ORIGINAL RESEARCH

Elucidation of the Anti-Lung Cancer Mechanism of Xiao'ai Jiedu Prescription Based on Network Pharmacology and Molecular Docking

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ABSTRACT

Objective • Network pharmacology is an emerging discipline that applies computational methods to understand drug actions and interactions with multiple molecular targets. Xiao'ai Jiedu is a valued traditional Chinese medicine preparation for which the mechanism of action is not yet established. This study aims to explore the mechanism of Xiao'ai Jiedu in treating lung cancer through network pharmacology.

Methods • First, the Traditional Chinese Medicine Systems Pharmacology (TCMSP) data platform was used to analyze the target treatment results of different medicinal materials in Mr. Zhou's cancer prescriptions. Then, functional enrichment analysis was performed to conduct a secondary analysis of the dissemination of cancer biological and pharmacological information in the human body. The Cancer Genome Atlas (TCGA) was used to obtain several cancer-aggressive target groups, and their transcription RNA was extracted for collection. The CIBERSORT evaluation method was used to conduct a Spearman correlation analysis on the data processing results. Then the matching degree between the experimental cells and the principle of drug treatment was analyzed to improve the statistical analysis.

Results • Pharmacology research results showed that the network can accurately eliminate cancer detoxification targeted target correlation set, and through the data interpretation found that four different gene transcription have significant influence on lung cancer. The findings also confirmed that the degree of immune cell infiltration has a key role in lung cancer The study summarizes the active ingredients and their targets and mechanisms of action of the elimination of Xiao'ai Jiedu formula for the treatment of lung cancer.

Conclusion • Network pharmacology can carry on the processing of the data, find the key to conform to the goal of research data, and the corresponding results are obtained, and the development of network pharmacology is not limited to, the study of lung cancer. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Cancer has been a persistent problem in the history of human medicine since its discovery.[1] Current methods for the treatment of cancer in humans have adverse effects on both physical and mental health.[2] The subsequent development of targeted cancer treatment involves the identification of components on the surface of cancer cells.[3] Among different cancer types, lung cancer has a very high fatality rate, and it is associated with the highest cancer-linked mortality in most countries.[4-5] The early detection of the disease is not always enough to ensure improved chances of patient survival. In fact, at the time of diagnosis, most lung cancer cases are locally advanced or metastatic,[6] and potentially effective treatments need to be explored to enhance the clinical management of lung cancer.

Traditional Chinese Medicine (TCM) is becoming more and more popular in tumor treatment due to its multi-component, multi-link, multi-target, and multi-system regulation advantages.[7] In Chinese clinical practice of oncology, TCM is combined with modern medicine to improve efficacy and reduce adverse effects.[8] Xiao'ai Jiedu

prescription is an anti-cancer TCM prescription that Professor Zhou got from the theory of TCM and several years of medical practice. This prescription includes seven different herbs: Radix pseudostellariae, Radix ophiopogonin, Hedyotis, silkworm, centipede, mountain mushroom, and August herb. The main idea of the prescription is the TCM theory of Yin and Yang harmony and the halal methodology of removing stasis. The auxiliary herbs used in the prescription need to be differentiated according to the treatment of cancer. The mechanism of the effect of the Cancer Removing and Detoxifying Formula on cancer has not been elucidated but the effects of its main ingredients on cancer have been found in some studies. The main ingredients of Xiao'ai Jiedu have been found to inhibit cancer cells, reduce the activity of cancer cells, resist the expression of certain factors in cancer cells, and increase the body's autonomous clearance ability.[9,10] Therefore, it is necessary to study the potential mechanism of the anti-lung cancer effect of Xiao'ai Jiedu formula.

