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Research Progress of Traditional Chinese Medicine in Regulating Tumor Associated Macrophages in Gastric Cancer

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Abstract: ***Gastric cancer (GC) is one of the multiple malignant tumors of the digestive tract. Most patients with gastric cancer have no obvious discomfort in the early stage, and once discovered, they are mostly in the middle and late stages, and the morbidity and mortality rate are increasing year by year. Its occurrence and development depend on a variety of mechanisms, among which tumor microenvironment (TME) and tumor-associated macrophages (TAMs) have attracted more and more attention. Tumor-associated macrophages affect the occurrence and development of tumors and are closely related to tumor prognosis by inducing apoptosis, promoting autophagy, promoting angiogenesis, and immune escape. In recent years, traditional Chinese medicine (TCM) has been widely studied and applied to the field of cancer, and it has been found that TCM mainly exerts its anti-gastric cancer effects by inhibiting the proliferation, metastasis and angiogenesis of cancer cells, promoting apoptosis of cancer cells, inducing autophagy of tumor cells, and immune function. As one of the effective treatment methods, traditional Chinese medicine can not only regulate TAMs to inhibit tumor growth, but also the active ingredients and targets may become a new research direction in the field of immunotherapy. Therefore , this review describes the tumor-associated macrophages and their roles in gastric cancer progression, and combs and summarizes the molecular targets and mechanisms of action of different kinds of TCM monomers, TCM combinations, and novel TCM preparations against gastric cancer, so as to provide a mechanistic references for the clinical treatment of gastric cancer with TCM, and to explore the potential of TCM in preventing gastric cancer and related diseases.***

Keywords: Gastric cancer, Tumor-associated macrophages, Traditional Chinese medicine, Research progress**.**

1. Introduction

Gastric cancer (GC)is the fifth largest cancer threatening human health and the fourth cause of death from cancer [1]. The main reason why the mortality rate of GC remains high is that the early detection, early diagnosis and early treatment of gastric cancer are still difficult [2]. GC is a multi-risk factor disease including lifestyle, environmental risk factors, Helicobacter pylori infection, socioeconomic status, dietary factors - high intake of salty and smoked foods, as well as low intake of fruit and vegetable, dietary fiber intake. In addition, smoking, alcohol consumption, obesity, less physical activity, radiation, gastroesophageal reflux, family history of disease and genetic susceptibility are also risk factors for GC [3]. However, the cause of GC remains unclear.

The classic pathological transformation process of GC is “chronic non-atrogenic gastritis → chronic atrophic gastritis → intestinal epithelial metaplasia → dysplasia/intraepithelial neoplasia → gastric cancer” [4]. The mechanism of GC “inflammatory-cancer transformation” has not been fully understood, but a consensus has been reached for long-term stimulation of chronic inflammation as a risk factor for the development of gastric cancer [5]. Some scholars use bioinformatics methods to reveal the key genes and pathways of chronic gastritis-gastric cancer “inflammation and cancer transformation” from the molecular level to reveal the pathogenesis of gastric cancer, and also reveal the close relationship between gastritis and gastric cancer [6]. Gastric mucositis-cancer transformation refers to the irreversible destruction of the structure and function of the gastric mucosa on the basis of chronic inflammation, inducing abnormal proliferation and genetic mutations of specific cells, and then gradually transforming into malignancy, ultimately leading to the occurrence of gastric cancer [7], [8]. At present, there are two main pathological pathways known for the occurrence of gastric cancer [9], [10]: one is intestinal metaplasia, characterized by intestinal cells; The other is a spastic peptide-expressing metabiotic-metaplastic mucinous cell lineage.

2. Tumor Associated Macrophages

Macrophages can affect the function and cell-to-cell communication of gastric epithelial cells through their derived cell vesicles [11], the occurrence of intestinal metaplasia (IM) may be driven by a chronic inflammatory environment involving macrophages [12]. Research finding [13], Deoxycholic acid-stimulated macrophages can promote spasmolytic polypeptide expressing metaplasia (SPEM) and IM formation, indicating that macrophages play an important regulatory role in the evolution of IM. Both SPEM and IM are important risk factors for gastric cancer, and there is increasing evidence that IM may originate from SPEM [14]. In the chronic inflammatory damage response of gastric mucosa, macrophage-related phenotype infiltration is one of the decisive factors affecting the malignant progression of SPEM and is closely related to the occurrence of gastric cancer [15].

