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Advances in the Pathogenesis and Treatment of Esophageal Cancer with Traditional Chinese Medicine

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Abstract

Esophageal cancer (EC) is one of the common malignancies with high morbidity and mortality. Despite the effectiveness of modern medical interventions such as surgery, radiotherapy, and chemotherapy in treating EC, complications and adverse reactions still exist. Traditional Chinese medicine (TCM) plays a crucial role in preventing and treating malignant tumors by employing its unique approach based on syndrome differentiation and the concept of wholism. Numerous fundamental experiments and clinical studies have provided substantial evidence supporting the beneficial effects of TCM in managing EC. The pathogenesis of EC and the potential mechanism of TCM intervention in EC treatment are summarized in this review, aiming to offer a novel perspective for EC therapy.

Keywords: pathogenesis, esophageal cancer, traditional Chinese medicine

1. Introduction

Esophageal cancer (EC) is one of the most common malignant tumors, and according to the statistics of the World Health Organization, the incidence and mortality of esophageal cancer in the world ranks 7th and 6th, respectively [1]. Developing countries have a higher incidence of EC with over half of cases occurring in China [2]. Modern medicine offers three major treatment options for EC: surgery, chemotherapy, and radiotherapy. While effective in controlling the deterioration rate of EC, these treatments come with side effects that cannot be ignored. Surgical resection is only preferred in the early stage of EC, but due to the atypical early symptoms, most patients with EC have been metastasized and unresectable when diagnosed. Despite their obvious curative effect, radiotherapy and chemotherapy cause side effects such as digestive tract reactions, immune suppression, and organic damage related to esophagitis that seriously affect subsequent treatment and impair the life quality of patients.

An increasing body of research now demonstrates the distinct advantages of traditional Chinese medicine (TCM) in the treatment of EC, as it effectively improves the 5 year survival rate of patients by inhibiting cancer cell growth, slowing disease progression, enhancing immune function, and reducing the risk of recurrence and metastasis [3-5]. Moreover, when combined with chemo-radiotherapy, the low-toxicity TCM can enhance treatment efficacy while minimizing toxicity [6]. This review aims to discuss and summarize the pathogenesis of EC and explore potential mechanisms underlying TCM intervention to identify new targets and perspectives for EC treatment, thereby promoting the modern research of traditional Chinese medicine.

2. The Pathogenesis of EC

The pathogenesis of EC is multifactorial, involving gene mutations, tumor microenvironment, dietary habits, chronic adverse stimulation, immune inflammation, and autophagy [7-8].

2.1 Gene Mutation

In human cells, TP53 is a crucial tumor suppressor gene that inhibits the proliferation of damaged cells by initiating gene repair and inducing programmed cell apoptosis. TP53 mutations primarily consist of genetic mutations and loss of heterozygosity, which can be detected in over 50% of human tumors [9]. Notably, TP53 deletion plays a significant role in the occurrence and progression of EC, particularly esophageal adenocarcinoma, leading directly to a substantial decline in patient survival rates [10]. The mutation rate of TP53 among EC patients in Linzhou,

China was approximately 70%, while the highest incidence of mutation was France (84%) [11-12]. According to studies on esophageal cancer-related risk factors (susceptibility factors), food carcinogens may act as inducers for TP53 mutation, with benzopyrene present in cigarette smoke also implicated in this process [13].

The phosphatase and tensin homolog deleted on chromosome ten (PTEN) is the first identified gene with bispecific phosphatase activity that can inhibit tumorigenesis [14]. Some scholars argue that variations in PTEN protein expression are closely associated with the pathological characteristics of EC, exhibiting statistical significance in relation to infiltration level, differentiation degree, lymph node metastasis, and pTNM (Pathologic Tumor-Node-Metastasis) staging of EC [15-16]. Furthermore, it has been observed that patients with high expression of PTEN gene in tumor nucleus have a lower survival rate compared to those with low expression [17-19]. Therefore, the expression of PTEN gene could serve as a crucial indicator for invasion and tumor migration of EC cells. Additionally, it can be utilized to assess therapeutic efficacy and clinical prognosis.