In recent years, network pharmacology has become a promising approach to studying the mechanism of action of Chinese medicines in TCM research.[11] There are more and more network pharmacology research platforms based on the Internet, and the data obtained from different platforms are also very different. By utilizing multiple authoritative databases to map drug-target disease networks, network pharmacology helps to explore the complex and multifaceted interactions between drugs and the human body.[12]

Thus, it is an innovation to use the expression of medical practice data of network pharmacology combined with the clinical manifestations of Xiao'ai Jiedu prescription to study the mechanism of its action and its effect on cancer. Although the development of network pharmacology has not taken place long before, it has experienced several important data revolutions in the process of its development.[13,14] The data upload and disclosure of clinical medicine have a great influence on the rapid interpretation of the action of Xiao'ai Jiedu prescription for lung cancer. At present, only a few studies are exploring the mechanism of action of Chinese medicine on lung cancer in China using network pharmacology, however, their direction of focus is different.[15,16] Literature findings show that the prescription can inhibit lung cancer and even eliminate some cancer cells under specific circumstances (suitable auxiliary medicinal materials and natural environment matching).[17]

The current study is based on the rapid development of network pharmacology, using different pharmacological research platforms to provide data to get cancer detoxification-related pharmacological data. Subsequently, network pharmacology was employed to forecast the potential targets and pathways of the Xiao'ai Jiedu prescription implicated in the biological process of anti-lung cancer. This study makes use of the network pharmacological analysis method in the new era, which can not only be used to study lung cancer, but can also be used in other pharmacological studies, and can improve the efficiency of pharmacological research, and make breakthrough contributions in treating other complex and challenging pathological conditions.

MATERIALS AND METHODS

Prediction of Targets of Xiao'ai Jiedu Prescription

Xiao'ai Jiedu Prescription contains the following 7 kinds of TCM: Baihuasheshecao, Shancigu, Jiangcan, Wugong, Taizishen, Maidong, Bayuezha. The above herbal medicines were searched in Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) (http://lsp.nwu.edu.cn/tcmsp.php) and subjected to toxic metabolokinetics (ADME) screening to identify the chemical components contained in these TCMs. Based on the predicted oral bioavailability (OB) and drug-likeness (DL) values of each constituent, the screened chemical components were text-mined with OB ≥30% and DL ≥0.18 as the screening thresholds, and characterized as potential active ingredients of Xiao'ai Jiedu prescription. The targets corresponding to the active ingredients were downloaded, and the English names of the active ingredients were obtained through the PubChem database and literature search.

Prediction of Targets for Lung Cancer

We used online tools such as GeneCards (http://www.genecards.org/) and Online Mendelian Inheritance in Man (OMIM, http://www.omim.org/) to find potential therapeutic targets for lung cancer. The search conditions were set to "gene" and "Homo sapiens," and the authenticity of the related genes was determined by a literature search. To improve the accuracy of the forecast in the GeneCards database, we only selected the target with a relevance score >20.

Functional Enrichment Analysis

The Database for Annotation, Visualization, and Integrated Discovery (DAVID) (https://david.ncifcrf.gov/), a widely used web-based genomic functional annotation tool, was used for functional analysis of the potential therapeutic targets of cinobufotalin injection. Gene ontology (GO) analysis and the Kyoto Encyclopedia of Genes and Genomics (KEGG) pathway analysis in the DAVID online tool were used for exploring gene function.

RNA-seq data acquisition

The Cancer Genome Atlas (https://portal.gdc.cancer.gov/), the largest database of cancer gene information, holds data including gene expression data, miRNA expression data, copy number variation, DNA methylation, SNPs, and so on. We downloaded the raw mRNA expression data for lung cancers. A total of 1149 samples were collected, including 108 normal specimens and 1041 cancer specimens.

Analysis of immune cell infiltration

The cell-type identification by estimating relative subsets of RNA transcripts (CIBERSORT) method is a widely used method for the evaluation of immune cell types in the microenvironment. The method is based on the principle of support vector regression and back-convolutional analysis of the expression matrix of immune cell subtypes. It contains 547 biomarkers distinguishing 22 human immune cell

phenotypes, including T-cell, B-cell, plasma cell, and myeloid cell subpopulations. In this study, patient data were analyzed using the CIBERSORT algorithm, which was used to infer the relative proportions of the 22 immune-infiltrating cells and to perform a Spearman's correlation analysis of gene expression and immune cell content.

Simulated Molecular docking

We collected the small molecule compounds of the main active ingredients of Chinese medicine in mol2 format, downloaded the crystal structures of structurally complete, high-resolution, ligand-bearing targets from the PDB protein database, and imported the data into Autodock software to perform molecular docking. The binding energies and hydrogen bond numbers were calculated.

Statistical Methods

Statistical analysis was performed using R language (version 4.0). All statistical tests were bilateral, and $P < .05$ was statistically significant.