As innate immune cells, macrophages play an important role in the progression of inflammation and tumorigenesis and development, as well as in inflammation treatment and tumor immunotherapy [16]. Macrophages, derived from monocytes in the peripheral blood circulation, play a vital role in fighting infection, maintaining tissue homeostasis, and protecting our

body through the function of phagocytosis and digestion of foreign substances [17], [18]. The Tumor microenvironment (TME) of GC is composed of various cellular components such as tumor-associated macrophages, fibroblasts, endothelial cells and extracellular matrix [19]. Macrophages entering and participating in the formation of TME are called tumor macrophages (TAMs), and are the main component of the immune environment in TME [20]. The infiltration of TAMs in the TME is closely related to the progression and prognosis of gastric cancer [16], and its polarization status depends on the regulation of cytokines in the TME [17]. TAMs have two polarized activation states, the classical M1 polarization phenotype with tumor suppression and the selectively activated M2 polarization phenotype with tumor-promoting function [21]. M1 macrophages are typically induced by pathogens, lipopolysaccharides, GM-CSF, tumor necrosis factor-α (TNF-α), Th1 cytokines, and interferon γ (IFN-γ) [22]. The markers that best characterize M1 macrophages are CD64 (high-affinity Fcγ receptor I) and CD80 (a T lymphocyte-activating antigen) [23]. They can produce pro-inflammatory cytokines (such as IL-1β, IL-6, TNF-α, and type I IFN) and chemokines (such as CXCL1, CXCL5, CCL2, CCL3, CCL11, CCL19, and CX3CL1, etc.) to induce Th1 response activation and promote complement-mediated phagocytosis and type I inflammation [24]. M2 macrophages are often polarized by Th2 responses in inflammatory environments [24]. Macrophage colony-stimulating factor (M-CSF), IL-4, IL-10, IL-13, or a combination of these factors are able to polarize macrophages to an M2-like phenotype. M2-like macrophages are identified primarily based on the expression of CD11b+ and CD209+, a C-type lectin [23]. In GC-TME, M2 mainly secretes IL-6, IL-8, and IL-10, which affects tumor growth, angiogenesis, invasion, and immune escape [17].

3. The Relationship Between Tumor - Associated Macrophages and Gastric Cancer

TAMs not only provide structural support and promote tumor growth in the tumor matrix, but also affect tumorigenesis and tumor cell growth by producing a variety of signaling molecules (such as cytokines, chemokines, growth factors, and other signaling molecules) and regulating various signaling pathways [25]. TAM can affect the occurrence and progression of gastric cancer in both directions by constructing TME, affecting tumor-associated angiogenesis, promoting cell proliferation, invasion and metastasis, immune escape, confering chemotherapy resistance, inhibiting anti-tumor immune responses, and interacting with the microbiota in the stomach [26]. In GC, M2 polarization of TAM is induced in the TME, and inhibition of M1 polarization is an important factor in GC progression [19]. Therefore, targeting M2-like TAMs and depleting them in the TME or reversing M2-like TAMs to an M1-like phenotype, which directly enhances their cytotoxicity and indirectly stimulates cytotoxic T cells to eliminate tumor cells, is a potential strategy for GC immunotherapy [27,28].

4. The Traditional Chinese Medicine's Understanding of Gastric Cancer

Traditional Chinese medicine believes that GC belongs to the categories of "accumulation", "symptoms", "heart and abdominal accumulation", and the pathogenesis elements such as deficiency, stasis, phlegm, and poison are recognized by most scholars. Long-term disease and stasis is the beginning of the pathogenesis of gastric cancer stasis, long-term stasis and toxicity is the key to promoting the pathogenesis of GC stasis and toxicity, and stasis and toxicity interconnection is the core of promoting the progression of gastric cancer [29]. The treatment method of "removing stasis and detoxifying" in traditional Chinese medicine has significant advantages in the treatment of GC, by changing the TME, affecting related signaling molecules, and then regulating the phenotype of GC-TAMs [30]. This treatment not only inhibits tumor growth, but also enhances the therapeutic effect of other therapeutic drugs on tumors [31]. In addition, it can also improve metabolism, enhance immunity, reduce the pathological reaction of tumors, and improve prognosis by regulating the intestinal flora of the body. As one of the effective measures for the prevention and treatment of GC, traditional Chinese medicine can not only regulate tumor-related cell polarization, improve TME, and then inhibit tumor growth, but also its active ingredients and related targets are new research directions of immunotherapy [32,33]. Therefore, traditional Chinese medicine may inhibit the growth progression of GC by regulating TAMs or become an important way to treat gastric cancer.