NOTCH1, located on chromosome 9 (9q34.3), is the most frequently mutated proto-oncogene in EC cells. The protein encoded by NOTCH1 is a member of the type I transmembrane protein family and plays a regulatory role in nuclear transcription while also functioning as cell surface receptor that determines cell differentiation direction. Numerous studies have demonstrated the involvement of the NOTCH1 pathway in EC pathogenesis through epithelial-mesenchymal transition (EMT), enhancing tumor cell invasion ability. Gene sequencing of EC cells revealed frequencies of NOTCH1 mutations ranging from 8% to 21%, predominantly resulting in functional loss of the EGF-like ligand-binding region by affecting the region [20-21]. Sequencing cancer cells from 104 EC patients identified a close association between NOTCH1 mutations and degree of cell differentiation, tumor progression, lymph node metastasis, poor clinical treatment response, and shortened survival time [22].

The PIK3CA gene, encoding the p110α protein as the catalytic subunit of phosphoinositide 3-kinase, is located on chromosome 3 (region 3q26). In tumors, missense mutations in the PIK3CA gene predominantly occur in exons 9 and 20, resulting in coding protein alterations [23]. The mutation rate ranges from 2.2% to 21.0% in EC cells, affecting only a small subset of cancer cells. It has been reported that wild-type patients exhibit superior clinical therapeutic efficacy and tumor-free survival compared to those with PIK3CA exon 9 and/or exon 20 mutations, with these mutations showing some association with age, sex, tumor differentiation, smoking, and alcohol consumption [24-25]. However, conflicting findings suggest that exon 9 mutation does not significantly correlate with clinicopathological factors such as age, sex, tumor differentiation or aggressiveness; instead overexpression of the PIK3CA gene is correlated with lymph node metastasis in EC cells and survival among female patients [26].

The CCND1 (Cyclin D1) gene is located on chromosome 11 (region 11q13), comprising of 5 exons, and its mutant form is predominantly amplified in EC cells. CCND1/pRb/ppRb participates in cell cycle regulation by activating the downstream signaling pathway of E2F, thereby shortening the cell cycle duration and playing a pivotal role in tumorigenesis. It has been reported that CCND1 is overexpressed in 30.0% to 72.7% of EC patients, and amplification of CCND1 is closely associated with lymph node metastasis, resulting in poor clinical treatment response, increased likelihood of post-treatment recurrence, and reduced overall survival [27-28]. Currently there is growing attention towards the single nucleotide polymorphism (SNP) at position 870 within the CCND1 gene as it contributes to the pathological process of EC. SNP represents a germline mutation occurring prior to tumor cell formation; specifically, the G to A substitution at position 870 leads to aberrant cell cycle progression and subsequent tumor development [29].

The XRCC1 gene, located on chromosome 19 (19q13.2-13.3), comprises of 17 exons in its structural organization. The protein encoded by XRCC1 binds to damaged DNA and facilitates repair in the presence of DNA polymerase beta, PNK, and DNAL ligase III. Mutations in XRCC1 can directly impact DNA repair function. A meta-analysis has revealed a significant association between the XRCC1 exon 6 C26304T (Arg194Trp) polymorphism and EC [30]. Additionally, elevated expression of the XRCC1 gene has been observed in certain EC cells, serving as an independent risk factor influencing clinical survival outcomes for patients. Therefore, detection results of the XRCC1 gene within cancer cells can serve as a basis for prognostic evaluation of EC [31].

2.2 Interference by Long Non-Coding RNA (LncRNA)

In recent years, numerous studies have demonstrated the pivotal role of LncRNAs as oncogenes or tumor suppressor in transcriptional and post-transcriptional mechanisms during tumorigenesis. Specifically, LncRNAs can modulate the transcription of genes associated with EC by participating in DNA methylation, histone modification, and chromatin remodeling.

DNA methylation is associated with alterations in LncRNA expression during tumorigenesis. The Glutathione S-transferase Pi Gene (GSTP1) plays a crucial regulatory role in detoxification and protection against oxidative damage. LINC01419 binds to the promoter region of GSTP1, resulting in GSTP1 methylation and subsequent

inhibition of its expression, thereby diminishing the chemical sensitivity of EC cells towards 5-Fluorouracil (5-FU) [32].