RESULTS

Effective components and targets of Xiao'ai Jiedu prescription

From the TCMSP databases, the compounds, and corresponding targets of each TCM component in Xiao'ai Jiedu prescription were obtained. A total of 12 effective components met the screening conditions. Baihuasheshecao contains 5 effective components; Maidong contains 3 effective components; Shancigu contains 3 effective components; Taizishen contains 5 effective components; and, Wugong contains 1 effective component. The above active components corresponded to 110 targets (Figure 1).

Identification of Potential Targets for Lung Cancer

Thereafter, from GeneCards and OMIM databases, we obtained 884 targets for lung cancer. The VENN graph was used to perform repetitive screening of the above two newly refined databases to find the possible mechanism of lung cancer treatment in them. The results are demonstrated by the Cytoscape diagram, as shown in Figure 2.

GO analysis and KEGG signaling pathway analysis of the target genes

The gene expression pathways of targeted cells were analyzed concerning the biological information database of Kyoto University in Japan, mainly about the signal combing of cell environmental factors, cell growth information transmission factors, and the coordinated and unified path analysis of biological systems. Threshold: the minimum overlap is 3.8, and a path analysis is considered valid if the acquisition probability is less than 0.01. 14 pathways were less than 20-log10 to target cell points and the other pathways were more affected by glandular responses (prostate cancer, bioglandular development), biohormonal responses, and possibly lipid-atherosclerosis pathways. By eliminating

Figure 1. Drug Targets Interaction

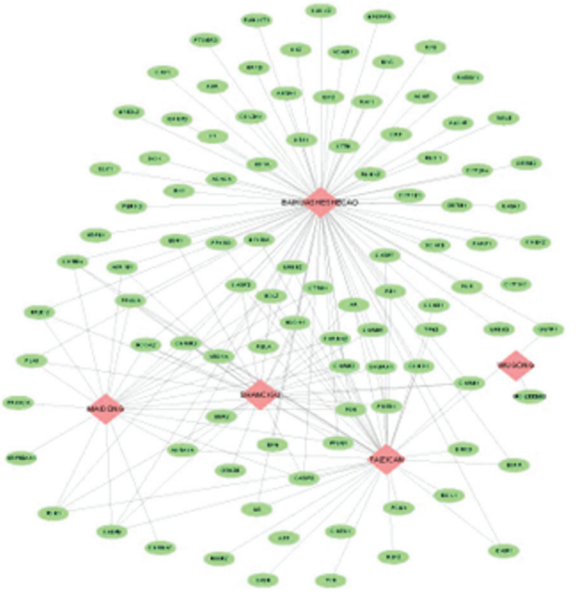


Figure 2. VENN of Repetitive Filtering

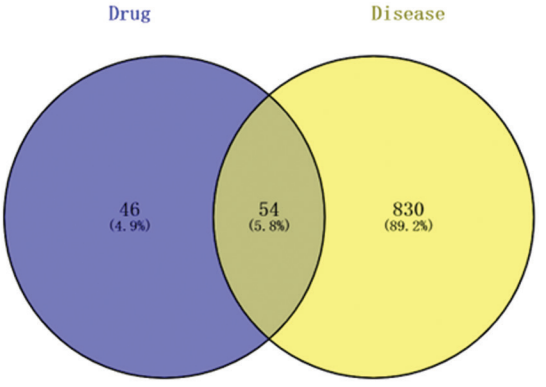


Figure 3. Functional Enrichment Analysis of the Target Genes. A: GO enrichment analysis; B: KEGG pathway analysis

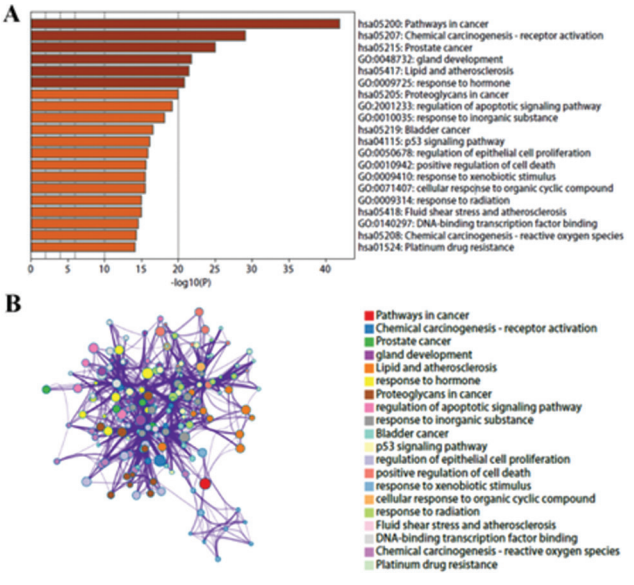


Figure 4. Influence of Different Medicinal Materials on the Environment of Immune Cell Infiltration

