Traditional Chinese Medicine Therapy for Esophageal Cancer: A Literature Review

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Abstract

Esophageal cancer (EC) is the sixth leading cause of cancer-related deaths worldwide. Western medicine has played a leading role in its treatment, but its prognosis remains unsatisfactory. Therefore, the development of effective therapies is important. Traditional Chinese medicine (TCM) has been practiced for thousands of years, and involves taking measures before diseases occur, deteriorate, and recur. Interestingly, there is growing evidence that TCM can improve the therapeutic effects in reversing precancerous lesions, inhibiting the recurrence and metastasis of EC. In this article, we review traditional Chinese herbs and formulas that have preventive and therapeutic effects on EC, summarize the application and research status of TCM in patients with EC, and discuss its shortcomings and prospects in the context of translational, evidence-based, and precision medicine.

Keywords

esophageal cancer, traditional Chinese medicine, complementary and alternative medicine, therapy, mechanism

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Introduction

There are an estimated 604000 new esophageal cancer (EC) cases and 544000 deaths each year, and the incidence and mortality rates of EC are ranked seventh and sixth in the world, respectively.¹ EC is mainly classified as esophageal squamous cell carcinoma (ESCC) or esophageal adenocarcinoma (EAC), of which ESCC accounts for about 90% with a 5-year survival rate of 10%,² and 30% to 40% of cases have local or distant metastasis once found.^{3,4} Smoking, excessive alcohol consumption, red meat, salted meat, fried food, Barrett's esophagus, gastroesophageal reflux disease, and obesity can increase the risk of EC.^{5,6} At present, EC is mainly treated by surgical resection, radio-therapy, chemotherapy, molecular targeted therapy, and immunotherapy, but the prognosis is still poor.⁷⁻⁹

Traditional Chinese medicine (TCM) originated in ancient China. It has experienced different stages of prosperity, decline, and revival (Figure 1) during over 5000s of years of medical practice. The main guiding concept of "seeking the root of the disease (Zhibing Qiuben)" is from a classic ancient book named "Huang Di Nei Jing." Under the overall and individualized concept,^{10,11} TCM teaches that *qi*, *xue*, *yin*, and *yang* are the basic materials to maintain

human life activities, and the occurrence of diseases is due to their imbalance. The body is like a "soil environment," and cancer cells are like "seeds." TCM not only can directly eliminate carcinogenic "seeds,"¹² but also improve the "soil environment" to make the body no longer suitable for "seed" growth.¹³⁻¹⁶ Maintaining esophageal patency (*tongjiang* in TCM) is beneficial in the therapeutic method. The key pathological factors of EC are deficiency (*xu*), stasis (*yu*), heat (*re*), and poison (*du*). Therefore, therapies such as replenishing *qi*, promoting blood circulation, invigorating the spleen and kidney, regulating *qi* and phlegm, and clearing heat and toxic substances are needed. Compared with Western medicine, TCM plays a supplementary and alternative role in EC, which has gained a satisfactory effect and

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Figure 1. The prosperity, decline, and revival of TCM. TCM sprouted in Xia dynasty, gradually developed and flourished in Tang, Song, Ming, and Qing dynasties. In 1912, TCM declined because of the impact of western medicine. Until 1950, TCM gradually revived. In 2003, TCM achieved good results in the fight against atypical pneumonia, which made it come to the fore. In 2015, the Nobel Prize of artemisinin research promoted TCM internationalization process. During COVID-19 in 2019, TCM's advantages became even more apparent in improving symptoms and reducing mortality, which has received extensive international attention and recognition.

attracted widespread attention.¹⁷⁻²¹ In this article, we review the application status and mechanistic research of TCM and discuss its shortcomings and prospects in the context of integrated medicine, precision medicine, and evidence-based medicine.²²⁻²⁶