LncRNAs function as guides for recruiting histone modifying enzymes to specific genomic regions, such as promoters and enhancers, thereby regulating chromatin modification. LncRNA Cancer Susceptibility Candidate 9 (CASC9) exhibits a significantly elevated expression in esophageal squamous cell carcinoma, making it one of the most prominent candidates for further investigation. It has been observed that LncRNA CASC9 can suppress Programmed Cell Death 4 (PDCD4) by facilitating the recruitment of EZH2, a subunit of Repressive Complex 2 (PRC2), thus promoting proliferation of EC cells [33]. Apart from EZH2 recruitment, CASC9 modulates overexpression of Laminin Gamma 2 (LAMC2) by enhancing H3K27ac levels at the promoter region and interacting with the transcriptional coactivator Creb-binding Protein (CBP). Furthermore, activation of FAK-PI3K/AKT signaling pathway promotes epithelial-to-mesenchymal transition (EMT), leading to increased proliferation and metastasis in EC cells [34].

2.3 Tumor Microenvironment

Myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), and other cell populations within the tumor microenvironment (TME) facilitate immune escape of cancer cells by secreting cytokines and activating pro-inflammatory pathways, thereby promoting the malignant progression of EC. Additionally cancer-associated fibroblasts (CAFs) secrete growth factors that alter the extracellular matrix, establish tumor niches, and enhance cell migration and invasion. Tumor-associated macrophages (TAMs) also exhibit pro-tumorigenic functions including angiogenesis induction and tumor cell invasion. Studies have demonstrated that the interplay between cytokines and MDSCs in the TME plays a pivotal role in EC development. Pro-inflammatory molecules such as IL-1β, IL-16, and PGE2, along with other secreted factors like VEGF activate MDSCs [35]. The expression of MAEL gene and inflammatory factor IL-8 can be upregulated in EC tissues through the TGF-β/Smad2/3 pathway, facilitating recruitment of MDSCs to tumor tissues and contributing to EC occurrence [36].

Previous studies have demonstrated an up-regulation of Foxp3 expression in both peripheral blood and esophageal mucosal tissues of patients with EC, which has been closely related to poor prognosis [37]. The infiltration of Tregs holds prognostic significance and is implicated in tumor invasion, metastasis, as well as reduced survival rates following chemotherapy [38-40]. Moreover, a study investigating preclinical and clinical neoadjuvant chemotherapy in EC patients revealed that the presence of Tregs impeded immune surveillance against cancer. Notably, the persistence of Tregs within residual tumors post-treatment not only correlated with pathological response but also influenced cancer-specific survival. One potential mechanism involves direct inhibition of IL-2 by Foxp3 while promoting CTLA-4 and CD25 expression [41].

It has been found that miRNAs in esophageal squamous cell carcinoma actively participate in the transformation of fibroblasts into CAFs [42]. CAFs possess the ability to reconstruct the TME through their involvement in promoting angiogenesis, cytokine secretion, induction of EMT, reconstitution of extracellular matrix components, and activation of inflammatory cytotropic EC progression [43].

2.4 Esophageal Injury Caused by Unhealthy Living and Eating Habits

Unhealthy dietary and lifestyle habits, along with esophageal diseases such as esophageal achalasia, esophagitis, gastroesophageal reflux disease, esophageal leukoplakia, and other factors can lead to damage of the esophageal mucosa and inflammation, thereby increasing the risk of developing EC. A study analyzing 2714 Japanese patients with achalasia and achalasia related esophageal dysphoria (EMDs) revealed that individuals with achalasia have a relatively higher susceptibility to EC [44]. Furthermore, Kaplan-Meier analysis demonstrated that apart from having a prolonged history of achalasia, advanced age, male gender, and alcohol consumption are significant risk factors for EC. Obesity can elevate abdominal pressure leading to gastroesophageal reflux which damages the esophageal mucosa and induces Barrett's Esophagus. The incidence of esophagealcancer in patients with Barrett's Esophagus is much higher compared to the general population [45]. An investigation conducted on the Korean population indicated that abdominal obesity could increase the likelihood of developing EC [46].

