the cystine/glutamate antiporter system x_c^-. This suppression of GSH, together with inhibition of GPX4-mediated lipid peroxide scavenging, enhances phospholipid peroxidation in tumor cells [61]. In addition, resveratrol specifically targets the mitochondrial USP36-superoxide dismutase 2 (SOD2) axis, promoting SOD2 destabilization, ROS and iron accumulation, ultimately inducing ferroptosis and suppressing tumor growth both *in vitro* and *in vivo* [62]. In addition, resveratrol modulates the tumor immune microenvironment by regulating toll-like receptor 4 (TLR4) expression. Li et al. [63] reported that resveratrol binds to TLR4, contributing to the activation of innate immunity and enhancing tumor cell clearance. Furthermore, it suppresses tumor development by promoting $CD8^+$ T-cell expansion and increasing the production of cytotoxic factors such as IL-18 [64]. With regard to EMT regulation, resveratrol inhibits GLI1 in the Hedgehog signaling pathway, leading to downregulation of Snail and N-cadherin and upregulation of E-cadherin, thereby reversing EMT [65]. Additionally, resveratrol exerts anti-angiogenic effects by reducing VEGF expression in a dose-dependent manner [66].

Bacaliin

Baicalin, a flavonoid compound derived from *Scutellaria baicalensis*, exhibits broad multi-target activity against GC. It significantly enhances GC cell sensitivity to ferroptosis by promoting the accumulation of ROS. For example, baicalin in combination with 5-fluorouracil significantly increases intracellular ROS and upregulates ferroptosis-related genes [67]. This regulation further activates tumor suppressor p53 and the SLC7A11/GPX4/ROS axis, thereby amplifying ferroptosis [68]. In addition to ferroptosis, baicalin modulates the tumor immune microenvironment. It induce apoptosis via NF-κB/NLRP3 pathway activation and enhance T and macrophage activation via pro-inflammatory cytokines secretion, thus augmenting immune surveillance [69]. Baicalin also downregulates the expression of EMT-related markers, such as N-cadherin and vimentin, while upregulating E-cadherin expression, thereby inhibiting the migration and invasion of GC cells [70]. Additionally, baicalin inhibits the EMT process in GC cells through modulation of the miR-7/FAK/AKT signaling pathway [71]. Finally, baicalin inhibits angiogenesis by suppressing HIF-1α and its downstream target VEGF in tumor microenvironment [72].

Tanshinone IIA

Tanshinone IIA (Tan IIA), a diterpenoid quinone extracted from *Salvia miltiorrhiza*, exhibits potent anti-GC activity through multi-target mechanisms. In GC cells, Tan IIA markedly elevates lipid peroxide accumulation and depletes GSH - key hallmarks of ferroptosis. Research has shown that Tan IIA significantly increases lipid peroxidation and ROS levels in GC cells by upregulating p53 protein expression and downregulating SLC7A11, while reducing the levels of GSH and cysteine, thereby inducing ferroptosis. Moreover, the effect of Tan IIA can be reversed by ferroptosis inhibitors, such as Fer-1, further confirming that its inhibition of stemness and proliferation in GC cells occurs via ferroptosis [73, 74]. Tan IIA also regulates the tumor immune microenvironment. Its water-soluble derivative, sodium Tan IIA sulfonate, has been shown to augment anti-PD-1 efficacy by promoting the infiltration of $CD8^+$ T cells, suppressing the activity of Foxp3+ Tregs, and ameliorating the immunosuppression within the tumor milieu [75]. With respect to EMT, Tan IIA inhibits cell migration and invasion in SGC-7901 and MKN-28 cells by suppressing the EMT transcription factor forkhead box protein M1 (FOXM1) and its downstream targets, matrix metalloproteinase-2 (MMP-2) and MMP-9, thereby restoring E-cadherin expression [76].

