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Exploration on the mechanism of quercetin in treating breast duct dilation based on network pharmacology

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Abstract: Dilation of mammary duct is a chronic nonbacterial inflammation of the breast based on breast duct obstruction, secondary breast duct dilation, periductal inflammation, and plasma cell infiltration.Dilation of mammary duct is a chronic nonbacterial inflammation of the breast based on breast duct obstruction, secondary breast duct dilation, periductal inflammation, and plasma cell infiltration. To analyze the mechanism of quercetin in the treatment of Dilation of mammary duct based on network pharmacology and further explore the modern pharmacological action of quercetin, The related targets of "quercetin" were screened from the TCMSP database; Relevant targets of " Dilation of mammary duct 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 targe. Conclusion: There are138 nodes and 2608 edges in the PPI network. These targets mainly include AKT1, IL-6, TP53, TNF, VEGFA, CASP3, IL1B, EGFR, JUN, etc. The results of GO enrichment analysis showed that quercetin is involved in 666 biological processes, 98 cellular composition, and 128 molecular functions. It mainly plays a role in AGE-RAGE signaling pathway in diabetic complications, Pathways in cancer, Lipid and atherosclerosis, and other pathways, Conclusion: Quercetin exerts anti-inflammatory effects in Dilation of mammary duct through multiple pathways and multiple targets, which is a new option for the treatment of Dilation of mammary duct.

1. Introduction

Dilation of mammary duct is a chronic nonbacterial inflammation of the breast based on breast duct obstruction, secondary breast duct dilation, periductal inflammation, and plasma cell infiltration [1-3]. It often occurs in non-lactating women, accounting for 4% to 5% of all benign breast diseases, and is more common in women aged 25 to 40 years, especially in the first 5 years of pregnancy [4-

6]. Its clinical manifestations are nipple discharge, subareolar mass, local pain and discomfort in the breast, and easy to form fistulas after suppuration and rupture, which is difficult to heal for a long time [7-8]. Western medicine treatment is mainly based on drugs and surgery, but at present, there is a lack of Western drugs with definite efficacy in clinical practice, and surgical resection will not only affect the appearance of the breast, but also have a high recurrence rate. With the transformation of treatment mode and the accumulation of medication experience, people have recognized the clinical value of traditional Chinese medicine in the treatment of this disease [9]. Quercetin has anti-inflammatory, antibacterial, anticancer, antioxidant, immune function regulation and cardiovascular protection, and has high value in the treatment of this disease, but the relevant mechanism of quercetin in the treatment of plasma cell mastitis is not clear. Network pharmacology uses biomolecular network methods to analyze the pharmacological branch of "multi-component, multi-target, multi-pathway" synergy between drugs and diseases and targets, which is consistent with the principles of traditional Chinese medicine in the treatment of complex diseases. In this paper, the potential chemical components and possible mechanisms of quercetin in the treatment of dilation of mammary duct were discussed.

2. Method

2.1. Screening of targets of quercetin action

Using "quercetin" as the search term, retrieve from the TCM system pharmacology analysis platform TCMSP database (https://old. tcmsp-e. com/tcmsp. php). After removing duplicates, standardize the target name using the database UniProt (https: //www. uniprot. org/) to obtain quercetin, target data [10-11].

2.2. Screening and analysis of targets for mammary duct dilation action

To investigate the disease target associated with mammary duct dilation, a search was conducted in the GeneCards database (https://www.genecards.org/) using the search term 'dilation of mammary duct.' This inquiry aimed to retrieve pertinent information regarding the condition linked to mammary duct dilation."

2.3. Screening of the intersection targets of quercetin and mammary duct dilation

In order to identify potential therapeutic targets, we employed VENNY2.1, a versatile tool for comparative analysis. Our objective was to elucidate the shared molecular targets between quercetin, a bioactive compound, and the disease state characterized by mammary duct dilation. This endeavor was undertaken to ascertain the convergence of quercetin's pharmacological effects with the pathogenesis of mammary duct dilation, ultimately facilitating the exploration of its therapeutic potential. Subsequently, a Venn diagram was generated to visually represent the overlapping targets between quercetin and the disease condition, contributing to a comprehensive understanding of their molecular interplay.