A large number of studies have shown that TCM monomers and their active ingredients, TCM compounds and other TCM can regulate the signaling molecules in the TME of GC and its related diseases, regulate related signaling pathways, affect the polarization and phenotype of TAMs, and effectively inhibit the occurrence and development of GC. This paper aims to summarize the relevant mechanisms of TCM in the treatment of GC by modulating TAMs, explore the future development direction of TCM regulation of macrophages in the treatment of GC, and provide theoretical support for the clinical treatment and further research of GC.

5. Research Status of Traditional Chinese Medicine on Gastric Cancer

5.1 Traditional Chinese Medicine Monomer and Its Active Ingredients

5.1.1 Polysaccharides

Astragalus has been widely proven to play a role in the prevention and treatment of gastric cancer through a variety of pathways. Astragalus polysaccharide is one of its main active ingredients, and its anti-cancer effect is particularly significant. Yanling Liu and others found [34], Astragalus polysaccharide activates macrophages through TLR4/R0S/ MAPKs/NF-kB, polarizes them into Ml-type macrophages, thereby inhibiting proliferation and migration, and inducing apoptosis of gastric cancer cells. In addition, studies have shown that astragalus polysaccharide can independently induce apoptosis in gastric cancer cells, and has the effect of promoting apoptosis of gastric cancer cells and chemotherapy sensitizer [35].

5.1.2 Flavonoids

Diosmetin (DIO) is a natural flavonoid with antitumor effects. DIO inhibits the growth and invasion of GC cells by inhibiting the TRAF2/NF-κB signaling pathway and interfering with the polarization of M2 phenotypic macrophages [36].

Flavokawain B(FKB) is a compound of medicinal value isolated and extracted from Alpinia pricei Hayata [37]. Previous studies have confirmed its therapeutic effect and therapeutic potential for a variety of cancers. Research has shown that [38] FKB can weaken the polarization-inducing ability of M2 macrophages in gastric cancer cells, activate the TGF-β1/SMAD4 pathway, inhibit the survival and proliferation of GC cells, and promote their apoptosis. In addition, Hseu Y C et al. confirmed [39] FKB has chemopreventive and anti-cancer activities, and other chemotherapy drugs have synergistic effects.

5.1.3 Alkaloids

Qingfeng Vine was first seen in the "Tu Jing Ben Cao" compiled by Song Su in the Song Dynasty. Green vine is derived from the traditional Chinese medicine Qingfeng vine, and as the main component, it plays anti-inflammatory, anti-immune, anti-tumor and other effects. Vine can reduce the expression of IL-6, affect TME, inhibit the polarization of TAMs to M2 phenotype, weaken the survival and migration ability of gastric cancer cells, and reduce the risk of immunosuppression by TME [40].

Sophorae Flavescentis Radix has the effect of clearing away heat and dampness, detoxifying, and is widely used in the prevention and treatment of gastric cancer and has unique advantages. Matrine is a bioactive alkaloid extracted from bitter ginseng, which has a wide range of anti-tumor, anti-inflammatory and other effects. Matrine acts on macrophages and CD8+ T cells, induces TAM polarization to M1-TAMs through the TLR4/IRF3 axis, inhibits M2-TAMs polarization, and reshapes the immune microenvironment of gastric cancer [41].

Paclitaxel (PTX) is a tricyclic diterpenoid compound naturally produced in the bark and needles of yew. Studies have shown that PTX can transform M2 polarization to M1 polarization in human PBMC-derived macrophages through TLR4, while low-dose PTX accelerates M1 macrophage polarization through the TLR4/NF-κBp65 signaling pathway [42].

5.1.4 Triterpenes

Ganoderma lucidum is the fruiting body of the Ganoderma family and contains large amounts of polysaccharides, triterpenoids, sterols, and proteins. Its active ingredients have been widely proven to play a role in the prevention and treatment of gastric cancer through a variety of effector targets and by regulating multiple pathways [43]. Ganodermanontriol (GAN) is a natural small molecule component of Ganoderma lucidum and is one of the main components of Ganoderma lucidum. GANs can regulate M2 polarization in tumor-associated macrophages after inhibition of STAT6 phosphorylation, thereby inhibiting tumor progression [44].

