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Exploring the mechanism of quercetin on cervical cancer based on network pharmacology and molecular docking

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Abstract: *Cervical cancer is one of the major cancers that endanger women's lives. At present, the means of treatment are still limited. Traditional Chinese medicine and its ingredients, as a new direction, provide new ideas for the treatment of cervical cancer. Quercetin, as the main ingredient in many traditional Chinese medicines, may be a new ingredient in the treatment of cervical cancer. Based on network pharmacology and molecular docking technology, this paper analyzes the mechanism of quercetin in the treatment of cervical cancer, and further explores the modern pharmacological action of quercetin. The related targets of "quercetin" were screened from the TCMSP database; Relevant targets of "cervical cancer" were screened from Genecards database. After the common protein target information of the two was obtained through venny, the protein interaction network was constructed using Cytoscape software, and the hub gene was screened. Use David platform to conduct GO, KEGG and other enrichment analysis on the same target. Finally, molecular docking technology was used to test the accuracy.There are 128 nodes and 911 edges in the PPI network, among which AKT1, TNF, JUN, TP53, IL-6, VEGFA, EGFR, RELA, CASP3 and other targets rank higher. The enrichment analysis results of GO and KEGG showed that the effect of quercetin on cervical cancer mainly involves biological processes such as positive regulation of gene expression, response to drug, positive regulation of translation, DNA-template, etc. The signal path mainly includes AGE-RAGE signaling path in radial applications, TNF signaling path, IL-17 signaling path, etc. Molecular docking results show that quercetin is associated with AKT1, TP53, TNF- α The binding degree of iso-target and quercetin is good. It is enriched in KEGG pathway. It reveals the potential target and mechanism of quercetin acting on cervical cancer, hoping to develop new drugs for treating cervical cancer.*

Keywords: *quercetin; network pharmacology; cervical carcinoma; molecular docking; Action mechanism*

Cervical cancer is a common malignant tumor in women, which is one of the main factors leading to female death [1].At present, the treatment of cervical cancer is still limited, and surgical treatment is still the main method of treatment. After surgery, radiotherapy, chemotherapy and other adjuvant therapies are given to a certain extent [2].However, there are still some problems in the treatment at this stage, such as recurrence and metastasis after surgery, and excessive adverse reactions of adjuvant treatment such as radiotherapy and chemotherapy. Therefore, the search for new drugs and targets for the treatment of cervical cancer is still one of the current research hotspots.Quercetin is a kind of flavonoid compound widely existing in nature, which is often distributed in diffusa diffusa, camellia and other plants [3].Modern research has found that quercetin has anticancer, anti-inflammatory, antioxidant and other effects. [4] A study found that quercetin can interfere with the growth of human cervical cancer cell hela. Its main mechanism of action is to promote apoptosis and achieve anti-tumor effect by down-regulating the medium-term MK-mRNA, up-regulating the expression of Casepase-3 mRNA and its protein [5].Network pharmacology is a new subject that integrates pharmacology, bioinformatics and other interdisciplinary disciplines. We can systematically analyze the relationship between drugs from drug-disease-target. Now it has been widely used in the prediction of the active ingredients of traditional Chinese medicine and the study of the mechanism of action.In this paper, the key target and action pathway of quercetin in the treatment of cervical cancer are explored by means of network pharmacology and molecular docking [6]. It provides a theoretical basis for subsequent experimental verification and clinical application.

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1. Method

1.1. Screening of targets of quercetin action

With "quercetin" as the search term, in the TCM system pharmacology analysis platform TCMSP database (https://old.tcmsp-e.com/tcmsp.php) Retrieval [7]. According to the principle of pharmacokinetics, oral bioavailability (oralbioavailability, OB) 30%, drug (DL) 0.18 were selected. After removing duplicates, the target name was standardized by database Uniprot (https://www.uniprot.org/) to obtain quercetin, target data [8].

