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 604,000 new esophageal cancer (EC) cases and 544,000 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, radiotherapy, 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 (tongji-ang 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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Integrative Cancer Therapies attracted widespread attention.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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-Tang\textsuperscript{29} and Sha-Shen-Mai-Dong-Tang,\textsuperscript{30} which supplement \textit{qi} and nourish \textit{yin}, can inhibit the growth of EC cells. Xiao-Chai-Hu-Tang\textsuperscript{31} and Qi-Zhu-Yu-Ling-Tang\textsuperscript{32} soothe the liver and regulate \textit{qi}. They can prevent EC cell proliferation and improve clinical symptoms. Bu-Qi-Yun-Pi-Tang\textsuperscript{30} and Liu-Wei-Di-Huang-Wan\textsuperscript{33} are classical prescriptions for invigorating the spleen and tonifying the kidney. They can prevent the progression of EC. Formulas such as Qi-Ge-San\textsuperscript{34} and Tong-You-Tang\textsuperscript{30} 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,\textsuperscript{37} and chronic inflammatory and mucosal hyperplasia are important factors for the gradual development of the esophageal epithelium into dysplasia.\textsuperscript{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.\textsuperscript{50}

Randomized controlled trials showed that Kang-Ai-Yi-Pian (Dioscorea Bulbifera L, Polygonum Bistorta L,
Table 1. Ancient Classical Formulas for the Treatment of EC.

| 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 (Jujuabae Fructus) | Soothing liver and relieving depression          | Shang-han-lun[^37] |
| Ban-Xia-Xie-Xin-tang | Banxia (Pinellia Ternata), Huanglian (Coptidis rhizoma), Huangqin (Scutellariae Radix), Gancao (Licorice), Dazao (Jujuabae Fructus), Renshen (Panax Ginseng C. A. Mey) | Harmonize liver and spleen, acrid opening and bitter downbearing | Shang-han-lun[^37] |
| Xuan-Fu-Dai-Zhe-Tang | Xuanfuhua (Inulae Flos), Banxia (Pinellia Ternata), Gancao (Licorice), Renshen (Panax Ginseng C. A. Mey), Daizheshi (Ruddle ocher), Shengjiang (Zingiber Officinale Roscoe), Dazao (Jujuabae Fructus) | Nourishing qi, harmonizing stomach, and depressing qi | Shang-han-lun[^37] |
| Sheng-Yang-Yi-Wei-Tang | Huangqi (Hedysarum Multijugum Maxim), Banxia (Pinellia Ternata), Renshen (Panax Ginseng C. A. Mey), Gancao (Licorice), Fangfeng (Saposhnikoviae Radix), Baishao (Paeoniae Radix Alba), Qianghuo (Notopterygyi Rhizoma Et Radix), Duhuo (Radix Angelicae Biserratae), Chenpi (Citrus Reticulata), Fuling (Tuckahoe), Zexie (Oriental Waterplantain Rhizome), Chaihu (Radix Bupleuri), Baizhu (Atractylodes macrocephala Koidz), Huanglian (Coptidis rhizoma), | Tonifying spleen and stomach, clearing heat, and draining dampness | Pi-wei-lun[^38] |
| Tong-You-Tang     | Taoren (Persicæ Semen), Honghua (Carthami Flos), Shengdihuang (Rehmannia glutinosa), Shudihuang (Rehmanniae Radix Praeparata), Danggui (Angelicae Sinensis Radix), Gancao (Licorice), Shengma (Cimicifugae Fuguea) | Nourishing yin and blood, and promoting blood circulation | Pi-wei-lun[^38] |
| Sha-Shen-Mai-Dong-Tang | Shashen (Root of straight ladybell), Yuzhu (Polygonati Odotari Rhizoma), Gancao (Licorice), Sangye (Mori Folium), Madong (Ophiopogon Panisus), Baihoutou (Lablab Semen Album), Tianhuafen (Trichosanthis Radix) | Tonifying lung and stomach, nourishing qi and yin | Wen-bing-tiao-bian[^19] |
| Qi-Ge-San         | Shashen (Root of straight ladybell), Danshen (Radix Salviae), Fuling (Tuckahoe), Chuanbeimu (Fritillariae Irideae Bulbus), Yujin (Curcumae Radix), Shanren (Amomum Aurantiacum H. T. Tsai Et S. W. Zhao), Heye (Folium Nelmabini) | Nourishing qi and yin, relieving depression, and removing phlegm | Yi-xue-xin-wu[^40] |
| Tong-Qiao-Huo-Xue-Tang | Chishao (Radix Saposhnikoviae Rubra), Chuanxiong (Chuanxiong Rhizoma), Taoren (Persicae Semen), Dazao (Jujuabae Fructus), Honghua (Carthami Flos), Laocang (Alii Fistulost Bulbus), Shengjiang (Zingiber Officinale Roscoe), Shexiang (Mush) | Promoting blood circulation and dissolving stasis | Yi-lin-gai-cuo[^41] |
| Liu-Wei-Di-Huang-Wan | Shudihuang (Rehmanniae Radix Praeparata), Shanyourou (Coronis Officinalis), Mudanpi (Cortex Moutan), Shanyao (Rhizaoma Dioscoreae), Fuling (Tuckahoe), Zexie (Oriental Waterplantain Rhizome) | Nourishing yin and tonifying kidney | Xiao-er-yao-zeng-zhi-jue[^42] |
| Bu-Zhong-Yi-Qi-Tang | Huangqi (Hedysarum Multijugum Maxim), Baizhu (Atractylodes macrocephala Koidz), Chenpi (Citrus Reticulata), Shengma (Cimicifugae Fuguea), Chaihu (Radix Bupleuri), Ren (Panax Ginseng C. A. Mey), Gancao (Licorice), Danggui (Angelicae 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 Chinensis Cortex), Zhizi (Gardeniae Fructus) | Clearing heat and poison, and draining dampness | Zhou-hou-bei-jia-fang[^44] |
| Sheng-Xian-Tang   | Huangqi (Hedysarum Multijugum Maxim), Zhouli (Anemarrheneae Rhizoma), Chaihu (Radix Bupleuri), Jiegeng (Platyodon Grandiflorus), Shengma (Cimicifugae Fuguea) | Tonifying lung, nourishing qi, and elevating qi | Yi-xue-zhong-zhong-can-xi-lu[^45] |
| Wen-Dan-Tang      | Banxia (Pinellia Ternata), Zhuru (Caulis bambusae in taenias), Zhishi (Aurantii Fructus Immaturus), Chenpi (Citrus Reticulata), Gancao (Licorice), Fuling (Tuckahoe) | Regulating qi, harmonizing stomach, and removing phlegm | San-yan-ji-yi-bing-zheng-fang-lun[^46] |
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. Acrid opening and bitter down-bearing herbs (such as Pinellia Ternata, Scutellariae Radix, Cotidis Rizoma, Zingiberis Rizoma, 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. 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). 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, Hedyotis 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 gastroscopical pathology was 94.2% (49/52), with no cancerous findings. 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 thunbergi, 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.