Ancient Classical Formulas for the Treatment of EC

Although EC itself was not described in ancient China, TCM was applied to improve clinical symptoms such as dysphagia.^{27,28} Meanwhile, ancient Chinese herbal formulas gradually developed from single herbs to multiple drugs (formulas). Some ancient classical formulas have preventive and therapeutic effects on EC. For example, Liu-Jun-Zi-Tang²⁹ and Sha-Shen-Mai-Dong-Tang,³⁰ which supplement *qi* and nourish *yin*, can inhibit the growth of EC cells. Xiao-Chai-Hu-Tang³¹ and Qi-Zhu-Yu-Ling-Tang³² soothe the liver and regulate *qi*. They can prevent EC cell proliferation and improve clinical symptoms. Bu-Qi-Yun-Pi-Tang³⁰ and Liu-Wei-Di-Huang-Wan³³ are classical prescriptions for invigorating the spleen and tonifying the kidney. They can prevent the progression of EC. Formulas

such as Qi-Ge-San³⁴ and Tong-You-Tang³⁰ remove phlegm, dampness, blood stasis, and poisonous substances, which can strengthen the body to resist disease (Table 1).

Modern Application and Research of TCM in EC

TCM for Prevention of EC Occurrence and Metastasis

EC mostly develops from esophageal squamous epithelial dysplasia,⁴⁷ and chronic inflammatory and mucosal hyperplasia are important factors for the gradual development of the esophageal epithelium into dysplasia.^{48,49} Clinical studies have shown that TCM has promise in preventing EC. For example, a randomized controlled trial showed that Fu-Fang-Cang-Dou-Wan (Atractylodes Rhizome, Radix Sophorae Tonkinensis, and green tea) can reduce the 2-year cancer rate, cellular DNA content, and proliferation index of patients with severe hyperplasia of esophageal epithelial cells.⁵⁰

Randomized controlled trials showed that Kang-Ai-Yi-Pian (Dioscorea Bulbifera L, Polygonum Bistorta L,