1.2. Screening and analysis of targets for cervical cancer action

The word "Cervical cancer" as the search term was searched in the GeneCards database (https://www.genecards.org/) to obtain the data of the disease target of cervical cancer [9].

1.3. Screening of the intersection targets of quercetin and cervical cancer

The data of the targets of quercetin and the targets of cervical cancer disease were obtained using VENNY2.1 to obtain the intersection targets of quercetin and cervical cancer and generate a Wayn diagram [10].

1.4. Construction of the component-disease-target network map

Quercetin, disease, and action target guide Cytoscape 3.7.1 software to construct drugactive ingredient-target-disease, network diagram.The relationship between the drug composition and the target of action was visualized.

1.5. Protein-protein interaction (PPI) network construction

The common targets of drugs and diseases were introduced into STRING database https://cn.string-db.org/), the species was set as "Homo sapiens", the protein interaction (protein-protein interaction, PPI) network was obtained, and further imported into Cytoscape3.7.1 software for topological analysis to select the core targets for the treatment of cervical cancer.

1.6. Enrichment analysis of the GO function and KEGG signaling pathway

GO function and KEGG were performed using the DAVID database (https://david.ncifcrf. gov /), and signaling pathway enrichment analysis. The GO functional annotations include biological processes (biological process, BP), cellular components (cell component, CC), and molecular functions (molecularfunction, MF). $P < 0.05$ was used as the screening condition to select the leading signaling pathways, and the bubble map was plotted for visualization.

1.7. Active ingredient-target molecule docking

In order to verify the results of the network pharmacological analysis, the core targetsAKT1, P53, and TNF-α were selected as receptors, and quercetin was selected as ligands for molecular docking.Retrieve the SDF structure file of the compound through the Pubchem website (https://pubchem.ncbi.nlm.nih.go), convert the SDF file into a PDB file using Open Bable software, and retrieve AKT1, P53, TNF-α from the Potein Data Bank (https://www.rcsb.org/) database, PYMOL2.3.4 software was used to take water from the acceptor protein, AutoDockTools software was used to hydrogenate the acceptor protein, balance charge and other modifications, and AutoDock Vina 1.1.2 was used to molecular docking between the receptor protein and the ligand small molecule, and the binding energy could be scored for analysis. The lower the binding energy, the better the affinity between the two and the more stable the conformation.

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2. Results

2.1. Intersection target of quercetin and cervical cancer

Through searching the genecard database, a total of 7819 targets of cervical cancer was retrieved, and the venny map was drawn by cross-comparison with quercetin targets, and 133 common targets were obtained. (See Figure 1)

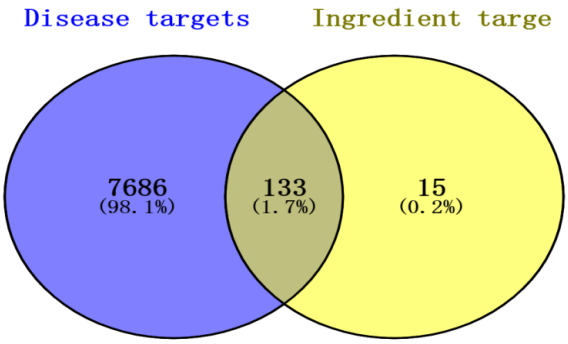

Figure 1: Target map of quercetin and cervical cancer

2.2. Construction of disease-component-target network

Quercetin, disease and action target were introduced into the Cytascape 7.1 software to construct the drug active component-target-disease network diagram. Visualize the relationship between drug components and action targets. (See Figure 2)