Betulinic acid (BA) is a biologically active pentacyclic triterpenoid compound isolated from birch trees [45]. BA inhibits gastric cancer stemness by regulating GRP78/TGF-β1 in gastric cancer cells, promoting the polarization of TAMs to M1 and M2, and inhibiting macrophage-derived IL-6 signaling in the tumor microenvironment [46].

5.1.5 Saponins

Panax ginseng C. A. Mey. It is the dried root and rhizome of perennial perennial root herbaceous plants in the Pentaceae family. Its main active ingredient, ginsenoside, has good antitumor activity and can play a good inhibitory role in the proliferation, invasion and migration of gastric cancer cells. Ginsenoside Rg3 can induce macrophages in mouse tumor tissues to polarize to M1 and inhibit their polarization to M2, thereby relieving the immunoepidemic suppression, strengthening the immune response, and killing tumors [47].

5.1.6 Hemiterpenes

Atractylodes has a long history of clinical application, first in the "Shennong Materia Medica", and has been used in many classic recipes in ancient and modern times. Because of its effect of strengthening the spleen and nourishing qi, dryness, dampness and water, it is often used to treat spleen and stomach diseases. Atractylodes internal lipid II. is one of the main active ingredients retained under conventional decoction of Atractylodes [48]. The study showed that atractylactone II. inhibited the proliferation and migration of gastric cancer by reducing the activity of p-PI3K, inducing the polarization of TAMs to M1 type [49].

5.1.7 Glycyrrhizinate

Licorice is a herb widely used in food and medicine, and the triterpenoid glycyrrhizic acid isolated and extracted from licorice can produce glycyrrhizinic acid (GA) through human metabolism. As the main metabolite of glycyrrhizic acid, GA has strong pharmacological activities, including anti-inflammatory, hepatoprotective, antiviral, antioxidant, anti-allergic, etc. Magnesium isoglycyrrhizate (MgIG) is a fourth-generation formulation of glycyrrhizic acid, which has better efficacy and fewer side effects than previous glycyrrhizic acid preparations. Research has shown that

Magnesium isoglycyrrhizate can indirectly induce the secretion of tumor cells and directly regulate the polarization of TAMs to M1 in the gastric cancer microenvironment, inhibiting the growth of gastric cancer and promoting apoptosis [50].

5.1.8 Saturated fats

Palmitic acid (PA) is a saturated fatty acid that accounts for 20-30% of the body's total fatty acids and can be obtained from the diet or synthesized by the body. There is evidence that PA has the ability to regulate phenotypic switching in macrophages and has antitumor effects [51]. Studies have shown that the combination therapy of PA and IFN-γ regulates macrophage polarization through the TLR4 pathway, enhancing M1-like macrophages and reducing M2-like macrophages. In addition, the combined strategy impairs the proliferation and migration activity of GCCs in vitro and in

vivo, thereby inhibiting GC progression [52].