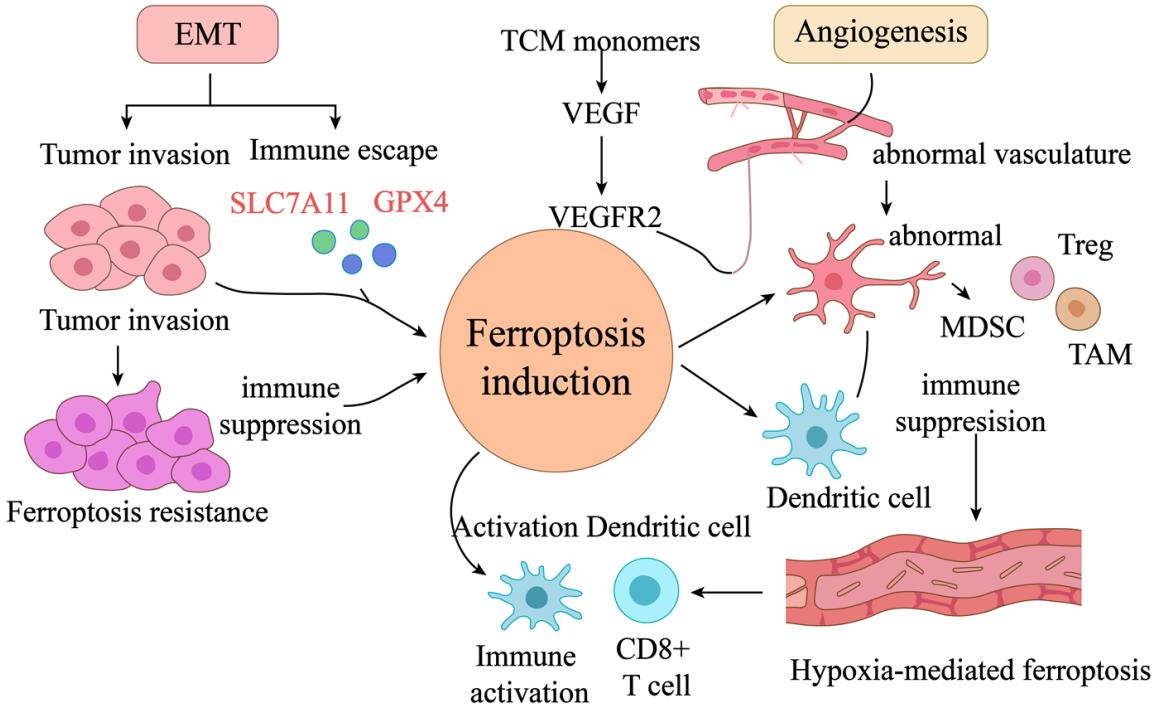

Figure 5. Dual-targeted strategy in GC: a schematic of coordinated regulation among EMT, angiogenesis, ferroptosis, and immune activation.

Tan IIA also reverses EMT by suppressing PI3K/Akt/ERK phosphorylation and downregulating Snail and Slug. In addition, Tan IIA exerts anti-angiogenic effects by inhibiting STAT3 phosphorylation, reducing VEGF secretion, and suppressing tumor neovascularization [77].

Ginsenoside Rg3

Ginsenoside Rg3, a bioactive saponin derived from *Panax ginseng* (also known as Korean ginseng), has demonstrated potent anti-GC effects through multi-target regulation. It downregulates GPX4 and SLC7A11, thereby impairing antioxidant defenses, enhancing lipid peroxidation, and inducing ferroptosis [78]. By inhibiting NF-κB pathway, Rg3 reduces immune evasion and strengthens immune surveillance [79]. Additionally, the combination of ginsenoside Rg3 and stimulator of interferon genes (STING) agonists synergistically suppress tumor cell growth and migration [80]. In terms of EMT regulation, ginsenoside Rg3 reverses EMT through upregulation of E-cadherin and downregulation of N-cadherin and vimentin, alongside inhibition of the PI3K/Akt/mTOR pathway [81, 82]. In addition, ginsenoside Rg3 exerts anti-angiogenic effects by suppressing the transcription and secretion of VEGF, cyclooxygenase-2 (COX-2), and HIF-1α, thereby weakening neovascularization and depriving tumors of essential nutrients [83].