Formulas	Herbs	TCM therapeutic principles	Reference
Er-Chen-Tang	Banxia (Pinellia Ternata), Chenpi (Citrus Reticulata), Fuling (Tuckahoe), Gancao (Licorice)	Invigorating spleen and draining dampness	Tai-ping-hui-min-he-ji-ju- fang ³⁵
Si-Wu-Tang	Shudihuang (Rehmanniae Radix Praeparata), Baishao (Paeoniae Radix Alba), Danggui (Angelicae Sinensis Radix), Chuanxiong (Chuanxiong Rhizoma)	Tonifying yin and blood	Xian-shou-li-shang-xu- duan-mi-fang ³⁶
Xiao-Chai-Hu-Tang	Chaihu (Radix Bupleuri), Gancao (Licorice), Banxia (Pinellia Ternata), Renshen (Panax Ginseng C. A. Mey), Huangqin (Scutellariae Radix), Shengjiang (Zingiber Officinale Roscoe), Dazao (lujubae Fructus)	Soothing liver and relieving depression	Shang-han-lun ³⁷
Ban-Xia-Xie- Xin-tang	Banxia (Pinella Ternata), Huanglian (Coptidis rhizoma), Huangqin (Scutellariae Radix), Ganjiang (zingiberis Rhizoma), Gancao (Licorice), Dazao (Jujubae Fructus), Renshen (Panax Gineene C A Mev)	Harmonize liver and spleen, acrid opening and bitter downbearing	Shang-han-lun ³⁷
Xuan-Fu-Dai- Zhe-Tang	Zursung Community), Banxia (Pinellia Ternata), Gancao (Licorice), Renshen (Panax Ginseng C. A. Mey), Daizheshi (Ruddle ocher), Shengjiang (Zingiber Officinale Roscoe), Dazao (Juinhae Furrus)	Nourishing <i>qi,</i> harmonizing stomach, and depressing <i>qi</i>	Shang-han-lun ³⁷
Sheng-Yang- Yi-Wei-Tang	Huangqi (Hedyarum Multijugum Maxim), Banxia (Pinellia Ternata), Renshen (Panax Ginseng Luangqi (Hedyarum Multijugum Maxim), Banxia (Pinellia Ternata), Renshen (Paeoniae Radix C. A. Mey), Gancao (Licorice), Fangfeng (Saposhnikoviae Radix), Baishao (Paeoniae Radix Alba), Qianghuo (Notopterygii Rhizoma Et Radix), Duhuo (Radix Angelicae Biseratae), Chenpi (Citrus Reticulata), Fuling (Tuckahoe), Zexie (Oriental Waterplantain Rhizome), Chaihu (Radix Bupleuri), Baizhu (Atractylodes macrocephala Koidz), Huanglian (Coptidis	Tonifying spleen and stomach, clearing heat, and draining dampness	Pi-wei-lun ³⁸
Tong-You-Tang	Taoren (Rehman), Taoren (Persicea Semen), Honghua (Carthami Flos), Shengdihuang (Rehmannia glutinosa), Shudihuang (Rehmanniae Radix Praeparata), Danggui (Angelicae Sinensis Radix), Gancao (Licorice) Shenema (Cimicifiusae Rhizona)	Nourishing <i>yin</i> and blood, and promoting blood circulation	Pi-wei-lun ³⁸
Sha-Shen-Mai- Dong-Tang	Shaken (Root of straight ladybel), Yuzhu (Polygonati Odorati Rhizoma), Gancao (Licorice), Sangye (Mori Follum), Maidong (<i>Ophiopogon japonicus</i>), Baibiandou (Lablab Semen Album), Tianhuafen (Trichosanchis Radix)	Tonifying lung and stomach, nourishing <i>qi</i> and <i>yin</i>	Wen-bing-tiao-bian ³⁹
Qi-Ge-San	Shashen (Root of straight ladybell), Danshen (Radix Salviae), Fuling (Tuckahoe), Chuanbeimu (Fritiliariae Irrhosae Bulbus), Yujin (Curcumae Radix), Sharen (Amomum Aurantiacum H. T. Tsai Et S. W. Zhao), Heve (Folium Nelumbinis)	Nourishing <i>qi</i> and <i>yin</i> , relieving depression, and removing phleem	Yi-xue-xin-wu ⁴⁰
Tong-Qiao- Huo-Xue-Tang	Chishao (Radix Paeoniae Rubra), Chuanxiong (Chuanxiong Rhizoma), Taoren (Persicae Semen), Dazao (Jujubae Fructus), Honghua (Carthami Flos), Laocong (Allii Fistulost Bulbus), Sheneijane (Zineiber Officinale Roscoe), Shexiane (Musk)	Promoting blood circulation and dissolving stasis	Yi-lin-gai-cuo ⁴¹
Liu-Wei-Di-Huang- Wan	Shudihuang (Rehmanniae Radix Praeparata). Shanyurou (Cornus Officinalis), Mudanpi (Cortex Moutan), Shanyao (Rhizoma Dioscoreae), Fuling (Tuckahoe), Zexie (Oriental Waterplantain Rhizome)	Nourishing <i>yin</i> and tonifying kidney	Xiao-er-yao-zheng-zhi-jue ⁴²
Bu-Zhong- Yi-Qi-Tang	Huangqi (Hedysarum Multijugum Maxim), Baizhu (Atractylodes macrocephala Koidz), Chenpi (Citrus Reticulata), Shengma (Cimicifugae Rhizoma), Chaihu (Radix Bupleuri), Renshen (Panax Ginsens C. A. Mev). Gancao (Licorice). Danagui (Anvelicae Sinensis Radix)	Invigorating spleen and Stomach, and tonifying qi	Nei-wai-shang-bian- huo-lun ⁴³
Huang-Lian-Jie- Du-Tang	Huanglian (Coptidis rhizoma), Huangqin (Scutellariae Radix), Huangbai (Phellodendri Chinrasis Cortex), Zhizi (Gardeniae Fructus)	Clearing heat and poison, and draining dampness	Zhou-hou-bei-ji-fang ⁴⁴
Sheng-Xian-Tang	Huangqi (Hedysarum Multijugum Maxim), Zhimu (Anemarrhenae Rhizoma), Chaihu (Radix Bupleuri), Jiegeng (Platycodon Grandiflorus), Shengma (Cimicifugae Rhizoma)	Tonifying lung, nourishing <i>qi</i> , and elevating <i>qi</i>	Yi-xue-zhong-zhong- can-xi-lu ⁴⁵
Wen-Dan-Tang	Banxia (Pinellia Ternata), Zhuru (Caulis bambusae in taeniis), Zhishi (Aurantii Fructus Immaturus), Chenpi (Citrus Reticulata), Gancao (Licorice), Fuling (Tuckahoe)	Regulating <i>qi</i> , harmonizing stomach, and removing phlegm	San-yin-ji-yi-bing- zheng-fang-lun ⁴⁶

Table I. Ancient Classical Formulas for the Treatment of EC.