3. Treatment of EC with TCM

The treatment of EC in traditional Chinese medicine (TCM) primarily relies on syndrome differentiation. TCM prescriptions, oral liquid, injections, and monomers are often combined with surgical interventions, radiotherapy, and chemotherapy to effectively reduce postoperative metastasis and recurrence rates as well as the incidence of radiochemotherapy resistance and associated adverse reactions.

3.1 Treatment of EC with TCM Solely

The ethanol extract of TCM *Cochinchina momordica seed*, *p*-Hydroxylcinnamaldehyde, demonstrated efficacy against the proliferation of EC cells both in vitro and in vivo by inducing cancer cell differentiation [47].

Baohuoside I, a flavonoid monomer constituent derived from the TCM *Cortex periplocae*, exhibits inhibitory effects on cell proliferation and induces apoptosis in the human EC cell line Eca109 both in vitro and in vivo by down-regulating the expression of survivin gene [48].

The flavonoid component Oroxin A derived from TCM *Xyloside* exhibits potent antioxidant, antibacterial, anticancer, and antiviral activities. Notably, Oroxin A exerts a significant inhibitory effect on the proliferation of EC cells by specifically targeting the upstream protein kinase JAK2 within the JAK2/STAT3 pathway and down-regulating $STAT3^{Tyr705}$, $STAT3^{Ser727}$ as well as phosphorylation levels of $NF\text{-}\kappa B^{Ser907}$ [49].

Naringin, an extract derived from TCM *Poncirus trifoliata*, up-regulated the expression levels of Bax, cytochrome C (CytC), Caspase-3 and Caspase-9 in EC cell line Eca109, while concurrently down-regulating the expression level of Bcl-2. These findings suggest a proapoptotic effect against EC cells. Additionally, treatment with Naringin resulted in a gradual decrease in the phosphorylation ratios of p-STAT3/STAT3, p-AKT/AKT and p-JAK2/JAK2 in Eca109 cells. Collectively, these results indicate that Naringin can modulate the JAK/STAT signaling pathway by regulating the protein levels of p-STAT3, STAT3, p-AKT, AKT, p-JAK2 and JAK2 [50].

The Qige powder, developed by Cheng Zhongling, a renowned medical scientist during the Qing Dynasty, was formulated specifically for the treatment of dysphagia and emerged as a representative prescription for managing EC. Recent studies have demonstrated that Qige powder exhibits inhibitory effects on the growth of EC9706 cells and attenuates the impact of EC cells on dendritic cell maturation through modulation of the STAT3 signaling pathway [51].

Curcumin, a plant polyphenol derived from curcuma plants' roots, exerts diverse anti-EC effects including pro-apoptotic, anti-proliferation and anti-angiogenic effects through its modulation of multiple signaling pathways such as PI3K-AKT, NF-κB, Notch, JAK/STAT, and AMPK [52].

Chlorogenic acid, a key active constituent of TCMs like *Lonicera japonica*, exerts significant antibacterial, anti-inflammatory, and antitumor effects. Previous studies have demonstrated that Chlorogenic acid hinders the progression of EC by down-regulating the expression of BMI1, SOX and Notch1-SOX2 positive-feedback loop [53].

Tetrastigma Hemsleyani Radix flavone, an extract derived from TCM *Tetrastigma hemsleyanum*, was observed to suppress the migration and invasion of EC9706 cells by down-regulating Notch1 expression [54].

Hawthorn procyanidins are a diverse group of polyphenolic oligomeric compounds derived from varying levels of catechins or epicatechins in hawthorn fruit (*Crataegus pinnatifida*). These procyanidins exhibit inhibitory effects on the phosphorylation of PI3K and activation of AKT in Eca109 cells, thereby reducing Cox-2 expression, which facilitates cancer cell proliferation, while enhancing the expression of pro-apoptotic protein Caspase-3, leading to apoptosis in Eca109 cells [55].

Hesperitin, one of the primary active constituents found in TCM orange peel, has been shown to induce G0/G1 cell cycle arrest and significantly inhibit the proliferation and invasion of Eca109. These effects may be attributed to the inhibition of PI3K/AKT, cyclin D1, MMP-2 and MMP-9, as well as the up-regulation of phosphorylated PTEN and p21 in Eca109 cells following hesperidin treatment [56].