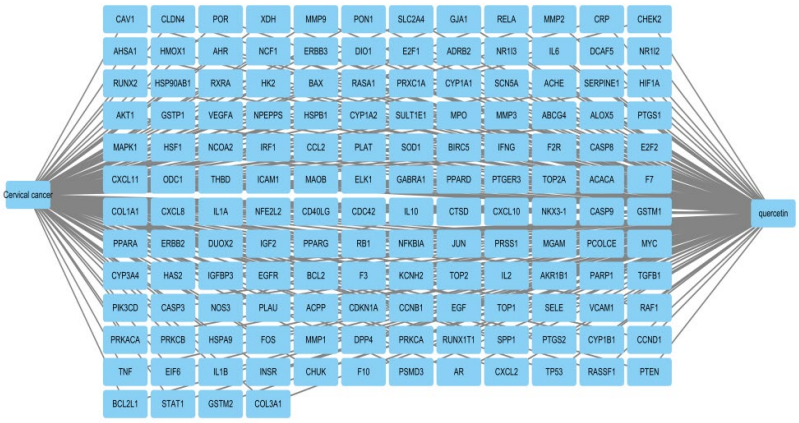

Figure 2: Schematic diagram of component-disease-target

2.3. PPI network for quercetin treatment of cervical cancer

The common targets of drugs and diseases are imported into the STRING database, analyzed by using the Cytoscape 7.1 software, and screened according to the degreevalue to obtain the core targets, with 128 nodes and 911 edges. These targets mainly include AKT1, TNF, JUN, TP53, IL-6, VEGFA, EGFR, RELA, CASP3, etc. These targets may be the core targets of quercetin in the treatment of cervical cancer. (See Figure 3)

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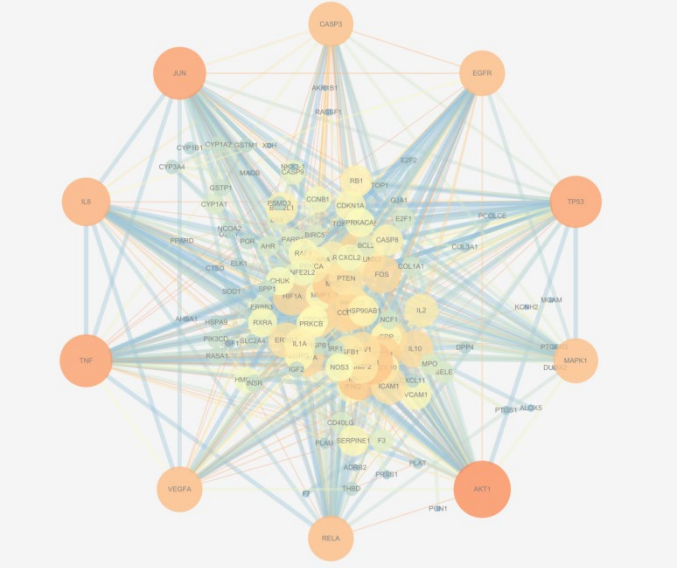

Figure 3: PPI network of quercetin and cervical cancer intersection targets(The node represents the target protein, and the edge represents the relationship between protein and protein. The darker the color and the larger the shape of the node, the greater the degree value)

2.4. GO function and KEGG pathway analysis

The common drug targets were imported into DAVID database for GO enrichment analysis, including 74 entries for biological process, 69 entries for cell components and 128 entries for molecular function. Among them, biological process involves positive regulation of gene expression, response to drug, positive regulation of translation, DNA-templated, etc., and cell components involve extracellar space, extracellar region, macropolar complex, etc. Molecular function involves such processes as enzyme bindingand protein binding. Visualization is carried out according to the first five plots of P value from small to large. (See Figure 4)

