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Research Progress on Traditional Chinese Medicine and Extracts for Treating Laryngeal Cancer

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Abstract: Laryngeal cancer is one of the common malignant tumors of the respiratory tract, most of which occur in the hypopharynx, among which the piriform fossa is the most common. Patients with subglottic laryngeal cancer lose the best treatment time because there are no obvious symptoms, while surgery is still the main treatment for early-stage tumors, and chemotherapy and immunotherapy are adjuvant in the middle and advanced stages. Among them, polysaccharides of traditional Chinese medicine have a significant effect on inhibiting tumors, which has the characteristics of multi-perspective and multi-mechanism synergistic effect, which can avoid drug resistance, and is a new field of natural medicine with great research value and development potential. Traditional Chinese medicine and its extracts mainly treat laryngeal cancer by inhibiting cell cycle and apoptosis, intervening in the metabolism of laryngeal cancer cells, affecting the microenvironment and metastasis of laryngeal cancer cells, and inhibiting the angiogenesis and metastasis of laryngeal cancer cells. This article provides a brief overview of the basic research on the treatment of laryngeal cancer with traditional Chinese medicine and extracts in recent years.

Keywords: Laryngeal cancer; Traditional Chinese medicine; Cellular metabolism; Tumor microenvironment; Drug resistance

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1. Foreword

Laryngeal carcinoma (LC) is the most common malignant tumor in the head and neck region, accounting for approximately 5% of all malignant tumors nationwide [1]. Primary risk factors include smoking, chronic laryngitis, and air pollution. Statistics indicate regional variations in incidence rates. Domestic reports show higher prevalence in northern regions, with urban areas exhibiting higher rates than rural areas, and heavy industrial cities demonstrating higher incidence than light industrial cities [2,3]. Clinical management primarily involves comprehensive treatment combining surgical resection with radiotherapy and chemotherapy. Most laryngeal carcinoma patients may experience adverse effects post-surgery, such as dysphagia, pharyngeal or esophageal stenosis, and vocal cord dysfunction [4].

Traditional Chinese medicine offers multifaceted, multi-targeted advantages in cancer treatment. By integrating traditional Chinese medicine with modern medicine, herbal remedies can exert distinct therapeutic effects at various stages of tumor development, thereby enhancing patients' quality of life. As TCM treatment for tumors becomes increasingly

standardized, many of the proprietary Chinese medicines mentioned in this paper are gradually entering public awareness, such as herbal extracts like baicalin and tanshinone. Currently, TCM has established a comprehensive system for cancer treatment, with numerous domestic and international studies demonstrating its efficacy against tumors through various experimental methods [5]. This paper aims to summarize previous findings on how TCM inhibits tumor cells and the associated inhibitory pathways, providing a foundation for future TCM anti-tumor applications.

2. Effects of traditional Chinese medicines and extracts on the cell cycle and apoptosis of laryngeal cancer cells

Scutellaria baicalensis is a perennial herb whose roots are used medicinally. Flavonoids constitute its most potent active components. Baicalin induces high expression of miR-125b-5p in AMC-NH-8 laryngeal carcinoma cells, thereby enhancing the levels of pro-apoptotic proteins Bax, cleaved-caspase-3, and cytochrome c levels while simultaneously promoting apoptosis by reducing the expression of the anti-apoptotic protein Bcl-2. This provides preliminary evidence for the potential application of baicalin as an anticancer drug for treating laryngeal carcinoma [6].

Salvia miltiorrhiza exhibits broad-spectrum antitumor activity, with tanshinone II being one of its primary active components. Tanshinone IIA intervention significantly increases apoptosis rates and autophagosome numbers in human laryngeal carcinoma Hep-2 cells, markedly downregulates Bcl-2 expression, and upregulates Bax, cleaved Caspase-3, LC3-I, LC3-II expression, elevates Bax/Bcl-2 and LC3-II/LC3-I ratios, and reduces PI3K, Akt, and mTOR phosphorylation levels [7]. Studies have also demonstrated that Tanshinone IIA inhibits proliferation of human laryngeal carcinoma Hep-2 cells and induces G2/M phase arrest [8].