Rhizoma Menispermi, Selfheal, Dahurian Patrinia Herb, and Cortex Dictamni) could reduce the transformation rate of severe esophagus epithelial cell hyperplasia by 52.2% and 47.3% at 3 and 5 years, respectively.⁵¹ Acrid opening and bitter down-bearing herbs (such as Pinellia Ternata, Scutellariae Radix, Coptidis Rhizoma, Zingiberis Rhizoma, Panax Ginseng C. A. Mey, Licorice, Jujubae Fructus) not only had a reversal effect on esophagus mucosal dysplasia (2-month and 1-year cure rates were 71.7% and 70.0%, respectively), but also improved clinical symptoms.⁵² The total effective rate of Qing-Re-Huo-Xue-He-Ji (Hedysarum Multijugum Maxim, Angelicae Sinensis Radix, Radix Paeoniae Rubra, Sophora Tonkinensis, Radix Sophorae Flavescentis, Hawthorn, Fructus Akebiae, *Tianlong*) on gastroscopy pathology in patients with esophageal mucosal dysplasia after 3 months of intervention was 82.76% (24/29).⁵³ In a non-randomized controlled trial Jia-Wei-Liu-Wei-Di-Huang-Tang (Rehmanniae Radix Praeparata, Cornus Officinalis, Rhizoma Dioscoreae, Oriental Waterplantain Rhizome, Tuckahoe, Cortex Moutan, Barbed Skullcap Herb, Hedvotis Diffusa, Prunella Asiatica, Oyster Shell) was used to treat patients with esophageal epithelial hyperplasia (mild, moderate and severe) for 3 to 6 months; the total effective rate of gastroscopic pathology was 94.2% (49/52), with no cancerous findings.⁵⁴ It can be seen that TCM has anti-EC potential and has direct inhibitory and reversal effects on esophageal epithelial hyperplasia. In addition, in terms of prevention of recurrence and metastasis of EC by TCM herbs, a non-randomized controlled trial reported that Jia-Wei-Qi-Ge-San (Salvia miltiorrhiza, Root Of Straight Ladybell, Radix Curcumae, Amomum Villosum, Poria Cocos, Fritillaria thunbergii, Radix Scrophulariae, Rehmannia Glutinosa, Ophiopogon japonicus, lotus leaf, and floating wheat) could reduce the 1-year recurrence and metastasis rates by 9.4% and 19.6% (respectively), prolong disease-free-survival, and improve the quality of life of patients after radical resection of EC.55

TCM Combined With Modern Medicine for EC Therapy

Surgery and chemoradiotherapy, as the main treatments for EC, have toxic side effects and affect the daily quality of life of patients.⁵⁶⁻⁵⁹ It is reported that TCM combined with Western medicine can improve the efficacy of such treatments and prolong survival.⁶⁰ For instance, 3 randomized controlled trials have shown that Bu-Yi-San-Jie-Yin can improve postoperative symptoms of fatigue, slurred speech, shortness of breath, fatigue, and spontaneous sweating and the levels of immune and nutritional indicators (P < 0.05) after EC radical resection.⁶¹ Xiao-Ai-Ping combined with S-1 and cisplatin could improve the response rate and disease control rate, prolong progression-free-survival (PFS) and overall survival (OS) of patients