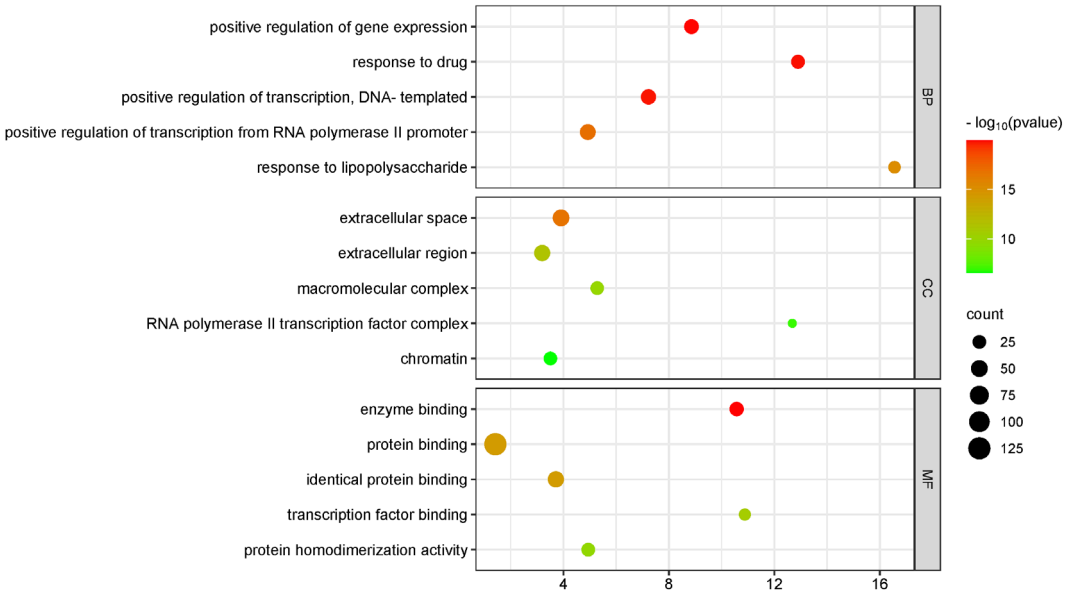

Figure 4: Schematic diagram of GO enrichment analysis results

The enrichment analysis of KEGG pathway obtained 172 pathways, mainly involving AGE-RAGE signaling pathway in diabetic applications, TNF signaling pathway, IL-17 signaling pathway, etc.. (See Figure 5)

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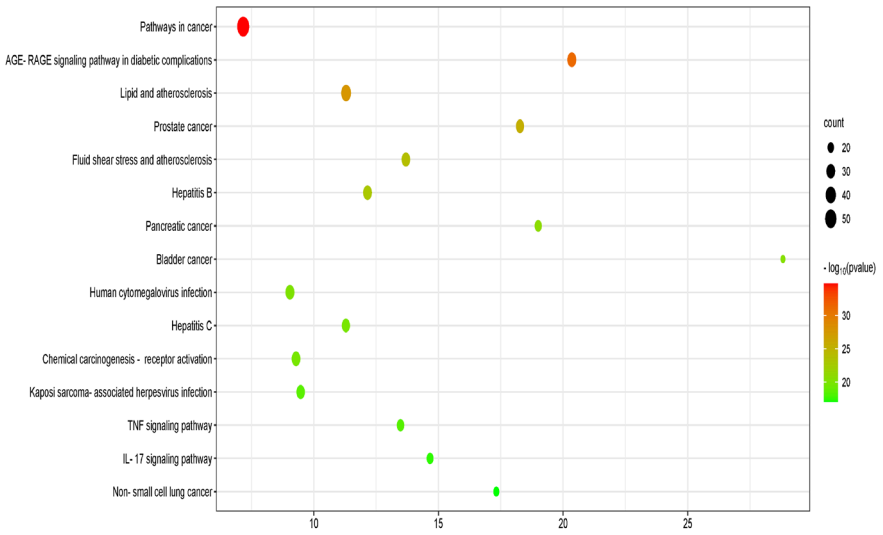

Figure 5: Bubble diagram of KEGG pathway analysis of quercetin treatment of cervical cancer

