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Exploring the Effects and Molecular Mechanisms of Curcumin on Esophageal Cancer based on Network Pharmacology

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Abstract: ***This study used a network pharmacology approach to analyze the potential role of Curcumin in esophageal squamous cell carcinoma (ESCC). Compared with traditional ESCC treatments, which often have single targets, limited efficacy, and significant side effects. These properties may compensate for the shortcomings of conventional drugs. The study constructed the Curcumin target network and PPI network, systematically analyzing its core targets and related pathways, providing a theoretical foundation for the development of Curcumin as a new drug for the prevention and treatment of ESCC.***

Keywords: Curcumin, Esophageal cancer, Network pharmacology, Molecular mechanisms**.**

1. Introduction

According to GLOBOCAN survey, esophageal cancer is the 11th new cancer and the 7th cause of cancer death in the world in 2022, of which the number of incidence rate of esophageal cancer in China accounted for 43.8% of the world, and the number of deaths accounted for 42.1% of the world [1-4]. Most patients with esophageal cancer require extensive treatment, including chemotherapy, radiotherapy, and/or surgical resection. Patients with advanced or metastatic esophageal cancer receive palliative chemotherapy; human epidermal growth factor receptor 2 (HER2)-positive patients may also benefit from trastuzumab therapy. and the overall burden of disease is still very heavy [5-7].

Curcumin is a natural polyphenolic compound extracted from the rhizome of turmeric, a plant in the ginger family [8,9]. Studies have shown that curcumin exhibits significant advantages in a number of areas, including neuroprotection, antioxidant, anti-inflammatory and anticancer, making it a hot research topic in the field of health prevention [10-13]. However, its specific mechanism of action in the treatment of esophageal cancer has not been fully elucidated. In this study, we investigated the potential targets and mechanism of action of curcumin in the treatment of esophageal cancer based on network pharmacology, and provided research ideas for its development as a new drug against esophageal cancer.

2. Methods

2.1 Collecting Curcumin Targets

The SMILES number of curcumin was obtained from PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and the SMILES number was imported into SuperPred database (http://bioinformatics.charite.de/superpred) to obtain the the target of action of the active ingredient.

2.2 Collection of ESCC Disease-related Targets

The GeneCards database (https://www.genecards.org/) was searched and screened for esophageal cancer-related pathogenic targets using “esophageal squamous cell carcinoma” as keywords. To obtain the intersection targets of curcumin and ESCC, Venny2.1 software (https://bioinfogp.cnb.csic.es/tools/venny/index.html) was used to import curcumin component targets and esophageal cancer causative targets to obtain the intersection targets and to draw a Wayne diagram.

2.3 “Curcumin-intersecting Target” Network Construction

The intersecting targets and curcumin components were imported into Cytoscape 3.10.0 software, and a network diagram of “curcumin-intersecting targets” was constructed to analyze the relationship between curcumin and intersecting targets.

2.4 Constructing a Protein PPI Network

Using the STRING database (https://stringdb.org/), the intersecting targets of curcumin and esophageal cancer were imported, and the protein species was set to “Homo sapiens” to obtain the protein-protein interaction network works (PPI) of the intersecting targets. The protein-protein interaction network works (PPI) of the intersecting target was obtained.

2.5 GO and KEGG Enrichment Analysis

The intersected targets were imported into Metascape platform (http://metascape.org) for GO functional enrichment and KEGG pathway enrichment analysis, and the species setting was “Homo sapiens” with the screening criterion of $P<0.01$. The enrichment results were visualized on the microbiology platform (http://metascape.org) to analyze the main biological processes and signaling pathways involved. The enrichment results were visualized through the microbiology platform (http://www.bioinformatics.com.cn) to analyze the main biological processes and metabolic pathways involved. Among them, different color nodes represented different types of enrichment results, while their

size was positively correlated with the degree of significance.

