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ARTICLE

Integrated network pharmacology and bioinformatics to identify the therapeutic target and molecular mechanisms of Ze-Qi Decoction on lung adenocarcinoma

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Abstract

Lung adenocarcinoma (LUAD) is the most common histological subtype of primary lung cancer and has recently been reorganized into a spectrum ranging from preinvasive lesions to invasive adenocarcinoma. As a classic and famous prescription of Synopsis of the Golden Chambers, Ze-Qi Decoction (ZQD) has been proved to be an effective prescription for treating LUAD in clinic, however, the pharmacological mechanisms underlying the beneficial effects remain obscure. In this study, we explored the pharmacological mechanisms of ZQD against LUAD via network pharmacology analysis. ZQD may regulate LUAD by regulating core target genes, such as STAT3, MAPK3, MYC, ESR1, RELA, MAPK1 and JUN, and acting on multiple key pathways, such as the human cytomegalovirus infection, chemical carcinogenesis-receptor activation, and PI3K-Akt signaling pathway.

Keywords: lung adenocarcinoma;Ze-Qi Decoction;network pharmacology; molecular docking;RELA

Lung cancer continues to be the leading cause of cancer mortality in the world[1]. According to cytological classification, lung cancer can be further subdivided into the following two types, namely, primary small cell lung cancer (SCLC) and primary nonspecific small cell lung cancer (NSCLC) of which the incidence of NSCLC can be as high as about 85% or more[2]. Lung adenocarcinoma (LUAD) is one of the most commonly used human histological subtypes in the diagnosis of NSCLC[3]. The early clinical manifestations of

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LUAD are relatively insidious, while in the middle and advanced stages, local invasion or distant metastasis occurs, and its treatment effect is poor, and the estimated 5-year survival rate is less than 21%[4]. With the successive identification of oncogenic driver genes in lung cancer series, molecular targeted therapy plays an important role in the treatment of advanced NSCLC, which has greatly improved the prognosis of people with positive driver genes. In recent years, with the major breakthrough of immunotherapy in the field of lung cancer, the 5-year overall survival of some patients with negative driver genes has been significantly extended. However, due to the obvious adverse reactions of molecular targeted therapy and immunotherapy[5], easy drug resistance and high medical costs made it is still a refractory disease worldwide. At present, there are still many deficiencies in the conventional treatment of NSCLC. Therefore, it is urgent to study the molecular mechanisms of NSCLC and find efficient and safe therapeutic drugs. In recent years, there have been more and more clinical trials and basic researches on the treatment of NSCLC with traditional Chinese medicine (TCM), which providing new ideas and methods for NSCLC treatment.

Ze-Qi Decoction (ZQD) is a classic traditional Chinese medicine prescription consisting of nine types of herbal medicines, including Herba Euphorbiae Helioscopiae, Rhizoma Pinelliae, Rhizoma Zingiberis Recens, Rhizoma Cynanchi Stauntonii, Herba Salviae Chinesnsis, Radix Glycyrrhizae, Radix Sutellariae, Radix Ginseng, and Ramulus Cinnamomi, combined in a ratio of 30:15:10:10:10:6:6:6:6 by weight. ZQD has been used to treat lung adenocarcinoma for over 20 years in clinical practice, and its curative effect is considered credible. However, the chemical constituents of ZQD have not been revealed because of their complexity, which has significantly hindered the systematic clarification of the efficacy of the materials and quality evaluation.

Network pharmacology is an emerging discipline in recent years. It is a systematic analysis method based on the interaction of diseases, drugs, active ingredients, target genes, and target proteins. The complex synergistic functions and associations also coincide with the notable features of the holistic treatment of modern Chinese medicine and the systemic synergistic treatment of drugs in the treatment of disease processes[6], which can more clearly and intuitively represent the system of the drug itself and its related compounds. The use of network pharmacology can more clearly and intuitively show the complex synergistic relationship between the drug itself and the compound[7]. To this end, this study is aimed at studying the main drugs and their active chemical constituents, traditional Chinese medicine ZQD used in the treatment of primary lung adenocarcinoma through the technical system of modern network pharmacology technology and drug molecular information docking. The potential target structure and molecular information pathway provide the basis for the further research and development of the safety of the traditional Chinese medicine ZQD and the evaluation of the clinical use of the drug.