2.5. Molecular docking results

Combine quercetin with AKT1, TP53 and TNF- α Through molecular docking, it was found that quercetin and AKT1, TP53, TNF- α The binding degrees of the three targets were - 8.2 kcal/mol, - 6.2 kcal/mol, and - 5.1 kcal/mol, respectively, which were less than - 5 kcal/mol, suggesting that the intermolecular binding activity was very good. Through molecular docking, it was proved that quercetin and AKT1, TP53, TNF- α The protein can bind effectively. (See Figure 6 and Table 1)

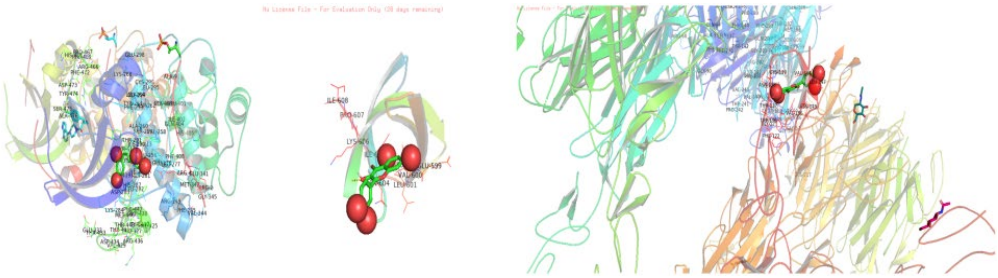

Figure 6: Quercetin and AKT1, TP53, TNF-α molecular docking

Table 1: Binding degree of quercetin with AKT1, TP53 and TNF

ACTIVE INGREDIENTS	AKT1	P53	TNF- A
QUERCETIN	-8.2kcal/mol	-6.2kcal/mol	-5.1kcal/mol

3. Discussion

This paper uses network pharmacology and molecular docking technology to explore the potential mechanism of quercetin in the treatment of cervical cancer. The results of network pharmacology showed that AKT1, TP53, TNF- α May be the key target of quercetin in the treatment of cervical cancer.Among them, AKT1 gene encodes serine/threonine protein kinase, which is a member of AKT family. AKT1/protein kinase B signal channel regulates cell proliferation and growth, and promotes tumor occurrence. This also suggests that AKT1 may be one of the targets of quercetin in the treatment of cervical cancer [11-12].P53 is the protein expressed by TP53, and TP53 is the gene of chromosome 17. p53 is a tumor suppressor protein and transcription factor, which can regulate cell division, prevent the division of cells with DNA mutation or damage, and transmit apoptosis signals to these cells through transcriptional regulation, thus preventing tumor formation. It can respond to cell stress or DNA damage and activate multiple transcription targets. P53 can coordinate a variety of reactions, including cell cycle arrest, DNA repair, metabolic changes, antioxidant effect, anti-angiogenesis, autophagy,

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aging and apoptosis [13-14].KEGG analysis showed that quercetin treatment of cervical cancer may be related to AGE-RAGE signal pathway.Glycation plays an important role in the development of cancer. The glycosylation of biological macromolecules leads to the development of advanced glycation end products (AGEs), which makes tumor cells proliferate in the process of carcinogenesis by activating transcription factors and releasing cytokines. The receptor for advanced glycation end products (RAGE) binds to its different ligands. The activation of downstream signal pathways ultimately leads to the pathophysiological status of diabetes, aging, neuropathy and cancer, as well as the activation of transcription factors. Studies have found that RAGE and s-RAGE levels may be biomarkers for the activation of ligand RAGE pathway and tumorigenesis [15-16].Therefore, the possibility of providing potential supplementary basis for the occurrence of cancer is very high, which may be a new target of treatment intervention.

4. Result

To sum up, this study uses the method of network pharmacology to screen the key targets of quercetin in the treatment of cervical cancer, and uses the molecular docking analysis method to verify the action mode of quercetin on the key targets. Based on the enrichment pathway, quercetin may regulate gene expression through multiple pathways and multiple targets to achieve the effect of treating cervical cancer.This study will carry out subsequent cell experiments and animal experiments to verify the mechanism of quercetin in the treatment of cervical cancer.

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