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with advanced EC compared with chemotherapy alone.⁶² Concurrent chemoradiotherapy combined with Qing-Fei-Qu-Yu-Tang in patients with advanced EC could reduce the incidence of radiation pneumonitis and radiation lung damage and improve the survival and quality of life of patients (P < .05).⁶³ A retrospective clinical study determined that chemoradiotherapy and β -elemene can improve the OS, PFS, and 3-year survival of patients with ESCC, which provides a basis for the clinical application of β elemene herbs, such as Zedoary.⁶⁴

TCM Improves EC Patients' Symptoms

In patients with EC, ginseng and Astragalus Membranaceus are often used to improve appetite and fatigue. Pinellia ternata and Ruddle Ocher can improve nausea. Concha Arcae and cuttlebone are applied to improve acid heartburn and rhubarb and Areca Catechu are used to improve constipation.^{65,66} Cancer-related pain is the most common symptom in patients with advanced incurable EC, mostly secondary to dysphagia or local tumor spread.⁶⁷ Two meta-analyses and one overview of systematic reviews have shown that Compound Kushen Injection can relieve cancer-related pain, including lung cancer, EC, liver cancer, gastric cancer, and other cancers.⁶⁸⁻⁷⁰ Two randomized controlled trials showed that Nourishing Yin and Unblocking Meridians Recipe (Radix Asparagi, Radix Ophiopogonis, Radix Scrophulariae, Radix Rehmanniae, Radix Bupleuri, Fructus Aurantii Immaturus, Rhizoma Corydali, Rhizoma Cy, Radix Paeoniae, Radix Angelicae Sinensis, Radix Notoginseng, Pericarpium Citri Reticulatae Viride, Semen Persicae, Radix Glycyrrhizae) can enhance the analgesic effect of opioids.⁷¹ Aitongping Capsule (Manyleaf Paris Rhizome, pillbug, Reddish Jackinthepulpit Rhizome, Giant Typhonium Rhizome, Olibanum, immature long pepper fruit, Rhizoma corydalis and others) exerts a central analgesic effect by increasing plasma β -endorphin content and decreasing cAMP levels, and improves the quality of life to a certain extent.72

Anti-EC Mechanisms of TCM

Inhibition of Cell Proliferation and Induction of Cell Senescence

Aberrant cell proliferation is a hallmark of cancer.⁷³ Studies have shown that lupeol acetate and baohuoside-I, the active ingredients of Cortex Periplocae Radicis, can inhibit the proliferation of EC cells by downregulating the expression of β -catenin and its downstream proteins.^{74,75} β -elemene (an active ingredient of Curcumae Longae Rhizoma) can inhibit the proliferation of ESCC by regulating hTERT expression mediated by long non-coding RNA.⁷⁶ In addition, Chinese herbal medicines and their active ingredients,



Figure 2. Mechanism of TCM against EC.

such as Momordicae Semen (*Mubiezi*), curcumin (an active ingredient of Curcumae Longae Rhizoma) and Jia-Wei-Tong-You-Tang (Persicae Semen, Carthami Flos, Cimicifugae Rhizoma, Arecae Semen, Scutellariae Barbatae Herba, and *Hedyotis Diffusae* Herba) can also inhibit cell proliferation to exert anti-EC effects.⁷⁷⁻⁷⁹ The mechanism of action of TCM against EC is detailed in Figure 2.

Senescence is an irreversible state of cell cycle arrest. Accumulating evidence suggests that the induction of cellular senescence is an effective method in cancer therapy.^{80,81} Interestingly, studies have shown that gypenoside L (a saponin isolated from *Gynostemma pentaphyllum*) could promote aging-related cytokines (such as IL-1 α , IL-6, TIMP-1, CXCL-1, and CXCL-2) and aging-related cyclins (p21 and p27) by increasing the activity of SA- β galactosidase, resulting in cells arrested in the S phase. Coincidentally, pathways regulating cellular senescence have an impact on the development of ESCC. Among them, p38 MAPK activation may be a key link during malignant carcinogenesis and transformation of ESCC 82; the MAPK/ ERK pathway can inhibit the proliferation and invasion of ESCC cells by targeting MAP3K9.83 NF-KB signaling is overactivated in ESCC cells, and its inhibition leads to decreased cell growth and cell proliferation.⁸⁴ Another

study showed that gypenoside L can induce senescence in EC cells by activating the p38, ERK, MAPK, and NF- κ B pathways.⁸⁵