3. Analysis of Results

3.1 Effects of Curcumin

The targets were collated and de-emphasized in the SuperPred database to obtain 106 action targets.

3.2 Acquisition of ESCC-related Targets

A total of 3784 targets related to ESCC were obtained after searching and screening in GeneCards database. Comparison and analysis with curcumin targets showed that there were 166 targets of curcumin for ESCC (Figure 1).

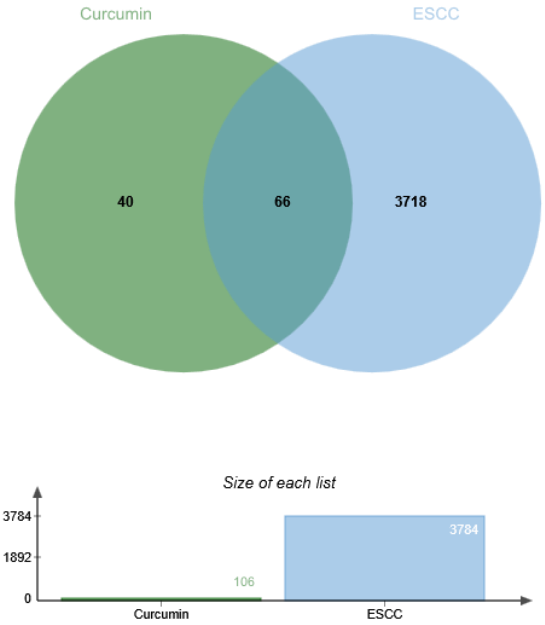

Figure 1: Curcumin for ESCC Intersecting Targets Wayne's Chart

3.3 PPI Network

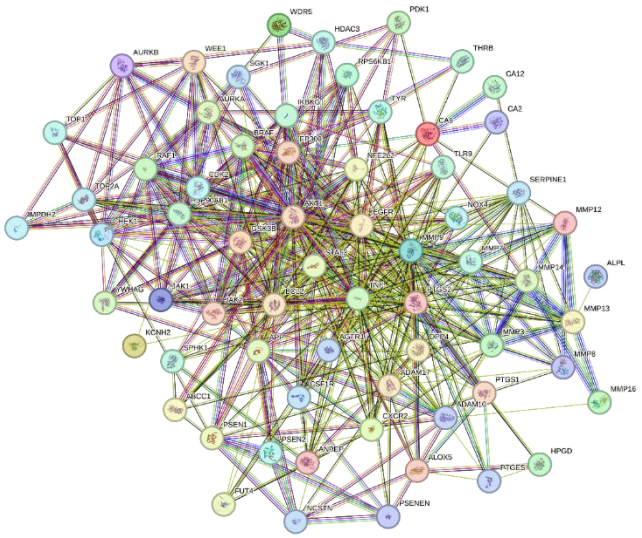

Figure 2: PPI network curcumin for ESCC intersection targets

After importing the PPI network "TSV" file obtained from String database into Cytoscape 3.10.0 software, the key target points are screened by Centiscape 2.2 plug-in, and the key target point PPI network map is plotted, and the larger the area of the circle, and the more the color tends to be darker, the larger the degree value (degree) is. The larger the circle area and the darker the color converge to indicate the larger the degree value (degree). The PPI network graph of common targets of curcumin for ESCC had 66 nodes, 473 edges, and the average node degree: 14.3 (Figure 2).

3.4 GO Function and KEGG Pathway Enrichment

The analysis utilized the Metascape platform to perform GO functional enrichment analysis of intersecting targets for curcumin treatment of ESCC, and the top 20 entries were screened for visualization based on the P value (Figure 3). The GO enrichment analysis generated 1578 entries for biological process (BP), 66 entries for cellular component (CC), and 71 entries for molecular function (MF). The intersecting targets were highly relevant to inflammation regulation; extracellular matrix remodeling; protease activity regulation; and membrane structural domains and cellular connectivity. KEGG pathway enrichment analysis was performed on the intersecting targets of curcumin treatment for ESCC using the Metascape platform (Figure 4), and 119 functional entries for KEGG enrichment analysis were obtained, and the top 20 entries were screened according to the P-value for visualization and analysis. Involving Alzheimer disease; PI3K-Akt signaling pathway, Prostate cancer, Human cytomegalovirus infection, EGFR tyrosine kinase inhibitor resistance and Pathways of neurodegeneration - multiple diseases, etc.