Compound Kushen injection is primarily utilized for the management of cancer-related pain and bleeding. Additionally, it has demonstrated efficacy in reducing tumor volume, mitigating pathological damage to tumor tissue in rats, and inhibiting the expression of VEGF, bFGF, p-PI3K, and p-AKT [57].

Forsythin, one of the primary bioactive compounds found in TCM *Forsythia vahl*, has been shown to significantly reduce the expression levels of p-PI3K, p-AKT, Bcl-2, and MMP-9 in esophageal epithelial malignant transition cells and Eca109 cells at of 10 and 100 μmol/L. Moreover, a concentration of 100 μmol/L Forsythin markedly increases the expression level of p21 protein in these cell lines. These findings suggest that Forsythin exhibits significant inhibitory effects on the proliferation, migration, and invasion abilities of esophageal epithelial malignant transition cells as well as Eca109 cells [58].

Celastrol, a triterpenoid compound found in *Tripterygium wilfordii*, has been demonstrated to inhibit tumor growth in EC by triggering both exogenous and endogenous apoptotic pathways. Mechanism studies have shown that Celastrol induces DR5-dependent exogenous apoptosis and NoxA-dependent endogenous apoptosis of EC cells

through transcriptional activation of ATF4. Furthermore, the FOXO3A-Bim pathway is implicated in Celastrol-induced endogenous apoptosis of EC cells [59].

Alantolactone, a sesquiterpene lactone compound extracted from TCM *Inulae Radix*, up-regulated the expression of Bax, Cleaved Caspase 3, and Caspase 3 while down-regulating the expression of Bcl-2 in EC9706 cells. Additionally, it decreased the expression levels of migration and invasion related proteins MMP-7, MMP-9, Vimentin, and zinc finger transcription factor 1. Moreover, Alantolactone significantly down-regulated β-catenin expression leading to reduced downstream target c-Myc and cyclin D1. It is evident that Alantolactone exerts its antitumor effect through the inhibition of the Wnt/β-catenin signaling pathway [60].

Podophyllotoxin, an active compound derived from TCM *Dysosma versipellis*, exhibits antitumor activity in EC by effectively suppressing the activation of the Wnt signaling pathway and down-regulating the expression of Wnt, β-catenin, as well as p-GSK3β/GSK3β [61].

The triterpenoid compound Demethylzelasteral, extracted from the root bark of *Tripterygium wilfordii,* induces G2/M phase arrest in esophageal squamous cancer cells. Treatment with Demethylzelasteral significantly up-regulates the expression of e-cadherin while down-regulating the expression of N-cadherin, Vimentin, MMP-9, β-catenin and c-Myc in esophageal squamosal cancer cells [62]. These findings suggest that Demethylzelasteral inhibits proliferation and migration of EC cells through modulation of the Wnt/β-catenin pathway.

Bufalin, an active component of TCM *Toad venom*, plays a crucial role in inhibiting angiogenesis and the growth of cancer stem cells. It has been reported that Bufalin effectively suppresses the proliferation, migration, and invasion of Eca109 cells in a concentration-dependent manner. RNA-seq analysis revealed up-regulation of PIAS3 expression in the Bufalin-treated group. Furthermore, down-regulation of PIAS3 attenuated STAT3 inhibition, leading to increased p-STAT3 expression. These findings suggest that Bufalin may exert its effects on Eca109 cells through modulation of the PIAS3/STAT3 signaling pathway [63].

Cryptotanshinone, an active component of TCM *Salvia miltiorrhiza*, effectively induces apoptosis in EC cell line HCE-4. Western blot analysis revealed that Cryptotanshinone down-regulates the expression of p-ERK, p-AKT, and Bcl-2 by modulating the MAPK and AKT signaling pathways, thereby promoting apoptosis in HCE-4 cells [64].

Marsdenia tenacissima extract, derived from a single Chinese medicinal plant, has been utilized in the treatment of esophageal and gastric cancers. This extract exhibits the ability to induce cell cycle arrest in EC cells, inhibit cell proliferation, and down-regulate the expression of cyclin D1/D2/D3, cyclin-dependent Kinase 2/4/6, as well as phosphorylated retinoblastoma protein. Moreover, Marsdenia tenacissima can effectively attenuate the activation of p-ERK, p-JNK and phosphorylated p38 proteins, thereby demonstrating its inhibitory potential against MAPK signaling pathways including ERK, JNK and p38 [65].