Table 1: Mechanisms of Chinese herbal monomers regulating the action of TAMs

Type	Ingredient	Molecular Target	Mechanism of action (TAMs polarization direction + pathway/phenotype)	Bibliography
Polysaccharides	Astragalus polysaccharide	TNF-α↑, IL-6↑, XCL10↑, iNOS↑, IL-1β↑, CD86↑, ROS↑MAPKs↑and NF-kB↑	Activation of TLR4/R0S/MAPKs/NF-kB pathway and M1↑, inhibition of cell proliferation and migration, and induction of apoptosis	[34]
Flavonoids	Diosmetin	Ki-67↓, N-cadherin↓, TRAF2↓, p-NF-κB↓, NF-κB↓	TRAF2/NF-κB, M2↓	[36]
	Flavokawain B	Bcl-2↓, Bax protein ↓, Arg-1↓, CD206↓, TGF-β1↑, SMAD4↑, TSPAN12↑	Activate TGF-β1/SMAD4 pathway, inhibit cell proliferation, promote apoptosis, and M2↓	[38]
Alkaloids	Green vine	STAT6↓, C/EBPβ↓, C/EBPβ↓, IL-6 ↓	Inhibitory CEBE/β/IL-6 Axis, M2 ↓	[40]
	Matrine	INOS↑, IFN-β↑, IL-12α↑, Arg-1↓, CD206↓, IL-10↓, Granzyme B↑, TNF-α↑, Perforation ↑, D-1↓, Tim-3↓, Lag-3↓	TLR4/IRF3 Axis, M1↑, M2↓	[41]
	Paclitaxel	VEGF-A↓, VEGF-CmRNAs↓, IL-10↓, Arg-1↓, CD163mRNAs↓	TLR4/NF-κB, p65, M1↑	[42]
Triterpenes	Ganodermanontriol	Arg-1↓, IL-10↓, CD206↓	STAT6, M2 ↓	[44]
	Betulinic acid	TGF-β1↓, OCT4↓, IL-6↓	Inhibit TGF-β/Smad2/3 signaling, M1↑, M2↓	[46]
Saponins	Ginsenoside Rg3	iNOS↑, IL-12↑, Arg1↓	M1↑, M2↓, Induce apoptosis and autophagy	[47]
Hemiterpenes	Atractylodes II	CD86↑, TNF-α↑, HLA-DRA↑, CD80mRNA↑, CD206↓, IL-6↓, TGFβmRNA↓	p-PI3K, M1↑, M2↓	[49]
Glycyrrhizinate	Magnesium isoglycyrrhizate	IL6↓, TGF-β↓, TNF-α↓, VEGF-A↓, IL10↓, IL12↑	NF-κB, M2→M1	[50]
Saturated fats	Palmitic acid	iNOS↑, IL-6↑, TNF-α↑, IL-1β↑, CD206↓, IL-10↓, ARG-1↓, IL–6↓	TLR4 pathway, M1↑, M2↓	[52]

Note: ↑ Increase; ↑ Decrease; → Reverse.

5.2 Traditional Chinese Medicine Compound and Its Active Ingredients

5.2.1 Strengthen the spleen and increase qi

The spleen and nourishing prescription is an empirical prescription created by Professor Liu Shenlin, a famous Chinese medicine doctor in the country, based on decades of clinical experience, according to the core pathogenesis of gastric cancer "spleen deficiency and stasis", and is a commonly used clinical prescription in Jiangsu Provincial Hospital of Traditional Chinese Medicine. Qingmin Sun et al. found that it can inhibit the activity of PI3Kγ, affect the expression of p-C/EBP-β and p-NF-κB, promote the reversal of TAMs from M2 to M1, and promote the apoptosis of gastric cancer cells [53]. Shanshan Zheng et al. found that the spleen and nourishing formula degraded gastric cancer cells IDH1 by regulating TAM exosomes, reducing the circulating metabolism level of tricarboxylic acids in gastric cancer cells, promoting ROS accumulation, inducing apoptosis of gastric cancer, and then inhibiting the development of gastric cancer [54].

Yiqi and spleen and blood stasis are another clinical experience prescription of Professor Shenlin Liu. Based on the pathogenesis of gastric cancer patients, Professor Liu used the theory of "strengthening the spleen and qi, eliminating symptoms and dispersing knots", to create a prescription for nourishing qi, strengthening the spleen and reducing blood stasis. Jian Wu et al. found that this formula has an inhibitory effect on gastric cancer, and can be synergistic with 5-FU to further regulate the expression of N-cadherin, E-cadherin, Snail, Slug and Vimentin in tumor tissue, promote the reversal of the M2 phenotype to M1 phenotype of TAMs in gastric cancer, inhibit the growth of gastric cancer, and improve the epithelial mesenchymal transformation of gastric cancer [55]. Another study by Jian Wu et al. found that after the combination of this formula with 5-Fu, it can significantly reduce the expression of snail, N-cadherin and slug genes/proteins in tumor-bearing mice, reduce the epithelial mesenchymal transformation of tumors, promote the reversal from M2 macrophages to M1 type, inhibit lung metastasis of gastric cancer, and reduce the toxic side effects of chemotherapy [56].

Clinical studies have proved that Jian pi yi qi prescription has good efficacy in the treatment of gastric cancer. Min Chen et al. showed that this prescription may reduce the number of TAMs and M2 phenotype in tumor-bearing mice through the PI3K/AKT pathway, inhibit epithelial mesenchymal transformation in tumors, and inhibit the proliferation and metastasis of transplanted tumor cells in mice [57]. Xi Zou et al. found that this prescription can regulate the CXCL12-CXCR4 axis and reduce the adhesion and invasion ability of human gastric cancer cells MGC-803 [58]. In addition, the spleen and nourishing the positive symptom can effectively inhibit the invasion, migration and adhesion ability of gastric cancer cell line MGC-803 by regulating the transcription factor Snail to affect EMT transformation [59].