In summary, TCM monomers demonstrate unique potential in regulating ferroptosis and immune surveillance, while simultaneously targeting EMT and angiogenesis. Their multi-target actions offer promising strategies for the development of novel therapeutic approaches against GC.

Dual-target treatment strategy: intervening in EMT and angiogenesis

GC is a highly heterogeneous malignancy, with progression closely linked to enhanced EMT and angiogenesis. These processes represent critical events in GC progression and metastasis. Emerging evidence suggests that EMT and angiogenesis are not only pivotal in tumor biology but also interconnected with ferroptosis and immune surveillance, forming a multidimensional regulatory network and providing diverse therapeutic targets (**Figure 5**). Recent evidence suggest that ferroptosis and immune surveillance can modulate EMT and angiogen-

esis, thereby restraining tumor progression. Thus, a dual-target intervention strategy, simultaneously inducing ferroptosis and remodeling the immune microenvironment with TCM monomers, is expected to become a new treatment strategy for GC.

EMT regulation: the core barrier between ferroptosis and immune escape

EMT is a process in which epithelial cells lose their polarity and intercellular adhesion while acquiring motility. This phenotypic plasticity is crucial for tumor invasion and metastasis. Research has demonstrated that EMT increases the invasiveness and migration of tumor cells but also alters their susceptibility to ferroptosis [84]. EMT inhibits ferroptosis through both common and distinct mechanisms. On one hand, EMT-related transcription factors such as Snail, ZEB1, and Twist1 upregulate SLC7A11 and GPX4 expression, thereby enhancing the cellular antioxidant capacity and reducing lipid peroxidation, ultimately suppressing ferroptosis [85]. On the other hand, dysregulation of iron metabolism genes, such as the aberrant expression of ferritin heavy chain and ferroportin, reduces intracellular free iron level, further restraining ferroptosis and promoting EMT-associated phenotypes [86]. Tumor cells invade tissue and escape immune detection through many mechanisms that are activated by EMT. During EMT, tumor cells significantly upregulate PD-L1 expression by activating multiple signaling pathways. PD-L1 binds to PD-1 on T cells, inhibiting their activation and proliferation, thereby weakening anti-tumor immunity and facilitating immune escape [87]. In addition, EMT promotes the recruitment of Treg cells and M2 macrophages, establishing an immunosuppressive tumor microenvironment [88]. In summary, EMT serves as a central barrier linking ferroptosis resistance and immune escape, underscoring its importance as a therapeutic target in GC.

Angiogenesis: an obstacle to ferroptosis and immune activation

Angiogenesis is essential for the sustained growth and metastasis of GC. Tumor cells secrete VEGF, which, together with HIF-1α, activates the VEGFR2 signaling and promotes neovascularization. These new vessels not only supply oxygen and nutrients but also exhibit structural abnormalities, leading to leakiness and hypoxia, which restricts immune cell infiltration and supports tumor immune escape [89]. VEGF exerts both angiogenic properties and immunosuppression effects by blocking the functions of antigen-presenting cells and effector T cells [90]. In addition, tumor angiogenesis recruits immunosuppressive cells, such as regulatory T cells, myeloid-derived suppressor cells (MDSC), and TAMs [91]. One study pointed out that tumor cells stabilize HIF-1α under hypoxic conditions, which upregulates the protein levels of SLC7A11 and GPX4, leading to decreased Fe^{2+} release, ROS production, and lipid peroxidation, thereby inhibiting ferroptosis [92]. Furthermore, HIF-1α enhances the mRNA translation of SLC7A11 by managing the transcription of YTH N6-Methyladenosine RNA Binding Protein 1 (YTHDF1), further elevating GPX4 expression and significantly reducing ferroptosis induced by hypoxia [93].

Ferroptosis-immunity crosstalk: the core mechanism of the dual-target strategy

TCM monomers exert anti-GC effects through regulating ferroptosis and immune surveillance, forming the basis of a novel dual-target strategy. The bidirectional crosstalk between immune system and ferroptosis is central to this approach, as it not only inhibits tumor growth but also enhances anti-tumor immunity.