Dihydroartemisin, a semi-synthetic derivative of Artemisin, has been reported to significantly inhibit the proliferation and migration of Eca109, KYSE150 and TE1 cells. Moreover, Dihydroartemisin down-regulates human telomerase reverse transcriptase (hTERT) expression at mRNA and protein levels in a time- and dose-dependent manner [66].

Icaritin, a hydrolytic product derived from TCM *Epimedium brevicornu*, has recently been demonstrated to dose-dependently inhibit the proliferation, migration and invasion of esophageal cancer stem cells. This effect may be attributed to its modulation of cell apoptosis and the expression levels Wnt and Hedgehog signaling pathways [67].

3.2 Treatment of EC with TCM Combined with Chemoradiotherapy

Chemoradiotherapy is considered an effective therapeutic approach for the treatment of EC; however, it may lead to adverse reactions such as esophageal mucosal damage, bone marrow suppression, radiation esophagitis, loss of appetite, early satiety and dysphagia. These not only diminish patients' quality of life but also potentially interrupt their treatment. Combining TCM with chemoradiotherapy has been shown to mitigate the occurrence of these adverse reactions while enhancing treatment efficacy and improving patients' life quality.

Liujunzi decoction, a traditional TCM prescription, exhibits a synergistic effect on inhibiting the proliferation of EC9706 cells through the combination with Stattic, a STAT3 protein phosphorylation inhibitor. This effect is attributed to the blocking activity of Liujunzi Decoction against IL-6 [68].

Hesperetin effectively inhibits the expression of phosphorylated PI3K/AKT, cyclin D1, MMP-2 and MMP-9, while enhancing the expression of phosphorylated PTEN and p21 in Eca109 cells. Subsequent investigations revealed that the combination of hesperetin with 5-fluorouracil (5-FU) significantly down-regulates Bcl-2 protein

levels and up-regulates Bax protein levels in Eca109 cells, suggesting a novel therapeutic approach for EC treatment [56].

The compound Capilliposide C, derived from TCM *Capillary wormwood*, exhibits a significant enhancement in the anti-proliferation and apoptosis effect of Oxaliplatin against EC cells. Co-administration of Oxaliplatin with Capilliposide C leads to a reduction in the expression levels of PI3K, p-Akt, p-mTOR, Bcl-2, and Bcl-XL while up-regulating the expression of Bax and Caspase-3. These findings suggest that Capilliposide C enhances the anticancer effects of Oxaliplatin by modulating the PI3K/AKT/mTOR pathway [69].

The TCM monomer Artemisinin demonstrates remarkable anticancer, antiparasitic, and antiviral activities. Additionally, Artemisinin significantly enhances the anticancer effect of Oxaliplatin in Eca109 cells, suggesting that this combination therapy may be a novel treatment for EC [70].

Sinomenine, derived from the TCM *Sinomenium acutum*, has been extensively utilized in the treatment of rheumatism due to its minimal side effects. Recent studies have demonstrated that the combination of Sinomenine and 5-FU exhibits a synergistic effect on EC, surpassing the individual efficacy of Sinomenine or 5-FU alone, while not increasing adverse reactions [71]. Furthermore, Sinomenine induces mitochondrial membrane potential disruption, leading to caspase-dependent cellular apoptosis.

The involvement of NF-κB in the induction of chemical resistance, which can be activated by chemotherapy agents in various cancer cell lines including EC cells, has been demonstrated. Both TCM monomers quercetin and curcumin have the ability to target the NF-κB signaling pathway and enhance the efficacy of chemotherapeutic drugs on EC [72, 73].

Compared to radiotherapy alone, the addition of compound Kushen injection significantly ameliorates symptoms in patients with EC, such as fatigue and constipation, reduces the incidence of radiation esophagitis, improves patients' life quality, and enhances the efficacy of radiotherapy [74]. It has been reported that berberine, a TCM monomer, effectively inhibits the hypoxic microenvironment in cancer cells and RAD51-induced HIF-1α expression. Consequently, it promotes radio-sensitivity in cancer cells and restores sensitivity of EC cells to radiation [75].