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

In the pursuit of a comprehensive understanding of the relationship between drug composition and the target of action, we employed Cytoscape 3.7.1 software. The objective of this endeavor was to construct a network diagram encapsulating the intricate interplay among quercetin, the disease of interest, and the corresponding action targets. This network visualization was meticulously designed

to elucidate the intricate connections between the drug's active ingredient, its target of action, and the specific disease under investigation. Such a visual representation serves as a valuable tool for gaining insights into the complex pharmacological mechanisms at play.

2.5. 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 dilation of mammary duct.

2.6. 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 (molecular function, MF). P <0. 05 was used as the screening condition to select the leading signaling pathways, and the bubble map was plotted for visualization.

3. Results

3.1. Intersection target of quercetin and dilation of mammary duct

Through searching the genecard database, a total of 4676 targets of dilation of mammary duct were retrieved, and the venny map was drawn by cross-comparison with quercetin targets, and 118 common targets were obtained. See Figure 1.

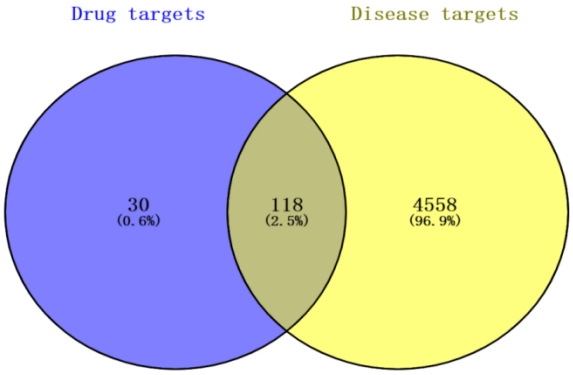

Figure 1: Quercetin and Dilation of mammary duct share targets

3.2. Construction of disease-component-target network

Quercetin, diseases, and action targets were incorporated into Cytoscape 7. 1 software to construct a network diagram of drug active components, targets, and associated diseases. The visualization of this network illustrates the relationship between drug components and action targets. See Figure 2.

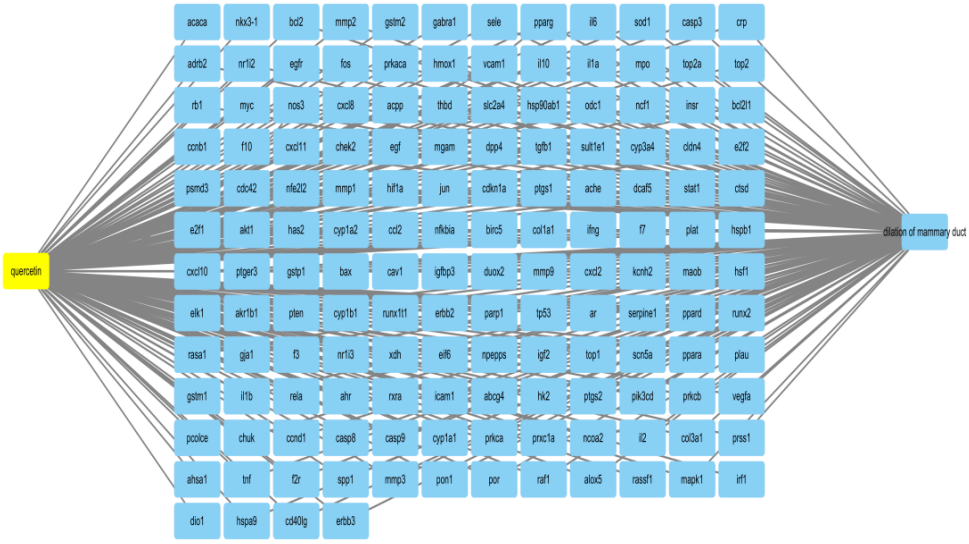

Figure 2: Schematic diagram of component-disease-target

3.3. PPI network for quercetin treatment of 2. 1dilation of mammary duct

The shared targets of the drug and diseases were imported into the STRING database and analyzed using Cytoscape 7. 1 software. The analysis involved filtering based on degree values to identify core targets, resulting in 138 nodes and 2608 edges in the network. These targets mainly include AKT1, IL-6, TP53, TNF, VEGFA, CASP3, IL1B, EGFR, JUN, etc. These targets may be the core targets of quercetin in the treatment of dilation of mammary duct, as shown in Figure 3.