Aconitine (Esc) is a coumarin derivative. Modern pharmacology indicates that aconitine possesses anti-inflammatory, antioxidant, and antitumor effects. Esc inhibits proliferation, migration, and survival of human laryngeal carcinoma Hep-2 cells, while inducing apoptosis and causing G1 cell cycle arrest in these cells. *In vivo* results further indicate that Esc primarily suppresses tumor growth and tumor weight in nude mice via the JAK/STAT signaling pathway [9].

Curcumin is a polyphenol extracted from turmeric rhizomes. Relevant animal studies have demonstrated that curcumin, GLUT-1AS-ODN, or their combination exhibits synergistic effects on radiosensitivity by promoting death in laryngeal carcinoma cells [10].

3. Effects of traditional Chinese medicines and extracts on the metabolism of laryngeal cancer cells

Many researchers believe that alterations in cellular metabolism constitute hallmarks of the cancer phenotype, as these metabolic changes characterize malignant transformation. Consequently, studying interventions that disrupt tumor cell metabolism holds significant importance. Metabolomics involves comprehensive investigation of metabolites such as monosaccharides, amino acids, small lipids, and cofactors. Both energy and redox balance play pivotal roles in cellular metabolism [11,12]. As metabolic research in head and neck cancers gains increasing recognition, we can identify tumor cells by detecting altered metabolites [13,14].

Rhizoma paridis saponins is a natural extract of *Polygonatum multiflorum*, used as an anticancer agent in traditional Chinese medicine and serving as the active component of rhizoma paridis saponins II. It exhibits potent antitumor activity against various cancers including hepatocellular carcinoma and lung cancer [15,16]. paridis saponins II inhibits proliferation and metastasis of head and neck squamous cell carcinoma (HNSCC) by suppressing the nitric oxide metabolic pathway. Paridis saponins II suppresses the viability and motility of head and neck squamous cell carcinoma cell lines, cancer stem cells, and primary cultured fibroblasts by inducing autophagy and apoptosis through targeting NOS3 and a series of metabolic changes *in vivo* and *in vitro* [17].

Ursolic acid derivatives is an ethnic medicinal herb used in Guangxi Zhuang medicine, renowned for its extensive therapeutic applications in treating throat diseases. *In vitro* and *in vivo* experiments revealed that extracts from Ursolic acid derivatives significantly inhibit the proliferation and migration of laryngeal cancer cells without exhibiting notable toxicity. The therapeutic effect of Ursolic acid derivatives filiforme extract against laryngeal carcinoma is mediated by activating the mitochondrial pathway, inhibiting the Akt/mTOR pathway, and inducing endoplasmic reticulum stress [18].

4. Effects of traditional Chinese medicines and extracts on the microenvironment and metastasis of laryngeal cancer cells

The tumor microenvironment (TEM) comprises cellular and non-cellular components, such as various immune cells, cancer-associated fibroblasts (CAFs), endothelial cells, extracellular matrix, and tumor stromal cells and matrix components including neurons and nerve fibers [19]. Research indicates that tumor progression depends not only on genetic alterations or epigenetic modifications in cancer cells but is also regulated by components of the tumor microenvironment (TEM). The tumor microenvironment plays a crucial role in tumor development and metastasis [20].

Astragalus is one of the most commonly used traditional Chinese medicines in clinical practice. Matrix metalloproteinases (MMPs) are a multi-gene family of metalloproteinases dependent on metal ions, serving as a major protein family involved in tumor metastasis and influencing the tumor cell microenvironment. Professor Dong and his team validated that the active components of Astragalus act on core genes within the MMP family, including MMP1, MMP3, and MMP10. This confirms Astragalus's potential role in the metastatic process of laryngeal cancer cells [21]. Ginsenoside (PDS) are protopanaxadiol-type extracts derived from ginseng stems and leaves. *In vitro* studies indicate that PDS inhibits proliferation, migration, and epithelial-mesenchymal transition in Hep2 laryngeal carcinoma cells by suppressing the Wnt/β-catenin pathway [22].

Brucea javanica is a heat-clearing and toxin-eliminating herb. Its constituents include β-sitosterol, luteolin, bristol, and other components. β-Sitosterol exerts effects in cancer cells such as promoting apoptosis, influencing the cell cycle, and exhibiting anti-proliferative, anti-invasive, anti-angiogenic, and anti-metastatic activities [23]. Wu Zhongbiao et al. confirmed through network pharmacology combined with *in vitro* experiments that Brucea javanica exhibits multi-compound, multi-target, and multi-pathway anti-laryngeal cancer effects. Among these, signaling pathways such as the PI3K-Akt pathway and the p53 pathway may play roles in reducing platinum resistance, promoting apoptosis, inhibiting proliferation, preventing metastasis, and regulating the cell cycle [24].