Ferroptotic cell death facilitates the release of tumor-related antigens and DAMPs. Research indicates that DAMPs such as high mobility group box 1 (HMGB1), adenosine triphosphate (ATP), and calreticulin released from ferroptotic cells activate DCs, promote antigen cross-presentation, and strengthen $CD8^+$ T cell-mediated anti-tumor immunity [94]. Liang et al. [95] demonstrated that ferroptosis induction enhances T cell-mediated anti-tumor immunity through DAMP release, DC activation, and antigen presentation enhancement. However, tumor cells evade immune surveillance via leveraging angiogenesis and EMT. The activation of EMT-related transcription factors increases invasiveness and reduce ferroptosis sensitivity by upregulating antioxidant defenses. Together, reduced ferroptosis sensitivity and excessive ROS accumulation foster an immunosuppressive microenvironment, thereby accelerating GC progression.

Recent studies have shown that TCM monomers such as quercetin, curcumin, and oleanolic acid enhance ferroptosis sensitivity in GC cells and reshape the immune microenvironment by promoting $CD8^+$ T cell infiltration and functional recovery. The interplay between ferroptosis induction and immune activation suggests that one process can potentiate the other, establishing a positive feedback loop. Based on this correlation, a dual-target strategy that involves EMT and angiogenesis represents a promising strategy to overcome therapeutic resistance in GC.

In essence, EMT and angiogenesis not only drive GC progression but also influence treatment responses by modulating ferroptosis and immunity. Substances derived from TCM, through their ability to regulate iron metabolism, lipid peroxidation, and immune cell infiltration, disrupt EMT and angiogenesis. By inducing ferroptosis and activating anti-tumor immunity, TCM monomers hold promising potential for clinical translation in GC treatment.

Summary and prospect

GC is a prevalent malignancy of the digestive system, characterized by high postoperative recurrence, extensive metastasis, and resistance to targeted therapies. EMT endows cancer cells with invasive and metastatic capacities, while angiogenesis supplies essential nutrients and oxygen, thereby facilitating immune evasion and tumor dissemination. Recently, ferroptosis and tumor immune surveillance have emerged as critical components of comprehensive cancer treatment. This review highlights the therapeutic potential of TCM monomers in GC by elucidating their roles in inducing ferroptosis and enhancing immune surveillance. Furthermore, it proposes a dual-target strategy against EMT and angiogenesis to advance comprehensive treatment paradigm.

TCM monomers are bioactive compounds with well-defined chemical structures that are isolated and purified from traditional Chinese herbal medicines. These natural products not only possess diverse structural features and high biological safety but also exhibit diverse pharmacological activities, including antioxidant, anti-inflammatory, apoptosis-regulating, and immune-activating effects. Recent studies have demonstrated that TCM monomers promote gastric cancer cell death by modulating ferroptosis-related molecules and improve the tumor immune microenvironment by enhancing immune recognition and cytotoxic activity. Moreover, they effectively inhibit EMT and angiogenesis, thereby blocking tumor invasion, metastasis, and nutrient supply, ultimately achieving synergistic anti-cancer effects through multi-targeted regulation.

Despite these advances, several challenges remain. The precise mechanisms underlying ferroptosis-immunity crosstalk are not fully understood, animal models are limited in their ability to recapitulate the human tumor microenvironment, and clinical validation of TCM monomers remains insufficient. Future research should focus on multi-omics integration, optimization of animal models, large-scale clinical validation, and more refined molecular mechanism research to provide a stronger foundation for the clinical application of TCM monomers in GC treatment.

In conclusion, TCM monomers broaden the scope of cancer therapeutics by providing a theoretical rationale for integrating ferroptosis induction with immune surveillance in precision oncology. Combining natural ferroptosis inducers with immunostimulatory agents leverages the advantage of “multi-target, system-level” of TCM for GC. Breakthroughs in mechanisms research, clinical evaluation framework, and intelligent dosage technologies will be critical to establishing TCM monomers as a distinct and indispensable modality in GC treatment and global precision oncology.

Disclosure of conflict of interest

None.

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