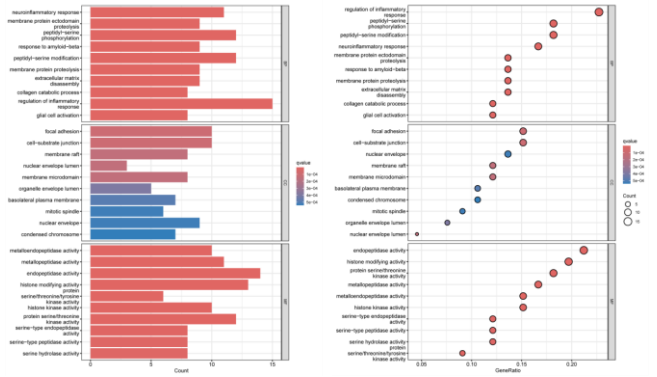

Figure 3: GO enrichment analysis

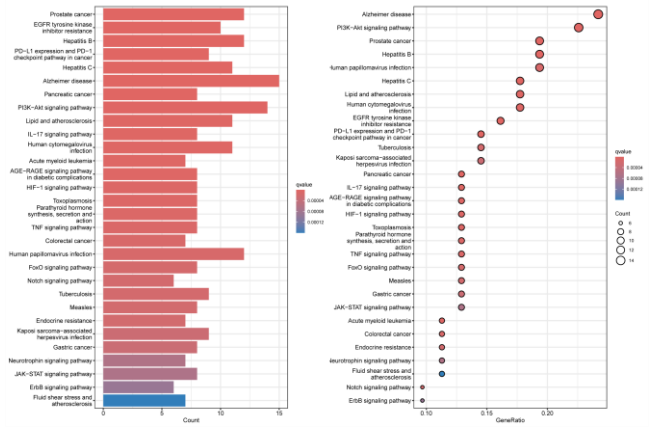

Figure 4: KEGG enrichment analysis graph

4. Discussion

Esophageal cancer ranks as the sixth leading cause of cancer

deaths globally, with high incidence and mortality rates [1]. The histologic subtypes of the disease show significant geographic heterogeneity, with esophageal squamous cell carcinoma (ESCC) dominating in Asia and Africa [13,14]. Despite the development of a comprehensive treatment system that includes radical surgery, systemic chemotherapy, precision radiotherapy, molecular targeted therapy, and immune checkpoint inhibitors, the five-year survival rate of ESCC patients remains low due to the prevalence of proliferative and metastatic tumor cells and drug resistance. Therefore, in-depth elucidation of prognostic biomarkers and innovative therapeutic targets is of great clinical value [15-17].

A technical approach based on network pharmacology to explore the potential targets of action and signaling pathways of curcumin against esophageal squamous carcinoma (ESCC). Key molecules such as CDK2, STAT3, BCL2, HIF-1α, and TNF-α were found to be significantly associated with the pathological process of ESCC [18-20]. As a key kinase in the regulation of cell cycle progression, CDK2 is mostly over-activated in malignant tumors due to increased gene copy number, abnormal accumulation of cyclin, or inhibitory factor dysfunction, which in turn induces cell cycle disorders and malignant proliferation. The STAT3 signaling axis plays a central role in ESCC evolution by regulating tumor microenvironmental homeostasis and immune escape mechanisms, and abnormally elevated BCL2 protein levels have been shown to be directly associated with ESCC chemoresistance and invasive phenotype. During the tumor hypoxic stress response, HIF-1α acts as a core regulatory element to drive malignant biological behaviors such as metabolic pattern switching, pro-angiogenesis, and invasion and metastasis, and its expression intensity is significantly and positively correlated with the risk of distal metastasis and resistance to treatment in ESCC. The pro-inflammatory factor TNF-α regulates the invasive and metastatic potential of tumor cells by reshaping the homeostasis of the immune microenvironment. The above molecular targets are involved in the development of ESCC through the regulation of cell cycle dynamics, apoptosis and escape mechanisms, and microenvironmental interactions, and have important therapeutic target translational value [21-23].