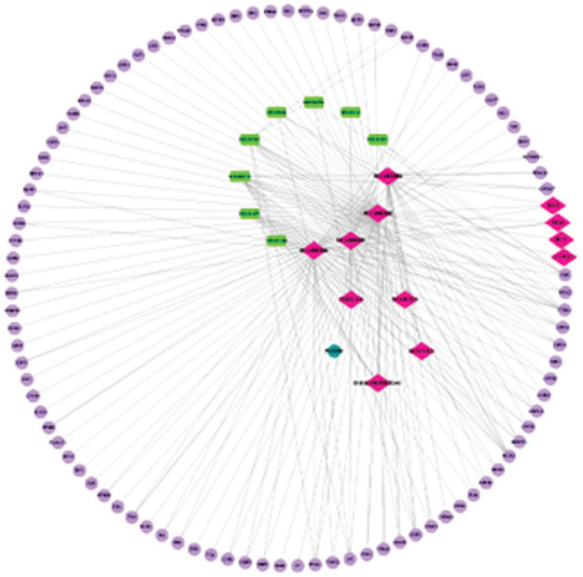
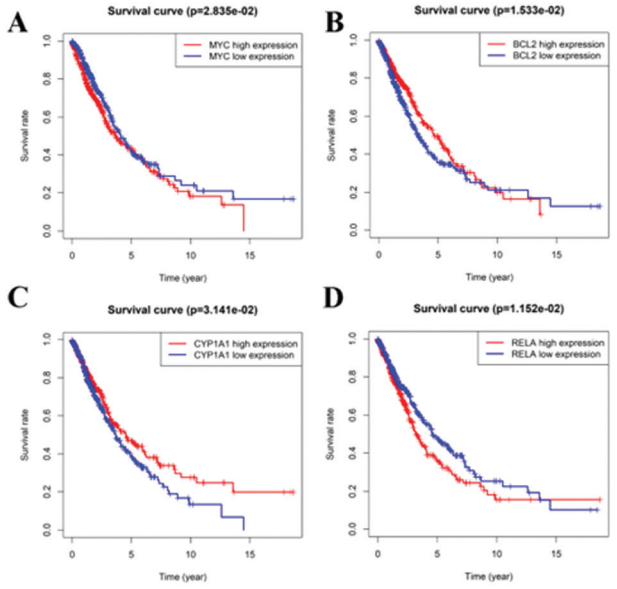


Figure 5. Survival Time of Cancer Cells with Different Expression Levels of Genes. A: MYC; B: BCL2; C: CYP1A1; D: RELA



cancer detoxification treatment for lung cancer, we found a way to process the impact of DNA-binding transcription factor binding, and p53 signaling pathway, reactions to inorganic matter, apoptosis signaling pathways regulate these paths, explain cancer detoxification through the inhibition of cancer cell gene transcription, reduce cancer cells in response to the inorganic matter, affect the control path to treat lung cancer cell apoptosis, as shown in Figure 3.

Analysis of the factors of Xiao'ai Jiedu prescription influencing immune cell infiltration

To investigate the relationship between target genes and immune cell infiltration, CIBERSORT methods were applied. As shown in Figure 4, different medicinal materials have different effects on the environment of immune cell infiltration. Although centipede among auxiliary medicinal materials has good effects in some specific environments, their scope of application is small and is not well applicable compared to other medicinal materials. The medicinal properties of ophiopogon can be widely applied to the environment of the immune system to effectively complete the task. Among the selected target sites, there was at least one medicine or medicine component corresponding to it. The medicine component data corresponding to NOCA2 was the most obvious but the transcription degree of immune cells affected by NOCA2 was not high. MOL001659 and MOL001670-MOL002045 are not affected by medicinal materials in many ways, and they have less intersection with other auxiliary medicinal materials. This may be because they are related to the changes in the environment of immune cell infiltration but the ingredients of the medicinal materials do not have a high level of influence on them. On the other hand, MOL000006, MOL001689, MOL000098, and MOL000358 have a deep impact on the environment of immune cells, and different medicinal materials can affect these targets, but the degree of impact is different. The results showed that BCL2, RELA, MYC, and CYP1A1 had the most obvious effects, which were closely related to other targets, and the effects of the ingredients of medicinal materials were not low. Therefore, the following study was conducted to analyze the infiltration of these four types of cells into the living environment.