Fuzheng Detoxification Formula is an in-hospital preparation used in the treatment of gastric cancer by the Department of Oncology of Guang'anmen Hospital of China Academy of Chinese Medical Sciences, which has the effects of strengthening the spleen and qi, nourishing the kidneys and generating blood, clearing away heat, detoxifying and anti-cancer. Studies have shown that Fuzheng Jiefang can reduce the expression level of CD206 in TAMs cells by regulating the P38MAPK/MK2 pathway, improve the polarization of M2 TAMs cells caused by aging CAFs, reduce immunosuppression, and inhibit the growth of gastric cancer [60]. Chengjing Zhang et al. found that this prescription can reduce the expression of TEMs cells in tumor tissue, regulate the expression of Argl, IL-10, VEGF, TNF-α, and COX-2, inhibit the formation of tumor blood vessels, inhibit the progression of gastric cancer, and reduce the recurrence and metastasis rate [61].

5.2.2 Activate blood circulation and dissolve blood stasis

E`Lian Granules is the experience of Professor Cai Gan, a famous old Chinese medicine doctor in China, in the

treatment of gastric precancerous lesions and gastric cancer, Early clinical trials have shown that this prescription can effectively alleviate patients' clinical symptoms, reduce the pathological progression of gastric mucosa, and improve patients' quality of life. Studies have shown that this prescription can inhibit the M2 polarization of tumor-associated macrophages (TAMs) through the NF-κB signaling pathway, thereby weakening the precancerous lesions of the stomach in rats and reducing the occurrence and progression of gastric cancer [62].

Table 2: Mechanisms of Chinese medicine compounding on the regulation of TAMs

Efficacy	Compound	molecular target	Mechanism of action	Bibliography
Strengthen the spleen and increase qi	spleen and nourishing prescription	p-PI3Kγ↓, p-C/EBP-β↓, p-NF-κB↑, BaxProtein↑, Bcl-2Protein↓Bcl-2/BaxProtein ratio↓, Cleaved-caspase3/caspase3Protein ratio↑	M2→M1, Induce apoptosis and autophagy	[53]
	Yiqi and spleen and blood stasis	E-cadherin↑, N-cadherin↓, Vimentin mRNA↓	M1↑, M2↓	[55]
	Jian pi yi qi prescription	P-AKT↓, P-PDK↓, P-MTOR↓	PI3K/AKT, M1↑, M2↓	[57]
	Fuzheng Detoxification Formula	CD11b↓, CD206↓, P38MAPK↓, MK2↓	P38MAPK/MK2, M2↓	[60]
Activate blood circulation and dissolve blood stasis	E`Lian Granules	Arg-1↓, iNOS↓, Arg-1/iNOS↓, p-p65↓, p65↓, p-IκBα↓, IκBαmRNA↑	NF-κB, M2↓	[62]
Clears heat and detoxifies	Qing Heat Elimination Fang	CD206↓, IFN-γ↓, IL-13↓, IL-4↓, TNF-α↓, miR-29a-3p↑	miR-29a-3p/HDAC4, M2↓	[63]

Note: ↑ Increase; ↑ Decrease; → Reverse.

5.2.3 Clears heat and detoxifies

Qing Heat Elimination Fang is an empirical formula explored and summarized by the Department of Oncology of the First Clinical School of Zhejiang University of Traditional Chinese Medicine after long-term clinical practice, which has the effect of clearing away heat and detoxifying, dissolving phlegm and dispersing condensation. Studies have shown that the Qing Heat Elimination Fang regulates the polarization of M2 macrophages by regulating miR-29a-3p/HDAC4, reversing the polarization of the M2 phenotype, and inhibiting the growth of gastric cancer tumors, providing a unique and innovative treatment method for gastric cancer [63]. Other studies have shown that it can inhibit the expression of NF-κB protein in tumor-bearing mouse tumor tissues and play an anti-tumor angiogenesis effect [64].