Induction of Autophagy and Apoptosis

Autophagy is a mechanism by which cellular materials are degraded by lysosomes. It has opposing and context-dependent roles in cancer, and is proposed as a therapeutic approach for tumors.⁸⁶ Ursolic acid can inhibit the growth and metastasis of EC cells by reactive oxygen species (ROS)-mediated autophagy.⁸⁷ Echinatin (an active ingredient of licorice), dihydroartemisinin (an active ingredient of Artemisinin), and ginsenoside Rk3 (an active ingredient of ginseng and Notoginseng Ginseng) can induce autophagy and exert anti-EC effects by inhibiting the Akt/mTOR signaling pathway.⁸⁸⁻⁹⁰

Moreover, apoptosis, a biological process in which multiple factors induce programed cell death, has also been shown to be a promising effective way to prevent cancer growth and progression.⁹¹ Studies have shown that TCM can induce apoptosis to inhibit EC progression. For example, Jaridonin, the active ingredient of *Isodon rubescens*, has been reported to induce apoptosis by inducing ROS Hexandrum Root, has an apoptotic effect on ESCC cells by increasing ROS levels and inducing the JNK/p38 signaling pathway.⁹³ The PI3K/AKT/mTOR signaling pathway is key in the oncogenic process of ESCC and has potential value for prognostic markers and treatment of ESCC.⁹⁴ Matrine (an active ingredient of *Sophora flavescens*), casticin (the main active ingredient of *Vitex* spp.), oridonin (an active ingredient of Rabdosia Rubescens), and ginsenoside Rg5 (a major active ingredient of red ginseng) can induce apoptosis through the BID-mediated mitochondrial pathway,⁹⁵ the JNK signaling pathway,⁹⁶ the PI3K/ AKT/mTOR and Ras/Raf pathways,⁹⁷ and the PI3K/PKB signaling pathway,⁹⁸ respectively.

Inhibition of Metastasis and Angiogenesis

Metastasis is the real cause of malignant tumor characteristics⁹⁹ and causes 90% of cancer-related deaths.¹⁰⁰ Studies have shown that berberine (an active ingredient of Coptidis Rhizoma) can inhibit EC cell migration by downregulating the expression of CCR7 and CXCR4.¹⁰¹ Curcumin (an active ingredient of Curcumae Longae Rhizoma), can inhibit the formation of the lipid raft-associated Rac1/PI3K/ Akt signaling complex to improve Sdf-1 α induced EC cell invasion.¹⁰² In addition, epithelial-to-mesenchymal transition (EMT) is a key factor in the regulation of tumor cell metastasis.¹⁰³ Interestingly, Qi-Ge-San and Cinobufotalin injection can inhibit EMT by inhibiting the expression of Gas6/axl and the activation of the Snail/Twist pathway, respectively.^{104,105}

Angiogenesis is a necessary condition for tumor growth and metastasis. Inhibiting angiogenesis and tumor vascular supply can contribute to the control of tumor cell growth and metastasis.¹⁰⁶ Scholars have speculated that the overexpression of PDGFR- α is associated with tumor-related angiogenesis and progression.¹⁰⁷ The PDGFR- α expression rates of EAC and ESCC are 91% and 100%, respectively. VEGF expression is closely related to angiogenesis, disease progression, and prognosis in ESCC.^{108,109} Studies have shown that Qi-Ge-San¹¹⁰ and Liu-Jun-Zi-Tang¹¹¹ can reduce cellular angiogenesis. Among them, Qi-Ge-San may exert anti-EC effects by downregulating EGFR, PDGFR, VEGF, and PLC- γ 1 expression.¹¹²