Endoplasmic reticulum stress refers to the microenvironment generated by cellular transcriptional and metabolic abnormalities, disrupting endoplasmic reticulum homeostasis in stromal cells and infiltrating leukocytes. These alterations induce a persistent state of endoplasmic reticulum stress [25]. *Hedyotis diffusa* polysaccharide extract may inhibit endoplasmic reticulum autophagy in Hep-2 cells, thereby enhancing sensitivity to the endoplasmic reticulum stress-apoptosis signaling pathway. This mechanism reduces Hep-2 cell proliferation capacity, exerting an antitumor effect [26].

5. Effects of traditional Chinese medicines and extracts on angiogenesis and metastasis in laryngeal cancer cells

Angiogenesis is a complex dynamic process influenced by molecular factors that play a crucial role in tumor growth, such as invasion and migration. The most commonly used anti-angiogenic agents include monoclonal antibodies and tyrosine kinase inhibitors (TKIs), both targeting the vascular endothelial growth factor (VEGF) pathway [27]. Numerous studies have also demonstrated that increased tumor microvascular density (MVD) correlates with markedly heightened malignant potential, including tumor invasion and metastasis [28].

Luteolin is a flavonoid compound, and integrin β1 is considered a downstream molecule of luteolin. Animal studies

indicate that luteolin enhances radiosensitivity by inhibiting cell proliferation, reduces integrin β1 expression, suppresses angiogenesis during radiotherapy, and inhibits tumor growth. Concurrently, luteolin significantly decreases VEGF protein expression, thereby exerting antitumor effects [29].

Isoliquiritigenin, a natural flavonoid compound primarily derived from licorice root, exhibits biological activity in inhibiting cancer proliferation, arresting cell cycle progression, suppressing angiogenesis, blocking metastasis, and inducing apoptosis. Researchers applied isoliquiritinide to two human laryngeal carcinoma cell lines, Hep-2 and TU212, using wound healing assays and Transwell migration/invasion assays. Results demonstrated that isoliquiritinide possesses the ability to inhibit tumor cell migration and invasion [30]. Furthermore, additional experiments validated that isoliquiritinib inhibits gastric cancer cell invasion through cellular assays, primarily by downregulating the expression of proteins in the PI3K/Akt signaling pathway and its downstream matrix metalloproteinase MMP-9 [31].

It is well known that vascular endothelial growth factor (VEGF) is a key mediator of angiogenesis and can bind to two VEGF receptors expressed on vascular endothelial cells. In healthy individuals, VEGF promotes angiogenesis during embryonic development and is crucial for wound healing in adults [32]. Curcumin inhibits VEGF levels in the laryngeal squamous cell line HEp-2 by acting on STAT-3. Consequently, curcumin has been demonstrated to suppress the growth, proliferation, migration, and angiogenesis of laryngeal cells. It also inhibits angiogenesis by suppressing JAK-2 expression and pSTAT-3 production [33].

6. Outlook

In summary, traditional Chinese medicine (TCM) and its active components demonstrate broad potential in laryngeal cancer treatment through multiple mechanisms, including inducing apoptosis, inhibiting proliferation, blocking invasion and metastasis, and regulating tumor metabolism and microenvironment. However, compared to chemical drugs, TCM exhibits greater complexity in composition, posing greater challenges for studying its mechanisms of action. Current research predominantly remains confined to cellular and animal studies, lacking robust clinical data. Mechanistic investigations also tend to focus on established pathways, with depth and innovation requiring further enhancement. Moving forward, emerging technologies such as systems biology and network pharmacology should be leveraged to unravel the multi-target interaction networks of TCM. Concurrently, rigorous clinical trials must be actively promoted to validate efficacy and safety, thereby accelerating the establishment of a scientifically grounded and standardized theoretical and clinical framework for TCM in the prevention and treatment of laryngeal cancer.

Disclosure statement

The authors declare no conflict of interest.

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