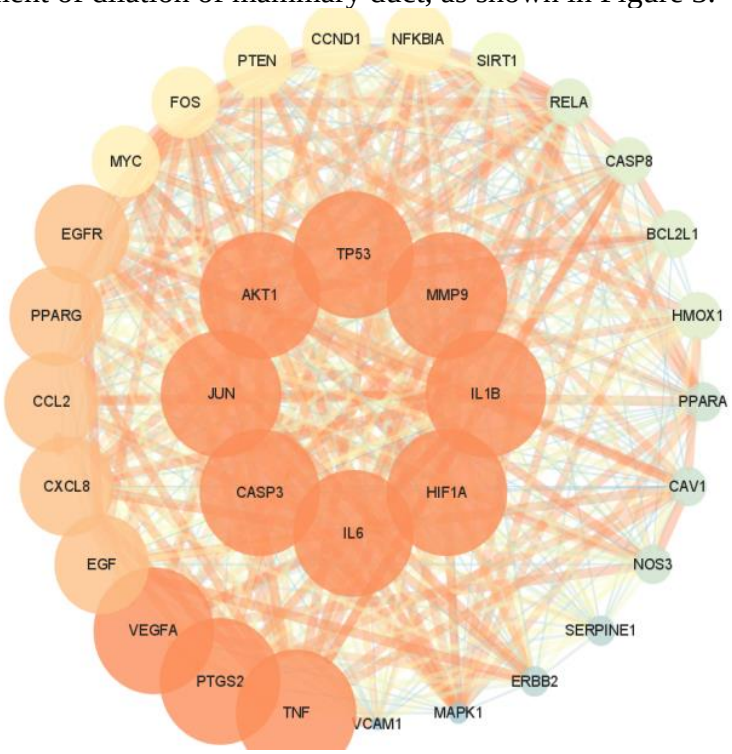

Figure 3: PPI network of quercetin and Dilation of mammary duct intersection targets

3.4. GO function and KEGG pathway analysis

The shared drug targets were imported into the DAVID database for Gene Ontology (GO) enrichment analysis, including 666 entries for biological process, 98 entries for cellular components, and 128 entries for molecular function. Among them, biological process involves positive regulation of gene expression, positive regulation of transcription, DNA-templated, negative regulation of apoptotic process etc. and cell components involve extracellular space, extracellular region, macromolecular complex, etc. Molecular function involves such processes as enzyme binding, protein binding, identical protein binding, Visualization was performed based on the first five plots of P-values, arranged in ascending order, as depicted in Figure 4. The enrichment analysis of the KEGG pathway yielded 170 pathways, mainly involved AGE-RAGE signaling pathway in diabetic complications, Pathways in cancer, Lipid and atherosclerosis, etc., as shown in Figure 5.

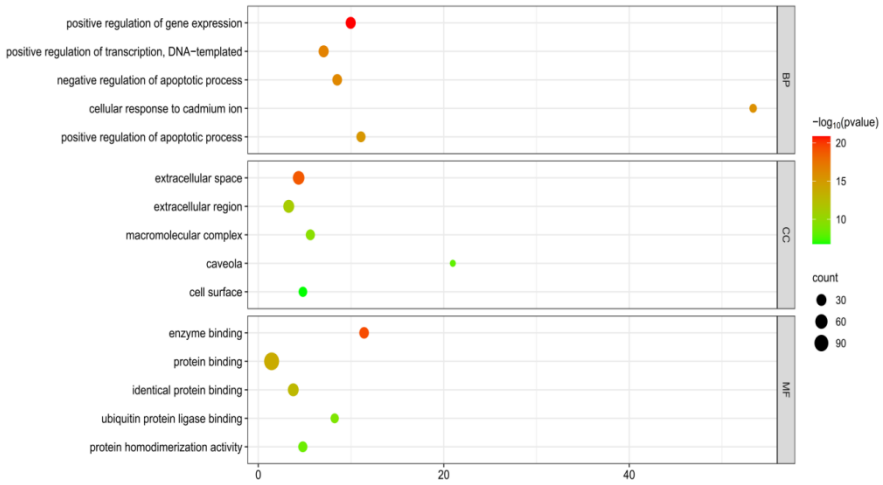

Figure 4: Schematic diagram of GO functional enrichment analysis of quercetin in the dilation of mammary duct