**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. It is reported that TCM combined with Western medicine can improve the efficacy of such treatments and prolong survival. 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. 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 with advanced EC compared with chemotherapy alone. 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). 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.

**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. Cancer-related pain is the most common symptom in patients with advanced incurable EC, mostly secondary to dysphagia or local tumor spread. 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. Two randomized controlled trials showed that Nourishing Yin and Unblocking Meridians (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. Ationping Capsule (Manyleaf Paris Rhizome, pillbug, Reddish Jackinthe pulp 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.

**Anti-EC Mechanisms of TCM**

**Inhibition of Cell Proliferation and Induction of Cell Senescence**

Aberrant cell proliferation is a hallmark of cancer. 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. 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. In addition, Chinese herbal medicines and their active ingredients,
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 Diffusa* 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-1α, 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; the MAPK/ERK pathway can inhibit the proliferation and invasion of ESCC cells by targeting MAP3K9; NF-κB 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-κB 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
Inhibition of Metastasis and Angiogenesis

Metastasis is the real cause of malignant tumor characteristics and causes 90% of cancer-related deaths. Studies have shown that berberine (an active ingredient of Coptidis Rhizoma) can inhibit EC cell migration by downregulating the expression of CCR7 and CXCR4. 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 expression in EC. 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. Scholars have speculated that the overexpression of PDGFR-α is associated with tumor-related angiogenesis and progression. 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. Studies have shown that 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.

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. Studies have shown that Compound Radix Sophorae Flavescentis Injection (Radix Sophorae Flavescentis, Radix Polygoni Multiflori, Trogopterus Dung) can improve the levels of CD3+T, CD4+T, and CD4+CD8+ T cells and strengthen cellular immune function in elderly EC patients undergoing chemoradiotherapy. Zhenqi Fuzheng Granules can increase the levels of CD3+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. Qi-Ge-San can reduce the EC inhibitory effect on DCs by inhibiting the STAT3 signaling pathway. At the same time, Treg cells are also involved in the development of tumors by inhibiting tumor immunity. A study has shown that Lian-Hua-Shen-Jia-Fang (Forsythiae Fructus, Codonopsis Radix, Cortex Periplocae) can slow down the process of precancerous esophageal lesions by inhibiting the expression of Treg cells.

Conclusions

The prognosis of patients with advanced EC remains unsatisfactory. The 5-year survival rate is approximately 5%. 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. 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. Accordingly, whether TCM plays a positive role in reversing targeted and immuno-therapy 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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