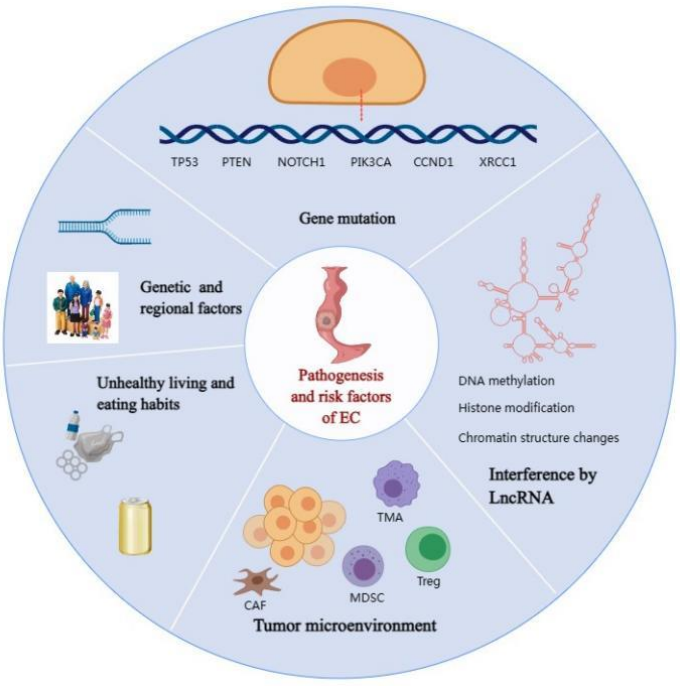

Figure 1. The main pathogenesis of EC including genetic factors, regional characteristics, gene mutation, RNA interference, tumor microenvironment, and unhealthy living and eating habits

4. Conclusions

Currently, the pathogenesis of EC remains incompletely understood. Despite the favorable clinical efficacy achieved by surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy in treating EC,

complications and adverse reactions persist. With its unique approach based on syndrome differentiation and concept of wholism, TCM plays a significant role in the prevention and treatment of malignant tumors. In recent years, numerous basic experiments and clinical studies have substantiated the beneficial effects of TCM in managing EC. Presently, the modernization of TCM is the general trend of the development of TCM. The multi-component and multi-target nature of TCM necessitate further exploration to elucidate its mechanisms for preventing and treating EC, thus highlighting the importance of molecular biology and information biology in revealing the mechanism of TCM treatment.

In conclusion, the pathogenesis of EC involves a combination of genetic factors, regional characteristics, gene mutation, RNA interference, tumor microenvironment, and unhealthy lifestyle habits (Figure 1). Identifying changes in relevant indicators associated with these pathogenic factors can facilitate the application of TCM interventions for EC. TCM can be used as monotherapy or as an adjunct to radiochemotherapy in the treatment of EC (Table 1 and Table 2), thereby enhancing overall response rates, quality of life, and patient survival. Therefore, greater emphasis should be placed on integrating TCM into the prevention and treatment strategies for EC to further enhance clinical efficacy.