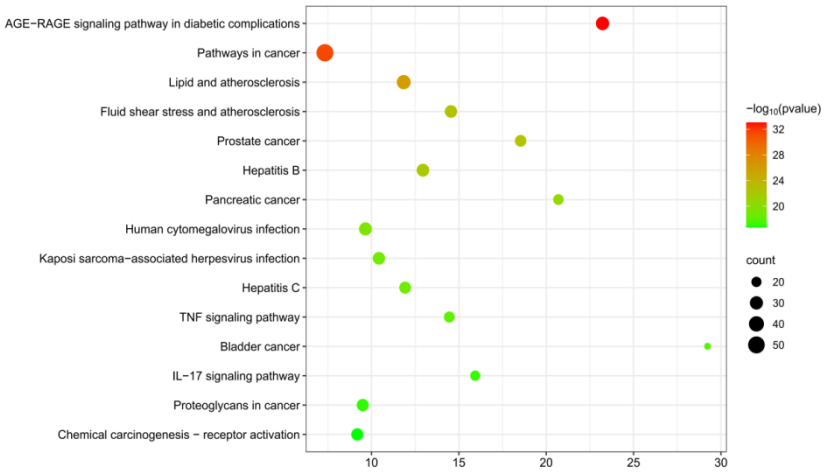

Figure 5: Bubble plot of KEGG pathway analysis for quercetin therapy dilation of mammary duct

3.5. Molecular docking result

The binding ability of AKT1 and IL-6, the top targets in the PPI network, to quercetin was predicted. The target protein was used as the receptor, the active ingredient was used as the ligand, and the lowest binding energy was used as the docking result of the target protein and ligand. If the binding energy is less than -5. 0kcal/mol, it indicates that the target protein and the active ingredient bind well, and the smaller the binding energy, the better the docking. According to the docking results, the binding energies of both components and targets are less than zero, indicating that both components and targets have good binding activity. The binding energy between quercetin and IL-6 was -5. 12kcal/mol, the lowest binding energy, and the best binding ability. The binding energy of quercetin and AKT1 was -4. 35kcal/mol, indicating a good binding ability. Studies confirmed that the core targets docking well with quercetin. See Figure 6 and Figure 7.