Survival analysis of immune cell infiltration

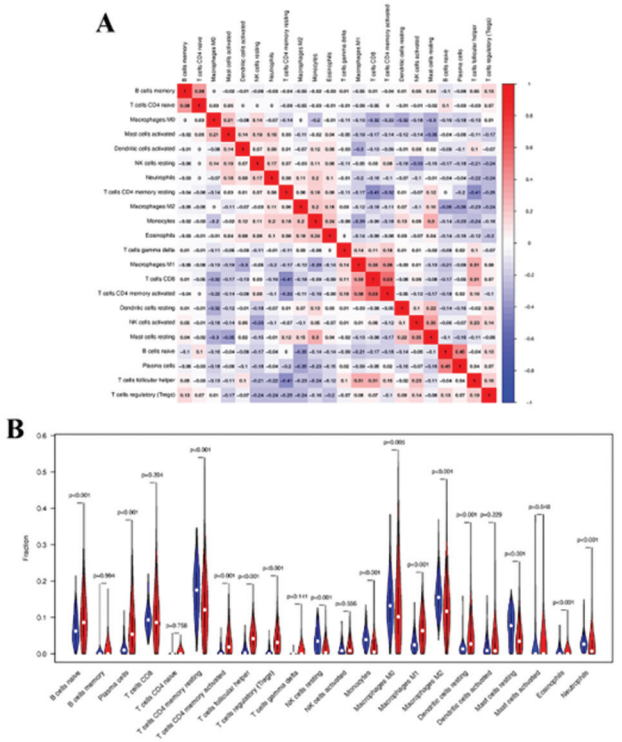
In the previous section, the factors of different ingredients of medicinal materials influencing targets in the environment of immune cell infiltration were analyzed, and four genes playing a decisive role in cancer cells were obtained: MYC, BCL2, CYP1A1, and RELA. This section will analyze the influence of these different gene expression degrees on the survival of cancer cells, and the results are shown in Figure 5.

Correlation analysis and evaluation of immune cell infiltration environment

The main gene expression affected by the Xiao'ai Jiedu formula was analyzed for the survival of cancer cells in the infiltrating environment, followed by the correlation analysis of different immune cells in the infiltrating tumor microenvironment, and then the expression of the main gene was evaluated. Correlation analysis and comparison are shown in Figure 6. The results show the expression correlation between different immune cells in the infiltrating environment, where a positive value indicates a positive correlation, a larger value indicates a stronger positive correlation, a negative value indicates a negative correlation and a smaller negative value indicates a greater negative correlation.

After analyzing the correlation of the different immune cells in the infiltrating environment, it is necessary to evaluate the expression of major genes. The results are shown

Figure 6. Immune Cell Infiltration Environment. A: Immune cell correlation map; B: Immune cell comparison



in Figure 7. The data in the figure show that the expression of these four genes is differentially associated with different immune cell infiltration. The correlation of BCL2 gene expression with T cells, CD4, and dendritic cells is the highest, with the absolute value of correlation reaching 0.16. However, the correlation with monocytes and eosinophils is relatively low, and the finding may be relevant in future lung cancer treatment studies.

The expression of the CYP1A1 gene is the most correlated with Macrophages M0 and T cells regulatory cells, the absolute value of correlation is 0.16, while the absolute value of correlation with eosinophils cells is the lowest, only 0.08. MYC gene expression was most correlated with NK cell resting and mast cell resting, the absolute value of correlation was 0.20, while the absolute value of correlation with eosinophils cell was only 0.10. RELA gene expression was most correlated with T cells regulatory and T cells gamma delta expression, with the absolute value of correlation reaching 0.20, while the absolute value of correlation with mast cells was the lowest, only 0.10.