The effective components and predicted targets of ZQD were obtained through the Traditional Chinese Medicine Systems Pharmacology and Analysis Platform (TCMSP) database. The disease database was used to screen the disease targets of LUAD. We also used Cytoscape 3.7.2 software to construct a "Traditional Chinese Medicine-Active Ingredient-Target" network. The obtained key targets were uploaded to the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database for protein-protein interaction (PPI) network analysis. Bioconductor software and R x 64 4.0.0 software were then used

to perform GO functional enrichment analysis and KEGG pathway enrichment analysis on the targets. Molecular docking of core protein-ligand interactions was modeled using AutoDock Vina software.

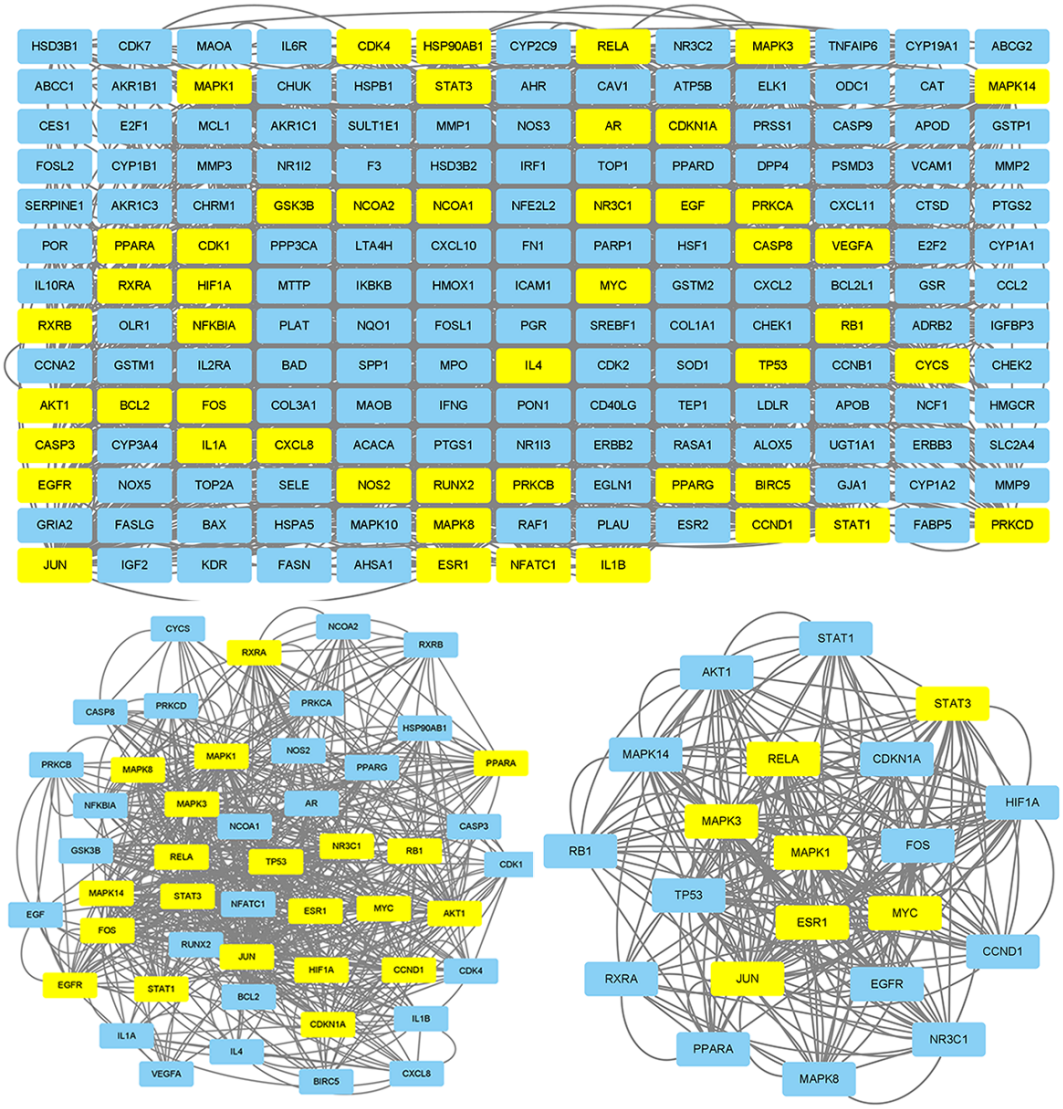

Figure 1. PPI network of predicted targets of ZQD against LUAD

The analysis revealed 151 active compounds and 228 potential targets of ZQD from the pharmacological database of Chinese medicine system and analysis platform (TCMSP) and 8907 related