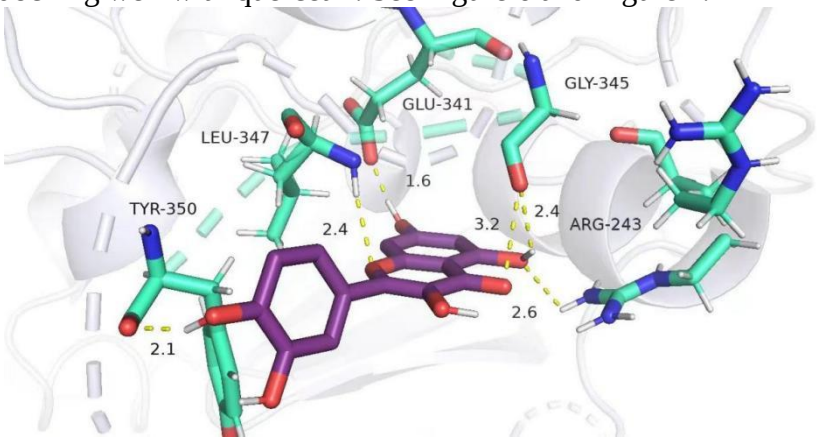

Figure 6: Quercetin docking with AKT1 target molecules

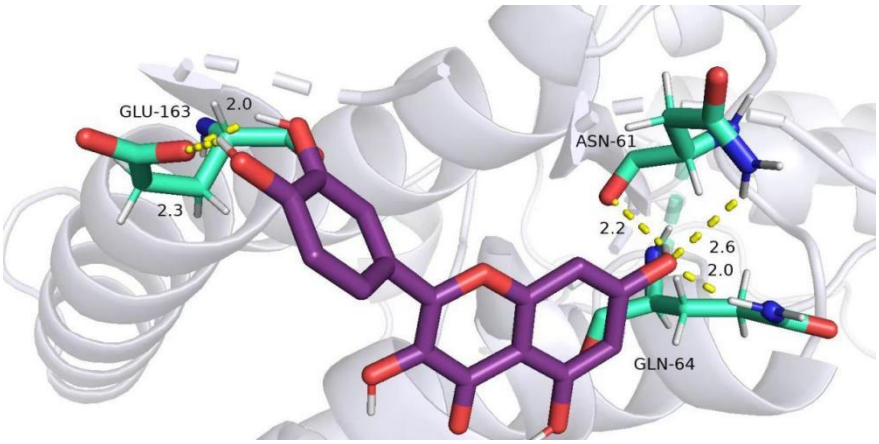

Figure 7: Molecular docking of quercetin with the core target

4. Discussion

In this review, the potential mechanism of quercetin in the treatment of dilation of mammary duct was explored using network pharmacology and molecular docking techniques. Network pharmacological results showed that AKT1, IL-6, TP53 may be key targets for quercetin in the treatment of dilation of mammary duct. AKT1 is a protein shock. One particular subtype of Enzyme B, known as AKT, assumes a pivotal role in modulating downstream signaling pathways involving glycogen synthase kinase 3 (GSK-3β), caspase-9 and the pro-apoptotic protein Bad. This intricate regulatory cascade orchestrated by AKT governs fundamental cellular processes, including but not

limited to cell growth, differentiation, apoptosis and angiogenesis [12-13]. The multifaceted actions of AKT underscore its significance in orchestrating cellular responses and physiological functions. IL-6 is a member of the pro-inflammatory cytokine family that induces the expression of a variety of proteins responsible for acute inflammation and plays an important role in the proliferation and differentiation of human cells [14]. The p53 protein, encoded by the gene TP53, also regulates many metabolic pathways in glucose, lipid, and amino acid metabolism by inducing the ability of precancerous cell apoptosis, cell cycle arrest, and aging, allowing cells to adapt and survive under mild metabolic stress [15].

According to KEGG analysis, TNF signaling pathway and IL-17 signaling pathway may be the key pathways of quercetin action and dilation of mammary duct, Tumor necrosis factor (TNF), also known as TNF-α, is a cytokine that can directly kill tumor cells without obvious cytotoxicity to normal cells [16]. It is involved in systemic inflammatory response and is one of the cytokines that make up the acute phase response. It is primarily produced by activated macrophages, although many other types of cells such as CD4 + lymphocytes, NK cells, neutrophils, mast cells, eosinophils, and neurons can also produce TNF [17]. There are two types of TNF-binding receptors, TNFR1 (TNF-receptor type 1) and TNFR2 (TNF-receptor type 2) [18]. TNFR1 is expressed in most tissues and can be fully activated by the soluble trimer form TNF, whereas TNFR2 is commonly found in cells of the immune system. Upon binding, TNF triggers the activation of many pathways, including the NFkB and MAPK pathways. The key role of interleukin-17 (IL-17) and T-helper 17 (T(H)17) cells in tissue inflammation, autoimmunity, and host defense, Its pathway inhibitors have yielded positive results in inflammatory diseases such as psoriasis, rheumatoid arthritis and ankylosing spondylitis [19].

In summary, this study uses a network pharmacological method to screen the key targets of quercetin in the treatment of dilation of mammary duct, Based on the enrichment pathway, Quercetin may be used to treat dilation of mammary duct through multiple pathways and multiple targets. This study will carry out subsequent cell experiments and animal experiments to verify the mechanism of quercetin in the treatment of dilation of mammary duct.

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