Table 1. Treatment of EC with TCM solely

TCM (monomers/ prescriptions)	Resources of TCM	Effect	Target or pathway
p-Hydroxylcinnamaldehyde [47]	*Cochinchina momordica seed*	Inhibit the proliferation of EC cells	-
Baohuoside I [48]	*Cortex periplocae*	Inhibit the proliferation and induce apoptosis of EC cells	Survivin gene
Oroxin A [49]	*Xyloside*	Inhibit the proliferation of EC cells	JAK2
Naringin [50]	*Poncirus trifoliata*	Induce apoptosis of EC cells	STAT3, AKT, JAK2
Qige powder [51]	*Adenophora stricta, Salvia miltiorrhiza, Poria cocos, Fritillaria cirrhosa, Curcuma aromatic, Amomum villosum Lour, Nelumbo nucifera Gaertn*	Inhibit the proliferation of EC cells	STAT3
Curcumin [52]	*Curcuma longa*	Pro-apoptotic, anti-proliferation and anti-angiogenic effect	PI3K-Akt, NF-κB, Notch, JAK/STAT and AMPK
Chlorogenic acid [53]	*Lonicera japonica*	Inhibit the proliferation of EC cells	Notch1-SOX2 positive-feedback loop
Tetrastigma Hemsleyani Radix flavone [54]	*Tetrastigma hemsleyanum*	Inhibit the migration and invasion of EC cells	Notch1
Hawthorn procyanidin [55]	*Crataegus pinnatifida*	Inhibit the proliferation and induce apoptosis of EC cells	Cox-2
Hesperidin [56]	Orange peel	Inhibit the proliferation and invasion of EC cell	PI3K/AKT, cyclin D1, MMP-2 and MMP-9
Compound Kushen injection [57]	*Sophora flavescens, Heterosmilax japonica kunth*	Reduce the tumor volume, pathological injury degree of tumor tissue	VEGF, bFGF, PI3K and AKT
Forsythin [58]	*Forsythia vahl*	Inhibit the proliferation, migration and invasion of EC cells	PI3K, AKT, Bcl-2, MMP-9
Celastrol [59]	*Tripterygium wilfordii*	Induce apoptosis of EC cells	DR5, NoxA, FOXO3A-Bim
Alantolactone [60]	*Inulae Radix*	Induce apoptosis and inhibit the migration and invasion of EC cells	Wnt/β-catenin signaling pathway
Podophyllotoxin [61]	*Dysosma versipellis*	Inhibit the proliferation of EC cells	Wnt signaling pathway
Demethylzelasteral [62]	*Tripterygium wilfordii*	Inhibit the proliferation and migration of EC cells	Wnt/β-catenin pathway
Bufalin [63]	*Toad venom*	Inhibit angiogenesis and cancer stem cell growth	PIAS3/STAT3 signaling pathway
Cryptotanshinone [64]	*Salvia miltiorrhiza*	Induce apoptosis of EC cell	MAPK and AKT

			signaling pathways
Marsdenia tenacissima extract [65]	*Marsdenia tenacissima*	Induce EC cell cycle arrest and inhibit cell proliferation	MAPK pathway
Dihydroartemisin [66]	*Artemisia annua*	Inhibit the proliferation and migration of EC cells	hTERT
Icaritin [67]	*Epimedium brevicornu*	Inhibit the proliferation, migration and invasion of EC cells	Wnt and Hedgehog signaling pathways

Table 2. Treatment of EC with TCM combined with chemoradiotherapy

TCM combined therapy	Resources of TCM	Effect	Target or pathway
Liujunzi Decoction and STAT3 inhibitor Stattic [68]	*Panax ginseng, Atractylodes macrocephala, Poria cocos, Glycyrrhiza uralensis, Pinellia ternata*	Synergistic effect on inhibiting the proliferation of EC cell	IL-6
Hesperetin and 5-fluorouracil [56]	Orange peel	Inhibit the proliferation of EC cells	Bcl-2, Bax
Capilliposide C and oxaliplatin [69]	*Capillary wormwood*	Enhance the anticancer effects of oxaliplatin	PI3K/AKT/mTOR pathway
Artemisinin and oxaliplatin [70]	*Artemisia annua*	Enhance the anticancer effects of oxaliplatin	-
Sinomenine and 5-fluorouracil [71]	*Sinomenium acutum*	Synergistic effect on EC	-
Quercetin and 5-fluorouracil [72]	*Flos Sophorae Immaturus*	Enhance the effect of chemotherapeutic drugs on EC	NF-κB signaling pathway
Curcumin and CPT-11 [73]	*Curcuma longa*	Enhance the effect of chemotherapeutic drugs on EC	NF-κB signaling pathway
Compound Kushen injection combined with radiotherapy [74]	*Sophora flavescens, Heterosmilax japonica kunth*	Improve the symptoms, life qualities and radiotherapy effect of patients	-
Berberine combined with radiotherapy [75]	*Coptis chinensis*	Restore the sensitive of EC cells to radiotherapy	RAD51

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Conflict of interest

No potential conflict of interest was reported by the authors.

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