Correlation analysis of core gene expression and molecular docking of different genes

The core genes studied in this paper are BCL2, CYP1A1, MYC, and RELA. Next, we studied their correlation in molecular docking of different genes, and the results are shown in Figure 8. The molecular docking correlation analysis diagram of MYC is enlarged to obtain the correlation analysis of MYC on SLC40A1 and NFE2L2. The scatter plot

Figure 7. Correlation Between CIBERSORT and Expression of Genes. A: Correlation between CIBERSORT and expression of BCL2; B: Correlation between CIBERSORT and expression of CYP1A1; C: Correlation between CIBERSORT and expression of MYC; D: Correlation between CIBERSORT and expression of RELA

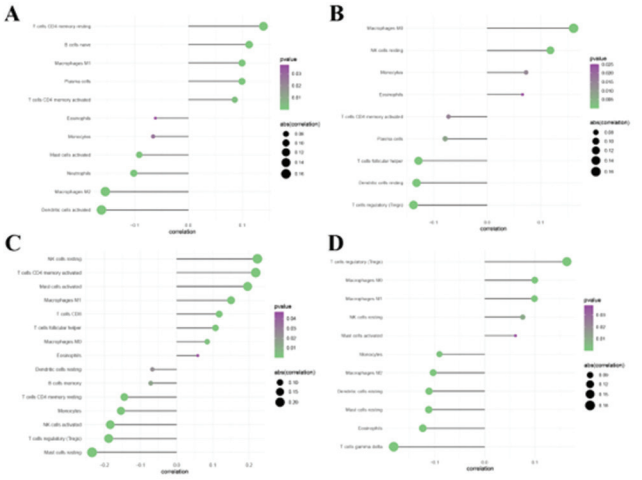


Figure 8. Correlation Analysis of Docking of Different Gene Molecules

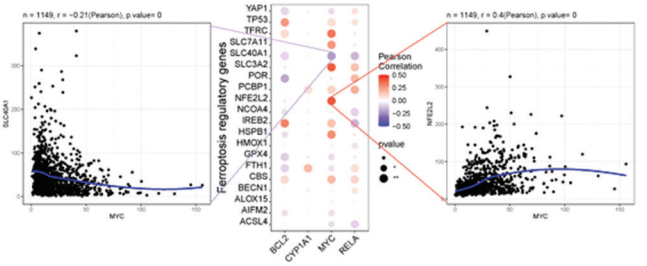
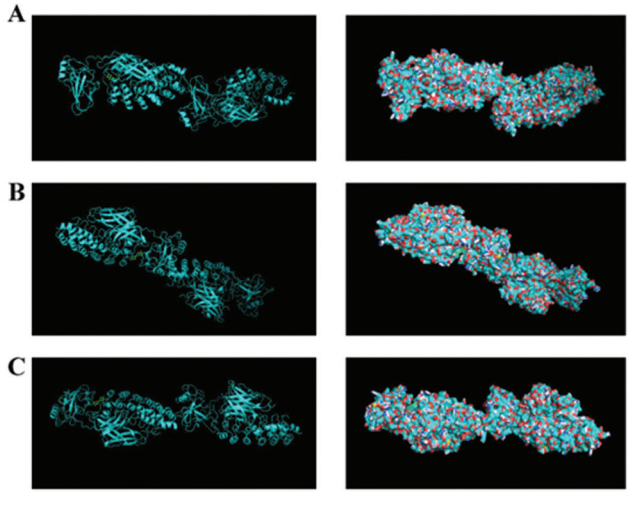


Figure 9. Molecular Docking. A: RELA+quercetin; B: RELA+acacetin; C: RELA+luteolin



in the figure shows that the correlation analysis of MYC on SLC40A1 and NFE2L2 has a divergent trend, and the fitting results of the overall regression analysis are not the same. Moreover, the analysis result of CYP1A1 was the least

obvious among these gene analyses, indicating the correlation of molecular docking analysis of the CYP1A1 gene was not high. BCL2, CYP1A1, and RELA genes had little correlation with NFE2L2 but the MYC gene had a high correlation with NFE2L2 molecular docking. This result verified the conclusion in the previous chapter that different genes have different effects on the infiltration of different immune cells.