Improving Drug Resistance

Drug resistance is a common phenomenon during cancer chemotherapy and is one of the causes of poor prognosis. The development of multidrug resistance in tumor cells is closely related to the expression of P-gp and MRP.^{113,114} In addition, TCM and its active ingredients, such as Cinobufotalin Injection and curcumin, can improve drug resistance and enhance the sensitivity of EC cells to chemotherapeutic drugs by inhibiting the expression of P-gp and MRP.^{105,115} Luteolin may also reverse multidrug resistance by inhibiting the FAK/Src/PI3K/Akt signaling pathway in ESCC cells.¹¹⁶ Studies have shown that downregulation of microRNA-138 expression is associated with cell resistance.^{117,118} Survivin is a target gene of microRNA-138, and EC cancer cells with elevated survivin protein expression are drug-resistant. α -Solanine (an active ingredient of Solanum Nigrum Linn) can promote the chemosensitivity of EC cells to 5-fluorouracil/cisplatin by upregulating microRNA-138 expression and downregulating survivin expression.¹¹⁹

Regulation of Immune Function

Immune escape, triggered by T cell reduction or dysfunction, is one of the mechanisms by which cancer cells avoid the immune system.¹²⁰ Studies have shown that Compound Radix Sophorae Flavescentis Injection¹²¹ (Radix Sophorae Flavescentis, Radix Polygoni Multiflori, Trogopterus Dung) can improve the levels of CD3+, CD4+, and CD4+/CD8+ T cells and strengthen cellular immune function in elderly EC patients undergoing chemoradiotherapy. Zhenqi Fuzheng Granules¹²² can increase the levels of CD3⁺, CD4⁺, and CD8⁺ T cells and enhance the immune capacity of EC patients. In addition, mature dendritic cells (DCs), as antigen-presenting cells in the immune system, have an ultra-strong ability to acquire antigens and present them to T cells.¹²³ Qi-Ge-San can reduce the EC inhibitory effect on DCs by inhibiting the STAT3 signaling pathway.¹²⁴ At the same time, Treg cells are also involved in the development of tumors by inhibiting tumor immunity.¹²⁵ A study has shown that Lian-Hua-Shen-Jia-Fang (Forsythiae Fructus, Trichosanthis Radix, Codonopsis Radix, and Cortex Periplocae) can slow down the process of precancerous esophageal lesions by inhibiting the expression of Treg cells.126

Conclusions

The prognosis of patients with advanced EC remains unsatisfactory. The 5-year survival rate is approximately 5%.¹²⁷ With more EC-relevant clinical trials being carried out in recent years, targeted and non-targeted immunotherapies have been gradually developed. It is expected that these therapies combined with surgery, radiotherapy, and chemotherapy, will be the future of multimodal treatment for EC.^{128,129} However, drug resistance in targeted immunotherapy is an unavoidable and complicated problem. TCM plays an important role in immune and targeted therapies, such as synergism and attenuation, improvement of drug sensitivity, and even reversal of drug resistance. For example, studies have demonstrated that TCM has unique advantages in reversing the acquired drug resistance of EGFR tyrosine kinase inhibitors in lung cancer.¹³⁰ Accordingly, whether TCM plays a positive role in reversing targeted and immunotherapy drug resistance in EC treatment remains a valuable problem to be solved. Moreover, it is worth exploring the mechanisms of TCM in the EC microenvironment and its effect on oral and intestinal flora.

TCM has shown great potential for the treatment of EC. It is well-suited to the complex mechanism of EC because of its natural complexity. However, there is also a wider dilemma: due to the multiple targets and pathways of TCM, the anti-EC mechanisms of most Chinese herbs have not been fully elucidated. It is necessary to explore regulatory networks associated with TCM mechanisms with the help of multidisciplinary, large-sample, and multi-omics techniques. Meanwhile, TCM is at a disadvantage in setting clinical pathways and guidelines for EC due to the lack of high-quality evidence-based studies, which greatly limits the application and development of TCM. In the future, high-quality randomized clinical trials with larger sample sizes across multiple centers need to be performed to improve this.

Author Contributions

LC and XW conceived the work. LC, XW, and GZ wrote and drafted the manuscript. LC, XW, GZ, and JL discussed and edited the manuscript. SL, HW, JW, and TL assisted in revising the second edition. JL funded the study. All authors read and approved the final version of the manuscript.

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