The multi-target mechanism of action of curcumin (Curcumin) was analyzed by GO enrichment analysis system. In the biological process (BP), curcumin was significantly enriched in the regulation of neuroinflammatory response, extracellular matrix catabolism and β-amyloid metabolism pathway, suggesting that curcumin plays a dual role of neuroprotection and antitumor effects by inhibiting microglial activation, remodeling the tumor microenvironment and interfering with amyloid deposition. In terms of molecular function (MF), curcumin targeted serine-type endopeptidase, metalloendopeptidase and histone modifying enzyme activities, suggesting that it can inhibit cancer progression by regulating protease-mediated inflammatory signaling (e.g. NF-κB) and epigenetic modifications (e.g. histone acetylation) [24-26]. Cellular component (CC) analysis showed that curcumin mainly acted on structures such as membrane rafts, basolateral plasma membrane, and nuclear periplasm, implying that it affects transmembrane signaling and DNA repair processes by interfering with dynamic assembly of cell membranes and chromatin remodeling in the nucleus.

KEGG pathway enrichment analysis revealed the multidimensional mechanism of action of curcumin. In cancer-related pathways, curcumin was significantly enriched in PI3K-Akt, JAK-STAT and ErbB signaling pathways, indicating that it could exert broad-spectrum anticancer effects by inhibiting PI3K-mediated cell proliferation, blocking STAT3 phosphorylation-driven immune escape, and reversing EGFR tyrosine kinase resistance. In terms of inflammation and immune regulation, curcumin targets IL-17 and AGE-RAGE pathways, suggesting that it attenuates chronic inflammation and diabetic complications by inhibiting pro-inflammatory factors (e.g., IL-6, TNF-α) and accumulation of advanced glycosylation end products (AGEs). In addition, the enrichment of infectious disease pathways (e.g., HPV infection, tuberculosis) supports that curcumin enhances resistance to infection by modulating the host immune response or directly inhibiting pathogen protein expression.

It is worth noting that curcumin intervenes in pathways related to neurodegenerative diseases (e.g., Alzheimer's disease) and metabolic disorders (e.g., atherosclerosis), highlighting its cross-disease regulatory properties. Its mechanism of action covers immune microenvironment remodeling, epigenetic modification and cell cycle regulation, reflecting the synergistic effect of "multi-target-multi-pathway". These results provide a molecular basis for curcumin to prevent esophageal cancer and other complex diseases, especially for the development of combined therapeutic regimens (e.g. chemotherapy/ immunotherapy sensitization). In the future, we need to verify the regulation of key pathway nodes (e.g., Akt, STAT3) through functional experiments and promote clinical translational research, so as to fully utilize the therapeutic potential of curcumin as a natural multifunctional compound.

Curcumin, as a natural polyphenolic compound, has certain advantages in the anti-ESCC effect. Compared with the problems of single target of action, limited clinical efficacy and many side effects of clinically used ESCC drugs, the natural compound curcumin's multiple pathways, multiple targets, strong bioavailability and blood-brain-barrier penetration will be helpful to make up for the shortcomings of traditional ESCC therapeutic drugs. In this study, we constructed a curcumin target network and a PPI network with the help of network pharmacology to systematically understand the core targets and related pathways of curcumin against ESCC, which provides a theoretical basis for the development of curcumin as a new drug against ESCC.

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