Molecular docking

From the research species in the previous section, we selected the RELA gene as the main gene to carry out molecular docking analysis, and the results are shown in Figure 9. The molecular docking results of quercetin were the most irregular, and the arrangement of its targets was also disorderly. Although the molecular docking results of acasetine and luteolin showed some irregular characteristics, they showed Ziranguize molecular docking results in some regions, which were quite different.

DISCUSSION

In recent years, the need for innovative medical research methods have increased. Instead of using traditional local data analysis as the main source of clinical medical data, it is also necessary to connect different databases from around the world to reflect different clinical realities. Network pharmacology is a popular effective means of exploring mechanisms in pharmacological research.[18] The continuous breakthrough of human computing ability and the revolutionary change brought by quantum computing makes it possible to process and analyze huge data. Among them, the use of network pharmacology is particularly important for the continuous development of cancer treatment. Xiao'ai Jiedu prescription has a great influence on the mechanism of lung cancer treatment with the potential to develop new strategies for lung cancer treatment. Therefore, this study adopted a research method based on network pharmacology to study the mechanism of Xiao'ai Jiedu prescription in the treatment of lung cancer.

In this study, by introducing the core content of network pharmacology and combining it with previous research, various data needed for this research were extracted from different databases, and then different targets for lung cancer treatment were extracted from these databases, and the influence of Xiao'ai Jiedu prescription on lung cancer gene expression was analyzed. The relationship between the survival environment of immune cells and the survival rate of cancer cells in an infiltrating environment was studied. Finally, the docking analysis of important gene receptors was completed by using molecular docking technology, and the new receptors were designed and generated.

The results found that MYC, BCL2, CYP1A1, and RELA were the key targeted genes to this formula. The expression levels of these four genes have different effects on the survival of cancer cells; however, high levels of expression of all four genes do not imply the inhibition of cancer cell survival and show different gene characteristics under different environments. MYC is causally involved in the growth, progression and maintenance of cancers of diverse origins.[19] The low expression of the MYC gene can also inhibit the survival of cancer cells, and its impact on the survival rate of cancer cells is the same as observed during its high expression.[20] However, when the survival rate of cancer cells is lower than 20%, the low expression of the MYC gene does not affect the survival of cancer cells. The influence of the level of BCL2 gene expression on the survival rate of cancer cells is not constant. The effect of the high expression of the BCL2 gene on the survival of cancer cells is not as good as that of low expression of the BCL2 gene in the first few years, but after 10 years, the effect is significantly better than that of the low expression of BCL2 gene. The low expression of the BCL2 gene had a significant inhibitory effect on the survival of cancer cells in the initial five years but the inhibitory effect was significantly reduced after five years, which may be due to stimulation of resistance among the cancer cells.[21-22] The high expression and low expression of the CYP1A1 gene have the same influence on the survival of cancer cells but the low expression of the CYP1A1 gene has a more obvious inhibitory effect on cancer cells.[23] The results of gene sensitivity analysis were different. From the fourth year, the slope of the low expression of the CYP1A1 gene to inhibit the survival of cancer cells has changed, and the inhibition is more obvious. This indicates that the low expression form of the stimulus is more beneficial for the treatment of lung cancer.

The development of network pharmacology can promote the development of a variety of complex clinical medical research that requires a large amount of data support. The most important thing is that it can not only be used in the study of drug composition mechanism, but can also be used in the key research of drug properties, cell binding, and transport after optimization. The detailed mechanism of Xiao'ai jiedu prescription in treating lung cancer or cancer will be unveiled in further studies under the joint efforts of all scholars. This will help to create new paths and means for cancer treatment, which is promising for mankind in the future.

CONCLUSION

Network pharmacology can help to perform data processing to achieve the goal of the intended research. It is a powerful tool that helps to identify the interaction of medicinal compounds and their targets and understand the mechanism of drug action. The potential of network pharmacology is immense and its role is not just limited to the study of lung cancer.

AUTHOR DISCLOSURE STATEMENT

The authors declare that they have no competing interests.

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AUTHOR CONTRIBUTIONS

Jin-Shu Fang and Jian-Yi Huang conceived the study design and the content concept; Liu Li and Ping-ping Zhai performed the data collection, and extraction and analyzed the data. Mian-Hua Wu and Wen-Ting Li interpreted and reviewed the data and drafts. Mian-Hua Wu and Wen-Ting Li reviewed the final draft.

AVAILABILITY OF DATA AND MATERIALS

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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