targets of LUAD from the GeneCards and Online Mendelian Inheritance in Man (OMIM) databases. Furthermore, 215 common targets of ZQD against LUAD were identified, and these common targets were used to construct a protein-protein interaction (PPI) network. The visual PPI network was constructed by Cytoscape software. The top seven genes from PPI according to degree value are STAT3, MAPK3, MYC, ESR1, RELA,

MAPK1 and JUN. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment were applied to reveal the potential targets and signaling pathways involved in ZQD against LUAD, especially the human cytomegalovirus infection, chemical carcinogenesis-receptor activation, and PI3K-Akt signaling pathway. In addition, molecular docking revealed that naringenin, quercetin, licochalcone a, luteolin, wogonin, isorhamnetin, and kaempferol displayed strong binding to STAT3, MAPK3, MYC, ESR1, RELA, MAPK1 and JUN.

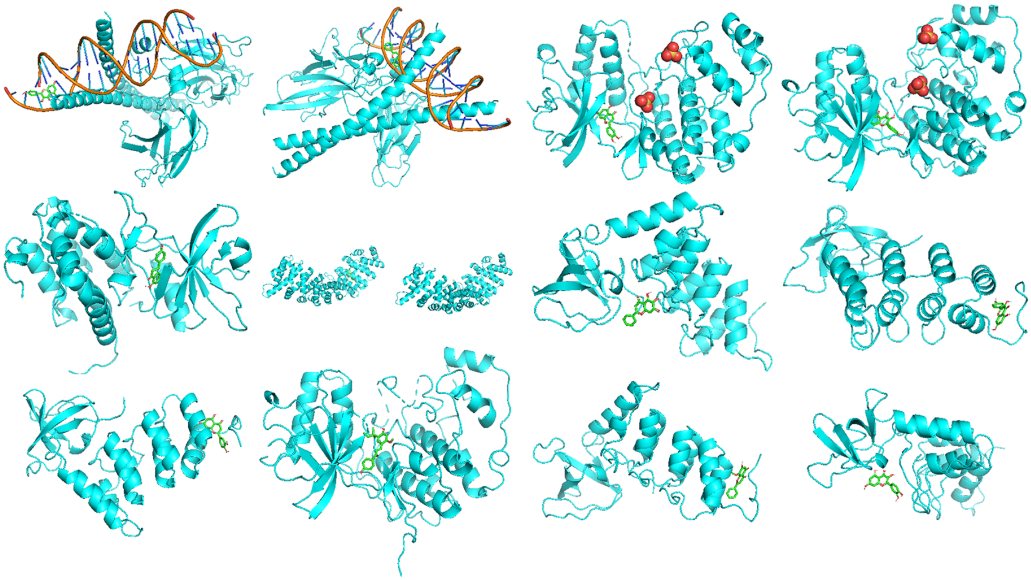

Figure 2. Molecular docking diagram of chemical composition to target

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