5.3 New Chinese Medicine Preparation

TCM for the treatment of GC has its own unique advantages, and emerging nanodrugs can help it work better. The nanodrug delivery system can realize multi-drug delivery, delay drug resistance, promote combined application, reduce toxic side effects, enhance preoperative and intraoperative imaging guidance, thereby enhancing the efficacy, and provide a very potential solution to the shortcomings of current gastric cancer drug treatment methods, such as poor single-agent efficacy, many toxic side effects and easy drug resistance. Jing Wang et al. used paclitaxel (PTX) as a model drug and nanocrystals as the preparation form to design a new nanopreparation with high drug content, good stability and significant tumor cell targeting performance - folic acid-modified phospholipid-coated paclitaxel nanocrystals (PTXNC@FA), which have good application potential and are expected to be used to shrink tumors before surgery, increase the chance of gastric preservation, and improve the quality of life of patients after surgery [65]. Xiaohai Song et al. produced a polymer nano-drug BPGP@CAP based on enzyme-reactive branched sugar polymers to produce a polymer nano-drug that exerts a strong anti-tumor effect on GC after co-delivery of GC through the polymer drug delivery system [66]. Yaqian Zhou et al. prepared and studied polydopamine (XA)-loaded polydopamine (XA) nanoparticles (PDA-XA-NPs) with high adhesion and high bioavailability, enabling GC to be treated with oral drugs [67]. The combination of nanodrug delivery systems with naringenin can significantly improve the problems of low water solubility, low oral bioavailability and instability caused by its hydrophobicity and crystallization, and then exert its anti-inflammatory and anti-cancer pharmacological effects more effectively [68].

6. Conclusion and Outlook

TAMs play a crucial role in the occurrence and development of GC. Macrophages are induced into the tumor microenvironment to become TAMs, and are regulated by TME to polarize into M1 and M2 types. The secretion of inflammatory mediators, phagocytosis and killing of target cells by M1 macrophages have a strong indirect and direct killing effect on gastric cancer cells, and their high infiltration in tumor tissues is often associated with a better prognosis. M2 macrophages participate in immunomodulation, angiogenesis, and promote tumor growth by expressing immune checkpoint ligands of T cells and releasing inhibitory cytokines. The associated phenotypes of regulated, reversed, and depleted TAMs are considered to be potential directions for the treatment of gastric cancer. As one of the effective means of treating GC, traditional Chinese medicine can regulate the phenotype of TAMs, reverse M2 TAMs to M1 and deplete M2 TAMs, thereby inducing autophagy and apoptosis of tumor cells and inhibiting their growth progress. Although the current research has achieved certain results, there are still great shortcomings and room for improvement in the research related to the regulation of TAMs in traditional Chinese medicine: (1) Experimental research is not in-depth enough: At present, most of the mechanisms of action of traditional Chinese medicine drugs focus on affecting the polarization of TAMs, and there are few studies on whether it affects the recruitment, infiltration, metastasis, etc. of macrophages in the tumor microenvironment, and whether it affects the formation of tumor microenvironment. (2) There are few drug-pair compatibility studies: At present, the research on the regulation of TAMs in traditional Chinese medicine is mainly based on traditional Chinese medicine monomers, and there are few compounds of traditional Chinese medicine. Due to the large number of compound drugs and the difficulty of matching, there are few studies on drug compatibility. (3) Difficulty in extracting active

ingredients of traditional Chinese medicine: At present, most of the effective methods of traditional Chinese medicine for the treatment of GC are compound preparations, and multi-flavored traditional Chinese medicine is compatible to form compound formulas, with a variety of preparation forms. Its components are mixed, which is difficult to effectively extract and accurately study, so related research is still restricted. (4) There are few studies on traditional Chinese medicine compounds: At present, most of the research on the treatment of GC by traditional Chinese medicine compounds focuses on strengthening the spleen and nourishing qi, and there are few studies on compounds related to other functions. (5) There is little research on new preparations of traditional Chinese medicine: nanodrugs can solve tumor targeting problems and participate in immune synergy due to their own advantages, bringing hope for tumor immunotherapy [69]. Traditional Chinese medicine monomers and their active ingredients are expected to be combined with nanodrugs to create new nanopreparations of traditional Chinese medicine, which can better target and accurately treat tumors. As medical workers, we still need to continue to conduct in-depth research, explore more directions, and start from more dimensions to optimize the treatment plan of GC, improve the prognosis and quality of life of gastric cancer patients, and reduce the harm of the disease. At the same time, in-depth study of the role of traditional Chinese medicine in the prevention and treatment of GC is also of great significance and value.

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